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# Total Synthesis of Furospongolide and Related Furanolipid Analogues as Potential Anti-tumour Agents



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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

**Donal P. Harrold, B.Sc.**

A Thesis presented for the Degree of
Doctor of Philosophy
to
THE NATIONAL UNIVERSITY OF IRELAND, CORK.

Department of Chemistry
University College Cork

*Supervisor: Dr. Stuart G. Collins*
*Head of Department: Prof. Michael Morris*

*December 2013*

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*Abbreviations* *i*

*Appendices can be found on a CD attached to this thesis*

## DECLARATION BY CANDIDATE

I declare that this thesis contains my own work and has not been submitted for another degree, either at University College Cork, or elsewhere

_____

Donal P. Harrold

## Acknowledgements

I would like to take this opportunity to sincerely thank all the people who helped me throughout my academic years in UCC. First and foremost, I would like to express my sincere gratitude to my supervisor Dr. Stuart Collins for all his help, encouragement and support throughout my research project and especially during the writing of my thesis. He is a true friend who I'm personally indebted to. Special thanks to Dr. Dan McCarthy and Dr. Lorraine Bateman for NMR work conducted; Dr. Florence McCarthy and Mick O' Shea for the mass spectrometry service; Dr. Nuala Maguire for HPLC assistance; Helen Kelly and Barry O'Mahony for microanalysis and the technical staff in the chemistry department.
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Donal P. Harrold

## Abstract

This thesis details the design, development and execution of innovative methodology in the total synthesis of the terpene-derived marine natural product, furospongolide. It also outlines the synthetic routes used to prepare a novel range of furanolipids derivatives and subsequent evaluation of their potential as antitumour agents.

The first chapter is a review of the literature describing efforts undertaken towards the synthesis of biologically active furanosesterterpenoid marine natural products. A brief discussion on the sources and biological activity exhibited by furan natural products is also provided. In addition, a concise account of the role of hypoxia in cancer, and the increasing interest in HIF-1 inhibition as a target for chemotherapeutics is examined.

The second chapter discusses the concise synthesis of the marine HIF-1 inhibitor furospongolide, which was achieved in five linear steps from (*E,E*)-farnesyl acetate. The synthetic strategy features a selective oxidation reaction, a Schlosser $sp^3$-$sp^3$ cross-coupling, a Wittig cross-coupling and an elaborate one-pot selective reduction, lactonisation and isomerization reaction to install the butenolide ring. The structure-activity relationship of furospongolide was also investigated. This involved the design and synthesis of a library of structurally modified analogues sharing the same C1-C13 subunit. This was achieved by exploiting the brevity and high level of convergence of our synthetic route together with the readily amenable structure of our target molecule. Exploiting the Schlosser cross-coupling allowed for replacement of furan with other heterocycles in the preparation of various furanolipid and thiophenolipid derivatives. The employment of reductive amination and Wittig chemistry further added to our novel library of structural derivatives.

The third chapter discusses the results obtained from the NCI from biological evaluation From a collection of 28 novel compounds evaluated against the NCI-60 cancer cell array, six drug candidates were successfully selected for further biological evaluation on the basis of antitumour activity. COMPARE analysis revealed a strong correlation between some of our design analogues and the blockbuster anticancer agent tamoxifen, further supporting the potential of furanolipids in the treatment of breast cancer.

The fourth chapter, details the full experimental procedures, including spectroscopic and analytical data for all the compounds prepared during this research.

To Mom and Dad

“Live as if you were to die tomorrow. Learn as if you were to live forever.”

*Mahatma Gandi*

# Chapter 1

# *Introduction*

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# 1.1 Background

## 1.1.1 Overview

The purpose of this introduction is to give a comprehensive overview on both the chemical and biological significance of furanolipids to modern day science. With respect to the latter, a furanolipid based natural product known as furospongolide was isolated from an Indonesian marine sponge and was found to possess promising antitumour activity towards the treatment of breast cancer. Today, furospongolide is recognised as a small molecule inhibitor of hypoxia-induced HIF-1 activation, which has recently become an attractive target for advanced stage cancer therapy. In this chapter, we will discuss the role of hypoxia in cancer, and the increasing interest in HIF-1 inhibition as a target for chemotherapeutics. In addition, we will examine recent advances in the discovery and development of small molecule inhibitors that target the HIF-1 pathways as potential antitumour agents.

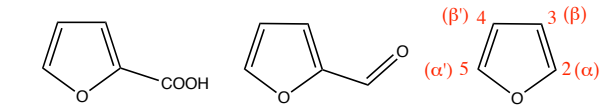
As furospongolide is a member of a large family of terpene-derived furanosesterterpenoids, we will be reviewing the literature describing efforts undertaken towards the synthesis of structurally related sesterterpenoids, focusing on completed total syntheses of biologically active marine natural products. This review will provide us with innovative methodology to achieve the concise total synthesis of furospongolide as well as promising concepts to alter its structure and increase its potency as an antitumour agent.

We will begin this chapter by discussing the history of furan, its physical and chemical properties; traditional and modern methods towards the synthesis of this heterocycle as well as describing some diverse biologically active natural products containing furan(s).

### 1.1.2 History of Furan

The earliest furan compound discovered is pyromucic acid **1**, more commonly known as furoic or furan-2-carboxylic acid (***Figure 1.1***). Pyromucic acid **1** was first isolated by Carl Wilhelm Scheele in 1780 by the dry distillation of mucic acid. In 1832 furfural **2**, or furan-2-carbaldehyde, was obtained by the action of sulfuric acid and manganese dioxide on sugar, but these furans were not related until 1860, when furfural **2** was oxidized to furoic acid **1** with silver oxide (***Scheme 1.1***).[1,2] Furan **3** itself was first prepared by Heinrich Limpricht in 1870 by treating barium furoate with soda lime.[3]

In 1922 furfural **2** became commercially available, economically and in large-scale quantities from Quaker Oats Company from the acid hydrolysis of cereal waste. At this time the outlets for furfural **2** was limited except for its occasional use in perfume, but its low cost and availability greatly stimulated the search for uses. Today furfural **2** is still produced from agricultural by-products like sugarcane bagasse and corncobs and is the usual starting material for commercial preparation of other simple furans. This industrially used method of preparation of furans is rare as it is based on a renewable starting material rather than on oil, gas, or coal.[4-6]



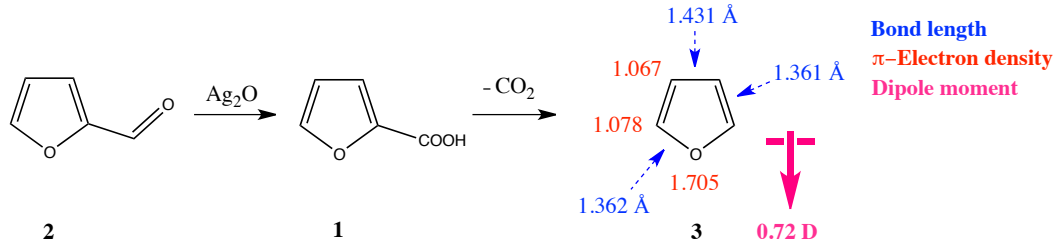

*Furan-2-carboxylic acid* **1** *Furan-2-carbaldehyde* **2** *Furan* **3**

***Figure 1.1***

The positions in the furan ring are usually numbered, but in older literature a less convenient lettering system was sometimes used as illustrated in ***Figure 1.1***. The compounds commonly known as furoic acid **1** and furfural **2** could therefore be named furan-2-carboxylic acid and furan-2-carbaldehyde respectively.[1]

### 1.1.3 Physical properties of furan

Furan **3** itself is a colourless, volatile and highly flammable oil (b.p. 31-36 $^{o}$C), which is slightly soluble in water and miscible with most organic solvents. The arrangement of the atoms in the ring was proved by Baeyer in 1877 following the conversion of furfural **2** into furan **3** as exemplified in ***Scheme 1.1.***[1]




***Scheme 1.1***

Furan cannot be accurately represented by classical structure **3**, as it is best considered as a resonance hybrid of the formulae **3a-3d**. The furan molecule is far from a regular pentagon in shape and the bond lengths suggest that structure **3** is the major contributor to the resonance hybrid (***Figure 1.2***).[1]

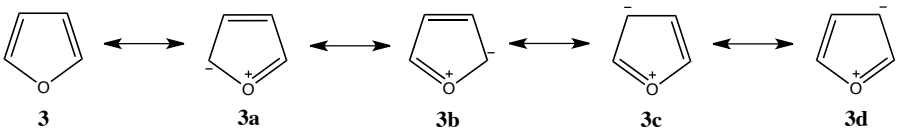
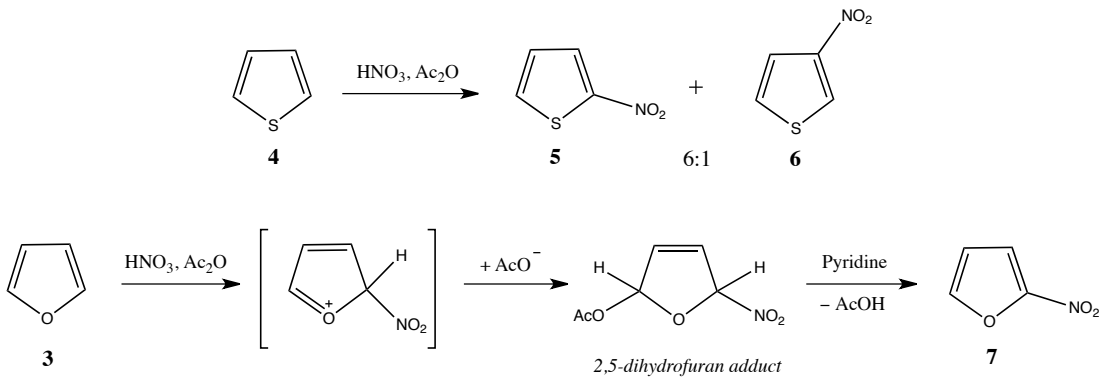



***Figure 1.2***

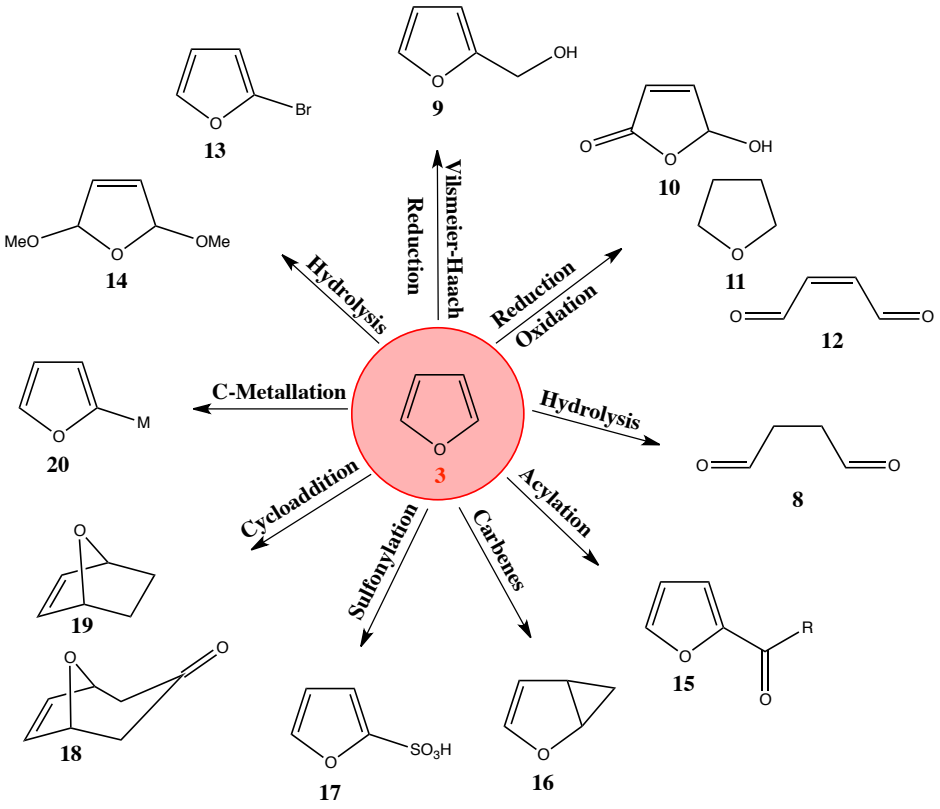
### 1.1.4 Chemical properties of furan

Furan **3** and thiophene **4** can usefully be examined in parallel, comparing one with the other and with pyrrole.[7] Furan **3** is an electron-rich heterocycle and is generally less reactive than pyrrole towards electrophiles (by a factor of about $10^5$) although it is still much more reactive than benzene. Although furan **3** clearly exhibits aromatic stabilisation, its resonance energy (~16 kcal/mol) is significantly less than that of benzene (~36 kcal/mol), and thus it can be converted to non-aromatic derivatives under fairly mild conditions (most like a 1,3-diene). In the trio of heteroaromatic systems, furan **3** is much less aromatic than pyrrole (~22 kcal/mol) and thiophene **4** (~30 kcal/mol) is the most synthetically flexible of the aromatic heterocycles. For example, thiophene **4** undergoes normal nitration, with selectivity for α-substitution (**5**) rather than β-substitution (**6**) similar to pyrrole. In contrast, furan **3** tends to produce 2,5-dihydrofuran adducts (stable isolatable intermediate) in which the elements of the attacking agent have added to the heterocycle with subsequent loss of aromaticity. The aromatic substitution product **7** can be easily obtained from the adduct by base-induced loss of acetic acid as shown in ***Scheme 1.2***.[1,6,7] Nitration of furan illustrates how both addition-elimination and normal substitution mechanisms can operate together.




***Scheme 1.2:*** *Nitration of thiophene and furan using acetyl nitrate.*

One attribute that makes furan **3** such a useful building block is its ability to undergo a wide range of reactions and serve as a precursor to many important substructures (***Scheme 1.3***). Combined with its easy accessibility and its unique reactivity, furan **3** has achieved a prominent role in synthetic chemistry.




***Scheme 1.3***

The ring of furan **3** is opened easily by acids and can be hydrolysed under acidic conditions to give the saturated dicarbonyl derivative **8**. Furan **3** can be converted to alcohol **9** through a Vilsmeier-Haack reaction followed by subsequent reduction. Furan **3** is susceptible to reduction and oxidation reactions and can provide the unsaturated dialdehyde **12** by oxidative cleavage with *meta*-chloroperbenzoic acid. The cycloaddition of furan **3** with singlet oxygen gives cyclic peroxides, which break down with loss of carbon dioxide revealing five-membered lactones (**10**), which are a very common occurrence in nature and are usually referred to as butenolides. Catalytic hydrogenation of furan leads to the formation of tetrahydrofuran derivatives (**11**), which are also common features in a vast array of natural products. Furan **3** reacts rapidly with bromine in dioxane at 0 $^{o}$C to form 2-bromofuran **13**. However, if a nucleophilic solvent like methanol was employed, furan can be oxidised to a stable adduct, 2,5-dihydro-2,5-dimethoxyfuran **14** resulting from nucleophilic displacement of the bromide.[7] Furan **3** is the least aromatic 5-membered ring and therefore reacts readily

with electron-deficient dienophiles to afford oxabicyclo[2.2.1]heptane derivatives (**19**). Furan also participates in [4+3] cycloadditions with oxyallyl cations to give oxabicyclo[3.2.1]octane derivatives (**18**). In furan **3**, the 2 and 5 positions are the sites of maximum π-electron density as a result of electron donation from the heteroatom and consequently they are the favoured positions for sulfonylation (**17**), acetylation (**15**), metallation (**20**) and condensation reactions (**9**) (***Scheme 1.3***).

### 1.1.5 Synthesis of furans and thiophenes

Numerous routes have been developed for the ring synthesis of thiophenes and furans. With respect to the latter, two classical methods of furan ring synthesis are the *Paal-Knorr synthesis* and the *Feist-Benary synthesis* (***Figure 1.3***).

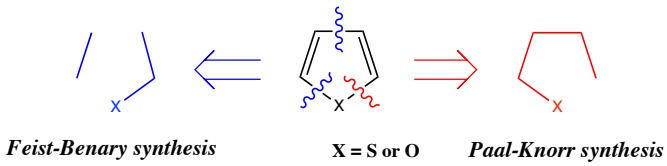
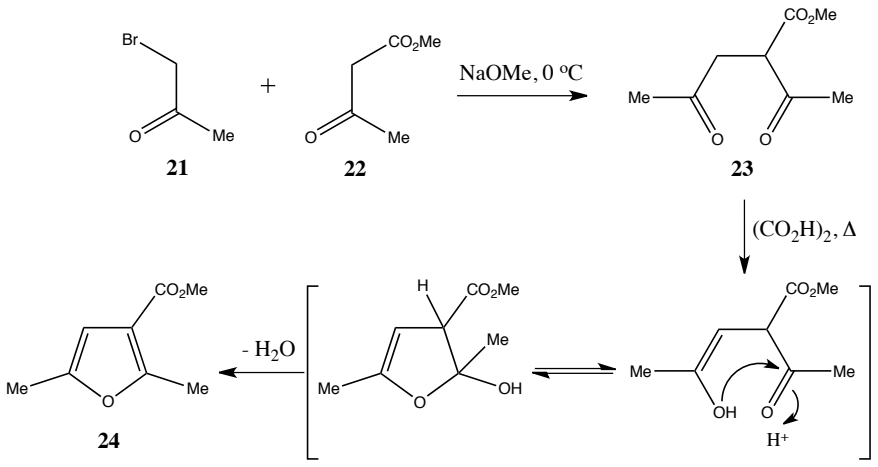


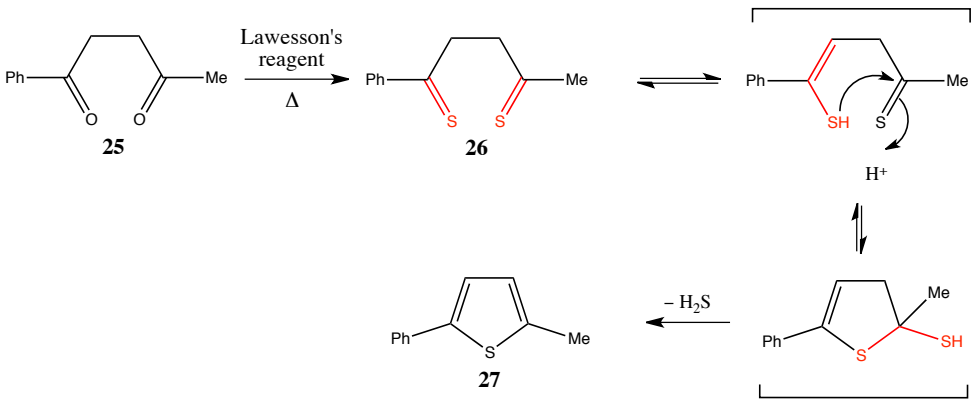

***Figure 1.3***

One of the most important methods in organic chemistry for the synthesis of furans, thiophenes and pyrroles from 1,4-dicarbonyl compounds through a dehydration reaction is known as a *Paal-Knorr synthesis.* Although the *Paal-Knorr synthesis* has seen widespread use, the mechanism wasn't fully understood until it was elucidated by van Amarnath *et al.* in the 1995.[8] The most likely sequence has intramolecular addition of enolic oxygen to the other carbonyl group requiring, loss of water to provide furan **24**. 1,4-Diketones **23** can be obtained in several ways; the alkylation of a 1,3-keto-ester **22** with α-haloketone **21** is one such method as demonstrated below in ***Scheme 1.4***.



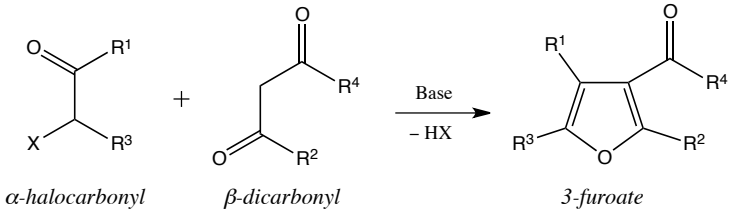

***Scheme 1.4:*** *Paal Knorr synthesis.*

The synthetic strategy for the preparation of the thiophene ring through *Paal Knorr* methodology first involves exposure of an appropriate 1,4-dicarbonyl precursor to conditions that convert a carbonyl group into a thiocarbonyl group (**25**-**26**). The reagent of choice for this transformation is Lawesson's reagent as it is more soluble in organic solvents than traditional thionation reagents like phosphorous pentasulfide. To date there is still confusion whether both carbonyl groups are converted, but exactly comparable sequences lead to the aromatic thiophene **27**, with loss of $H_2S$ (if both have been thionated) or $H_2O$ (if one has been thionated) (***Scheme 1.5***).[7]




***Scheme 1.5***

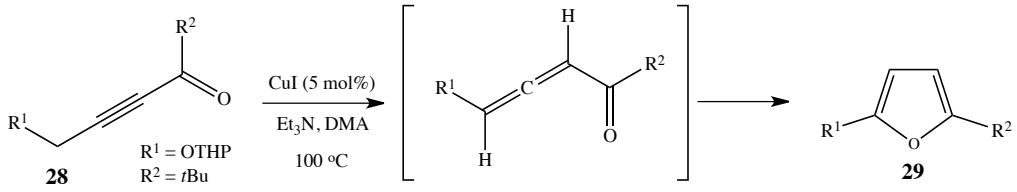
Conversely, the *Feist-Benary synthesis* occurs when an α-halocarbonyl reacts with a β-dicarbonyl in the presence of base. The resulting product is a 3-furoate that incorporates substituents present in both starting materials (***Scheme 1.6***).[5,6,9,10]




***Scheme 1.6:*** *Feist-Benary synthesis.*

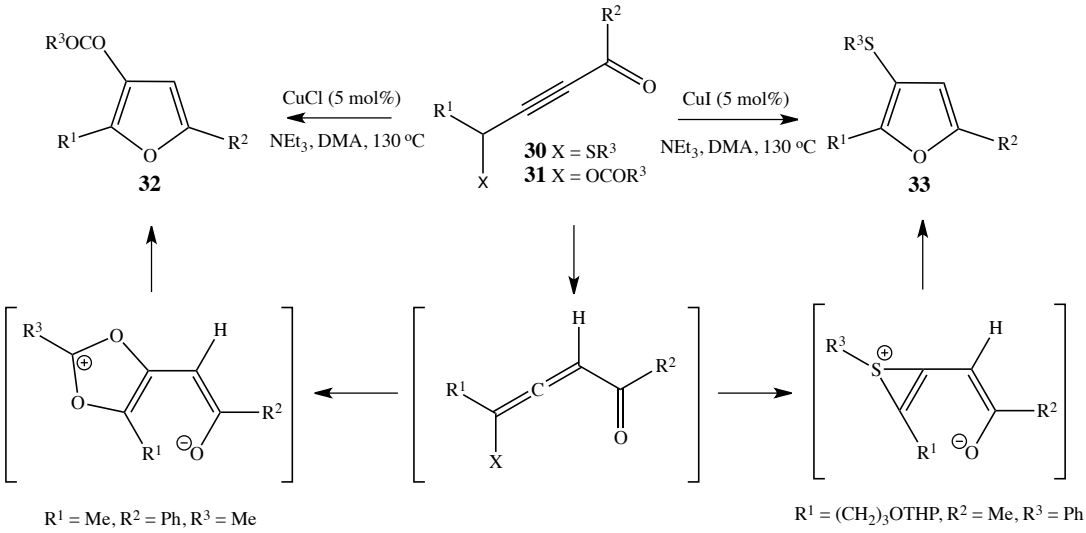
A common use of the *Feist-Benary furan synthesis* is for the preparation of 2-substituted-3-furoates. The most popular synthetic target is the furan originally prepared by Benary *et al.*, namely ethyl 2-methyl-3-furoate ($R^1$ and $R^3$ = H; $R^2$ = Me; $R^4$ = Et, ***Scheme 1.6***).[11] Although the *Paal-Knorr* synthesis and the *Feist-Benary* have proven very useful for the synthesis of furan derivatives, there are some limitations, including the difficulty in accessing furans that contain sensitive functional groups (unstable to basic conditions) and the inability to provide furans with high flexibility regarding their substitution pattern. For this reason, the development of innovative and more efficient methods for the synthesis of highly functionalized furans under milder conditions remains an area of on-going interest. Functionalised furans are frequent subunits in a variety of biological active molecules and are useful intermediates in synthetic chemistry.[12-14] A well-known approach for the synthesis of functionalised furans is transition metal-catalysed cyclisation of alkynyl,[15,16] alkenyl,[17] or allenyl ketones,[18] alcohols or epoxides.[19-21]

With respect to alkynyl ketones (**28**), Gevorgyan *et al.* investigated their utility as readily available starting materials for the synthesis of 2,5-disubstituted furans (**29**).[22] The Cu(I)-catalysed and base-assisted cycloisomerisation is believed to proceed via an intermediary allenyl isomer. This method yields disubstituted furans possessing different functional groups, such as alkenes, ethers, acetals, esters and alcohols (***Scheme 1.7***).



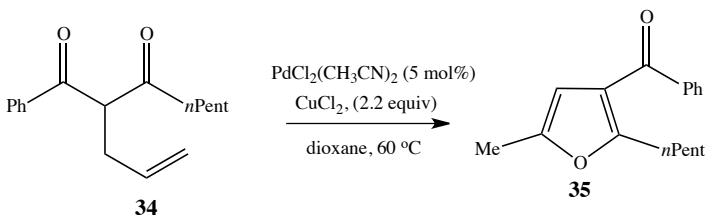

***Scheme 1.7*: *Cu(I)-catalysed synthesis of 2,5-disubstituted furans.***

An extension of this methodology was further achieved by Gevorgyan *et al.* for the preparation of trisubstituted furans **32** and **33** by employing 4-thio and 4-acyloxybut-2-ynones **30** and **31** in an innovative, Cu(I)-catalysed, synthetic route as illustrated in ***Scheme 1.8.***[23,24]




***Scheme 1.8:*** *Synthesis of 3-thio- and 3-acyloxy-substituted furans. 1,2 migration has been proposed as the key step in the copper-catalysed propargyl-propenyl isomerisation in the synthesis of trisubstituted furans.*[25]

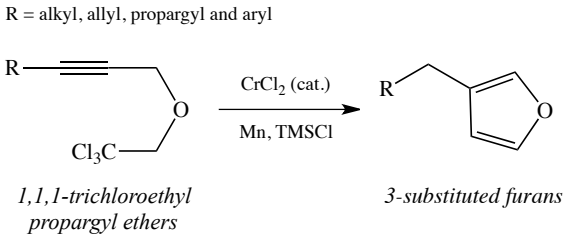
Since olefins are more readily available than are alkynes and allenes, Widenhoefer *et al.* exploited alkenyl substrates as suitable starting materials for the transition metal catalysed synthesis of furan *via* heterocyclization.[26] In this scenario, α-alkenyl-β-diketone **34** underwent furan formation using a Pd(II) source and $CuCl_2$ as an oxidant to afford the trisubstituted furan **35** (***Scheme 1.9***).




**34** **35**

***Scheme 1.9:*** *Palladium-catalysed oxidative alkoxylation of an α-alkenyl-β-diketone to form a functionalised trisubstituted furan.*[25]

Synthesis of simple 3-substituted furans can be achieved *via* reductive annulation of 1,1,1-trichloroethyl propargyl ethers employing catalytic $Cr(II)Cl_2$ regenerated by Mn/TMSCl (***Scheme 1.10***).[27] This reaction is synthetically useful in the synthesis of 3-substituted natural products.




***Scheme 1.10:*** *Reductive annulation using catalytic Cr(II) regenerated from Mn/TMSCl*

The field of furan synthesis has attracted significant interest in the last century with the emergence of many natural and pharmaceutically important furan-containing substances.[28] The literature is saturated with concise methodology for accessing mono-, di-,tri-, or tetra-substituted furans and will continue to rapidly advance with the discovery of more complex and challenging furan containing natural products. An extensive review by Kirsch *et al*. on recent developments in the synthesis of polysubstituted furans in available in the literature.[25]

### 1.1.6 Natural products containing the furan ring

The furan ring system is found in many naturally occurring compounds, either as a fully unsaturated structure or in a reduced or partly reduced form. The majority of the naturally occurring compounds containing a fully unsaturated furan ring are terpenoid in character; like the di-substituted rosefuran **37** (rose oil) and mono-substituted perillene **36** (secondary plant metabolite). However, simple furan-containing natural products like furfuryl thiol **41** (aroma in roasted coffee) do exist. Furans that occur in nature in a reduced or otherwise modified form include pentose sugars such as ribose **38** and deoxyribose **39**, which are components of nucleic acids and several types of unsaturated γ-lactone like ascorbic acid **40** (vitamin C) as seen in ***Figure 1.4***.[6,29]

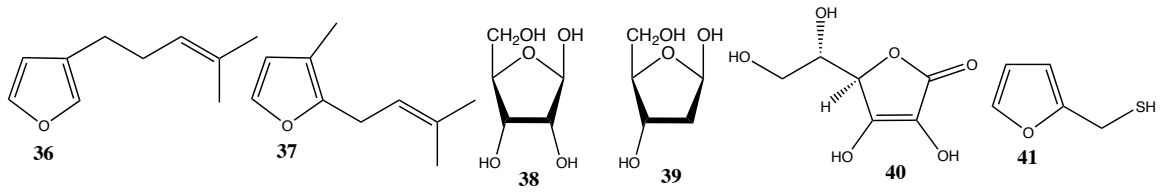
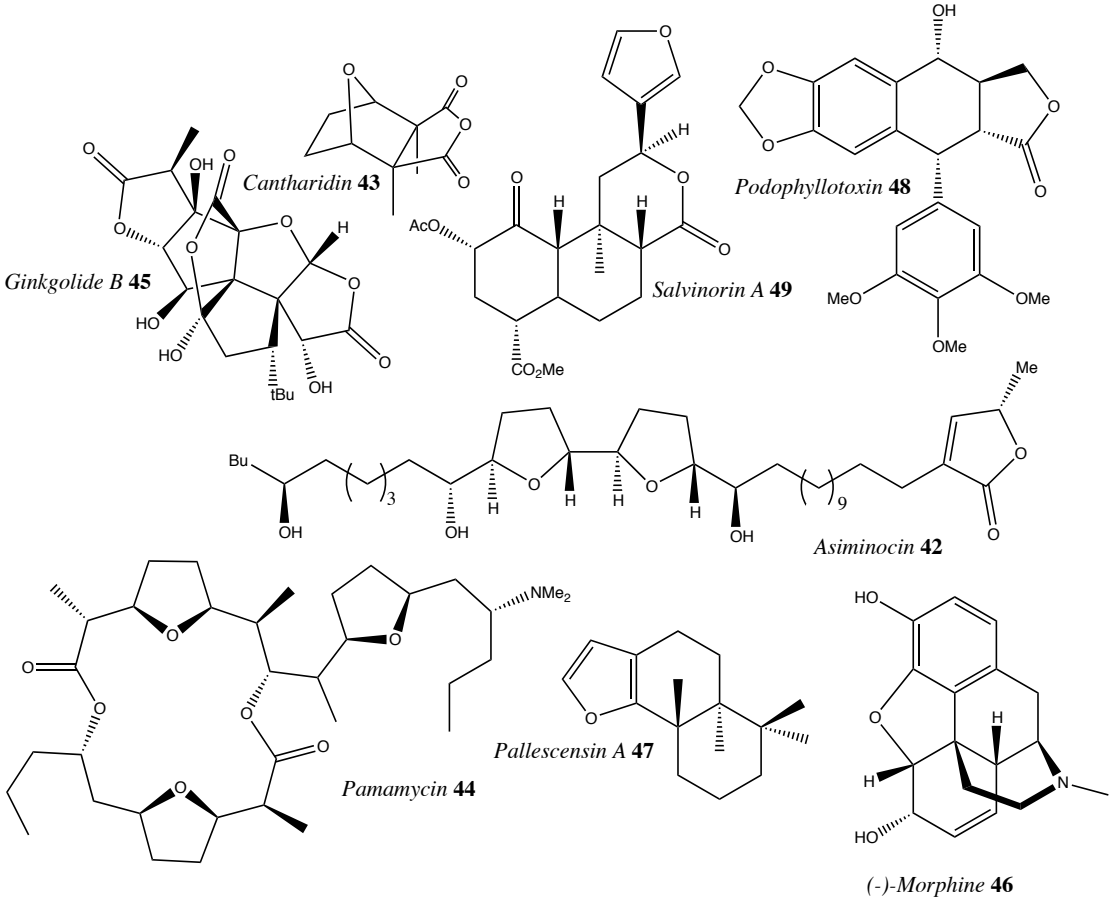



***Figure 1.4***

The furan ring is also present in a huge variety of natural products, such as polyketides, phenylpropanoids, alkaloids and terpenes. In general, the natural compounds containing the furan rings and its derivatives (di, tetrahydro, γ-lactone) have been found in all classes of terrestrial (fungi, bacteria, insects, plants) and marine (bacteria, fungi, algae, mollusc, sponge, seaweed) organisms.[30]

The different structural types of natural products with furan rings cover the acetogenins (asimicin),[31] morphinanes (morphine), cembranolides (deoxypukalide),[32] manzamine-related alkaloid (nakadomarin),[33] macrolide antibiotics, polycyclic ethers, lignans (podophyllotoxin), ginkgolides (ginkgolide B),[34,35] quassinoids, limonoids, furanflavonides, furanoquinones, steroidal glycosides (cephalostatins,[36] ritterazines[37]), macrodiolides (pamamycin),[38] among others.[30] ***Table 1.1*** shows representative examples of the families of natural products containing furans.

***Table 1.1:*** *Illustrates examples of the families of natural products containing furans**




| Product | Natural source | Biological activity |
|---|---|---|
| Asiminocin **42** | *Asimina triloba* | Antitumour, pesticidal, antimalarial[39] |
| Cantharidin **43** | *Mylabris phalerata* | Hepatocarcinoma[40] |
| Pamamycin **44** | *Streptomyces alboniger* | Antibiotic[41] |
| Ginkgolide B **45** | *Ginkgo biloba* | Dementia and age related cognitive decline[35,42] |
| Morphine **46** | *Daphniphyllum calycinum* | Analgesic[43] |
| Pallescensin A **47** | *Disidea pallescens* | Defence[44] |
| Podophyllotoxin **48** | *Podophyllum* | Cytotoxic, antviral[45] |
| Salvinorin A **49** | *Salvia divinorum* | Psychoactive[46] |

*** Data sourced from 'Heterocycles in Natural Product Synthesis' by Boto *et al.*[30]**

## 1.1.7 Isolation of furospongolide

### 1.1.7.1 Introduction to furan derivatives isolated

The transcription factor hypoxia-inducible factor-1 (HIF-1) has stimulated significant interest as a novel molecular target for anticancer drug discovery. Following its discovery by Goldberg and Semenza *et al.* in the early 90's,[47,48] numerous clinical trials strongly support HIF-1 as a valid molecular target for drug discovery in the treatment of tumour hypoxia.[49,50] Hypoxia influences many aspects of the biology of tumours and is directly associated with resistance to therapy, tumour progression, and patient mortality.[51] Inhibition of HIF-1 activation has been shown to suppress the growth and spread of hypoxic tumours.[52] To the best of our knowledge, despite extensive drug discovery research, there is no approved drug that directly targets tumour hypoxia.[53] The majority of small molecule HIF-1 inhibitors discovered and developed in recent times are indirect inhibitors of HIF-1 activation.[54]

Marine natural products have recently become an extraordinary resource for the discovery of new anticancer agents that effectively suppress numerous antitumour molecular targets. Several research programs have begun to examine their potential as HIF-1 activation inhibitors.[52,55,56] Thus far, cell-based and *in-vitro* high-throughput screening has been effective in identifying new compounds that inhibit HIF-1. At the forefront of these investigations has been Dale. G. Nagle. His research group extensively explored the biomedical potential of marine natural products as new sources of drug leads for the treatment of cancer, whereby the group developed new molecular-based bioassays to investigate natural products for their potential to supplement existing chemotherapeutic agents.

Using a human breast carcinoma T47D cell-based reporter assay, Nagle *et al.* evaluated the HIF-1 inhibitory activity of over 15,000 natural product-rich extracts from various marine organisms and plants obtained from the NCI Open Repository. This screening effort has yielded an array of structurally diverse natural product-derived HIF-1 inhibitors such as manassantin B **50**,[57] 7-hydroxyneolamellarin A **52**,[58,59] laurenditerpenol **51**,[60,61] and tetrahydroisoquinoline alkaloids klugine **53** and emetine **54** (***Figure 1.5***).[62]

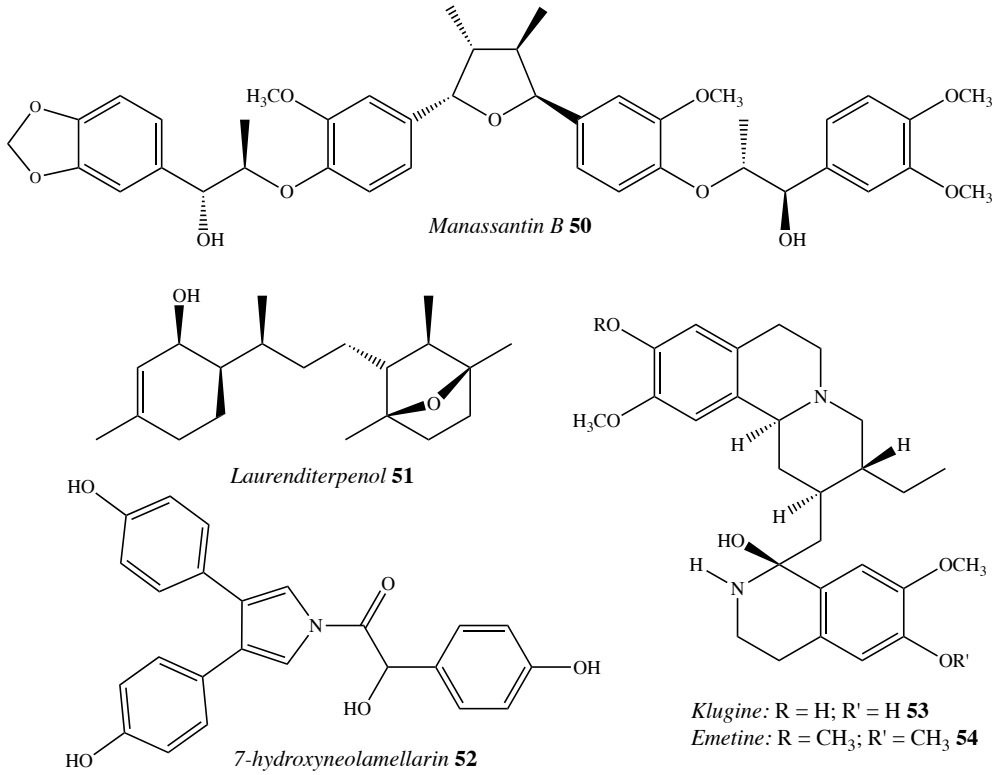
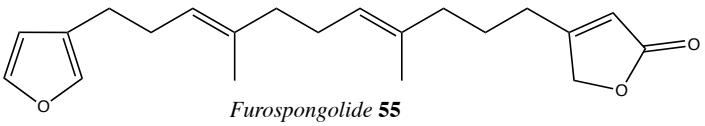



***Figure 1.5***

As part of this molecular-targeted antitumour drug discovery program, an active extract of the tropical marine sponge *Lendenfeldia sp.* (5 $\mu$g $mL^{-1}$) collected from shallow water in Saipan was found to inhibit hypoxia (1% $O_2$)-induced HIF-1 activation by 91%. Bioassay-guided chromatographic separation of this active extract from the NCI Open Respository of marine invertebrate extracts yielded the terpene-derived furanolipid furospongolide **55**, one novel scalarane sesterterpene **56** and two previously reported scalaranes **57** and **58** as illustrated in ***Figure 1.6***.[63-65]



*A photo of Lendenfeldia sp. which has been taken from the Wild Singapore website.*[66]



*Furospongolide* **55**

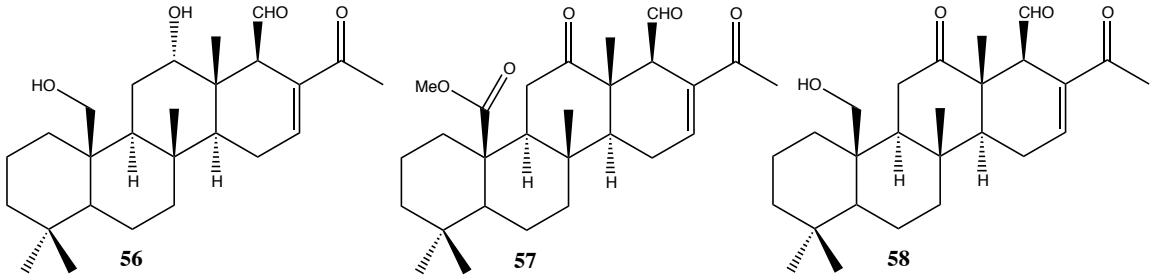



***Figure 1.6:*** *Illustration of the four components* ***55-58*** *isolated from an active extract of the marine sponge Lendenfeldia sp.*

The first reported isolation of furospongolide **55** was by Kashman *et al.* in 1980 from the marine sponge *Dysidea herbacea* collected in the Gulf of Suez (Red Sea).[64] Following spectroscopic analysis of the $C_{21}$ metabolite **55**, data was consistent with the presence of a α,β-unsaturated-γ-lactone and a furan ring joined at the terminal ends of a linear carbon skeleton. The close relationship between **55** and the furospongin family led to the name, furospongolide **55**.[64,67]

### 1.1.7.2 Biological evaluation of furospongolide

The compounds **55-58** isolated from the active marine extract were tested independently in a concentration-response study to determine their effect on HIF-1 activation in T47D and PC-3 (human prostate tumour) cell-based reporter assay (***Figure 1.6***).[52] Among the four *Lendenfeldia sp.* metabolites isolated, furospongolide **55** was the only relatively non-cytotoxic inhibitor of hypoxia (1% $O_2$)-induced HIF-1 activation with an $IC_{50}$ value of 2.9 $\mu$M in the T47D breast tumour cell line (***Figure 1.7***). Disappointingly, the three scalaranes **56-58** were found to be cytotoxic, showing only a narrow therapeutic window between the HIF-1 inhibitory activity and the suppression of cell proliferation/viability in T47D cells.

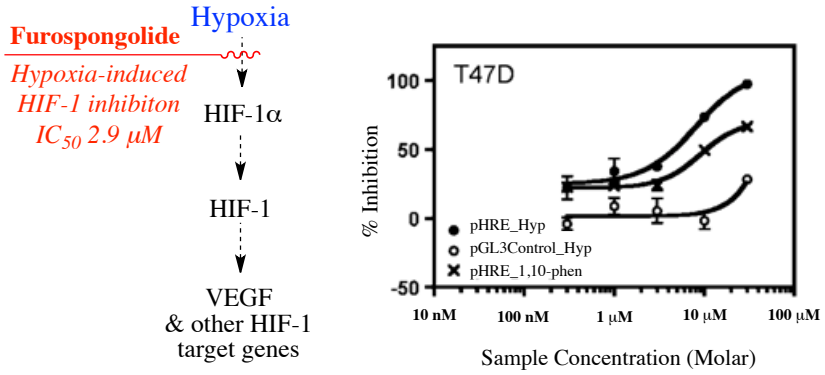



***Figure 1.7:*** *Concentration response effect of furospongolide **55** on HIF-1 activity in T47D cell reporter assays as reported by Liu et al.*[52] *"pHRE_Hyp": cells were transfected with the pHRE-TK-Luc reporter; "pGL3Control_Hyp": cells transfected with the control plasmid pGL3-Control; "pHRE_1,10-phen": Cells treated with a hypoxia mimetic, 1,10-phenanthroline (10 μM).*

Utilising cutting edge molecular mechanism-targeted bioassay techniques, furospongolide **55** was found to suppress HIF-1 activation by inhibiting the hypoxia induction of HIF-1α protein. Furospongolide **55** was shown to block the hypoxia-induced production of the downstream HIF-1 target secreted Vascular Endothelial Growth Factor (VEGF) in a concentration dependant manner as illustrated in ***Figure 1.8.*** Surprisingly, furospongolide **55** only weakly inhibited the induction of HIF-1α protein by 1,10-phenanthroline (chemical hypoxia). Thus, **55** selectively inhibits hypoxic activation of HIF-1 by blocking the induction of HIF-1α protein.

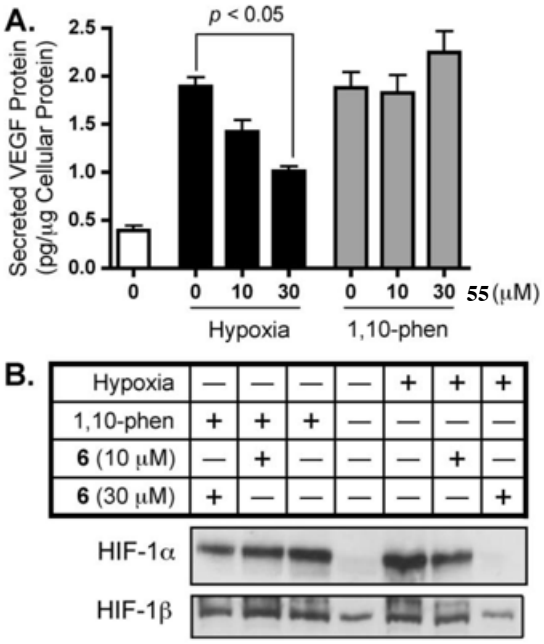



***Figure 1.8:*** *Furospongolide **55** inhibited hypoxia induction of HIF-1 target VEGF protein (**A**) and blocks the induction of nuclear HIF-1α protein accumulation (**B**) as reported by Liu et al.*[52]

The generation of mitochondrial reactive oxygen species (ROS) at complex III in hypoxic cells is generally believed to play a vital role in HIF-1 regulation. Mitochondria electron transport chain (ETC) inhibitors constitute one group of recently recognised small-molecule HIF-1 inhibitors.[68,69] Inhibitors of the mitochondrial ETC could block the production of ROS-mediated signalling processes that stabilize HIF-1α protein under hypoxic conditions. Liu *et al.* used a Clark-type electrode system to measure mitochondrial respiration in the same T47D cells that were used to examine HIF-1 activation. Furospongolide **55** inhibited cellular oxygen consumption at concentrations as low as 10$\mu$M (38% inhibition) in a concentration dependant manner as illustrated in ***Figure 1.9***.[52] Additional mechanistic studies indicated that furospongolide **55** inhibits hypoxia-induced HIF-1 activity by blocking NADH-ubiquinone oxidoreductase (complex 1)-mediated mitochondrial electron transfer, thereby suppressing tumour cell respiration and hypoxic ROS generation.[52]

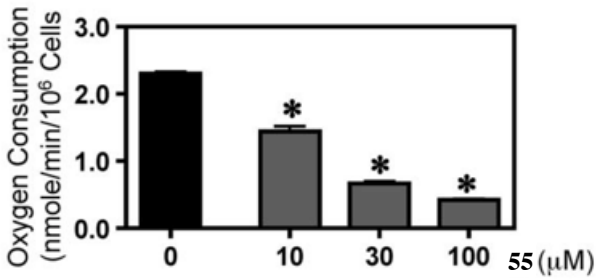



***Figure 1.9:*** *Furospongolide* ***55*** *inhibited oxygen consumption in T47D cells by disrupting the mitochondrial electron chain at complex I as reported by Liu et al.*[52]

Interestingly in 2013, Sagar *et al.* made a hypothesis linking furospongolide **55** to angiogenesis via the VEGF. Inhibition of VEGF has been shown in studies to block angiogenesis in tumour cells.[70] Thus it was proposed by Sagar *et al.* that furospongolide **55** could potentially be used as a drug to block angiogenesis in solid tumours (***Figure 1.10***).

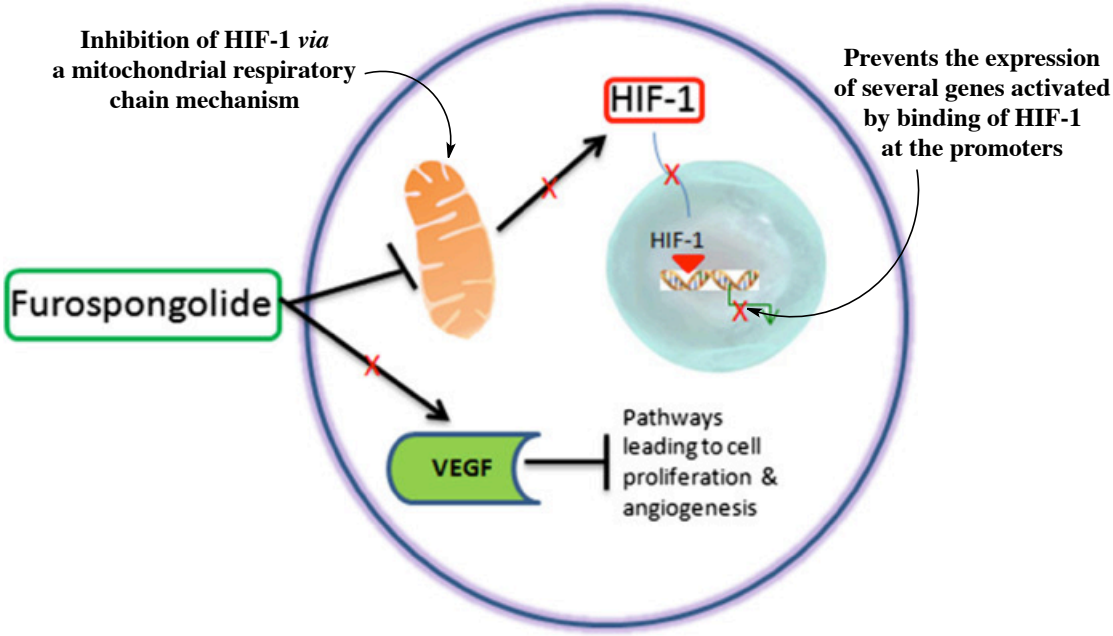



***Figure 1.10****: A basic summary of the possible mechanism of action of furospongolide* ***55*** *in a tumour cell as depicted by Sagar et al.*[70]

While furospongolide **55** represents only a moderate potency inhibitor ($IC_{50}$ 2.9 $\mu$M), it is the first marine-derived furanolipid found to inhibit hypoxia-induced HIF-1 activation. The molecular target of **55** is linked with possible mitochondrial-associated toxicity and together with its arresting bioactivity and unusual natural structure, makes this furanolipid an attractive target for total synthesis, structural modification and possible pharmaceutical optimisation in the development of a potent anticancer agent.[52,56]

## 1.1.8 Biological Background

### 1.1.8.1 Cancer

Cancer is a term used to describe diseases in which abnormal cells divide without control and are able to invade other tissues. There are more than 100 different types of cancer and they are classified by the organ or type of cell in which they start. All cancers begin in cells, the body's basic unit of life. When the genetic material (DNA) of a cell becomes damaged or changed, this results in mutations that affect normal cell growth and division. When this happens, cells do not die when they should, and new cells form when the body does not need them, effectively forming a mass of tissue called a tumour. Cells that invade nearby tissues and spread to other parts of the body are cancerous and the spread of cancer from one part of the body to another is called metastasis.

A report from the National Cancer Registry of Ireland (NCRI) and the Central Statistics Office (CSO) shows the incidence, survival and mortality rates in Ireland from all cancers for men and women in 2013, the most recent reporting period available.[71] According to the statistics, it is estimated that one in three people will develop cancer during their lifetime. Worryingly, an average of 30,000 new cases of cancer are diagnosed each year in Ireland and this number is expected to rise dramatically to over 40,000 per year by 2020. The five most common cancers in Ireland are non-melanoma skin cancer, prostate cancer, breast cancer, bowel cancer and lung cancer respectively. The average incidence of each of these cancers between 2009 and 2010 inclusive is illustrated below in ***Figure 1.11***.

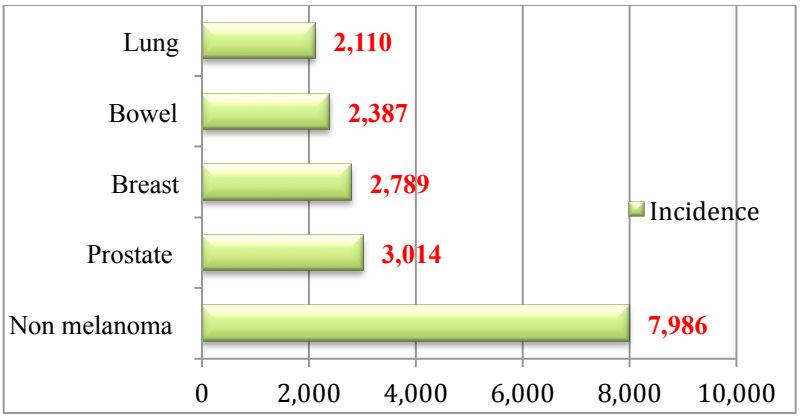



***Figure 1.11:*** *Illustration of the average incidence of the five most common cancers in Ireland between 2008 and 2010 inclusive.*

The most common type of cancer in Ireland is non-melanoma skin cancer across both genders. Excluding skin cancer however, breast cancer was the most common among women (2,767) while prostate cancer was the most common cancer among men (3,014) (***Figure 1.11***). With respect to cancer mortality, cancer accounts for 25% of the annual death toll making it the second most common cause of death in Ireland. According to the most recent figures, 8,316 people died from cancer in 2010. Worldwide this figure was as high as 7.6 million. Thankfully, with recent advances in medical research and the implementation of new treatment options for patients, cancer is viewed as a condition from which people survive. Statistically speaking, 42% of men and 50% of women diagnosed with cancer currently survive for five years and longer. Amazingly, it is estimated that 280,000 people, diagnosed between 1995-2009, have survived their cancer in Ireland. Cancer is still a major problem and it goes without saying that numerous laboratories around the world are investing huge time and energy into addressing this problem by continually developing new and more innovative treatment options for cancer patients.

### 1.1.8.2 Hypoxia

Hypoxia is a common feature of most tumours that profoundly affects the biological behaviour, response to therapy and prognosis of human cancers.[72,73] The presence of hypoxia in solid tumours has been recognised for more than 50 years.[72] Hypoxia occurs when cells are located too far from a functional blood vessel for adequate supply of oxygen due to rapid cancer cell proliferation and the formation of blood vessels that are structurally and functionally abnormal. In the most extreme cases, oxygen supply is below that required for survival, resulting in cell death and the establishment of a selection of cancer cells in which the apoptotic pathways are inactivated and anti-apoptotic pathways are activated.[51,74,75] These hypoxic cells are generally more resistant to killing by radiation and chemotherapy, are more invasive and metastatic, resistant to apoptosis, and genetically unstable.[72,73] One of the major advances in cancer research over the last two decades has been the discovery of Hypoxia Inducible Factors (HIF), a family of transcription factors crucially involved in the response of mammalian cells to oxygen deprivation.[48] The discovery of HIF-1 as a crucial player of the response to hypoxia has changed the perspective on how to target hypoxia for the development of cancer therapeutics by turning a strength of cancer cells into their Achilles' heel.[72] Clinical studies in cancer patients indicate that the expression of HIF-1 is directly correlated with poor patient prognosis and activation of HIF-1 contributes to advanced disease stages (malignant behaviour) and therapeutic resistance. Conversely, inhibition of HIF-1 activation has been shown to suppress growth, survival and metastatic spread of hypoxic tumours.[52,56]

### 1.1.8.3 Hypoxia Inducible Factor (HIF)

Since its discovery in 1992 by Semenza *et al.*, HIF-1 has been the subject of thousands of published studies.[50] It is widely accepted among experts that the Hypoxia Inducible Factor is the primary transcription factor activated by hypoxia and is responsible for orchestrating a number of cellular responses such as angiogenesis and glycolysis that are important to tumour cell survival under hypoxic conditions. Hypoxia-inducible factor-1 is a heterodimeric transcriptional factor consisting of a HIF-1α (120-kDa) and a HIF-1β subunit (80-kDa).[53,76] HIF-1 is a member of the rapidly growing Per-ARNT-Sim (PAS) family of basic helix-loop-helix (bHLH) transcription factors which is activated during dimerisation of HIF-1α and HIF-

1β (***Figure 1.12***).[76] HIF-1α is a protein that in humans is encoded by the HIF-1α gene. HIF-1α plays a major role in activating gene transcription, which is important for maintaining homeostasis under hypoxic conditions and is an obvious target for development of novel cancer therapeutics.

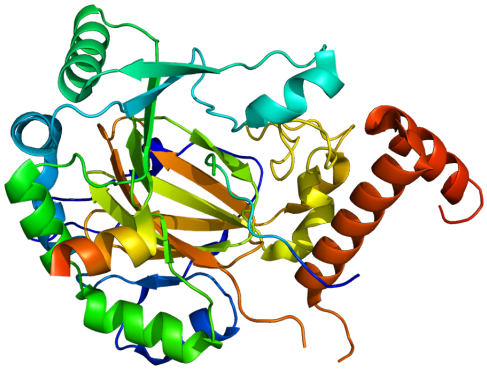


***Figure 1.12:*** *Structure of the transcriptional factor HIF-1α.*

The level of HIF-1α protein is directly regulated by intracellular oxygen concentration. In the presence of oxygen (normoxic conditions) HIF-1α protein is rapidly degraded, while it is stabilized in the absence of oxygen (hypoxic conditions). HIF-1β protein on the other hand is always present (constitutively expressed). Upon hypoxic induction and activation, HIF-1α protein levels are dramatically increased and undergo heterodimerisation with HIF-1β protein. This activates HIF-1, which subsequently binds to the hypoxia response element (HRE) present in the promoters of target genes, which ultimately control angiogenesis, anaerobic metabolism, cell survival and metastasis as well as other cellular functions.

More than seventy target genes that are activated by HIF-1 have been identified.[77] These genes are involved in many aspects of cancer progression, angiogenesis, cell survival, glucose metabolism and invasion. These include genes encoding for vascular endothelial growth factor (VEGF), erythropoietin (EPO) and many numerous enzymes involved in glucose, iron and nucleotide metabolism. Hypoxia-inducible factor 1 (HIF-1) is therefore a master regulator of this adaptive response to hypoxia.[78] Given the central role that HIF-1-driven transcription factor activity has in compensating for loss of oxygen, it is clear that

modulation of that activity could be a potent mechanism for treating a wide range of hypoxia-related pathologies. A simplified representation of the processes influenced by HIF-1 was provided by Quintero *et al.* and is exemplified in ***Figure 1.13***.

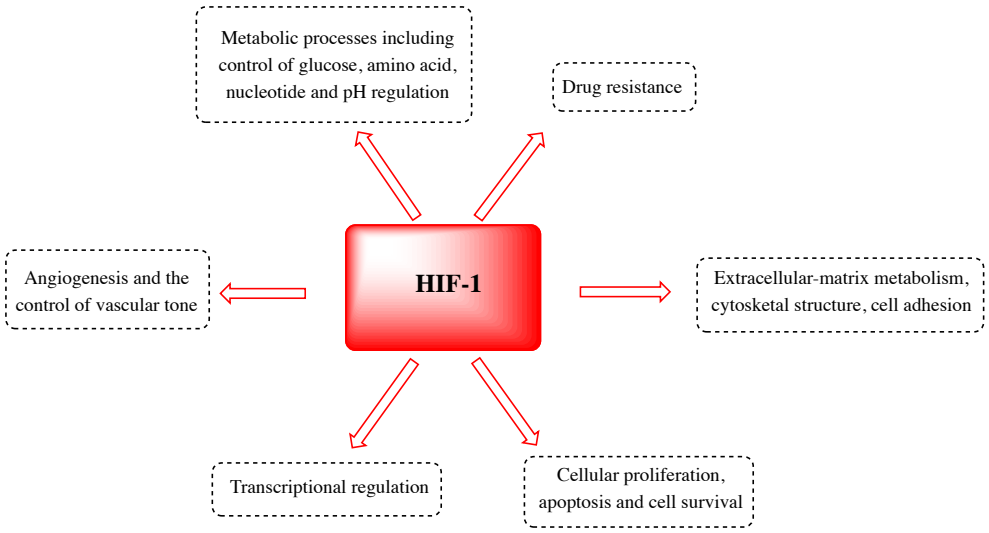



***Figure 1.13***

With respect to HIF-α, three homologs have been identified: HIF-1α, HIF-2α and HIF-3α.[53,79] HIF-2α is closely related to HIF-1α and both are able to interact with hypoxia response elements, to up-regulate transcriptional activity. By contrast, HIF-3α is involved in down-regulation of the hypoxic response via an alternatively spliced transcription factor, which may function as an inhibitor of HIF-1α adding to the complexity in the regulation of hypoxia-inducible genes by the HIF family of transcription factors.[80,81]

HIF-1α has two transactivation domains located in its COOH-terminal half, which are termed the $NH_2$-terminal transactivation domain or N-TAD (amino acids 531-575) and the COOH-terminal transactivation domain or C-TAD (amino acids 786-826) as illustrated in ***Figure 1.14***.[82]

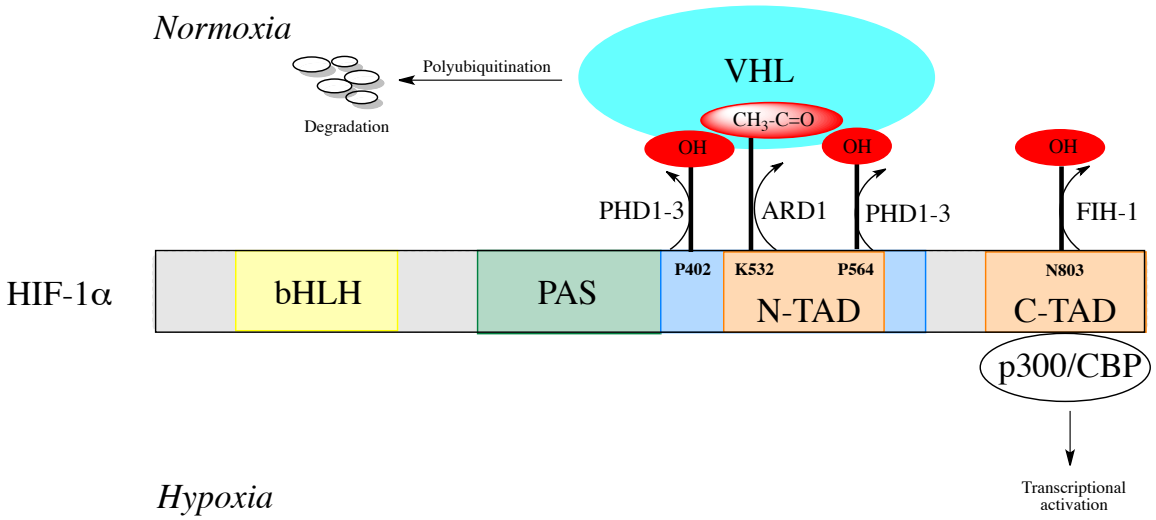



***Figure 1.14:*** *Oxygen-dependant regulation of HIF-1α activity adapted from Xia et al. with some minor modifications.*[53,83]

The C-TAD of HIF-1α plays a key role in modulating the transcriptional activation of HIF-1α under hypoxic conditions. On the other hand, N-TAD is involved in the stabilisation of HIF-1α under anoxic conditions. Under hypoxia, the C-TAD is able to interact with transcriptional co-activators like p300/CBP at N803. However under normoxic conditions, hydroxylation of N803 is mediated by an asparaginyl hydroxylase, known as factor inhibiting HIF-1 (FIH-1), which prevents HIF-1α from interacting with the transcriptional co-activator p300/CBP (***Figure 1.14***).[84]

The von Hippel-Lindau protein (pVHL) is involved in the regulation of HIF-1α. Under normoxic conditions, oxygen-dependant hydroxylation of proline residues $Pro^{402}$ and $Pro^{564}$ in HIF-1α by three prolyl-4-hydroxylase domain containing enzymes (PHD1-3) is required for binding of the von Hippel-Lindau tumour-suppressor protein, which is the recognition component of an E3 ubiquitin-protein ligase. VHL binding is also promoted by acetylation of K532 residue by the ARD1 acetyltransferase. This prolyl-hydroxylation 'tags' HIF-1α protein for polyubquitination mediated by the pVHL E3 ubiquitin ligase complex, followed by rapid degradation through a 26S proteasome-dependent mechanism (***Figure 1.14***).[85]

Under hypoxic conditions, the rate of N803 and K532 hydroxylation decreases dramatically and VHL protein can no longer bind to HIF-1α that is not prolyl-hydroxylated, resulting in a decreased rate of HIF-1 degradation. As previously stated, p300/CBP can now bind to HIF-1α that is not asparaginyl-hydroxylated, resulting in transcriptional activation of HIF-1 target genes (***Figure 1.14***).[53,83]

### 1.1.8.4 Hypoxia-induced mitochondrial reactive oxygen species

Natural product-based small molecule inhibitors of the mitochondrial electron transport chain (ETC) have been found to inhibit hypoxia-induced HIF-1 activation.[68,69,86-88] The mechanism is not fully understood, but several opposing theories have emerged to explain the role of mitochondria in the regulation of HIF-1 activation.[89,90] Under hypoxic conditions, reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide are produced by the Qp site of mitochondrial complex III (***Figure 1.15***). These hypoxia-induced ROS are believed to function as signalling molecules that oxidise the catalytic Fe(II) in Fe(II)-dependent HIF-prolyl hydroxylase that is essential in the initial steps of ubiquitin-mediated proteasomal degradation of HIF-1α protein.[68,86,87,91,92] Furthermore, mitochondrial ROS have also been linked to the inhibition of the Fe(II)-dependent asparaginyl hydroxylase [factor inhibiting HIF, (FIH)] which interferes with HIF-1 transcriptional activation by hydroxylating the N803 asparagine in the C-TAD of HIF-1α (***Figure 1.14***).

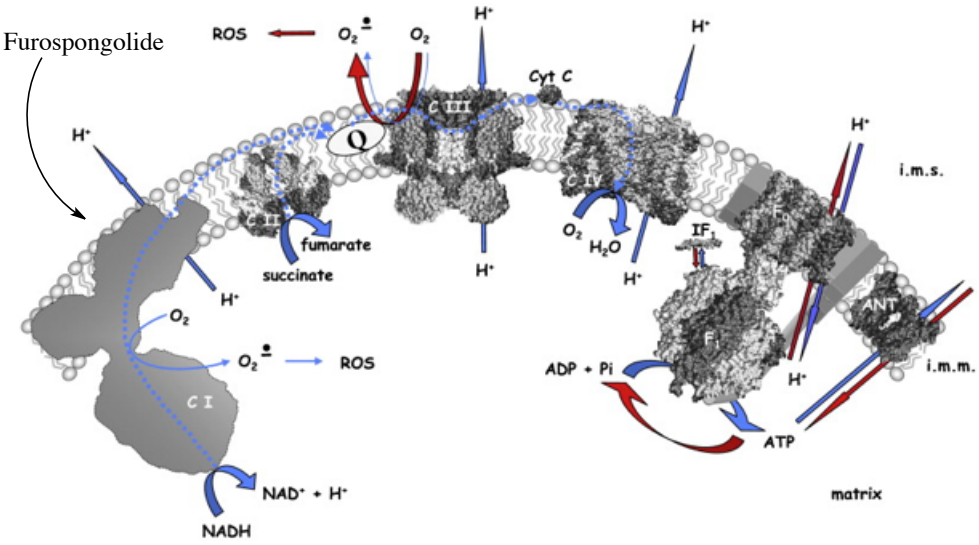



***Figure 1.15:*** *The mitochondria of hypoxic cells release superoxide from the Qp site of mitochondria complex III. This prevents the transfer of electrons required to drive the hypoxia-induced production of reactive oxygen species at complex III. The marine natural product furospongolide* ***55*** *inhibits the mitochondrial electron transport chain at the NADH-ubiquinone oxidoreductase (complex I) site.*[56]

As previously stated in ***Section 1.1.7.2***, it has been postulated that the mechanism through which furospongolide **55** inhibits hypoxia-induced HIF-1 activity is linked to inhibition of the mitochondrial ETC by suppressing the production of ROS signalling pathways in hypoxic tumours. This stabilises HIF-1α protein by preventing proteasomal degradation under hypoxic conditions and activates HIF-1 by interfering with the ability of asparaginyl hydroxylase to suppress HIF-1 activation.

### 1.1.8.5 Small molecule HIF-1 inhibitors and chemoprevention

In brief, the progression of cancer is correlated with the development of hypoxic regions within solid tumours. HIF-1 is a transcriptional factor activated by hypoxia, which orchestrates the expressions of specific genes associated with conferring radio- and chemo resistance while simultaneously inducing angiogenesis, enhancing tumour development and promoting metastasis. As a result, HIF-1 has emerged as a key molecular target for anticancer drug discovery.[56] Over the last decade intense efforts has been made to investigate natural products that can be potentially used as HIF-1 inhibitors. In general, natural products have been a major source of new drugs for centuries and statistics show that nearly 50% of approved anticancer agents are derived directly or indirectly from natural products.[93] The importance of natural products in drug discovery has been discussed in several reviews and reports.[94-97]

As our knowledge of the tumour cell continues to expand, stronger evidence suggests that inhibition of the HIF-1 pathway represents an attractive approach to cancer therapy. Recently, numerous laboratories have joined in the race to discover small molecule HIF-1 inhibitors,[72,98,99] most of which use a synthetic or commercial compound library-based screening approach. Small molecules aim to suppress tumour hypoxia and to increase the susceptibility of tumour cells to radiotherapy and chemotherapy thereby improving patient outcome. They also serve as important molecular probes to investigate the pathways that regulate HIF-1 activity. Xia *et al.* disclosed a review on recent advances in discovery and development of small molecule HIF-1 inhibitors.[53] Representative HIF-1 inhibitors discovered from compound library screening efforts include topotecan,[100] echinomycin,[101] chetomin,[102] a benzopyran derivative 103D5R, analogues of emetine and actinomycin D,[103] a pyrroloquinoline derivative DJ12,[104] and a group of structurally diverse compounds including alkyliminophenylacetates that affect mitochondrial function.[105] For many of these, the mechanism of action has been established and involves a reduction of HIF-1$\alpha$ mRNA or protein levels, HIF-1 DNA-binding activity, or HIF-1 mediated transactivation of target genes (***Table 1.2***).[74]

***Table 1.2:*** *Anticancer agents that inhibit HIF-1 activity**

| Mechanism of action | Drug molecule |
|---|---|
| Decrease HIF-1α mRNA levels | GL331[106] |
| Decrease HIF-1α protein levels | Ibuprofen, Celecoxib[107] |
| Topoisomerases | Topotecan[100] |
| Cyclin-dependent kinases | Flavopiridol[108] |
| Microtubule targeting agents | 2-Methoxyestradiol[109] |
| Decreased binding of HIF-1 to DNA | Echinomycin,[101] DJ12[104] |
| Decreased HIF-1 mediated transactivation | Bortezomib,[110] Chetomin[102] |
| Inhibits mitochondrial ETC | Laurenditerpenol,[60] Furospongolide[52] |
| Unknown | Manassantins,[57] 103D5R[111] |

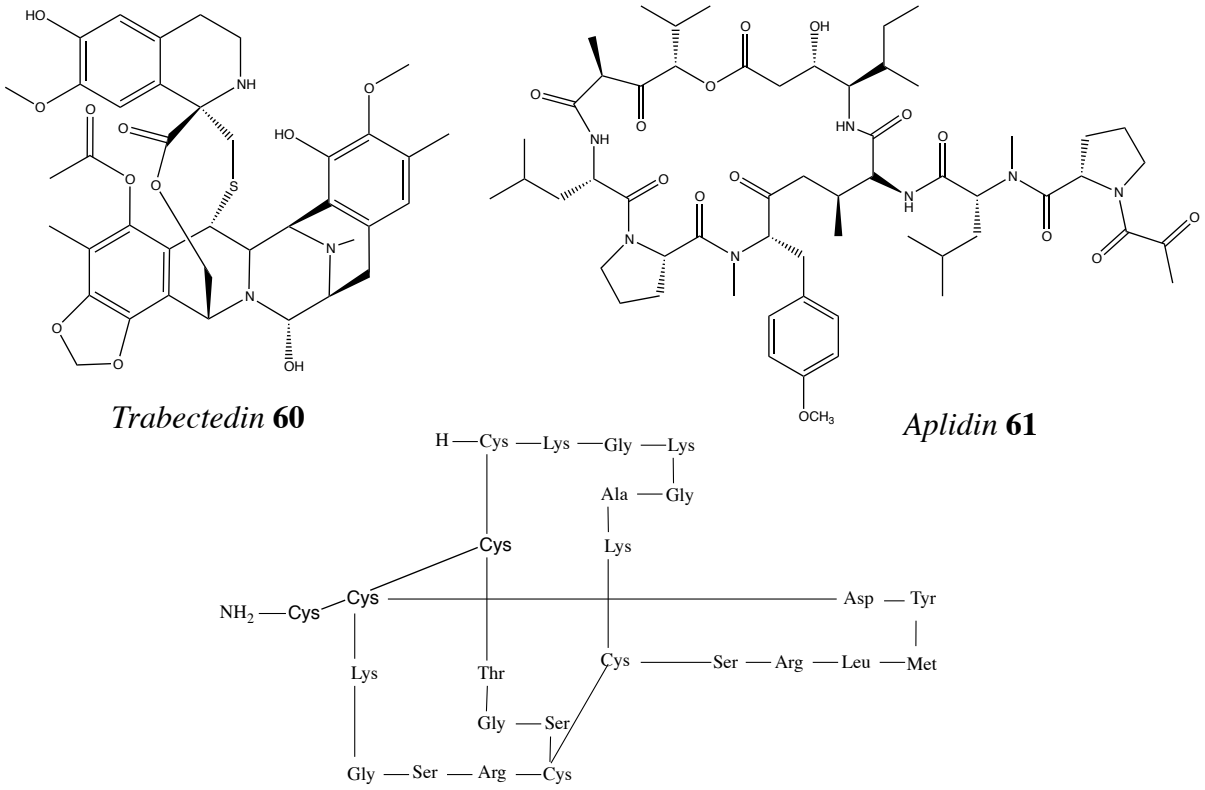
*** Information was sourced from a review by Semenza *et al.*[74]**

Unfortunately, many of the identified compounds have poor water solubility and are very toxic and therefore cannot be used in human therapy. Using a natural product chemistry-based approach, several groups have discovered chemically and mechanistically diverse HIF-1 inhibitors. Some of these HIF-1 inhibitors function at low nanomolar concentrations (e.g. manassantins) with a wide therapeutic window between their HIF-1 inhibitory activity and cytotoxicity.[56,57] A number of fantastic reviews have been published discussing natural compounds with HIF-1 inhibitory activity that have been discovered to date.[112-114]

### 1.1.8.6 HIF-1 inhibitors from marine life

The potential of marine life as a source of novel molecules for the treatment of human diseases is extraordinary. Recent technological and methodological advances in structure elucidation, organic synthesis and biological assay has resulted in the isolation and clinical evaluation of various novel anticancer agents from marine organisms.[115,116] Natural products, especially those from terrestrial plants and microbes, have long been a traditional source of drug molecules (morphine and penicillin). Modern pharmaceutical discovery programmes are indebted to natural products as active compounds from plants and microbes represent an invaluable pipeline for new investigational drugs.[117,118] On the other hand, marine organisms possess a greater molecular diversity than their terrestrial counterparts due to their longer evolutionary history. Recent research has discovered that marine life produce more antibiotic, anticancer and anti-inflammatory substances than any group of organisms on land.[119] The major problem with developing drugs from a marine source is that procurement or manufacture of quantities of rare compounds to ensure a sustainable supply to industry was essentially a bottleneck. Sponges and their microbial fauna are largely unculturable, and the valuable compounds they produce must be extracted and purified from specimens collected by hand from shallow to deep waters. Nevertheless, the unrivalled potential of marine natural products as antitumour agents has inspired innovative solutions to the supply problem ranging from aquaculture to total synthesis.[120]

The past two decades has seen a dramatic increase in the number of preclinical anticancer lead compounds from diverse marine life enter human clinical trials (***Figure 1.16***). Ziconotide **59** (Prialt®, Elan Pharmaceuticals), a peptide originally discovered in a tropical cone snail (*Conus magus*) was the first marine-derived compound to be approved in the US in December 2004 for the treatment of pain (non opioid and non NSAID analgesic).[121,122] In October 2007, trabectedin **60** (Yondelis®, PharmaMar) became the first marine anticancer drug to be approved in the EU.[123] Currently, the antitumour agent plitidepsin **61** (Aplidin®, PharmaMar) is in phase III clinical trials for the treatment of multiple myeloma.[124,125]




*Trabectedin* **60** *Aplidin* **61**

*Ziconotide* **59**

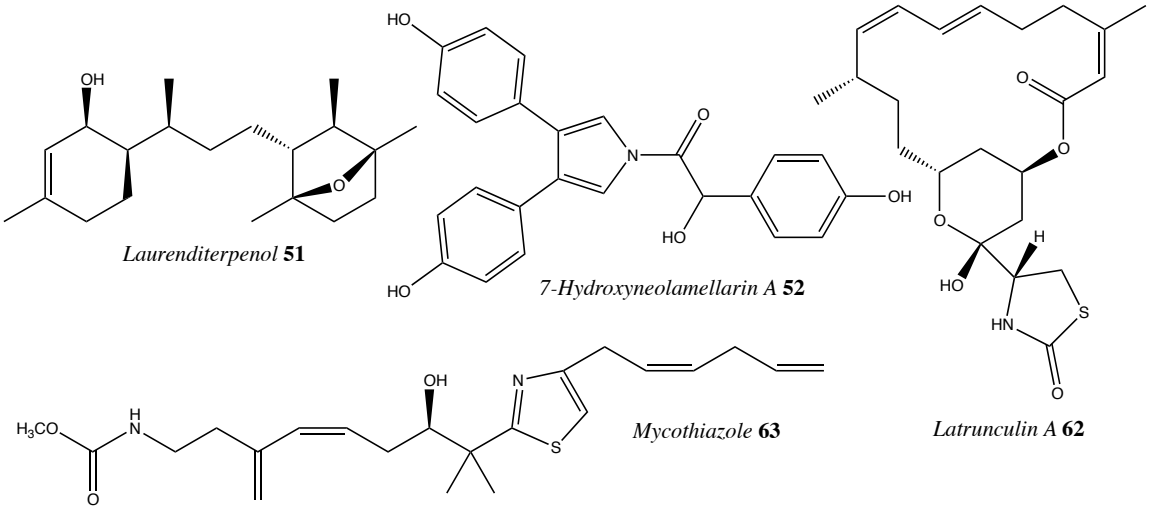
***Figure 1.16:*** *Marine derived pharmaceutical drugs.*

Numerous other marine natural products, primarily invertebrates (e.g., sponges, tunicates, bryozoans, and mollusks) have shown potent antimitotic and/or antitumour properties and have advanced to late-stage clinical trials.[123,126] The literature has many comprehensive reviews discussing the importance of marine natural products in anticancer drug discovery.[115,116,119,127] With respect to Aplidin® **61**, links have been made which suggest it functions as an inhibitor of HIF-1 activation by suppressing the expression of HIF and angiogenesis-related HIF-1 target genes *in vivo*.[128,129]

Several research programs have recently begun to examine marine natural products as a potential source of HIF-1 activation inhibitors.[56,112] The first marine natural product found to inhibit hypoxia-induced HIF-1 activation was laurenditerpenol **51**, a diterpene first isolated in 2004 from the marine red algae *Laurencia intricate* (***Table 1.3, Entry 1***).[60] Interestingly,

despite having little to no structural homology, both laurenditerpenol **51** and furospongolide **55** inhibit hypoxia-induced HIF-1 activation in breast cancer cells by inhibiting NADH-ubiquinone oxidoreductase-mediated mitochondrial signalling pathways.[52,56,60] Bioassay-guided isolation has since yielded an array of HIF-1 inhibitors from sponges and other marine organisms. Two good examples include the macrolide macrolide latrunculin A **62**, isolated from a Red Sea sponge *Negombata magnifica,*[130] which is now commercially available from Sigma Aldrich,[131] and the phenolic pyrrole alkaloid 7-hydroxyneolamellarin A **52** isolated from the sponge *Dendrilla nigra* (***Table 1.3, Entry 2*** and ***3***).[58] Within our research group, studies are currently in progress towards the synthesis and biological evaluation of novel neolamellarin analogues as potential antitumour agents.[132] To date, the most potent marine natural product inhibitor of hypoxia induced HIF-1 activation is mycothiazole **63**, a polyketide isolated in 2002 from the marine sponge *Cacospongia mycofifiensis* (***Table 1.3, Entry 4***).[133,134] As illustrated in ***Table 1.3***, these marine natural products vary widely in potency and selectivity to target HIF-1 and ultimately tumour hypoxia.

***Table 1.3:*** *Marine natural products found to inhibit hypoxia-induced HIF-1 activation in T47D human breast cancer cells*.*




*Laurenditerpenol* **51** *7-Hydroxyneolamellarin A* **52** *Latrunculin A* **62**

*Mycothiazole* **63**

| Entry | Product | Natural source | $IC_{50}$ value |
|---|---|---|---|
| 1 | Laurenditerpenol **51** | *Laurencia intricata* | 0.4 μM |
| 2 | 7-Hydroxyneolamellarin **52** | *Dendrilla nigra* | 1.9 μM |
| 3 | Latrunculin A **62** | *Negombata magnifica* | 6.7 μM |
| 4 | Mycothiazole **63** | *Cacospongia mycofijiensis* | 1 nM |

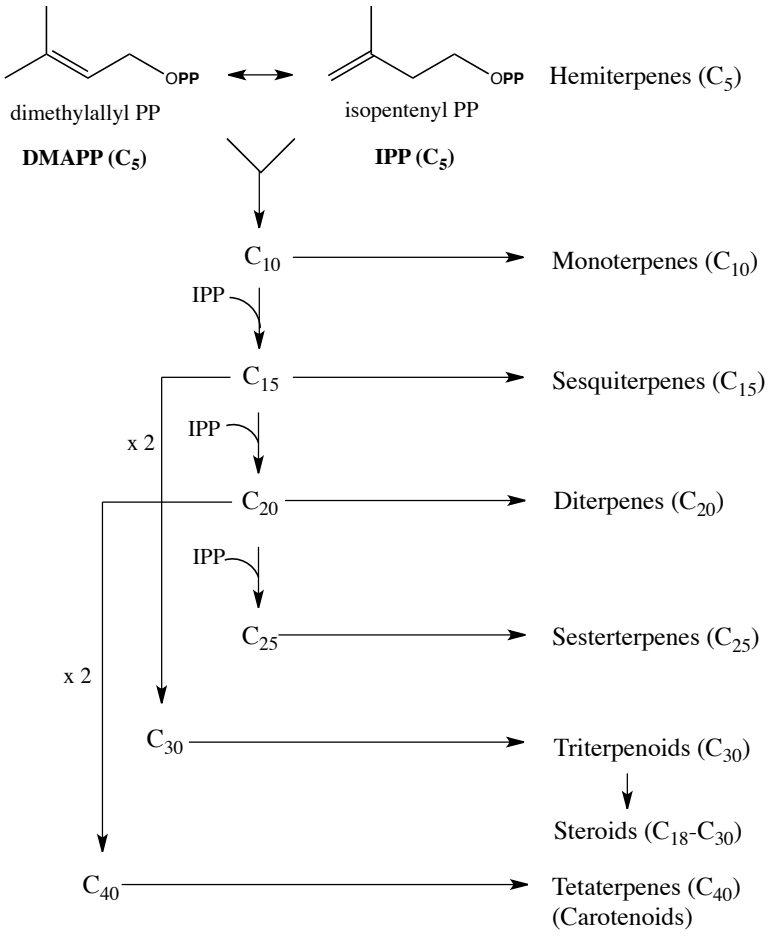
*** Data sourced from a review on marine natural products as HIF-1 inhibitors by Nagle *et al.*** [56]

One of the intended applications of natural product-based HIF-1 inhibitors is as adjunct agents to be used in combination with other cancer treatment options.[56] Preclinical studies strongly support this treatment regime of combining HIF-1 inhibition with radiation and chemotherapy to improve patient outcome.[56,135,136] As the exploration for HIF-1 targeted antitumour natural products continues to expose innovative lead compounds, a greater prospect of identifying a potent clinically useful inhibitor of HIF-1 activation is at hand.

## 1.1.9 Sesterterpenoids

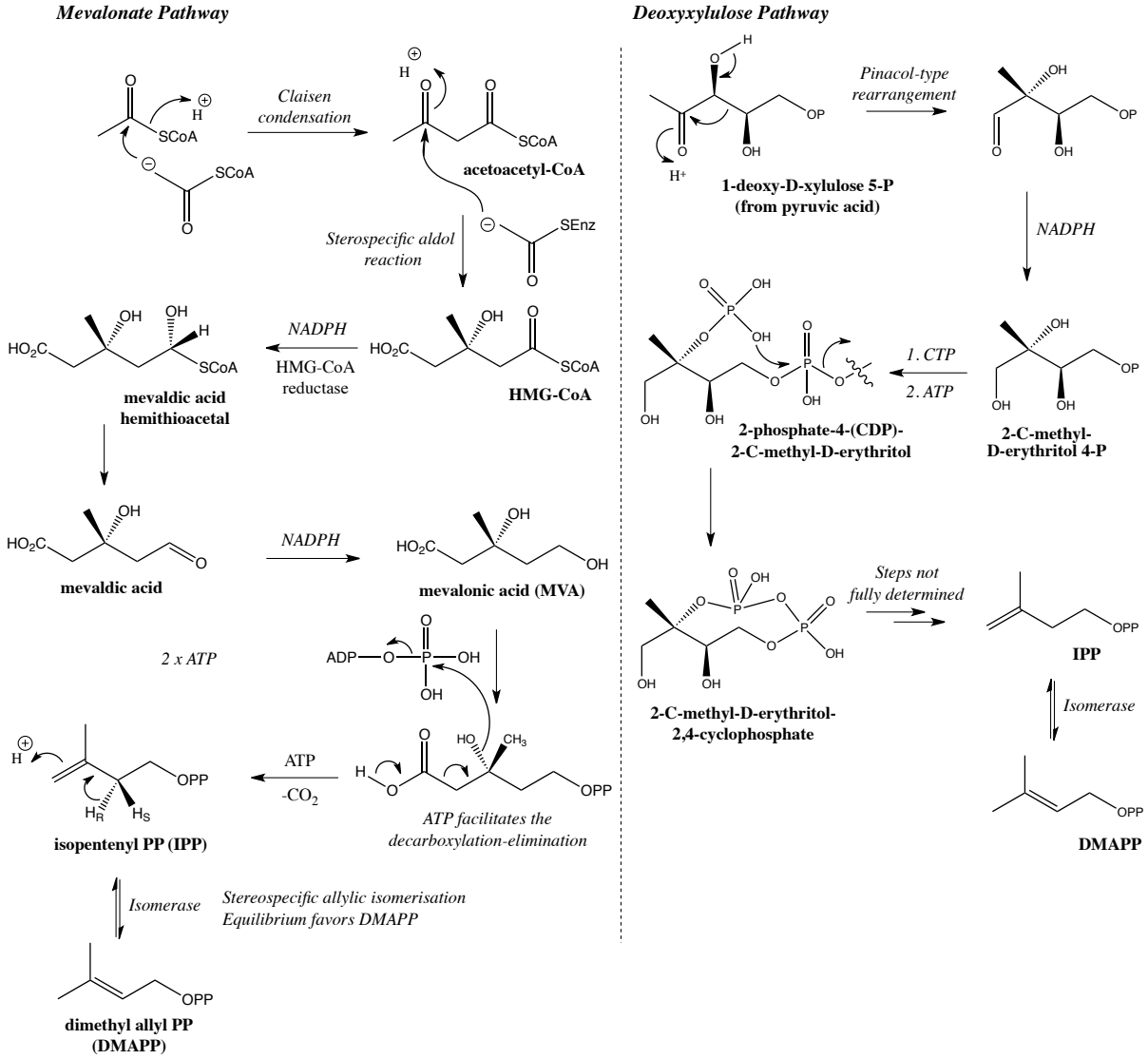
### 1.1.9.1 Introduction to sesterterpenoids

Terpenes are an enormous class of natural products spanning well over 30,000 members. They have been used throughout history for a broad variety of purposes including perfumes, medicine and flavouring.[137] Terpenoids are derived from $C_5$ isoprene units joined in a head to-tail fashion. Typical structures contain carbon skeletons represented by $(C_5)_n$, and are classified as hemiterpenes ($C_5$), monoterpenes ($C_{10}$), sesquiterpenes ($C_{15}$), diterpenes ($C_{20}$), sesterterpenes ($C_{25}$), triterpenes ($C_{30}$) and tetraterpenes ($C_{40}$) as illustrated in ***Scheme 1.11***.[137]



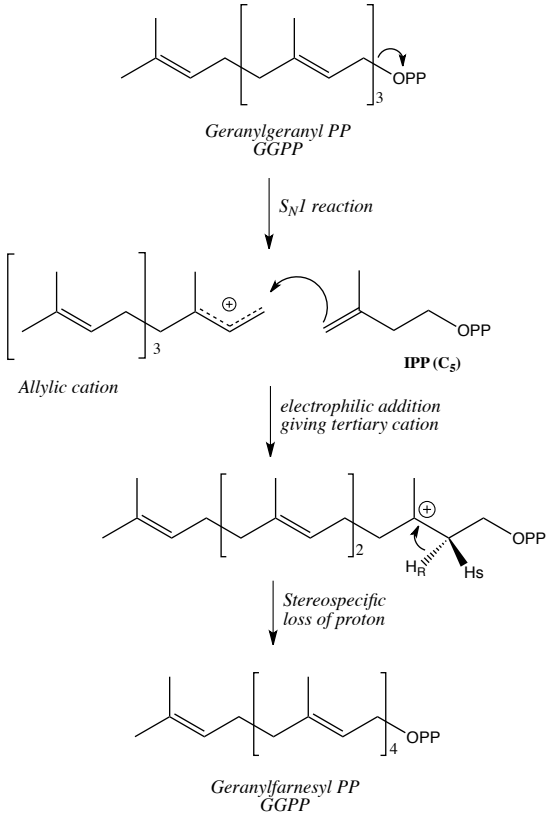

***Scheme 1.11***

The two biosynthetic pathways leading to terpenoids are the mevalonate pathway and the more recently discovered mevalonate-independent deoxyxylulose pathway for the production of isopentyl diphosphate (IPP) and dimethyl allyl diphosphate (DMAPP), which are the biochemically active isoprene units (***Scheme 1.12***).[137]




***Scheme 1.12:*** *The chemistry of the mevalonate and deoxyxylulose pathway as by Dewick et al.*[137]

Within the terpenoid family, sesterterpenoids probably form the smallest class, comprising less than a thousand known compounds.[137,138] They comprise of two and a half (sester in latin) terpene units, which for historic reasons were defined as pieces made of ten carbons. As such, sesterterpenoids contain 25 (or slightly fewer) carbon atoms. Their sources are widespread, having been isolated from terrestrial fungi, lichens, higher plants, insects and various marine organisms especially sponges.[138]




***Scheme 1.13***

Sesterterpenoids are a group of pentaprenyl substances formed from combination of geranylgeranyl diphosphate (GGPP) and IPP *via* the enzyme prenyl transferase, which yields geranylfarnesyl diphosphate (GFPP). This is believed to involve ionisation of GGPP to the allylic cation, addition to the double bond of IPP, followed by loss of a proton. This produces a sesterterpene diphosphate, geranylfarnesyl PP, in which the new double bond is *trans* (*E*) (***Scheme 1.13***).

### 1.1.9.2 Synthetic approaches towards sesterterpenoids

Terpenoids have played a important role in developing organic synthesis as far back as Komppa's pioneering work on camphor in the early 1900's.[139,140] Many important concepts in organic chemistry such as Wagner-Meerwein rearrangements, Diels-Alder reactions, or polyolefin cyclization, were first explored with members of this large natural product class. With huge advancements in organic synthesis in recent years, complex terpenoids have been targeted and their total syntheses must now number in the hundreds.[141]

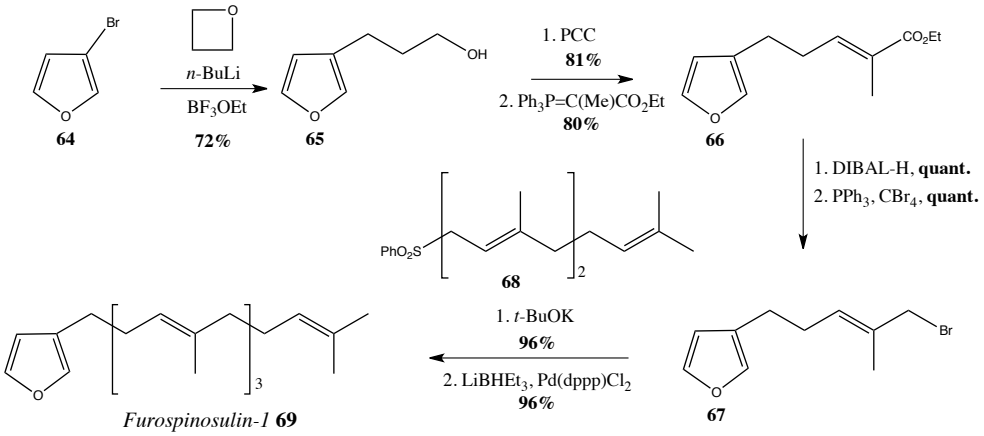
Sesterterpenoids represent an attractive target for both biomedical and synthetic purposes,[142,143] as this structurally complex terpenoid family exhibit diverse biological activity such as anti-inflammatory,[144] cytotoxic, anticancer,[145] antimicrobial,[146,147] antitubercular,[148,149] and anti-biofilm activities.[150] They exhibit inhibitory activity against parasitic protozoa,[151] suppression of the expression of cyclooxygenase-2 and inducible nitric oxide synthase,[152] and act as inhibitors of hypoxia-inducible factor-1 (HIF-1).[112] The natural products of the sesterterpenoid subclass possess a linear carbon chain, which in most cases has been partially oxidized leading to cyclization at the terminal ends of the terpenoid chain resulting in furans and/or lactones. Although numerous linear sesterterpenoids have been reported,[138,153,154] very few have been targeted by synthetic chemists to date.[141]

In this short section, I will be reviewing efforts undertaken towards the synthesis of linear and bicarbocyclic sesterterpenoids, focusing on completed total syntheses of marine natural products, which have shown promising biological activity towards the treatment of human related diseases.

A number of reviews have been published by Hanson *et al.* and Liu *et al.*, which extensively cover the isolation, structure and biological evaluation of sesterterpenoid marine natural products from 1970 to 2013.[138,153,155-157]

### *1.1.9.2.1 Synthesis of furospinosulin-1*

Marine organisms, particularly sponges, have continued to provide a source of linear sesterterpenoids.[157] The terminal units often comprise either of a furan, a γ-lactone or a tetronic acid moiety. Furospinosulin-1 **69** was first isolated in 1972 from the marine sponge *Ircinia spinosula* by Cimino *et al.* and has very recently shown promising activity as a hypoxia-selective growth inhibitor following its isolation from an Indonesian marine sponge *Dactylospongia elegans*.[158,159] Furospinosulin-1 **69** showed selective antiproliferative activity against DU145 human prostate cancer cells under hypoxic conditions and exhibited antitumour activity at a level of 10-50 mg $kg^{-1}$ after oral administration to a mouse model inoculated with sarcoma S180 cells. Mechanistic analysis revealed that **69** suppressed the transcription of the insulin-like growth factor-2 gene (IGF-2), which is selectively induced under hypoxic conditions through presentation of the binding of nuclear protein to the Sp1 consensus sequence in the IGF-2 promoter region.[158] These intriguing bioactivities prompted Kotoku *et al.* to develop a concise total synthesis of furospinosulin-1 **69** and further investigate its structural-activity relationship (***Scheme 1.14***).[160]

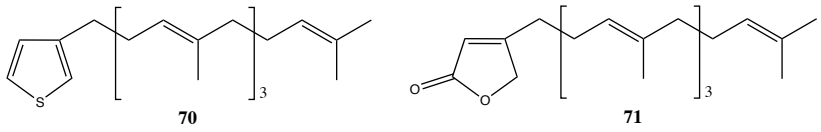



***Scheme 1.14***

The first geometry-selective total synthesis of furospinosulin-1 **69** is illustrated in ***Scheme 1.14***. The route-defining step involved a sulfone-mediated cross coupling reaction between allylic bromide **67** and the known farnesyl phenylsulfone **68**. The allylic bromide **67** was conveniently prepared from commercially available 3-bromofuran **64**. The first step involved

reacting trimethyleneoxide with the derived organolithium species of 3-bromofuran **64** to afforded 3-substituted furan alcohol **65**. Oxidation and subsequent Wittig olefination provided the enoate **66**. Diisobutylaluminium hydride reduction of the ester moiety in **66** and subsequent bromination with $CBr_4/PPh_3$ under standard Appel conditions furnished the allylic bromide **67**. The coupling reaction between the allylic bromide **67** and the sulfone **68** proceeded smoothly using potassium *tert*-butoxide. Subsequent reductive desulfonylation using Super-Hydride® lithium triethylborohydride in the presence of $Pd(dppp)Cl_2$ successfully furnished furospinosulin-1 **69** in seven linear steps from **64**. Since furospinosulin-1 **69** is structurally similar to furospongolide **55**, quite a number of synthetic transformations discussed here can be utilised in the synthesis of our target molecule **55** especially methodology for attaching the furan moiety to the lipophilic terpenoid sidechain.

Living organisms produce sesterterpenoids for certain physiological functions. Given the different selection pressures under which organisms have evolved over time, an enormous number of structural diversity is expected. With regard to furospinosulin-1 **69**, both the butenolide derivative **71** and the thiophene derivative **70** have been isolated from marine origin and have shown interesting bioactivity (***Figure 1.17***).[161,162]




**70** **71**

***Figure 1.17***

The butenolide **71** was first isolated from the Caribbean sponge, *Thorecta horridus* and has been found to possess marked inflammatory activity inducing the release of histamine and cause oedema in the paw of test animals.[157,161] On the other hand, the thiophene sesterterpene **70** has recently been isolated from an active extract from the Sikao Bay sponge *Xestospongia sp*.[162] Surprisingly, this was the first reported discovery and isolation of a thiophene containing sesterterpene produced by a marine sponge. Worth mentioning, sulfur is often found in marine natural products in the form of the isothiocyanate, thiocyanate, thioacetate,

thiol, sulfone and sulphate functional groups, whereas the thiazole is a common natural heterocyclic moiety.[162] Furthermore, sesterterpenoid **70**, which is almost identical in structure to furospinosulin-1 **69** was found to be cytotoxic against Vero cells.[162]

With regard to the length of the acyclic terpenoid chain, two structural derivatives of furospinosulin-1 **69** have been isolated from the marine sponge *Ircinia spinosula,* difurospinosulin **75** and furospinosulin-3 **73** ***(Figure 1.18)***.[159] Interestingly, it has been suggested by Cimino *et al.* that difurospinosulin **75** could be derived from the $C_{35}$ linear furanoterpene, furospinosulin-3 **73** by the loss of four carbon atoms following biological inter-conversions involving enzyme catalysed oxidation, reduction and proton initiated cyclisation. Similarly, it has been proposed that anhydrofurospongin-1 **74** can be derived from the $C_{25}$ linear furanoterpene, furospinosulin-1 **72** through an identical metabolic pathway. Further enzyme catalysed oxidation would potentially afford furospongolide **55**.

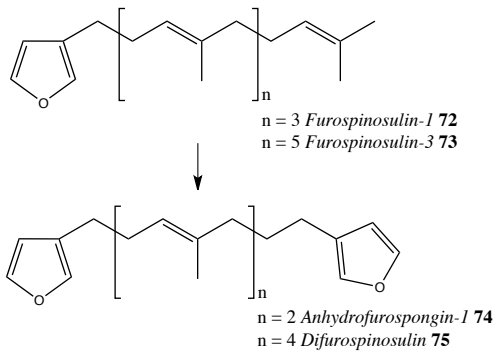



***Figure 1.18***

When furospongolide **55** was isolated back in 1980 by Kashman *et al.* from the marine sponge *Dysidea herbacea,* furanoterpenes that terminated in a lactone ring were completely unknown in the $C_{21}$-furanoterpene series but not unfamiliar in other marine metabolites.[64,163] In the last 3 decades, very few novel sesterterpenoids encompassing both a furan and lactone ring have been isolated from marine life. One obvious example is the $C_{22}$ lactone **77**, which is associated with furospongolide **55** both in structure and origin as it was isolated from the same species of Madagascan sponges of the genus *Lendenfeldia (**Figure 1.19**)*.[164]

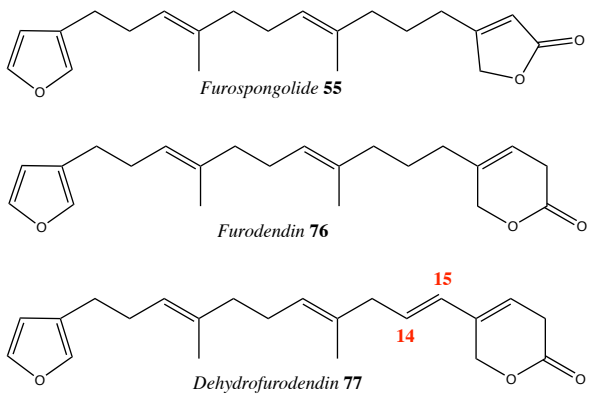



***Figure 1.19***

Dehydrofurodendin **77** contains a β,γ-unsaturated-δ-lactone ring which is extremely rare among marine metabolites and in fact only exists in dehydrofurodendin **77**, furodendin **76** and in another $C_{21}$ terpenoid. The $C_{22}$ lactone, furodendin **76**, has been reported in the sponge *phyllosponngia dendyi*.[165] It should be noted that dehydrofurodendin **77** differs from furodendin **76** only in the additional double bond at $C_{14}$-$C_{15}$, which probably results from oxidation occurring at a late stage in the biosynthesis. Interestingly, dehydrofurodendin **77** has been found to be a potent inhibitor of HIV-1 RT-associated DNA polymerase activity. It is important to highlight here how making simple changes to the structure of the molecule can affect its bioactivity and alter its therapeutic potential.

#### *1.1.9.2.2 Synthesis of variabilin*

As previously stated, the terminal units of linear sesterterpenoids often comprise of a furan, lactone or a tetronic acid moiety. These natural products presumably occur following partial oxidation of the linear chain followed by cyclisation. Quite a number of the sesterterpenoid family contain a tetronic acid moiety and show strong antibiotic activity against *staphylococcus aureus*.[155] Common examples are variabilin **78** from *Ircinia variabilis*,[166] its double bond isomer strobilinin **79** from *Ircinia strobilina*,[167] and fasciculatin **80** from *Ircinia fasciculate* (***Figure 1.20)***[168]

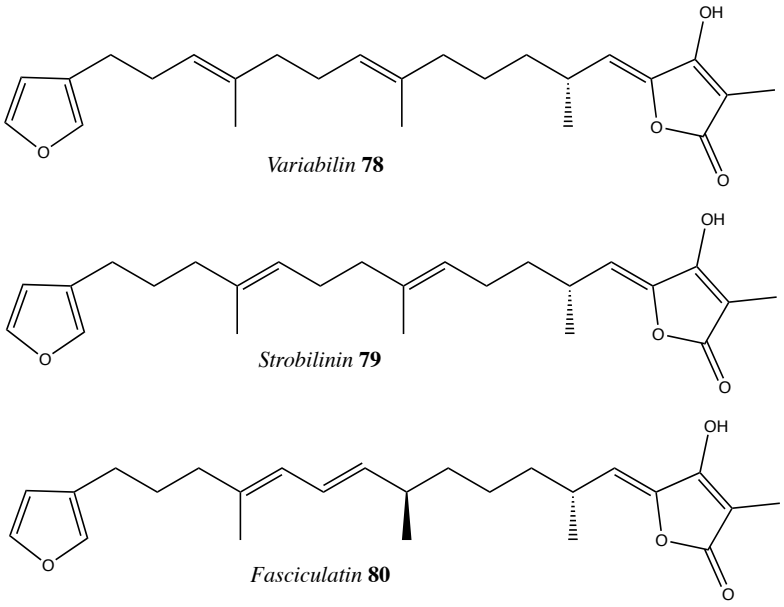
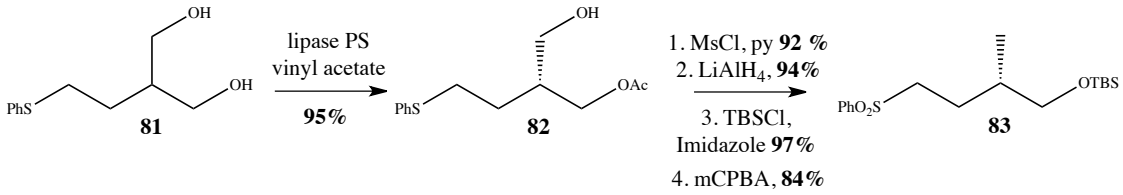



***Figure 1.20***

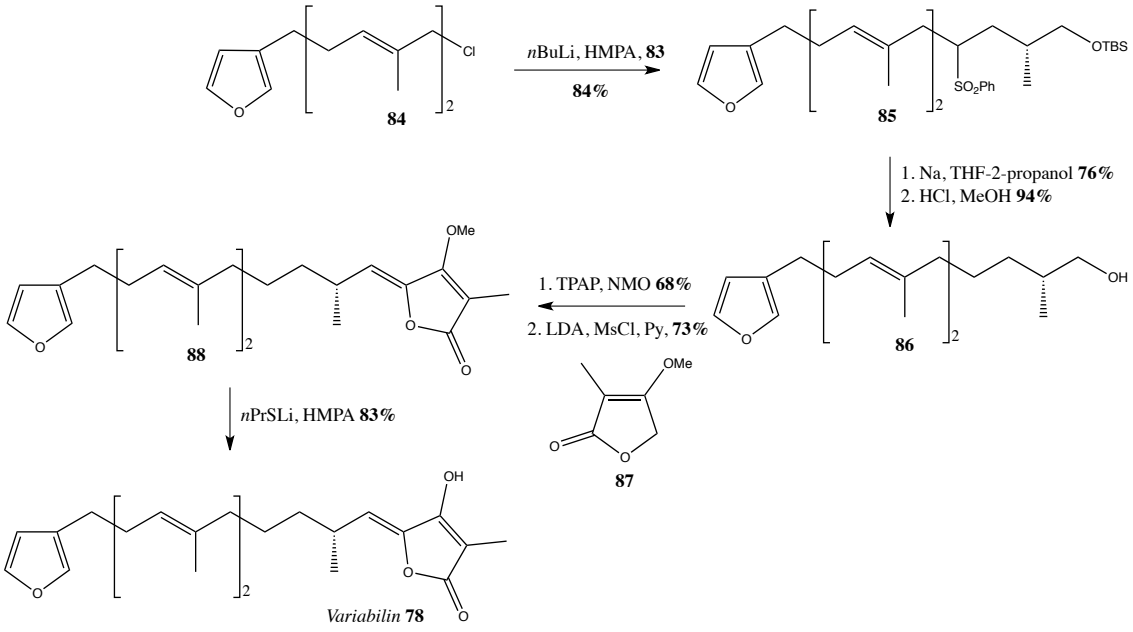
Variabilin **78** was first isolated by Flaukner *et al.* in 1973 from the marine sponge *Ircinia variabilis* (*I. variabilis*).[169] A variety of geometric, stereo- and regioisomers of this natural product and other related types have since been isolated and have shown to possess remarkable antiviral and cytotoxic activity.[170-173] Variabilin **78** is recognised as a novel RGD-containing antagonist of glycoprotein IIb-IIIa and a platelet aggregation inhibitor.[174] It is also a dual inhibitor of human secretory and cytosolic phospholipase $A_2$ ($PLA_2$) with anti-inflammatory activity.[172]

More than 30 years after its isolation, the naturally occurring linear furansesterterpene tetronic acid, (18*S*)-variabilin **78** was first synthesised by Yoda *et al.*[171]



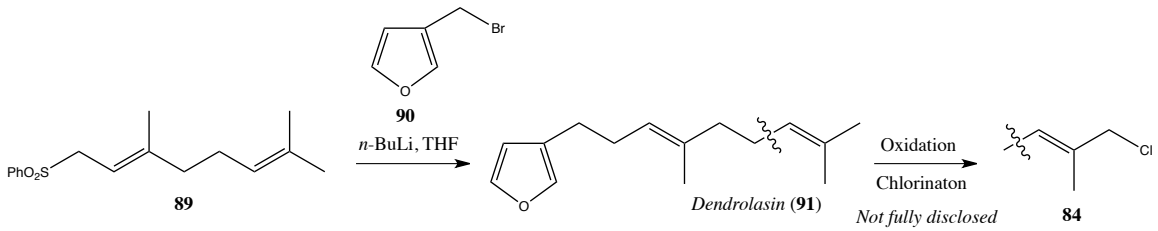

***Scheme 1.15***

The synthetic route began with the lipase PS-catalysed asymmetric desymmetrization of the 1,3-propanediol **81** to furnish the mono acetate **82** in both high chemical and enantiomeric excesses (98% ee) respectively, to install the sole stereocenter (***Scheme 1.15***). The mono-acetate **82** was converted into the silyl ether **83** through a three-step sequence and was subsequently coupled with the furanyl side chain **84** leading to the silyl sulfone **85 (*Scheme 1.16*)**.




***Scheme 1.16:*** *Total synthesis of variabilin **78** by Yoda et al.*[171]

Oddly, the synthesis of the furanyl side chain **84** was not fully disclosed in the report by Takabe *et al.* It is presumed that **84** was prepared by furanylation of allylic sulfone **89** with 3-furylmethyl bromide **90** through an $sp^3$-$sp^3$ cross coupling reaction to afford dendrolasin **91** followed sequentially by allylic oxidation and chlorination chemistry (***Scheme 1.17***).

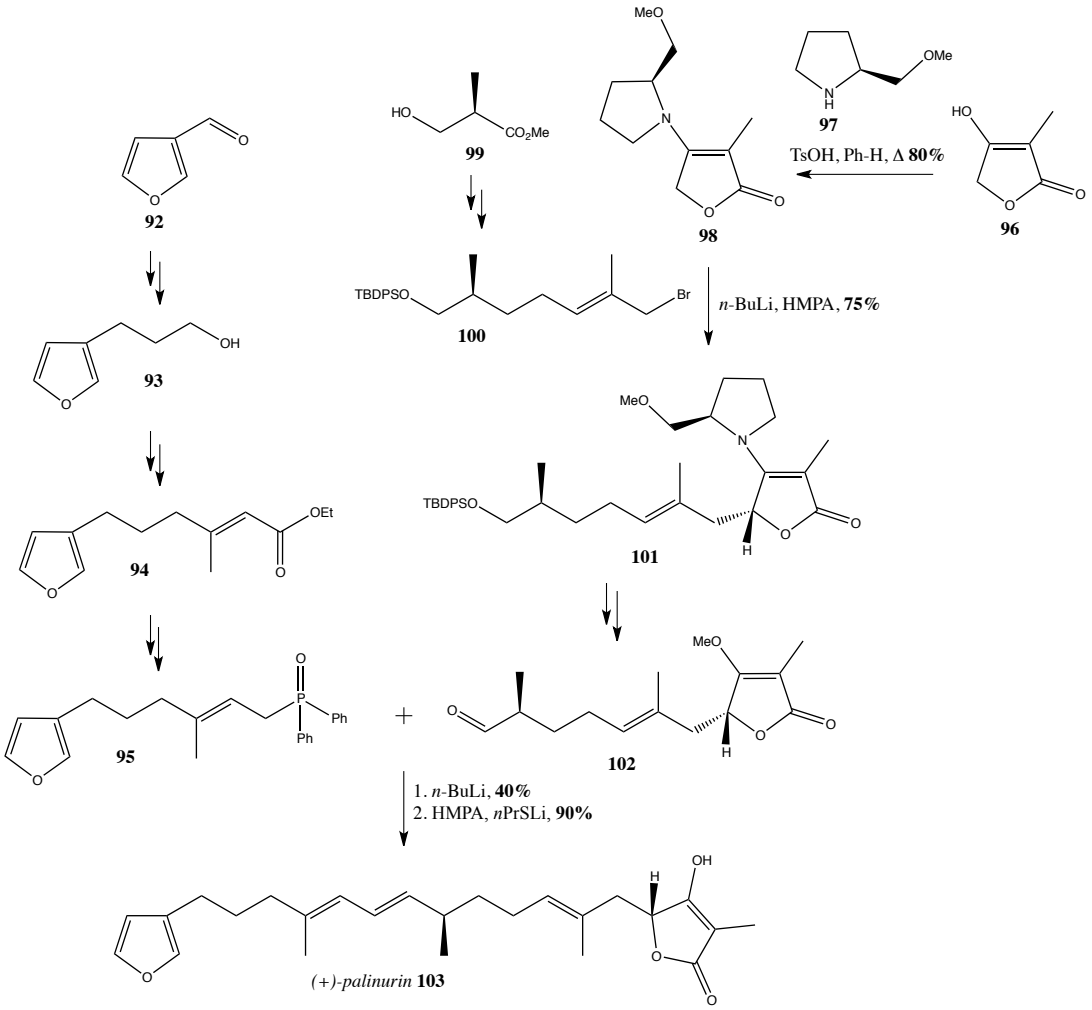



***Scheme 1.17:*** *Preparation of the furanyl side chain **84**.*

Compound **85** was then subjected to desulfonylation and deprotection chemistry to furnish **86**, the chiral segment of variabilin **78** (***Scheme 1.16***). In order to introduce the conjugated tetronic acid moiety, a coupling reaction of **86** after TPAP-induced oxidation to an aldehyde intermediate was effected with methyl tetronate **87** in the presence of LDA. Finally, dehydroxylation under basic conditions and demethylation of **88** completed the first asymmetric synthesis of variabilin **78** (***Scheme 1.16***).

### *1.1.9.2.3 Synthesis of palinurin*

Similar to variabilin **78**, the first reported isolation of (+)-palinurin **103** was from the Mediterranean marine sponge *Ircinia variabilis*.[175] Palinurin **103** has emerged as a non-ATP competitive glycogen synthase kinase 3β (GSK-3β) inhibitor, a kinase implicated in Alzheimer's disease.[176-178] Recently, Gomez *et al.* accomplished the first enantioselective synthesis of (+)-palinurin **103** starting from commercially available furaldehyde **92** and (*R*)-Roche ester **99**.[179] The key step in the synthesis was a Horner-Wadsworth-Emmons reaction to construct the alkene unit by coupling the phosphine oxide **95** and the tetronic moiety **102** (***Scheme 1.18***).




***Scheme 1.18:*** *Total synthesis of palinurin* ***103*** *by Gomez et al.*[179]

Preparation of the phosphine oxide **95** involved 9 linear steps from furaldehyde **92** (***Scheme 1.18***). The 3-substituted furan alcohol **93** was prepared by a Wittig reaction of **92** followed sequentially by reduction and catalytic hydrogenation. The alcohol **92** was converted to its corresponding iodide and then nitrile before reacting it with methyllithium to afford a ketone substrate, which was subjected to a Horner-Wadsworth-Emmons reaction to obtain the α,β-unsaturated ester **94**. Reduction of **94** with DIBAL-H gave the corresponding allylic alcohol, which was finally converted into phosphine oxide **95**.

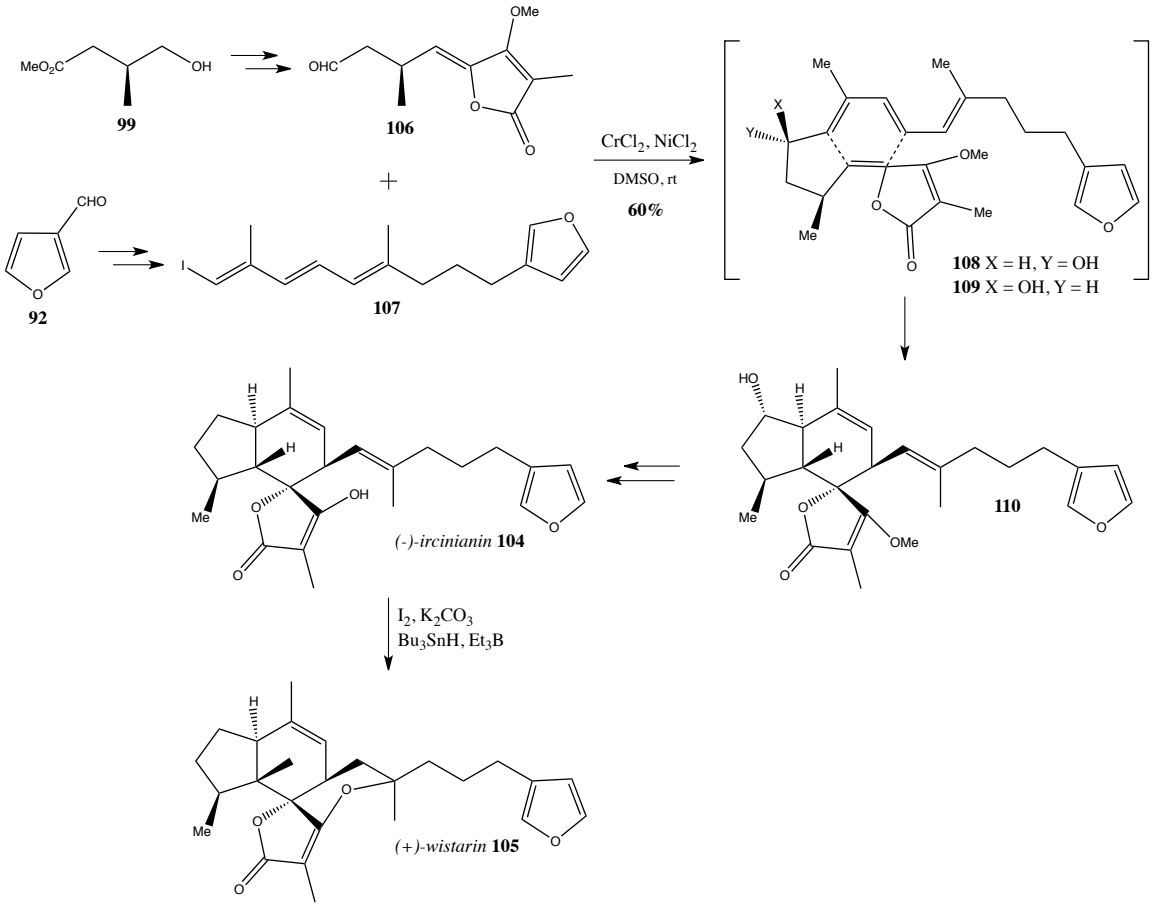
Preparation of the requisite tetronic moiety **102** began with reacting methyl tetronic acid **96** with pyrrolidine **97** under Dean-Stark conditions to afford the chiral enamino-furanone **98**. Cross coupling of **98** with the allylic bromide **100** under the influence of the chiral tether provided the chiral furanone **101**. Removal of the silyl protecting group using TBAF and the chiral auxiliary with aqueous hydrochloric acid gave the corresponding alcohol, which was subsequently reacted with methanol under Mitsunobu conditions followed by Swern oxidation to afford the target aldehyde **102**.

With respect to the Wittig-Horner reaction, treatment of phosphine oxide **95** with *n*-butyllithium generated its corresponding anion, which was subsequently coupled with the aldehyde **102**. Finally, demethylation concluded the first enantioselective total synthesis of palinurin **103** (***Scheme 1.18***).

#### *1.1.9.2.4 Synthesis of (-)-ircinianin and (+)-wistarin*

Two bicarbocyclic sesterterpenoids marine natural products, (-)-ircinianin **104** and its cyclic isomer (+)-wistarin **105** have been the subject of numerous synthetic studies.[180-182] (-)-Ircinianin **104** was isolated in 1977 by Hofheinz *et al.* from the marine sponge, *genus Ircinia,*[183] while (+)-wistarin **105** was isolated from the marine sponge, *Ircinia wistarii*,[184] by Gregson *et al.* in 1982. Despite the additional complexity in structure, both **104** and **105** are members of the same family of furanosesterterpenetetonic acids as variabilin **78** and palinurin **103**. As expected, much of the same methodology previously described for **78** and **103** was utilised in the synthesis of **104** and **105**. The first total synthesis of ircinianin **104** was achieved in 1986 by Takeda *et al.* inspired by a biogenetic hypothesis proposed by Hofheinz *et al.* on the construction of the spirotetronic ring by intramolecular Diels-Alder

(IMDA) cyclisation.[183] Uenishi *et al.* revised this route almost eleven years later, completing an enantioselective synthesis of (-)-ircinianin **104** in 1997 as illustrated in ***Scheme 1.19***.




***Scheme 1.19:*** *Total synthesis of (-)-ircinianin* **104** *and (+)-wistarin* **105** *by Uenishi et al.*[182]

Biogenetically, it was assumed that (-)-ircinianin **104** was formed enzymatically or thermally by intramolecular Diels-Alder reaction from an acyclic tetronic acid precursor similar in structure to **108** in nature.[182] The key step therefore in the synthesis of **104** involved a $NiCl_2$-$CrCl_2$ mediated coupling reaction of aldehyde **106** and conjugated triene **107**. The synthesis of the chiral aldehyde **106** began from (*R*)-Roche ester **99** (***Scheme 1.19***) with preparation of the γ-methylene-butenolide substructure in a similar fashion to that shown previously for variabilin **78** (***Scheme 1.16***). Likewise, synthesis of the conjugate triene **107** was achieved using a similar pathway previously described for palinurin **103** (***Scheme 1.18***).

The Nozaki-Hiyama-Kishi (NHK) reaction of **106** and **107**, followed by an intramolecular Diels-Alder reaction furnished the tricyclic adduct **110**. Interestingly, Ueniski *el al* observed that isomer **108** obtained from the NHK reaction was spontaneously cyclised to **110**, whereas the isomer **109** remained unreacted under the same conditions and could easily be isolated from the reaction mixture. Finally, Barton deoxygenation and demethylation led to (-)-ircinianin **104** (***Scheme 1.19***). Moreover, intramolecular iodo-etheration for the formation of a tetrahydropyran ring followed by radical-induced reductive deiodination accomplished the total synthesis of (+)-wistarin **105 (*Scheme 1.19*)**. It is worth noting that wistarin **105** was the first example of a sesterterpenoid that occurs naturally in both enantiomeric forms.[185]

### *1.1.9.2.5 Synthesis of ircinin-4*

The 2,4-disubstituted furan motif is present in various physiologically active natural products such as **111-114** isolated from marine sources. Ircinin-4 **111** is a member of a large family of furanoterpenes, some of which are illustrated in ***Figure 1.21*** and deserve mentioning due to issues related to their biosynthesis,[186] and more importantly, because of the interesting biological effects exerted by these compounds.[187-189]

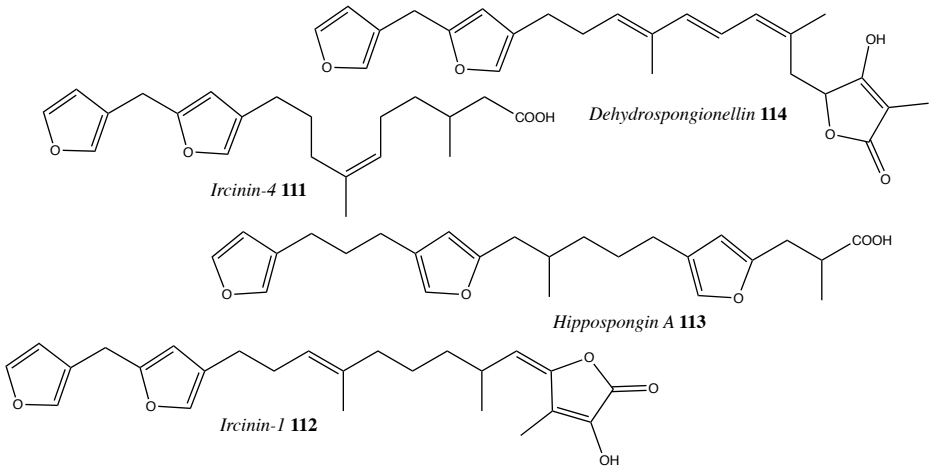
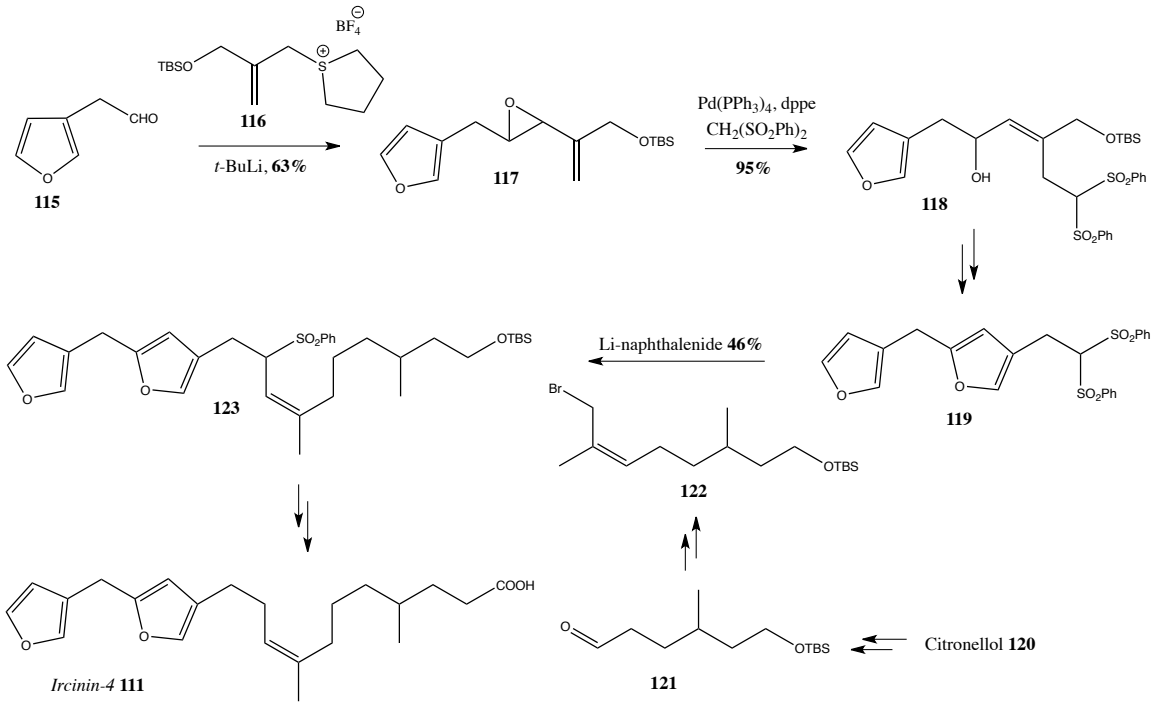



***Figure 1.21:*** *2,4-Disubtituted furanosesterterpenoid marine natural products.*

The first total synthesis of ircinin-4 **111** was achieved by Frustner *et al.* in 1999,[188] almost two decades after its isolation from the Mediterranean marine sponge *Ircinia oros* by Cimino *et al*.[190] Synthesis of ircicin-4 **111** began with the preparation of segment **119**. Reaction of 3-furylacetaldehyde **115** with the sulfur ylide of **116** formed by deprotonation with *tert*-butyllithium gave the epoxide **117** (***Scheme 1.20***). The functionalised sulfonium salt **116** was a valuable building block frequently used within Furstner's research group especially in the concise synthesis of the antitumour alkaloid roseophilin.[191,192]




***Scheme 1.20:*** *The first total synthesis of the marine natural product ircinin-4* ***111****.*

Synthesis of the allylic alcohol **118** was innovatively accomplished *via* a palladium catalysed ring opening of the vinyloxirane **117** employing $Pd(PPh_3)_4$. The mechanism involved deprotonation of bis(phenylsulfonyl)methane by the alkoxide unit of the π-allylpalladium complex resulting in regioselective attack at the electrophilic organopalladium species to furnish **118**. Transformation of **118** into the desired furanylmethylfuran **119** was achieved by temporary protection of **118** as a THP acetal followed by desilylation and selective oxidation. Subsequent treatment of the resulting aldehyde with aqueous hydrochloric acid cleanly furnished the furanylmethylfuran **119 (*Scheme 1.20*)**.

Segment **122** was prepared in 4 linear steps from commercially available citronellol **120** (***Scheme 1.20***). The two initial steps involved O-silylation and oxidation using ozone to furnish the aldehyde **121**. A modified Wittig reaction delivered the (*Z*)-configurated allyl alcohol as a single isomer.[193-195] The final step in the synthesis of the allylic bromide **122** involved a bromination reaction using NBS.

Reductive metalation of bis-sulfone **119** with lithium naphthalenide followed by addition of the allylic bromide **122** provided the desired coupling product **123**. Desulfonylation and deprotection chemistry gave the corresponding primary alcohol. Due to the inherent labile nature of the furan to oxidation, transformation to ircinin-4 **111** was successfully achieved employing a carefully controlled two-step protocol using PDC and silver nitrate (***Scheme 1.20***).

#### *1.1.9.2.6 Synthesis of (+)-manoalide and related monocarbocyclic derivatives*

Monocarbocyclic sesterterpenoids are an important series of marine sponge metabolites belonging to the sesterterpene class. (+)-Manoalide **124** is the parent compound in this series and was first isolated in 1980 by Scheuer *et al.* from a Pacific sponge *Luffariella variablis*.[196] One year later, Scheuer *et al.* reported three additional related metabolites from the same Pacific sponge, namely secomanoalide **125**, (*E*)-neomanoalide **126** and (*Z*)-neomanoalide **127**. All three compounds, as well as the parent compound, displayed antibacterial activity against *Gram*-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) (***Figure 1.22***).

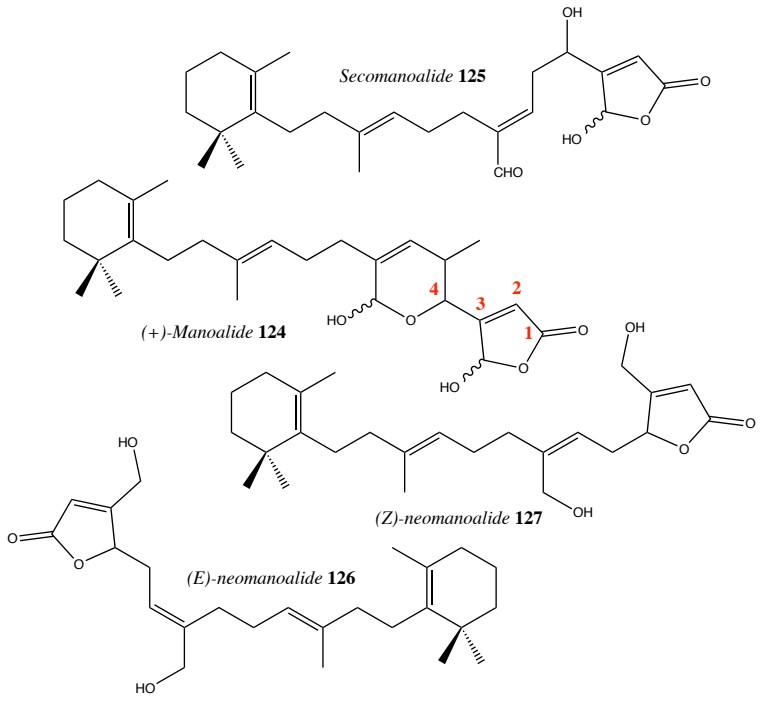
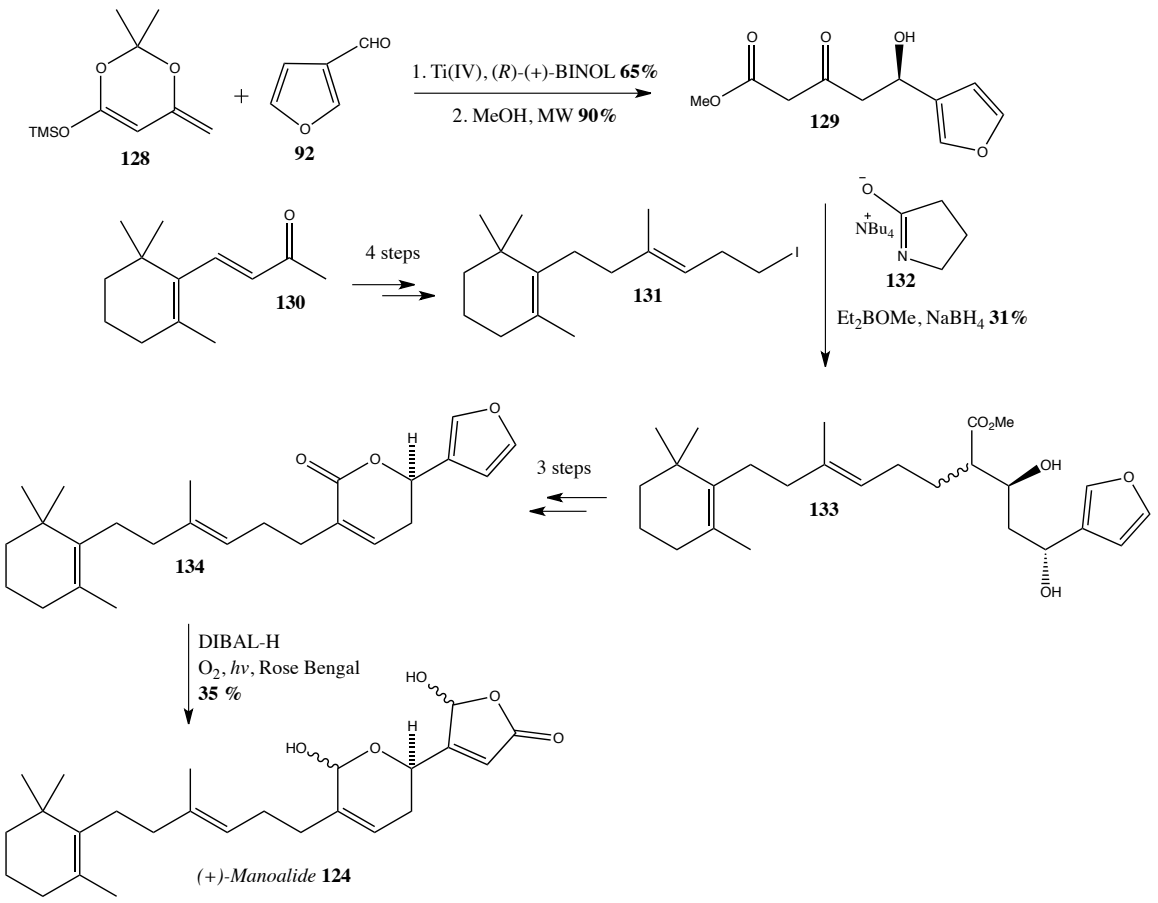



***Figure 1.22***

Since its discovery, (+)-manoalide **124** has attracted considerable attention from synthetic organic chemists with the first reported racemic synthesis in 1985 by Katsumara *et al.,*[197] which was followed by six additional syntheses of the racemate by the groups of Garst,[198] Katsamura,[199] Kocienski,[200] and Hoffmann.[201] The structure of manoalide **124** is relatively simple as it only embodies one defined stereogenic center. The interesting fact about manoalide **124** is its biological profile, showing fantastic activity as a potent and irreversible inhibitor of phospholipase $A_2$, which is the enzyme that catalyses arachidonic acid release in the formation of pro-inflammatory factors.[202,203] Despite the number of syntheses available, only two enantioselective routes towards (+)-manoalide **124** have been reported in the literature. [204,205]

The first enantioselective synthesis of manoalide **124** was accomplished by Soriente *et al.* nearly twenty years after its isolation (***Scheme 1.21***).[204] The alkyl iodide **131** was prepared from β-ionone **130** utilizing the same synthetic procedure first reported by Hoffmann *et al*.[201] The second subunit **129** bearing the stereogenic centre with the desired (*R*)-configuration was prepared in two steps as illustrated in ***Scheme 1.21***.

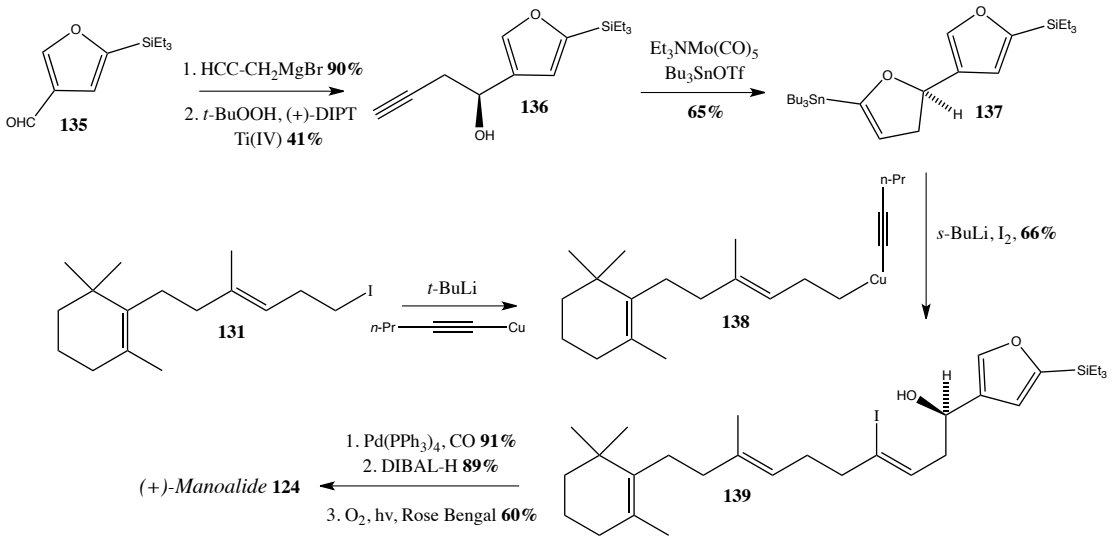



***Scheme 1.21:*** *First enantioselective synthesis of (+)-manoalide* **124** *reported by Soriente et al.*[204]

The stereogenic centre at C(4) was introduced by exploiting an aldol condensation reaction.[206] Subjecting 3-furylaldehyde **92** and silyloxydiene **128** to a mixture of Ti(O*i*-Pr)$_4$ and (*R*)-BINOL gave the corresponding aldol (65% yield, 88% *ee*), which was subsequently converted to its corresponding ester **129** by microwave irradiation (***Scheme 1.21***).[206]

The alkylation reaction between homoallyl iodide **131** and the ester **129** required the presence of tetrabutylammonium salt **132** as a phase transfer catalyst to furnish, after diastereoselective ketone reduction, furan **133**. An ensuing three-step protocol generated lactone **134** *via* ester hydrolysis, acetylation with simultaneous lactonization and finally elimination of acetate in the presence of DBU. Treatment with DIBAL-H to afford the lactol followed by photooxygenation of the furan moiety successfully furnished (+)-manoalide **124** (***Scheme 1.21***).

Four years later in 2003, Kocienski *et al.* reported the second enantioselective synthesis of (+)-manoalide **124** (***Scheme 1.22***).[205] In contrast to Sodano's methodology, the stereogenic centre was introduced using a Sharpless kinetic resolution. Similar to Sodano's synthesis, Kocienski's route employed the same homoallyl iodide **131**, which was prepared from β-ionone **130** but using a different 8 step procedure.

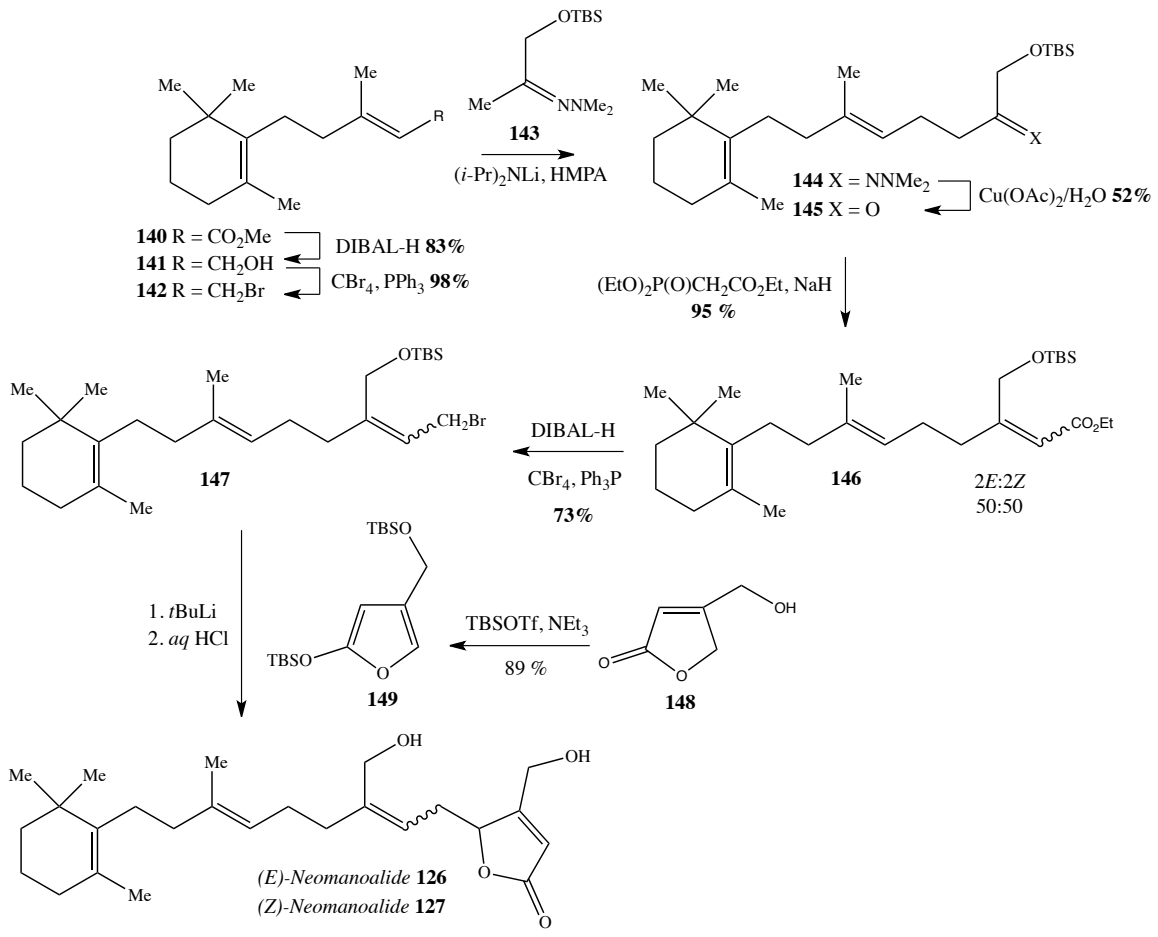



***Scheme 1.22:*** *Second enantioselective synthesis of (+)-manoalide* **124** *reported by Kocienski et al.*[205]

The second subunit was derived from furyl aldehyde **135**, which was reacted with propargyl magnesium bromide to afford a racemic propargylic alcohol. Sharpless asymmetric epoxidation of the alcohol subsequently afforded the desired (*R*)-configured alcohol **136** in 41% yield. Successive Mo-catalysed cycloisomerisation in the presence of $Bu_3SnOTf$ led to the vinyl stannane **137**, which is the key intermediate for the Cu-mediated 1,2-metalate rearrangement. To facilitate this cross coupling reaction, the vinyl lithium species of **137** was generated *in-situ* using *s*-butyllithium, which was subsequently added to the mixed cuprate **138** previously prepared from homoallyl iodide **131** employing *t*-butyllithium and 1-pentynylcopper. The vinyl cuprate species was quenched with iodine to generate vinyl iodide **139**. The last three steps in the synthetic route involved a palladium-catalysed carbonylation reaction to afford a lactone, which was subsequently reduced to its corresponding lactol using

DIBAL-H. Similar to Sodano *et al.*, the final step was a photooxidation of the furan moiety using rose bengal to furnish (+)-manoalide **124 (*Scheme 1.22*)**.
Manoalide **124** was licensed to Allergan Pharmaceuticals and reached phase II clinical trials as a topical antipsoriatic. Its development was however discontinued due to formulation problems. The compound is now commercially available as a biochemical standard tool to block the action of $PLA_2$.[207,208]

With regard to the first synthesis of (*E*)-neomanoalide **126** and (*Z*)-neomanoalide **127**, this was first achieved by Jefford and Boukouvalas *et al.* in 1994.[209] Charles Jefford and John Boukouvalas have been involved in the synthesis of a number of synthetically novel furanolipid marine natural products in the last two decades. With respect to the the early 90's, they applied versatile furanolate technology which worked efficiently for the synthesis of γ-lactone and furan natural products like freelingnite,[210] (+/-)-eldanolide and siphonodictidine.[211,212] Logically, this methodology, which is illustrated in ***Scheme 1.23***, was again utilised in the concise synthesis of (*E*)-neomanoalide **126** and (*Z*)-neomanoalide **127**.




***Scheme 1.23:*** *Concise synthesis of (E)-neomanoalide **126** and (Z)-neomanoalide **127** as developed by Jefford et al.*[209]

The key step in preparation of *(E)*-neomanoalide **126** and *(Z)*-neomanoalide **127** involved attachment of the two coupling partners **147** and **149**. This was achieved by generating the 5-lithio derivative of **149** using *tert*-butyllithium and subsequent cross coupling with **147**. Furan **149** was prepared from the γ-lactone **148** by treatment with (*tert*-butyl)dimethylsilyl trifluoromethanesulfonate in the presence of triethylamine.

Preparation of the allyl bromide **147** was accomplished by modifying and extending the side chain of (*E*)-methyl monocyclofarnesate **140 (*Scheme 1.23*)**. Reduction and bromination of **140** gave the bromide **142**. The hydroxy acetone element of the molecule was attached by employing hydrazone **143.** The anion of **143** was generated *in-situ* by the action of lithium

diisopropylamine and alkylated with **142** to give hydrazone **144**. Hydrolysis with copper acetate gave the ketone **145** which was submitted to a Wittig reaction with ethyl (diethoxyphosphoryl)acetate to furnish both the 2*E* and 2*Z*-isomers of ethyl ester **146** in a 1:1 ratio, which were separated by column chromatography. Each isomer was converted separately to its corresponding (2*E*)- and (2*Z*)-bromide **147** (***Scheme 1.23***).

Following attachment of the two coupling partners **147** and **149**, hydrolysis with aqueous hydrochloric acid successfully delivered (*Z*)-neomanoalide **127** or (*E*)-neomanoalide **126** depending on the isomer of **147** employed (***Scheme 1.23***).

### 1.1.9.3 Summary

Herein, I have reported on the total synthesis of a variety of biologically active sesterterpenoid marine natural products of varying complexity ranging from simple linear furanolipid molecules like furospinosulin-1 **69** to more complex molecules containing stereogenic centers and cyclic systems like (-)-ircinianin **104** and **(+)-**wistarin **105**. All syntheses reported in this section feature much of the repertoire of modern chemistry, including elaborate intramolecular Diels-Alder reactions and exciting transition-metal catalysed C-C-bond formations and rearrangements. As we reflect on the syntheses featured in the section, a number of plausible methods to achieve the concise total synthesis furospongolide **55** have been identified. Elegant concepts for introducing the furan and butenolide ring onto a central linchpin unit have been discussed as well as exciting and convenient functional group transformation reactions. These reactions will all be considered as practical approaches towards the synthesis of our target molecule **55**.

Despite the uniqueness of each sesterterpenoid reported in this section, they all have a common structural homology containing either/both a furan or lactone ring, which must at some level be connected to their inherent biological activity. This comparative study between sesterterpenoids provided promising concepts on how to amend the structure of furospongolide **55** to increase its potency as an antitumour agent. Standard oxidation and reduction chemistry can also be performed on our target molecule **55** to alter its structure to imitate other known biological active marine natural products.

As new members of the sesterterpenoid family are continually being discovered, and largely forgotten ones unearthed, modern synthetic chemistry will continue to be developed and refined to meet the needs for synthetically targeting these important and attractive molecules of this fascinating class of natural products.

