Novel synthetic routes to furan fatty acids and their analogues

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Novel Synthetic Routes to Furan Fatty Acids and Their Analogues

Yamin Wang

Supervisors: Dr Gareth J. Pritchard and Dr Marc C. Kimber

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Thesis Abstract

Furan and its derivatives are commonly found in numerous compounds such as natural products, polymers and medicines. The furan ring system is not only the core component to many natural products, but also serves as a key synthetic intermediate to access other more complex molecules. Among furan derivatives, furan fatty acids (F-acids) are an important class of natural products which are widely distributed in nature, and occupy a unique place in the field of medicinal chemistry because of their potent biological and pharmacological activity.

This thesis examines the development of novel approaches towards highly substituted furans, with the ultimate goal of applying novel and high efficiency methods to the synthesis of F-acids and their derivatives.

The first total synthesis of a natural product, an F-acids metabolite originally isolated from shark (*Lamna ditropis*) bile,\(^1\) was accomplished by the utilisation of an iodocyclisation of the corresponding 3-alkyne-1,2-diol to construct the furan nucleus; the synthetic route will be discussed in this thesis.

Through the study of palladium-catalysis of a formal cyclisation to construct the furan ring system, a general route to access different F-acids has been developed. Splitting the F-acids into relatively simple fragments allows for easy preparation and modification of two fragments to produce a range of F-acids. The synthetic route was then applied to the formal synthesis of a natural product, F-acid F\(_6\). After optimisation of the synthetic route, total synthesis of F-acids F\(_4\), F\(_6\) and their analogues was accomplished.
Acknowledgments

Firstly, I would like to express my special thanks of gratitude to my dear supervisor, Gareth Pritchard, for providing me a much-coveted and influential research and practice platform, for the trust, assistance, motivation and inspiration you have provided me over the last four years, and for paving the way for my research and its outcomes. I would also like to thank my dear second supervisor, Marc Kimber, for your kindness help, wise guidance and intimate support all along these years. In these ‘endless’ total syntheses, I really appreciate your encouragement and help. Thanks to both of you, letting me have an insight into the variety of beer in the pub.

I want to say thank you to so many members of staff in the department, for your help and support over these years.

I am also grateful to my fellow colleagues and friends I have met in the ground floor organic chemistry lab during my PhD, especially Sam, Ross, Carlos, Yubai, Bo, Bea, Shuqi, Yassir, Dani and Kay. Special thanks to dear Nat and Robert for the proofreading of my thesis, the help of during my daily lab work.

I would like to thank my parents for your continuously support and encouraging me through this journey of discovery in the UK. Thank you for everything!

A big thanks to my gorgeous wife, Yingying. I love you!
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Arachidonic acid</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>Butyllithium</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylidene acetone</td>
</tr>
<tr>
<td>DCC</td>
<td>$N,N'$-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCU</td>
<td>Dicyclohexylurea</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaenoic Acid</td>
</tr>
<tr>
<td>Dibal-H</td>
<td>Diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(Diphenylphosphino)ethane</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Ionisation</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>EPA</td>
<td>Eicosapentaenoic Acid</td>
</tr>
<tr>
<td>Equiv.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>F-acids</td>
<td>Furan Fatty Acids</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas Chromatography–Mass Spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-red</td>
</tr>
<tr>
<td>LOX</td>
<td>Lipoxygenase</td>
</tr>
<tr>
<td>J</td>
<td>Coupling Constant</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>min.</td>
<td>Minutes</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesylate</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass to Charge Ratio</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NASID</td>
<td>Nonsteroidal Anti-inflammatory Drug</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-Toluenesulfonate</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated Fatty Acid</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>TBDPSCI</td>
<td>tert-Butyldiphenylsilyl Chloride</td>
</tr>
<tr>
<td>TBSCI</td>
<td>tert-Butyldimethylsilyl Chloride</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-(n)-Propylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosylate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra Violet</td>
</tr>
</tbody>
</table>
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Introduction
1.0 Introduction to Furan Fatty Acids

1.1 Inflammation and Fatty Acids

Inflammation, one of the primary responses of the body’s innate immune system after tissue injury and infection, has been associated with a number of human diseases. Generally, inflammation can be divided into acute inflammation and chronic inflammation. The acute inflammation, the most commonly encountered inflammatory response, is an immediate effect and self-limiting. If a continued response is required, chronic inflammation may develop and can continue for weeks or months.

The inflammatory response is a necessary and an important part of the immune response, which consists of the release of pro-inflammatory mediators, and a resolution phase where the system is returned to normal. It is always accompanied with a variety of symptoms such as redness, swelling, heat, pain, vasodilation and diapedesis. These symptoms are the direct results of the interaction and activation of various cellular components and chemicals found in the blood and tissues (Figure 1). Tissue damage stimulates mast cells to release a variety of inflammatory mediators such as histamine, chemotactic factors and prostaglandins. Inflammatory mediators mainly trigger three actions, vasodilation, chemotaxis and increased vascular permeability. These actions eventually lead to target tissue healing.
Chronic inflammation may have numerous consequences associated with increased risk of chronic disease. Chronic inflammation has been reported to be an underlying disorder in a wide range of diseases including asthma, diabetes, rheumatoid arthritis, Alzheimer’s disease, cardiovascular disease and cancer.

For the treatment of chronic inflammation, steroids (e.g. dexamethasone) and nonsteroidal anti-inflammatory drugs (NASIDs) such as aspirin and ibuprofen are widely used. However, long-term use of corticosteroids drugs has been recognized to produce a dependence and lead to side effects such as adrenal function decline.
Prostaglandins, inflammatory mediators produced in response to mast cell stimulation, are able to cause pain and increased vascular permeability. The mechanism of action of NASIDs in the body is considered to be via the inhibition of the arachidonic acid metabolic pathway from arachidonic acid to prostaglandins (Figure 3). NASIDs block the production of prostaglandins by inhibiting enzyme cyclo-oxygenase (COX), thereby inhibiting inflammation and reducing pain and fever. Unlike NASIDs, steroids achieve their anti-inflammatory abilities by inhibiting the production of phospholipase from mast cells.

Figure 2. Steroids and NASIDs drugs.

Figure 3. Arachidonic acid metabolic pathway.
The classic major fatty acids isolated from lipids such as ω-3 polyunsaturated fatty acids (PUFAs) have been extensively studied and it has been proved to have an important role in biological activity. Two representative ω-3 PUFAs, eicosapentaenoic acid (EPA) 4 and docosahexaenoic acid (DHA) 5, have been determined as the active components of marine food and fish oils (Figure 4). Research indicates that EPA and DHA play a protective role in inflammatory diseases (e.g. inflammatory bowel diseases and rheumatoid arthritis).  

![Figure 4. The chemical structures of EPA, DHA and AA.](image)

The anti-inflammatory activity of ω-3 PUFAs is thought to inhibit the metabolic pathway from arachidonic acid (AA) 6 to inflammatory mediators (prostaglandins and leukotrienes). ω-3 PUFAs such as EPA and DHA are competitive substrates for COX and 5-lipoxygenase (LOX) enzymes, thereby decreasing production of inflammatory mediators from mast cells.

In terms of these ω-3 PUFAs, especially of EPA and DHA, are the major components of lipids of fish and fish oil. For a long time, it has been assumed that ingestion of ω-3 PUFAs leads to the protective properties of fish and fish oil diets against chronic inflammatory diseases. Until last three decades, studies have recognized that other trace bioactive fatty acids in lipids are related to the anti-inflammatory activity as well as ω-3 PUFAs.
1.2 Furan Fatty Acids (F-acids)

F-acids, mainly isolated from fish lipids, are widely found in plants, marine and fresh water fish. F-acids occur as minor compounds in the lipids of different samples. F-acids are a class of heterocyclic lipid components with a furan moiety in the central part of the molecule. Reports on minor F-acids in literature are rather scarce, although they are considered as particularly valuable natural products.

1.2.1 Introduction

It is only since the 1970s that F-acids were discovered and studied. Prior to this, F-acids were confused with some PUFAs. Determination of GC retention indices was the most common method used to identify fatty acids in earlier research, in which there are no obvious differences between the GC retention indices of F-acids and PUFAs. In 1974, Glass et al. first discovered F-acids in the Northern pike (Esox Lucius) by using EI mass spectrometry for compound characterization, which allowed for unequivocal distinction between F-acids and PUFAs. After that, F-acids were found widely distributed in nature, particularly in fish, cod liver oil, marine bacteria, plants and even food fats. For example, F-acids F5 7 and F6 8 were two representative F-acids detected in the New Zealand green-lipped mussel Perna canaliculus (Figure 5).
F-acids are a large group of tri- or tetra-substituted furan derivatives, which typically carry a propyl or pentyl side chain in one ɑ-position and an unbranched long fatty acid chain in the other ɑ-position. Either both β-positions of the furan ring are substituted by a methyl group or else there is only one methyl group in the β-position adjacent to the long chain. Because of the low stability of F-acids, they are often converted to fatty acid methyl esters to avoid degradation in analysis. F-acids methyl esters demonstrate very characteristic mass spectra, which provide complete structural information of F-acids. According to their increasing GC elution times of the methyl esters, the F-acids are numbered (Table 1).

<table>
<thead>
<tr>
<th>Number</th>
<th>Compound</th>
<th>m</th>
<th>n</th>
<th>R</th>
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<tr>
<td>1</td>
<td>F_1</td>
<td>2</td>
<td>8</td>
<td>CH₃</td>
</tr>
<tr>
<td>2</td>
<td>F_2</td>
<td>4</td>
<td>8</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>F_3</td>
<td>4</td>
<td>8</td>
<td>CH₃</td>
</tr>
<tr>
<td>4</td>
<td>F_4</td>
<td>2</td>
<td>10</td>
<td>CH₃</td>
</tr>
<tr>
<td>5</td>
<td>F_5</td>
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<td>10</td>
<td>H</td>
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<tr>
<td>6</td>
<td>F_6</td>
<td>4</td>
<td>10</td>
<td>CH₃</td>
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<td>7</td>
<td>F_7</td>
<td>4</td>
<td>12</td>
<td>H</td>
</tr>
<tr>
<td>8</td>
<td>F_8</td>
<td>4</td>
<td>12</td>
<td>CH₃</td>
</tr>
</tbody>
</table>

Table 1. Structures of the most abundant F-acids.

Unlike the abundant F-acids listed above, some unsaturated F-acids were detected from many marine sponges (e.g. *Aplysina fistulairs* and *Strongylophora durissima*). These
F-acids were found to be unusual in comparison with the most abundant F-acids, in that a highly unsaturated side chain is replaced in one \( \alpha \)-position of the furan ring. In 1991, Ciminello et al. found that these F-acid esters from extracts of marine sponge *Dictyonella incise* show a high anti-inflammatory activity in vivo and in vitro experiments (Figure 6).  

![Figure 6. Furan fatty acids isolated from marine sponge *Dictyonella incise*.](image)

At an early stage, F-acids were thought to be produced in animals, such as fish. In 1983, research on the metabolism of F-acids in fish by Sand and co-worker proved that fish produced neither the furan ring nor the alkyl side chain of furan fatty acids. Then it was recognized that plants and algae synthesise F-acids, and F-acids accumulate in animal tissues after intake of food.

The generation of F-acids in nature is very complicated and quite different in each case of different sources. A variety of studies have indicated that the formation of F-acids is Ca\(^{2+}\) dependent. The activation and regulation of some lipoxygenase isoenzymes can be controlled by the presence of Ca\(^{2+}\) ion. The enzyme lipoxygenase (LOX) is taking part in the initial step of F-acid formation as a source for lipid peroxidation (Scheme 1). Linoleic acid 11 is the precursor of the carbon skeleton of F-acids carrying a pentyl side chain by formation of a hydroperoxide at C-13 to afford the intermediate 12. Then the oxygen atom from peroxide group reacts with the conjugated diene by elimination of water to generate a five-membered ring 13, which is then converted to a furan ring by double bond rearrangement. During F-acids biosynthesis, the \( \beta \)-methyl
groups derived from periodic incorporation of methylmalonyl coenzyme A (methylmalonyl-CoA) into 14. Eventually, methylation of \( \beta \)-positions in the furan ring is able to yield the F-acid \( \text{F}_3 \) 15.\(^{19,22}\)

Scheme 1. Biosynthesis of F-acid \( \text{F}_3 \) from linolenic acid.\(^{22}\)

The biosynthetic route demonstrates the generation of F-acids with a pentyl side chain. However, it does not explain how those F-acids with a propyl side chain are generated. Originally, it was assumed that F-acids with a propyl chain were derived from a hydroperoxide in C-12 of Linoleic acid. In 1993, Batna et al. found that propyl F-acid \( \text{F}_1 \) 17 is synthesised from a different source, 9,12-hexadecadienoic acid 16, in a very similar biosynthetic route (Scheme 2).\(^{21}\)

Scheme 2. Biosynthesis of \( \text{F}_1 \) from 9,12-hexadecadienoic acid.\(^{21}\)
1.2.2 Anti-inflammatory activity of F-acids

Ciminiello and co-workers found high inflammatory activity of F-acid sterol esters through observing the release of histamine from rat peritoneal cells. The ability to release histamine from rat peritoneal cells was increased dramatically after the administration of F-acids. However, they did not give a detailed mechanism to explain the relations among the F-acids, histamine and inflammation.

A very important breakthrough was achieved in 2011, Wakimoto et al. developed a semisynthetic preparation and examined the anti-inflammatory activity of F-acids in a rat model of adjuvant-induced arthritis. In this research, lipid extracts of the green-lipped mussel have well-described anti-inflammatory activity due to the presence of F-acids.

Lyprinol® is a natural marine extract comprising of a combination of lipid groups, which is extracted from the freeze-dried stabilized New Zealand green-lipped mussel *Perna canaliculus*. It has been confirmed to have great anti-inflammatory activity when given to animals and humans, and is being eagerly pursued as an alternative to NSAIDs without any known side effects. The lipid-rich extract was found to have a large number of lipid classes, such as free fatty acids, polar lipids and sterol esters. The fatty acid in this mussel mainly consists of ω-3 PUFAs including DHA and EPA. F-acids were also found in the extract.

At first, it was considered that the anti-inflammatory activity of the green-lipped mussel was caused by DHA and EPA, via the inhibition of both the COX and 5-lipoxygenase arachidonate oxygenation pathways. However, some other mussel species with similar concentrations of ω-3 PUFAs did not show the same anti-inflammatory effect. Thus, the group hypothesized that other unstable F-acids remained to be identified as the potential anti-inflammatory components in the green-lipped mussel.

The group examined the F-acids anti-inflammatory effect in a rat model of adjuvant-
induced arthritis in comparison with that of EPA, Lyprinol® and a commercially available NSAID, naproxen. Female Wistar rats were sensitized via injection of *Mycobacterium butyricum* with squalene into the right hind limb. At day 10 after arthritis induction, test materials were administered orally for 5 days then the suppressive effect was observed via determination of the increase in the volume of the rear left paw between the beginning and the end of dosing.\(^1\)

The suppression of the rear left paw swelling by the administration of EPA ethyl ester did not show a big difference even at a high dose. While the administration of F\(_6\) ethyl ester inducing significant inhibition proved that F\(_6\) is a much more potent anti-inflammatory component than EPA in green-lipped mussel. Moreover, F\(_6\) ethyl ester showed a stronger suppression than naproxen at the same dose.\(^1,25\)

The mechanisms of F-acids in biological system are not fully understood, but some assumptions had been proposed that they are acting as strong scavengers of radicals.\(^4,26,27\) Such a characteristic of F-acids allow for the suppression of lipid peroxidation, the initial event of oxidative stress induced inflammation, thereby leading to their anti-inflammatory activity.\(^4,18,27,28\) In a recent study, it was considered that incorporation of F-acids into cell membrane phospholipids is able to suppress the production of inflammatory mediators by affecting key enzymes in the AA metabolic pathway.\(^29,30\)
### 2.0 Furans

#### 2.1 Furan

Furans are an important family of heterocyclic compounds containing a five-membered aromatic ring structure, of which four are carbon atoms and one is an oxygen atom.\(^{31}\) The parent compound, furan, is a planar five-membered aromatic ring (Figure 7). Furan atoms are numbered from 1 to 5 starting with oxygen atom as number 1 and then increasing values counterclockwise.\(^{32}\) Due to the symmetry of the furan ring system, α-position (C2 or C5) and β-position (C3 or C4) are frequently used in furan molecules to identify the relative position of carbon atoms to other substituents.

![Figure 7](attachment:chemical_structure_of_furan.png)

Figure 7. Chemical structure of furan.