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# Chapter 2

# *Chemical*

# *Results and Discussion*

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# 2.1 Aims and objectives

## 2.1.1 Project overview

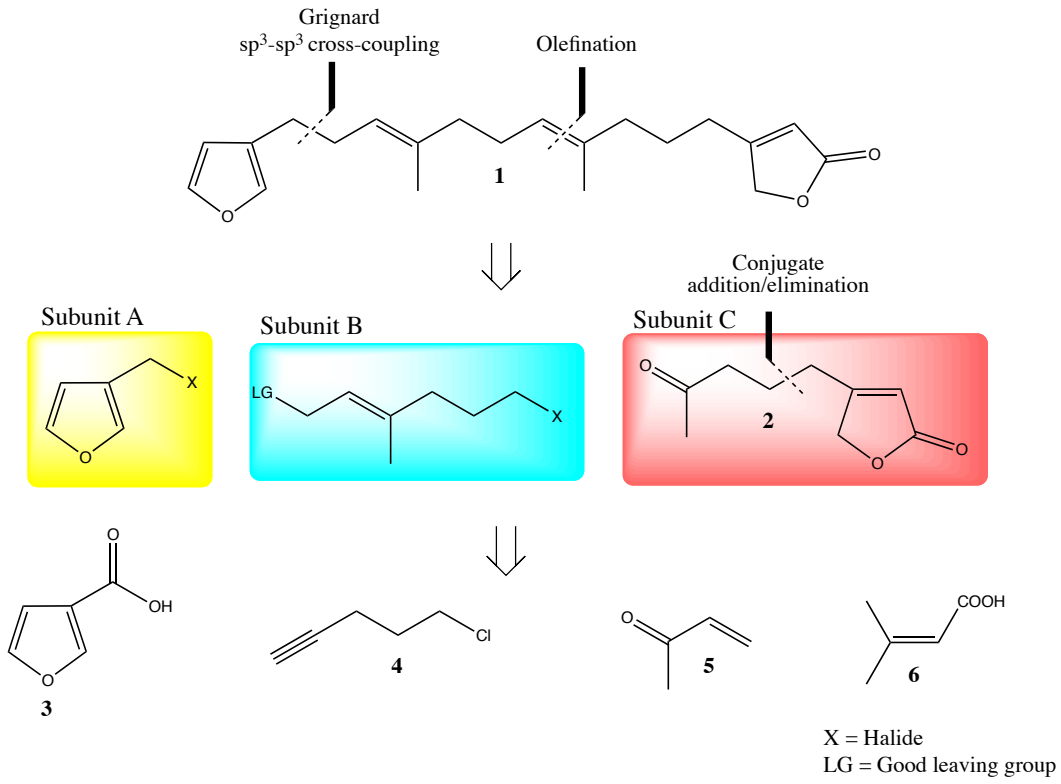
Recently identified as a structurally unique inhibitor of HIF-1 activation with an $IC_{50}$ value of 2.9 μM, furospongolide became an attractive target for synthesis, structural modification and pharmaceutical optimisation in the development of a potent antitumour agent.[1] Furospongolide was first isolated and characterised in 1980 following its isolation from the marine sponge *Dysidea herbacea*.[2] This terpene-derived furanolipid natural product has been the subject of many recent reviews describing its potential as a chemotherapeutic agent.[1,3-5]

The design and execution of a concise total synthesis of furospongolide **1** was the primary objective of this project. This would involve developing an elegant retrosynthetic plan that would incorporate contemporary methodology in the construction of the furanolipid backbone and innovative concepts in order to introduce the butenolide ring. A significant proportion of the methodology described in our introduction in the synthesis of furanosesterterpenoids (***Section 1.1.9***) will be utilised in the preparation of furospongolide and structurally related analogues. Its relatively simple and readily amenable structure makes furospongolide an ideal candidate for the construction of designed analogues as well as other biologically important furanosesterterpenes sharing the same C1-C13 subunit.[6]

As there is little information about the structure-requirement for the hypoxia-selective growth inhibitory activity of furospongolide **1**, we intend to elucidate its structural-activity relationship through synthesis and biological evaluation of an extensive library of structurally modified analogues. Future scope of the project can then look towards amending our target molecule to improve potency and minimise toxic effects against various cancer cells lines.

## 2.2 Synthesis of furospongolide (1st Generation)

Our 1st generation retrosynthetic plan for furospongolide **1** hinged upon three C-C bond disconnections to the furanolipid backbone breaking the molecule down into 3 precursor fragments labelled **subunit A, B** and **C** as illustrated in ***Scheme 2.1***. All three precursor fragments can be prepared from commercially available starting material from Sigma Aldrich (**3, 4, 5** and **6**). With respect to our coupling strategy, it is envisioned that the furan moiety would be attached to **subunit B** (central linchpin) through a Grignard $sp^3$-$sp^3$ cross coupling reaction. **Subunit C** would then be attached to the furanolipid backbone *via* a Wittig reaction. With respect to **subunit C**, it is intended that this fragment will be prepared through a conjugate addition/elimination reaction (***Scheme 2.1***).



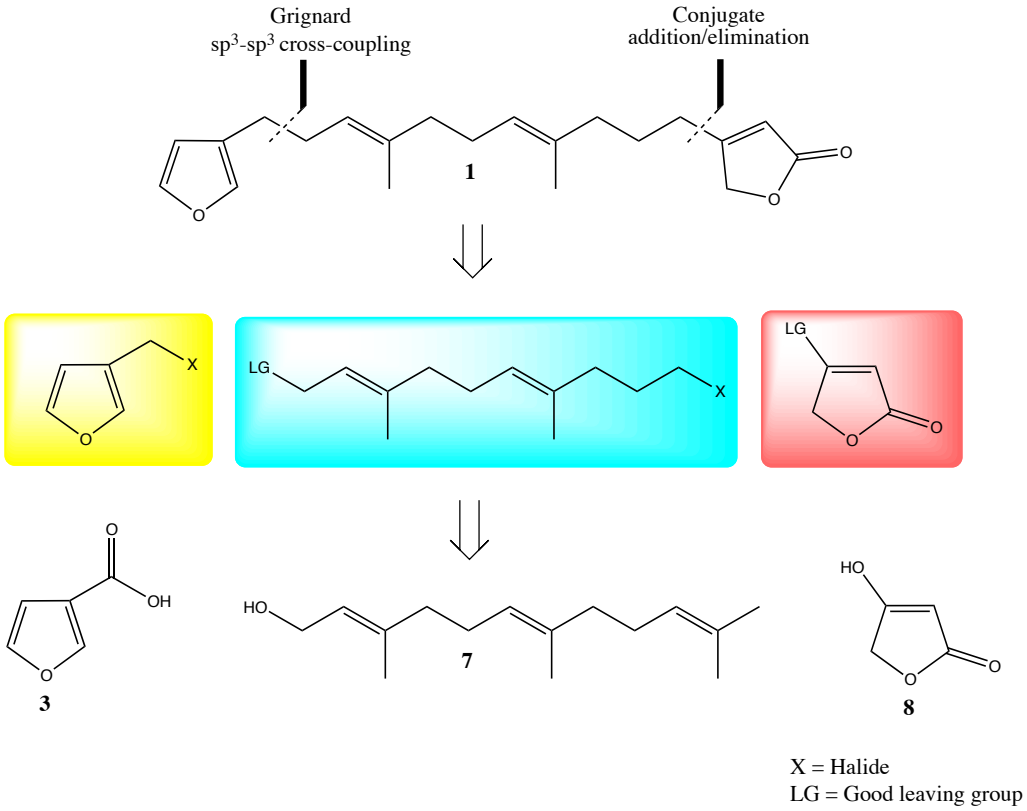

***Scheme 2.1:*** *1st generation retrosynthetic analysis of furospongolide **1**.*

Disappointingly, 1st generation synthesis of furospongolide **1** was unsuccessful and the results obtained from our synthetic endeavours are described in detail in ***Appendix I***.

Our retrosynthetic plan looked deceptively straightforward on paper, however considerable difficulty was encountered with two synthetic steps in the synthetic strategy. The first problematic step was in the synthesis of **subunit C** through the conjugate addition/elimination reaction. After numerous failed attempts, the coupling strategy and precursor starting materials were altered slightly to encompass a Grignard cross coupling reaction, which was also unsuccessful. The second challenge in our 1st generation synthesis of furospongolide **1** was the Wittig reaction (***Scheme 2.1***). Preliminary investigations were focused on studying the stereochemical outcome of the Wittig reaction and manipulating the reaction conditions to achieve high stereochemical purity of the trans isomer during olefin synthesis. Disappointingly this was not achievable and a mixture of the *E* and *Z* isomer was obtained following the cross coupling reaction.

Noteworthy, the methodology employed in the preparation of **subunit A** as well as the Grignard $sp^3$-$sp^3$ cross coupling reaction (***Scheme 2.1***) successfully made its transition to 2nd generation synthesis of furospongolide **1 (*Scheme 2.2*)**.

## 2.3 Synthesis of furospongolide (2nd Generation)




***Scheme 2.2:*** *2nd generation retrosynthetic analysis of furospongolide **1**.*

The 2nd generation retrosynthetic plan for furospongolide **1** hinged upon making two C-C bond disconnections to the furanolipid backbone breaking the molecule down into three precursor fragments as illustrated in ***Scheme 2.2***. **Subunit A** (furan moiety), **subunit B** (central linchpin) and **subunit C** (α,β-unsaturated γ-lactone) can be prepared from commercially available starting material from Sigma Aldrich (**3, 7** and **8**). With respect to the coupling strategy, it was envisioned that attachment of the furan moiety (**subunit A**) to the central linchpin (**subunit B**) will be achieved by means of Grignard $sp^3$-$sp^3$ cross coupling while the crucial addition of the butenolide fragment to the furanolipid backbone will be achieved by means of a conjugate addition/elimination reaction.

### 2.3.1 Synthesis of subunit A

The 3-substituted furyl moiety is present in numerous natural products isolated from both terrestrial and aquatic organisms,[7] such as perillene **9**,[8] dendrolasin **10**,[8,9] ambliol-A **11**,[10] ambliol-B **12**,[10] and furospongolide **1** (***Figure 2.1***).[1,2]

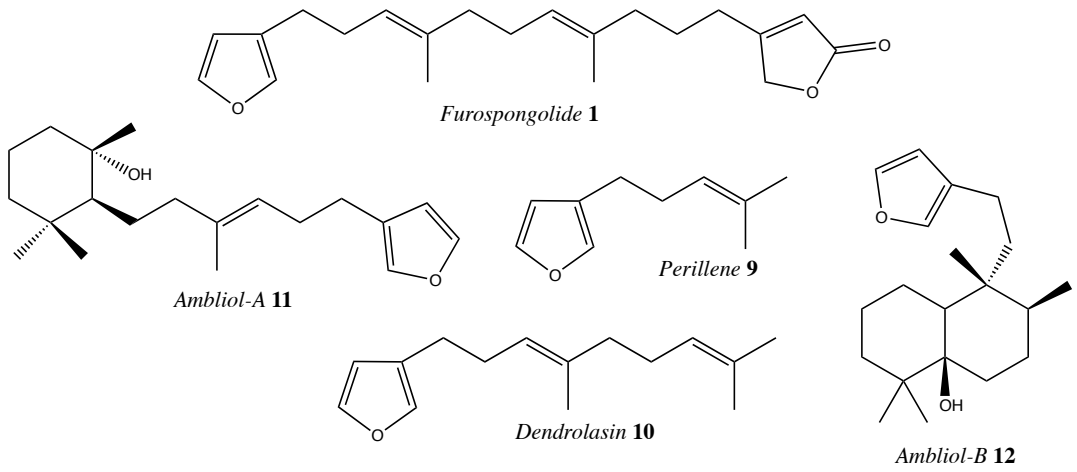
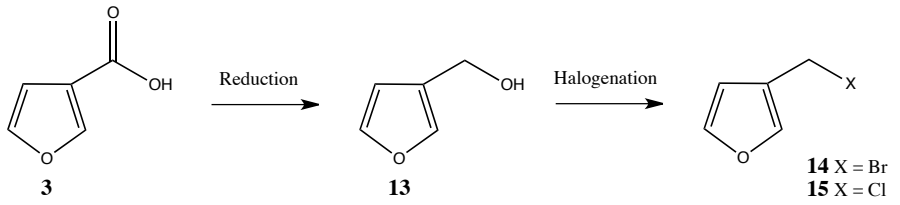



***Figure 2.1***

The simplest approach in the preparation of 3-substituted furans has involved the reaction of a Grignard reagent with an appropriate electrophile. To address this matter, synthetic endeavours began with the requisite Grignard precursor (**subunit A**), which can be prepared in two synthetic steps as illustrated in ***Scheme 2.3***.

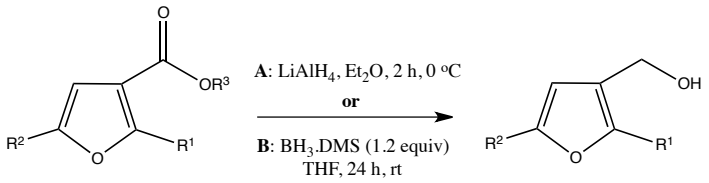



***Scheme 2.3****: Synthetic route to the requisite Grignard precursor (**subunit A**).*

### 2.3.1.1 Synthesis of 3-furylmethanol derivatives

3-Furylmethanol **13** was synthesised by reduction of commercially available 3-furoic acid **3** using 1.3 equivalents of lithium aluminium hydride (LAH) in diethyl ether over a 2 hour reaction period at 0 °C adhering to the procedure for this compound by Sherman *et al.* (***Table 2.1.***).[11]

***Table 2.1.*** *Synthesis of 3-furylmethanol derivatives.*




(**3**, **16, 17**) (**13, 18, 19**)

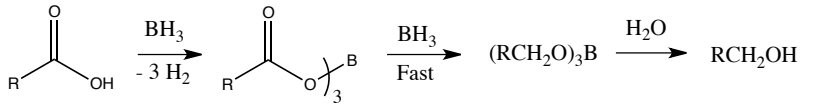
| Entry | SM | $R^1$ | $R^2$ | $R^3$ | LAH(eq) | Method | Product | Yield |
|---|---|---|---|---|---|---|---|---|
| **1** | **3** | H | H | H | 1.5 | A | **13** | 73% [a,d] |
| **2** | **3** | H | H | H | - | B [c] | **13** | 76% [b] |
| **3** | **16** | $CH_3$ | $CH_3$ | H | 1.9 | A | **18** | 74% [a] |
| **4** | **16** | $CH_3$ | $CH_3$ | H | - | B | **18** | 76% [b] |
| **5** | **17** | $CH_3$ | H | $CH_3$ | 2.0 | A [c] | **19** | 79% [a] |

**a: Crude yield of alcohol, no purification required.**
**b: Isolated yield following purification by column chromatography on silica gel.**
**c: 1.2 equivalents of $BH_3$.DMS was always used.**
**d: Yields for this reaction were inconsistent.**

From practical experience, it became apparent that a larger excess of lithium aluminium hydride (1.5 equivalents) was necessary to ensure complete reduction of the acid **3** to its corresponding alcohol **13** (***Table 2.1, Entry 1***). The desired product, 3-furylmethanol **13** was obtained in good yield (73%) as a colourless oil, which was essentially pure by $^1$H NMR analysis, thus avoiding the need for further purification by column chromatography.

$^1$H NMR spectroscopy confirmed the formation of 3-furylmethanol **13** with the disappearance of the broad acid O*H* at $\delta_H$ 9.50 ppm and the presence of a 2H singlet at $\delta_H$ 4.57 ppm characteristic of the methylene group adjacent to the furan ring (ArC*H*$_2$OH). IR spectroscopy was also consistent with literature findings with absorptions at $\nu_{max}$ 3337 cm$^{-1}$ (OH) and $\nu_{max}$ 1023 cm$^{-1}$ (C-O) respectively.[11]

Noteworthy, this method of reduction was inconsistent at providing 3-furylmethanol **13** in good yield (73%). Sometimes, yields as low as 29% were recorded. The formation of excessive inorganic salts together with the water-soluble nature of 3-furylmethanol **13** resulted in potential loss in yield during workup. For this reason, attention was averted to the use of an electrophilic reducing agent like borane dimethyl sulfide complex ($BH_3$.DMS) which offers an attractive and facile reduction of carboxylic acids to primary alcohols (as illustrated in ***Scheme 2.4***).[12] The reduction involves initial formation of a triacylborate with concomitant evolution of hydrogen gas ($H_2$) followed by fast hydride transfer to the carbonyl carbon to furnish, after workup, the corresponding primary alcohol.




R = 3- Furyl moiety

***Scheme 2.4***

Following established precedent,[13] the borane complex (1.2 equivalents) was gently stirred with 3-furoic acid **3** at room temperature over a 24 hour period in dry tetrahydrofuran and subsequent purification by column chromatography afforded the desired alcohol **13** in 76% yield as a colourless oil (***Table 2.1, Entry 2***). Despite the longer reaction time and need for purification, in our hands the use of borane dimethyl sulfide complex as a reducing agent was a practically easier, more consistent and higher yielding method for the preparation of 3-furylmethanol **13** from its corresponding acid **3**. The borane complex was therefore employed as the reagent of choice for future work in this area.

Following on from the success of the above reaction, attention was shifted to the reduction of the 3-furyl analogues. 2,5-Dimethyl-3-furylmethanol **18** was cleanly obtained in good yield (74%) as a light yellow oil following reduction of commercially available 2,5-dimethyl-3-furoic acid **16** using 1.9 equivalents of lithium aluminium hydride in diethyl over 2 hours at 0 $^{o}$C (***Table 2.1, Entry 3***). A larger excess of lithium aluminium hydride was required to achieve full reduction to the desired alcohol **18** when compared to the literature procedure by Trahanovsky *et al.* for this compound.[14] Surprisingly in this scenario, the reduction of the

acid **16** using lithium aluminium hydride was relatively consistent giving averaging yields between 70-74%. $^1$H NMR analysis verified the synthesis of compound **18** with the appearance of a broad 2H singlet at $\delta_H$ 4.42 ppm characteristic of the methylene protons alpha to the furan ring (ArC*H*$_2$OH). The two 3H singlets characteristic of the methyl groups at the C-2 and C-5 α-positions on the furan ring were shifted marginally upfield from $\delta_H$ 2.26 ppm and $\delta_H$ 2.55 ppm to a 6H singlet at $\delta_H$ 2.24 ppm.Characteristic absorption bands were also observed in the IR spectrum of **18** at $\nu_{max}$ 3338 cm$^{-1}$ (OH) and at $\nu_{max}$ 1002 cm$^{-1}$ (CO).

For comparative reasons, synthesis of 2,5-dimethyl-3-furylmethanol **18** was also achieved using borane dimethyl sulfide complex while following previously described reaction conditions (***Table 2.1, Entry 4***).[13] The desired alcohol **18** was furnished in 76% yield following purification by column chromatography on silica gel. Reduction of the acid **16** using borane dimethyl sulfide complex again exhibited improvements in yield and consistency in addition to being an easier method of reduction in practice.

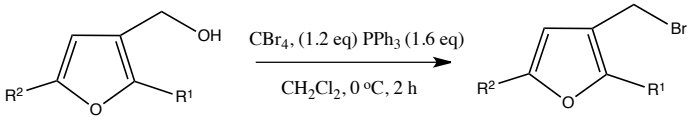
2-Methyl-3-furylmethanol **19** was successfully synthesised by reduction of commercially available methyl 2-methyl-3-furan-carboxylate **17** using lithium aluminium hydride in diethyl ether over a 2 hour period at 0 $^o$C (***Table 2.1, Entry 5***). A larger excess of lithium aluminium hydride (2.0 equivalents) was once again essential to achieve complete reduction to the alcohol **19** when compared to literature precedent.[15] 2-Methyl-3-furylmethanol **19** was obtained in good yield (79%) as a light yellow oil, which was pure by spectroscopic analysis, thus avoiding the need for further purification by column chromatography. $^1$H NMR analysis confirmed the synthesis of compound **19** with the disappearance of mono-methyl ester peak at $\delta_H$ 3.83 ppm (ArCO$_2$C*H*$_3$) and the appearance of a 2H singlet at $\delta_H$ 4.47 ppm characteristic of the methylene group adjacent to the furan ring (ArC*H*$_2$OH). The methyl protons on the α-position of the furan ring were shifted upfield from $\delta_H$ 2.58 ppm to $\delta_H$ 2.28 ppm (ArC*H*$_3$) following reduction of the ester functionality. IR spectroscopy was consistent with earlier observed trends having strong absorption bands at $\nu_{max}$ 3353 cm$^{-1}$ (OH) and at $\nu_{max}$ 1046 cm$^{-1}$ (CO).

Following the successful synthesis of the 3-furylmethanol derivatives (**13, 18-19**) via a reduction reaction, attention was shifted to the subsequent preparation of the appropriate halide as previously illustrated in ***Scheme 2.3***.

### 2.3.1.2 Bromination of 3-furylmethanol derivatives

Carbon tetrabromide ($CBr_4$) looked promising from a search of the literature as an appropriate brominating reagent for the conversion of primary alcohols to alkyl bromides in good yield.[16,17] Following the procedure reported for this compound by Wang *et al.*,[16] synthesis of 3-furylmethyl bromide **14** was conducted by stirring 3-furylmethanol **13** in triphenylphosphine (1.6 equivalents) and carbon tetrabromide (1.2 equivalents) over a 2 hour reaction period at 0 °C in dichloromethane (***Table 2.2, Entry 1***).

***Table 2.2.*** *Synthesis of 3-furylmethyl bromide derivatives using $CBr_4/PPh_3$.*




(**13, 18, 19**) (**14, 20, 21**)

| Entry | SM | $R^1$ | $R^2$ | Product | % Conversion [a] |
|---|---|---|---|---|---|
| 1 | **13** | H | H | **14** | 71% |
| 2 | **19** | $CH_3$ | H | **20** | 66% |
| 3 | **18** | $CH_3$ | $CH_3$ | **21** | 65% |

**a: % Conversion was estimated by $^1$H NMR integration of the crude product.**

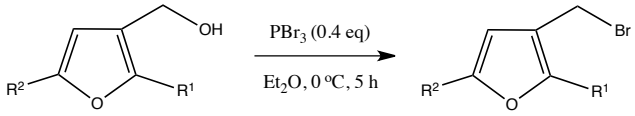
Although a significant amount of triphenylphosphine oxide was generated from this reaction, removal of this by-product by column chromatography was trivial and 3-furylmethyl bromide **14** was successfully isolated as a colourless oil. Unfortunately following $^1$H NMR spectroscopy, another impurity peak was identified at $\delta_H$ 6.83 ppm, which relates to bromoform, an undesirable by-product of the Appel bromination reaction (C*H*$Br_3$). The presence of this impurity affected both the purity and yield of the isolated product. Purification by column chromatography was generally unsuccessful at removing this impurity, as its $R_f$ value was identical to the desired product **14**. $^1$H NMR integration estimated that preparation to 3-furylmethyl bromide **14** was achieved in 71% conversion ***(Table 2.2, Entry 1)***.

$^1$H NMR spectroscopy was consistent with literature findings with the disappearance of a broad 2H singlet at $\delta_H$ 4.57 ppm and the presence of a distinctive sharp 2H signal at $\delta_H$ 4.38 ppm, assigned to the methylene protons adjacent to the bromide (C*H*$_2$Br).[16] A similar result was encountered when 2-methyl-3-furylmethanol **19** and 2,5-dimethyl-3-furylmethanol **18** were exclusively brominated using the same reaction precedent as previously described (***Table 2.2, Entry 2 and 3***).[16] Following purification by column chromatography and subsequent $^1$H NMR spectroscopy, it became apparent that both 2-methyl-3-furylmethyl bromide **20** and 2,5-dimethyl-3-furylmethyl bromide **21** were contaminated with bromoform (C*H*Br$_3$), which was present at $\delta_H$ 6.83 ppm in the $^1$H NMR spectrum. Preparation of 2-methyl-3-furylmethyl bromide **20** (***Table 2.2, Entry 2***) and 2,5-dimethyl-3-furylmethyl bromide **21** (***Table 2.2, Entry 3***) was achieved in 66% and 65% conversion respectively as determined by $^1$H NMR integration.

When subjected to Grignard conditions, bromoform can potentially act as a substrate (electrophile) or competing Grignard reagent in the ensuing cross coupling reaction.[18] Solely for this reason, an alternative brominating reagent was employed for the synthesis of our 3-furylmethyl bromide derivitives.

An alternative method was uncovered in the literature for the high yielding conversion of primary alcohols to alkyl bromides using phosphorous tribromide ($PBr_3$).[19-21] 3-Furylmethyl bromide **14** was successfully synthesised by stirring 3-furylmethanol **13** in phosphorous tribromide (0.4 equivalents) over a 5 hour reaction period in diethyl ether at 0 °C (***Table 2.3, Entry 1***). From $^1$H NMR spectroscopy, the crude product was deemed pure, however column chromatography was carried out to ensure complete removal of all impurities prior to the Grignard reaction. 3-furylmethyl bromide **14** was isolated as a stable colourless oil in yields averaging 79% of the theoretical. The only potential problem encountered was the low boiling point of 3-furylmethyl bromide **14**, which required care in removal of solvent *in vacuo* due to potential loss in yield. This reaction involves a simple and straightforward procedure with a good yield and should be employed in future for the synthesis of 3-furylmethyl bromide derivatives.

***Table 2.3.*** *Synthesis of 3-furylmethyl bromide derivatives using $PBr_3$.*




(**13, 18, 19**) (**14, 20, 21**)

| Entry | SM | $R^1$ | $R^2$ | Product | Yield [a] |
|---|---|---|---|---|---|
| 1 | **13** | H | H | **14** | 79% |
| 2 | **18** | $CH_3$ | $CH_3$ | **21** | 85% |
| 3 | **19** | $CH_3$ | H | **20** | 86% |

**a: Isolated yield following purification by column chromatography on silica gel.**

The same synthetic procedure was employed in the synthesis of 2,5-dimethyl-3-furylmethyl bromide **21** from 2,5-dimethyl-3-furylmethanol **18** (***Table 2.3, Entry 2***). The desired product was isolated as a colourless oil in yields averaging 85% of the theoretical ensuing column chromatography on silica gel. Noteworthy, this novel bromide **21** must be used immediately in the next step following synthesis and purification due to its susceptibility to uncontrolled deterioration. When stored over a short period of time (freezer under $N_2$ blanket), bromide **21** will become an unworkable viscous black tar. $^1$H NMR analysis confirmed the synthesis of 2,5-dimethyl-3-furylmethyl bromide **21** with the disappearance of the broad 2H singlet at $\delta_H$ 4.42 ppm and the appearance of a sharp 2H singlet at $\delta_H$ 4.32 ppm associated with the methylene protons alpha to the bromide (Ar$CH_2$Br). The methyl groups at the C-2 and C-5 α-positions of the furan ring appeared in parallel as two 3H singlet (2 x $CH_3$) at $\delta_H$ 2.21 ppm and $\delta_H$ 2.22 ppm, only differing slightly from that of the alcohol **18** at $\delta_H$ 2.24 ppm (6H, s).

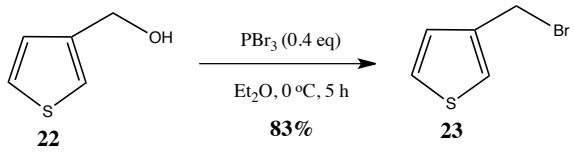
The same synthetic procedure was employed in the synthesis of 2-methyl-3-furylmethyl bromide **20** from 2-methyl-3-furylmethanol **19** (***Table 2.3, Entry 3***). The desired product was isolated as a colourless oil in 86%, which was consistent with literature values.[22] Similar to compound **21**, the 2-methyl-3-furylmethyl bromide **20** must be used immediately in the next step following synthesis and purification due to uncontrolled deterioration (but to a lesser extent than 2,5-dimethyl-3-furylmethyl bromide **21)**. $^1$H NMR analysis confirmed the synthesis of 2-methyl-3-furyl-methyl bromide **20** with the disappearance of the broad 2H singlet at $\delta_H$ 4.47 ppm and the appearance of a sharp 2H singlet at $\delta_H$ 4.36 ppm associated with the methylene group alpha to the bromide (Ar$CH_2$Br). IR analysis of our 3-furylmethyl

bromide derivatives **14, 20** and **21** showed a common trend with the disappearance of the hydroxyl OH stretch in the region of $\nu_{max}$ 3337-3353 $cm^{-1}$ (***Table 2.3, Entry 1, 2 and 3***).

### 2.3.1.3 Bromination of 3-thiophenemethanol

In order to develop an extensive library of structural analogues for biological evaluation, exclusive synthesis of furanolipid based natural products seemed constrictive and therefore work was extended to include the thiophene ring. Various 3-substituted thiophene analogues could be prepared systematically by introducing 3-(bromomethyl)thiophene **23** as an alternative to 3-furylmethyl bromide derivatives in **subunit A**.

3-(Bromomethyl)thiophene **23** was successfully synthesised following treatment of commercially available 3-thiophenemethanol **22** with phosphorous tribromide (0.4 equivalents) over a 5 hour reaction period in diethyl ether at 0 $^{o}$C (***Scheme 2.5***).[23]




***Scheme 2.5***

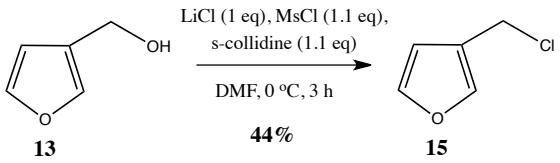
The desired product **23** was obtained as a stable colourless oil in 83% yield, which was deemed pure by $^{1}$H NMR spectroscopy. However purification by column chromatography was employed to ensure absolute purity prior to the Grignard chemistry. $^{1}$H NMR spectroscopy was consistent with the literature findings for **23** with the disappearance of a broad 2H doublet at $\delta_H$ 4.68 ppm and the appearance of a sharp 2H singlet at $\delta_H$ 4.53 ppm assigned to the methylene group adjacent to bromine (Ar$CH_2$Br).[23] Caution had to be taken when handling 3-(bromomethyl)thiophene **23** as it is a mild lachrymator. That said, bromide **23** is significantly more stable when compared to it 3-furyl derivatives **20** and **21**. Principally the bromide **23** was developed by Campaigne *et al.* as a Grignard precursor where he acknowledged the good compliancy and efficacy of the 3-thienyl Grignard reagent in cross

coupling reactions.[23] The 3-furyl/thienyl methyl bromide derivatives **14, 20, 21** and **23** were subsequently used in the ensuing Grignard cross coupling reaction towards the synthesis of furospongolide **1** and other 3-substituted furan and thiophene molecules.

### 2.3.1.4 Chlorination of 3-furylmethanol derivatives

According to literature reading, the most common Grignard precursor in the synthesis of furanolipid synthetic natural products has been derived from 3-furylmethyl chloride **15**.[24-28] In order to evaluate and compare its potential against the bromide **14** and determine the most appropriate Grignard precursor for the preparation of 3-substituted furans, synthetic endeavours towards the synthesis of the chloride **15** commenced.

A neat method was found in the literature for synthesis of allylic chlorides from their corresponding alcohols in excellent yield.[29] Adhering to the procedure by Collington *et al.*,[29] 3-furylmethyl choride **15** was successfully synthesised following treatment of 3-furylmethanol **13** with lithium chloride (LiCl), methanesulfonyl chloride (MsCl) and 2,4,6-trimethylpyridine (s-collidine) in dimethylformamide (DMF) over a three hour reaction period at 0 $^{o}$C (***Scheme 2.6***).

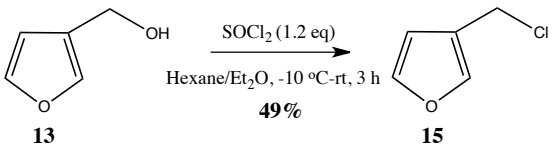



**13** **15**

***Scheme 2.6***

$^{1}$H NMR analysis of the crude product revealed a two-component mixture consisting of the desired chloride **15** and unreacted starting material **13** in a 6:1 ratio. Following purification by column chromatography the desired chloride **15** was obtained as a colourless oil in 44% yield. The reaction was repeated following the same conditions applied previously, however the same conclusive result was obtained. In order to force the reaction to completion the reagent equivalents were doubled, which disappointingly only led to an adverse effect on the yield due to decomposition of the sensitive alcohol **13**.[30]

According to literature research, the most common and standard method for the chlorination of 3-substituted furyl alcohols has been through the use of thionyl chloride ($SOCl_2$).[11,15,26,30,31] The most cited procedure described for this compound is by Sherman *et al.* and involves treatment of 3-furylmethanol **13** with thionyl chloride in a stirring solution of pyridine and diethyl ether at -10 $^oC$.[11] In our hands this reaction was capricious affording the chloride **15** in yields ranging from 25-50%. Numerous variations in the procedure were investigated, including inverse addition of alcohol **13** to a thionyl chloride-pyridine mixture as described by Miller *et al.* and substitution of benzotriazole for pyridine as described by Retey *et al.*[26,31] The most reproducible method for synthesis of 3-furylmethyl chloride **15** using thionyl chloride involved adding this reagent (1.2 equivalents) dropwise in distilled hexane to a stirring solution of alcohol **13** in diethyl ether at -10 $^oC$ in the absence of base followed by a three hour stir at room temperature (as illustrated in ***Scheme 2.7***).




**13** **15**

***Scheme 2.7***

$^1H$ NMR analysis deemed the crude product sufficiently pure for use in further transformations, however purification by column chromatography was undertaken to ensure the absolute purity of the product. The title chloride **15** was isolated as a colourless oil in 49% yield, which is consistent with literature values.[11]

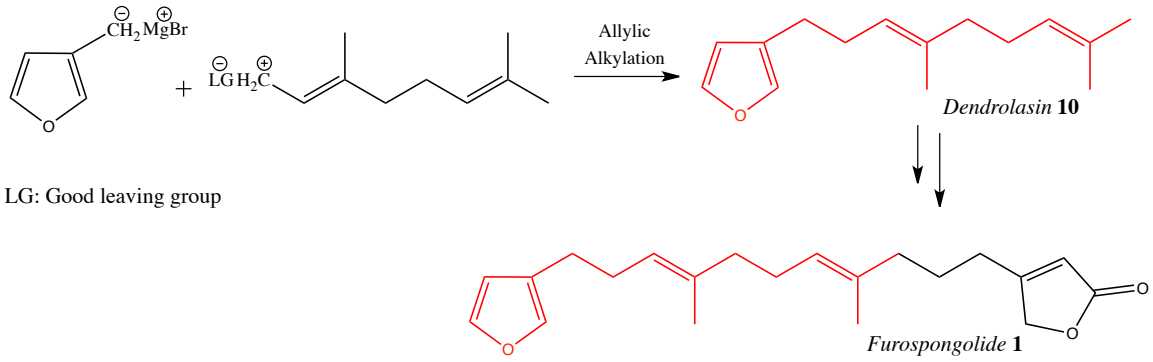
Spectroscopic analysis was also consistent with literature findings with the disappearance of a broad 2H doublet at $\delta_H$ 4.68 ppm and the appearance of a sharp 2H singlet at $\delta_H$ 4.48 ppm assigned to the methylene group adjacent to chloride (Ar$CH_2$Cl).[11,26]

With respect to the general preparation of **subunit A**, synthesis of the 3-furylmethyl bromide **14** using phosphorous tribromide offered a more consistent, practically easier and higher yielding method for the large scale preparation of a stable Grignard precursor reagent (***Table 2.3, Entry 1***). Large-scale preparation of 3-furylmethyl chloride **15** was found to be relatively inconsistent and quite problematic at providing the chloride **15**, which decomposed quite

rapidly at room temperature to a viscous black tar as previously noted by Winberg *et al*.[15] Taken all this into consideration, the bromide **14** was the obvious choice and the most appropriate Grignard precursor reagent for the ensuing $sp^3$-$sp^3$ cross coupling step.

### 2.3.2 Optimisation of the Grignard $sp^3$-$sp^3$ cross coupling reaction

An important milestone in the strategy towards the synthesis of our target molecule **1** was to devise a logical method for coupling the Grignard precursor with a suitable terpenoid derived precursor molecule in a convenient high yielding reaction. Having already successfully synthesised the requisite Grignard precursor **14**, the next essential step was to prepare an ideal electrophilic coupling companion for the Grignard cross coupling reaction (***Scheme 2.8***).



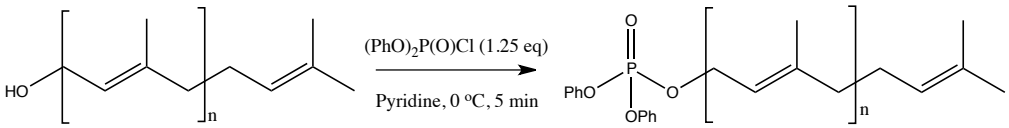

***Scheme 2.8***

Since its first isolation in 1957 from the ant Lasius (*Dendro Lasius*) fuliginosus Latr,[9] dendrolasin **10** has become one of the most popular synthetic targets among the heterocyclic sesquiterpenes.[21,32-38] As illustrated in ***Scheme 2.8***, dendrolasin **10** is the basic constituent in the structural template of furospongolide **1**. This simple furanolipid natural product therefore became an attractive initial target for establishing effective methodology for attaching the furan moiety in the synthesis of furanolipid natural products. Among the numerous methods reported in the literature (Negishi coupling,[33] Stille coupling,[39] and oxygenation of conjugated dienes[37]) for its synthesis, the most clear and concise route involved a Grignard cross coupling. The electrophilic substrate could essentially be derived from commercially available geraniol **24** by attaching a leaving group in the allylic position to facilitate the allylic alkylation reaction (***Scheme 2.8***).

### 2.3.2.1 Synthesis of acyclic terpene diphenyl phosphates

According to the literature,[40-42] geranyl diphenyl phosphate **25** seemed like a good coupling partner and starting point for preliminary synthetic studies, so different methodology into the preparation of phosphate esters was thus explored.

***Table 2.4.*** *Preparation of allyl phosphates.*




**24** n = 1
**7** n = 2

**25** n = 1
**26** n = 2

| Entry | Alcohol | Product | Crude ratio | % Yield [a] |
|---|---|---|---|---|
| 1 | **24** | **25** | 5:95 | 76% |
| 2 | **7** | **26** | 1:99 | 92% |

Many important highly functionalised molecules in nature contain phosphate esters, especially those based upon carbohydrate residues. As well as serving a critical role in maintaining vital biological processes, phosphate esters have been incorporated into many important pharmaceutical agents such as Honvan® used in the treatment of prostate cancer.

There are several approaches for the preparation of phosphate esters.[43] According to the literature the most direct approach involves reacting the appropriate alcohol with a chlorophosphate in the presence of a proton scavenger.[44-46] As illustrated in ***Table 2.4*****, Entry 1**, geraniol **24** was stirred in the presence of diphenylphosphoryl chloride (1.25 equivalents) and pyridine (0.5 mL/mmol) at 0 $^{o}$C. Conversion of geraniol **24** to its corresponding phosphate ester **25** was almost instantaneous with complete consumption of starting material evident by thin layer chromatography after 5 minutes. A similar result was encountered by Jones *et al.* when studying the rates of phosphorylation of various primary alcohol substrates.[45] Similar to our observations, he noted that the rate of phosphorylation reaches an optimum after a 5 min period and decreases gradually over time. The phosphate ester **25** was successfully prepared in 76% yield. $^{1}$H NMR analysis indicated a minor trace of starting material (~ 5%) present in the crude product (2H doublet at $\delta_H$ 4.16 ppm). It is well documented in the literature that purification of diphenylphosphate esters by column

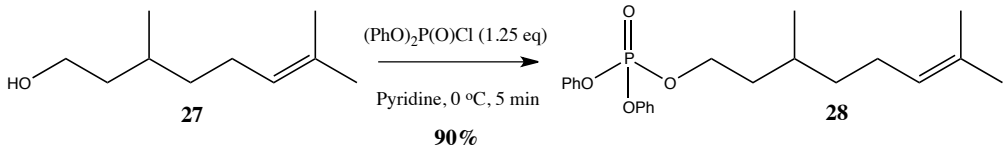
chromatography is not feasible due to the inherent susceptibility of phosphate esters to decomposition, resulting in dramatic loss of yield.[45]

$^{1}$H NMR spectroscopy confirmed the synthesis of geranyl diphenyl phosphate **25** with the shift downfield of the characteristic 2H doublet of geraniol **24** from $\delta_H$ 4.16 ppm to a 2H multiplet at $\delta_H$ 4.71-4.82 ppm associated with the allylic methylene protons adjacent to the newly formed phosphate ester functionality. $^{31}$P NMR spectroscopy consisted of a distinctive singlet at $\delta_p$ -11.5 ppm. IR analysis was also consistent with published data showing characteristic strong absorption bands associated with the P=O group at $\nu_{max}$ 1287 cm$^{-1}$ and P-O-Ph group at $\nu_{max}$ 1192 cm$^{-1}$ and $\nu_{max}$ 1163 cm$^{-1}$ respectively.[44,45] As illustrated in ***Scheme 2.8***, it was envisioned that sesquiterpenes like dendrolasin **10** could potentially be accessed following the reaction of geranyl diphenyl phosphate **25** with an appropriate 3-furyl Grignard reagent. Simply by varying the electrophilic coupling companion in the reaction from **25** to farnesyl diphenyl phosphate **26** would potentially allow access to ambliofuran,[10] a naturally occurring sesterterpenoid marine natural product (please refer to ***Table 2.16***, ***page 219***).

Farnesyl diphenyl phosphate **26** was successfully synthesized in 92% yield from commercially available farnesol **7** by obeying the optimized reaction conditions outlined above for the phosphorylation reaction (***Table 2.4, Entry 2***).[45] Purification by column chromatography on silica gel was deemed unnecessary, and the colourless oil was sufficiently pure to be carried through to the next reaction.

$^{1}$H NMR spectroscopy was consistent with literature findings and thus confirming the synthesis of farnesyl diphenylphosphate **26** with a shift in the characteristic 2H doublet of farnesol **7** downfield from $\delta_H$ 4.15 ppm to a 2H multiplet at $\delta_H$ 4.68-4.82 ppm associated with allyllic methylene protons adjacent the phosphate ester.[46] $^{31}$P NMR spectroscopy showed a distinctive singlet at $\delta_p$ -11.8. IR analysis contained characteristic strong absorption bands associated with the P=O group at $\nu_{max}$ 1290 cm$^{-1}$ and P-O-Ph group at $\nu_{max}$ 1222 cm$^{-1}$, $\nu_{max}$ 1192 cm$^{-1}$ and $\nu_{max}$ 1162 cm$^{-1}$, which are consistent with published data.[44,47]

On a separate note, additional work was carried out in this area to help understand and address the perceived difficulty in achieving full conversion of geraniol **24** to its corresponding phosphate ester **25** (***Table 2.4, Entry 1***). Citronellol **27** is almost identical in structure to geraniol **24** except it lacks allylic alcohol functionality. It was proposed that this allylic site on geraniol **24** was influencing the reaction progress and impeding full conversion to its corresponding phosphate ester **25**. To test this theory, citronellyl diphenylphosphate **28** was prepared from commercially available citronellol **27** under the optimised conditions of the phosphorylation reaction (***Scheme 2.9***).



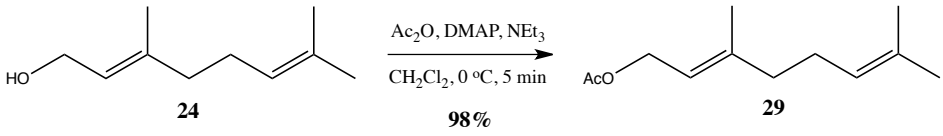

***Scheme 2.9***

As illustrated in ***Scheme 2.9***, the novel phosphate ester **28** was successfully synthesised as a colourless oil in 90 % yield. Interestingly, full conversion of **27** to **28** was achieved with only a minimal trace of starting material (0.02%) in the $^{1}$H NMR spectra of the crude product. From this result, it is possible to postulate that the allylic alcohol functionality is impeding the phosphorylation reaction.

$^{1}$H NMR spectroscopy confirmed the synthesis of citronellyl diphenylphosphate (**28**) with a shift downfield of the characteristic 2H multiplet (C*H*$_2$OH) of citronellol (**27)** from $\delta_H$ 3.61-3.76 ppm to $\delta_H$ 4.20-4.36 ppm respectively. IR analysis showed strong absorption bands associated with the P=O group at $\nu_{max}$ 1292 cm$^{-1}$ and P-O-Ph group at $\nu_{max}$ 1193 cm$^{-1}$ and $\nu_{max}$ 1165 cm$^{-1}$. $^{31}$P NMR spectroscopy consisted of a distinctive singlet at $\delta_p$ -11.8 ppm associated with the phosphate ester.

### 2.3.2.2 Synthesis of geranyl acetate

Recently an acetate ester leaving group has been utilised more frequently in the literature as the optimal electrophilic partner for the synthesis of 3-substituted furyl analogues.[25,28] (*E,E*)-Geranyl acetate **29** is a commercially available starting material from Sigma Aldrich and may offer a superior alternative to geranyl diphenylphosphate **25** as a coupling partner in the preparation of dendrolasin **10**. For convenience, (*E,E*)-geranyl acetate **29** was successfully synthesised from commercially available geraniol **24** following treatment with acetic anhydride ($Ac_2O$), 4-Dimethylaminopyridine (DMAP) and triethylamine in dry dichloromethane at 0 $^oC$ over a 5 minute period adhering to a procedure described for this compound by Watson *et al.* (***Scheme 2.10***).[48]



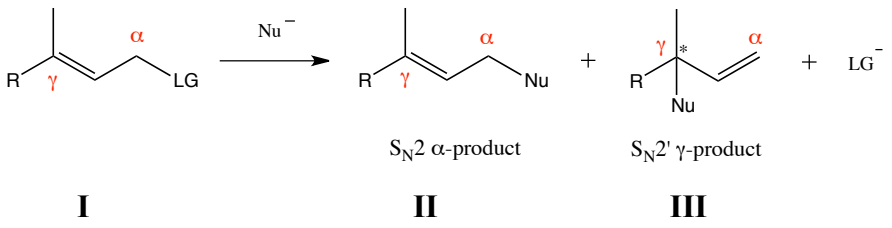

***Scheme 2.10***

The desired acetate ester **29** was cleanly obtained as a colourless oil in 98% following general workup and was used in the next transformation without further purification. $^1H$ NMR analysis confirmed the formation of the desired product **29** with a shift downfield of the 2H doublet at $\delta_H$ 4.15 ppm (*J* 7.0) to a 2H doublet at $\delta_H$ 4.59 ppm (*J* 7.1) associated with the allylic methylene protons. The IR spectrum showed the disappearance of the hydroxyl OH stretch at $\nu_{max}$ 3350 $cm^{-1}$ and the appearance of a carbonyl absorption stretch at $\nu_{max}$ 1742 $cm^{-1}$.

Geranyl acetate **29** was found to be significantly more stable than geranyl diphenylphosphate **25**. The latter was susceptible to deterioration when stored over long periods. The acetate **29** was subsequently used in the ensuing Schlosser $sp^3$-$sp^3$ cross coupling reaction with 3-furylmethylmagnesium bromide **14a** towards the synthesis of dendrolasin **10**. It is worth noting that **a** of **14a** denotes the Grignard reagent of 3-furylmethyl bromide **14**. Similarly, other Grignard reagents that were prepared during our research are symbolised in the same way.

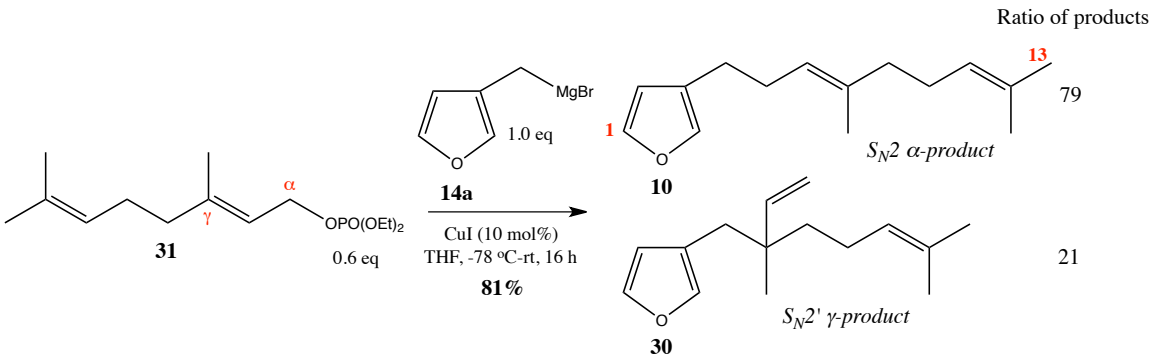
### 2.3.2.3 Allylic alkylation of geranyl diphenyl phosphate

The reaction of allylic substrates with Grignard reagents in the presence of a copper catalyst is a useful and efficient method for the formation of new C-C bonds.[49-53] More commonly known as an allylic alkylation reaction,[54] this transformation is fascinating since the reaction of a carbon nucleophile and substrate with a leaving group in the allylic position can give two different products, the $S_N2$- or α-product and the $S_N2$'- or γ-product (***Scheme 2.11***). Control on the regiochemistry of this reaction is a challenging problem in organic synthesis. As illustrated in ***Scheme 2.11***, the $S_N2$ product is formed by direct displacement of the leaving group of **I** in a typical $S_N2$ fashion affording **II**, while the $S_N2$' product is formed by displacement of the leaving group of **I** involving an allylic shift of the double bond affording **III**.




***Scheme 2.11:*** *Regioselectivity of the allylic alkylation reaction.*

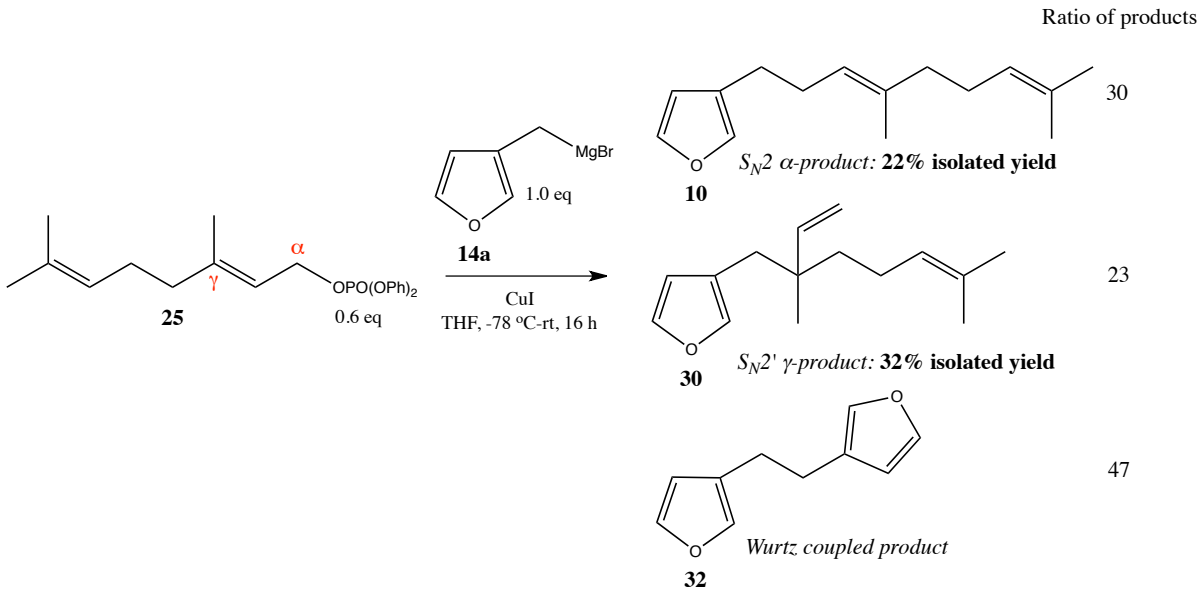
The development of methods that give rise to a controlled C-C bond formation at either the α or γ positions has attracted much attention. In the cross-coupling reaction of allylic substrates, the regioselectively has been actively studied with a variety of leaving groups,[55,56] but to a lesser extent with phosphate leaving groups.[40-42,55] To the best of our knowledge, the first synthesis of dendrolasin **10** using an allylic alkylation reaction was performed in 1982 by Araki *et al.* as illustrated in ***Scheme 2.12***.[41,42]




***Scheme 2.12:*** *Results obtained by Araki et al. for the regio-controlled geranylation of 3-furylmethylmagnesium bromide using copper(I) iodide.*

As previously discussed, dendrolasin **10**, a natural product originally isolated from ants representing the C1-C13 unit (***Scheme 2.8***), was viewed as an initial target in this project from which furospongolide **1** could be potentially obtained.[9] Despite the obvious formation of the regioisomer or γ-product **30**, this methodology seemed like a valid starting point for synthetic endeavours towards the preparation of dendrolasin **10**.

Following a procedure described for this compound by Araki *et al.*,[42] the Grignard reagent was prepared by dropwise addition of 1 equivalent of 3-furylmethyl bromide **14** onto magnesium turnings (2 equivalents) at -10 °C over a 10 minute period followed sequentially by a 1 hour stir at room temperature. The Grignard reagent of **14** was subsequently reacted with 0.6 equivalents of geranyl diphenylphosphate **25** at -78 °C using copper(I) iodide (10 mol%) as a catalyst in anhydrous tetrahydrofuran under inert nitrogen atmosphere as summarised in ***Scheme 2.13***.




***Scheme 2.13***

The reaction was monitored by thin layer chromatography and complete consumption of starting material was evident after 16 hours at room temperature. Following workup, $^{1}$H NMR analysis of the crude product revealed a three component mixture consisting of the dendrolasin **10**, isodendrolasin **30** and 1,2-di(furan-3-yl)ethane **32** in a 30:23:47 ratio of products respectively (***Figure 2.13***). Purification by column chromatography on silica gel successfully isolated all three components independently (achievable due to the non-polar nature of the crude mixture).

Dendrolasin **10** was successfully isolated as a colourless oil in 22% yield. Spectroscopic characteristics were consistent with those reported in the literature,[41] with the appearance of characteristic furanoid peaks in the $^{1}$H NMR spectrum at $\delta_H$ 7.33 ppm [t, *J* 1.6, C(1)*H*], $\delta_H$ 7.21 ppm [s, C(4)*H*] and $\delta_H$ 6.27 ppm [s, C(2)*H*]. Further evidence was observed with the appearance of an apparent 2H triplet at $\delta_H$ 2.45 ppm [*J* 7.6, C(5)$H_2$] and an apparent 2H quartet at $\delta_H$ 2.24 ppm [*J* 7.3, C(6)$H_2$] associated with the methylene protons alpha and beta to the furan ring respectively (***Figure 2.2***).

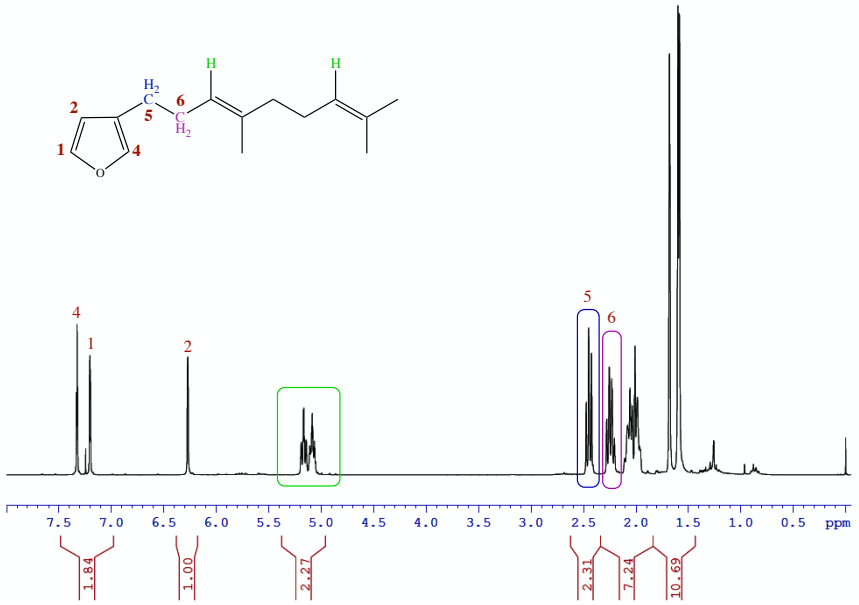



***Figure 2.2:*** *$^{1}H$ NMR spectrum of dendrolasin **10** ($CDCl_3$, 300 MHz).*

The least polar fraction isolated following chromatography was isodendrolasin **30** as a colourless oil in 32% yield. The regioisomer had a distinctive absorption pattern in the $^{1}H$ NMR spectrum succeeding the assembly of the terminal vinyl functionality, which was consistent with literature findings.[42] Due to spin-spin splitting of the terminal alkenyl protons, an ABX system was revealed with a 1H doublet of doublets at $\delta_H$ 5.77 ppm associated with the vinylic C(12)*H* proton ($H_X$ of the ABX system, $J_{BX}$ 17.6, $J_{AX}$ 10.8). The signals for the terminal alkenyl C(13)$H_2$ protons were independently observed as 1H doublet of doublets at $\delta_H$ 4.89 ppm (trans proton, $H_B$ of the ABX system, $J_{BX}$ 17.6, $J_{AB}$ 1.4) and $\delta_H$ 5.00 ppm (cis proton, $H_B$ of the ABX system, $J_{AX}$ 10.8, $J_{AB}$ 1.4) and were easily identified by their unique vicinal coupling constants (***Figure 2.3***). The methylene protons adjacent to the furan ring at C(5)$H_2$ were observed as a 2H singlet at $\delta_H$ 2.41 ppm (***Figure 2.3***).

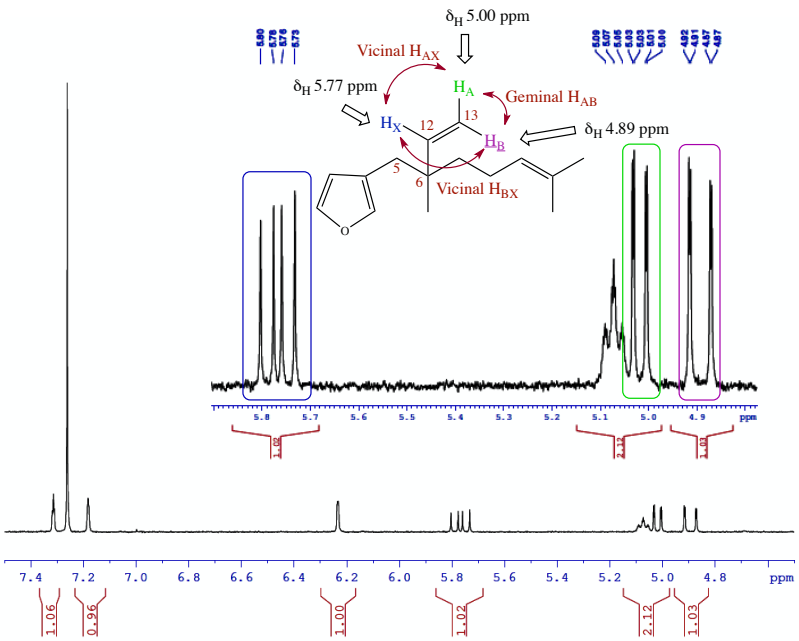



***Figure 2.3:*** *$^{1}H$ NMR spectrum of isodendrolasin **30** showing characteristic absorption patterns ($CDCl_3$, 400 MHz).*

The most polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. $^{1}$H NMR analysis confirmed the formation of the Wurtz coupling product **32** with the appearance of a distinctive 4H singlet at $\delta_H$ 2.68 ppm [2 x C(5)$H_2$] corresponding to the symmetrical methylene protons adjacent to the furan in the dimer **32**.$^{13}$C NMR spectroscopy was also consistent with the disappearance of the peak at $\delta_C$ 23.6 ppm associated with bromide **14** and the appearance of a peak further downfield at $\delta_C$ 25.5 ppm [$C$(5)$H_2$] (***Figure 2.4***).[25,57]

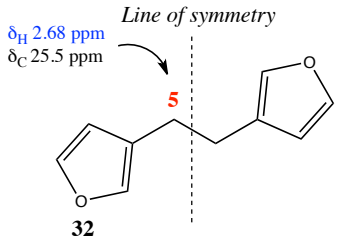
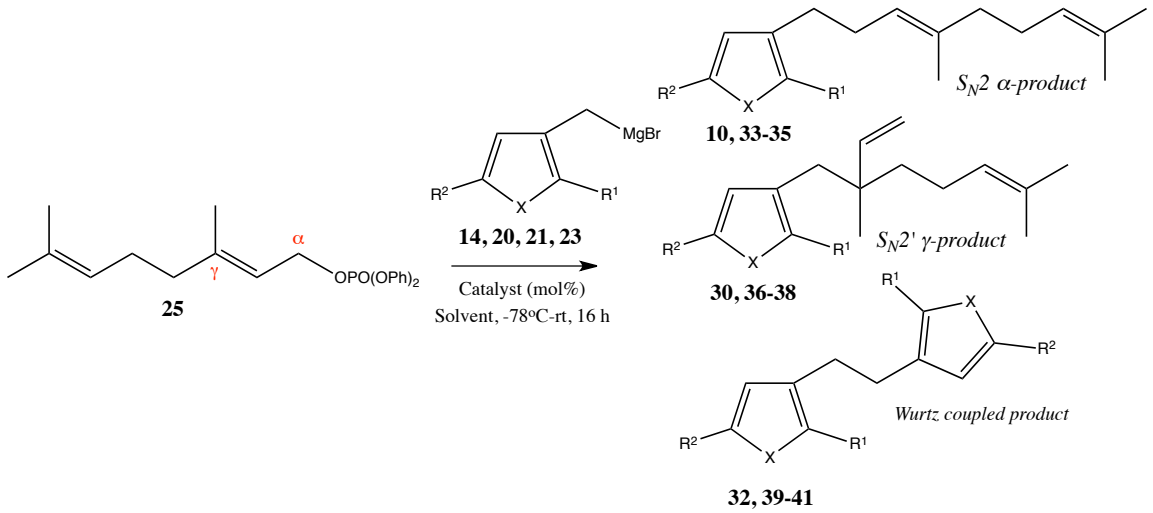



***Figure 2.4***

When comparing the findings obtained by Araki *et al.* in his original studies to the results we achieved (***Scheme 2.12 and Scheme 2.13***), both the yield and regioisomeric ratio were noticeably different despite following his procedure verbatim. The only major difference was we used geranyl diphenyl phosphate **25** instead of that geranyl diethyl phosphate **31** as the electrophilic substrate for the reaction. Surprisingly, Araki *et al.* never encountered or commented on the formation of the Wurtz coupled product **32** during his synthesis of dendrolasin **10 (*Scheme 2.12*)**. With respect to our research, the Wurtz coupled product was an unavoidable side product formed during the synthesis of Grignard reagents from allylic halides. It is worth noting that the yield for the cross coupling reaction was considerably dimished due to complex and rather laborous chromatography in independantly isolating the α- and γ-isomers. Despite the interesting occurance of isodendrolasin **30**, formation of this regioisomeric by-product was not ideal. Nevertheless, attention was shifted to evaluating the potential of the other Grignard reagents in the allylic alkylation reaction with geranyl diphenyl phosphate **25** as shown in ***Table 2.5***.

***Table 2.5**: Transition metal catalysed allylic alkylation reaction of geranyl diphenyl phosphate **25** with Grignard reagents.*




| Entry | $R^1$ | $R^2$ | X | Catalyst (mol%) | Ratio [a] $S_N2$:$S_N2$' | Yield [b] (α-product) | Yield [b] (γ-product) |
|---|---|---|---|---|---|---|---|
| **1** | H | H | O | CuI (10) | 57:43 | 22 % (**10**) | 32% (**30**) |
| **2** | H | H | S | CuI (10) | 75:25 | 39% (**33**) | 10% (**36**) |
| **3** | $CH_3$ | $CH_3$ | O | CuI (10) | - | - (**34**) | - (**37**) |
| **4** | $CH_3$ | H | O | $NiBr_2$ (5) | 75:25 | 43% (**35**) | 13% (**38**) |

**a: Determined by $^1$H NMR integration of the crude product.**
**b: Isolated yield after purification by column chromatography.**

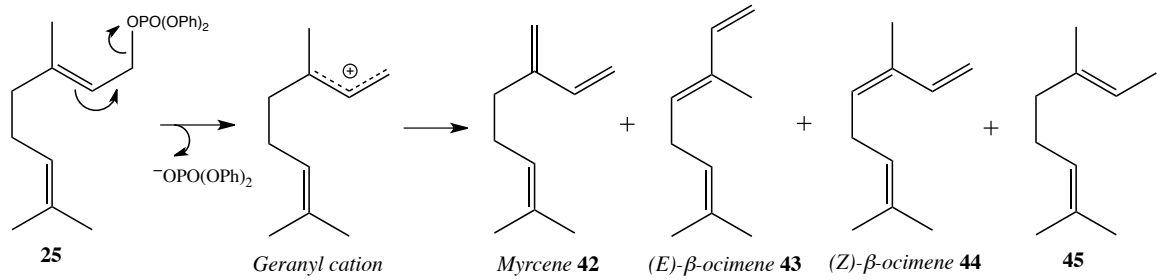
With respect to ***Entry 2***, following the same procedure described previously by Araki *et al.*, the Grignard reagent of 3-thienylmethyl bromide **23** was reacted with geranyl diphenylphosphate **25** employing copper(I) iodide (10 mol%) as a catalyst at -78 $^o$C in anhydrous tetrahydrofuran under inert nitrogen atmosphere ***(Table 2.5, Entry 2)***. As expected, following workup and spectroscopic analysis of the crude product, $^1$H NMR integration revealed a three component mixture consisting of the desired cross coupled product **33**, its corresponding regioisomer **36** and the Wurtz coupled product **39** in a 3:1:1 ratio of products respectively. All three components were independently isolated following column chromatography on silica gel (100% hexane). The novel 3-substituted thiophene **33** was obtained as a colourless oil in 39% yield. Spectroscopic analysis confirmed the synthesis of **33** with the appearance of a 2H triplet at $\delta_H$ 2.66 ppm [*J* 7.6, C(5)$H_2$] and a 2H quartet at $\delta_H$

2.31 ppm [*J* 7.4, C(6)$H_2$]. Noteworthy, thiophene is a less electronegative heterocycle and has higher resonance energy compared to furan thus shifting the adjacent methylene hydrogens at C(5)$H_2$ further downfield.

The novel regioisomer **36** was isolated as a colourless oil in 10% yield, which had the shortest retention time and showed characteristic signals in the $^1$H NMR spectrum (identical to those observed for isodendrolasin **30** in ***Figure 2.3***) for a terminal vinyl group (ABX system) at $\delta_H$ 5.78 ppm (1H, dd, $J_{BX}$ 17.5, $J_{AX}$ 10.8), $\delta_H$ 5.02 ppm (1H, dd, $J_{AX}$ 10.8, $J_{AB}$ 1.4) and $\delta_H$ 4.87 ppm (1H, dd, $J_{BX}$ 17.5, $J_{AB}$ 1.4) in addition to a methylene singlet adjacent to the furan ring at $\delta_H$ 2.63 ppm [C(5)$H_2$]. The Wurtz coupled product **39**, was isolated as a white crystalline solid having the longest retention time and was identified by the appearance of a distinctive 4H singlet at $\delta_H$ 2.96 ppm in the $^1$H NMR spectrum.

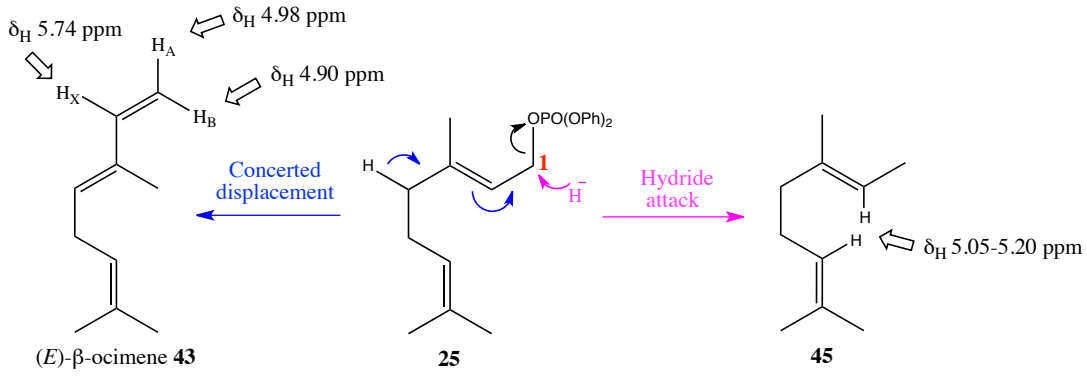
Interestingly, the Grignard reagent influenced the regioselectivity of the allylic alkylation reaction. 3-Thienylmethylmagnesium bromide **23a** favoured attack at the α-position more so than the corresponding furan Grignard reagent **14a**. However with that said, undesired formation of the regioisomer **36** was still occurring which was having a detrimental effect on the yield due to rather complex and arduous chromatography.

For ***Entry 3,*** despite numerous attempts, preparation of 2,5-dimethyl substituted furanolipid **34** was not achieved while adhering to the standard protocol illustrated in ***Table 2.5***. It became apparent following purification and subsequent spectroscopic analysis that the Grignard reagent of 2,5-dimethyl-3-furylmethyl bromide **21** was undergoing complete Wurtz cross coupling to the dimer **40**. This was confirmed with the appearance of a distinctive 4H singlet at $\delta_H$ 2.41 ppm in the $^1$H NMR spectrum. This effectively prevented Grignard cross coupling with the acetate ester substrate **25**. Interestingly, following flash chromatography, a complex range of acyclic monoterpenes were isolated following decomposition of unreacted geranyl diphenyl phosphate **25** *in situ* (***Scheme 2.14)***.[46,58,59] According to Haley *et al.*,[58] a variety of acyclic terpenoids (**42**,**43**,**44** and **45)** are formed following ionization of phosphate ester **25** to give an intermediate geranyl cation followed consecutively by elimination of the appropriate proton as shown in (***Scheme 2.14)***.




***Scheme 2.14***

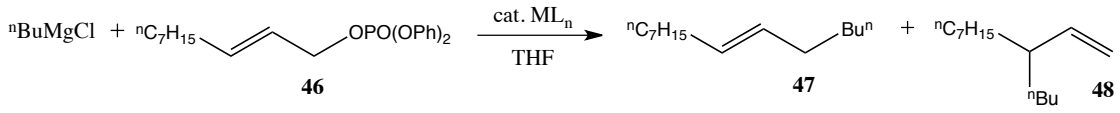
The least polar fraction isolated by chromatography consisted seemingly of 3 monoterpenes, which possessed spectroscopic characteristics similar to those reported for acyclic myrcene **42**, (*E*)-β-ocimene **43** and (*Z*)-β-ocimene **44**.[59] According to spectroscopic analysis, (*E*)-β-ocimene **43** was the major decomposition product formed following concerted displacement of the proton at C(4)$H_2$ (***Scheme 2.15***). The $^1$H NMR spectrum of **43** showed characteristic absorptions patterns of a terminal vinyl group with the appearance of a 1H doublet of doublets at $\delta_H$ 5.74 ppm ($J_{BX}$ 17.5, $J_{AX}$ 10.8), 4.98 ppm ($J_{AX}$ 10.8, $J_{AB}$ 1.5) and 4.90 ppm ($J_{BX}$ 17.5, $J_{AB}$ 1.5) (***Scheme 2.15***). The more polar fraction contained the acyclic diene **45**, which was possibly formed by nucleophilic attack by a hydride ion at the derived allylic carbonium ion (***Scheme 2.15***).[58] Spectroscopic characteristics were consistent with literature findings.[58]




***Scheme 2.15***

According to a more recent report by Yanagisawa *et al.* who was studying the effect of transition metal-catalysts on substitution reactions between allylic phosphates and Grignard reagents, it is possible to achieve $S_N2$-selective Grignard coupling with primary allylic diphenyl phosphates using either a nickel ($NiBr_2$) or iron [$Fe(acac)_3$] based catalyst (***Table 2.6, Entry 1*** *and* ***2***).[55] In sharp contrast, a catalytic amount of CuCN•2LiCl was found to promote a $S_N2$'-selective coupling reaction ***(Table 2.6, Entry 3)***.

***Table 2.6:*** *Cross coupling reaction of (E)-2-decenyl-1-diphenylphosphate* ***46*** *with* $^{n}$*BuMgCl in the presence of various transition metal catalysts as reported by Yanagisawa et al.*[55]




46 47 48

| Entry | $ML_n$ [a] | Conditions | %Yield [b] | $S_N2$ (47): $S_N2$'(48) |
|---|---|---|---|---|
| **1** | $Fe(acac)_3$ [c] | -76 °C, 1 h | 94 | 99:1 |
| **2** | $NiBr_2$ | -73 °C, 2 h | 93 | 99:1 |
| **3** | CuCN•2LiCl | -76 °C, 1 h | 98 | 1:99 |

**a: Metal catalyst (0.05-0.1 eq)**
**b: Isolated yield**
**c: acac = acetylacetonate.**

This report illustrated that it is possible to achieve greater regiocontrol over the allylic alkylation reaction simply by varying the transition metal catalyst. Despite the fact that catalytic loading is one of many important factors controlling the regioselectivity of this C-C bond formation reaction, we were interested to identify if employing either iron(III) acetylacetonate [$Fe(acac)_3$] or nickel(II) bromide ($NiBr_2$) as an alternative to copper(I) iodide in the geranylation of 3-furylmethylmagnesium bromide **14a** can promote the chemoselective synthesis of dendrolasin **10** ($\alpha$-product) over its corresponding regioisomeric byproduct **30** ($\gamma$-product).

In the case of ***Table 2.5, Entry 4***, following a procedure described in the literature for a similar compound by Yanagisawa *et al.*,[55] the Grignard reagent of 2-methyl-3-furylmethyl bromide **20** (2 equivalents) was reacted with geranyl diphenylphosphate **25** (1 equivalent) using nickel(II) bromide (5 mol%) as a catalyst at -78 $^{o}$C. $^{1}$H NMR analysis of the crude product revealed a three component mixture consisting of the desired cross coupled product **35**, its corresponding regioisomer **38** and the Wurtz coupled product **41** in a 38:12:50 ratio of products respectively. All three components were independently isolated following column chromatography on silica gel (100% hexane). The novel 2-methyl-furanolipid **35** was obtained as a colourless oil in 43% yield. Successful coupling was confirmed following the appearance of the 2H triplet at $\delta_H$ 2.35 ppm [$J$ 7.4, C(5)$H_2$] in the $^{1}$H NMR spectrum. An upfield shift was also observed for the methyl protons on the α-position of the furan ring from a 3H singlet at $\delta_H$ 2.28 ppm to $\delta_H$ 2.20 ppm (ArC$H_3$).

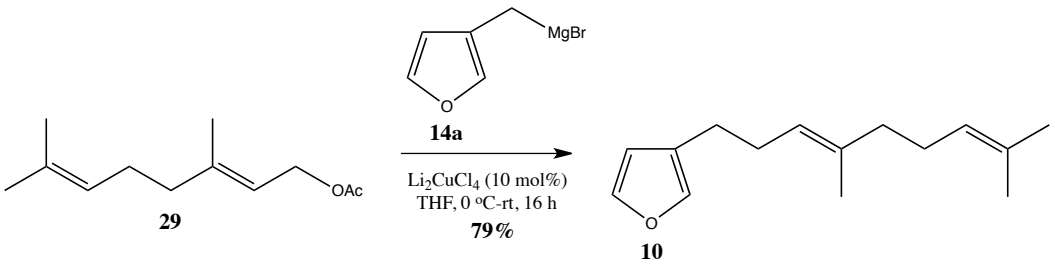
The novel regioisomer **38** was isolated as a colourless oil in 13% yield, which had the shortest retention time and showed characteristic signals in the $^{1}$H NMR spectrum of a terminal vinyl group (ABX system) at $\delta_H$ 5.76 ppm [1H, dd, $J_{BX}$ 17.5, $J_{AX}$ 10.8], $\delta_H$ 5.00 ppm [1H, dd, $J_{AX}$ 10.8, $J_{AB}$ 1.4] and $\delta_H$ 4.88 ppm (1H, dd, $J_{BX}$ 17.5, $J_{AB}$ 1.4) in addition to a methylene singlet adjacent to the furan ring at $\delta_H$ 2.32 ppm. The novel Wurtz coupled product **41**, was isolated as a colourless oil having the longest retention time and was identified by the appearance of a distinctive 4H singlet at $\delta_H$ 2.50 ppm in the $^{1}$H NMR spectrum.

Primarily due to the uncontrolled formation of the γ-isomer, a different electrophilic coupling partner was introduced instead of geranyl diphenyl phosphate **25** in the Grignard $sp^3$-$sp^3$ cross coupling reaction**.** Geranyl acetate **29** seemed like the ideal candidate, which showed promising potential at regioselectively affording the α-product through a Schlosser cross coupling reaction.[28,50]

### 2.3.2.4 Allylic alkylation of geranyl acetate (Schlosser cross coupling)

A convenient method was described by Schlosser *et al.* for the exclusive synthesis of the α-substituted product following $sp^3$-$sp^3$ cross coupling of a Grignard reagent with an allylic acetate in the presence of Kochi's catalyst ($Li_2CuCl_4$).[50] This simple and effective method for the formation of C-C bonds was further studied by Backvall *et al.* where recommendations were made on how to selectively control the regiochemistry of $Li_2CuCl_4$-catalysed Grignard reactions with allylic acetates to favour α-substitution.[49]

Following a modified procedure described in the literature for a similar compound by Kolympadi *et al.*,[28] the Schlosser cross coupling of geranyl acetate **29** with 3-furylmethylmagnesium bromide **14a** was performed in the presence of Kochi's catalyst ($Li_2CuCl_4$, 10 mol%) in anhydrous tetrahydrofuran at 0 $^oC$ as illustrated in ***Scheme 2.16***.[49,50,60]




***Scheme 2.16***

Following workup, $^1H$ NMR analysis of the crude residue revealed a two component mixture consisting of dendrolasin **10** and the Wurtz homocoupled product **32** in a 85:15 ratio of products respectively. Fortunately, following purification by column chromatography on silica gel, dendrolasin **10** was successfully isolated as a colourless oil in 79% yield with no trace of the γ-substituted by-product **30** (***Scheme 2.16***). Spectroscopic analysis was consistent with those reported in the literature.[9,42,61]

Formation of the Wurtz coupling product **32** was still a residing issue despite employing various techniques to control and supress dimerization. Unfortunately, allyl Grignard reagents form very stable Grignard radicals and are notoriously susceptible to Wurtz coupling.[62] Improvements were made to limit the formation of the Wurtz homocoupled product **32** which involved slow addition of the bromide **14** (~2 hours) to a large excess (>10

equivalents) of freshly ground magnesium which has been activated by use of the entrainment method (1,2-dibromoethane as a co-reactant).[62-64] This methodology imparted better control over Grignard synthesis to ensure at least one full equivalent was successfully reacted with the allylic ester (limiting reagent). The catalyst, dilithium tetrachlorocuprate ($Li_2CuCl_4$) first developed by Kochi *et al.* and commonly employed in coupling reactions between Grignard reagents and alkyl halides,[60] was convenient to use since it is soluble in most organic solvents and is rapidly reduced to copper(I) salts by the Grignard reagent.[49]

To summarise, the Schlosser $sp^3$-$sp^3$ cross coupling reaction had numerous practical advantages, but most notably it permitted the regio-controlled copper-catalysed α-substitution of an allylic acetate with a Grignard reagent at mild temperatures in high yield. This innovative methodology imparted an exciting and convenient gateway for the construction of an extensive library of 3-substituted furan/thiophene analogues, which will be discussed in detail in a later section.

### 2.3.3 Synthesis of subunit C

#### 2.3.3.1 Synthesis of β-tetronic acid(s)

The α,β-unsaturated γ-lactone moiety occurs in numerous natural products isolated from both aquatic and terrestrial life.[65,66] More commonly referred to as butenolides, they occupy literally a central position between butyrolactones and furan structures both in terms of synthetic chemistry and biosynthesis. Encompassing both fatty acid and terpenoidal biosynthetic origins, these compounds display a broad and diverse range of biological and pharmacological activities including strong antibiotic, antihelmatic, antifungal, antitumour, antiviral and anti-inflammatory properties.[67,68] The simplest examples include the fatty acid derived buttercup metabolite protoanemonin **49** and the butter flavour metabolite bovolide **50** to more complex terpenoid derived natural products like freelingyne **51**,[69] variabilin **52**,[70] the $PLA_2$ inhibitor manoalide **53**,[71] and the cardiac glycoside digitoxin **54** (***Figure 2.5***).[72] Therefore, γ-lactones represent remarkable lead structures for the development of new drugs.[67,68]

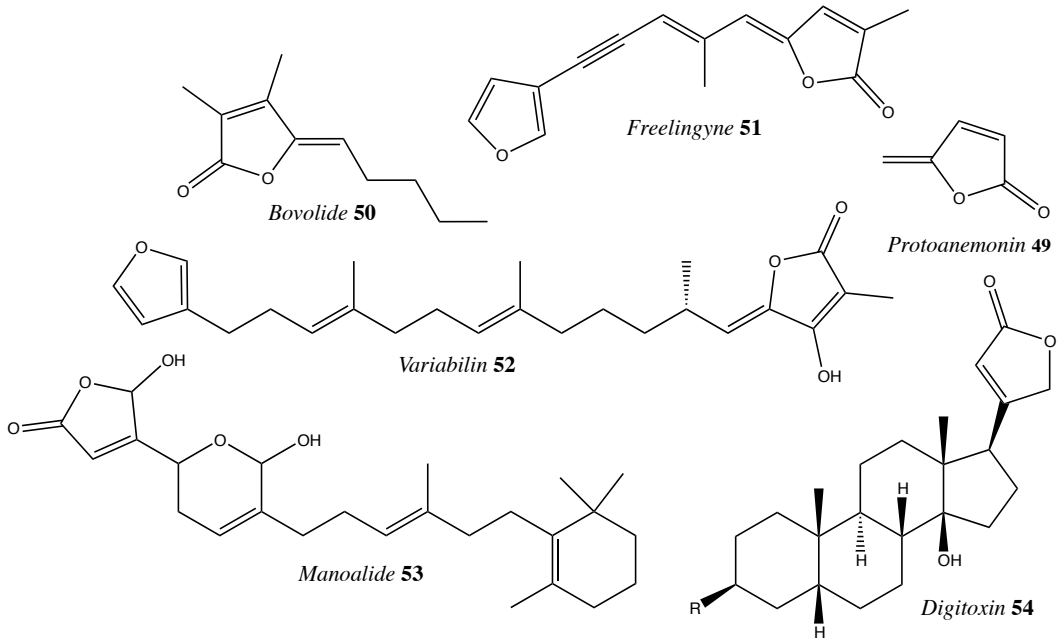
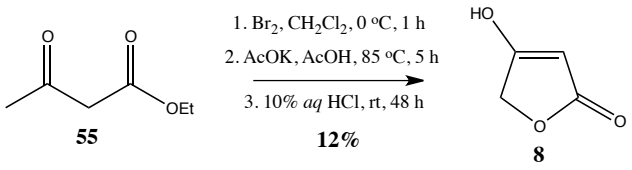



***Figure 2.5:*** Natural products containing a γ-lactone moiety.

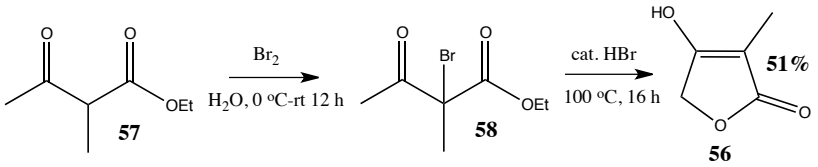
As illustrated in 2nd generation retrosynthesis, it was envisioned that **subunit C** would be synthesised from commercially available β-tetronic acid **8** (***Scheme 2.2***). Since tetronic acid **8** is quite an expensive starting material to begin with, we decided to investigate if it could be synthesised from a cheaper more readily available starting material. Numerous synthetic routes to **8** have been devised in the literature,[73-76] however most of which have shortcomings primarily due to low yields or poor reproducibility. A neat method was found in the literature,[77] which addressed the large-scale preparation of β-tetronic acid **8** from a β-ketoester **55** derivative bearing a γ-halogen atom in modest yield (***Scheme 2.17***).[76-78]




***Scheme 2.17:*** *'One pot' fashioned preparation of β-tetronic acid.*[77]

The procedure for the one-pot preparation of **8** by Momose *et al.* was followed verbatim, which involved the bromination of ethyl acetoacetate **55** using bromine solution ($Br_2$),[77] subsequent transformation into the corresponding acetoxy ester using potassium acetate (AcOK) followed by an acid induced lactonisation reaction employing 10% aqueous hydrochloric acid. In our hands, the one-pot synthesis of **8** was extremely problematic leading to a poor overall yield of 12 %. The first major difficulty encountered was the complete removal of deposited potassium bromide following the acetoxylation reaction. This together with a rather laborious workup, involving selective extraction of a highly hydrophilic lactone **8** from an aqueous mother liquor effectively led to a diminished yield. However with that said, Momose *et al.* only achieved an overall yield of 38-40% from this one-pot synthesis.[77] In retrospect, it is a much more viable option to acquire this substrate **8** from a commercially available source as opposed to enduring a complicated, multi-step, poor yielding and labour intensive one-pot preparation reaction. $^1$H NMR analysis confirmed the formation of tetronic acid **8** with the appearance of 2H doublet at $\delta_H$ 4.67 ppm [*J* 1.1, C(5)$H_2$] associated with the γ-methylene protons and a 1H triplet at $\delta_H$ 4.96 ppm [*J* 1.1, C(3)*H*] assigned to the α-vinylic proton in the lactone ring.

In order to derivatise the terminal end of furospongolide **1** and make further expansions to the synthetic library of compounds for biological testing, a structural analogue of **subunit C** was prepared. Methyl tetronic acid **56** was successfully synthesised in a two-step synthetic pathway from commercially available ethyl 2-methylacetoacetate **57** following a procedure described for this compound by Tambar *et al.*[79] The synthetic methodology was almost identical to the preparation of tetronic acid **8** as it involved the synthesis of a key intermediate, 2-bromo-2-methyl-3-oxobutanoate **58**, which was obtained following treatment of ethyl 2-methylacetoacetate **57** with 1.05 equivalents of bromine (***Scheme 2.18***).[80-82]




***Scheme 2.18***

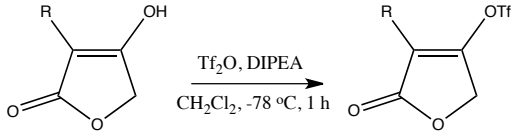
The bromoketone **58** was obtained as a yellow oil, which according to $^1$H NMR analysis was sufficiently pure for use in the next transformation. Spectroscopic characteristics were consistent with those described in the literature with the disappearance of the 1H quartet at $\delta_H$ 4.02 ppm [*J* 7.1, C(2)*H*] associated with the acidic α-proton within the dicarbonyl and a corresponding downfield shift of the 3H doublet at $\delta_H$ 1.35 ppm (*J* 7.2) to a 3H singlet at $\delta_H$ 2.45 ppm associated with the methyl protons adjacent to the bromide [C(2)C$H_3$].[79]

Subsequent acid induced lactonisation of the bromoketone intermediate **58** with hydrobromic acid (48% w/v in water) furnished methyl tetronic acid **56** as a white solid in a moderate yield of 51% over two steps (***Scheme 2.18***). This yield was slightly lower than that obtained by Tambar *et al.* in his original studies (79%).[79] To ensure complete conversion to the γ-lactone **56**, the bromoketone **58** was subjected to two additional sixteen-hour refluxes at 100 $^o$C. Spectroscopic characteristics were consistent with those described in the literature with the appearance of a 2H singlet at $\delta_H$ 4.57 ppm associated with the γ-methylene protons within the lactonic ring [C(5)$H_2$].[79]

### 2.3.3.2 Synthesis of triflate tetronic acid(s)

As illustrated in 2nd generation retrosynthesis (***Scheme 2.2***), it was envisaged that attachment of the α,β-unsaturated γ-lactone moiety to the furanolipid backbone would be accomplished through a conjugate addition/elimination reaction between the alkyl Grignard reagent of **subunit B** and the vinyl triflate of **subunit C**. According to the literature, triflate tetronic acid **57** has been employed as an efficient substrate in a range of Grignard and palladium catalysed C-C bond formation reactions.[25,82-86] Following established precedent,[85] tetronic acids **8** and **56** were readily converted to their corresponding triflates **57** and **58** in 67% and 79% yields respectively following treatment with triflic anhydride in dry dichloromethane at -78 $^{o}$C as illustrated in ***Table 2.7, Entry 1*** and ***2***.

***Table 2.7:*** *Preparation of triflate tetronic acids.*




(**8, 56**) (**57, 58**)

| Entry | R | Product | Yield (%) [a] |
|---|---|---|---|
| **1** | H | **57** | 67% |
| **2** | $CH_3$ | **58** | 79% |

**a. Yields following column chromatography.**

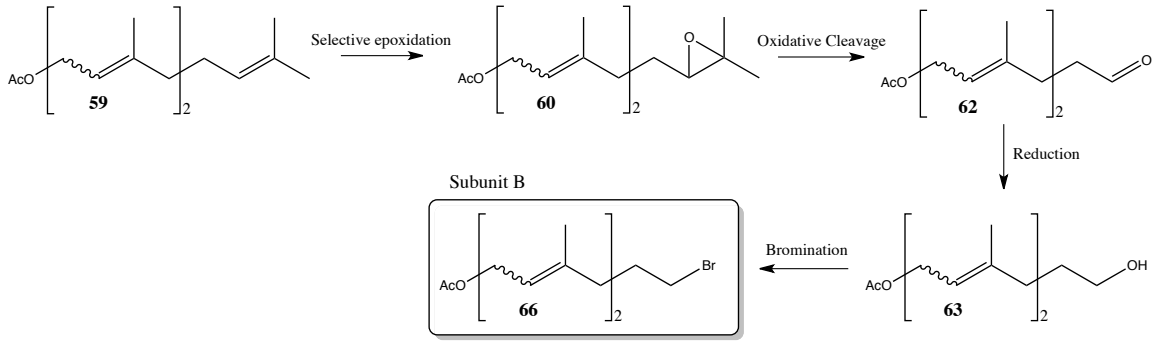
Spectroscopic characteristics were consistent with literature findings for **57** and **58** with the downfield shift of the γ-methylene protons within the lactonic ring from a 2H singlet in the region $\delta_H$ 4.57-4.67 ppm to a 2H doublet at $\delta_H$ 4.90 ppm (*J* 1.8) and to a 2H quartet at $\delta_H$ 4.92 ppm (*J* 1.8) respectively.[85] Interestingly, the coupling of fluorine to carbon was observed in the $^{13}$C NMR spectrum of **58** with the appearance of a quartet at $\delta_C$ 118.4 ppm ($J_{FC}$ 321 Hz, $CF_3$) as a result of substitution of the quaternary carbon with three fluorine atoms. This effect was also observed for **57** with a quartet at $\delta_C$ 118.8 ppm ($J_{FC}$ 322 Hz, $CF_3$).[84] Noteworthy, following triflation of the tetronic acids **57** and **58**, absorption bands were identified in the IR spectrum characteristics of an α,β-unsaturated γ-lactone at $\nu_{max}$ 1770 cm$^{-1}$ and $\nu_{max}$ 1763-1760 cm$^{-1}$ indicating successfully trapping of the enolate. The triflates **57**

and **58**, which are surprisingly stable over long periods of time were subsequently used when required in the conjugate addition/elimination reaction with a suitable Grignard reagent.

## 2.3.4 Synthesis of acetate protected subunit B

### 2.3.4.1 Acetylation of naturally occurring farnesol

To be brief, 2nd generation retrosynthesis was designed around **subunit B** (central linchpin). Following the problems encountered in 1st generation synthesis, a major initiative was to introduce a complete difunctional interlinking subunit, which already incorporated the sequiterpenoid framework with three isoprene units in the (*E,E*)-configuration. A convenient and well-established precedent was found in the literature for the 4-step transformation of commercially available farnesyl acetate **59** to the difunctional terpene **66** denoted as **subunit B**.[87,88] This synthetic pathway involved an elaborate oxidation procedure for the selective epoxidation of the terminal alkene bond of farnesyl acetate **59** as illustrated in ***Scheme 2.19***.

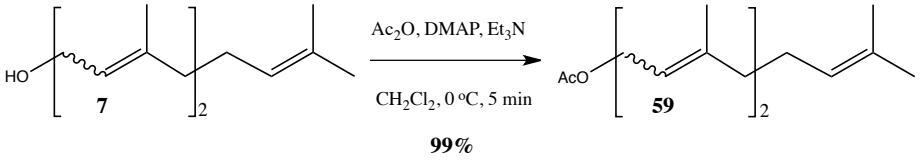



***Scheme 2.19:*** *Synthetic route for accessing* ***subunit B 66*** *from commercially available farnesyl acetate* ***59*** *in 4 linear steps.*

Synthetic endeavours began with the preparation of farnesyl acetate **59**. Despite being a commercially available starting material from Sigma Aldrich, it was more economically viable to prepare the acetate ester **59** from commercially available farnesol **7**. Farnesol **7** was purchased from Sigma Aldrich in the form of a mixture of stereoisomers containing 52% of the (*E,E)*-isomer, 42% of the (*Z,E*)-isomer and 6% other(s) as determined by high

performance liquid chromatography (***Appendix V***). This starting material was employed in preliminary studies towards the preparation of furospongolide **1** in order to test and optimise the synthetic route before purchasing the exceedingly more expensive *E,E* farnesol **7**.

By employing standard acetylation conditions as described for this compound by Snyder *et al.,*[89,90] farnesyl acetate **59** was successfully synthesised following treatment of farnesol **7** with 1.2 equivalents of acetic anhydride ($Ac_2O$), 1.5 equivalents of triethylamine ($Et_3N$) and a catalytic trace (1 mol%) of 4-dimethylaminopyridine (DMAP) at 0 $^oC$ over a 5 min reaction (***Scheme 2.20***).



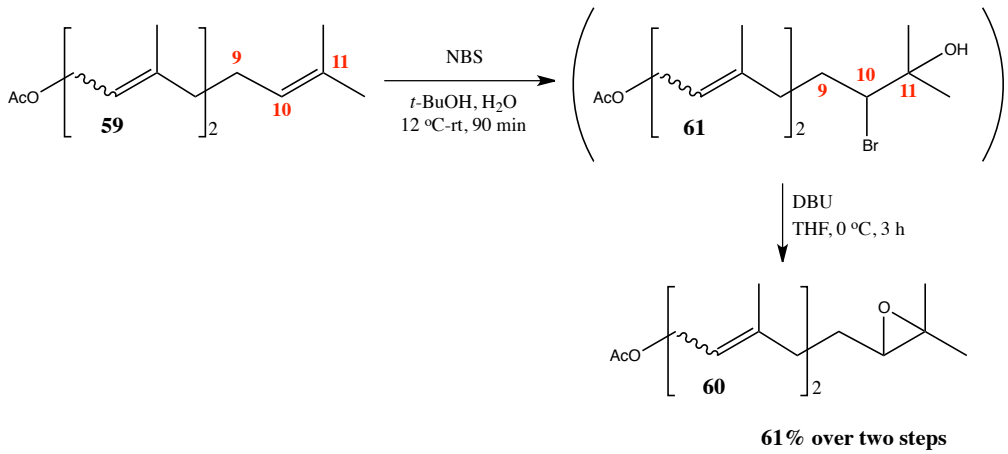

***Scheme 2.20***

Recovered as a colourless non-viscous oil in 99% yield post work-up, $^1H$ NMR analysis of the crude product indicated acceptable purity avoiding the need for further purification by column chromatography. $^1H$ NMR analysis confirmed the synthesis of farnesyl acetate **59** with a characteristic shift downfield of allylic methylene protons [C(1)$H_2$] from a 2H doublet at $\delta_H$ 4.15 ppm (*J* 6.9) to $\delta_H$ 4.59 ppm (*J* 7.2). IR analysis was also consistent with literature findings with the disappearance of the hydroxyl OH stretch at $\nu_{max}$ 3349 $cm^{-1}$ and the appearance of a carbonyl absorption stretch at $\nu_{max}$ 1739 $cm^{-1}$.[91] Following the successful synthesis of farnesyl acetate **59**, synthetic efforts towards the synthesis of acetate-protected **subunit B 66** commenced.

### 2.3.4.2 Selective epoxidation of farnesyl acetate

(+/-)-10,11-Epoxyfarnesyl acetate **60** was first prepared by Van Tamelen *et al.*,[87] using essentially the same procedure as illustrated in ***Scheme 2.21***, which was based on his earliest finding that *N*-bromosuccinimide in a polar solvent is a powerful and selective oxidant for functionalising the terminal alkene bond of squalene.[92] Van Tamelen *et al.* has since applied this methodology to produce terminally epoxidised mono-, sequi-, di-, and triterpene systems for biosynthetic studies and bio-organic synthesis.[93,94]

Adhering to a more contemporary procedure,[88] the desired bromohydrin intermediate **61** was successfully synthesised as a stable faint yellow oil following treatment of farnesyl acetate **59** with 1.1 equivalents of *N*-bromosuccinimide (NBS) in aqueous *tert*-butyl alcohol (*t*BuOH) over a 90 min period at room temperature (***Scheme 2.21***).




***Scheme 2.21***

The crude product was sufficiently pure by spectroscopic analysis and used immediately in the next transformation. Evidence for the formation of the desired product **61** was observed in the $^{1}$H NMR spectrum with the appearance of the distinctive 1H doublet of doublets at $\delta_H$ 3.96 ppm (*J* 11.4, 1.9), characteristic of the singular proton adjacent to the bromide [C(10)*H*Br]. The alkene region at $\delta_H$ 5.14-5.40 ppm was now only integrating for two hydrogens and the $^{13}$C NMR spectrum showed a low frequency chemical shift for both C(10) and C(11) from $\delta_C$ 123.6 ppm and $\delta_C$ 131.3 ppm to $\delta_C$ 70.7 ppm and $\delta_C$ 72.5 ppm respectively.

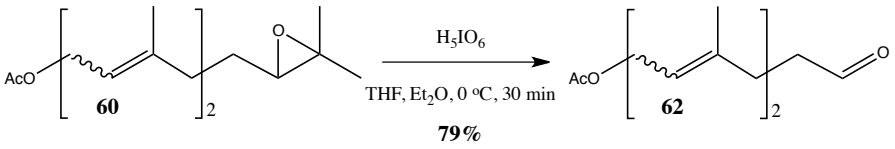
This reaction illustrated how selective oxidation can be achieved on a trisubstituted double bond system like farnesyl acetate **59**, with exclusive formation of the monobromohydrin **61** resulting from regioselective attack at the terminal double bond.[95]

The bromohydrin intermediate **61** can be easily cyclized to its corresponding epoxide **60** upon exposure to a weak base. The attack of the *in situ* generated alkoxide on the adjacent halide proceeds with a single inversion.[96,97] According to the literature,[87-90,98] the most common reagent employed to carry out this type of reaction is potassium carbonate ($K_2CO_3$). A major drawback reported in the literature for using potassium carbonate is undesired removal of the acetate ester functionality,[88,89,98] which would potentially require an additional acetylation step to obtain the desired product **60**. Recently however, employing a base like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium hydride (NaH) has been a more contemporary approach for avoiding such qualms.[91,99]

(+/-)-10,11-epoxyfarnesyl acetate **60** was successfully synthesised following treatment of the bromohydrin intermediate **61** with 1,8-diazabicyclo[5.4.0]undec-7-ene in tetrahydrofuran over a 3 hour reaction period at 0 $^{o}$C (***Scheme 2.21***).[99] Following purification by column chromatography on silica gel the epoxide **60** was isolated as a colourless oil in 61% yield, which was calculated from the theoretical over two steps. Spectroscopic analysis was consistent with literature data,[89,91] with the appearance of a distinctive 1H triplet at $\delta_H$ 2.70 ppm (*J* 6.2), characteristic of the proton adjacent to epoxide. Concurrently, a chemical shift was also apparent in the $^{13}$C NMR spectrum from $\delta_C$ 70.7 ppm to $\delta_C$ 64.2 ppm associated with C(10) in the ether linkage.

### 2.3.4.3 Oxidative cleavage of (+/-)-10,11-epoxyfarnesyl acetate

The epoxide **60** was converted to the corresponding aldehyde **62** through an oxidative cleavage reaction following treatment with 1.2 equivalents of periodic acid ($H_5IO_6$) in tetrahydrofuran at 0 $^oC$ over a 30 minute period and following the procedure described for this compound by Labadie *et al.* (***Scheme 2.22***).[88]

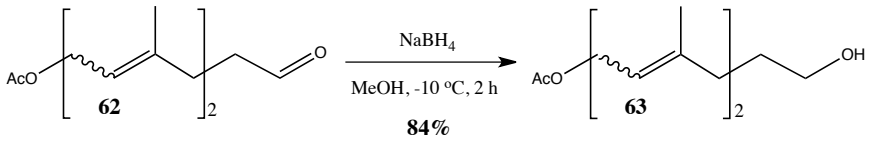



***Scheme 2.22***

Upon workup and subsequent purification by column chromatography on silica gel, the desired aldehyde **62** was isolated as a faint yellow oil in 79% yield. $^1H$ NMR analysis confirmed the synthesis of the aldehyde **62** with the appearance of a distinctive 1H triplet at $\delta_H$ 9.75 ppm (*J* 1.9) assigned to the newly formed aldehyde proton. Both $^{13}C$ NMR and IR analysis were also consistent,[88] with a peak at $\delta_C$ 202.6 ppm and a carbonyl absorption band at $\nu_{max}$ 1727 $cm^{-1}$ respectively. $^1H$ NMR integration revealed a 60:40 ratio of stereoisomers, from analyzing the peaks at $\delta_H$ 9.75 ppm (*E*,*E* isomer) and $\delta_H$ 9.79* (*Z*,*E* isomer) respectively. Noteworthy, this aldehyde **62** became an expedient building block in the synthesis of a novel range of terpene amine analogues by exploiting reductive amination chemistry, which will be discussed in a later section (***Section 2.9.5***). For the meantime, it was used accordingly in the forthcoming reduction reaction.

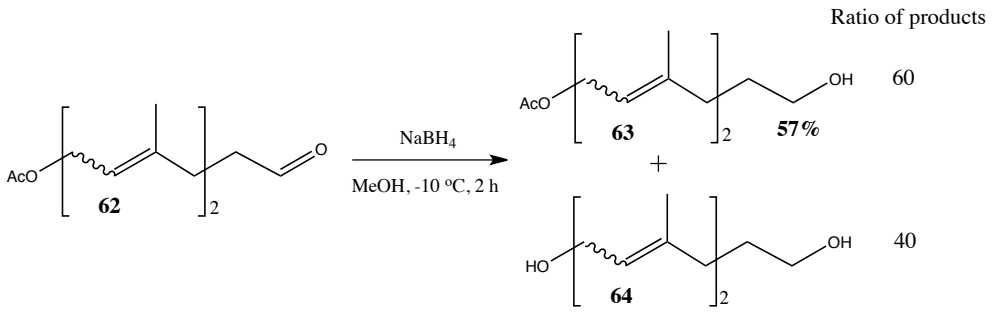
### 2.3.4.4 Reduction of 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate

The aldehyde **62** was successfully reduced to its corresponding primary alcohol **63** by employing 1.2 equivalents of sodium borohydride ($NaBH_4$) in freshly distilled methanol over a two hour reaction period at -10 $^oC$ and adhering to the procedure described for this compound by Labadie *et al.* (***Scheme 2.23***).[88]



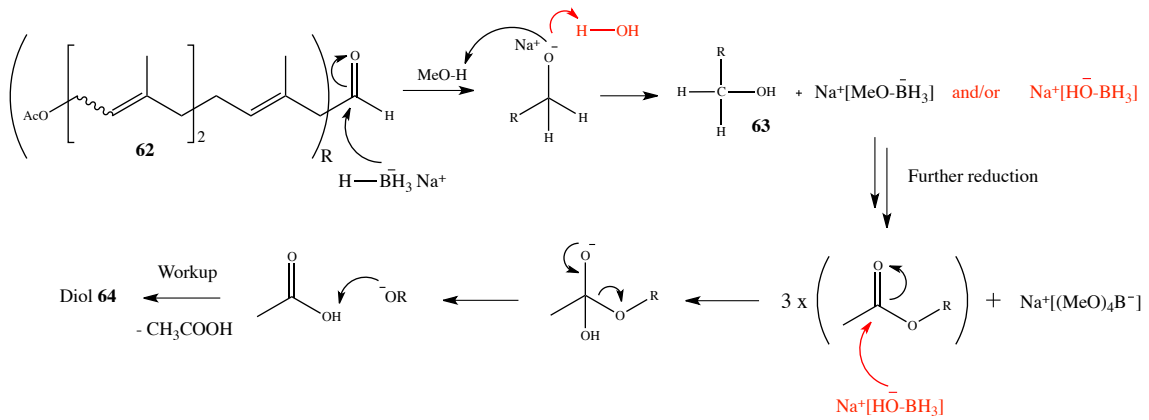

***Scheme 2.23***

Recovered as a colourless oil in 84% yield after work-up, $^1H$ NMR analysis of the crude product indicated acceptable purity for use in further transformations thus avoiding the need for purification by column chromatography. $^1H$ NMR analysis confirmed the synthesis of the alcohol **63** with the disappearance of the 1H triplet at $\delta_H$ 9.75 ppm (*J* 1.9) and the appearance of a 2H multiplet at $\delta_H$ 3.58-3.67 ppm assigned to the methylene protons alpha to the hydroxyl group (C*H*$_2$OH). $^{13}C$ NMR spectroscopy also revealed a low frequency chemical shift from $\delta_C$ 202.6 ppm to $\delta_C$ 62.6 ppm associated with carbon atom at C(10), while IR analysis displayed a characteristic hydroxyl absorption stretch at $\nu_{max}$ 3410 $cm^{-1}$. Disappointingly, on replicating the reaction and following to the conditions illustrated in ***Scheme 2.23***, undesired removal of the acetate ester-protecting group occurred (***Scheme 2.24***). This problem arose primarily because reagent grade methanol was used instead of freshly distilled methanol in the reduction reaction. From practical experience, ensuring the absolute purity of the aldehyde **62** and the use of distilled methanol are crucial factors to avoid undesired removal of the protecting group and the ultimate success of the reduction reaction to **63**. $^1H$ NMR analysis of the crude product indicated a 60:40 ratio of alcohol **63** and diol **64** respectively (***Scheme 2.24***). However it must be noted that these ratios shift dramatically depending on the scale of the reaction i.e. quantity of sodium borohydride and methanol used.




***Scheme 2.24***

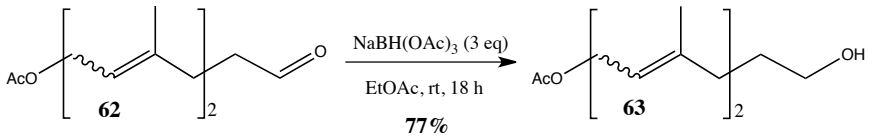
Purification by column chromatography isolated the acetate alcohol **63** as a colourless oil in 57% yield with spectroscopic characteristics consistent with those previously reported. In order to try and understand how undesired removal of the acetate ester was occurring during the reduction of the aldehyde **62** a comprehensive look at the reaction mechanism was undertaken (***Scheme 2.25***). It is postulated that a borohydride-water intermediate complex labelled as $Na^{+}[HO\text{-}BH_3]$ is forming following reduction of the aldehyde **62** to its corresponding alcohol **63** *in-situ*. This intermediate complex is then undergoing nucleophilic attack at the acetate ester protecting group leading to formation of the diol **64** (***Scheme 2.25)***. Surprisingly, this problem wasn't encountered by Labadie *et al.* in his original studies.[88] However there is some evidence in the literature for the reduction of esters using sodium borohydride in methanol.[100-102]




***Scheme 2.25*** *An illustrative mechanism for the reduction of aldehyde* ***62*** *to its corresponding alcohol* ***63*** *using sodium borohydride in methanol. It also provides a theory on how diol* ***64*** *is being formed.*

Disappointingly, selective re-protection of diol **64** following its isolation by column chromatography was not feasible using standard acetylation conditions. The diol **64** was however salvaged and returned back into the synthetic route through a secondary pathway, which will be discussed later in ***Section 2.3.8.1***.

An alternative method for the reduction of aldehydes was found in the literature and involved the use of a milder reducing agent.[103] Following a procedure described for a related compound by Lu *et al.,*[103] aldehyde **62** was successfully reduced using 3 equivalents of sodium triacetoxyborohydride [$NaBH(OAc)_3$] in distilled ethyl acetate as shown in ***Scheme 2.26***.

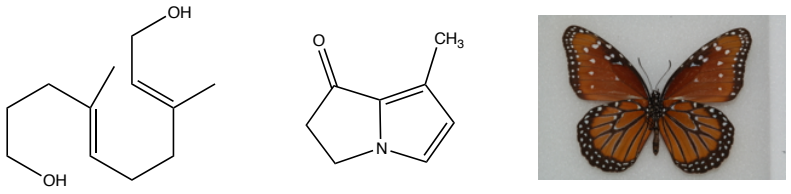



***Scheme 2.26***

In comparison to sodium borohydride, despite requiring a 18 hour reaction at room temperature, exclusive synthesis of the alcohol **63** was achieved in a slightly lower yield of

77% with no apparent formation of the diol **64** following $^{1}$H NMR analysis of the crude product. This procedure offered a valid standby method for the synthesis of alcohol **63**.

Interestingly on reviewing the literature, the diol **64** in question is a sesquiterpene natural product, first isolated in 1969 by Pliske *et al.* from the "hairpencils" of some species of male *Danaid* butterflies.[104] The diol **64** was one of two substances isolated and identified from the male of the queen butterfly *Danaus gilippus berenice* (***Figure 2.6***). The other substance identified from the secretion was a pyrrolizidine ketone known as danaidone **65**, which acts as the chemical messenger that induces the females to mate.[105] The function of the diol **64** is currently uncertain and its thought to serve as a glue that sticks the male aphrodisiac secretion which is transferred by way of tiny "duct" particles from its "hairpencils" to the female during courtship.[104] However implications have been made that the diol **64** (due to structural similarities with farnesol) may function to mimic the juvenile hormone in the adult butterfly and thus stimulate yolk deposition during oogenesis.[104,106]



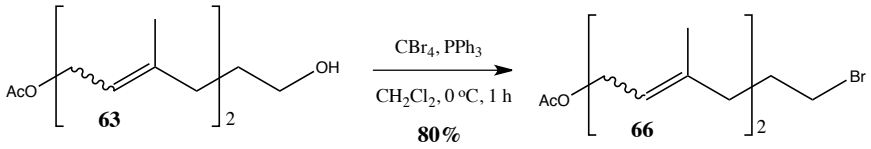

*Diol* **64** *Danaidone* **65** *Danaus gilippus berenice*

***Figure 2.6:*** *The diol* ***64*** *and the ketone* ***65*** *(danaidone) found in the pheromonal secretion from the male of the queen butterfly (Danaus gilippus berenice).*[104]

Since its isolation, numerous synthetic preparations of the diol **64** have been reported in the literature.[107-110] $^{1}$H NMR spectroscopy was consistent with these literature findings with the shift downfield of a distinctive 2H doublet at $\delta_H$ 4.59 ppm ($J$ 7.4) to a 2H doublet at $\delta_H$ 4.15 ppm ($J$ 7.0) associated with the allylic methylene protons.[107,108] $^{13}$C NMR and IR analysis was also consistent with the disappearance of a distinctive ester peak at $\delta_C$ 171.2 ppm and a carbonyl stretch at $\nu_{max}$ 1739 cm$^{-1}$ respectively.

### 2.3.4.5 Bromination of 10-hydroxy-3,7-dimethyldeca-2,6-dien-1-yl acetate

The last step in the preparation of acetate-protected **subunit B 66** was a bromination reaction. The bromide **66** was conveniently prepared in 80% yield from the alcohol **63** using 1.5 equivalents of carbon tetrabromide ($CBr_4$) and 1.2 equivalents of triphenylphosphine ($PPh_3$) in dry dichloromethane over a 1 hour period at 0 $^oC$ (as illustrated in ***Scheme 2.27***).




***Scheme 2.27***

Following recommendations made by Zoretic and Kocienski *et al.*, [111,112] mild bromination with $CBr_4$-$PPh_3$ was preferred categorically over $PBr_3$ giving much cleaner and higher yielding related products.[111,112] As previously noted in ***Section 2.3.1.2***, the crude product was contaminated with the presence of triphenylphosphine oxide and bromoform, which are two by-products of the Appel bromination reaction. On this occasion however, both impurities were easily removed by column chromatography without enduring undesired co-elution. The bromide **66** was isolated as a colourless oil, which was stable over long periods of time when stored in a freezer under inert atmosphere.

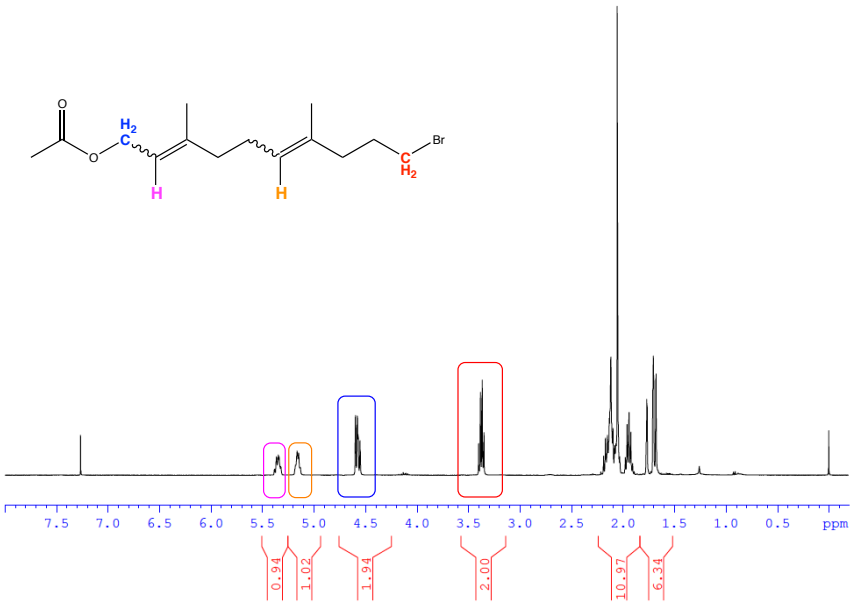


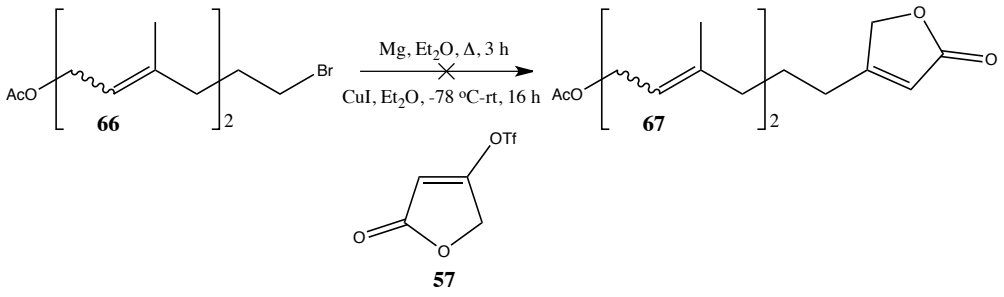

***Figure 2.7:*** *$^{1}$H NMR spectrum of bromide* ***66*** *($CDCl_3$, 300 MHz).*

$^{1}$H NMR analysis confirmed the formation of the novel bromide **66** with an upshift of the 2H multiplet at $\delta_H$ 3.58-3.67 ppm to a 2H triplet at $\delta_H$ 3.37 ppm (*J* 7.1) associated with the methylene protons adjacent to the bromide [C(10)*H*$_2$Br] (***Figure 2.7***). Likewise, $^{13}$C NMR showed a low frequency shift from $\delta_C$ 62.6 ppm to $\delta_C$ 33.4 ppm at *C*(10)Br due to the change in the electronegativity around the α-substituent. The bromide **66** was surprisingly stable and could be stored over long periods of time without any sign of deterioration.

To summarise, synthesis of acetate protected **subunit B 66** was accomplished in 4 linear steps in 33% overall yield from commercially available farnesyl acetate **59**. The bromide **66** was subsequently utilized as a Grignard precursor in the ensuing conjugate addition/elimination reaction.

### 2.3.5 Initial attempts at coupling acetate protected subunit B and subunit C

As previously illustrated in 2nd generation retrosynthesis (***Scheme 2.2***), attachment of the butenolide to the furanolipid backbone would involve a conjugate addition/elimination reaction between the Grignard derived cuprate of acetate protected **subunit B** and the vinyl triflate of **subunit C** (***Scheme 2.28).*** Coupling of these subunits would mark an important milestone in the synthesis of our target molecule **1**.




***Scheme 2.28***

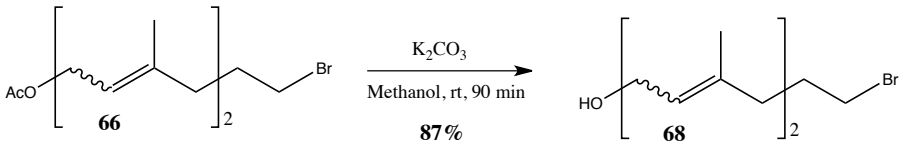
Following a procedure described by Molander *et al.* for a similar type of cross coupling reaction, the bromide **66** was converted to its corresponding Grignard derived cuprate following treatment with magnesium and copper iodide (1.15 equivalents) respectively before the addition of the vinyl triflate **57** dropwise at -78 $^{o}$C.[83] Unfortunately, spectroscopic analysis of the crude product indicated that the desired cross coupled product was not formed. It became apparent following further investigation that the Grignard reagent of **66** underwent nucleophilic attack at the acetate ester functionality leading to a complex range of unidentifiable products. This was confirmed by $^{1}$H NMR analysis with the disappearance of the 2H doublet at $\delta_H$ 4.59 ppm associated with the allylic methylene protons adjacent to the acetate ester.

As previously discussed in the synthesis of dendrolasin **1** (***Section 2.3.2.4***), acetate esters are a common leaving group frequently used in Grignard cross coupling reactions for the formation of new carbon-carbon bonds. In order to facilitate the Grignard cross coupling reaction, it was imperative a more durable protecting group was introduced in place of the acetate ester. Silyl ethers are well-established protecting groups in organic synthesis and are a

common choice to mask hydroxyl groups in Grignard precursors.[113] The *tert*-butyldimethylsilyl (TBDMS) group is a popular alternative to trimethylsilyl (TMS) group for protection of hydroxyl groups, especially since TBDMS is reported to be $10^4$ times more stable against hydrolysis than TMS.[114,115]

### 2.3.6 Synthesis of TBS protected subunit B

Acetate esters are extremely convenient protecting groups in organic chemistry due to the simple way they can be introduced and subsequently removed without ensuing complications. The allylic alcohol **68** was successfully prepared from it's corresponding acetate ester **66** following treatment with 3 equivalents potassium carbonate ($K_2CO_3$) in methanol at room temperature (***Scheme 2.29***).

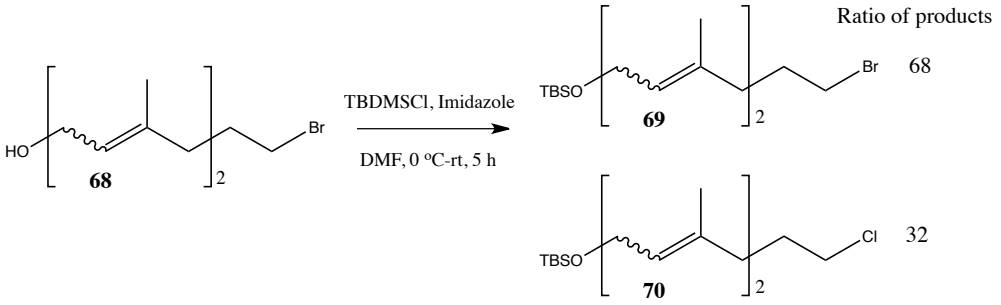



***Scheme 2.29***

The reaction was monitored by thin layer chromatography and after 90 minutes of stirring at room temperature, the reaction was complete. The novel allylic alcohol **68** was cleanly obtained as a light yellow oil in 87 % yield following workup. $^1$H NMR analysis confirmed the formation of **68** with a shift of the 2H doublet at $\delta_H$ 4.59 ppm (*J* 7.4) to $\delta_H$ 4.16 ppm (*J* 6.9) characteristic of the allylic methylene protons. The $^{13}$C NMR spectrum showed the disappearance of the distinctive high frequency carbonyl peak at $\delta_C$ 171.1 ppm and the IR spectrum displayed the emergence of a hydroxyl absorption peak at $\nu_{max}$ 3335 cm$^{-1}$ following the disappearance of the carbonyl absorption peak at $\nu_{max}$ 1739 cm$^{-1}$.

Following removal of the acetate, the hydroxyl functionality of **68** was temporarily masked by employing a *tert*-butyldimethylsilyl ether protecting group. The first report of the TBDMS group for protection of hydroxyl groups dates back to 1972,[114] where the reaction of *tert*-butyldimethylsilyl chloride (TBDMSCl) in dimethylformamide (DMF) was reported to take place very slowly with alcohols and gave unsatisfactory yields. However, the addition of 2

equivalents of imidazole was found to lead to a smooth reaction with high yields.[114,115] A more contemporary procedure was adopted from the literature,[116] which involved the sequential treatment of the allylic alcohol **68** with 1.05 equivalents of *tert*-butyldimethyl silyl chloride and imidazole (2 equivalents) in dry DMF at 0 $^{o}$C (***Scheme 2.30***). Please note that the abbreviation for the *tert*-butyldimethyl silyl protecting group is TBS, which is consistent with the literature.[25,88,117,118]



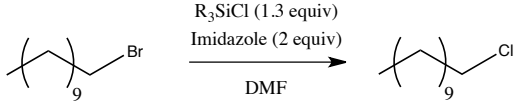

***Scheme 2.30:***

The reaction was monitored by thin layer chromatography and after a five hour stir at room temperature, complete consumption of starting material **68** was evident. Interestingly, the $^{1}$H NMR spectrum of the crude product revealed a two-component mixture of products consisting of the desired silyl ether protected bromide **69** and its corresponding chloride **70**. Purification by column chromatography was unsuccessful at separating the two components and therefore isolated the bromide **69** and chloride **70** in a 68:32 ratio of products respectively as determined by $^{1}$H NMR integration.

$^{1}$H NMR analysis confirmed the successful synthesis of the novel silyl bromide **69** with the appearance of a 6H singlet at $\delta_H$ 0.07 ppm [Si(C$H_3$)$_2$] and a 9H singlet at $\delta_H$ 0.91 ppm [SiC(C$H_3$)$_3$] corresponding to the methyl groups on the silyl ether. Likewise, a marginal but characteristic shift was observed from a 2H doublet at $\delta_H$ 4.16 ppm (*J* 6.9) to $\delta_H$ 4.19 ppm (*J* 6.4) associated with the allylic methylene protons adjacent to the silyl ether functionality. IR analysis showed the disappearance of the OH stretch at $\nu_{max}$ 3335 cm$^{-1}$ and the presence of two strong absorption bands at $\nu_{max}$ 1254 cm$^{-1}$ (SiCH$_3$) and $\nu_{max}$ 1065 cm$^{-1}$ (SiO) associated with the silicon atom.

Evidence for the formation of the novel chloride **70** was apparent in the $^{1}$H NMR spectrum with the appearance of a 2H triplet at $\delta_H$ 3.49 ppm [*J* 6.7, C(10)$H_2$Cl] in tandem with the bromide **69** at $\delta_H$ 3.37 ppm [*J* 6.7, C(10)$H_2$Br]. The $^{13}$C NMR spectrum also displayed the existence of a distinctive peak at $\delta_C$ 44.5 ppm [*C*(10)$H_2$Cl] in conjunction with a peak at $\delta_C$ 33.4 ppm [*C*(10)$H_2$Br]. The mass spectrum was quite "busy" showing strong indications for the presence of two multi-isotopic elements. The distinctive pattern for bromine **69** was evident with two isotope peaks at 243.4 ($^{79}$Br) and 245.4 ($^{81}$Br) in nearly a 1:1 ratio. The chloride **70** produced a similar pattern with two isotope peaks at 199.4 ($^{35}$Cl) and 201.3 ($^{37}$Cl) in a 3:1 ratio respectively. Fortuitously, this reagent was intended to be a Grignard precursor so the presence of a halide mixture was somewhat acceptable. With respect to rationalising this result, Peyrat *et al.* reported that when a bromide substrate is treated with a trialkylsilyl chloride reagent in the presence of imidazole and in dimethylformamide,[119] displacement of the bromine atom by chlorine is recognised. He conveyed how treatment of 1-bromoundecane **71** with 1.3 equivalents of trimethylsilyl chloride (TMSCl) in dimethylformamide at 90 $^{o}$C in the presence of two equivalents of imidazole would afford the corresponding chloride **72** in quantitative yields (***Table 2.8 Entry 2***). Furthermore, this halide exchange was also possible using *tert*-butyldimethylsilyl chloride in lieu of TMSCl, even though the reaction was slightly slower as illustrated in ***Table 2.8 Entry 4***.

***Table 2.8:*** *Reaction conditions employed in the halide exchange preparation of alkyl chloride **72** from alkyl bromide **71** by Peyrat et al.*[119]



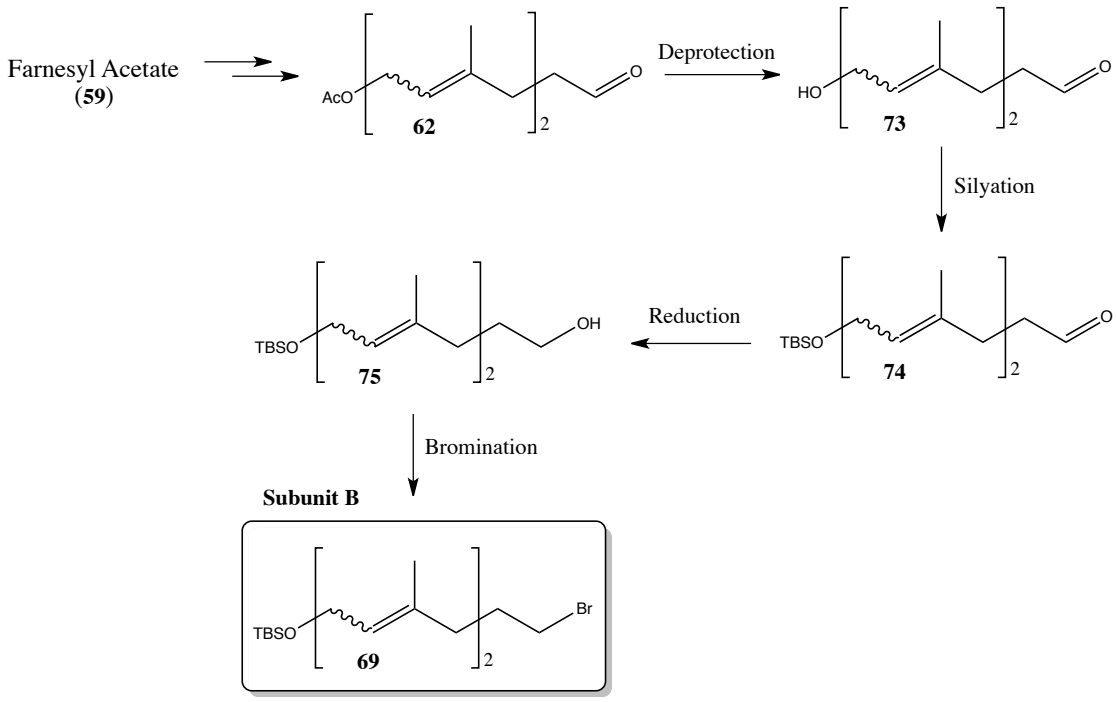

**71** **72**

| Entry | $R_3SiCl$ | Temp ($^{o}$C) | 72:71[a] 2.5 h | 72:71[a] 24 h |
|---|---|---|---|---|
| **1** | TMSCl | rt | 32:68 | 76:23 |
| **2** | TMSCl | 90 | 100:0 (**1 h**) | |
| **3** | TBDMSCl | rt | 24:76 | 63:37 |
| **4** | TBDMSCl | 60 | 86:14 | 100:0 |

**a: Ratios were obtained by GC analysis.**

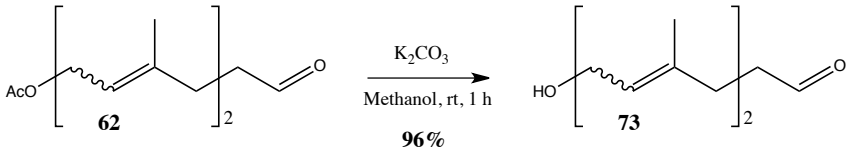
Disappointingly, exclusive conversion of the allylic alcohol **68** to its corresponding silyl ether protected bromide **69** using standard silylation conditions is essentially unattainable on this occasion due to the competing halide exchange reaction (***Scheme 2.30***). Alas, it was decided to try and introduce the silyl ether protecting group at an earlier stage in the preparation of **subunit B** in order to avoid problematic side reactions.

Ideally the best point for introduction of the silyl ether protecting group was following the synthesis of the acetate aldehyde **62** as illustrated in ***Scheme 2.31***. Masking of the hydroxyl group at this step would avoid competing halide exchange chemistry and produce a protecting group sufficiently stable enough to avoid undesired removal to its corresponding diol **64** during the impending reduction reaction.




***Scheme 2.31***

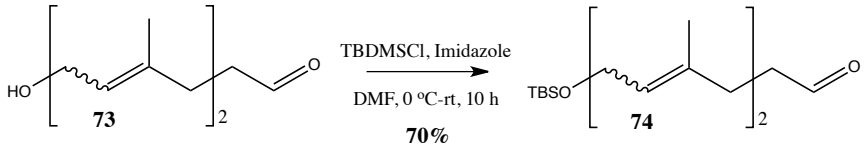
Following established precedent,[88,120] 10-hydroxy-4,8-dimethyldeca-4,8-dienal **73** was successfully synthesised in 96% yield following treatment of the acetate ester **62** with potassium carbonate in methanol over a one hour period at room temperature (***Scheme 2.32***).




***Scheme 2.32***

The allylic alcohol **73** was cleanly obtained as a light yellow oil, thus avoiding the need for further purification by column chromatography. $^{1}$H NMR spectroscopy was consistent with literature findings,[88,121,122] showing a shift of the 2H doublet at $\delta_H$ 4.59 ppm (*J* 7.4) to $\delta_H$ 4.14 ppm (*J* 6.8) characteristic of the allylic methylene protons. The $^{13}$C NMR spectrum showed the disappearance of the distinctive high frequency carbonyl peak at $\delta_C$ 171.1 ppm and the IR spectrum displayed the emergence of a hydroxyl absorption peak at $\nu_{max}$ 3392 cm$^{-1}$ following the disappearance of the carbonyl absorption peak at $\nu_{max}$ 1738 cm$^{-1}$.

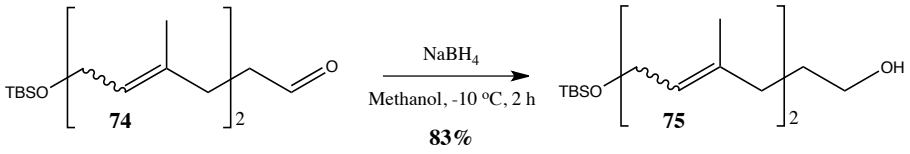
As illustrated in ***Scheme 2.31*** the next step in the synthesis of the TBS protected **subunit B 69** was a silylation reaction. Following a procedure described for this compound by Labadie *et al.*,[88] the allylic alcohol **73** was treated with *tert*-butyldimethylsilyl chloride and imidazole in dry dimethylformamide at 0 $^{o}$C with stirring over a 10 hour reaction period at room temperature (***Scheme 2.33***).




***Scheme 2.33***

Purification by column chromatography on silica gel furnished the desired silyl ether **74** as a colourless oil in 70% yield. $^1$H NMR analysis was consistent with literature findings,[120] with the appearance of a 6H singlet at $\delta_H$ 0.07 ppm [Si(C$H_3$)$_2$], a 9H singlet at $\delta_H$ 0.90 ppm [SiC(C$H_3$)$_3$] and a 2H doublet at $\delta_H$ 4.19 ppm (*J* 6.3), all correlating with successful attachment of the silyl ether functionality.

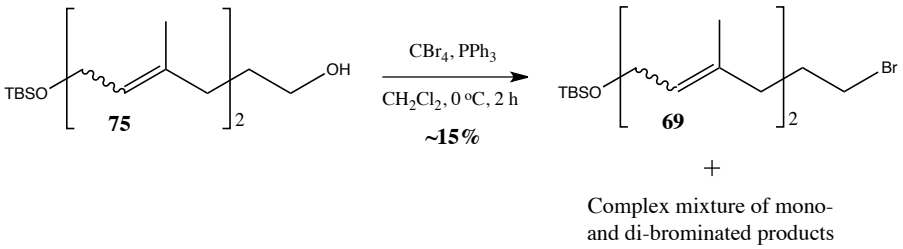
The next step involved a reduction reaction where the alcohol **75** was successfully synthesised in 83% yield following treatment of the aldehyde **74** with sodium borohydride in methanol at -10 $^o$C over a 2 hour period following the procedure described for this compound by Labadie *et al.* (***Scheme 2.34***).[88]




***Scheme 2.34***

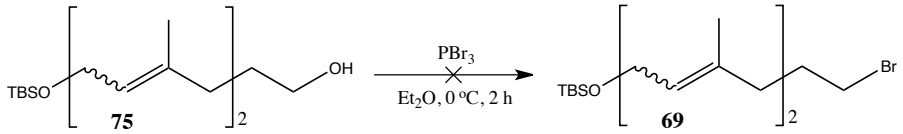
Upon workup, the crude product **75** was deemed sufficiently pure to be used in the next transformation without further purification by flash chromatography. $^1$H NMR analysis confirmed the formation of the desired product **75** with the disappearance of a distinctive 1H triplet at $\delta_H$ 9.75 ppm (*J* 1.9) and the subsequent appearance of a 2H multiplet at $\delta_H$ 3.57-3.65 ppm corresponding to the methylene protons adjacent to the hydroxyl group [C(1)$H_2$OH]. IR spectrum was also consistent with the disappearance of the strong carbonyl absorption band at $\nu_{max}$ 1728 cm$^{-1}$ and the presence of a broad OH stretch at $\nu_{max}$ 3362 cm$^{-1}$.
In contrast to the acetate ester **62**, reduction of TBS-protected aldehyde **74** using sodium borohydride in reagent grade methanol cleanly obtained the corresponding alcohol **75** in good yield showing no signs of undesired deprotection to the diol by-product **64** (as previously encountered in ***Section 2.3.4.4***).

The final step in the synthesis of TBS protected **subunit B** was the Appel bromination reaction. Adhering to previously successfully precedent (***Scheme 2.27***), the alcohol **75** was treated sequentially with carbon tetrabromide and triphenylphophine in dry dichloromethane at room temperature as illustrated in ***Scheme 2.35***.




***Scheme 2.35***

The reaction was monitored by thin layer chromatography and it became apparent after two hours that a second reaction had taken place concurrently to the desired bromination reaction. Interestingly, $^{1}$H NMR spectroscopy of the crude product revealed a complex mixture consisting of starting material **75**, the desired bromide **69** and a variety of mono- and di-brominated products undoubtedly resulting from undesired removal of the silyl ether protecting group. Due to the complexity of the crude mixture, purification by column chromatography was considered pointless and unfeasible. Alternatively, the bromination reaction was attempted using phosphorous tribromide in diethyl ether at 0 $^{o}$C as shown in ***Scheme 2.36***.




***Scheme 2.36***

On this occasion no trace of the desired compound **69** was evident in the $^{1}$H NMR spectrum of the crude product with complete removal of the silyl ether protecting group to a complex range of mono and di-brominated products as previously encountered with the Appel bromination reaction (***Scheme 2.35***). Since silyl ethers are commonly removed following treatment with tetra-*n*-butylammonium fluoride (TBAF) as a source of fluoride anion, in essence both $PBr_3$ and $CBr_4$-$PPh_3$ can provide a free bromine anion, which is available for nucleophilic attack at the silyl ether leading to a pentavalent silicon center, which is permitted due to hybridization with the vacant d-orbitals of silicon.[123] The driving force behind this reaction is the formation of the strong Si-Br bond (***Figure 2.8***).

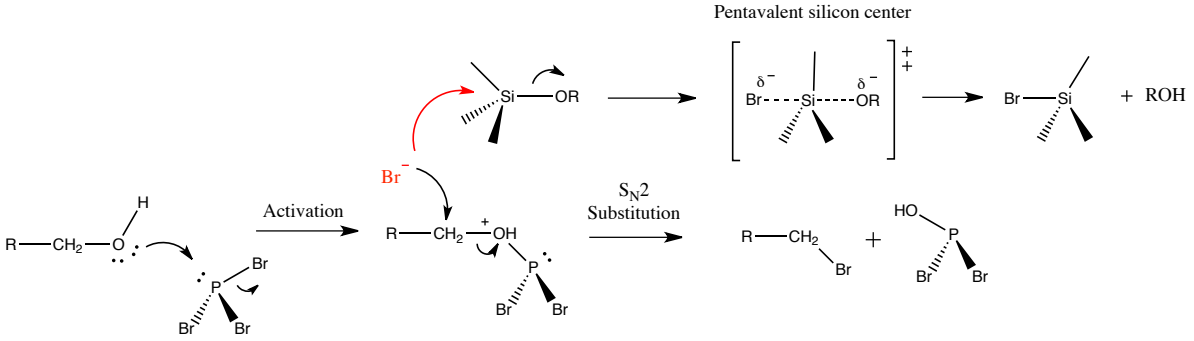


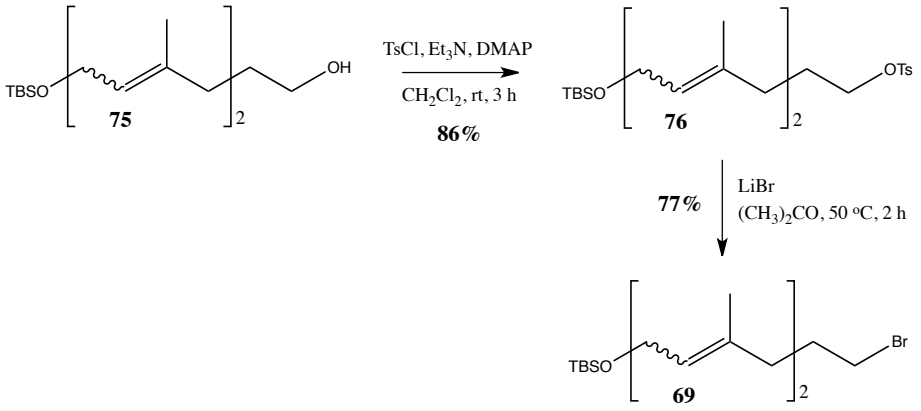

***Figure 2.8:*** *Putative mechanism for halide anion-induced desilylation in an aprotic environment during a bromination reaction using phosphorous tribromide.*

Disappointingly, convenient preparation of bromide **69** through the Appel bromination reaction or alternatively using $PBr_3$ could not be achieved in this scenario due to the presence of the silyl protecting group. A milder, more resourceful method for brominating the primary alcohol was thus required.

### 2.3.6.1 Preparation of alkyl halides of TBS protected subunit B

It became apparent that the use of a common laboratory reagent generally employed for the conversion of a primary alcohol to its corresponding halide would be ineffective at accomplishing this transformation cleanly and successfully. An attractive approach to avoid such a problem is illustrated in ***Scheme 2.37***, which involved converting the alcohol **75** to its

corresponding toyslate **76** followed by subsequent treatment with lithium bromide (LiBr) through a Finkelstein type reaction.




***Scheme 2.37***

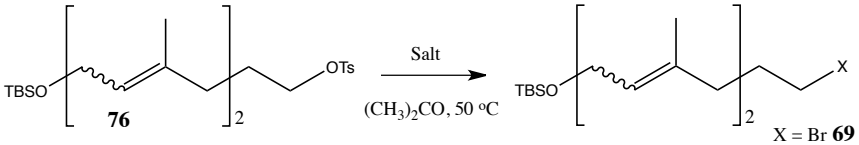
Tosylation was successfully accomplished in 86% yield following treatment of the alcohol **75** with 1 equivalent of *para*-toluenesulfonyl chloride (TsCl), 3 equivalents of triethylamine ($Et_3N$), and a catalytic trace of dimethylaminopyridine (DMAP) in dry dichloromethane at room temperature. The reaction was monitored by thin layer chromatography and complete consumption of starting material **75** was evident after 3 hours. Following workup, this novel tosylate **76** was cleanly obtained as a colourless oil and used in the next transformation without further purification. $^1$H NMR analysis confirmed the formation of the toyslate **76** with the appearance of a 2H doublet at $\delta_H$ 7.35 ppm (*J* 8.4) and $\delta_H$ 7.79 ppm (*J* 8.3) associated with the phenyl protons. A downfield shift of the 2H multiplet at $\delta_H$ 3.57-3.65 ppm to a distinctive 2H triplet at $\delta_H$ 3.99 ppm [*J* 6.4, C(1)$H_2$] was also evident and relates to the methylene protons adjacent to the sulfonate [C$H_2$OSO$_2$]. IR analysis was beneficial showing strong absorption bands at $\nu_{max}$ 1364 cm$^{-1}$ (asymmetric $SO_2$), $\nu_{max}$ 1178 cm$^{-1}$ (symmetric $SO_2$) and $\nu_{max}$ 836 cm$^{-1}$ (S-O-C stretching).

Having successfully activated the alcohol **75** via a tosylation reaction, the next step involved treatment of the tosylate **76** with 2 equivalents of lithium bromide in refluxing acetone over a two hour period (***Scheme 2.37***). Upon workup, this novel bromide **69** was obtained as a light yellow oil in 77% yield, which by $^1$H NMR spectroscopy was sufficiently pure for use in

further transformations. $^{1}$H NMR analysis confirmed the formation of the bromide **69** with the upshift of the 2H triplet at $\delta_H$ 3.99 ppm (*J* 6.4) to a 2H triplet at $\delta_H$ 3.37 ppm (*J* 6.7, C*H*$_2$Br) and the disappearance of the phenyl protons at $\delta_H$ 7.35 ppm (2H, d, *J* 8.4) and $\delta_H$ 7.79 ppm (2H, d, *J* 8.3). $^{13}$C NMR was also consistent with a low frequency chemical shift from $\delta_C$ 70.1 ppm to $\delta_C$ 33.4 ppm characteristic of the carbon alpha to the bromide [*C*(10)H$_2$Br].

Activation of the primary alcohol via tosylation and subsequent reaction with lithium bromide is a very convenient and efficient method for the preparation of alkyl bromide in neutral conditions. A key advantage of this type of transformation is how it can be exploited to produce both the iodide **77** and chloride **70** in addition to the bromide **69** of **subunit B** (***Table 2.9***). Since **subunit B** was synthetically designed to function as a Grignard precursor, it is indeed convenient to have all three novel halides in ones armoury for more troublesome coupling reactions.

***Table 2.9:*** *Preparation of alkyl halides of TBS protected* ***subunit B****.*




| Entry | Salt | Time | Product | Yield (%) a |
|---|---|---|---|---|
| **1** | LiBr | 2 h | **69** | 77% |
| **2** | NaI | 2 h | **77** | 76% |
| **3** | LiCl | 16 h | **70** | 84% |

**a: Crude yield of halide product, no purification required.**

The iodide **77** was prepared in 76% yield following the same general procedure as previously expressed for the bromide **69** with the exception of sodium iodide being employed as the source of iodide anion (***Table 2.9, Entry 2***). Following a 2 hour reflux and subsequent workup, the iodide **77** was isolated as a light yellow oil, which by $^{1}$H NMR spectroscopy was sufficiently pure for use in further transformations. Due to the heavy atom effect on the iodide-bearing carbon (α-substituent), a considerable low frequency shift was observed in the

$^{13}C$ NMR spectrum at C(10) from $\delta_C$ 70.1 ppm to $\delta_C$ 6.7 ppm. As expected, the most characteristic peak in the $^{1}H$ NMR spectrum was observed as a 2H triplet at $\delta_H$ 3.14 ppm (*J* 7.1) associated with the methylene protons alpha to the iodide [C(10)$H_2$I] ***(Figure 2.9)***.

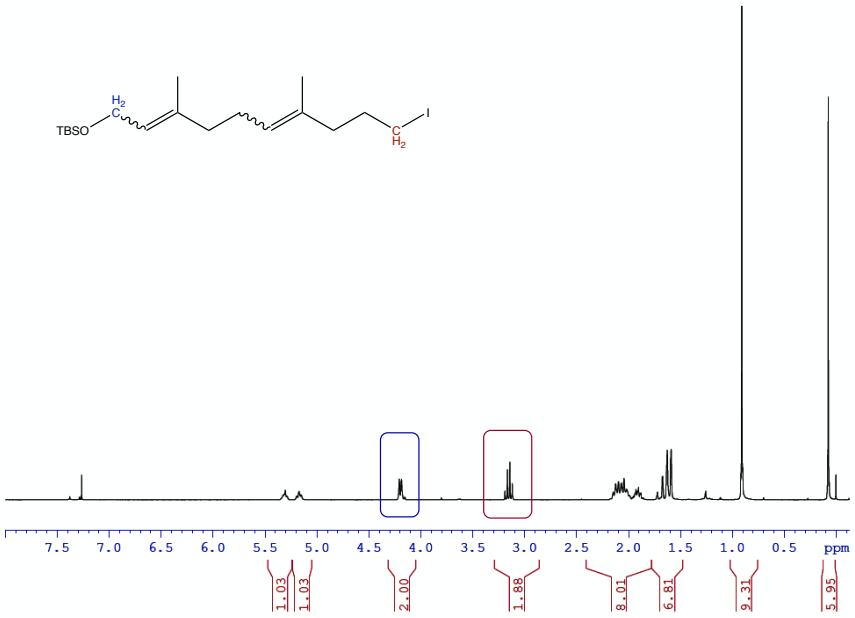
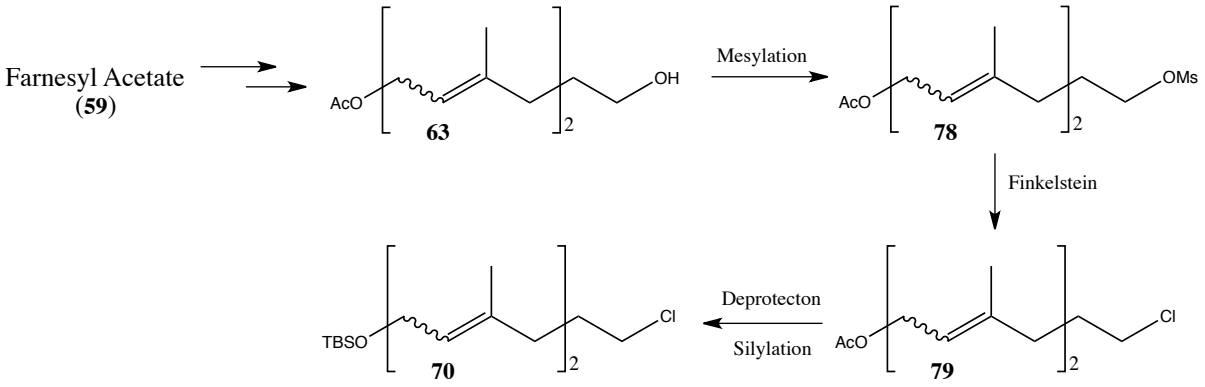



***Figure 2.9:*** *$^{1}H$ NMR spectrum of iodide 77 ($CDCl_3$, 300 MHz).*

The chloride **70** was prepared in a similar fashion to the previous two halides, however on this occasion a longer reaction time of 16 hours was necessary to achieve full conversion from the tosylate **76** using lithium chloride (LiCl) as determined by TLC analysis (***Table 2.9, Entry 3***). The chloride **70** was cleanly obtained as a colourless oil in 84% yield requiring no additional purification by column chromatography. The $^{1}H$ NMR spectrum was almost identical to the iodide **77** and bromide **69** previously described except for a characteristic 2H triplet at $\delta_H$ 3.42 ppm (*J* 6.3). Activation of the alcohol **75** via tosylation and subsequent halogenation using the appropriate inorganic salt is an attractive and convenient route for the high yielding preparation of alkyl halides without undesired removal of the silyl ether protecting group. To summarise, synthesis of TBS protected **subunit B** was accomplished in 7 linear steps from commercially available farnesyl acetate **59**. Our **subunit B** halides **69,70** and **77** were subsequently used as Grignard precursors in the conjugate addition/elimination reaction with a suitable vinyl triflate.

### 2.3.6.2 Alternative synthesis of TBS protected subunit B (chloride)

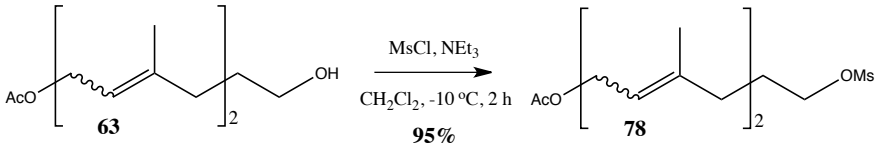
Alternatively, the chloride **70** was also prepared in a 7 step synthetic route from commercially available farnesyl acetate **59** as illustrated in ***Scheme 2.38.*** It should be noted that this synthetic pathway was devised and successfully performed well before the development of the route described above in ***Section 2.3.6.1***.




***Scheme 2.38***

Access to the chloride **70** was achieved in this regard via activation of the alcohol **63** through a mesylation reaction followed by treatment with lithium chloride (***Scheme 2.38***). To facilitate the Grignard cross coupling reaction, a silyl ether protecting group was introduced to replace the acetate ester. The route to the preparation of the chloride **70** afforded three novel terpene analogues **78, 79** and **80**.

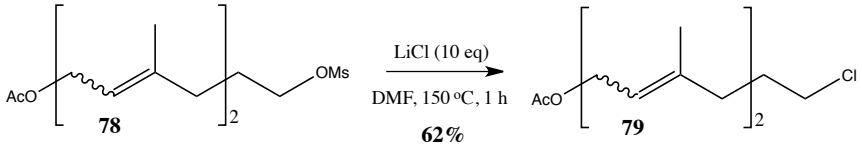
As illustrated in ***Scheme 2.38***, the first step involved converting the alcohol **63** to its corresponding mesylate **78**, which was achieved using 1.25 equivalents of methanesulfonyl chloride (MsCl) and 1.1 equivalents of triethylamine while following a procedure described for a related compound by Murtagh *et al.* (***Scheme 2.39***).[124]




***Scheme 2.39***

The reaction was monitored by thin layer chromatography and consumption of starting material **63** was apparent after 2 h at -10 $^{o}$C. Following workup, the mesylate **78** was obtained in 95% yield as a yellow oil, which by $^{1}$H NMR spectroscopy was sufficiently pure for use in the next transformation. Activation of the alcohol **63** was observed in the $^{1}$H NMR spectrum with a significant shift downfield of a 2H multiplet at $\delta_H$ 3.58-3.67 ppm to a 2H triplet at $\delta_H$ 4.20 ppm (*J* 6.5) and in the $^{13}$C NMR spectrum with a high frequency shift from $\delta_C$ 62.6 ppm to $\delta_C$ 69.6 ppm both of which are associated with the methylene group adjacent to the mesylate [C(10)$H_2$OMs]. The characteristic peaks for the mesylate functionality were also observed in the $^{1}$H NMR spectrum as a 3H singlet at $\delta_H$ 3.00 ppm [$SO_2CH_3$]. The IR spectrum showed the disappearance of the hydroxyl group stretch at $\nu_{max}$ 3410 cm$^{-1}$ and the appearance of a strong sulfonate absorption band at $\nu_{max}$ 1175 cm$^{-1}$.