A general rule proposed by Hückel in 1931 indicates that aromaticity is observed in cyclically conjugated systems of \(4n + 2\) \(\pi\)-electrons, in which \(n\) is a positive integer.\(^{33}\) Furan, consisting of four sp\(^2\) hybridized carbon atoms and one sp\(^2\) hybridized oxygen atom, has an uninterrupted cycle of p-orbitals.\(^{32,34,35}\) The p-orbital of each carbon atom contributes one electron to form a \(\pi\)-bond with an adjacent carbon atom. One of the two lone pairs of the oxygen atom lie in the same plane of furan ring, the other being orthogonal to the plane of the ring, thereby leading to a delocalized 6 \(\pi\)-electron system which gives the furan ring its aromatic character.\(^{34}\)

Due to the oxygen lone pair being tightly held by the highly electronegative oxygen atom, the mesomeric representations 19-22 contribute little to the electronic structure of furan (Scheme 3).
The highly electronegative oxygen atom in furan holds on to electron density more tightly than its nitrogen or sulfur analogues, pyrrole and thiophene, leading to the great tendency to electrophilic aromatic substituted products. Electrophilic substitutions preferentially take place at the α-position rather than the β-position, as is evident from the resonance structures shown in Scheme 4. The intermediate formed by α-position attack can be described by three resonance structures 23-25, which is greater than two resonance structures 27-28 of the intermediate produced by β-position attack. Therefore the α-substitution intermediate is more stable, and so by Hammond’s Postulate the rate determining transition state is also lower in energy leading to the observed kinetic preference in these reactions.

As an important family of heterocyclic compounds, furans are widely distributed throughout nature and synthetic materials alike. A brief literature search yields numerous compounds containing the furan ring system possessing an enormous range
of pharmacological activities (Figure 8).\textsuperscript{36–40} Natural products containing the furan ring, such as furoscrobiculin B \textsuperscript{30} and rubifolide \textsuperscript{31} were isolated from soft corals and basidiomycetes of mushrooms, respectively.\textsuperscript{38,39} Nitrofurantoin \textsuperscript{32} is an antibiotic and is used in treating urinary tract infection.\textsuperscript{36} Prazosin \textsuperscript{33} is a sympatholytic drug used for treatment of posttraumatic stress disorder and high blood pressure.\textsuperscript{35} Cefuroxime \textsuperscript{34}, as a second-generation cephalosporin antibiotic, has provided a remarkable therapeutic effect for treatment of Lyme’s disease.\textsuperscript{40}

![Structures of several natural and pharmaceutical products containing furan framework](image)

\textbf{Figure 8.} Structures of several natural and pharmaceutical products containing furan framework.\textsuperscript{36–40}

\section*{2.2 Syntheses of Furans}

There are a vast number of furan containing compounds, varying from simple mono-substituted furans such as furfural \textsuperscript{35} which is an important industrial raw material and synthetic precursor to dozens of compounds, to the more complex tetrasubstituted furans such as galerucella pheromone \textsuperscript{38} (a natural product isolated from leaf beetle) (Figure 9).\textsuperscript{34,41,42}
The difference in the substitution patterns of furans leads to the diversity in the synthesis strategy. Generally, there are two main strategies to the synthesis of the furan nucleus in organic chemistry. The first strategy is the construction of the furan ring itself, and the second involves the functionalization of related furan nuclei to access target compounds. Some fundamentally and characteristically different approaches are reviewed as follows.

### 2.2.1 Construction of furan rings

There are numerous synthetic mythologies and strategies reported to form the substituted furan ring by cyclisation in the literature, starting from a variety of substrates, and being mediated by different catalysts (Figure 10). Typical core components of these substrates include 1,4-diketones, 1,4-alkynediols, enals, enyne acetates, 3-alkyne-1,2-diols, alk-1-yynyl oxiranes, etc.
One of the classical and most important approaches for the preparation of furans is the Paal-Knorr reaction \((\text{Scheme 5})\).\(^{45,51}\) The target furan ring is formed by the cyclisation of 1,4-diketones 39 mediated by acids. The reaction is proposed to proceed by protonation of one carbonyl by acid, followed by cyclisation \textit{via} attack of the carbonyl with formation of the enol to give intermediate 41. Subsequent dehydration results in the formation of furan 43. This reaction is limited by the availability of the appropriate 1,4-diketones and the use of harshly acidic conditions and high temperatures.\(^{51}\)
Knight and his group have produced two approaches to F-acids from alkyne containing substrates (e.g. 3-alkyne-1,2-diols). The corresponding β-iodofurans were delivered through 5-*endo-dig* cyclisation of 3-alkyne-1,2-diols 44 using iodine (Scheme 6). The reaction was proposed to proceed by coordination of the alkyne by iodine, followed by cyclisation via attack of a hydroxyl group to deliver 47. Subsequently protonolysis and dehydration yielded the β-iodofuran 45. One key factor of this reaction was to introduce the halogen atom to the furan ring, which made it possible for further modifications at this position by various reactions (e.g. halogen-metal exchange and coupling reaction). This reaction generally proceeded smoothly; however, the synthesis of 3-alkyne-1,2-diols is lengthy and by-products such as the corresponding 2,4-diiodofuran were obtained in some cases.
The Knight group also reported the silver-catalysed cycloehydration of 3-alkyne-1,2-diols 44 into trisubstituted furans 49 (Scheme 7). The reaction was proposed to proceed by activation of the alkyne by Ag(I), followed by cyclisation, protonolysis and dehydration to yield the target furan. This reaction can also be catalysed by some other metal catalysts such as Pd, Au, Cu, etc.

Tsuji et al. described a palladium-catalysed cyclisation of 2-alkynyl carbonates 50 with \( \beta \)-keto esters 51 (Scheme 8). In this report, various tetra-substituted furans were formed via this successive nucleophilic cyclisation under neutral conditions. In addition, the authors demonstrated that 2-(1-alkynyl)oxiranes undergo the same reaction with \( \beta \)-keto esters to give highly substituted furans in good yields. More recently, Yoshida and
co-workers also reported work on palladium-catalysed cyclisation, using the same conditions to form a range of heterocycles including pyrroles, benzofurans and chromans.

Scheme 8. Reagents: (a) Pd$_2$(dba)$_3$·CHCl$_3$, dppe, THF, 65 °C, 2 h; (b) aqueous HCl, THF, 1 h.

The mechanism of the furan annelation was proposed by the authors (Scheme 9). The 2-alkynyl carbonate 50 is transformed to the π-propargylpalladium complex 53 by reaction with the palladium catalyst. Subsequently nucleophilic attack of the β-keto ester 51 gives the π-allylpalladium intermediate 54. Subsequent intramolecular nucleophilic attack of the oxygen ion to the π-allylpalladium species proceed regioselectively at the substituted carbon to form compound 55. A final isomerisation step forms tetrasubstituted furan 52.

Recently, Moran and co-workers developed a similar trisubstituted furan formation by gold-catalysed cyclisation of $\beta$-alkynyl $\beta$-ketoesters (Scheme 10). The reaction is proposed to be alkyne activation by Au(III) and subsequent intramolecular attack by the ketone to form the intermediate 59. Protodemetallation regenerates the catalyst and forms the heterocycle 60, which isomerises to the trisubstituted furan 57. The reaction generally works quite well achieving good yields (68%-93%) and was shown to have a wide substrate scope.

Interestingly, compared with Moran’s method, Zheng and Gujarathi reported a silver-catalysed one pot tetrasubstituted furan synthesis directly from propargylic alcohols 61 and 1,3-dicarbonyl compounds 62 (Scheme 11). The reaction involves two steps, propargylation and cycloisomerisation. The reaction starts by silver-catalysed dehydroxylation of propargylic alcohol 61 to give a propargylic cation, which is subsequently trapped by 62 to deliver intermediate 63. Then it undergoes a similar path.
as Moran’s method, through alkyne activation by Ag(I) and subsequent 5-exo-dig intramolecular attack by the ketone carbonyl to form a heterocycle. After protonolysis and isomerisation, the furan 64 is formed. The authors also proved the mechanism by the successive isolation of the intermediate 63 in the report.

\[
\begin{align*}
(61) & \quad (62) & \quad a \\
(63) & \quad (64)
\end{align*}
\]

**Scheme 11.** Reagents: (a) AgSbF₆, toluene, 90 °C; Cs₂CO₃, toluene, 0 °C, 12 h.⁶¹

### 2.2.2 Functionalisation of related furan nuclei

Reactions with existing furan ring systems are able to eliminate the need for the step of forming the heterocycle nucleus and therefore improve the synthesis efficiency. Reactions including halogenation, nitration, acylation, alkenylation, metallation, *etc.* are commonly applied in this strategy.⁶²,⁶³

Among these reactions, metal-catalysed cross coupling reactions between furan C-H bonds and unsaturated hydrocarbons constitute an attractive methodology in furan synthesis.⁶⁴,⁶⁵ A key feature of this methodology is that it avoids the otherwise necessary prefuctionalisation by means of aromatic halogenation.⁶⁶,⁶⁷

In 1981, Fujiwara and co-workers reported palladium-catalysed alkenylation of furans with various olefins to produce mono-alkenylated products (Scheme 12).⁶⁷ The reaction is regioselective and stereoselective, giving the α-substituted E isomers 66 as major products. The reaction is able to give alkenylated products in just one step, thereby eliminating the need to convert the heterocycles into their aldehyde derivatives or halides before alkenylation.⁶⁸ However, this reaction always gave Z isomers (1%-
7\%\) under the reaction condition and achieved desired products in poor yields (3\%-39\%).

![Scheme 12](image)

**Scheme 12.** Reagents: (a) Pd(OAc)$_2$, Cu(OAc)$_2$, dioxane, acetic acid, 100 °C, 8 h.$^{67}$

Recently, Zhang *et al.* have developed an optimized palladium-catalysed coupling reaction in the presence of AgOAc and pyridine (**Scheme 13**).$^{68}$ This method gave high regioselectivity and stereoselectivity, and delivered the desired α-substituted $E$ products in good yields (76\%-90\%).

![Scheme 13](image)

**Scheme 13.** Reagents: (a) Pd(OAc)$_2$, AgOAc, pyridine, 120 °C, 12 h.$^{68}$

Alternatively, Reetz and Sommer reported gold-catalysed hydroarylation of electron-rich and –poor alkynes with various furans (**Scheme 14**).$^{65}$ Reactions were carried out under mild conditions resulting in high degrees of Z-selectivity. The mechanism of this reaction was believed to involve activation of the alkyne by the cationic gold complex, and nucleophilic attack of the furan from the opposite side, leading to the generation of a vinylgold intermediate 73. Subsequent specific protonation forms the desired Z-double bond and give the product 71. The authors demonstrated that several gold complexes and different co-catalysts can also mediate the reaction. Although other
metal catalysts (e.g. Pt, Zr and Pd salts) have been reported to be active in such reactions,\textsuperscript{44} the low catalyst loading (1 mol% Au) in this method is highly favourable.

Scheme 14. Reagents: (a) Ph$_3$PAuCl, AgSbF$_6$, CH$_3$NO$_2$, r.t., 3 h.\textsuperscript{65}
3.0 Previous Synthetic Routes to F-acids

The chemical synthesis of F-acids has been studied since their identification in the 1970s. However, reports of F-acids synthesis are rather scarce, and most of them are multiple steps and low efficiency. Hence, isolation of F-acids from natural source is still the most important and common method in quantitative analysis of F-acids until now. Therefore, efficient synthesis of F-acids is a very challenging job and has broad prospects.

Schlenk’s routes to F-acids F₆ and F₇

The first total synthesis of F-acids was reported in 1979 by Schlenk et al. starting from two commercial available materials, 3,4-bis(acetoxymethyl)furan 74 and 3-methyl-2-furoate 80, respectively. Schlenk’s approaches to F-acids were simple and straightforward, and mainly involved the generation of alkylfuran and the introduction of the long side side chain. For the synthesis of F₆, acylation of 74 with valeric anhydride gave the butyl ketone 75. Subsequent Wolff-Kishner reduction formed pentylfuran diol 76, which was converted to di-chloride 77 with phosgene. The dimethyl furan 78 was obtained by simple reduction of di-chloride 77. The long side chain was introduced by lithiation and reaction with 1-chloro-10-iododecane. The F-acid F₆ 8 was achieved by reaction with Li and subsequent carbonation (Scheme 15). However, the introduction of the long side chain and subsequent carbonation occurred in two steps with a disappointing yield of 18%.
Scheme 15. Reagents: (a) [H\textsubscript{3}C(CH\textsubscript{3})CO\textsubscript{2}O, BF\textsubscript{3}, benzene, r.t., 5 h; (b) N\textsubscript{2}H\textsubscript{4}, KOH, (HOCH\textsubscript{2}CH\textsubscript{2})\textsubscript{O}, 190 °C, 4h (60%, 2 steps); (c) COCl\textsubscript{2}, toluene, r.t., 4 h; (d) LiAlH\textsubscript{4}, ether, reflux, 1.5 h (76%, 2 steps); (e) n-BuLi, THF, 0 °C; 1-chloro-10-iododecane, ether, r.t. 5 h (58%); (f) Li, CO\textsubscript{2}, MeOH, ether , 0 °C, 2 h (32%).

For the synthesis of F\textsubscript{5}, acylation of 3-methyl-2-furoate 80 followed by reduction gave intermediate 82. Subsequent decarboxylation by using copper gave 2,4-alkylfuran 83. The desired F-acid F\textsubscript{5} 7 was then delivered by undergoing same procedures as above (Scheme 16).

Scheme 16. Reagents: (a) [H\textsubscript{3}C(CH\textsubscript{3})CO\textsubscript{2}O, BF\textsubscript{3}, benzene, r.t., 5 h (20%); (b) N\textsubscript{2}H\textsubscript{4}, KOH, (HOCH\textsubscript{2}CH\textsubscript{2})\textsubscript{O}, 190 °C, 4 h (85%); (c) Cu, 190 °C, 0.5 h (51%); (d) n-BuLi, THF, 0 °C; 1-chloro-10-iododecane, ether, r.t. 5 h (48%); (f) Li, CO\textsubscript{2}, MeOH, ether , 0 °C, 2 h (56%).
Bach’s route to F₅

In 1997, Bach et al. demonstrated a short synthesis of F₅ using 4,5-dibromofurfural 85 as starting material (Scheme 17). The α-bromide of the furan was replaced through a regioselective Pd(0)-catalysed coupling reaction with alkyne 86 to generate the corresponding furan 87. The unsaturated side chain was then introduced by Wittig olefination of the α-aldehyde, and the methyl group was introduced from the β-bromide by Pd(0)-catalysed coupling with MeZnCl. Subsequent palladium-catalysed hydrogenation of the multiple bonds, generated the benzyl ester 89. Eventually, the synthesis was completed after prolonged reaction time of the hydrogenolytic deprotection to gave F₅ 7.

Mascal’s route to F₄

In 2015, Mascal et al. described a total synthesis of F₄ starting from 5-(chloromethyl)furfural 90 in seven steps with a 60% overall yield (Scheme 18). Protection of the aldehyde using 1-butanol and concentrated HCl gave the acetal 91,
followed by Ni-catalysed coupling reaction lead to a 3-C side chain at α-position. Subsequent deprotection and Wittig reaction of compound 92 gave the 11-C side chain at the other α-position, which was transformed to furan 93 under hydrogenation conditions. Reaction between paraformaldehyde and furan 93 gave corresponding methyl ester at both β-positions. The synthesis of F₄ 94 was completed hydrolysis of the methyl ester with aqueous sodium hydroxide.

Scheme 18. Reagents: (a) BuOH, HCl (cat.), 99%; (b) EtMgCl, Ni (acac)₂, DAE, THF, -30 °C; (c) HCl/H₂O, (83%, 2 steps); (d) (9-carboxynonyl)triphenylphosphonium iodide, LiHMDS, THF/DMSO; (e) H₂, Pd/C, THF, (92%, 2 steps); (f) paraformaldehyde, HBr, AcOH; (g) H₂, Pd/C, THF/H₂O, (80%, 2 steps).²⁷

Wakimoto’s semisynthetic preparation of F₆

Despite the development and improvement of chemistry synthesis of F-acids after decades, it is still not convenient when large amount of pure F-acids required. Catabolism of furan fatty acids to degradation products provides an alternative approach for research.³⁷

Wakimoto et al. developed a semisynthetic preparation of F₆-ester starting from a shark metabolite 95 (Figure 11), which was highly accumulated in shark (Lamna ditropis) bile (ca. 10% dry weight).¹ In this case the presence of an electron-withdrawing group conjugated to the tetra-substituted furan ring means the metabolite is relatively stable. Besides, the olefinic bond is useful for chemical modification.
Following a general method, furan fatty acid metabolite 95 was isolated from shark bile. Fischer esterification afforded the methyl ester, which was oxidised by a Lemieux-Johnson oxidation to give corresponding furfural derivative. Wittig olefination followed by hydrogenolysis delivered a tetra-substituted furan with a terminal methyl ester 96. The methyl ester was transformed to the aldehyde by diisobutylaluminium hydride (DIBAL) reduction. Then the 6-C side chain underwent a second Wittig olefination, resulting in the desired 11-C side chain. Subsequent hydrogenolysis with H₂ and Pd/C, generated the target compound F₆ ethyl ester 97 (Scheme 19). As indicated above, F-acids, especially those with two β-methyl substituents, are quite unstable and prone to degradation during analysis, F₆ esters are used instead of direct using F₆ in analysis.