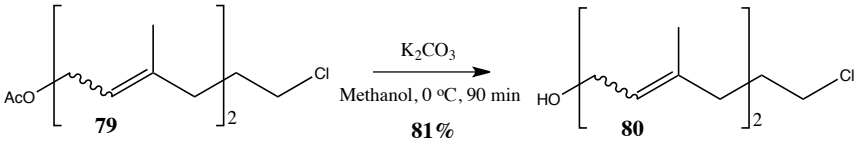
The next step involved a chlorination reaction, which was successfully accomplished following treatment of the mesylate **78** with 10 equivalents of lithium chloride in refluxing dimethylformamide over a 1 hour period as shown in ***Scheme 2.40***.




***Scheme 2.40***

Purification by column chromatography following acid workup furnished the chloride **79** as a colourless oil in 62% yield. Conversion to the chloride **79** was confirmed by $^{1}$H NMR analysis with the disappearance of the singlet at $\delta_H$ 3.00 ppm [$SO_2CH_3$] and an upfield shift of the 2H triplet at $\delta_H$ 4.20 ppm to $\delta_H$ 3.50 ppm [*J* 6.7, C(10)$H_2$Cl]. Following synthesis of the chloride **79**, it was paramount that a silyl ether protecting group was introduced to facilitate the impending Grignard cross coupling reaction.

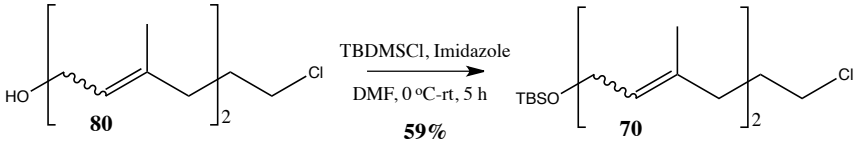
In order to address this matter, the acetate ester functionality was subsequently removed by employing previously successful reaction conditions, which involved treatment of the acetate **79** with potassium carbonate in methanol at 0 $^{o}$C over 90 minutes (***Scheme 2.41***).




***Scheme 2.41***

Post workup, the novel allylic alcohol **80** was cleanly obtained as a stable light yellow oil in 81% yield. Further purification was deemed unnecessary and the alcohol **79** was subsequently used in the next reaction. $^{1}$H NMR analysis confirmed the synthesis of **80** by the appearance of the characteristic 2H doublet at $\delta_H$ 4.16 ppm (*J* 6.9) associated with the allylic methylene protons.

Following a procedure reported for a related compound by Labadie *et al.,*[88] conversion of the alcohol **80** to its corresponding silyl ether **70** was accomplished in 59% yield following treatment with *tert*-butyldimethylsilyl chloride and imidazole in dry dimethylformamide at 0 $^{o}$C as illustrated in ***Scheme 2.42***.

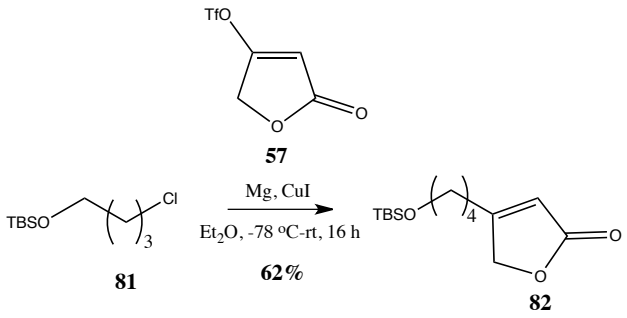



***Scheme 2.42***

The reaction was monitored by thin layer chromatography and after a 5 hour reaction at room temperature, workup followed by subsequent purification by column chromatography afforded the silyl ether **70** as a colourless oil. Spectroscopic characteristics were consistent with those previously described in ***Section 2.3.6.1***. Noteworthy, since the substrate for the silyation reaction already contained a chloride, no undesired halide exchange could occur following treatment with *tert*-butyldimethylsilyl chloride. The chloride **70** was subsequently utilised as a Grignard precursor for the ensuing conjugate addition/elimination reaction with vinyl triflate **57** towards the synthesis of furospongolide **1**.

### 2.3.7 Attempted coupling of TBS protected subunit B with subunit C

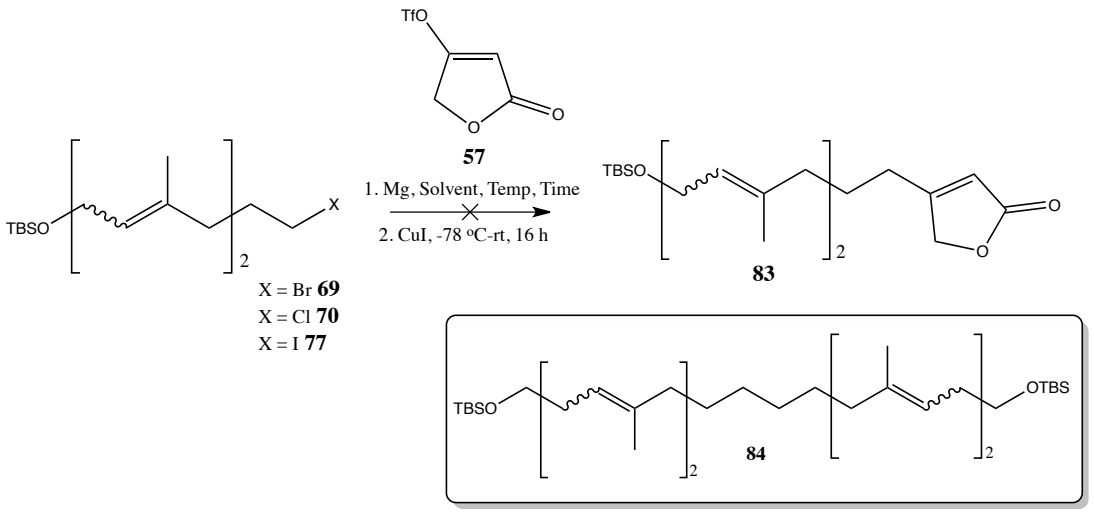
Having successful synthesised TBS protected **subunit B**, the next crucial step was to determine if our halides **69,70** and **77** could effectively undergo a cross coupling reaction with vinyl triflate **57** towards the synthesis of our target molecule **1**. As previously described in ***Section 2.3.5***, it was envisioned that attachment of the butenolide to the central linchpin would involve a conjugate addition/elimination reaction. A similar reaction was performed by Molander *et al.* where he prepared a β-substituted butenolide **82** in good yield (62%) through a conjugate addition reaction involving vinyl triflate **57** and the Grignard derived cuprate of *tert*-butyl-(4-chlorobutoxy)dimethylsilane **81** as illustrated in ***Scheme 2.43***.[83,125]




***Scheme 2.43.*** *A conjugate addition/elimination reaction preformed by Molander et al.*[83,125]

Our synthetic endeavours towards the synthesis of the β-substituted butenolide **83** began with using the bromide **69**/chloride **70** mixture as the Grignard precursor (68:32 ratio respectively) (***Table 2.10, Entry 1***). Just to recap, this mixture of products was formed following an unforeseen Finkelstein-type halide exchange reaction during O-silylation of **68** using *tert*-butyldimethylsilyl chloride in dimethylformamide (***Scheme 2.30***). Using to the procedure described by Molander *et al.*, the Grignard reagent was prepared by slow addition of the bromide **69**/chloride **70** mixture to a stirring suspension of pre-activated magnesium (3 equivalents) in diethyl ether at room temperature before refluxing at 40 $^{o}$C over a 3 hour period.[83,125] The vinyl triflate **57** was subsequently added dropwise to the Grignard derived cuprate at -78 $^{o}$C (***Table 2.10, Entry 1).***

***Table 2.10:*** *Conjugate addition/elimination reaction between the Grignard derived cuprate of TBS protected* ***subunit B*** *and* ***subunit C****.*



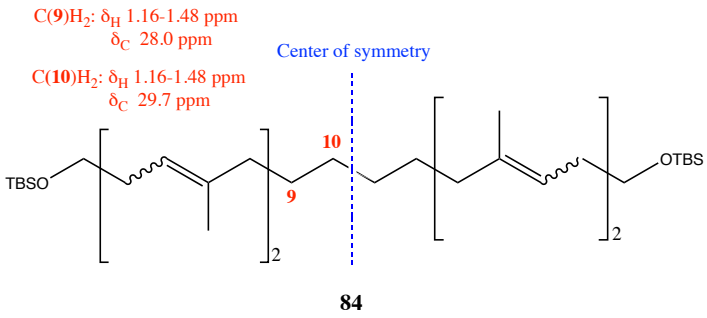

| Entry | SM | Solvent | Temp | Time |
|---|---|---|---|---|
| **1** | **69**/**70** [a, b] | $Et_2O$ | 40 °C | 3 h |
| **2** | **77** [a] | $Et_2O$ | 40 °C | 3 h |
| **3** | **69** [a] | $Et_2O$ | 40 °C | 3 h |
| **4** | **69** [a, b] | THF | 0 °C | 6 h |

**a: Major product formed was the Wurtz dimer 84.**
**b: Recovery of unreacted halide starting material.**

Disappointingly upon workup, spectroscopic analysis revealed that the desired β-substituted butenolide **83** was not formed (***Table 2.10, Entry 1***). Interestingly, no trace of the bromide **69** and the vinyl triflate **57** were evident in the $^1$H NMR spectrum of the crude product. Furthermore, chloride **70** was recovered unchanged from the reaction informing us that its corresponding Grignard reagent was never formed. From experience, the chloride **70** was found to be extremely troublesome at generating the Grignard reagent despite numerous attempts with the recovery of starting material in all cases. On further spectroscopic analysis it became apparent that the bromide **69** was converted to the Wurtz homo-coupled product **84** following Grignard synthesis. Interestingly, the vinyl triflate **57** was converted to its corresponding bromide **85** and iodide **86** following unanticipated *in-situ* halogenation (***Scheme 2.44***). $^1$H NMR analysis of the crude product therefore indicated a four component

mixture consisting of the Wurtz homo-coupled product **84**, 4-bromofuran-2(5*H*)-one **85**, 4-iodofuran-2(5*H*)-one **86** and unreacted chloride starting material **70** in a 31:35:6:28 ratio respectively.

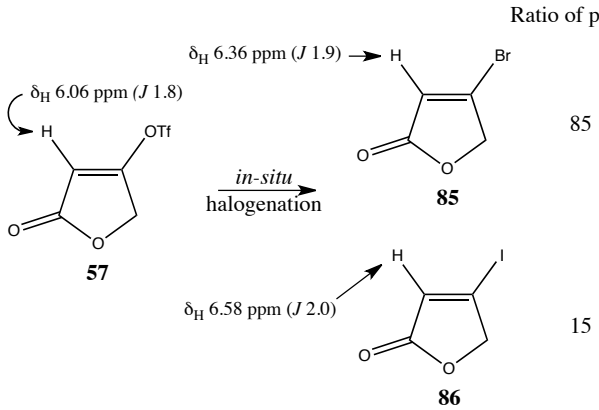
The least polar fraction isolated by flash chromatography was the Wurtz cross-coupled product **84** as a colourless oil. $^1$H NMR analysis confirmed dimerization with the disappearance of the methylene proton signal adjacent to the bromide at $\delta_H$ 3.37 ppm (*J* 6.7) and the appearance of a 8H multiplet at $\delta_H$ 1.16-1.48 ppm associated with the 2 sets of methylene hydrogens at C(10)$H_2$ and C(9)$H_2$ as shown in ***Figure 2.10***.




**84**

***Figure 2.10:*** *Spectroscopic characteristics for the Wurtz coupled product* ***84****.*

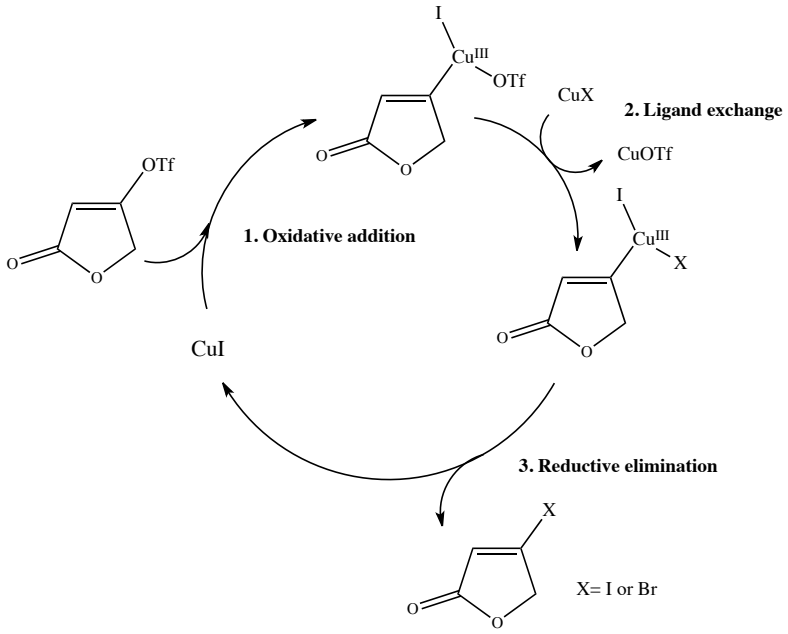
Due to identical $R_f$ values, the most polar fraction isolated was a co-eluted mixture consisting of 4-bromofuran-2(5*H*)-one **85** and 4-iodofuran-2(5*H*)-one **86** in a 85:15 ratio of products respectively (***Scheme 2.44***).




***Scheme 2.44:*** *Characteristic $^1$H NMR signals for iodide* ***86*** *and bromide* ***85*** *following in-situ halogenation of the vinyl triflate* ***57****.*

$^1$H NMR analysis confirmed the presence of the iodide **86** and the bromide **85** with the appearance of a distinctive 1H triplet at $\delta_H$ 6.58 ppm and $\delta_H$ 6.36 ppm respectively, assigned to the α-vinylic proton which is consistent with literature findings (***Scheme 2.44***).[126,127]

This unanticipatedj organom but equally interesting halogenation reaction prompted us to query how this process of converting the vinyl triflate **57** to its corresponding vinyl halides **85** and **86** was occurring. It could be postulated that formation of the vinyl halides *in-situ* maybe occurring through a transition metal-mediated carbon–halogen reductive elimination process, which is also well documented in the literature.[128-131] Since the iodide **86** was formed in accordance with the bromide **85**, this might suggest that a Cu(I)-mediated halogen exchange reaction is occurring (***Scheme 2.45***). The first step involves the formation of a copper(III) intermediate by oxidative addition of the vinyl triflate to copper(I) iodide. Ligand exchange and reductive elimination subsequently affords the vinyl halide with regeneration of the catalyst.[129]




***Scheme 2.45:*** *Possible mechanistic pathway for a transition-metal-catalysed halide exchange reaction as depicted by Sheppard et al.*

With respect to ***Table 2.10, Entry 2***, the reaction was repeated, except on this occasion the iodide **77** was employed as the Grignard precursor. Disappointingly, following workup, $^{1}$H NMR analysis of the crude product indicated a two-component mixture of products consisting of the Wurtz homocoupled product **84** and the butenolide iodide **86** in a 55:45 ratio of products respectively with no evidence for the formation of the desired alkylated butenolide **83**. In this scenario, complete conversion of the iodide **77** to its corresponding Wurtz homocoupled product **84** occurred as well as full conversion of the triflate **57** to its corresponding iodide **86**. Both compounds were isolated following flash chromatography and spectroscopic data was consistent with those previously described.

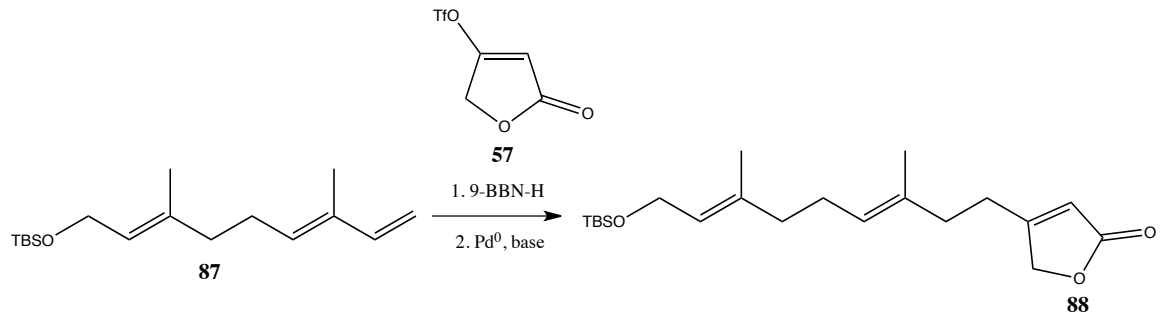
In the case of ***Entry 3***, the pure bromide **69** was employed as the Grignard precursor for the cross coupling reaction. The reaction protocol was performed in the same manner as the previous two entries (***Table 2.10***). Similar to the iodide **77**, complete conversion of the bromide **69** to the Wurtz coupled product **84** occurred. As expected, the vinyl triflate **57** was also completely consumed *in-situ* and subsequently converted to its corresponding bromide butenolide **85** and iodide butenolide **86** in a 93:7 ratio of products respectively (similar to ***Scheme 2.45***).

With respect to ***Entry 4***, various techniques were employed to control and suppress dimerization. It should be noted that ***Entry 4*** is only one example of numerous attempts to try and minimise the formation of the Wurtz homo-coupled product **84** by varying the reaction conditions during Grignard synthesis. On this occasion, magnesium turnings (3 equivalents) were vigorously stirred in the absence of solvent overnight and activated by the sequential addition of iodine and 1,2-dibromoethane followed by sonication and reflux before the exceedingly slow addition of the bromide **69** over a 30 minute period. Following a reaction protocol described for a related compound by Kanazawa *et al.*,[132] the Grignard reagent was generated over a 6 h period at 0 $^{o}$C and the conjugate addition in the presence of copper(I) iodide (1.15 equivalents) to the vinyl triflate **57** was performed as previously stated.
Unfortunately, no trace of the desired β-substituted butenolide **83** was observed following spectroscopic analysis of the crude product.$^{1}$H NMR analysis revealed a four component mixture of products consisting of the Wurtz cross coupled product **84**, 4-bromofuran-2(5*H*)-

one **85**, 4-iodofuran-2(5*H*)-one **86** and unreacted bromide starting material **69** in a 12:35:7:46. Despite implementing milder conditions for the generation of the Grignard reagent, which ultimately resulted in the recovery of a considerable amount of unreacted bromide starting material **69** (~65%) upon workup and chromatography, undesired Wurtz coupling (~35%) still occurred. This reaction illustrates how notoriously labile the Grignard reagent of **69** is to Wurtz homocoupling.

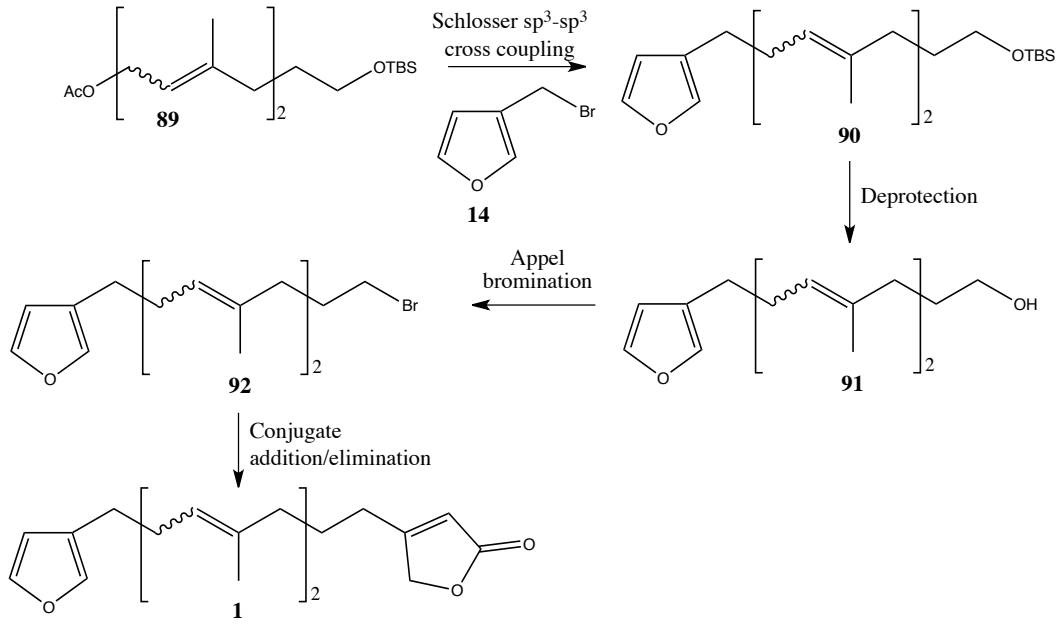
To conclude, the TBS-protected **subunit B** halides **69, 70** and **77** were undeniably ineffective as Grignard precursors for copper catalysed conjugate addition reactions with a vinyl triflate **57**. This was entirely due to the uncontrolled formation of the Wurtz dimer **84** following generation of the Grignard reagent. Surprisingly, both Molander *et al.* and Hanson *et al.* never reported the formation of the Wurtz coupled product despite using an unstabilised primary alkyl halide (***Scheme 2.43***).[125,133]

At this stage in the project, attachment of the butenolide moiety (**subunit C**) to the central linchpin (**subunit B**) *via* a Grignard cross coupling reaction was problematic. Following encouraging reports in the literature, a *B*-alkyl Suzuki-Miyaura cross coupling was an ideal alternative approach for accessing 3-substituted butenolides through an $C(sp^3)$-$C(sp^2)$ cross coupling reaction. Disappointingly, preliminarily attempts to join alkene **87** and vinyl triflate **57** towards the synthesis of 3-substituted butenolide **88** under Pd(0) catalysed Suzuki-Miyaura conditions were generally unsuccessfully and the results of our synthetic endeavours can be seen in more detail in ***Appendix 1***, ***Section 5.2.2***.



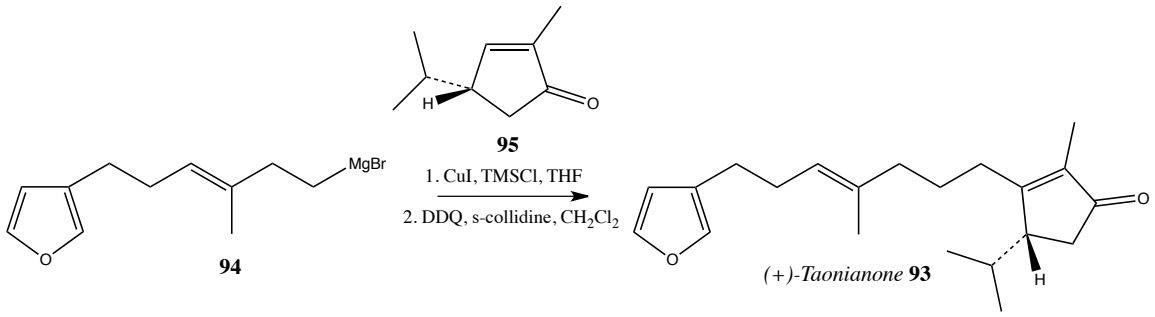

***Scheme 2.46:*** *The B-alkyl Suzuki-Miyaura cross coupling reaction.*

The next option was to attach the furan moiety first to the central linchpin subunit before attempting the conjugate addition reaction (***Scheme 2.47***). Even though silyl-protected alkyl halides are very common Grignard precursors in organic synthesis, it could be postulated that the silyl ether functional group may be interfering on some level with the generation and stability of the Grignard reagent. In order to avoid the use of silyl protecting group chemistry at the allylic position of **subunit B**, a new synthetic pathway towards the synthesis of our target molecule **1** was devised, which is shown in ***Scheme 2.47***.




***Scheme 2.47***

According to a recent report by Kanazawa *et al.* during the synthesis of a furanoditerpene marine natural product (+)-taonianone **93**, successful generation of the 3-furyl Grignard reagent **94** from its corresponding homoallylic bromide was achieved and added conjugately to enone **95** using copper(I) iodide as illustrated in ***Scheme 2.48***.[132]



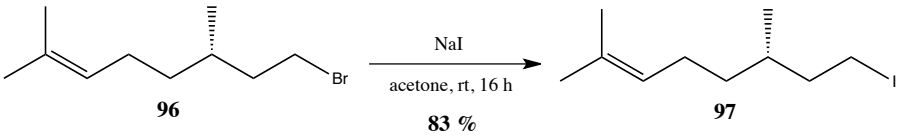

***Scheme 2.48***

Intriguingly, Kanazawa *et al.* commented on the competing formation of the Wurtz dimer during Grignard synthesis of **94**, however the cross coupling reaction towards the synthesis of (+)-taonianone **93** could still be successfully achieved.

It was therefore decided to try and attach the furan moiety to the central linchpin first before attempting the conjugate reaction with the vinyl triflate **57** in a similar type manner to that described by Kanazawa *et al.* in the synthesis of (+)-taonianone **93 (*Scheme 2.48*)**.[132] However, before we set about synthesising the furanolipid bromide **92** as the ideal coupling partner for vinyl triflate **57** in the synthesis of our target molecule **1**, it was imperative that we first assess if our methodology and conditions for the conjugate addition reaction were correct. To address this issue, a variety of test Grignard reactions were performed using citronellyl bromide **96**, chloride **99** or iodide **97** as the precursor Grignard reagent.

### 2.3.7.1 Synthesis of citronellyl halides

(S)-(+)-Citronellyl iodide **97** was successfully prepared from commercially available (S)-(+)-citronellyl bromide **96** following treatment with sodium iodide in acetone under standard Finkelstein conditions according to a procedure described for this compound by Kouwer *et al.* (***Scheme 2.49***).[134,135]

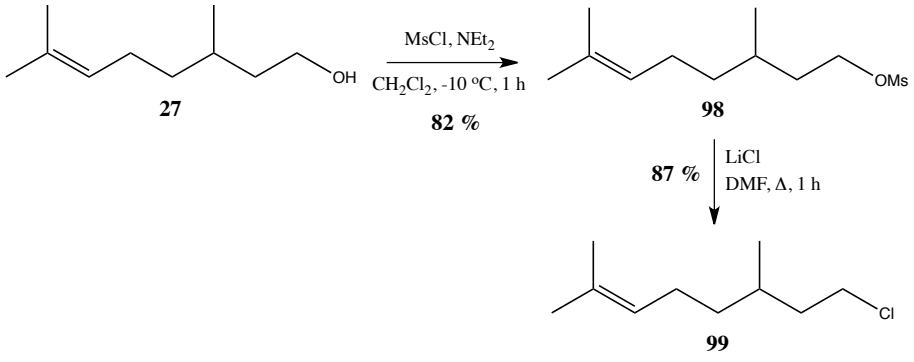



**96** **97**

***Scheme 2.49***

The desired iodide **97** was furnished as a colourless oil in 83% yield, which was deemed pure by spectroscopic analysis and used in the next transformation without further purification. $^{1}$H NMR analysis confirmed the formation of the iodide **97** with the shift upfield of the 2H multiplet at $\delta_H$ 3.35-3.50 in the bromide **96** to a 2H multiplet at $\delta_H$ 3.12-3.29 [C(1)$H_2$] assigned to the methylene protons adjacent to the iodide. Due to the heavy atom effect of the α-substituent, a low frequency chemical shift to $\delta_C$ 5.1 ppm was also observed at C(1) in the $^{13}$C NMR spectrum.

Citronellyl chloride **99** was successfully prepared in a two-step synthetic pathway from commercially available citronellol **27** as shown in ***Scheme 2.50***.




**27** **98** **99**

***Scheme 2.50***

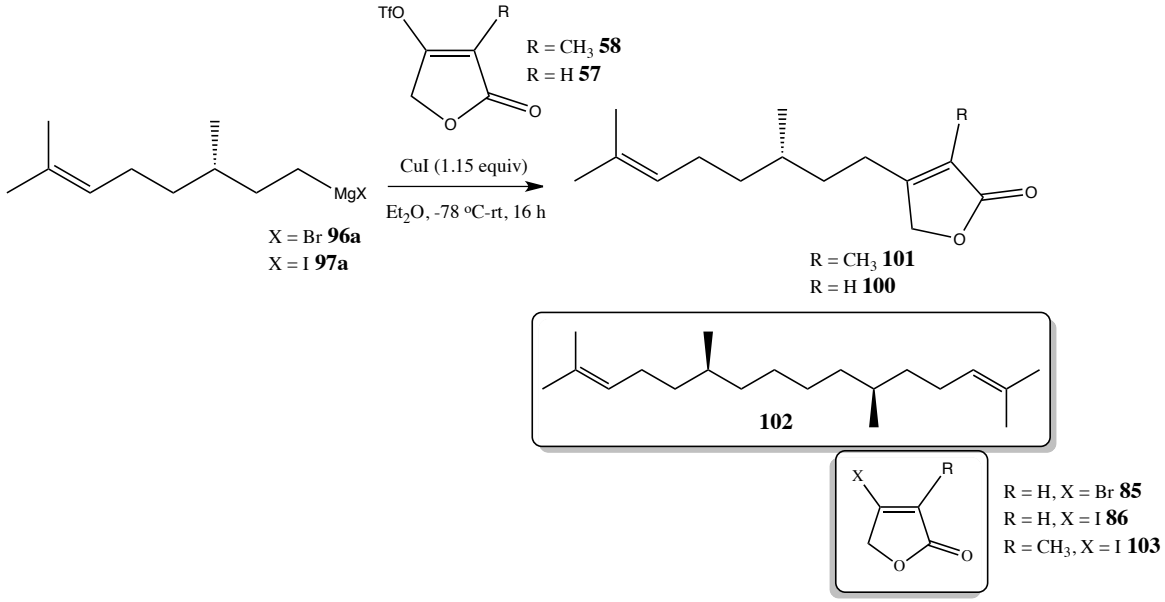
The first step involved a standard mesylation reaction in which citronellol **27** was treated with methanesulfonyl chloride and triethylamine in dichloromethane at -10 $^{o}$C following a procedure described for this compound by Murtagh *et al.*[124] The mesylate **98** was cleanly furnished as a yellow oil in 82% yield, which was sufficiently pure by $^{1}$H NMR spectroscopy for use in the next step. $^{1}$H NMR analysis was consistent with literature finding with the appearance of a 3H singlet at $\delta_H$ 3.00 ppm [$SO_2CH_3$] and a significant shift downfield of the α-methylene protons from a 2H multiplet at $\delta_H$ 3.60-3.75 ppm to $\delta_H$ 4.19-4.32 ppm. The IR spectrum displayed the appearance of characteristic asymmetric and symmetric sulfonate group stretching at $\nu_{max}$ 1355 cm$^{-1}$ and 1176 cm$^{-1}$ respectively.

The mesylate **98** was subsequently treated with lithium bromide in refluxing dimethylformamide over a 1 hour period adhering to a procedure described for this compound by Gembus *et al.* (***Scheme 2.50***).[136] Following purification by flash chromatography on silica gel, the desired chloride **99** was isolated as a colourless oil in 87% yield. $^{1}$H NMR analysis was consistent with literature findings with the appearance of a 2H multiplet at $\delta_H$ 3.48-3.63 ppm assigned to the α-methylene protons [C(1)$H_2$].[136] The three citronellyl halides **96**, **97** and **99** were subsequently used as Grignard precursors in the ensuing conjugate addition/elimination reaction with a suitable vinyl triflate substrate.

### 2.3.7.2 Synthesis of β-substituted butenolides

β-substituted butenolides represent remarkable lead structures for the development of new drugs. The general procedure for the synthesis of β-substituted butenolides through a conjugate addition/elimination reaction was adopted from Molander *et al.* and involved reacting the Grignard derived cuprate of the citronellyl halide with a suitable vinyl triflate as illustrated in ***Table 2.11***.[133]

***Table 2.11:*** *Synthesis of β-substituted butenolides via a conjugate addition/elimination reaction.*




| Entry | SM | R | Product | % Yield [a,b] |
|---|---|---|---|---|
| **1** | **97** | H | **100** | 26% |
| **2** | **96** | H | **100** | 38% |
| **3** | **96** | $CH_3$ | **101** | 67% |

**a: Purification by column chromatography on silica gel.**
**b: Isolated yield following column chromatography on silica gel.**

With respect to both the bromide **96** and the iodide **97**, the Grignard reagent was generated by slow addition of the halide to pre-activated magnesium in diethyl ether followed by a 3 hour reflux at 40 $^{o}$C. TLC analysis was useful in establishing a point when consumption of the halide was complete.

In the case of ***Entry 1***, following workup, spectroscopic analysis of the crude product revealed that the desired β-substituted butenolide **100** had successfully been formed, with purification by flash chromatography affording the pure product **100** as a colourless oil in 26% yield. It should be noted that a considerable amount of the Wurtz cross-coupled product **102** was formed in the reaction. Any unreacted vinyl triflate **57** was converted *in-situ* to its corresponding iodide **86** with spectroscopic characteristics matching those previously reported.

Confirmation of the successful preparation of the novel β-substituted butenolide **100** was evident from $^{1}$H NMR spectroscopy with the appearance of a multiplet at $\delta_H$ 2.35-2.50 ppm associated with the methylene group adjacent to the butenolide ring at C(6)$H_2$. Distinctive α,β-unsaturated lactone peaks were also observed in the $^{1}$H NMR spectrum as a 1H multiplet at $\delta_H$ 5.81-5.85 ppm and a 2H doublet at 4.73 ppm (*J* 1.8) associated with the α– and γ-hydrogens respectively. Further evidence was obtained from IR spectroscopy with the appearance of characteristic α,β-unsaturated carbonyl stretching frequencies at $\nu_{max}$ 1780 cm$^{-1}$ and $\nu_{max}$ 1751 cm$^{-1}$ (***Figure 2.11***).

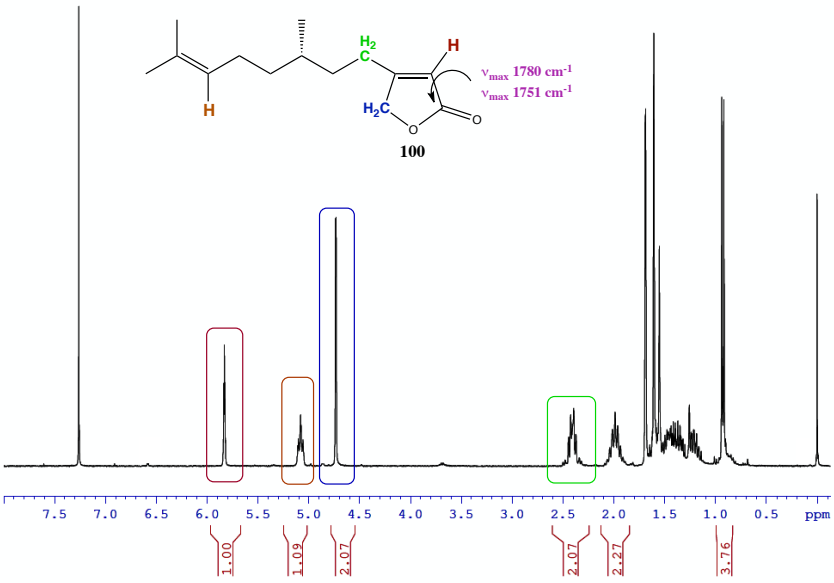



***Figure 2.11:*** *$^{1}$H NMR spectrum of β-substituted butenolide **100** ($CDCl_3$, 300MHz).*

For comparative reasons, the bromide **96** was employed as the Grignard precursor reagent and the cross coupling reaction was repeated as mentioned previously (***Table 2.11, Entry 2***). Following purification by column chromatography the desired β-substituted butenolide **100** was isolated as a colourless oil in 38% yield with spectroscopic characteristics consistent with those described in ***Figure 2.11***. As previously observed for the iodide **97**, the reaction was considerably hampered by the formation of the Wurtz dimer **102** and any unreacted vinyl triflate **57** was converted to its corresponding bromide (**85**) and iodide (**86**). By comparison, bromide **96** was found to be a better Grignard precursor reagent for the cross coupling reaction as it afforded the β-substituted butenolide **100** in a higher yield when equated against iodide **97**.

With respect to ***Entry 3***, the bromide **96** was employed as the Grignard precursor and the methyl tetronic acid triflate **58** was used as the substrate in the preparation of β-substituted butenolide **101**. Adhering to the same reaction protocol, the desired butenolide **101** was successfully isolated as a colourless oil in 67% yield following purification by flash chromatography. The Wurtz dimer **102** and the iodo butenolide **103** were also isolated following purification by chromatography. The Wurtz dimer **102** was easily identified by $^{1}H$ NMR analysis with a 14H multiplet at $\delta_H$ 1.03-1.46 ppm associated with the methylene protons at C(8)$H_2$, C(7)$H_2$, C(6)$H$ and C(5)$H_2$ (***Figure 2.12***).

Spectroscopic characteristics for the novel iodo butenolide **103** were as expected and its formation was confirmed with the appearance of a distinctive quaternary carbon signal at $\delta_C$ 113.9 ppm, which is indicative of the iodide **103** [C(4)] (***Figure 2.12***).

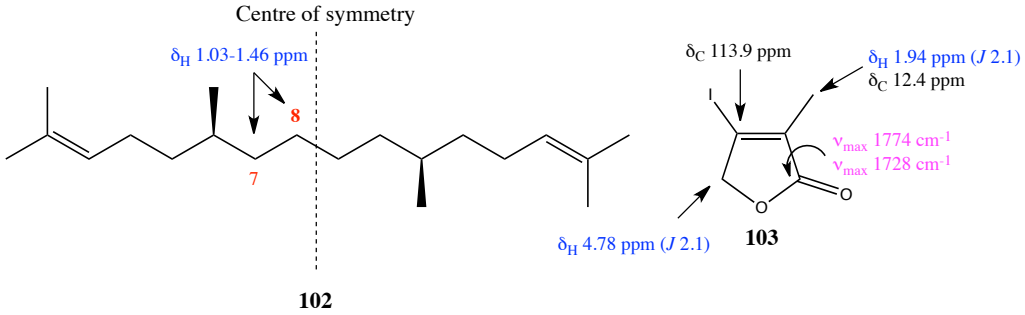



***Figure 2.12***

Spectroscopic characteristics for **101** were similar to those described for **100** with the appearance of a 2H multiplet at $\delta_H$ 2.30-2.50 ppm assigned to the methylene protons adjacent to the butenolide [C(6)$H_2$] and a 2H broad singlet at $\delta_H$ 4.65 ppm assigned to the γ-hydrogens. The only major difference was the appearance of a 3H singlet at $\delta_H$ 1.83 ppm associated with the methyl group at the α-position of the butenolide ring (***Figure 2.13***).

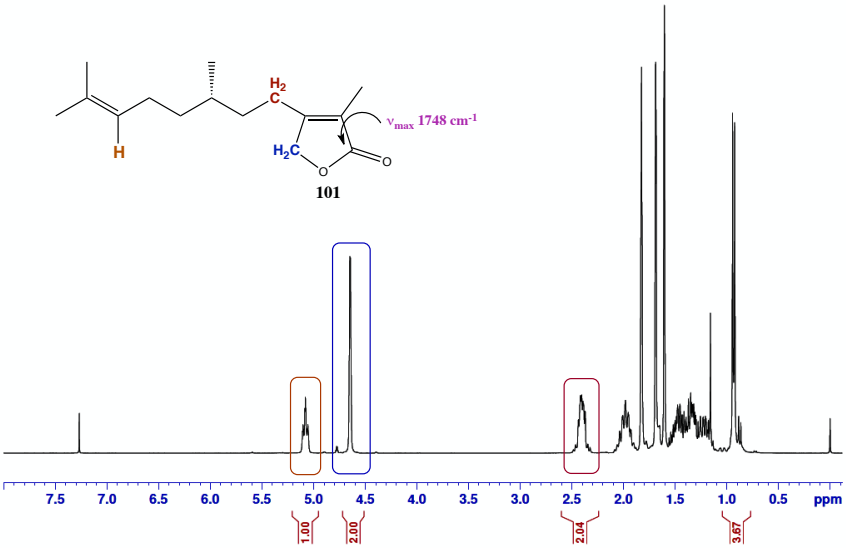
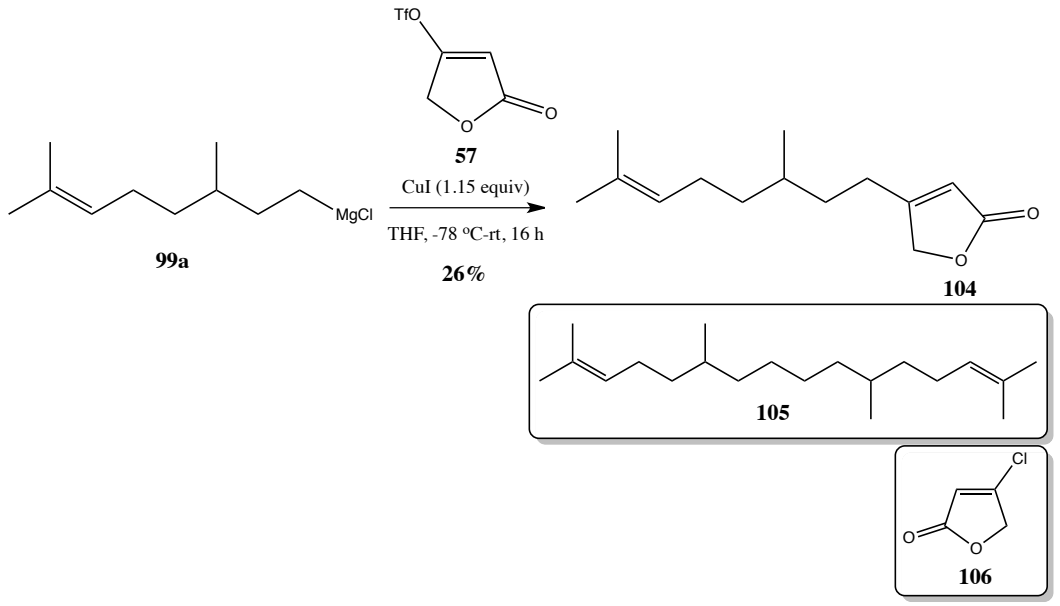



***Figure 2.13:*** *$^1$H NMR spectrum of β-substituted butenolide* ***101*** *($CDCl_3$, 300 MHz).*

Finally, citronellyl chloride **99** was also utilised as a Grignard precursor in the preparation of β-substituted butenolide **104** following the same reaction protocol as previously described (***Scheme 2.51***).



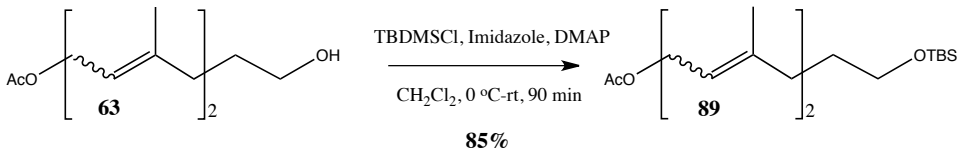

***Scheme 2.51***

Purification by flash chromatography afforded the novel β-substituted butenolide **104** as a colourless oil in 26% yield. Spectroscopic characteristics were consistent with those reported for **100** as illustrated in ***Figure 2.11***. Disappointingly, the Wurtz dimer **105** was the major product formed in this reaction. Interestingly, the chloro butenolide **106** was exclusively formed with no trace of its corresponding iodide **86**. Spectroscopic characteristics for the chloride **106** matched those reported in the literature with the appearance of a distinctive 1H triplet at $\delta_H$ 6.18 ppm (*J* 1.9) assigned to the vinylic proton.

Having shown that β-substituted butenolides can be successfully prepared through a conjugate addition/elimination reaction, the next important step was to prepare protected **subunit B 89** as the ideal central linchpin subunit in the synthesis of our target molecule **1** as previously illustrated in **Scheme 2.47**.

### 2.3.8 Synthesis of protected subunit B

The alcohol **63** was successfully converted to its corresponding silyl ether **89** following treatment with *tert*-butyldimethylsilyl chloride, imidazole and 4-dimethylaminopyridine in distilled dichloromethane at 0 $^{o}$C following the procedure described for this compound by Tarselli *et al.* (***Scheme 2.52***).[118]

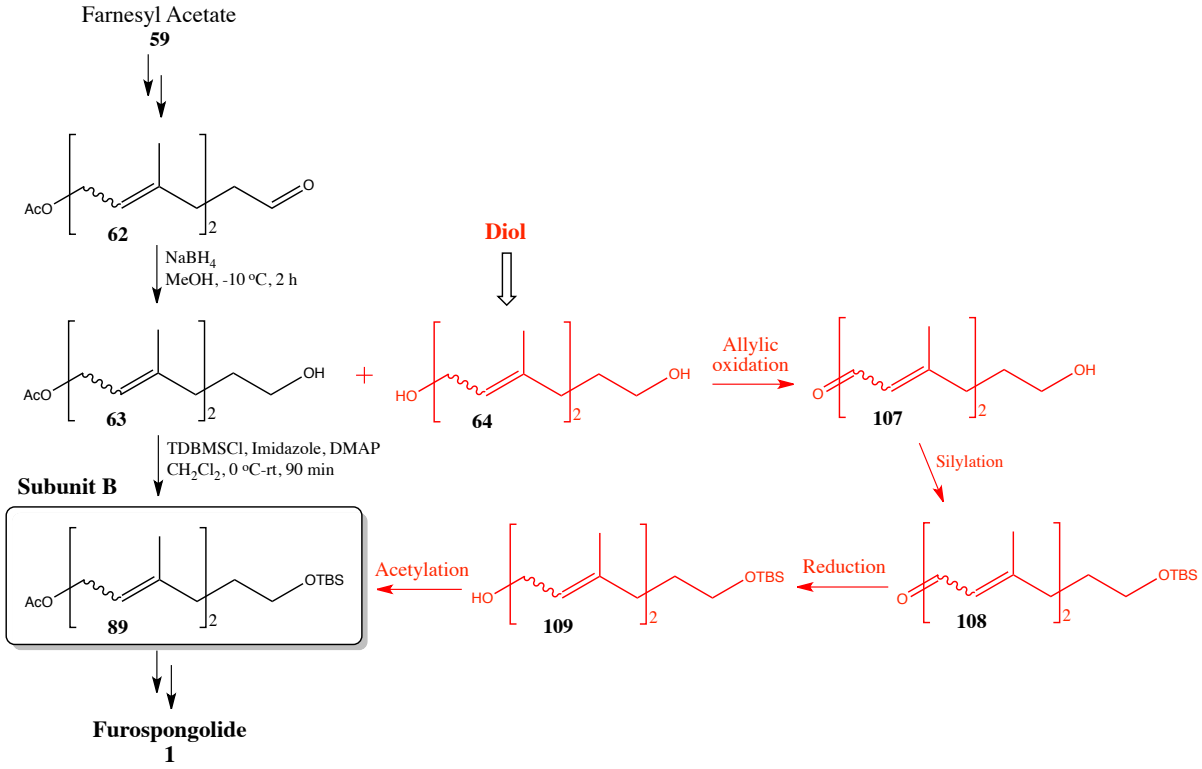



***Scheme 2.52***

The silyl ether **89** was isolated as a colourless oil in yields averaging 85% of the theoretical following purification by column chromatography on silica gel. Despite being a good yield, Tarselli *et al.* described isolation of the silyl ether **89** in 97% yield post purification. $^{1}$H NMR analysis confirmed the synthesis of the silyl ether **89** with the disappearance of a distinctive 2H multiplet at $\delta_H$ 3.58-3.67 ppm and the appearance of a 2H triplet at $\delta_H$ 3.58 ppm (*J* 6.6) assigned to the methylene protons adjacent to the silyl ether functionality. Succession of the broad hydroxyl absorption stretch at $\nu_{max}$ 3410 cm$^{-1}$ with characteristic silicon absorption stretches at $\nu_{max}$ 1233 cm$^{-1}$ and $\nu_{max}$ 1100 cm$^{-1}$ was also apparent in the IR spectrum. This bifunctional substrate **89** was subsequently used for the ensuing Schlosser sp$^3$-sp$^3$ cross coupling reaction.

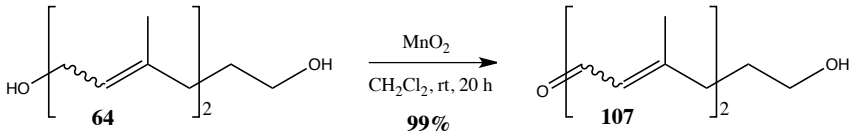
### 2.3.8.1 Alternative synthesis of protected subunit B

As previously discussed, during the reduction of aldehyde **62** using sodium borohydride in non-distilled methanol, undesired removal of the acetate ester protecting group occurred resulting in the formation of the diol **64**. Unfortunately, the presence of two hydroxyl groups made selective acetylation of the alcohol at the allylic position essentially unachievable. In order to regenerate protected **subunit B 89** from diol **64** to assist second-generation synthesis of furospongolide **1**, a four step synthetic route was devised as exemplified in ***Scheme 2.53***.




***Scheme 2.53:*** *Recycling diol **64** back into the synthetic route towards furospongolide **1**.*

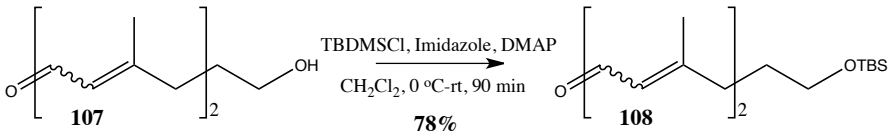
Our synthetic endeavours began with the selective oxidation of the allylic alcohol **64** to its corresponding aldehyde **107** utilising manganese dioxide ($MnO_2$) as illustrated in ***Scheme 2.54***.




***Scheme 2.54***

Following modification of a published procedure for this compound by Miles *et al.*,[137] the diol **64** was vigorously stirred over a 20 hour period in dry dichloromethane with 10 equivalents of activated manganese dioxide ($MnO_2$) at room temperature (***Scheme 2.54***). Upon removal of the excess manganese dioxide by filtration, the dienal **107** was obtained as a light yellow viscous oil in 99% yield, which by spectroscopic analysis was sufficiently pure for use in further transformations. $^1$H NMR analysis revealed a 67:33 mixture of the (*E,E*) and other isomer(s) following integration of the peaks at $\delta_H$ 9.99 ppm and $\delta_H$ 9.90 ppm respectively. $^1$H NMR analysis was consistent with literature findings for the dienal **107** with the appearance of a distinctive 1H doublet at $\delta_H$ 9.99 ppm [*J* 8.1, C(1)*H*O].[137] This relatively low-field chemical shift for the allylic hydrogen is primarily due to the increased deshielding effect exerted by the unsaturated aldehyde. Concurrently, a significant downfield shift was noted for the neighbouring alkenyl proton at C(2)*H* from a 1H multiplet at 5.30-5.38 ppm in **64** to a 1H doublet at $\delta_H$ 5.89 ppm (*J* 8.1) in **107**. IR and $^{13}$C NMR analysis was also consistent with a conjugated carbonyl absorption stretch at a low wavenumber of $\nu_{max}$ 1668 $cm^{-1}$ and a high frequency signal at $\delta_C$ 191.4 ppm respectively.

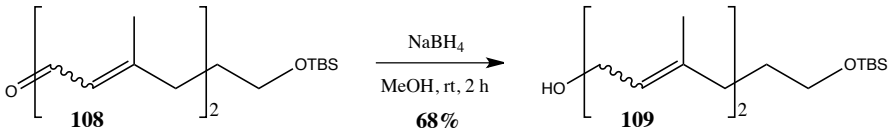
The dienal **107** was subsequently converted to its corresponding silyl ether **108** following treatment with 1.2 equivalents of *tert*-butyldimethylsilyl chloride, 1.6 equivalents of imidazole and a catalytic amount of 4-dimethylaminopyridine (5 mol%) in dry dichloromethane at 0 $^o$C following a procedure described for a related compound by Cole *et al.* (***Scheme 2.55***).[117]




***Scheme 2.55***

The reaction was monitored by thin layer chromatography and complete consumption of starting material **107** was evident after 90 minutes at room temperature. Purification by flash chromatography afforded the desired silyl alcohol **108** in 78% yield as a light yellow oil. $^{1}$H NMR analysis confirmed the formation of the novel silyl ether **108** with the marginal but notable shift of the 2H multiplet at $\delta_H$ 3.55-3.68 ppm to a 2H triplet at $\delta_H$ 3.58 ppm (*J* 6.2) associated with the methylene protons adjacent to the silyl ether [C(10)$H_2$SiO-]. IR analysis showed the disappearance of the hydroxyl group stretch at $\nu_{max}$ 3419 cm$^{-1}$ and the subsequent appearance of absorption bands at $\nu_{max}$ 1255 cm$^{-1}$ ($SiCH_3$) and $\nu_{max}$ 1100 cm$^{-1}$ (SiO) associated with the silicon atom. Silylation of primary alcohols under the conditions illustrated in ***Scheme 2.55*** was in practice a considerably more convenient, higher yielding and faster method for the preparation of TBS silyl ethers when compared to the older more conventional method involving TBDMSCl in dimethylformamide, which was previously employed.

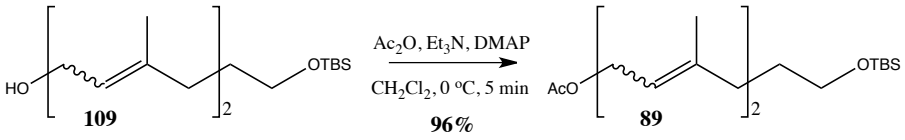
The next step involved reduction of TBS protected dienal **108** to its corresponding alcohol **109** following treatment with sodium borohydride in methanol at -10 $^{o}$C over a two hour period and using a procedure described for this compound by Tarselli *et al.* (***Scheme 2.56***).[118]




***Scheme 2.56***

The alcohol **109** was isolated as a faint yellow oil in 68% yield post workup, which was deemed pure by $^1$H NMR analysis avoiding the need for further purification by flash chromatography. $^1$H NMR analysis confirmed the formation of the alcohol **109** with the disappearance of the 1H doublet at $\delta_H$ 9.99 ppm (*J* 8.1) and the subsequent appearance of a characteristic 2H doublet at $\delta_H$ 4.15 ppm (*J* 6.9) relating to the allylic methylene protons [C(1)$H_2$].

The last step in synthetic sequence involved converting the alcohol **109** to its corresponding acetate ester **89** employing standard acetylation conditions and following established precedent as illustrated in ***Scheme 2.57***.[138]



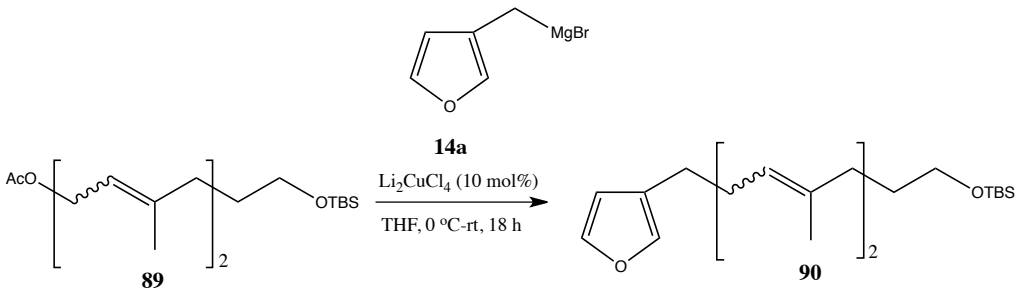

***Scheme 2.57***

The acetate ester **89** was isolated as a colourless oil in 96% yield following purification by flash chromatography. Spectroscopic characteristics were consistent with those previously reported for compound **89**. Successful conversion to the acetate ester **89** was easily identified in the $^1$H NMR spectrum with the appearance of the distinctive 2H doublet at $\delta_H$ 4.59 ppm (*J* 7.1). Additional evidence was observed in the IR spectrum with the appearance of a carbonyl absorption stretch at $\nu_{max}$ 1743 cm$^{-1}$ and the disappearance of the hydroxyl stretch at $\nu_{max}$ 3336 cm$^{-1}$.

To summarise, the naturally occurring diol **64** was successfully transformed in 4 synthetic steps to protected **subunit B** (central linchpin), which was subsequently utilised in the Schlosser cross coupling reaction with **subunit A**. This synthetic route offered a viable pathway for reincorporation of diol **64** back into 2$^{nd}$ generation synthesis of furospongolide **1** following its unexpected formation during a sodium borohydride reduction reaction as shown in ***Scheme 2.24, page 110.***

### 2.3.9 Coupling subunit A and protected subunit B

The next essential step was to attach the furan moiety to the intervening linker chain. Employing the same methodology described by Backvall *et al.* and previously utilised in the synthesis of dendrolasin (***Section 2.3.2.4***),[51] the Grignard derived cuprate of 3-furylmethyl bromide **14** was reacted with the acetate **89** under standard Schlosser conditions in the presence of Kochi's catalyst ($Li_2CuCl_4$, 10 mol%) as summarised in ***Scheme 2.58***.[50,60]




***Scheme 2.58***

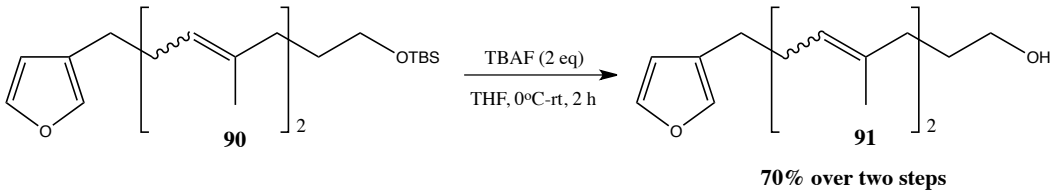
The Grignard reagent was prepared under standard conditions by reacting 3-furylmethyl bromide **14** with activated magnesium turning in distilled tetrahydrofuran at -10 $^{o}$C over a 5 hour period. In an attempt to minimise the formation of the Wurtz coupling product **32**, slow dropwise addition of the bromide **14** over a two hour period to a large excess of magnesium (10 equivalents), which had been activated by the entrainment method was implemented.[63] The Grignard reagent was subsequently added at 0 $^{o}$C to a stirring mixture of the acetate **89** and dilithium tetrachlorocuprate (II) solution (10 mol%) in tetrahydrofuran (***Scheme 2.58***). Following an 18 hour stir at room temperature and workup, $^{1}$H NMR analysis of the crude product indicated that the reaction proceeded smoothly to furnish a two component mixture consisting of the desired furanolipid **90** in conjunction with the Wurtz coupled product, 1,2-di-3-furylethane **32** in a 85:15 ratio of products respectively. No trace of allylic acetate starting material **89** was evident in the spectrum confirming complete conversion to cross-coupled product **90**.

Disappointingly, flash chromatography in neat hexane resulted in minor co-elution with 1,2-di-3-furylethane **32** (matching $R_f$ values). Due to minor difficulty in separation of the Wurtz coupling product **32**, the mixture (<5% Wurtz product **32**) was used in the next transformation without further purification.

The furanolipid **90** is a known compound, although no spectroscopic data is available in the literature.[138] $^1$H NMR analysis confirmed the synthesis of furanolipid **90** with the appearance of a 2H triplet at $\delta_H$ 2.45 ppm [*J* 7.6, C(5)$H_2$] and a 2H quartet at $\delta_H$ 2.24 ppm [*J* 7.3, C(6)$H_2$] assigned to the methylene protons alpha and beta to the furan ring respectively. Collectively, $^{13}$C NMR and IR analysis supported the elimination of the acetate ester functionality with the disappearance of the carbonyl peak at $\delta_C$ 171.1 ppm and $\nu_{max}$ 1743 cm$^{-1}$ respectively.

### 2.3.10 Preparation of the furanolipid Grignard precursor

Having successfully appendaged the furan moiety and accessed the desired furanolipid skeleton, the next important step involved unmasking of the hydroxyl functionality by removal of the silyl ether protecting group. Tetra-*n*-butylammonium fluoride (TBAF) was employed and added to a stirring solution of the furanolipid silyl ether **90** in tetrahydrofuran at 0 $^o$C followed by a two hour stir at room temperature (***Scheme 2.59***).

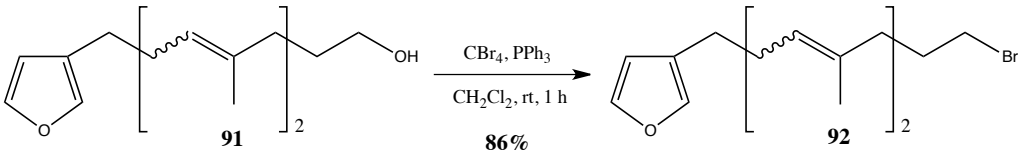



***Scheme 2.59***

Purification by column chromatography provided the furanolipid alcohol **91** as a colourless oil in 70% yield, which was calculated from the theoretical over two steps [Schlosser cross coupling (***Scheme 2.58***) and desilylation (***Scheme 2.59***)]. At this stage, following successful deprotection and the resulting change in the $R_f$ value for the furanolipid alcohol **91**, complete removal of the Wurtz coupled product **32** was achieved without any difficulty.

Takabe *et al.* previously prepared compound **91**,[138] although no spectroscopic data was available in the literature. To clarify the unmasking of the hydroxyl functionality, $^1$H NMR analysis displayed a downfield shift of the α-methylene protons [C(15)$H_2$] adjacent to the hydroxyl functionality from a 2H triplet at $\delta_H$ 3.58 ppm (*J* 6.6) in **90** to a 2H triplet at $\delta_H$ 3.62 ppm (*J* 6.4). A broad OH stretch at $\nu_{max}$ 3339 cm$^{-1}$ was also evident in the IR spectrum succeeding the disappearance of the characteristic silicon absorption stretches. It should be noted that cleavage of the OTBS group was also performed using aqueous hydrochloric acid solution (1M) as an alternative to TBAF. However from experience it was concluded that TBAF provided the alcohol **91** in a more reliable, higher yielding and faster reaction.

Synthesis of the furanolipid alcohol **91** marked a significant milestone in the overall scope of the project. Having successfully constructed the furanolipid backbone by coupling the furan moiety with **subunit B** (central difunctional linchpin), the next impending step was to convert the furanolipid alcohol **91** to its corresponding bromide **92**. This was successfully accomplished following treatment of the furanolipid alcohol **91** with carbon tetrabromide and triphenylphosphine in distilled dichloromethane while observing standard Appel protocol (***Scheme 2.60***).[139,140]




***Scheme 2.60***

The progress of the reaction was monitored by thin layer chromatography, and after one hour the reaction was quenched, worked up and the residue was purified by column chromatography on silica gel to afford the novel furanolipid bromide **92** as a faint yellow oil in 86% yield (***Scheme 2.60***). The bromide **92** was surprisingly stable, which on storage could be used when necessary without any sign of deterioration over a long period of time. It is worth noting that in this scenario, purification of the furanolipid bromide **92** by column chromatography was straightforward with separation of triphenylphosphine oxide and

bromoform from the product **92**. Despite Takabe *et al.* previously synthesising compound **92**, no spectroscopic data was once again available in the literature.[138] As anticipated, addition of the electron-withdrawing group reduced the electron density at neighbouring hydrogens [C(15)$H_2$] causing a chemical shift to appear in the $^1$H NMR spectrum of the furanolipid bromide **92** at a relatively low field from a 2H triplet at $\delta_H$ 3.62 ppm (*J* 6.4) in **91** to a 2H triplet at $\delta_H$ 3.36 ppm (*J* 6.0) in **92** (***Figure 2.14***). Further evidence was provided by IR analysis with the disappearance of the broad OH absorption peak at $\nu_{max}$ 3339 cm$^{-1}$. All other spectroscopic characteristics were as expected and the furanolipid bromide **92** was used accordingly in the ensuing Grignard cross coupling reaction.

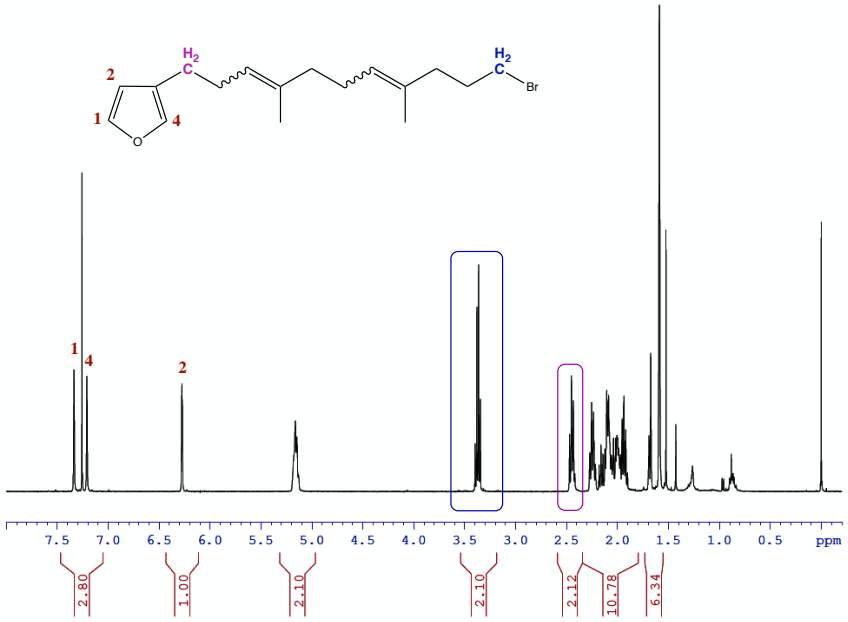
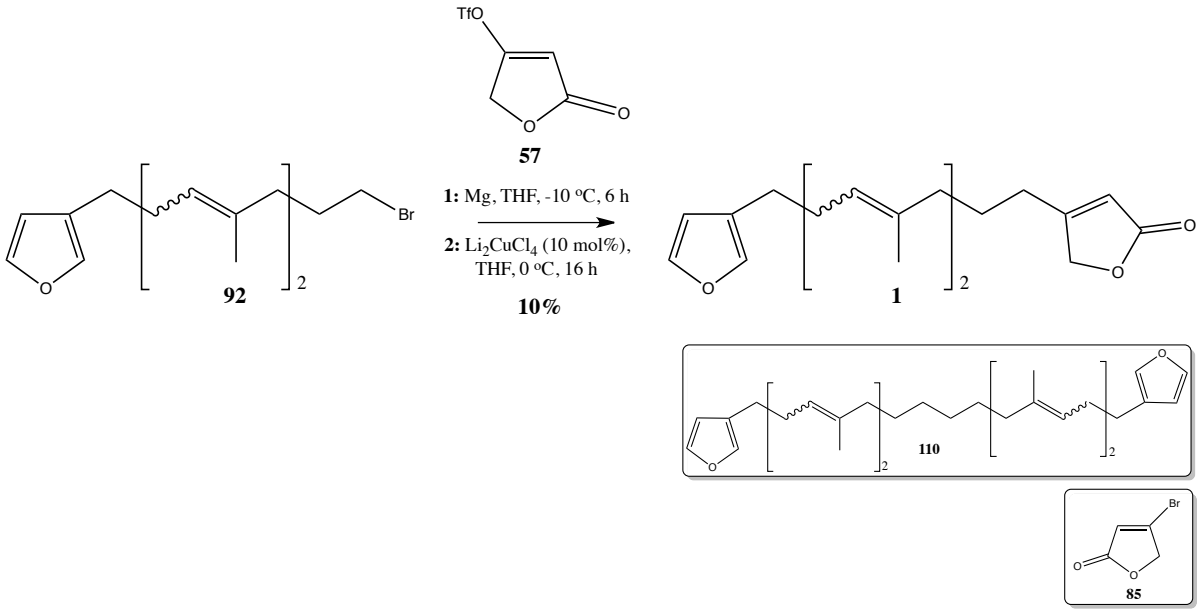



***Figure 2.14:*** *$^1$H NMR spectrum of furanolipid bromide* ***92*** *(CDCl$_3$, 300MHz).*

### 2.3.11 Synthesis of furospongolide (conjugate addition/elimination)

The last phase in the 8 linear step synthesis of furospongolide **1** from commercially available farnesyl acetate **59** involved an $C(sp^3)$-$C(sp^2)$ cross coupling reaction to attach the butenolide moiety to the furanolipid backbone. It was envisaged that formation of this carbon-carbon bond linkage would be accomplished through a conjugate addition/elimination reaction involving the Grignard-derived cuprate of furanolipid bromide **92** with triflate tetronic acid **57** as shown in ***Scheme 2.61***.




***Scheme 2.61***

The Grignard reagent was prepared by addition of the furanolipid bromide **92** onto activated magnesium turning in freshly distilled tetrahydrofuran under inert atmosphere at -10 $^oC$. In an attempt to minimise the formation of the Wurtz coupling product **110**, exceedingly slow and rigorous dropwise addition of the bromide **92** over a two hour period to a 10 fold excess of freshly ground and activated magnesium powder was employed. Thin layer chromatography indicated complete consumption of the bromide starting material **92** after a 6 hour reaction period at -10 $^oC$. Due to its practical benefits previously described in ***Section 2.3.2.4***, dilithiumtetracuprate (II) solution ($Li_2CuCl_4$) was employed as the catalyst for the cross coupling reaction. Following standard protocol,[28,132] the freshly prepared Grignard reagent was added dropwise to a stirring solution of **57** and dilithiumtetracuprate (II) solution (10 mol%) in distilled tetrahydrofuran at 0 $^oC$. Formation of furospongolide **1** was evident

after 1 hour following thin layer chromatography. Nevertheless the reaction was left stirring at room temperature overnight to ensure complete conversion. Upon workup, analysis of the crude product revealed a 3 component mixture consisting of the Wurtz coupled product **110**, 4-bromofuran-2(5*H*)-one **85** and furospongolide **1** in a 7:4:1 ratio of products as determined by $^{1}$H NMR analysis. The crude residue was subsequently purified by column chromatography on silica gel to furnish furospongolide **1** as a colourless oil in 10% yield. Spectroscopic characteristics were consistent with those reported in the literature by Kashman *et al.* and Boukouvalas *et al.*[2,25] $^{1}$H NMR analysis confirmed the synthesis of furospongolide **1** with an upfield shift of the α-vinylic proton of **57** from a 1H triplet at $\delta_H$ 6.06 ppm (*J* 1.8) to a 1H multiplet at $\delta_H$ 5.81-5.88 ppm in **1**. Likewise, an upfield shift was also observed for the 2H doublet at $\delta_H$ 4.90 ppm in **57** to a 2H multiplet at $\delta_H$ 4.70-4.76 ppm in **1** allocated to the γ-methylene protons of the butenolide ring. The most remarkable shift observed was for the methylene protons adjacent to the butenolide [C(15)$H_2$] from a 2H triplet at $\delta_H$ 3.36 ppm (*J* 6.0) in **92** to a 2H multiplet at $\delta_H$ 1.64-1.75 ppm in **1**, essentially confirming successful attachment of the butenolide. Similarly, a chemical shift was observed at C15 from $\delta_C$ 33.4 ppm to $\delta_C$ 25.2 ppm in the $^{13}$C NMR spectrum. Further evidence was also obtained from IR spectroscopy with the appearance of distinctive α,β-unsaturated carbonyl stretching frequencies at $\nu_{max}$ 1780 cm$^{-1}$ and $\nu_{max}$ 1748 cm$^{-1}$ (***Figure 2.15***). Furospongolide **1** was found to contain 47% of the (*E*,*E*)-isomer, 43% of the (*Z*,*E*)-isomer and 10% other(s) as determined by HPLC analysis (***Appendix V***).

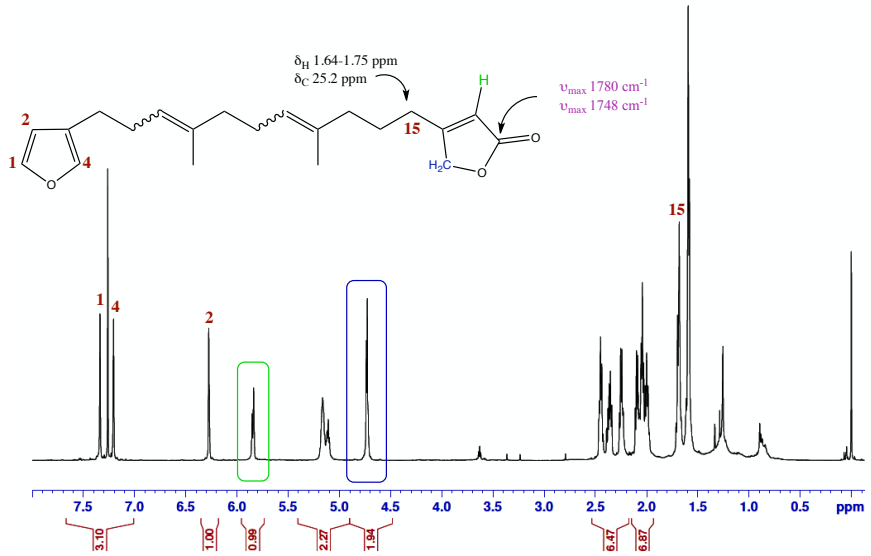



***Figure 2.15:*** *$^1$H NMR spectrum of furospongolide* ***1*** *($CDCl_3$, 600MHz) including other characteristic spectroscopic data.*

The most polar fraction isolated following flash chromatography was 4-bromofuran-2(5*H*)-one **85** as a white crystalline solid with spectroscopic characteristics consistent with those previously reported.[127] It became apparent following spectroscopic analysis that uncontrolled Wurtz coupling had taken place and only a minor amount of the desired Grignard-derived cuprate of furanolipid bromide **92** successfully coupled with the vinyl triflate **57**. Despite using a 2 equivalent excess of the Grignard reagent over the substrate, a large quota of the vinyl triflate **57** was left unreacted and was subsequently converted to its corresponding bromide **85** *in-situ* through a Finkelstein type halide exchange reaction as previously discussed in ***Section 2.3.7***.

The least polar fraction following flash chromatography was the Wurtz coupled dimer **110**, which was isolated as a non-viscous colourless oil. Dimerization was confirmed by $^1$H NMR analysis with the appearance of a 4H multiplet at $\delta_H$ 1.20-1.34 ppm [C(14)$H_2$] and $\delta_H$ 1.34-1.46 ppm [C(15)$H_2$] associated with the methylene hydrogens alpha and beta to the newly formed C-C bond respectively (***Figure 2.16***). With respect to the latter, theoretically a quintet should be observed at C(15)$H_2$ due to symmetrical nature of the molecule at this position,

however accurate assignment was not possible due to complications for the other stereoisomer(s). Concurrently, a low frequency chemical shift was also observed in the $^{13}C$ NMR spectrum from $\delta_C$ 30.9 ppm and $\delta_C$ 33.4 ppm in the bromide **92** to $\delta_C$ 20.0 ppm and $\delta_C$ 20.2 ppm in **110** associated with C(14) and C(15) respectively.

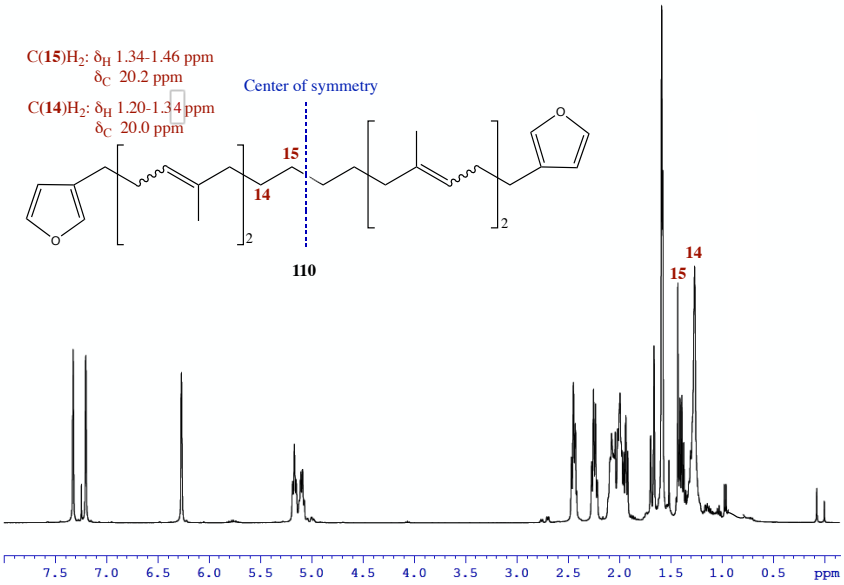
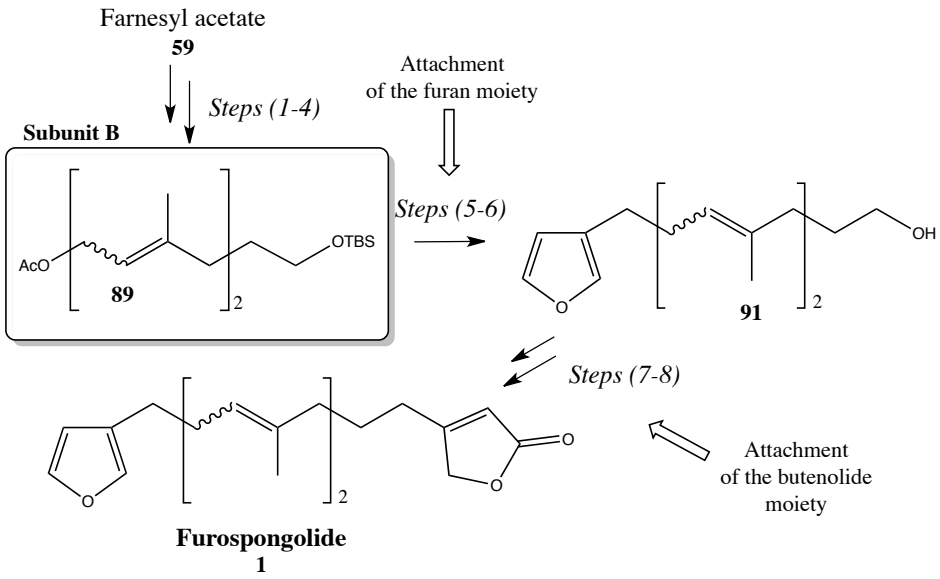



***Figure 2.16:*** *$^1H$ NMR spectrum of the Wurtz dimer **110** ($CDCl_3$, 300MHz) including other characteristic spectroscopic data.*

To summarise, synthesis of furospongolide **1** through the second-generation route involved 8 linear steps from commercially available farnesyl acetate **59** in an overall yield of 2%. Disappointingly, the last step in our linear route was considerably low yielding. It was obvious at this stage that a more effective method for introducing the butenolide ring to the furanolipid backbane was required. Nevertheless, the overall yield for our synthetic route set a benchmark that will hopefully be exceeded with further optimisation and development of our 2$^{nd}$ generation route.

## 2.4 Synthesis of furospongolide (Optimising 2nd Generation)

In order to develop a more concise route towards our target molecule **1**, it is necessary to re-evaluate the synthetic methodology in the hope of shortening the number of synthetic steps and thereby increasing the overall synthetic yield (***Scheme 2.62***).

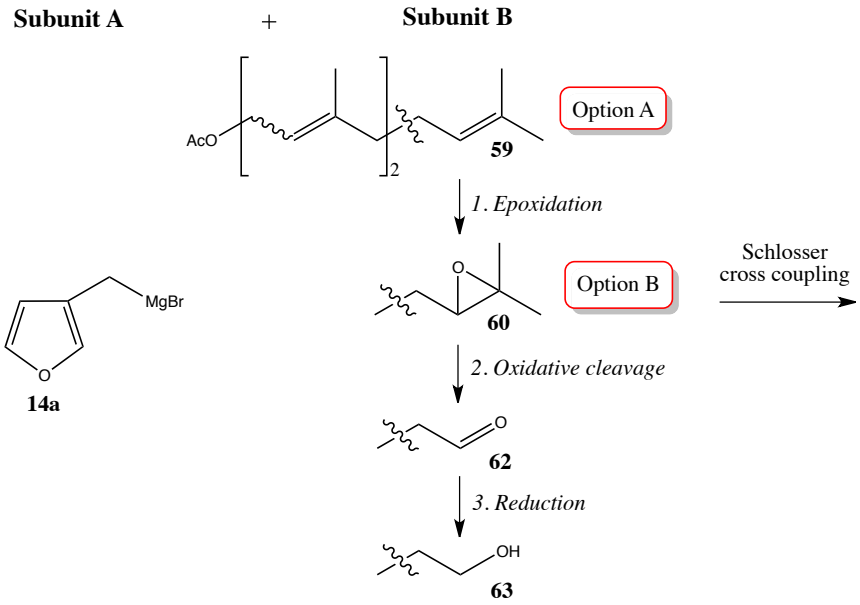



***Scheme 2.62:*** *Summary of 2nd generation synthesis of furospongolide **1** from farnesyl acetate **59** highlighting the protection and subsequent deprotection steps.*

Introduction of a protecting group adds additional steps to a synthetic scheme. Hence one should strive to keep the use of protecting groups to a minimum and avoid them if possible. With respect to our synthetic route, avoiding protecting group chemistry would remove two synthetic steps and improve the overall yield of our linear route (***Scheme 2.62, Steps 4 and 6***). This is only hypothetically achievable if assembly of the target molecule (**1)** is not drastically changed to facilitate this concept. In our case, protecting group chemistry was introduced to mask the hydroxyl group after selectively functionalising the terminal end of farnesyl acetate **59** in 3 steps (***Scheme 2.62, Step 4***). Otherwise known as **subunit B**, difunctional compound **89** was an aptly stable substrate for the Grignard cross coupling reaction. The protecting group was subsequently removed to furnish the furanolipid alcohol **91**, which was transformed in two linear steps to furospongolide **1** (***Scheme 2.62, Steps 7-8***). The immediate

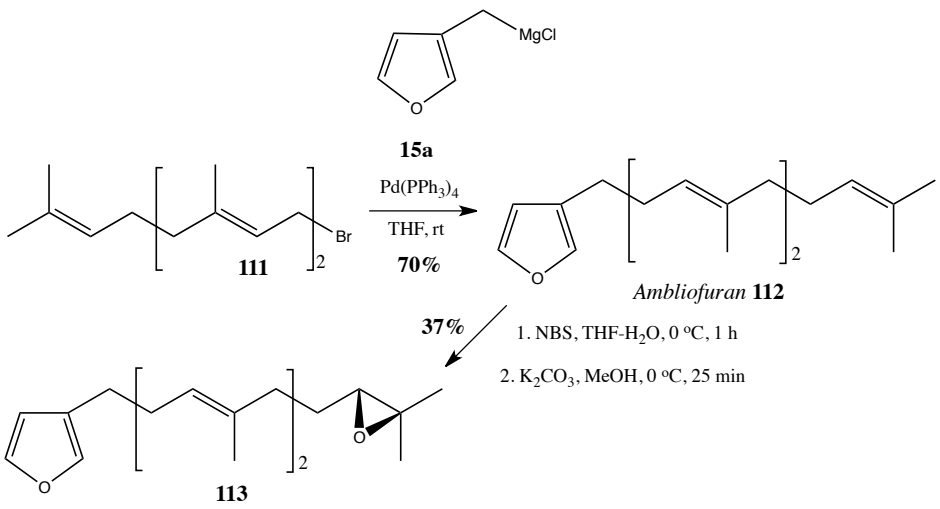
challenge was to identify if protecting group chemistry was essential to our synthetic strategy and if not, at what point would attachment of the furan ring to the lipophilic backbone be feasible.

Returning back to the linear synthetic strategy, the most obvious step to introduce the furan ring at first glance was option A (***Scheme 2.63***). Attachment of the furan moiety to farnesyl acetate **59** looked appealing, as nucleophilic substitution by the Grignard reagent was restricted to the allylic position thus avoiding the need for protecting group chemistry. On consideration of option A as a hypothetical approach towards synthesising furospongolide **1** in 6 linear steps, two problems were uncovered from literature research. The first problem was minor enough and was the basis for why attachment of the furan was carried out on protected **subunit B 89**. A good converging synthesis is one where two or more fragments are prepared separately and joined at the latest possible stage of the synthetic strategy. One would strive to design a synthetic route where ease in synthesis, product turnover and cost are all addressed. Despite being a commercially available compound, 3-furoic acid **3**, which is the precursor component of **subunit A 14** is not cheap and coupling it at such an early stage is not financially recommended.




***Scheme 2.63*** *Deciding at what point in the linear route to attach the furan moiety (**subunit A**) to the lipophilic linker unit (**subunit B**) via the Schlosser $sp^3$-$sp^3$ cross coupling reaction.*

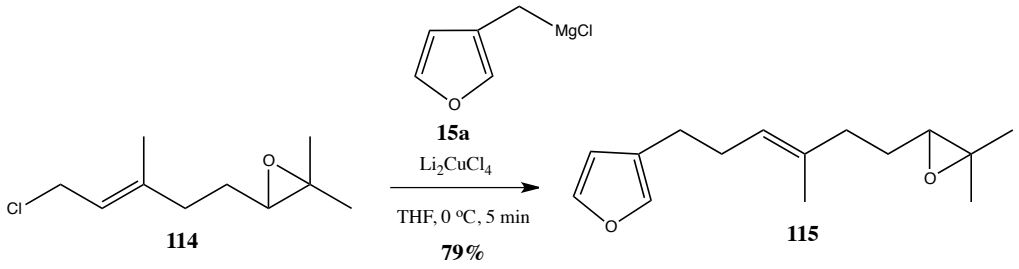
The main reason for avoiding option A for attachment of the furan ring is due to the apparent instability of ambliofuran **112** to the selective oxidation reaction in our synthetic route. According to the work of Zhao *et al.* synthesis of epoxide **113** from ambliofuran **112** resulted in a relatively poor yield of **113** (37%) due to the susceptibility of the furyl nucleus to oxidation as a competing reaction (***Scheme 2.64***).[87,141-143]




***Scheme 2.64:*** *Zhao et al. methodology for the synthesis of 3-furyl olefin* ***112*** *and epoxide* ***113****.*[144]

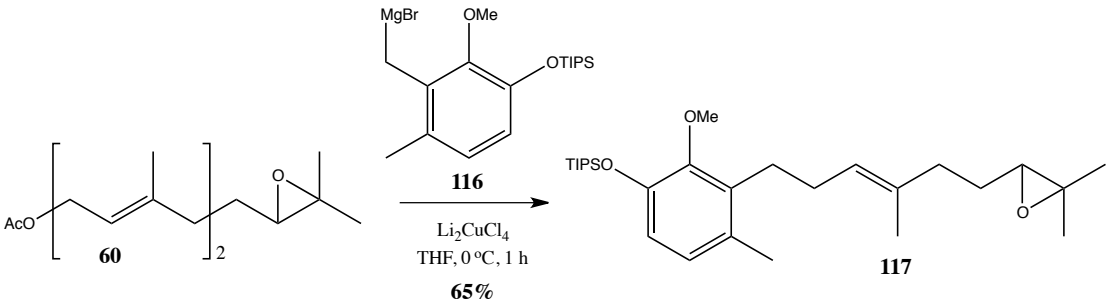
### 2.4.1 Synthesis of furanolipid epoxide

The next point of access for attachment of the furan to the lipophilic chain was at (+/-)-10,11-epoxyfarnesyl acetate **60** (***Scheme 2.63, option B***). One serious point of concern was immediately apparent. In contrast to farnesyl acetate **59**, (+/-)-10,11-epoxyfarnesyl acetate **60** has two possible sites for attack. It is well documented in the literature that epoxides can react with cuprates prepared from Grignard reagents or organolithium compounds through ring opening via nucleophilic substitution.[145-148] Thus, the crucial question of the chemoselectivity of allylic substitution versus epoxide ring opening has to be addressed. A promising report by Tanis *et al.* illustrated that a 3-furyl Grignard reagent **15a** in the presence of $Li_2CuCl_4$ reacted with high selectivity towards the allylic site of a halo epoxide **114**, furnishing 7,8-epoxydendrolasin **115** in high yield with no trace of epoxide cleavage (***Scheme 2.65***).[24,149]



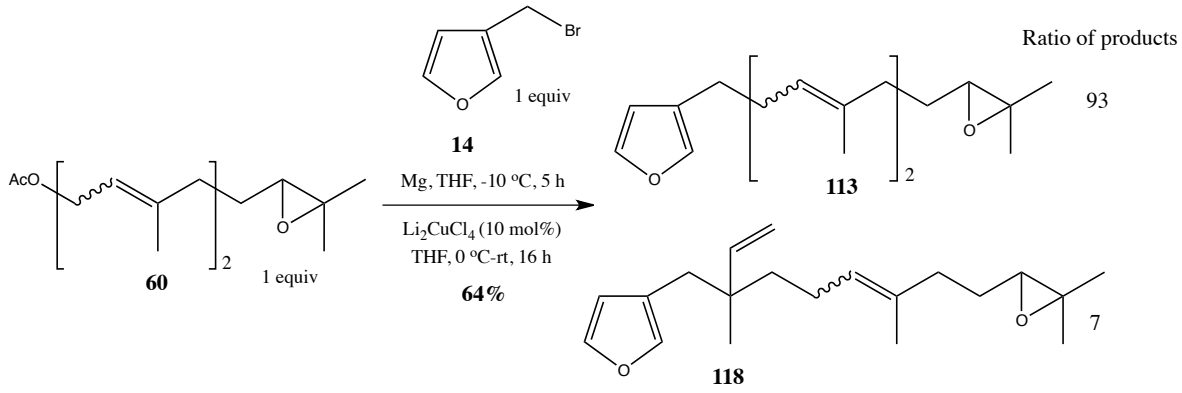

***Scheme 2.65***

Further evidence was provided by E. J. Corey's research group in the synthesis of Lupeol,[150] where our exact substrate farnesyl acetate epoxide **60** underwent position-selective copper promoted coupling with a Grignard reagent **116** to form cleanly the primary-primary coupled product **117** with no undesired attack at the epoxide as illustrated in ***Scheme 2.66***.




***Scheme 2.66***

Taking these findings into consideration it was concluded that option B was the most appropriate access point for attaching the furan moiety to the lipophilic interlinking chain. Following the procedure described for a related compound by Tanis *et al.*,[24] 3-furylmethyl magnesium bromide **14a** (1 equivalent) was reacted with 1 equivalent of the acetate **60** under Schlosser conditions in the presence of Kochi's catalyst ($Li_2CuCl_4$, 10 mol%) in tetrahydrofuran at 0 °C as summarised in ***Scheme 2.67***.[50]



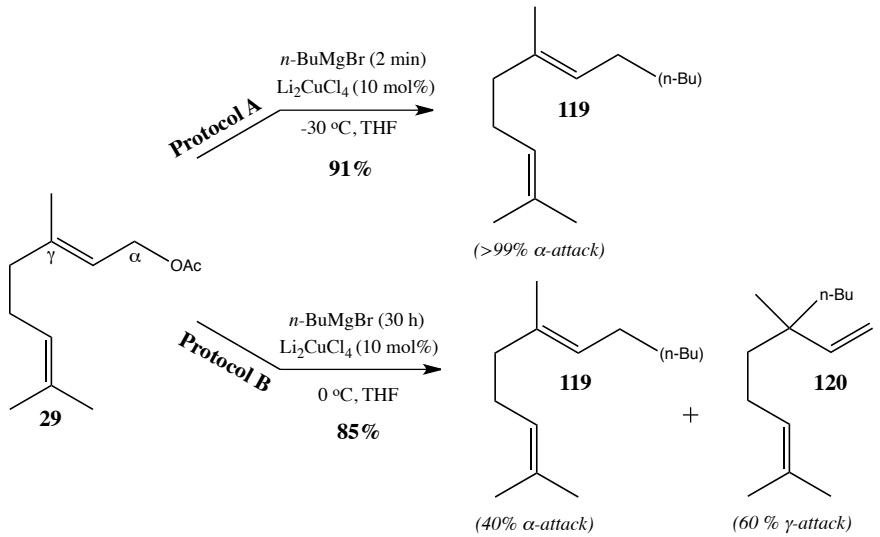

***Scheme 2.67***

Upon workup, $^1$H NMR spectroscopy of the crude product revealed a four component mixture consisting of desired cross coupled product **113**, its corresponding regioisomer **118**, the Wurtz coupled product **32**, and unreacted starting material **60**. As expected, the copper-catalyzed Grignard reagent reacted exclusively at the allylic acetate with no undesired attack at the epoxide functionality following analysis. Purification of the crude mixture by column

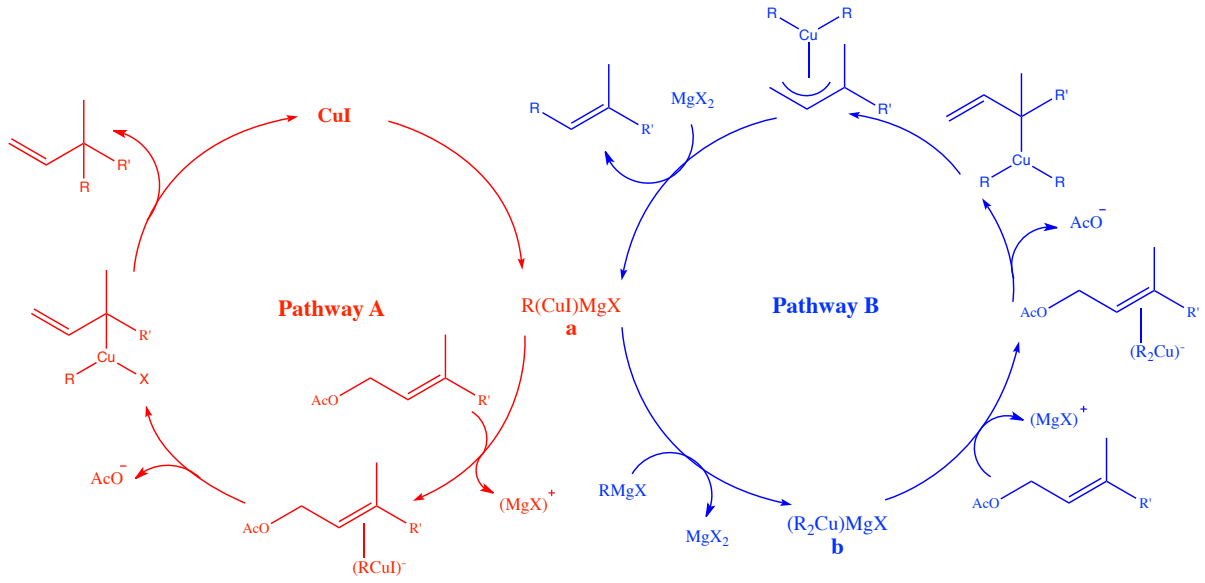
chromatography on silica gel afforded an inseparable two-component mixture consisting of desired cross-coupled product **113** and its corresponding regioisomer **118** as a colourless oil in 64% yield. $^{1}$H NMR integration revealed a 93:7 ratio of the α-substituted **113** to the γ-substituted product **118**. The yield for this reaction was determined based on the consumption of acetate **60**. The weight of unreacted acetate **60** isolated by column chromatography was determined and subtracted from the initial weight of acetate **60** charged at the beginning of the reaction. This resulted in a change to the theoretical yield value. This method of yield determination has been previously reported in the literature.[28] This protocol was employed in order to avoid undesired attack of the Grignard reagent at the epoxide site in the final product and to ultimately determine the most accurate yield for the reaction. Recovered acetate ester **60** was re-used in the next Schlosser coupling reaction.

The formation of the regioisomer **118** was an unanticipated result and the reason for the occurrence of **118** was due to a large excess of catalyst used in the reaction (>10 mol% $Li_2CuCl_4$). Backvall *et al.* demonstrated that the regiochemistry of $Li_2CuCl_4$-catalysed Grignard reactions with primary allylic acetates can be controlled and depends on three important factors.[49] With respect to ***Scheme 2.68A***, in order to favour regioselective α-substitution (**119)**, (1) *fast addition of the Grignard reagent*, (2) *low reaction temperature and* (3) *low concentration of the catalyst* is necessary (***Protocol A***). Conditions that favour γ-substitution (**120)** are the exact opposite and include (1) *slow addition of the Grignard reagent,* (2) *increased reaction temperature and* (3) *high concentration of the catalyst* (***Protocol B)***.

***A***




***B***




***Scheme 2.68A:*** *Studies preformed by Backvall et al. into controlling the regiochemisty of copper-catalysed reactions between Grignard reagents and allylic substrates.*[49] ***Scheme 2.68B:*** *A likely mechanism for the dual regiocontrol in the $Li_2CuCl_4$-catalysed Grignard reaction with an allylic acetate. Both mechanistic pathways are directly influenced by the concentration of copper catalyst employed.*[49]

The major factor controlling the regioselectivity of the allylic alkylation reaction is the concentration of catalyst. According to the mechanism proposed by Backvall *et al.*, when high concentrations of copper catalyst are employed, this favours the formation of the monoalkylcopper species ***a*** **(*Scheme 2.68B*)**. If this species predominates, then the reaction mechanism will follow ***Pathway A*** resulting in the formation of the γ-isomer. ***Pathway B*** occurs when a higher concentration of Grignard reagent is employed. This results in the formation of the dialkylcopper species **b**, which ultimately favours the formation of the α-isomer **(*Scheme 2.68B, Pathway B*)**. Backvall and Goering *et al.* have provided a more comprehensive insight into the mechanistic pathways controlling the regioselectivity of $Li_2CuCl_4$-catalysed Grignard reactions.[49,51,52]

$^1$H NMR analysis was consistent with literature findings for the synthesis of 3-furyl epoxide **113** with the appearance of a 2H triplet at $\delta_H$ 2.45 ppm [*J* 7.5, C(5)$H_2$] and a 2H quartet at $\delta_H$ 2.24 ppm [*J* 7.3, C(6)$H_2$] characteristic of the methylene protons alpha and beta to furan ring.[144] Further evidence was provided by IR spectroscopy with the disappearance of the distinctive carbonyl absorption stretch at $\nu_{max}$ 1738 cm$^{-1}$.

With respect to the regioisomer **118**, very distinct absorption patterns were observed in the $^1$H NMR spectrum succeeding the assembly of a vinyl functionality in compound **118**. Due to spin-spin splitting of the terminal alkenyl protons, an ABX system was revealed with a distinctive 1H doublet of doublets at $\delta_H$ 5.77 ppm associated with the vinylic C(16)*H* proton ($H_X$ of the ABX system, $J_{BX}$ 17.6, $J_{AX}$ 10.8). The signals for the terminal alkenyl C(17)$H_2$ protons were independently observed as doublet of doublets at $\delta_H$ 4.90 ppm (trans proton, $H_B$ of the ABX system, $J_{BX}$ 17.6, $J_{AB}$ 1.3) and $\delta_H$ 5.02 ppm (cis proton, $H_B$ of the ABX system, $J_{AX}$ 10.8, $J_{AB}$ 1.3) respectively and were easily identified by their unique vicinal coupling constants (***Figure 2.17***).

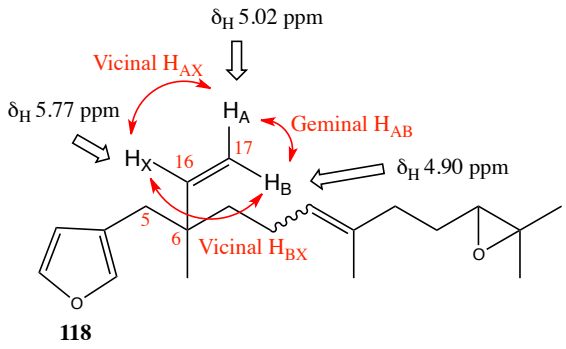
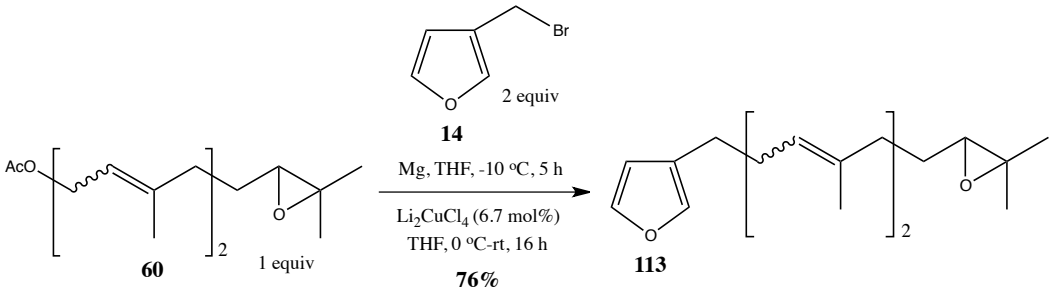



***Figure 2.17:*** *Characteristic spectroscopic patterns of the regioisomer* ***118****.*

In order to control the regioselectivity, the reaction conditions were manipulated slightly to favor exclusive formation of the α-substituted product **113**. From experience, only ~1/3 of bromide **14** is essentially converted to active Grignard reagent (i.e. limiting reagent). Bearing this in mind, the ideal concentration of copper catalyst to promote α-substitution was estimated to be 6.7 mol% of $Li_2CuCl_4$. The motive behind reducing catalytic loading was to essentially compensate for loss in active Grignard reagent due to uncontrolled Wurtz coupling. A similar protocol was employed by E. J. Corey's research group in the synthesis of Lupeol (***Scheme 2.66***).[150]

With respect to our work, 2 equivalents of the Grignard reagent prepared from 3-furylmethyl bromide **14** was reacted with 1 equivalent of the acetate epoxide **60** in the presence of $Li_2CuCl_4$ (6.7 mol%) under the standard conditions of the Schlosser cross coupling reaction as illustrated in ***Scheme 2.69***.[50]



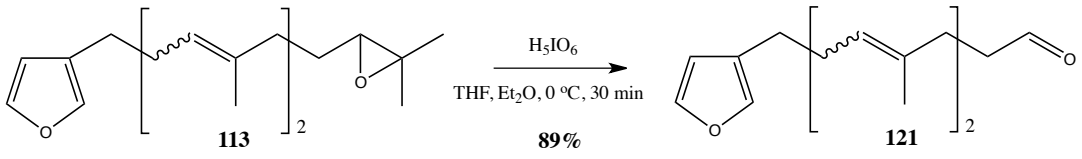

***Scheme 2.69***

Fortunately following workup, $^{1}H$ NMR analysis of the crude product confirmed the synthesis of 3-furyl epoxide **113** with no trace of the γ-substituted product **118** detected. Following purification by column chromatography, the desired furanolipid epoxide **113** was isolated as a colourless oil in 76% yield (based on consumed acetate **60**) without any product arising from epoxide ring opening and essentially as a single isomer. Spectroscopic characteristics were consistent with those previously reported by Zhao *et al*.[144]

The unreacted acetate epoxide **60** was subsequently isolated intact and recycled back into the next Schlosser cross coupling reaction. The optimised reaction conditions for the Schlosser cross coupling reaction offered a convenient, clean and high yielding method for the exclusive preparation of furanolipid epoxide **113** derivatives devoid of the γ-substituted product **118**. This methodology should be utilised in future for the synthesis of 3-furyl epoxyolefins and related structural analogues.

### 2.4.2 Synthesis of furanolipid aldehyde

The next step in the linear strategy was a periodic acid mediated oxidative cleavage reaction. Adhering to an established procedure previously described for a related compound by Labadie *et al.,*[88] the furanolipid aldehyde **121** was successfully synthesised following treatment of the epoxide **113** with periodic acid at 0 $^{o}C$ under inert nitrogen atmosphere over a 30 minute reaction period (***Scheme 2.70***).



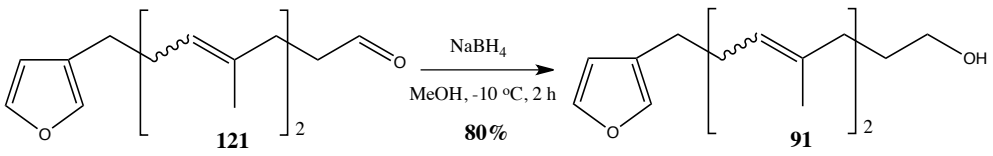

***Scheme 2.70***

From experience, it was established that in order to achieve clean, high yielding cleavage of the epoxide **113** to its corresponding aldehyde **121**, the epoxide **113** needs to be dissolved in diethyl ether as opposed to tetrahydrofuran and added rapidly to a pre-cooled and vigorously

stirring solution of the periodic acid dissolved in tetrahydrofuran. Purification by column chromatography furnished the novel furanolipid aldehyde **121** as a colourless oil in 89% yield. The $^{1}$H NMR spectrum of **121** was as expected revealing the disappearance of the 1H triplet at $\delta_H$ 2.70 ppm [*J* 6.3, C(15)*H*] associated with the oxirane proton and the appearance of a distinctive 1H triplet at $\delta_H$ 9.74 ppm [*J* 1.9, C(15)HO] characteristic of proton adjacent to the aldehyde. The $^{13}$C NMR spectrum showed a high frequency chemical shift at C(15) from $\delta_C$ 64.2 ppm to $\delta_C$ 202.8 ppm following functional group transformation. IR analysis was also consistent with the presence of a strong carbonyl absorption stretch at $\nu_{max}$ 1727 cm$^{-1}$. $^{1}$H NMR integration revealed a 70:30 mixture of the *E,E* and other isomer(s) following integration of the peaks at $\delta_H$ 9.74 ppm and $\delta_H$ 9.78 ppm respectively. Noteworthy, aldehyde **121** became a very important intermediate for the preparation of a number of furanolipid analogues for biological testing, which will be addressed in detail in a later section.

### 2.4.3 Synthesis of furanolipid alcohol

The furanolipid aldehyde **121** was subsequently reduced to its corresponding alcohol **91** following treatment with sodium borohydride in methanol at -10 $^{o}$C over a 2 hour reaction period (***Scheme 2.71***).[88]




***Scheme 2.71***

Upon workup and purification by column chromatography, the desired furanolipid alcohol **91** was isolated as a colourless oil in 80% yield. $^{1}$H NMR spectroscopy confirmed the synthesis of **91** with the disappearance of the distinctive 1H triplet at $\delta_H$ 9.74 ppm and the appearance of the 2H triplet at $\delta_H$ 3.62 ppm (*J* 6.4) corresponding to the protons adjacent to the hydroxyl group of the furanolipid alcohol **91**. Further evidence was provided by IR spectroscopy with

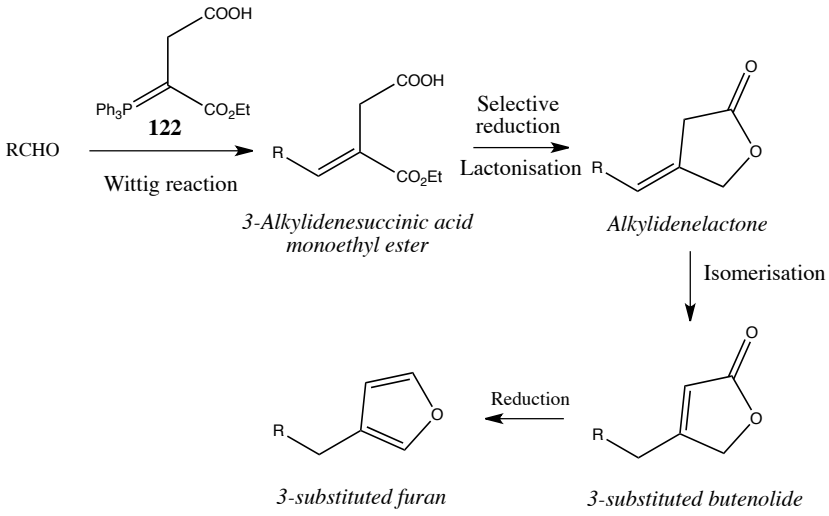
the disappearance of the distinctive carbonyl absorption peak at $\nu_{max}$ 1727 $cm^{-1}$ and appearance of strong absorptions stretch at $\nu_{max}$ 3339 $cm^{-1}$ associated with the alcohol (*OH*). Clean conversion to furanolipid alcohol **91** was achieved using a mild selective nucleophilic reducing reagent like sodium borohydride in this scenario. Attachment of the furan ring prior to the reduction reaction is a necessary step in order to avoid unnecessary protecting group chemistry due to the inherent instability of the acetate ester during borohydride reduction as previously discussed in ***Section 2.3.4.4***. The alcohol **91** can be later converted to its corresponding bromide **92** as the Grignard precursor for the conjugate addition/elimination reaction with triflate tetronic acid **57** as previously illustrated in ***Scheme 2.60*** and ***Scheme 2.61*** respectively.

Fortunately, 2nd generation synthesis allowed for complete removal of protecting group chemistry without drastic manipulation of the linear route. To summarise, following optimisation of 2nd generation synthesis of furospongolide **1**, a more concise synthetic route has been developed involving six linear steps from farnesyl acetate **59** in 3% overall yield.

Despite successfully removing two synthetic steps from our linear route, further optimisation was still required especially with respect to the final step, which was the Grignard cross coupling reaction. It was paramount that a more comprehensive and efficient method for attaching the butenolide to the furanolipid backbone was introduced.

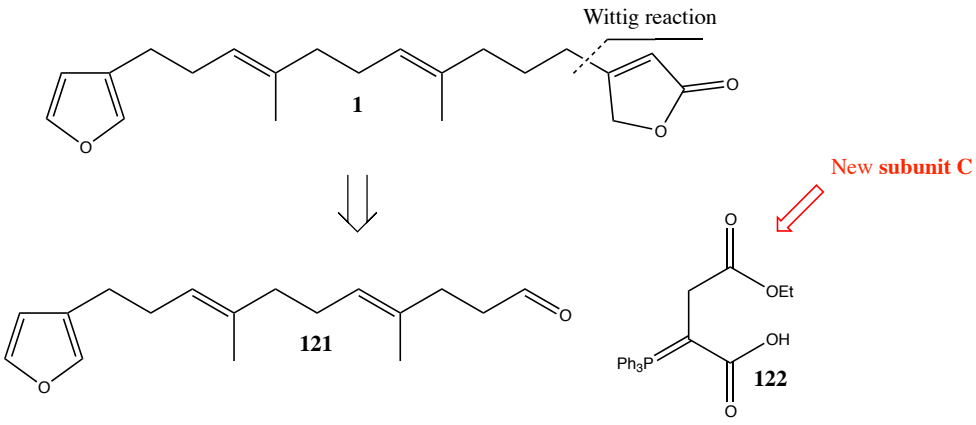
## 2.5 Concise synthesis of furospongolide (2nd Generation)

In 1977, McMurry *et al.* developed an elegant and novel method for the preparation of 3-substituted butenolides and 3-substituted furans in organic synthesis.[151] A generalised schematic of the synthetic pathway is shown below in ***Scheme 2.72***.




***Scheme 2.72:*** *Illustration of the linear pathway for the preparation of 3-substituted butenolides and 3-substituted furans from primary aldehydes as established by McMurry et al.*[151]

The reaction pathway ultimately hinged upon two chemical transformations to furnish the 3-substituted butenolide. The first of which was a Wittig reaction between ylide **122** and an aldehyde substrate to afford a 3-alkylidenesuccinic acid monoethyl ester. The second reaction involved selective reduction of the ester and subsequent lactonisation to afford the alkylidenelactone, which can be easily isomerised to the more stable butenolide. If desired, the butenolide can be conveniently reduced to its corresponding furan (***Scheme 2.72***). It was envisioned that this elegant methodology could be utilised to prepare furospongolide **1** from furanolipid aldehyde **121** as illustrated in ***Scheme 2.73***.

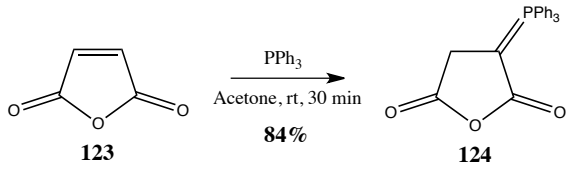



***Scheme 2.73:*** *2nd generation retrosynthesis revisited: Attachment of* ***subunit C*** *to the furanolipid backbone will now involve a Wittig reaction.*

Since the synthesis of aldehyde **121** has already been accomplished, attention was shifted towards the preparation of the ylide **122**.

### 2.5.1 Synthesis of subunit C (ylide)

Synthesis of the ylide **122** can be achieved in a high yielding two step synthetic route for commercially available maleic anhydride **123** following a procedure described for this compound by Hudson *et al*. The first step involves treatment of maleic anhydride **123** with triphenyl phosphine in an equimolar ratio at room temperature in dry acetone (***Scheme 2.74***).[152]

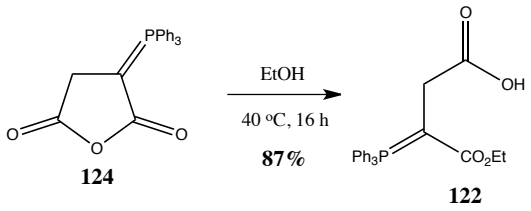



***Scheme 2.74***

The phosphorane began to precipitate almost immediately and the reaction had reached completion after 30 minutes as indicated by TLC analysis. Following isolation by suction filtration, the anhydride **124** was furnished as a pale yellow solid in 84% yield, which was consistent with literature findings.[153]

$^1$H NMR spectroscopy confirmed the synthesis of **124** with the disappearance of the distinctive 2H singlet associated with the two symmetrically equivalent vinylic protons in maleic anhydride and the appearance of a 15H multiplet at $\delta_H$ 7.48-7.72 ppm characteristic of the phenyl protons in tandem with a 2H singlet at $\delta_H$ 3.22 ppm characteristic of the C(4)$H_2$ protons. Likewise, IR spectroscopy was consistent with literature values showing characteristic ester carbonyl group absorptions in the IR spectrum at 1794 cm$^{-1}$ and 1711 cm$^{-1}$, which differ slightly in comparison to the anhydride starting material **123**. The melting point of **124** also matched reported literature data, having a range of 185-189 $^o$C (lit. mp 185-187 $^o$C). Its worth noting that 2-triphenylphosphoranylidenesuccinic anhydride **124** is a commercially available compound from Sigma Aldrich.

According to the work of Hudson *et al.*,[152] the desired monoethyl ester ylide **122** can be obtained by subjecting the anhydride **124** to an overnight stir in absolute ethanol at room temperature (***Scheme 2.75***).



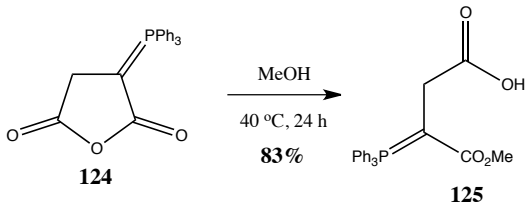

***Scheme 2.75***

In our hands however, these mild conditions were completely inadequate at inducing esterification of the anhydride **124** to the monoester **122** as indicated by $^1$H NMR analysis of the crude product showing only minor traces of the desired product **122** in a spectrum almost completely saturated with starting material **124**. The reaction mixture was resubmitted to the same conditions, however on this occasion heat was applied. After an overnight stir at 40 $^o$C, TLC analysis indicated that complete consumption of the anhydride **124** had occurred. Facile

workup and recrystallization from ethyl acetate provided the monoester **122** as an off-white granular solid in yields averaging 87% of the theoretical. It is worth noting that the monoethyl ester Wittig reagent **122** is thermally unstable and subjecting the anhydride **124** to refluxing temperatures (78 $^{o}$C) over prolonged periods resulted in a poor yield of the desired product **122**.[151,152]

$^{1}$H NMR analysis confirmed the formation of the desired product **122** with a shift upfield of the 2H singlet at $\delta_H$ 3.22 ppm to a 2H doublet at $\delta_H$ 2.91 ppm (*J* 14.5) associated with the methylene protons adjacent to the carboxylic acid. Interestingly, due to the anticlinal relationship between phosphorous at its neighboring methylene protons at C(3)$H_2$, a sharp doublet ($J_{P\text{-}H}$ 14.5) instead of a predicted singlet was observed in the $^{1}$H NMR spectrum.[154] A broad singlet at $\delta_H$ 9.30 (COO*H*), a sharp quartet at $\delta_H$ 3.87 ppm (*J* 7.1) and a triplet at $\delta_H$ 0.81 ppm (*J* 7.1) were also consistent with literature findings.[154] Further evidence was available from IR spectroscopy with the presence of a broad carboxylic acid O–H absorption band in the region of $\nu_{max}$ 3500-2500 cm$^{-1}$, centered at about $\nu_{max}$ 3000 cm$^{-1}$ and an ester carbonyl group absorptions at $\nu_{max}$ 1736 cm$^{-1}$ (C=O) and $\nu_{max}$ 1606 cm$^{-1}$ (CO). Similar to the anhydride, the $^{13}$C NMR spectrum of **122** was quite unique showing heteronuclear $^{13}$C-$^{31}$P coupling to three neighbouring carbons ($^{1}J_{CP}$ 84.0 to $^{3}J_{CP}$ 5.4). It should be noted that elemental analysis of **122** was outside acceptable limits. This ylide **122**, referred to more commonly in the literature as betaine,[152] was subsequently used in the ensuing condensation reaction with furanolipid aldehyde **121**.

Treatment of 2-triphenylphosphoranylidenesuccinic anhydride **124** with different alcohol substrates is a convenient and ideal way of producing monoester ylide derivatives. Equally, the monomethyl ester derivative **125** was synthesised following the reaction of anhydride **124** with dry methanol over a 24 hour period at 40 $^{o}$C while adhering to a procedure described for this compound by Doulut *et al.* (***Scheme 2.76***).[153]



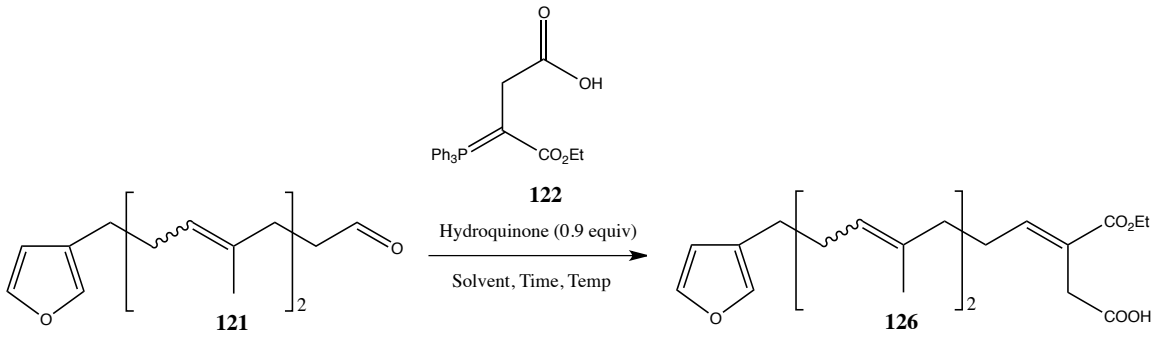

***Scheme 2.76***

Upon workup and recrystallization from ethyl acetate, the monomethyl ester **125** was furnished as a pale yellow granular solid in 83% yield. The $^{1}$H NMR spectrum of the monomethyl ester **125** was virtually identical to that of the monoethyl ester **122** except for the sharp 3H singlet associated with the methyl ester protons at $\delta_H$ 3.37 ppm. The melting point of **125** also matched reported literature data, having a range of 149-152 $^{o}$C (lit.[153] mp 150-152 $^{o}$C). Use of ylide **125** as a Wittig reagent will be discussed in a later section (***Scheme 2.108, page 248***). The ylide derivatives **122** and **125** were surprisingly stable and could be stored over long periods of time without any sign of deterioration.

### 2.5.2 Synthesis of 3-alkylidenesuccinic acid mono esters

As illustrated in ***Scheme 2.73,*** it was envisaged that attachment of **subunit C 122** to the furanolipid backbone would be achieved through a Wittig cross coupling reaction. Following a concept developed by McMurry *et al.,*[151] and a more contemporary procedure described by Serra *et al.*,[155] the synthesis of 3-alkylidenesuccinic acid monoethyl ester **126** was performed by treatment of furanolipid aldehyde **121** with 1.2 equivalents of the ylide **122** and 0.9 equivalents of hydroquinone sequentially in toluene at room temperature (***Table 2.12, Entry 1***).

***Table 2.12:*** *Optimising the reaction conditions of the Wittig reaction.*




| Entry | Time | Temp | Solvent | Ylide (eq) | Ratio 126:121 | Yield [a] |
|---|---|---|---|---|---|---|
| **1** | 70 h | rt-40 °C | Toluene | 1.2 | 70:30 | 43% |
| **2** | 70 h | 50 °C | Benzene | 2.4 | 95:5 | 63% |
| **3** | 70 h | rt | Toluene | 2.4 | 99:1 | 61% |
| **4** | 24 h | rt | Toluene | 2.4 | 99:1 | 66% |

***a*: Isolated yield following purification by column chromatography on silica gel (10-50% ethyl acetate in hexanes gradient).**

With respect to ***Entry 1***, TLC analysis after 24 hours revealed only minor conversion to the succinic acid monoethyl ester **126** had occurred. In order to increase the rate of conversion, the reaction was heated to 40 °C. Disappointingly after a 70 hour reaction period, $^{1}$H NMR analysis of the crude product revealed a 70:30 ratio of product **126** to starting material **121** respectively. Purification by column chromatography afforded the desired product **126** as a colourless oil in 43% yield (***Table 2.12, Entry 1***).

In the case of ***Entry 2***, benzene was substituted for toluene as the solvent for the reaction following promising reports from Paquette *et al.*[156] Benzene had also been the solvent of choice by McMurry *et al.* in his original studies towards the synthesis of 3-substituted butenolides.[151] The equivalents of ylide **122** were increased 2-fold (2.4 equivalents) in order to saturate the aldehyde **121** and encourage condensation. Following a 70 hour reaction at 50 °C, TLC analysis indicated almost complete conversion to the desired product **126**. Following workup, $^{1}$H NMR integration of the crude product revealed a 95:5 ratio of the half ester **126** and aldehyde **121** respectively. Purification by flash chromatography isolated the desired product **126** as colourless oil in 63% yield.

The optimum conditions for the condensation reaction can be seen in the case of ***Entry 3*** when the reaction was performed in toluene over 70 hours at room temperature. Under these mild conditions the desired product **126** was isolated following flash chromatography in 61% yield (***Table 2.12, Entry 3***). Interestingly, when the reaction was conducted on a larger scale, a slightly better result was obtained (***Entry 4***). In this scenario, the reaction time was reduced to 24 hours and the isolated yield of **126** was 66% following flash chromatography. Benzene therefore offered no real advantages over toluene and presents a considerably greater health risk. Disappointingly, the isolated yield was still moderate at 66% for the half ester **126** when compared to other research groups using similar conditions and reaction substrates.[151,155-157] Nevertheless, ***Entry 4*** encompasses the optimised reaction conditions for mild conversion of furanolipid aldehyde **121** to its corresponding half ester **126** in moderate yield and should be employed in future reactions of this type.

$^{1}$H NMR analysis confirmed the formation of **126** with a shift upfield of the 1H triplet at $\delta_H$ 9.74 ppm (*J* 1.9) to $\delta_H$ 6.97 ppm [*J* 7.4, C(15)*H*] associated with the newly formed vinyl proton adjacent to the half ester. A classic $A_3X_2$ splitting pattern was identified as a 2H quartet at $\delta_H$ 4.20 ppm (*J* 7.1) and a 3H triplet at $\delta_H$ 1.28 ppm (*J* 7.1) characteristic of the monoethyl ester functionality. The methylene protons adjacent to the carboxylic acid functionality were found to shift slightly downfield to a sharp 2H singlet at $\delta_H$ 3.38 ppm when compared to the 2H doublet at $\delta_H$ 2.91 ppm (*J* 14.5) in the ylide **122** (***Figure 2.18***). Further evidence was available from IR spectroscopy with disappearance of the aldehyde group stretch at $\nu_{max}$ 1727 cm$^{-1}$ and the appearance of a broad intense band peaking at $\nu_{max}$ 1714 cm$^{-1}$ incorporating the carboxylic acid and α,β-unsaturated ester. This was confirmed by $^{13}$C NMR spectroscopy with the appearance of signals at $\delta_C$ 176.9 ppm and $\delta_C$ 167.0 ppm associated with the carboxylic acid and α,β-unsaturated ester respectively (***Figure 2.18***). Please note that a $^{1}$H NMR spectrum of ester **126** can be seen in ***Figure 2.26, page 197***.

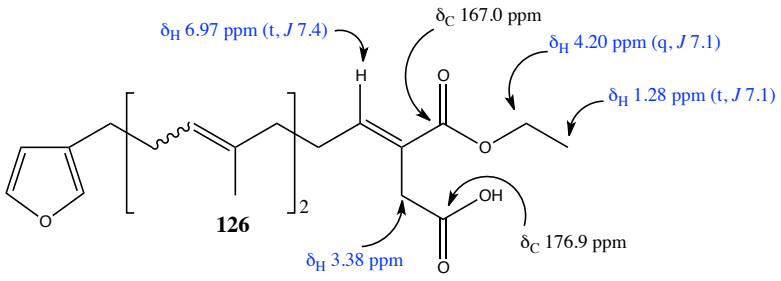
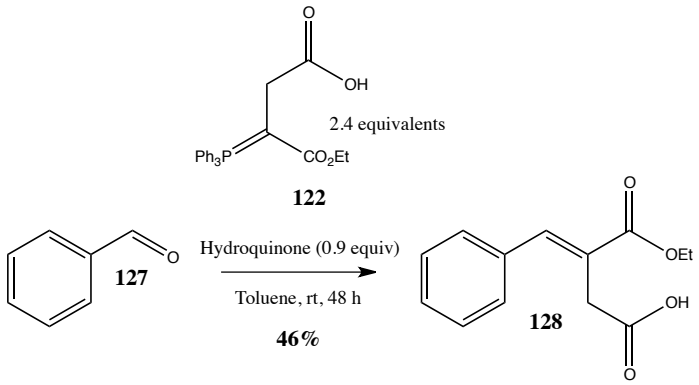



***Figure 2.18:*** *Characteristic spectroscopic data for furanolipid half ester* ***126****.*

According to the literature, an attractive feature for the use of this ylide **122** was the high stereoselective fashion in which 3-alkylidenesuccinic acid monoethyl esters are produced upon condensation with an aldehyde substrate.[156,157] With respect to the half ester **126,** the *E*-isomer has been assigned at the newly formed double bond following NOE studies. Similar to Roder *et al.*, the vinylic hydrogen atom was found to be invariably cis to the carbethoxy substituent.

For comparative purposes, 1-ethyl 4-hydrogen 2-benzylidenesuccinate **128** was prepared following treatment of commercially available benzaldehyde **127** with 2.4 equivalents of the ylide **122** and 0.9 equivalents of hydroquinone in dry toluene at room temperature while adhering to the optimised protocol for the Wittig reaction as aforementioned (***Scheme 2.77).***[158]




***Scheme 2.77***

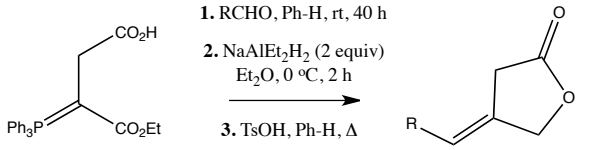
TLC analysis indicated complete conversion to the desired product **128** following a 48 hour reaction period. Purification by column chromatography on silica gel was quite laborious with minor co-elution occurring with triphenylphosphine oxide resulting in isolation of **128** as an off-white crystalline solid in a poor isolated yield of 46%. $^{1}$H NMR analysis was consistent with literature findings for the synthesis of the monoethyl ester **128** with a shift upfield of a 1H singlet at $\delta_H$ 10.02 ppm to $\delta_H$ 7.93 ppm [1H, s, C(5)*H*], associated with the newly formed vinyl proton adjacent to the half ester.[152,159] The methylene protons adjacent to the carboxylic acid functionality were shifted slightly downfield to a sharp 2H singlet at $\delta_H$ 3.59 ppm C(2)$H_2$ as expected while IR spectroscopy displayed the disappearance of aldehyde absorption peak at $\nu_{max}$ 1731 cm$^{-1}$ (C=O) and the appearance of the ester absorption stretch at $\nu_{max}$ 1709 cm$^{-1}$.

Following the successful synthesis of the furanolipid half ester **126** and the benzyl half ester **128** through the Wittig cross coupling reaction, synthetic efforts were now shifted to the selective reduction reaction. It is worth noting that the benzyl half ester **128** played an important role as a model substrate for optimization of the ensuing reduction reaction. The precious furanolipid half ester **126** was preserved and only used when the reaction conditions for the reduction reaction were successfully optimized and validated.

### 2.5.3 Synthesis of β-alkylidene-γ-lactones

As formerly discussed, the next step in the synthetic sequence involves selective reduction of the ester moiety in the presence of a carboxylic acid functionality to its corresponding allylic alcohol followed by subsequent lactonisation to the β-alkylidene-γ-lactone (***Scheme 2.72***). The methodology behind this transformation was developed by McMurry *et al.* where in a short communication,[151] it was stated how successful synthesis of β-alkylidene-γ-lactone analogues can be achieved in good yield (60-78%, over two steps) by employing a two fold excess of sodium diethyldihydroaluminate ($NaAlEt_2H_2$) in diethyl ether followed by a short reflux of the resultant hydroxy acid in benzene with a trace of *p*-toluenesulfonic acid to induce lactonisation (***Table 2.13***).

***Table 2.13:*** *Illustration of the results obtained by McMurry et al. in the synthesis of β-alkylidene-γ-lactone analogues from aldehydes.*[151]



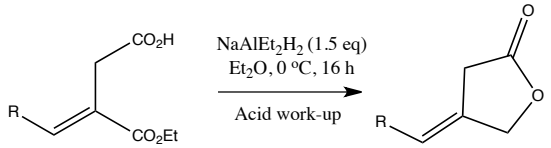

**122** **131-133**

| RCHO (SM) | % Yield [a] |
|---|---|
| $C_6H_5CHO$ **(127)** | 65 (**131**) |
| *n*-$C_6H_{13}CHO$ **(129)** | 78 (**132**) |
| $(CH_3)_2CCHCH_2CHO$ **(130)** | 60 (**133**) |

**a: Isolated yield following column chromatography on silica gel.**

There were two major shortcomings for employing sodium diethyldihydroaluminate in the selective reduction of an half ester substrate to its corresponding γ-hydroxy acid. To begin with, sodium diethyldihydroaluminate is not the most common reducing agent in use today due to its difficulty in handling and it is only commercially available as a 25 wt. % in toluene from selected commercial sources.[160,161] Lastly, on further review of the literature,[157] sodium diethyldihydroaluminate was not found to be as effective a reducing agent as McMurry had previously implied for the reduction of esters. In a report described by Roder *et al.,*[157] sodium diethyldihydroaluminate was employed in the synthesis of an extensive library of β-alkylidene-γ-lactones (***Table 2.14***).

***Table 2.14:*** *Illustration of the results obtained by Roder et al. in the synthesis of β-alkylidene-γ-lactone analogues from their corresponding half esters.*[157]



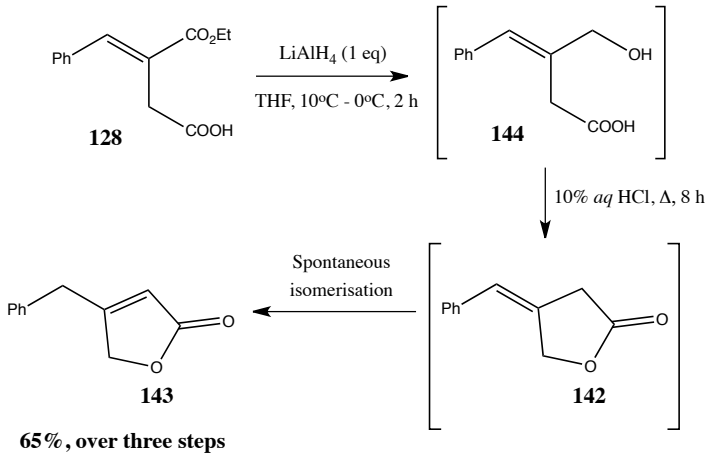

**134-137** **138-141**

| R | % Yield [a] |
|---|---|
| Me **(134)** | 37% **(138)** |
| Et **(135)** | 36% **(139)** |
| $Me(CH_2)_2CH_2$ **(136)** | 30% **(140)** |
| $Me(CH_2)_3CH_2$ **(137)** | 30% **(141)** |

**a: Isolated yield following column chromatography**

As shown in ***Table 2.14***, the yields recovered by Roder *et al.* for the selective reduction reaction and resultant acidic induced lactonisation were moderate at best and yields averaged between 30-37% for a variety of linear acyclic half ester substrates. In contrast to McMurry *et al.*, 1.5 equivalents of $NaAlEt_2H_2$ was used by Roder *et al.* and the reduction time was greatly increased to 16 hours in diethyl ether at 0 $^oC$. This protocol was implemented to avoid further reduction of the γ-hydroxy acid to its corresponding diol. On the back of these findings, the pursuit of a more appropriate reducing agent commenced.

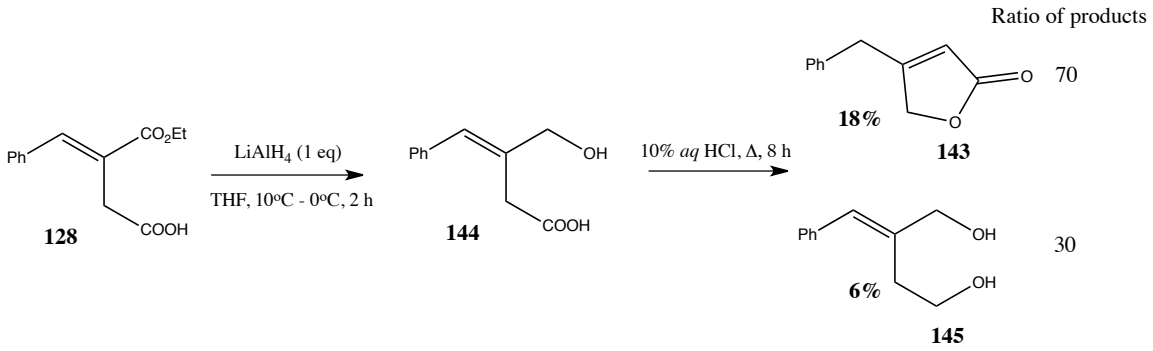
On further examination of the literature, an alternative procedure was reported for the chemoselective reduction of half esters. Muraoka *et al.* described the efficient and selective reduction of (*E*)-1-ethyl 4-hydrogen 2-benzylidenesuccinate **128** with lithium aluminium hydride. The γ-hydroxy acid **144** was subsequently converted to its corresponding benzyl butenolide **143** by the action of hydrochloric acid in 65% overall yield from starting material **128** (***Scheme 2.78***).[158] It should be noted, since the β-alkylidene-γ-lactone **142** has a benzylic proton at C(5)*H*, isomerisation to the more stable butenolide **144** occurs spontaneously. Normally, an addition step employing a base is required to induce this transformation.




***Scheme 2.78***

Lithium aluminium hydride ($LiAlH_4$) was a surprising choice of reagent as it usually imparts relatively low levels of chemoselectivity.[162] However with that said, $LiAlH_4$ has a strong affinity towards strong electrophiles and together with the use of only one equivalent of the hydride reducing agent may chemoselectively furnish the desired γ-hydroxy acid **144**.

In our hands, preliminary investigations involved repeating the above reaction conditions described by Muraoka *et al.* to become familiar with the reduction reaction procedure.[158] Reduction of **128** was performed using 1 equivalent of lithium aluminium hydride in diethyl ether at -10 °C to 0 °C over a two hour reaction period under inert atmosphere **(*Scheme 2.79*)**.




***Scheme 2.79***

Upon workup, spectroscopic analysis of the crude light yellow oil revealed a multipart mixture with the desired γ-hydroxy acid **144** identified as the major product. Due to the relative instability of the γ-hydroxy acid **144**, further purification by column chromatography was deemed inappropriate and the acid **144** was used in the next transformation without further purification. Despite **144** being a synthetically known compound in the literature,[158] this γ-hydroxy acid **144** was only described as an intermediate and no spectroscopic information was available for its characterisation. $^{1}$H NMR analysis indicated that the desired γ-hydroxy acid **144** was formed with a shift upfield of the 1H singlet at $\delta_H$ 7.93 ppm to $\delta_H$ 6.74 ppm associated with the vinylic proton at C(5)*H*. Further evidence could be seen with the disappearance of distinctive monoethyl ester peaks and the appearance of a 2H singlet at $\delta_H$ 4.30 ppm associated with the allylic methylene protons.

The last step involved an acid induced lactonisation reaction to convert γ-hydroxy acid **144** to its corresponding β-alkylidene-γ-lactones **142**. Spontaneous isomerisation of intermediate **142** to butenolide **143** can also be achieved through acid reflux (one-pot)**.** Following a procedure described for this compound by Muraoka *et al.*,[158] the crude γ-hydroxy acid intermediate **144** was dissolved in tetrahydrofuran and acidified to pH 2 by the action of 10% aqueous hydrochloric acid (***Scheme 2.79***).

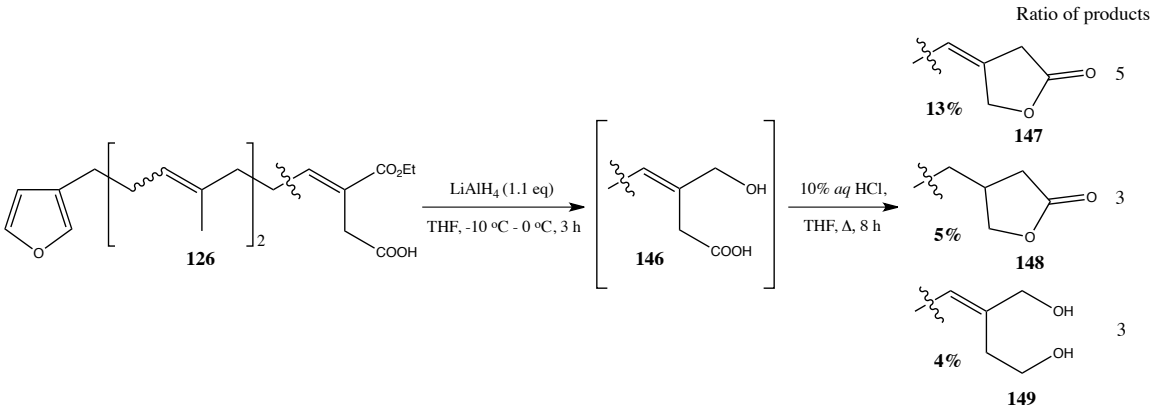
The progress of the reaction was monitored by TLC analysis and after 8 hours at reflux, the reaction was allowed to warm to room temperature. Upon workup, $^{1}$H NMR analysis of the crude product indicated a complex mixture consisting mainly of the desired benzyl butenolide **143** and it corresponding diol **145** in a 70:30 ratio of products respectively. The desired compound **143** was isolated following column chromatography on silica gel as a colourless oil in 18 % yield, calculated from the theoretical over three steps (***Scheme 2.79***).

Spectroscopic characteristics matched literature data for **143** with appearance of a 2H multiplet at $\delta_H$ 4.69-4.73 ppm and a 1H muliplet at $\delta_H$ 5.78-5.84 ppm associated with the γ-methylene hydrogens and the α-olefinic proton in the lactonic ring.[158] IR analysis was also consistent with three sharp and strong bands at $\nu_{max}$ 1782 cm$^{-1}$, $\nu_{max}$ 1748 cm$^{-1}$ and $\nu_{max}$ 1641 cm$^{-1}$, which are characteristic of a five membered α,β-unsaturated γ-lactone.

The most polar fraction isolated following column chromatography on silica gel was (*E*)-2-phenylmethylidene-1,4-butanediol **145** as a viscous yellow oil in 6% yield (***Scheme 2.79***). Spectroscopic characteristics matched those described in the literature with the presence of a 2H triplet at $\delta_H$ 3.81 ppm (*J* 5.9) and $\delta_H$ 2.62 ppm (*J* 5.9) associated with the methylene protons alpha and beta to the newly formed primary alcohol respectively.[163,164] IR analysis was also consistent with the disappearance of the strong and broad carboxylic acid stretching at $\nu_{max}$ 3500-2400 $cm^{-1}$.

A yield of 18% was considered a relatively poor result compared to the 65% yield obtained by Muraoka *et al.*, despite following his procedure verbatim. Surprisingly, Muraoka *et al.* never encountered or commented on the formation of the diol **145** in his original finding. Nevertheless, primarily for comparative reasons, synthetic endeavours towards the selective reduction of furanolipid half ester **126** employing $LiAlH_4$ began.

The reaction conditions illustrated in ***Scheme 2.80*** were employed in the selective reduction and subsequent acid induced lactonisation of furanolipid half ester **126** to its corresponding lactone **147** following the procedure previously described by Muraoka *et al.*[158]




***Scheme 2.80***

According to the literature,[165] reduction of carboxylic acids with one equivalent of lithium aluminium hydride consumes three of the four available nucleophilic hydrides due to the acidic hydrogen of the COOH unit reacting first. On this occasion a slight excess of lithium aluminium hydride (1.1 equivalents) was employed to ensure full reduction to the desired γ-

hydroxy acid intermediate complex **146** (***Scheme 2.80***). The reaction was complete after 3 hours at 0 $^{o}$C as indicated by TLC analysis and the excess hydride was quenched using ethyl acetate. As previously discussed, due to the inherent instability of the acid intermediate **146** to self-lactonisation and possible undesired deterioration following the reduction reaction, isolation and characterization was never attempted and subsequent acid induced lactonisation was employed on the crude material. The acidity of the reaction mixture was adjusted to pH 1 using 10% aqueous hydrochloric acid and the γ-hydroxy acid **146** was subjected to an 8 hour reflux in tetrahydrofuran as illustrated in ***Scheme 2.80***.

Following workup, $^{1}$H NMR spectroscopy of the crude product showed a three-component mixture consisting of the desired lactone **147**, its corresponding diol **149** and its corresponding saturated lactone **148** in a 5:3:3 ratio of products respectively (***Scheme 2.80***). Purification by column chromatography on silica was successful with isolation of the three components independently with no undesired co-elution. The least polar fraction isolated was the desired furanolipid lactone **147** as a light yellow oil in 13 % yield (***Scheme 2.80***). As expected, no trace of furospongolide **1** was observed in the crude product following acid reflux. In this scenario, spontaneous isomerisation of β-alkylidene-γ-lactone **147** to **1** was not possible. In contrast to ***Scheme 2.79***, an additional step employing base is required to successfully achieve this transformation.

$^{1}$H NMR analysis confirmed the synthesis of the novel furanolipid lactone **147** with disappearance of characteristic monoethyl ester peaks at $\delta_H$ 1.28 ppm (*J* 7.1) and $\delta_H$ 4.20 ppm (*J* 7.1) and the appearance of a 2H multiplet at $\delta_H$ 4.77-4.84 ppm assigned to the γ-methylene protons in the lactone ring. Further evidence was identified with a significant shift upfield of the vinylic proton at $\delta_H$ 6.97 ppm (*J* 7.4) in the half ester **126** to a 1H multiplet at $\delta_H$ 5.35-5.50 ppm in the furanolipid lactone **147**. IR analysis was also consistent with the presence of two sharp and strong bands at $\nu_{max}$ 1780 cm$^{-1}$ and $\nu_{max}$ 1725 cm$^{-1}$ characteristic of the γ-lactone ring.

The second fraction isolated following flash chromatography was the saturated lactone **148** as a light yellow oil in 5% yield (calculated from the theoretical). $^{1}$H NMR analysis confirmed the formation of the saturated γ-lactone **148** with the appearance of a ABX pattern

in the $^1$H NMR spectrum. As a result of the chiral carbon at C16 with a tetrahedral stereo-center* adjacent to the two diastereotopic methylene hydrogens (geminal protons) labeled as **$H_A$** and **$H_B$**, spin-spin splitting occurred with the appearance of 1H doublet of doublets at $\delta_H$ 3.88-3.94 ppm [$\delta_H$ 3.91 ppm, *J* 8.9, 7.3, C(19)$H_A$] and $\delta_H$ 4.38-4.44 ppm [$\delta_H$ 4.41 ppm, *J* 8.9 Hz, 7.4 Hz, C(19)$H_B$] (***Figure 2.19***). Normally these signals would appear as two independent clean doublet of doublets as a result of coupling with the neighboring proton, which appears as a 1H multiplet at $\delta_H$ 2.48-2.58. However, since the furanolipid saturated lactone **148** is present as a mixture of isomers (*E,E* and *E,Z*), the proton peak is described over a range rather than specifying the peak to one specific point in the $^1$H NMR spectrum. It should be noted that a pure sample of the furanolipid saturated lactone **148** was synthesised in a forthcoming reaction and a more comprehensive NMR study was performed on the molecule showing cleaner and more precise spectroscopic characteristics (***Figure 2.28***). The IR spectrum of **148** exhibited a sharp absorption band of the lactone carbonyl group at $\nu_{max}$ 1780 cm$^{-1}$ and the absorption band for C=C of an unsaturated lactone ring which is expected around $\nu_{max}$ 1660 cm$^{-1}$ was not observed.

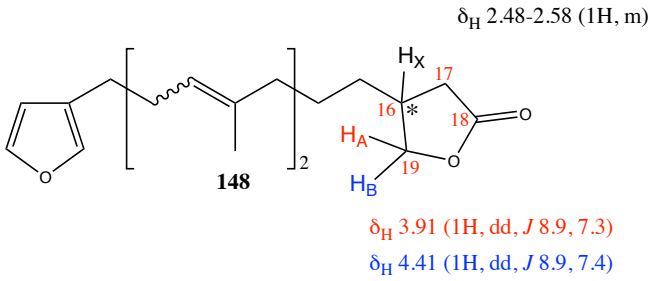
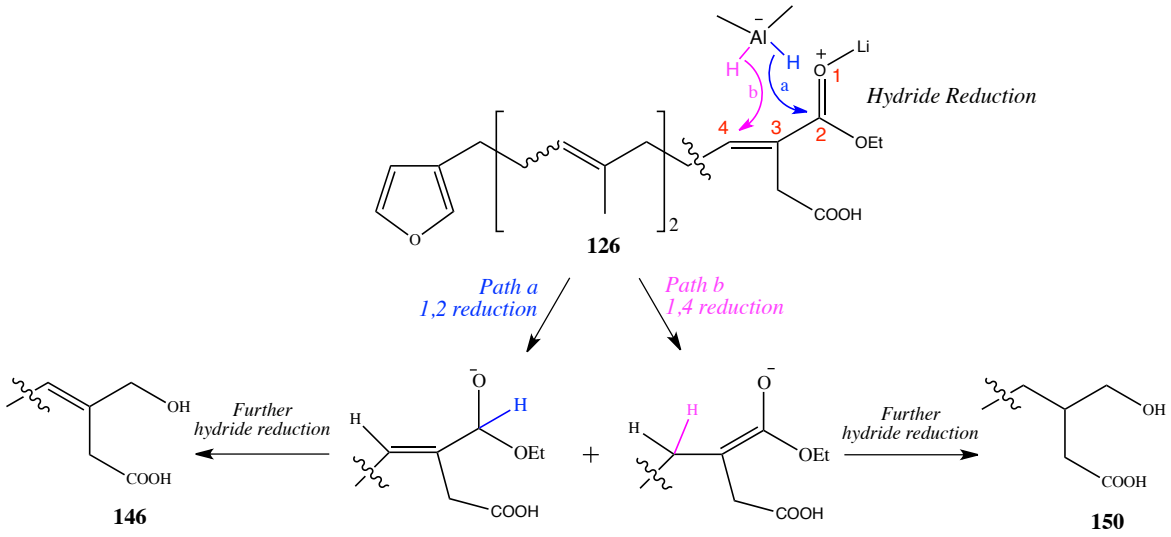


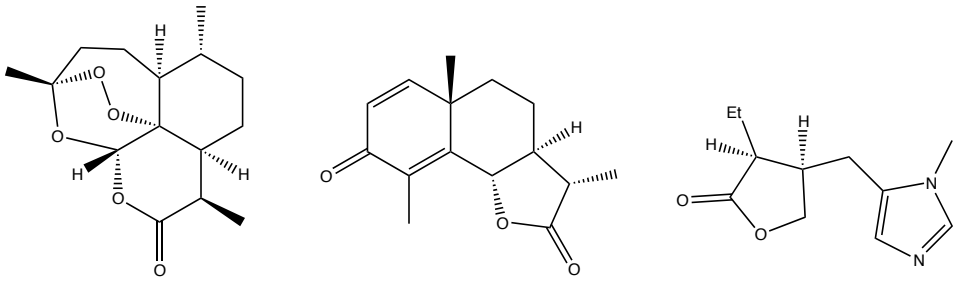

***Figure 2.19***

Reduction of α,β unsaturated carbonyl derivatives poses a potential problem in organic chemistry. With respect to the half ester **126**, reduction using a hydride reducing agent can potentially lead to either the desired allylic alcohol **146** via normal 1,2-reduction (delivery of the hydride to the carbonyl) or to the saturated alcohol **150** via 1,4-reduction (delivery of the hydride to the alkenyl carbon) as shown in ***Scheme 2.81.***[166]




***Scheme 2.81:*** *Hydride reduction of α,β-unsaturated ester* ***126*** *including generalized mechanism.*

If reduction proceeds via coordination of the aluminum to the carbonyl oxygen, 1,2-reduction occurs via **path A** to give **146**, which is the usual pathway. However, if the β-carbon is polarized with a positive dipole, a hydride can also be delivered to the β-carbon via **path B** (a six membered transition state). This pathway leads to 1,4 conjugate addition, and **150** is the product (***Scheme 2.81***). Fascinatingly from literature reading, saturated lactones display interesting biological activities and are used in many areas, especially medicine, pharmacology, perfume making and pesticides. Artemisinin **151** (treatment of malaria), santonin **152** (anthelmintic) and pilocarpine **153** (parasympathomimetic) are examples of compounds endowed with valuable biological activity, which contain a saturated lactone ring (***Figure 2.20***).[167-169] Saturated γ-lactones are of great interest and can have a valuable potential for new biologically active compounds. For this reason, the saturated lactone **148** became an interesting compound to send for biological testing.