Scheme 19. Reagents: (a) H₂SO₄, MeOH; (b) NaIO₄, OsO₄, H₂O, r.t., 2 d; (c) CH₃(CH₂)₃PPh₃⁺Br⁻, NaN(SiMe₃)₂, CH₂Cl₂, -78 °C, 3 h; (d) Pd-C/H₂, CH₂Cl₂, 5 min; (e) DIBAL-H, CH₂Cl₂, -78 °C, 2 h; (f) EIOCO(CH₂)₃PPh₃⁺Br⁻, NaN(SiMe₃)₂, CH₂Cl₂, 2 h; (g) Pd-C/H₂ 5 min.
Marson’s route to $F_5$

The above syntheses are all of the type where an existing furan nucleus is synthetically modified to afford the desired F-acids. Marson and Harper demonstrated a total synthesis of $F_5$ by using commercially available cycloundecanone 98 (Scheme 20) as starting material.\(^{72}\) Addition of lithium acetylide to ketone 98, followed by hydration of the acetylene and dehydration of the terminal alcohol initially gave 1-acetyl-1-cyclododecene 99. Addition of heptynyl lithium and alkene epoxidation afforded compound 100 with the tertiary allylic alcohol and epoxide group. The cyclisation of furan was then achieved by using catalytic acid and mercury(II) to give 101. After that, the aldehydic group was oxidised with pyridinium dichromate to deliver $F_5$.\(^7\) Eventually, the total synthesis of $F_5$ is thus obtained a total yield of 12% with six steps.

![Scheme 20](image)

**Scheme 20.** Reagents: (a) Lithium acetylide, THF, r.t. 1.5 h (75%); (b) aq.HCOOH, reflux, 3h (64%); (c) heptynyllithium, 20 °C, 4h (68%); (d) aq. tert-butyl hydroperoxide, VO(acac)$_2$, r.t., 4h (69%); (e) Hg(II), aq. H$_2$SO$_4$ (88%); (f) PDC, r.t., 6h (65%).\(^{72}\)

Knight’s routes to F-acids $F_5$ and $F_6$

The Knight group published a series of papers about the 5-endo cyclisation mode and have defined an approach to form $F_5$ and $F_6$ by using silver- or iodine-catalyse 5-endo-dig cyclisation of suitably functionalized 3-alkyne-1,2-diols.\(^{49,52,69,73}\) The group
succeeded in achieving a total synthesis of F₅ and F₆ with the same alkyne-diol precursor in 2008. Mono-TBS 102 was prepared by Baeyer-Villiger oxidation of cyclododecanol, hydrolysis of the resulting lactone, silylation and LiAlH₄ reduction (60% overall yield of 4 steps). Oxidation of the terminal hydroxyl group of mono-TBS compound 102 generated an aldehyde, which following a Gignard reaction with ethynylmagnesium bromide delivered the alkylnol 104. After temporary protection of the alcohol group with Ac₂O, alkyne hydration was followed by treatment with catalytic sodium gold(III) chloride and methanol to deliver the hydroxyl ketone 106. Reaction with heptynyllithium then afforded the required 1,2-alkyne-diol 107 in excellent yield. The synthesis of the 3-alkyne-1,2-diol precursor is thus obtained with five steps (Scheme 21).

Scheme 21. Reagents: (a) PCC, Celite, CH₂Cl₂, 20 °C, 2 h (87%); (b) HCCMgBr, THF, (93%); (c) Ac₂O, DMAP, pyridine, 20 °C, 16 h, (88%); (d) NaAuCl₄·2H₂O (cat.), aq. MeOH, reflux, 5 h (79%); (e) C₅H₁₁CCLi, THF, -78 °C−0 °C (95%).
With 3-alkyne-1,2-diol precursor 107 in hand, the 2,3,5-trisubstituted furan moiety 108 was formed by silver-catalysed cyclisation in excellent yield (97%). The total synthesis of F_5 7 was achieved by TBAF deprotection and PDC oxidation (Scheme 22).^{73}

![Scheme 22](image)

**Scheme 22.** Reagents: (a) AgNO_3-SiO_2, CH_2Cl_2, 20 °C, 5 h (97%); (b) TBAF, THF, 20 °C, 1.5 h (90 %) then 5 PDC, Celite, DMF, 20 °C, 8 h (85%).

For the synthesis of F_6, the tetra-substituted furan 109 was prepared by iodocyclisation of 1,3-alkyne-diol precursor 107. Metal-halogen exchange using butyllithium, followed by alkylation with methyl iodide gave the dimethyl furan. The total synthesis of F_6 8 was completed by TBAF deprotection and PDC oxidation as above (Scheme 23).^{73}

![Scheme 23](image)

**Scheme 23.** Reagents: (a) 3NaHCO_3, dry EtOAc, then 3I_2, 20°C, 1h (87%); (b) BuLi, THF, -78 °C, 5 min then MeI (90%); (c) TBAF, THF, 20 °C, 1.5 h (90 %) then 5 PDC, Celite, DMF, 20 °C, 8 h (85%).

Recently, the Knight group reported optimised syntheses of F-acids F_5 and F_6 in contract to their previous approaches, in order to develop approaches that are suitable for producing the F-acids on large scale.^{69}
The two new approaches to F_5 and F_6 still use silver- or iodine-catalyse 5-endo-dig cyclisation of 3-alkyne-1,2-diols as before. The key intermediate, 3-alkyne-1,2-diol 114, was prepared in five steps (Scheme 24). Starting from commercially available material undec-10-enal 110, addition of ethylmagnesium bromide to aldehyde gave the propargylic alcohol. After temporary protection of the alcohol group to generate compound 111, alkyne hydration was followed by use of catalytic sodium gold(III) chloride and methanol to deliver the hydroxyl ketone 113. Key intermediate 1,3-alkyne-diol 114 was achieved by reaction with heptyllithium.

For the synthesis of F_5, the trisubstituted furan 115 was formed by silver-catalysed cyclisation of 3-alkyne-1,2-diol 110 in excellent yield (100%). Through cross metathesis of the furan 115 with benzyl acrylate, which was able to introduce the additional carbon atom and carboxylate group, unsaturated benzyl ester 116 was formed. The total synthesis of F_5 7 was completed by hydrogenation (Scheme 25). The key feature of this new approach was it completely avoided the step of transformation from primary alcohol to carboxylic acid.
Scheme 25. Reagents: (a) AgNO₃-SiO₂, CH₂Cl₂, 20 °C, 4 h (100%); (b) benzyl acrylate, Grubbs II, CH₂Cl₂, reflux, 2 h (89%); (c) H₂, Pd/C, MeOH, 1h, (83%).

For the synthesis of F₆, the β-iodofuran 117 was prepared by iodocyclisation of 1,3-alkyne-diol precursor 114. Metal-halogen exchange using methyllithium gave the dimethyl furan 118. The total synthesis of F₆ 8 was completed by same procedures as above (Scheme 26).

Scheme 26. Reagents: (a) I₂, NaHCO₃, THF, 20 °C, 1 h (85%); (b) MeLi.LiBr.OEt, THF, -78 °C, 0.5 h (90%); (c) benzyl acrylate, Grubbs II, CH₂Cl₂, reflux, 2 h (87%); (c) H₂, Pd/C, MeOH, 1h, (91%).

Tsukasa’s route to F₂

Tsukasa reported a total synthesis of F₂ by the cyclisation of an acetal (Scheme 33). The acetal 122, which was prepared from hexanal 120 and 1,1-diethoxy-2-methyl-2-
propene 121 *via* a radical addition reaction, was heated in the presence of silica-magnesia beads to give furan 83. Then it was converted to furfural derivative 123 by a Vilsmeier-Haack reaction using DMF and POCl₃ in a 90% yield, followed by Wittig reaction to give compound 124. Eventually, the target F-acid F₂ 125 was delivered by hydrogenation and hydrogenolytic deprotection.

Scheme 27. Reagents: (a) Benzoyl peroxide, 90 °C, 4 h (72%); (b) Silica-magnesia cat., 250 °C, 4 h (60%); (c) DMF, POCl₃, 0 °C-r.t., 3 h (90%); (d) Ph₃=CH(CH₂)₆COOMe, DMF, NaOCH₃, r.t. 5 h (73%); (e) MeOH, Pd/C, r.t. (f) NaOH (92%, two steps).
4.0 Aims

As reviewed in introduction, F-acids exhibited potent activity in vivo anti-inflammatory test and have been proposed to have a potential therapeutic effect for the treatment of inflammatory disorders. However, the limited natural availability of F-acids has hindered their research and applications. Also, most of the current synthetic preparation of F-acids required too many steps leading to insufficient material for comprehensive testing.

The first aim of this research was to accomplish the first total synthesis of a natural product, a structural metabolite of F-acids accumulated in shark bile, which can serve as precursor in the semisynthetic preparation of F₆ developed by Wakimoto et al.¹

Once the synthesis of F-acids metabolite had been developed, the research will focus on the development of a novel synthetic route to the preparation of F-acids. This is to be accomplished by splitting the F-acids into easy relatively simple fragments, which allow for easy preparation and modification of two fragments to produce a range of target F-acids. It is also the intention to develop a route which is capable to produce a series of relevant F-acids analogues to allow for biological testing.
Results and Discussion
5.0 First Total Synthesis of F-acids metabolite

Furan dicaboxylic acid 95, a structure metabolite of F-acids, is highly accumulated in shark (Lamna ditropis) bile. It was the starting material of Wakimoto et al.’s semisynthetic preparation of F-acids. However, to the best of our knowledge, no synthetic approaches to furan dicaboxylic acid 95 have ever been reported. The initial aim of this research was to develop a synthetic route for the chemical synthesis of this natural product. With the knowledge gained from previous syntheses of furans and F-acids, a retrosynthetic plan for this project was developed and investigated (Scheme 28).

![Scheme 28. Retrosynthetic plan for the synthesis of F-acids metabolite 95.](image)

The retrosynthetic plan for the synthesis of F-acid metabolite 95 involves several key intermediates. As was illustrated in the introduction, 5-endo-dig cyclisations of 3-alkyne-1,2-diols using iodine as the electrophile proceeded smoothly to deliver the corresponding β-iodofurans. The 3-alkyne-1,2-diol intermediate 130 was the starting
material intended to undergo iodocyclisation to give β-iodofuran 129. The β-iodofuran 129 itself was considered as an intermediate to access dimethyl furan 128, accessible by halogen-metal exchange or by replacing the iodine using a coupling reaction. The introduction of a protected unsaturated acidic side chain to form tetrasubstituted furan 126 was highlighted as a potentially challenging step.

5.1 Preparation of the 3-Alkyne-1,2-diol Intermediate

Research began by firstly aiming towards the formation of 3-alkyne-1,2-diol intermediate 130. With the knowledge gained from Knight’s route to 3-alkyne-1,2-diols, the retrosynthetic plan of 130 splits the molecule into two fragments; ketone intermediate 131 and alkyne intermediate 132 (Scheme 29).

![Scheme 29. Retrosynthetic plan for the synthesis of 3-alkyne-1,2-diol 130.](image)

The ketone intermediate 131 was constructed from 3,4-dihydro-2H-pyran 133 and hydroxyacetone 134 as there was already a literature precedent for the same compound that showed good yields. By utilizing PPTS as a catalyst, the reaction proceeded smoothly as reported and pure product was obtained as a colourless oil in a good yield of 88% after the purification via column chromatography (Scheme 30). Analytical and spectroscopic data was in agreement with that reported in literature.
The next part in the synthesis of the 3-alkyne-1,2-diol intermediate 130 was the preparation of alkyne intermediate 132, starting with the esterification of commercial available 6-heptynoic acid 135 to give 136 in an 87% yield (Scheme 31). The Steglich esterification is a very effective method for the esterification of carboxylic acids with DCC as a coupling reagent and DMAP as a catalyst\(^{76,77}\). It proceeded smoothly without any difficulties and resulted in excellent yields. The product and starting material displayed significant different polarities by TLC. Pure compound 136 was obtained as a light yellow oil after column chromatography. \(^1\)H NMR confirmed the conversion by the presence of a new peak at \(\delta 3.68\) ppm corresponding to the protons of the methyl group.

The Steglich esterification however, produced a large amount of by-product along with the desired product (Scheme 32).\(^{78}\) The carboxylic acid 135 reacted with DCC to form an \(O\)-acyl isourea, which was more reactive than the free acid. Subsequent attack by the alcohol at the carbonyl carbon of the \(O\)-acyl isourea intermediate 142, formed \(N,N'\)-
dicyclohexylurea (DCU) 144 and ester 136. The by-product was mostly removed by filtration, but trace amounts remained and were difficult to remove.

![Scheme 32](image)

*Scheme 32.* Proposed mechanism of the Steglich esterification.

A sodium borohydride-methanol system was then used to reduce the ester 136 to the primary alcohol 145 *(Scheme 33).* The alcohol product 145 was prepared by heating a solution of ester 136 in the presence of NaBH₄ and MeOH in THF. The reflux time was extended from one hour to three hours. This provided the reaction sufficient time to go to completion and increased the yield from 52% to 82%. The alcohol product 145 was isolated as a colourless oil after aqueous work-up. The ¹H and ¹³C NMR spectrum show
the product to be pure after purification by silica column. Peaks representing the protons of the methyl group of 136 were not present in the $^1$H NMR. IR spectroscopy was used to help characterise the product and a peak at $v$ 3583 cm$^{-1}$ corresponding to the OH group.

Before the coupling reaction between alkyne 132 and ketone 131, the alcohol group of 145 need to be protected and initially, a $t$-butydimethylsilyl group (TBS) was used to protect the terminal hydroxyl group (Scheme 34). As expected the reaction proceeded smoothly in good yield (80%). The product 146 was easily isolated after aqueous work-up. The $^1$H and $^{13}$C NMR spectra illustrated the product to be pure after purification by silica column chromatography. $^1$H NMR confirmed this by the presence of peaks at $\delta$ 0.07 ppm and 0.91 ppm corresponding to the protons of the methyl and $t$-butyl groups of the silyl ether respectively.

Therefore, there was now just one step away from synthesising the target alkynediol. Protected alcohol 146 was then proposed to be coupled to ketone 131 (Scheme 35). Lithiated alkyne was formed by using $^n$BuLi to deprotonate the terminal alkyne. Then
ketone 131 was added to the resulting mixture. After aqueous work-up, the residue was dissolved in methanol containing p-toluenesulfonic acid monohydrate (pTSA·H₂O) in order to remove the tetrahydropyran group. Unfortunately, signals for the desired product were not seen in the crude ¹H NMR spectrum. This was confirmed by ¹H NMR spectrum as the expected peaks at δ 0.07 ppm and 0.91 ppm representing the protons of two types of methyl groups from TBS group were absent. Hence, the silyl ether protecting group (TBS) has been removed by methanol and pTSA monohydrate.

Scheme 35. Reagents: (a) nBuLi, THF, 0 °C, 0.5 h; (b) 131, 0 °C, 1 h; (c) pTSA monohydrate, MeOH, r.t., 2 h.

Then t-butyldiphenylsilyl (TBDPS) group was selected to protect the OH group of 145 as it is less prone to the removal under acidic conditions than TBS. Following the procedure employed for TBS protection, the reaction proceeded smoothly without any difficulties and resulted in excellent yields of the protected alcohol (89%) (Scheme 36). ¹H NMR confirmed this by the presence of peaks at δ 1.08 ppm representing the protons of the tert-butyl group and at δ 7.38-7.68 ppm representing the protons of the phenyl groups of the TBDPS group.