*Artemisinin* **151** *Santonin* **152** *Pilocarpine* **153**

***Figure 2.20***

As expected, the furanolipid diol **149** was the most polar fraction isolated after column chromatography as a light yellow viscous oil. $^{1}$H NMR analysis confirmed the formation of the diol by-product **149** with the appearance of a 2H triplet at $\delta_H$ 3.71 ppm [*J* 5.9, C(18)$H_2$] and at $\delta_H$ 2.42 ppm [*J* 5.9, C(17)$H_2$] associated with the neighboring methylene hydrogens alpha and beta to the newly formed alcohol functionality respectively. A distinctive 1H singlet was also present at $\delta_H$ 4.04 ppm, which is assigned to the allylic hydrogens at C(19)$H_2$ (***Figure 2.21***). Conclusive evidence could be seen in the IR spectrum with no carbonyl absorption stretching and a broad OH stretch at $\nu_{max}$ 3338 cm$^{-1}$.

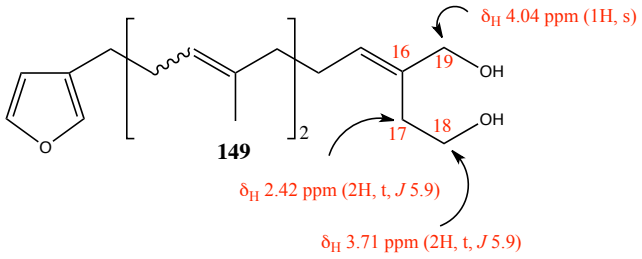


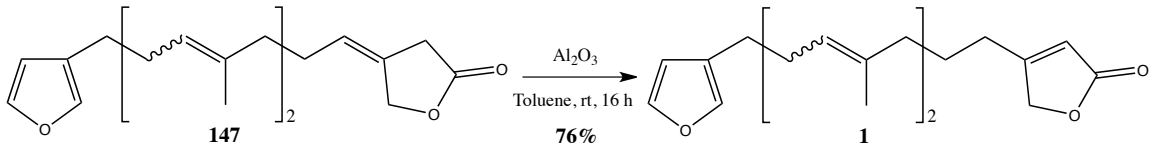

***Figure 2.21***

In our hands, using lithium aluminium hydride as a chemoselective-reducing agent was essentially unsuccessful. Conversion of the half ester **126** to its corresponding γ-hydroxy acid **146** was achieved and following acid induced lactonisation afforded the desired lactone **147** in a relatively poor yield of 13%. Unfortunately the half ester **126** embodies an α,β-unsaturated carbonyl functionality, which is susceptible to undesired 1,4 reduction in addition to desired 1,2 reduction resulting in the formation of the saturated lactone **148**.

Formation of the diol **149** was a clear example of the sheer inability of $LiAlH_4$ to function as a chemoselective reducing agent. The formation of these two by-products significantly diminished the yield and ultimate success of the reaction. It was imperative that a superior chemoselective reducing agent was employed for this transformation. Nevertheless, attention was momentarily shifted to the last step in the synthesis of furospongolide **1**, which was a base induced isomerisation reaction.

### 2.5.4 Synthesis of furospongolide (isomerisation using $Al_2O_3$)

The last step in the synthesis of furospongolide **1** was a based induced isomerisation reaction. Various methods are reported in the literature for carrying out this transformation. The simplest and most practically appealing procedure involved the use of neutral aluminium trioxide ($Al_2O_3$). Furospongolide **1** was successfully synthesised following treatment of lactone **147** with neutral $Al_2O_3$ in dry toluene overnight and following a modified literature precedent described for a related compound by McMurry *et al.* (***Scheme 2.82***).[151]




***Scheme 2.82***

The only modification made from McMurry's original procedure was that toluene was employed instead of benzene as the reaction solvent for handling reasons. Following a 16 hour stir at room temperature, the desired product **1** was obtained as a colourless oil in 76% yield, which was deemed pure by $^1H$ NMR analysis avoiding the need for further purification by column chromatography. Spectroscopic analysis was consistent with literature data for the synthesis of furospongolide **1**.[2,25] The $^1H$ NMR spectrum revealed successful isomerisation to the conjugated lactone **1** with a significant downfield shift of the 2H multiplet at $\delta_H$ 3.09-3.17 ppm in **147** to a 1H multiplet at $\delta_H$ 5.80-5.87 ppm associated with the newly fashioned α-olefinic proton within the butenolide ring. Likewise, there was a significant upfield shift of

the 1H multiplet at $\delta_H$ 5.35-5.50 ppm to a 2H multiplet at $\delta_H$ 1.60-1.75 ppm associated with the methylene protons adjacent to the butenolide ring at C(15)$H_2$ (***Figure 2.22***). Further evidence was provided by $^{13}$C NMR with a considerable chemical shift from $\delta_C$ 31.3 ppm to $\delta_C$ 115.4 ppm at *C*(17)H following isomerisation. Similarly, a shift upfield was observed at *C*15 from $\delta_C$ 124.3 ppm to $\delta_C$ 25.2 ppm (***Figure 2.23***). Lastly, the IR spectrum contained two strong and sharp carbonyl absorption peaks at $\nu_{max}$ 1780 cm$^{-1}$ and $\nu_{max}$ 1748 cm$^{-1}$ emblematic of an α,β-unsaturated γ-lactone ring.

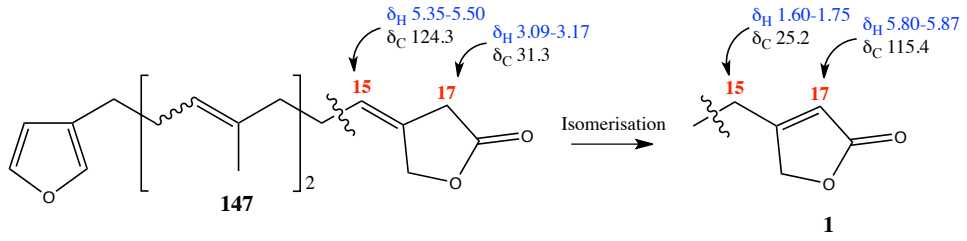


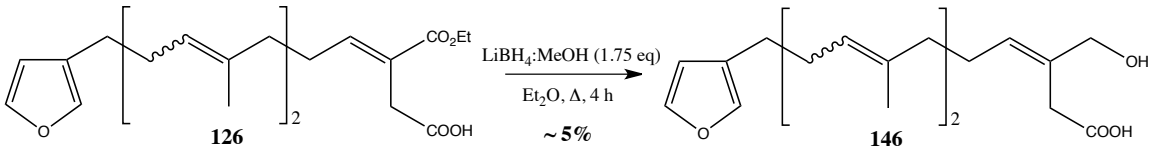

***Figure 2.22:*** Spectroscopic data endorsing isomerisation to the α,β-unsaturated γ-lactone.

Successful construction of the butenolide ring in this manner marked a significant milestone in the overall scope of the project. Regardless of the problems encountered with the selective reduction reaction, this route offered a concise and genuinely effective method for the preparation of furospongolide **1**.

### 2.5.5 Selective reduction revisited

Work was resumed on the selective reduction reaction in order to find a more efficient chemoselective reducing agent for conversion of the half ester **126** to its corresponding γ-hydroxy acid **146**. With respect to metal hydride reduction, $LiAlH_4$ was explored to no great avail showing no selective hydride transfer affinity towards the ester functionality. Lithium borohydride was another metal hydride reducing agent commonly used for the selective reduction of esters in the presence of acids.[170-174] Despite having relatively slow reduction rates, it displays much greater chemoselectively than lithium aluminium hydride. The reactivity of lithium borohydride is dependant on the reaction medium (diethyl ether > THF

> 2-propanol), which is attributed to the availability of the lithium counter-ion for coordination to the substrate, promoting reduction. On that note, Saoi *et al.* recommended the use of an ether-methanol solvent system in conjunction with lithium borohydride ($LiBH_4$-MeOH-$Et_2O$),[175] which would greatly enhance the reducing power and chemoselective nature of the reaction. Following his procedure exactly,[175] an equimolar proportion of methanol and lithium borohydride (1.75 equivalents) were refluxed in addition to the half ester substrate **126** in diethyl ether as shown in ***Scheme 2.83***.



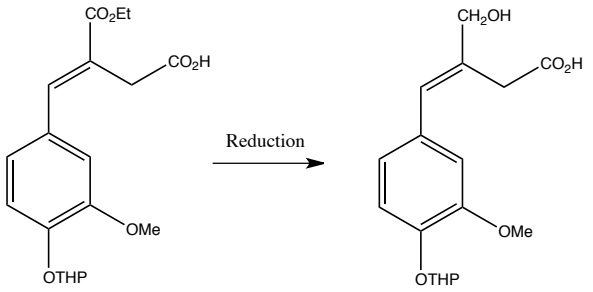

***Scheme 2.83***

The reaction progress was monitored by TLC analysis and after a four hour reaction period, complete consumption of starting material **126** was observed and the reaction was quenched. Disappointingly, $^1$H NMR spectroscopy of the crude product revealed only a minor trace (>5%) of the desired γ-hydroxy acid **146** had formed indicated by the appearance of a characteristic singlet at 3.22 ppm and 4.13 ppm in the $^1$H NMR spectrum, which is consistent with previous spectroscopic findings. Nevertheless, the major compound formed was an unidentified product possibly formed following uncontrolled degradation.

The next option as a hydride reducing agent capable of achieving chemoselective reduction was a bulky alkali metal trialkylaluminium hydride. Described as an "ate" complex in the literature,[176-178] lithium diisobutyl-*n*-butylaluminium hydride which is derived from the equimolar addition of diisobutylaluminium hydride and *n*-butyllithium has been reported to provide a convenient method for chemoselective conversion of esters to alcohols in the presence of carboxylic acids.[176-178] Most metal hydride reducing agents do not allow employment of a stoichiometric amount of hydride ion reminiscent of lithium aluminium hydride and lithium borohydride, which were addressed previously. According to the literature,[176-178] the use of 3 equivalents (1 equivalent to neutralize the acid and 2 equivalents to effect reduction) of the "ate" complex, which has only one active hydride, is superb to

achieve selective formation of the allylic alcohol. Fortuitously, on further literature research, Lee *et al.* who was trying to synthesise a "Novel Hapten-Protein Conjugate" encountered a similar problem when trying to selectively reduce half ester **154** to its corresponding allylic alcohol **155** as summarised in ***Table 2.15***.[177]

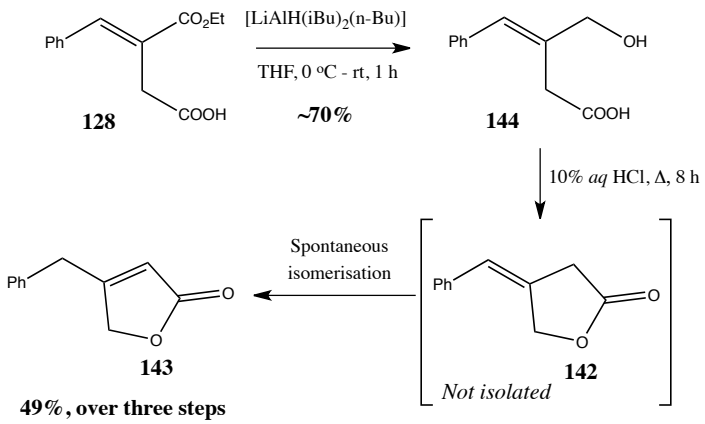
***Table 2.15:*** *Results obtained by Lee et al. for the selective reduction of half ester* ***154*** *to alcohol* ***155*** *employing a variety of different metal hydride reducing agents.*[177]




**154** **155**

| Entry | Reducing agent | Yield |
|---|---|---|
| **1** | $LiBH_4$ | Trace |
| **2** | $LiAlH_4$ | 20% |
| **3** | $LiAlH_2(OEt)_2$ | 40% |
| **4** | "ate" complex | 85% |

Interestingly, results obtained by Lee *et al.* matched those achieved in this research especially in the case of lithium borohydride (***Entry 1***) and lithium aluminium hydride (***Entry 2***). In an attempt to refabricate the results obtained by Lee *et al.* and to assess the potential of the "ate" complex, Lee's conditions were employed in the chemoselective reduction of 1-ethyl 4-hydrogen 2-benzylidenesuccinate **128** to its corresponding benzyl butenolide **143** (***Scheme 2.84***). The benzyl half ester **128** was the perfect candidate due to its close structural resemblance with compound **154**. The "ate" complex [$LiAlH(i\text{Bu})_2(n\text{-Bu})$] was generated *in-situ* and added to the half ester **128** in anhydrous tetrahydrofuran at 0 $^oC$ over 30 minutes (***Scheme 2.84***).[176]

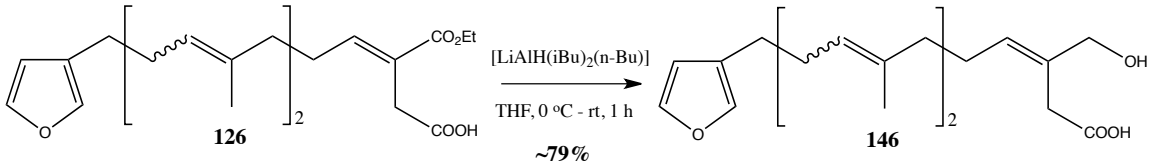



***Scheme 2.84***

The reaction was monitored by TLC analysis and after 1 hour at room temperature the reaction was quenched and analysed by $^1$H NMR spectroscopy, which revealed that the desired γ-hydroxy acid **144** was formed in ~70% yield as a crude yellow oil. Purification of the allylic alcohol **144** was deemed unnecessary due to the inherent instability of this complex to self-induced lactonisation, which is well documented in the literature.[158,177] Spectroscopic data for the γ-hydroxy acid **144** was consistent with those previously described.

The γ-hydroxy acid **144** was subsequently converted to its corresponding α,β-unsaturated-γ-lactone **143** through intermediate **142** following successive lactonisation and isomerisation reactions. This was achieved following treatment of **144** with 10% aqueous hydrochloric acid in refluxing tetrahydrofuran over an 8 hour period (***Scheme 2.84***). $^1$H NMR analysis of the crude product indicated a two-component mixture consisting of the benzyl butenolide **143** and an unknown impurity in a 78:22 ratio of products respectively. Purification by column chromatography on silica gel afforded the desired butenolide **143** in 49% yield. The second component was an unknown impurity isolated as a light yellow oil. It was presumed that the unknown compound isolated was the corresponding saturated lactone resulting from 1,4 reduction of the α,β-unsaturated ester **128**. However, spectroscopic analysis did not fit the profile with the appearance of a two distinctive 2H triplets at $\delta_H$ 3.59 ppm (*J* 6.6) and $\delta_H$ 3.69 ppm (*J* 6.3) in the $^1$H NMR spectrum.

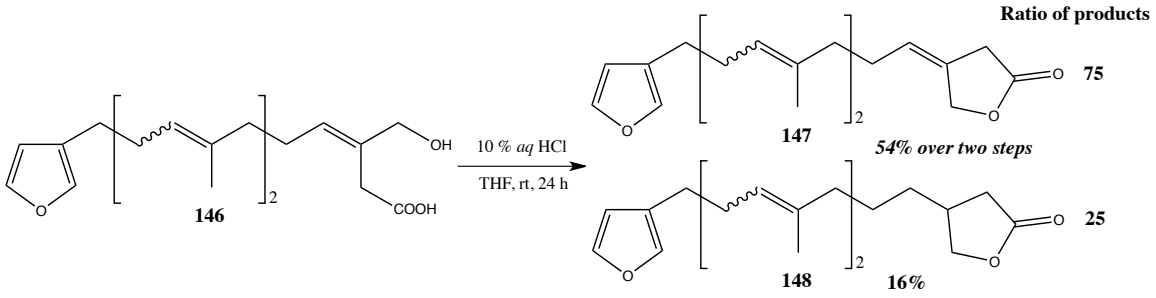
Following the successful synthesis of **143**, attention was shifted to the reduction of the furanolipid half ester **126** employing the same methodology as previously described above in ***Scheme 2.84***.




***Scheme 2.85***

The furanolipid ester **126** was treated with the aluminium "ate" complex at 0 $^{o}$C in tetrahydrofuran over a 30 minute period and after an additional 1 hour stir at room temperature, TLC analysis indicated complete consumption of starting material **126**. Aqueous workup involved the use of sodium potassium tartrate (Rochelle's salt) to effectively break up emulsions caused by the aluminium-based hydride reagent. This essentially made the extraction process significantly easier and the desired γ-hydroxy acid **146** was furnished as a light yellow oil in ~79% yield. In contrast, the workup employed by Lee *et al.* was arduous and gave poor recovery of the product following extraction. $^{1}$H NMR analysis revealed successful synthesis of **146** with spectroscopic characteristics matching those previously described. Noteworthy, on this occasion, the crude product was remarkably cleaner compared to the lithium aluminium hydride reduction. Due to inherent instability of the allylic alcohol **146**, further purification by chromatography was deemed unnecessary and it was subsequently used in the subsequent transformation.

With a view to improving the procedure for the acid induced lactonisation reaction, it became apparent that subjecting the γ-hydroxy acid **146** to harsh reaction conditions (refluxing tetrahydrofuran) is not beneficial. In general, complexes of this type can be lactonised by stirring the substrate in tetrahydrofuran under acidic conditions.[174,179,180] By employing milder conditions, greater control can be obtained and thus avoid undesired degradation or by-product formation.




***Scheme 2.86***

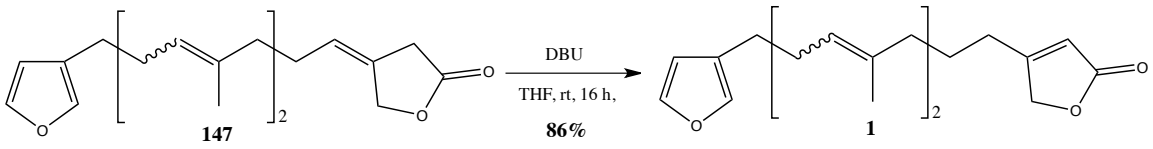
As conveyed in ***Scheme 2.86***, the acidity of the reaction was adjusted to pH 1 using 10% aqueous hydrochloric acid and the substrate was stirred in tetrahydrofuran for 24 hours. Spectroscopic analysis of the crude product following aqueous workup revealed a two-component mixture consisting of the lactone **147** and its corresponding saturated lactone **148** in a 75:25 ratio of products respectively. Purification by column chromatography on silica gel furnished the lactone **147** as a colourless oil in 54% yield calculated from the theoretical over two steps. Spectroscopic data was consistent with those previously described.

The more polar fraction was the saturated lactone **148**, which was isolated as a colourless oil in 16% yield. Spectroscopic characteristic were identical to those previously described showing unique splitting patterns for the γ-methylene protons [C(19)$H_2$] appearing as two doublet of doublets at $\delta_H$ 3.91 ppm (*J* 8.9, 7.3) and $\delta_H$ 4.41 ppm (*J* 8.9, 7.4). This phenomenon transpired following formation of a new chiral center at *C*(16)H following undesired 1,4 reduction as formerly discussed.

### 2.5.6 Synthesis of furospongolide (base induced isomerisation)

On the topic of optimization and refining reaction conditions, a new procedure was adopted for introducing conjugation into the lactone ring. Previously, neutral aluminium trioxide was used as a mild and trivial method for carrying out this transformation (***Scheme 2.82***). Following literature research,[181-184] base induced isomerisation is a more contemporary approach to isomerisation, which is generally performed using a non nucleophilic base like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Simply stirring the γ-lactone **147** in a 2

equivalent excess of DBU in tetrahydrofuran at room temperature was sufficient to afford furospongolide **1** as a light yellow oil (***Scheme 2.87***).



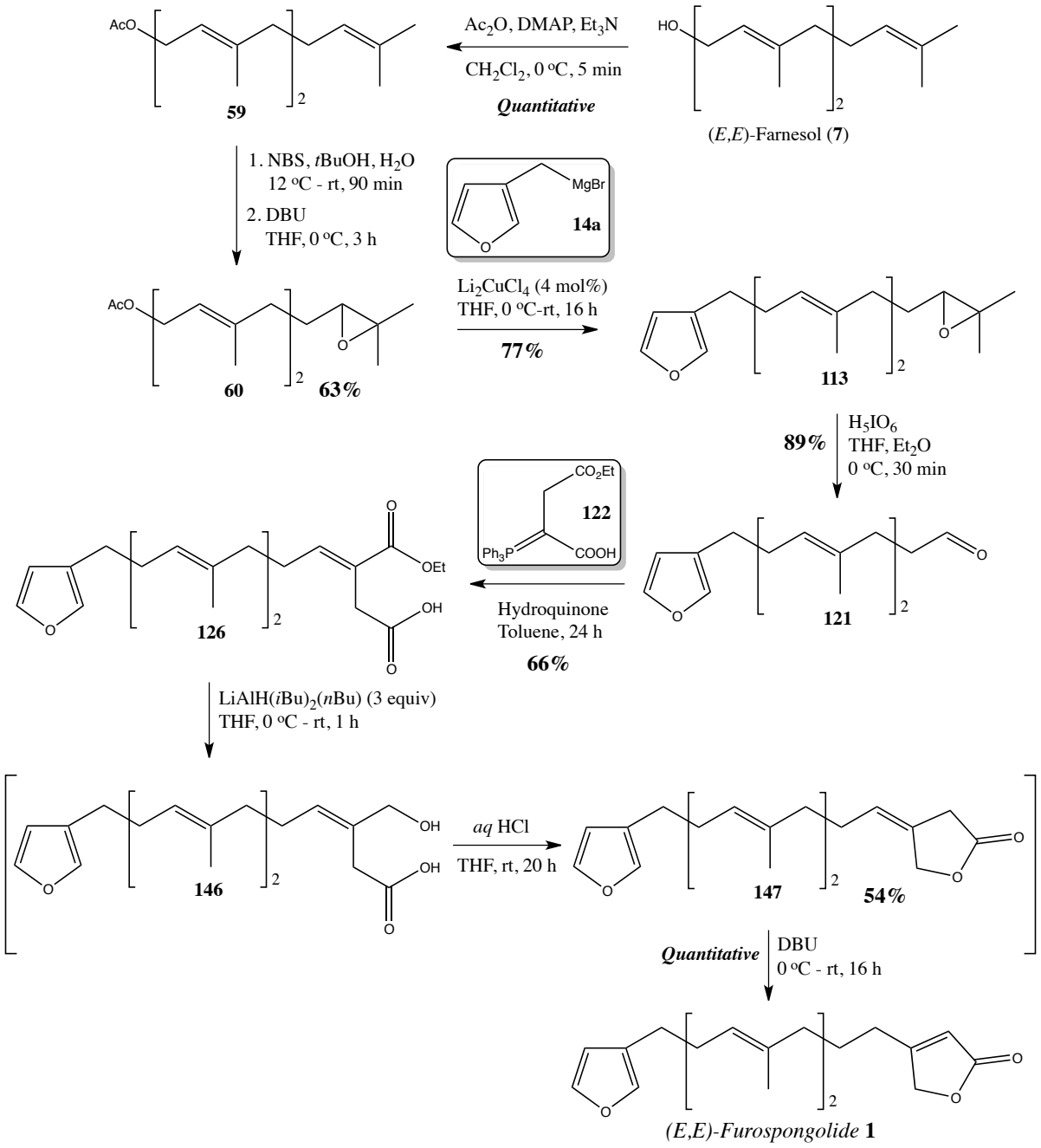

***Scheme 2.87***

Purification by column chromatography on silica gel followed workup despite the crude product of **1** looking essentially pure by $^{1}$H NMR analysis. Satisfyingly, furospongolide **1** was isolated as a colourless oil in 86% yield with spectroscopic characteristics consistent with those previously described and reported in the literature.[2,25]

In comparison to $Al_2O_3$, DBU offered a simple, clean and high yielding approach for shifting the double bond into conjugation. Nevertheless, DBU furnished furospongolide **1** in a slightly higher yield and therefore will be employed in future as standard practice for carrying out transformations of this type. Inclusive of the selective reduction of the half ester **126** followed sequentially by acid induced lactonisation and base induced isomerisation, the target compound furospongolide **1** was prepared in 47% yield over three steps. In brief, our total synthesis of furospongolide **1** was successfully accomplished in a 7 linear step sequence in 12.9 % overall yield from commercially available farnesyl acetate **59**.

## 2.6 Synthesis of (*E,E*)-furospongolide

With the successful establishment of viable methodology that allows access to our target molecule **1** in 7 linear steps, it was now imperative that the pure (*E,E*)-isomer is prepared in order to achieve our goal of the total synthesis of (*E,E*)-furospongolide **1** in a concise linear pathway. Complete spectroscopic comparisons can then be made against naturally occuring furospongolide **1** isolated for the marine sponge *Dysidea herbacea*.[2] The linear route for our total synthesis of (*E,E*)-furospongolide **1** is illustrated in ***Scheme 2.88***.




***Scheme 2.88***

The route began with the preparation of (*E,E*)-farnesyl acetate **59**. This was accomplished using commercially available *trans, trans* farnesol **7** and employing standard acetylation conditions.[89,91] A HPLC trace of **7** was first carried out to confirm the purity of the starting

material (***Appendix V***). The desired acetate ester **59** was isolated quantitatively as a colourless oil and used in the next transformation without further purification. As expected, the NMR spectrum of acetate **59** was considerably cleaner with greater peak definition permitting a more accurate assessment and characterisation of the molecule.

(*E,E*)-Farnesyl acetate **59** was subjected to the standard conditions of the regioselective epoxidation reaction,[87] following established methodology developed by Van Tamellen *et al.*[88,98] Through the action of *N*-bromosuccinimide, the bromohydrin intermediate was successfully synthesised as a light yellow oil with exclusive oxidation at the terminal non-allylic double bond. The epoxide **60** was subsequently generated following treatment with DBU and isolated as a colourless oil in 63% yield following column chromatography on silica gel. As shown in ***Figure 2.23***, the oxirane proton appears as a distinctive 1H triplet at $\delta_H$ 2.70 ppm (*J* 6.2).

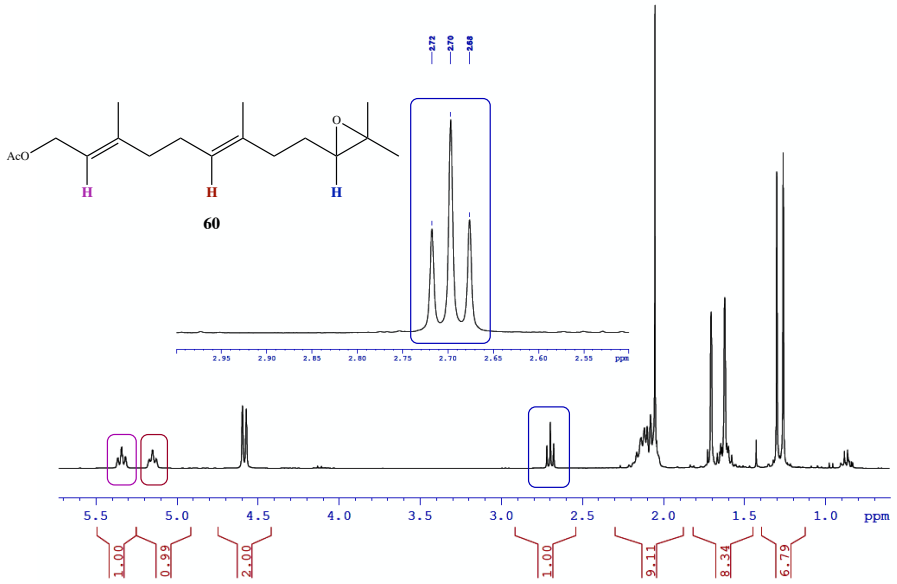



***Figure 2.23:*** *$^1$H NMR spectrum of (+/-)-10,11-epoxyfarnesyl acetate **60** ($CDCl_3$, 300 MHz).*

Attachment of the furan moiety to (+/-)-10,11-epoxyfarnesyl acetate **60** was accomplished by means of the Schlosser $sp^3$-$sp^3$ cross coupling reaction. However in this scenario, the concentration of Kochi's copper catalyst ($Li_2CuCl_4$, 3.9 mol%) was slightly reduced compared to previous reactions following recommendations from Gansauer *et al.*[185] As expected, cross coupling of acetate **60** with the Grignard reagent of **14** proceeded smoothly to

furnish the desired furanolipid epoxide **113** in high diastereoselectivity as a colourless oil in 77% yield post purification by flash chromatography with no trace of epoxide ring opening or the allylic isomer. Spectroscopic characteristics were consistent with those previously described (***Figure 2.24***).

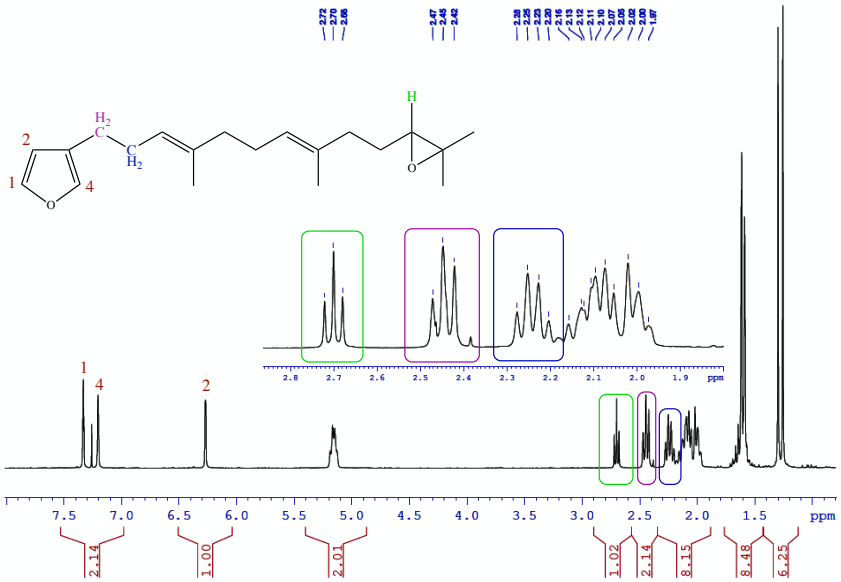



***Figure 2.24:*** *$^{1}$H NMR spectrum of furanolipid epoxide **113** ($CDCl_3$, 300 MHz).*

The furanolipid epoxide **113** was converted to its corresponding aldehyde **121** following treatment with periodic acid through an oxidative cleavage reaction.[88] Purification by column chromatography on silica gel afforded the furanolipid aldehyde **121** as a colourless oil in 89% yield (***Figure 2.25***).

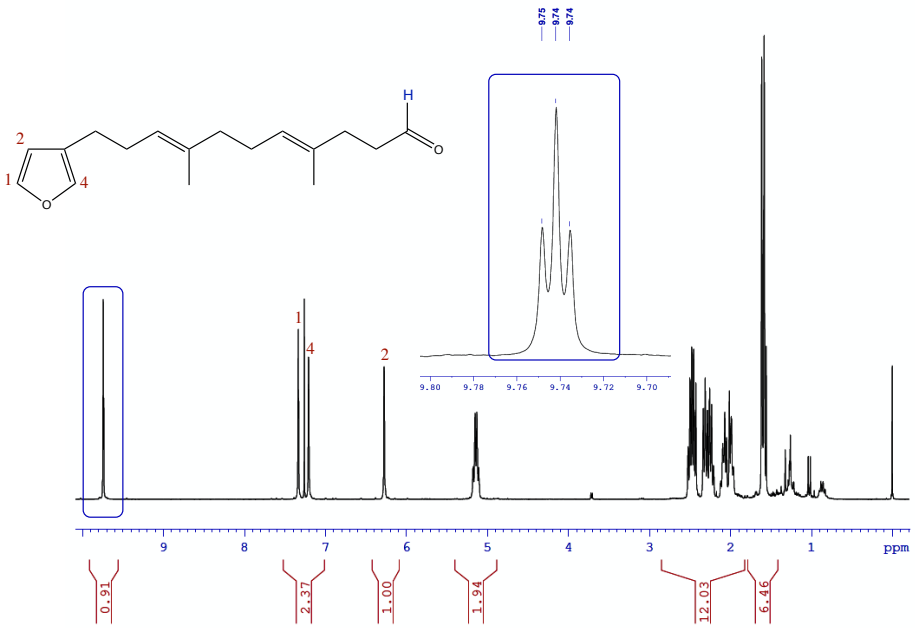



***Figure 2.25:*** *$^{1}H$ NMR spectrum of furanolipid aldehyde **121** ($CDCl_3$, 300 MHz).*

Attachment of the butenolide ring to the furanolipid backbone was accomplished by implementing innovative methodology originally developed by McMurry *et al.*[151] The first step involved a Wittig reaction where furanolipid aldehyde **121** was cross-coupled with ylide **122** following our optimised procedure. The furanolipid half ester **126** was furnished as a light yellow oil in 66% yield post chromatography (***Figure 2.26***).

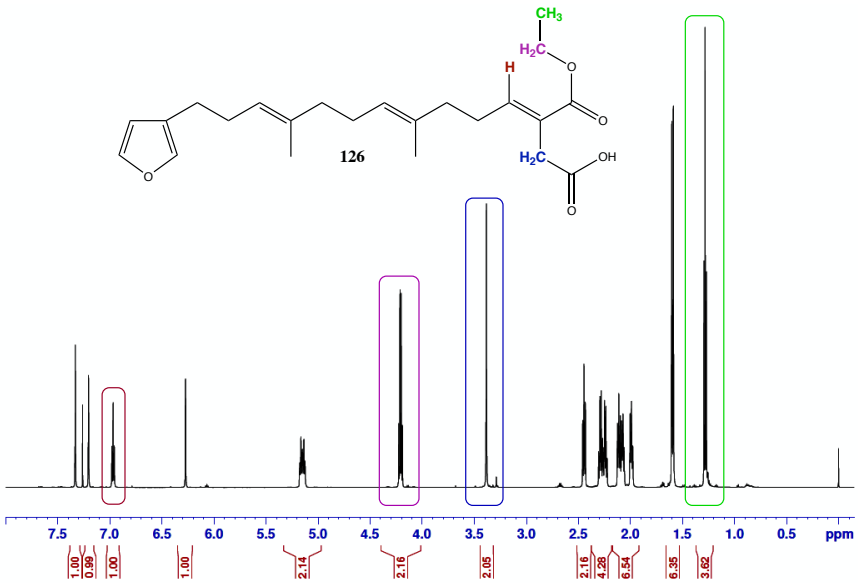



***Figure 2.26:*** *$^{1}$H NMR spectrum of furanolipid half ester* ***126*** *($CDCl_3$, 600 MHz).*

With the carbon skeleton in place, the next step was to selectively reduce the ester **126** followed by consecutive lactonisation and isomerisation reactions to furnish the butenolide moiety. The chemoselective reduction was successfully achieved employing a lithium trialkylaluminium hydride reagent or 'ate' complex generated *in situ* by the equimolar addition of DIBAL-H and *n*-butyllithium.[176] Adhering to previously successful conditions,[177] the γ-hydroxy acid **146** was furnished as a colourless oil, which was used directly in the next transformation without further purification.

Acid induced lactonisation to **147** was performed using 10% aqueous hydrochloric acid in tetrahydrofuran. This transformation can either be achieved by acid workup in a separating funnel or simply stirring the γ-hydroxy acid **146** under acidic conditions in the reaction flask.[157] Both methods afford the lactone **147** in a similar isolated yield of 54% (yield calculated for the reductive-lactonisation reaction post column chromatography) but the latter is more frequently performed according to the literature for related compounds.[174,179-181]

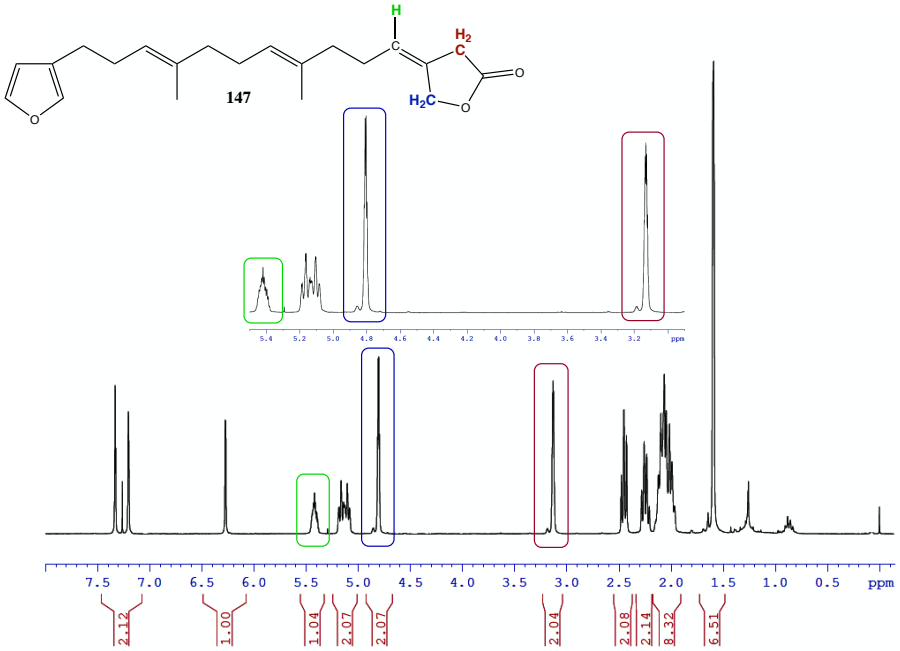



***Figure 2.27:*** *$^{1}$H NMR spectrum of furanolipid lactone **147** ($CDCl_3$, 300 MHz).*

An inevitable feature of this reaction was the formation of the saturated lactone **148** following undesired 1,4 reduction at the α,β-unsaturated ester functionality. This by-product **148** was isolated as a colourless oil in 18% yield post chromatography. The saturated lactone **148** was subsequently sent for biological evaluation to the NCI in order to establish its potential as an antitumour agent. Furthermore, a comparative study between (*E,E*)-furospongolide **1** and the furanolipid saturated lactone **148** will provide intriguing information on the importance of the butenolide ring to the structure activity relationship of our target molecule **1**.

The $^{1}$H NMR spectrum of **148** was quite unique displaying four doublets of doublets at different chemical shifts in an **ABX** and **CDX** pattern. The hydrogen at C(16)*H* responsible for this phenomenon was observed as a 1H multiplet at $\delta_H$ 2.50-2.58 ppm (***Figure 2.28***). It is worth noting that the methylene group at C(17)$H_2$ ($J_{CD}$17.1 Hz) had a larger geminal coupling constant compared to C(19)$H_2$ ($J_{AB}$ 8.88 Hz). The geminal coupling is larger than expected because the methylene protons at C(19)$H_2$ are alpha to the carbonyl group in saturated lactone **148**. The effect is especially large when the line joining the two coupled protons is parallel to the neighboring π orbital.[186]

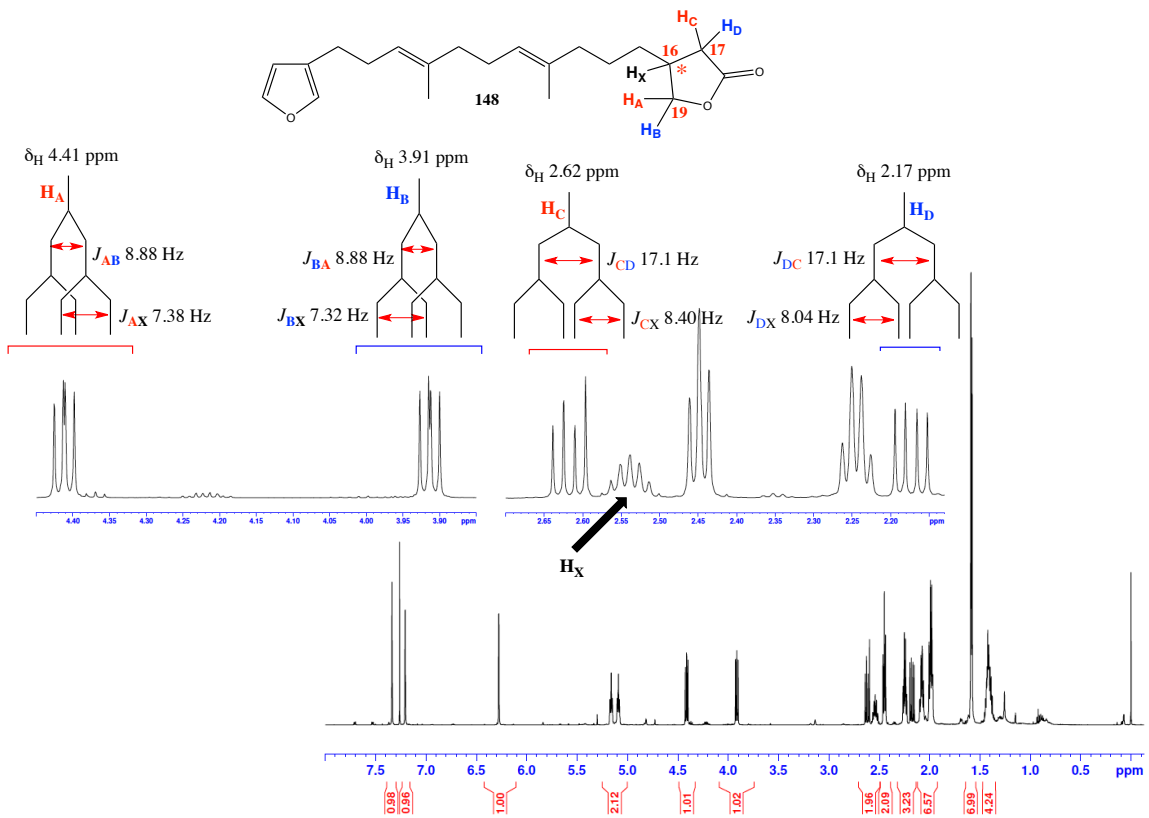



***Figure 2.28:*** *$^{1}H$ NMR spectrum of furanolipid lactone* ***148*** *($CDCl_3$, 600 MHz) including a stick diagram representing the ABX and CDX pattern formed by the methylene protons at C(19)$H_2$ and C(17)$H_2$ respectively.*

Pleasingly, base induced enolisation using DBU successfully provided furospongolide **1** as a colourless oil in 99% yield, which was deemed pure by $^{1}$H NMR spectroscopy. Nevertheless, purification by column chromatography was employed to ensure the absolute purity of the natural product. This was further confirmed with the appearance of one peak in a HPLC trace of our target compound **1** (***Appendix V***). Spectroscopic data for **1** were in good agreement with those previously reported in the literature both for its initial discovery by Kashman *et al.* from the marine sponge *Dysidea heracea* and its first total synthesis by Boukouvalas *et al.* (***Figure 2.29***).[2,25]

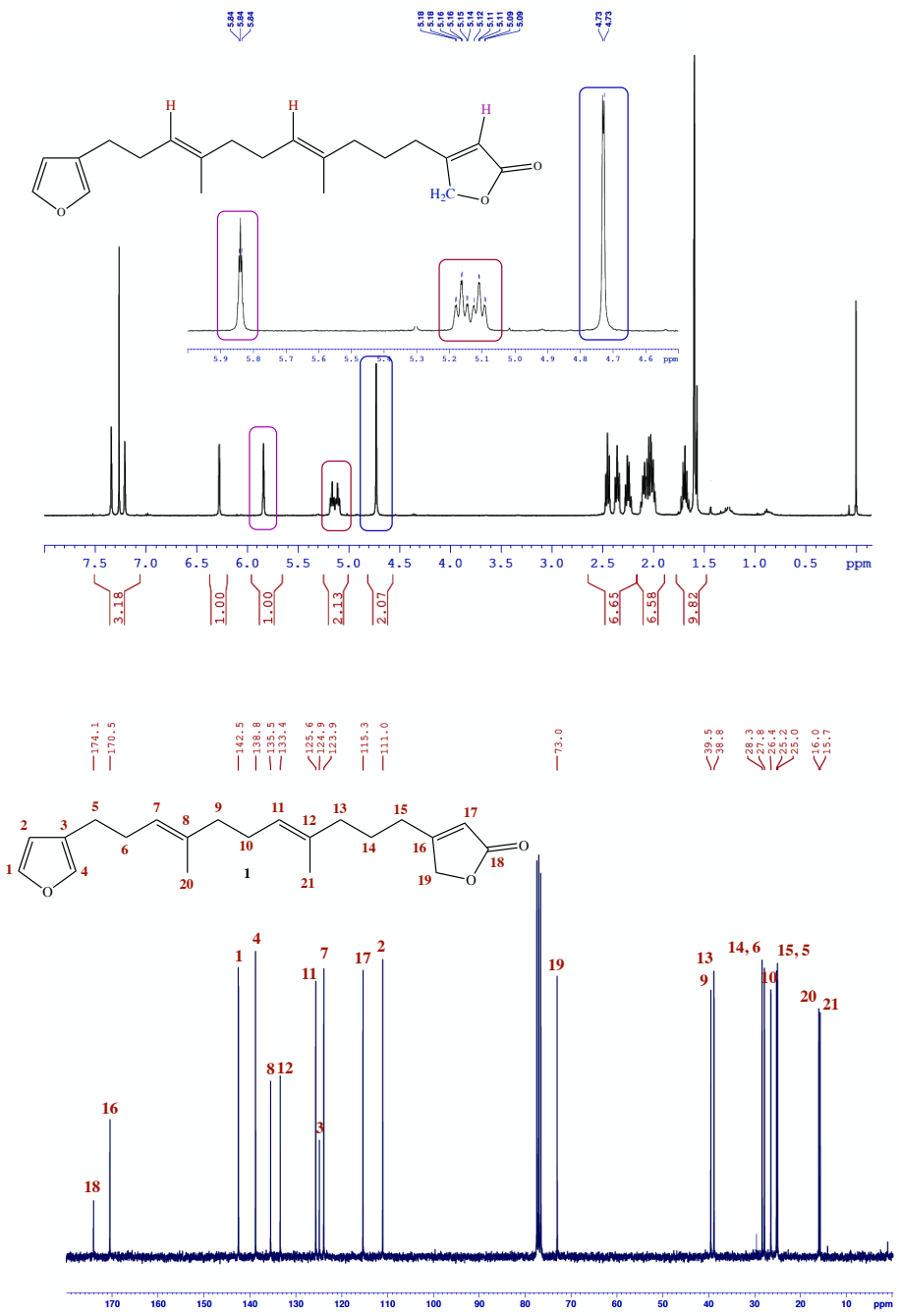
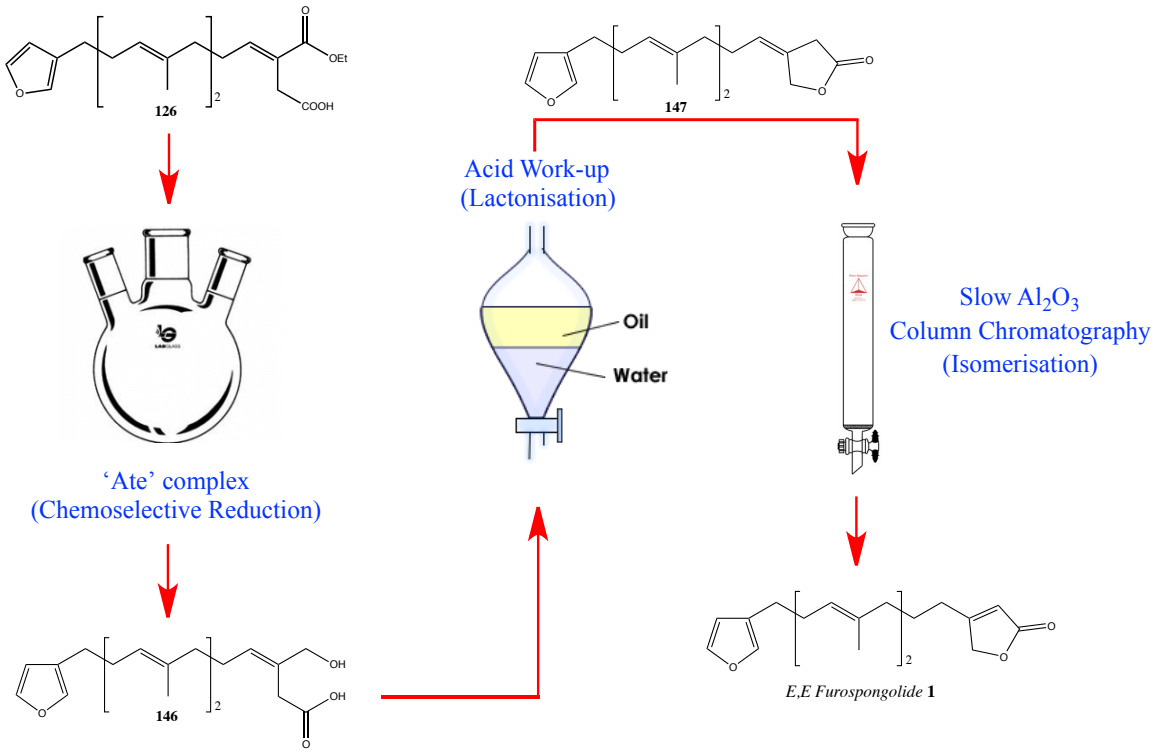


***Figure 2.29:*** *$^{1}H$ NMR and $^{13}C$ NMR spectrum of furospongolide **1** ($CDCl_3$, 300 MHz, 75.5 MHz).*

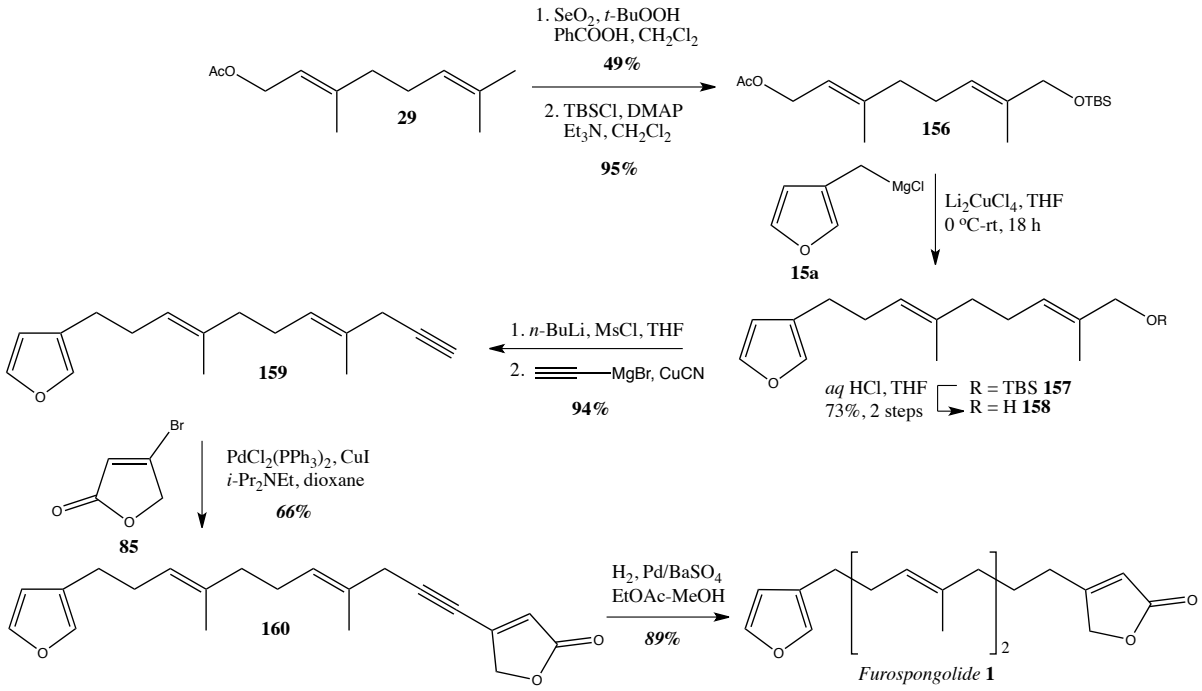
Remarkably, it is also possible to induce isomerisation to the conjugate system by slow neutral alumina column chromatography, as previously encountered by McMurry *et al.* in his original studies.[151] Surprisingly, slow silica gel flash chromatography was ineffective at carrying out this transformation. On the back of these findings, one could postulate that our total synthesis of furospongolide **1** has been achieved in five linear steps from (*E,E*)-farnesyl acetate **59** as opposed to a seven step synthetic sequence (***Scheme 2.89***).




***Scheme 2.89:*** *One-pot synthesis of furospongolide **1** from furanolipid half ester **126**.*

To summarise, our total synthesis of isomerically pure (*E,E*)-furospongolide **1** has been achieved in 5 linear steps and 14.3% overall yield from (*E,E*)-farnesyl acetate **59**. This is a highly convergent, concise and flexible synthetic route, which is readily amenable to the preparation of structural analogues as well as other biologically important furanolipids sharing the same carbon framework.

Disappointingly during my research, the first synthesis of the marine HIF-1 inhibitor furospongolide **1** was achieved by Boukouvalas *et al.* in late 2011.[25] The eight linear step sequence was accomplished in 19% overall yield from commercially available geranyl acetate **29** as illustrated in ***Scheme 2.90***. Completion of our linear route was accomplished in early 2012. In contrast to the synthetic route developed by Boukouvalas *et al.*,[25] our route only involved 5 linear synthetic steps, two C-C bond formation steps and avoided the use of protecting group chemistry and the employment of palladium as a catalyst. Each linear step in our route was also conducted under mild conditions (***Scheme 2.90***).

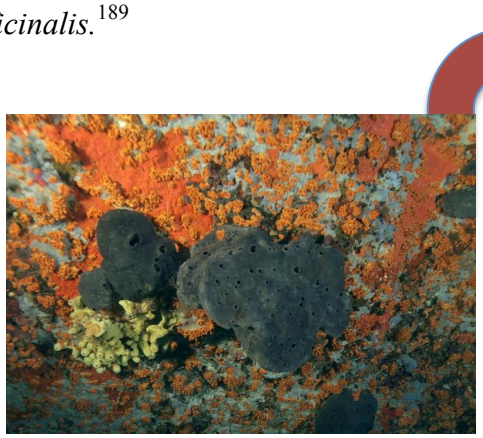



***Scheme 2.90:*** *The first total synthesis of the marine HIF-1 inhibitor furospongolide **1** as developed by Boukouvalas et al.*[25]

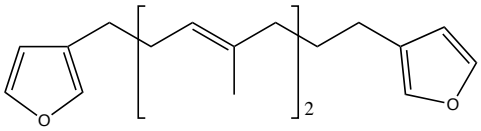
Unfortunately, the overall yield acquired by Boukouvalas *et al.* for his synthetic route was slightly higher than ours despite an 8 linear step synthesis. Future work will look at further optimising our synthetic route in the hope of increasing the overall yield.

## 2.7 Synthesis of anhydrofurospongin-1

Anhydrofurospongin-1 **164** is a marine natural product almost identical in structure to furospongolide **1**. The first reported isolation and subsequent characterisation of this difuranoterpene was in 1971 by Cimino *et al.* from the marine sponges *Spongia officinalis* and *Hippospongia communis*.[187] Since its discovery, anhydrofurospongin-1 **164** has been isolated from a number of other marine sponges like *Spongia agaricina* collected near Tarifa Island in Spain.[188] Interestingly, both furospongolide **1** and anhydrofurospongin-1 **164** were isolated from the same marine extract collected off the Sicily coast by Manzo *et al.* when he was studying the terpene metabolite pattern of the Mediterranean marine sponge *Spongia officinalis.*[189]



*Spongia officinalis*



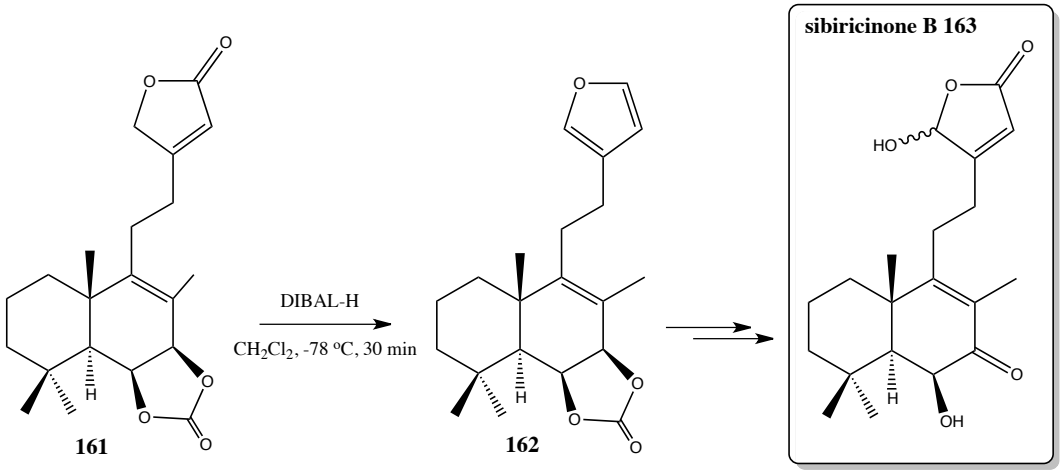
*Anhydrofurospongin-1* **164**

***Figure 2.30:*** *Anhydrofurospongin-1 isolated from the marine sponge Spongia officinalis by Cimino et al.*[187]

It may be plausible that within the marine ecosystem, these two metabolites are interconverted through a series of enzyme catalysed oxidation and reduction reactions between the furan ring and the unsaturated γ-lactone *in vivo*.[190] Surprisingly, to the best of our knowledge, no synthetic preparation of anhydrofurospongin-1 **164** has been reported in the literature to date.

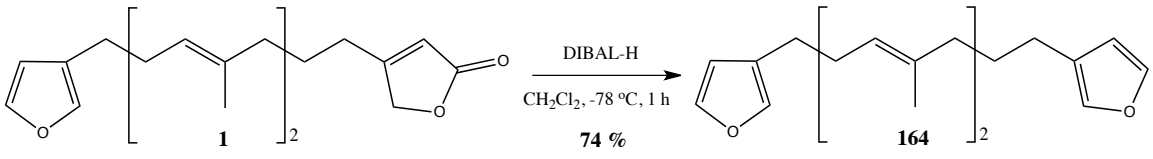
Having successfully synthesised (*E,E*)-furospongolide **1** through 2nd generation synthesis, the next synthetic goal was to convert the α,β-unsaturated γ-lactone in **1** to its corresponding 3-substituted furan in **164** *via* a reduction reaction. In summary, the first synthesis of the

marine natural product anhydrofurospogin-1 **164** can be fundamentally achieved by extending second generation synthesis of (*E,E*)-furospongolide **1** by one synthetic step. According to the literature, the most common reagent employed for achieving this type of transformation is diisobutylaluminium hydride (DIBAL-H).[151,190-194] This reagent was adopted by Marcos *et al.* during the synthesis of sibiricinone B **163**, a natural product isolated from the motherwort plant *Leonorus sibericus* where it is utilised today as a cough syrup and antipyretic for treatment of malaria (***Scheme 2.91***).[191]




***Scheme 2.91***

Following the procedure described by Macros *et al.*, furospongolide **1** was successfully converted to anhydrofurospongin-1 **164** using 4.2 equivalents of diisobutylaluminium hydride in dry dichloromethane at -78 °C as illustrated in ***Scheme 2.92***.




***Scheme 2.92***

The reaction progress was monitored by thin layer chromatography, while maintaining the reaction temperature below -78 $^{o}$C. Complete consumption of **1** was evident after 1 hour and the reaction was subsequently quenched and worked-up using a saturated solution of Rochelle's salt. Sodium potassium tartrate is an excellent ligand for aluminium and breaking up aluminium emulsions.[195] Purification by column chromatography on silica gel afforded anhydrofuranosponin-1 **164** as a colourless oil in a good yield of 74%.

Spectroscopic characteristics were consistent with those reported by Cimino *et al.* for the marine natural product **164** with the disappearance of characteristic α,β-unsaturated γ-lactone signals at $\delta_H$ 5.82-5.86 ppm [1H, m, C(17)*H*] and $\delta_H$ 4.73 ppm [2H, d, *J* 1.7, C(19)$H_2$].[187] The $^1$H NMR spectrum now displayed the presence of 2 β-methylene-substituted furan rings with a 2H broad singlet at $\delta_H$ 7.34 ppm and $\delta_H$ 7.20 ppm attributed to four α-hydrogens [C(1)H, C(4)H, C(18)H andC(19)H] and a 2H broad singlet at $\delta_H$ 6.26 ppm assigned to two β-hydrogens [C(2)H and C(17)H] as illustrated in ***Figure 2.31***.

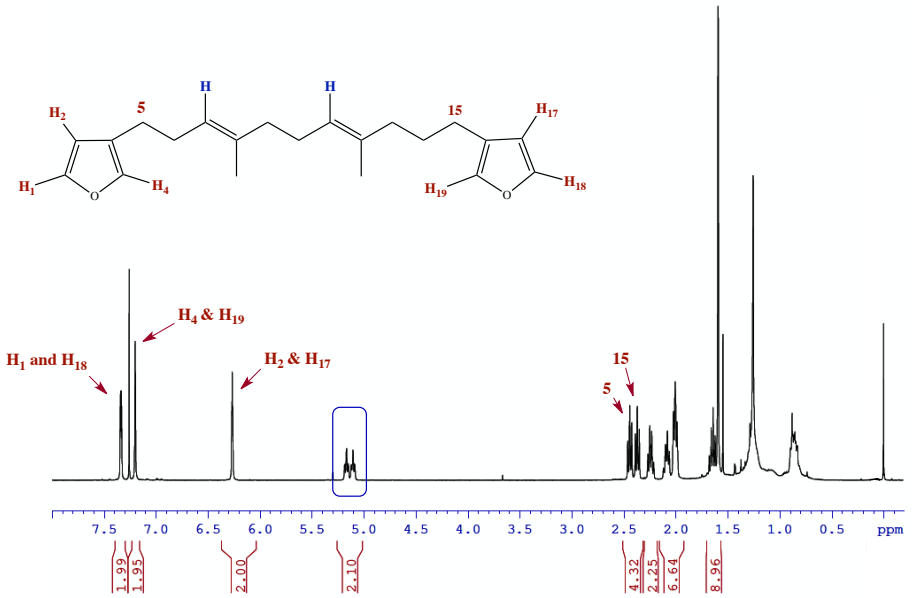



***Figure 2.31:*** *$^1$H NMR spectrum of anhydrofurospongin-1* ***164*** *($CDCl_3$, 300 MHz).*

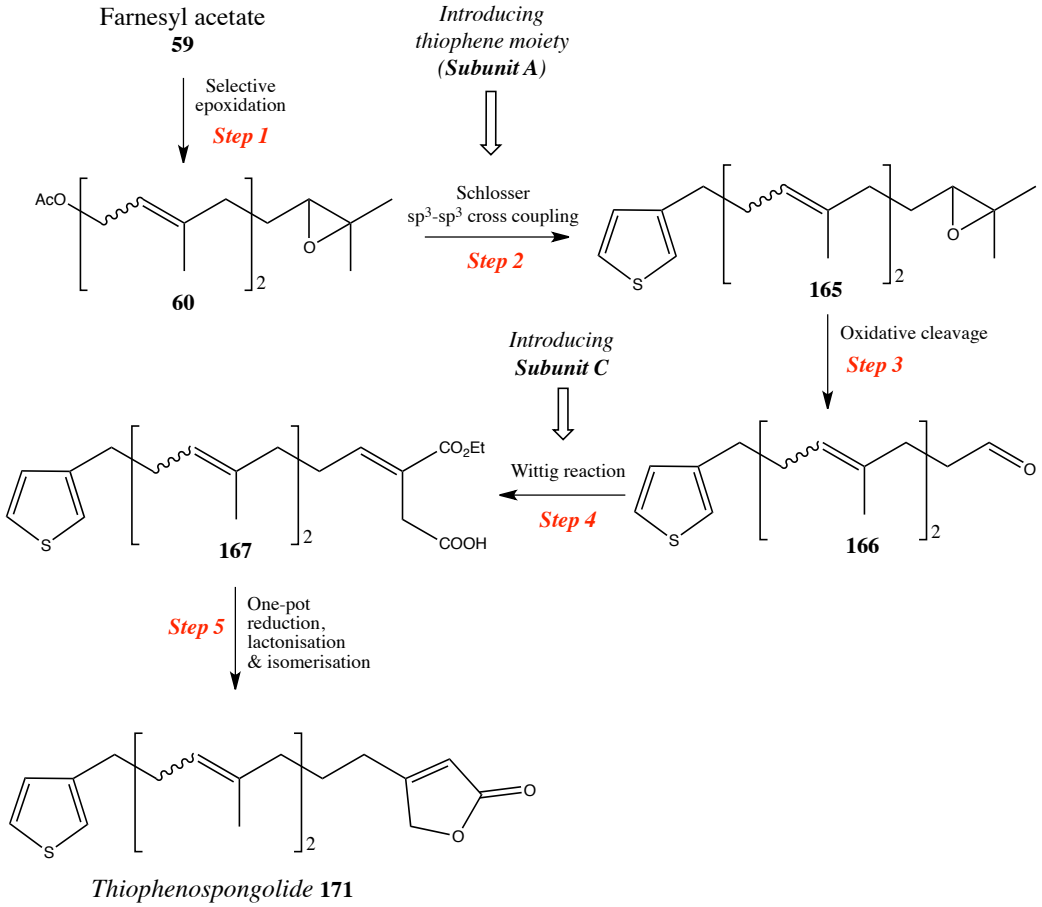
Formation of the furan ring triggered a change in the electronic environment causing a shift downfield for the α-methylene protons adjacent to the heterocycle at C(15)$H_2$ from a 2H quintet at $\delta_H$ 1.69 ppm to a distinctive 1H triplet at $\delta_H$ 2.37 ppm (*J* 7.6) (***Figure 2.31***). Additional spectroscopic evidence for the disappearance of the α,β unsaturated γ-lactone was observed with no carbonyl absorption peak in the IR spectrum and the disappearance of signals at $\delta_C$ 174.1 ppm and $\delta_C$ 170.5 ppm in the $^{13}C$ NMR spectrum.

To summarise, the first synthesis of anhydrofurospongin-1 **164** was accomplished in 6 linear steps and in 10.6% yield from (*E,E*)-farnesyl acetate. Preparation of this marine derived natural product was achieved by exploiting 2$^{nd}$ generation synthesis of furospongolide and extending the route by one additional step. It will be intriguing to identify following biologically evaluation, which of our two synthetic natural products (**1** and **164**) possess the greater antitumour activity. This SAR study will also help determine if the butenolide ring is important to the activity profile of furospongolide **1**.

## 2.8 Synthesis of thiophenospongolide

With the successful establishment of viable methodology that allows access to furospongolide **1** in 5 synthetic steps, it was now possible to proceed with the next stage of the synthetic strategy. Exploiting our synthetic route to develop novel furanolipid structural derivatives of **1** for the purpose of biological testing. Furthermore, we were extremely interested in preparing novel thiophenolipids and evaluating there potential as antitumour agents.

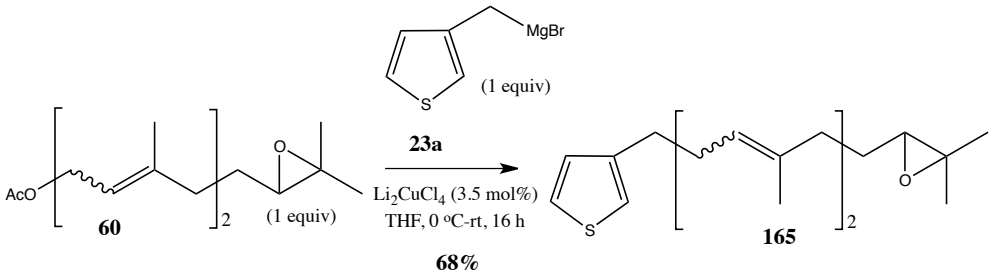
Merely by introducing the thiophene ring as an alternative to the furan ring in **subunit A**, synthesis of thiophenospongolide **171** from farnesyl acetate **59** was successfully achieved while obeying our established methodology developed during 2nd generation synthesis of furospongolide **1** (***Scheme 2.3***).




***Scheme 2.92:*** *Summary of the synthetic route towards thiophenospongolide **171**.*

For the same reason furospongolide **1** got its name,[2] this novel thiophenolipid was christened thiophenospongolide **171** by our group as its carbon skeleton embodies both a *thio*phene heterocycle and a buten*olide* ring. To the best of our knowledge, compound **171** is novel and has never been isolated from a natural source (i.e. aquatic or terrestrial life).

The initial step (*Step 2*) of this derivatisation study towards the preparation of thiophenospongolide **171** involved attachment of the thiophene moiety to (+/-)-10,11-epoxyfarnesyl acetate **60** employing established Schlosser $sp^3$-$sp^3$ cross coupling precedent as illustrated in ***Scheme 2.94***.[24,49,50]

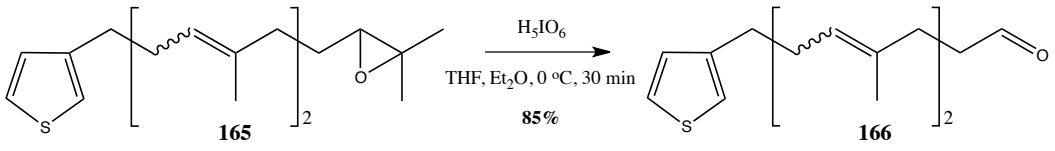



***Scheme 2.94***

The Grignard reagent was prepared in the usual manner from 3-thienylmethyl bromide **23** (1 equiv) and was added to the acetate **60** (1 equiv) in the presence of Kochi's catalyst ($Li_2CuCl_4$, 3.5 mol%) at 0 $^oC$ (***Scheme 2.94***).[60] Upon workup, after a 16 hour reaction at room temperature, $^1H$ NMR analysis of the crude product indicated a three component mixture consisting of the desired cross coupled product **165**, 1,2-di(thiophen-3-yl)ethane **39** and unreacted epoxide starting material **60** in a 43:4:53 ratio respectively. Purification by flash chromatography isolated the novel thiophenolipid epoxide **165** as a yellow oil in 68% yield (based on the consumed acetate **60**) with no trace of its corresponding γ-substituted by-product or allylic isomer detected as previously encountered in ***Scheme 2.67***. In a similar fashion to furanolipid epoxide **113**, the yield for thiophenolipid **165** was calculated by re-evaluating the theoretical yield following isolation of unreacted acetate ester **60** by chromatography.

Successful coupling was confirmed by $^{1}$H NMR spectroscopy with the appearance of a 3H multiplet at $\delta_H$ 2.59-2.75 ppm representing the hydrogens alpha to the thiophene at C(5)$H_2$ conjointly with the lone oxirane proton adjacent to the epoxide at C(15)*H*. The 2H quartet associated with the hydrogens beta to the furan [C(6)$H_2$] was also present at $\delta_H$ 2.31 ppm (*J* 7.3). Collectively, $^{13}$C NMR and IR analysis supported the elimination of the acetate ester functionality with the disappearance of the carbonyl peak at $\delta_C$ 171.1 ppm and $\nu_{max}$ 1739 cm$^{-1}$ respectively. Having successfully assembled the requisite C1-C15 segment, work was now focused on constructing the butenolide ring at the terminal end of the thiophenolipid backbone.

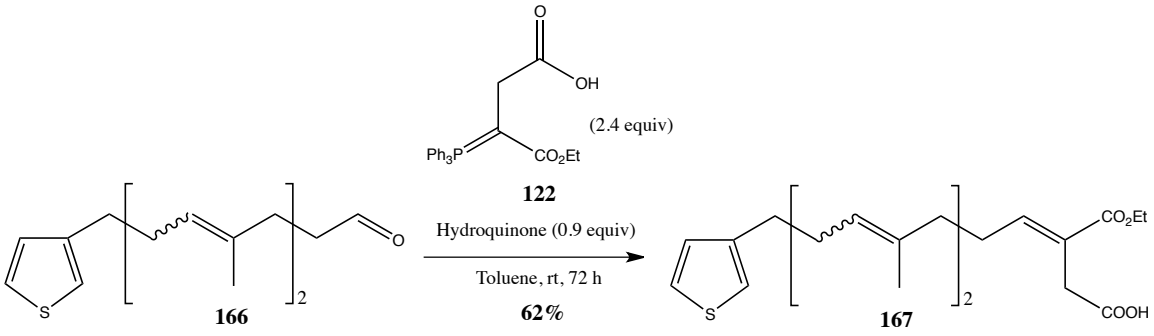
The next step involved converting the epoxide **165** to its corresponding aldehyde **166** following the standard precedent for a periodic acid-induced oxidative cleavage reaction as shown in ***Scheme 2.95***.[88]




***Scheme 2.95***

Purification by column chromatography on silica gel afforded the thiophenolipid aldehyde **166** as a light yellow oil in 85 % yield. $^{1}$H NMR spectroscopy confirmed the formation of the aldehyde **166** with the disappearance of the oxirane signal and the appearance of a distinctive 1H triplet at $\delta_H$ 9.74 ppm (*J* 1.9) assigned to the aldehyde proton. $^{1}$H NMR analysis revealed a 77:23 ratio of *E,E* and other isomer(s) following integration of the distinctive aldehyde peak at $\delta_H$ 9.74 ppm (*J* 1.9) and $\delta_H$ 9.77 ppm* (*J* 1.8) respectively. IR analysis displayed the disappearance of the epoxide stretch at $\nu_{max}$ 1123 cm$^{-1}$ and the appearance of a strong carbonyl stretch at $\nu_{max}$ 1727 cm$^{-1}$. The thiophenolipid aldehyde **166** became a versatile building block for the synthesis of thiopenolipid structural derivatives, which will be addressed in a later section (***Section 2.9.7***).

The next critical step in the synthetic route involved a cross coupling reaction between the thiophenolipid aldehyde **166** and the ylide **122**, which was successfully achieved while using our optimised conditions of the Wittig reaction as illustrated in ***Scheme 2.96***.

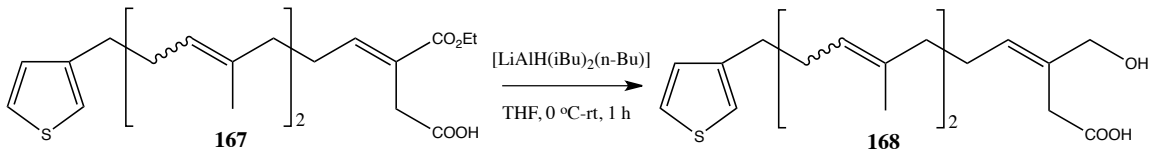



***Scheme 2.96***

Purification by flash chromatography neatly isolated the thiophenolipid monoethyl ester **167** as a viscous light yellow oil in 62% yield (which replicated previous results obtained with the furan derivative in ***Table 2.12, Entry 3***). Similar to the ester **126**, a longer reaction time of 72 hours was required to achieve full conversion to the half ester **167**. It is well documented in the literature that transformations of this type require longer reaction times which can vary depending on the substrate involved and the conditions employed for the cross coupling.[155]

$^1$H NMR analysis confirmed the synthesis of thiophenolipid monoethyl ester **167** with a shift upfield of a 1H triplet at $\delta_H$ 9.74 ppm (*J* 1.9) to $\delta_H$ 6.97 ppm (*J* 7.2), associated with the newly formed vinyl proton adjacent to the half ester at C(15)*H*. Coupling was also evident with a downfield shift in the methylene protons adjacent to the carboxylic acid functionality from a 2H doublet at $\delta_H$ 2.91 ppm (*J* 14.9) in the ylide **122** to a 2H singlet at $\delta_H$ 3.39 ppm [C(17)*H*] and the appearance of a broad 1H singlet associated with the carboxylic acid (COO*H*) at $\delta_H$ 10.1 ppm. Additional evidence was available from IR spectroscopy with the disappearance of an aldehyde absorption peak at $\nu_{max}$ 1727 cm$^{-1}$ (C=O) and the appearance of an α,β-unsaturated ester absorption stretch at $\nu_{max}$ 1715 cm$^{-1}$ and the broad acid (OH) absorption band at $\nu_{max}$ 3600-2400 cm$^{-1}$.

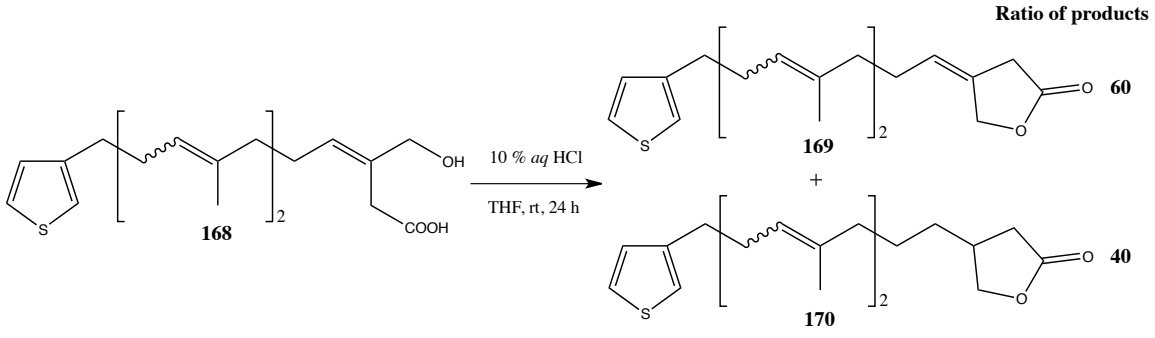
The last crucial step in the preparation of thiophenospongolide **171** was a one-pot reduction, lactonisation and isomerisation reaction. Utilizing our established methodology, the half ester **167** was selectively reduced to its corresponding γ-hydroxy acid **168** following treatment with 3.5 equivalents of the 'ate' complex at 0 $^{o}$C as summarised in ***Scheme 2.97***.




***Scheme 2.97***

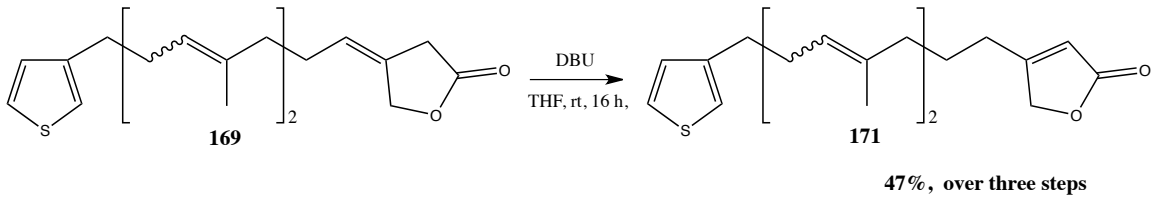
Workup was executed in the usual manner using sodium potassium tartrate (Rochelle's salt). $^{1}$H NMR analysis of the crude residue revealed that the desired γ-hydroxy acid **168** was formed with the appearance of a distinctive 2H signlet at $\delta_H$ 4.14 ppm [C(19)$H_2$] and an upfield shift of the vinylic proton at C(15)*H* from a 1H triplet at $\delta_H$ 6.97 ppm (*J* 7.2) to a 1H multiplet at $\delta_H$ 5.60-5.70 ppm. Due to the ability of **168** to readily lactonise, the γ-hydroxy acid **168** was charged to the ensuing acid induced lactonisation reaction without further purification by column chromatography.

By adjusting the acidity of the reaction mixture to pH 1 using 10% aqueous hydrochloric acid, the corresponding thiophenolipid lactone **169** was successfully prepared following a 24 hour stir at room temperature as shown in ***Scheme 2.98***.




***Scheme 2.98***

Following workup, $^1$H NMR integration revealed a two component mixture consisting of the desired lactone **169** and its corresponding lactone **170** in a 60:40 ratio of products respectively. $^1$H NMR analysis confirmed the synthesis of **169** with the appearance of a 2H multiplet at $\delta_H$ 3.10-3.17 ppm [C(17)$H_2$] and at $\delta_H$ 4.78-4.84 ppm [C(19)$H_2$] associated with the $\alpha$ and $\gamma$–methylene protons of the lactonic ring respectively. Separation of the crude mixture by flash chromatography was deemed unwise at this stage, as the ensuing base-induced isomerisation reaction would have no detrimental affect on the saturated lactone by-product **170**. Immediately, the crude mixture consisting of **169** and **170** was treated with 1,8-diazabicycloundec-7-ene in tetrahydrofuran at room temperature while using the conditions previously utilised in the synthesis of furospongolide **1** (***Scheme 2.99***).




***Scheme 2.99***

To our delight, purification by column chromatography on silica gel neatly isolated thiophenospongolide **171**, as a light yellow oil in 47%. The $^1$H NMR spectrum was similar to furospongolide **1** with the disappearance of the 1H multiplet at $\delta_H$ 5.37-5.48 ppm and a significant and distinctive shift of the $\alpha$-methylene protons [C(17)$H_2$] at $\delta_H$ 3.10-3.17 ppm to a vinylic 1H multiplet at $\delta_H$ 5.81-5.87 ppm essentially confirming isomerisation (***Figure 2.32***). The IR spectrum contained characteristic $\alpha,\beta$-unsaturated lactone absorption stretches at $\nu_{max}$ 1781 cm$^{-1}$ and $\nu_{max}$ 1751 cm$^{-1}$.

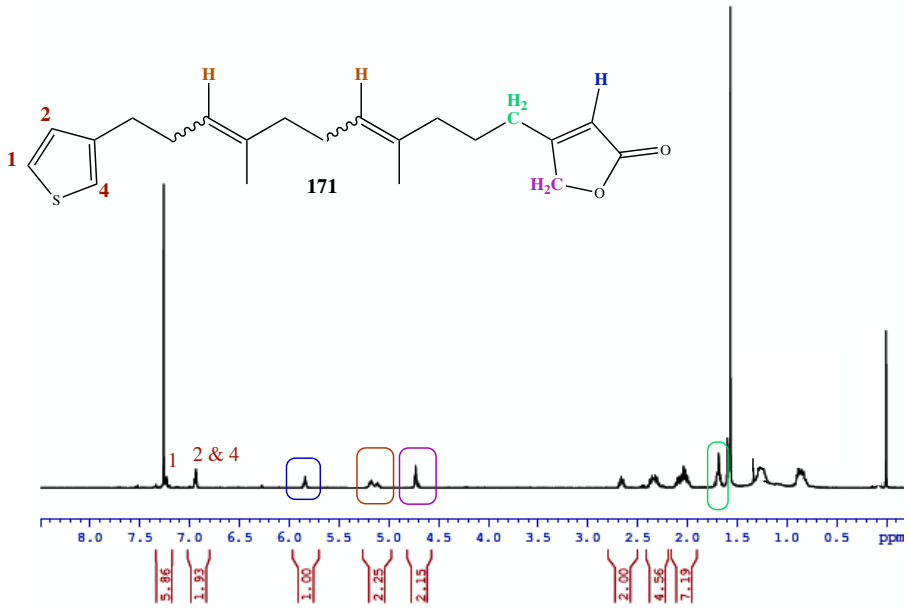


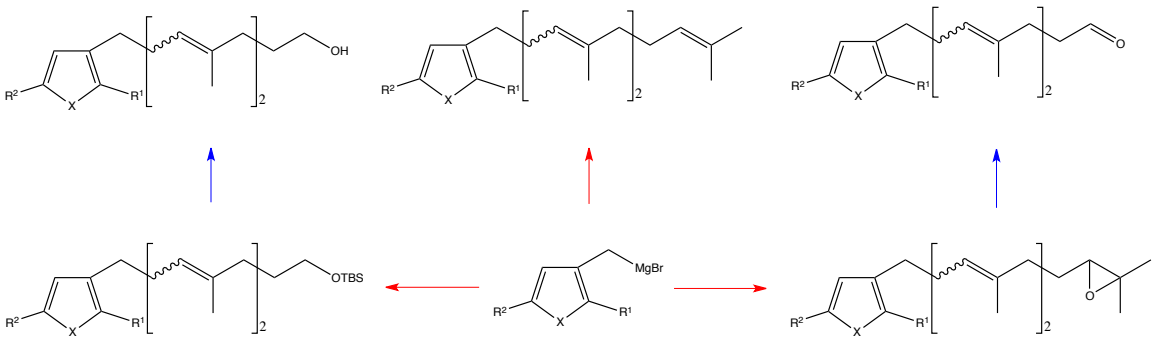

***Figure 2.32:*** *$^{1}H$ NMR spectrum of thiophenospongolide **171** ($CDCl_3$, 300 MHz).*

The least polar fraction, the saturated lactone **170**, was independently isolated as a light yellow oil in 26% yield (overall yield calculated from the theoretical over two transformations)*. Spectroscopic characteristics were similar to those previously described for the furanolipid saturated lactone **148** with the appearance of a 1H multiplet at $\delta_H$ 3.87-3.95 ppm ($\delta_H$ 3.91 ppm, dd, *J* 8.9, 7.3,) and $\delta_H$ 4.38-4.45 ppm ($\delta_H$ 4.41 ppm, dd, *J* 8.9, 7.3,) characteristic of the γ-methylene hydrogens [C(19)$H_2$]. Fundamentally these signals should be clean doublet of doublets due to a spin-spin splitting interaction with the neighbouring proton. However, due to the mixture of isomers, accurate assignment of the peaks was not possible.

To summarise, our total synthesis of thiophenospongolide **171** was accomplished in 5 linear steps from commercially available farnesyl acetate **59** in 11.2% overall yield. Having successfully established a viable synthetic route, future work will look towards synthesising (*E,E*)-thiophenospongolide **171** and optimising the synthetic route to improve the overall yield.

## 2.9 Synthesis of terpene, 3-substituted furanolipid or thiophenolipid analogues

With the successful establishment of a viable synthetic route towards the synthesis of furospongolide **1** and thiophenospongolide **171**, attention was now turned to derivatisation of the linear pathway in the development of an extensive library of novel compounds for biological testing. To achieve this goal, the simplest approach for accessing novel 3-substituted furan and thiophene derivatives of biological interest involved exploiting the Schlosser $sp^3$-$sp^3$ cross coupling reaction and introducing different analogues of **subunit A** systematically at various different points in the synthetic route as exemplified in ***Scheme 2.100***.




***Scheme 2.100:*** *Utilising the Schlosser $sp^3$-$sp^3$ cross coupling reaction to access both 3-substituted furan and thiophene analogues.*

This study will provide valuable information on the structural-activity relationship (SAR) of our target molecule **1**. For instance, how important is the furan heterocycle and/or the butenolide ring to its bioactivity? To date, very little is actually known about the SAR profile of furospongolide **1** (***Figure 2.33***).

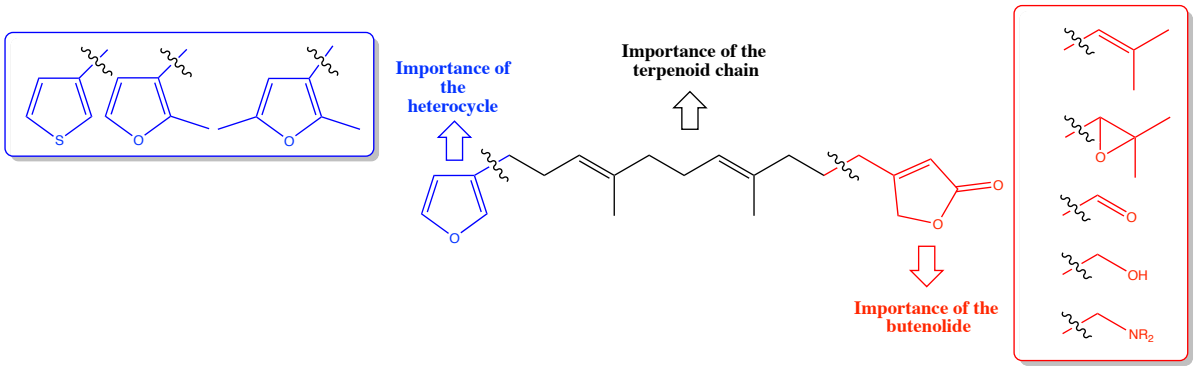



***Figure 2.33***

Liu *et al.* reported that when furospongolide **1** was hydrolysed to its open lactone form **172** (***Figure 2.34***), almost complete loss of HIF-1 activity was observed in the T47D cell-based reporter assay.[1] It should be noted that acid **172** is identical in structure to γ-hydroxy acid **146** apart from the position of the double bond. Furthermore, Dai *et al.* reported how a furanolipid **173** isolated from the same marine sponge as furospongolide **1** (*Lendenfeldia* sp.) was essentially inactive showing no significant inhibition of HIF-1 activation (***Figure 2.34***).[196]

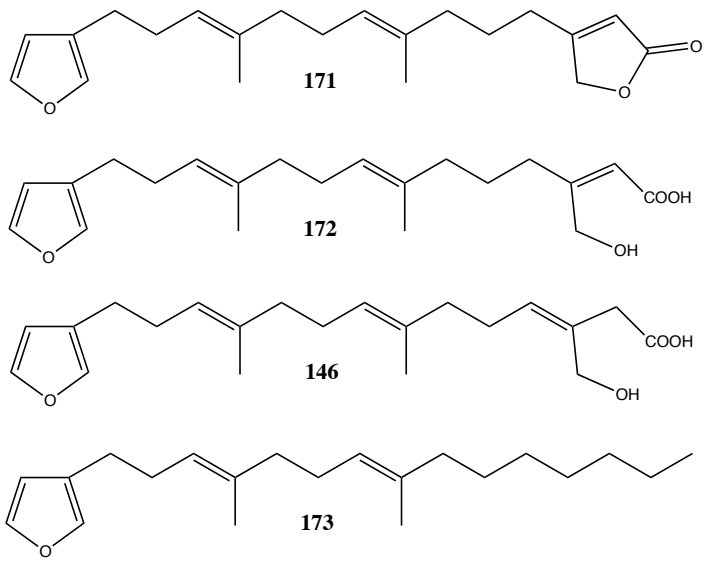



***Figure 2.34***

This information conveys the significance of the butenolide ring to its inherent bioactivity. With that said, it would be completely inaccurate to assume that all furanosesterterpenoid lacking a butenolide moiety are essentially biological inactive. As alluded to in my introduction (***Section 1.1.9.2***), furanosesterterpenoids are a highly promising and underexploited class of compounds in the field of anticancer chemotherapy. In order to analyse the detailed structure-activity relationship around the aromatic ring, our synthetic endeavours began with the synthesis of 3-substituted furan and thiophene olefins.

### 2.9.1 Synthesis of 3-substituted furanolipid and thiophenolipid olefins

Ambliofuran **112** is a natural product first isolated from the marine sponge *Dysidea amblia* by Walker *et al.*[10] Since its reported discovery in 1981, this linear diterpene has appeared as a fundamental metabolite isolated from numerous marine sponges.[197-200] Furthermore, this furanolipid **112** has been isolated from the marine sponge *Dysidea herbacea*, the same species from which furospongolide **1** was first isolated and characterised.[197] Interestingly, ambliofuran **112** was screened for antitumour activity by Higa *et al.* in the early 90's and found to be weakly cytotoxic against P388, A-549 human lung carcinoma and HT-29 human colon adenocarcinoma cells.[197]

It has been postulated in the literature,[10,201] that this simple linear diterpene may function as the precursor building block to more complex cyclic and/or linear metabolites. Tischler *et al.* suggested that ambliofuran **112** serves as a starting point in the biosynthesis of the other four compounds **174-177** isolated from the marine sponge *Dysidea amblia* (as shown in ***Figure 2.35***).[201]

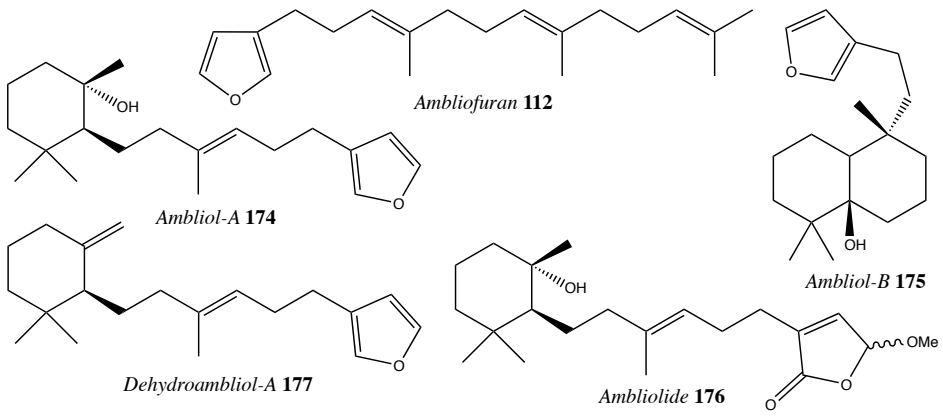
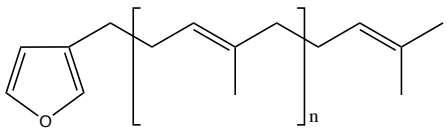



***Figure 2.35***. *Five metabolites isolated from the marine sponge Dysidea amblia.*[197] *The proposed biogenetic origin of metabolites from ambliofuran* ***112*** *precursor.*[201]

As suggested by Tischler *et al.*, functionalisation of **112** can be addressed by subsequent biological inter-conversions involving enzyme catalysed oxidations and reductions while cyclisation can be explained by proton initiated cyclisation of ambliofuran **112 (*Figure 2.35*)**.[201] Taking all this into consideration, would it be correct to propose that the biosynthesis of furospongolide **1** in Nature's hands originates from ambliofuran **112** as a precursor building block?

Like dendrolasin **10**, the synthesis of ambliofuran **112** has been explored in great detail. (***Figure 2.36***).[144,197,202-205] Furthermore, ambliofuran **112** is a structural analogue of the sesterterpenoid hypoxia-selective growth inhibitor, furospinosulin-1 **178** (four iterative isoprene units),[206,207] which was previously discussed in ***Section 1.1.9.2.1***

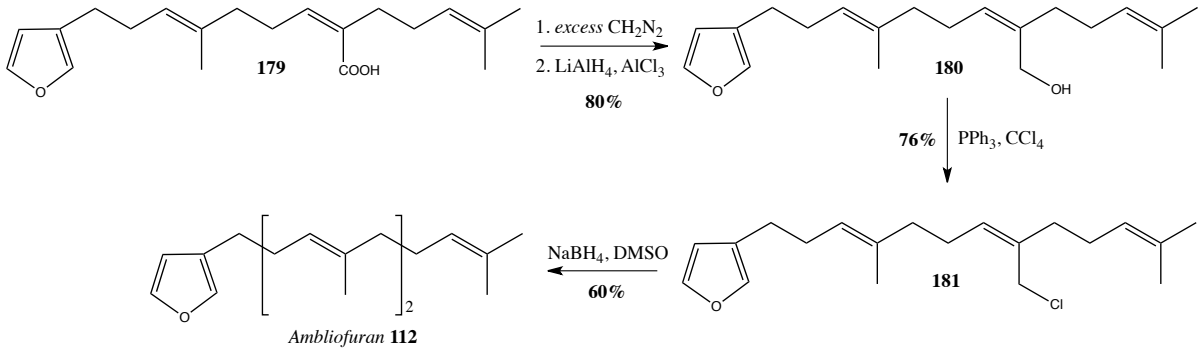



n=1 Dendrolasin **10**
n=2 Ambliofuran **112**
n=3 Furospinosulin-1 **178**

***Figure 2.36***

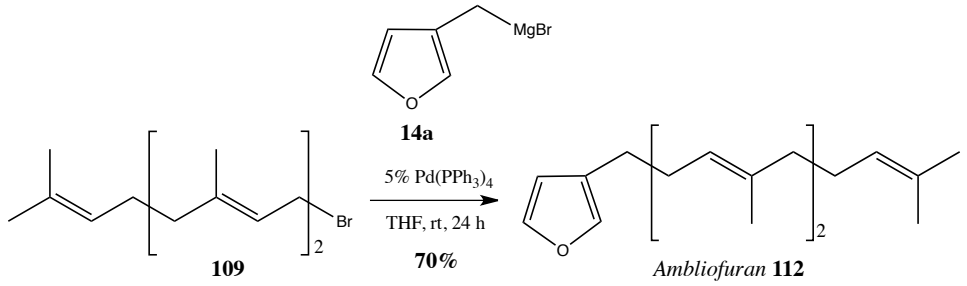
The intriguing bioactivities for 3-substituted furan olefins (**10**, **112** and **178**) prompted us to engage in a synthetic study towards the preparation of ambliofuran **112** and other novel structurally related analogues. This study would also aid in understanding the structure-activity relationship of furospongolide **1** and the importance of the furan ring.

To the best of our knowledge, the first reported preparation of ambliofuran **112** was by Sharma *et al.* in 1984, which was a semi-synthesis from naturally occurring furanoditerpene acid **179** as illustrated in ***Scheme 2.101***.[204]




***Scheme 2.101:*** *First semi-synthesis of ambliofuran **112** as reported by Sharma et al.*[204]

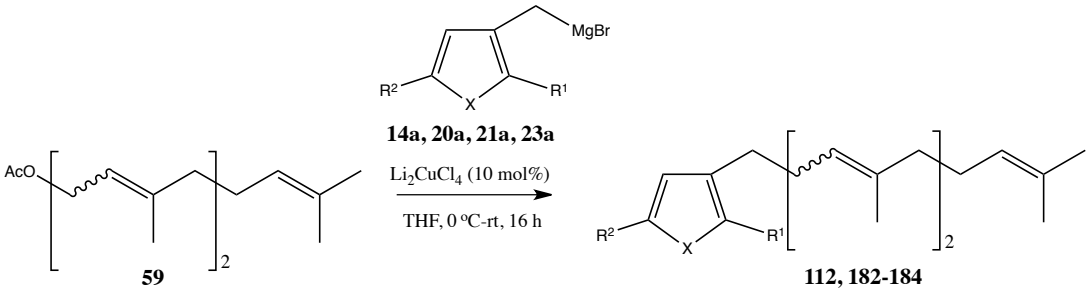
Overtime, with advancements in organic chemistry, more direct methods for the synthesis of 3-substituted furans have been developed as illustrated in ***Scheme 2.102,*** which involves a regioselective Grignard cross coupling reaction using tetrakis(triphenylphosphine)palladium(0) as a catalyst.[144,208]




***Scheme 2.102***

Similar to the latter example, ambliofuran **112** was conveniently prepared within our research group by coupling farnesyl acetate **59** with 3-furylmethyl magnesium bromide **14a** employing dilithium tetrachlorocuprate (II) solution (10 mol%) as the catalyst *via* the Schlosser $sp^3$-$sp^3$ cross coupling reaction (***Table 2.16, Entry 1***).[25,28]

***Table 2.16***: *Synthesis of ambliofuran **112** and other 3-subtituted furan and thiophene olefins via Schlosser $sp^3$-$sp^3$ cross coupling of farnesyl acetate **59** with various Grignard reagents.*




| Entry | $R^1$ | $R^2$ | X | Product | Ratio [c] Product: Wurtz | Yield [a] |
|---|---|---|---|---|---|---|
| **1** | H | H | O | **112** | 85:15 | 76% |
| **2** | H | H | S | **182** | 83:17 | 81% |
| **3** | $CH_3$ | H | O | **183** | 63:37 | 82% |
| **4** | $CH_3$ | $CH_3$ | O | **184** | 69:31 | 66% |

**a: Isolated yield following purification by column chromatography.**
**c: Ratio was estimated by $^1$H NMR integration of the crude product.**

With respect to ***Entry 1***, the reaction proceeded smoothly giving exclusive formation of the α-substituted product as determined by $^1$H NMR analysis of the crude product. The Wurtz coupling product **32** was visibly evident in the crude product and was subsequently removed by column chromatography on silica gel as the least polar fraction. Ambliofuran **112** was successfully isolated as a non-viscous colourless oil in 76% yield and spectroscopic characteristics were consistent with those previously reported in the literature.[10,209]

By exploiting this synthetic methodology, it was feasible to prepare structural analogues of ambliofuran **112** simply by varying the Grignard reagent as shown in ***Table 2.16, Entry 2,3 and 4***). Column chromatography on silica gel was implemented to remove the Wurtz by-product, which was formed in incessant ratios depending on the Grignard reagent employed.

All three terpenoid analogues **182, 183** and **184** were isolated pure as non-viscous colourless oils in good yields as shown in ***Table 2.16***.

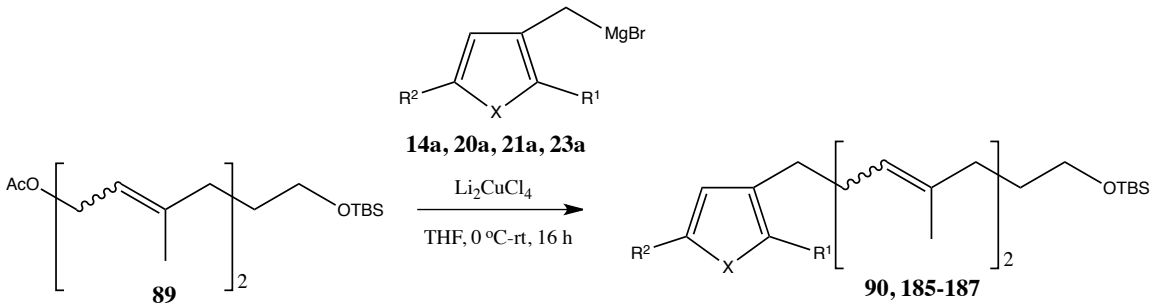
$^{1}$H NMR analysis confirmed successful synthesis of the 3-substituted furan and thiophene analogues (**112, 182-184**) with the appearance of a 2H triplet in the region $\delta_H$ 2.28-2.66 ppm (*J* 7.2-7.5) characteristic of the α-methylene protons adjacent to the heterocycle at C(5)$H_2$. With respect to the ambliofuran **112**, a 2H quartet at $\delta_H$ 2.25 ppm (*J* 5.3) was observed characteristic of the β-methylene protons at C(6)$H_2$. Collectively, $^{13}$C NMR and IR analysis supported the elimination of the acetate ester functionality with the disappearance of the carbonyl peak at $\delta_C$ 171.1 ppm and $\nu_{max}$ 1742 cm$^{-1}$ respectively.

Furanolipid and thiophenolipid olefins **182**, **183** and **184** were sent to the NCI for biological evaluation in order to establish key information about the SAR profile of furospongolide **1** and the results will be discussed in ***Section 3.1.3.1***.

### 2.9.2 Synthesis of 3-substituted furanolipid and thiophenolipid alcohols

Continuing the synthetic derivatisation theme, attention was now focused on developing a novel series of 3-substituted furanolipid and thiophenolipid alcohols. In order to access the alcohol derivatives, the furano/thiophenolipid silyl ether derivatives will be prepared first followed by subsequent deprotection to unmask the hydroxyl group. With respect to ***Table 2.17***, the Grignard reagent was prepared in the usual manner and added to the acetate **89** in the presence of Kochi's catalyst (10 mol%) at 0 $^{o}$C.

***Table 2.17:*** *Results obtained from the cross coupling of acetate **89** with various Grignard reagents via Schlosser $sp^3$-$sp^3$ cross coupling reaction.*



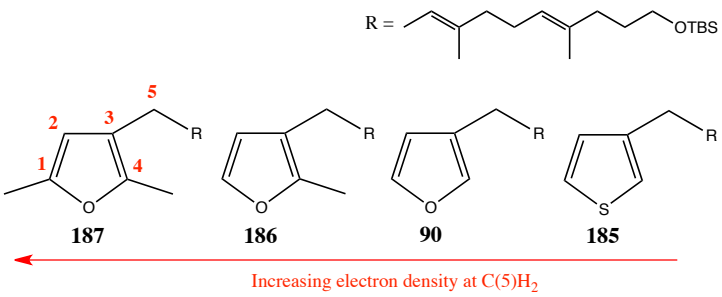

| Entry | $R^1$ | $R^2$ | X | Product | Ratio [c] Product: Wurtz | %Yield |
|---|---|---|---|---|---|---|
| **1** | H | H | O | **90** | 85:15 | 77% [b] |
| **2** | H | H | S | **185** | 82:18 | 71% [a] |
| **3** | $CH_3$ | H | O | **186** | 2:1 | 69% [b] |
| **4** | $CH_3$ | $CH_3$ | O | **187** | 68:32 | 59% [b] |

**a: Isolated yield following purification by chromatography.**
**b: % Conversion determined by $^1$H NMR analysis.**
**c: Ratio was estimated by $^1$H NMR integration of the crude product.**

With respect to furanolipid silyl ether **90** (***Entry 1***), this compound was previously prepared during second generation synthesis of furospongolide **1** for accessing the furanolipid alcohol **91**. The alcohol **91** was subsequently brominated where it was used as a precursor Grignard reagent in the conjugate addition/elimination cross coupling with the vinyl triflate **57** (*please refer to **Section 2.3.10***).

In all four cases, $^{1}$H NMR analysis of the crude product indicated complete consumption of starting material to afford a two-component mixture consisting of the desired cross coupled product and its corresponding Wurtz coupled product in their respective ratios as indicated in ***Table 2.17***. Fortunately, no trace of the γ-isomer (regioisomer) was observed following spectroscopic analysis. Purification by column chromatography on silica gel (100% hexane) was in most cases challenging (***Table 2.17, Entry 1, 3 and 4***) due to similar $R_f$ values between the product and its corresponding Wurtz homocoupled product. Due to undesired co-elution, yields were calculated by $^{1}$H NMR integration. In the case of ***Entry 1***, only minor co-elution occurred (<5%). However with respect to ***Entry 3*** (11%) and ***Entry 4*** (32%), co-elution occurred to a greater extent. Instead of arduous repetitive chromatography, the furano/thiophenolipid analogues (**90, 185-187)** were converted to their corresponding alcohols (**91, 188-190)** to make purification slightly easier.

With respect to the TBS protected furanolipid analogues (**90, 185-187**), $^{1}$H NMR analysis confirmed the successful coupling with the appearance of a 2H triplet in the region $\delta_H$ 2.28-2.45 ppm (*J* 7.5-7.6). Interestingly, using NMR spectroscopy it was possible to observe how varying the substitution around the heterocycle could influence the electron density around the adjacent methylene group [*C*(5)$H_2$] as illustrated in ***Figure 2.37***.



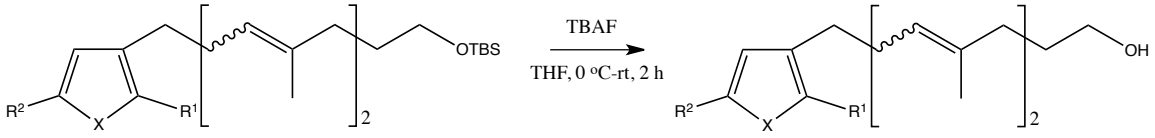

| | | | | |
|---|---|---|---|---|
| $\delta_H$ C(5)$\underline{H}_2$ | 2.28 (*J* 7.6) | 2.35 (*J* 7.6) | 2.45 (*J* 7.5) | 2.66 (*J* 7.3) |
| $\delta_C$ $\underline{C}$(5)$H_2$ | 25.1 | 25.1 | 25.1 | 30.4 |

***Figure 2.37***

With respect to 2,5-dimethyl furanolipid **187**, due to the electron donating effect of the two methyl groups at the α-positions on the furan ring, a greater shielding effect is generated at C(5)$H_2$, causing the peak at $\delta_H$ 2.28 ppm (*J* 7.6) to appear further upfield relative to **90** at $\delta_H$ 2.45 ppm (*J* 7.6). As expected, the same dictating effect was observed for 2-methyl-furanolipid **186**, with a 2H triplet at $\delta_H$ 2.35 ppm [*J* 7.6, C(5)$H_2$] due to a slightly weaker electron donating effect from the lone α-methyl group. Since sulfur is a less electronegative atom than oxygen, the methylene protons adjacent to the thiophene ring of **185** appeared further downfield as a 2H triplet at $\delta_H$ 2.66 ppm (*J* 7.2) relative to the furan (***Figure 2.37***). This interesting observation was also evident in the $^{13}C$ NMR spectrum with the peak at C(5) adjacent to the thiophene appearing at $\delta_H$ 30.4 ppm, which is at a higher chemical frequency when compared to the furan at $\delta_H$ 25.1 ppm (***Figure 2.37***). The IR spectrum showed no carbonyl absorption stretch at $\nu_{max}$1743 $cm^{-1}$.

Following successfully attachment of the appropriate heterocycle to the central linchpin **89**, the next reaction was the desilylation reaction to unmask the hydroxyl group. Removal of the silyl protecting group was achieved using tetra-*n*-butyl ammonium fluoride in tetrahydrofuran over a 2 hour reaction period at room temperature using predetermined methodology (***Table 2.18***).

***Table 2.18:*** *Results obtained following the removal of the silyl protecting group with TBAF.*




**90,185-187** **91,188-190**

| Entry | $R^1$ | $R^2$ | X | Product | Yield [a] |
|---|---|---|---|---|---|
| **1** | H | H | O | **91** | 91% |
| **2** | H | H | S | **188** | 78% |
| **3** | $CH_3$ | H | O | **189** | 86% |
| **4** | $CH_3$ | $CH_3$ | O | **190** | 66% |

**a: Isolated yield following purification by column chromatography.**

Purification by column chromatography on silica gel successfully isolated the desired furano/thiophenolipid analogues (**91, 188-190**) independent of the Wurtz homocoupled product. With respect to ***Entry 4***, a low isolated yield of 66% was encountered for alcohol **190**. It is worth noting that 2,5-dimethyl substituted furanolipid **190** was slightly unstable with obvious signs of decomposition by $^{1}$H NMR analysis after one week under storage. The other three alcohols (**91, 188-189**) could be stored under an inert nitrogen atmosphere in a freezer and used when desired without any evidence of degradation.

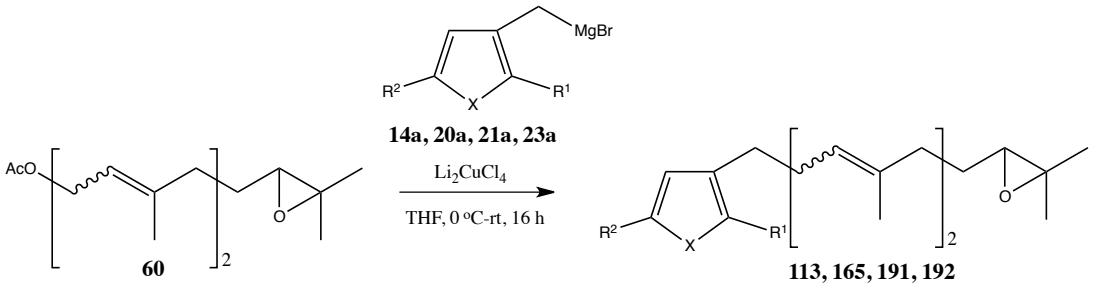
In all four cases, $^{1}$H NMR analysis confirmed the effective removal of the silyl protecting group with the appearance of a 2H triplet at $\delta_H$ 3.62 [*J* 6.4, C(15)$H_2$], slightly downfield from the 2H triplet at $\delta_H$ 3.58 ppm (*J* 6.6) in the corresponding silyl ether. IR spectroscopy displayed the appearance of a hydroxyl group stretch in the region $\nu_{max}$ 3339-3343 cm$^{-1}$.

The furano/thiophenolipid analogues **188** and **189** were subsequently sent for biological testing to establish their potential as antitumour agents and answer key information about the SAR profile of furospongolide **1**.

### 2.9.3 Synthesis of 3-substituted furanolipid and thiophenolipid epoxides

The synthesis of 3-substituted furanolipid and thiophenolipid epoxides were the next series to be investigated (***Table 2.19***). Epoxides are widely versatile building blocks in organic synthesis,[210] which are present in several bioactive compounds.[211]

***Table 2.19:*** *Results obtained from the cross coupling of epoxygeranyl acetate* ***60*** *with various Grignard reagents via Schlosser $sp^3$-$sp^3$ cross coupling reaction.*




| Entry | $R^1$ | $R^2$ | X | $Li_2CuCl_4$ | Product | Yield |
|---|---|---|---|---|---|---|
| **1** | H | H | O | 6.7 mol % | **113** | 76% [a] |
| **2** | H | H | S | 3.5 mol % | **165** | 68% [a] |
| **3** | $CH_3$ | H | O | 10 mol % | **191** [c] | 60% [b] |
| **4** | $CH_3$ | $CH_3$ | O | 3.3 mol % | **192** [d] | 58% [b] |

**a: Isolated yield following purification by column chromatography.**
**b: % Conversion as determined by $^1$H NMR integration.**
**c: Reaction furnished both the α- and γ-isomer in a 92:8 ratio of products respectively.**
**d: Product contained product and unreacted bromide starting material in a 88:12 ratio respectively.**

With respect to ***Entry 1*** and ***Entry 2***, these results were formerly presented when addressing the total synthesis of furospongolide **1** and thiophenospongolide **171** respectively. Encouraged by the success of previous reports and in order to expand the furanolipid library, the same methodology was employed in the synthesis of furanolipid epoxides **191** and **192**.

In the case of ***Entry 3***, the concentration of copper catalyst ($Li_2CuCl_4$) employed was too high (10 mol%) for the Schlosser cross coupling reaction resulting in a minor formation of the γ-isomer **193**.[49,50] As previously encountered in ***Section 2.4.1,*** following flash chromatography, $^1$H NMR analysis revealed an inseparable two-component mixture consisting of the desired cross-coupled product **191** and its corresponding γ-regioisomer **193** in a 92:8 ratio of products respectively (***Figure 2.38***).[49] The concentration of Kochi's catalyst

was amended (decreased ~3 fold) for further cross coupling reactions of this type (***Table 2.19***). $^{1}$H NMR integration indicated that conversion to epoxide **191** was achieved in 60%. Despite the presence of the γ-isomer **193**, the epoxide **191** was used in the next transformation without further purification.

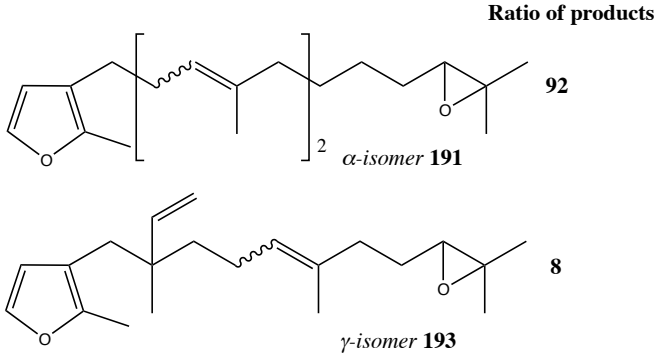



***Figure 2.38:*** *Ratio of α-isomer **191** and γ-isomer **193** as determined by $^{1}$H NMR integration.*

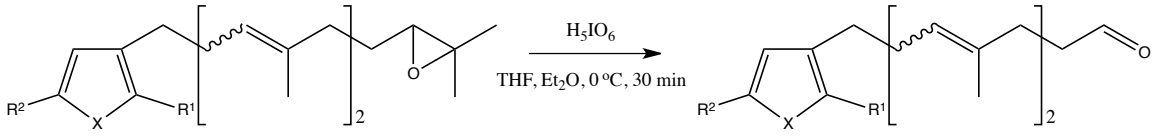
With respect to ***Entry 4***, purification by flash chromatography afforded the desired product **192** as a colourless oil with no trace of the γ-isomer in the $^{1}$H NMR spectrum. However it must be noted that minor co-elution of the epoxide **192** with unreacted bromide starting material **21** occurred in a 88:12 ratio respectively. Conversion to **192** was achieved in 58%. Further purification was deemed unnecessary at this stage and the epoxide **192** was used accordingly in the next transformation. It was envisioned that the bromide **21** would be removed by chromatography following the oxidative cleavage reaction.

With the exception of ***Entry 3***, following the conditions seen in ***Table 2.19***, furano/thiopenolipid epoxides **113**, **165** and **192** were obtained in high regioselectively with no products arising from epoxide opening following the reaction of various Grignard reagents with stable and readily available (+/-)-10,11-epoxygeranyl acetate **60**. $^{1}$H NMR analysis confirmed the formation of furanolipid epoxides **191** and **192** with the appearance of a 2H triplet in the region $\delta_H$ 2.28-2.35 ppm assigned to the methylene group adjacent to the furan at C(5)$H_2$. IR analysis showed the disappearance of the carbonyl absorption stretch at $\nu_{max}$ 1727 cm$^{-1}$ and the appearance of a characteristic oxirane (C-O) absorption stretch in the region $\nu_{max}$ 1123-1138 cm$^{-1}$.

### 2.9.4 Synthesis of 3-substituted furanolipid and thiophenolipid aldehydes

The aldehydes used in the preparation of furospongolide **1** and thiophenospongolide **171** are featured in ***Entry 1*** and ***Entry 2*** respectively. The methodology employed in their synthesis was utilised in the synthesis of 2-methyl substituted furanolipid aldehyde **194** and 2,5-dimethyl substituted furanolipid aldehyde **195** from their corresponding epoxides **191** and **192** following treatment with periodic acid at 0 $^{o}$C over a 30 minute period as illustrated in ***Table 2.20***.

***Table 2.20:*** *Synthesis of furano/thiophenolipid aldehyde analogues via periodic acid induced oxidative cleavage of furano/thiophenolipid epoxide substrates.*




**113,165,191-192** **121,166,194-195**

| Entry | $R^1$ | $R^2$ | X | Product | Yield |
|---|---|---|---|---|---|
| **1** | H | H | O | **121** | 80% [a] |
| **2** | H | H | S | **166** | 85% [a] |
| **3** | $CH_3$ | H | O | **194** | 75% [b] |
| **4** | $CH_3$ | $CH_3$ | O | **195** | 53% [a] |

**a: Isolated yield following purification by column chromatography.**
**b: Yield determined by $^1$H NMR integration following column chromatography.**

In the case of ***Entry 3***, a two-component mixture consisting of the epoxide **191** and its corresponding γ-regioisomer **193** were successfully converted to their respective aldehydes **194** and **196** in a 88:12 ratio of products. Following flash chromatography, $^1$H NMR analysis of the inseparable mixture indicated that the desired aldehyde **194** was synthesised in 75% yield as a faint yellow oil. The presence of this inseparable γ-isomer **196** made further transformations essentially pointless and advancing derivatisation studies on 2-methyl substituted furanolipids were temporarily abandoned.

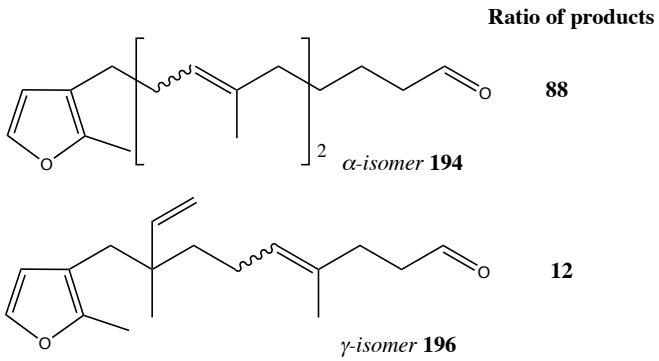



***Figure 2.39:*** *Ratio of α-isomer **194** and γ-isomer **196** as determined by $^{1}$H NMR integration.*

With respect to ***Entry 4***, the aldehyde **195** was successfully isolated as a light yellow oil in 53% yield following purification by column chromatography on silica gel. As intended, the bromide side product **21** carried through from the previous reaction was successfully removed. However, it must be noted that following purification, the furanolipid **195** was notoriously susceptible to degradation even when stored in the dark, under inert atmosphere at freezing temperatures over short periods of time. Due to the inherent instability of this aldehyde **195**, engaging in further transformations with this compound was impractical and thus abandoned.

$^{1}$H NMR analysis confirmed the synthesis of all four aldehydes **121, 166, 194** and **195** with the loss of the characteristic oxirane proton signal at $\delta_H$ 2.71 ppm (1H, t, *J* 6.2) and the appearance of a distinctive 1H triplet at $\delta_H$ 9.74 ppm (*J* 1.9) corresponding with the aldehyde group at C(15)*H*. This transformation was also observed by $^{13}$C NMR and IR spectroscopy with a high frequency chemical shift of the peak at *C*15 from $\delta_C$ 64.2 ppm to the region $\delta_C$ 202.6-202.8 ppm and the emergence of a strong carbonyl absorption stretch in the region $\nu_{max}$1727-1728 cm$^{-1}$ respectively.

### 2.9.5 Synthesis of terpene amines

The amine group is one of the most frequently found functional groups in today's armory of commercially available drugs. Amine based pharmaceutical drugs cover a diverse range in the treatment of human ailments like pain relief (codeine **197**), obesity (sibutramine **200**), cancer (gefitinib **201**), Parkinson's (procyclidine **202**), Alzheimer's (rivastigmine **199**) and HIV (lopinavir **203**) just to name a few (***Figure 2.40***). Like many pharmaceuticals, compounds containing an amine can have physicochemical attributes that present obstacles to their safe and effective delivery to desired sites of action. Amines are generally considered to be amenable to derivatisation reactions and thus provide a "synthetic handle" that can be exploited in chemical modifications.

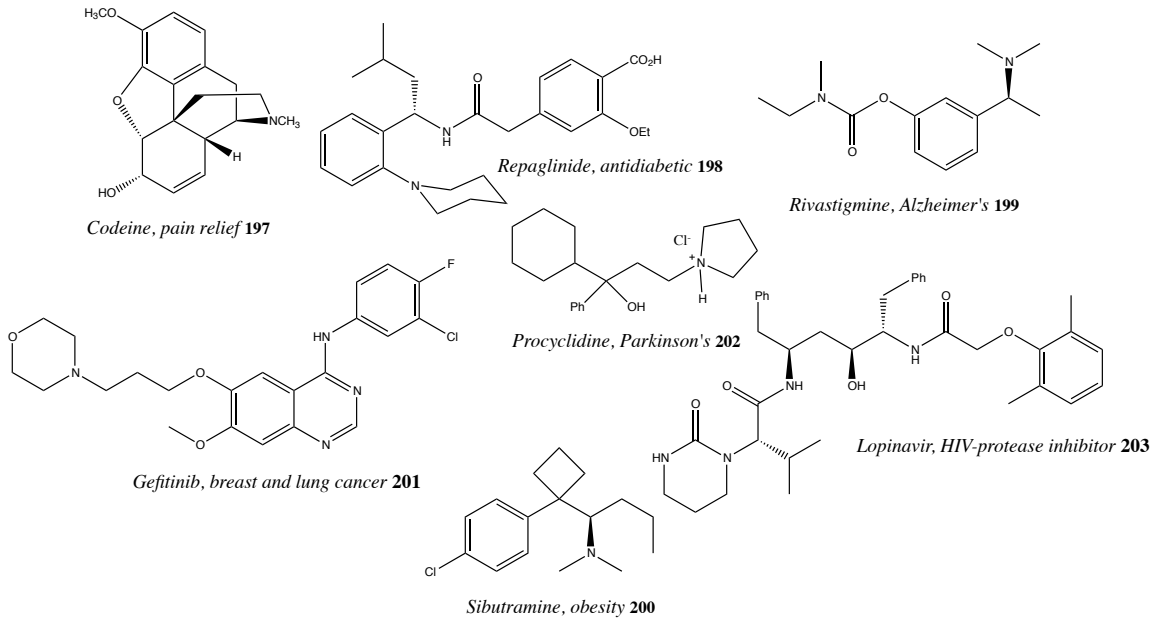
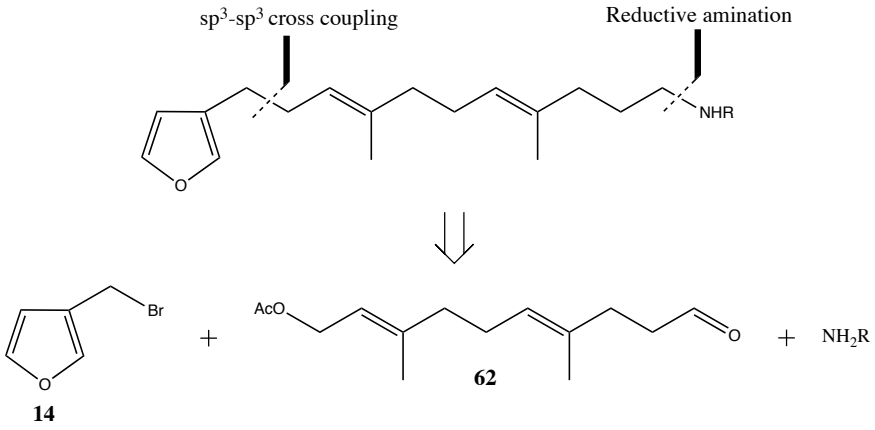



***Figure 2.40:*** *Amine based pharmaceutical drugs.*

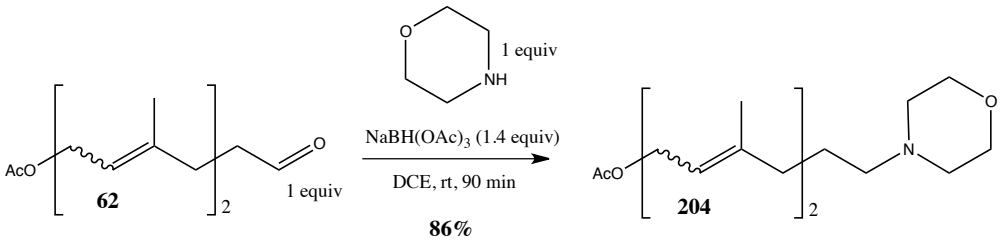
Reductive amination is a valuable and important tool used in organic chemistry for introducing amine functionality into an organic compound containing an aldehyde or ketone. Since an important part of the project involves structural derivatisation of the furanolipid skeleton, reductive amination seemed like a fantastic avenue to explore in the development of novel compounds for biological testing (***Scheme 2.103***). Our retrosynthetic plan for the synthesis of furanolipid amines involved a two-step synthetic strategy. Attachment of the

furan fragment was the crucial step and to avoid complications caused by the aldehyde functionality during the Grignard cross coupling reaction, the reduction amination reaction was performed first. Noteworthy, the synthesis of nitrogen-containing compounds in the terpene series is of considerable interest because these substances may possess a wide range of biological action.




***Scheme 2.103:*** *Retrosynthetic plan for the synthesis of furanolipid amine molecules.*

Following an established protocol comprehensively cited in the literature by Abdel *et al.*,[212] aldehyde **62** was converted to its corresponding amine **204** following treatment with 1 equivalent of morpholine in the presence of 1.3 equivalents of sodium triacetoxyborohydride in dry dichloroethane (DCE) at room temperature under inert nitrogen atmosphere as shown in ***Scheme 2.104***.




***Scheme 2.104***

The reaction was monitored by TLC analysis and complete consumption of starting material **62** was evident after 90 minutes. Upon workup, the novel tertiary amine **204** was furnished as a yellow oil in 86 % yield, which was deemed pure by spectroscopic analysis thus avoiding the need for purification by column chromatography. $^{1}$H NMR spectroscopy confirmed the formation of the tertiary amine **204** with the disappearance of the distinctive aldehyde triplet at $\delta_H$ 9.78 ppm (*J* 1.9) and the subsequent appearance of a 2H multiplet at $\delta_H$ 2.24-2.36 ppm assigned to the newly formed methylene protons adjacent to the amine at C(10)$H_2$. Other characteristic signals observed in the $^{1}$H NMR spectrum were the two 4*H* multiplets at $\delta_H$ 2.35-2.55 ppm and $\delta_H$ 3.65-3.77 ppm corresponding to the methylene groups alpha [C(1')$H_2$] and beta [C(2')$H_2$] to the nitrogen in the morpholine ring respectively. The $^{13}$C NMR spectrum displayed the four methylene groups within the morpholine ring, as overlapping singlets at $\delta_C$ 53.8 ppm [*C*(1')$H_2$] and $\delta_C$ 70.0 ppm [*C*(2')$H_2$] respectively, in addition to a significant low frequency chemical shift from $\delta_C$ 202.6 ppm to $\delta_C$ 58.7 ppm associated with the α-carbon signal at *C*(10)$H_2$ adjacent to the morpholine ring.

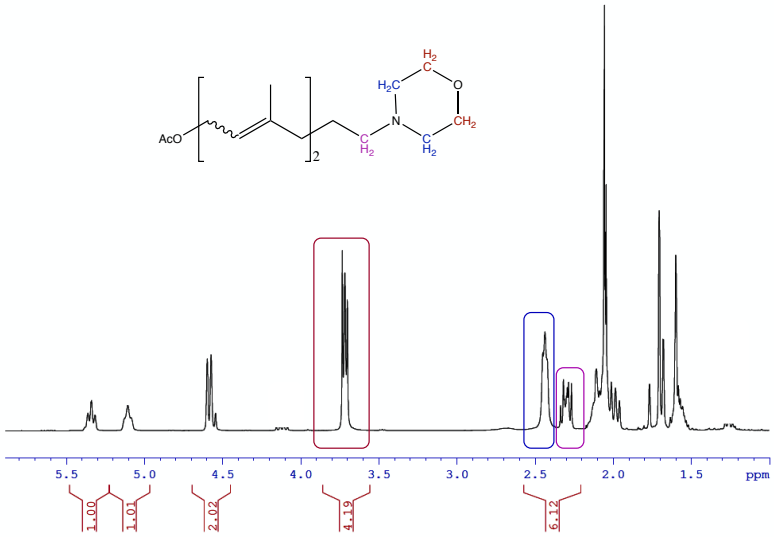
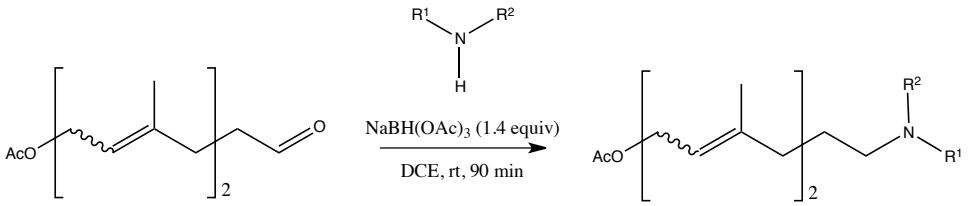



***Figure 2.41:*** *$^{1}$H NMR spectrum of* ***204*** *($CDCl_3$, 300 MHz).*

***Table 2.21:*** *Preparation of secondary and tertiary terpene amines via reductive amination.*




**62** **204-212**

| Entry | Amine | Product | Yield [a] |
|---|---|---|---|
| **1** | Morpholine | **204** | 86% |
| **2** | Piperidin-4-yl methanol | **205** | 80% |
| **3** | Diethylamine | **206** | 82% |
| **4** | Aniline | **207** | 90% |
| **5** | Diisopropylamine | **208** | 73% |
| **6** | Dipropylamine | **209** | 80% |
| **7** | 4-Fluoroaniline | **210** | 86% |
| **8** | Piperidine | **211** | 90% |
| **9** | Piperazine | **212** | 6%[b,c] |

**a: Crude yield of amine product, no purification required.**
**b: Two-component mixture: monomer and dimer in a 12:88 ratio respectively.**
**c: The yield and ratio of products was determined by integration of the $^1$H NMR spectrum of the crude product.**

Following the procedure outlined above in ***Table 2.21***, a variety of secondary and tertiary terpene amines (**204-211**) were successfully synthesised in good yield with the exception of **212**. The low yield associated with ***Entry 9*** is primarily due to undesired formation of the dimer **213** (***Figure 2.42***). Piperazine has two equivalent secondary amino groups, which are available for reductive amination. This led to the formation of a two-component mixture consisting of the monomer **212** and dimer **213** in a 12:88 ratio of products respectively as determined by $^1$H NMR analysis of the crude product. Since only a minor quantity of the desired product **212** (~6%) was present in the crude mixture, purification by column chromatography was not performed. Dimerization to **213** was evident from $^1$H NMR analysis with the appearance of an 8H multiplet at $\delta_H$ 2.36-2.65 ppm assigned to the methylene protons at C(1')$H_2$ (***Figure 2.42***). Further evidence for the formation of a symmetrical molecule **213** was observed with the appearance of a 4H multiplet at $\delta_H$ 2.25-2.36 ppm

associated with the methylene hydrogens adjacent to the piperazine ring [C(10)$H_2$]. Evidence for the formation of the monomer **212** was also observed in the $^1$H NMR spectrum at $\delta_H$ 2.93 ppm which is consistent with literature findings for a related compound (***Figure 2.42***).[212] High resolution mass spectrometry found the molecular ion peak for the dimer **213** at 530.4090.

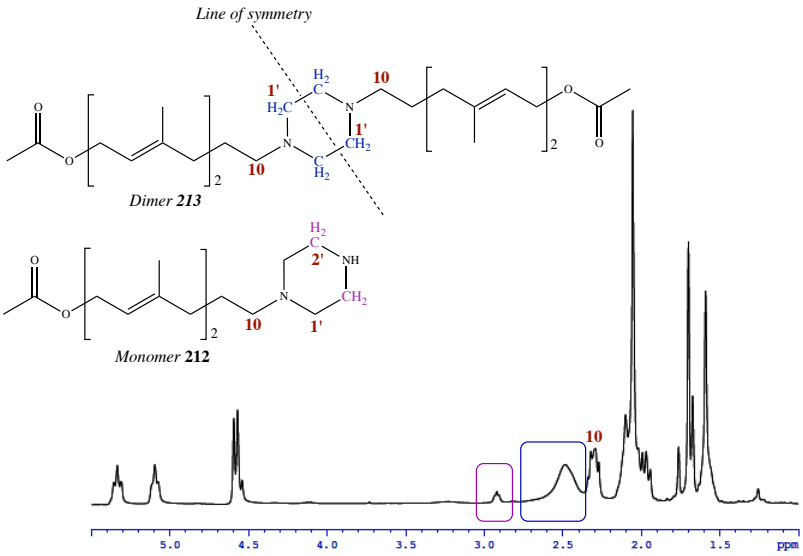
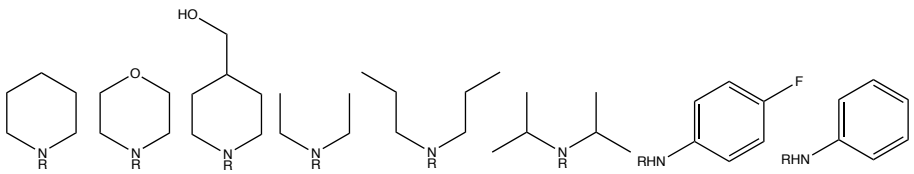



***Figure 2.42:*** *Expansion of the $^1$H NMR spectrum of piperazine dimer **213** and piperazine monomer **212** with characteristics signals labelled.*

With respect to the mono-alkylated terpene amines (***Table 2.21, Entry 1-8***), $^1$H NMR analysis confirmed the formation of each amine with the disappearance of the aldehyde peak at $\delta_H$ 9.78 ppm and the appearance of a 2*H* multiplet in the region $\delta_H$ 2.18-2.48 ppm corresponding to the methylene hydrogens [C(10)$H_2$] adjacent to the amine. However with respect to ***Entry 4*** and ***Entry 7***, the methylene protons at C(10)$H_2$ appeared further downfield in the $^1$H NMR spectrum as a distinctive triplet at $\delta_H$ 3.08 ppm and $\delta_H$ 3.04 ppm due to a stronger deshielding effect applied on the neighbouring methylene group by aniline (**207**) and fluoroaniline (**210**) respectively. Furthermore in the $^{13}$C NMR spectrum, depending on the amine group attached, slightly different chemical shift values were observed at *C*10 in the region $\delta_C$ 43.5-59.2 ppm as illustrated in ***Figure 2.43***.



| | 211 | 204 | 205 | 206 | 209 | 208 | 210 | 207 |
|---|---|---|---|---|---|---|---|---|
| $\delta_C$ $\underline{C}$**(10) ppm** | **59.2** | **58.7** | **58.7** | **52.5** | **53.9** | **45.2** | **44.2** | **43.5** |

***Figure 2.43***

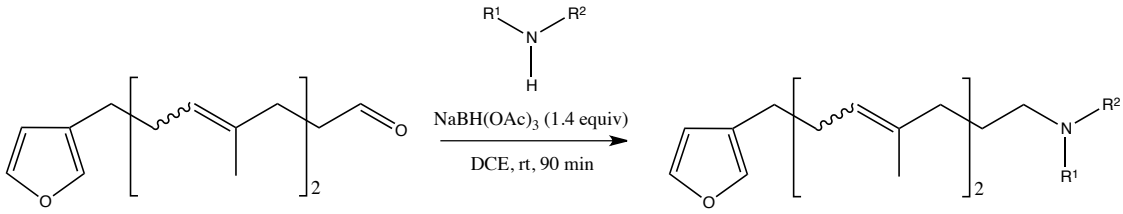
Having successfully fashioned the amine moiety to the terminal end of compound **62**, the next essential step was to attach the furan ring. However, at this point in the project, we were having difficulty developing an effective coupling regime for attaching the furan moiety to the terpene fragment (central linchpin). Since coupling reactions of 3-furylmethylmagnesium bromide **14a** with geranyl diphenyl phosphate **25** using copper(I) iodide (10 mol%) as a catalyst provided the desired product **10** along with undesired formation of its corresponding regioisomers **30** in relatively poor yield (***Scheme 2.13***), it was decided to put this reaction on hold until superior methodology was uncovered.

Overtime, with the implementation of the Schlosser cross coupling as a standard for attachment of the furan to the central linchpin and the concise and elegant 2$^{nd}$ generation synthesis of furospongolide **1**, it became apparent that the most appropriate and contemporary method for the synthesis of furanolipid amines involved utilising the furanolipid aldehyde **121** as a fundamental building block which already encompasses the desired C1-C15 subunit. As previously described, large quantities of the aldehyde **121** can be synthesised on demand from farnesyl acetate **59** in 3 linear steps. Since the reductive amination reaction has already been studied in considerable detail (***Table 2.21***), access to furanolipid amines from the aldehyde **121** seemed straightforward.

### 2.9.6 Synthesis of furanolipid amines

As outlined in the previous section, the furanolipid aldehyde **121** was successfully converted to a range of furanolipid amines **214-222** following treatment with sodium triacetoxyborohydride and the appropriate amine in dry dichloroethane over a 90 minute period at room temperature as illustrated in ***Table 2.22***.

***Table 2.22:*** *Preparation of furanolipid amines.*




**121** **214-222**

| Entry | Amine | Product | % Yield |
|---|---|---|---|
| 1 | 2-(Piperazin-1-yl)ethanol | **214** | 77%[a] |
| 2 | Piperidin-4-yl methanol | **215** | 71%[a] |
| 3 | Thiomorpholine | **216** | 85%[a] |
| 4 | Morpholine | **217** | 79%[a] |
| 5 | Pyrrolidine | **218** | 84%[a] |
| 6 | 4-Fluoroaniline | **219** | 83%[a] |
| 7 | Piperidine | **220** | 82%[a] |
| 8 | Diethylamine | **221** | 33%[b] |
| 9 | 2-(Piperazin-1-yl)ethanamine | **222** | ~6%[c,d] |

***a:*** **Crude yield of amine product, no purification required.**
***b*: Purified by column chromatography.**
**c: Two-component mixture: monomer and dimer in a 8:92 ratio respectively.**
**d: The yield and ratio of products was determined by integration of the $^1$H NMR spectrum of the crude product.**

Each furanolipid amine **214-220** (***Entry 1-7***) was cleanly obtained in good yield, which was deemed pure by $^1$H NMR analysis, thus avoiding the need for purification by column chromatography. In the case of ***Entry 8***, $^1$H NMR analysis of the crude product revealed a two-component mixture consisting of the furanolipid amine **221** and starting material **121** in a 80:20 ratio respectively. Rather laborious column chromatography ensued and the title compound **221** was isolated in a low yield of 33%. In order to avoid the unnecessary need for

purification, it is paramount that a 1:1 ratio of the aldehyde and amine is employed in the reductive amination reaction.

In the case of ***Entry 9***, NMR spectroscopy showed clear indication for the formation of a dimer **223** as a result of alkylation at both the primary and secondary amine sites of 2-(piperazin-1-yl)ethanamine (***Figure 2.44***). Disappointingly, only a minor amount of the desired amine product **222** (~6%) was evident in the $^{1}$H NMR spectrum of the crude product. Evidence for the formation of the monomer **222** was observed as a 2H multiplet at $\delta_H$ 2.83 ppm in the $^{1}$H NMR spectrum which is consistent with literature findings for a related compound.[212] High resolution mass spectrometry also found the molecular ion peak for both the monomer **222** and dimer **223** at 374.3094 and 618.5001 respectively.

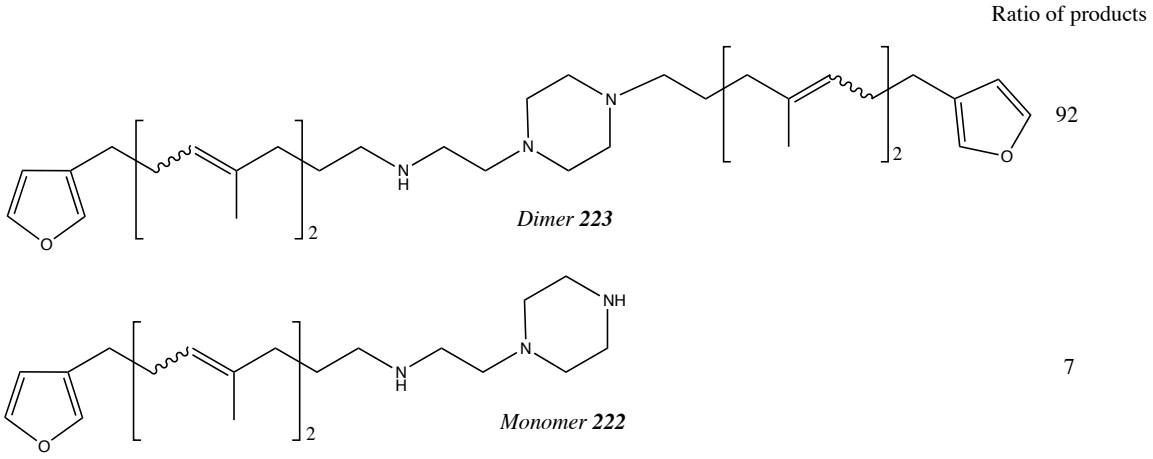
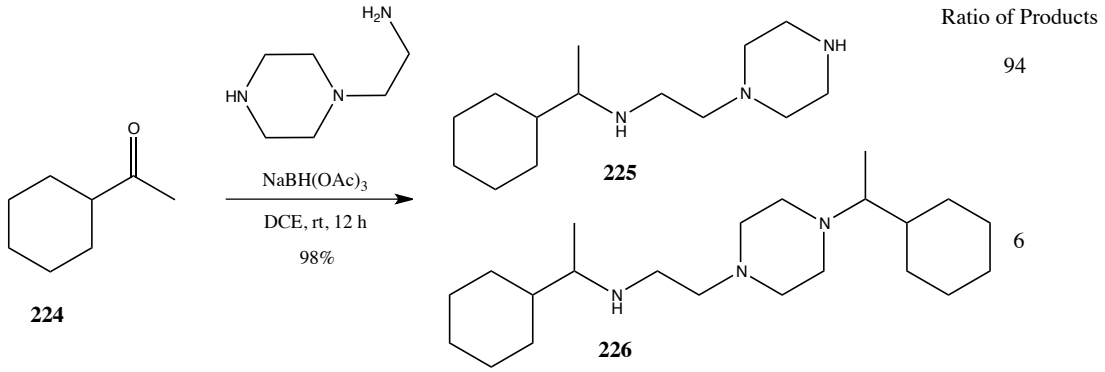



***Figure 2.44***

Interestingly, Abdel *et al.* performed a similar reaction using 2-(piperazin-1-yl)ethanamine in a reductive amination reaction with acetylcyclohexane **224**.[212] In direct contrast to our results, the desired mono-addition component **225** was the major product formed in the reaction with only a minor amount for the di-addition product **226** formed as shown in ***Scheme 2.105***.




***Scheme 2.105***

With respect to the furanolipid amines **214-221** (***Entry 1-8***), a common trend was observed in the $^{1}$H NMR spectrum for each compound with the disappearance of the triplet at $\delta_H$ 9.74 ppm (*J* 1.9) and the subsequent appearance of a 2H multiplet in the region $\delta_H$ 2.12-3.05 ppm assigned to the methylene protons at C(15)$H_2$ adjacent to the amine functionality (***Figure 2.45***). It should be noted that this region in the $^{1}$H NMR spectrum may include other methylene proton peaks like C(5)$H_2$ and C(6)$H_2$ depending on the compound described. As previously encountered for the terpene amines, this region is quite broad primarily due to the diverse electronic environments introduced following attachment of different amine groups to the terminal end of the furanolipid backbone. This is particularly obvious in the case of the fluoroaniline derivative **219** with the appearance of a distinctive 2H triplet at $\delta_H$ 3.03 ppm [*J* 7.0, C(15)$H_2$]. Further evidence was available from IR and $^{13}$C NMR spectroscopy with the disappearance of the carbonyl absorption peak at $\nu_{max}$ 1727 cm$^{-1}$ and a low frequency chemical shift at *C*(15)$H_2$ from $\delta_C$ 202.7 ppm to $\delta_C$ 44.3-59.1 ppm respectively (***Figure 2.45*).**

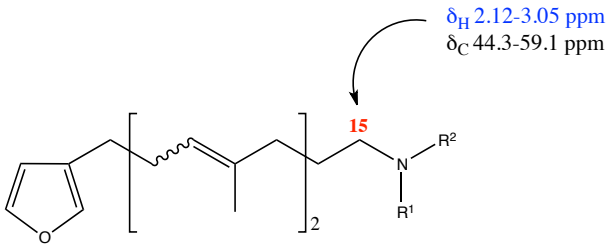



***Figure 2.45***

An interesting observation was made when characterising furanolipid piperidin-4-yl methanol **215**. According to the $^{1}$H NMR spectrum, the methylene protons directly adjacent to the nitrogen [2 x C(1')$H_2$] which should theoretically be equivalent, appeared as two sets of multiplets in the region of $\delta_H$ 1.82-2.12 ppm and $\delta_H$ 2.88-3.02 ppm. On further examination of the literature, it was uncovered that piperidine has two distinguishable chair conformations.[213] One with the N-R bond in the axial position, and the other in the equatorial position as seen in ***Figure 2.46***. After much controversy during the 1950s-1970s, the equatorial conformation was found to be more stable by 0.72 kcal/mol in the gas phase.[214] Many possible conformers for **215** are possible some of which are shown in ***Figure 2.46***

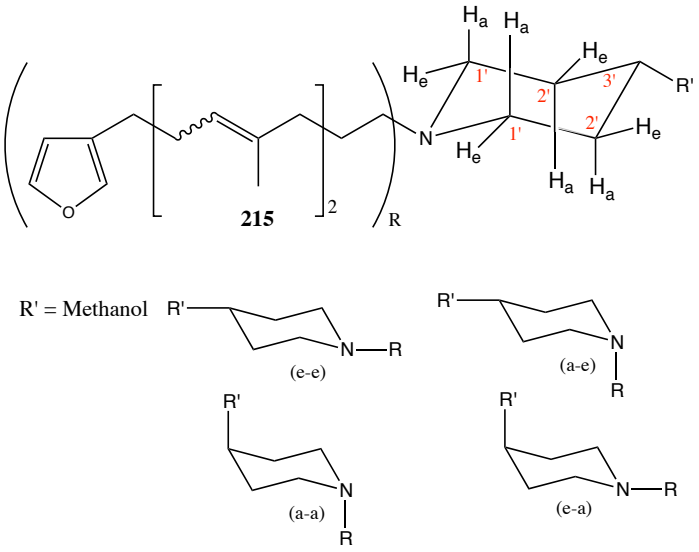



***Figure 2.46:*** *Conformations of furanolipid piperidin-4-yl methanol* ***215*** *showing atomic numbering.*

According to Alver *et al.*,[213,215] the equatorially oriented protons at C(1')$H_e$ appear at higher frequency field regions compared to axially oriented protons at C(1')$H_a$. This phenomenom is due to magnetic anisotropy where electron circulation is stronger in some orientations of a molecule in the magnetic field compared with others. In the case of compound **215**, the axial orientated protons are in a higher electron density enviroment and are shielded to a greater extent compared to equatorial orientated protons. Evidence for the existence of this phenomenon in furanolipid amine **215** can be observed using a HETCOR experiment as

illustrated in ***Figure 2.47***. Surprisingly, this phenomenon was only observed for furanolipid piperidin-4-yl methanol **215**. In the case of piperidine **220**, the $^{1}$H NMR spectrum showed only one multiplet in the region $\delta_H$ 2.35-2.52 ppm [integrates for a 6H multiplet as its intertwined with C(5)$H_2$] assigned to the equivalent protons alpha to the nitrogen at C(1')$H_2$.