Scheme 36. Reagents: (a) TBDPSCI, imidazole, dichloromethane, 0 °C-r.t., 16 h, (89%).
With compound 148 in hand, the next step was attempted to produce the alkynediol derivative using nBuLi to deprotonate the terminal alkyne, initiating the reaction. However, the initial acetal deprotection conditions (methanol/p-TSA and methanol/PPTS) were found to be problematic to deliver the desired product. After using ethanol/PPTS as deprotection conditions, the reaction was able to deliver the desired product 149 (Scheme 37). This was confirmed via 1H NMR spectroscopy, and all the peaks representing the protons of TBDPS group were observed. The singlet at δ 1.45 ppm represents the protons of the methyl group adjacent to the tetra-substituted carbon which is connected to the alkyne carbon. The doublet at δ 3.46 ppm in the proton spectrum of 149 represents the protons of the carbon adjacent to the terminal hydroxyl group. IR spectroscopy was also used to help characterise the product with a peak at ν 3583 cm⁻¹ corresponding to the hydroxyl group.

Scheme 37. Reagents: (a) nBuLi, THF, 0 °C, 1 h; (b) 131, 0 °C, 4 h; (c) PPTS, EtOH, 55 °C, 3 h, (77%).

In order to improve the yields, optimisation of the reaction conditions was carried out (Table 2). The reaction mixture was allowed to stir with nBuLi for one hour prior to the addition of 131. This was to allow for complete deprotonation the alkyne moiety of 148, leading to the corresponding lithiated species. Eventually, the 3-alkyne-1,2-diol 149 was obtained a good 77% yield (Table 2, entry 5).
### Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time(^a) (h)</th>
<th>Time(^b) (h)</th>
<th>Yield(^c)</th>
</tr>
</thead>
<tbody>
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<td>2</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3.5</td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>4</td>
<td>77%</td>
</tr>
</tbody>
</table>

*Table 2. Optimisation conditions for the synthesis of 149.\(^a\) Reaction time after added \(^n\)BuLi; \(b\) reaction time after added 146; \(c\) The overall yield.*

...In summary, the 3-alkyne-1,2-diol intermediate 149 was delivered within five steps (49% overall yield) (Scheme 38).

**Scheme 38.** Reagents: (a) DCC, DMAP, MeOH, CH\(_2\)Cl\(_2\), r.t., 3 h, (87%); (b) NaBH\(_4\), MeOH, THF, reflux, 3 h, (82%); (c) TBDPSCl, imidazole, CH\(_2\)Cl\(_2\), 0 °C-r.t., 16 h, (89%); (d) 133, PPTS, CH\(_2\)Cl\(_2\), r.t., 16 h, (62%); (e) \(^n\)BuLi, THF, 0 °C, 1 h; (f) 131, 0 °C, 4 h; (g) PPTS, EtOH, 55 °C, 3 h, (77%, 3 steps).
5.2 Optimisation of the Iodocyclisation

After the success of obtaining alkynediol intermediate 149, the second part of this project was continued, which applied 5-endo-dig cyclisations towards to the natural product target.

Using literature conditions for a similar iodocyclisation, the synthesis of β-iodofuran intermediate 150 was attempted (Scheme 39). Using acetonitrile as solvent, 3.3 equivalents of iodine and sodium hydrogen carbonate were used. After aqueous work-up, crude product was obtained as a brown oil. Several spots, including starting material, were observed by TLC. Three singlet peaks at δ 1.04 ppm, 1.06 ppm and 1.08 ppm were found in the crude 1H NMR spectrum, thus further purification was required.

![Scheme 39. Reagents: (a) I₂, NaHCO₃, MeCN, r.t., 1 h, (3%).]

There were challenges when it came to purification of the mixture. It was nearly impossible to isolate the desired product due to two major compounds with similarly low polarity. Pure compound 150 (3%) was obtained through preparative thin layer chromatography. Through analysis of the 1H NMR, peaks due to protons from the TBDPS group were observed. A singlet peak at δ 1.94 ppm corresponding to the protons of the β-methyl group was found. Another singlet peak at δ 7.17 ppm corresponding to α-proton of the furan ring was observed as well. IR spectroscopy was also used to help characterise the product; the absence of a broad OH stretch in the ν 3600 cm⁻¹ region indicated that the diol group of starting material was no long present.

Though the target β-iodofuran was delivered, this step was found to be problematic. It
was not only the low yield of product, but also the presence and properties of the major by-product. In this reaction, the $\beta$-iodofuran 150 contained an unsubstituted $\alpha$ position, meaning that it was more prone to subsequent electrophilic substitution by the residual molecular iodine resulting in the by-product diiodofuran. TLC analysis indicated that the polarity of $\beta$-iodofuran 150 and diiodofuran are similar. The most notable feature in the $^1$H NMR spectra of 150 is that the singlet peak at $\delta$ 7.17 ppm corresponding to the proton at the $\alpha$ position of the furan ring; this is not present in the by-product diiodofuran.

Due to the low yields and significant quantities of diiodofuran, optimisation of the reaction conditions was then investigated (Table 3).

Entries 1 to 8 were carried out at room temperature, which proved to be an inefficient, and often unsuccessful, means of effecting the transformation. Reduction of the reaction time to 0.5 hours (Entries 3 and 4) led to unsuccessful iodocyclisation. A marked increase in reaction time to 20 hours (Entries 7 and 8) effected the iodocyclisation, with almost complete conversion of the starting material, however only the undesired diiodofuran by-product was obtained as observed in the crude $^1$H NMR spectrum.

In order to decrease the tendency of the desired iodofuran to undergo electrophilic substitution with the residual molecular iodine, a reduction in temperature to 0 °C was implemented (Entries 9-11). Entries 9 to 11 were desired to react at 0 °C. Iodocyclisation was not favorable when carried out when THF was employed as the solvent, with only trace quantities of products being visible in the crude $^1$H NMR. Although entry 11 produced a low yield, it was first to show a relatively small amount of the by-product. Comparing entry 1 and entry 11, it can be seen that low temperature aids in reducing the quantity of the undesirable by-product.

Other reaction variables were then considered, such as the reduction in the number of
I₂ equivalents. The reasoning behind this is that there would be less chance for the diiodofuran to form due to limiting the quantity of residual iodine present in the reaction to undergo electrophilic substitution.

A big step forward was gained, as shown in entry 18, when half of the initial equivalents of iodine and NaHCO₃ were used which resulted in a higher yield (12%) with only trace by-product observed after 16 hours.

Whilst a drastic improvement over previous attempts, the yield was still poor. Modification of reagent concentrations led to a dramatic change in reaction yield. A dramatic change occurred (Entry 19), when the reaction proceeded at a concentration of 1 mL/mmol; it produced a yield of 38% without any by-product being observed. Another three experiments (Entries 20, 21 and 22) were attempted whilst modifying concentration or reaction time. Eventually, the optimum reaction conditions (1.6 I₂; 1.6 NaHCO₃; 1 mL/mmol MeCN; 0 °C; 40 h) was found with an improved yield of 45% (Entry 21) (Scheme 40).

![Scheme 40](image)

**Scheme 40.** Reagents: (a) I₂, NaHCO₃, MeCN, 0 °C, 40 h, (45%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>conc. (mL/mmol)</th>
<th>NaHCO₃ equiv.</th>
<th>I₂ equiv.</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield</th>
<th>Yield b</th>
<th>Yield%</th>
</tr>
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<td>3.3</td>
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<td>r.t.</td>
<td>2</td>
<td>3%</td>
<td>8%</td>
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</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
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<td>r.t.</td>
<td>2</td>
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</tr>
<tr>
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<td>3.3</td>
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<td>r.t.</td>
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<td>-</td>
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<td>r.t.</td>
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<td>-</td>
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<td>r.t.</td>
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<tr>
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<td>-</td>
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</table>

Table 3. Optimisation of iodocyclisations. (a) All of the solvents were used anhydrous; (b) Determined by $^1$H NMR spectroscopy.

Though this reaction obtained a relatively satisfactory result, other approaches were attempted to explore alternative routes in this research. Bromine was considered to be able to induce the same cyclisation as iodine; herein N-bromosuccinimide (NBS) was chose to act as an electrophilic reagent in the cyclisation (Scheme 41). However, it failed to yield 151. TLC analysis showed no different products were present in the mixture. This was also confirmed by crude $^1$H NMR spectroscopy, and starting material 149 was recovered from the reaction. The succinimide route was not pursued further because of the lack of success.