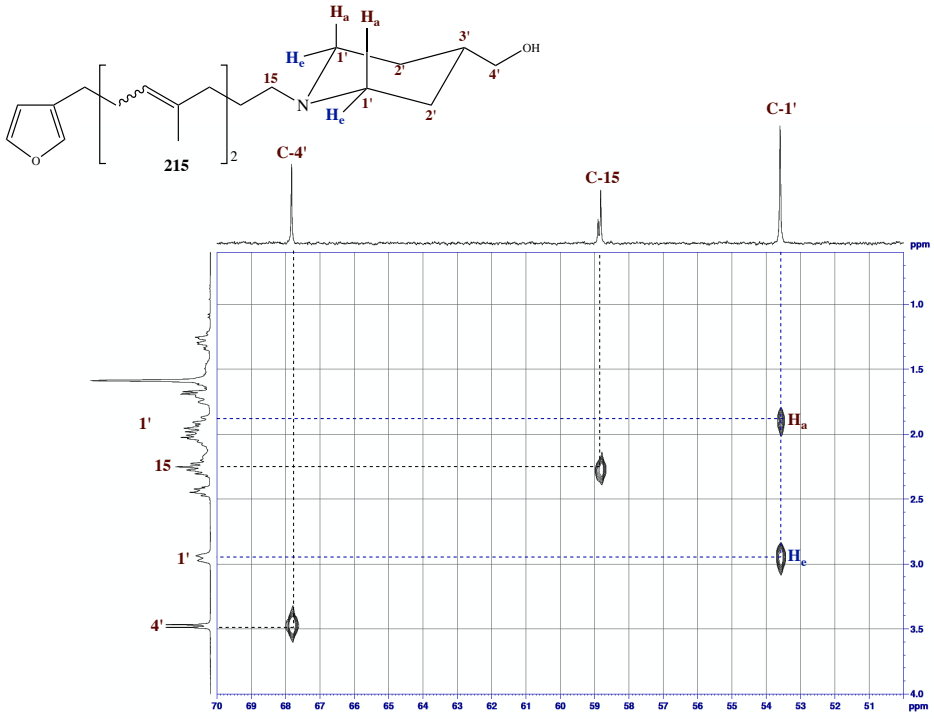


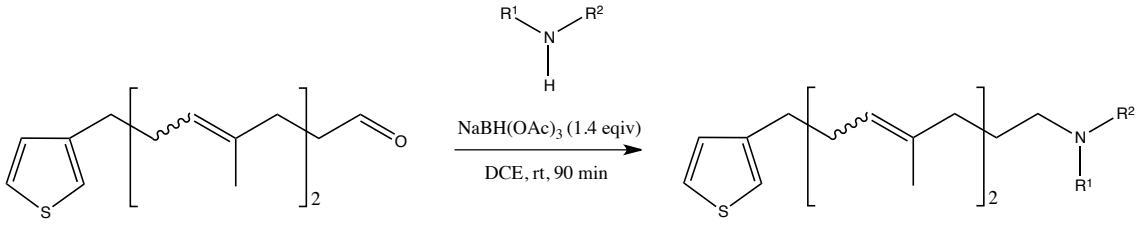

***Figure 2.47:*** *2D HETCOR spectrum of furanolipid piperidin-4-yl methanol* ***215*** *[$^{13}$C DEPT 45 NMR and $^{1}$H NMR (300MHz)].*

The furanolipid amines **214-221** were surprisingly very stable compounds which could be stored over long period without any sign of deterioration. A number of furanolipid amines (**214-220**) were subsequently sent to the National Cancer Institute for biological evaluation and the results will be discussed in ***Section 3.1.3.2***.

### 2.9.7 Synthesis of thiophenolipid amines

In light of the successful synthesis of a range of novel furanolipid amine derivatives using reductive amination chemistry, it was decided to extend this work to include the thiophene moiety. Simply by using thiophenolipid aldehyde **166** instead of furanolipid aldehyde **121** in the reductive amination reaction, it was possible to develop a novel series of thiophenolipid amine derivatives as shown below in ***Table 2.23***.

***Table 2.23:*** *Preparation of thiophenolipid tertiary amines.*




**166** **227-232**

| Entry | Amine | Product | % Yield [a] |
|---|---|---|---|
| 1 | 2-(Piperazin-1-yl)ethanol | **227** | 83% |
| 2 | Thiomorpholine | **228** | 82% |
| 3 | Morpholine | **229** | 71% |
| 4 | Piperidin-4-yl methanol | **230** | 90% |
| 5 | Pyrrolidine | **231** | 95% |
| 6 | 2-(Piperazin-1-yl)ethanamine | **232** | ~6% [b,c] |

**a: Crude yield of alkylated product, no purification required.**
**b: Two-component mixture: monomer and dimer in a 7:93 ratio respectively.**
**c: The yield and ratio of products was determined by $^1$H NMR integration of the crude product.**

Following an established precedent described by Abdel *et al.*, a novel series of thiophenolipid amines (**227-231)** (***Entry 1-5***) were successfully synthesised in good yield, and deemed pure by $^1$H NMR analysis thus avoiding the need for purification by flash chromatography. With respect to ***Entry 6***, the dimer **233** was once again the major product formed for the reaction of the aldehyde **166** with 2-(piperazin-1-yl)ethanamine as previously encountered in ***Table 2.22, Entry 9***.

The $^{1}$H NMR spectrum of each thiophenolipid amine **227-231** (***Entry 1-5***) displayed a similar spectroscopic trend (previously observed for the furanolipid amine series) with the disappearance of the triplet at $\delta_H$ 9.74 ppm (*J* 1.9) associated with the aldehyde proton at C(15)*H* and the appearance of a 2H multiplet in the region $\delta_H$ 2.20-2.70 ppm alongside C(6)$H_2$ which results in an integration value accounting for four hydrogen's. $^{13}$C NMR spectroscopy was also consistent with a shift upfield of the carbon signal at *C*(15)$H_2$ from $\delta_C$ 202.5 ppm to $\delta_C$ 58.2-59.0 ppm (***Figure 2.48***).

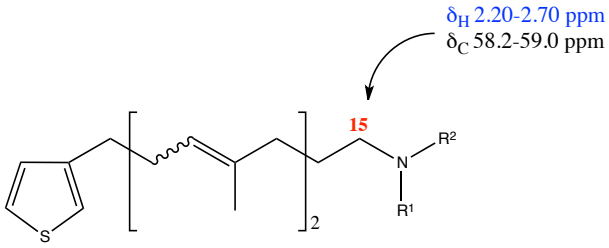



***Figure 2.48***

With respect to ***Entry 4***, spectroscopic analysis of **230** revealed the same phenomenon as previously noted for **215** with the appearance of two sets of multipets in the region of $\delta_H$ 1.82-2.15 ppm and $\delta_H$ 2.85-3.05 ppm, resulting from an apparent difference in the chemical shift value between equatorial [C(1')$H_e$] and axial [C(1')$H_a$] oriented protons assigned to the methylene protons adjacent to the nitrogen atom.

Similar to the furanolipid amines, a number of thiophenolipid amines (**227-230)** were sent to the National Cancer Institute for biological evaluation and the results will be discussed in ***Section 3.1.3.2***.

### 2.9.8 Synthesis of furanolipid amides

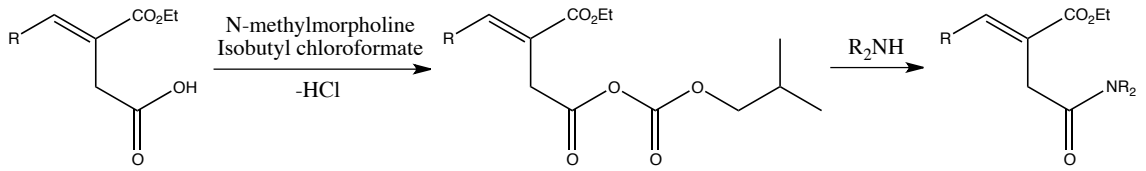
Like amines, amides are abundant in nature and are present in numerous well know drug molecules including penicillin, LSD, Lipitor, Diazepam and barbiturates. Amides also function as a key-linking moiety in proteins and peptide drug products. A variety of amide-based pharmaceutical drugs, which have appeared on the pharmaceutical market are shown in ***Table 2.24***.

***Table 2.24:*** *Pharmaceutical drugs containing an amide moiety.*

| **Drug** | Treatment | **Drug** | Treatment | **Drug** | Treatment |
|---|---|---|---|---|---|
| **Acebutolol** | Arrhythmias | **Capecitabine** | Breast cancer | **Moricizine** | Arrhythmias |
| **Acetaminophen** | Inflammatory pain | **Conivaptan** | Hyponatremia | **Piroxicam** | Rheumatoid arthritis |
| **Acetazolamide** | Epileptic seizures | **Dutasteride** | Prostatic hyperplasia | **Rifabutin** | Tuberculosis |
| **Arformoterol** | COPD | **Ertapenem** | Antibiotic | **Rifaximin** | Diarrhoea |
| **Atorvastatin** | Cholesterol | **Flutamide** | Prostate cancer | **Sorafenib** | Kidney cancer |
| **Bentiromide** | Pancreatic therapy | **Formoterol** | Asthma | **Tocainide** | Arrhythmias |
| **Bicalutamide** | Prostate cancer | **Lefunomide** | Rheumatoid arthritis | **Vorinostat** | T-cell lymphoma |
| **Bupivacaine** | Local anaesthetic | **Mepivacaine** | Local anaesthetic | **Zafirlukast** | Asthma |

Conversion of carboxylic acids to amides is a very common reaction in organic chemistry especially in the area of peptide synthesis. In practice, this transformation is usually performed through a mixed anhydride intermediate (***Scheme 2.106***). The use of anhydrides for the formation of peptides bonds dates to the very beginning of synthetic peptide chemistry.[216] Isobutyl chloroformate has become the most widely used reagent for the preparation of mixed anhydrides for peptide synthesis as it provides rapid reaction rates at low temperature, good yields of readily purifiable products, easily removable side-products from a low cost reagent which is commercially available.

In the field of peptide chemistry, the term “mixed anhydride” usually relates to the mixed carbonic acid anhydride method of peptide synthesis which involves the use of an isobutyl chloroformate and *N*-methylmorpholine as shown in ***Scheme 2.106***.

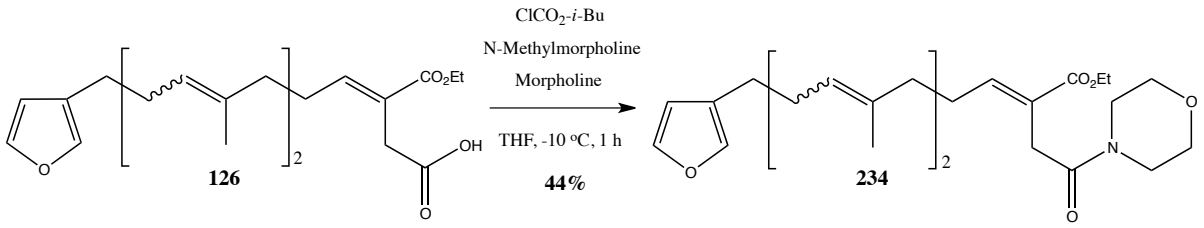



*Mixed Carbonic Acid Anhydride*

***Scheme 2.106:*** *Preparation of a mixed anhydride and its reaction with an amine derivative to form an amide.*

The first step in the synthesis of an amide is the formation of the mixed anhydride. This activation step involves the reaction of a carboxylic acid derivative with an acid chloride (isobutyl chloroformate) in the presence of a tertiary amine (*N*-methylmorpholine) in an inert solvent. The purpose of *N*-methylmorpholine is essentially to neutralise the hydrochloric acid liberated during the reaction. A mixed carbonic acid anhydride is formed which acts as an acylating agent and subsequently undergoes condensation with an amine substrate to give the desired amide product and a carboxylic acid by-product.

A very useful compound prepared during the 2$^{nd}$ generation synthesis of furospongolide **1** was the furanolipid half ester **126**, which was surprisingly stable and was readily amenable to the preparation of designed analogues. The half ester **126** was an ideal candidate for structural modification in the development of a novel series of furanlipid amides as it contains a carboxylic acid functional group at the terminal end of the molecule. Following a procedure comprehensively cited in the literature by Plattner *et al.*, [217] the furanolipid half ester **126** was treated sequential with 1.4 equivalents of isobutyl chloroformate and 1.3 equivalents *N*-methylmorpholine in anhydrous tetrahydrofuran at -10 $^{o}$C followed by subsequent addition of morpholine (***Scheme 2.107***).




***Scheme 2.107***

The reaction was monitored by TLC analysis and after 1 hour, complete consumption of starting material was observed. Upon work-up, $^{1}$H NMR analysis of the crude product indicated complete conversion of **126** to its corresponding amide **234**. Following purification by column chromatography on silica gel the desired furanolipid amide **234** was successfully isolated as a colourless oil in 44% yield.

$^{1}$H NMR spectroscopy confirmed the synthesis of **234** with the disappearance of the 1H broad singlet at $\delta_H$ 9.6 ppm associated with the carboxylic acid O*H* and the subsequent appearance of a 8H multiplet at $\delta_H$ 3.52-3.80 ppm associated with the methylene protons within the morpholine ring [2 x C(1')$H_2$ and 2 x C(2')$H_2$]. A marginal but notable upfield shift from $\delta_H$ 3.38 ppm to $\delta_H$ 3.33 ppm was observed with the methylene protons adjacent to the amide at C(17)$H_2$ (***Figure 2.49***). $^{13}$C NMR spectroscopy revealed a chemical shift from $\delta_C$ 176.9 ppm to $\delta_C$ 168.8 ppm associated with a change in the carbonyl group from an acid to amide at *C*(18)$H_2$. Further evidence was also observed in the IR spectrum with the disappearance of the broad carboxylic acid O*H* stretch in the region $\nu_{max}$ 3300-2500 cm$^{-1}$ and the appearance of a strong carbonyl absorption peak at $\nu_{max}$ 1659 cm$^{-1}$ characteristic of tertiary amide (C=O).

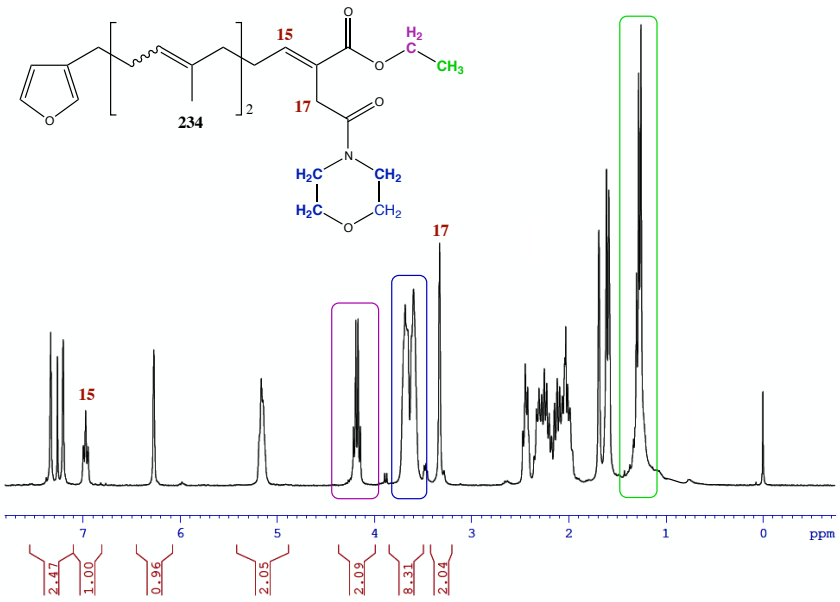
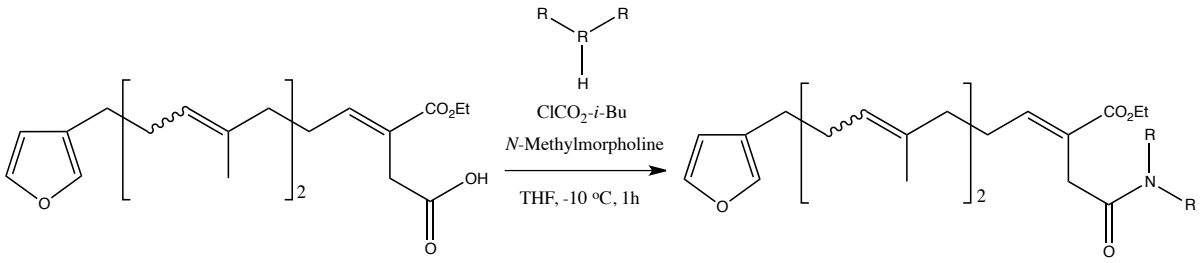



***Figure 2.49:*** *$^1$H NMR spectrum of furanolipid amide **234** ($CDCl_3$, 300 MHz).*

Following the successful synthesis of **234**, it was decided to construct a novel series of furanolipid amide derivatives employing the same reaction conditions as above (***Table 2.25***).

***Table 2.25*** *Preparation of furanolipid tertiary amides.*




**126** **234-237**

| Entry | Amine | Product | % Yield [a] |
|---|---|---|---|
| 1 | Morpholine | **234** | 44% |
| 2 | Thiomorpholine | **235** | 40% |
| 3 | 2-(Piperazin-1-yl)ethanol | **236** | 44% |
| 4 | Piperidine | **237** | 44% |

**a: Isolated yield of acylated product post purification by chromatography.**

A variety of tertiary furanolipid amides **234-237** were successfully synthesised in moderate yield post purification by flash chromatography (***Entry 1-4***). Each reaction was complete after 1 hour at -10 $^{o}$C as indicated by TLC analysis. It should be noted that reactions of this type are generally low yielding as reported by Plattner *et al.* (~48%).[217] Spectroscopic analysis was consistent with data previously reported for the furanolipid amide **234** with a low frequency chemical shift observed in the $^{13}$C NMR spectrum from $\delta_C$ 176.9 ppm to $\delta_C$ 168.3-168.6 ppm associated with carbonyl group (deshielded due to oxygen) at *C*18. A minor shift was observed for the 2H singlet from $\delta_H$ 3.38 ppm to $\delta_H$ 3.33-3.34 ppm assigned to the methylene protons alpha to the amide at C(17)$H_2$, which are slightly de-shielded by the carbonyl group (***Figure 2.50***). The IR spectrum was also consistent with the appearance of a strong carbonyl absorption peak in the region of $\nu_{max}$ 1645-1655 cm$^{-1}$ characteristic of a tertiary amide.

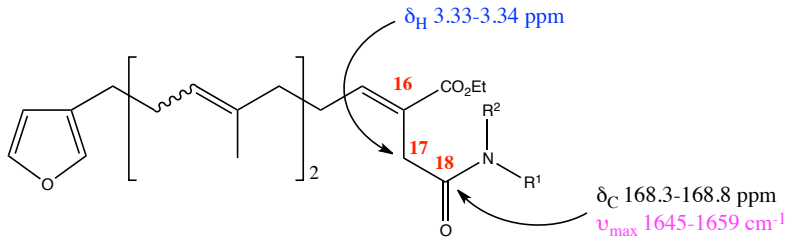



***Figure 2.50***

With respect to ***Entry 2***, the $^{1}$H NMR spectrum of **235** was almost identical to **234** with the exception of the methylene protons adjacent to the sulfur atom in the thiomorpholine ring. As expected, these protons are present further upfield appearing as a 4H multiplet in the region $\delta_H$ 2.53-2.72 ppm [C(2')$H_2$] due to the sulfur atom being less electronegative than oxygen.

In the case of ***Entry 3***, distinctive peaks were observed for the 2-(piperazin-1-yl)ethanol functional group in the $^{1}$H NMR spectrum of **236** with a 2H triplet [*J* 4.8, C(4')$H_2$] in the region of $\delta_H$ 3.55-3.58 ppm and a 2H triplet in the region of $\delta_H$ 2.38-2.62 ppm [*J* 5.3, C(3')$H_2$] characteristic of the methylene protons α and β to the hydroxyl group respectively. Noteworthy, these triplet signals were broadened slightly due to slow intermolecular exchange of the neighbouring hydroxyl proton.

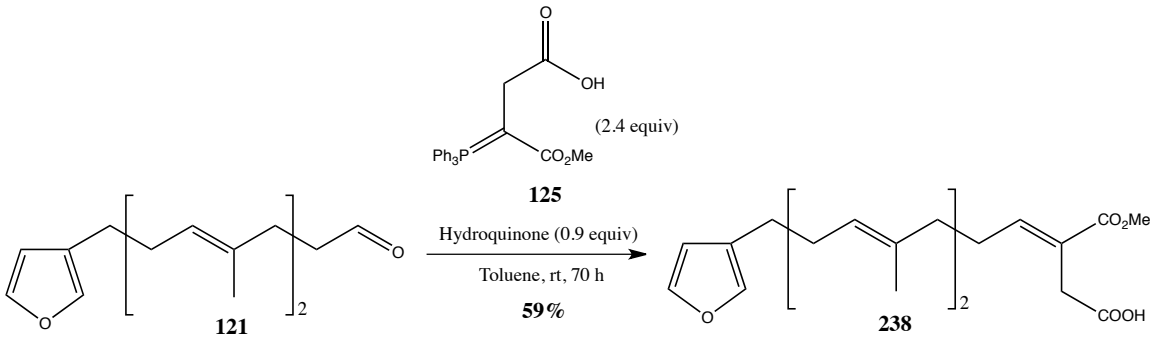
In the $^1$H NMR spectrum of **237** (***Entry 4***), distinctive peaks were also observed for the piperidine functional group with a 6H multiplet in the region of $\delta_H$ 1.45-1.72 ppm [2 x C(2')$H_2$ and C(3')$H_2$] characteristic of the methylene protons β and γ to the nitrogen. The α-methylene protons adjacent to the nitrogen were also observed as a 4H multiplet at $\delta_H$ 3.43-3.60 ppm.

The furanolipid amides **234-237** were very stable compounds and could be stored over long periods of time without undesired deterioration. Furanolipid amides **234**, **235** and **237** were subsequently sent to the NCI for biological evaluation.

### 2.9.9 Synthesis of furanolipid alkenyl analogues

Making reference to both 2$^{nd}$ generation synthesis of furospongolide **1** and the synthesis of furanolipid amines via reductive amination chemistry, the furanolipid aldehyde **121** has become a fundamental building block in the preparation of furanolipid structural analogues. With respect to 2$^{nd}$ generation synthesis, the furanolipid aldehyde **121** was utilized as a substrate in a Wittig type reaction with betaine **122** as previously shown in ***Table 2.12***. In order to make further additions to our library of furanolipid analogues for biological testing, furanolipid aldehyde **121** was exploited once again by means of the Wittig reaction in the synthesis of furanolipid alkenyl analogues.

The furanolipid monomethyl ester **238** was prepared following treatment of (*E,E*)-furanolipid aldehyde **121** with ylide **125** while adhering to our optimised conditions of the Wittig reaction as illustrated in ***Scheme 2108.***

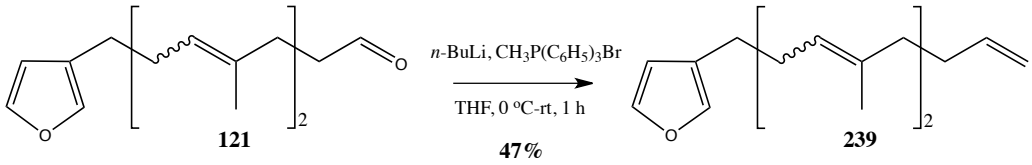



***Scheme 2.108***

Complete conversion of the furanolipid aldehyde **121** to the monomethyl ester **238** was reached after 70 hours as indicated by TLC analysis. Following purification by flash chromatography, the desired monomethyl ester **238** was isolated as a colourless oil in a moderate yield of 59%. The *E*-configuration was assigned at the new double bond following an NOE experiment, which indicated that the vinylic hydrogen in the product was invariably cis to the carbethoxy substitutent following condensation of the aldehyde with ylide **125**.[156,157]

$^1$H NMR analysis confirmed the synthesis of the half ester **238** with a shift upfield of a 1H triplet at $\delta_H$ 9.74 ppm (*J* 1.9) to $\delta_H$ 6.97 ppm (*J* 7.4), associated with the newly formed vinyl proton adjacent to the half ester. Further evidence was observed with the appearance of a broad 1H singlet at $\delta_H$ 9.8 ppm associated with the carboxylic acid (COO*H*) and a distinctive 3H singlet at $\delta_H$ 3.76 ppm [C(19)$O_2$C$H_3$] associated with the methyl ester. The methylene protons adjacent to the carboxylic acid functionality were also shifted slightly downfield from a 2H doublet at $\delta_H$ 2.91 ppm (*J* 14.9) to a sharp 2H singlet at $\delta_H$ 3.39 ppm [C(17)$H_2$]. IR spectroscopy was also consistent with the disappearance of aldehyde absorption peak at $\nu_{max}$ 1727 cm$^{-1}$ (C=O) and the appearance of an α,β-unsaturated ester absorption stretch at $\nu_{max}$ 1717 cm$^{-1}$.

Utilising a procedure previously encountered in the synthesis of alkene **87** by Cole *et al.* (***Appendix I, Section 5.2.1***),[117] the phosphorus ylide [$H_2C^-$-$^+P(C_6H_5)_3$] generated from the reaction of *n*-butyllithium (1.05 equivalents) and methyltriphenylphosphonium bromide (1.21 equivalents) was reacted with furanolipid aldehyde **121** at 0 $^o$C in anhydrous tetrahydrofuran as shown in ***Scheme 2.109***.

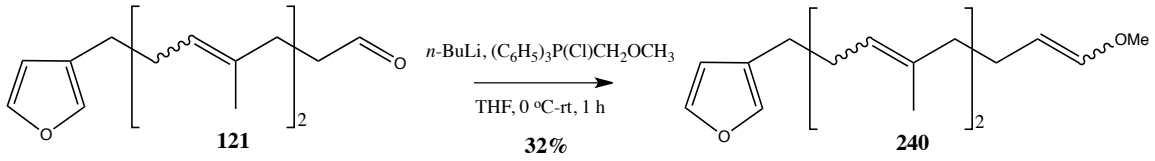



***Scheme 2.109***

The reaction was monitored by TLC analysis and after 1 hour at room temperature, complete consumption of starting material **121** was evident and the reaction was worked-up in the usual manner. Purification by column chromatography on silica gel afforded the novel triene **239** as a colourless non-viscous oil in 47% yield. Since methyltriphenylphosphonium bromide was employed as a Wittig reagent, no stereochemistry was introduced around the new alkene bond.

Distinct absorption patterns were observed in the $^{1}$H NMR spectrum of **239** following the assembly of the terminal alkene bond. Due to spin-spin splitting of the vinylic protons, a ABX system was observed with the appearance of a distinctive 1H doublet of doublets at $\delta_H$ 5.77 ppm associated with the vinyl C(15)*H* proton ($H_X$ of the ABX system, $J_{BX}$ 17.0, $J_{AX}$10.3). The signals for the vinyl C(16)$H_2$ protons were individually observed as 1H doublet of doublets at $\delta_H$ 4.93 ppm ($H_A$ of the ABX system, $J_{AX}$ 10.3, $J_{AB}$ 1.9) and $\delta_H$ 5.00 ppm ($H_B$ of the ABX system, $J_{BX}$17.0, $J_{AB}$ 1.9) respectively and could be easily distinguished by their unique vicinal and geminal coupling constants. Furthermore, $^{13}$C NMR spectroscopy showed a significant low frequency chemical shift from $\delta_C$ 202.7 ppm to $\delta_C$ 125.3 ppm [*C*(15)*H*] and the IR spectrum showed the disappearance of the carbonyl absorption stretch at $\nu_{max}$1727 cm$^{-1}$.

Employing the same reaction conditions as before, the furanolipid aldehyde **121** was reacted with the phosphorus ylide of (methoxymethyl)triphenylphosphonium chloride as shown in ***Scheme 2.110***.




***Scheme 2.110***

Upon workup after a one hour reaction at room temperature, $^{1}$H NMR analysis of the crude product indicated a two-component mixture consisting of the desired furanolipid **240** and an unknown impurity in a 56:44 ratio of products respectively. Purification by flash chromatography isolated the desired enol ether **240** as a light yellow oil in 32% yield (***Scheme 2.110***).

The stereochemical outcome of the Wittig reaction was a 2:1 ratio of the *E* and *Z* isomer as determined by $^{1}$H NMR integration of the peaks at $\delta_H$ 3.49 ppm and $\delta_H$ 3.57 ppm respectively assigned to the methyl protons on the vinyl ether (OC*H*$_3$). The isomers were distinguishable by their unique coupling constants, following analysis of the peaks at $\delta_H$ 4.26-4.38 ppm (*J* 6.2, 1.0, *Z* isomer, *minor*) and $\delta_H$ 4.60-4.80 ppm (*J* 12.6, 3.5, *E* isomer, *major*) associated with the β-proton at C(15)*H* in the vinyl ether (OC*H*$_3$) (***Figure 2.51***).

The signal assigned to the *Z*-isomer of the α-proton in the vinyl ether [C(16)*H*] was identified as a 1*H* doublet in the region $\delta_H$ 5.82-5.89 ppm (*J* 6.2, *minor*). The corresponding *E*-isomer was observed further downfield in the region $\delta_H$ 6.20-6.34 ppm (1H, m, *major*) alongside the furan peak at C(2)*H* in the $^{1}$H NMR spectrum (***Figure 2.51***).

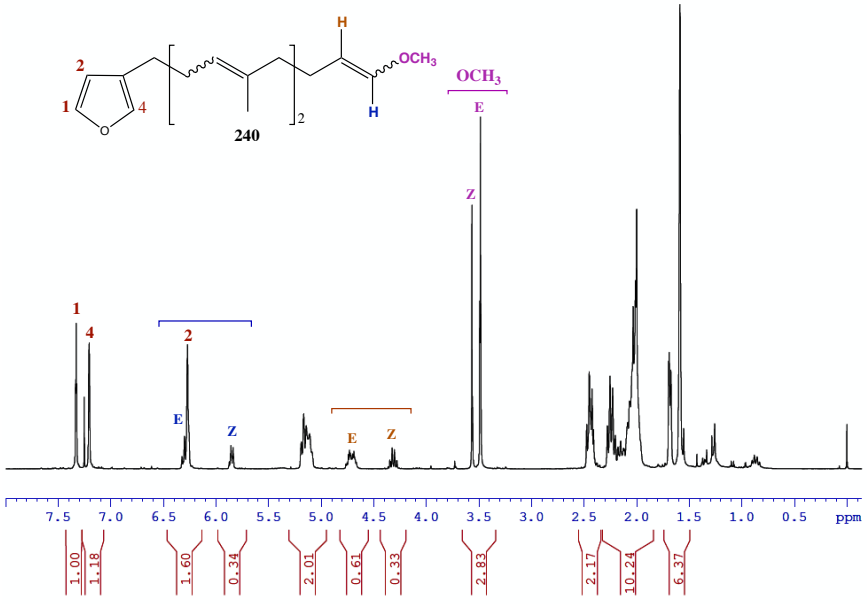



***Figure 2.51:*** *$^{1}$H NMR spectrum of furanolipid enol ether* ***240*** *($CDCl_3$, 300MHz).*

Unfortunately the yield for the reaction was significantly diminished due to the formation of an undesired by-product **241**. The structure of this by-product was putatively assigned as 3-(4,8-dimethyldodeca-3,7,10-trien-1-yl)furan following spectroscopic analysis (***Figure 2.52***).

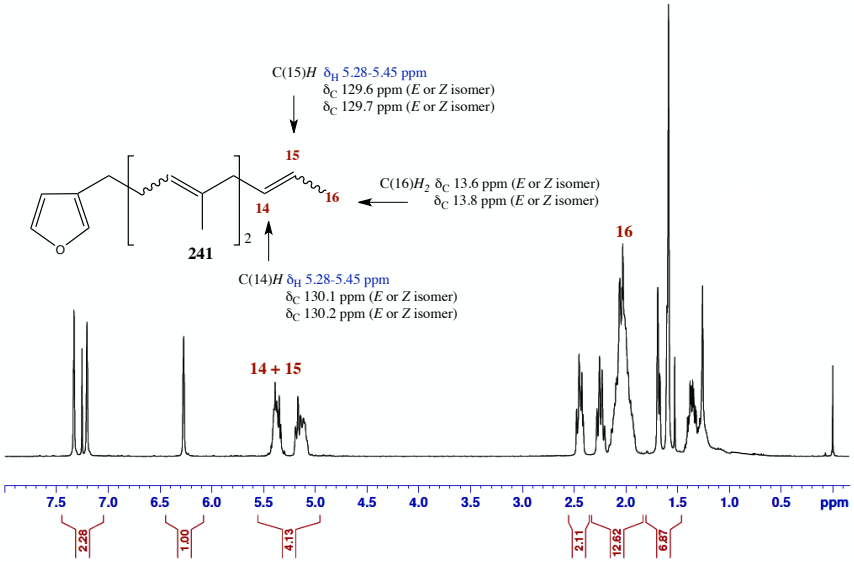



***Figure 2.52:*** *$^{1}$H NMR spectrum of furanolipid **241** ($CDCl_3$, 300MHz).*

Formation of this by-product **241** may have occurred following undesired loss of the methoxy functionality. Both NMR analysis and high-resolution mass spectrometry supported the structure of **241** with the appearance of a molecular ion peak at *m/z* 259.1995 $[M+H]^+$ respectively. $^{1}$H NMR spectroscopy supported the putative structure with the appearance of a 2H multipet at δ 5.28-5.45 associated with the olefinic protons at C(14)*H* and C(15)*H* (***Figure 2.52***).

The aldehyde **121** is a fantastic building block, which was effectively utilised as a substrate in Wittig reactions to construct furanolipid structural analogues for biological testing. With respect to the furanolipid alkenyl analogues, compound **240** was the only compound sent for biological evaluation to the NCI.

## 2.13 Conclusion

Our approach to the total synthesis of (*E,E*)-furospongolide **1** is outlined in ***Scheme 2.53.*** This sesterterpenoid marine natural product was successfully prepared in 5 linear steps and 14.3% overall yield from commercially available (*E,E*)-farnesyl acetate **59**.

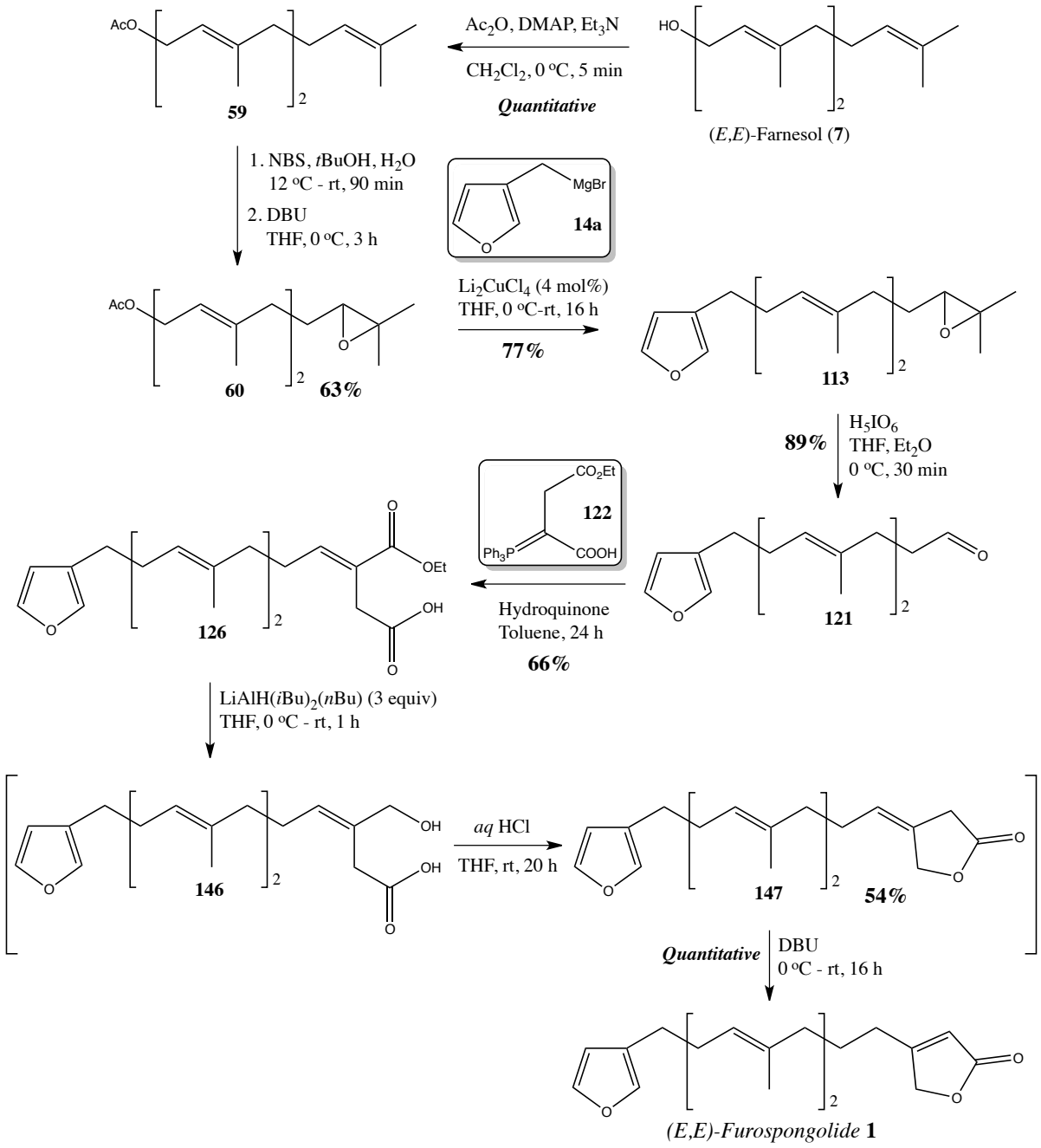



***Figure 2.53***

Furospongolide **1** has been recently identified as a structurally unique inhibitor of HIF-1 activation ($IC_{50}$ value of 2.9 μM). It inhibits HIF-1 activity by selectivity blocking NADH-ubiquinone oxidoreductase (complex I)-mediated mitochondrial electron transfer, thereby suppressing tumour cell respiration and reactive oxygen species generation.[1] On the basis of its known chemotherapeutic potential as a HIF-1 inhibitor, furospongolide **1** was the primary target for total synthesis.

The key step in our synthetic pathway was an innovative one-pot reduction, lactonisation and isomerisation reaction to elegantly connect the butenolide moiety onto the furanolipid backbone. Disappointingly, during our research, Boukouvalas *et al.* achieved the first total synthesis of furospongolide **1** in late 2011.[25] The eight linear step sequence was accomplished in 19% overall yield from commercially available geranyl acetate **29** (***Table 2.25, Entry 5***). Despite having a lower overall yield, our synthetic route offered a shorter, more convergent and milder method for the synthesis of the hypoxia signalling inhibitor furospongolide **1**. Our route involved only two C-C bond formation steps and completely avoided the utilisation of protecting group chemistry and the employment of palladium as a catalyst. We are confident that with further optimisation, we can achieve a higher yielding linear pathway comparable to Boukovalas *et al.*

As expected with most total syntheses, preparation of our target molecule, furospongolide **1** in a high yielding synthetic pathway required a significant amount of research, development and optimisation work (***Table 2.25***).

***Table 2.25:*** *A basic summary of our synthetic endeavours towards the synthesis of furospongolide **1**.*

| Entry | Generation | Linear Steps | Yield |
|---|---|---|---|
| **1** | 1st | - | - |
| **2** | 2nd | 8 [a] | 2% [c] |
| **3** | 2nd | 6 [a] | 3% [c] |
| **4** | 2nd | 5 [a] | 14.3% [d] |
| **5** | - | 8 [b] | 19% [d,e] |

Increasing optimisation, yield and purity

**a: Linear steps from farnesyl acetate 59**
**b: Linear steps from geranyl acetate 29**
**c: Mixture of isomers: 47% of the (*E,E*)-isomer, 43% of the (*Z,E*)-isomer and 10% of other(s)**
**d: Pure (*E,E*)-furospongolide 1**
**e: Work performed by Boukouvalas et al.[25]**

While limited success was achieved through our 1st generation synthetic route (***Appendix 1***), it provided us with a wealth of knowledge in synthetic transformations and helped us construct a more elegant 2nd generation retrosynthetic plan for the concise synthesis of our target molecule **1** ***(Table 2.25, Entry 1)***. Following extensive efforts, furospongolide **1** was first prepared within our research group in 8 linear steps and in 2% overall yield from farnesyl acetate **59 (*Table 2.25, Entry 2*)**. Unfortunately, the synthetic route featured a low yielding conjugate addition/elimination reaction for attaching the butenolide moiety, which was the sole reason for the poor overall yield for our linear route. With a view towards improving our 2nd generation synthetic route, we avoided the use of protecting group chemistry and successfully reduced our linear route by two synthetic steps and increased the overall yield to 3% (***Table 2.25, Entry 3***). With respect to **Entry 2** and **3,** furospongolide **1** was prepared as a mixture of isomers containing 47% of the (*E,E*)-isomer, 43% of the (Z,E)-isomer and 10% of other(s) as determined by HPLC analysis (***Appendix V***). Finally, by introducing a more innovative method for attaching the butenolide to the furanolipid backbone *via* a Wittig reaction, the total synthesis of (*E,E*)-furospongolide **1** was successfully achieved in 5 linear steps and in 14.3% yield from (*E,E*)-farnesyl acetate (***Table 2.25, Entry 4***). The brevity and high level of convergence of our 2nd generation route was possible from continuous optimisation. For comparative reasons, **Entry 5** describes the results obtained by Boukouvalas *et al.* in the first total synthesis of **1**.[25]

Throughout the extent of our research, we successfully synthesised a number of well-known natural products from both marine and plant sources (***Table 2.26***).

***Table 2.26:*** *A list of the natural products successfully prepared during our research.*

| **Natural Product** | **Origin** | **Biological Activity** | **Novel** | **Overall yield (*Linear Steps*)** |
|---|---|---|---|---|
| Furospongolide **1** | *Lendenfeldia sp.* | Inhibitor of HIF-1 activation | N[25] | 14.3% (*5*) [a] |
| Dendrolasin **10** | *Dendro lasius* | Defence | N[37] | 79% (*1*) [b] |
| Ambliofuran **112** | *Dysidea amblia* | Unknown | N[204] | 76% (*1*) [a, c] |
| Diol **64** | *Danaus gilippus berenice* | Glue | N[107] | 38.9 % (*4*) [a, c] |
| Anhydrofuro spongin-1 **164** | *Spongia officinalis* | Unknown | Y | 10. 6% (*6*) [a] |

**a: Linear steps from farnesyl acetate 59**
**b: Linear steps from geranyl acetate 29**
**c: Mixture of isomers**

Simple furanolipid natural products like dendrolasin **10** and ambliofuran **112** were prepared in high yield by exploiting the Schlosser $sp^3$-$sp^3$ cross coupling reaction (***Table 2.26, Entry 2* and *3***). Some of these natural products listed in ***Table 2.26*** possess fascinating biological activity profiles like diol **64**. This compound functions as a glue that aids in transferring the male aphrodisiac onto the queen butterfly during courtship. Diol **64** was successfully prepared in 38.9 % yield and in 4 linear steps from farnesyl acetate **59**. Herein, we also reported on the first total synthesis of anhydrofurospongin-1 **164**, which was accomplished in 6 linear steps and in 10.6% yield from (*E,E*)-farnesyl acetate (***Table 2.26, Entry 5***). Preparation of this synthetically novel marine derived natural product was achieved by exploiting our 2nd generation synthetic route for **1**.

Other synthetic achievements within this project were the preparation of a range of novel furanolipid derivatives, through a number of tailored and modified synthetic routes. We successfully generated an extensive library of over 40 novel furanolipid and thiophenolipid structural analogues of furospongolide **1**. Applying our 2nd generation synthetic methodology and varying the heterocycle along the linear pathway allowed access to an attractive, novel and biologically useful range of furanolipid and thiophenolipid olefins, alcohols, epoxides and aldehydes (*as summarised in* ***Figure 2.54***).

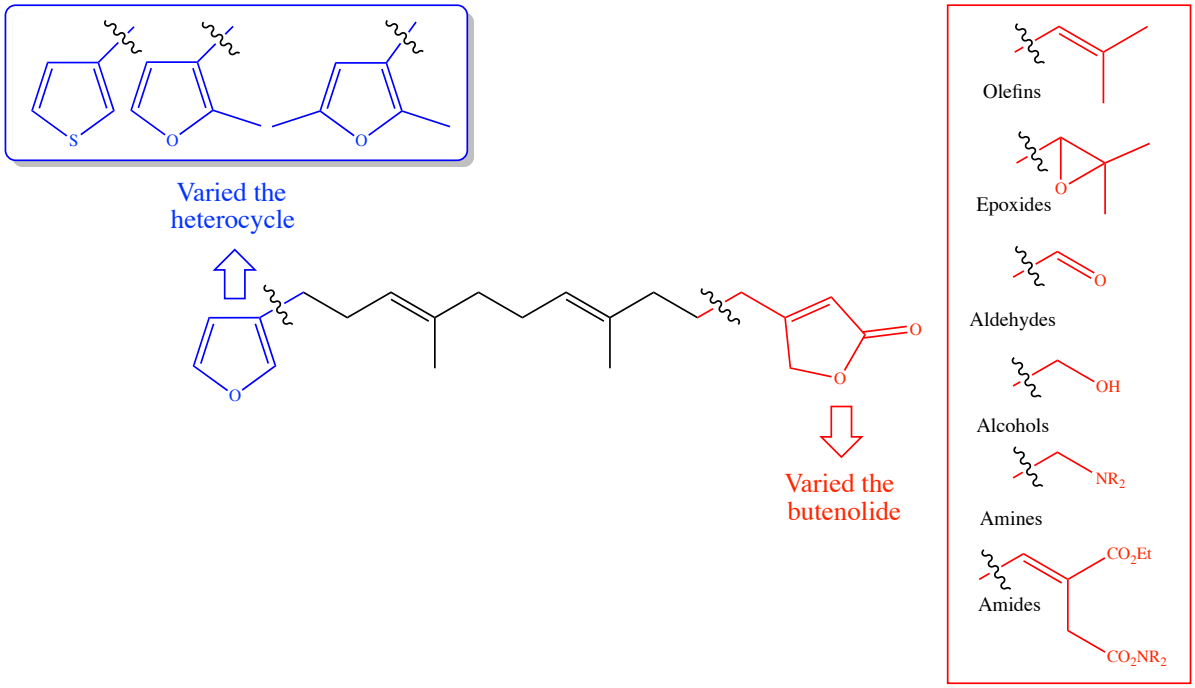



***Figure 2.54***

Thiophenospongolide is a good example of a novel design analogue of **1**, prepared by exchanging furan with thiophene. The relatively simple structure of furospongolide **1** made structural modification possible.

An extremely important building block in the synthesis of structural related analogues of **1** was furanolipid aldehyde **121.** This compound gave access to a novel series of furanolipid amine derivatives (reductive amination reaction) and a novel series of alkenyl derivatives (Wittig reaction). Similarly, thiophenolipid aldehyde **166** was utilised for the same purpose in

the preparations of a novel series of thiophenolipid amine derivatives *via* the reductive amination reaction.

A second important building block used in the synthesis of furanolipid analogues was furanolipid ester **126.** The half ester **126** was converted to a novel series of furanolipid amide derivatives *via* peptide chemistry.

To conclude, we have successfully prepared our target molecule (*E,E*)-furospongolide **1** in a concise high yielding synthetic route from (*E,E*)-farnesyl acetate **59**. An extensive library of related furanolipid structural analogues were also prepared. A number of these compounds were subsequently sent for biological testing through the National Cancer Institute and the results of this evaluation are discussed in ***Chapter 3***.

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# Chapter 3

# *Biological*

# *Results and Discussion*

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## 3.1 Biological Evaluation

The primary aim of this project was to accomplish the total synthesis of furospongolide in a concise, high yielding synthetic pathway and also prepare an extensive range of related furanolipid analogues. An additional and equally important objective was to evaluate the chemotherapeutic potential of our furanolipid analogues, which are an unexploited class of compound in the area of anticancer research. Following collaboration with the NCI, we successfully assessed the chemotherapeutic potential of 28 novel furanolipid and thiophenolipid analogues. As alluded to in ***Section 1.1.9***, the diverse range of biological activity exhibited by furanolipid marine natural products is remarkable and warrants further investigation. Surprisingly, synthetic chemists have targeted very few marine natural products for synthetic and biological purposes.

With respect to our research, furospongolide **1** was the prime target for total synthesis and biological evaluation due to its potency as a hypoxia-selective HIF-1 inhibitor in previous studies.[1] In this section, we hope to further evaluate the chemotherapeutic potential of furospongolide **1** across the NCI-60 tumour cell line panel and investigate its structure-activity relationship *via* comparative studies with structurally related furanolipid analogues. This will help us understanding what functionality is key to its inherent bioactivity. This is a crucial step in the development of a more potent antitumour agent. Furthermore, its simple structure made it readily amenable to the preparation of designed analogues. Our analogues will also be biologically evaluated with the primary goal of identifying promising lead compounds encompassing promising antitumour activity. In parallel to evaluating the chemotherapeutic potential of our designed analogues, we hope to investigate and identify a biological mechanism of action associated with this important class of compounds.

### 3.1.1 Development Therapeutic Program

As the drug discovery and developmental arm of the National Cancer Institute (NCI), the Developmental Therapeutics Program (DTP) plans, conducts and facilitates development of therapeutic agents for the treatment of cancer and AIDS. DTP's overall goal is to turn "molecules into medicine for the public health". Areas of support by DTP are discovery, development and pathways to development for the intramural and the extramural community.[2]

The Development Therapeutics Program, originally created by Congress in 1955 as the Cancer Chemotherapy National Service Center (CCNSC), operates a progressive, tiered *in vitro* and *in vivo* anti-cancer compound screening program for single pure compounds with the goal of identifying and evaluating novel chemical leads and biological mechanisms of action.[3] In addition to its anti-cancer screening program, DTP operates a Natural Products Repository (NPR), which contains the largest and most diverse natural products extracts collection in the world. It houses close to 170,000 extracts from samples of more than 70,000 plants and 10,000 marine organisms collected from more than 25 countries, plus more than 30,000 extracts of diverse bacteria and fungi. The natural products stored in DTP's repository are screened against the NCI human tumor cell line assay for potential anticancer activity shortly after their collection. So far, about 4,000 natural-source extracts have shown *in vitro* activity against human cancer cells, making them worthy of further study by DTP researchers. This repository of both synthetic and pure natural products provides a rich resource for discovery of novel research probes for molecular target manipulation, and new potential leads for drug discovery research and development. Since its establishment, DTP has played an intimate role in the discovery or development of more than 40 U.S. licensed chemotherapeutic agents, with the rest coming directly from the pharmaceutical industry. Some examples of these anticancer agents, developed with DTP involvement are shown in ***Table 3.1***. [2,4-10]

***Table 3.1:*** *Anticancer agents developed with DTP involvement**

| Year | Drug | Year | Drug | Year | Drug |
|---|---|---|---|---|---|
| **2010** | *Eribulin* | **1988** | *Ifosfamide* | **1970** | *Mithramycin* |
| **2009** | *Romidepsin* | **1987** | *Mitoxantrone* | **1969** | *Procarbazine* |
| **2004** | *Erbitux* | **1983** | *Etoposide* | **1967** | *Hydroxyurea* |
| **2003** | *Velcade* | **1982** | *Streptozotocin* | **1966** | *Thioguanine* |
| **1998** | *Ontak* | **1979** | *Daunorubicin* | **1964** | *Actinomycin D* |
| **1996** | *Topotecan* | **1978** | *Cisplatin* | **1963** | *Vincristine* |
| **1995** | *All-t-retinoic acid* | **1977** | *BCNU* | **1962** | *Fluorouracil* |
| **1992** | ***Taxol*** | **1976** | *CCNU* | **1961** | *Vinblastine* |
| **1991** | *Pentostatin* | **1975** | *Dacarbazine* | **1959** | *Cyclophosphamide* |
| **1990** | *Hevamisole* | **1974** | *Adriamycin* | **1961** | *Chloroambucil* |
| **1989** | *Carboplatin* | **1973** | *Bleomycin* | | |

***Table was adapted from the NCI website.**

Paclitaxel **274** is one of the most widely prescribed anticancer drugs on the market (***Table 3.1***). Paclitaxel **274** is a natural product isolated from the bark of the Pacific yew tree, *Taxus brevifolia* from which it got its trademark name, taxol (***Figure 3.1***).[11] It was first discovered by researchers working under a joint U.S. Department of Agriculture-National Cancer Institute grant and it was a DTP contractor who formulated the drug for use in clinical trials.[12-14] Paclitaxel **274** is a mitotic inhibitor and is used today in cancer chemotherapy in the treatment of patients with lung, ovarian, breast, head and neck cancer, and advanced forms of Kaposi's sarcoma. [15-17]

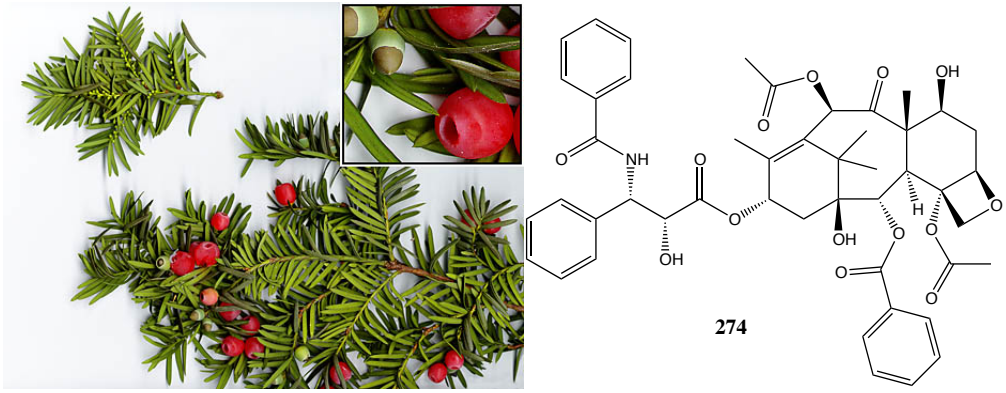
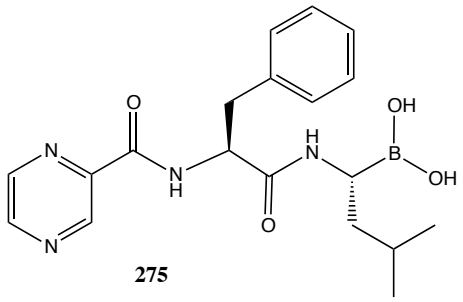



***Figure 3.1:*** *Paclitaxel (Taxol®) **274** and the Pacific yew tree, Taxus brevifolia.*

Bortezomib **275** is another DTP success story, which was screened and formulated by DTP in cooperation with its commercial sponsor (***Figure 3.2***). Approved by the Food and Drug Administration (FDA) in 2003, it was the first treatment in more than a decade to be approved for patients with multiple myeloma. It took only 8 years from initial NCI-60 hit identification of the novel proteasome inhibitor bortezomib **275** – a COMPARE negative (distinct anti-cancer mode of action) agent – in 1995 to full FDA approval.[8,10,18-20]




**275**

***Figure 3.2:*** *Bortezomib (Velcade®)* ***275.***

Many academic and private industry laboratories, which engage in drug discovery face financial and technical burdens that keep promising therapeutic agents from reaching the pharmaceutical market. DTP functions primarily as a public screening service for anticancer drug activity which help the academic and private sectors to overcome various therapeutic development barriers. As a consequence of this relationship, DTP has been intimately involved in the discovery or development of more than 70 percent of the anticancer therapeutics on the market today.[5-7,21,22]

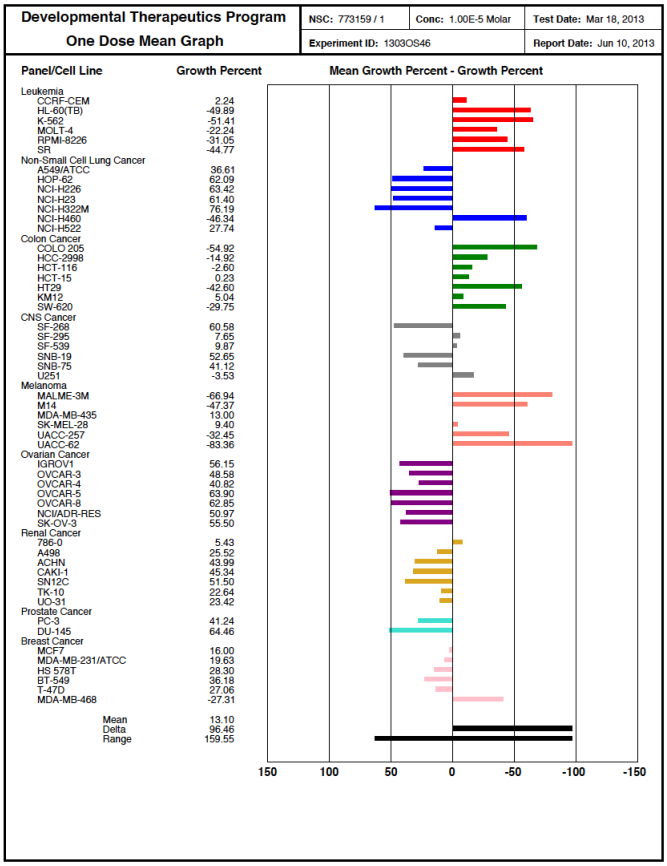
### 3.1.2 NCI-60 cancer cell line screening program

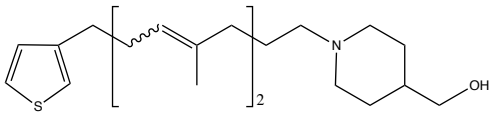
The U.S National Cancer Institute's Developmental Therapeutics Programme (DTP) 60 human tumour cell line service (NCI-60) was developed in the late 1980's as a strategic high-throughput screening tool for *in vitro* anti cancer drug activity.[9] Cytotoxicity data for in excess of 100,000 compounds across diverse cancer lines has been classified, following this approach.

This project is designed to screen up to 3,000 compounds per year for potential anticancer activity. The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. These cell lines were selected partly on pragmatic terms: those selected behaved best under typical assay conditions. The aim is to prioritize for further evaluation, synthetic compounds or natural product samples showing selective growth inhibition or cell killing of particular tumor cell lines.

This screen is unique in that the complexity of a 60 cell line dose response produced by a given compound results in a biological response pattern which can be utilized in pattern recognition algorithms. Using these algorithms, it is possible to assign a putative mechanism of action to a test compound, or to determine that the response pattern is unique and not similar to that of any of the standard prototype compounds included in the NCI database. In addition, following characterization of various cellular molecular targets in the 60 cell lines, it may be possible to select compounds most likely to interact with a specific molecular target.[23]

The screening is a two-stage process, beginning with the evaluation of all compounds against the 60 cell lines at a single dose of 10 μM, which is known as a one-dose NCI-60 screen. *In vitro* activity of each compound in the human tumour cell line is displayed in the form of a 'mean graph', consisting of a series of horizontal bar graphs representing units of nominal growth precent, deviating from the arithmetic mean growth for the entire 60 cell line panel ('0'). (***Figure 3.3***)




**230**

***Figure 3.3:*** *NCI-60 cancer cell line screen 'mean graph' of* ***230****.*

In each case, graphs which extend to the right (-) signify more selective cytotoxicity or positive growth inhibition, while those which extend to the left (+) of centre line indicate a chemoprotective or non-cytotoxic effect on individual cell lines.

Compounds that exhibit significant growth inhibition and satisfy the threshold inhibition criteria (<50%) are evaluated against the 60 cell line panel at five concentration levels, which is known as a 5-dose NCI-60 screen (***Figure 3.4***). Patterns of total panel activity can be correlated with those of over 100,000 compounds within a NCI-60 database, to reveal key mechanisms of action using the COMPARE program.

This screen is performed by a 5 x 10 fold serial dilution of a 100 μM stock solution prepared at the same time as the one-dose sample. The results are displayed on a graph showing the three response parameters; $GI_{50}$, TGI and $LG_{50}$ (***Figure 3.4***).

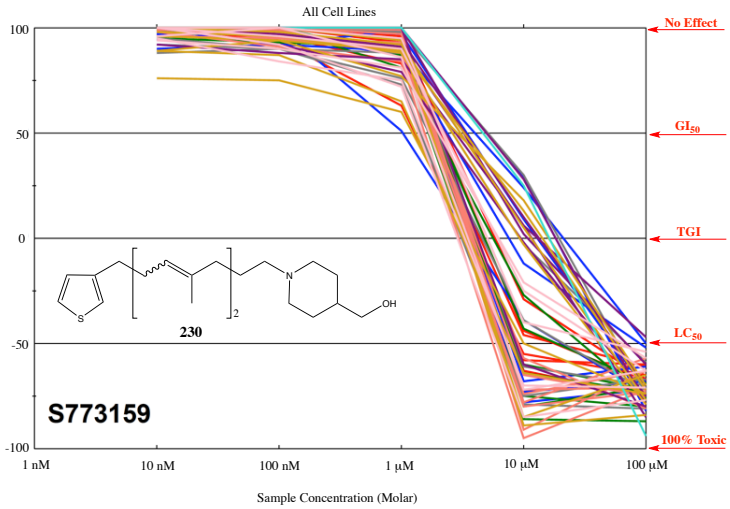



***Figure 3.4:*** *NCI-60 'five dose graph/dose response curve' of* ***230*** *for all cancer cell lines.*

The three characteristic *in vitro* parameters, $GI_{50}$ (concentration at which growth of 50% of cells present is fully arrested), TGI (concentration for total inhibition or 0% cell growth) and $LC_{50}$ (lethal concentration causing death in 50% of cells originally present), are calculated for each cell line in response to the presence of the different drug candidates.

Following recommendations by the Biological Review Committee, compounds that exhibit useful activity profiles may progress to *in vivo* hollow-fibre testing in mouse models and further xenograft assays, with successful drug candidates eventually authorised by the Drug Development Group to enter NCI clinical development.

### 3.1.3 NCI-60 one-dose screen results

#### 3.1.3.1 Furanolipid and thiophenolipid general derivatives

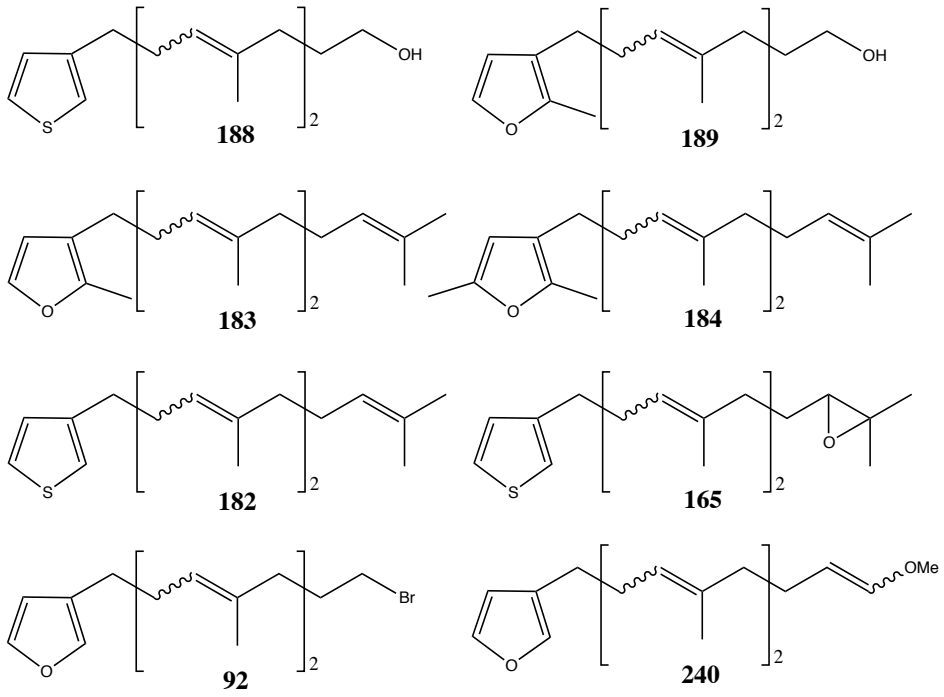
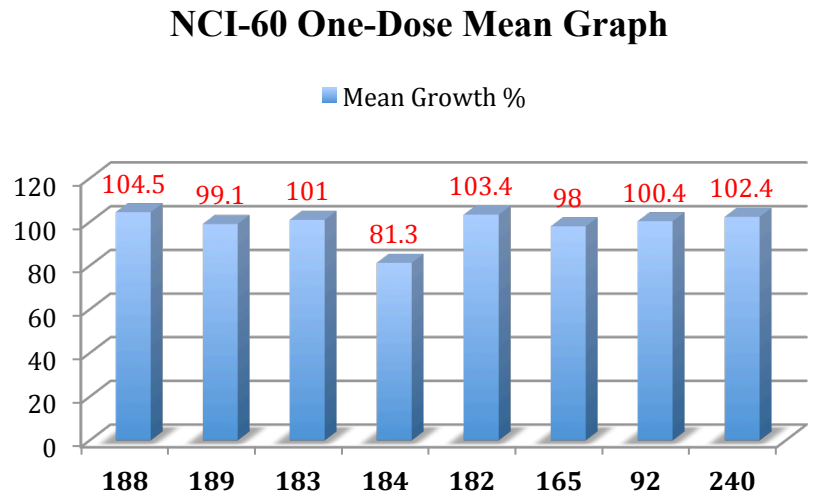



***Figure 3.5:*** *Series of furanolipid and thiophenolipid derivatives submitted to the DTP for in vitro NCI-60 cell line screening.*

The furanolipid and thiophenolipid general analogues displayed in ***Figure 3.5*** were successfully investigated for initial one-dose (10 μM) tumour cell line activity, and the pattern of quantifiable growth inhibition of these agents on the NCI-60 human tumour cell line panel is outlined herein. It should be noted that none of the above compounds exhibited the necessary biological activity required for five-dose screening by the NCI.

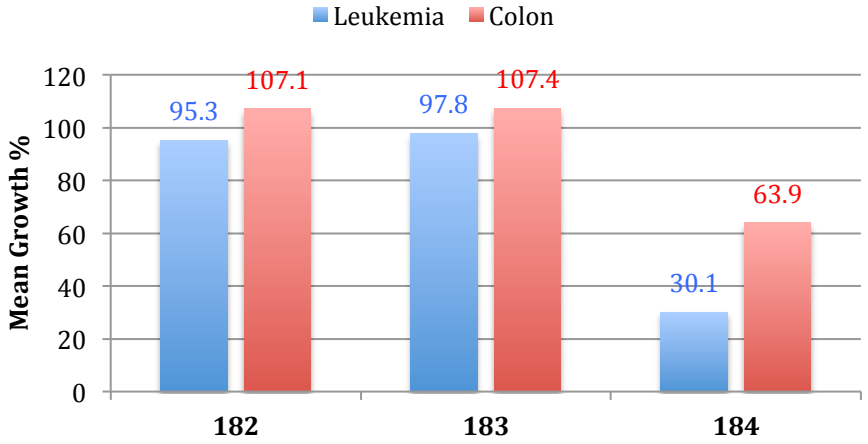
The one-dose mean graphs obtained for each of the compounds depicted in ***Figure 3.5*** are presented in ***Appendix III***. Evaluation of these one-dose mean graphs revealed that 2,5 dimethyl substituted furan **184** exhibited the greatest overall biological activity when compared to other compounds tested in this series (***Figure 3.6***).

***Figure 3.6.*** *Illustration of NCI-60 mean growth percent for our furanolipid and thiophenolipid general derivatives.*

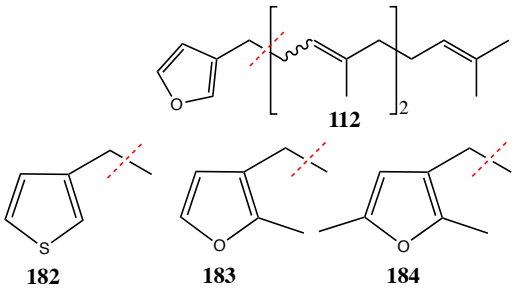



As portrayed in ***Figure 3.6***, the furanolipid and thiophenolipid derivatives displayed no significant biological activity except in the case of 2,5-dimethyl substituted furan **184**. In a comparative study between our olefin derivatives **182**, **183** and **184,** compound **184** proved to be highly selective against both leukaemia and colon cancers, revealing a noticeable pattern of growth inhibition for their respective cancer cell lines (***Figure 3.7***).

***Figure 3.7.*** *Illustration of mean growth percent in leukaemia and colon cancer cells when exposed to furanolipid and thiophenolipid olefins* ***182***, ***183*** *and* ***184.***



As previously stated in ***Section 2.9.1***, Higa *et al.* found ambliofuran **112** to be weakly cytotoxic in lung (P388, A-549) and colon (HT-29) cancer cells.[24] Likewise from our studies, a similar biological pattern was observed for both the 2-methyl substituted furan **183** and thiophene compound **182** showing no antitumour activity against the NCI-60 cell array (***Figure 3.8***).




| **Mean growth %** | **103.4** | **101.0** | **81.3** |
|---|---|---|---|

*Increasing antitumour activity*

***Figure 3.8:*** *The effect of varying the furan ring of ambliofuran **112** on antitumour activity.*

This provides fascinating information about the structure-activity relationship of ambliofuran **112** and the importance of the furan ring. Substitution of the ring at both the 2- and 5-positions (**184**) showed a marked improvement in biological activity. Furthermore, mono-methylation of the furan ring at the 2-position (**183**) or exchanging in a thiophene ring (**182**) was found to have no impact on antitumour activity in either case (***Figure 3.8***). In general, our furanolipid and thiophenolipid olefin derivatives were biological inactive as inhibitors of tumour cell line growth (except **184**). Likewise, as illustrated in ***Figure 3.6***, oxidation of the terminal alkene bond to epoxide **165** and alcohols **188** and **189** was found to show no significant enhancement in biological activity. Similarly, this was also the case when the functionality was changed to a bromide (**92**) or a methyl ether (**240**) (***Figure 3.6***).

### 3.1.3.2 Furanolipid and thiophenolipid amine analogues

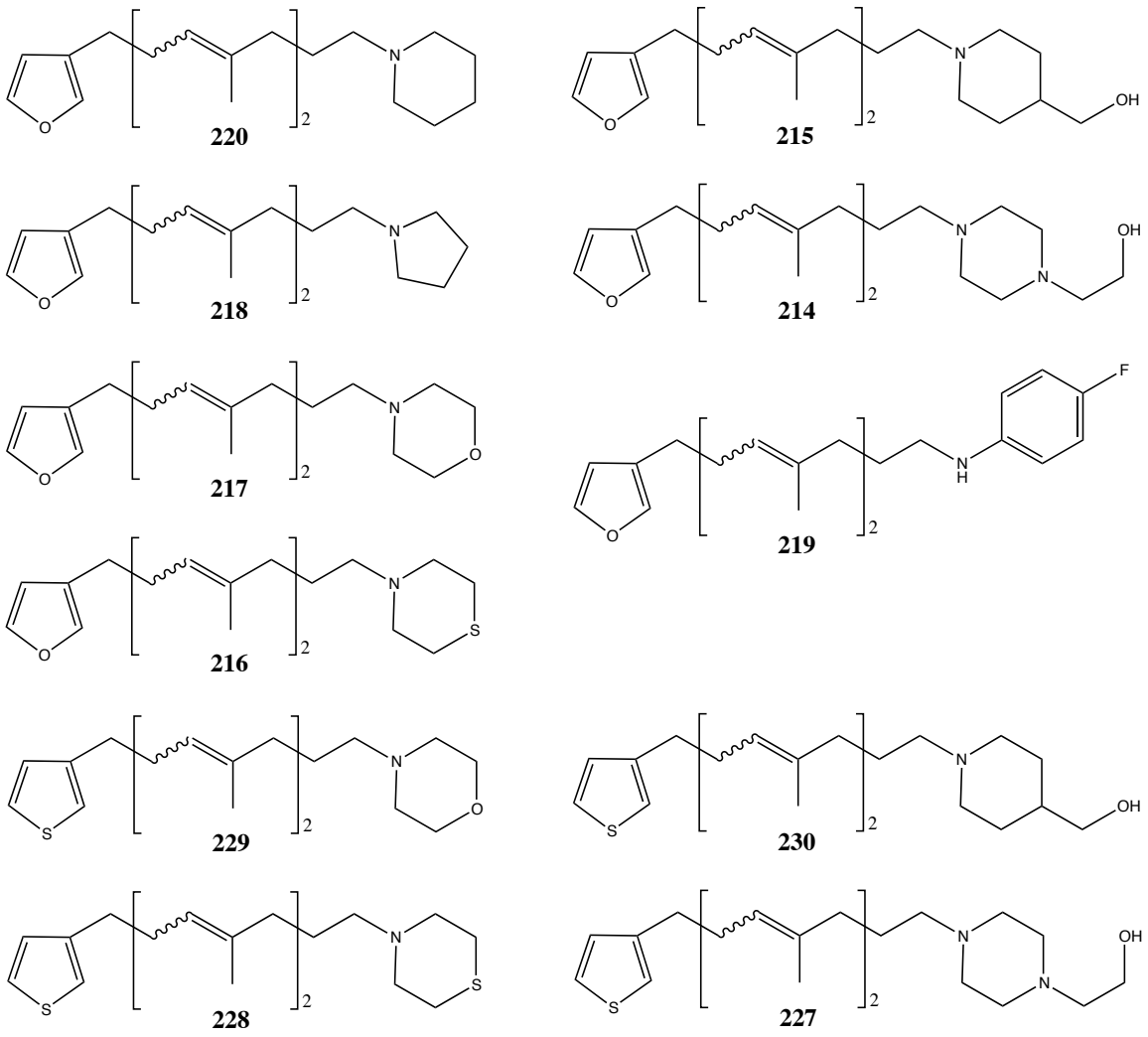
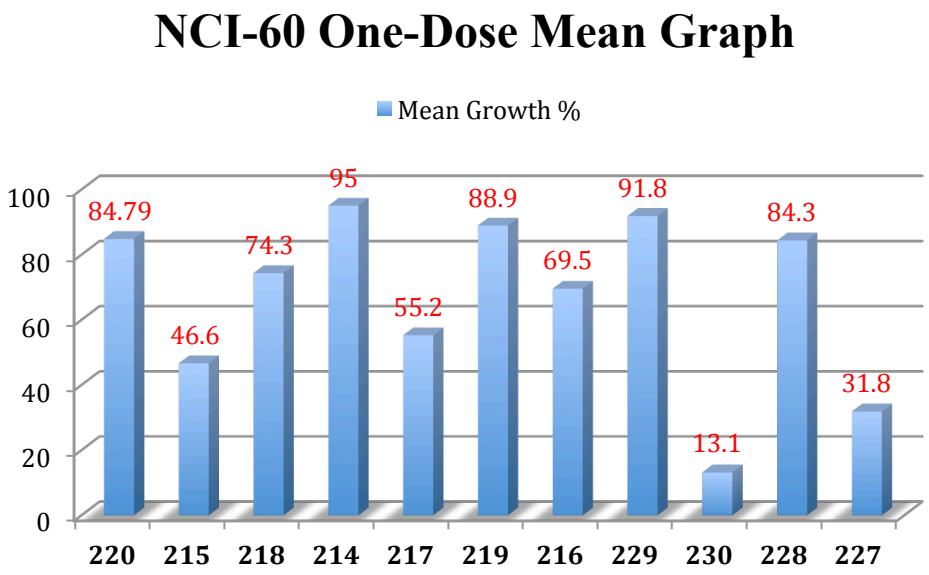


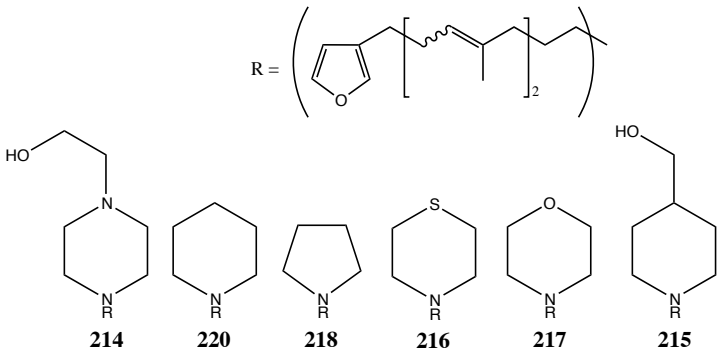

***Figure 3.9:*** *Series of furanolipid and thiophenolipid amines submitted to the DTP for NCI-60 cell line screening.*

The furanolipid and thiophenolipid amines shown in ***Figure 3.9*** were successfully investigated for one-dose tumour cell line activity on the NCI-60 cell array. The distinctive pattern of growth inhibition of these agents is outlined herein. It should be noted that furanolipid amines **215** and **217** as well as thiophenolipid amines **227** and **230** exhibited a broad range of biological activity, and to our delight, were accepted for five-dose screening by the NCI.

The one-dose mean graphs obtained for each of the compounds depicted in ***Figure 3.9*** are presented in ***Appendix III***. Evaluation of these one-dose mean graphs revealed a number of interesting and distinctive patterns for biological activity. In particular, the piperidine methanol derivative **230**, which demonstrated the greatest overall inhibition of tumour growth in this series. This is clearly evident in ***Figure 3.10***, which illustrates the enhanced growth inhibition of our furanolipid and thiophenolipid amine series; the overall NCI-60 mean growth percent is plotted for each compound.

***Figure 3.10:*** *Illustration of NCI-60 mean growth percent for our furanolipid and thiophenolipid amines.*





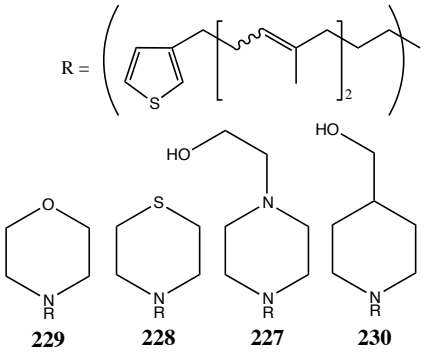

| Mean growth % | 95 | 84.8 | 74.3 | 69.5 | 55.2 | 46.6 |
|---|---|---|---|---|---|---|

*Increasing antitumour activity*

***Figure 3.11:*** *The effect of different furanolipid amine derivatives on antitumour activity.*

Utilising the one-dose mean data (***Figure 3.10***), we successfully analysed and studied the structure-activity relationship of our furanolipid amine derivatives (***Figure 3.11***). As expected, making minor structural modifications by varying the amine substituent had a remarkable impact on antitumour activity. Furanolipid piperazine ethanol **214** had the weakest activity profile. Interestingly, the five membered ring of pyrrolidine **218** was more active than its corresponding 6 membered ring derivative piperidine **220**. Introducing an electronegative atom/hydrogen bond accepter like sulfur or oxygen triggered a dramatic improvement in antitumour activity especially in the case of morpholine derivative **217**. The most pronounced inhibition of tumour growth was observed for piperidine methanol derivative **215**. Tumour growth was inhibited to an average of 46.6% across all NCI-60 cancer cell lines following exposure (***Figure 3.11***). Furanolipid amines **215** and **217** surpassed the minimum requirement for five-dose testing and were accepted for further evaluation through by the NCI. The results of the five-dose screen for compound **215** are discussed in ***Section 3.1.4.1***. Unfortunately, the five-dose screening results for compound **217** will not feature in this thesis as we are still awaiting the results of the 5-dose screen from the NCI.

A number of interesting observations were made following a comparative study between our furanolipid and thiophenolipid amine derivatives. Surprisingly, on this occasion, thiophenolipid morpholine **229** and thiomorpholine **228** were found to be relatively biologically inactive. In this scenario, complete loss of antitumour activity was observed when the furan ring was exchanged with thiophene (***Figure 3.12***).




| **Mean growth %** | **91.8** | **84.3** | **31.8** | **13.1** |
|---|---|---|---|---|

*Increasing antitumour activity*

***Figure 3.12:*** *The effect of different thiophenolipid amine derivatives on antitumour activity.*

Conversely, piperazine ethanol **227** was found to considerably increase its biological profile following interchange of heterocycles (95% to 31.8%). As expected, piperidine methanol **230** was the most active thiophenolipid derivative tested. Exchanging furan (**215**) for thiophene (**230**) dramatically improved antitumour activity by blocking tumour growth across all 60 cancer cells line to an average of 13.1% (***Figure 3.12***). Thiophenolipids **227** and **230** surpassed the minimum requirement for five-dose testing and were accepted for further evaluation through by the NCI. The results of the five-dose screen for compounds **230** and **227** are discussed in ***Section 3.1.4.2*** and ***Section 3.1.4.3*** respectively.

With regard to selectivity, furanolipid and thiophenolipid amine derivatives **215**, **227** and **230** exhibited distinctive biological activity for three cancer types in particular; leukaemia, colon and melanoma cancers (***Table 3.2***).

***Table 3.2:*** *One-dose screen of our furanolipid and thiophenolipid amines against leukaemia, colon and melanoma cancer.*

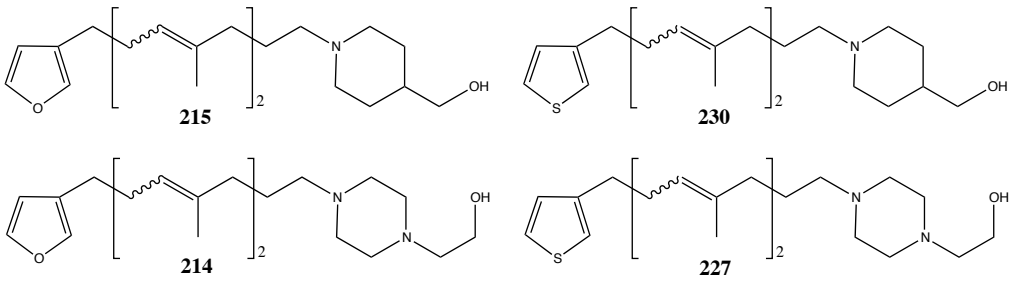
| Entry | Compound | Tumour site | Growth %* | Mean Growth % |
|---|---|---|---|---|
| 1 | **220** | Leukaemia | 80.56 | 84.79 |
| | | Colon | 85.06 | |
| | | Melanoma | 89.97 | |
| 2 | **215** | Leukaemia | 11.64 | 46.63 |
| | | Colon | 21.55 | |
| | | Melanoma | 19.07 | |
| 3 | **218** | Leukaemia | 48.15 | 74.26 |
| | | Colon | 73.95 | |
| | | Melanoma | 86.05 | |
| 4 | **214** | Leukaemia | 85.18 | 95.01 |
| | | Colon | 93.88 | |
| | | Melanoma | 99.29 | |
| 5 | **217** | Leukaemia | 30.26 | 55.18 |
| | | Colon | 43.38 | |
| | | Melanoma | 60.09 | |
| 6 | **219** | Leukaemia | 55.62 | 88.94 |
| | | Colon | 93.37 | |
| | | Melanoma | 97.05 | |
| 7 | **216** | Leukaemia | 59.46 | 69.48 |
| | | Colon | 62.22 | |
| | | Melanoma | 78.08 | |
| 8 | **229** | Leukaemia | 85.85 | 91.79 |
| | | Colon | 92.94 | |
| | | Melanoma | 95.19 | |
| 9 | **230** | Leukaemia | -32.85 | 13.10 |
| | | Colon | -19.93 | |
| | | Melanoma | -34.62 | |
| 10 | **228** | Leukaemia | 66.02 | 84.27 |
| | | Colon | 86.66 | |
| | | Melanoma | 89.14 | |
| 11 | **227** | Leukaemia | -14.56 | 31.77 |
| | | Colon | -0.61 | |
| | | Melanoma | 6.06 | |

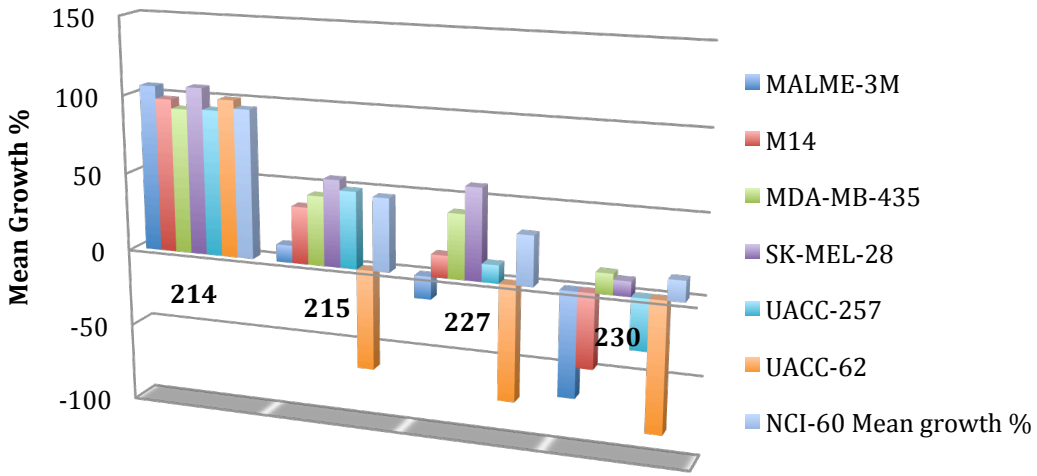
*Initial compound concentration of 10 μM.

From evaluation of ***Table 3.2***, it can be seen that furanolipid amines **215** and **217** as well as thiophenolipid amines **230** and **227** exhibited the greatest inhibition of growth across the three cell lines featured. With respect to our thiophenolipid amine derivatives **230** and **227**, complete inhibition of tumour growth was observed on exposure to leukaemia, colon and melanoma cancers in addition to pronounced cytotoxicity at 10 μM. The furanolipid amine derivatives **215** and **217** also showed encouraging antitumour activity but were noticeably less potent (***Table 3.2***).

As a result of the promising antitumour activity observed for our furanolipid amine **215** and our thiophenolipid amines **227** and **230**, we decided to explore even deeper and identify if these compounds have selectivity towards one specific tumour cell line. Due to structure similarity, compound **214** was included in this study. With respect to melanoma cancer, the UACC-62 cell line (a malignant cell line) showed the greatest sensitivity to our amine derivatives **215**, **227** and **230** (***Figure 3.13***). These compounds exhibited outstanding antitumour activity with tumour cell line mortality was as high as 83%. The remarkable selective inhibition exhibited in the UACC-62 cell line is illustrated in ***Figure 3.13***.

***Figure 3.13:*** *Illustration of growth percent for 6 melanoma cell lines and NCI-60 mean growth percent following exposure to amines* ***214***, ***215***, ***227*** *and* ***230***.



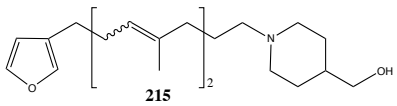
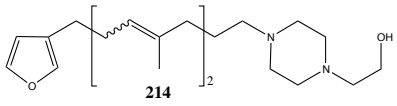
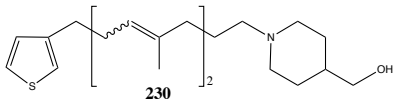
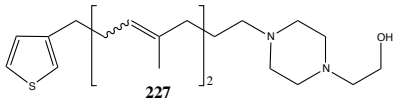




Surprisingly, furanolipid amine **214**, which is almost identical in structure to thiophenolipid **227,** exhibited no growth inhibition in the UACC-62 cancer cell line (100.18%). In this scenario, replacement of the thiophene ring with a furan ring resulted in complete loss of biological activity (***Figure 3.13***).

Nevertheless, the positive selectivity of furanolipid **215** and thiophenolipid amines **227** and **230** for melanoma cancer in this screening process and the UACC-62 cell line in particular is encouraging and will be explored further in future work. Melanoma is a dangerous form of skin cancer, which begins in melanocytes and can easily spread to other parts of the body.

Another distinctive pattern observed during the evaluation of furanolipids amines **215** and thiophenolipid amines **227** and **230** was the promising antitumour activity displayed in both leukaemia and colon cancer cell lines (***Appendix III***). For illustrative purposes, ***Table 3.3*** exemplifies just a few of the cells lines in which our amine molecules were found to exhibit remarkable growth inhibition.

***Table 3.3:*** *One-dose screen of our furanolipid and thiophenolipid amines against leukaemia and colon cancer cells*

| Entry | Compound | NCI-60 Cell line | Tumour site | Growth %* |
|---|---|---|---|---|
| 1 |  **215** | HL-60(TB) | | 17.19 |
| | | K-562 | Leukaemia | -15.79 |
| | | SR | | 2.60 |
| | | COLO 205 | | -21.44 |
| | | HCT-15 | Colon | 25.54 |
| | | HT29 | | 6.48 |
| 2 |  **214** | HL-60(TB) | | 85.43 |
| | | K-562 | Leukaemia | 69.53 |
| | | SR | | 83.51 |
| | | COLO 205 | | 99.77 |
| | | HCT-15 | Colon | 99.49 |
| | | HT29 | | 82.35 |
| 3 |  **230** | HL-60(TB) | | -49.89 |
| | | K-562 | Leukaemia | -51.41 |
| | | SR | | -44.77 |
| | | COLO 205 | | -54.92 |
| | | HCT-15 | Colon | 0.23 |
| | | HT29 | | -42.60 |
| 4 |  **227** | HL-60(TB) | | -38.27 |
| | | K-562 | Leukaemia | -27.35 |
| | | SR | | -29.08 |
| | | COLO 205 | | -9.20 |
| | | HCT-15 | Colon | -22.22 |
| | | HT29 | | -34.37 |

*Initial compound concentration of 10 μM

In most cases, close to complete inhibition of tumour growth was observed (***Table 3.3***). Furthermore, minor to moderate cytotoxicity was observed across specific leukaemia (K-562, highlighted) and colon cancer (COLO 205, highlighted) cell lines following exposure to our compounds. The excellent activity displayed in the leukaemia [HL-60(TB), K-562 and SR] and colon [COLO 205, HCT-15 and HT29] cancer cell lines warrants further investigation at a five-dose level.

### 3.1.3.3 Furanolipid and thiophenolipid ester and/or amide derivatives

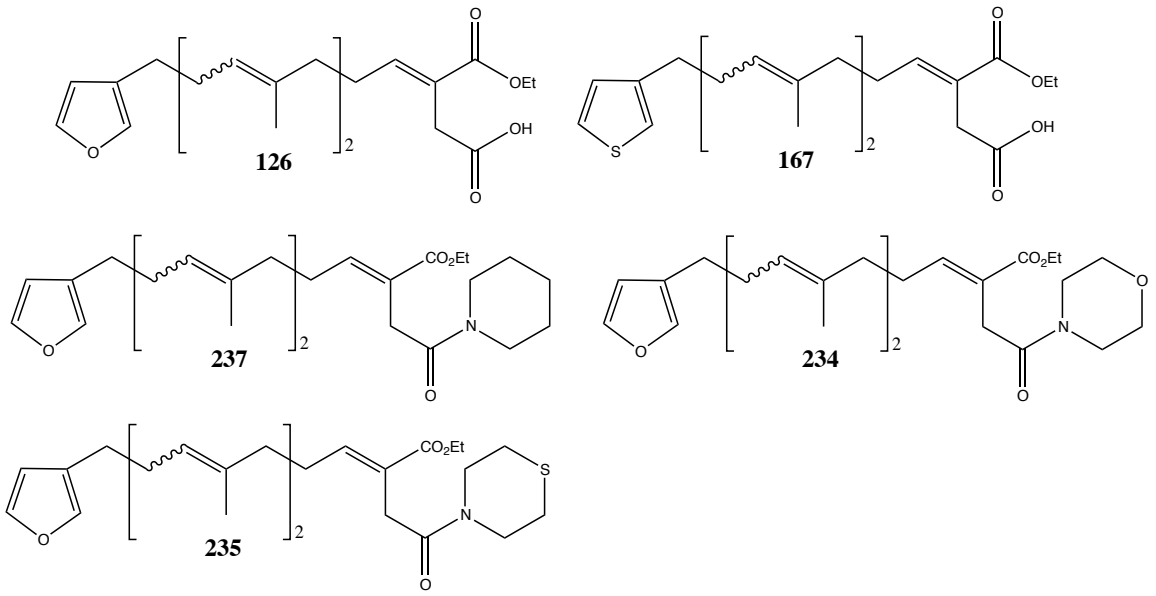
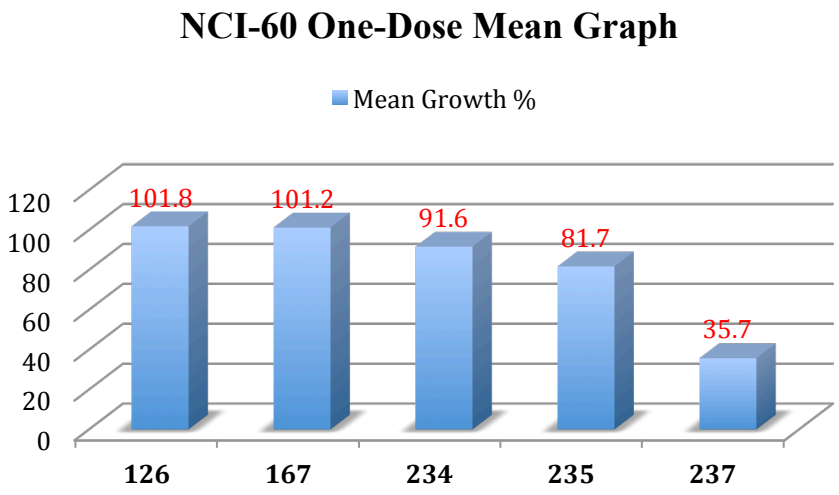



***Figure 3.14:*** *Series of furanolipid and thiophenolipid ester and furanolipid amide derivatives submitted to the DTP for NCI-60 screening.*

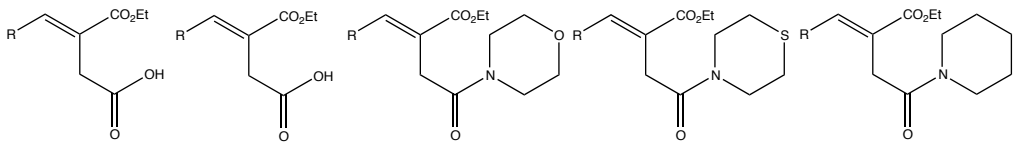
The furanolipid and thiophenolipid ester and furanolipid amide derivatives displayed in ***Figure 3.14*** were investigated for initial one-dose tumour cell line activity on the NCI-60 human tumour cell line panel. It should be noted that furanolipid amide **237** exhibited a broad range of biological activity, and to our delight, has been accepted for five-dose screening by the NCI. The one-dose mean graphs obtained for each of the compounds depicted in ***Figure 3.14*** are presented in ***Appendix III***. Evaluation of these one-dose mean graphs revealed a number of interesting and distinctive patterns for biological activity. Particularly, the amide

derivatives **234**, **235** and **237** which demonstrated greater overall inhibition of tumour growth compared to the ester derivatives **126** and **167** as illustrated in ***Figure 3.15***.

***Figure 3.15:*** *Illustration of NCI-60 mean growth percent for the furanolipid and thiophenolipid ester and furanolipid amide derivatives.*




The furanolipid (**126**) and thiophenolipid (**167**) ester derivatives were found to be biologically inactive showing no measurable growth inhibition across the NCI-60 cell array (***Figure 3.15***). As previously discussed in ***Section 2.9.8***, introducing an amide functionality into a half ester substrate is a resourceful way to increase the bioactivity of a compound as the molecule more closely resembles an amino acid (***Figure 3.16***).[25]




| | 126 | 167 | 234 | 235 | 237 |
|---|---|---|---|---|---|
| **Growth %** | **101.8** | **101.2** | **91.6** | **81.7** | **35.7** |

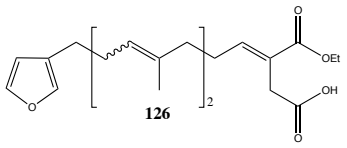
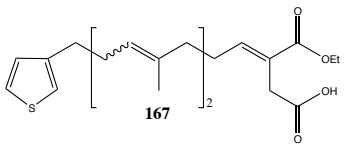
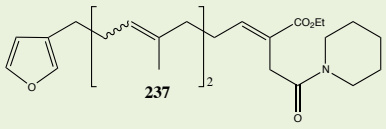
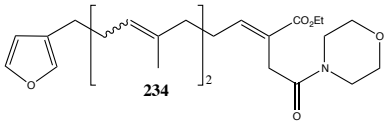
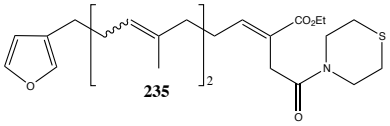
*Increasing antitumour activity*

***Figure 3.16:*** *The effect of introducing an amide functionality on antitumour activity.*

With respect to structure-activity relationship, introducing the morpholine (**234)** and thiomorpholine (**235)** ring system was shown to marginally increase antitumour activity compared to their corresponding ester derivative **126**. Interestingly, thiomorpholine (**235**), which is a less electronegative ring system than morpholine (**234**) was found to block tumour growth to a slightly greater extent (91.6% to 81.7%). Furthermore, when the electronegative atom/hydrogen bond acceptor unit is completely removed from compound **234** (oxygen) and **235** (sulfur) like in the case of piperidine **237**, a remarkable increase in antitumour activity (35.7%) is observed (***Figure 3.16***). This may suggest that an undesired hydrogen bonding interaction could be taking place within the binding pocket of the enzyme blocking a biological response (putative). Future work will look towards preparing a series of furanolipid amide derivatives similar in structure to **237** (lacking an electronegative atom) using rapid parallel synthesis in the quest of discovering a more potent drug lead for the treatment of cancer. Compound **237** surpassed the minimum requirement for five-dose testing and was accepted for further evaluation through by the NCI. Unfortunately, the five-dose testing results for compound **237** will not be featured in this report as we are still awaiting information from the NCI.

With regard to selectivity, compound **237** exhibited distinctive biological activity for non-small cell lung cancer (***Table 3.4***). The greatest antitumour activity was observed in the A549/ATCC, NCI-H322M and NCI-H460 cell lines (*highlighted*). On exposure to piperidine **237** at a concentration of 10 μM, tumour growth was completely inhibited with pronounced tumour cell line mortality as high as 92 % (***Table 3.4, Entry 3***). It should be noted that this was the highest recorded value for tumour cell line cytotoxicity across all our compounds for one specific cell line.

***Table 3.4:*** *One-dose screen of our furanolipid and thiophenolipid esters and furanolipid amide derivatives against non-small cell lung cancer.*

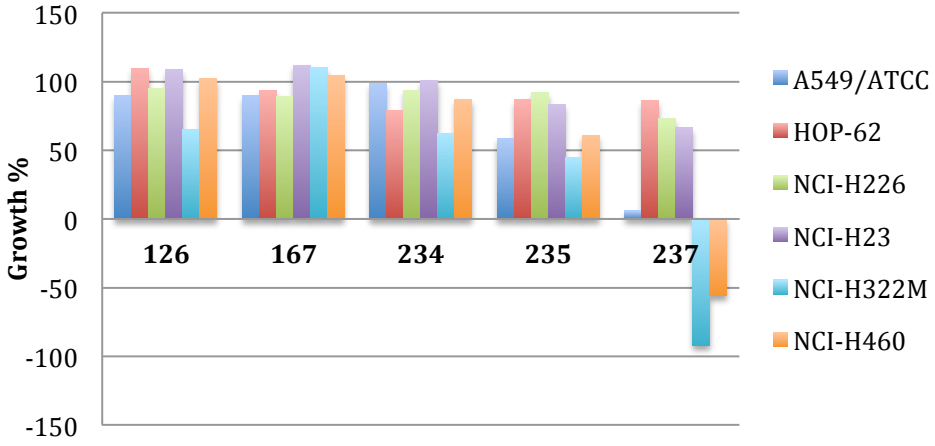
| Entry | Compound No | NCI-60 cell-lines | Growth %* | Mean cell-line Growth % |
|---|---|---|---|---|
| 1 |  **126** | A549/ATCC | 89.92 | 95.09 |
| | | HOP-62 | 109.76 | |
| | | NCI-H226 | 94.91 | |
| | | NCI-H23 | 108.54 | |
| | | NCI-H322M | 65.42 | |
| | | NCI-H460 | 101.96 | |
| 2 |  **167** | A549/ATCC | 89.58 | 99.82 |
| | | HOP-62 | 93.35 | |
| | | NCI-H226 | 89.36 | |
| | | NCI-H23 | 111.82 | |
| | | NCI-H322M | 110.06 | |
| | | NCI-H460 | 104.75 | |
| 3 |  **237** | A549/ATCC | 5.91 | 13.86 |
| | | HOP-62 | 85.97 | |
| | | NCI-H226 | 73.05 | |
| | | NCI-H23 | 66.44 | |
| | | NCI-H322M | -91.81 | |
| | | NCI-H460 | -56.40 | |
| 4 |  **234** | A549/ATCC | 98.43 | 86.97 |
| | | HOP-62 | 79.02 | |
| | | NCI-H226 | 93.81 | |
| | | NCI-H23 | 101.19 | |
| | | NCI-H322M | 62.07 | |
| | | NCI-H460 | 87.30 | |
| 5 |  **235** | A549/ATCC | 58.60 | 81.45 |
| | | HOP-62 | 86.67 | |
| | | NCI-H226 | 91.86 | |
| | | NCI-H23 | 83.63 | |
| | | NCI-H322M | 44.64 | |
| | | NCI-H460 | 60.93 | |

*Initial compound concentration of 10 μM

As expected, morpholine **234** and thiomorpholine **235** showed marginal antitumour activity while furanolipid ester **126** and thiophenolipid ester **167** were completely inactive.

The remarkable selective inhibition exhibited by **237** in the A549/ATCC, NCI-H322M and NCI-H460 cell lines is clearly portrayed in ***Figure 3.17***.

***Figure 3.17:*** *Illustration of growth percent of six non-small cell lung cancer cell lines for compounds* ***126***, ***167***, ***234***, ***235*** *and* ***237***.




This result further highlights the impressive biological activity displayed by furanolipid piperidine **237** and the need for future synthetic and biological studies into these amide derivatives.

### 3.1.3.4 Furospongolide and related structural analogues

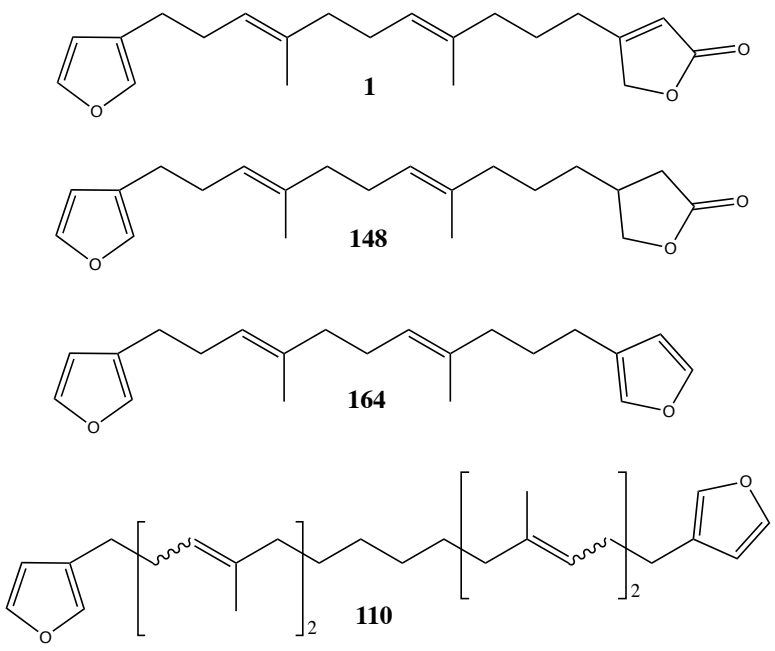
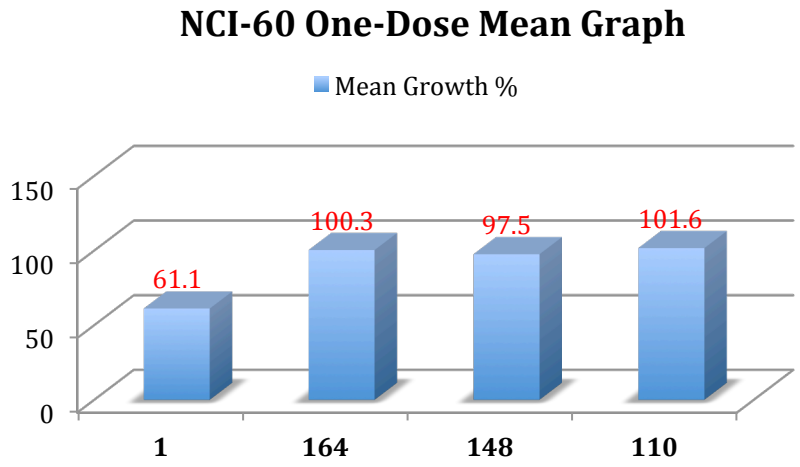



***Figure 3.18:*** *Furosponogolide* ***1****, anhydrofurospongin-1* ***164*** *and related structural derivatives submitted to the DTP for NCI-60 screening.*

Furospongolide **1**, anhydrofurospongin-1 **164** and related structural derivatives displayed in ***Figure 3.18*** were successfully investigated for initial one-dose (10 μM) tumour cell line activity. The one-dose mean graphs obtained for each of the compounds depicted in ***Figure 3.18*** are presented in ***Appendix III***. Evaluation of these one-dose mean graphs revealed a number of interesting findings especially with respect to the structure-activity relationship of furospongolide **1**.

***Figure 3.19:*** *Illustration of NCI-60 mean growth percent for* furospongolide **1**, anhydrofurospongin-1 **164** and related structural derivatives **148** and **110**.




With respect to NCI-60 mean growth %, furospongolide **1** was the only compound found to exhibit pronounced antitumour activity. When minor alterations were made at the butenolide moiety like in the case of compound **148** and **164**, complete loss of antitumour activity was observed (***Figure 3.19***). Despite only having moderate potency (61.1%, 10 μM), furospongolide **1** was accepted by the NCI for five-dose testing. Unfortunately at this time, we are unable to discuss the results of **1** at a 5-dose level across the NCI-60 cell line panel as we are still awaiting the results from the NCI.

As alluded to in the introduction, furospongolide **1** is a structurally unique inhibitor of HIF-1 activation with an $IC_{50}$ of 2.9 μM in T47D breast tumour cells (***Section 1.1.7.1***). These intriguing bioactivities prompted us to engage in a synthetic study in order to supply a sufficient amount of **1** for further biological study and the development of a more potent chemotherapeutic agent. As there has been only minor information about the hypoxia-selective growth inhibitory activity of **1** in the literature,[1,26,27] we decided to elucidate the structure-activity relationship of **1** through synthesis and biological evaluation of some structurally related analogues (***Figure 3.20***).

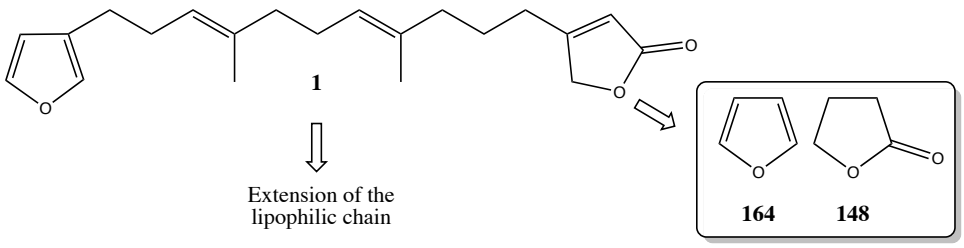
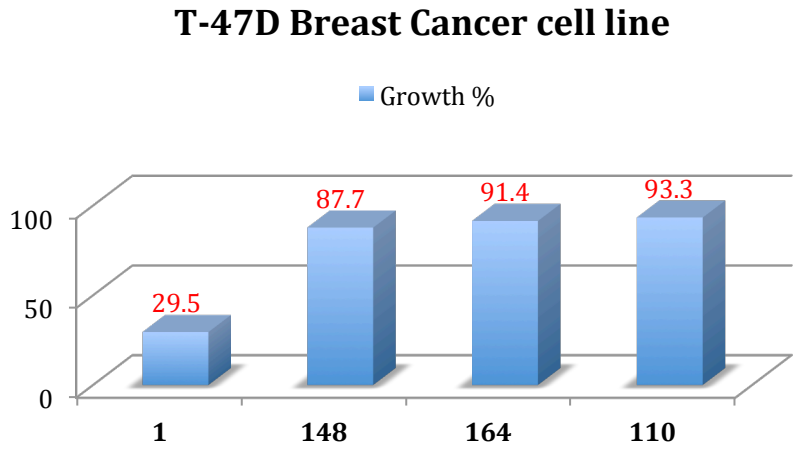



***Figure 3.20:*** *Minor modifications were made to furospongolide **1** in order to biologically assess the importance of the butenolide moiety to its antitumour activity.*

Nagle and Boukouvalas *et al.* have recent proposed that the butenolide moiety of furospongolide **1** is the key structural feature behind its biological activity. [1,26,27] In order to address this, we looked at the NCI-60 one-dose mean graph for **1**, particularly its effect on the breast cancer cell line T-47D and compared it with 3 closely related structural derivatives (***Figure 3.21***).

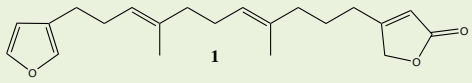
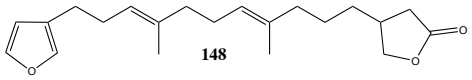
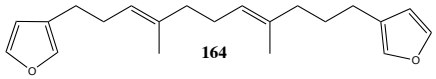
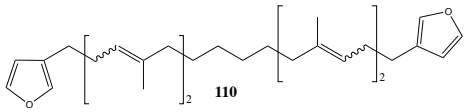
***Figure 3.21:*** *Illustration of NCI-60 one-dose growth percent for furospongolide **1**, anhydrofurospongin-1 **164** and related structural derivatives **148** and **110** on the T-47D human breast cancer cell line.*



Furospongolide **1** was found to block the growth of T-47D breast cancer cells to 29.5% at a standard concentration of 10 μM. Interestingly, when conjugation was removed from the α,β-unsaturated lactone as in the case of the saturated lactone **148**, almost complete loss of biological activity occurred. T-47D cancer cell line growth was 87.7 % following treatment with compound **148** at a concentration of 10 μM (***Figure 3.21, Table 3.5***). Furthermore, when the lactone function was completely removed from the furanolipid backbone and exchanged with a furan moiety like in the case of the marine natural product anhydrofurospongin-1 **164**, T-47D cancer cell line growth was even higher at 91.4 % (***Figure 3.21, Table 3.5***).

Finally, just to remark on the length of the lipophilic terpenoid chain and its importance to the biological activity of furospongolide **1**. Compound **110** is similar in structure to anhydrofurospongin-1 **164** as it terminates with a furan ring at both ends but is different due to an extra extension in the intervening terpenoid chain (***Figure 3.18***). T-47D cancer cell line growth was the highest at 93.3 % of the 4 compounds tested in this particular series (***Figure 3.21, Table 3.5***). It should be noted that further work would be required in this area in order to make more comprehensive assessments about the importance of the lipophilic sidechain to the biological profile of furospongolide **1**.

***Table 3.5:*** *One-dose screen of furospongolide **1** and related derivatives against Breast Cancer cell lines.*

| Entry | Compound No | NCI-60 cell-lines | Growth %* | Mean cell-line Growth % |
|---|---|---|---|---|
| 1 |  **1** | MCF7 | 43.90 | 49.74 |
| | | MDA-MB-231 | 58.68 | |
| | | HS 578T | 63.26 | |
| | | BT-549 | 80.73 | |
| | | T-47D | 29.48 | |
| | | MDA-MB-468 | 22.40 | |
| 2 |  **148** | MCF7 | 90.55 | 95.6 |
| | | MDA-MB-231 | 92.63 | |
| | | HS 578T | 97.54 | |
| | | BT-549 | 107.61 | |
| | | T-47D | 87.70 | |
| | | MDA-MB-468 | 97.40 | |
| 3 |  **164** | MCF7 | 98.63 | 100.80 |
| | | MDA-MB-231 | 100.05 | |
| | | HS 578T | 101.18 | |
| | | BT-549 | 107.11 | |
| | | T-47D | 91.40 | |
| | | MDA-MB-468 | 106.45 | |
| 4 |  **110** | MCF7 | 105.76 | 101.79 |
| | | MDA-MB-231 | 99.05 | |
| | | HS 578T | 105.69 | |
| | | BT-549 | 106.53 | |
| | | T-47D | 93.30 | |
| | | MDA-MB-468 | 100.40 | |

*Initial compound concentration of 10 μM*

These results confirmed that the intact butenolide ring is essential to the antitumour activity profile of furospongolide **1** since both the saturated lactone **148** and difuran **164** derivatives were found to be both biologically inactive (as previously suggested by Nagle and Boukouvalas) following a comparitive study.[1,26,27] Future work in this area will look towards modifing the furan ring and the interlinking terpenoid chain in order to amend the antitumour potential of furospongolide **1**.

### 3.1.4 NCI-60 five-dose screen results

Compounds that were successfully chosen for five-dose testing were tested against the NCI-60 cell panel at five concentrations ranging from 10 nM to 100 μM. Dose-response curves were generated for cell growth inhibition as a function of inhibitor concentration for each cell line following extrapolation of the data. The three characteristic *in vitro* parameters, $GI_{50}$, TGI and $LC_{50}$ were calculated for each cell line in response to the presence of the different drug candidates.

#### 3.1.4.1 Five-dose data for furanolipid 215

Having shown significant promise in initial one-dose screening (***Figure 3.10***), furanolipid **215** was accepted for five-dose screening and tested at five different concentrations against the NCI-60 cell array. Inhibition across the cell line panel was in a dose-dependant manner as illustrated in ***Figure 3.22***, with $GI_{50}$ values predominantly in the low micromolar range (***Appendix IV***).

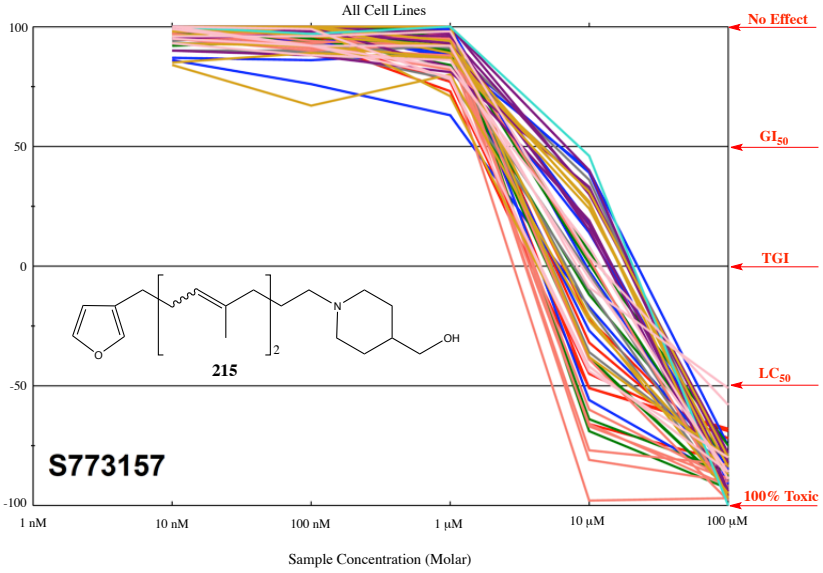



***Figure 3.22:*** *Dose-response curve for furanolipid* ***215***

The curve showed the steady inhibition of growth in all cancer cell lines on exposure to compound **215** at concentrations above 1 μM. As the concentration of compound **215** is steadily increased towards 100 μM, the $LC_{50}$ parameter is reached across all NCI-60 tumour cell lines (***Figure 3.22***). Therefore there is only a short therapeutic window between the

inhibition of tumour growth and cell viability on exposure to compound **215**. This drug is therefore cytotoxic at moderate concentrations (>1 μM) showing no cytostatic characteristics. Furthermore, at a concentration of 10 μM, close to 100% cytotoxicity (98%) was observed in the SK-MEL-5 melanoma cell line having a $LC_{50}$ value of 5.39 μM (***Figure 3.23***). Noteworthy, the UACC-62 melanoma cell line, which showed complete inhibition of tumour growth in addition to cell line death of 64% in the one-dose screen (***Figure 3.13***), likewise showed a similar value in five-dose testing (10 μM, 66% cell death) and also had one of the lowest $GI_{50}$ (1.77 μM) and TGI (3.73 μM) values, illustrating a consistency across screens (***Figure 3.23***).

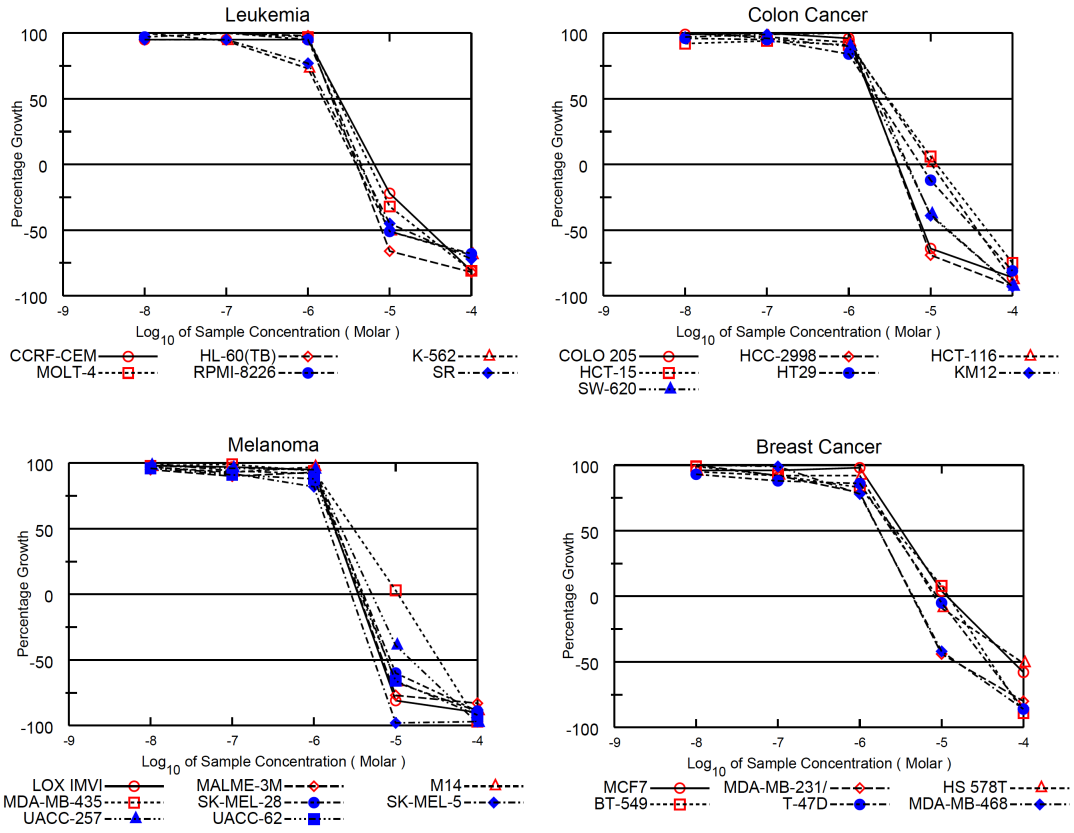



***Figure 3.23:*** *Dose-response curves of furanolipid* ***215*** *against leukaemia, colon, melanoma and breast cancer cell lines.*

With regard to selectivity, the MDA-MB-435 cell line was slightly more resistant to the cytotoxic agent **215** than other melanoma cell lines screened (***Figure 3.23***)**.** Recently**,** a number of studies have suggested that loss of wild-type (wt) *p53* function may be a major reason underlying failure to respond to radiotherapy and chemotherapy in various human cancers.[28-30] Many, although not all *in vitro* studies suggest that tumour cells lacking *p53* function are resistant to cytotoxic agents and radiation compared with cells with wt *p53*.[28-31] MDA-MB-435 is a ductal carcinoma cell line that is lacking *p53* function and this factor may have had an impact on cellular sensitivity to our cytotoxic agent. More information is obviously required before we make a connection between the activity of our cytotoxic agent **215** and how it is directly influenced by *p53* status**.**

The MDA-MB-435 cell line was originally reported as a breast carcinoma cell but has recently been reclassified as a melanoma cell line. Conversely, two closely related breast tumour cell lines called MDA-MB-231 and MDA-MB-468 both lacking *p53* function were found to have the highest sensitivity to our cytotoxic agent **215** (***Figure 3.23***). This is in direct contrast to our previous theory on the impact of *p53* status on cellular sensitivity to our drug candidate **215**.

With regard to the dose response curve for colon cancer, a graduation in sensitivity of each cell line was observed (***Figure 3.23***). COLO-205 and HCC-2998 cell lines were the most sensitive having an $IC_{50}$ value in the range 7.8-8.2 μM (similar to one-dose data, ***Table 3.3***). Not surprising, both of these cell lines have a mutant (mu) *p53* gene. Likewise, colon cell lines with a functional wt *p53* gene like HCT-15 and HCT-116 were more resistant to our cytotoxic agent having an $IC_{50}$ value in the range 37.6-48.9 μM.

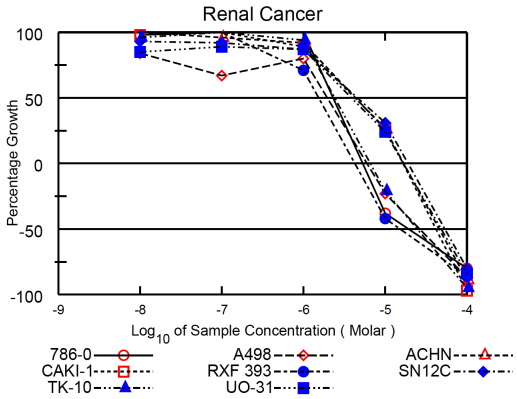



***Figure 3.24:*** *Dose-response curves of furanolipid* ***215*** *against renal cancer cell lines.*

The dose-response curves of **215** against renal cancer produced a visible divergence in tumour cell line sensitivity, which not surprisingly can be directly related to the presence of a functional wt *p53* gene (***Figure 3.24***). Tumour cells lines lacking *p53* function like TK-10, RXF393 and 786-0 were found to be slightly more sensitive to our cytotoxic agent **230** having an $LC_{50}$ value in the range 15.2-24.6 μM. In contrast, tumour cells lines containing a functional wt *p53* gene like CAK-1, ACHN and UO31 were found to be more resistant having an $LC_{50}$ value in the range 41.8-48.8 μM. This observation is contradictory of the views put forward by O'Conner *et al.* and Lu *et al.*.[29] However other studies in the literature have produced results similar to ours on the relationship between *p53* status and chemoselectivity.[28,30]

Interestingly, about half of all human tumours carry mu *p53*. Novel drugs that target mu *p53*-carrying tumours are thus urgently needed. Restoration of wt *p53* function should trigger massive apoptosis in tumour cells and thus eradicate tumours as illustrated in ***Figure 3.25***).[32,33]

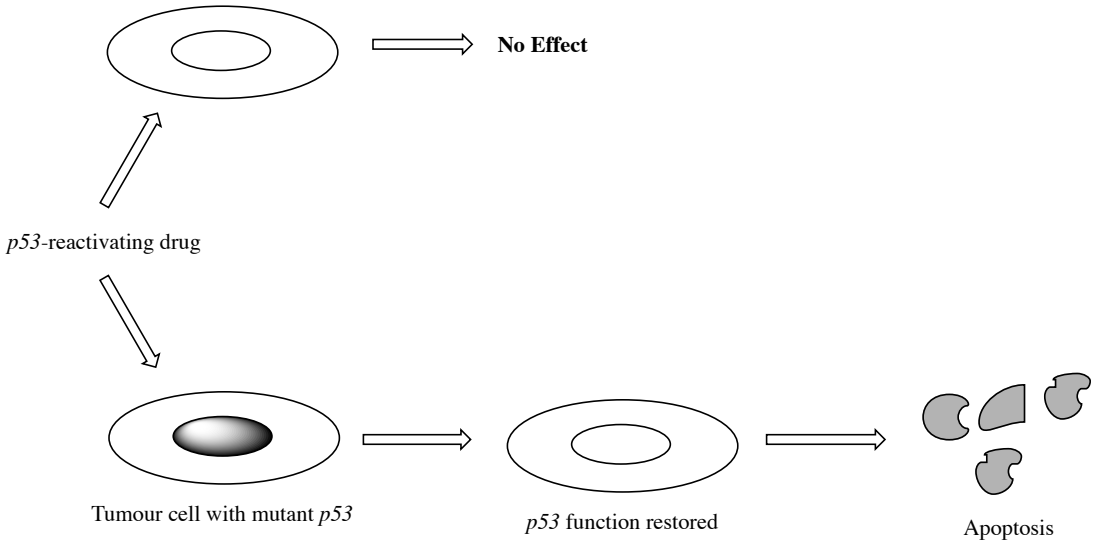



***Figure 3.25:*** *Possible molecular mechanism for mu p53 reactivation by small molecules. Introduction of the mu p53-reactivation drug will induce apoptosis, while normal tissue will be unharmed. Diagram was adapted from Selivanova et al.*[32,34]

Various types of small molecules have been identified that can restore native conformation and wild-type function to mu *p53*. Mutant p53 reactivation by small molecules is a rapidly evolving field of translational cancer research with obvious potential for the development of novel efficient anticancer drugs. Small molecules that selectively target mu *p53* are represented in ***Figure 3.26***.[32,35]

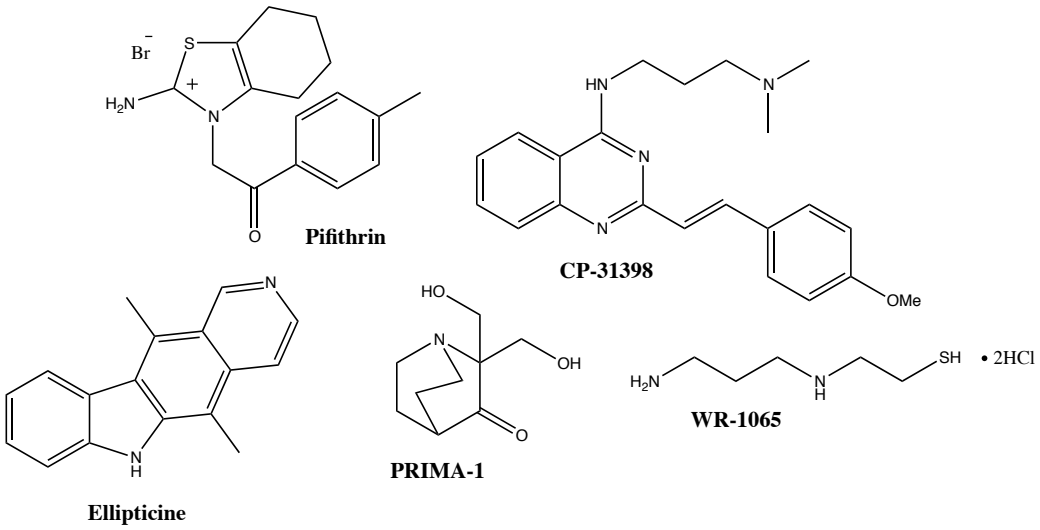



***Figure 3.26:*** *Small molecules used for targeting wt or mu p53.*[35]

Pifithrin is a synthetic compound that blocks *p53* expression at the transcriptional level and CP-31398 was the first compound reported with the ability to alter mu *p53* to wt *p53* conformation (***Figure 3.26***). Ellipticine and WR-1065 have the ability to restore mu *p53* transcription function. PRIMA-1 is able to restore the DNA-binding property of a wide range of mu *p53* protein (***Figure 3.26***).[32]

The results of our 5-dose screen suggest that furanolipid **215** maybe functioning as a small molecule similar to those described in ***Figure 3.26*** (all tertiary amines) with the ability to reactivate mu *p53*. This hypothesis is based on the fact that tumour cell lines lacking p53 function (mu *p53*) were found to be more sensitive to our cytotoxic agent **215.** Obviously they are other factors involved here which need to be address and more research is required before we can state a definitive correlation between *p53* status and cellular sensitivity and a possible mechanistic role of our cytotoxic agent **215** in mu *p53* reactivation.

### 3.1.4.2 Five-dose data for thiophenolipid amine 230

With the lowest mean growth in the one-dose screen, thiophenolipid amine **230** was an obvious choice for further biological evaluation. Similar results to those described for furanolipid amine **215** were observed from the five-dose response curve of cytotoxic agent **230** (***Appendix IV***). It was gratifying to observe that thiophenolipid amine **230** was also a cytotoxic agent at concentrations above 1 μM (***Figure 3.27***).

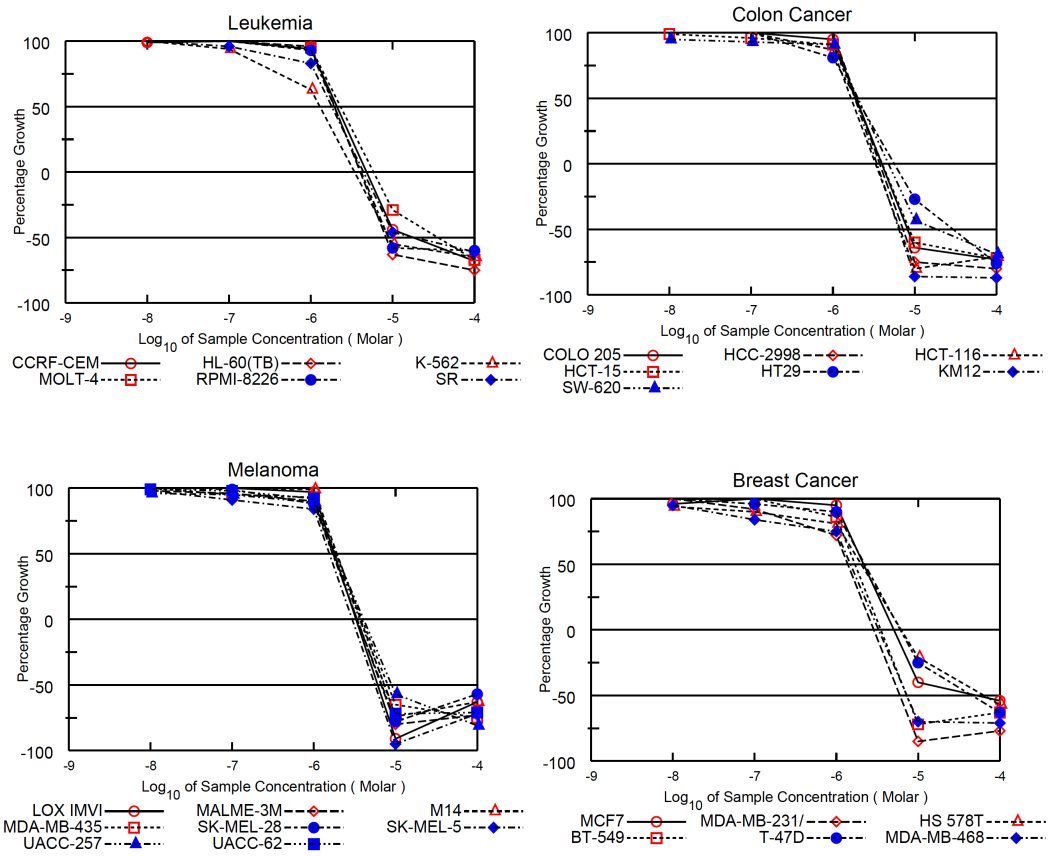



***Figure 3.27:*** *Dose-response curves of thiophenolipid **230** against leukaemia, colon, melanoma and breast cancer cell lines.*

The dose-response curve for our cytotoxic agent **230** against leukaemia, melanoma, colon and breast cancer were comparable with a steep almost linear curve showing no selectivity between individual cancer cell lines. With respect to melanoma cancer, at a concentration of 10 μM, the $LC_{50}$ parameter was reached across all cell lines with close to 100% toxicity in LOX IMVI (91%) and SK-MEL-5 (95%) tumour cell lines. These are addition melanoma cell lines that were not present in the one-dose screen (***Figure 3.13***). Remarkably, further

increments in concentration had no addition effect on toxicity possibly due to a solubility issue (***Figure 3.27***). With regard to breast cancer (***Figure 3.27***), the MDA-MB-231 and MDA-MB-468 once again showed the highest sensitivity to our compound **230 (**$IC_{50}$ in the range 6.0-7.32 μM**)**, comparable to compound **215** (***Figure 3.23***).

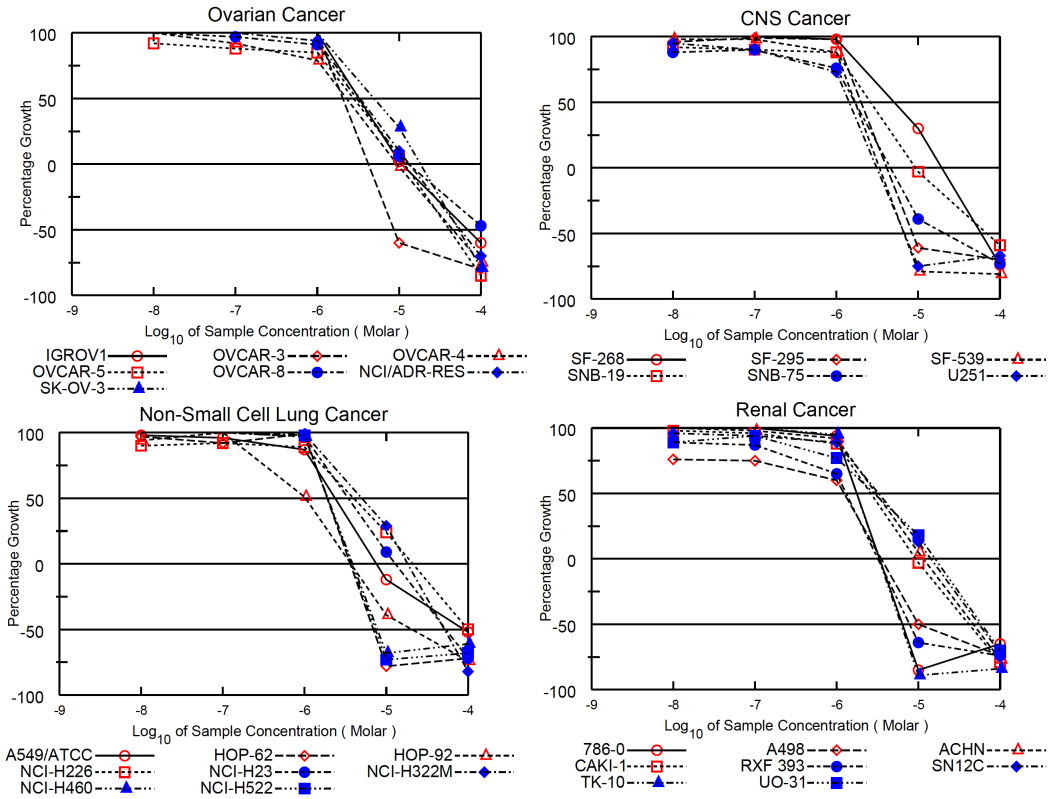



***Figure 3.28:*** *Dose-response curves of thiophenolipid* ***230*** *against ovarian, CNS, NSCLC and renal cancer cell lines.*

Similar to compound **215**, there was a distinct division down the middle for the sensitivity of renal cancer cell lines for our cytotoxic agent **230 (*Figure 3.28*)**. Once again, tumour cells lines lacking *p53* function like TK-10, RXF393 and 786-0 were found to be more sensitive to our cytotoxic agent **230** having an $LC_{50}$ value in the range 6.2-9.9 μM. Tumour cells lines containing a functional wt *p53* gene like CAK-1, ACHN and UO31 were found to be more resistant having an $LC_{50}$ value in the range 41.2-59.7 μM. Please note that thiophenolipid **230** was considerably more potent than its furan derivative **215**.

With regard to the other cell lines, both central nervous system (CNS) cancer and non-small cell lung cancer (NSCLC) showed a typical graduation in activity/selectivity following exposure to our cytotoxic agent **230**. An interesting outlier was observed in the dose response curve for NSCLC. Inhibition of the growth in the HOP-92 cancer cell line was initiated in the nanomolar range with a $GI_{50}$ value of 1.02 μM. This is the lowest recorded value in our five-dose screen. It is worth noting that the HOP-92 cell line lacks *p53* function (mu *p53*).

An outlier was also observed in the dose response curve for ovarian cancer. The OVCAR-3 cell line, which is lacking *p53* function, was found to be considerably more sensitive ($LC_{50}$ of 8.73 μM) to our cytotoxic agent **230** in comparison to all other ovarian cancer cell lines ($LC_{50}$ of 41.3 μM-100 μM).

### 3.1.4.3 Five-dose data for thiophenolipid amine 227

With the second-lowest mean growth in the one-dose screen, thiophenolipid amine **227** was an excellent candidate for further biological evaluation. As illustrated in ***Figure 3.29,*** the dose-response curve is similar in shape to those previously observed for compound **215** and **230** with $GI_{50}$ values in the low micromolar range (<10 μM) and pronounced cytotoxic effects observed across all cell lines (***Appendix IV***). Furthermore, a narrow therapeutic window between tumour cell line inhibition and cell viability was observed for all three compounds tested in five-dose NCI-60 screen.

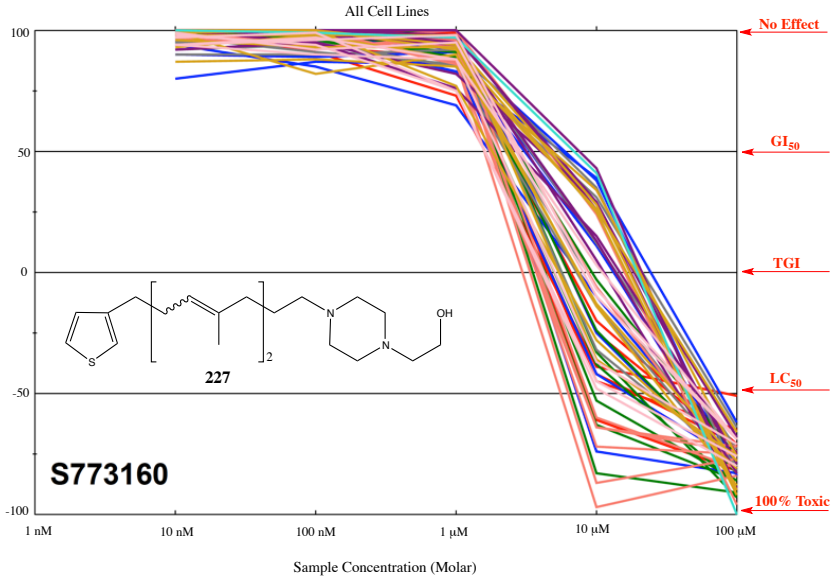



***Figure 3.29:*** *Dose-response curve for thiophenolipid* ***227.***

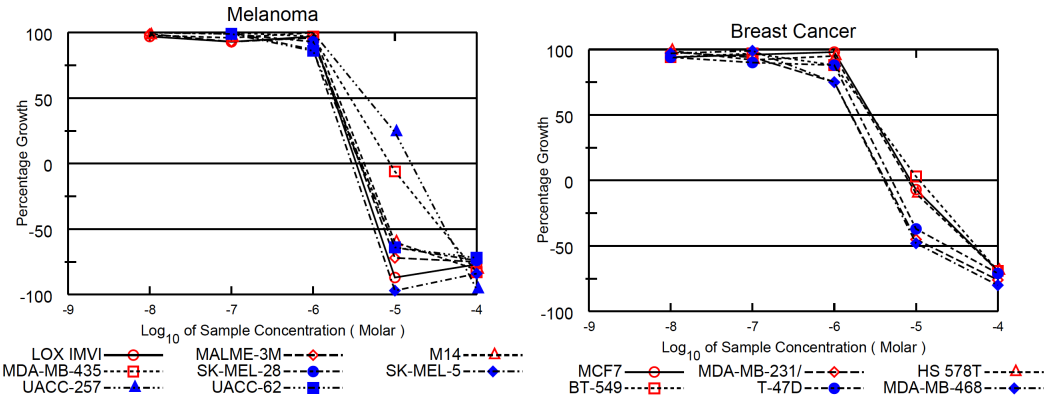



***Figure 3.30:*** *Dose-response curves of thiophenolipid* ***227*** *against melanoma and breast cancer cell lines.*

The dose-response curve for our cytotoxic agent **227** against breast and melanoma cancers (***Figure 3.30***) was comparable with amines **215** (***Figure 3.23***) and **230** (***Figure 3.27***). At a concentration of 10 μM, close to 100% cytotoxicity was observed in the SK-MEL-5 (-97%) and LOX IMVI (-87%) having an $IC_{50}$ value in the range 5.5-6.3 μM. With regard to breast cancer, the MDA-MB-231 and MDA-MB-468 cell lines exhibiting the greatest sensitivity **(**$IC_{50}$ in the range 11.8-14.1 μM**).**

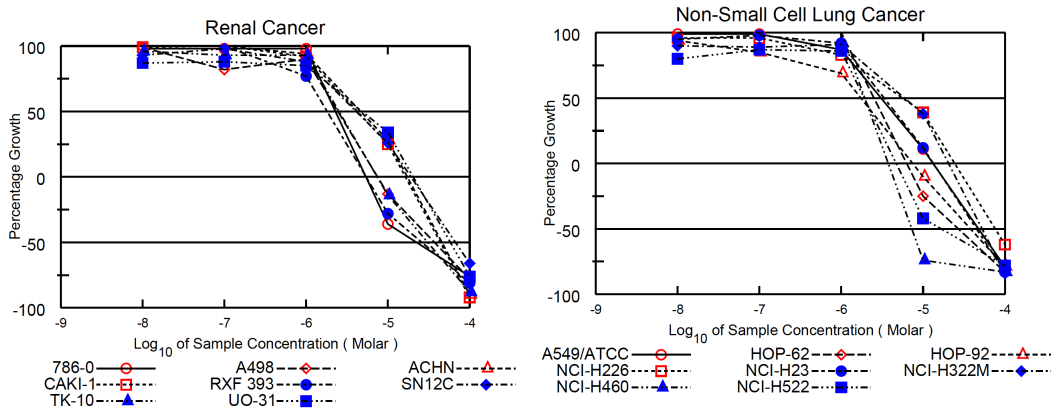



***Figure 3.31:*** *Dose-response curves of thiophenolipid **227** against renal and NSCLC cell lines.*

Interestingly as illustrated in ***Figure 3.31***, the dose response curve for thiophenolipid **227** against renal cancer was almost identical to that previously seen for furanolipid **215** and thiophenolipid **230**. Gratifyingly, a divergence in tumour cell line sensitivity was observed and this phenomenon can be directly related once again to the presence of a functional wt *p53* gene. In contrast to furanolipid **230,** thiophenolipid **227** was significantly less potent towards renal cells having an $IC_{50}$ value in the range 22.2-66.9 μM across all 8 cell lines.

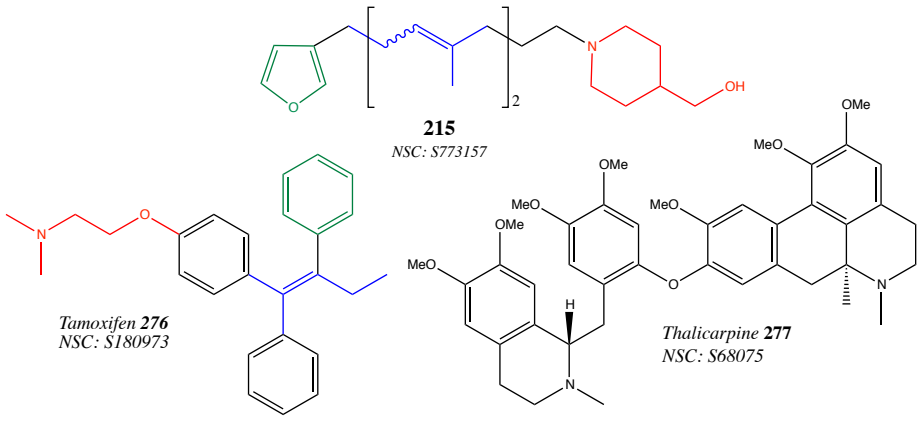
With respect to the dose response curve for NSCLC, inhibition of growth in HOP-92 cancer cells was initiated in the nanomolar range with a $GI_{50}$ value of 1.73 μM (similar to **215**). Furthermore, in a comparative study, all 8-tumour cell lines had an identical trend in selectively for all three compounds screened (**215**, **227** and **230**). The NCI-H226, NCI-H322M and NCI-H23 cell lines were the most resistant while the NCI-H460, NCI-H522 and HOP-62 were the most sensitive to our cytotoxic agents. Unfortunately, we were unable to find a logical explanation for this consistency in selectivity.

### 3.1.4.4 COMPARE analysis

The COMPARE algorithm was developed by the NCI to aid in predicting a biochemical mechanism of action from the *in vitro* antitumor screen.[21] By comparing the mean graph cytotoxicity profile for a certain antitumour agent having a known mechanism of action with those of single compounds not previously characterized, it is possible to identify new agents with cytotoxicity profiles similar to that of "seed", and which, therefore putatively share the same mechanism of action.[36]

In order identify a possible mechanism of action of our cytotoxic agent **215**, a COMPARE analysis was carried out. The COMPARE algorithm demonstrated a good correlation between furanolipid **215** and tamoxifen **276**, a blockbuster drug used in the treatment of breast cancer. A connection was also observed with thalicarpine **277**, which is a vinca alkaloid with antineoplastic activity (***Table 3.6***).

***Table 3.6:*** *Correlation of furanolipid* ***215*** *with tamoxifen* ***276*** *and thalicarpine* ***277*** *using COMPARE.*




| Correlation | Compound | Level |
|---|---|---|
| 0.673 | Tamoxifen **276** | $GI_{50}$ |
| 0.722 | Tamoxifen **276** | TGI |
| 0.645 | Tamoxifen **276** | $LC_{50}$ |
| 0.632 | Thalicarpine **277** | TGI |

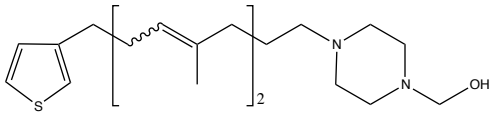
A definitive correlation was seen between **215** and tamoxifen **276** at all three-dose response parameters indicating the existence of a similar biological mode of action. Tamoxifen **276** is a selective estrogen receptor modulator (SERM) which functions as an antagonist that competitively inhibits the binding of estradiol at estrogen receptors resulting in a reduction in DNA synthesis and cellular response to estrogen. Unfortunately, there is no report or evidence in the literature, which identifies tamoxifen **276** as an inhibitor of HIF-1 activation. It is therefore likely that compound **215** is blocking tumour growth through a different mechanistic pathway to furospongolide **1 (*Section 1.1.7.2*)**. One can only putatively assume that **215** resembles tamoxifen **276** with regard to a mechanism of action. Furthermore, tamoxifen **276** and furanolipid **215** are both small molecules that contain a tertiary amine group (***Table 3.6***, colour coordinated).

However with that said, on review of the dose response curves of our three drug candidates against breast cancer we found that tumour cell lines MDA-MB-468 and MDA-MB-231 were remarkably more sensitive to our cytotoxic agent (***Figure 3.23***). These are triple-negative breast cancer cell lines meaning they don't express the genes for estrogen receptor, progesterone and Her-2/neu. Since tamoxifen **276** is a selective ER modulator that acts as a partial estrogen antagonist, it is essentially ineffective in the treatment of triple-negative breast cancer (lacking ER-receptor). If our amine cytotoxic agents exert their biological response through a similar mechanistic pathway to tamoxifen **276**, how is it possible that triple-negative breast cancer cells are more sensitive to our cytotoxic agent **215**?

There are several other hypothetical mechanisms of action of tamoxifen **276** that may not be related to action through the ER on the basis of basic laboratory studies. These include a biological response activity with a modulation by inhibition of natural killer activity (NKT), inhibition of protein kinase C (PKC),[37] a decrease in insulin-like growth factor (IGF-1) levels,[38] and antiangiogenic activity.[39] It was rather pleasing to identify a strong correlation between amine **215** and tamoxifen **276**. From COMPARE analysis, we know that at a certain molecular level, both drugs have a similar mechanism of action. However more work is required in this area to determine the exact pathway.

To our delight, a strong correlation was also observed between thiophenolipid **227** and tamoxifen **276** at all three-dose response parameters using the COMPARE algorithm (***Table 3.7***).

***Table 3.7**: Correlation of thiophenolipid **227** with tamoxifen **276** and thalicarpine **277**.*




**227**

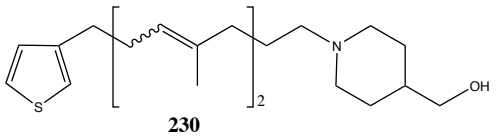
*NSC: S773160*

| Correlation | Compound | Level |
|---|---|---|
| 0.647 | Tamoxifen **276** | $GI_{50}$ |
| 0.699 | Tamoxifen **276** | TGI |
| 0.71 | Tamoxifen **276** | $LC_{50}$ |
| 0.56 | Thalicarpine **277** | TGI |

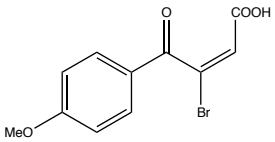
Interestingly, thalicarpine **277** featured once again in our COMPARE analysis. Thalicarpine binds to and inhibits p-glycoprotein, the multidrug resistance efflux pump. It is also known to induce single-strand breaks in DNA and induce cell cycle arrest in tumour cells.[40] It should be noted that correlation with thalicarpine **277** was not strong enough to implicate **227** as a possible inhibitor of p-glycoprotein. Furthermore, according to the literature, thalicarpine **277** and tamoxifen **276** are mechanistically unalike, showing no affinity to a similar biologically pathway. The results illustrated in ***Table 3.7,*** do however suggest a related mechanism of action between tamoxifen **276** and thiophenolipid **227**. This was expected since both **227** and **215** are structurally similar compounds.

Surprisingly, thiophenolipid ***230*** did not show the same relationship with tamoxifen **276** when analysed using the COMPARE algorithm (***Table 3.8***).

***Table 3.8****: Correlation of thiophenolipid* ***230*** *with tamoxifen* ***276****, thalicarpine* ***277*** *and cytembena* ***278****.*




**230**
*NSC: S773160*




*Cytembena* **278**
*NSC: S104801*

| Correlation | Compound | Level |
|---|---|---|
| 0.639 | Cytembena **278** | TGI |
| 0.602 | Thalicarpine **277** | TGI |
| 0.589 | Tamoxifen **276** | TGI |

The closest correlation was observed with cytembena **278**, which is an antitumour agent used in the treatment of ovarian and breast cancer.[41] According to the NCI website, its mechanism of action is currently unknown (***Table 3.8***). The fall off in correlation with tamoxifen **276** was surprising since all three compounds share a similar structural homology. The potency of compound **230** is significantly higher than **215** and **227**, which may be interfering with its mechanistic role.

### 3.1.5 Conclusion

From the 28 compounds submitted to the NCI for biological screening, 6 compounds possessed the necessary cytotoxic profile to progress to five-dose testing. The initial one-dose screen was extremely useful as it helped differentiate between compounds that possessed and lacked biological activity. Although not as detailed as results obtained from five-dose assay, one-dose screening was a valuable tool in identifying promising leads for future work.

Biological evaluation of furospongolide **1** revealed a number of important findings. Our target molecule **1** was found to have moderate potency as a chemotherapeutic agent blocking tumour growth to 61% across the entire NCI-60 cell line panel at a standard concentration of 10 μM. Furthermore, furospongolide **1** was found to be selective towards the T47D breast tumour cell line inhibiting growth to 29.5% (10 μM). On the basis of its activity profile, furosponglide **1** was accepted for further evaluation at a 5-dose level through the NCI. Preliminary studies into the structure-activity relationship of furospongolide **1** established that the butenolide ring is indeed essential to its antitumour activity. This was determined by comparing the one-dose NCI-60 mean growth data of furospongolide **1** against structurally related compounds having an altered butenolide moiety. In order to optimise its structure, future work will look at modifying the furan ring and/or lipophilic sidechain of furospongolide **1** with the ultimate goal of developing a more potent hypoxia-targeting anti-tumour drug candidate.

The most active compounds tested in the one-dose NCI-60 screen were our furanolipid and thiophenolipid amine derivatives with 4 out of 11 compounds successfully accepted for five-dose screening. These compounds are similar in structure to furospongolide **1** as they share the same C1-C13 subunit. In contrast, these design analogues terminate in a tertiary amine group as apposed to a butenolide ring. This structural change resulted in a considerable increase in antitumour activity especially in the case of furanolipid **215,** which blocked tumour growth to 47% across the entire NCI-60 cell line panel (10 μM). Furthermore, exchanging a furan ring for a thiophene ring further increased the potency of our amine analogues. Thiophenolipid amines **227** and **230** showed remarkable antitumour activity

inhibiting tumour growth across the NCI-60 cell array to 31.8% and 13.1% (10 μM) respectively. Future synthetic studies within our research group will look at preparing an extended novel library of furanolipid and thiophenolipid amine derivatives using reductive amination chemistry with the overall goal of identifying even more potent antitumour agents. The last compound accepted for 5-dose testing was furanolipid amide **237**. According to one-dose data, **237** blocked tumour growth to 36% (10 μM). Amide **237** was selective towards non-small cell lung cancer cells particularly the A549/ATCC, NCI-H322M and NCI-H460 cell lines.

With regard to five-dose screening, amine derivatives **215**, **227** and **230** were found to be cytotoxic showing no cytostatic activity and displayed an identical pattern of tumour cell line chemoselectivity across the NCI-60 cell array. A relationship between *p53* status and cellular sensitivity was also observed. Tumour cell lines lacking *p53* function (mu *p53*) were found to be more sensitive to our cytotoxic agents. The best example of this was the visible divergence in tumour cell line sensitivity observed in the dose response curve of furanolipid amine **215** against renal cancer (***Figure 3.24***). This trend was concurrently observed for amine derivatives **227** and **230**. The impact of *p53* status on cellular sensitivity was also remarked in breast, colon, NSCLC and ovarian cancer cell lines. These results suggest that our tertiary amine cytotoxic agents **215**, **227** and **230** may function to rescue *p53* function by altering mu *p53* to wt *p53* conformation and thus inducing apoptosis in cancer cells. We need to carry a lot more work to confirm this putative theory and learn more about their molecular mechanism of action. Reactivation of mu *p53* in tumours has emerged as an attractive strategy for novel tumour therapies. Its allure lies in the fact that 50% of human cancers carry mu *p53* and that such tumours often show increased resistance to chemotherapy and radiotherapy in comparison to wt *p53*. Mutant *p53* reactivation by small molecules is thus a rapidly evolving field of translational cancer research with obvious potential for the generation of more efficient and specific anti-cancer drugs.

With respect to elucidating a possible biological mechanism of action, COMPARE analysis revealed a close correlation between tamoxifen **276** and our amine compounds **215**, **227** and **230**. Since tamoxifen **276** is an antagonist of the estrogen receptor in breast tissue, this

theoretically implies that our cytotoxic agents exert their antitumour activity through a related mechanistic pathway. In theory, this was an exciting discovery and future work will look at identifying the precise biological pathway that connects tamoxifen **276** to our amine drug candidates in the hope of developing a blockbuster chemotherapeutic agent with a biological activity profile similar to tamoxifen **276** for the treatment of breast cancer and/or other diseases.

To conclude, it is evident from our research that furanosesterterpenoids like furospongolide mark an important class of natural products to be targeted for total synthesis, structural modification and biological evaluation. Whether these small molecules function as inhibitors of HIF-1 activation, re-activators of mutant *p53* protein or as selective estrogen receptor modulators, they possess attractive bioactivities, which can be grafted to offer enormous potential in the development of novel chemotherapeutic agents.

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# Chapter 4

## *Experimental*

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## 4.1 General procedures

All solvents were distilled prior to use by the following method: dichloromethane was distilled from phosphorous pentoxide; ethyl acetate was distilled from potassium carbonate; ethanol and methanol were distilled from magnesium in the presence of iodine and stored over 3 Å molecular sieves; hexane was distilled prior to use; tetrahydrofuran was freshly distilled from sodium and benzophenone. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used as supplied unless otherwise stated. All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated.

$^{1}$H (300 MHz, 400 MHz, 500MHz and 600MHz) and $^{13}$C (75 MHz, 125.7 MHz and 150.7 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR, 400 NMR, 500 NMR and 600 NMR spectrometer. Spectra were recorded at room temperature (~20 $^{o}$C) unless otherwise stated, in deuterated chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-$d_6$) using tetramethylsilane (TMS) as an internal standard. Chemical shifts ($\delta_H$ and $\delta_C$) are expressed in parts per million (ppm) relative to the reference peak. Coupling constants (*J*) are expressed in Hertz (Hz). Splitting patterns in $^{1}$H NMR spectra are designated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and m (multiplet). $^{13}$C NMR spectra were calibrated using the solvents signals, i.e. $CDCl_3$: $\delta_C$ 77.0 ppm, DMSO-$d_6$: $\delta_C$ 39.5 ppm, and were assigned (CH, $CH_2$, $CH_3$) with the aid of DEPT experiments. All spectroscopic details for compounds previously made were in agreement with those previously reported unless otherwise indicated.

Infrared spectra were recorded as a thin film on sodium chloride plates for liquids or a potassium bromide (KBr) disc for solids on a Perkin Elmer Spectrum 1000 FT-IR spectrometer. Melting points were measured in a uni-melt Thomas Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography was carried out on precoated silica gel plates (Merck 60 $PF_{254}$), and visualisation was achieved by UV light detection (254 nm) or vanillin staining. Wet flash column chromatography was performed using Kieselgel silica gel 60, 0.040 – 0.063 mm (Merck).

Enantiopurity of the compounds was determined by reverse phase high performance liquid chromatography (HPLC) performed on a YMC-Pack® ODS-A column. Details of the column conditions and mobile phase employed are included in ***Appendix V***. HPLC analysis was performed on a waters alliance 2690 seperations module.

The Microanalysis Laboratory, National University Ireland, Cork, performed elemental analysis using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analyser. Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole spectrometer (QAA102) in electrospray ionisation (ESI) mode using 50% acetonitrile – water containing 0.1% formic acid as eluent. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionisation (ESI) mode using 50% acetonitrile – water containing 0.1% formic acid as eluent. Samples (max. 1 mg) were dissolved in acetonitrile.

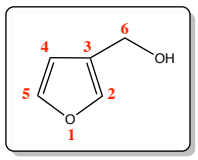
Farnesol was purchased from Alfa Aesar in the form of a mixture of stereoisomers containing 51% of the (*E*,*E*)-isomer, 40% of the (*Z*,*E*)-isomer and 9% of the other isomer(s) as determined by HPLC analysis (***Appendix V***). An asterisk (*) indicates the signal of the (*Z*,*E*) isomer.

# 4.2 Synthesis of subunit A

## 4.2.1 Synthesis of 3-furylmethanol derivatives

### 4.2.1.1 Synthesis of 3-furylmethanol 13

**Method A: Reduction using lithium aluminium hydride.[1]**



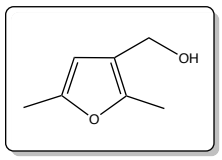

A solution of 3-furoic acid **3** (1.00 g, 8.92 mmol) in diethyl ether (15 mL) was added dropwise to a stirring solution of lithium aluminium hydride (0.51 g, 13.49 mmol, 1.5 equiv) in diethyl ether (30 mL) under inert nitrogen atmosphere at 0 °C. The reaction mixture was left stirring for an additional 2 h at 0 °C. The reaction was quenched cautiously with water (15 mL) and aqueous sodium hydroxide (20%, 15 mL) was added. The reaction mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title alcohol **13** (0.63 g, 73%) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[1,2] $\nu_{max}/cm^{-1}$ (film) 3337 (OH), 2940, 2881, 1503, 1158, 1023 (CO), 875, 795; $\delta_H$ ($CDCl_3$, 300 MHz) 4.57 [2H, s, C(6)$H_2$], 6.44 [1H, s, C(4)*H*], 7.41 [1H, t, *J* 1.7, C(5)*H*], 7.41-7.44 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 56.7 [$CH_2$, *C*(6)$H_2$], 109.8 [CH, *C*(4)H], 125.2 [C, *C*(3)], 139.9 [CH, *C*(2)H], 143.5 [CH, *C*(5)H]; HRMS (ESI+): Exact mass calculated for $C_5H_7O_2$ $(M+H)^+$ 99.0368. Found 99.0364 $(M+H)^+$; m/z (ESI+) 99.04 $(M+H)^+$.

**Method B: Reduction using borane dimethyl sulfide complex.[3]**

Borane dimethyl sulfide complex (1 mL, 0.81 g, 10.7 mmol, 1.2 equiv) in tetrahydrofuran (5 mL) was added dropwise to a stirring solution of 3-furoic acid **3** (1.0 g, 8.92 mmol) in tetrahydrofuran (5 mL) under inert nitrogen atmosphere at 0 $^oC$. The mixture was allowed to warmed to room temperature and stirred for 24 h. The reaction mixture was diluted carefully with water (10 mL) followed by the sequential addition of solid sodium chloride and sodium carbonate (1:1, 9 g). The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to afford the title alcohol **13** (0.66 g, 76%) as a colourless oil. Spectroscopic characteristics were consistent with those previous described in **Method A** above.

### 4.2.1.2 Synthesis of 2,5-dimethyl-3-furylmethanol 18

**Method A: Reduction using lithium aluminium hydride.[1]**

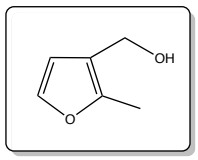



The title compound was synthesised according to the procedure described for 3-furylmethanol **13** using 2,5-dimethyl-3-furoic acid **16** (1.0 g, 7.14 mmol) and lithium aluminium hydride (0.51 g, 13.5 mmol, 1.9 equiv) in diethyl ether (45 mL) to afford the title alcohol **18** (0.66 g, 74%) as a faint yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[4] $\nu_{max}/cm^{-1}$ (film) 3338 (OH), 2922, 2879, 1639, 1586, 1432, 1257, 1211, 1146, 1002 (CO); $\delta_H$ ($CDCl_3$, 400MHz) 2.24 (6H, s, 2 x C*H*$_3$), 4.42 [2H, s, C(6)*H*$_2$], 5.94 [1H, s, C(4)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.5 (*C*H$_3$), 13.4 (*C*H$_3$), 56.8 [$CH_2$, C(6)$H_2$], 106.6 [CH, *C*(4)H], 119.4 [C, *C*(3)], 147.3 [C, *C*(2) or *C*(5)], 150.0 [C, *C*(2) or *C*(5)]; HRMS (ESI+): Exact mass calculated for $C_7H_{11}O_2$ $(M+H)^+$ 127.0759. Found 127.0755 $(M+H)^+$; m/z (ESI-) 125.1 $(M-H)^-$.

**Method B: Reduction using borane dimethyl sulfide complex.[3]**

The title compound was synthesised according to the procedure described for 3-furylmethanol **13** using borane–dimethyl sulfide complex (4.1 mL, 3.25 g, 42.8 mmol, 1.2 equiv) and 2,5-dimethyl-3-furoic acid **16** (5.0 g, 35.7 mmol) in tetrahydrofuran (50 mL) to give a crude residue which was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the title alcohol **18** (3.39 g, 76%) as a faint yellow oil. Spectroscopic characteristics were consistent with those previous described in **Method A** above.

### 4.2.1.3 Synthesis of 2-methyl-3-furylmethanol 19 [1]

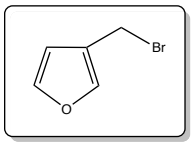



The title compound was synthesised according to the procedure described for 3-furylmethanol **13** using methyl 2-methyl-3-furancarboxylate **17** (1.00 g, 7.14 mmol) and lithium aluminium hydride (0.55 g, 14.52 mmol, 2 equiv) in diethyl ether (45 mL) to afford the title alcohol **19** (0.64 g, 79%) as a faint yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[5] $\nu_{max}/cm^{-1}$ (film) 3353 (OH), 2923, 1629, 1516, 1417, 1211, 1139, 1046, 999, 893; $\delta_H$ ($CDCl_3$, 400MHz) 2.28 [3H, s, C(2)C*H*$_3$], 4.47 [2H, s, C(6)*H*$_2$], 6.37 [1H, d, *J* 1.8, C(4)*H*], 7.26 [1H, d, *J* 1.8, C(5)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.6 [$CH_3$, C(2)*C*H$_3$], 56.6 [$CH_2$, *C*(6)$H_2$], 110.9 [CH, *C*(4)H], 118.8 [C, *C*(3)], 140.5 [CH, *C*(5)H], 149.3 [C, *C*(2)]; HRMS (ESI+): Exact mass calculated for $C_6H_9O_2$ $(M+H)^+$ 113.0603. Found 113.0601 $(M+H)^+$; m/z (ESI-) 111.1 $(M-H)^-$.

## 4.2.2 Synthesis of 3-furylmethyl bromide derivatives

### 4.2.2.1 Synthesis of 3-furylmethyl bromide 14

**Method A: Bromination using carbon tetrabromide/triphenyl phosphine.[2]**




Triphenyl phosphine (1.65 g, 6.3 mmol) was added portion wise to a stirring solution of 3-furylmethanol **13** (0.40 g, 4.0 mmol) and carbon tetrabromide (1.60 g, 4.8 mmol) in dichloromethane (10 mL) at 0 °C. After the addition was complete, the mixture was stirred for an additional 2 h before the solvent was removed under reduced pressure. The residue was taken up in diethyl ether (10 mL) and the reaction mixture filtered. The filter cake was washed with diethyl ether (4 x 10 mL) and the combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the title bromide **14** (0.46 g, 71% conversion)§ as a colourless oil. An impurity peak was present at $\delta_H$ 6.83 in the $^1$H NMR spectrum, which was attributed to bromoform ($CHBr_3$). Other spectroscopic characteristics were consistent with those reported in the lierature.[2] $\delta_H$ ($CDCl_3$, 400 MHz) 4.38 [2H, s, C(6)$H_2$], 6.45 [1H, s, C(4)*H*], 6.83 (1H, s, $CHBr_3$), 7.40 [1H, t, *J* 1.7, C(2)*H*], 7.46-7.49 [1H, m, C(5)*H*].

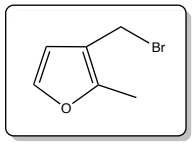
§ % Conversion was calculated from $^1$H NMR integration of the isolated mixture.

**Method B: Bromination using phosphorous tribromide.[6,7]**

Phosphorus tribromide (0.86 mL, 2.46 g, 9.09 mmol, 0.4 equiv) was added dropwise to a stirring solution of 3-furylmethanol **13** (2.23 g, 22.7 mmol) in diethyl ether (250 mL) at 0 °C. The solution was stirred for 5 h at 0 °C before water (40 mL) was added and the solution was extracted with diethyl ether (4 x 30 mL). The combined organic extracts were washed successively with water (40 mL), aqueous sodium hydrogen carbonate (10%, 40 mL), and brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to afforded the title bromide **14** (2.89 g, 79%) as a colourless oil; $\nu_{max}$/cm$^{-1}$ (film) 2927, 2855, 1508, 1213, 1162, 1074, 1020, 875, 793, 648; $\delta_H$ ($CDCl_3$, 400 MHz) 4.38 [2H, s, C(6)$H_2$], 6.45 [1H, s, C(4)*H*], 7.40 [1H, t, *J* 1.7, C(2)*H*], 7.46-7.49 [1H, m, C(5)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 23.6 [$CH_2$, *C*(6)$H_2$], 110.9 [CH, *C*(4)H], 122.5 [C, *C*(3)], 140.8 [CH, *C*(2)H], 143.8 [CH, *C*(5)H]. m/z (ESI+) 81.1 $(M-Br)^+$.

### 4.2.2.2 Synthesis of 2-methyl-3-furylmethyl bromide 20

**Method A: Bromination using carbon tetrabromide/triphenyl phosphine.[2]**




The title compound was synthesised according to the procedure described for 3-furylmethyl bromide **14** using triphenyl phosphine (0.62 g, 2.38 mmol), 2-methyl-3-furylmethanol **19** (0.17 g, 1.53 mmol) and carbon tetrabromide (0.64 g, 1.92 mmol) in dichloromethane (10 mL). The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford the title bromide **20** (0.17 g, 66% conversion)§ as a faint yellow oil. An inseparable impurity peak was present at $\delta_H$ 6.83 ppm in the $^1$H NMR spectra, which was attributed to bromoform ($CHBr_3$). Other spectroscopic characteristics were consistent with those reported in the literature.[8] $\delta_H$ ($CDCl_3$, 400MHz) 2.28 [3H, s, C(2)C$H_3$], 4.36 [2H, s, C(6)$H_2$], 6.34 [1H, d, *J* l.9, C(4)*H*], 6.83 (1H, s, C*H*$Br_3$), 7.24 [1H, d, *J* 1.9, C(5)*H*].

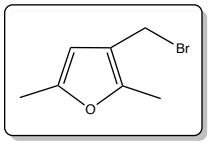
§ % Conversion was calculated from $^1$H NMR integration of the isolated mixture.

**Method B: Bromination using phosphorous tribromide.[6,7]**

The title compound was synthesised according to the procedure described for 3-furylmethyl bromide **14** using phosphorus tribromide (0.17 mL, 0.48 g, 1.78 mmol, 0.4 equiv), 2-methyl-3-furylmethanol **19** (0.50 g, 4.46 mmol) in diethyl ether (50 mL) to give a crude yellow oil, which was purified by column chromatography on silica gel (3% ethyl acetate in hexanes) to afford the title bromide **20** (0.69 g, 86%) as a colourless oil. Spectroscopic characteristics were consistent with those reported in the literature;[8] $\nu_{max}$/cm$^{-1}$ (film) 2921, 1619, 1515, 1413, 1212, 1130; $\delta_H$ ($CDCl_3$, 300MHz) 2.28 [3H, s, C(2)C$H_3$], 4.36 [2H, s, C(6)$H_2$], 6.34 [1H, d, *J* l.9, C(4)*H*], 7.24 [1H, d, *J* 1.9, C(5)*H*]. $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.6 [$CH_3$, *C*(2)*C*$H_3$], 25.0 [$CH_2$, *C*(6)$H_2$], 111.3 [CH, *C*(4)H], 116.6 [C, *C*(3)], 140.7 [CH, *C*(5)H], 150.4 [C, *C*(2)]; HRMS (ESI+): Exact mass calculated for $C_6H_7O$ $(M\text{-}Br)^-$ 95.0521. Found 95.0492 $(M\text{-}Br)^-$; m/z (ESI+) 95.0 $(M\text{-}Br)^+$.

### 4.2.2.3 Synthesis of 2,5-dimethyl-3-furylmethyl bromide 21

**Method A: Bromination using carbon tetrabromide/triphenyl phosphine.[2]**



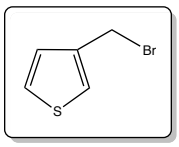

The title compound was synthesised according to the procedure described for 3-furylmethyl bromide **14** using triphenyl phosphine (1.84 g, 7.0 mmol), 2,5-dimethyl-3-furylmethanol **18** (0.63 g, 4.5 mmol) and carbon tetrabromide (1.87 g, 5.63 mmol) in dichloromethane (10 mL) at 0 °C. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford the title bromide **21** (0.55 g, 65% conversion)§ as a faint yellow oil. An inseparable impurity was present at $\delta_H$ 6.83 ppm in the $^1$H NMR spectra which was attributed to bromoform ($CHBr_3$): $\delta_H$ ($CDCl_3$, 300MHz) 2.22 [6H, s, C(2)C$H_3$ and C(5)C$H_3$], 4.32 [2H, s, C(6)$H_2$], 5.92 [1H, s, C(4)*H*], 6.83 (1H, s, C*H*$Br_3$).

§ % Conversion was calculated from $^1$H NMR integration of the isolated mixture.

**Method B: Bromination using phosphorous tribromide.[6,7]**

The title compound was synthesised according to the procedure described for 3-furylmethyl bromide **14** using phosphorus tribromide (0.22 mL, 0.64 g, 2.35 mmol, 0.4 equiv) and 2,5-dimethyl-3-furylmethanol **18** (0.74 g, 5.87 mmol) in diethyl ether (60 mL) to afford a crude yellow oil, which was purified by column chromatography on silica gel (3% ethyl acetate in hexanes) to afford the title bromide **21** (0.94 g, 85%) as a colourless oil; $\nu_{max}$/cm$^{-1}$ (film) 2922, 1634, 1589, 1433, 1239, 1212, 900, 926, 779, 633; $\delta_H$ ($CDCl_3$, 300MHz) 2.21 (3H, s, C$H_3$), 2.22 (3H, s, C$H_3$), 4.32 [2H, s, C(6)$H_2$], 5.92 [1H, s, C(4)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.5 (*C*$H_3$), 13.4 (*C*$H_3$), 25.7 ($CH_2$, *C*(6)$H_2$), 107.0 [C, *C*(4)H], 117.2 [C, *C*(3)], 148.5 [C, *C*(2) or *C*(5)], 150.4 [C, *C*(2) or *C*(5)]; HRMS (ESI+): Exact mass calculated for $C_7H_9O$ $(M\text{-}Br)^+$ 109.0653. Found 109.0657 $(M\text{-}Br)^+$; m/z (ESI+) 109.2 $(M\text{-}Br)^+$.

### 4.2.2.4 Synthesis of 3-(bromomethyl)thiophene 23

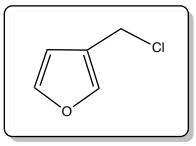



The title compound was synthesised according to the procedure described for 3-furylmethyl bromide **14** using phosphorus tribromide (0.34 mL, 0.95 g, 3.5 mmol, 0.4 equiv), 3-thiophenemethanol **22** (1.00 g, 8.76 mmol) in diethyl ether (60 mL) to afford the title bromide **23** (1.29 g, 83%) as a colourless oil. Spectroscopic characteristics were consistent with those reported in the literature;[9] $\nu_{max}$/cm$^{-1}$ (film) 3100, 2963, 1415, 1239, 1213, 784, 649; $\delta_H$ ($CDCl_3$, 400MHz) 4.53 [2H, s, C(6)$H_2$], 7.13 [1H, d, *J* 4.9, C(4)*H*], 7.26-7.34 [2H, m, C(2)*H* and C(5)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 27.4 [$CH_2$, *C*(6)$H_2$], 124.4 [CH, *C*(2)H or *C*(5)H], 126.7 [CH, *C*(2)H or *C*(5)H], 128.2 [CH, *C*(4)H], 138.1 [C, *C*(3)]; m/z (ESI+) 96.8 $(M\text{-}Br)^+$.

## 4.2.3 Synthesis of 3-furylmethyl chloride derivatives

### 4.2.3.1 Synthesis of 3-furymethyl chloride 15

**Method A: Chlorination using lithium chloride, mesyl chloride and 2,4,6-collidine.[10]**




Lithium chloride (44 mg, 1.02 mmol) dissolved in dimethylformamide (3 mL) was added to a stirring mixture of the 3-furylmethanol **13** (0.1 g, 1.02 mmol) and 2,4,6-collidine (0.15 mL, 0.14 g, 1.12 mmol) under inert nitrogen atmosphere at room temperature. On cooling to 0 $^{o}$C, a cloudy white suspension was formed on treatment with methanesulfonyl chloride (0.1 mL, 0.16 g, 1.11 mmol). Stirring was continued at 0 $^{o}$C for an additional 3 h before the reaction mixture was poured over ice water (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined extracts were washed successively with saturated copper nitrate solution (4 x 10 mL). This was continued until no further intensification of the blue copper solution occurred, indicating complete removal of 2,4,6-collidine. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a two-component mixture consisting of the title chloride **15** and unreacted starting material **13** in a 6:1 ratio of products respectively. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to afford the title chloride **15** (52 mg, 44%) as a colourless oil. Spectroscopic characteristics were consistent with those reported in the literature;[1,11] $\nu_{max}/cm^{-1}$ (film) 2920, 2861, 1600, 1503, 1160, 1088, 1061, 1021, 875, 796, 717; $\delta_H$ ($CDCl_3$, 300Mz) 4.48 [2H, s, C(6)$H_2$], 6.45 [1H, s, C(4)*H*], 7.40 [1H, t, *J* 1.7, C(5)*H*], 7.45-7.47 [1H, m, C(2)*H*]; m/z (ESI+) 81.2 $(M\text{-}Cl)^+$.

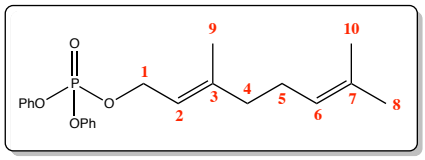
**Method B: Chlorination using thionyl chloride.**

A solution of thionyl chloride (0.54 mL, 0.873 mg, 7.34 mmol) in hexane (5 mL) was added dropwise to a stirring solution of 3-furylmethanol **13** (0.60 g, 6.17 mmol) in diethyl ether (5 mL) at -10 $^{o}$C. The reaction was allowed to warm to room temperature following complete addition and stirring was continued for an additional 3 h. The reaction was quenched cautiously with water (10 mL) and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude yellow oil was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to afford the title chloride **15** (0.32 g, 49%) as a colourless oil. Spectroscopic characteristics are consistent with those previously described in **Method A** above.

# 4.3 Optimisation of the Grignard $sp^3$-$sp^3$ cross coupling reaction

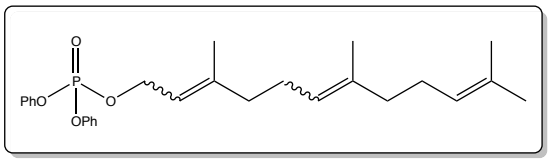
## 4.3.1 Synthesis of acyclic terpene diphenyl phosphates

### 4.3.1.1 Synthesis of (*E*)-3,7-dimethylocta-2,6-dien-1-yl diphenyl phosphate 25[12]




Diphenyl phosphoryl chloride (0.84 mL, 1.09 g, 4.0 mmol) was added dropwise to a stirring mixture of geraniol **24** (0.5 g, 3.24 mmol) and pyridine (1.6 mL, 1.57 g, 19.9 mmol) at 0 °C. TLC analysis after 5 min showed complete consumption of starting material and the reaction was quenched with water (5 mL). The reaction mixture was extracted with diethyl ether (2 x 10 mL) and the combined organic extracts were washed successively with aqueous sulfuric acid (10%, 10 mL), aqueous sodium hydrogen carbonate (10%, 10 mL), water (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title phosphate **25** (0.95 g, 76%) as a colourless oil. $^1$H NMR analysis showed a minor trace of unreacted starting material **24** (> 5%). Spectroscopic characteristics were consistent with those reported in the literature;[13] $\nu_{max}$/cm$^{-1}$ (film) 2967, 2923, 1591, 1490, 1287 (P=O), 1192 (P-O-Ph), 1163 (P-O-Ph), 1000 (P-O-C), 951; $\delta_H$ ($CDCl_3$, 300MHz) 1.59 [3H, s, C$H_3$], 1.67 [3H, s, C$H_3$], 1.68 [3H, s, C$H_3$], 1.94-2.16 [4H, m, C(4)$H_2$ and C(5)$H_2$], 4.16* (2H, d, *J* 6.4), 4.71-4.82 [2H, m, C(1)$H_2$], 5.00-5.13 [1H, m, C(6)*H*], 5.40 [1H, td, *J* 7.3, 1.2, C(2)*H*], 7.13-7.40 (10H, m, Ar*H*); $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.5 (*C*H$_3$), 17.7 (*C*H$_3$), 25.7 (*C*H$_3$), 26.2 [CH$_2$, *C*(5)H$_2$], 39.5 [CH$_2$, *C*(4)H$_2$], 65.8 [CH$_2$, d, $^2J_{CP}$ 6.2, *C*(1)H$_2$], 118.1 [CH, d, $^3J_{CP}$ 6.2, *C*(2')H] 120.1 [CH, d, $^4J_{CP}$ 4.9, *C*(3')H], 123.6 [CH, *C*(2)H or *C*(6)H], 125.2 [CH, d, *J* 1.0, *C*(4')H], 129.7 [CH, *C*(2)H or *C*(6)H], 132.0 [C, *C*(3) or *C*(7)], 144.0 [C, *C*(3) or *C*(7)], 150.6 [C, d, $^2J_{CP}$ 7.2, *C*(1')]; $\delta_p$ ($CDCl_3$, 121.5 MHz) –11.5; m/z (ESI+) 137.3 [M-PO(OPh)$_2$]$^+$.

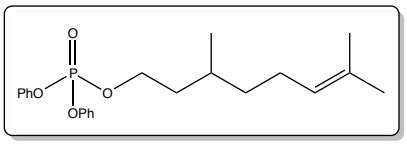
### 4.3.1.2 Synthesis of 3,7,11-trimethyldodeca-2,6,10-trien-1-yl diphenyl phosphate 26[12]




The title compound was synthesised according to the procedure described for geranyl diphenyl phosphate **25** using diphenyl phosphoryl chloride (0.58 mL 0.76 g, 2.81 mmol), farnesol **7** (0.50 g, 2.25 mmol) and pyridine (1.12 mL, 1.10 g, 14.0 mmol) to give farnesyl diphenyl phosphate **26** (0.94 g, 92%) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported.[14] $\nu_{max}$/cm$^{-1}$ (film) 2967, 2919, 2857, 1669, 1590, 1490, 1454, 1290 (P=O), 1222 (P-O-Ph), 1192 (P-O-Ph), 1163 (P-O-Ph), 1010 (P-O-C), 953; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 (6H, s), 1.68 (6H, s), 1.74* (6H, s), 1.92-

2.18 [8H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(9)$H_2$], 4.68-4.82 [2H, m, C(1)$H_2$], 5.00-5.15 [2H, m, C(6)*H* and C(10)*H*], 5.40 [1H, td, *J* 7.3, 1.2, C(2)*H*], 7.10-7.40 (10H, m, Ar*H*); $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 16.5 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 17.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 25.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.1 [$CH_2$, *C*(9)$H_2$], 26.6 [$CH_2$, *C*(5)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 39.7 [$CH_2$, *C*(8)$H_2$], 65.8 [$CH_2$, d, $^2J_{CP}$ 6.2, *C*(1)$H_2$], 118.1 [CH, d, $^3J_{CP}$ 6.4, *C*(2')H], 120.1 [CH, d, $^4J_{CP}$ 4.9, *C*(3')H], 123.5 [CH, *C*(10)H], 124.2 [CH, *C*(2)H or *C*(6)H], 125.2 [CH, d, $^5J_{CP}$ 1.0, *C*(4')H], 129.7 [CH, *C*(2)H or *C*(6)H], 131.4 [C, *C*(11)], 135.6 [C, *C*(3) or *C*(7)] 144.1 [C, *C*(3) or *C*(7)], 150.6 [C, d, $^2J_{CP}$ 7.1, *C*(1')]; Characteristics peaks for the other isomer(s)* 16.5 (*C*$H_3$), 17.7 (*C*$H_3$), 23.4 (*C*$H_3$), 23.6 (*C*$H_3$), 25.8 (*C*$H_3$), 26.0 (*C*$H_2$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 26.7 (*C*$H_2$), 32.0 (*C*$H_2$), 32.1 (*C*$H_2$), 39.8 (*C*$H_2$), 65.5 (*C*$H_2$), 119.1 (*C*H), 123.2 (*C*H), 124.1 (*C*H), 124.3 (*C*H), 129.3 (*C*H), 131.4 (*C*), 131.6 (*C*), 135.8 (*C*), 136.0 (*C*), 140.0 (*C*); $\delta_p$ ($CDCl_3$, 121.5 MHz) –11.8; m/z (ESI+) 205.2 $[M\text{-}(OPh)_2PO]^+$.

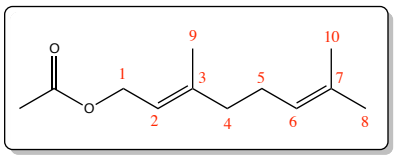
### 4.3.1.3 Synthesis of 3,7-dimethyloct-6-en-1-yl diphenyl phosphate 28




The title compound was synthesised according to the procedure described for geranyl diphenyl phosphate **25** using diphenyl phosphoryl chloride (0.83 mL, 1.07 g, 4.0 mmol), citronellol **27** (0.5 g, 3.12 mmol) and pyridine (1.6 mL, 1.57 g, 19.9 mmol) to give citronellyl diphenyl phosphate **28** (1.11 g, 90%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 3067, 2964, 2919, 1593, 1490, 1457, 1292 (P=O), 1193 (P-O-Ph), 1165 (P-O-Ph), 1053, 1022 (P-O-C), 951, 770, 689; $\delta_H$ ($CDCl_3$, 300MHz) 0.88 [3H, d, *J* 6.4, C(9)$H_3$], 1.05-1.40 [2H, m, C(4)$H_2$], 1.40-1.82 [9H, m, C(2)$H_2$ and C(3)*H* and containing 2 x 3H, s, C(8)$H_3$ and C(10)$H_3$], 1.83-2.08 [2H, m, C(5)$H_2$], 4.20-4.36 [2H, m, C(1)$H_2$], 5.06 [1H, td, *J* 7.1, 1.4, C(6)*H*], 7.10-7.42 (10H, m, Ar*H*); $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 19.2 [$CH_3$, *C*(9)$H_3$], 25.3 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 28.9 [CH, *C*(3)H], 36.9 [$CH_2$, *C*(4)$H_2$], 37.0 ($CH_2$, d, $^3J_{CP}$ 6.9, *C*(2)$H_2$), 67.8 [$CH_2$, d, $^2J_{CP}$ 6.6, *C*(1)$H_2$], 120.1 [CH, d, $^3J_{CP}$ 4.9, *C*(2')H], 124.4 [CH, *C*(6)H], 125.3 [CH, d, $^5J_{CP}$ 0.9, *C*(4')H], 129.8 [CH, $^4J_{CP}$ 1.0, *C*(3')H], 132.0 [C, *C*(7)], 150.7 [C, d, $^2J_{CP}$ 7.2, *C*(1')]; $\delta_p$ ($CDCl_3$, 162.0 MHz) –11.8; HRMS (ESI+): Exact mass calculated for $C_{22}H_{29}O_4P$ $(M+H)^+$ 389.1882. Found 389.1868 $(M+H)^+$; m/z (ESI+) 389.1 $(M+H)^+$.

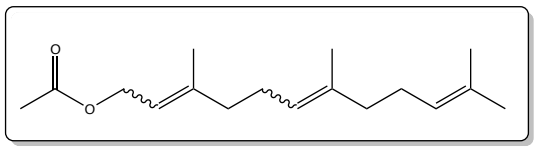
## 4.3.2 Synthesis of acyclic terpene acetate esters

### 4.3.2.1 Synthesis of (*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate 29 [15]



Geraniol **24** (5.00 g, 32.4 mmol) dissolved in dichloromethane (90 mL) was treated sequentially with triethylamine (6.8 mL, 4.92 g, 48.6 mmol), 4-dimethylaminopyridine (40 mg, 1 mol%) and acetic anhydride (3.7 mL, 3.97 g 38.9 mmol) at 0 °C. After 5 min, the reaction mixture was poured into water (50 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layers was washed with water (3 x 50 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give geranyl acetate **29** (6.2 g, 98% yield) as a colourless oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[15,16] $\nu_{max}/cm^{-1}$ (film) 2969, 2926, 2858, 1742 (C=O), 1444, 1379, 1366, 1233, 1024 (CO), 955; $\delta_H$ ($CDCl_3$, 400 MHz) 1.60 (3H, s, C$H_3$), 1.68 (3H, s, C$H_3$), 1.70 (3H, s, C$H_3$), 1.98-2.16 [7H, m, C(4)$H_2$ and C(5)$H_2$ and containing 3H, s, C(O)C$H_3$], 4.59 [2H, d, *J* 7.1, C(1)$H_2$], 5.08 [1H, td, *J* 6.8, 1.2, C(6)*H*], 5.34 [1H, td, *J* 7.1, 1.2, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.4 (*C*$H_3$), 17.7 (*C*$H_3$), 21.0 [$CH_3$, *C*(O)*C*$H_3$], 25.6 (*C*$H_3$), 26.3 [$CH_2$, *C*(5)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 118.3 [CH, *C*(2)H], 123.7 [CH, *C*(6)H], 131.8 [C, *C*(7)], 142.2 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$].

### 4.3.2.2 Synthesis of 3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate 59 [17,18]



The title compound was synthesized according to the procedure described above for **29** using farnesol **7** (2.00 g, 9.0 mmol), triethylamine (1.9 mL, 1.37 g, 13.5 mmol), 4-dimethylamino pyridine (0.01 g, 1 mol%), and acetic anhydride (1.02 mL, 1.10 g 10.8 mmol) to afford farnesyl acetate **59** (2.36 g, 99%) as a non-viscous colourless oil, which was used without further purification. Spectroscopic characteristics were consistent with those reported in the literature;[19] $\nu_{max}/cm^{-1}$ (film) 2967, 2927, 2858, 1739 (C=O), 1446, 1379, 1233 (CO), 1024 (CO); $\delta_H$ ($CDCl_3$, 400 MHz) 1.60 (6H, s), 1.61* (6H, s), 1.68 (3H, s), 1.71 (3H, s), 1.77* (3H, s), 1.92-2.18 [11H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(9)$H_2$ and containing 3H, s, C(O)C$H_3$], 4.53-4.62 [2H, m, C$H_2$* and containing 2H, d, *J* 7.2, C(1)$H_2$], 5.03-5.15 [2H, m, C(6)*H* and C(10)*H*], 5.30-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 16.4 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 17.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 25.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.2 [$CH_2$, *C*(9)$H_2$], 26.6 [$CH_2$, *C*(5)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 39.7 [$CH_2$, *C*(8)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 118.3 [CH, *C*(2)H], 123.6 [CH, *C*(10)H], 124.3 [CH, *C*(6)H], 131.3 [C, *C*(11)], 135.6 [C, *C*(7)], 142.2 [C,

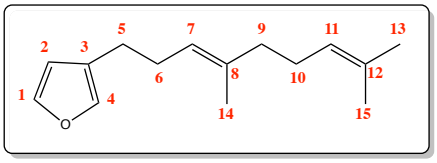
*C*(3)], 171.1 [C, *C*(O)CH$_3$]; Characteristics peaks for the other isomer(s)* 16.0 (*C*H$_3$), 17.6 (*C*H$_3$), 23.3 (*C*H$_3$), 23.5 (*C*H$_3$), 25.7 (*C*H$_3$), 26.1 (*C*H$_2$), 26.4 (*C*H$_2$), 26.6 (*C*H$_2$), 26.7 (*C*H$_2$), 31.9 (*C*H$_2$), 32.0 (*C*H$_2$), 32.1 (*C*H$_2$), 32.4 (*C*H$_2$), 39.5 (*C*H$_2$), 39.8 (*C*H$_2$), 61.1 (*C*H$_2$), 118.3 (*C*H), 119.1 (*C*H), 119.2 (*C*H), 123.4 (*C*H), 124.2 (*C*H), 124.3 (*C*H), 124.4 (*C*H), 131.3 (*C*), 131.5 (*C*), 135.4 (*C*), 135.8 (*C*), 135.9 (*C*), 142.6 (*C*), 171.1 (*C*); m/z (ESI+): 265.4 $(M+H)^+$.

### 4.3.3 Synthesis of sesquiterpenoid furan and thiophenolipid derivatives

The following numbering template was used in characterising our furanolipid and thiophenolipid molecules. The numbering system described in ***Section 4.3.3*** is consistent with the literature for the assignment of terpenoid compounds.[20-23]

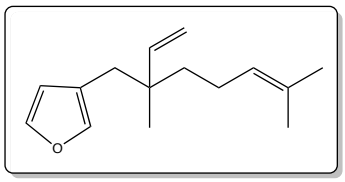
#### 4.3.3.1 Synthesis of (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)furan 10

**Method A: Grignard sp$^3$-sp$^3$ cross coupling using copper(I) iodide catalyst.[24]**

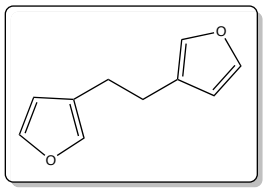



A solution of 3-furylmethyl bromide **14** (0.20 g, 1.24 mmol) in tetrahydrofuran (2 mL) was added dropwise to a stirring solution of magnesium turnings (0.06 g, 2.50 mmol) in tetrahydrofuran (0.5 mL) at -10 °C. After addition was complete, the mixture was gradually warmed to room temperature and stirred for an additional 1 h. To remove the excess magnesium, the resulting Grignard solution was transferred by a syringe to a second flask and added to a stirring suspension of copper iodide (15 mg, 0.08 mmol, 10 mol%) in tetrahydrofuran (1 mL) at -10 °C. The reaction mixture was stirred for 30 min before it was cooled to -78 °C. A solution of (*E*)-3,7-dimethylocta-2,6-dien-1-yl diphenyl phosphate **25** (0.29 g, 0.77 mmol) in tetrahydrofuran (2 mL) was added dropwise to the reaction mixture over 10 min at -78 °C. After addition was complete, the reaction mixture was gradually warmed to room temperature and left stir overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a three-component mixture consisting of dendrolasin **10**, isodendrolasin **30** and 1,2-di(furan-3-yl)ethane **32** in a 30:23:47 ratio of products respectively. The crude yellow oil was purified by column chromatography on silica gel (100% hexane) to afford dendrolasin **10** as a colourless oil (35 mg, 22%). Spectroscopic characteristics are consistent with those reported in the literature;[24-26] $\nu_{max}$/cm$^{-1}$ (film) 2923 (CH), 2852 (CH), 1650, 1463, 1428, 1377, 1204, 1113, 1075; $\delta_H$ ($CDCl_3$, 400 MHz) 1.59 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.95-2.12 [4H, m, C(9)*H*$_2$ and C(10)*H*$_2$], 2.24 [2H, q, *J* 7.3, C(6)*H*$_2$], 2.45

[2H, t, *J* 7.6, C(5)$H_2$], 5.09 [1H, td, *J* 6.8, 1.3, C(7)*H*], 5.17 [1H, td, *J* 7.0, 1.3, C(11)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 (*C*$H_3$), 17.7 (*C*$H_3$), 25.0 [$CH_2$, *C*(5)$H_2$], 25.7 (*C*$H_3$), 26.7 [$CH_2$, *C*(10)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(11)H], 124.3 [CH, *C*(7)H], 125.0 [C, *C*(3)], 131.3 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; HRMS (ESI+): Exact mass calculated for $C_{15}H_{22}O$ $(M+H)^+$ 219.1749. Found 219.1757 $(M+H)^+$; m/z (ESI+) 219.1 $(M+H)^+$.



The least polar fraction, 3-(2,6-dimethyl-2-vinyl-5-heptenyl)furan **30** (52 mg, 32%) was also isolated as a colourless oil. Spectroscopic characteristic for isodendrolasin **30** were consistent with those reported in the literature.[27] $\nu_{max}/cm^{-1}$ (film) 2960, 2926, 2851, 1640, 1463, 1375, 1203, 1071, 1029; $\delta_H$ ($CDCl_3$, 400 MHz) 0.97 [3H, s, C(14)$H_3$], 1.23-1.35 [2H, m, C(7)$H_2$], 1.58 [3H, s, C(11)$H_3$ or C(15)$H_3$], 1.67 [3H, s, C(11)$H_3$ or C(15)$H_3$], 1.91 [2H, m, C(8)$H_2$], 2.41 [2H, s, C(5)$H_2$], 4.89 [1H, dd, B of the ABX system $J_{BX}$ 17.6, $J_{AB}$ 1.4, C(13)$H_2$], 5.00 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.4, C(13)$H_2$], 5.07 [1H, td, *J* 7.1, 1.6, C(9)*H*], 5.77 [1H, dd, X of the ABX system $J_{BX}$ 17.6, $J_{AX}$ 10.8, C(12)*H*], 6.23 [1H, s, C(2)*H*], 7.18 [1H, s, C(4)*H*], 7.32 [1H, t, *J* 1.5, C(2)*H*]; HRMS (ESI+): Exact mass calculated for $C_{15}H_{22}O$ $(M+H)^+$ 219.1749. Found 219.1760 $(M+H)^+$; m/z (ESI+) 219.1 $(M+H)^+$.



The most polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those reported in the literature.[28,29] $\nu_{max}/cm^{-1}$ (film) 2925, 2860; $\delta_H$ ($CDCl_3$, 300 MHz) 2.68 [4H, s, 2 x C(5)$H_2$], 6.27 [2H, s, 2 x C(2)*H*], 7.21 [2H, s, 2 x C(4)*H*], 7.35 [2H, t, *J* 1.6, 2 x C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 25.5 [$CH_2$, *C*(5)$H_2$] 110.9 [CH, *C*(2)H], 125.5 [C, *C*(3)], 134.0 [CH, *C*(4)H], 142.7 [CH, *C*(1)H]; HRMS (ESI+): Exact mass calculated for $C_{10}H_{11}O_2$ $(M+H)^+$ 163.1852. Found 163.1852 $(M+H)^+$; m/z (ESI+) 163.2 $(M+H)^+$.

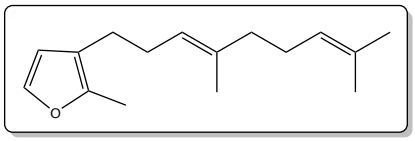
**Method B: Schlosser $sp^3$-$sp^3$ cross coupling using $Li_2CuCl_4$ catalyst.[29,30]**

Freshly ground magnesium (1.04 g, 42.7 mmol) was flame heated, allowed to cool to room temperature and activated by successively adding a crystal of iodine and a solution of 1,2-dibromoethane (0.1 mL) in tetrahydrofuran (7 mL) under inert nitrogen atmosphere. The mixture was refluxed for at 1 h, and then cooled to -10 °C. A solution of 3-furylmethyl bromide **14** (0.69 g, 4.27 mmol) in tetrahydrofuran (3 mL) was then added dropwise over a period of 1 h. Vigorous stirring was continued for 4 h at –10 °C. In a separate reaction flask, dilithium tetrachlorocuprate(II) solution (0.1

M in tetrahydrofuran, 1.33 mL, 1.33 mmol, 10 mol%) was added to a stirring solution of (*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate **29** (0.26 g, 1.33 mmol) in tetrahydrofuran (3 mL) at room temperature. After cooling to 0 °C, the freshly prepared Grignard reagent in tetrahydrofuran was added over 20 min at 0 °C. After 10 min, the reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h before quenching with brine (3 mL). The mixture was extracted with ethyl acetate (3 x 15 mL). The organic layer was separated, washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a two-component mixture consisting of the desired cross coupled product **10** and 1,2-di(furan-3-yl)ethane **32** in a 85:15 ratio of products respectively. The crude yellow oil was purified by column chromatography on silica gel (100% hexanes) to afford the dendrolasin **10** (0.23 g, 79%) as a colourless oil. Spectroscopic characteristics are consistent with those described in **Method A**.

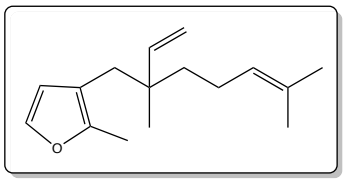
The most polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.3.3.1***.[28,29]

### 4.3.3.2 Synthesis of (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-2-methylfuran 35

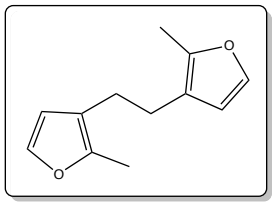


The title compound was synthesised following the procedure described for (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)furan **10** using 2-methyl-3-furylmethyl bromide **20** (0.50 g, 2.86 mmol), magnesium turnings (0.28 g, 11.4 mmol), nickel(II) bromide (16 mg, 0.07 mmol, 5 mol%) and (*E*)-3,7-dimethylocta-2,6-dien-1-yl diphenyl phosphate **25** (0.55 g, 1.43 mmol) in tetrahydrofuran (13 mL) to afford a three-component mixture consisting of the title cross coupled product **35**, its corresponding structural regioisomer **38** and 1,2-bis(2-methylfuran-3-yl)ethane **41** in a 38:12:50 ratio of products respectively. The crude yellow oil was purified by column chromatography on silica gel (100% hexanes) to afford the title furanolipid **35** (143 mg, 43%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2967, 2923, 2857, 1513, 1448, 1377, 1139, 894, 726; $\delta_H$ ($CDCl_3$, 300MHz) 1.57 [3H, s, C(14)$H_3$ or C(15)$H_3$], 1.60 [3H, s, C(14)$H_3$ or C(15)$H_3$], 1.68 [3H, s, C(13)$H_3$], 1.90-2.25 [9H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and containing 3H, s, C(4)C$H_3$], 2.35 [2H, t, *J* 7.4, C(5)$H_2$], 5.09 [1H, td, *J* 6.8, 1.4, C(7)*H*], 5.15 [1H, td, *J* 7.0, 1.3, C(11)*H*], 6.20 [1H, d, *J* 1.8, C(2)*H*], 7.20 [1H, d, *J* 1.8, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.4 [$CH_3$, C(4)*C*$H_3$], 16.0 [$CH_3$, *C*(14)$H_3$ or *C*(15)$H_3$], 17.7 [$CH_3$, *C*(14)$H_3$ or *C*(15)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(13)$H_3$], 26.7 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 111.6 [CH, *C*(2)H], 118.7 [C, *C*(3)H], 123.7 [CH, *C*(11)H], 124.3 [CH, *C*(7)H], 131.3

[C, *C*(12)], 135.7 [C, *C*(8)], 139.6 [CH, *C*(1)H], 147.2 [C, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_{16}H_{25}O$ $(M+H)^+$ 233.1905. Found 233.1904 $(M+H)^+$; m/z (ESI+): 233.3 $(M+H)^+$.

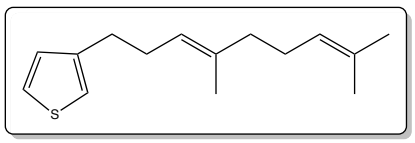


The least polar fraction, 3-(2,6-dimethyl-2vinyl-5-heptenyl)-2methylfuran **38** (43 mg, 13%) was isolated as a colourless oil. $\nu_{max}/cm^{-1}$ (film) 2923, 2853, 1513, 1453, 1377; $\delta_H$ ($CDCl_3$, 300 MHz) 0.96 [3H, s, C(14)$H_3$], 1.25-1.38 [2H, m, C(7)$H_2$], 1.58 [3H, s, C(11)$H_3$ or C(15)$H_3$], 1.67 [3H, s, C(11)$H_3$ or C(15)$H_3$], 1.90 [2H, q, *J* 15.7, 8.1, C(8)$H_2$], 2.19 [3H, s, C(4)C$H_3$], 2.32 [2H, s, C(5)$H_2$], 4.88 [1H, dd, B of the ABX system $J_{BX}$ 17.5, $J_{AB}$ 1.4, C(13)$H_2$], 5.00 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.4, C(13)$H_2$], 5.07 [1H, td, *J* 7.1, 1.4, C(9)*H*], 5.76 [1H, dd, X of the ABX system $J_{BX}$ 17.5, $J_{AX}$ 10.8, C(12)*H*], 6.15 [1H, d, *J* 1.8, C(2)*H*], 7.19 [1H, d, *J* 1.8, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.9 [$CH_3$, C(4)*C*$H_3$], 17.6 (*C*$H_3$), 22.0 [$CH_3$, *C*(14)$H_3$], 23.1 [$CH_2$, *C*(8)$H_2$] 25.7 (*C*$H_3$), 37.1 [$CH_2$, *C*(5)$H_2$], 40.4 [$CH_2$, *C*(7)$H_2$], 41.1 [C, *C*(6)], 112.0 [$CH_2$, *C*(13)$H_2$], 113.5 [CH, *C*(2)H], 115.4 [C, *C*(3)], 124.9 [CH, *C*(9)H], 131.1 [C, *C*(10)], 139.1 [C, *C*(1)], 146.7 [C, *C*(12)H], 148.9 [C, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_{16}H_{25}O$ $(M+H)^+$ 233.1905. Found 233.1910 $(M+H)^+$; m/z (ESI+): 233.3 $(M+H)^+$.



The least polar fraction, 1,2-bis(2-methylfuran-3-yl)ethane **41** was isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2858, 1514, 1446, 1205, 1184, 1138, 894, 731. $\delta_H$ ($CDCl_3$, 300 MHz) 2.09 [6H, s, 2 x C(4)C$H_3$], 2.50 [4H, s, 2 x C(5)$H_2$], 6.15 [2H, d, *J* 1.8, 2 x C(2)*H*], 7.20 [2H, d, *J* 1.8, 2 x C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.2 [$CH_3$, C(4)*C*$H_3$], 25.8 [$CH_2$, *C*(5)$H_2$], 111.5 [CH, C(2)H], 118.2 [C, C(3)], 139.7 [CH, C(1)H], 147.6 [C, C(4)$CH_3$]; HRMS (ESI+): Exact mass calculated for $C_{12}H_{15}O_2$ $(M+H)^+$ 190.1072. Found 190.1066 $(M+H)^+$.

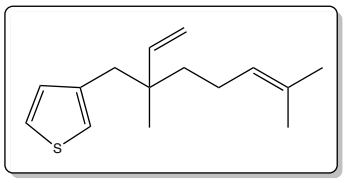
### 4.3.3.3 Synthesis of (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)thiophene 33



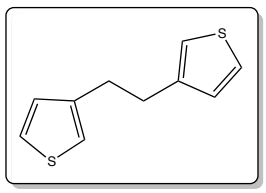
The title compound was synthesised following the procedure described for (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)furan **10** using 3-thienylmethyl bromide **23** (0.50 g, 2.82 mmol), magnesium turnings (0.14 g, 5.65 mmol), copper(I) iodide (32 mg, 0.17 mmol, 10 mol%), (*E*)-3,7-dimethylocta-2,6-dien-1-yl diphenyl phosphate **25** (0.67 g, 1.69 mmol) in diethyl ether (14 mL) to afford a three-component mixture consisting of the title cross coupled product **33**, its corresponding structural regioisomer **36** and 1,2-di(thiophen-3-yl)ethane **39** in a 3:1:1 ratio of products respectively.

The crude yellow residue was purified by column chromatography on silica gel (100% hexanes) to afford the title thiophenolipid **33** as a colourless oil (154 mg, 39%); $\nu_{max}/cm^{-1}$ (film) 2966, 2921, 2854, 1444, 1376, 1239, 1108, 1080; $\delta_H$ ($CDCl_3$, 300 MHz) 1.57 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.90-2.12 [4H, m, C(9)*H*$_2$ and C(10)*H*$_2$], 2.31 [2H, q, *J* 7.4, C(6)*H*$_2$], 2.66 [2H, t, *J* 7.6, C(5)*H*$_2$], 5.09 [1H, td, *J* 6.8, 1.4, C(7)*H*], 5.18 [1H, td, *J* 7.0, 1.2, C(11)*H*], 6.91-6.97 [2H, m, C(4)*H* and C(2)*H*], 7.20-7.28 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 (*C*H$_3$), 17.7 (*C*H$_3$), 25.7 (*C*H$_3$), 26.7 [$CH_2$, *C*(10)H$_2$], 29.0 [$CH_2$, *C*(6)H$_2$], 30.4 [$CH_2$, *C*(5)H$_2$], 39.7 [$CH_2$, *C*(9)H$_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(11)H], 124.3 [CH, *C*(7)H], 125.0 [CH, *C*(1)H], 128.4 [CH, *C*(2)H], 131.4 [C, *C*(12)], 135.8 [C, *C*(8)], 142.8 [C, C(3)]; HRMS (ESI+): Exact mass calculated for $C_{15}H_{23}O$ $(M+H)^+$ 235.1520. Found 235.1524 $(M+H)^+$; m/z (ESI+) 235.4 $(M+H)^+$.

- The reaction was repeated following the same procedure and conditions as above and identical regioselective results were obtained.

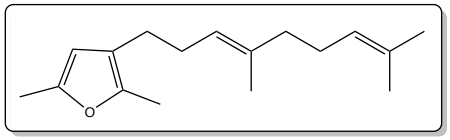


The least polar fraction, 3-(2,6-dimethyl-2vinyl-5-heptenyl)thiophene **36** (40 mg, 10%) was also isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2966, 2925, 2854, 1640 (C=C), 1458 (C=C, Ar); $\delta_H$ ($CDCl_3$, 300 MHz) 0.96 [3H, s, C(14)*H*$_3$], 1.26-1.36 [2H, m, C(7)*H*$_2$] 1.58 [3H, s, C(11)*H*$_3$ or C(15)*H*$_3$], 1.67 [3H, s, C(11)*H*$_3$ or C(15)*H*$_3$], 1.85-2.05 [2H, m, C(8)*H*$_2$], 2.63 [2H, s, C(5)*H*$_2$], 4.87 [1H, dd, B of the ABX system $J_{BX}$ 17.5, $J_{AB}$ 1.4, C(13)*H*$_2$], 5.02 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.4, C(13)*H*$_2$], 5.07 [1H, td, *J* 7.1, 1.4, C(9)*H*], 5.78 [1H, dd, X of the ABX system $J_{BX}$ 17.5, $J_{AX}$ 10.8, C(12)*H*], 6.86-6.92 [2H, m, C(2)*H* and C(4)*H*], 7.16-7.21 [1H, m, C(1)H]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.6 (*C*H$_3$), 22.3 [$CH_3$, *C*(14)H$_3$], 23.0 [$CH_2$, *C*(8)H$_2$] 25.7 (*C*H$_3$), 40.4 [$CH_2$, *C*(7)H$_2$], 40.5 [C, *C*(6)], 42.0 [$CH_2$, *C*(5)H$_2$], 112.2 [$CH_2$, *C*(13)H$_2$], 122.4 [CH, *C*(4)H], 124.0 [CH, *C*(9)H], 124.9 [CH, *C*(1)H], 130.2 [CH, *C*(2)H], 131.2 [C, *C*(10)], 138.9 [C, *C*(3)], 146.7 [CH, *C*(12)H]; HRMS (ESI+): Exact mass calculated for $C_{15}H_{23}S$ $(M+H)^+$ 235.1520. Found 235.1521 $(M+H)^+$; m/z (ESI+): 235.1 $(M+H)^+$.

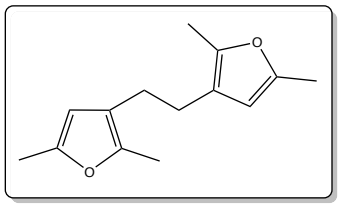


The most polar fraction, 1,2-di(thiophen-3-yl)ethane **39** was isolated as a white crystalline solid. $\nu_{max}/cm^{-1}$ (film): 2921, 2856, 1452, 1409, 1078, 781; $\delta_H$ ($CDCl_3$, 300 MHz) 2.96 [4H, s, 2 x C(5)*H*$_2$], 6.91-6.96 [4H, m, 2 x C(2)*H* and 2 x C(4)*H*], 7.22-7.28 [2H, m, 2 x C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 31.3 [$CH_2$, *C*(5)H$_2$] 120.4 [CH, *C*(4)H], 125.3 [CH, *C*(1)H], 128.2 [CH, *C*(2)H], 142.0 [C, *C*(3)]; HRMS (ESI+): Exact mass calculated for $C_{10}H_{11}S_2$ $(M+H)^+$ 195.0302 Found 195.0315 $(M+H^+)$; m/z (ESI+) 195.0 $(M+H)^+$.

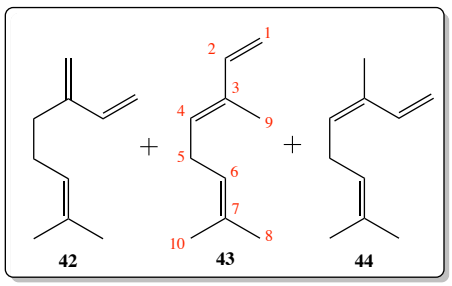
### 4.3.3.4 Synthesis of (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-2,5-dimethylfuran 34



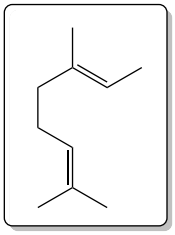
Synthesis of the title compound was attempted following the procedure described for (*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)furan **10** using 2,5-dimethyl-3-furylmethyl bromide **21** (0.25 g, 1.32 mmol), magnesium turnings (0.07 g, 2.65 mmol), copper iodide (15 mg, 0.08 mmol, 10 mol%) and (*E*)-3,7-dimethylocta-2,6-dien-1-yl diphenyl phosphate **25** (0.31 g, 0.79 mmol) in tetrahydrofuran (6 mL) to afford a complex mixture consisting primarily of 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** and multiple degradation products with no apparent evidence for the formation of the title cross coupled product **34**. The crude residue was purified by column chromatography on silica gel (100% hexanes).



The least polar fraction, 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** was isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2922 (CH), 2856, 1583, 1451, 1257, 1190, 924, 796; $\delta_H$ ($CDCl_3$, 300 MHz) 2.08 [6H, s, 2 x C(4)C*H*$_3$], 2.21 [6H, s, 2 x C(1)C*H*$_3$], 2.41 [4H, s, 2 x C(5)*H*$_2$], 5.75 [2H, s, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.2 [$CH_3$, C(4)*C*H$_3$], 13.4 [$CH_3$, C(1)*C*H$_3$], 26.0 [$CH_2$, *C*(5)H$_2$], 107.3 [CH, C(2)H], 119.1 [C, C(3)], 145.3 [C, C(4)CH$_3$], 149.0 [C, C(1)CH$_3$]; Exact mass calculated for $C_{14}H_{19}O_2$ $(M+H)^+$ 219.1307 Found 219.1310 ($M+H^+$); m/z (ESI+) 219.1 $(M+H)^+$.




The least polar fraction comprised of a complex mixture of acyclic monoterpenes putatively assigned as myrcene **42**, (*E*)-β-ocimene **43**, and (*Z*)-β-ocimene **44**, which were isolated as a non viscous colourless oil. The major compound of the three component mixture was (*E*)-β-ocimene **43** and spectroscopic data for this compound was consistent with those reported in the literature.[14,31] $\nu_{max}/cm^{-1}$ (film) 2968, 2926, 2856, 1452, 1376, 911; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 1.67 (3H, s, C*H*$_3$), 1.95-2.15 [2H, m, C(5)*H*$_2$], 4.90 [1H, dd, B of the ABX system $J_{BX}$ 17.5, $J_{AB}$ 1.5, C(1)*H*$_2$], 4.98 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.5, C(1)*H*$_2$], 5.02-5.20 [2H, m, C(4)*H* and C(6)*H*], 5.74 [1H dd, X of the ABX system $J_{BX}$ 17.5, $J_{AX}$ 10.8, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.2 (*C*H$_3$), 17.7 (*C*H$_3$), 22.6 (*C*H$_3$), 26.6 [$CH_2$, *C*(5)H$_2$], 111.4 [$CH_2$, *C*(1)H$_2$], 130.9 [C, *C*(4)], 131.2 [C, *C*(7)], 136.3 [C, *C*(3)], 147.2 [C, *C*(2)].

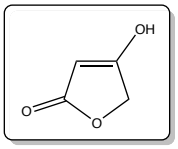


The less polar fraction, was putatively assigned as (*E*)-2,6-dimethylocta-2,6-diene **45**, which was isolated as a colourless oil. Spectroscopic data was consistent with those reported in the literature and was subsequently tentatively assigned.[14] $\nu_{max}/cm^{-1}$ (film) 2967, 2917, 2856, 1444, 1376, 1108; $\delta_H$ ($CDCl_3$, 300 MHz) 1.60 (6H, s, C$H_3$), 1.68 (3H, s, C$H_3$), 1.90-2.15 [7H, m, C(4)$H_2$ and C(5)$H_2$ and C(1)$H_3$], 5.05-5.20 [2H, m, C(2)*H* and C(6)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.1 (*C*$H_3$), 16.0 (*C*$H_3$), 17.7 (*C*$H_3$), 25.7 (*C*$H_3$), 26.8 [$CH_2$, *C*(5)$H_2$], 39.8 [$CH_2$, *C*(4)$H_2$], 124.3 [CH, *C*(2)H or *C*(6)H], 124.4 [CH, *C*(2)H or *C*(6)H], 131.3 [C, *C*(3)], 135.1 [C, *C*(7)].

# 4.4 Synthesis of subunit C

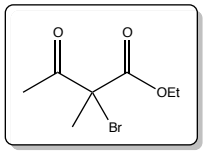
## 4.4.1 Synthesis of tetronic acid derivatives

### 4.4.1.1 Synthesis of 4-hydroxyfuran-2(5H)-one 8 [32,33]

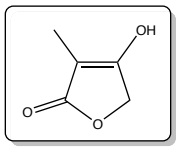



A solution of bromine (3.96 mL, 12.28 g, 0.077 mol) in dichloromethane (4 mL) was added dropwise to a stirring solution of ethyl acetoacetate **55** (10 g, 0.077 mol) in dichloromethane (45 mL) at 0 $^oC$ over a period of 1 h, and the mixture was stirred for an additional 25 min at room temperature and then aerated by passage of dry air for 1 h. Potassium acetate (22.67 g, 0.231 mol) and acetic acid (77 mL) were added to the reaction mixture, and the contents of the reaction flask was heated to 85 $^oC$ for 5 h. On cooling to room temperature, deposited potassium bromide was removed by filtration and the filtrate was concentrated under reduced pressure. The crude residue was dissolved up in 10% aqueous hydrochloric acid (103 mL) and stirred at room temperature for 48 h. The reaction mixture was evaporated under reduced pressure, and the resulting residue was washed with toluene (20 mL), ethyl acetate (20 mL) and extracted with ethanol (3 x 20 mL). Evaporation of the ethanol extracts under reduced pressure afforded β-tetronic acid **8** as a yellow crystalline solid. The crystalline residue was recrystallized from ethyl acetate to furnish β-tetronic acid **8** (940 mg, 12.2 %) as pale yellow crystalline solid. Spectroscopic characteristics were consistent with those reported in the literature;[32-34] mp 137-141 $^oC$, *lit*[34] mp 141-142 $^oC$; Found C, 49,77, H, 4.19, $C_4H_4O_3$ requires C, 48.01, H, 4.03; $\nu_{max}/cm^{-1}$ (KBr) 2984, 2695, 1561, 1448, 1183; $\delta_H$ (DMSO-$d_6$, 400 MHz) 4.67 [2H, d, *J* 1.1, C(5)$H_2$], 4.96 [1H, t, *J* 1.1, C(3)*H*]; $\delta_C$ (DMSO-$d_6$, 75.5 MHz) 67.8 [$CH_2$, *C*(5)$H_2$], 87.6 [CH, *C*(3)H], 174.2 [C, *C*(2)], 180.4 [C, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_4H_5O_3$ $(M+H)^+$ 101.0239. Found 101.0234 $(M+H)^+$; m/z (ESI+) 101.1 $(M+H)^+$

### 4.4.1.2 Synthesis of 4-hydroxy-3-methylfuran-2(5H)-one 56 [35]



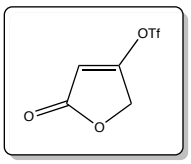

Bromine (3.75 mL, 11.6 g, 72.8 mmol) was added dropwise over a 2 h period to a stirring solution of ethyl 2-methylacetoacetate **57** (10 g, 69.4 mmol) in water (20 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirring was continued for additional 12 h. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford ethyl 2-bromo-2-methyl-3-oxobutanoate **58** (13.7 g, 89 %) as a yellow oil, which was used in the next step without further purification. Spectroscopic characteristics are consistent with those previously reported;[35,36] $\nu_{max}/cm^{-1}$ (film) 2987, 1727, 1251; $\delta_H$ ($CDCl_3$, 300 MHz) 1.31 [3H, t, *J* 7.1, C(O)$CH_2CH_3$], 1.98 [3H, s, C(4)$H_3$], 2.45 [3H, s, C(2)$CH_3$], 4.29 [1H, dq, *J* 7.2, 0.8, C(O)$CH_2CH_3$]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 13.8 [$CH_3$, C(O)$CH_2CH_3$], 25.2 [$CH_3$, C(2)$CH_3$ or *C*(4)$H_3$], 25.7 [$CH_3$, C(2)$CH_3$ or *C*(4)$H_3$], 62.7 [C, *C*(2)], 63.1 [$CH_2$, C(O)$CH_2CH_3$], 168.2 [C, *C*(1)], 198.2 [C, *C*(3)].




Hydrogen bromide (48% w/v in water, 4 drops) was added to a stirring solution of ethyl 2-bromo-2-methyl-3-oxobutanoate **58** at room temperature. The reaction mixture was heated to reflux (100 °C) and stirred for 16 h. On cooling to room temperature, the reaction mixture was suction filtered and rinsed with ethyl acetate (3 x 20 mL). The concentrated filtrate was resubmitted to the reaction conditions twice. The filtrates from the three reaction cycles were combined to afford the title lactone **56** (5.05 g, 51% over two steps) as a white solid. Spectroscopic characteristics are consistent with those previously reported;[35,36] mp 182-184 °C, *lit*[35] mp 185 °C; Found C, 52.78, H, 5.28, $C_5H_6O_3$ requires C, 52.63, H, 5.30; $\nu_{max}/cm^{-1}$ (KBr) 2984, 2695, 1598, 1448; $\delta_H$ (DMSO-$d_6$, 400 MHz) 1.59 [3H, s, C(3)C$H_3$], 4.57 [2H, s, C(5)$H_2$]; $\delta_C$ (DMSO-$d_6$, 75.5 MHz) 5.9 [$CH_3$, C(3)$CH_3$], 66.5 [$CH_2$, *C*(5)$H_2$], 94.4 [C, *C*(3)], 172.9 [C, *C*(2)], 175.3 [C, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_5H_7O_3$ $(M+H)^+$ 115.0395. Found 115.0399 $(M+H)^+$; m/z (ESI+) 115.2 $(M+H)^+$.

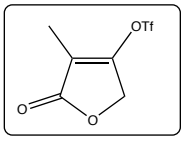
## 4.4.2 Synthesis of triflate tetronic acid derivatives

### 4.4.2.1 Synthesis of 5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate 57 [37-39]




*N,N*-Diisopropylethylamine (0.87 mL, 0.65 g, 5.0 mmol) and triflic anhydride (1M in dichloromethane, 5.0 mL, 5.0 mmol) were added sequentially to a stirring solution of 4-hydroxyfuran-2(5*H*)-one **8** (0.50 g, 5.0 mmol) in dichloromethane (40 mL) at -78 $^{o}$C. The reaction mixture was allowed to warm to room temperature over 1 h. On cooling, the reaction mixture was diluted with dichloromethane (40 mL) and water (40 mL). The organic layer was washed with water (3 x 20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give the title triflate **57** (0.79 g, 67%) as a light yellow oil. Spectroscopic characteristics are consistent with those previously reported.[37,40,41] $\nu_{max}$/cm$^{-1}$ (film) 1790 (C=O), 1760 (C=O), 1652 (C=C), 1442, 1301, 1223, 1131, 1052; $\delta_H$ ($CDCl_3$, 300 MHz) 4.90 [2H, d, *J* 1.8, C(5)$H_2$], 6.06 [1H, t, *J* 1.8, C(3)*H*].

### 4.4.2.2 Synthesis of 4-methyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate 58 [37]



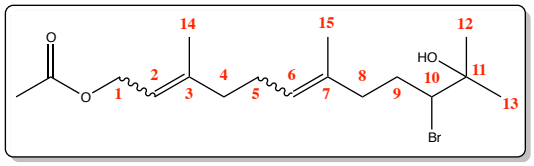

The title compound was prepared following the procedure described for **57** using *N,N*-diisopropylethylamine (0.61 mL, 0.45 g, 3.5 mmol), 4-hydroxy-3-methylfuran-2(5*H*)-one **56** (0.40 g, 3.5 mmol) triflic anhydride (1M in dichloromethane, 3.5 ml, 3.5 mmol) in dichloromethane (25 mL) at -78 $^{o}$C. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the title triflate **58** (0.68 g, 79%) as a faint yellow oil. Spectroscopic characteristics are consistent with those previously reported;[37-39] $\nu_{max}$/cm$^{-1}$ (film) 1790 (C=O), 1763 (C=O), 1712, 1435, 1309, 1223, 1137, 1045; $\delta_H$ ($CDCl_3$, 300 MHz) 1.95 [3H, t, *J* 2.0, C(3)C$H_3$], 4.92 [2H, q, *J* 2.0, C(5)$H_2$], $\delta_C$ ($CDCl_3$, 75.5 MHz) 7.5 [$CH_3$, C(3)*C*H$_3$], 66.6 [$CH_2$, C(5)*C*H$_2$], 117.1 [$CH_3$, *C*(3)CH$_3$], 118.4 [C, q, $^1J_{FC}$ 321.1, *C*F$_3$], 160.3 [C, *C*(2)], 170.2 [C, *C*(4)].

# 4.5 Synthesis of subunit B

For the purpose of characterisation, compounds were numbered according to their name unless otherwise stated in the literature. Farnesol was purchased from Alfa Aesar in the form of a mixture of stereoisomers containing 51% of the (*E*,*E*)-isomer, 40% of the (*Z*,*E*)-isomer and 9% of the other isomer(s) as determined by HPLC analysis (***Appendix V***). An asterisk (*) indicates the signal of the (*Z,E*) isomer. When possible, the ratio of isomers was estimated by $^{1}$H NMR analysis.

## 4.5.1 Synthesis of acetate protected subunit B

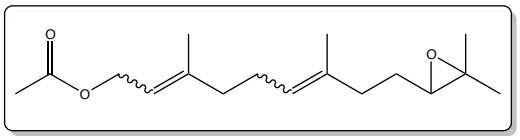
### 4.5.1.1 Synthesis of 10-bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl acetate 61 [42,43]




Farnesyl acetate **59** (2.00 g, 7.56 mmol) was dissolved in *tert*-butanol (70 mL) at 12 $^{o}$C and water (120 mL) was added until saturation. External cooling was removed and *N*-bromosuccinimide (1.48 g, 8.32 mmol) was added portion-wise over 30 mins with vigorous stirring. The mixture was allowed to stir for 90 min at room temperature before the solution was concentrated under reduced pressure. The aqueous residue was extracted with diethyl ether (4 x 20 mL). The extracts were combined, washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude bromohydrin intermediate **61** as a yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[19,42,44] $\nu_{max}$/cm$^{-1}$ (film) 3446 (OH), 2974, 1732 (C=O), 1446, 1368, 1236 (CO), 1025 (CO); $\delta_H$ ($CDCl_3$, 400 MHz) 1.34 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.35 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.60 [3H, s, C(13)$H_3$ or C(14)$H_3$], 1.65-1.88 [5H, m, C(9)$H_2$ and C$H_3$* and containing 3H, s, C(13)$H_3$ or C(14)$H_3$], 1.90-2.25 [8H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.96 [1H, dd, *J* 11.4, 1.9, C(10)*H*], 4.54-4.63 [2H, m, C$H_2$* and containing 2H, d, *J* 7.2, C(1)$H_2$], 5.14-5.24 [1H, m, C(6)*H*], 5.30-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.8 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 16.5 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.0 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.1 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.5 [$CH_2$, *C*(5)$H_2$], 32.0 [$CH_2$, *C*(9)$H_2$], 38.1 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 70.7 [CH, *C*(10)H], 72.5 [C, *C*(11)], 118.5 [CH, *C*(2)H], 125.4 [CH, *C*(6)H], 133.6 [C, *C*(7)], 142.0 [C, *C*(3)], 171.2 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 15.3 (*C*$H_3$), 17.6 (*C*$H_3$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 23.5 (*C*$H_3$), 23.6 (*C*$H_3$), 25.7 (*C*$H_2$), 25.9 (*C*$H_2$), 26.2 (*C*$H_2$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 29.6 (*C*$H_2$), 30.5 (*C*$H_2$), 31.5 (*C*$H_2$), 32.2 (*C*$H_2$), 32.3 (*C*$H_2$), 32.5 (*C*$H_2$), 38.2 (*C*$H_2$), 39.8 (*C*$H_2$), 58.4 (*C*$H_2$), 61.1 (*C*$H_2$), 61.3 (*C*$H_2$), 65.9 (*C*$H_2$), 70.5 (*C*H), 70.6 (*C*H), 70.8 (*C*H), 118.5 (*C*H),

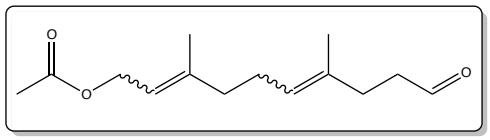
124.3 (*C*H), 124.4 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 133.7 (*C*), 134.0 (*C*), 142.0 (*C*), 142.4 (*C*).

### 4.5.1.2 Synthesis of the (+/-) 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate 60 [42,45]



A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.47 mL, 1.5 g, 9.83 mmol) dissolved in tetrahydrofuran (5 mL) was added to a stirring solution of the crude bromohydrin residue **61** in tetrahydrofuran (25 mL) at 0 °C. The reaction was warmed to room temperature and monitored by TLC analysis. After 3 h, the tetrahydrofuran was evaporated under reduced pressure. The crude residue was suspended in hexane and washed with water (3 x 20 mL). The combined aqueous layers were back extracted with hexane (20 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (1-15% ethyl acetate gradient in hexanes) to provide the title epoxide **60** (1.30 g, 61% over 2 steps) as a colourless oil. $^1$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*. Spectroscopic characteristics are consistent with those previously reported;[18,19] $\nu_{max}$/cm$^{-1}$ (film) 2927, 1739 (C=O), 1727 (C=O), 1449, 1379, 1367, 1233 (CO), 1123 (C-C-O), 1024 (CO), 956, 873, 681; $\delta_H$ ($CDCl_3$, 300 MHz) 1.26 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.27* (3H, s), 1.30 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.31* (3H, s), 1.56-1.68 [5H, m, C(9)$H_2$ and containing 3H, s, C(13)$H_3$ or C(14)$H_3$], 1.71 [3H, s, C(13)$H_3$ or C(14)$H_3$], 1.77* (3H, s), 2.02-2.24 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.70 [1H, t, *J* 6.2 C(10)*H*], 2.71* (2H, t, *J* 6.3), 4.53-4.62 [2H, m, C$H_2$* and containing 2H, d, *J* 7.4, C(1)$H_2$], 5.09-5.20 [1H, m, C(6)*H*], 5.30-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 16.5 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 18.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 24.9 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 27.4 [$CH_2$, *C*(9)$H_2$], 36.3 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 58.3 [C, *C*(11)], 61.4 [$CH_2$, *C*(1)$H_2$], 64.2 [CH, *C*(10)H], 118.4 [CH, *C*(2)H], 124.3 [CH, *C*(6)H], 134.6 [C, *C*(7)], 142.1 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 14.1 (*C*$H_3$), 18.7 (*C*$H_3$), 22.7 (*C*$H_3$), 23.3 (*C*$H_3$), 23.5 (*C*$H_3$), 26.0 (*C*$H_2$), 26.3 (*C*$H_2$), 26.6 (*C*$H_2$), 26.9 (*C*$H_2$), 27.4 (*C*$H_2$), 28.5 (*C*$H_2$), 31.6 (*C*$H_2$), 32.1 (*C*$H_2$), 39.7 (*C*$H_2$), 58.4 (*C*$H_2$), 61.1 (*C*$H_2$), 64.1 (*C*$H_2$), 118.3 (*C*H), 119.2 (*C*H), 119.3 (*C*H), 124.0 (*C*H), 125.1 (*C*H), 134.9 (*C*), 142.0 (*C*), 142.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{17}H_{29}O_3$ $(M+H)^+$ 281.2117. Found 218.2126 $(M+H)^+$; m/z (ESI+): 281.4 $(M+H)^+$.

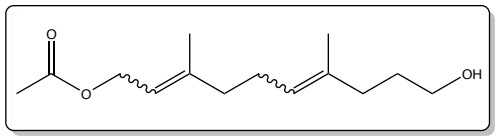
### 4.5.1.3 Synthesis of 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate 62 [42,45]



A solution of 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (0.80 g, 2.85 mmol) dissolved in diethyl ether (15 mL) was added rapidly to a stirring solution of periodic acid (0.78 g, 3.4 mmol) in tetrahydrofuran (3 mL) at 0 °C. The reaction was monitored by TLC analysis and quenched after 30 min with saturated aqueous sodium thiosulfate solution (10 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (1-15% ethyl acetate gradient in hexanes) to provide the title aldehyde **62** (0.68 g, 79%) as a faint yellow oil. $^1$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*. Spectroscopic characteristics are consistent with those previously reported.[18,19,46] $\nu_{max}/cm^{-1}$ (film) 2966, 2920, 1738 (C=O), 1727 (C=O), 1446, 1381, 1367, 1235 (CO), 1024 (CO), 955; $\delta_H$ ($CDCl_3$, 300 MHz) 1.62 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.76* (3H, s), 1.98-2.18 [7H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.28-2.40 [2H, m, C(8)$H_2$], 2.45-2.57 [2H, m, C(9)*H*], 4.53-4.62 [2H, m, C$H_2$* and containing 2H, d, *J* 7.4, C(1)$H_2$], 5.05-5.20 [1H, m, C(6)*H*], 5.27-5.42 [1H, m, C(2)*H*], 9.75 [1H, t, *J* 1.9, C(10)$H_2$], 9.79* (1H, t, *J* 1.7); $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.1 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.0 [$CH_2$, *C*(5)$H_2$], 31.8 [$CH_2$, *C*(8)$H_2$], 39.3 [$CH_2$, *C*(4)$H_2$], 42.1 [$CH_2$, *C*(9)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 118.5 [CH, *C*(2)H], 124.8 [CH, *C*(6)H], 133.3 [C, *C*(7)], 141.9 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$], 202.6 [CH, *C*(10)H]; Characteristics peaks for the other isomer(s)* 16.1 (*C*$H_3$), 16.5 (*C*$H_3$), 23.0 (*C*$H_3$) 23.5 (*C*$H_3$), 24.2 (*C*$H_2$), 24.3 (*C*$H_2$), 26.0 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 31.7 (*C*$H_2$), 31.9 (*C*$H_2$), 32.1 (*C*$H_2$), 39.5 (*C*$H_2$), 42.3 (*C*$H_2$), 61.0 (*C*$H_2$), 61.1 (*C*$H_2$), 119.3 (*C*H), 119.4 (*C*H), 124.5 (*C*H), 125.7 (*C*H), 125.9 (*C*H), 133.8 (*C*), 141.8 (*C*), 142.2 (*C*), 142.3 (*C*), 202.1 (*C*), 202.2 (*C*), 202.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{19}O$ $(M+H\text{-}HOAc)^+$ 179.1431. Found 179.1429 $(M+H\text{-}HOAc)^+$; m/z (ESI+): 239.3 $(M+H)^+$.

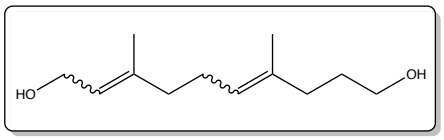
### 4.5.1.4 Synthesis of 10-hydroxy-3,7-dimethyldeca-2,6-dien-1-yl acetate 63 [42]

**Method A: Sodium borohydride reduction in methanol.**



Sodium borohydride (0.08 g, 2.15 mmol) was added in small portions to a stirring solution of 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (0.43 g, 1.79 mmol) in freshly distilled methanol* (30 mL) at -10 $^{o}$C. The mixture was stirred for an additional 2 h at -10 $^{o}$C before the reaction was quenched with ice-cold water (10 mL). The reaction mixture was concentrated under reduced pressure and the aqueous residue was saturated with solid sodium chloride and extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (20-50% ethyl acetate gradient in hexanes) to afford the title alcohol **63** (0.36 g, 84%) as a colourless oil. $^1$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*. Spectroscopic characteristics are consistent with those previously reported;[42] $\nu_{max}$/cm$^{-1}$ (film) 3410 (OH), 2938, 2867, 1739 (C=O), 1669, 1446, 1381, 1367, 1236 (CO), 1024 (CO), 954; $\delta_H$ ($CDCl_3$, 400 MHz) 1.58-1.73 [8H, m, C(9)$H_2$ and C$H_2$* and containing 2 x 3H, s, C(11)$H_3$ and C(12)$H_3$], 1.76* (3H, s), 2.02-2.18 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.58-3.67 [2H, m, C(10)$H_2$], 4.53-4.62 [2H, m, C$H_2$* and containing 2H, d, *J* 7.4, C(1)$H_2$], 5.09-5.18 [1H, m, C(6)*H*], 5.30-5.38 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.0 [$CH_2$, *C*(5)$H_2$], 30.6 [$CH_2$, *C*(9)$H_2$], 35.9 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 62.6 [$CH_2$, *C*(10)$H_2$], 118.4 [CH, *C*(2)H], 124.1 [CH, *C*(6)H], 135.1 [C, *C*(7)], 142.0 [C, *C*(3)], 171.2 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.5 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 23.6 (*C*$H_3$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.0 (*C*$H_2$), 28.1 (*C*$H_2$), 30.7 (*C*$H_2$), 30.9 (*C*$H_2$), 31.0 (*C*$H_2$), 32.0 (*C*$H_2$), 32.5 (*C*$H_2$), 39.7 (*C*$H_2$), 61.2 (*C*$H_2$), 62.7 (*C*$H_2$), 62.8 (*C*$H_2$), 118.3 (*C*H), 119.1 (*C*H), 119.2, (*C*H), 123.8 (*C*H), 124.7 (*C*H), 124.9 (*C*H), 135.2 (*C*), 135.4 (*C*), 135.6 (*C*), 142.1 (*C*), 142.4 (*C*), 142.5 (*C*), 171.3 (*C*); HRMS (ESI+): Exact mass calculated for $C_{14}H_{25}O_3$ $(M+H)^+$ 241.1804. Found 241.1809 $(M+H)^+$; m/z (ESI+) 181.3 $(M+H\text{-}HOAc)^+$.

* When HPLC grade methanol was employed as the solvent for this reaction while adhering to the same general procedure as described above, a two-component mixture consisting of the title alcohol **63** and its corresponding diol **64** in a 60:40 ratio of products respectively was formed following $^1$H NMR analysis of the crude material. The crude residue was purified by column chromatography on silica gel (20-50% ethyl acetate gradient in hexanes) to afford the title alcohol **63** (0.98 g, 57%) as a colourless oil. Spectroscopic characteristics were consistent with those previously described above.

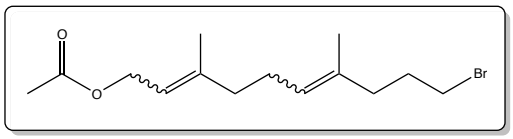



The more polar fraction, 3,7-dimethyldeca-2,6-diene-1,10-diol **64** (0.49 g) was isolated as a viscous colourless oil. $^{1}$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*. Spectroscopic characteristics were consistent with those reported in the literature;[47-49] $\nu_{max}/cm^{-1}$ (film) 3398 (OH), 2937, 1448, 1378, 1367, 1047; $\delta_H$ ($CDCl_3$, 300 MHz) 1.58-1.77 [8H, m, C(9)$H_2$ and C$H_3$* containing 2 x 3H, s, C(11)$H_3$ and C(12)$H_3$], 1.90-2.20 [8H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and 2 x O*H*], 3.61* (2H, t, *J* 6.3), 3.63 [2H, t, *J* 6.2, C(10)$H_2$], 4.08-4.18 [2H, m, C$H_2$* and containing 2H, d, *J* 7.0, C(1)$H_2$], 5.07-5.22 [1H, m, C(6)*H*], 5.34-5.50 [1H, m, C(2)*H*]. $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.8 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 30.8 [$CH_2$, *C*(9)$H_2$], 36.1 [$CH_2$, *C*(8)$H_2$], 39.3 [$CH_2$, *C*(4)$H_2$], 59.3 [$CH_2$, *C*(1)$H_2$], 62.6 [$CH_2$, *C*(10)$H_2$], 124.1 [CH, *C*(6)H], 124.6 [CH, *C*(2)H], 135.2 [C, *C*(7)], 138.9 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 15.8 (*C*$H_3$), 15.9 (*C*$H_3$), 23.2 (*C*$H_3$), 23.3 (*C*$H_3$), 23.6 (*C*$H_3$), 25.8 (*C*$H_2$), 26.1 (*C*$H_2$), 26.7 (*C*$H_2$), 28.0 (*C*$H_2$), 28.1 (*C*$H_2$) 30.1 (*C*$H_2$), 30.4 (*C*$H_2$), 30.9 (*C*$H_2$), 31.7 (*C*$H_2$), 32.3 (*C*$H_2$), 35.8 (*C*$H_2$), 39.6 (*C*$H_2$), 58.8 (*C*$H_2$), 58.9 (*C*$H_2$), 59.3 (*C*$H_2$), 62.2 (*C*$H_2$), 62.8 (*C*$H_2$), 123.6 (*C*H), 124.2 (*C*H), 124.3, (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 135.1 (*C*), 135.4 (*C*), 135.6 (*C*), 139.4 (*C*), 140.1 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{21}O$ $(M+H-H_2O)^+$ 181.1587. Found 181.1584 $(M+H-H_2O)^+$; m/z (ESI+) 181.4 $(M+H-H_2O)^+$.

**Method B: Sodium triacetoxyborohydride reduction in ethyl acetate.[50]**

A solution of 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (50 mg, 0.21 mmol) in ethyl acetate (2 mL) was added slowly at room temperature to a stirring solution of sodium triacetoxyborohydride (134 mg, 0.63 mmol) in ethyl acetate (5 mL). The mixture was allowed to stir at rt for 18 h before it was diluted with ethyl acetate (10 mL) and quenched with water (10 mL). The organic phase was separated and the aqueous fraction was extracted with ethyl acetate (2 x 10 mL). The combined ethyl acetate extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title alcohol **63** (39 mg, 77%) as a colourless oil. Spectroscopic characteristics were consistent with those previously reported above in **Method A**.

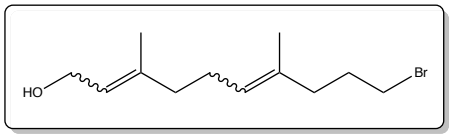
### 4.5.1.5 Synthesis of 10-bromo-3,7-dimethyldeca-2,6-dien-1-yl acetate 66 [51]



Carbon tetrabromide (2.0 g, 6.0 mmol) was added in small portions to a stirring solution of 10-hydroxy-3,7-dimethyldeca-2,6-dien-1-yl acetate **63** (0.96 g, 4.0 mmol) and triphenylphosphine (1.26 g, 4.8 mmol) in dichloromethane (40 mL) at room temperature. The reaction mixture was stirred for 1 h, and dichloromethane was removed under reduced pressure. Water (20 mL) was added and the resulting aqueous layer was extracted with diethyl ether (3 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the title bromide **66** (0.97 g, 80%) as a colourless oil. $^1$H NMR integration revealed a 62:38 mixture of (*E*,*E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2964, 2935, 1739 (C=O), 1443, 1380, 1366, 1234 (CO), 1023 (CO); $\delta_H$ ($CDCl_3$, 400 MHz) 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.71 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.76* (3H, s), 1.85-2.00 [2H, m, C(9)$H_2$], 2.00-2.22 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.37 [2H, t, *J* 7.1 C(10)$H_2$], 3.38* (2H, t, *J* 6.8), 4.56* (2H, d, *J* 7.6), 4.59 [2H, d, *J* 7.4, C(1)$H_2$], 5.08-5.24 [1H, m, C(6)*H*], 5.28-5.42 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.1 [$CH_2$, *C*(5)$H_2$], 31.0 [$CH_2$, *C*(9)$H_2$], 33.4 [$CH_2$, *C*(10)$H_2$], 37.8 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 118.5 [CH, *C*(2)H], 125.1 [CH, *C*(6)H], 133.5 [C, *C*(7)], 142.0 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.5 (*C*$H_3$), 23.2 (*C*$H_3$), 23.5 (*C*$H_3$), 23.6 (*C*$H_3$), 30.8 (*C*$H_2$), 30.9 (*C*$H_2$), 33.5 (*C*$H_2$), 37.8 (*C*$H_2$), 39.7 (*C*$H_2$), 61.1 (*C*$H_2$), 119.3 (*C*H), 124.8 (*C*H), 125.7 (*C*H), 125.9 (*C*H), 133.7 (*C*), 133.9 (*C*), 134.0 (*C*), 142.4 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{79}Br$ (M+H-HOAc)$^+$ 243.0743. Found 243.0753 (M+H-HOAc)$^+$; m/z (ESI+) 243.2 [($C_{12}H_{20}{}^{79}Br$)$^+$, 79%], 245.2 [($C_{12}H_{20}{}^{81}Br$)$^+$, 100%].

## 4.5.2 Synthesis of TBS protected subunit B

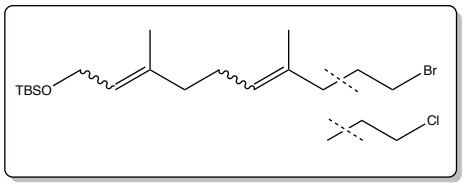
### 4.5.2.1 Synthesis of 10-bromo-3,7-dimethyldeca-2,6-dien-1-ol 68



Potassium carbonate (0.25 g, 1.78 mmol) was added to a stirring solution of 10-bromo-3,7-dimethyldeca-2,6-dien-1-yl acetate **66** (0.18 g, 0.59 mmol) in methanol (10 mL) at room temperature. After 90 min, the reaction contents were poured into water (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were then washed with water (10 mL), brine

(10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title bromide **68** (0.14 g, 87%) as a light yellow oil, which was used without further purification. $^1$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 3335, 2963, 2931, 2856, 1445, 1380, 1248, 1000; $\delta_H$ ($CDCl_3$, 300 MHz) 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.75* (3H, s), 1.86-2.22 [8H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(9)$H_2$], 3.37 [2H, t, *J* 6.7, C(10)$H_2$], 3.39* (2H, t, *J* 6.7), 4.11* (2H, d, *J* 7.1), 4.16 [2H, d, *J* 6.9, C(1)$H_2$], 5.11-5.22 [1H, m, C(6)*H*], 5.37-5.50 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.8 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.2 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 30.8 [$CH_2$, *C*(9)$H_2$], 33.4 [$CH_2$, *C*(10)$H_2$], 37.8 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 59.4 [$CH_2$, *C*(1)$H_2$], 123.6 [CH, *C*(2)H], 125.3 [CH, *C*(2)H], 133.4 [C, *C*(7)], 139.5 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.3 (*C*$H_3$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 23.5 (*C*$H_3$), 26.2 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 30.1 (*C*$H_2$), 30.2 (*C*$H_2$), 30.8 (*C*$H_2$), 32.2 (*C*$H_2$), 33.6 (*C*$H_2$), 37.8 (*C*$H_2$), 39.7 (*C*$H_2$), 59.0 (*C*$H_2$), 123.5 (*C*H), 124.5 (*C*H), 125.0 (*C*H), 125.9 (*C*H), 126.0 (*C*H), 133.6 (*C*), 134.0 (*C*), 134.3 (*C*), 139.5 (*C*), 139.8 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{79}Br$ $(M+H-H_2O)^+$ 243.0748. Found 243.0751 $(M+H-H_2O)^+$; m/z (ESI+) 243.1 [$(C_{12}H_{20}{}^{79}Br)^+$, 79%], 245.1 [$(C_{12}H_{20}{}^{81}Br)^+$, 100%].

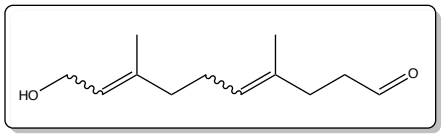
### 4.5.2.2 Synthesis of 10-bromo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene 69




Imidazole (0.22 g, 3.2 mmol) and *tert*-butyldimethylsilyl chloride (0.26 mg, 1.7 mmol) were sequentially added to a stirring solution of 10-bromo-3,7-dimethyldeca-2,6-dien-1-ol **68** (0.42 g, 1.6 mmol) in dimethylformamide (3 mL) at 0 °C. The reaction mixture was stirred for 1 h before it was allowed to warm to room temperature and stirring was continued for an additional 5 h. The reaction was then quenched with water (5 mL) at 0 °C and extracted with diethyl ether (3 x 10 mL). The extract was washed with water (4 x 10 mL), saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% ethyl acetate gradient in hexanes) to afford an inseparable two-component mixture (0.30 g) as a colourless oil, consisting of the title bromide **69** and its corresponding chloride **70** in a 68:32 ratio of products respectively; $\nu_{max}$/cm$^{-1}$ (film) 2957, 2930, 2857, 1463, 1383, 1254 ($SiCH_3$), 1107, 1065 (SiO), 836, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 0.07 [6H, s, Si(C$H_3$)$_2$], 0.91 [9H, s, SiC(C$H_3$)$_3$], 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.63 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.72* (3H, s), 1.76-2.22 [8H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(9)$H_2$], 3.37 [2H, t, *J* 6.7, C(10)$H_2$**Br**], 3.38*

(2H, t, *J* 6.7), 3.49 [2H, t, *J* 6.7, C(10)$H_2$**Cl**], 3.51* (2H, t, *J* 6.7), 4.16* (2H, d, *J* 6.6), 4.19 [2H, d, *J* 6.4, C(1)$H_2$], 5.10-5.22 [1H, m, C(6)*H*], 5.26-5.36 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.0 [$CH_3$, Si(*C*$H_3$)$_2$], 15.8 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.3 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 18.4 [C, Si*C*$(CH_3)_3$], 26.0 [$CH_2$, SiC(*C*$H_3$)$_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 30.9 [$CH_2$, *C*(9)$H_2$], 33.4 [$CH_2$, *C*(10)$H_2$**Br**], 37.8 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 44.5 [$CH_2$, *C*(10)$H_2$**Cl**], 60.3 [$CH_2$, *C*(1)$H_2$], 124.6 [CH, *C*(2)H], 125.4 [CH, *C*(6)H], 133.2 [C, *C*(7)], 137.3 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 16.3 (*C*$H_3$), 23.2 (*C*$H_3$) 23.4 (*C*$H_3$), 26.6 (*C*$H_2$), 30.2 (*C*$H_2$), 32.1 (*C*$H_2$), 32.4 (*C*$H_2$), 33.5 (*C*$H_2$), 37.9 (*C*$H_2$), 39.7 (*C*$H_2$), 44.5 (*C*$H_2$), 59.9 (*C*$H_2$), 124.7 (*C*H), 125.2 (*C*H), 125.4 (*C*H), 133.4 (*C*), 133.7 (*C*), 136.7 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{79}Br$ $(M\text{-}TBSO)^+$ 243.0748. Found 243.0747 $(M\text{-}TBSO)^+$; m/z (ESI+) 243.4 [$(C_{12}H_{20}{}^{79}Br)^+$, 100%], 245.4 [$(C_{12}H_{20}{}^{81}Br)^+$, 97%], 199.4 [$(C_{12}H_{20}{}^{35}Cl)^+$, 100%], 201.3 [$(C_{18}H_{35}{}^{37}Cl)^+$, 32%].

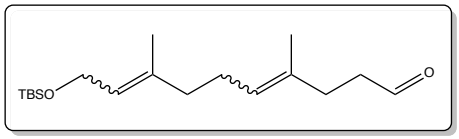
### 4.5.2.3 Synthesis of 10-hydroxy-4,8-dimethyldeca-4,8-dienal 73 [52]




Potassium carbonate (0.52 g, 3.77 mmol) was added to a stirring solution of 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (0.30 g, 1.26 mmol) in methanol (30 mL) at room temperature. After 1 h, water was added (10 mL) and methanol was evaporated under reduced pressure. The aqueous residue was saturated with solid sodium chloride and extracted with ethyl acetate (4 x 10 mL). Combined organic were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title allylic alcohol **73** (0.24 g, 96%) as a light yellow oil, which was used without purification. $^1$H NMR integration of the crude product revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*. Spectroscopic characteristics are consistent with those reported in the literature;[42,53,54] $\nu_{max}$/cm$^{-1}$ (film) 3392, 2918, 1723, 1447, 1385, 1009; $\delta_H$ ($CDCl_3$, 300 MHz) 1.62 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.65 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.69* (3H, s), 1.74* (3H, s), 1.98-2.20 [4H, m, C(7)$H_2$ and C(6)$H_2$], 2.25-2.40 [2H, m, C(3)$H_2$], 2.45-2.57 [2H, m, C(2)$H_2$], 4.10* (2H, d, *J* 7.1), 4.14 [2H, d, *J* 6.8, C(10)$H_2$], 5.04-5.24 [1H, m, C(5)*H*], 5.30-5.50 [1H, m, C(9)*H*], 9.74 [1H, t, *J* 1.9, C(1)*H*], 9.77* (1H, t, *J* 1.7); $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.1 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.3 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 26.3 [$CH_2$, *C*(6)$H_2$], 31.7 [$CH_2$, *C*(3)$H_2$], 39.2 [$CH_2$, *C*(7)$H_2$], 41.9 [$CH_2$, *C*(2)$H_2$], 59.2 [$CH_2$, *C*(10)$H_2$], 123.9 [CH, *C*(9)H], 124.7 [CH, *C*(5)H], 133.7 [C, *C*(4)], 139.1 [C, *C*(8)], 203.0 [C, *C*(1)H]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 22.6 (*C*$H_3$), 23.0 (*C*$H_3$), 23.3 (*C*$H_3$), 24.2 (*C*$H_2$), 24.3 (*C*$H_2$), 25.9 (*C*$H_2$), 26.1 (*C*$H_2$), 31.5 (*C*$H_2$), 31.8 (*C*$H_2$), 32.0 (*C*$H_2$), 39.5 (*C*$H_2$), 41.8 (*C*$H_2$), 42.2 (*C*$H_2$), 58.8 (*C*$H_2$), 58.9 (*C*$H_2$), 123.5 (*C*H), 123.8 (*C*H), 124.1 (*C*H), 124.7 (*C*H), 125.2 (*C*H), 126.0 (*C*H), 126.1 (*C*H), 133.2 (*C*), 138.7 (*C*), 139.0 (*C*), 139.3 (*C*),

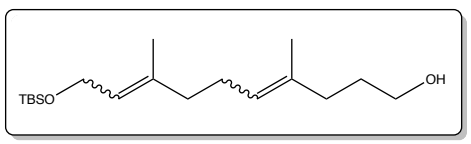
202.2 (*C*H) 202.3 (*C*H), 202.7 (*C*H), 203.1 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{12}H_{19}O$ $(M+H-H_2O)^+$ 179.1431. Found 179.1422 $(M+H-H_2O)^+$; m/z (ESI+): 179.5 $(M+H-H_2O)^+$.

### 4.5.2.4 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dienal 74 [42,55]




Imidazole (0.27 g, 4.0 mmol) and *tert*-butyldimethylsilyl chloride (0.61 g, 4.0 mmol) dissolved in dimethylformamide (9 mL) were added sequentially to a stirring solution of 10-hydroxy-4,8-dimethyldeca-4,8-dienal **73** (1.36 g, 6.93 mmol) in dimethylformamide (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stir for 3 h. Additional portions of imidazole (0.27 g, 4.0 mmol) and *tert*-butyldimethylsilyl chloride (0.61 g, 4.0 mmol) dissolved in dimethylformamide (9 mL) were added in sequence and stirring was continued at room temperature for additional 10 h. The mixture was poured into saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (4 x 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give the title silylated aldehyde **74** (1.50 g, 70%) as colorless oil. $^1$H NMR integration revealed a 60:40 mixture of (*E,E*) and other isomer(s)*. Spectroscopic characteristics are consistent with those reported in the literature;[52,56] $\nu_{max}/cm^{-1}$ (film) 2956, 2929, 2857, 1728, 1670, 1472, 1463, 1387, 1255 ($SiCH_3$), 1109, 1066 (SiO), 1006, 836, 776; $\delta_H$ ($CDCl_3$, 400 MHz) 0.07 [6H, s, Si(C$H_3$)$_2$], 0.90 [9H, s, SiC(C$H_3$)$_3$], 1.62 [6H, s, C(11)$H_3$ and C(12)$H_3$], 1.68* (3H, s), 1.71* (3H, s), 1.96-2.16 [4H, m, C(7)$H_2$ and C(6)$H_2$], 2.26-2.38 [2H, m, C(3)$H_2$], 2.44-2.56 [2H, m, C(2)$H_2$], 4.15* (2H, d, *J* 6.5), 4.19 [2H, d, *J* 6.3, C(10)$H_2$], 5.10-5.20 [1H, m, C(5)*H*], 5.26-5.35 [1H, m, C(9)*H*], 9.75 [1H, t, *J* 1.9, C(1)*H*], 9.78* (1H, t, *J* 1.8); HRMS (ESI+): Exact mass calculated for $C_{18}H_{35}O_2Si$ $(M+H)^+$ 311.2406. Found 311.2410 $(M+H)^+$; m/z (ESI+): 179.5 $(M-TBSO)^+$.

### 4.5.2.5 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-ol 75 [42]

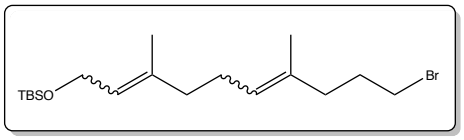



Sodium borohydride (13 mg, 0.34 mmol) was added in small portions to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dienal **74** (88 mg, 0.28 mmol) in methanol (5 mL) at -10 $^o$C. The mixture was allowed to stir at -10 $^o$C for 2 h before water (5 mL) was added and methanol was removed under reduced pressure. The aqueous residue was saturated with solid NaCl and extracted with diethyl ether (4 x 15 mL). The combined organic

extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title alcohol **75** (74 mg, 83 %) as a colourless oil, which was used without further purification. $^1$H NMR integration revealed a 60:40 mixture of (*E,E*) and other isomer(s)*. Spectroscopic characteristics are consistent with those previously reported;[56,57] $\nu_{max}$/cm$^{-1}$ (film) 3362, 2930, 2858, 1472, 1255 ($SiCH_3$), 1066 (SiO), 836, 776; $\delta_H$ ($CDCl_3$, 400 MHz) 0.07 [6H, s, Si(C*H*$_3$)$_2$], 0.91 [9H, s, SiC(C*H*$_3$)$_3$], 1.58-1.74 [8H, m, C(9)*H*$_2$ and C*H*$_3$* and containing 2 x 3H, s, C(11)*H*$_3$ and C(12)*H*$_3$], 1.72* (3H, s), 1.97-2.15 [6H, m, C(3)*H*$_2$ and C(6)*H*$_2$ and C(7)*H*$_2$], 3.57-3.65 [2H, m, C(1)*H*$_2$], 4.17* (2H, d, *J* 6.5), 4.19 [2H, d, *J* 6.3, C(10)*H*$_2$], 5.10-5.18 [1H, m, C(5)*H*], 5.26-5.35 [1H, m, C(9)*H*]; HRMS (ESI+): Exact mass calculated for $C_{18}H_{37}O_2Si$ $(M+H)^+$ 313.2563. Found 313.2554 $(M+H)^+$; (m/z) (ESI-) 311.4 $(M-H)^-$.

### 4.5.2.6 Synthesis of 10-bromo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene 69 [58]

**Method A: Bromination using $CBr_4/PPh_3$.**




Carbon tetrabromide (0.11 g, 0.32 mmol) was added in small portions to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-ol **75** (100 mg, 0.32 mmol) and triphenylphosphine (84 mg, 0.32 mmol) in dichloromethane (30 mL) at room temperature. The reaction mixture was stirred for 1 h, and dichloromethane was removed under reduced pressure. Water (10 mL) was added and the resulting aqueous layer was extracted with diethyl ether (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. $^1$H NMR spectroscopy of the crude material revealed a complex mixture of products resulting from undesired deprotection of the silyl-protecting group. A minor trace (< 15%) of the title bromide **69** was evident in the $^1$H NMR spectrum.

**Method B: Bromination using $PBr_3$.**

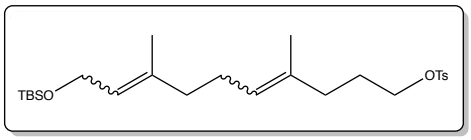
Phosphorous tribromide (12 μL, 35 mg, 0.128 mmol) was added to a stirring solution of **75** (100 mg, 0.32 mmol) in diethyl ether (10 mL) in the dark at 0 $^o$C. The reaction mixture was stirred for 2 h before water (5 mL) was added and the solution was extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed successively with water (10 mL), aqueous sodium hydrogen carbonate (10%, 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. $^1$H NMR spectroscopy of the crude material revealed a complex mixture of products resulting from

undesired deprotection of the silyl-protecting group with no evidence for the formation of the desired compound **69** was observed.

**Method C: Finkelstein reaction.**

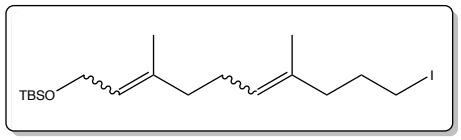
Lithium bromide (0.28 g, 3.27 mmol) was added to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-yl 4-methylbenzenesulfonate **76** (0.73 g, 1.64 mmol) (Please note that the experimental data for compound **76** is described in Section ***4.3.2.7***) in acetone (5 mL) at room temperature. The resulting solution was stirred vigorously and heated to 50 $^{o}$C for 2 h. After this time, the solution was cooled, filtered and acetone was removed under reduced pressure. The residue was taken up in hexane (20 mL) and the solution was washed with water (3 x 20 mL), saturated aqueous sodium thiosulfate (1 x 10 mL), brine (1 x 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title bromide **69** (0.53 g, 77%) as a light yellow oil. $^{1}$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2930, 2858, 1254, 1065, 836, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 0.07 [6H, s, Si(C$H_3$)$_2$], 0.91 [9H, s, SiC(C$H_3$)$_3$], 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.62 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.72* (3H, s), 1.85-2.22 [8H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(9)$H_2$], 3.37 [2H, t, *J* 6.7, C(10)$H_2$], 3.38* (2H, t, *J* 6.9), 4.16* (2H, d, *J* 6.5), 4.19 [2H, d, *J* 6.3, C(1)$H_2$], 5.10-5.22 [1H, m, C(6)*H*], 5.26-5.36 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.0 [$CH_3$, Si(*C*H$_3$)$_2$], 15.8 [$CH_3$, *C*(11)H$_3$ or *C*(12)H$_3$], 16.3 [$CH_3$, *C*(11)H$_3$ or *C*(12)H$_3$], 18.4 [C, Si*C*(CH$_3$)$_3$], 26.0 [$CH_2$, SiC(*C*H$_3$)$_3$], 26.2 [$CH_2$, *C*(5)H$_2$], 30.9 [$CH_2$, *C*(9)H$_2$], 33.4 [$CH_2$, *C*(10)H$_2$], 37.8 [$CH_2$, *C*(8)H$_2$], 39.4 [$CH_2$, *C*(4)H$_2$], 60.3 [$CH_2$, *C*(1)H$_2$], 124.6 [CH, *C*(2)H], 125.4 [CH, *C*(6)H], 133.2 [C, *C*(7)], 136.7 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* -3.6 (*C*H$_3$), 14.1 (*C*H$_3$), 15.3 (*C*H$_3$), 16.2 (*C*H$_3$), 16.4 (*C*H$_3$), 18.4 (*C*H$_3$), 22.6 (*C*H$_3$), 23.2 (*C*H$_3$), 23.4 (*C*H$_3$), 25.6 (*C*H$_3$), 26.2 (*C*H$_2$), 26.6 (*C*H$_2$), 30.8 (*C*H$_2$), 31.1 (*C*H$_2$), 31.6 (*C*H$_2$), 32.1 (*C*H$_2$), 33.5 (*C*H$_2$), 39.7 (*C*H$_2$), 59.4 (*C*H$_2$), 59.9 (*C*H$_2$), 123.6 (*C*H), 124.7 (*C*H), 125.2 (*C*H), 125.3 (*C*H), 125.4 (*C*H), 126.0 (*C*H), 126.2 (*C*H), 133.4 (*C*), 136.6 (*C*), 137.3 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{79}Br$ (M-TBSO)$^+$ 243.0748. Found 243.0742 (M-TBSO)$^+$; m/z (ESI+) 243.1 [($C_{12}H_{20}{}^{79}Br$)$^+$, 97%], 245.1 [($C_{12}H_{20}{}^{81}Br$)$^+$, 100%].

### 4.5.2.7 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-yl 4-methylbenzenesulfonate 76




Triethylamine (0.94 mL, 0.68 g, 6.73 mmol) and 4-dimethylaminopyridine (15 mg, 0.11 mmol, 5 mol%) were added sequentially to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-ol **75** (0.70 g, 2.24 mmol) in dichloromethane (10 mL) at room temperature. *para*-Toluenesulfonyl chloride (0.43 g, 2.24 mmol) was added and the resulting solution was stirred at room temperature for 3 h. The solution was diluted with dichloromethane (35 mL) and washed successively with aqueous hydrochloric acid solution (1M, 20 mL), water (4 x 30 mL) and brine (30 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure to give the title tosylate **76** (0.86 g, 86%) as a colourless oil, which was used without further purification. $^1$H NMR integration of the crude product revealed a 60:40 mixture of (*E*,*E*) and the other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2929, 2857, 1472, 1364 [asymmetric $SO_2$], 1255 ($SiCH_3$), 1178 [symmetric $SO_2$], 1099, 1065 (SiO), 836 (S-O-C stretching); $\delta_H$ ($CDCl_3$, 300 MHz) 0.07 [6H, s, Si(C$H_3$)$_2$], 0.90 [9H, s, SiC(C$H_3$)$_3$], 1.50-1.62 [6H, m, C$H_3$* and containing 2 x 3H, s, C(11)$H_3$ or C(12)$H_3$], 1.65-1.80 [2H, m, C(2)$H_2$], 1.88-2.12 [6H, m, C(3)$H_2$ and C(6)$H_2$ and C(7)$H_2$], 2.45 [3H, s, ArC$H_3$], 3.99 [2H, t, *J* 6.4, C(1)$H_2$], 4.00* (2H, t, *J* 6.5), 4.14* (2H, d, *J* 6.5), 4.19 [2H, d, *J* 6.4, C(10)$H_2$], 5.02 [1H, t, *J* 6.2, C(5)*H*], 5.12* (1H, t, *J* 6.2), 5.22-5.33 [1H, m, C(9)*H*], 7.35 (2H, d, *J* 8.4, Ar*H*), 7.79 (2H, d, *J* 8.3, Ar*H*); $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.0 [$CH_3$, Si(*C*$H_3$)$_2$] 15.8 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 18.4 [C, Si*C*(CH$_3$)$_3$] 21.7 [$CH_3$, ArC$H_3$], 26.0 [C, SiC(*C*H$_3$)$_3$], 26.3 [$CH_2$, *C*(2)$H_2$], 27.0 [$CH_2$, *C*(6)$H_2$], 35.1 [$CH_2$, *C*(3)$H_2$], 39.4 [$CH_2$, *C*(7)$H_2$], 60.3 [$CH_2$, *C*(10)$H_2$], 70.1 [$CH_2$, *C*(1)$H_2$], 124.5 [CH, *C*(9)H], 125.3 [CH, *C*(5)H], 127.9 [CH, Ar-*C*H], 129.8 [CH, Ar-*C*H], 133.3 [C, *C*(4)], 136.7 [C, *C*(8)], 144.6 [C, Ar-*C*]; Characteristics peaks for the other isomer(s)* 16.3 (*C*H$_3$), 23.1 (*C*H$_3$), 26.0 (*C*H$_2$), 27.2 (*C*H$_2$), 39.6 (*C*H$_2$), 70.3 (*C*H$_2$), 124.7 (*C*H), 126.1 (*C*H), 129.8 (*C*H), 133.2 (*C*), 133.3 (*C*), 136.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{25}H_{43}O_4SSi$ $(M+H)^+$ 467.2651. Found 467.2666 $(M+H)^+$; m/z (ESI+) 467.3 $(M+H)^+$.

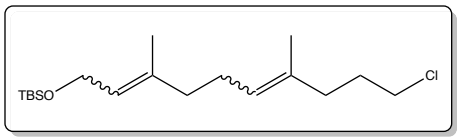
### 4.5.2.8 Synthesis of 10-iodo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **77** [58]




Sodium iodide (0.53 g, 3.54 mmol) was added to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-yl 4-methylbenzenesulfonate **76** (0.79 g, 1.77 mmol) in acetone (10 mL) at room temperature. The reaction mixture was vigorously stirred and heated to 50 $^{o}$C for 2 h. After this time, the reaction mixture was cooled, filtered and concentrated under reduced pressure. The residue was taken up in hexane (10 mL) and washed successively with water (20 mL), saturated aqueous sodium thiosulfate (10 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure to give the title iodide **77** (0.56 g, 76%) as a yellow oil. $^1$H NMR integration of the crude product revealed a 60:40 mixture of (*E*,*E*) and the other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2956, 2929, 2856, 1472, 1462, 1445, 1382, 1255 ($SiCH_3$), 1064 (SiO), 836, 776; $\delta_H$ ($CDCl_3$, 300 MHz) 0.07 [6H, s, Si(C$H_3$)$_2$], 0.91 [9H, s, SiC(C$H_3$)$_3$], 1.59 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.63 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.67* (3H, s), 1.72* (3H, s), 1.84-1.97 [2H, m, C(9)$H_2$], 1.97-2.20 [6H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$], 3.14 [2H, t, *J* 7.1, C(10)$H_2$], 3.16* (2H, t, *J* 7.0), 4.18* (2H, d, *J* 6.6), 4.20 [2H, d, *J* 6.4, C(1)$H_2$], 5.10-5.22 [1H, m, C(6)*H*], 5.25-5.36 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.0 [$CH_3$, Si(*C*H$_3$)$_2$], 6.7 [$CH_2$, *C*(10)H$_2$], 15.8 [$CH_3$, *C*(11)H$_3$ or *C*(12)H$_3$], 16.3 [$CH_3$, *C*(11)H$_3$ or *C*(12)H$_3$], 18.5 [C, Si*C*(CH$_3$)$_3$], 26.1 [C, SiC(*C*H$_3$)$_3$], 26.2 [$CH_2$, *C*(5)H$_2$], 31.6 [$CH_2$, *C*(9)H$_2$], 39.4 [$CH_2$, *C*(4)H$_2$], 40.0 [$CH_2$, *C*(8)H$_2$], 60.3 [$CH_2$, *C*(1)H$_2$], 124.6 [CH, *C*(2)H], 125.5 [CH, *C*(6)H], 133.1 [C, *C*(7)], 136.7 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 6.6 (*C*H$_3$), 16.4 (*C*H$_3$), 23.3 (*C*H$_3$), 23.4 (*C*H$_3$), 26.3 (*C*H$_2$), 26.6 (*C*H$_2$), 32.0 (*C*H$_2$), 32.1 (*C*H$_2$), 32.5 (*C*H$_2$), 39.7 (*C*H$_2$), 60.0 (*C*H$_2$), 124.6 (*C*H), 125.3 (*C*H), 126.2 (*C*H), 133.4 (*C*), 136.6 (*C*); HRMS (ESI+): Exact mass calculated for $C_{18}H_{36}OISi$ $(M+H)^+$ 423.1580. Found 423.1749 $(M+H)^+$. m/z (ESI+) 291.1 $(M-TBSO)^+$.

### 4.5.2.9 Synthesis of 10-chloro-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene 70 [58]

**Method A**

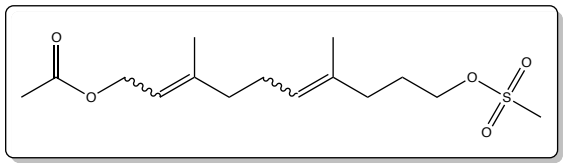



Lithium chloride (10 mg, 0.12 mmol) was added to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-yl 4-methylbenzenesulfonate **76** (5 mg, 0.01 mmol) in acetone (2 mL) at room temperature. The resulting solution was stirred vigorously and heated to 50 $^{o}$C for 16 h. After this time, the reaction mixture was cooled, filtered and concentrated under reduced pressure. The residue was taken up in hexane (5 mL) and washed successively with water (3 x 5 mL), saturated aqueous sodium thiosulfate (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the title chloride **70** (3.1 mg, 84%) as a colourless oil, which was used in the next step without further purification. $^1$H NMR integration of the crude product revealed a 60:40 mixture of (*E*,*E*) and the other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2928, 2856, 1464, 1380, 1362, 1255 ($SiCH_3$), 1109, 1066 (SiO); $\delta_H$ ($CDCl_3$, 400 MHz) 0.07 [6H, s, Si(C$H_3$)$_2$], 0.91 [9H, s, SiC(C$H_3$)$_3$], 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.62 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.67* (3H, s), 1.72* (3H, s), 1.80-1.90 [2H, m, C(9)$H_2$], 1.94-2.20 [6H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$], 3.49 [2H, t, *J* 6.3, C(10)$H_2$], 3.44* (2H, d, *J* 6.5), 4.16* (2H, d, *J* 6.4), 4.19 [2H, d, *J* 6.3, C(1)$H_2$], 5.10-5.22 [1H, m, C(6)*H*], 5.25-5.35 [1H, m, C(2)*H*]; HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{35}Cl$ $(M\text{-}TBSO)^+$ 199.1249. Found 199.1243 $(M\text{-}TBSO)^-$; m/z (ESI+) 199.1 [$(C_{12}H_{20}{}^{35}Cl)^+$, 100%], 201.1 [$(C_{18}H_{35}{}^{37}Cl)^+$, 35%].

**Method B**

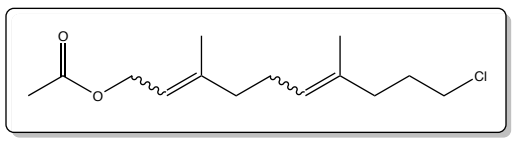
Imidazole (4 mg, 0.06 mmol) and *tert*-butyldimethylsilyl chloride (8 mg, 0.06 mmol) were sequentially added to a stirring solution of 10-chloro-3,7-dimethyldeca-2,6-dien-1-ol **80** (9 mg, 0.05 mmol) in dimethylformamide (3 mL) at 0 °C. The reaction mixture was stirred for 1 h before it was allowed to warm to room temperature and stirring was continued for an additional 5 h. The reaction was then quenched with water (5 mL) at 0 °C and extracted with diethyl ether (3 x 5 mL). The extract was washed with water (4 x 10 mL), saturated aqueous sodium hydrogen carbonate (5 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (2% ethyl acetate in hexane) to afford the title chloride **70** (9 mg, 59%) as a colourless oil. $^1$H NMR integration of the crude product revealed a 65:35 mixture of (*E*,*E*) and the other isomer(s)*. Spectroscopic characteristics were consistent with those previously described in **Method A** above.

### 4.5.2.10 Synthesis of 3,7-dimethyl-10-(methylsulfonyloxy)deca-2,6-dien-1-yl acetate 78 [59]



Methanesulfonyl chloride (0.07 mL, 0.10 g, 0.93 mmol) was added to a stirring solution of 10-hydroxy-3,7-dimethyldeca-2,6-dien-1-yl acetate **63** (0.18 g, 0.75 mmol) in dichloromethane (5 mL) at -10 $^{O}$C. Triethylamine (0.13 mL, 0.10 g, 0.85 mmol) was then added dropwise over 5 min. The mixture was stirred at -10 $^{o}$C for 2 h before quenching with aqueous sodium hydroxide (50%, 1 mL) and water (10 mL). The phases were separated, and the organic phase was washed with aqueous hydrochloric acid (1M, 5 mL), water (20 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title mesylate **78** (0.23 g, 95%) as a yellow oil, which was used directly in the next step without further purification; $\nu_{max}/cm^{-1}$ (film) 2938, 1736 (C=O), 1356, 1236, 1175 (S=O), 1024, 958, 927; $\delta_H$ ($CDCl_3$, 300 MHz) 1.61 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.69* (3H, s), 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.77* (3H, s), 1.78-1.92 [2H, m, C(9)$H_2$], 1.90-2.20 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.00 [3H, s, S(O)$_2$C$H_3$], 4.20 [2H, t, *J* 6.5, C(10)$H_2$], 4.21* (2H, t, *J* 6.5), 4.53-4.63 [2H, m, C$H_2$* and containing 2H, d, *J* 7.1, C(1)$H_2$], 5.02-5.22 [1H, m, C(6)*H*], 5.28-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 26.0 [$CH_2$, *C*(5)$H_2$], 27.2 [$CH_2$, *C*(9)$H_2$], 35.9 [$CH_2$, *C*(8)$H_2$], 37.2 [$CH_3$, S(O)$_2$*C*$H_3$], 39.2 [$CH_2$, *C*(4)$H_2$], 61.2 [$CH_2$, *C*(1)$H_2$], 69.6 [$CH_2$, *C*(10)$H_2$], 118.5 [CH, *C*(2)H], 125.0 [CH, *C*(6)H], 133.4 [C, *C*(7)], 141.7 [C, *C*(3)], 170.9 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.4 (*C*$H_3$), 23.0 (*C*$H_3$), 23.4 (*C*$H_3$), 25.9 (*C*$H_2$), 27.3 (*C*$H_2$), 27.4 (*C*$H_2$), 31.6 (*C*$H_2$), 31.9 (*C*$H_2$), 37.3 (*C*$H_3$), 39.5 (*C*$H_2$), 60.9 (*C*$H_2$), 61.1 (*C*$H_2$), 69.6 (*C*$H_2$), 118.4 (*C*H), 118.5 (*C*H), 119.3, (*C*H), 124.3 (*C*H), 124.8 (*C*H), 125.9 (*C*H), 133.4 (*C*), 133.8 (*C*), 141.8 (*C*), 142.2 (*C*); HRMS (ESI+): Exact mass calculated for $C_{13}H_{23}O_3S$ (M+H-HOAc)$^+$ 259.1363. Found 259.1360 (M+H-HOAc)$^+$; m/z (ESI+) 259.2 (M+H-HOAc)$^+$.

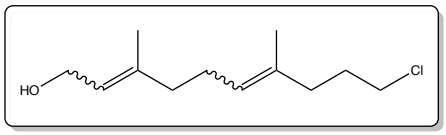
### 4.5.2.11 Synthesis of 10-chloro-3,7-dimethyldeca-2,6-dien-1-yl acetate 79



Lithium chloride (0.24 g, 5.65 mmol) was added to a stirring solution of 3,7-dimethyl-10-(methylsulfonyloxy)deca-2,6-dien-1-yl acetate **78** (0.17 g, 0.53 mmol) in dimethylformamide (4 mL) at room temperature. The resulting mixture was refluxed for 1h at 150 $^{o}$C with vigorous stirring before being cooled and poured into an iced mixture of aqueous hydrochloric acid (1M, 2 mL) and hexane (10 mL) with stirring. The aqueous layer was extracted with hexane (3 x 10 mL) and the combined organic phase was washed successively with

saturated aqueous sodium hydrogen carbonate (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2% ethyl acetate in hexane) to afford the title chloride **79** (91 mg, 62%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2935, 2857, 1740 (C=O), 1445, 1381, 1366, 1234, 1024, 956; $\delta_H$ ($CDCl_3$, 300 MHz) 1.62 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.71 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.77* (3H, s), 1.78-1.94 [2H, m, C(9)$H_2$], 1.95-2.25 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.50 [2H, t, *J* 6.7, C(10)$H_2$], 3.52* (2H, t, *J* 6.5), 4.52-4.64 [2H, m, C$H_2$* and containing 2H, d, *J* 7.2, C(1)$H_2$], 5.08-5.21 [1H, m, C(6)*H*], 5.28-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.1 [$CH_2$, *C*(5)$H_2$], 30.7 [$CH_2$, *C*(9)$H_2$], 36.6 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 44.6 [$CH_2$, *C*(10)$H_2$Cl] 61.4 [$CH_2$, *C*(1)$H_2$], 118.4 [CH, *C*(2)H], 125.0 [CH, *C*(6)H], 133.7 [C, *C*(7)], 142.1 [C, *C*(3)], 171.2 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.5 (*C*$H_3$), 23.2 (*C*$H_3$), 28.9 (*C*$H_2$) 30.8 (*C*$H_2$), 31.0 (*C*$H_2$), 39.7 (*C*$H_2$), 47.7 (*C*$H_2$), 125.8 (*C*H), 133.8 (*C*); HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{37}Cl$ $(M+H\text{-}HOAc)^+$ 199.1249. Found 199.1245 $(M+H\text{-}HOAc)^+$; m/z (ESI+) 199.4 [$(C_{14}H_{23}{}^{35}Cl)^+$, 100%], 201.3 [$(C_{12}H_{20}{}^{37}Cl)^+$, 34%].

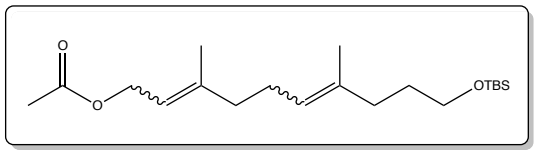
### 4.5.2.12 Synthesis of 10-chloro-3,7-dimethyldeca-2,6-dien-1-ol 80




Potassium carbonate (32 mg, 0.23 mmol) was added to a stirring solution of 10-chloro-3,7-dimethyldeca-2,6-dien-1-yl acetate **79** (20 mg, 0.08 mmol) in methanol (4 mL) at 0 $^oC$. The reaction mixture was allowed warm to room temperature and stirring was continued for 90 min. The reaction contents were poured into water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title chloride **80** (13.5 mg, 81%) as a light yellow oil, which was used without further purification. $\nu_{max}/cm^{-1}$ (film) 3339 (OH), 2959, 2920, 2856, 1444, 1307, 1002; $\delta_H$ ($CDCl_3$, 400 MHz) 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.75* (3H, s), 1.80-1.90 [2H, m, C(9)$H_2$], 1.98-2.20 [6H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$], 3.50 [2H, t, *J* 6.7, C(10)$H_2$], 3.51* (2H, t, *J* 6.6), 4.11* (2H, d, *J* 7.1), 4.16 [2H, d, *J* 6.9, C(1)$H_2$], 5.10-5.22 [1H, m, C(6)*H*], 5.38-5.45 [1H, m, C(2)*H*]; HRMS (ESI+): Exact mass calculated for $C_{12}H_{20}{}^{35}Cl$ $(M+H\text{-}H_2O)^+$ 199.1249. Found 199.1243 $(M+H\text{-}H_2O)^+$; m/z (ESI+) 199.4 [$(C_{12}H_{20}{}^{35}Cl)^+$, 100%], 201.4 [$(C_{12}H_{20}{}^{37}Cl)^+$, 36%].

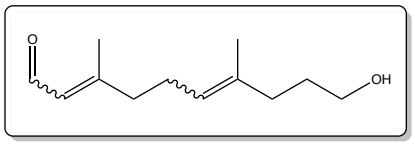
## 4.5.3 Synthesis of protected subunit B

### 4.5.3.1 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-yl acetate 89 [60]



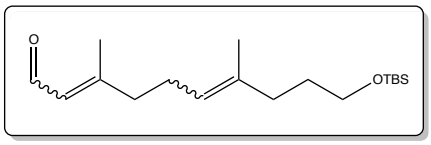

Imidazole (0.60 g, 8.9 mmol), 4-dimethylaminopyridine (70 mg, 5 mol%), and *tert*-butyldimethylsilyl chloride (0.98 g, 6.5 mmol) were added sequentially to a stirring solution of 10-hydroxy-3,7-dimethyldeca-2,6-dien-1-yl acetate **63** (1.42 g, 5.9 mmol) in dichloromethane (60 mL) at 0 °C. The solution was allowed to warm to room temperature over 1 h, and after an additional 30 min, water (20 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 25 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2-5% ethyl acetate gradient in hexanes) to afford the title silyl ether **89** (1.79 g, 85%) as a colourless oil. Spectroscopic characteristics were consistent with those reported in the literature;[60] $\nu_{max}/cm^{-1}$ (film) 2931 (CH), 2858, 1743 (CO), 1447, 1384, 1365, 1233 ($SiCH_3$), 1100 (SiO), 1024, 995, 837, 776; $\delta_H$ ($CDCl_3$, 400 MHz) 0.05 [6H, s $Si(CH_3)_2$], 0.90 [9H, s, $SiC(CH_3)_3$], 1.53-1.65 (5H, m, C(9)$H_2$ and $CH_2$* and containing 3H, s, C(11)$H_3$ or C(12)$H_3$], 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.77* (3H, s), 1.95-2.15 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)$CH_3$], 3.58 [2H, t, *J* 6.6 C(10)$H_2$], 3.59* (2H, t, *J* 6.4), 4.53-4.62 [2H, m, $CH_2$* and containing 2H, d, *J* 7.1, C(1)$H_2$], 5.10 [1H, t, *J* 6.5, C(6)*H*], 5.34 [1H, t, *J* 7.1, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.3 [$CH_3$, $Si(CH_3)_2$], 16.0 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.5 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 18.4 [C, $SiC(CH_3)_3$], 21.1 [$CH_3$, $C(O)CH_3$], 26.0 [$CH_3$, $SiC(CH_3)_3$] 26.2 [$CH_2$, *C*(5)$H_2$], 31.2 [$CH_2$, *C*(9)$H_2$], 35.8 [$CH_2$, *C*(8)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 62.9 [$CH_2$, *C*(10)$H_2$], 118.3 [CH, *C*(2)H], 123.7 [CH, *C*(6)H], 135.2 [C, *C*(7)], 142.2 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 18.3 (*C*), 22.6 ($CH_3$), 23.4 ($CH_3$), 23.5 ($CH_3$), 26.0 ($CH_3$), 26.6 ($CH_2$), 28.1 ($CH_2$), 31.3 ($CH_2$), 32.1 ($CH_2$), 39.8 ($CH_2$), 61.1 ($CH_2$), 63.0 ($CH_2$), 119.1 (*C*H), 123.4 (*C*H), 124.4 (*C*H), 135.5 (*C*), 135.6 (*C*), 142.2 (*C*); HRMS (ESI+): Exact mass calculated for $C_{20}H_{39}O_3Si$ $(M+H)^+$ 355.2668. Found 355.2659 $(M+H)^+$; m/z (ESI+) 355.4 $(M+H)^+$.

### 4.5.3.1 Synthesis of 10-hydroxy-3,7-dimethyldeca-2,6-dienal 107 [61]




3,7-dimethyldeca-2,6-diene-1,10-diol **64** (1.98 g, 9.96 mmol) was dissolved in dichloromethane (10 mL) and added to a stirring suspension of manganese dioxide (8.7 g, 99.6 mmol) in dichloromethane (90 mL) at room temperature. The reaction progress was monitored by TLC analysis. After 20 h, the mixture was filtered through a bed of celite and washed with dichloromethane (5 x 30 mL). The solvent was removed under reduced pressure to afford the title dienal **107** (1.93 g, 99%) as a light yellow oil, which was used in the next step without further purification. Spectroscopic characteristics are consistent with those previously reported;[61] Spectroscopic characteristics are consistent with those previously reported. $^1$H NMR integration indicated a 67:33 ratio of the (*E,E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 3419 (OH), 2937, 2862, 1668 (C=O), 1446, 1381, 1195, 1059; $\delta_H$ ($CDCl_3$, 300 MHz) 1.40-1.80 [5H, m, C(9)$H_2$ and C$H_3$* and containing 3H, s, C(12)$H_3$], 1.97-2.65 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(11)$H_3$], 3.55-3.68 [2H, m, C(10)$H_2$], 5.05-5.20 [1H, m, C(6)*H*], 5.89 [1H, d, *J* 8.1, C(2)*H*], 9.90* (1H, d, *J* 8.2), 9.99 [1H, d, *J* 8.1, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(12)$H_3$], 17.6 [$CH_3$, *C*(11)$H_3$], 25.6 [$CH_2$, *C*(5)$H_2$], 30.7 [$CH_2$, *C*(9)$H_2$], 35.8 [$CH_2$, *C*(8)$H_2$], 40.5 [$CH_2$, *C*(4)$H_2$], 62.6 [$CH_2$, *C*(10)$H_2$], 122.9 [CH, *C*(6)H], 127.5 [CH, *C*(2)H], 136.2 [C, *C*(7)], 163.8 [C, *C*(3)], 191.4 [C, *C*(1)HO]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 17.7 (*C*$H_3$), 23.3 (*C*$H_3$), 25.1 (*C*$H_2$), 25.4 (*C*$H_2$), 26.8 (*C*$H_2$), 28.0 (*C*$H_2$), 30.8 (*C*$H_2$), 32.5 (*C*$H_2$), 32.9 (*C*$H_2$), 35.8 (*C*$H_2$), 40.7 (*C*$H_2$), 62.6 (*C*$H_2$), 122.5 (*C*H), 123.4 (*C*H), 123.7 (*C*H), 127.4 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 136.3 (*C*), 136.9 (*C*), 137.0 (*C*), 163.9 (*C*), 191.0 (*C*H), 191.4 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{12}H_{21}O_2$ $(M+H)^+$ 197.1542. Found 197.1533 $(M+H)^+$; m/z (ESI+): 197.4 $(M+H)^+$.

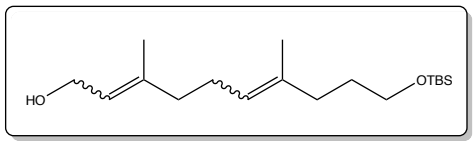
### 4.5.3.3 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dienal 108




Imidazole (0.96 g, 14.1 mmol), 4-dimethylamino pyridine (0.05 g, 0.44 mmol, 5 mol%), and *tert*-butyldimethylsilyl chloride (1.56 g, 10.3 mmol) were added sequentially to a stirring solution of 10-hydroxy-3,7-dimethyldeca-2,6-dienal **107** (1.71 g, 8.71 mmol) in dichloromethane (95 mL) at 0 °C. The solution was allowed to warm to room temperature and stirring was continued for an additional 90 min. Water (20 mL) was added and the reaction mixture was extracted with dichloromethane (4 x 30 mL). The organic layers were combined and washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to

afford the title silyl ether **108** (2.1 g, 78%) as a light yellow oil $^1$H NMR integration revealed a 67:33 mixture of (*E*,*E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2954, 2930, 2858, 1678 (C=O), 1463, 1444, 1255 (SiCH$_3$), 1194 1100 (SiO), 836, 776; $\delta_H$ ($CDCl_3$, 500 MHz) 0.05 [6H, s, Si(C*H*$_3$)$_2$], 0.90 [9H, s, SiC(C*H*$_3$)$_3$], 1.53-1.70 [5H, m, C(9)*H*$_2$ and C*H*$_3$* and containing 3H, s C(12)*H*$_3$], 1.95-2.10 [2H, m, C(4)*H*$_2$], 2.12-2.28 [7H, m, C(5)*H*$_2$ and C(8)*H*$_2$ and containing 3H, s C(11)*H*$_3$], 3.58 [2H, t, *J* 6.2, C(10)*H*$_2$], 3.59* (2H, t, *J* 6.6), 5.03-5.15 [1H, m, C(6)*H*], 5.88 [1H, d, *J* 8.0, C(2)*H*], 9.90* [1H, d, *J* 8.2], 9.99 [1H, d, *J* 8.0, C(1)*H*]; $\delta_C$ ($CDCl_3$, 125.8 MHz) -5.3 [CH$_3$, Si(*C*H$_3$)$_2$] 16.1 [CH$_3$, *C*(12)H$_3$], 17.6 [CH$_3$, *C*(11)H$_3$], 18.3 [C, Si*C*(CH$_3$)$_3$] 25.9 [CH$_2$, *C*(5)H$_2$], 26.0 [C, SiC(*C*H$_3$)$_3$], 31.1 [CH$_2$, *C*(9)H$_2$], 35.8 [CH$_2$, *C*(8)H$_2$], 40.6 [CH$_2$, *C*(4)H$_2$], 62.8 [CH$_2$, *C*(10)H$_2$], 122.5 [CH, *C*(6)H], 127.4 [CH, *C*(2)H], 136.4 [C, *C*(7)], 163.7 [C, *C*(3)], 191.2 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 14.1 (*C*H$_3$), 17.6 (*C*H$_3$), 18.3 (*C*), 23.3 (*C*H$_3$), 25.5 (*C*H$_2$), 25.7 (*C*H$_2$), 25.9 (*C*H$_3$), 27.1 (*C*H$_2$), 28.1 (*C*H$_2$), 31.2 (*C*H$_2$), 32.6 (*C*H$_2$), 40.9 (*C*H$_2$), 122.1 (*C*H), 123.3 (*C*H), 127.5 (*C*H), 128.6 (*C*H), 136.6 (*C*), 136.9 (*C*), 137.1 (*C*), 163.7 (*C*), 163.8 (*C*), 190.7 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{18}H_{35}O_2Si$ $(M+H)^+$ 311.2406. Found 311.2396 $(M+H)^+$; m/z (ESI+): 311.3 $(M+H)^+$.

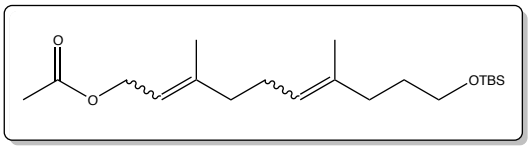
### 4.5.3.4 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-ol 109




Sodium borohydride (0.28 g, 7.5 mmol) was added in small portions to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dienal **108** (1.93 g, 6.22 mmol) in methanol (70 mL) at –10 °C. The reaction mixture was allowed to stir for 2 h at –10 °C before water (10 mL) was added. Solvent was removed under reduced pressure and the aqueous residue was saturated with sodium chloride and extracted with diethyl ether (4 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO4) and concentrated at reduced pressure to afford the title allylic alcohol **109** (1.32 g, 68 %) as a faint yellow oil, which was used without further purification. $^1$H NMR integration indicated a 67:33 ratio of the (*E,E*) and other isomer(s)*. Spectroscopic characteristics were consistent with those reported in the literature;[60] $\nu_{max}$/cm$^{-1}$ (film) 3336 (OH), 2928, 1472, 1386, 1255 (SiCH$_3$), 1100 (SiO), 1006, 835, 776; $\delta_H$ ($CDCl_3$, 300 MHz) 0.05 [6H, s Si(C*H*$_3$)$_2$], 0.90 [9H, s, SiC(C*H*$_3$)$_3$], 1.55-1.65 (5H, m, C(9)*H*$_2$ and containing 3H, s, C(11)*H*$_3$ or C(12)*H*$_3$], 1.68 [3H, s, C(11)*H*$_3$ or C(12)*H*$_3$], 1.75* (3H, s), 1.95-2.18 [6H, m, C(4)*H*$_2$ and C(5)*H*$_2$ and C(8)*H*$_2$], 3.58 [2H, t, *J* 6.6, C(10)*H*$_2$], 3.59* (2H, t, *J* 6.5), 4.10* (2H, d, *J* 7.2), 4.15 [2H, d, *J* 6.9, C(1)*H*$_2$], 5.11 [1H, t, *J* 6.7, C(6)*H*], 5.42 [1H, t, *J* 6.9, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.3 [CH$_3$, Si(*C*H$_3$)$_2$], 16.0 [CH$_3$, *C*(11)H$_3$ or *C*(12)H$_3$], 16.3 [CH$_3$, *C*(11)H$_3$ or *C*(12)H$_3$], 18.4 [C, Si*C*(CH$_3$)$_3$], 26.0 [CH$_3$, SiC(*C*H$_3$)$_3$] 26.3 [CH$_2$, *C*(5)H$_2$], 31.2 [CH$_2$, *C*(9)H$_2$], 35.8 [CH$_2$, *C*(8)H$_2$],

39.5 [$CH_2$, *C*(4)$H_2$], 59.4 [$CH_2$, *C*(1)$H_2$], 62.9 [$CH_2$, *C*(10)$H_2$], 123.4 [CH, *C*(2)H], 124.6 [CH, *C*(6)H], 135.1 [C, *C*(7)], 139.7 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 16.3 (*C*$H_3$), 18.3 (*C*), 23.4 (*C*$H_3$), 26.1 (*C*$H_3$), 26.5 (*C*$H_2$), 28.1 (*C*$H_2$), 31.3 (*C*$H_2$), 32.0 (*C*$H_2$), 39.8 (*C*$H_2$), 59.0 (*C*$H_2$), 63.0 (*C*$H_2$), 123.6 (*C*H), 123.8 (*C*H), 124.4 (*C*H), 135.4 (*C*); HRMS (ESI+): Exact mass calculated for $C_{18}H_{37}O_2Si$ $(M+H)^+$ 313.2563. Found 313.2555 $(M+H)^+$; m/z (ESI+): 313.4 $(M+H)^+$.

### 4.5.3.5 Synthesis of 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-yl acetate 89 [19]

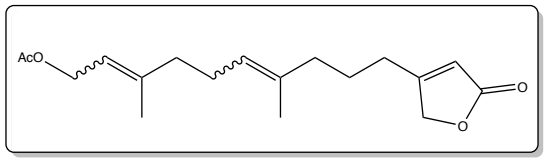



10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-ol **109** (1.19 g, 3.81 mmol) was dissolved in dichloromethane (30 mL) and treated sequentially with triethyl amine (0.8 mL, 0.58 g, 5.71 mmol), 4-dimethylaminopyridine (5 mg, 1 mol%), and acetic anhydride (0.43 mL, 0.47 g 4.6 mmol) at 0 °C. After 5 min, the reaction mixture was poured into water (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were then washed with water (4 x 30 mL), brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3% ethyl acetate gradient in hexanes) to afford the title acetylated product **89** (1.29 g, 96%) as a colourless oil. Spectroscopic characterstics are consistent with those previously reported in ***Section 4.5.3.1***.[60]

# 4.6 Coupling of subunit B and subunit C

## 4.6.1 Attempted coupling of acetate protected subunit B with subunit C

### 4.6.1.1 Attempted synthesis of 4-(10-acetoxy-4,8-dimethyldeca-4,8-dien-1-yl)furan-2(5*H*)-one 67

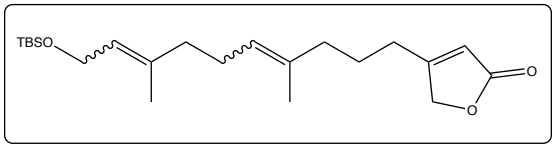



Freshly ground magnesium (43 mg, 1.8 mmol) was flame heated, allowed to cool to room temperature and activated by successive addition of an iodine crystal and 1,2-dibromoethane (2-3 drops) in diethyl ether at room temperature. In a separate dry flask was added 10-bromo-3,7-dimethyldeca-2,6-dien-1-yl acetate **66** (0.30 g, 1.0 mmol) in diethyl ether (3 mL). Approximately one-third of this solution was added to the dry magnesium powder along with additional 1,2-dibromoethane (2 drops). The remaining bromide solution was added at such a rate as to maintain the reflux throughout the addition (approx. 15 min.). Using external heating, the solution was kept at reflux for 3 h. On cooling to room temperature, the freshly prepared Grignard reagent was transferred into a separate flask containing a stirring suspension of copper(I) iodide (95 mg, 0.5 mmol) in diethyl ether (2 mL) at 0 $^{o}$C. The solution was stirred for 1 h at 0 $^{o}$C before cooling to -78 $^{o}$C. A solution of 5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate **57** (146 mg, 0.6 mmol) in diethyl ether (2 mL) was then added dropwise over 10 mins. Following complete addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. $^{1}$H NMR analysis of the crude product revealed that the desired cross coupled product **67** was not formed. The crude residue was subsequently purified by column chromatography on silica gel (5-10% ethyl acetate gradient in hexanes). The acetate starting material **66** underwent putative degradation following Grignard synthesis to a complex unidentifiable product(s). The triflate starting material **57** was isolated unchanged with spectroscopic data consistent with those previously reported in ***Section 4.4.2.1***.

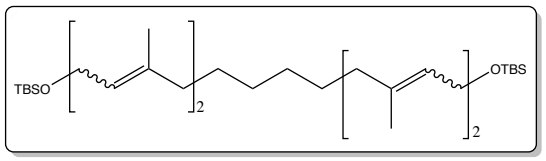
## 4.6.2 Attempted coupling of TBS protected subunit B with subunit C

### 4.6.2.1 Attempted synthesis of 4-(10-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethyldeca-4,8-dien-1-yl)furan-2(5H)-one 83

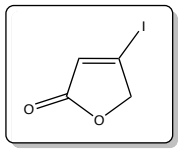
**Method A: Conjugate addition using iodide 77.**[62,63]




Freshly ground magnesium (15 mg, 0.62 mmol) was flame heated, allowed to cool to room temperature and activated by successive addition of an iodine crystal and 1,2-dibromoethane (2 drops) in diethyl ether (2 mL) under inert nitrogen atmosphere. In a separate dry flask was added 10-iodo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **77** (0.2 g, 0.47 mmol) in diethyl ether (3 mL). Approximately one-third of this solution was added to the activated magnesium powder at room temperature along with additional 1,2-dibromoethane (2 drops). The remaining iodide **77** was added at such a rate as to maintain the reflux throughout the addition. Using external heating, the solution was kept at reflux (40 $^{o}$C) for 3 h. The solution was cooled to room temperature and then transferred via syringe into a separate reaction flask containing a stirring suspension of copper(I) iodide (45 mg, 0.24 mmol) in diethyl ether (3 mL) at 0 $^{o}$C. The solution was stirred for 1 h at 0 $^{o}$C before being cooled to -78 $^{o}$C. A solution of trifluoro-methanesulfonic acid,5-oxo-2,5-dihydrofuran-3-yl ester **57** (48 mg, 0.21 mmol) in diethyl ether (4 mL) was added dropwise over 10 min. The solution was stirred for 30 mins at -78 $^{o}$C before the reaction was allowed to warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the reaction mixture was extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a two-component mixture consisting of the Wurtz coupled product **84** and 4-iodofuran-2(5*H*)-one **86** in a 55:45 ratio of products respectively. $^{1}$H NMR analysis revealed complete consumption of starting material in addition to confirming the unsuccessfully synthesis of the desired cross-coupled product **83**. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) and the two components where isolated and characterized as follows.




The least polar fraction, the Wurtz coupled product **84** was isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2957, 2930, 2858, 1463, 1254, 1065, 836, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 0.07 [12H, s, 2 x Si(C$H_3$)$_2$], 0.91 [18H, s, 2 x SiC(C$H_3$)$_3$], 1.16-1.48 [8H, m, 2 x {C(9)$H_2$ and C(10)$H_2$}], 1.58 [6H, s, 2 x {C(11)$H_3$ or C(12)$H_3$}], 1.62 [6H, s, 2 x {C(11)$H_3$ or C(12)$H_3$}], 1.66* (6H, s), 1.72* (6H, s), 1.88-2.18 [12H, m, 2 x {C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$}], 4.13-4.24 [4H, m, C$H_2$* and containing 2H, d, *J* 6.6, 2 x C(1)$H_2$], 5.03-5.20 [2H, m, 2 x C(6)*H*], 5.22-5.36 [2H, m, 2 x C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.0 [$CH_3$, Si(*C*$H_3$)$_2$], 15.8 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.3 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 18.4 [C, Si*C*(CH$_3$)$_3$], 26.0 [$CH_2$, SiC(*C*$H_3$)$_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 28.0 [$CH_2$, *C*(9)$H_2$], 29.7 [$CH_2$, *C*(10)$H_2$], 37.8 [$CH_2$, *C*(4)$H_2$ or *C*(8)$H_2$], 41.8 [$CH_2$, *C*(4)$H_2$ or *C*(8)$H_2$], 60.3 [$CH_2$, *C*(1)$H_2$], 123.9 [CH, *C*(2)H], 124.5 [CH, *C*(6)H], 135.2 [C, *C*(7)], 136.8 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* - 5.4 (*C*$H_3$), 14.0 (*C*$H_3$), 14.1 (*C*$H_3$), 15.9 (*C*$H_3$), 16.0 (*C*$H_3$), 21.0 (*C*$H_2$), 21.1 (*C*$H_2$), 22.7 (*C*$H_3$), 23.3 (*C*$H_3$) 23.4 (*C*$H_3$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 28.0 (*C*$H_2$), 29.2 (*C*$H_2$), 29.3 (*C*$H_2$), 29.4 (*C*$H_2$), 29.5 (*C*$H_2$), 29.6 (*C*$H_2$), 31.8 (*C*$H_2$), 31.9 (*C*$H_2$), 32.3 (*C*$H_2$), 33.8 (*C*$H_2$), 39.7 (*C*$H_2$), 39.8 (*C*$H_2$), 44.1 (*C*$H_2$), 60.0 (*C*$H_2$), 123.5 (*C*H), 123.8 (*C*H), 124.4 (*C*H), 124.7 (*C*H), 125.2 (*C*H), 135.5 (*C*), 135.7 (*C*), 135.8 (*C*) 136.9 (*C*), 137.4 (*C*); HRMS (ESI+): Exact mass calculated for $C_{30}H_{55}OSi^+$ (M-TBSO)$^-$ 459.4017. Found 459.4046 (M-TBSO)$^-$.




The most polar fraction, 4-iodofuran-2(5*H*)-one **86** was isolated as white crystalline needles. Spectroscopic characteristics are consistent with those reported in the literature.[64] mp 108–111 °C, *lit*.[64] 109-110 °C; $\nu_{max}/cm^{-1}$ (KBr) 2924 (CH), 2852, 1774 (C=O), 1728 (C=O), 1585 (C=C), 1442, 1249, 1153, 1001, 856; $\delta_H$ ($CDCl_3$, 300 MHz) 4.86 [2H, d, *J* 2.0, C(5)$H_2$], 6.58 [1H, t, *J* 2.0, C(3)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 78.8 [$CH_2$, *C*(5)$H_2$], 118.0 [C, *C*(4)], 129.5 [CH, *C*(3)H], 171.1 [C, *C*(2)]. HRMS (ESI+): Exact mass calculated for $C_4H_4{}^{127}IO_2$ $(M+H)^+$ 210.9256. Found 210.9280 $(M+H)^+$; m/z (ESI+): 211.2 $(M+H)^+$.

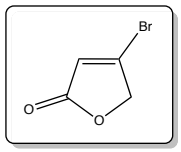
**Method B: Conjugate addition using a bromide 69/chloride 70 mixture.[62,63]**

The attempted synthesis of the title compound **83** was carried out following the procedure described above in **Method A** using magnesium powder (46 mg, 1.9 mmol), a mixture of 10-bromo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **69** and 10-chloro-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **70** in a 68:32 ratio (0.22 g, 0.62 mmol), copper(I) iodide (59 mg, 0.31 mmol), trifluoro-methanesulfonic acid,5-oxo-2,5-dihydrofuran-3-yl ester **57** (63 mg, 0.27 mmol) in diethyl ether to afford four-component mixture consisting of the Wurtz coupled product **84**, 4-

bromofuran-2(5*H*)-one **85**, 4-iodofuran-2(5*H*)-one **86** and unreacted chloride starting material **70** in a 31:35:6:28 ratio respectively. $^1$H NMR analysis revealed complete consumption of bromide starting material **69** in addition to confirming the unsuccessfully synthesis of the desired cross coupled product **83**. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes).

The least polar fraction, the Wurtz coupled product **84** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A** above.

The less polar fraction, **70** was isolated pure and spectroscopic characteristics were consistent with those previously described in ***Section 4.5.2.9***.




The more polar fraction, 4-bromofuran-2(5*H*)-one **85** was isolated as white crystalline needles. Spectroscopic characteristics are consistent with those reported in the literature.[65,66] mp 74-76 °C *lit*.[66] 76 °C; $\nu_{max}$/cm$^{-1}$ (KBr) 2922 (CH), 2857, 1776 (C=O), 1749 (C=O), 1585 (C=C); $\delta_H$ ($CDCl_3$, 300 MHz) 4.87 [2H, d, *J* 1.9, C(5)$H_2$], 6.36 [1H, t, *J* 1.9, C(3)*H*].

**Method C: Conjugate addition using the bromide 69.[62,63]**

The attempted synthesis of the title compound **83** was carried out following the procedure described above in **Method A** using freshly ground magnesium (18 mg, 0.72 mmol), 10-bromo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **69** (0.20 g, 0.53 mol), copper(I) iodide (51 mg, 0.27 mmol), trifluoro-methanesulfonic acid, 5-oxo-2,5-dihydrofuran-3-yl ester **57** (54 mg, 0.23 mmol) in diethyl ether to afford four-component mixture consisting of the Wurtz coupled product **84**, 4-bromofuran-2(5*H*)-one **85**, 4-iodofuran-2(5*H*)-one **86** and unreacted bromide starting material **69** in a 45:51:4 ratio respectively. $^1$H NMR confirmed the unsuccessfully synthesis of the desired cross coupled product **83**. The crude residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes).

The least polar fraction, the Wurtz coupled product **84** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A** above.

The most polar fraction consisted of a co-eluted mixture of 4-bromofuran-2(5*H*)-one **85** and 4-iodofuran-2(5*H*)-one **86** isolated as white crystalline needles. Spectroscopic characteristics were consistent with those previously described above.

**Method D: Conjugate addition using the bromide 69.**[62,63]

Magnesium turnings (29 mg, 1.2 mmol) were thoroughly dried using a heat gun before been vigorously stirred overnight under inert nitrogen atmosphere in the absence of solvent. The magnesium was subsequently activated by the addition of an iodine crystal and 1,2-dibromoethane in tetrahydrofuran (2 mL) at room temperature. The contents of the flask were subjected to sonication for 30 mins before heating to reflux (70 $^{o}$C) for an additional 1 h. A solution of 10-bromo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **69** (0.13 g, 0.35 mmol) in tetrahydrofuran was then added at -10 $^{o}$C over 30 mins in tetrahydrofuran (1 mL) and the contents were further stirred at 0 $^{o}$C for 6 h. The solution was warmed to room temperature and then transferred via syringe into a separate flask containing a stirring suspension of copper(I) iodide (17 mg, 0.09 mmol) in tetrahydrofuran (3 mL) at 0 $^{o}$C. The solution was stirred for 1 h at 0 $^{o}$C before being cooled to -78 $^{o}$C. A solution of **57** (18 mg, 0.08 mmol) in tetrahydrofuran (4 mL) was added dropwise over 10 min. The solution was stirred for 30 mins at -78 $^{o}$C before the reaction was allowed to warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the reaction mixture was extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a four-component mixture consisting of the Wurtz coupled product **84**, 4-bromofuran-2(5*H*)-one **85**, 4-iodofuran-2(5*H*)-one **86** and bromide starting material **69** in a 12:35:7:46 ratio respectively. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes).

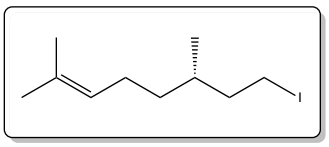
The least polar fraction, the Wurtz coupled product **84** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A** above.

The less polar fraction, 10-bromo-1-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-diene **69** was isolated pure and spectroscopic characteristics were consistent with those previously described in ***Section 4.5.2.6***.

The most polar fraction consisted of a co-eluted mixture of 4-bromofuran-2(5*H*)-one **85** and 4-iodofuran-2(5*H*)-one **86** isolated as white crystalline needles. Spectroscopic characteristics were consistent with those previously described above.

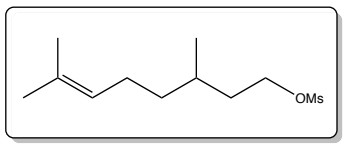
## 4.6.3 Synthesis of citronellyl halides

### 4.6.3.1 Synthesis of (*S*)-(+)-citronellyl iodide 97 [67]



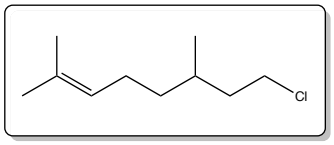
Sodium iodide (1.71 g, 11.4 mmol) was added to a stirring solution of (*S*)-(+)-citronellyl bromide **96** (1.0 g, 4.56 mmol) in acetone (10 mL) and the resulting suspension was vigorously stirred in the dark at room temperature overnight. After this time, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in hexane (20 mL) and the solution was washed with saturated aqueous sodium thiosulfate (10 mL), water (3 x 20 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a (*S*)-(+)-citronellyl iodide **97** (1.0 g, 83%) as a colourless oil, which was used in the next step without further purification. Spectroscopic characteristics are consistent with those previously reported;[68] $\nu_{max}/cm^{-1}$ (film) 2964, 2925, 2859, 1451, 1378, 1189; $\delta_H$ ($CDCl_3$, 400 MHz) 0.89 [3H, d, *J* 6.6, C(9)$H_3$], 1.11-1.40 [2H, m, C(4)$H_2$] 1.50-1.72 [8H, m, C(2)$H_2$ and containing 2 x 3H, s C(8)$H_3$ and C(9)$H_3$], 1.80-2.10 [3H, m, C(3)*H* and C(5)$H_2$], 3.12-3.29 [2H, m C(1)$H_2$], 5.09 [1H, t, *J* 7.1, C(6)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 5.1 [$CH_2$, *C*(1)$H_2$], 17.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 18.7 [$CH_3$, *C*(9)$H_3$], 25.3 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 33.6 [CH, *C*(3)H], 36.3 [$CH_2$, *C*(4)$H_2$], 40.9 [$CH_2$, *C*(2)$H_2$], 124.5 [CH, *C*(6)H], 131.5 [C, *C*(7)]; HRMS (ESI+): Exact mass calculated for $C_{10}H_{20}{}^{127}I$ $(M+H)^+$ 267.0610. Found 267.0603 $(M+H)^+$.

### 4.6.3.2 Synthesis of citronellyl chloride 99 [59,69,70]




Methanesulfonyl chloride (0.96 mL, 1.41 g, 12.3 mmol) was added to a stirring solution of citronellol **27** (1.7 g, 10.9 mol) in dichloromethane (21 mL) at room temperature. The reaction mixture was cooled to -10 $^oC$ and triethylamine (1.9 mL, 1.37 g, 13.5 mmol) was added dropwise over 10 min. After 1 h at -10 $^OC$, the reaction was quenched with aqueous sodium hydroxide (50%, 10 mL) and water (20 mL). The phases were separated, and the organic phase was washed with aqueous hydrochloric acid (1M, 20 mL), water (20 mL) brine (20 mL) and dried ($MgSO_4$). The reaction mixture was concentrated under reduced pressure to afford citronellyl mesylate **98** (2.08, 82%) as a yellow oil, which was used in the next step without further purification. Spectroscopic characteristics are consistent with those previously reported;[59] $\nu_{max}/cm^{-1}$ (film) 2966, 2918, 1459, 1355 (S=O), 1176 (S=O), 975, 944, 891, 824; $\delta_H$ ($CDCl_3$, 300 MHz) 0.94 [3H, d, *J* 6.4, C(9)$H_3$], 1.10-1.44 [2H, m, C(2)$H_2$ or C(4)$H_2$] 1.50-1.72 [8H, m, C(2)$H_2$ or C(4)$H_2$ and containing 2 x 3H, s C(8)$H_3$ and C(9)$H_3$], 1.72-1.87 [1H, m, C(3)*H*],1.87-2.10 [2H, m, C(5)$H_2$], 3.00 [3H, s,

$SO_2CH_3$], 4.19-4.32 [2H, m C(1)$H_2$], 5.08 [1H, mt, *J* 7.1, C(6)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 19.2 [$CH_3$, *C*(9)$H_3$], 25.3 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 29.0 [CH, *C*(3)H], 35.9 [$CH_2$, *C*(2)$H_2$ or *C*(4)$H_2$], 36.8 [$CH_2$, *C*(2)$H_2$ or *C*(4)$H_2$], 37.4 [$CH_3$, $SO_2CH_3$], 68.5 [$CH_2$, *C*(1)$H_2$], 124.3 [CH, *C*(6)H], 131.6 [C, *C*(7)].

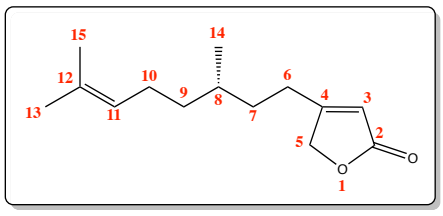



Lithium chloride (3.62 g, 85.4 mmol) was added to a stirring solution of citronellyl mesylate **98** (2.0 g, 8.54 mmol) in dimethylformamide (30 mL) at room temperature. The resulting mixture was vigorously stirred at refluxed (150 $^oC$) for 1 h before being cooled and poured into an iced mixture of aqueous hydrochloric acid (1M, 20 mL) and hexane (40 mL). The aqueous layer was extracted with hexane (3 x 20 mL) and the combined organic phase was washed with saturated sodium hydrogen carbonate (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give the title chloride **99** (1.30 g, 87%) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[69,70] $\nu_{max}/cm^{-1}$ (film) 2965, 2928, 2874, 1452, 1379, 1287, 727, 659; $\delta_H$ ($CDCl_3$, 400 MHz) 0.91 [3H, d, *J* 6.5, C(10)$H_3$], 1.10-1.40 [2H, m, C(2)$H_2$ or C(4)$H_2$] 1.50-1.74 [8H, m, C(2)$H_2$ or C(4)$H_2$ and containing 2 x 3H, s C(8)$H_3$ and C(9)$H_3$], 1.74-1.86 [1H, m, C(3)*H*], 1.90-2.08 [2H, m, C(5)$H_2$], 3.48-3.63 [2H, m C(1)$H_2$], 5.09 [1H, mt, *J* 7.1, C(6)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 19.0 [$CH_3$, *C*(9)$H_3$], 25.3 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(8)$H_3$ or *C*(10)$H_3$], 30.1 [CH, *C*(3)H], 36.7 [$CH_2$, *C*(4)$H_2$], 39.7 [$CH_2$, *C*(2)$H_2$], 43.3 [$CH_2$, *C*(1)$H_2$], 124.5 [CH, *C*(6)H], 131.4 [C, *C*(7)].

## 4.6.4 Synthesis of β-substituted butenolides

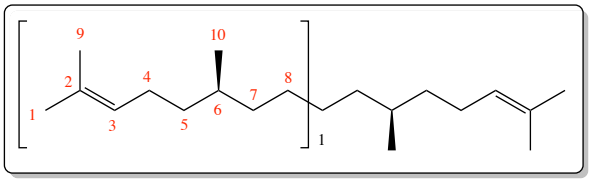
### 4.6.4.1 Synthesis of (*S*)-4-(3,7-dimethyloct-6-en-1-yl)furan-2(5*H*)-one 100

**Method A: Grignard $sp^3$-$sp^2$ cross coupling using (*S*)-(+)-citronellyl iodide 97.[62,63]**




Freshly ground magnesium (0.05 g, 2.1 mmol) was flame heated, allowed to cool to room temperature and activated by successively addition of an iodine crystal and 1,2-dibromoethane (2 drops) in diethyl ether (2 mL) under inert nitrogen atmosphere. A solution of (*S*)-(+)-citronellyl iodide **97** (0.5 g, 1.9 mmol) in diethyl ether (4 mL) was added at such a rate as to maintain the reflux throughout the addition (*approx*. 20 min). Using external heating, the solution was kept at reflux for 3 h. On cooling to room temperature, the freshly prepared Grignard reagent was transferred via syringe

into a separate reaction flask containing a stirring suspension of copper(I) iodide (0.150 g, 0.77 mmol) in diethyl ether (4 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before being cooled to -78 °C. A solution of 5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate **57** (0.16 g, 0.67 mmol) in diethyl ether (4 mL) was added dropwise over 10 min. Following addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a three-component mixture consisting of the desired cross coupled product **100**, 4-iodofuran-2(5*H*)-one **86** and the Wurtz coupled product **102** in a 14:30:56 ratio of products respectively. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give the title lactone **100** (38 mg, 26%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2925 (CH), 2859, 1780 (C=O), 1751 (C=O), 1638 (C=C), 1450, 1170; 1032; $\delta_H$ ($CDCl_3$, 300 MHz) 0.93 [3H, d, *J* 6.3, C(14)$H_3$], 1.10-1.66 [8H, m, C(7)$H_2$ and C(8)*H* and C(9)$H_2$ and containing 3H, s C(13)$H_3$ or C(15)$H_3$], 1.69 [3H, s, C(13)$H_3$ or C(15)$H_3$], 1.85-2.10 [2H, m, C(10)$H_2$], 2.35-2.50 [2H, m, C(6)$H_2$], 4.73 [2H, d, *J* 1.8, C(5)$H_2$], 5.08 [1H, td, *J* 7.1, 1.4, C(11)*H*], 5.81-5.85 [1H, m, C(3)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.7 [$CH_3$, *C*(13)$H_3$ or *C*(15)$H_3$], 19.2 [$CH_3$, *C*(14)$H_3$], 25.4 [$CH_2$, *C*(10)$H_2$], 25.7 [$CH_3$, *C*(13)$H_3$ or *C*(15)$H_3$], 26.2 [$CH_2$, *C*(6)$H_2$], 32.1 [CH, *C*(8)H], 34.3 [$CH_2$, *C*(7)$H_2$], 36.7 [$CH_2$, *C*(9)$H_2$], 73.0 [$CH_2$, *C*(5)$H_2$], 115.3 [CH, *C*(3)H], 124.3 [CH, *C*(11)H], 131.6 [C, *C*(12)], 170.8 [C, *C*(4)], 174.1 [C, *C*(2)]; HRMS (ESI+): Exact mass calculated for $C_{14}H_{23}O_2$ $(M+H)^+$ 223.1698. Found 223.1685 $(M+H)^+$; m/z (ESI+) 223.4 $(M+H)^+$.




The least polar fraction, (6*S*,11*S*)-2,6,11,15-tetramethylhexadeca-2,14-diene **102** was isolated as a non-viscous colourless oil.[71] Found: C, 85.11%; H, 13.64%, $C_{10}H_{20}$ requires C, 86.25%; H, 13.75%; $\nu_{max}/cm^{-1}$ (film) 2964, 2926, 2856, 1458, 1377; $\delta_H$ ($CDCl_3$, 300 MHz) 0.85 [6H, d, *J* 6.4, 2 x C(10)$H_3$] 1.03-1.46 [14H, m, 2 x {C(5)$H_2$ and C(6)*H* and C(7)$H_2$ and C(8)$H_2$}], 1.60 [6H, s, 2 x {C(1)$H_3$ or C(9)$H_3$}], 1.68 [6H, s, 2 x {C(1)$H_3$ or C(9)$H_3$}], 1.82-2.10 [4H, m, 2 x C(4)$H_2$], 5.11 [2H, t, *J* 7.1, 2 x C(6)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.6 (*C*$H_3$), 19.6 (*C*$H_3$), 25.6 [$CH_2$, *C*(4)$H_2$], 25.7 (*C*$H_3$), 27.4 [$CH_2$, *C*(8)$H_2$], 32.4 [$CH_2$, *C*(6)$H_2$], 37.0 [$CH_2$, *C*(5)$H_2$ or *C*(7)$H_2$], 37.2 [$CH_2$, *C*(5)$H_2$ or *C*(7)$H_2$], 125.1 [CH, *C*(3)H], 130.9 [C, *C*(2)]. m/z (ESI+) 320.3 $(M+H)^+$. The HRMS value was outside acceptable limits and thus omitted from the experimental.

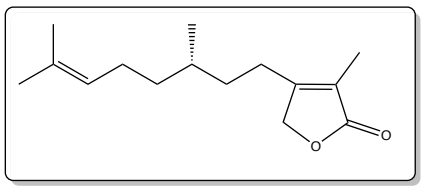
The most polar fraction, 4-iodofuran-2(5*H*)-one **86** was isolated as white crystalline solid. Spectroscopic characteristics were consistent with those previously described in ***Section 4.6.2.1***.

**Method B: Grignard $sp^3$-$sp^2$ cross coupling using (*S*)-(+)-citronellyl bromide 96.**[62,63,72]

Freshly ground magnesium (0.08 g, 3.1 mmol) was flame heated, allowed to cool to room temperature and activated by successively addition of an iodine crystal and 1,2-dibromoethane (2 drops) in diethyl ether (2 mL) under inert nitrogen atmosphere. A solution of (*S*)-(+)-citronellyl bromide **96** (0.5 g, 1.9 mmol) in diethyl ether (3 mL) was added dropwise at room temperature and the solution was stirred for an additional 6 h. On cooling to room temperature, the freshly prepared Grignard reagent was transferred via syringe into a separate reaction flask containing a stirring suspension of copper(I) iodide (0.217 g, 1.14 mmol) in diethyl ether (4 mL) at 0 $^{o}$C. The reaction mixture was stirred for 1 h at 0 $^{o}$C before being cooled to -78 $^{o}$C. A solution of 5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate **57** (0.23 g, 1.0 mmol) in diethyl ether (4 mL) was added dropwise over 10 min. Following addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a four-component mixture consisting of the desired cross coupled product **100**, 4-iodofuran-2(5*H*)-one **86**, 4-bromofuran-2(5*H*)-one **85** and the Wurtz coupled product **102** in a 18:24:10:48 ratio. The residue was purified by column chromatography on silica gel (5-10% ethyl acetate gradient in hexanes) to give the title lactone **100** (72 mg, 38%) as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A** above.

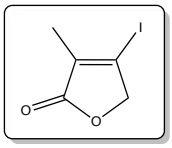
The most polar fraction consisted of a co-eluted mixture of 4-bromofuran-2(5*H*)-one **85** and 4-iodofuran-2(5*H*)-one **86** isolated as white crystalline needles. Spectroscopic characteristics were consistent with those previously described in ***Section 4.6.2***.1.

### 4.6.4.2 Synthesis of (*S*)-4-(3,7-dimethyloct-6-en-1-yl)-3-methylfuran-2(5*H*)-one 101 [62]



The title compound was prepared according to the procedure described for **100** using magnesium (0.08 g, 3.1 mmol), (*S*)-(+)-citronellyl bromide **96** (0.50 g, 2.28 mmol), copper(I) iodide (0.22 g, 1.14 mmol), 4-methyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate **58** (0.250 g, 0.99 mmol) in diethyl ether (14 mL) to afford a three-component mixture consisting of the desired cross coupled product **101**, the Wurtz coupled product **102** and 4-iodo-3-methylfuran-2(5*H*)-one **103** in a 60:22:18 ratio of products respectively. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to give

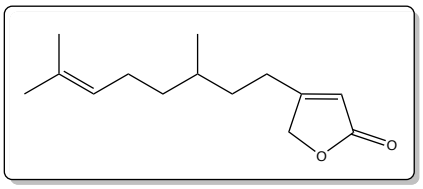
the title lactone **101** (157 mg, 67%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2924, 2859, 1748 (C=O), 1678 (C=C), 1453, 1379, 1339, 1179, 1033, 759, 734; $\delta_H$ ($CDCl_3$, 300 MHz) 0.93 [3H, d, *J* 6.3, C(14)$H_3$], 1.10-1.60 [5H, m, C(7)$H_2$ and C(8)*H* and C(9)$H_2$], 1.61 [3H, s, C(13)$H_3$ or C(15)$H_3$], 1.69 [3H, s, C(13)$H_3$ or C(15)$H_3$], 1.83 [3H, s, C(3)C$H_3$], 1.85-2.10 [2H, m, C(10)$H_2$], 2.30-2.50 [2H, m, C(6)$H_2$], 4.65 [2H, brs, C(5)$H_2$], 5.08 [1H, td, *J* 7.1, 1.4, C(11)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 8.5 [$CH_3$, C(3)*C*$H_3$], 17.7 [$CH_3$, *C*(13)$H_3$ or *C*(15)$H_3$], 19.2 [$CH_3$, *C*(14)$H_3$], 24.7 [$CH_2$, *C*(6)$H_2$], 25.4 [$CH_2$, *C*(10)$H_2$], 25.7 [$CH_3$, *C*(13)$H_3$ or *C*(15)$H_3$], 32.3 [CH, *C*(8)H], 34.6 [$CH_2$, *C*(7)$H_2$], 36.6 [$CH_2$, *C*(9)$H_2$], 71.4 [$CH_2$, *C*(5)$H_2$], 122.7 [CH, *C*(3)$CH_3$], 124.3 [CH, *C*(11)H], 131.6 [C, *C*(12)], 160.7 [C, *C*(4)], 175.6 [C, *C*(2)]; HRMS (ESI+): Exact mass calculated for $C_{15}H_{25}O_2$ $(M+H)^+$ 237.1855. Found 237.1851 $(M+H)^+$. m/z (ESI+) 237.2 $(M+H)^+$.



The most polar fraction, 4-iodo-3-methylfuran-2(5*H*)-one **103** (21 mg) was isolated as white crystalline needles. 1774 (C=O), 1728 (C=O), $\delta_H$ ($CDCl_3$, 300 MHz) 1.94 [3H, t, *J* 2.1, C(3)C$H_3$], 4.78 [2H, q, *J* 2.1, C(5)$H_2$]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 12.4 [$CH_3$, C(3)*C*$H_3$], 76.3 [$CH_2$, *C*(5)$H_2$], 113.9 [C, *C*(4)], 135.4 [C, *C*(3)], 170.4 [C, *C*(2)]. HRMS (ESI+): Exact mass calculated for $C_5H_6IO_2$ $(M+H)^+$ 224.9334. Found 224.9349 $(M+H)^+$; m/z (ESI+) 224.9 $(M+H)^+$.

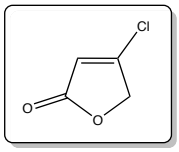
The least polar fraction, (6*S*,11*S*)-2,6,11,15-tetramethylhexadeca-2,14-diene **102** was isolated as a colourless non-viscous oil. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.6.4.1***.

### 4.6.4.3 Synthesis of 4-(3,7-dimethyloct-6-en-1-yl)furan-2(5H)-one 104 [62,63]



The title compound was prepared according to the procedure described for **100** using magnesium (0.150 g, 6.13 mmol) citronellyl chloride **99** (1.0 g, 5.74 mmol), copper(I) iodide (0.420 g, 2.20 mmol), 5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate **57** (0.40 g, 1.91 mmol) in tetrahydrofuran (20 mL) to afford a three-component mixture consisting of the desired cross coupled product **104**, the Wurtz coupled product **105**, and 4-chlorofuran-2(5*H*)-one **106** in a 14:69:17 ratio of products respectively. The residue was purified by column chromatography on silica gel (5-10% ethyl acetate gradient in hexanes) to give the title lactone **104** (112 mg, 26%) as a colourless oil. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.6.4.1***.

The least polar fraction, (6*S*,11*S*)-2,6,11,15-tetramethylhexadeca-2,14-diene **105** was isolated as a colourless non-viscous oil. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.6.4.1***.

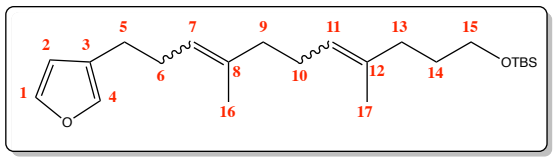



The most polar fraction, 4-chlorofuran-2(5*H*)-one **106** was isolated as white crystalline needles. Spectroscopic characteristics are consistent with those previously reported.[73] mp 67–71 °C; $\nu_{max}/cm^{-1}$ (KBr) 2964 (CH), 1780 (C=O), 1748 (C=O), 1600 (C=O), 1263, 1015, 802; $\delta_H$ ($CDCl_3$, 300 MHz) 4.87 [2H, d, *J* 1.9, C(5)$H_2$], 6.18 [1H, t, *J* 1.9, C(3)*H*].

## 4.7 Coupling of subunit A and subunit B

The following numbering template was used in spectroscopically characterising the furanolipid molecule(s). This numbering system is commonly used in the literature to assign furanolipid compounds.[20-23,29]

### 4.7.1 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)furan 90 [29,30,74,75]



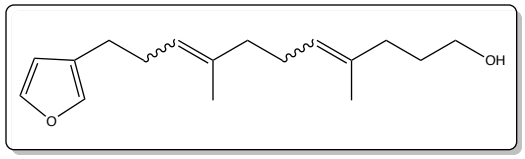

Freshly ground magnesium (3.0 g, 124.3 mmol) was flame heated, allowed to cool to room temperature and activated by successively adding a crystal of iodine and a solution of 1,2-dibromoethane (0.4 mL) in tetrahydrofuran (20 mL) under inert nitrogen atmosphere. The mixture was refluxed for 1 h, and then cooled to -10 °C. A solution of 3-furylmethyl bromide **14** (2.0 g, 12.4 mmol) in tetrahydrofuran (9 mL) was then added dropwise over a period of 1 h. Vigorous stirring was continued for 5 h at –10 °C. In a separate reaction flask, dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahrdrofuran, 3.24 mL, 0.324 mmol, 10 mol%) was added to a stirring solution of 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-yl acetate **89** (1.15 g, 3.24 mmol) in tetrahydrofuran (9 mL) at room temperature. On cooling to 0 °C, the freshly prepared Grignard reagent in tetrahydrofuran was added over 30 min. The reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h. The reaction was quenched with brine (9 mL) and poured into ethyl acetate (15 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a two-component mixture consisting of the title

furanolipid silyl ether **90** and 1,2-di-3-furylethane **32** in a 85:15 ratio of products respectively. The crude residue was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes), to afford the title furanolipid silyl ether **90** (0.94 g) as a colourless oil. Minor co-elution with 1,2-di-3-furylethane **32** was encountered (>5%). Due to difficulties in fully separating the Wurtz coupled product **32** at this stage, the mixture was used as it was for the subsequent reaction; $\nu_{max}/cm^{-1}$ (film) 2930 (CH), 2858, 1463, 1385, 1255 ($SiCH_3$), 1101 (SiO), 1027, 836, 776; $\delta_H$ ($CDCl_3$, 300 MHz) 0.05 [6H, s, $Si(CH_3)_2$], 0.90 [9H, s, $SiC(CH_3)_3$], 1.56 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.57-1.70 [5H, m, C(14)$H_2$ and $CH_3$* and containing 3H, s, C(16)$H_3$ or C(17)$H_3$], 1.92-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.6, C(5)$H_2$], 3.58 [2H, t, *J* 6.6, C(15)$H_2$], 3.55* (2H, t, *J* 6.5), 5.02-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 7.20 [1H, s, C(4)*H*], 7.32 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.3 [$CH_3$, $Si(CH_3)_2$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 18.4 [C, $SiC(CH_3)_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.0 [$CH_3$, $SiC(CH_3)_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 31.2, [$CH_2$, *C*(14)$H_2$], 35.8 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 63.0 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.2 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.7 [C, *C*(12)], 135.8 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 23.4 ($CH_3$), 25.3 ($CH_2$), 26.4 ($CH_2$), 26.5 ($CH_2$), 28.1 ($CH_2$), 28.4 ($CH_2$), 31.3 ($CH_2$), 32.0 ($CH_2$), 40.0 ($CH_2$), 63.1 ($CH_2$), 123.8 (*C*H), 124.1 (*C*H), 124.5 (*C*H), 135.0 (*C*), 135.7 (*C*), 135.9 (*C*), 142.7 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{23}H_{41}O_2Si$ $(M+H)^+$ 377.2876. Found 377.2863 $(M+H)^+$; m/z (ESI+) 377.4 $(M+H)^+$.

The less polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.3.3.1***. [29,76]

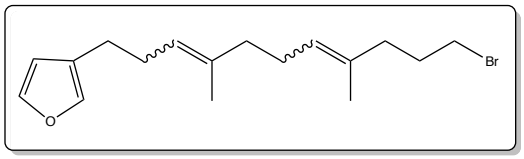
# 4.8 Preparation of the furanolipid Grignard precursor

## 4.8.1 Synthesis of 3-(11-hydroxy-4,8-dimethylundeca-3,7-dien-1-yl)furan 91 [60,74]




Tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 4.94 mL, 4.94 mmol, 2 equiv) was added to a stirring solution of 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)furan **90** (0.93 g, 2.47 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 2 h before water (20 mL) and ethyl acetate (20 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a two-component mixture consisting of the title furanolipid alcohol **91** and 1,2-di(furan-3-yl)ethane **32** in a 9:1 ratio respectively. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes) to afford the title alcohol **91** [0.59 g, 70% over two steps (Schlosser cross coupling and desilylation)] as a yellow oil. $^1$H NMR integration indicated a 67:33 ratio of the (*E,E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 3339 (OH), 2923 (CH), 2856, 1501, 1449, 1382, 1164, 1064, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.55-1.72 [8H, m, C(14)$H_2$ and C$H_2$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.93-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 3.62 [2H, t, *J* 6.4 C(15)$H_2$], 3.63* [2H, t, *J* 6.4), 5.07-5.20 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.8 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 29.8 [$CH_2$, *C*(14)$H_2$], 32.0 [$CH_2$, *C*(15)$H_2$], 36.0 [$CH_2$, *C*(13)$H_2$], 39.8 [$CH_2$, *C*(9)$H_2$], 41.9 [$CH_2$, *C*(13)$H_2$], 111.1 [CH, *C*(2)H], 123.7 [CH, *C*(7)H], 124.9 [CH, *C*(11)H], 125.0 [C, *C*(3)], 135.4 [C, *C*(12)], 135.8 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 16.1 (*C*$H_3$), 23.3 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 28.1 (*C*$H_2$), 28.4 (*C*$H_2$), 30.9 (*C*$H_2$), 31.9 (*C*$H_2$), 39.9 (*C*$H_2$), 63.0 (*C*$H_2$), 123.9 (*C*H), 124.6 (*C*H), 125.0 (*C*H), 134.7 (*C*), 134.9 (*C*), 135.6 (*C*), 135.8 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{17}H_{27}O_2$ $(M+H)^+$ 263.2011. Found 263.2003 $(M+H)^+$; m/z (ESI+) 263.4 $(M+H)^+$.

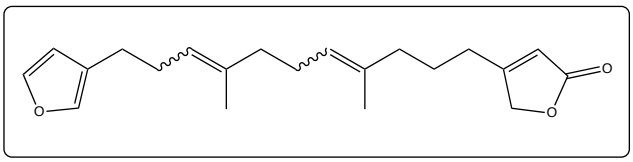
### 4.8.2 Synthesis of 3-(11-bromo-4,8-dimethylundeca-3,7-dien-1-yl)furan 92




Carbon tetrabromide (0.80 g, 2.40 mmol) was added in small portions to a stirring solution of 3-(11-hydroxy-4,8-dimethylundeca-3,7-dien-1-yl)furan **91** (0.42 g, 1.6 mmol) and triphenylphosphine (0.55 g, 2.08 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred for an additional 1 h before dichloromethane was removed under reduced pressure. The crude residue was taken-up in hexane (10 mL) and the resulting solids were removed by filtration. Concentration of the filtrate under reduced pressure followed by subsequent column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) provided the title bromide **92** (0.47 g, 86%) as a faint yellow oil. $^1$H NMR integration indicated a 67:33 ratio of the (*E,E*) and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2919 (CH), 2855 (CH), 1501, 1445, 1383, 1248, 1164, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 [6H, s, C(16)$H_3$ and C(17)$H_3$], 1.67* (3H, s), 1.70* (3H, s), 1.85-2.20 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 3.36 [2H, t, *J* 6.0, C(15)$H_2$], 3.38* (2H, t, *J* 6.7), 5.10-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 7.20 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.5, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.8 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 30.9 [$CH_2$, *C*(14)$H_2$], 33.4 [$CH_2$, *C*(15)$H_2$], 37.8 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 111.1 [CH, *C*(2)H], 124.0 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.7 [CH, *C*(11)H], 133.0 [C, *C*(12)], 135.5 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 16.1 (*C*$H_3$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.4 (*C*$H_2$), 30.2 (*C*$H_2$), 31.1 (*C*$H_2$), 31.9 (*C*$H_2$), 33.2 (*C*$H_2$), 33.5 (*C*$H_2$), 37.9 (*C*$H_2$), 39.9 (*C*$H_2$), 124.0 (*C*H), 124.7 (*C*H), 125.0 (*C*), 125.5 (*C*H), 126.5 (*C*H), 133.2 (*C*), 133.3 (*C*), 133.5 (*C*), 135.7 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{17}H_{26}BrO$ $(M+H)^+$ 325.1167. Found 325.1157 $(M+H)^+$; m/z (ESI+) 263.4 $(M+H)^+$.

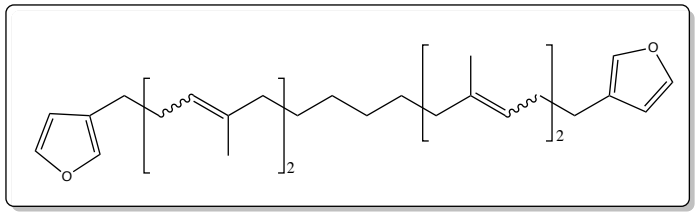
# 4.9 Synthesis of furospongolide (conjugate addition/elimination)

## 4.9.1 Synthesis of furospongolide 1



Freshly ground magnesium (0.27 g, 11.2 mmol) was flame heated, allowed to cool to room temperature and activated by successively adding a crystal of iodine and a solution of 1,2-dibromoethane (0.5 mL) in tetrahydrofuran (2 mL) under inert nitrogen atmosphere. The mixture was refluxed for 1 h and then cooled to -10 °C. A solution of 3-(11-bromo-4,8-dimethylundeca-3,7-dien-1-yl)furan **92** (0.36 g, 1.12 mmol) in tetrahydrofuran (2 mL) was then added dropwise over a period of 2 h. The reaction was warmed to room temperature and stirring was continued for a further 6 h. In a separate reaction flask, dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 0.56 mL, 0.056 mmol) was added to a stirring solution of 5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate **57** (0.13 g, 0.56 mmol) in tetrahydrofuran (2 mL) at room temperature. On cooling to 0 °C, the freshly prepared Grignard reagent in tetrahydrofuran was added over 30 min. The reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h. The reaction was quenched with brine (10 mL) and poured into ethyl acetate (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a three-component mixture consisting of furospongolide **1**, the Wurtz coupled product **110** and 4-bromofuran-2(5*H*)-one **85** in a 1:7:4 ratio of products respectively. The residue was subjected to column chromatography on silica gel (1-10% ethyl acetate gradient in hexanes) to afford furospongolide **1** (18 mg, 10 %) as a colourless oil. Furospongolide **1** was found to contain 47% of the (*E,E*)-isomer, 43% of the (*Z,E*)-isomer and 10% other(s) as determined by HPLC analysis (***Appendix V***). Spectroscopic characteristics were consistent with those reported in the literature;[29,77] $\nu_{max}/cm^{-1}$ (film) 2926 (CH), 2856, 1780 (C=O), 1748 (C=O)), 1637 (C=C), 1501, 1447, 1380, 1169, 1025, 888, 874; $\delta_H$ ($CDCl_3$, 600 MHz) 1.58* (3H, s), 1.60 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.64-1.75 [2H m, C(14)$H_2$], 1.95-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.25 [2H, q, *J* 7.5, C(6)$H_2$], 2.35 [2H, t, *J* 7.5 C(15)$H_2$], 2.45 [2H, t, *J* 7.5 C(5)$H_2$], 4.70-4.76 [2H, m, C(19)$H_2$], 5.05-5.25 [2H, m, C(7)*H* and C(11)*H*], 5.81-5.88 [1H, m, C(17)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 150.9 MHz) 15.7 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.2 [$CH_2$, *C*(15)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.9 [$CH_2$, *C*(6)$H_2$], 28.4 [$CH_2$, *C*(14)$H_2$], 38.9 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 73.1 [$CH_2$, *C*(19)$H_2$], 111.0 [CH, *C*(2)H], 115.4 [CH, *C*(17)H], 123.9 [CH, *C*(7)H], 124.9 [C, *C*(3)], 125.7 [CH, *C*(11)H],

133.4 [C, *C*(12)], 135.5 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 170.5 [C, *C*(16)], 174.2 [C, *C*(18)]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.1 (*C*$H_3$), 25.0 (*C*$H_2$), 25.2 (*C*$H_2$), 25.3 (*C*$H_2$), 25.4 (*C*$H_2$), 26.4 (*C*$H_2$), 27.9 (*C*$H_2$), 28.1 (*C*$H_2$), 28.2 (*C*$H_2$), 28.4 (*C*$H_2$), 29.4 (*C*$H_2$), 29.7 (*C*$H_2$), 30.2 (*C*$H_2$), 30.7 (*C*$H_2$), 30.9 (*C*$H_2$), 31.1 (*C*$H_2$), 31.4 (*C*$H_2$), 31.8 (*C*$H_2$), 31.9 (*C*$H_2$), 32.1 (*C*$H_2$), 32.2 (*C*$H_2$), 38.9 (*C*$H_2$), 39.0 (*C*$H_2$), 39.8 (*C*$H_2$), 62.8 (*C*$H_2$), 63.0 (*C*$H_2$), 111.0 (*C*H), 115.4 (*C*H), 123.9 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.0 (*C*H), 125.5 (*C*H), 125.6 (*C*H), 133.5 (*C*), 133.7 (*C*), 135.2 (*C*), 135.4 (*C*), 135.5 (*C*), 135.6 (*C*), 135.7 (*C*), 138.8 (*C*H), 142.6 (*C*H), 170.4 (*C*), 170.5 (*C*), 174.1 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_3$ $(M+H)^+$ 329.2117. Found 329.2102 $(M+H)^+$; m/z (ESI+): 329.2 $(M+H)^+$.



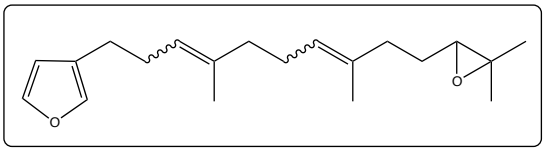
The least polar fraction, 3,3'-(4,8,15,19 tetramethyldocosa-3,7,15,19-tetraene-1,22-diyl)difuran **110** was isolated as a non viscous colourless oil; $\nu_{max}/cm^{-1}$ (film) 2959, 2928, 2857, 1454, 1380, 1165, 1066, 1026, 874, 777; $\delta_H$ ($CDCl_3$, 400 MHz) 1.20-1.35 [4H, m, 2 x C(15)*H*$_2$], 1.34-146 [4H, m, 2 x C(14)*H*$_2$], 1.60 [12H, s, 2 x {C(16)*H*$_3$ and C(17)*H*$_3$}], 1.68* (6H, m), 1.71* (6H, m), 1.90-2.15 [12H, m, 2 x {C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$}], 2.27 [4H, q, *J* 7.3, 2 x C(6)*H*$_2$], 2.46 [4H, t, *J* 7.5 2 x C(5)*H*$_2$], 5.05-5.24 [4H, m, 2 x {C(7)*H* and C(11)*H*}], 6.28 [2H, s, 2 x C(2)*H*], 7.21 [2H, s, 2 x C(4)*H*], 7.34 [2H, t, *J* 1.6, 2 x C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.8 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 20.0 [$CH_2$, *C*(14)$H_2$], 20.2 [$CH_2$, *C*(15)$H_2$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 39.8 [$CH_2$, *C*(13)$H_2$], 41.9 [$CH_2$, *C*(9)$H_2$], 111.1 [CH, *C*(2)H], 123.7 [CH, *C*(7)H], 124.1 [CH, *C*(11)H], 125.0 [C, *C*(3)], 135.1 [C, *C*(12)], 135.8 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 13.7 (*C*$H_3$), 13.8 (*C*$H_3$), 14.1 (*C*$H_3$), 14.2 (*C*$H_3$), 18.8 (*C*$H_3$), 22.7 (*C*$H_3$), 22.8 (*C*$H_3$), 23.4 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.9 (*C*$H_2$), 28.4 (*C*$H_2$), 29.1 (*C*$H_2$), 29.5 (*C*$H_2$), 29.8 (*C*$H_2$), 32.0 (*C*$H_2$), 32.1 (*C*$H_2$), 33.8 (*C*$H_2$), 34.7 (*C*$H_2$), 36.5 (*C*$H_2$), 39.6 (*C*$H_2$), 40.0 (*C*$H_2$), 41.8 (*C*$H_2$), 111.1 (*C*H), 123.8 (*C*H), 124.0 (*C*H), 124.5 (*C*H), 124.9 (*C*H), 125.3 (*C*H), 135.4 (*C*), 135.6 (*C*), 136.0 (*C*), 137.2 (*C*H), 142.6 (*C*H); HRMS (ESI+) Exact mass calculated for $C_{34}H_{51}O_2$ $(M+H)^+$ 491.3889. Found 491.3870 $(M+H)^+$; m/z (ESI+): 491.4 $(M+H)^+$.

The most polar fraction, 4-bromofuran-2(5*H*)-one **85** was isolated was a white crystalline solid. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.6.2.1***.

# 4.10 Synthesis of furospongolide (Optimising 2nd generation)

## 4.10.1 Synthesis of 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)furan 113

**Method A**



Freshly ground magnesium (10.0 g, 0.41 mol, 20 equiv) was flame heated, allowed to cool to room temperature and activated by successively adding a crystal of iodine and a solution of 1,2-dibromoethane (1.2 mL) in tetrahydrofuran (70 mL) under inert nitrogen atmosphere. The mixture was refluxed for 1 h, and then cooled to -10 °C. A solution of 3-furylmethyl bromide **14** (6.6 g, 41.0 mmol, 2 equiv) in tetrahydrofuran (32 mL) was then added dropwise over a period of 2 h. Vigorous stirring was continued for 5 h at –10 °C. In a separate reaction flask, dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 13.7 mL, 1.37 mmol, 6.7 mol%) was added to a stirring solution of 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (5.75 g, 20.5 mmol, 1 equiv) in tetrahydrofuran (100 mL) at room temperature. After cooling to 0 °C, the freshly prepared Grignard reagent in tetrahydrofuran was added over 45 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h before quenching with brine (30 mL). The mixture was poured into ethyl acetate (50 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a three-component mixture consisting of the desired furanolipid epoxide **113**, 1,2-di(furan-3-yl)ethane **32** and unreacted starting material **60** in a 83:7:11 ratio respectively. The residue was purified by column chromatography on silica gel (0-10% ethyl acetate gradient in hexanes) to give the title furanolipid epoxide **113** as a colourless oil (4.26 g, 76% based on the consumed acetate). $^1$H NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers*. Spectroscopic characteristics were consistent with those reported in the literature; $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2856 (CH), 1450, 1378, 1026(CO), 874, 779; $\delta_H$ ($CDCl_3$, 300 MHz) 1.26 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.30 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.50-1.73 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(18)$H_3$ and C(19)$H_3$], 1.90-2.22 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 2.70 [1H, t, *J* 6.2, C(15)*H*], 2.72* (1H, t, *J* 6.4), 5.10-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.1 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 18.8 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 24.9 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.5 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 36.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 58.4 [C, *C*(16)], 64.2 [CH, *C*(15)H], 111.1 [CH,

*C*(2)H], 123.8 [CH, *C*(7)H], 124.8 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.1 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H]; Characteristic peaks for other isomer(s)* 16.0 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.4 (*C*$H_2$), 28.4 (*C*$H_2$), 28.5 (*C*$H_2$), 31.9 (*C*$H_2$), 39.9 (*C*$H_2$), 64.1 (*C*H), 123.9 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 125.6 (*C*H), 134.3 (*C*), 135.8 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{20}H_{31}O_2$ $(M+H)^+$ 303.2324. Found 303.2312 $(M+H^+)$; m/z (ESI+): 303.4 $(M+H)^+$.

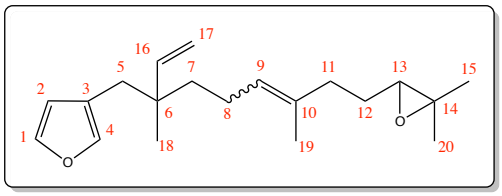
The least polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic characteristics are consistent with those reported in ***Section 4.3.3.1***.

The most polar fraction, 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** was isolated unchanged as a yellow oil and was recycled back into the next cross coupling reaction. The percentage yield was calculated from a revised theoretical yield figure due to isolation of unreacted starting material **60** from the reaction mixture.[30]

**Method B**[78]

The title furanolipid epoxide **113** was prepared following the procedure described in **Method A** using freshly ground and activated magnesium (2.59 g, 106.4 mmol, 10 equiv), 3-furylmethyl bromide **14** (1.71 g, 10.64 mmol, 1 equiv), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 10.7 mL, 1.07 mmol, 10 mol%) and 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (2.98 g, 10.64 mmol, 1 equiv) in tetrahydrofuran (28 mL) to afford a four-component mixture consisting of the desired cross coupled product **113**, its corresponding regioisomer **118**, the Wurtz coupled product **32** and starting material **60**. The crude residue was purified by column chromatography on silica gel (0-10% ethyl acetate in hexanes) to afford an inseparable two-component mixture (0.684 g, 64% based on the consumed acetate) consisting of desired cross-coupled product **113** (59% conversion)§ and its corresponding regioisomer **118** (4.5% conversion)§ as a colourless oil (*approx.* ratio of 93:7, as determined from $^1$H NMR integration). Spectroscopic characteristics are consistent with those previously reported in **Method A**.

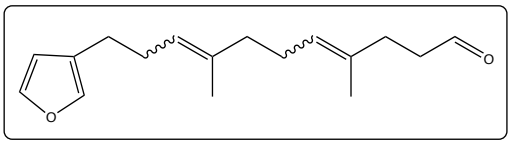
§ % Conversion was determined by $^1$H NMR analysis of the isolated inseperable mixture.



3-(8-(3,3-dimethyloxiran-2-yl)-2,6-dimethyl-2-vinyloct-5-en-1-yl)furan **118** was tentatively assigned from the $^{1}$H NMR spectrum of the purified two-component mixture of cross-coupled products; $\delta_H$ ($CDCl_3$, 400 MHz) 0.97 [3H, s, C(18)$H_3$], 1.27 [3H, s, C(15)$H_3$ or C(20)$H_3$], 1.31 [3H, s, C(15)$H_3$ or C(20)$H_3$], 1.50-1.73 [5H, m, C(12)$H_2$ and containing 3H, s, C(19)$H_3$], 1.86-2.22 [6H, m, C(7)$H_2$ and C(8)$H_2$ and C(13)$H_2$], 2.41 [2H, s, C(5)$H_2$], 2.68-2.75 [1H, m, C(13)*H*], 4.90 [1H, dd, B of the ABX system $J_{BX}$ 17.6, $J_{AB}$ 1.3, C(17)$H_2$], 5.02 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.3, C(17)$H_2$], 5.10-5.22 [1H, m, C(9)*H*], 5.76* [1H, dd, X of the ABX system $J_{BX}$ 17.6, $J_{AX}$ 10.8, C(16)$H_2$], 5.77 [1H, dd, X of the ABX system $J_{BX}$ 17.6, $J_{AX}$ 10.8, C(16)$H_2$], 6.23 [1H, s, C(2)*H*], 7.18 [1H, s, C(4)*H*], 7.31 [1H, t, *J* 1.6, C(1)*H*].

The least polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic data was consistent with those previously reported in ***Section 4.3.3.1***.

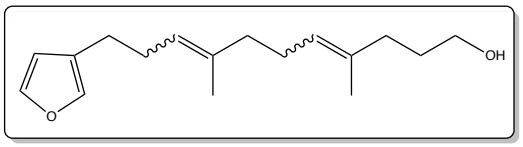
### 4.10.2 Synthesis of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan 121



A solution of 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)furan **113** (3.49 g, 11.55 mmol) in diethyl ether (80 mL) was added rapidly to a stirring solution of periodic acid (3.16 g, 13.86 mmol) in tetrahydrofuran (16 mL) at 0 °C. The reaction was monitored by TLC analysis and quenched after 30 min with saturated aqueous sodium thiosulfate (25 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) to provide the title aldehyde **121** (2.67 g, 89 %) as a colourless oil. $^{1}$H NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers*; $\nu_{max}$/cm$^{-1}$ (film) 2920 (CH), 2856 (CH), 1727 (C=O), 1501, 1446, 1384, 1164, 1066, 1025, 874, 781; $\delta_H$ ($CDCl_3$, 300 MHz) 1.58 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.61 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.68* (3H, s), 1.94-2.15 [4H, m, C(9)$H_2$ and C(10)$H_2$], 2.18-2.36 [4H, m, C(6)$H_2$ and C(13)$H_2$], 2.38-2.55 [4H, m, C(5)$H_2$ and C(14)$H_2$], 5.08-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*], 9.74 [1H, t, *J* 1.9, C(15)*H*], 9.78* (1H, t, *J* 1.8); $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.4 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 31.8 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 42.1 [$CH_2$,

*C*(14)$H_2$], 111.1 [CH, *C*(2)H], 124.0 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.3 [CH, *C*(11)H], 133.0 [C, *C*(12)], 135.4 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 202.8 [CH, *C*(15)H]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 21.3 (*C*$H_3$), 23.1 (*C*$H_3$), 23.4 (*C*$H_3$), 24.3 (*C*$H_2$), 24.7 (*C*$H_2$), 25.3 (*C*$H_2$), 28.4 (*C*$H_2$), 29.7 (*C*$H_2$), 31.5 (*C*$H_2$), 31.8 (*C*$H_2$), 32.0 (*C*$H_2$), 34.3 (*C*$H_2$), 39.6 (*C*$H_2$), 39.7 (*C*$H_2$), 42.3 (*C*$H_2$), 111.1 (*C*H), 123.8 (*C*H), 124.1 (*C*H), 124.7 (*C*H), 124.9 (*C*H), 126.4 (*C*H), 132.9 (*C*), 133.2 (*C*), 135.4 (*C*), 135.6 (*C*), 142.6 (*C*H), 202.4 (*C*H), 202.7 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{17}H_{25}O_2$ $(M+H)^+$ 261.1855. Found 261.1849 $(M+H)^+$; m/z (ESI+) 261.2 $(M+H)^+$.

### 4.10.3 Synthesis of 3-(11-hydroxy-4,8-dimethylundeca-3,7-dien-1-yl)furan 91



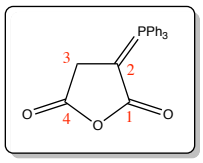

Sodium borohydride (4 mg, 0.09 mmol) was added to a stirring solution of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (20 mg, 0.08 mmol) in methanol (2 mL) at -10 $^oC$. The mixture was stirred for an additional 2 h at -10 $^oC$ before the reaction mixture was quenched with ice-cold water (10 mL) and solvent was removed under reduced pressure. The aqueous residue was saturated with solid sodium chloride and extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the title alcohol **91** (16 mg, 80%) as a colourless oil. $^1H$ NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers*. Spectroscopic characteristics were consistent with those previously reported in ***Section 4.8.1***.

# 4.11 Concise synthesis of furospongolide (2nd generation)

## 4.11.1 Synthesis of subunit C (Ylide)

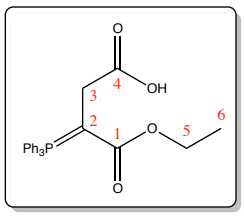
For the purpose of characterisation, the numbering and naming of these compounds were as described in the literature.[79-81]

### 4.11.1.1 Synthesis of 2-triphenylphosphoranylidenesuccinic anhydride 124 [80]




Maleic anhydride **123** (5.0 g, 0.051 mol) dissolved in acetone (25 mL) was added dropwise via a dropping funnel to a stirring solution of triphenylphosphine (13.3 g, 0.051 mol) in acetone (50 mL) at room temperature. The phosphorane began to precipitate almost immediately and after 30 min, the reaction mixture was filtered and washed with acetone (4 x 20 mL) and diethyl ether (2 x 20 mL) to afford the title anhydride **124** (15.4 g, 84%) as a pale yellow crystalline solid, which was used in the next step without further purification. Spectroscopic characteristics are consistent with those previously reported;[80] mp: 185-189 °C, Lit[80] mp 185-187; Found: C, 73.71; H, 4.87, $C_{22}H_{17}O_3P$ requires C, 73.33; H, 4.76; $\nu_{max}/cm^{-1}$ (film) 1794 (C=O), 1711 (C=O), 1438, 1323, 1108; $\delta_H$ ($CDCl_3$, 300 MHz) 3.22 [2H, s, C(3)$H_2$], 7.48-7.72 [15H, m, Ar*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 33.7 [C, d, $^1J_{CP}$ 135.5, *C*(2)], 37.1 [$CH_2$, d, $^2J_{CP}$ 11.7, *C*(3)$H_2$], 124.0 [C, d, $^1J_{CP}$ 114.2, *C*(1')], 129.5 [CH, d, $^2J_{CP}$ 12.7, *C*(3')H], 133.3 [CH, *C*(4')H], 133.4 [CH, $^3J_{CP}$ 10.8, *C*(2')H], 167.4 [C, $^3J_{CP}$ 18.1, *C*(1)], 172.8 [C, $^2J_{CP}$ 19.7, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_{22}H_{18}O_3P$ $(M+H)^+$ 361.0994. Found 361.0990 $(M+H)^+$; m/z (ESI+) 361.2 $(M+H)^+$.

### 4.11.1.2 Synthesis of ethoxy-oxo-2-(triphenylphosphoranylidene)-4-butanoic acid 122 [79,81,82]

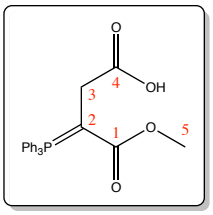



2-Triphenylphosphoranylidenesuccinic anhydride **124** (5.5 g, 15.3 mmol) was suspended in ethanol (50 ml) in a one-neck round bottom flask fitted with a reflux condenser and the reaction mixture was gently heated to 40 °C and stirred for 24 h. Evaporation of ethanol under reduced pressure and recrystallization from ethyl acetate gave the title monoethyl ester **122** (5.4 g, 87%) as an off-white granular solid. Spectroscopic characteristics are consistent with those previously reported;[81,83] mp: 122-125 °C, Lit[81] mp 126-127; Found: C, 70.27; H, 5.74, $C_{24}H_{23}O_4P$ requires C, 70.93; H, 5.70; $\nu_{max}/cm^{-1}$ (KBr): 3500-2500 (br, OH), 1736 (C=O), 1606 (CO); $\delta_H$ ($CDCl_3$, 300 MHz) 0.81 [3H, t, *J* 7.1, C(6)$H_3$], 2.91 [2H, d, $J_{P-H}$ 14.5, C(3)$H_2$], 3.87 [2H, q, *J* 7.1, C(5)$H_2$], 7.50-7.75 [15H, m, Ar*H*], 9.30 [1H, brs, COO*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 13.8 [$CH_3$, *C*(6)$H_3$], 35.3 [$CH_2$, d, $^2J_{CP}$

3.9 *C*(3)$H_2$], 39.5 [C, d, $^1J_{CP}$ 84.0, *C*(2)], 61.2 [$CH_2$, *C*(5)$H_2$], 122.5 [C, d, $^1J_{CP}$ 89.9, *C*(1')], 129.5 [CH, d, $^3J_{CP}$ 12.6, *C*(3')H], 133.6 [CH, d, $^2J_{CP}$ 2.9, *C*(2')H], 133.8 [CH, d, $^4J_{CP}$ 3.9, *C*(4')H], 170.7 [C, d, $^3J_{CP}$ 5.4, *C*(4)], 172.8 [C, d, $^2J_{CP}$ 7.1 *C*(1)]; HRMS (ESI+): Exact mass calculated for $C_{24}H_{24}O_4P$ $(M+H)^+$ 407.1412. Found 407.1417 $(M+H)^+$; m/z (ESI+) 407.1 ($M+H^+$).

It should be noted that elemental analysis of **122** was outside acceptable limits.

### 4.11.1.3 Synthesis of methoxy-oxo-2-(triphenylphosphoranylidene)-4-butanoic acid 125 [80,82]



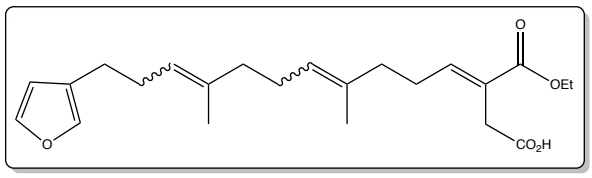

The title compound was prepared according to the procedure described for **122** using 2-Triphenylphosphoranylidenesuccinic anhydride **124** (3.00 g, 8.33 mmol) and methanol (20 mL) to afford the recrystallized title ester **125** (2.70 g, 83%) as a pale yellow granular solid. Spectroscopic characteristics are consistent with those previously reported;[80] mp 149-152, Lit[80] mp 150-152; Found: C, 70.46; H, 5.42, $C_{23}H_{21}O_4P$ requires C, 70.40; H, 5.39; $\nu_{max}/cm^{-1}$ (KBr): 2940, 2912, 1729 (C=O), 1565; $\delta_H$ ($CDCl_3$, 300 MHz) 2.91 [2H, d, $J_{P-H}$ 14.9, C(3)$H_2$], 3.37 [3H, s, C(5)$H_3$], 7.48-7.76 [15H, m, Ar*H*], 9.18 [1H, brs, COO*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 35.0 [$CH_2$, d, $^2J_{CP}$ 4.9, *C*(3)$H_2$], 39.2 [C, d, $^1J_{CP}$ 90.3, *C*(2)], 51.7 [$CH_2$, *C*(5)$H_2$], 123.1 [C, d, $^1J_{CP}$ 90.3, *C*(1')], 129.4 [CH, d, $^3J_{CP}$ 12.6, *C*(3')H] 133.4 [CH, d, $^4J_{CP}$ 2.9, *C*(4')H], 133.7 [CH, d, $^2J_{CP}$ 9.8, *C*(2')H], 171.3 [C, d, $^3J_{CP}$ 6.8, *C*(4)], 173.2 [C, d, $^2J_{CP}$ 6.5, *C*(1)]; HRMS (ESI+): Exact mass calculated for $C_{23}H_{22}O_4P$ ($M+H^+$) 393.1256. Found 393.1252 ($M+H^+$); m/z (ESI+) 393.2 ($M+H^+$).

## 4.11.2 Synthesis of furospongolide (Wittig reaction)

For the purpose of characterisation, the name and the numbering of these compounds were as described in the literature.

### 4.11.2.1 Synthesis of 3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan 126

**Method A: Employing toluene and 1.2 equivalents of ylide 122.[84]**




A solution of 4-ethoxy-4-oxo-3-(triphenylphosphoranylidene)butanoic acid **122** (94 mg, 0.23 mmol, 1.2 equiv) in toluene (1 mL) and hydroquinone (19 mg, 0.17 mmol, 0.9 equiv) were sequentially added to a stirring solution of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (50 mg, 0.19 mmol) in toluene (3 mL) at room temperature. After 24 h stir at room temperature, the reaction mixture was heated to 40 $^{o}$C and stirring was maintained for a further 46 h. The reaction mixture was filtered and solvent was carefully removed under reduced pressure to afford a two component mixture consisting of the desired cross coupled product **126** and unreacted starting material **121** in a 70:30 ratio respectively. The residue was purified by column chromatography on silica gel (10-50% ethyl acetate in hexanes) to furnish the title ester **126** (32 mg, 43%) as a colourless oil. $^{1}$H NMR integration revealed a 70:30 mixture of *E,E* and other isomers*; $\nu_{max}$/cm$^{-1}$ (film) 3300-2500 (OH), 1714 (C=O), 1446, 1378, 1287, 1198; $\delta_H$ ($CDCl_3$, 300 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2CH_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.69* (3H, s), 1.93-2.16 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.16-2.36 [4H, m, C(6)$H_2$ and C(14)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 3.38 [2H, s, C(17)$H_2$], 4.20 [2H, q, *J* 7.1, C(19)$O_2CH_2CH_3$], 5.08-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 6.97 [1H, t, *J* 7.4, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.5, C(1)*H*], 9.6 [1H, brs, COO*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.2 [$CH_3$, C(19)$O_2CH_2CH_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.6 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 32.3 [$CH_2$, *C*(17)$H_2$], 38.1 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 61.0 [$CH_2$, C(19)$O_2CH_2CH_3$], 111.1 [CH, *C*(2)H], 123.9 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.5 [CH, *C*(11)H], 133.4 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 145.9 [CH, *C*(15)H], 167.0 [C, *C*(19)=O, ester], 176.9 [C, *C*(18)=O, acid]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.0 (*C*$H_3$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.5 (*C*$H_2$), 28.4 (*C*$H_2$), 30.4 (*C*$H_2$), 31.9 (*C*$H_2$), 32.0 (*C*$H_2$), 39.8 (*C*$H_2$), 60.6, (*C*$H_2$) 111.1 (*C*H), 116.0 (*C*H), 124.0 (*C*H), 124.6 (*C*H), 124.9 (*C*), 125.0 (*C*), 125.2 (*C*H), 125.4 (*C*H), 126.4 (*C*H), 133.3 (*C*), 133.7 (*C*), 135.4 (*C*), 135.8 (*C*), 142.6 (*C*H), 145.6 (*C*H), 145.8 (*C*H);

HRMS (ESI+): Exact mass calculated for $C_{23}H_{33}O_5$ $(M+H)^+$ 389.2328. Found 389.2320. $(M+H)^+$; m/z (ESI+) 389.3 $(M+H)^+$.

**Method B: Employing benzene and 2.4 equivalents of ylide 122.**[85]

A solution of 4-ethoxy-4-oxo-3-(triphenylphosphoranylidene)butanoic acid **122** (112 mg, 0.28 mmol, 2.4 equiv) in benzene (1 mL) and hydroquinone (12 mg, 0.10 mmol, 0.9 equiv) were sequentially added to a stirring solution of **121** (30 mg, 0.12 mmol) in benzene (2 mL) at room temperature. The reaction was heated to 50 $^oC$ and stirring was maintained for 70 h. The reaction mixture was filtered and solvent was carefully removed under reduced pressure to afford a two component mixture consisting of the ester **126** and unreacted aldehyde **121** in a 95:5 ratio respectively. The residue was purified by column chromatography on silica gel (10-50% ethyl acetate gradient in hexanes) to afford the title ester **126** (28 mg, 63%) as a colourless oil. $^1H$ NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers*. Spectroscopic characteristics were consistent with those in **Method A**.

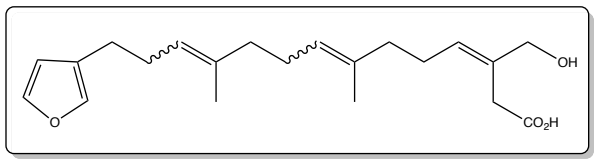
**Method C: Employing toluene and 2.4 equivalents of ylide 122.**

A solution of 4-ethoxy-4-oxo-3-(triphenylphosphoranylidene)butanoic acid **122** (0.38 g, 0.92 mmol, 2.4 equiv) in toluene (2 mL) and hydroquinone (0.04 g, 0.35 mmol, 0.9 eqiuv) were sequentially added to a stirring solution of **121** (0.10 g, 0.38 mmol) in toluene (3 mL) at room temperature. The reaction progress was monitored by TLC analysis and consumption of the aldehyde starting material was complete after 70 h. The reaction mixture was filtered and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (10-50% ethyl acetate gradient in hexanes) to afford the title ester **126** (91 mg, 61%)* as a colourless oil. $^1H$ NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers*. Spectroscopic characteristics were consistent with those previously reported in **Method A**.

*A yield of 66% was obtained for **126** on a batch that was processed later. The reaction time was also reduced to 24 h.

### 4.11.2.2 Synthesis of 3-(13-carboxy-12-(hydroxymethyl)-4,8-dimethyltrideca-3,7,11-trien-1-yl)furan 146

**Method A: 'Ate' complex reduction.**




*n*-Butyllithium (2.45 M in hexane, 0.44 mL, 1.08 mmol) was added dropwise to a stirring solution of diisobutylaluminium hydride (1.00 M in hexane, 1.10 mL, 1.08 mmol) in tetrahydrofuran (2 mL) at 0 $^{o}$C under inert nitrogen atmosphere. After 1h, the ate complex (0.3M in tetrahydrofuran-hexane) was transferred by syringe and added to a stirring solution of 3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan **126** (140 mg, 0.36 mmol) in tetrahydrofuran (5 mL) over 30 min at 0 $^{o}$C. Following addition, the reaction was allowed to warm to room temperature and stirring was continued for 1 h. The reaction was treated with saturated aqueous sodium potassium tartrate (10 mL) and stirring was continued for an additional 2 h. The reaction was poured into brine (10 mL), the layers were separated and the aqueous layer was extracted with diethyl ether (6 x 10 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title alcohol **146** as a light yellow oil. Due to the instability of the title complex, the crude product was carried through to the next step without further purification. $\nu_{max}/cm^{-1}$ (film) 3146, 2925, 2856, 1588, 1440, 1165, 1065, 1026, 874, 771; $\delta_H$ ($CDCl_3$, 400 MHz) 1.59 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.90-2.20 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.24 [2H, q, *J* 7.7 C(6)$H_2$], 2.45 [2H, t, *J* 7.6, C(5)$H_2$], 3.22 [2H, s, C(17)$H_2$], 4.13 [2H, s, C(19)$H_2$], 5.11 [1H, t, *J* 7.0, C(7)*H* or C(11)*H*], 5.16 [1H, t, *J* 6.7, C(7)*H* or C(11)*H*], 5.55-5.70 [1H, m, C(15)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, s, C(1)*H*]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{31}O_4$ $(M+H)^+$ 347.2222. Found 329.2225 $(M+H)^+$.

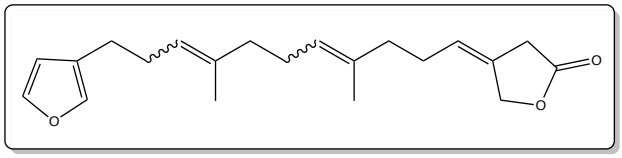
**Method B: $LiBH_4$-MeOH reduction.[86]**

Lithium borohydride (10 mg, 0.44 mmol, 1.7 equiv) and methanol (18 μL, 14 mg, 0.44 mmol) was added sequentially to a stirring solution of **126** (0.10 g, 0.26 mmol) in diethyl ether (4 mL) at room temperature. The reaction mixture was heated to refluxed and stirred for 4 h before it was allowed to cool to room temperature. The reaction was quenched with water (1 mL), $NH_4Cl$ (1 mL) and aqueous hydrochloric acid (1M, 0.1 mL) at 0 $^{o}$C. The reaction mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. $^1$H NMR analysis of the crude product indicated complete consumption of starting material, however only a minor trace (> 5%) of the title alcohol **146** was

identified. The major product from the reaction was an unidentifiable reduced product.

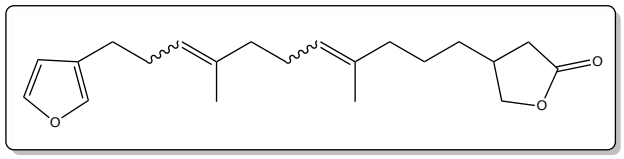
### 4.11.2.3 Synthesis of 3-(4,8-dimethyl-11-(5-oxodihydrofuran-3(2H)-ylidene)undeca-3,7-dien-1-yl)furan 147

**Method A: Lithium aluminium hydride reduction.**[87]

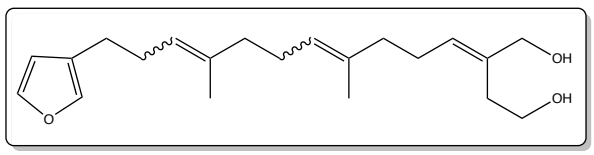


A solution of 3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan **126** (0.35 g, 0.90 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added slowly to a stirring solution of lithium aluminium hydride (39 mg, 1.02 mmol, 1.1 equiv) in tetrahydrofuran (2 mL) at -10 $^{o}$C. After addition, the reaction mixture was stirred at 0 $^{o}$C for 3h. The excess hydride was decomposed with ethyl acetate (2 mL) and the resulting mixture was acidified to pH 1 using *aqueous* hydrochloric acid (10%) and a pH meter. A condenser was fitted to the reaction vessel and the mixture was heated to reflux for 8 h. On cooling to room temperature, water (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined and washed successively with saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL) and concentrated under reduced pressure to afford a three-component mixture consisting of the desired lactone **147**, its corresponding diol **149** and its corresponding saturated lactone **148** in a 5:3:3 ratio of products respectively. The residue was purified by column chromatography on silica gel (10-50% ethyl acetate gradient in hexanes) to give the title lactone **147** (39 mg, 13.2%), which was the least polar fraction as a light yellow oil; $\nu_{max}$/cm$^{-1}$ (film) 2924, 2856, 1780 (C=O), 1725 (C=O), 1501, 1439, 1381, 1167, 1022, 874, 840, 780; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.69* (3H, s), 1.90-2.17 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.25 [2H, q, *J* 7.3, C(6)$H_2$], 2.39-2.50 [2H, m, C(5)$H_2$], 3.09-3.17 [2H, m, C(17)$H_2$], 4.77-4.84 [2H, m, C(19)$H_2$], 5.04-5.22 [2H, m, C(7)*H* and C(11)*H*], 5.35-5.50 [1H, m, C(15)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.7 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(14)$H_2$], 28.1 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 31.3 [$CH_2$, *C*(17)$H_2$], 38.6 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 72.3 [$CH_2$, *C*(19)$H_2$], 111.1 [CH, *C*(2)H], 123.9 [CH, *C*(7)H], 124.3 [CH, *C*(15)H], 124.9 [C, *C*(3)], 125.2 [CH, *C*(11)H], 128.6 [C, *C*(16)], 133.7 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 175.6 [C, *C*(18)]; Characteristics peaks for the other isomer(s)* 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 30.9 (*C*$H_2$), 31.9 (*C*$H_2$), 124.2 (*C*H), 124.7 (*C*H), 125.1 (*C*H), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_3$

$(M+H)^+$ 329.2117. Found 329.2118 $(M+H)^+$; m/z (ESI+) 329.3 $(M+H)^+$.



The more polar fraction, 3-(4,8-dimethyl-11-(5-oxotetrahydrofuran-3-yl)undeca-3,7-dien-1-yl)furan **148** was isolated (15 mg, 5%) as a light yellow oil; $\nu_{max}/cm^{-1}$ (film) 2926, 2857, 1780 (C=O), 1501, 1446, 1382, 1257, 1168, 1065, 1024, 874, 838, 780, 725; $\delta_H$ ($CDCl_3$, 600 MHz) 1.33-1.50 [4H, m, C(14)$H_2$ and C(15)$H_2$], 1.58 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.66* (3H, s), 1.69* (3H, s), 1.94-2.12 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.13-2.21 [1H, m, C*H** and containing 1H, dd, J 17.1, 8.0 C(17)*H*], 2.25 [2H, q, *J* 7.2, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 2.48-2.58 [1H, m, C(16)*H*], 2.58-2.67 [1H, m, C*H** and containing 1H, dd, *J* 17.1, 8.4, C(17)*H*], 3.88-3.94 [1H, m, C*H** and containing 1H, dd, *J* 8.9, 7.3, C(19)*H*], 4.38-4.44 [1H, m, C*H** and containing 1H, dd, *J* 8.9, 7.4, C(19)*H*], 5.06-5.20 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6 C(1)*H*]; $\delta_C$ ($CDCl_3$, 150 MHz) 15.8 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.6 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 32.6 [$CH_2$, *C*(15)$H_2$], 34.5 [$CH_2$, *C*(17)$H_2$], 35.7 [CH, *C*(16)H], 39.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 73.4 [$CH_2$, *C*(19)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.0 [CH, *C*(11)H], 134.1 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 177.3 [C, *C*(18)]; Characteristics peaks for the other isomer(s)* 16.1 (*C*$H_3$), 22.7 (*C*$H_2$), 23.3 (*C*$H_2$), 23.4 (*C*$H_2$), 25.0 (*C*$H_2$), 25.3 (*C*$H_2$), 25.7 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.4 (*C*$H_2$), 29.4 (*C*$H_2$), 29.7 (*C*$H_2$), 31.4 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 32.6 (*C*$H_2$), 32.9 (*C*$H_2$), 34.5 (*C*$H_2$), 34.6 (*C*$H_2$), 35.7 (*C*$H_2$), 39.4 (*C*$H_2$), 39.9 (*C*$H_2$), 73.3 (*C*$H_2$), 73.4 (*C*$H_2$), 111.1 (*C*H), 124.0 (*C*H), 124.6 (*C*H), 124.8 (*C*H), 125.6 (*C*H), 134.3 (*C*), 134.4 (*C*), 135.2 (*C*), 135.5 (*C*), 135.8 (*C*), 138.8 (*C*H), 142.6 (*C*H), 177.2 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{31}O_3$ $(M+H)^+$ 331.2273. Found 331.2267 $(M+H)^+$; m/z (ESI+) 331.4 $(M+H)^+$.



The most polar fraction, 3-(14-hydroxy-12-(hydroxymethyl)-4,8-dimethyltetradeca-3,7,11-trien-1-yl)furan **149** was isolated as a light yellow viscous oil (12 mg). $^1H$ NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers*; $\nu_{max}/cm^{-1}$ (film) 3338 (OH), 2926, 2857, 1447, 1381, 1165, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.69* (3H, s), 1.90-2.20 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.24 [2H, q, *J* 7.2, C(6)$H_2$], 2.42 [2H, t, *J* 5.9, C(17)$H_2$], 2.45 [2H, t, J 7.4, C(5)$H_2$], 3.71 [2H, t, *J* 5.9, C(18)$H_2$], 4.04 [2H, s, C(19)$H_2$], 5.02-5.20 [2H, m, C(7)*H* and C(11)*H*], 5.51-5.59 [1H, m, C(15)*H*], 6.28 [1H, s, C(2)*H*], 7.20 [1H, s, C(4)*H*],

7.34 [1H, s, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.9 [$CH_2$, *C*(6)$H_2$], 28.4 [$CH_2$, *C*(14)$H_2$], 38.9 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 73.3, 111.1 [CH, *C*(2)H], 123.8 [CH,n *C*(7)H], 124.8 [CH, *C*(11)H], 125.0 [C, *C*(3)], 131.3 [$CH_2$, *C*(15)$H_2$], 134.3 [CH, *C*(12)], 135.7 [CH, *C*(8)], 136.0 [C, *C*(3)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 14.2, 15.8 (*C*$H_3$), 16.0 (*C*$H_3$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 28.4 (*C*$H_2$), 31.4 (*C*$H_2$), 32.4 (*C*$H_2$), 39.3 (*C*$H_2$), 39.9 (*C*$H_2$), 60.6, (*C*$H_2$) 123.9 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 125.4 (*C*H), 125.6 (*C*H), 131.0 (*C*H), 131.1 (*C*H), 131.2 (*C*H), 134.4 (*C*), 134.5 (*C*), 134.6 (*C*), 135.6 (*C*), 135.8 (*C*), 136.2(*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{33}O_3$ $(M+H)^+$ 333.2430. Found 333.2445 $(M+H)^+$; m/z (ESI+) 333.3 $(M+H)^+$.

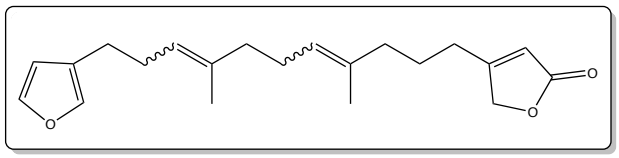
**Method B: Lactonisation of 146 succeeding "ate" complex reduction.**

The crude residue was taken up in tetrahydrofuran (5 mL) and water (1 mL) was added. The acidity of the mixture was adjusted to pH 1 using *aqueous* hydrochloric acid (10%) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and extracted with diethyl ether (4 x 10 mL) and the combined organic layers were washed successively with saturated aqueous sodium hydrogen carbonate (3 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a two-component mixture as a yellow oil consisting of the title lactone **147** and its corresponding saturated lactone **148** in a 75:25 ratio of products respectively. The crude yellow oil was purified by column chromatography on silica gel (0-10% ethyl acetate gradient in hexane) to afford the title lactone **147** (64 mg, 54%) as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A**.

The more polar fraction, 3-(4,8-dimethyl-11-(5-oxotetrahydrofuran-3-yl)undeca-3,7-dien-1-yl)furan **148** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A**.

### 4.11.2.4 Synthesis of furospongolide 1

**Method A: Neutral aluminium trioxide.**[85]



Neutral aluminium trioxide was added to a stirring solution of **147** (19 mg, 0.058 mmol) in toluene (5 mL) at room temperature. After 16 h, the reaction mixture was filtered and the solvent was removed under reduced pressure to afford furospongolide **1** (14.4 mg, 76 %) as a colourless oil. Furospongolide **1** was found to contain 47% of the (*E,E*)-isomer, 43% of the (*Z,E*)-isomer and 10% other(s) as determined by HPLC analysis (***Appendix V***). Spectroscopic characteristics are consistent with those previously reported.[29,77] $\nu_{max}/cm^{-1}$ (film) 2926, 2856, 1780 (C=O), 1748 (C=O), 1637 (C=C), 1501, 1447, 1380, 1169, 1025, 888, 874; $\delta_H$ ($CDCl_3$, 300 MHz) 1.60 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.60-1.75 [2H m, C(14)$H_2$], 1.94-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.25 [2H, q, *J* 7.2, C(6)$H_2$], 2.35 [2H, t, *J* 7.6, C(15)$H_2$], 2.39-2.50 [2H, m, C(5)$H_2$], 4.69-4.75 [2H, m, C(19)$H_2$], 5.05-5.25 [2H, m, C(7)*H* and C(11)*H*], 5.80-5.87 [1H, m, C(17)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.7 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.2 [$CH_2$, *C*(15)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.9 [$CH_2$, *C*(6)$H_2$], 28.4 [$CH_2$, *C*(14)$H_2$], 38.9 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 73.0 [$CH_2$, *C*(19)$H_2$], 111.0 [CH, *C*(2)H], 115.4 [CH, *C*(17)H], 123.9 [CH, *C*(7)H], 124.9 [C, *C*(3)], 125.7 [CH, *C*(11)H], 133.4 [C, *C*(12)], 135.5 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 170.4 [C, *C*(16)], 174.2 [C, *C*(18)]; Characteristics peaks for the other isomer(s)* 23.2 (*C*$H_3$), 26.4 (*C*$H_2$), 27.9 (*C*$H_2$), 28.2 (*C*$H_2$), 29.7 (*C*$H_2$), 31.1 (*C*$H_2$), 31.8 (*C*$H_2$), 38.9 (*C*$H_2$), 39.8 (*C*$H_2$), 124.1 (*C*H), 124.7 (*C*H), 125.6 (*C*H), 126.3 (*C*H), 135.7 (*C*), 142.5 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_3$ $(M+H)^+$ 329.2117. Found 329.2102 $(M+H)^+$; m/z (ESI+) 329.2 $(M+H)^+$.

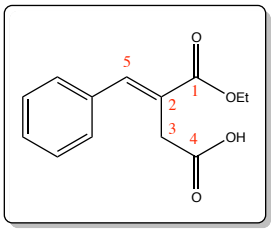
**Method B: DBU**.

1,8-diazabicycloundec-7-ene (57 µL, 58 mg, 0.38 mmol) was added dropwise to a stirring solution of the lactone **147** (50 mg, 0.15 mmol) in tetrahydrofuran (3 mL) at room temperature. After 16 h, the reaction mixture was cooled to 0 $^oC$ and quenched with the addition of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to give furospongolide **1** (43 mg, 86%) as a colourless oil. Spectroscopic characteristics are consistent with those previously described in **Method A**.

## 4.11.3 Synthesis of 4-benzyl-2,5-dihydrofuran-2-one

For the purpose of characterisation, the name and the numbering of these compounds were as described in the literature.[87]

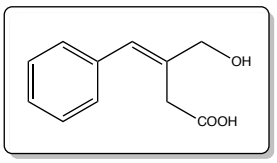
### 4.11.3.1 Synthesis of 1-ethyl 4-hydrogen 2-benzylidenesuccinate 128 [81,84,85,88,89]




The title compound was synthesised according to the procedure described for **122** (**Method C**) using ethoxy-oxo-2-(triphenylphosphoranylidene)-4-butanoic acid **122** (5.0 g, 12.3 mmol, 2.4 equiv), hydroquinone (0.51 g, 4.62 mmol, 0.9 equiv), benzaldehyde **127** (0.53 mL, 0.54 g, 5.13 mmol) in toluene (12 mL) at room temperature over 48 h. The residue was subjected to column chromatography on silica gel (30-50% ethyl acetate gradient in hexanes) to afford the title ester **128** (0.49 g, 46%) as an off white crystalline solid. Spectroscopic characteristics are consistent with those previously reported;[90] $\nu_{max}/cm^{-1}$ (film); 3500-2400 (OH), 1709 (C=O), 1413, 1374, 1273, 1204, 1099, 1022, 767, 698; $\delta_H$ ($CDCl_3$, 400 MHz) 1.35 [3H, t, *J* 7.1, C(1)OCH$_2$C*H*$_3$], 3.59 [2H, s, C(3)*H*$_2$], 4.31 [2H, q, *J* 7.1 C(1)C*H*$_2$CH$_3$], 7.32-7.46 [5H, m, Ar*H*], 7.93 [1H, s, C(5)*H*]; HRMS (ESI+): Exact mass calculated for $C_{13}H_{15}O_4$ $(M+H)^+$ 235.0970. Found 235.0966 ($M+H^+$); m/z (ESI+) 235.3 $(M+H)^+$.

### 4.11.3.2 Synthesis of 3-hydroxymethyl-4-phenylbut-3-enoic acid 144

**Method A: Selective reduction using $LiAlH_4$.[87]**



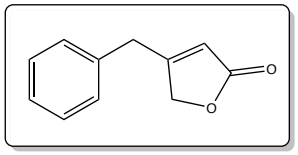

A solution of 1-ethyl 4-hydrogen 2-benzylidenesuccinate **128** (350 mg, 1.49 mmol) in tetrahydrofuran (3 mL) was added slowly to a stirring suspension of lithium aluminium hydride (57 mg, 1.49 mmol) in tetrahydrofuran (2 mL) at -10 $^oC$ and the reaction mixture was stirred at 0°C for 2 h. The excess of hydride was decomposed with ethyl acetate (2 mL) before water (5 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined and concentrated under reduced pressure to afford a crude mixture as a light yellow oil with the major product identified as the title γ-hydroxy acid **144**. Due to the relative instability of the title complex,[91] it was used immediately in the next step without further purification and characterization. Spectroscopic data was extracted from a spectrum of the crude mixture; $\delta_H$ ($CDCl_3$, 300 MHz) 3.32 [2H, s, C(3)*H*$_2$], 4.30 [2H, s, C(1)*H*$_2$], 4.66 [1H, brs, O*H*], 6.74 [1H, s, C(5)*H*], 7.18-7.38 [5H, m, Ar*H*].

**Method B: Selective reduction using an "ate" complex.**[91,92]

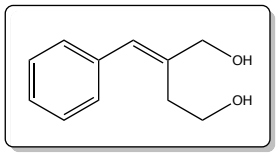
The title compound was synthesised according to the procedure described for **122** using *n*-butyllithium (2.50 M in hexane, 0.9 mL, 2.24 mmol, 3.5 equiv), diisobutylaluminium hydride (1.0 M in hexane, 2.24 mL, 2.24 mmol, 3.5 equiv) and 1-ethyl 4-hydrogen 2-benzylidenesuccinate **128** (150 mg, 0.64 mmol, 1 equiv) in tetrahydrofuran (5 mL) to afford the title γ-hydroxy acid **144** (86 mg, 70 %) as a crude yellow oil, which was used immediately in the next step without further purification. Spectroscopic characteristics were consistent with those described in **Method A**.

### 4.11.3.3 Synthesis of 4-benzyl-2,5-dihydrofuran-2-one 143

**Method A: Lactonisation/isomerisation of 144 succeeding $LiAlH_4$ reduction.**[87]



The crude γ-hydroxy acid **144** was dissolved in tetrahydrofuran (5 mL) and acidified with *aqueous* hydrochloric acid (10%) to pH 2. The reaction mixture was heated under reflux at 85 $^{o}$C for 8 h before cooling to room temperature and extracting with ethyl acetate (3 x 10 mL). The combined organic extracts were washed successively with saturated aqueous sodium hydrogen carbonate (10 mL) brine (10 mL), and evaporated under reduced pressure to afford a complex mixture of products consisting primarily of the title benzyl butenolide **143** and its corresponding diol **145** in a 70:30 ratio respectively. The residue was purified by column chromatography on silica gel (3-30% ethyl acetate gradient in hexanes) to afford the title benzyl butenolide **143** (47 mg, 18%) as a colourless oil. Spectroscopic characteristics were consistent with those previously reported in the literature;[87] $\nu_{max}/cm^{-1}$ (film); 3031 (OH), 2929 (CH), 1782 (C=O), 1748 (C=O), 1641, 1603 (C=C), 1496, 1454, 1344, 1248, 1169, 1125, 1030, 887, 763, 700; $\delta_H$ ($CDCl_3$, 300 MHz) 3.74 [2H, s, C(6)$H_2$], 4.69-4.73 [2H, m, C(5)$H_2$], 5.78-5.84 [1H, m, C(3)*H*], 7.10-7.40 [5H, m, Ar*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 35.3 [$CH_2$, *C*(6)$H_2$], 72.7 [$CH_2$, *C*(5)$H_2$], 116.6 [$CH_2$, *C*(3)$H_2$], 127.5 [CH, Ar*C*H], 128.7 [CH, Ar*C*H], 129.1 [CH, Ar*C*H], 135.6 [C, Ar*C*], 169.0 [C, *C*(4)], 173.7 [C, *C*(2)]; HRMS (ESI+): Exact mass calculated for $C_{11}H_{11}O_2$ $(M+H)^+$ 175.0759 Found 175.0751 $(M+H)^+$; m/z (ESI+) 173.3 $(M-H)^+$.



The most polar fraction, 2-phenylmethylidene-1,4-butanediol **145** (17 mg, 6%) was isolated as a viscous yellow oil. Spectroscopic characteristics are consistent with those previously reported;[93,94] $\nu_{max}/cm^{-1}$ (film); 3324 (OH), 2925, 1668, 1455, 1028; $\delta_H$ ($CDCl_3$, 300 MHz) 2.62 [2H, t, *J* 5.9, C(3)$H_2$], 3.81 [2H, t, *J* 5.9, C(4)$H_2$], 4.25 [2H, s, C(1)$H_2$], 6.65 [1H, s, C(5)*H*], 7.15-7.40 [1H, s, C(5)*H*]; $\delta_C$

($CDCl_3$, 75.5 MHz) 32.9 [$CH_2$, *C*(3)$H_2$], 61.8 [$CH_2$, *C*(4)$H_2$], 68.6 [$CH_2$, *C*(1)$H_2$], 126.9 [CH, Ar*C*H], 128.3 [CH, Ar*C*H], 128.7 [CH, Ar*C*H], 129.9 [CH, *C*(5)H], 137.0 [C, Ar*C*], 139.0 [C, *C*(2)]; HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_2$ $(M+H)^+$ 179.0994. Found 179.0990 $(M+H)^+$; m/z (ESI+) 179.2 $(M+H)^+$.

**Method B: Lactonisation/isomerisation of 144 succeeding "ate" complex reduction.**[87]

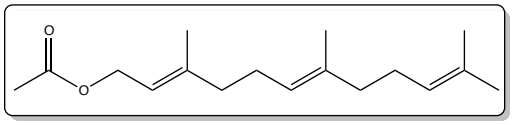
The crude γ-hydroxy acid **144** was taken up in tetrahydrofuran (5 mL) and water (1 mL) was added. The acidity of the mixture was adjusted to pH 1 using aqueous hydrochloric acid solution (10 %) and the reaction mixture was heated to reflux and stirred for 16 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and extracted with diethyl ether (4 x 10 mL). The combined organic layers were washed successively with sodium hydrogen carbonate (3 x 10 mL), brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a two-component mixture consisting of the title benzyl butenolide **143** and an unknown impurity in a 78:22 ratio of products respectively. The crude residue was purified by column chromatography on silica gel (10-30% ethyl acetate gradient in hexanes) to afford the title benzyl butenolide **143** (54 mg, 49 % over three steps) as a colourless oil. Spectroscopic characteristics were consistent with those previously described in **Method A**.

The most polar fraction was an unknown impurity isolated as a light yellow oil. Characteristic peaks associated with the unknown impurity were identified by $^1$H NMR analysis of the crude product. $\delta_H$ ($CDCl_3$, 300 MHz) 1.65-1.77 (2H, m), 1.83-1.93 (1H, m), 3.59 (2H, t, *J* 6.6), 3.69 (2H, t, *J* 6.3), 7.10-7.40 (5H, m, Ar*H*).

## 4.12 Synthesis of (*E,E*)-furospongolide

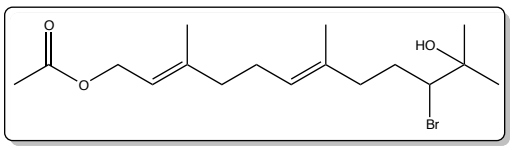
Note: In order to synthesis (*E,E*)-furospongolide, *trans,trans*-farnesol **7** was purchased from Sigma Aldrich.

### 4.12.1 Synthesis of (2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate 59 [18]



The title compound was prepared following the procedure described previously for **59** using *trans,trans*-farnesol **7** (2.0 g, 9.0 mmol), triethylamine (1.88 mL, 1.37 g, 13.5 mmol), 4-dimethylaminopyridine (0.06 g, 0.49 mmol, 5 mol%) and acetic anhydride (1.02 mL, 1.10 g 10.8 mmol) in dichloromethane (40 mL) to afford *trans,trans*-farnesyl acetate **59** (2.37 g, *quantitative*) as a colourless oil, which was used in the next step without further purification. Spectroscopic characteristics are consistent with those reported in the literature.[19] *trans,trans*-Farnesyl acetate **59** is commercially available from Sigma Aldrich. $\nu_{max}/cm^{-1}$ (film) 2967, 2920, 2858, 1742 (C=O), 1446, 1378, 1366, 1233, 1023 (CO), 956, 833; $\delta_H$ ($CDCl_3$, 300 MHz) 1.60 (6H, s), 1.68 (3H, s), 1.71 (3H, s), 1.90-2.18 [11H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(9)$H_2$ and containing 3H, s, C(O)C$H_3$], 4.59 [2H, d, *J* 7.1, C(1)$H_2$], 5.03-5.15 [2H, m, C(6)*H* and C(10)*H*], 5.35 [1H, td, *J* 7.1, 1.2, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 16.4 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 17.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 25.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.2 [$CH_2$, *C*(9)$H_2$], 26.7 [$CH_2$, *C*(5)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 39.7 [$CH_2$, *C*(8)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 118.3 [CH, *C*(2)H], 123.6 [CH, *C*(10)H], 124.3 [CH, *C*(6)H], 131.3 [C, *C*(11)], 135.5 [C, *C*(3)], 142.2 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$].

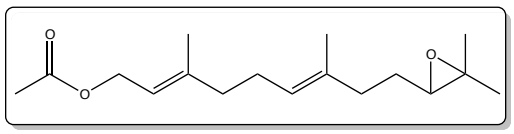
### 4.12.2 Synthesis of (2*E*,6*E*)-10-bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl acetate 61[42,43]




The title compound was prepared following the procedure described previously for **61** using *trans,trans*-farnesyl facetate **59** (2.30 g, 8.70 mmol), *N*-bromosuccinimide (1.70 g, 9.60 mmol) in *tert*-butanol (80 mL) and water (140 mL) to give the crude bromohydrin intermediate **61** as a faint yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[44] $\nu_{max}/cm^{-1}$ (film) 3446 (OH), 2974, 1732 (C=O), 1446, 1368, 1236; $\delta_H$ ($CDCl_3$, 400 MHz) 1.34 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.35 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.60 [3H, s, C(13)$H_3$ or C(14)$H_3$], 1.65-1.87 [5H, m, C(9)$H_2$ and containing 3H, s, C(13)$H_3$ or C(14)$H_3$], 1.90-2.25 [8H, m,

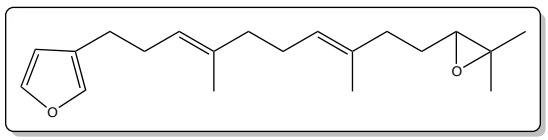
C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.96 [1H, dd, *J* 11.4, 1.9, C(10)*H*], 4.59 [2H, d, *J* 7.0, C(1)$H_2$], 5.19 [1H, td, *J* 6.3, 1.2 C(6)*H*], 5.35 [1H, td, *J* 7.1, 1.2, C(2)*H*].

### 4.12.3 Synthesis of (2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate 60 [45]



The title compound was prepared following the procedure described previously for **60** using 1,8-diazabicyclo[5.4.0]undec-7-ene (1.69 mL, 1.72 g, 11.3 mmol) and the bromohydrin intermediate **61** in tetrahydrofuran (35 mL) to afford the crude residue **60**, which was purified by column chromatography on silica gel (1-10% ethyl acetate gradient in hexanes) to provide the title epoxide **60** (1.51 g, 63% over 2 steps) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[18,19] $\nu_{max}$/cm$^{-1}$ (film) 2927, 1739 (C=O), 1449, 1379, 1367, 1233, 1123 (C-O), 1024, 956, 873, 681; $\delta_H$ ($CDCl_3$, 300 MHz) 1.26 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.30 [3H, s, C(12)$H_3$ or C(15)$H_3$], 1.54-1.68 [5H, m, C(9)$H_2$ and containing 3H, s, C(13)$H_3$ or C(14)$H_3$], 1.71 [3H, s, C(13)$H_3$ or C(14)$H_3$], 1.97-2.22 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.70 [1H, t, *J* 6.2, C(10)*H*], 4.58 [2H, d, *J* 7.1, C(1)$H_2$], 5.09-5.20 [1H, td, *J* 6.3, 1.2, C(6)*H*], 5.28-5.42 [1H, td, *J* 7.1, 1.2, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 16.5 [$CH_3$, *C*(13)$H_3$ or *C*(14)$H_3$], 18.7 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 24.9 [$CH_3$, *C*(12)$H_3$ or *C*(15)$H_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 27.4 [$CH_2$, *C*(9)$H_2$], 36.3 [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 58.3 [C, *C*(11)], 61.3 [$CH_2$, *C*(1)$H_2$], 64.1 [CH, *C*(10)H], 118.4 [CH, *C*(2)H], 124.2 [CH, *C*(6)H], 134.6 [C, *C*(7)], 142.0 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$]; HRMS (ESI+): Exact mass calculated for $C_{17}H_{29}O_3$ $(M+H)^+$ 281.2117. Found 218.2126 $(M+H)^+$; m/z (ESI+): 281.2 $(M+H)^+$.

### 4.12.4 Synthesis of (3*E*,7*E*)-3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)furan 113 [95,96]



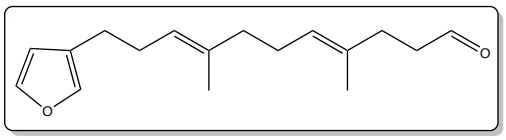
The title compound was prepared following the procedure described previously for **113** using freshly ground magnesium (1.92 g, 78.8 mmol), 1,2-dibromoethane (0.2 mL), 3-furylmethyl bromide **14** (1.27 g, 7.8 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 1.4 mL, 0.14 mmol, 3.9 mol%) and (2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (1.0 g, 3.6 mmol) in

tetrahydrofuran (47 mL) to afford a three-component mixture consisting of the desired title furanolipid epoxide **113**, 1,2-di(furan-3-yl)ethane **32** and unreacted starting material **60** in a 85:10:5 ratio of products respectively. The crude residue was purified by column chromatography on silica gel (0-10% ethyl acetate gradient in hexanes) to give the title furanolipid epoxide **113** (0.76 g, 77% based on the consumed acetate) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[97] $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2856 (CH), 1450, 1378, 1026 (CO), 874, 779; (Found C, 79.29; H, 9.95. $C_{20}H_{30}O_2$ requires C, 79.42; H, 10.0%); $\delta_H$ ($CDCl_3$, 300 MHz) 1.26 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.30 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.50-1.73 [8H, m, C(14)$H_2$ and containing 2 x 3H, s, C(18)$H_3$ and C(19)$H_3$], 1.90-2.22 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 2.70 [1H, t, *J* 6.2, C(15)*H*], 5.10-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 18.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 24.9 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.5 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 36.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 58.3 [CH, *C*(16)H], 64.2 [CH, *C*(15)H], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.8 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.1 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; HRMS (ESI+): Exact mass calculated for $C_{20}H_{31}O_2$ $(M+H)^+$ 303.2324. Found 303.2313 $(M+H)^+$; m/z (ESI+) 303.4 $(M+H)^+$.

The least polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic characteristics are consistent with those described in **Section 4.3.3.1**.[76]

The most polar fraction, (2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** was isolated as a colourless oil and subsequently used in the next reaction. The percentage yield was calculated from a revised theoretical yield figure due to isolation of unreacted starting material **60** from the reaction mixture.[30]

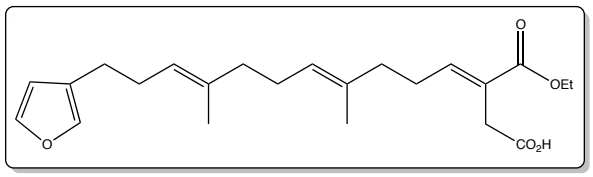
### 4.12.5 Synthesis of (3*E*,7*E*)-3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan 121



The title compound was prepared following the procedure described previously for **121** using **113** (0.60 g, 2.0 mmol) in diethyl ether (14 mL) and periodic acid (0.54 g, 2.4 mmol) in tetrahydrofuran (3 mL) to give a crude residue, which was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) to afford the title aldehyde **121** (0.46 g, 89%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2920 (CH), 2856 (CH), 1727 (C=O), 1501, 1446,

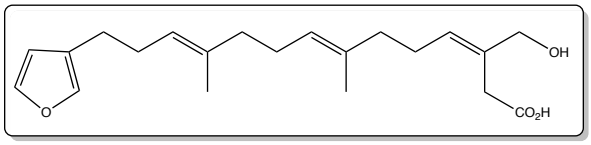
1384, 1164, 1066, 1025, 874, 781; (Found: C, 78.34; H, 9.42. $C_{17}H_{24}O_2$ requires C, 78.42; H, 9.29%); $\delta_H$ ($CDCl_3$, 300 MHz) 1.58 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.61 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.92-2.15 [4H, m, C(9)$H_2$ and C(10)$H_2$], 2.18-2.36 [4H, m, C(6)$H_2$ and C(13)$H_2$], 2.38-2.55 [4H, m, C(5)$H_2$ and C(14)$H_2$], 5.08-5.20 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*], 9.74 [1H, t, *J* 1.9, C(15)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.4 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 31.8 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 42.1 [$CH_2$, *C*(14)$H_2$], 111.1 [CH, *C*(2)H], 124.0 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.3 [CH, *C*(11)H], 133.0 [C, *C*(12)], 135.4 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 202.7 [CH, *C*(15)H]; HRMS (ESI+): Exact mass calculated for $C_{17}H_{25}O_2$ $(M+H)^+$ 261.1855. Found 261.1849 $(M+H)^+$; m/z (ESI+) 261.2 $(M+H)^+$.

### 4.12.6 Synthesis of (3*E*,7*E*,11*E*)-3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan 126



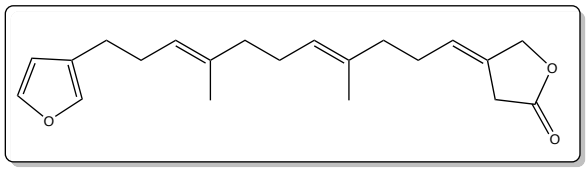

The title compound was prepared following the procedure described previously for **126** using **122** (1.31 g, 3.2 mmol, 2.4 equiv), hydroquinone (0.13 g, 1.2 mmol, 0.9 equiv) and (3*E*,7*E*)-3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (0.35 g, 1.35 mmol) in toluene (8 mL) to give a crude residue, which was purified by column chromatography on silica gel (10-50% ethyl acetate gradient in hexanes) to afford the title monoethyl ester **126** (0.35 g, 66%) as a light yellow oil; $\nu_{max}/cm^{-1}$ (film) 3300-2500 (OH), 1714 (CO), 1446, 1378, 1287, 1198, 1117, 1064, 1025; (Found C, 71.10; H, 8.33. $C_{23}H_{32}O_5$ requires C, 71.11; H, 8.33%); $\delta_H$ ($CDCl_3$, 300 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2CH_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.93-2.17 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.18-2.35 [4H, m, C(6)$H_2$ and C(14)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 3.38 [2H, s, C(17)$H_2$], 4.21 [2H, q, *J* 7.1, C(19)$O_2CH_2CH_3$], 5.07-5.25 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 6.97 [1H, t, *J* 7.4, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.2 [$CH_3$, C(19)$O_2CH_2CH_3$], 15.9 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.6 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 32.3 [$CH_2$, *C*(17)$H_2$], 38.1 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 61.0 [$CH_2$, C(19)$O_2CH_2CH_3$], 111.1 [CH, *C*(2)H], 123.9 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.5 [CH, *C*(11)H], 133.4 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 145.8 [CH, *C*(15)H], 167.1 [C, *C*(19)=O, ester], 176.4 [C, *C*(18)=O, acid]; HRMS (ESI+): Exact mass calculated for $C_{23}H_{33}O_5$ $(M+H)^+$ 389.2328. Found 389.2320 $(M+H)^+$; m/z (ESI+) 389.3 $(M+H)^+$.

### 4.12.7 Synthesis of (3*E*,7*E*,11*E*)-3-(13-carboxy-12-(hydroxymethyl)-4,8-dimethyltrideca-3,7,11-trien-1-yl)furan 146



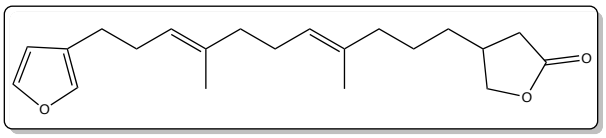

The title compound was prepared following the procedure described previously for **146** using *n*-butyllithium (2.5 M in hexane, 0.81 mL, 2.0 mmol), diisobutylaluminium hydride (1.0 M in hexane, 2.03 mL, 2.0 mmol), (3*E*,7*E*,11*E*)-3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan **126** (0.22 g, 0.6 mmol) in tetrahydrofuran (11 mL). The reaction was quenched with saturated sodium potassium tartrate (20 mL) and stirring was continued for 2 h. The reaction was worked up in the usual manner as previously stated. Due to the instability of the title complex **146**,[91] the crude product was carried through to the next step without further purification; $\nu_{max}/cm^{-1}$ (film) 3146 (OH), 2925 (CH), 2856, 1708 (C=O), 1588, 1440, 1165, 1065, 1026, 874, 771; $\delta_H$ ($CDCl_3$, 400 MHz) 1.59 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.90-2.20 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.24 [2H, q, *J* 7.7 C(6)$H_2$], 2.45 [2H, t, *J* 7.6, C(5)$H_2$], 3.22 [2H, s, C(17)$H_2$], 4.13 [2H, s, C(19)$H_2$], 5.11 [1H, t, *J* 7.0, C(11)*H*], 5.16 [1H, t, *J* 6.7, C(7)*H*], 5.55-5.70 [1H, m, C(15)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, s, C(1)*H*]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{31}O_4$ $(M+H)^+$ 347.2222. Found 347.2225 $(M+H)^+$; m/z (ESI+) 347.2 $(M+H)^+$.

### 4.12.8 Synthesis of (3*E*,7*E*,11*E*)-3-(4,8-dimethyl-11-(5-oxodihydrofuran-3(2H)-ylidene)undeca-3,7-dien-1-yl)furan 147




The title compound was prepared following the procedure described previously for **147** following treatment of the crude γ-hydroxy acid **146** with 10 % *aqueous* hydrochloric acid solution in tetrahydrofuran (5 mL) and water (1 mL) at room temperature over 20 h to give a two-component mixture consisting of the title furanolipid lactone **147** and its corresponding saturated lactone **148** in a 72:28 ratio of products respectively. The crude yellow oil was purified by column chromatography on silica gel (1-10% ethyl acetate gradient in hexanes) to afford the title lactone **147** (101 mg, 54% over two steps), which was isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2856, 1780 (C=O), 1725 (C=O), 1501, 1439, 1400, 1381, 1344, 1246, 1167, 1022, 874, 840, 780, 723; $\delta_H$ ($CDCl_3$, 400 MHz) 1.59 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.95-2.17 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.25 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 3.10-3.16 [2H, m, C(17)$H_2$], 4.78-

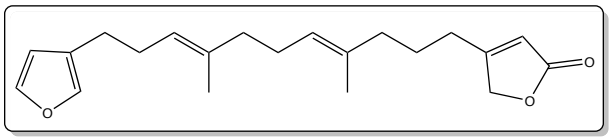
4.83 [2H, m, C(19)$H_2$], 5.11 [1H, td, *J* 6.8, 1.1, C(11)*H*], 5.16 [1H, td, *J* 7.0, 1.2, C(7)*H*], 5.36-5.50 [1H, m, C(15)*H*], 6.28 [1H, s, C(2)*H*], 7.20 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.7 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(14)$H_2$], 28.1 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 31.3 [$CH_2$, *C*(17)$H_2$], 38.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 72.3 [$CH_2$, *C*(19)$H_2$], 111.1 [CH, *C*(2)H], 123.9 [CH, *C*(7)H], 124.2 [CH, *C*(15)H], 124.9 [C, *C*(3)], 125.2 [CH, *C*(11)H], 128.6 [C, *C*(16)], 133.7 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 175.6 [C, *C*(18)]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_3$ $(M+H)^+$ 329.2117. Found 329.2118 $(M+H)^+$; m/z (ESI+) 329.4 $(M+H)^+$.



The more polar fraction, (3*E*,7*E*)-3-(4,8-dimethyl-11-(5-oxotetrahydrofuran-3-yl)undeca-3,7-dien-1-yl)furan **148** (34 mg, 18%) was isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2926 (CH), 2857, 1780 (C=O), 1501, 1446, 1382, 1257, 1168, 1065, 1024, 874, 838, 780, 725; (Found C, 75.91; H, 9.35. $C_{21}H_{30}O_3$ requires C, 76.33; H, 9.15%); $\delta_H$ ($CDCl_3$, 300 MHz)* 1.33-1.50 [4H, m, C(14)$H_2$ and C(15)$H_2$], 1.58 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.90-2.22 [7H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(17)*H*], 2.25 [2H, q, *J* 7.2, C(6)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 2.48-2.68 [2H, m, C(16)*H* and C(17)*H*], 3.91 [1H, dd, *J* 9.0, 7.1, C(19)*H*], 4.41 [1H, dd, *J* 9.0, 7.4, C(19)*H*], 5.10 [1H, td, *J* 6.8, 1.1, C(11)*H*], 5.16 [1H, td, *J* 7.0, 1.1, C(7)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.6 ($CH_2$, *C*(14)$H_2$), 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 32.6 [$CH_2$, *C*(15)$H_2$], 34.5 [$CH_2$, *C*(17)$H_2$], 35.7 [CH, *C*(16)H], 39.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 73.4 [$CH_2$, *C*(19)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.9 [C, *C*(3)], 124.9 [CH, *C*(11)H], 134.1 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 177.2 [C, *C*(18)]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{31}O_3$ $(M+H)^+$ 331.2273. Found 331.2267 $(M+H)^+$; m/z (ESI+) 331.4 $(M+H)^+$.

*$\delta_H$ ($CDCl_3$, 600 MHz) 1.33-1.50 [4H, m, C(14)$H_2$ and C(15)$H_2$], 1.58 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.94-2.12 [7H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.17 [1H, dd, *J* 17.1, 8.0, C(17)*H*], 2.25 [2H, q, *J* 7.3, C(6)$H_2$], 2.45 [2H, t, *J* 7.6, C(5)$H_2$], 2.50-2.58 [1H, m, C(16)*H*], 2.62 [1H, dd, *J* 17.1, 8.4, C(17)*H*], 3.91 [1H, dd, *J* 8.9, 7.4, C(19)*H*], 4.41 [1H, dd, *J* 8.9, 7.4, C(19)*H*], 5.09 [1H, td, *J* 6.9, 1.1, C(11)*H*], 5.16 [1H, td, *J* 7.0, 1.1, C(7)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6 C(1)*H*].

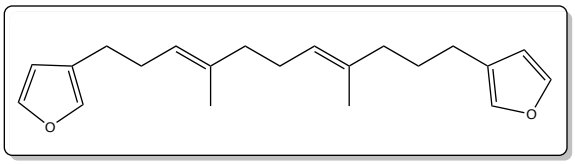
### 4.12.9 Synthesis of (3*E*,7*E*)-4-(4,8-dimethyl-11-(5-oxo-2,5-dihydrofuran-3-yl)undeca-3,7-dien-1-yl)furan 1



The title compound was prepared following the procedure described previously for **1** using 1,8-diazabicycloundec-7-ene (57 μL, 0.06 mg, 0.38 mmol) and **147** (0.05 g, 0.15 mmol) in tetrahydrofuran (2 mL) to give a crude yellow oil, which was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford furospongolide 1 (0.05 g, 99%) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[29,77] $\nu_{max}/cm^{-1}$ (film) 2926 (CH), 2856 (CH), 1779 (CO), 1749 (CO), 1639 (C=C), 1501, 1447, 1383, 1322, 1262, 1168, 1130, 1025, 886, 874, 854, 781, 725; (Found C, 76.73; H, 8.97. $C_{21}H_{28}O_3$ requires C, 76.79; H, 8.59%); $\delta_H$ ($CDCl_3$, 400 MHz) 1.60 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.69 [2H, quin, *J* 7.5, C(14)$H_2$], 1.96-2.14 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.25 [2H, q, *J* 7.5, C(6)$H_2$], 2.35 [2H, t, *J* 7.5, C(15)$H_2$], 2.45 [2H, t, *J* 7.5 C(5)$H_2$], 4.73 [2H, d, *J* 1.7, C(19)*H*], 5.11 [1H, td, *J* 7.0, 1.1, C(11)*H*], 5.16 [1H, td, *J* 7.0, 1.1, C(7)*H*], 5.82-5.86 [1H, m, C(17)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.7 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.2 [$CH_2$, *C*(15)$H_2$], 26.4 [$CH_2$, *C*(10)$H_2$], 27.8 [$CH_2$, *C*(6)$H_2$], 28.3 [$CH_2$, *C*(14)$H_2$], 38.8 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 73.0 [$CH_2$, *C*(19)$H_2$], 111.0 [CH, *C*(2)H], 115.3 [CH, *C*(17)H], 123.9 [CH, *C*(7)H], 124.9 [C, *C*(3)], 125.6 [CH, *C*(11)H], 133.4 [C, *C*(12)], 135.5 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 170.5 [C, *C*(16)], 174.1 [C, *C*(18)]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_3$ $(M+H)^+$ 329.2117. Found 329.2105 $(M+H)^+$; m/z (ESI+) 329.3 (M+H).

## 4.13 Synthesis of anhydrofurospongin-1

### 4.13.1 Synthesis of (3*E*,7*E*)-3,3'-(4,8-dimethylundeca-3,7-diene-1,11-diyl)difuran 164



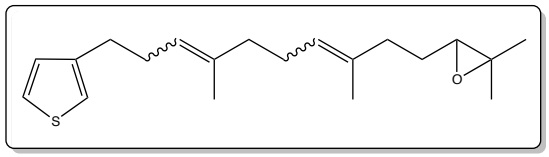
Diisobutylaluminium hydride (1M in hexane, 0.25 mL, 0.25 mmol, 4.2 equiv) was added to a stirring solution of furospongolide **1** (20 mg, 0.06 mmol) in dry dichloromethane (2 mL) under nitrogen atmosphere at -78$^{o}$C. After 1 h, methanol (1 mL) was added and the reaction was allowed warm to room temperature. A saturated solution of sodium potassium tartrate (5 mL) was added and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were washed successively with saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to afford anhydrofurospongin-1 **164** (14 mg, 74%) as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[98] $\nu_{max}$/cm$^{-1}$ (film) 2926, 2856, 1564, 1502, 1456, 1382, 1261, 1166, 1066, 1026, 874, 777, 722; (Found C, 80.35; H, 10.39. $C_{21}H_{28}O_2$ requires C, 80.72; H, 9.03%); $\delta_H$ ($CDCl_3$, 400 MHz) 1.59 [6H, s, C(20)$H_3$ and C(21)$H_3$], 1.59 [2H, quin, *J* 7.6, C(14)$H_2$], 1.94-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.4, C(6)$H_2$], 2.37 [2H, t, *J* 7.6, C(15)$H_2$], 2.44 [2H, t, *J* 7.6 C(5)$H_2$], 5.11 [1H, td, *J* 7.0, 1.2, C(11)*H*], 5.17 [1H, td, *J* 7.0, 1.2, C(7)*H*], 6.26 [2H, brs, C(2)*H* and C(17)*H*], 7.20 [2H, brs, C(4)*H* and C(19)*H*], 7.34 [2H, brs, C(1)*H* and C(18)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 24.2 [$CH_2$, *C*(15)$H_2$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.2 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 39.1 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 111.0 [CH, *C*(2)H or *C*(16)H], 111.1 [CH, *C*(2)H or *C*(16)H], 123.8 [CH, *C*(7)H], 124.6 [CH, *C*(11)H], 125.0 [C, *C*(3) or *C*(16)], 125.2 [C, *C*(3) or *C*(16)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H and *C*(19)H], 142.5 [CH, *C*(1)H or *C*(18)H], 142.6 [CH, *C*(1)H or *C*(18)H]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_2$ $(M+H)^+$ 313.2168. Found 313.2156 $(M+H)^+$; m/z (ESI+) 313.21 $(M+H)^+$.

It should be noted that elemental analysis for compound **164** was outside acceptable limits due to the presence of solvent in the sample.

# 4.14 Synthesis of thiophenospongolide

Note: The same numbering system previously shown for the furanolipid derivatives was used to number the thiophenolipid derivatives in this section.

## 4.14.1 Synthesis of 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)thiophene 165

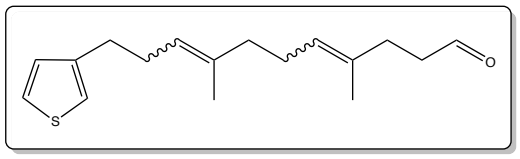


The title compound was prepared following the procedure described previously for **113** using magnesium (1.81 g, 74.6 mmol), 3-bromomethylthiophene **23** (1.32 g, 7.46 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 2.6 mL, 0.261 mmol, 3.5 mol%), 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (2.09 g, 7.46 mmol) in tetrahydrofuran (36 mL) to give a three-component mixture consisting of the title cross-coupled product **165,** 1,2-di(thiophen-3-yl)ethane **39** and unreacted epoxide starting material **60** in a 43:4:53 ratio of products respectively. The residue was purified by column chromatography on silica gel (0-10% ethyl acetate gradient in hexanes) to afford the title cross-coupled product **165** (0.85 g, 68% based on the consumed acetate) as a yellow oil. $^1$H NMR integration indicated a 78:22 ratio of *E,E* and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film); 2961 (CH), 2925, 2855, 1450, 1378, 1249, 1123 (C-O), 860, 836, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 1.26 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.27* (3H, s), 1.30 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.31* (3H, s), 1.53-1.74 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(18)$H_3$ and C(19)$H_3$], 1.90-2.23 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.31 [2H, q, *J* 7.3, C(6)$H_2$], 2.59-2.75 [3H, m, C(5)$H_2$ and C(15)*H*], 5.08-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.90-6.98 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 18.8 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 24.9 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.5 [$CH_2$, *C*(14)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 36.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 58.3 [C, *C*(16)], 64.2 [CH, *C*(15)H], 120.0 [CH, *C*(4)H], 123.8 [CH, *C*(7)H], 124.9 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.3 [CH, *C*(2)H], 134.1 [C, *C*(12)], 135.7 [C, *C*(8)], 142.7 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 18.7 (*C*$H_3$), 23.4 (*C*$H_3$), 24.9 (*C*$H_3$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.5 (*C*$H_2$), 28.6 (*C*$H_2$), 28.9 (*C*$H_2$), 29.6 (*C*$H_2$), 30.7 (*C*$H_2$), 31.9 (*C*$H_2$), 32.1 (*C*$H_2$), 39.9 (*C*$H_2$), 58.3 (*C*), 64.1 (*C*H), 64.2 (*C*H), 123.8 (*C*H), 124.3 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.7 (*C*H), 128.3 (*C*H), 134.1 (*C*), 134.3 (*C*), 135.6 (*C*), 135.8 (*C*) 142.7 (*C*); HRMS (ESI+): Exact mass calculated for $C_{20}H_{31}OS$ $(M+H)^+$ 319.2096. Found 319.2084 $(M+H)^+$; m/z (ESI+) 319.20 $(M+H)^+$.

The least polar fraction, 1,2-di(thiophen-3-yl)ethane **39** was isolated as a white crystalline solid. Spectroscopic characteristics were consistent with those previously described in ***Section 4.3.3.3.***

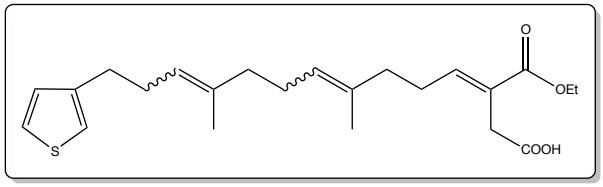
The most polar fraction, 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** was isolated pure and was used in subsequent reactions. The percentage yield was calculated from a revised theoretical yield figure due to isolation of unreacted starting material **60** from the reaction mixture.[30]

### 4.14.2 Synthesis of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene 166



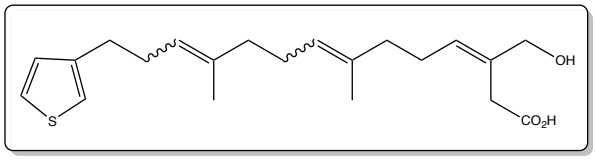

The title compound was prepared following the procedure described previously for **121** using 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)thiophene **165** (0.59 g, 1.85 mmol) and periodic acid (0.51 g, 2.22 mmol) in tetrahydrofuran (3 mL) and in diethyl ether (10 mL) to give a residue, which was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to provide the title aldehyde **166** (0.44 g, 85 %) as a faint yellow oil. $^1$H NMR integration revealed a 77:23 ratio mixture of *E*,*E* and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2919 (CH), 2854 (CH), 2720, 1727 (C=O), 1446, 1410, 1386, 1080, 835, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 1.57 [3H, s, C(16)*H*$_3$ or C(17)*H*$_3$], 1.61 [3H, s, C(16)*H*$_3$ or C(17)*H*$_3$], 1.68* (3H, s), 1.92-2.14 [4H, m, C(9)*H*$_2$ and C(10)*H*$_2$], 2.24-2.38 [4H, m, C(6)*H*$_2$ and C(13)*H*$_2$], 2.44-2.55 [2H, m, C(14)*H*$_2$], 2.66 [2H, t, *J* 7.6, C(5)*H*$_2$], 5.05-5.24 [2H, m, C(7)*H* and C(11)*H*], 6.90-6.98 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*], 9.74 [1H, t, *J* 1.9, C(15)*H*], 9.77* (1H, t, *J* 1.8); $\delta_C$ ($CDCl_3$, 300 MHz) 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 31.9 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 42.1 [$CH_2$, *C*(14)$H_2$], 120.0 [CH, *C*(4)H], 123.9 [CH, *C*(7)H], 125.0 [CH, *C*(1)H], 125.4 [CH, *C*(11)H], 128.3 [CH, *C*(2)H], 133.0 [C, *C*(12)], 135.5 [C, *C*(8)], 142.7 [C, *C*(3)], 202.6 [CH, *C*(15)H]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 23.1 (*C*$H_3$), 23.4 (*C*$H_3$), 24.3 (*C*$H_3$), 24.4 (*C*$H_3$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 30.7 (*C*$H_2$), 31.8 (*C*$H_2$), 32.0 (*C*$H_2$), 39.7 (*C*$H_2$), 42.3 (*C*$H_2$), 42.4 (*C*$H_2$), 124.0 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.5 (*C*H), 128.3(*C*H), 132.9 (*C*), 133.1 (*C*), 133.2 (*C*), 135.4 (*C*), 135.7 (*C*), 142.7 (*C*), 202.2 (*C*H), 202.3 (*C*H), 202.5 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{17}H_{25}OS$ $(M+H)^+$ 277.1626. Found 277.1616 $(M+H)^+$; m/z (ESI+) 277.3 $(M+H)^+$.

### 4.14.3 Synthesis of 3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)thiophene 167



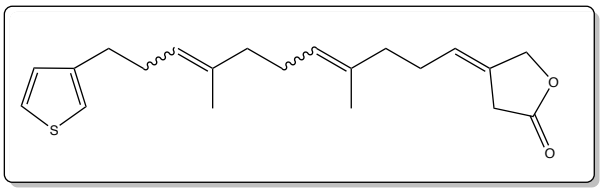

The title compound was prepared following the procedure described previously for **126** using 4-ethoxy-4-oxo-3-(triphenylphosphoranylidene)butanoic acid **122** (0.28 g, 0.69 mmol, 2.4 equiv), hydroquinone (29 mg, 0.26 mmol, 0.9 equiv), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (80 mg, 0.29 mmol, 1 equiv) in toluene (3 mL) at room temperature over 72 h to give a residue, which was purified by column chromatography on silica gel (10-50% ethyl acetate gradient in hexanes) to afford the title ester **167** (69 mg, 62 %) as a viscous light yellow oil. $^1$H NMR integration revealed a 77:23 ratio mixture of *E*,*E* and other isomer(s)*. $\nu_{max}$/cm$^{-1}$ (film) 3600-2400 (brm), 1715 (C=O), 1439, 1440, 1376, 1286, 1197, 1119, 1063, 771; $\delta_H$ ($CDCl_3$, 400 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2CH_3$], 1.57 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.68* (3H, s), 1.92-2.24 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24-2.37 [4H, m, C(6)$H_2$ and C(14)$H_2$], 2.66 [2H, t, *J* 7.4, C(5)$H_2$], 3.39 [2H, brs, C(17)*H*], 4.21 [2H, q, *J* 7.1, C(19)$O_2CH_2CH_3$], 5.08-5.24 [2H, m, C(7)*H* and C(11)*H*], 6.90-7.02 [3H, m, C(2)*H* and C(4)*H* and containing 1H, t, *J* 7.2 C(15)*H*], 7.20-7.25 [1H, m, C(1)*H*], 10.1 [1H, brs, COO*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.2 [$CH_3$, C(19)$O_2CH_2CH_3$], 16.0 [$CH_3$, *C*(20)$H_3$ and *C*(21)$H_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.6 [$CH_2$, *C*(14)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 31.8 [$CH_2$, *C*(17)$H_2$], 38.1 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 61.0 [$CH_2$, C(19)$O_2CH_2CH_3$], 120.0 [CH, *C*(4)H], 123.8 [CH, *C*(7)H], 125.0 [CH, *C*(1)H], 125.5 [CH, *C*(11)H], 128.4 [CH, *C*(2)H], 133.3 [C, *C*(16)], 133.4 [C, *C*(12)], 135.7 [C, *C*(8)], 142.8 [C, *C*(3)], 145.9 [CH, *C*(15)H], 167.1 [C, *C*(19)=O, ester], 176.4 [C, *C*(18)=O, acid]; Characteristics peaks for the other isomer(s)* 16.0 ($CH_3$), 23.2 ($CH_3$) 23.4 ($CH_3$), 26.5 ($CH_2$), 27.5 ($CH_2$), 28.9 ($CH_2$), 29.7 ($CH_2$), 30.7 ($CH_2$), 32.0 ($CH_2$), 39.8 ($CH_2$), 123.9 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 125.4 (*C*H), 126.4 (*C*H), 128.3 (*C*H), 132.1 (*C*), 133.7 (*C*), 135.5 (*C*), 135.8 (*C*), 145.7 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{23}H_{33}O_4S$ $(M+H)^+$ 405.2100. Found 405.2098 $(M+H)^+$; m/z (ESI+) 405.4 $(M+H)^+$.

### 4.14.4 Synthesis of 3-(13-carboxy-12-(hydroxymethyl)-4,8-dimethyltrideca-3,7,11-trien-1-yl)thiophene 168




The title compound was prepared following the procedure described previously for **146** using *n*-butyllithium (2.5 M in hexane, 0.062 mL, 0.156 mmol), diisobutylaluminium hydride (1.0 M in hexane, 0.16 mL, 0.156 mmol, 3.5 equiv), 3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)thiophene **167** (18 mg, 0.045 mmol) in tetrahydrofuran (2.5 mL). The reaction was quenched with saturated sodium potassium tartrate (2 mL) and worked up in the usual manner to afford the title γ-hydroxyl acid **168** as a crude yellow oil, which was used without further purification. $\nu_{max}/cm^{-1}$ (film) 3392 (OH), 2926 (CH), 2856, 1713 (C=O), 1456, 1379, 1261, 1081, 1020, 800; $\delta_H$ ($CDCl_3$, 400 MHz) 1.57 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.68* (3H, s), 1.92-2.22 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.31 [2H, q, *J* 7.4, C(6)$H_2$], 2.66 [2H, t, *J* 7.6, C(5)$H_2$], 3.23 [2H, s, C(17)$H_2$], 4.14 [2H, s, C(19)$H_2$], 5.05-5.25 [2H, m, C(7)*H* and C(11)*H*], 5.60-5.70 [1H, m, C(15)*H*], 6.91-6.97 [2H, m, C(2)*H* and C(4)*H*], 7.20-7.26 [1H, m, C(1)*H*].

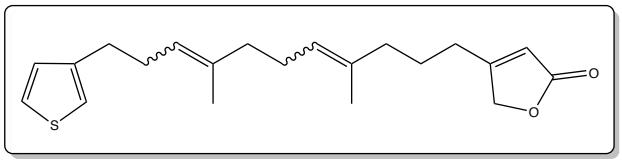
### 4.14.5 Synthesis of 3-(4,8-dimethyl-11-(5-oxodihydrofuran-3(2H)-ylidene)undeca-3,7-dien-1-yl)thiophene 169




The title compound was prepared following the procedure described previously for **147** following treatment of the crude γ-hydroxy acid **168** with 10 % *aqueous* hydrochloric acid solution (pH 1) in tetrahydrofuran (2 mL) and water (0.3 mL) to afford a two-component mixture (17 mg) as a faint yellow oil consisting of the title lactone **169** and its corresponding saturated lactone by-product **170** in a 60:40 ratio of products respectively. Purification was deemed unnecessary at this point and the crude mixture was carried forward to the succeeding reaction. Spectroscopic data for the title lactone **169** was extracted from the spectrum of the crude mixture. $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2856, 1780 (C=O), 1725 (C=O), 1439, 1381, 1167, 1022, 840, 780, 723, 679; $\delta_H$ ($CDCl_3$, 400 MHz) 1.58 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.68* (3H, s), 1.93-2.15 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.31 [2H, q, *J* 7.2, C(6)$H_2$], 2.66 [2H, t, *J* 7.1 C(5)$H_2$], 3.10-3.17 [2H, m, C(17)$H_2$], 4.78-4.84 [2H, m, C(19)$H_2$], 5.05-5.23 [2H, m, C(7)*H* and

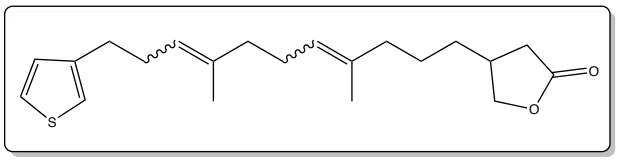
C(11)*H*], 5.37-5.48 [1H, m, C(15)*H*], 6.90-7.00 [2H, m, C(2)*H* and C(4)*H*], 7.20-7.26 [1H, m, C(1)*H*]; HRMS (ESI+): Exact mass calculated for $C_{21}H_{29}O_2S$ $(M+H)^+$ 345.1888. Found 345.1884 $(M+H^+)$. m/z (ESI+) 345.2 $(M+H)^+$.

### 4.14.6 Synthesis of 3-(4,8-dimethyl-11-(5-oxo-2,5-dihydrofuran-3-yl)undeca-3,7-dien-1-yl)thiophene 171



The title compound was prepared following the procedure described previously for furopongolide **1** using 1,8-diazabicyclo[5.4.0]undec-7-ene, (16.3 μL, 17 mg, 0.11 mmol), 3-(4,8-dimethyl-11-(5-oxodihydrofuran-3(2H)-ylidene)undeca-3,7-dien-1yl)thiophene **169** in tetrahydrofuran (1 mL) to afford a two-component mixture consisting of thiophenospongolide **171** and its corresponding saturated lactone by-product **170** in a 60:40 ratio of products respectively. The residue was purified by column chromatography on silica gel (1-10% ethyl acetate gradient in hexanes). The most polar fraction, thiophenospongolide **171** (7 mg, 47% over three transformations) was isolated as a faint yellow oil. $^1$H NMR integration revealed a 76:24 ratio mixture of *E*,*E* and other isomer(s)*; $\nu_{max}/cm^{-1}$ (film) 2926 (CH), 2856, 1781 (C=O), 1751 (C=O), 1639 (C=C), 1456, 1379, 1261, 1168, 1129, 1027, 886, 856, 782; $\delta_H$ ($CDCl_3$, 600 MHz) 1.57* (3H, s), 1.58 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.65-1.73 [2H, m, C(14)$H_2$], 1.95-2.13 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.27-2.40 [4H, m, C(6)$H_2$ and C(15)$H_2$], 2.66 [2H, t, *J* 7.1, C(5)$H_2$], 4.69-4.75 [2H, m, C(19)$H_2$], 5.08-5.22 [2H, m, C(7)*H* and C(11)*H*], 5.81-5.87 [1H, m, C(17)*H*], 6.92-6.97 [2H, m C(2)*H* and C(4)*H*], 7.22-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 150 MHz) 15.7 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.2 [$CH_2$, *C*(15)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.9 [$CH_2$, *C*(14)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 38.9 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 73.1 [$CH_2$, *C*(19)$H_2$], 115.4 [$CH_2$, *C*(17)$H_2$], 120.0 [CH, *C*(4)H], 123.8 [CH, *C*(7)H], 125.1 [CH, *C*(1)H], 125.2 [CH, *C*(11)H], 128.3 [CH, *C*(2)H], 133.4 [C, *C*(12)], 135.6 [C, *C*(8)], 142.7 [C, *C*(3)], 170.5 [C, *C*(16)], 174.2 [C, *C*(18), lactone]; Characteristics peaks for the other isomer(s)* 14.2 (*C*$H_3$), 16.0 (*C*$H_3$), 22.7 (*C*$H_3$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 23.4 (*C*$H_3$), 25.0 (*C*$H_2$), 25.3 (*C*$H_2$), 27.1 (*C*$H_2$), 27.9 (*C*$H_2$), 28.2 (*C*$H_2$), 28.4 (*C*$H_2$), 28.9 (*C*$H_2$), 29.4 (*C*$H_2$), 30.0 (*C*$H_2$), 30.4 (*C*$H_2$), 30.7 (*C*$H_2$), 31.8 (*C*$H_2$), 37.1 (*C*$H_2$), 38.9 (*C*$H_2$), 39.8 (*C*$H_2$), 111.1(*C*H), 115.3 (*C*H), 115.4 (*C*H), 123.9 (*C*H), 124.6 (*C*H), 124.8 (*C*H), 124.9 (*C*H), 125.6 (*C*H), 128.3 (*C*H), 133.5 (*C*), 133.7 (*C*), 135.4 (*C*), 135.5 (*C*), 135.7 (*C*), 142.6 (*C*), 170.3 (*C*), 170.4 (*C*), 174.1 (*C*); HRMS (ESI+): Exact

mass calculated for $C_{21}H_{29}O_2S$ $(M+H)^+$ 345.1888. Found 345.1879 $(M+H^+)$; m/z (ESI+) 345.2 $(M+H)^+$

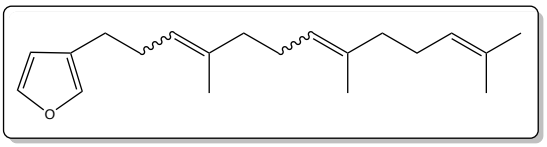


The least polar fraction, 3-(4,8-dimethyl-11-(5-oxotetrahydrofuran-3-yl)undeca-3,7-dien-1-yl)thiophene **170** was isolated (4 mg, 26% over two transformations) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2926, 2856, 1783 (C=O), 1459, 1379, 1261, 1168, 1020; $\delta_H$ ($CDCl_3$, 600 MHz) 1.35-1.50 [4H, m, C(14)$H_2$ and C(15)$H_2$], 1.66 [3H, s, C$H_3$* and C(20)$H_3$ or C(21)$H_3$], 1.69 [3H, s, C$H_3$* and C(20)$H_3$ or C(21)$H_3$], 1.95-2.12 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.14-2.21 [1H, m, C$H$* and containing 1H, dd, *J* 17.2, 7.9, C(17)$H$], 2.31 [2H, q, C(6)$H_2$], 2.45-2.58 [1H, m, C(16)$H$], 2.58-2.70 [3H, m C(5)$H_2$ and C(17)$H$], 3.87-3.95 [1H, m, C$H$* and containing 1H, dd, *J* 8.9, 7.3, C(19)$H$], 4.38-4.45 [1H, m, C$H$* and containing 1H, dd, *J* 8.9, 7.3, C(19)$H$], 5.05-5.22 [2H, m, C(7)$H$ and C(11)$H$], 6.92-6.97 [2H, m C(2)$H$ and C(4)$H$], 7.21-7.26 [1H, m, C(1)$H$]; $\delta_C$ ($CDCl_3$, 150.0 MHz) 15.8 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.6 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 32.6 [$CH_2$, *C*(15)$H_2$], 34.5 [$CH_2$, *C*(17)$H_2$], 35.7 [CH, *C*(16)H], 39.3 [$CH_2$, *C*(13)$H_2$], 39.9 [$CH_2$, *C*(9)$H_2$], 73.4 [$CH_2$, *C*(19)$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H or *C*(11)H], 125.0 [CH, *C*(1)H], 125.0 [CH, *C*(7)H or *C*(11)H], 128.3 [CH, *C*(2)H], 134.1 [C, *C*(8) or *C*(12)], 135.7 [C, *C*(8) or *C*(12)], 142.7 [C, *C*(3)], 177.3 [C, *C*(18)]; Characteristics peaks for the other isomer(s)* 14.2 (*C*$H_3$), 16.0 (*C*$H_3$), 22.7 (*C*$H_3$), 23.0 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 23.7 (*C*$H_3$), 25.5 (*C*$H_2$), 25.7 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.9 (*C*$H_2$), 29.7 (*C*$H_2$), 30.0 (*C*$H_2$), 30.4 (*C*$H_2$), 30.7 (*C*$H_2$), 31.4 (*C*$H_2$), 31.9 (*C*$H_2$), 32.9 (*C*$H_2$), 34.6 (*C*$H_2$), 35.7 (*C*$H_2$), 37.1 (*C*$H_2$), 38.7 (*C*$H_2$), 39.4 (*C*$H_2$), 73.3 (*C*$H_2$), 123.9 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.9 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 125.7 (*C*H), 134.2 (*C*), 134.4 (*C*), 135.6 (*C*), 135.8 (*C*), 177.2 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{31}O_2S$ $(M+H)^+$ 347.1967. Found 347.1970 $(M+H)^+$; m/z (ESI+) 347.2 $(M+H)^+$.

# 4.15 Synthesis of terpene, 3-substituted furan and thiophene analogues

## 4.15.1 Synthesis of furanolipid derivatives

### 4.15.1.1 Synthesis of 3-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)furan 112

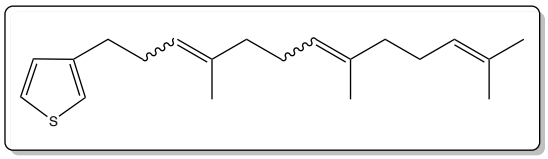


The title compound was prepared following the procedure described previously for **10** using magnesium (0.65 g, 26.6 mmol), 3-furylmethyl bromide **14** (0.43 g, 2.7 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 0.86 mL, 0.86 mmol, 10 mol%), farnesyl acetate **59** (0.23 g, 0.86 mmol) in tetrahydrofuran (8 mL) to afford a two-component mixture consisting of the desired cross-coupled product **112** and the Wurtz coupled product, 1,2-di(furan-3-yl)ethane **32** in a 85:15 ratio of products respectively. The residue was purified by column chromatography on silica gel (100% hexanes) to give the title furanolipid **112** (187 mg, 76%) as a colourless oil. $^{1}$H NMR integration indicated a 70:30 ratio of *E,E* and other isomer(s)*. Spectroscopic characteristics are consistent with those previously reported;[97,99] $\nu_{max}$/cm$^{-1}$ (film) 2921, 2856, 1513, 1447, 1377, 1139, 1065, 726; $\delta_H$ ($CDCl_3$, 300 MHz) 1.60 (9H, s, 3 x C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.92-2.14 [8H, m, C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$ and C(14)*H*$_2$], 2.25 [2H, q, *J* 5.3, C(6)*H*$_2$], 2.45 [2H, t, *J* 7.5, C(5)*H*$_2$], 5.05-5.22 [3H, m, C(7)*H* and C(11)*H* and C(15)*H*], 6.27 [1H, s, C(2)*H*], 7.20 [1H, s, C(4)*H*], 7.32 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(18)$H_3$ or *C*(19)$H_3$], 16.1 [$CH_3$, *C*(18)$H_3$ or *C*(19)$H_3$], 17.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)*C*$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 26.6 [$CH_2$, *C*(10)$H_2$ or *C*(14)$H_2$], 26.8 [$CH_2$, *C*(10)$H_2$ or *C*(14)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$ and *C*(13)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(15)H], 124.2 [CH, *C*(7)H or *C*(11)H], 124.4 [CH, *C*(7)H or *C*(11)H], 125.0 [C, *C*(3)], 131.2 [C, *C*(16)], 135.0 [C, *C*(8) or *C*(12)], 135.8 [C, *C*(8) or *C*(12)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 17.6 (*C*$H_3$), 22.7 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 25.5 (*C*$H_2$), 25.7 (*C*$H_2$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 26.6 (*C*$H_2$), 26.7 (*C*$H_2$), 28.4 (*C*$H_2$), 29.1 (*C*$H_2$), 29.4 (*C*$H_2$), 29.7 (*C*$H_2$), 31.6 (*C*$H_2$) (*C*$H_2$), 32.0 (*C*$H_2$), 32.3 (*C*$H_2$), 40.0 (*C*$H_2$), 110.9 (*C*H), 111.1 (*C*H), 124.1 (*C*H), 124.3 (*C*H), 124.4 (*C*H), 124.5 (*C*H), 124.6 (*C*H), 131.3 (*C*), 131.5 (*C*), 135.1 (*C*), 135.2 (*C*), 135.4 (*C*), 135.8 (*C*), 135.9 (*C*), 139.0 (*C*H), 142.6 (*C*H), 142.7 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{20}H_{31}O$ $(M+H)^+$ 287.2297. Found 287.2297 $(M+H)^+$; m/z (ESI+): 287.2 $(M+H)^+$.

The less polar fraction, 1,2-di(furan-3-yl)ethane **32** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously described in ***Section 4.3.3.1***.

## 4.15.2 Synthesis of thiophenolipid derivatives

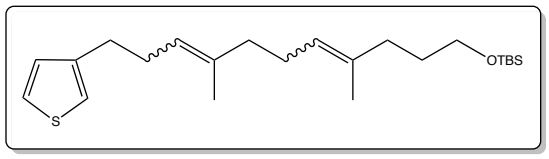
### 4.15.2.1 Synthesis of 3-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)thiophene 182



The title compound was prepared following the procedure described previously for **10** magnesium (0.60 g, 24.9 mmol), 3-bromomethylthiophene **23** (0.44 g, 2.49 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 0.77 mL, 0.077 mmol) and farnesyl acetate **59** (0.20 g, 0.78 mmol) in tetrahydrofuran (9 mL) to afford a two-component mixture consisting of the title cross-coupled product **182** and 1,2-di(thiophen-3-yl)ethane **39** in a 83:17 ratio of products as determine by $^1$H NMR integration of the crude product. The residue was purified by column chromatography on silica gel (neat hexanes) to afford the title cross-coupled product **182** (0.19 g, 81%) as a colourless oil; $\nu_{max}$/cm$^{-1}$ (film) 2965 (CH), 2924, 2855, 1448, 1377, 836, 773; $\delta_H$ ($CDCl_3$, 300 MHz) 1.57* (3H, s), 1.60 (9H, s, C$H_3$), 1.68 (3H, s, C$H_3$), 1.90-2.14 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.31 [2H, q, *J* 7.3, C(6)$H_2$], 2.66 [2H, t, *J* 7.2, C(5)$H_2$], 5.04-5.23 [3H, m, C(7)*H* and C(11)*H* and C(15)*H*], 6.90-6.98 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 17.7 [$CH_3$, *C*(17)$H_3$ or C(20)$H_3$], 25.7 [$CH_3$, *C*(17)$H_3$ or C(20)$H_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 26.8 [$CH_2$, *C*(14)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$ and *C*(13)$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.2 [CH, *C*(15)H], 124.4 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.4 [CH, *C*(2)H] 131.3 [C, *C*(16)], 135.0 [C, *C*(12)], 135.9 [C, *C*(8)], 142.8 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 23.4 (*C*$H_3$) 26.5 (*C*$H_2$), 26.7 (*C*$H_2$), 28.9 (*C*$H_2$), 30.7 (*C*$H_2$), 32.0 (*C*$H_2$), 39.7 (*C*$H_2$), 40.0 (*C*$H_2$), 124.1 (*C*H), 128.3 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{20}H_{31}S$ $(M+H)^+$ 303.2146. Found 303.2146 $(M+H)^+$; m/z (ESI+) 303.52 $(M+H)^+$.

The less polar fraction, 1,2-di(thiophen-3-yl)ethane **39** was isolated as a white crystalline solid and spectroscopic characteristics were consistent with those previously described in ***Section 4.3.3.3***.

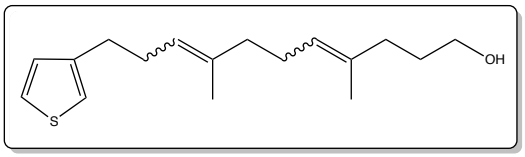
### 4.15.2.2 Synthesis of 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene 185




The title compound was prepared following the procedure described previously for **90** using magnesium (0.60 g, 24.9 mmol), 3-bromomethylthiophene **23** (0.44 g, 2.49 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 0.78 mL, 0.078 mmol) and 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-yl acetate **89** (0.28 g, 0.78 mmol) in tetrahydrofuran (9 mL) to afford a two-component mixture consisting of the desired cross-coupled product **185** and 1,2-di(thiophen-3-yl)ethane **39** in a 82:18 ratio of products. The residue was purified by column chromatography on silica gel (100% hexane) to afford the title cross-coupled product **185** (0.22 g, 71%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2929 (CH), 2857 (CH), 1670, 1472, 1463, 1386, 1255 (Si-$CH_3$), 1099 (Si-O), 837, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 0.05 [6H, s, Si($CH_3$)$_2$], 0.90 [9H, s, SiC($CH_3$)$_3$], 1.50-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.16 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.31 [2H, q, *J* 7.4, C(6)$H_2$], 2.66 [2H, t, *J* 7.3, C(5)$H_2$], 3.58 [2H, t, *J* 6.6, C(15)$H_2$], 3.60* (2H, t, *J* 6.5), 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.90-6.97 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) -5.2 [$CH_3$, Si($CH_3$)$_3$], 16.0 [$CH_3$, *C*(16)$H_3$ and *C*(17)$H_3$], 18.4 [C, Si*C*($CH_3$)$_3$], 26.0 [$CH_3$, SiC($CH_3$)$_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(15)$H_2$], 31.2 [$CH_2$, *C*(14)$H_2$], 35.8 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 62.9 [$CH_2$, *C*(15)$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.2 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.3 [CH, *C*(2)H], 134.7 [C, *C*(12)], 135.8 [C, *C*(8)], 142.8 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 18.3 (*C*$H_3$), 23.4 (*C*$H_3$) 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.1 (*C*$H_2$), 29.7 (*C*$H_2$), 30.2 (*C*$H_2$), 30.7 (*C*$H_2$), 31.3 (*C*$H_2$), 32.0 (*C*$H_2$), 39.9 (*C*$H_2$), 60.8 (*C*$H_2$), 63.1 (*C*$H_2$), 123.7 (*C*H), 124.1 (*C*H), 124.5 (*C*H), 125.0 (*C*H), 126.3 (*C*H), 126.8 (*C*H), 135.0 (*C*), 135.8 (*C*); HRMS (ESI+): Exact mass calculated for $C_{23}H_{41}OSSi$ $(M+H)^+$ 393.2603. Found 393.2635 $(M+H)^+$; m/z (ESI+) 393.26 $(M+H)^+$.

The less polar fraction, 1,2-di(thiophen-3-yl)ethane **39** was isolated as a white crystalline solid and spectroscopic characteristics were consistent with those previously described in ***Section 4.3.3.3***.

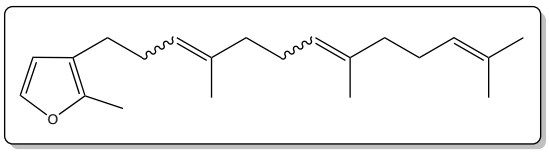
### 4.15.2.3 Synthesis of 3-(11-hydroxy-4,8-dimethylundeca-3,7-dien-1-yl)thiophene 188



The title compound was prepared following the procedure described previously for **91** using tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 0.49 mL, 0.49 mmol) and 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **185** (96 mg, 0.25 mmol) in tetrahydrofuran (5 mL). Purification by column chromatography on silica gel (10-20% ethyl acetate gradient in hexanes) provided the title alcohol **188** (53 mg, 78%) as a faint yellow oil; $\nu_{max}/cm^{-1}$ (film) 3339 (OH), 2923 (CH), 2856 (CH), 1501, 1449, 1382, 1164, 1065, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.74 [8H, m, C(14)$H_2$ and C$H_2$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.92-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.31 [2H, q, *J* 7.4, C(6)$H_2$], 2.66 [2H, t, *J* 7.4, C(5)$H_2$], 3.62 [2H, t, *J* 6.4, C(15)$H_2$], 3.64* (2H, t, *J* 6.4), 5.08-5.26 [2H, m, C(7)*H* and C(11)*H*], 6.90-6.98 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 26.4 [$CH_2$, *C*(10)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 30.7 [$CH_2$, *C*(14)$H_2$], 36.0 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 62.8 [$CH_2$, *C*(15)$H_2$], 120.0 [CH, *C*(4)H], 123.8 [CH, *C*(7)H], 124.7 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.4 [CH, *C*(2)H], 134.7 [C, *C*(12)], 135.7 [C, *C*(8)], 142.8 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 23.3 (*C*$H_3$), 26.5 (*C*$H_2$), 28.1 (*C*$H_2$), 29.7 (*C*$H_2$), 30.8 (*C*$H_2$), 30.9 (*C*$H_2$), 31.9 (*C*$H_2$), 39.9 (*C*$H_2$), 63.0 (*C*$H_2$), 123.8 (*C*H), 124.6 (*C*H), 125.5 (*C*H), 134.7 (*C*), 135.7 (*C*); HRMS (ESI+): Exact mass calculated for $C_{17}H_{27}OS$ $(M+H)^+$ 279.1783. Found 279.1770 $(M+H)^+$; m/z (ESI+) 279.2 $(M+H)^+$.

## 4.15.3 Synthesis of 2-methyl-furanolipid derivatives

### 4.15.3.1 Synthesis of 3-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-2-methylfuran 183

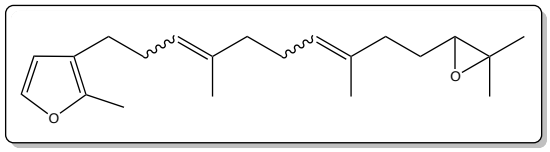


The title compound was prepared following the procedure described previously for **10** using magnesium (0.84 mg, 34.3 mmol), 2-methyl-3-furylmethyl bromide **20** (0.60 g, 3.43 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 1.07 mL, 0.107 mmol) and farnesyl acetate **59** (0.28 g, 1.07 mmol) in tetrahydrofuran (12 mL) to afford a two-component mixture of product consisting of the title cross-coupled product **183** and 1,2-bis(2-methylfuran-3-yl)ethane **41** in 63:37 ratio of products respectively. The residue was purified by column chromatography on silica gel (100% hexanes) to give the title furanolipid **183** (262 mg, 81.4 %) as a

colourless oil; $\nu_{max}/cm^{-1}$ (film) 2921 (CH), 2856, 1513, 1447, 1377, 1139, 1109, 1046, 894, 837, 726; $\delta_H$ ($CDCl_3$, 300 MHz) 1.57 (3H, s, C*H*$_3$), 1.60 (6H, s, C*H*$_3$), 1.61* (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.90-2.22 [13H, m, C(6)*H*$_2$ and C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$ and C(14)*H*$_2$ and containing 3H, s, C(4)C*H*$_3$], 2.35 [2H, t, *J* 7.5, C(5)*H*$_2$], 5.05-5.20 [3H, m, C(7)*H* and C(11)*H* and C(15)*H*], 6.20 [1H, d, *J* 1.8, C(2)*H*], 7.20 [1H, d, *J* 1.8, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.4 [$CH_3$, C(4)*C*$H_3$], 16.0 [$CH_3$, *C*(18)$H_3$ or *C*(19)$H_3$], 16.1 [$CH_3$, *C*(18)$H_3$ or *C*(19)$H_3$], 17.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 32.0 [$CH_2$, *C*(14)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$ and *C*(13)$H_2$], 111.6 [CH, *C*(2)H], 118.8 [C, *C*(3)], 123.7 [CH, *C*(7)H], 124.2 [CH, *C*(15)H], 124.4 [CH, *C*(11)H], 131.3 [C, *C*(16)], 135.0 [C, *C*(12)], 135.7 [C, *C*(8)], 139.6 [CH, *C*(1)H], 147.2 [C, *C*(4)]; Characteristics peaks for the other isomer(s)* 17.6 (*C*$H_3$), 23.4 (*C*$H_3$), 26.5 (*C*$H_2$), 26.8 (*C*$H_2$), 40.0 (*C*$H_2$), 125.0 (*C*H), 131.5 (*C*), 135.2 (*C*), 135.7 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{33}O$ $(M+H)^+$ 301.2531. Found 301.2522 $(M+H)^+$; m/z (ESI+) 301.3 $(M+H)^+$.

The least polar fraction, 1,2-bis(2-methylfuran-3-yl)ethane **41** was isolated as a colourless oil. Spectroscopic characteristics were consistent wit those previously described.

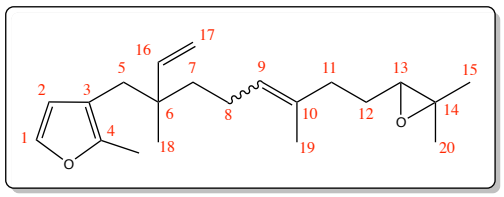
### 4.15.3.2 Synthesis of 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)-2-methylfuran 191



The title compound was prepared following the procedure described previously for **113** using magnesium (0.84 g, 34.3 mmol), 2-methyl-3-furylmethyl bromide **20** (0.60 g, 3.43 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 3.45 mL, 0.345 mmol, 10 mol%) and 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (0.97 g, 3.43 mmol) in terahydrofuran (18 mL) to afford a four-component mixture consisting of the title cross coupled product **191**, its corresponding regioisomer **193**, 1,2-bis(2-methylfuran-3-yl)ethane **41** and unreacted epoxide starting material **60** in a 18:2:11:69 ratio of products. The residue was purified by column chromatography on silica gel (0-10% ethyl acetate gradient in hexanes) to afford an inseparable mixture (218 mg, 65 % based on the consumed acetate) as a faint yellow oil consisting of the title furanolipid epoxide **191** (60% conversion)§ and its corresponding regioisomer **193** (5% conversion)§ in a 92:8 ratio of products as determined by $^1$H NMR integration. Spectroscopic data for the title epoxide **191** was extracted from the spectrum of the two-component mixture. $^1$H NMR integration indicated a 70:30 ratio of *E,E* and other isomer(s)*; $\nu_{max}/cm^{-1}$ (film) 2961 (CH), 2923, 2856, 1447, 1378, 1138 (C-O), 894, 727; $\delta_H$ ($CDCl_3$, 300 MHz)

1.26 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.27* (3H, s), 1.30 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.31* (3H, s), 1.54-1.72 [8H, m, C(14)$H_2$ and C$H_2$* and containing 2 x 3H, s, C(18)$H_3$ and C(19)$H_3$], 1.90-2.25 [11H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 3H, s, C(4)C$H_3$], 2.35 [2H, t, *J* 7.6, C(5)$H_2$], 2.70 [1H, t, *J* 6.2, C(15)*H*], 2.71* (1H, t, *J* 6.3), 5.10-5.20 [2H, m, C(7)*H* and C(11)*H*], 6.19 [1H, d, *J* 1.8, C(2)*H*], 7.20 [1H, d, *J* 1.8, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.4 [CH, C(4)*C*$H_3$], 16.0 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 18.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 24.9 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.4 [$CH_2$, *C*(14)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 36.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 58.3 [C, *C*(16)], 64.2 [CH, *C*(15)H], 111.6 [CH, *C*(2)H], 118.7 [C, *C*(3)], 123.8 [CH, *C*(7)H], 124.9 [CH, *C*(11)H], 134.1 [C, *C*(12)], 135.6 [C, *C*(8)], 139.6 [CH, *C*(1)H], 147.2 [C, *C*(4)$CH_3$]; Characteristics peaks for the other isomer(s)* 18.7 (*C*$H_3$), 23.3 (*C*$H_3$), 26.4 (*C*$H_2$), 27.5 (*C*$H_2$), 28.5 (*C*$H_2$), 28.8 (*C*$H_2$), 39.9 (*C*$H_2$), 64.1 (*C*H), 113.4 (*C*H), 123.9 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.7 (*C*H), 135.4 (*C*), 139.1 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{33}O_2$ $(M+H)^+$ 317.2481. Found 317.2471 $(M+H)^+$; m/z (ESI+) 317.2 $(M+H)^+$.

§ % Conversion was determined by $^1$H NMR analysis of the isolated inseperable mixture.

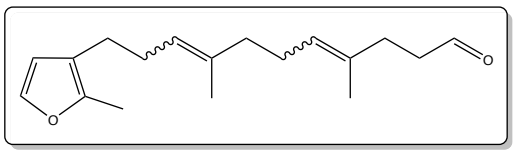



Characteristic peaks associated with the regioisomer, 3-(8-(3,3-dimethyloxiran-2-yl)-2,6-dimethyl-2-vinyloct-5-en-1-yl)-2-methylfuran **193** were extracted from the spectrum of the two-component mixture.; $\delta_H$ ($CDCl_3$, 300 MHz) 0.96 [3H, s, C(18)$H_3$], 4.88 [1H, dd, B of the ABX system $J_{BX}$ 17.6, $J_{AB}$ 1.3, C(17)$H_2$], 5.00 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.3, C(17)$H_2$] 5.76* [1H, dd, X of the ABX system $J_{BX}$ 17.6, $J_{AX}$ 10.8, C(16)*H*], 5.77 [1H, dd, X of the ABX system $J_{BX}$ 17.6, $J_{AX}$ 10.8, C(16)*H*], 6.14 [1H, d, *J* 1.8, C(2)*H*], 7.18 [1H, d, *J* 1.8, C(1)*H*].

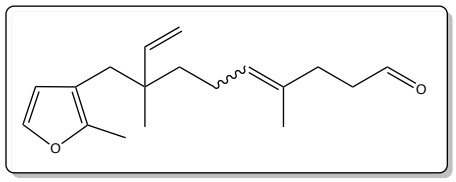
The least polar fraction, 1,2-bis(2-methylfuran-3-yl)ethane **41** was isolated as a colourless oil and spectroscopic characteristics were consistent with those previously described in ***Section 4.3.3.2***.

The most polar fraction, epoxyfarnesyl acetate **60** was isolated pure and was used in subsequent reactions. The percentage yield was calculated from a revised theoretical yield figure due to isolation of unreacted starting material **60** from the reaction mixture.[30]

### 4.15.3.3 Synthesis of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)-2-methylfuran 194

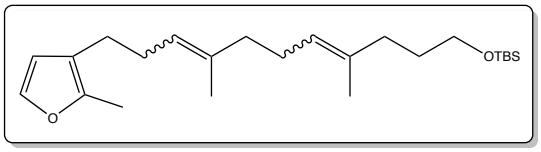


The title compound was prepared following the procedure described previously for **121** using 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)-2-methylfuran **191** (0.11 g, 0.35 mmol) and its corresponding regioisomer **193** in diethyl ether (3 mL) and periodic acid (0.10 g, 0.42 mmol) in tetrahydrofuran (1 mL). The residue was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to afford an inseparable mixture (81 mg, 85%) as a faint yellow oil consisting of the title aldehyde **194** (72 mg, 75%) and its corresponding regioisomer **196** (9 mg, 10%) in a 88:12 ratio of products. $^1$H NMR integration indicated a 70:30 ratio of *E,E* and other isomer(s)*. Spectroscopic data for the title aldehyde **194** was extracted from the spectrum of the two-component mixture; $\nu_{max}$/cm$^{-1}$ (film); 2923 (CH), 2856 (CH), 1728 (C=O), 1514, 1447, 1386, 1230, 1138, 894, 728; $\delta_H$ ($CDCl_3$, 300 MHz) 1.56 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.61 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.68* (3H, s), 1.80-2.58 [15H, m, C(5)$H_2$ and C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$ and containing 3H, s C(4)C$H_3$], 5.08-5.25 [2H, m, C(7)*H* and C(11)*H*], 6.19 [1H, d, *J* 1.8, C(2)*H*], 7.20 [1H, d, *J* 1.8, C(1)*H*], 9.74 [1H, t, *J* 1.9, C(15)*H*], 9.78* (1H, t, *J* 1.7); $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.4 [$CH_3$, C(4)*C*$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$]. 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.8 [$CH_2$, *C*(6)$H_2$], 31.9 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 42.1 [$CH_2$, *C*(14)$H_2$], 111.6 [CH, *C*(2)H], 118.7 [CH, *C*(3)H], 124.0 [CH, *C*(7)H], 125.4 [CH, *C*(11)H] 132.9 [C, *C*(12)], 135.4 [C, *C*(8)], 139.6 [CH, *C*(1)H], 147.2 [C, *C*(4)$CH_3$], 202.7 [CH, *C*(15)H], Characteristics peaks for the other isomer(s)* 14.1 (*C*$H_3$), 23.0 (*C*$H_3$), 24.3 (*C*$H_2$), 25.3 (*C*$H_2$), 26.4 (*C*$H_2$), 28.9 (*C*$H_2$), 29.1 (*C*$H_2$), 31.6 (*C*$H_2$), 31.7 (*C*$H_2$), 39.7 (*C*$H_2$), 42.3 (*C*$H_2$), 112.1 (*C*H), 113.4 (*C*H), 124.1 (*C*H), 126.0 (*C*H), 126.5 (*C*H), 132.8 (*C*), 135.3 (*C*), 139.1 (*C*H), 146.6 (*C*), 202.3 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{18}H_{27}O_2$ $(M+H)^+$ 275.2011. Found 275.2015 $(M+H)^+$; m/z (ESI+) 275.4 $(M+H)^+$.



Characteristic peaks for the regioisomer, 3-(2,6-dimethyl-9-oxo-2-vinylnon-5-en-1-yl)-2-methylfuran **196**; $\delta_H$ ($CDCl_3$, 300 MHz) 4.88 [1H, dd, B of the ABX system $J_{BX}$ 17.6, $J_{AB}$ 1.4, C(17)$H_2$], 5.00 [1H, dd, A of the ABX system $J_{AX}$ 10.8, $J_{AB}$ 1.4, C(17)$H_2$], 5.77 [1H, dd, X of the ABX system $J_{BX}$ 17.6, $J_{AX}$ 10.8, C(16)*H*], 6.14 [1H, d, *J* 1.8, C(2)*H*], 7.18 [1H, d, *J* 1.8, C(1)*H*], 9.77 [1H, t, *J* 1.7, C(15)*H*].

### 4.15.3.4 Synthesis of 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)-2-methylfuran 186

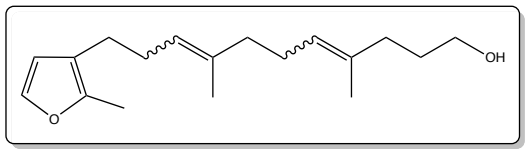



The title compound was prepared following the procedure described previously for **90** using magnesium (0.84 g, 34.3 mmol), 2-methyl-3-furylmethyl bromide **20** (0.60 g, 3.43 mmol), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 1.07 mL, 0.107 mmol) and 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-yl acetate **89** (0.38 g, 1.07 mmol) in tetrahydrofuran (12 mL) to afford a two-component mixture consisting of the title cross coupled product **186** and 1,2-bis(2-methylfuran-3-yl)ethane **41** in a 2:1 ratio of products. The residue was purified by column chromatography on silica gel (100% hexanes) to give a co-eluted two-component mixture (0.32 g) as a colourless oil consisting of the title furanolipid silyl ether **186** (69% conversion)§ and 1,2-bis(2-methylfuran-3-yl)ethane **41** in a 8:1 ratio of products respectively as determined by $^1$H NMR integration. The isolated co-eluted mixture was carried through to the next step without further purification. Spectroscopic data for the title aldehyde **186** was extracted from the spectrum of the two-component mixture; $\nu_{max}/cm^{-1}$ (film) 2929 (CH), 2858 (CH), 1448, 1255 (Si-$CH_3$), 1099 (Si-O), 837, 776, 727; $\delta_H$ ($CDCl_3$, 300 MHz) 0.05 [6H, s, Si(C$H_3$)$_2$], 0.90 [9H, s, SiC(C$H_3$)$_3$], 1.53-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.24 [11H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 3H, s, C(4)C$H_3$], 2.35 [2H, t, *J* 7.6, C(5)$H_2$], 3.58 [2H, t, *J* 6.6, C(15)$H_2$], 3.59* (2H, t, *J* 6.5), 5.05-5.20 [2H, m, C(7)*H* and C(11)*H*], 6.20 [1H, d, *J* 1.8, C(2)*H*], 7.20 [1H, d, *J* 1.8, C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) -5.3 [$CH_3$, Si($CH_3$)$_2$], 11.4 [$CH_3$, C(4)$CH_3$], 16.0 [$CH_3$, *C*(16)$H_3$ and *C*(17)$H_3$], 18.4 [C, Si*C*(C$H_3$)$_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.0 [C, SiC(*C*$H_3$)$_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 31.2, [$CH_2$, *C*(14)$H_2$], 35.8 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 62.9 [$CH_2$, *C*(15)$H_2$], 111.6 [CH, *C*(2)H], 118.7 [C, *C*(3)], 123.7 [CH, *C*(7)H], 124.2 [CH, *C*(11)H], 135.0 [C, *C*(12)], 135.7 [C, *C*(8)], 139.6 [CH, *C*(1)H], 147.2 [C, *C*(4)$CH_3$]; Characteristics peaks for the other isomer(s)* 11.2 (*C*$H_3$), 18.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 25.8 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.1 (*C*$H_2$), 31.3 (*C*$H_2$), 40.0 (*C*$H_2$), 63.1 (*C*$H_2$), 111.5 (*C*H) 118.2 (*C*), 123.8 (*C*H), 125.0 (*C*H), 134.7 (*C*), 135.6 (*C*), 139.7 (*C*H) 147.6 (*C*); HRMS (ESI+): Exact mass calculated for $C_{24}H_{43}O_2Si$ $(M+H)^+$ 391.3032. Found 391.3020 $(M+H)^+$.

§ % Conversion was determined by $^1$H NMR analysis of the co-eluted mixture.

The least polar fraction, 1,2-bis(2-methylfuran-3-yl)ethane **41** was isolated as a colourless oil. Spectral characteristics were consistent with those listed previously in ***Section 4.3.3.2***.

### 4.15.3.5 Synthesis of 3-(11-hydroxy-4,8-dimethylundeca-3,7-dien-1-yl)-2-methylfuran 189

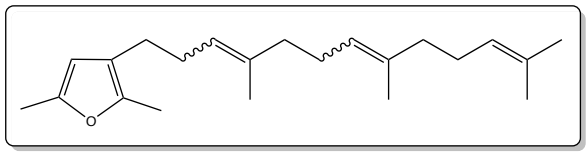



The title compound was prepared following the procedure described previously for **91** using tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.4 mL, 1.38 mmol), 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)-2-methylfuran **186** (0.27 g, 0.69 mmol) in tetrahydrofuran (9 mL) to afford a two-component mixture consisting of the title furanolipid alcohol **189** and 1,2-bis(2-methylfuran-3-yl)ethane **41** in a 94:6 ratio. The residue was purified by column chromatography on silica gel (1-10% ethyl acetate gradient in hexanes) to afford the title furanolipid alcohol **189** (0.16 g, 86%) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 3341 (OH), 2923 (CH), 1513, 1447, 1382, 1139, 1046, 1046, 894, 727; $\delta_H$ ($CDCl_3$, 300 MHz) 1.53-1.73 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.23 [11H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 3H, s, C(4)C$H_3$], 2.35 [2H, t, *J* 7.5, C(5)$H_2$], 3.62 [2H, t, *J* 6.4, C(15)$H_2$], 3.64* (2H, t, *J* 6.5), 5.05-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.20 [1H, d, *J* 1.7, C(2)*H*], 7.20 [1H, d, *J* 1.8, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.4 [$CH_3$, C(4)*C*$H_3$], 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.4 [$CH_2$, *C*(10)$H_2$], 28.8 [$CH_2$, *C*(6)$H_2$], 30.7 [$CH_2$, *C*(14)$H_2$], 36.0 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 62.8 [$CH_2$, *C*(15)$H_2$], 111.6 [CH, *C*(2)H], 118.7 [C, *C*(3)], 123.9 [CH, *C*(7)H], 124.7 [CH, *C*(11)H], 134.7 [C, *C*(8)], 135.5 [C, *C*(8)], 139.6 [CH, *C*(1)H], 147.2 [C, *C*(4)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.5 (*C*$H_2$), 28.1 (*C*$H_2$), 30.9 (*C*$H_2$), 31.9 (*C*$H_2$), 39.9 (*C*$H_2$), 63.0 (*C*$H_2$), 123.9 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 125.5 (*C*H), 134.7 (*C*), 134.8 (*C*), 135.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{18}H_{29}O_2$ $(M+H)^+$ 277.2168. Found 277.2155 $(M+H)^+$. m/z (ESI+) 227.2 $(M+H)^+$.

The least polar fraction, 1,2-bis(2-methylfuran-3-yl)ethane **41** was isolated as a colourless oil. Spectral characteristics were consistent with those described in ***Section 4.3.3.2***.

## 4.15.4 Synthesis of 2,5-dimethyl-furanolipid derivatives

### 4.15.4.1 2,5-dimethyl-3-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)furan 184

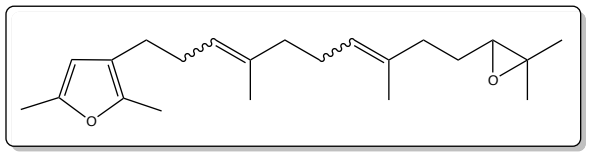


The title compound was prepared following the procedure described previously for **10** magnesium (0.90 g, 37.0 mmol), 2,5-dimethyl-3-furylmethyl bromide **21** (0.70 g, 3.70 mmol, 5 equiv), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 0.74 mL, 0.074 mmol) and farnesyl acetate **59** (0.20 g, 0.74 mmol, 1 equiv) in tetrahydrofuran (11 mL) to afford a two-component mixture consisting of the desired cross coupled product **184** and 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** in a 1:0.45 ratio of products respectively. The residue was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) to afford the title furanolipid **184** (152 mg, 66%) as a colourless oil; $\nu_{max}/cm^{-1}$ (film) 2964 (CH), 2926, 2856, 1702, 1449, 1376, 1170; $\delta_H$ ($CDCl_3$, 300 MHz) 1.58* (C*H*$_3$), 1.60 (6H, s), 1.68 (6H, s), 1.90-2.34 [18H, m, C(5)*H*$_2$ and C(6)*H*$_2$ and C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$ and C(14)*H*$_2$ and 2 x 3H, s, C(1)C*H*$_3$ and C(4)C*H*$_3$], 5.03-5.22 [3H, m, C(7)*H* and C(11)*H* and C(15)*H*], 5.78 [1H, s, C(2)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 11.3 [$CH_3$, C(4)*C*$H_3$], 13.4 [$CH_3$, C(1)*C*$H_3$], 16.0 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 17.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_3$, *C*(17)$H_3$ or *C*(20)$H_3$], 26.6 [$CH_2$, *C*(10)$H_2$], 26.8 [$CH_2$, *C*(14)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$ and *C*(13)$H_2$], 107.4 [CH, *C*(2)H], 119.4 [C, *C*(3)], 123.9 [CH, *C*(15)H], 124.2 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 131.2 [C, *C*(16)], 135.0 [C, *C*(12)], 135.5 [C, *C*(8)], 145.1 [C, *C*(4)$CH_3$], 148.9 [C, *C*(1)$CH_3$]; Characteristics peaks for the other isomer(s)* 14.1 (*C*$H_3$), 16.0 (*C*$H_3$), 17.6 (*C*$H_3$), 22.7 (*C*$H_3$), 23.4 (*C*$H_3$), 25.4 (*C*$H_2$), 25.7 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 26.7 (*C*$H_2$), 28.3 (*C*$H_2$), 28.9 (*C*$H_2$), 29.7 (*C*$H_2$), 32.0 (*C*$H_2$), 40.0 (*C*$H_2$), 107.4 (*C*H), 119.4 (*C*H), 123.2 (*C*H), 124.2 (*C*H), 124.3 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 131.3 (*C*), 131.5 (*C*), 135.1 (*C*), 135.3 (*C*), 135.5 (*C*), 135.7 (*C*). m/z (ESI+) 315.3 $(M+H)^+$.

The HRMS was outside acceptable limits so the data was omitted from the experimental.

The least polar fraction, 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** was isolated as a colourless oil. Spectroscopic characteristics were consistent with those previously described in ***Section 4.3.3.4***.

### 4.15.4.2 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)-2,5-dimethylfuran 192



The title compound was prepared following the procedure described previously for **10** using magnesium (2.70 g, 111.08 mmol), 2,5-dimethyl-3-furylmethyl bromide **21** (2.1 g, 11.08 mmol, 2 equiv), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 1.85 mL, 0.183 mmol, 3.3 mol%) and 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** (1.56 g, 5.55 mmol, 1 equiv) in tetrahydrofuran (42 mL) to afford a four-component mixture consisting of the desired cross coupled product **192**, 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40**, unreacted acetate starting material **60** and unreacted bromide starting material **21** in a 1:0.32:0.66:0.1 ratio of products respectively. The residue was subjected to column chromatography on silica gel (0-10% ethyl acetate gradient in hexanes) to give a co-eluted mixture (674 mg) as a faint yellow oil, consisting of the title furanolipid epoxide **192** and the bromide starting material **21** in the 88:12 ratio of products respectively. Conversion to the title product **192** was achieved in 58 % (based on the consumed acetate).§ Spectroscopic data for the title furanolipid epoxide **192** was extracted from the spectrum of the two-component mixture. $^1$H NMR integration also indicated a 74:26 ratio of the *E,E* and other isomer(s)*; $\nu_{max}/cm^{-1}$ (film) 2961 (CH), 2923, 2856 (CH), 1450, 1378, 1232 (CO), 1123 (CO); $\delta_H$ ($CDCl_3$, 300 MHz) 1.26 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.27* (3H, s), 1.30 [3H, s, C(17)$H_3$ or C(20)$H_3$], 1.31* (3H, s), 1.55-1.74 [8H, m, C(14)$H_2$ and containing 2 x 3H, s, C(18)$H_3$ and C(19)$H_3$], 1.90-2.34 [16H, m, C(5)$H_2$ and C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 2 x 3H, s, C(1)C$H_3$ and C(4)C$H_3$], 2.70 [1H, t, *J* 6.2, C(15)*H*], 2.71* (1H, t, *J* 6.3), 5.05-5.20 [2H, m, C(7)*H* and C(11)*H*], 5.78 [1H, s, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.4 [$CH_3$, C(4)*C*$H_3$], 13.5 [$CH_3$, C(1)*C*$H_3$], 16.0 [$CH_3$, C(18)*C*$H_3$ and C(19)*C*$H_3$], 18.8 [$CH_3$, C(17)*C*$H_3$ or C(20)*C*$H_3$], 24.9 [$CH_3$, C(17)*C*$H_3$ or C(20)*C*$H_3$], 25.2 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.5 [$CH_2$, *C*(14)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 36.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 58.3 [C, *C*(16)], 64.2 [CH, *C*(15)H], 107.4 [CH, *C*(2)H], 119.4 [C, *C*(3)], 124.0 [CH, *C*(7)H], 124.9 [CH, *C*(11)H], 134.1 [C, *C*(12)], 135.4 [C, *C*(8)], 145.1 [CH, *C*(4)$CH_3$], 148.9 [C, *C*(1)$CH_3$]; Characteristics peaks for the other isomer(s)* 11.5 (*C*$H_3$), 13.3 (*C*$H_3$), 16.0 (*C*$H_3$), 18.7 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 24.9 (*C*$H_3$), 25.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.4 (*C*$H_2$), 27.5 (*C*$H_2$), 28.8 (*C*$H_2$), 28.9 (*C*$H_2$), 31.9 (*C*$H_2$), 39.9 (*C*$H_2$), 58.2 (*C*H), 58.3 (*C*), 64.1 (*C*H), 107.2 (*C*H), 119.4 (*C*H), 124.1 (*C*H), 124.8 (*C*H), 125.7 (*C*), 134.1 (*C*), 135.3 (*C*); HRMS (ESI+): Exact mass calculated for $C_{22}H_{35}O_2$ $(M+H)^+$ 331.2637. Found 331.2631 $(M+H)^+$; m/z (ESI+) 331.3 $(M+H)^+$.

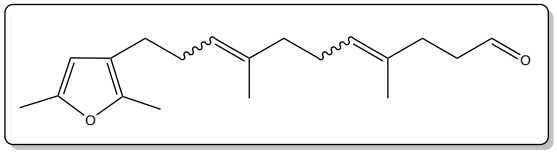
§ % Conversion was determined by $^1$H NMR analysis of the co-eluted mixture.

- Spectroscopic characteristics for the unreacted bromide starting material **21** were evident in the spectrum of the two-component mixture and were consistent with those previously reported in ***Section 4.2.2.3***.

The least polar fraction, 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** was isolated as a colourless oil. Spectroscopic characteristics are consistent with those previously described in ***Section 4.3.3.4***.

The most polar fraction, 9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate **60** was isolated pure and was used for subsequent reactions. The percentage yield was calculated from a revised theoretical yield figure due to isolation of unreacted starting material **60** from the reaction mixture.[30]

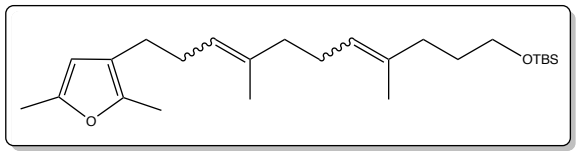
### 4.15.4.3 Synthesis of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)-2,5-dimethylfuran 195



The title compound was prepared following the procedure described previously for **121** using 3-(10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dien-1-yl)-2,5-dimethylfuran **192** (0.57 g, 1.75 mmol) in diethyl ether (10 mL) and periodic acid (0.48 g, 2.1 mmol) in tetrahydrofuran (3 mL) to afford a two-component mixture consisting of the title furanolipid aldehyde **195** and bromide starting material **21** in a 85:15 ratio of products respectively. The crude product was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to afford the title furanolipid **195** (270 mg, 53%) as a light yellow oil. $^1$H NMR integration also indicated a 74:26 ratio of the *E,E* and other isomer(s)*; $\nu_{max}$/cm$^{-1}$ (film) 2922 (CH), 2856 (CH), 1728 (C=O), 1584, 1448, 1383, 1233; $\delta_H$ ($CDCl_3$, 300 MHz) 1.57 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.61 [3H, s, C(16)$H_3$ or C(17)$H_3$], 1.68* (3H, s), 1.90-2.40 [16H, m, C(5)$H_2$ and C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 2 x 3H, s, C(1)C$H_3$ and C(4)C$H_3$], 2.44-2.55 [2H, m, C(14)$H_2$], 5.05-5.20 [2H, m, C(7)*H* and C(11)*H*], 5.78 [1H, s, C(2)*H*], 9.74 [1H, t, *J* 1.9, C(15)*H*], 9.78* (1H, t, *J* 1.8); $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.3 [$CH_3$, C(4)*C*$H_3$], 13.4 [$CH_3$, C(1)*C*$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 31.9 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 42.1 [$CH_2$, *C*(14)$H_2$], 107.4 [CH, *C*(2)H], 119.4 [C, *C*(3)], 124.1 [CH, *C*(7)H], 125.4 [CH, *C*(11)H], 132.9 [C, *C*(12)], 135.2 [C, *C*(8)], 145.1 [C, *C*(4)$CH_3$], 148.9 [C, *C*(1)$CH_3$], 202.6 [CH, *C*(15)H]; Characteristics peaks for the other isomer(s)* 11.5 (*C*$H_3$), 13.3 (*C*$H_3$), 13.4 (*C*$H_3$), 16.0 (*C*$H_3$), 22.1 (*C*$H_3$), 23.0 (*C*$H_3$), 23.4 (*C*$H_2$), 24.3 (*C*$H_2$), 25.4 (*C*$H_2$), 26.4 (*C*$H_2$), 28.8 (*C*$H_2$), 31.4 (*C*$H_2$), 31.7 (*C*$H_2$), 33.9 (*C*$H_2$), 39.4 (*C*$H_2$), 39.7 (*C*$H_2$), 42.1 (*C*$H_2$), 42.3 (*C*$H_2$), 107.2 (*C*H), 124.2 (*C*H), 125.0 (*C*H), 125.3 (*C*H), 132.8 (*C*), 133.1 (*C*), 135.1 (*C*), 135.4 (*C*), 149.0 (*C*), 149.7 (*C*),

150.1 (*C*), 202.3 (*C*H), 202.5 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{19}H_{29}O_2$ $(M+H)^+$ 289.2168. Found 289.2166 $(M+H)^+$; m/z (ESI+) 289.4 $(M+H)^+$.

### 4.15.4.4 Synthesis of 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)-2,5-dimethylfuran 187

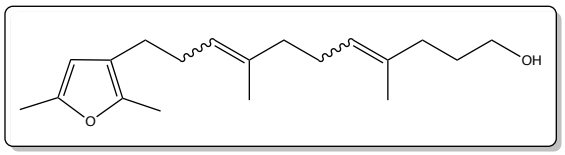



The title compound was prepared following the procedure described previously for **90** using magnesium (0.90 g, 37.0 mmol), 2,5-dimethyl-3-furylmethyl bromide **21** (0.70 g, 3.70 mmol, 5 equiv), dilithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 0.74 mL, 0.074 mmol) and 10-(*tert*-butyl-dimethyl-silyloxy)-3,7-dimethyldeca-2,6-dien-1-yl acetate **89** (0.26 g, 0.74 mmol) in tetrahydrofuran (11 mL) to afford a two-component mixture consisting of desired cross-coupled product **187** and 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** in a 1:0.44 ratio respectively. The residue was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) to give a co-eluted mixture (260 mg) as a colourless oil, consisting of title furanolipid silyl ether **187** (59% conversion)§ and 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** in 68:32 ratio of products respectively. Spectroscopic data for the title silyl ether **187** was extracted from the spectrum of the two-component mixture; $\nu_{max}/cm^{-1}$ (film) 2928 (CH), 2857, 1716, 1584, 1501, 1446, 1383, 1256 (Si-$CH_3$), 1100 (Si-O), 837, 776; $\delta_H$ ($CDCl_3$, 300 MHz) 0.05 [6H, s, Si(C$H_3$)$_2$], 0.90 [9H, s, SiC(C$H_3$)$_3$], 1.55-1.70 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.20 [11H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 3H, s, C(4)*C*H$_3$], 2.21 [3H, s, C(1)*C*H$_3$], 2.28 [2H, t, *J* 7.6, C(5)$H_2$], 3.58 [2H, t, *J* 6.6, C(15)$H_2$], 3.59* (2H, t, *J* 6.5), 5.05-5.20 [2H, m, C(7)*H* and C(11)*H*], 5.78 [1H, s, C(2)*H*]; HRMS (ESI+): Exact mass calculated for $C_{25}H_{45}O_2Si$ $(M+H)^+$ 405.3189. Found 405.3180 $(M+H)^+$; m/z (ESI+) 405.4 $(M+H)^+$.

§ % Conversion was estimated by $^1$H NMR integration of the co-eluted mixture.

The least polar fraction, 1,2-bis(2,5-dimethylfuran-3-yl)ethane **40** was isolated as a colourless oil. Spectroscopic characteristics are consistent with those previously described in ***Section 4.3.3.4***.

### 4.15.4.5 Synthesis of 3-(11-hydroxy-4,8-dimethylundeca-3,7-dien-1-yl)-2,5-dimethylfuran 190



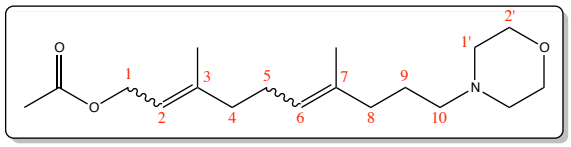

The title compound was prepared following the procedure described previously for **91** using tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.2 mL, 1.15 mmol), 3-(11-(*tert*-butyl-dimethyl-silyloxy)-4,8-dimethylundeca-3,7-dien-1-yl)-2,5-dimethylfuran **187** (0.23 g, 0.58 mmol) in tetrahydrofuran (8 mL) at 0 °C. Purification by column chromatography on silica gel (10-20% ethyl acetate gradient in hexanes) provided the title furanolipid alcohol **190** (0.11 g, 66%) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 3423 (OH), 2925 (CH), 2856 (CH), 1590, 1448, 1376, 1173, 1094, 1063, 842, 778; $\delta_H$ ($CDCl_3$, 400 MHz) 1.50-1.74 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.24 [16H, m, C(5)$H_2$ and C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and containing 2 x 3H, s, C(1)C$H_3$ and C(4)C$H_3$], 3.62 [2H, t, *J* 6.4, C(15)$H_2$], 3.64* (2H, t, *J* 5.5), 5.08-5.20 [2H, m, C(7)*H* and C(11)*H*], 5.77 [1H, s, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.3 [$CH_3$, C(4)*C*$H_3$], 13.4 [$CH_3$, C(1)*C*$H_3$], 15.8 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.2 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.9 [$CH_2$, *C*(6)$H_2$], 30.7 [$CH_2$, *C*(14)$H_2$], 36.0 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 62.8 [$CH_2$, *C*(15)$H_2$], 107.4 [CH, *C*(2)H], 119.4 [C, *C*(3)], 124.0 [CH, *C*(7)H], 124.7 [CH, *C*(11)H], 134.6 [C, *C*(12)], 135.4 [C, *C*(8)], 145.1 [C, *C*(4)$CH_3$], 148.9 [C, *C*(1)$CH_3$]; Characteristics peaks for the other isomer(s)* 14.1 (*C*$H_3$), 16.0 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.4 (*C*$H_2$), 25.7 (*C*$H_2$), 25.9 (*C*$H_2$), 26.4 (*C*$H_2$), 28.1 (*C*$H_2$), 29.4 (*C*$H_2$), 29.7 (*C*$H_2$), 30.9 (*C*$H_2$), 31.9 (*C*$H_2$), 33.2 (*C*$H_2$), 39.9 (*C*$H_2$), 42.0 (*C*$H_2$), 62.9 (*C*$H_2$), 124.1 (*C*H), 124.6 (*C*H), 124.9 (*C*H), 125.5 (*C*H), 134.7 (*C*), 134.8 (*C*), 135.3 (*C*), 135.5 (*C*), 135.7 (*C*); HRMS (ESI+): Exact mass calculated for $C_{19}H_{31}O_2$ $(M+H)^+$ 291.2324. Found 291.2314 $(M+H)^+$; m/z (ESI+) 291.4 ($M+H^+$).

- It should be noted that compound **190** was relatively unstable and was subject to undesired deterioration when stored over extended periods of time.

## 4.15.5 Synthesis of terpene amine derivatives

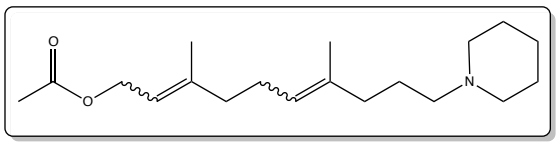
These transformations were essentially quantitative. Purification by chromatography was deemed unnecessary, with complete conversion to the amine. The following numbering template was used in characterising the amine molecule(s). The amines in this section were prepared from 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** and $^{1}$H NMR integration revealed a 60:40 mixture of (*E*,*E*) and other isomer(s)* for this compound. All amines prepared from aldehyde **62** will therefore contain a 60:40 mixture of (*E*,*E*) and other isomer(s)*

### 4.15.5.1 Synthesis of 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate 204



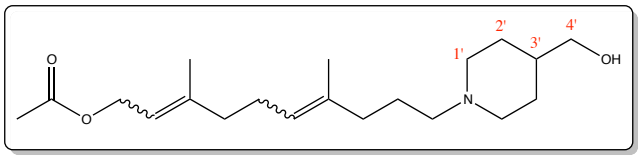

Sodium triacetoxyborohydride (125 mg, 0.59 mmol, 1.4 equiv) was added to a stirring solution of the aldehyde, 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol, 1 equiv) and morpholine (37 mg, 0.42 mmol, 1 equiv) in 1,2-dichloroethane (5 mL) under an inert nitrogen atmosphere at room temperature. TLC analysis after 1.5 h showed complete consumption of the aldehyde starting material **62** and the reaction was quenched using saturated sodium bicarbonate solution (5 mL). The organic layer was extracted into ethyl acetate (3 x 20 mL) and washed with water (2 x 20 mL) followed by brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the title amine **204** (110 mg, 86 %) as an yellow oil. $\nu_{max}/cm^{-1}$ (film) 2939 (CH), 2855 (CH), 2808 (CH), 1740 (C=O), 1446, 1366, 1234, 1119, 1024 (CO); $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.64 [5H, m, C(9)$H_2$ and containing 3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.77* (3H, s), 1.90-2.20 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.24-2.36 [2H, m, C(10)$H_2$], 2.35-2.55 [4H, m, 2 x C(1')$H_2$], 3.65-3.77 [4H, m, 2 x C(2')$H_2$], 4.50-4.65 [2H, m, C$H_2$* and containing 2H, d, *J* 7.3, C(1)$H_2$], 5.04-5.16 [1H, m, C(6)*H*], 5.28-5.42 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 24.7 [$CH_2$, *C*(9)$H_2$], 26.1 [$CH_2$, *C*(5)$H_2$], 37.3, [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 53.8 [$CH_2$, 2 x N*C*(1')$H_2$], 58.7 [$CH_2$, *C*(10)$H_2$], 61.3 [$CH_2$, *C*(1)$H_2$], 70.0 [$CH_2$, 2 x O*C*(2')$H_2$], 118.3 [CH, *C*(2)H or *C*(6)H], 123.9 [CH, *C*(2)H or *C*(6)H], 135.0 [C, *C*(7)], 142.1 [C, *C*(3)], 171.0 [CH, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 14.1 (*C*$H_3$), 16.5 (*C*$H_3$), 23.2 (*C*$H_3$), 23.5 (*C*$H_3$), 24.8 (*C*$H_2$), 26.0 (*C*$H_2$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 29.4 (*C*$H_2$), 29.7 (*C*$H_2$), 32.1 (*C*$H_2$), 32.3 (*C*$H_2$), 39.7 (*C*$H_2$), 43.4 (*C*$H_2$), 53.7 (*C*$H_2$), 58.7 (*C*$H_2$), 60.3 (*C*$H_2$), 61.1 (*C*$H_2$), 61.3 (*C*$H_2$), 119.1 (*C*H), 119.2 (*C*H), 123.6 (*C*H), 124.5 (*C*H), 124.7 (*C*H), 135.1 (*C*), 135.3 (*C*), 135.4 (*C*), 142.0 (*C*), 142.3 (*C*) 142.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{18}H_{32}NO_3$ $(M+H)^+$ 310.2382. Found 310.2383 $(M+H)^+$; m/z (ESI+) 310.23 $(M+H)^+$.

### 4.15.5.2 Synthesis of 3,7-dimethyl-10-(piperidin-1-yl)deca-2,6-dien-1-yl acetate 211



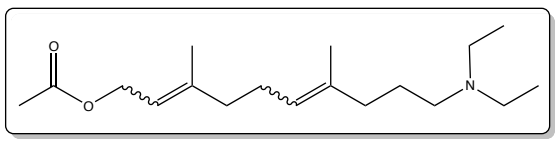
The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and piperidine (36 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **211** as an orange oil (116 mg, 90 %); $\nu_{max}/cm^{-1}$ (film) 2935 (CH), 2854 (CH), 2800 (CH), 2763, 1741 (C=O), 1444, 1379, 1366, 1232, 1123, 1024; $\delta_H$ ($CDCl_3$, 300 MHz) 1.34-1.50 [2H, m, C(3')$H_2$], 1.50-1.65 [9H, m, 2 x C(2')$H_2$ and C(9)$H_2$ and containing 3H, s, C(11)$H_3$ or C(12)$H_3$], 1.67* (3H, s), 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.76* (3H, s), 1.90-2.18 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.18-2.48 [6H, m, C(10)$H_2$ and containing 2 x C(1')$H_2$], 4.50-4.64 [2H, m, C$H_2$* and containing 2H, d, *J* 7.3, C(1)$H_2$], 5.03-5.14 [1H, m, C(6)*H*], 5.25-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 24.4 [$CH_2$, *C*(3')$H_2$], 25.1 [$CH_2$, *C*(9)$H_2$], 25.9 [$CH_2$, 2 x *C*(2')$H_2$], 26.1 [$CH_2$, *C*(5)$H_2$], 37.6, [$CH_2$, *C*(8)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 54.6 [$CH_2$, 2 x *C*(1')$H_2$], 59.2 [$CH_2$, *C*(10)$H_2$], 61.3 [$CH_2$, *C*(1)$H_2$], 118.3 [CH, *C*(2)H or *C*(6)H], 123.6 [CH, *C*(2)H or *C*(6)H], 135.2 [C, *C*(7)], 142.1 [C, *C*(3)], 171.0 [C, *C*(O)*C*$H_3$]; Characteristics peaks for the other isomer(s)* 14.2 (*C*$H_3$), 15.9 (*C*$H_3$), 16.5 (*C*$H_3$), 23.3 (*C*$H_3$), 23.5 (*C*$H_3$), 25.2 (*C*$H_2$), 26.0 (*C*$H_2$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 29.7 (*C*$H_2$), 32.1 (*C*$H_2$), 32.3 (*C*$H_2$), 37.6 (*C*$H_2$), 39.7 (*C*$H_2$), 54.6 (*C*$H_2$), 59.2 (*C*$H_2$), 60.3 (*C*$H_2$), 61.1 (*C*$H_2$), 61.3 (*C*$H_2$), 119.1 (*C*H), 119.2 (*C*H), 123.4 (*C*H), 124.3 (*C*H), 135.4 (*C*), 135.5 (*C*), 135.7 (*C*), 142.5 (*C*), 142.6 (*C*); HRMS (ESI+): Exact mass calculated for $C_{19}H_{34}NO_2$ $(M+H)^+$ 308.2590. Found 308.2587 $(M+H)^+$; m/z (ESI+) 308.4 $(M+H)^+$.

### 4.15.5.3 Synthesis of 10-(4-(hydroxymethyl)piperidin-1-yl)-3,7-dimethyldeca-2,6-dien-1-yl acetate 205




The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and piperidin-4-yl methanol (49 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **205** (114 mg, 80 %) as a orange oil; $\nu_{max}/cm^{-1}$ (film) 3402 (OH), 2921 (CH), 2807, 2771, 1740 (C=O), 1446, 1379, 1234, 1124, 1044; $\delta_H$ ($CDCl_3$, 300 MHz) 1.16-1.40 [2H, m, C(2')$H_2$], 1.40-1.82 [11H, m, C(9)$H_2$ and C(2')$H_2$ and C(3')$H$ and C$H_3$* and containing 2 x 3H, s, C(11)$H_3$ and C(12)$H_3$], 1.84-2.20 [11H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and C(1')$H_2$ and containing 3H, s, C(O)C$H_3$], 2.20-2.36 [2H, m, C(10)$H_2$], 2.88-3.02 [2H, m, C(1')$H_2$], 3.11 (1H, brs, O$H$), 3.46 [2H, d, $J$ 6.4, C(4')$H_2$], 4.50-4.64 [2H, m, C$H_2$* and containing 2H, d, $J$ 7.3, C(1)$H_2$], 5.04-5.16 [1H, m, C(6)$H$], 5.29-5.40 [1H, m, C(2)$H$]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, $C$(11)$H_3$ or $C$(12)$H_3$], 16.4 [$CH_3$, $C$(11)$H_3$ or $C$(12)$H_3$], 21.0 [$CH_3$, C(O)$C$H$_3$], 25.1 [$CH_2$, $C$(9)$H_2$], 26.1 [$CH_2$, $C$(5)$H_2$], 28.7 [$CH_2$, $C$(2')$H_2$], 37.6, [$CH_2$, $C$(8)$H_2$], 38.6 [CH, $C$(3')H], 39.5 [$CH_2$, $C$(4)$H_2$], 53.6 [$CH_2$, $C$(1')$H_2$], 58.7 [$CH_2$, $C$(10)$H_2$], 61.4 [$CH_2$, $C$(1)$H_2$], 67.5 [$CH_2$, $C$(4')$H_2$], 118.2 [CH, $C$(2)H], 123.8 [CH, $C$(6)H], 135.0 [C, $C$(7)], 142.2 [C, $C$(3)], 171.2 [C, $C$(O)CH$_3$]; Characteristics peaks for the other isomer(s)* 14.2 ($C$H$_3$), 15.8 ($C$H$_3$), 16.5 ($C$H$_3$), 23.3 ($C$H$_3$), 23.5 ($C$H$_3$), 25.1 ($C$H$_2$), 26.0 ($C$H$_2$), 26.3 ($C$H$_2$), 26.5 ($C$H$_2$), 28.8 ($C$H$_2$), 29.6 ($C$H$_2$), 32.1 ($C$H$_2$), 32.3 ($C$H$_2$), 39.7 ($C$H$_2$), 43.4 ($C$H$_2$), 58.8 ($C$H$_2$), 60.4 ($C$H$_2$), 61.1 ($C$H$_2$), 118.2 ($C$H), 119.1 ($C$H), 119.2 ($C$H), 123.6 ($C$H), 124.4 ($C$H), 124.6 ($C$H), 135.2 ($C$), 135.4 ($C$), 135.5 ($C$), 142.1 ($C$), 142.4 ($C$), 142.6 ($C$), 171.1($C$); HRMS (ESI+): Exact mass calculated for $C_{20}H_{36}NO_3$ $(M+H)^+$ 338.2695. Found 338.2697 $(M+H)^+$; m/z (ESI+) 338.4 $(M+H)^+$.

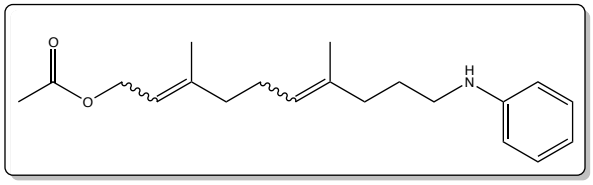
### 4.15.5.4 Synthesis of 10-(diethylamino)-3,7-dimethyldeca-2,6-dien-1-yl acetate 206




The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and diethylamine (31 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **206** (101 mg, 82 %) as an light yellow oil; $\nu_{max}/cm^{-1}$ (film) 2969 (CH), 2936, 2800, 1742 (C=O), 1448, 1381, 1367, 1232, 1024; $\delta_H$ ($CDCl_3$, 300 MHz) 1.02 [6H, t, $J$ 7.2, 2 x C(2')$H_3$],

1.45-1.64 [5H, m, C(9)$H_2$ and containing 3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.77* (3H, s), 1.88-2.20 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.33-2.45 [2H, m, C(10)$H_2$], 2.52 [4H, q, *J* 7.2, 2 x C(1')$H_2$], 4.50-4.64 [2H, m, C$H_2$* and containing 2H, d, *J* 7.3, C(1)$H_2$], 5.04-5.16 [1H, m, C(6)*H*], 5.28-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.6 [$CH_3$, *C*(2')$H_3$], 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 25.1 [$CH_2$, *C*(9)$H_2$], 26.1 [$CH_2$, *C*(5)$H_2$], 37.5, [$CH_2$, *C*(8)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 46.9 [$CH_2$, *C*(1')$H_2$], 52.5 [$CH_2$, *C*(10)$H_2$], 61.3 [$CH_2$, *C*(1)$H_2$], 118.2 [CH, *C*(2)H], 123.6 [CH, *C*(6)H], 135.2 [C, *C*(7)], 142.1 [C, *C*(3)] , 171.0 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 11.4 (*C*$H_3$), 14.2 (*C*$H_3$), 15.9 (*C*$H_3$), 23.3 (*C*$H_3$), 23.5 (*C*$H_3$), 25.2 (*C*$H_2$), 26.0 (*C*$H_2$), 26.5 (*C*$H_2$), 32.1 (*C*$H_2$), 32.3 (*C*$H_2$), 37.0 (*C*$H_2$), 37.6 (*C*$H_2$), 39.7 (*C*$H_2$), 43.4 (*C*$H_2$), 46.4 (*C*$H_2$), 46.8 (*C*$H_2$), 52.6 (*C*$H_2$), 52.8 (*C*$H_2$), 60.3 (*C*$H_2$), 61.1 (*C*$H_2$), 118.3 (*C*H), 119.1 (*C*H), 119.2 (*C*H), 123.4 (*C*H), 124.2 (*C*H), 124.4 (*C*H), 135.5 (*C*), 135.6 (*C*), 135.8 (*C*), 142.1 (*C*), 142.4 (*C*), 142.6 (*C*); HRMS (ESI+): Exact mass calculated for $C_{18}H_{34}NO_2$ $(M+H)^+$ 296.2590. Found 296.2589 $(M+H)^+$; m/z (ESI+) 296.4 $(M+H)^+$.

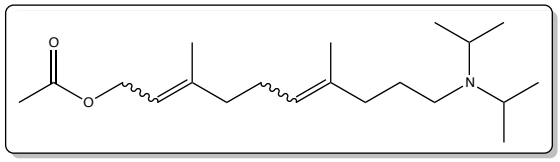
### 4.15.5.5 Synthesis of 3,7-dimethyl-10-(phenylamino)deca-2,6-dien-1-yl acetate 207



The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and aniline (39 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **207** (118 mg, 90 %) as an faint yellow oil; $\nu_{max}/cm^{-1}$ (film) 3402 (NH), 3053, 2932, 1732 (C=O), 1604, 1506, 1436, 1366, 1322, 1237, 1024, 749; $\delta_H$ ($CDCl_3$, 300 MHz) 1.62 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.64-1.79 [5H, m, C(9)$H_2$ and C$H_3$* and containing 3H, s, C(11)$H_3$ or C(12)$H_3$], 1.94-2.20 (9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 3.08 [2H, t, *J* 7.1, C(10)$H_2$], 3.10* (2H, t, *J* 7.0), 3.54 (1H, brs, N*H*), 4.50-4.64 [2H, m, C$H_2$* and containing 2H, d, *J* 7.0, C(1)$H_2$], 5.08-5.20 [1H, m, C(6)*H*], 5.28-5.40 [1H, m, C(2)*H*], 6.54-6.63 [2H, m, 2 x C(2')*H*] 6.63-6.73 [1H, m, C(4')*H*], 7.10-7.23 [2H, m, 2 x *C*(3')*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.5 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.1 [$CH_2$, *C*(5)$H_2$], 27.6 [$CH_2$, *C*(9)$H_2$], 37.1 [$CH_2$, *C*(8)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 43.5 [$CH_2$, *C*(10)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 112.7 [CH, *C*(2')H], 117.1 [CH, *C*(4')H], 118.4 [CH, *C*(2)H], 124.3 [CH, *C*(6)H], 129.2 [CH, *C*(3')H], 134.8 [C, *C*(7)], 142.1 [C, *C*(3)], 148.5 [C, *C*(1')], 171.2 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.1 (*C*$H_3$), 16.5 (*C*$H_3$),

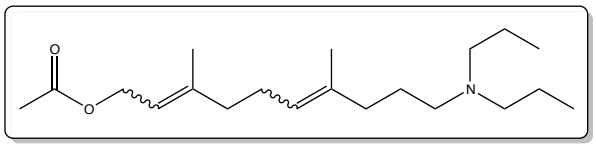
23.3 (*C*$H_3$), 23.5 (*C*$H_3$), 26.1 (*C*$H_2$), 26.5 (*C*$H_2$), 27.7 (*C*$H_2$), 29.7 (*C*$H_2$), 32.1 (*C*$H_2$), 39.7 (*C*$H_2$), 43.6 (*C*$H_2$), 43.8 (*C*$H_2$), 50.6 (*C*$H_2$), 61.1 (*C*$H_2$), 111.8 (*C*H), 112.7 (*C*H), 115.1 (*C*H), 117.2 (*C*H), 118.4 (*C*H), 118.5 (*C*H), 119.2 (*C*H), 124.0 (*C*H), 124.9 (*C*H), 125.1 (*C*H), 129.3 (*C*H), 134.9 (*C*), 135.2 (*C*), 142.1 (*C*), 142.5 (*C*), 148.4 (*C*); (Monomer) HRMS (ESI+): Exact mass calculated for $C_{20}H_{30}NO_2$ $(M+H)^+$ 316.2277. Found 316.2280 $(M+H)^+$. (Dimer) HRMS (ESI+): Exact mass calculated for $C_{34}H_{52}NO_4$ $(M+H)^+$ 538.3896. Found 538.3870 $(M+H)^+$. m/z (ESI+) 538.8.4 $(M+H)^+$.

### 4.15.5.6 Synthesis of 10-(diisopropylamino)-3,7-dimethyldeca-2,6-dien-1-yl acetate 208



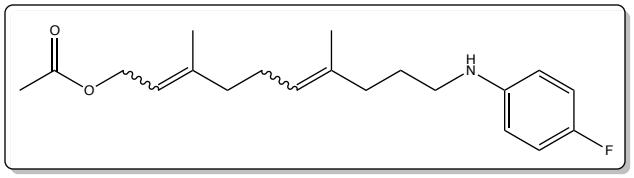
The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and diisopropylamine (42 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **208** (99 mg, 73%) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 2965, 1741 (C=O), 1448, 1382, 1365, 1233, 1162, 1024; $\delta_H$ ($CDCl_3$, 300 MHz) 1.00 [12H, d, *J* 6.6, 4 x C(2')*H*$_3$], 1.40-1.56 [2H, m, C(9)*H*$_2$], 1.60 [3H, s, C(11)*H*$_3$ or C(12)*H*$_3$], 1.68* (3H, s), 1.70 [3H, s, C(11)*H*$_3$ or C(12)*H*$_3$], 1.77* (3H, s), 1.88-2.20 [9H, m, C(4)*H*$_2$ and C(5)*H*$_2$ and C(8)*H*$_2$ and containing 3H, s, C(O)C*H*$_3$], 2.24-2.42 [2H, m, C(10)*H*$_2$], 3.01 [2H, septet, *J* 13.1, 6.6, 2 x C(1')*H*$_2$], 4.50-4.64 [2H, m, C*H*$_2$* and containing 2H, d, *J* 7.2, C(1)*H*$_2$], 5.03-5.20 [1H, m, C(6)*H*], 5.27-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 20.6 [$CH_2$, *C*(2')$H_3$]. 21.0 [$CH_3$, C(O)*C*$H_3$], 26.2 [$CH_2$, *C*(5)$H_2$], 29.6 [$CH_2$, *C*(9)$H_2$], 37.4 [$CH_2$, *C*(8)$H_2$], 39.8 [$CH_2$, *C*(4)$H_2$], 45.2 [$CH_2$, *C*(10)$H_2$], 58.6 [$CH_2$, *C*(1')H], 61.4 [$CH_2$, *C*(1)$H_2$], 118.2 [CH, *C*(2)H], 123.4 [CH, *C*(6)H], 135.6 [C, *C*(7)], 142.2 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 23.4 (*C*$H_3$), 23.5 (*C*$H_3$), 26.0 (*C*$H_2$), 26.1 (*C*$H_2$), 26.6 (*C*$H_2$), 29.6 (*C*$H_2$), 29.8 (*C*$H_2$), 31.8 (*C*$H_2$), 32.1 (*C*$H_2$), 37.4 (*C*$H_2$), 39.2 (*C*$H_2$), 39.5 (*C*$H_2$), 45.4 (*C*$H_2$), 48.6 (*C*$H_2$), 61.1 (*C*$H_2$), 118.3 (*C*H), 119.1 (*C*H), 123.2 (*C*H), 124.0 (*C*H), 135.7 (*C*), 135.9 (*C*), 142.2 (*C*); HRMS (ESI+): Exact mass calculated for $C_{20}H_{38}NO_2$ $(M+H)^+$ 324.2903. Found 324.2908 $(M+H)^+$; m/z (ESI+) 324.4 $(M+H)^+$.

### 4.15.5.7 Synthesis of 10-(dipropylamino)-3,7-dimethyldeca-2,6-dien-1-yl acetate 209



The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and dipropylamine (42 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **209** (108 mg, 80%) as a light yellow oil; $\nu_{max}/cm^{-1}$ (film) 2959, 2935, 2873, 2800, 1743 (C=O), 1458, 1380, 1366 1232, 1079, 1023; $\delta_H$ ($CDCl_3$, 300 MHz) 0.87 [6H, t, *J* 7.4, 2 x C(3')$H_3$], 1.36-1.58 [6H, m, C(9)$H_2$ and 2 x C(2')$H_2$], 1.60 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.68* (3H, s), 1.70 [3H, s, C(11)$H_3$ or C(12)$H_3$], 1.77* (3H, s), 1.88-2.20 [9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.30-2.44 [6H, m, C(10)$H_2$ and 2 x C(1')$H_2$], 4.50-4.64 [2H, m, C$H_2$* and containing 2H, d, *J* 7.3, C(1)$H_2$], 5.04-5.15 [1H, m, C(6)*H*], 5.29-5.40 [1H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 12.0 [$CH_3$, *C*(3')$H_3$], 16.0 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.5 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 20.2 [$CH_2$, *C*(2')H]. 21.1 [$CH_3$, C(O)*C*$H_3$], 25.3 [$CH_2$, *C*(9)$H_2$], 26.2 [$CH_2$, *C*(5)$H_2$], 37.6 [$CH_2$, *C*(8)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 53.9 [$CH_2$, *C*(10)$H_2$], 56.3 [$CH_2$, *C*(1')$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 118.2 [CH, *C*(2)H], 123.6 [CH, *C*(6)H], 135.5 [C, *C*(7)], 142.3 [C, *C*(3)], 171.1 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 23.4 (*C*$H_3$), 23.5 (*C*$H_3$), 25.5 (*C*$H_2$), 26.0 (*C*$H_2$), 26.4 (*C*$H_2$), 26.6 (*C*$H_2$), 29.8 (*C*$H_2$), 32.1 (*C*$H_2$), 32.4 (*C*$H_2$), 37.6 (*C*$H_2$), 39.8 (*C*$H_2$), 53.9 (*C*$H_2$), 54.2 (*C*$H_2$), 56.2 (*C*$H_2$), 61.1 (*C*$H_2$), 118.2 (*C*H), 119.1 (*C*H), 123.4 (*C*H), 124.3 (*C*H), 135.7 (*C*), 135.8 (*C*), 142.2 (*C*), 142.7 (*C*); HRMS (ESI+): Exact mass calculated for $C_{20}H_{38}NO_2$ $(M+H)^+$ 324.2903. Found 324.2916 $(M+H)^+$; m/z (ESI+) 324.4 $(M+H)^+$.

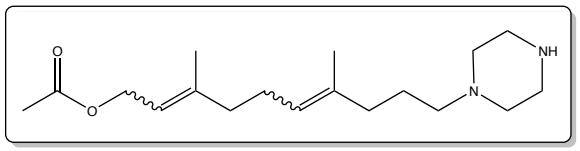
### 4.15.5.8 Synthesis of 10-(4-fluorophenylamino)-3,7-dimethyldeca-2,6-dien-1-yl acetate 210



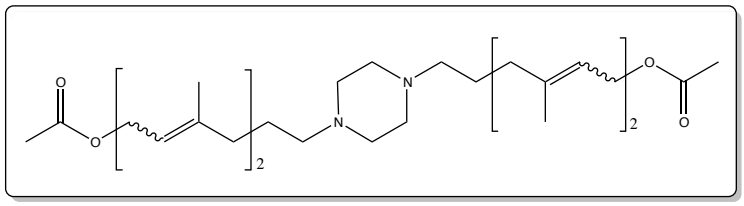
The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and 4-fluoroaniline (47 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **210** (120 mg, 86%) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 3398, 2934, 1732 (C=O), 1614, 1514, 1446, 1367, 1235, 1117, 1024; $\delta_H$ ($CDCl_3$, 300 MHz) 1.57-1.80 [8H, m, C(9)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(11)$H_3$ and C(12)$H_3$], 1.95-2.20 (9H, m, C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H,

s, C(O)C$H_3$], 3.04 [2H, t, *J* 6.0, C(10)$H_2$], 3.05* (2H, t, *J* 7.0), 3.52 (1H, brs, N*H*), 4.50-4.64 [2H, m, C$H_2$* and containing 2H, d, *J* 7.3, C(1)$H_2$], 5.08-5.20 [1H, m, C(6)*H*], 5.26-5.40 [1H, m, C(2)*H*], 6.45-6.57 [2H, m, 2 x C(2')*H*], 6.57-6.66* (2H, m), 6.88 [2H, t, *J* 8.8, 2 x C(3')*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.5 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.1 [$CH_3$, C(O)*C*$H_3$], 26.1 [$CH_2$, *C*(5)$H_2$], 27.5 [$CH_2$, *C*(9)$H_2$], 37.1 [$CH_2$, *C*(8)$H_2$], 39.5 [$CH_2$, *C*(4)$H_2$], 44.2 [$CH_2$, *C*(10)$H_2$], 61.4 [$CH_2$, *C*(1)$H_2$], 113.5 [CH, d, $^3J_{FC}$ 5.1, *C*(2')H], 115.6 [CH, d, $^2J_{FC}$ 22.3, *C*(3')H], 118.4 [CH, *C*(2)H], 124.3 [CH, *C*(6)H], 134.8 [C, C(7)], 142.1 [C, C(3)], 144.8 [C, d, $^4J_{FC}$ 1.6, *C*(1')], 155.7 [C, d, $^1J_{FC}$ 234.5, *C*(4')], 171.2 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 16.5 (*C*$H_3$), 23.3 (*C*$H_3$), 23.5 (*C*$H_3$), 26.1 (*C*$H_2$), 26.5 (*C*$H_2$), 27.6 (*C*$H_2$), 32.1 (*C*$H_2$), 39.7 (*C*$H_2$), 44.3 (*C*$H_2$), 44.4 (*C*$H_2$), 61.1 (*C*$H_2$), 113.5 (*C*H), 115.6 (*C*H), 116.0 (*C*H), 116.1 (*C*H), 118.4 (*C*H), 119.2 (*C*H), 124.0 (*C*H), 125.1 (*C*H), 134.8 (*C*), 135.1 (*C*), 142.0 (*C*), 142.5 (*C*), 144.8 (*C*) 155.7 (*C*); (Monomer) HRMS (ESI+): Exact mass calculated for $C_{20}H_{29}FNO_2$ $(M+H)^+$ 334.2182. Found 334.2171 $(M+H)^+$; m/z (ESI+) 334.21 $(M+H)^+$; (Dimer) HRMS (ESI+): Exact mass calculated for $C_{34}H_{51}FNO_4$ $(M+H)^+$ 556.3802. Found 556.3776 $(M+H)^+$; m/z (ESI+) 556.3 $(M+H)^+$.

### 4.15.5.9 Synthesis of 3,7-dimethyl-10-(piperazin-1-yl)deca-2,6-dien-1-yl acetate 212



The title compound was synthesised according to the procedure described for 3,7-dimethyl-10-morpholinodeca-2,6-dien-1-yl acetate **204** using sodium triacetoxyborohydride (125 mg, 0.59 mmol), 3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate **62** (100 mg, 0.42 mmol) and piperazine (36 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL). $^1$H NMR analysis of the crude product revealed a two component mixture consisting of the title amine **212** (7 mg, 6%) and its corresponding dimer **213** (55 mg, 42%) as a yellow oil in a 12:88 ratio of products respectively. The characteristic peak in $^1$H NMR spectrum associated with the monomer **212** was at $\delta_H$ ($CDCl_3$, 300 MHz) 2.93 [2H, t, *J* 4.6]. m/z (ESI+) 309.4 $(M+H)^+$.



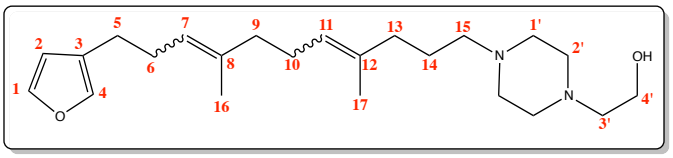
The dimer, piperazine-1,4-diylbis(3,7-dimethyldeca-2,6-diene-10,1-diyl) diacetate **213**; $\nu_{max}$/cm$^{-1}$ (film) 3370 (NH), 2939 (CH), 2809 (CH), 1741 (C=O), 1446, 1366, 1233, 1023; $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.80 [16H, m, 2x{C(9)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(11)$H_3$ and C(12)$H_3$}], 1.88-2.20 [18H, m, 2x{C(4)$H_2$ and C(5)$H_2$ and C(8)$H_2$ and containing 3H, s, C(O)C$H_3$], 2.25-2.36 [4H, m, 2 x C(10)$H_2$], 2.36-2.65 [8H,

m, 4 x C(1')$H_2$], 4.50-4.64 [4H, m, C$H_2$* and containing 2H, d, *J* 7.3, C(1)$H_2$], 5.00-5.15 [2H, m, C(6)*H*], 5.25-5.40 [2H, m, C(2)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 16.4 [$CH_3$, *C*(11)$H_3$ or *C*(12)$H_3$], 21.0 [$CH_3$, C(O)*C*$H_3$], 25.1 [$CH_2$, *C*(9)$H_2$], 26.1 [$CH_2$, *C*(5)$H_2$], 37.5, [$CH_2$, *C*(8)$H_2$], 39.4 [$CH_2$, *C*(4)$H_2$], 53.2 [$CH_2$, *C*(1')$H_2$], 58.4 [$CH_2$, *C*(10)$H_2$], 61.3 [$CH_2$, *C*(1)$H_2$], 118.3 [CH, *C*(2)H], 123.8 [CH, *C*(6)H], 135.1 [C, *C*(7)], 142.1 [C, *C*(3)], 171.0 [C, *C*(O)$CH_3$]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.5 (*C*$H_3$), 23.3 (*C*$H_3$), 23.5 (*C*$H_3$), 23.6 (*C*$H_3$), 24.8 (*C*$H_2$), 26.3 (*C*$H_2$), 26.5 (*C*$H_2$), 29.5 (*C*$H_2$), 32.1 (*C*$H_2$), 32.3 (*C*$H_2$), 39.7 (*C*$H_2$), 45.8 (*C*$H_2$), 54.2 (*C*$H_2$), 58.9 (*C*$H_2$), 61.1 (*C*$H_2$), 119.1 (*C*H), 119.2 (*C*H), 123.6 (*C*H), 124.4 (*C*H), 135.2 (*C*), 135.4 (*C*), 135.5 (*C*), 142.1 (*C*), 142.4 (*C*), 142.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{32}H_{54}N_2O_4$ $(M+H)^+$ 530.4084. Found 530.4090 $(M+H)^+$; m/z (ESI+) 530.4 $(M+H)^+$.

### 4.15.6 Synthesis of furanolipid amine derivatives

These transformations were essentially quantitative. Purification by chromatography was deemed unnecessary unless otherwise stated, with complete conversion to the amine. The following numbering template was used in characterising the furanolipid amine compound(s). The furanolipid amines in this section were prepared from 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** and $^{1}$H NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers* for this compound. All furanolipid amines prepared from furanolipid aldehyde **121** will therefore contain a 70:30 mixture of (*E*,*E*) and other isomer(s)*.

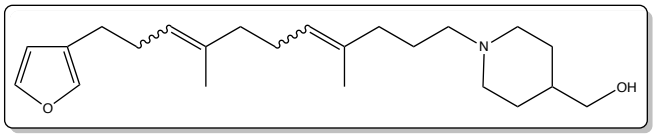
#### 4.15.6.1 Synthesis of 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)furan 214




Sodium triacetoxyborohydride (34 mg, 0.16 mmol, 1.4 equiv) was added to a stirring solution of the aldehyde, 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol, 1 equiv) and 2-(piperazin-1-yl)ethanol (15 mg, 0.12 mmol, 1 equiv) in 1,2-dichloroethane (5 mL) under an inert nitrogen atmosphere at room temperature. TLC analysis after 1.5 h showed complete consumption of the aldehyde starting material and the reaction was quenched using saturated sodium bicarbonate solution (5 mL). The organic layer was extracted into ethyl acetate (3 x 10 mL). The combined organic phase was washed with water (10 mL) followed by brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the title amine **214** (33 mg, 77 %) as a light yellow oil; $\nu_{max}/cm^{-1}$ (film) 3392 (OH), 2934 (CH), 2856 (CH), 1456, 1385, 1159, 1026, 874, 777; $\delta_H$ ($CDCl_3$, 300 MHz) 1.48-1.72 [8H, m, C(14)$H_2$ and C$H_3$* containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.16-2.70 [16H, m, C(5)$H_2$ and C(6)$H_2$ and C(15)$H_2$ and C$H_2$CH$_2$OH and 2 x C(1')$H_2$ and 2 x C(2')$H_2$], 2.90 [1H, s, O*H*], 3.68 [2H, t, *J* 5.4, CH$_2$C$H_2$OH], 5.05-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 15.9 [CH$_3$, *C*(16)H$_3$ or *C*(17)H$_3$], 16.1 [CH$_3$, *C*(16)H$_3$ or *C*(17)H$_3$], 25.1 [CH$_2$, *C*(5)H$_2$], 25.2 [CH$_2$, *C*(14)H$_2$], 26.5 [CH$_2$, *C*(10)H$_2$], 28.4 [CH$_2$, *C*(6)H$_2$], 37.5 [CH$_2$, *C*(13)H$_2$], 39.7 [CH$_2$, *C*(9)H$_2$], 52.9 [CH$_2$, *C*(1')H$_2$ or *C*(2')H$_2$], 53.3 [CH$_2$, *C*(1')H$_2$ or *C*(2')H$_2$] 57.7 [CH$_2$, CH$_2$CH$_2$OH], 58.4 [CH$_2$, *C*(15)H$_2$], 59.2 [CH$_2$, *C*H$_2$CH$_2$OH], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 15.9 (*C*H$_3$), 16.1 (*C*H$_3$), 23.3 (*C*H$_3$), 23.4 (*C*H$_3$), 23.5 (*C*H$_3$), 25.1 (*C*H$_2$), 25.3 (*C*H$_2$), 26.3 (*C*H$_2$), 26.4 (*C*H$_2$), 28.4 (*C*H$_2$), 29.6 (*C*H$_2$), 29.7 (*C*H$_2$), 31.9 (*C*H$_2$), 32.2

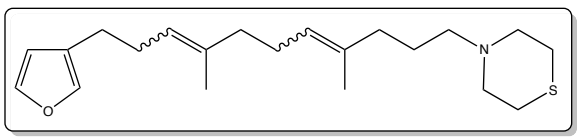
($CH_2$), 39.9 ($CH_2$), 58.4 ($CH_2$), 123.8 (*C*H), 124.3 (*C*H), 124.5 (*C*H), 124.6 (*C*H), 125.2 (*C*H), 134.8 (*C*), 135.6 (*C*) 135.9 (*C*), 142.6 (*C*); HRMS (ESI+): Exact mass calculated for $C_{23}H_{39}N_2O_2$ $(M+H)^+$ 375.3012. Found 375.3000 $(M+H)^+$; m/z (ESI+) 375.5 $(M+H)^+$.

### 4.15.6.2 Synthesis of 3-(11-(4-(hydroxymethyl)piperidin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)furan 215




The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 mg, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and piperidin-4-ylmethanol (13.3 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to furnish the title amine **215** (30 mg, 71 %) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 3368 (OH), 2921 (CH), 1446, 1379, 1044, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.15-1.80 [13H, m, C(14)$H_2$ and C(3')*H* and 2 x C(2')$H_2$ and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.82-2.12 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(1')$H_2$], 2.12-2.35 [4H, m, C(6)$H_2$ and C(15)$H_2$] 2.38-2.50 [2H, m, C(5)$H_2$], 2.88-3.02 [2H, m, C(1')$H_2$], 3.48 [2H, d, *J* 6.4, C(4')$H_2$], 5.04-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, brs, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 25.2 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 28.8 [$CH_2$, *C*(2')$H_2$], 37.7 [$CH_2$, *C*(13)$H_2$], 38.6 [$CH_2$, *C*(3')H], 39.7 [$CH_2$, *C*(9)$H_2$], 53.6 [$CH_2$, *C*(1')$H_2$], 58.8 [$CH_2$, *C*(15)$H_2$], 67.8 [$CH_2$, *C*(4')$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.7 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [C, *C*(4)H], 142.5 [C, *C*(1)H]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 23.5 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 28.4 (*C*$H_2$), 29.7 (*C*$H_2$), 32.0 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 58.9 (*C*$H_2$), 123.8 (*C*H), 124.3 (*C*H), 124.5 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 134.8 (*C*), 134.9 (*C*), 135.1 (*C*) 135.7 (*C*) 135.9 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{23}H_{38}NO_2$ $(M+H)^+$ 360.2903. Found 360.2904 $(M+H)^+$; m/z (ESI+) 360.4 $(M+H)^+$.

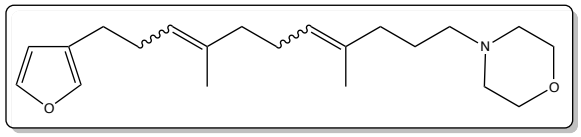
### 4.15.6.3 Synthesis of 3-(4,8-dimethyl-11-thiomorpholinoundeca-3,7-dien-1-yl)furan 216




The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 mg, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and thiomorpholine (12 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to afford the title amine **216** (34 mg, 85 %) as a yellow oil;

$\nu_{max}/cm^{-1}$ (film) 2918 (CH), 2855, 2808, 1501, 1447, 1322, 1280, 1123, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.48-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.14 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.18-2.38 [4H, m, C(6)$H_2$ and C(15)$H_2$], 2.45 [2H, t, *J* 7.4, C(5)$H_2$], 2.60-2.75 [8H, m, 2 x C(1')$H_2$ and 2 x C(2')$H_2$], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, brs, C(2)*H*], 7.21 [1H, brs, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 24.7 [$CH_2$, *C*(14)$H_2$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.0 [$CH_2$, *C*(2')$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 37.4 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 55.1 [$CH_2$, *C*(1')$H_2$], 59.1 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.5 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.0 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 23.5 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 28.4 (*C*$H_2$), 29.5 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 111.1 (*C*$H_2$), 123.9 (*C*H), 124.4 (*C*H), 124.6 (*C*H), 125.3 (*C*H), 134.7 (*C*), 134.8 (*C*), 135.0 (*C*) 135.6 (*C*), 135.9 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{34}NOS$ $(M+H)^+$ 348.2361. Found 348.2359 $(M+H)^+$; m/z (ESI+) 348.2 $(M+H)^+$.

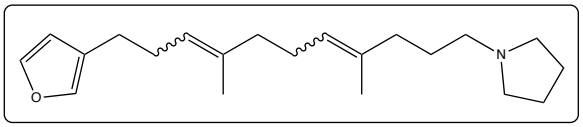
### 4.15.6.4 Synthesis of 3-(4,8-dimethyl-11-morpholinoundeca-3,7-dien-1-yl)furan 217




The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 mg, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and morpholine (10 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to afford the title amine **217** (30 mg, 79 %) as a light yellow oil; $\nu_{max}/cm^{-1}$ (film) 2934 (CH), 2855, 2808, 1501, 1446, 1381 1306, 1276, 1138, 1119, 1026, 874, 779; $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.15-2.55 [10H, m, C(5)$H_2$ and C(6)$H_2$ and C(15)$H_2$ and 2 x C(1')$H_2$], 3.67-3.78 [4H, m, 2 x C(2')$H_2$], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, brs, C(4)*H*], 7.34 [1H, t, *J* 1.5 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 24.8 [$CH_2$, *C*(14)$H_2$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 37.4 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 53.8 [$CH_2$, *C*(1')$H_2$], 58.8 [$CH_2$, *C*(15)$H_2$], 67.0 [$CH_2$, *C*(2')$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.5 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.5 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [C, *C*(4)H], 142.6 [C, *C*(1)H]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.1 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 28.4 (*C*$H_2$), 29.5 (*C*$H_2$), 29.7 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 123.8 (*C*H), 124.4 (*C*H), 124.6 (*C*H), 125.3 (*C*H), 134.7 (*C*), 134.8 (*C*), 134.9 (*C*), 135.6 (*C*)

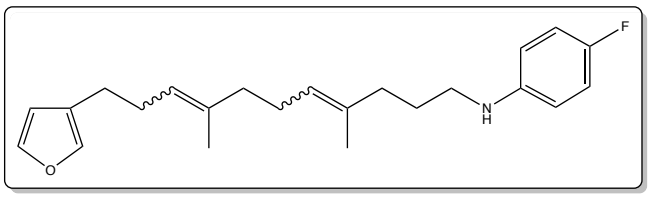
135.8 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{34}NO_2$ $(M+H)^+$ 332.2590. Found 332.2574 $(M+H)^+$; m/z (ESI+) 332.4 $(M+H)^+$.

### 4.15.6.5 Synthesis of 3-(4,8-dimethyl-11-(pyrrolidin-1-yl)undeca-3,7-dien-1-yl)furan 218



The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 g, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and pyrrolidine (8.2 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to afford the title amine **218** (31 mg, 84%) as a faint yellow oil; $\nu_{max}/cm^{-1}$ (film) 2932 (CH), 2857, 2786, 1447, 1383, 1164, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.74-1.87 [4H, m, 2 x C(2')$H_2$], 1.92-2.16 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.35-2.65 [8H, m, C(5)$H_2$ and C(15)$H_2$ and 2 x C(1')$H_2$], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 23.4 [$CH_2$, *C*(2')$H_2$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.0 [$CH_2$, *C*(14)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 37.6 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 54.2 [$CH_2$, *C*(1')$H_2$], 56.2 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 23.3 (*C*$H_3$), 25.3 (*C*$H_2$), 26.4 (*C*$H_2$), 27.2 (*C*$H_2$), 28.4 (*C*$H_2$), 29.8 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 56.4 (*C*$H_2$), 123.8 (*C*H), 124.3 (*C*H), 124.5 (*C*H), 125.1 (*C*H), 134.8 (*C*), 135.9 (*C*) 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{34}NO$ $(M+H)^+$ 316.2640. Found 316.2634 $(M+H)^+$; m/z (ESI+) 316.4 $(M+H)^+$.

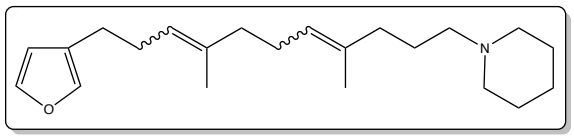
### 4.15.6.6 Synthesis of 3-(11-(4-fluorophenylamino)-4,8-dimethylundeca-3,7-dien-1-yl)furan 219



The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 mg, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and 4-fluoroaniline (13 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to afford the title amine **219** (34 mg, 83 %) as an intense yellow oil; $\nu_{max}/cm^{-1}$ (film) 3413 (NH), 2925 (CH), 2856, 1505, 1447, 1222, 1138, 1025, 819, 777; $\delta_H$ ($CDCl_3$, 300 MHz) 1.53-1.75 [8H, m, C(14)$H_2$ and C$H_3$*

and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.17 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.2, C(6)$H_2$], 2.44 [2H, t, *J* 7.5, C(5)$H_2$], 3.03 [2H, t, *J* 7.0, C(15)$H_2$], 3.05* [2H, t, *J* 6.9], 3.42 [1H, s, N*H*], 5.07-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 6.46-6.58 [2H, m, C(2')*H*], 6.82-6.93 [2H, m, C(3')*H*], 7.20 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.5, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.1 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.5 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 37.1 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 44.3 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 113.5 [CH, d, $^3J_{FC}$ 7.3, *C*(2')H], 115.6 [CH, d, $^2J_{FC}$ 22.1, *C*(3')H], 123.9 [CH, *C*(7)H], 124.9 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.3 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 144.8 [C, d, $^4J_{FC}$ 4.1, *C*(1')], 155.7 [C, d, $^1J_{FC}$ 235, *C*(4')]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 27.6 (*C*$H_2$), 27.8 (*C*$H_2$), 28.4 (*C*$H_2$), 29.3 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 44.3 (*C*$H_2$), 44.4 (*C*$H_2$), 44.5 (*C*$H_2$), 124.6 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.7 (*C*H), 134.4 (*C*), 134.5 (*C*), 134.6 (*C*), 135.6 (*C*) 135.8 (*C*); HRMS (ESI+): Exact mass calculated for $C_{23}H_{31}FNO$ $(M+H)^+$ 356.2311. Found 356.2320 ($M+H^+$); m/z (ESI+) 356.2 $(M+H)^+$.

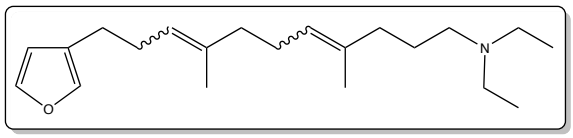
### 4.15.6.7 Synthesis of 3-(4,8-dimethyl-11-(piperidin-1-yl)undeca-3,7-dien-1-yl)furan 220



The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 mg, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and piperidine (10 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to afford the title amine **220** (31 mg, 82 %) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 2934, 2855, 2800, 1502, 1444, 1379,1156, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 300 MHz) 1.36-1.72 [14H, m, C(14)$H_2$ and C$H_3$* and C(3')$H_2$ and 2 x C(2')$H_2$ and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.15-2.35 [4H, m, C(6)$H_2$ and C(15)$H_2$], 2.35-2.52 [6H, m, C(5)$H_2$ and 2 x C(1')$H_2$], 5.00-5.25 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, brs, C(4)*H*], 7.34 [1H, t, *J* 1.6 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 24.3 [$CH_2$, *C*(3')$H_2$], 24.9 [$CH_2$, *C*(14)$H_2$], 25.1 [$CH_2$, *C*(5)$H_2$], 25.7 [$CH_2$, *C*(2')$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 37.6 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 54.5 [$CH_2$, *C*(1')$H_2$], 59.1 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 23.3 (*C*$H_3$), 24.4 (*C*$H_2$), 25.0 (*C*$H_2$), 25.3 (*C*$H_2$), 25.8 (*C*$H_2$), 25.9 (*C*$H_2$), 26.4 (*C*$H_2$), 28.4 (*C*$H_2$), 31.9 (*C*$H_2$), 32.3 (*C*$H_2$), 39.9 (*C*$H_2$), 59.2 (*C*$H_2$), 123.8 (*C*H), 124.3 (*C*H), 124.5 (*C*H), 124.9 (*C*H), 125.1

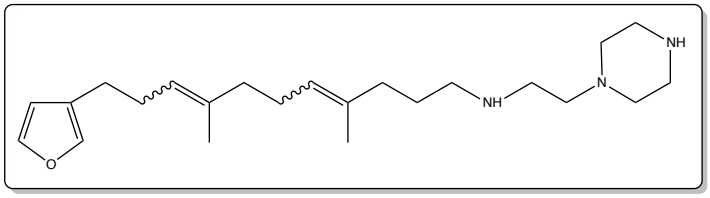
(*C*H), 134.9 (*C*), 135.7 (*C*) 135.9 (*C*); HRMS (ESI+): Exact mass calculated for $C_{22}H_{36}NO$ $(M+H)^+$ 330.2797. Found 330.2789 $(M+H)^+$; m/z (ESI+) 330.4 $(M+H)^+$.

### 4.15.6.8 Synthesis of 3-(11-(diethylamino)-4,8-dimethylundeca-3,7-dien-1-yl)furan 221

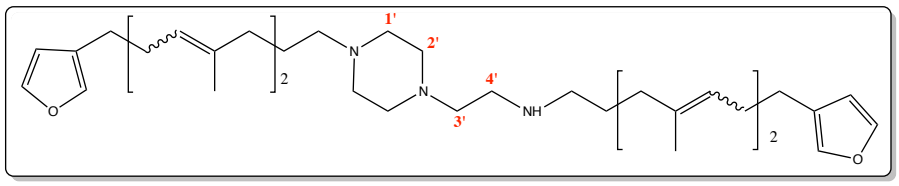


The title compound was synthesized according to the procedure described for **214** using sodium triacetoxyborohydride (34 mg, 0.16 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (30 mg, 0.12 mmol) and diethylamine (8.4 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) to afford a two component mixture consisting of the title furanolipid amine **221** and aldehyde starting material **121** in a 80:20 ratio of products. The crude residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes followed by 2-5% methanol gradient in dichloromethane) to afford the title amine **221** (12 mg, 33%) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 2966, 2927, 2854, 1451, 1382, 1026, 874, 778; $\delta_H$ ($CDCl_3$, 400 MHz) 1.00-1.15 [6H, t, *J* 7.2, 2 x C(2')$H_3$], 1.50-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.92-2.12 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, q, *J* 7.3, C(6)$H_2$], 2.38-2.53 [4H, m, C(5)$H_2$ and C(15)$H_2$], 2.54-2.72 [4H, m, 2 x C(1')$H_2$], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6 C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 11.2 [$CH_2$, *C*(2')$H_3$], 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 24.5 [$CH_2$, *C*(14)$H_2$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 37.5 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 46.7 [$CH_2$, *C*(1')$H_2$], 52.2 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.5 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.5 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 11.3 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 24.3 (*C*$H_2$), 25.3 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 27.1 (*C*$H_2$), 28.4 (*C*$H_2$), 29.7 (*C*$H_2$), 31.8 (*C*$H_2$), 31.9 (*C*$H_2$), 36.2 (*C*$H_2$), 39.4 (*C*$H_2$), 39.9 (*C*$H_2$), 42.1 (*C*$H_2$), 52.6 (*C*$H_2$), 123.8 (*C*H), 124.0 (*C*H), 124.4 (*C*H), 125.2 (*C*H), 125.3 (*C*H), 134.8 (*C*), 135.4 (*C*), 135.6 (*C*), 135.9 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{21}H_{36}NO$ $(M+H)^+$ 318.2797. Found 318.2784 $(M+H)^+$; m/z (ESI+) 318.4 $(M+H)^+$.

### 4.15.6.9 The attempted synthesis of 3-(4,8-dimethyl-11-((2-(piperazin-1-yl)ethyl)amino)undeca-3,7-dien-1-yl)furan 222



The synthesis of the title compound was attempted according to the procedure described for **214** using sodium triacetoxyborohydride (34.2 mg, 0.162 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan (30 mg, 0.115 mmol) **121** and 2-(piperazin-1-yl)ethanamine (14.9 mg, 0.115 mmol) in 1,2-dichloroethane (5 mL) to afford a crude yellow oil (31.2 mg, 73 %). $^{1}$H NMR analysis of the crude product revealed a two component mixture consisting of the title amine **222** (2 mg, 6%) and its corresponding dimer **223** (29 mg, 67%) in a 8:92 ratio of products respectively. The characteristic peak in the $^{1}$H NMR spectrum associated with the monomer **222** was at $\delta_H$ ($CDCl_3$, 300 MHz) 2.83 (2H, m); HRMS (ESI+): Exact mass calculated for $C_{23}H_{40}N_3O$ $(M+H)^+$ 374.3093. Found 374.3094 $(M+H)^+$; m/z (ESI+) 374.4 $(M+H)^+$. Spectroscopic characteristics for the dimer **223** are tentatively assigned below.

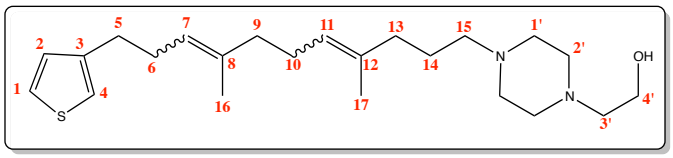


The dimer, 3-(11-((2-(4-(11-(furan-3-yl)-4,8-dimethylundeca-4,8-dien-1-yl)piperazin-1-yl)ethyl)amino)-4,8-dimethylundeca-3,7-dien-1-yl)furan **223**; $\nu_{max}$/cm$^{-1}$ (film) 3327 (NH), 2922 (CH), 1662, 1502, 1456, 1380, 1308, 1274, 1162, 1065, 1026, 874, 778, 738; $\delta_H$ ($CDCl_3$, 300 MHz) 1.46-1.74 [16H, m, 2 x {C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$}], 1.86-2.16 [12H, m, 2 x {C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$}], 2.16-2.90 [24H, m, C(3')$H_2$ and C(4')$H_2$ and 2 x {C(5)$H_2$ and C(6)$H_2$ and C(15)$H_2$ and C(1')$H_2$ and C(2')$H_2$}] 3.65 [1H, s, N*H*], 5.04-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.28 [2H, s, 2 x C(2)*H*], 7.21 [2H, s, 2 x C(4)*H*], 7.34 [2H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.3 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 37.5 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 45.5 [$CH_2$, *C*(4')$H_2$], 53.1 [$CH_2$, *C*(1')$H_2$ or *C*(2')$H_2$ or *C*(3')$H_2$], 53.2 [$CH_2$, *C*(1')$H_2$ or *C*(2')$H_2$ or *C*(3')$H_2$], 58.3 [$CH_2$, *C*(15)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 26.4 (*C*$H_2$), 26.7 (*C*$H_2$), 28.4 (*C*$H_2$), 29.6 (*C*$H_2$), 29.7 (*C*$H_2$), 31.9 (*C*$H_2$), 37.0 (*C*$H_2$), 39.9 (*C*$H_2$), 45.8 (*C*$H_2$), 123.8 (*C*H), 124.3 (*C*H), 124.5 (*C*H), 125.2 (*C*H), 125.6 (*C*H), 134.0 (*C*), 134.8 (*C*), 135.6 (*C*) 135.9 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{40}H_{63}N_3O_2$ $(M+H)^+$ 618.4999. Found 618.5001 $(M+H^+)$; m/z (ESI+) 618.4 $(M+H)^+$.

### 4.15.7 Synthesis of thiophenolipid amine derivatives

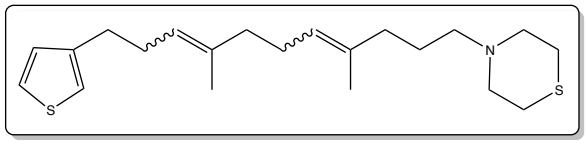
Note: The following numbering system was used to number our thiophenolipid amine derivatives in this section. The thiophenolipid amines in this section were prepared from 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** and $^1$H NMR integration revealed a 77:23 mixture of *E*,*E* and other isomers* for this compound. All thiophenolipid amines prepared from aldehyde **166** will therefore contain a 77:23 mixture of (*E*,*E*) and other isomer(s)*

#### 4.15.7.1 Synthesis of 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene 227



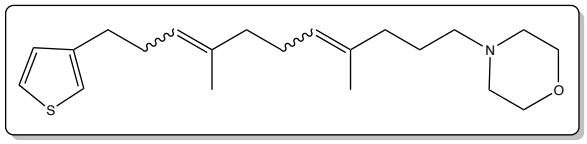

Sodium triacetoxyborohydride (33.2 mg, 0.15 mmol) was added to a stirring solution of 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (30 mg, 0.11 mmol) and 2-(piperazin-1-yl)ethanol (14.4 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL) under an inert nitrogen atmosphere at room temperature. TLC analysis after 1.5 h showed complete consumption of the aldehyde starting material and the reaction was quenched using saturated sodium bicarbonate solution (5 mL). The organic layer was extracted into ethyl acetate (3 x 10 mL) and washed successively with water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the title amine **227** (35 mg, 83 %) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 3371 (OH), 2935 (CH), 1447, 1156, 1058; $\delta_H$ ($CDCl_3$, 300 MHz) 1.48-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.88-2.14 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.23-2.38 [4H, m, C(6)$H_2$ and C(5)$H_2$], 2.40-2.70 [12H, m, C$H_2$CH$_2$OH and C(15)$H_2$ and C(1')$H_2$ and C(2')$H_2$], 3.19 [1H, s, O*H*], 3.68 [2H, t, *J* 5.4, CH$_2$C$H_2$OH], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.88-6.98 [2H, m, C(2)*H* and C(4)*H*], 7.19-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.0 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 37.5 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 52.7 [$CH_2$, *C*(1')$H_2$ or *C*(2')$H_2$], 53.0 [$CH_2$, *C*(1')$H_2$ or *C*(2')$H_2$] 57.7 [$CH_2$, CH$_2$*C*H$_2$OH], 58.2 [$CH_2$, *C*(15)$H_2$], 59.3 [$CH_2$, *C*H$_2$CH$_2$OH], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.5 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.3 [CH, *C*(2)H], 134.5 [C, *C*(12)], 135.8 [C, *C*(8)], 142.7 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 16.0 (*C*H$_3$), 23.3 (*C*H$_3$), 23.4 (*C*H$_3$), 24.9 (*C*H$_2$), 26.3 (*C*H$_2$), 26.4 (*C*H$_2$), 28.9 (*C*H$_2$), 29.5 (*C*H$_2$), 29.7 (*C*H$_2$), 30.7 (*C*H$_2$), 31.9 (*C*H$_2$), 39.9 (*C*H$_2$), 58.3 (*C*H$_2$), 123.8 (*C*H), 124.4 (*C*H), 125.1 (*C*H), 125.3 (*C*H), 128.3 (*C*H), 134.7 (*C*), 134.9 (*C*), 135.7 (*C*) 135.9 (*C*), 142.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{23}H_{39}N_2OS$ $(M+H)^+$ 391.2783. Found 391.2774 $(M+H)^+$; m/z (ESI+) 391.4 $(M+H)^+$.

### 4.15.7.2 Synthesis of 3-(4,8-dimethyl-11-thiomorpholinoundeca-3,7-dien-1-yl)thiophene 228



The title compound was synthesized according to the procedure described for 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **227** using sodium triacetoxyborohydride (33.2 mg, 0.15 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (30 mg, 0.11 mmol) and thiomorpholine (11.2 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **228** (32.4 mg, 82 %) as an orange oil; $\nu_{max}/cm^{-1}$ (film) 2922 (CH), 2808, 1448, 1121, 1017, 776; $\delta_H$ ($CDCl_3$, 300 MHz) 1.48-1.72 [8H, m, C(14)$H_2$ and C$H_3$* containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.14 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.23-2.38 [4H, m, C(6)$H_2$ and C(15)$H_2$], 2.60-2.78 [10H, m, C(5)$H_2$ and 2 x C(1')$H_2$ and 2 x C(2')$H_2$], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.88-7.00 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 24.7 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 28.0 [$CH_2$, *C*(2')$H_2$] 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 37.4 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 55.0 [$CH_2$, *C*(1')$H_2$], 59.0 [$CH_2$, *C*(15)$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.5 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.3 [CH, *C*(2)H], 134.5 [C, *C*(12)], 135.7 [C, *C*(8)], 142.7 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 24.9 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 29.5 (*C*$H_2$), 29.7 (*C*$H_2$), 30.7 (*C*$H_2$), 31.9 (*C*$H_2$), 39.9 (*C*$H_2$), 123.7 (*C*H), 124.4 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 125.3 (*C*H), 128.3 (*C*H), 134.7 (*C*), 134.9 (*C*), 135.7 (*C*) 135.8 (*C*), 142.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{34}NS_2$ ($M+H^+$) 364.2133. Found 364.2119 ($M+H^+$); m/z (ESI+) 364.3 ($M+H^+$).

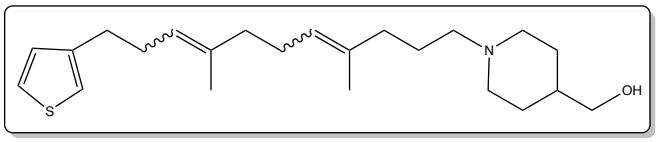
### 4.15.7.3 Synthesis of 3-(4,8-dimethyl-11-morpholinoundeca-3,7-dien-1-yl)thiophene 229



The title compound was synthesized according to the procedure described for 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **227** using sodium triacetoxyborohydride (33.2 mg, 0.15 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (30 mg, 0.11 mmol) and morpholine (9.5 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **229** (27 mg, 71 %) as a faint yellow; $\nu_{max}/cm^{-1}$ (film) 2931, 2854, 2808, 1446, 1376, 1276, 1138, 1119, 1009, 862, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.72 [8H, m, C(14)$H_2$ and C$H_3$* containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.90-2.13 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24-2.37 [4H, m, C(6)$H_2$ and

C(15)$H_2$], 2.37-2.50 [4H, m, 2 x C(1')$H_2$], 2.66 [2H, t, *J* 7.7, C(5)$H_2$], 3.67-3.76 [4H, m, 2 x C(2')$H_2$], 5.05-5.23 [2H, m, C(7)*H* and C(11)*H*], 6.88-7.00 [2H, m, C(2)*H* and C(4)*H*], 7.19-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 24.8 [$CH_2$, *C*(14)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 37.4 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 53.8 [$CH_2$, *C*(1')$H_2$], 58.8 [$CH_2$, *C*(15)$H_2$], 67.0 [$CH_2$, *C*(2')$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.5 [CH, *C*(7)H], 125.0 [CH, *C*(1)H], 128.4 [CH, *C*(2)H], 134.5 [C, *C*(12)], 135.8 [C, *C*(8)], 142.7 [C, *C*(3)H]; Characteristics peaks for the other isomer(s)* 16.1 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 23.4 (*C*$H_3$), 24.8 (*C*$H_2$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 29.5 (*C*$H_2$), 29.7 (*C*$H_2$), 30.7 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 123.7 (*C*H), 124.4 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 125.3 (*C*H), 128.3 (*C*H), 134.7 (*C*), 134.8 (*C*), 135.7 (*C*) 135.9 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{34}NOS$ $(M+H)^+$ 348.2361. Found 348.2362 $(M+H)^+$; m/z (ESI+) 248.3 $(M+H)^+$.

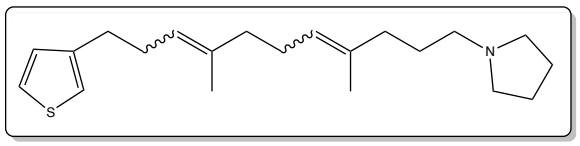
### 4.15.7.4 Synthesis of 3-(11-(4-(hydroxymethyl)piperidin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene 230




The title compound was synthesized according to the procedure described for 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **227** using sodium triacetoxyborohydride (33.2 mg, 0.15 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (30 mg, 0.11 mmol) and piperidin-4-yl methanol (12.5 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL) to give the title amine **230** (37 mg, 90 %) as a light red oil; $\nu_{max}/cm^{-1}$ (film) 3369 (OH), 2921 (CH), 1446, 1378, 1044, 835, 775 (CO); $\delta_H$ ($CDCl_3$, 300 MHz) 1.15-1.82 [13H, m, C(14)$H_2$ and C(3')*H* and 2 x C(2')$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.82-2.15 [8H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(1')$H_2$], 2.20-2.40 [4H, m, C(6)$H_2$ and C(15)$H_2$], 2.66 [2H, t, *J* 7.7, C(5)$H_2$], 2.85-3.05 [2H, m, C(1')$H_2$], 3.47 [2H, d, *J* 6.4, C(4')$H_2$], 5.05-5.23 [2H, m, C(7)*H* or C(11)*H*], 6.85-7.00 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.2 [$CH_2$, *C*(14)$H_2$], 26.4 [$CH_2$, *C*(10)$H_2$], 28.8 [$CH_2$, *C*(2')$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 37.7 [$CH_2$, *C*(13)$H_2$], 38.6 [$CH_2$, C(3')*H*], 39.7 [$CH_2$, *C*(9)$H_2$], 53.6 [$CH_2$, *C*(1')$H_2$] 58.8 [$CH_2$, *C*(15)$H_2$], 67.8 [$CH_2$, *C*(4')$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.4 [CH, *C*(2)H], 134.6 [C, *C*(12)], 135.8 [C, *C*(8)], 142.8 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 23.4 (*C*$H_3$), 25.2 (*C*$H_2$), 26.3 (*C*$H_2$), 28.8 (*C*$H_2$), 28.9 (*C*$H_2$), 29.0 (*C*$H_2$), 29.7 (*C*$H_2$), 30.7 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 39.9 (*C*$H_2$), 58.9 (*C*$H_2$), 123.7 (*C*H), 124.3 (*C*H), 124.5

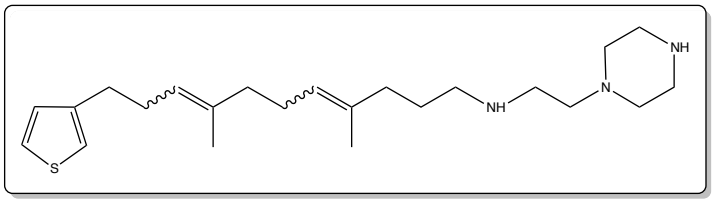
(*C*H), 125.1 (*C*H), 125.2 (*C*H), 128.3 (*C*H), 134.8 (*C*), 134.9 (*C*), 135.7 (*C*) 135.9 (*C*); HRMS (ESI+): Exact mass calculated for $C_{23}H_{38}NOS$ $(M+H)^+$ 376.2674. Found 376.2675 $(M+H)^+$; m/z (ESI+) 376.3 $(M+H)^+$.

### 4.15.7.5 Synthesis of 3-(4,8-dimethyl-11-(pyrrolidin-1-yl)undeca-3,7-dien-1-yl)thiophene 231

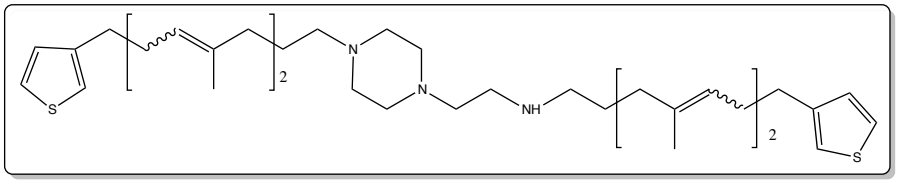


The title compound was synthesized according to the procedure described for 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **227** using sodium triacetoxyborohydride (33.2 mg, 0.15 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (30 mg, 0.11 mmol) and pyrrolidine (7.8 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL) under an inert to give the title amine **231** (34 mg, 95 %) as faint yellow oil; $\nu_{max}/cm^{-1}$ (film) 2931, 2876, 2786, 1448, 1384, 1149, 1128, 1080, 773; $\delta_H$ ($CDCl_3$, 300 MHz) 1.48-1.72 [8H, m, C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$], 1.88-2.14 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.22-2.36 [4H, m, C(6)$H_2$ and C(15)$H_2$], 2.36-2.78 [10H, m, C(5)$H_2$ and 2 x C(1')$H_2$ and 2 x C(2')$H_2$], 5.04-5.25 [2H, m, C(7)*H* and C(11)*H*], 6.85-7.00 [2H, m, C(2)*H* and C(4)*H*], 7.18-7.25 [1H, m, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 25.2 [$CH_2$, *C*(14)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 37.5 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 53.3 [$CH_2$, *C*(1')$H_2$ and *C*(2')$H_2$], 58.4 [$CH_2$, *C*(15)$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.3 [CH, *C*(2)H], 134.6 [C, *C*(12)], 135.8 [C, *C*(8)], 142.8 [C, *C*(3)H]; Characteristics peaks for the other isomer(s)* 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 26.4 (*C*$H_2$), 27.9 (*C*$H_2$), 28.9 (*C*$H_2$), 29.6 (*C*$H_2$), 29.7 (*C*$H_2$), 30.7 (*C*$H_2$), 31.9 (*C*$H_2$), 37.3 (*C*$H_2$), 39.9 (*C*$H_2$), 57.6 (*C*$H_2$), 124.3 (*C*H), 124.5 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 128.3 (*C*H), 134.5 (*C*), 134.8 (*C*); HRMS (ESI+): Exact mass calculated for $C_{21}H_{34}NS$ $(M+H)^+$ 332.2412. Found 332.2397 $(M+H)^+$; m/z (ESI+) 332.3 $(M+H^+)$.

### 4.15.7.6 The attempted synthesis of 3-(4,8-dimethyl-11-((2-(piperazin-1-yl)ethyl)amino)undeca-3,7-dien-1-yl)thiophene 232



The synthesis of the title compound was attempted according to the procedure described for 3-(11-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **227** using sodium triacetoxyborohydride (33.2 mg, 0.15 mmol), 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)thiophene **166** (30 mg, 0.11 mmol) and 2-(piperazin-1-yl)ethanamine (14 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL) to give a crude light yellow oil (37 mg, 88 %). $^1$H NMR analysis of the crude product revealed a two component mixture consisting of the title amine **232** (3 mg, 6%) and its corresponding dimer **233** (34 mg, 82%) in a 7:93 ratio of products respectively. The characteristic peak in the $^1$H NMR spectrum associated with the monomer **232** was at $\delta_H$ ($CDCl_3$, 300 MHz) 2.83 (2H, m); HRMS (ESI+): Exact mass calculated for $C_{23}H_{40}N_3S$ $(M+H)^+$ 390.2943 Found 390.2925 $(M+H^+)$; m/z (ESI+) 390.4 $(M+H)^+$. Spectroscopic characteristics for the dimer are tentatively assigned below.



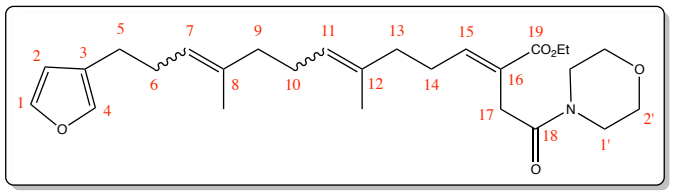
The dimer, 3-(11-((2-(4-(4,8-dimethyl-11-(thiophen-3-yl)undeca-4,8-dien-1-yl)piperazin-1-yl)ethyl)amino)-4,8-dimethylundeca-3,7-dien-1-yl)thiophene **233**; $\nu_{max}/cm^{-1}$ (film) 3369 (NH), 2933 (CH), 1447, 1158, 1011, 774; $\delta_H$ ($CDCl_3$, 300 MHz) 1.50-1.72 [16H, m, 2 x {C(14)$H_2$ and C$H_3$* and containing 2 x 3H, s, C(16)$H_3$ and C(17)$H_3$}], 1.72-1.85 [8H, m, 4 x C$H_2$], 1.90-2.14 [12H, m, 2 x {C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$}], 2.31 [4H, q, *J* 7.4, 2 x C(6)$H_2$], 2.35-2.46 [4H, m, 2 x C(15)$H_2$], 2.46-2.60 [8H, m, 4 x C$H_2$], 2.66 [4H, t, *J* 7.6, 2 x C(5)$H_2$], 2.83 [1H, s, N*H*], 5.05-5.23 [4H, m, 2 x {C(7)*H* and C(11)*H*}], 6.90-6.98 [4H, m, 2 x {C(2)*H* and C(4)*H*}], 7.18-7.25 [2H, m, 2 x C(1)*H*]; $\delta_C$ ($CDCl_3$, 300 MHz) 15.9 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 16.0 [$CH_3$, *C*(16)$H_3$ or *C*(17)$H_3$], 23.4 (*C*$H_2$), 26.6 [$CH_2$, *C*(10)$H_2$], 27.2 [$CH_2$, *C*(14)$H_2$], 29.0 [$CH_2$, *C*(6)$H_2$], 30.4 [$CH_2$, *C*(5)$H_2$], 37.7 [$CH_2$, *C*(13)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 54.2 (*C*$H_2$), 56.3 (*C*$H_2$), 56.4 [$CH_2$, *C*(15)$H_2$], 120.0 [CH, *C*(4)H], 123.7 [CH, *C*(7)H], 124.4 [CH, *C*(11)H], 125.0 [CH, *C*(1)H], 128.3 [CH, *C*(2)H], 134.7 [C, *C*(12)], 135.8 [C, *C*(8)], 142.8 [C, *C*(3)]; Characteristics peaks for the other isomer(s)* 23.3 (*C*$H_3$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.2 (*C*$H_2$), 27.3 (*C*$H_2$), 28.9 (*C*$H_2$), 29.8 (*C*$H_2$), 30.7 (*C*$H_2$), 31.9 (*C*$H_2$), 32.2 (*C*$H_2$), 40.0 (*C*$H_2$), 124.2 (*C*H), 124.5 (*C*H), 125.1 (*C*H), 128.3 (*C*H), 134.9 (*C*), 135.1

(*C*), 135.8 (*C*) 135.9 (*C*); HRMS (ESI+): Exact mass calculated for $C_{40}H_{63}N_2S_2$ $(M+H)^+$ 650.4542. Found 650.4566 $(M+H^+)$; m/z (ESI+) 650.4 $(M+H)^+$.

## 4.15.8 Synthesis of furanolipid amide derivatives

The same numbering system previously shown for our furanolipid derivatives was used to number the furanolipid amide derivatives in this section. The furanolipid amides were prepared from 3-(12-(carboxymethyl)-13-ethoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan **126** and $^1$H NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers* for this compound. All furanolipid amides prepared from **126** will therefore contain a 70:30 mixture of (*E*,*E*) and other isomer(s)*.

### 4.15.8.1 Synthesis of 3-(12-(ethoxycarbonyl)-4,8-dimethyl-14-morpholino-14-oxotetradeca-3,7,11-trien-1-yl)furan 234




*N*-Methylmorpholine (18.8 µL, 17 mg, 0.17 mmol) and isobutyl chloroformate (22.9 µL, 24 mg, 0.18 mmol) were added sequentially to a stirring solution of **126** (50 mg, 0.13 mmol) in tetrahydrofuran (2 mL) at -10 °C. After 5 min, morpholine (14.9 µL, 15 mg, 0.17 mmol) was added. Following 1 h at -10 °C, the solution was filtered and the filtrate was concentrated under reduced pressure. The residual white solid was dissolved in ethyl acetate (20 mL) and was washed successively with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to afford the title amide **234** (26 mg, 44%) as a viscous colourless oil. $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2856 (CH), 1706 (C=O), 1659 (C=O), 1435, 1377, 1275, 1208, 1117, 1066, 1025, 874, 781; $\delta_H$ ($CDCl_3$, 300 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2CH_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.61 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.70* (3H, s), 1.85-2.38 [10H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.45 [2H, t, *J* 7.4, C(5)$H_2$], 3.33 [2H, s, C(17)$H_2$], 3.52-3.80 [8H, m, 2 x C(1')$H_2$ and 2 x C(2')$H_2$], 4.18 [2H, q, *J* 7.1, C(19)$O_2CH_2CH_3$], 5.05-5.25 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 6.97 [1H, t, *J* 7.2, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.2 [$CH_3$, C(19)$O_2CH_2CH_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$,

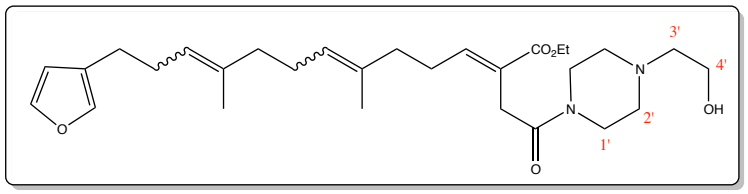
*C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.7 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 30.7 [$CH_2$, *C*(17)$H_2$], 38.2 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 42.3 [$CH_2$, *C*(2')$H_2$], 46.3 [$CH_2$, *C*(2')$H_2$], 60.7 [$CH_2$, C(19)$O_2$*C*$H_2$$CH_3$], 66.7 [$CH_2$, *C*(1')$H_2$], 66.9 [$CH_2$, *C*(1')$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.2 [CH, *C*(11)H], 126.4 [C, *C*(16)], 133.8 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 145.2 [CH, *C*(15)H], 167.3 [C, *C*(19)=O, ester], 168.8 [C, *C*(18)=O, amide]; Characteristics peaks for the other isomer(s)* 22.7 (*C*$H_3$) 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_3$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.6 (*C*$H_2$), 28.4 (*C*$H_2$), 29.4 (*C*$H_2$), 31.9 (*C*$H_2$), 39.8 (*C*$H_2$), 124.0 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 126.1 (*C*), 126.4 (*C*), 126.5 (*C*), 133.7 (*C*), 134.0 (*C*), 135.5 (*C*), 135.8 (*C*), 145.0 (*C*H), 145.1 (*C*H), 168.8 (*C*); HRMS (ESI+): Exact mass calculated for $C_{27}H_{40}NO_5$ $(M+H)^+$ 458.2906. Found 458.2902 $(M+H)^+$; m/z (ESI+) 458.2 $(M+H)^+$.

### 4.15.8.2 Synthesis of 3-(12-(ethoxycarbonyl)-4,8-dimethyl-14-oxo-14-thiomorpholinotetradeca-3,7,11-trien-1-yl)furan 235

The title compound was synthesized according to the procedure described for **234** using N-methylmorpholine (18.8 μL, 17 mg, 0.17 mmol), isobutyl chloroformate (29.9 μL, 24 mg, 0.18 mmol), **126** (50 mg, 0.13 mmol) and thiomorpholine (17.3 μL, 18 mg, 0.17 mmol) in tetrahydrofuran (2 mL) to give a crude residue which was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to afford the title ester **235** (25 mg, 40%) as a viscous colourless oil; $\nu_{max}/cm^{-1}$ (film) 2924 (CH), 2856 (CH), 1706 (C=O), 1655 (C=O), 1444, 1376, 1287, 1188, 1064, 1025, 874, 781; $\delta_H$ ($CDCl_3$, 300 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2C$*H*$_3$], 1.59 [3H, s, C(20)*H*$_3$ or C(21)*H*$_3$], 1.61 [3H, s, C(20)*H*$_3$ or C(21)*H*$_3$], 1.69* (3H, s), 1.92-2.36 [10H, m, C(6)$H_2$ and C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$ and C(14)*H*$_2$], 2.45 [2H, t, *J* 7.4, C(5)*H*$_2$], 2.53-2.72 [4H, m, 2 x C(2')*H*$_2$], 3.33 [2H, s, C(17)*H*$_2$], 3.78-3.92 [4H, m, 2 x C(1')*H*$_2$], 4.18 [2H, q, *J* 7.4, C(19)$O_2C$*H*$_2$$CH_3$], 5.08-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 6.97 [1H, t, *J* 7.3, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.3 [$CH_3$, C(19)$O_2CH_2$*C*$H_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.4 [$CH_2$, *C*(2')$H_2$], 27.7 [$CH_2$, *C*(14)$H_2$], 27.8 [$CH_2$, *C*(2')$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 31.0 [$CH_2$, *C*(17)$H_2$], 38.2 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 44.7 [$CH_2$, *C*(1')$H_2$], 48.6 [$CH_2$, *C*(2')$H_2$], 60.7 [$CH_2$, C(19)$O_2$*C*$H_2$*C*$H_3$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.2 [CH, *C*(11)H], 126.4 [C, *C*(16)], 133.7 [C, *C*(8)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 145.1 [CH, *C*(15)H], 167.3 [C, *C*(19)=O, ester], 168.6 [C, *C*(18)=O, amide];

Characteristics peaks for the other isomer(s)* 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_3$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.5 (*C*$H_2$), 28.4 (*C*$H_2$), 29.7 (*C*$H_2$), 30.6 (*C*$H_2$), 31.9 (*C*$H_2$), 39.8 (*C*$H_2$), 124.0 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 126.2 (*C*), 126.6 (*C*), 133.7 (*C*), 134.0 (*C*), 135.5 (*C*), 135.8 (*C*), 142.6 (*C*H), 144.9 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{27}H_{40}NO_4S$ $(M+H)^+$ 474.2678. Found 474.2674 $(M+H)^+$; m/z (ESI+) 474.2 $(M+H)^+$.

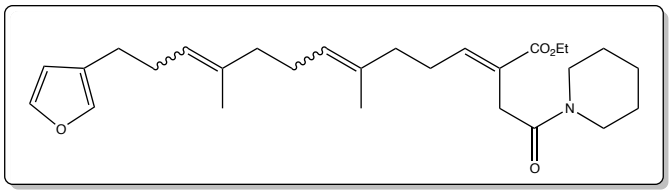
### 4.15.8.3 Synthesis of 3-(12-(ethoxycarbonyl)-14-(4-(2-hydroxyethyl)piperazin-1-yl)-4,8-dimethyl-14-oxotetradeca-3,7,11-trien-1-yl)furan 236




The title compound was synthesized according to the procedure described for **234** using N-methylmorpholine (18.8 µL, 17 mg, 0.17 mmol), isobutyl chloroformate (23.0 µL, 24 mg, 0.18 mmol), **126** (0.05 g, 0.13 mmol), 2-(piperazin-1-yl)ethanol (22.45 mg, 0.17 mmol) in tetrahydrofuran (2 mL) to give a crude residue which was purified by column chromatography on silica gel (30% ethyl acetate in hexanes to 5% methanol in dichloromethane as gradient) to afford the title ester **236** (28.4 mg, 44%) as a viscous light yellow oil; $\nu_{max}/cm^{-1}$ (film) 3428 (OH), 2930 (CH), 1694 (C=O), 1655 (C=O), 1436, 1389, 1289, 1131, 1065, 874, 767; $\delta_H$ ($CDCl_3$, 600 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2CH_3$], 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.61 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.69* (3H, s), 1.90-2.36 [10H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.38-2.62 [8H, m, C(5)$H_2$ and 2 x C(2')$H_2$ and containing 2H, t, *J* 5.3, C(3')$H_2$], 3.34 [2H, s, C(17)$H_2$], 3.55-3.58 [6H, m, 2 x C(1')$H_2$ and containing 2H, t, *J* 4.8, C(4')$H_2$], 4.18 [2H, q, *J* 7.1, C(19)$O_2CH_2CH_3$], 5.10-5.20 [2H, m, C(7)*H* and C(11)*H*], 6.28 [1H, s, C(2)*H*], 6.97 [1H, t, *J* 7.3, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 150.9 MHz) 14.3 [$CH_3$, C(19)$O_2CH_2CH_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.6 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 30.8 [$CH_2$, *C*(17)$H_2$], 38.2 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 41.9 [$CH_2$, *C*(1')$H_2$], 45.8 [$CH_2$, *C*(1')$H_2$], 52.6 [$CH_2$, *C*(2')$H_2$], 53.1 [$CH_2$, *C*(2')$H_2$], 57.7 [$CH_2$, *C*(4')$H_2$], 59.2 [$CH_2$, *C*(3')$H_2$], 60.7 [$CH_2$, C(19)$O_2CH_2CH_3$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.2 [CH, *C*(11)H], 126.5 [C, *C*(16)], 133.8 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 145.0 [CH, *C*(15)H], 167.3 [C, *C*(19)=O, ester], 168.6 [C, *C*(18)=O, amide]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 23.3 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 27.5 (*C*$H_2$), 27.6 (*C*$H_2$), 28.3 (*C*$H_2$), 29.7 (*C*$H_2$), 30.6 (*C*$H_2$), 31.9 (*C*$H_2$), 32.1 (*C*$H_2$), 39.8 (*C*$H_2$), 60.7 (*C*$H_2$), 124.0 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 125.1 (*C*H), 126.5 (*C*), 126.6 (*C*), 133.7 (*C*), 134.0 (*C*),

135.5 (*C*), 135.8 (*C*), 142.6 (*C*H), 144.9 (*C*H), 145.0 (*C*H), 168.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{29}H_{45}N_2O_5$ $(M+H)^+$ 501.3328. Found 501.3339 $(M+H)^+$; m/z (ESI+) 501.4 $(M+H)^+$.

### 4.15.8.4 Synthesis of 3-(12-(ethoxycarbonyl)-4,8-dimethyl-14-oxo-14-(piperidin-1-yl)tetradeca-3,7,11-trien-1-yl)furan 237

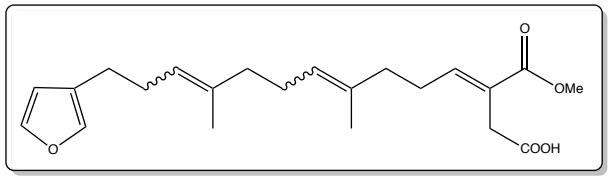



The title compound was synthesized according to the procedure described for **234** using N-methylmorpholine (18.8 μL, 17 mg, 0.17 mmol), isobutyl chloroformate (23.0 μL, 24 mg, 0.18 mmol), **126** (50 mg, 0.13 mmol), piperidine (17.1 μL, 15 mg, 0.17 mmol) in tetrahydrofuran (2 mL) to give a crude residue which was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to afford the title ester **237** (25.8 mg, 44%) as a light yellow oil; $\nu_{max}/cm^{-1}$ (film) 2929 (CH), 2856 (CH), 1709 (C=O), 1645 (C=O), 1442, 1376, 1279, 1206, 1063, 1025, 874, 780; $\delta_H$ ($CDCl_3$, 300 MHz) 1.28 [3H, t, *J* 7.1, C(19)$O_2CH_2CH_3$], 1.45-1.72 [12H, m, 2 x C(2')$H_2$ and C(3')$H_2$ and containing 2 x 3H, s, C(20)$H_3$ and C(21)$H_3$], 1.90-2.37 [10H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.45 [2H, t, *J* 7.4, C(5)$H_2$], 3.34 [2H, s, C(17)$H_2$], 3.43-3.60 [4H, m, 2 x C(1')$H_2$], 4.18 [2H, q, *J* 7.1, C(19)$O_2CH_2CH_3$], 5.08-5.22 [2H, m, C(7)*H* and C(11)*H*], 6.27 [1H, s, C(2)*H*], 6.94 [1H, t, *J* 7.3, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.6, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 14.2 [$CH_3$, C(19)$O_2CH_2CH_3$], 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 24.6 [$CH_2$, *C*(3')$H_2$], 25.0 [$CH_2$, *C*(5)$H_2$], 25.6 [$CH_2$, *C*(2')$H_2$], 26.5 [$CH_2$, *C*(2')$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 27.6 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 30.9 [$CH_2$, *C*(17)$H_2$], 38.3 [$CH_2$, *C*(13)$H_2$], 39.6 [$CH_2$, *C*(9)$H_2$], 43.1 [$CH_2$, *C*(1')$H_2$], 46.9 [$CH_2$, *C*(1')$H_2$], 60.6 [$CH_2$, C(19)$O_2CH_2CH_3$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.1 [CH, *C*(11)H], 126.9 [C, *C*(16)], 133.9 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 145.5 [CH, *C*(15)H], 167.4 [C, *C*(19)=O, ester], 168.3 [C, *C*(18)=O, amide]; Characteristics peaks for the other isomer(s)* 16.0 ($CH_3$), 23.2 ($CH_3$), 23.4 ($CH_3$), 25.3 ($CH_3$), 26.3 ($CH_2$), 26.4 ($CH_2$), 27.5 ($CH_2$), 28.4 ($CH_2$), 29.7 ($CH_2$), 30.6 ($CH_2$), 31.9 ($CH_2$), 32.1 ($CH_2$), 39.8 ($CH_2$), 123.9 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.9 (*C*H), 125.0 (*C*H), 127.0 (*C*), 127.1 (*C*), 134.1 (*C*), 135.5 (*C*), 135.8 (*C*), 142.6 (*C*), 144.3 (*C*H), 144.4 (*C*H), 144.5 (*C*H), 168.2 (*C*); HRMS (ESI+): Exact mass calculated for $C_{28}H_{42}NO_4$ $(M+H)^+$ 456.3114. Found 456.3104 $(M+H)^+$; m/z (ESI+) 456.3 $(M+H)^+$.

## 4.15.9 Synthesis of furanolipid alkenyl analogues

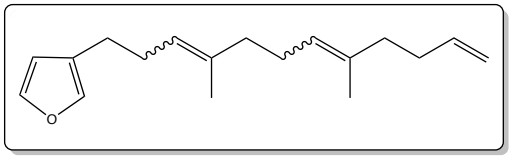
The same numbering system previously shown for our furanolipid derivatives was used in this section. With the exception of compound **238** [which was prepared from 3*E*,7*E*-3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121**], the furanolipid alkenyl analogues in this section were prepared from 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** and $^1$H NMR integration revealed a 70:30 mixture of *E*,*E* and other isomers* for this compound. All furanolipid alkenyl analogues prepared from **121** will therefore contain a 70:30 mixture of (*E*,*E*) and other isomer(s)*.

### 4.15.9.1 Synthesis of (3*E*,7*E*)-3-(12-(carboxymethyl)-13-methoxy-4,8-dimethyl-13-oxotrideca-3,7,11-trien-1-yl)furan 238



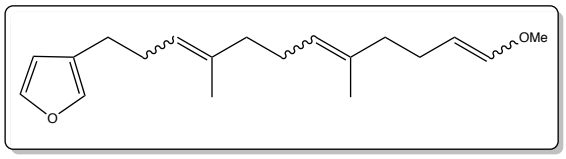

Methoxy-oxo-2-(triphenylphosphoranylidene)-4-butanoic acid **125** (0.18 g, 0.46 mmol, 2.4 equiv) was dissolved in toluene (1mL) and added sequentially with hydroquinone (19 mg, 0.17 mmol, 0.9 equiv) to a stirring solution of (3*E*,7*E*)-3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (0.05 g, 0.19 mmol) in toluene (2 mL) at room temperature. The reaction progress was monitored by TLC and after 70 h, the reaction mixture was filtered and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (10-50% ethyl acetate gradient in hexanes) to afford the title monomethyl ester **238** (42 mg, 59%) as a colourless oil; $\nu_{max}$/cm$^{-1}$ (film) 3500-2500 (br, OH), 1717 (C=O), 1439, 1291, 1205, 1065, 1026, 874, 775; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.60 [3H, s, C(20)$H_3$ or C(21)$H_3$], 1.90-2.15 [6H, m, C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$], 2.24 [2H, m, C(14)$H_2$], 2.31 [2H, q, *J* 7.5, C(6)$H_2$], 2.45 [2H, t, *J* 7.6, C(5)$H_2$], 3.39 [2H, s, C(17)$H_2$], 3.76 [3H, s, C(19)$O_2$C$H_3$], 5.13 [1H, t, *J* 6.9, 1.0, C(11)*H*], 5.16 [1H, t, *J* 7.0, 1.0, C(7)*H*], 6.28 [1H, s, C(2)*H*], 6.97 [1H, t, *J* 7.4, C(15)*H*], 7.21 [1H, s, C(4)*H*], 7.34 [1H, t, *J* 1.5, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 16.1 [$CH_3$, *C*(20)$H_3$ or *C*(21)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$], 26.5 [$CH_2$, *C*(10)$H_2$], 27.6 [$CH_2$, *C*(14)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 29.7 [$CH_2$, *C*(17)$H_2$], 38.0 [$CH_2$, *C*(13)$H_2$], 39.5 [$CH_2$, *C*(9)$H_2$], 52.2 [$CH_2$, C(19)$O_2$*C*$H_3$], 111.1 [CH, *C*(2)H], 123.9 [CH, *C*(7)H], 125.0 [C, *C*(3)], 125.5 [CH, *C*(11)H], 133.4 [C, *C*(12)], 135.6 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.6 [CH, *C*(1)H], 146.5 [CH, *C*(15)H], 167.9 [C, *C*(19)=O, ester], 173.7 [C, *C*(18)=O, acid]; Characteristics peaks for other isomer(s)* 14.1 (*C*$H_3$), 22.7 (*C*$H_3$), 29.4 (*C*$H_2$), 30.0 (*C*$H_2$), 31.9 (*C*$H_2$), 32.3 (*C*$H_2$), 37.1 (*C*$H_2$), 116.2 (*C*H), 128.5 (*C*H), 132.0 (*C*H), 132.1 (*C*H), 149.5 (*C*); HRMS (ESI+): Exact mass calculated for $C_{22}H_{31}O_5$ $(M+H)^+$ 375.2171. Found 375.2164 $(M+H)^+$; m/z (ESI-) 373.4 $(M-H)^-$.

### 4.15.9.2 Synthesis of 3-(4,8-dimethyldodeca-3,7,11-trien-1-yl)furan 239

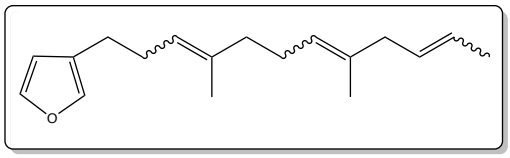


*n*-Butyllithium (2.45 M in hexane, 0.17 mL, 0.40 mmol) was added dropwise to a stirring suspension of methyltriphenylphosphonium bromide (0.17 g, 0.46 mmol) in tetrahydrofuran (3 mL) at 0 $^{o}$C. After 30 mins, 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (0.10 g, 0.38 mmol) in tetrahydrofuran (4 mL) was added over 1 min at 0 $^{o}$C. The reaction was allowed to warm to room temperature and stirring was continued for a further 1 h. The dull-orange reaction mixture was concentrated under reduced pressure. The crude residue was dissolved up in hexane (20 mL), the phosphine waste was filtered off and the solvent was again concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) to afford the title diene **239** (47 mg, 47%) as a non-viscous colourless oil; $\nu_{max}$/cm$^{-1}$ (film) 2921 (CH), 2856, 1513, 1447, 1377, 1139, 1065, 726; $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 [6H, s, C(17)*H*$_3$ and C(18)*H*$_3$], 1.69* (3H, s, C*H*$_3$), 1.92-2.19 [8H, m, C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$ and C(14)*H*$_2$], 2.24 [2H, q, *J* 7.3, C(6)H$_2$], 2.45 [2H, t, *J* 7.5, C(5)*H*$_2$], 4.93 [1H, dd, A of the ABX system $J_{AX}$ 10.3, $J_{AB}$ 1.9, C(16)*H*$_2$], 5.00 [1H, dd, B of the ABX system $J_{BX}$ 17.0, $J_{AB}$ 1.9, C(16)*H*$_2$], 5.07-5.24 [2H, m, C(7)*H* and C(11)*H*], 5.70-5.90 [1H, m, C*H** and containing 1H, dd, X of the ABX system $J_{BX}$ 17.0, $J_{AX}$ 10.3, C(15)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.5, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(18)H$_3$ and *C*(19)H$_3$], 25.0 [$CH_2$, *C*(5)H$_2$], 25.7 [$CH_3$, *C*(17)H$_3$ or *C*(20)H$_3$], 26.6 [$CH_2$, *C*(10)H$_2$], 26.8 [$CH_2$, *C*(14)H$_2$], 28.4 [$CH_2$, *C*(6)H$_2$], 39.1 [$CH_2$, *C*(13)H$_2$], 39.7 [$CH_2$, *C*(9)H$_2$], 111.1 [CH, *C*(2)H], 114.2 [$CH_2$, *C*(16)H$_2$], 123.8 [CH, *C*(7)H], 124.5 [CH, *C*(11)H], 125.0 [C, *C*(3)], 125.3 [CH, *C*(15)H], 134.5 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], Characteristics peaks for the other isomer(s)* 15.9 (*C*H$_3$), 23.3 (*C*H$_3$), 23.4 (*C*H$_3$), 25.3 (*C*H$_2$), 26.4 (*C*H$_2$), 28.4 (*C*H$_2$), 29.7 (*C*H$_2$), 31.3 (*C*H$_2$), 32.0 (*C*H$_2$), 32.3 (*C*H$_2$), 39.9 (*C*H$_2$), 111.1 (*C*H), 114.3 (*C*H$_2$), 114.4 (*C*H$_2$), 123.8 (*C*H), 124.4 (*C*H), 124.5 (*C*H), 124.6 (*C*H), 134.6 (*C*), 134.7 (*C*), 135.9 (*C*), 138.6 (*C*H), 138.7 (*C*H), 138.8 (*C*H), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{18}H_{27}O$ $(M+H)^+$ 259.2062. Found 259.2054 $(M+H)^+$; m/z (ESI+): 259.4 $(M+H)^+$.

### 4.15.9.3 Synthesis of 3-(12-methoxy-4,8-dimethyldodeca-3,7,11-trien-1-yl)furan 240




The title compound was synthesized according to the procedure described for 3-(4,8-dimethyldodeca-3,7,11-trien-1-yl)furan **239** using *n*-butyllithium (2.45 M in hexane, 0.165 mL, 0.40 mmol), (methoxymethyl) triphenylphosphonium chloride (160 mg, 0.46 mmol) and 3-(4,8-dimethyl-11-oxoundeca-3,7-dien-1-yl)furan **121** (100 mg, 0.38 mmol) in tetrahydrofuran (7 mL) to give a two-component mixture consisting of the desired vinyl ether **240** and an unknown impurity in a 56:44 ratio of products respectively. The residue was purified by column chromatography on silica gel (0-1% ethyl acetate gradient in hexanes) to give the title vinyl ether **240** (35 mg, 32%) as a light yellow oil. $^1$H NMR integration indicated a 2:1 ratio of the *E* and Z isomer at the newly formed double bond. $^1$H NMR integration also indicated a 70:30 ratio of the *E,E* and other isomer(s)*; $\nu_{max}/cm^{-1}$ (film); 3035, 2928 (CH), 2854 (CH), 1657, 1502, 1451, 1384, 1210 (CO), 1142, 1111 (CO), 1026, 934, 874, 779; $\delta_H$ ($CDCl_3$, 300 MHz) 1.60 [6H, s, C(17)$H_3$ and C(18)$H_3$], 1.68* (3H, s), 1.69* (3H, s), 1.90-2.33 [10H, m, C(6)$H_2$ and C(9)$H_2$ and C(10)$H_2$ and C(13)$H_2$ and C(14)$H_2$], 2.45 [2H, t, *J* 7.5, C(5)$H_2$], 3.49 [3H, s, OC$H_3$, *major*], 3.57 [3H, s, OC$H_3$, *minor*], 4.26-4.38 [1H, m, C*H** and containing 1H, dt, *J* 6.2, 1.0, C(15)*H, minor*], 4.60-4.80 [1H, m, C*H** and containing 1H, dt, *J* 12.6, 3.5, C(15)*H, major*], 5.04-5.22 [2H, m, C(7)*H* and C(11)*H*], 5.82-5.89 [1H, m, C*H** and containing 1H, d, *J* 6.2, C(16)*H, minor*], 6.20-6.34 [2H, m, C(16)*H* (*major*) and containing 1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.5, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 [$CH_3$, *C*(18)$H_3$ or *C*(19)$H_3$], 16.1 [$CH_3$, *C*(18)$H_3$ or *C*(19)$H_3$], 25.0 [$CH_2$, *C*(5)$H_2$ ], 26.4 [$CH_2$, *C*(14)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 28.4 [$CH_2$, *C*(6)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 41.0 [$CH_2$, *C*(13)$H_2$], 55.9 [$CH_3$, O*C*$H_3$, *major*], 59.5 [$CH_3$, O*C*$H_3$, *minor*], 102.8 [CH, *C*(15)H, *major*], 106.6 [CH, *C*(15)H, *minor*], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.6 [CH, *C*(11)H], 125.0 [C, *C*(3)], 134.6 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H], 145.9 [CH, *C*(16)H, *minor*], *146*.9 [CH, *C*(16)H, *major*]; Characteristics peaks for the other isomer(s)* 15.9 (*C*$H_3$), 16.0 (*C*$H_3$), 22.4 (*C*$H_2$), 23.2 (*C*$H_3$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 26.5 (*C*$H_2$), 28.5 (*C*$H_2$), 29.7 (*C*$H_2$), 31.8 (*C*$H_2$), 32.0 (*C*$H_2$), 32.3 (*C*$H_2$), 33.2 (*C*$H_2$), 39.6 (*C*$H_2$), 40.0 (*C*$H_2$), 55.8 (*C*$H_3$), 102.7 (*C*H), 102.8 (*C*H), 106.5 (*C*H), 106.6 (*C*H), 123.7 (*C*H), 123.8 (*C*H), 124.2 (*C*H), 124.3 (*C*H), 124.5 (*C*H), 124.6 (*C*H), 125.1 (*C*H), 125.3 (*C*H), 134.7 (*C*), 134.8 (*C*), 135.7 (*C*), 135.8 (*C*), 135.9 (*C*), 145.9 (*C*H), 146.0 (*C*H), 146.2 (*C*H), 147.0 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{19}H_{29}O_2$ $(M+H)^+$ 289.2168. Found 289.2167 $(M+H)^+$; m/z (ESI+): 289.4 $(M+H)^+$.



The less polar fraction was putatively assigned as 3-(4,8-dimethyldodeca-3,7,10-trien-1-yl)furan **241**, which was isolated as a colourless oil; $\nu_{max}/cm^{-1}$ (film); 2925 (CH), 2856 (CH), 1640, 1501, 1448, 1382, 1165, 1027, 911, 874, 777; (Found C, 83.45; H, 10.05 $C_{18}H_{26}O$ requires C, 83.67; H, 10.14%); $\delta_H$ ($CDCl_3$, 300 MHz) 1.59 [6H, s, C(17)*H*$_3$ and C(18)*H*$_3$], 1.67* (3H, s), 1.69* (3H, s), 1.86-2.18 [9H, m, C(9)*H*$_2$ and C(10)*H*$_2$ and C(13)*H*$_2$ and C(16)*H*$_3$], 2.24 [2H, q, *J* 7.3, C(6)*H*$_2$], 2.45 [2H, t, *J* 7.5, C(5)*H*$_2$], 5.04-5.24 [2H, m, C(7)*H* and C(11)*H*], 5.28-5.45 [2H, m, C(14)*H* and C(15)*H*], 6.27 [1H, s, C(2)*H*], 7.21 [1H, s, C(4)*H*], 7.33 [1H, t, *J* 1.5, C(1)*H*]; $\delta_C$ ($CDCl_3$, 75.5 MHz) 13.6 [$CH_3$, *C*(16)$H_3$, *major or minor*], 13.8 [$CH_3$, *C*(16)$H_3$, *major or minor*], 16.0 [$CH_3$, *C*(18)$H_3$ and *C*(19)$H_3$], 25.1 [$CH_2$, *C*(5)$H_2$], 26.6 [$CH_2$, *C*(10)$H_2$], 28.5 [$CH_2$, *C*(6)$H_2$], 39.7 [$CH_2$, *C*(9)$H_2$], 39.8 [$CH_2$, *C*(13)$H_2$], 111.1 [CH, *C*(2)H], 123.8 [CH, *C*(7)H], 124.3 [CH, *C*(11)H], 125.0 [C, *C*(3)], 129.6 [CH, *C*(15)H, *major or minor*], 129.7 [CH, *C*(15)H, *major or minor*], 130.1 [CH, *C*(14)H, *major or minor*], 130.2 [CH, *C*(14)H, *major or minor*], 134.8 [C, *C*(12)], 135.7 [C, *C*(8)], 138.8 [CH, *C*(4)H], 142.5 [CH, *C*(1)H]; Characteristics peaks for the other isomer(s)* 16.0 (*C*$H_3$), 22.7 (*C*$H_2$), 22.9 (*C*$H_2$), 23.4 (*C*$H_3$), 25.3 (*C*$H_2$), 25.8 (*C*$H_2$), 25.9 (*C*$H_2$), 26.4 (*C*$H_2$), 26.5 (*C*$H_2$), 28.4 (*C*$H_2$), 29.3 (*C*$H_2$), 29.7 (*C*$H_2$), 31.1 (*C*$H_2$), 31.2 (*C*$H_2$), 31.3 (*C*$H_2$), 31.9 (*C*$H_2$), 32.0 (*C*$H_2$), 32.1 (*C*$H_2$), 32.3 (*C*$H_2$), 34.7 (*C*$H_2$), 39.6 (*C*$H_2$), 40.0 (*C*$H_2$), 123.7 (*C*H), 124.2 (*C*H), 124.4 (*C*H), 124.5 (*C*H), 124.6 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 129.4 (*C*H), 129.5 (*C*H), 129.8 (*C*H), 130.0 (*C*H), 130.1 (*C*H), 130.2 (*C*H), 130.3 (*C*H), 130.4 (*C*H), 134.8 (*C*), 134.9 (*C*), 135.8 (*C*), 135.9 (*C*), 142.6 (*C*H); HRMS (ESI+): Exact mass calculated for $C_{18}H_{27}O$ $(M+H)^+$ 259.1984. Found 259.1995 $(M+H)^+$; m/z (ESI+): 259.4 ($M+H^+$).

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## Table of Abbreviations

| | |
|---|---|
| Å | angstrom |
| ABq | AB quartet |
| acac | acetylacetonate |
| aq. | aqueous |
| Ar | aryl |
| brd | broad doublet |
| brs | broad singlet |
| Bn | benzyl |
| Bu | butyl |
| *n*-BuLi | *n*-butyllithium |
| *t*-BuLi | *tert*-butyllithium |
| cat. | catalytic |
| CBP | CREB binding protein |
| $CDCl_3$ | deuterated chloroform |
| $CHCl_3$ | chloroform |
| $CH_2Cl_2$ | dichloromethane |
| CNS | central nervous system |
| COSY | correlation spectroscopy |
| d | doublet |
| dd | doublet of doublets |
| DCE | dichloroethane |
| DEPT | distortionless enhancement of polarisation transfer |
| DIBAL-H | diisobutylaluminium hydride |
| DIPEA | diisopropylethylamine |
| DMAP | *N*,*N*-dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DMSO-*d*6 | deuterated dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| dt | doublet of triplets |
| DTP | Developmental Therapeutics Program |
| eq | equivalents or equation where appropriate |
| ESI | electrospray ionisation |
| Ether/$Et_2O$ | diethyl ether |

| | |
|---|---|
| $Et_3N$ | triethylamine |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| EWG | electron withdrawing group |
| g | gram |
| $GI_{50}$ | 50% growth inhibition concentration |
| h | hour(s) |
| $H_2O_2$ | hydrogen peroxide |
| HCl | hydrochloric acid |
| HETCOR | heteronuclear correlation |
| HMBC | heteronuclear multiple bond correlation |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum correlation |
| Hz | hertz |
| *i-* | *iso* |
| $IC_{50}$ | 50% inhibition concentration |
| IR | infrared |
| *J* | coupling constant |
| $LC_{50}$ | 50% lethal concentration |
| Lit. | literature |
| m | multiplet |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| mg | milligram |
| MHz | megahertz |
| min | minutes |
| mL | millilitre |
| μM | micromolar |
| mmol | millimole |
| mol | mole |
| m.p. | melting point |
| mRNA | messenger ribonucleic acid |
| mu *p53* | mutant *p53* |
| nM | nanomolar |

| | |
|---|---|
| NBS | *N*-bromosuccinimide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear overhauser effect |
| NSCLC | non-small cell lung cancer |
| Nu | nucleophile |
| OAc | acetate |
| OTf | triflate |
| OTs | tosylate |
| PAS | PER-ARNT-SIM |
| PDB | protein data bank |
| Ph | phenyl |
| Pro | proline |
| *p*-TSA | *para*-toluenesulfonic acid |
| q | quartet |
| r.t. | room temperature |
| s | singlet |
| SAR | structure-activity relationship |
| t | triplet |
| TBAF | tetra-n-butylammonium fluoride |
| TBDMS | *tert*-butyldimethylsilyl |
| td | triplet of doublets |
| TGI | total growth inhibition |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| TMS | trimethylsilane |
| UV | ultraviolet |
| VEGF | Vascular Endothelial Growth Factor |
| wt *p53* | wild type *p53* |
| μ | micro |
| Δ | reflux |