![Scheme 41](image)

Scheme 41. Reagents: (a) NBS, NaHCO$_3$, MeCN, r.t., 2 h.

5.3 Synthesis of the Furan Acid Intermediate

The next part of this project was the introduction of a protected unsaturated acidic side chain to the furan ring of 150. Clearly there are a variety of different approaches to introduce C-C bond through the cleavage of C-H bond, such as palladium-catalysed cross-coupling reactions.\(^{64,71,79}\) In order to ensure that cross coupling reactions of $\beta$-iodofuran 150 were possible, a series of similar reactions were tested as practice to avoid the wastage of raw material.
The first intention was to repeat the work initial reported by Tsuji and co-workers (Scheme 42); 2-methylfuran was allowed to undergo oxidative cross coupling with acrylates in the presence of t-butyl perbenzoate and a catalytic amount of Pd(OCOPh)₂. A key feature of this coupling reaction was that the olefinic bond of the product is exclusively trans. Readily available Pd(OAc)₂ was selected to replace Pd(OCOPh)₂ as the catalyst in the coupling reactions. A solution of 2-methyl furan 152, ethyl acrylate 153, t-butyl perbenzoate and 5mol% Pd(OAc)₂ in glacial acetic acid was heated at 100 °C for 4 hours, TLC analysis showed that new products were present in the mixture. The coupled product 154 was isolated in 55% yield, after aqueous work-up and purification via column chromatography. ¹H NMR confirmed this by the presence of peaks at δ 7.37-7.34 ppm and 6.24-6.21 ppm corresponding to the protons of the carbon-carbon double bond. ¹H NMR analysis showed that both J coupling values of the carbon-carbon double bond were 15.6 Hz, indicating the trans double bond was present rather than the cis one.

Scheme 42. Reagents: (a) Pd(OAc)₂, PhCO₃t-Bu, AcOH, reflux, 4 h, (55%).

The olefin hydroarylation between hetercocylic C-H bonds and olefinic C-C bonds is an important synthetic methodology for the preparation of alkylated heterocycles. The gold-catalysed hydroarylation of ethyl propiolate 155 by 2-methyl furan 152 was also investigated as a potential replacement for the aforementioned palladium-catalysed oxidative cross coupling as it is quoted as being selective towards the cis product (Scheme 43). Readily available reagent AgOTf was selected to replace AgSbF₆ as the co-catalyst with Ph₃PAuCl in the reaction. This reaction proceeded smoothly without any difficulties and resulted in acceptable yields (49%). New products were observed...
on the TLC plate and compound 156 was obtained after purification via silica gel column chromatography. $^1$H NMR spectroscopy confirmed this by the presence of peaks at $\delta$ 6.75-6.72 ppm and 5.66-5.63 ppm corresponding to the protons of the carbon-carbon double bond. Traces of the different isomers were also identified via $^1$H NMR analysis.

![Scheme 43](image)

**Scheme 43.** Reagents: (a) Ph$_3$PAuCl, AgOTf, CH$_3$NO$_2$, r.t., 4 h, (52%).

| Entry | Au cat. (mol%) | Ag cat. (mol%) | Equiv. 155 | Time (h) | Yield (%) | [Z:E]$^a$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>3</td>
<td>0</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>7[&gt;99:1]</td>
</tr>
<tr>
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<td>1</td>
<td>1</td>
<td>10</td>
<td>4</td>
<td>52[&gt;99:1]</td>
</tr>
</tbody>
</table>

Table 4. Hydroarylation of 152. (a) Determined by $^1$H NMR spectroscopy.

Though this reaction mainly produces cis-compounds, the mild reaction conditions and simple operations are the most important advantages of the gold-catalysed hydroarylation of ethyl propiolate by furans.

The conversion of cis product 156 to 154 resulted in quantitative yields by utilizing iodine to isomerise the double bond (Scheme 44). The reaction process was monitored by $^1$H NMR. Doublet peaks at $\delta$ 6.74 ppm and 5.65 ppm representing the protons of the carbon-carbon double bond were removed after 5 hours (Figure 12). Spectra data
was consistent with that obtained from the palladium-catalysed coupling reaction of 152.

\[
\text{(156)} \quad \text{a} \quad \text{(154)}
\]

**Scheme 44.** Reagents: (a) I$_2$, CDCl$_3$, r.t., 5 h, (100%).

**Figure 12.** $^1$H NMR spectra of iodine induced isomerisation of 156.
With the knowledge gained from these reactions, the project continued to introduce side chain to \( \beta \)-iodofuran 150.

Initially, synthesis of the target product was attempted through the palladium catalysed cross-coupling reaction (Scheme 45). Following the procedure outlined in the literature, a dark oil was obtained after aqueous work-up. TLC analysis showed many products were recovered in the mixture. However, this reaction proved unsuccessful with neither starting material nor desired product being observed from the reaction. This might be due to the harsh reaction conditions, especially using acetic acid as the solvent, decomposing the \( \beta \)-iodofuran 150.

![Scheme 45](image)

Scheme 45. Reagents: (a) ethyl acrylate 153, Pd(OAc)\(_2\), PhCO\(_3\)-Bu, AcOH, reflux, 4 h.

Therefore, this research focused on the gold-catalysed reaction between 150 and ethyl propiolate 155. Using the same reaction conditions as before (Entry 1), the target furan was not obtained. The original conditions utilized an excess of furan, which was considered wasteful in this case. A trace amount of product was observed in the crude \(^1\)H NMR when the reaction time was prolonged to 8 hours. Optimisation of the reaction conditions was then carried out (Table 5).

When low quantities of ethyl propiolate were employed (Entries 1-4), conversion was unsuccessful. An increase to 10 equivalents of ethyl propiolate (Entry 5) led to the desired product being formed, however a yield of 6% was far from desirable. An increase in reaction time to 24 hours (Entry 8) saw an increase in the yield to 13%.
TLC analysis indicated there was a new compound present. Pure compound 158 was then obtained after purification and was confirmed by $^1$H and $^{13}$C NMR. Doublet peaks at $\delta$ 6.23 ppm and 6.19 ppm representing the proton of the carbon-carbon double bond were observed. The singlet peak at $\delta$ 7.17 ppm representing the proton of the furan ring of starting material was removed.

Scheme 46. Reagents: (a) ethyl propiolate 155, Ph$_3$PAuCl, AgOTf, CH$_3$NO$_2$, r.t., 24 h, (13%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv of 155</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>0.1</td>
<td>4</td>
<td>r.t.</td>
<td>-</td>
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<td>r.t.</td>
<td>trace</td>
</tr>
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<td>0.1</td>
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<td>100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>8</td>
<td>r.t.</td>
<td>trace</td>
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<td>r.t.</td>
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<td>r.t.</td>
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<td>8</td>
<td>10</td>
<td>24</td>
<td>r.t.</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 5. Optimisation for conditions.
In order to improve the yield of the gold-catalysed reaction, alternative gold catalysts were examined. (Acetonitrile) [(2-biphenyl)di-tert-butylphosphine] gold(I) hexafluoroantimonate, which is known as JohnPhos Au(MeCN)SbF$_6$ 159 (Figure 13), was tried to replace Ph$_3$PAuCl/AgOTf. This catalyst was used directly without the need for activation by silver salts. This reaction proceeded smoothly with an improved yield of 33% under the same conditions as scheme 46. Spectroscopic data was consistent with that obtained previously.

![Figure 13](Figure 13. JohnPhos Au(MeCN)SbF$_6$)

Work was then directed towards optimising the conditions of the Au(I)-catalysed hydroarylation of the iodofuran (Scheme 47). Table 6 shows some trends by different reaction conditions. When the concentration was increased to 6 mL/mol, the yield was decreased to 23% as shown in entry 3. Excess gold(I) catalyst had a negative effect on the reaction (Entries 4, 5 and 6). For example, neither starting material nor the desired product was isolated when using 50 mol % gold(I) catalyst (Entry 6).

Further optimisation showed that lower amounts of catalyst can be used, e.g., only 3 mol % of gold catalyst (Entry 7 and 8). Interestingly, the order of addition of iodofuran and ethyl propiolate slightly affected the yield of the reaction (Entry 7 and 8). Under the same conditions (3 mol % gold(I) catalyst, 10 equiv. of ethyl propiolate, r.t., 24 h), adding iodofuran first resulted in 37% yield of 158 (Entry 7).

Further experiments addressed the temperature issue but the results did not improve
(Entry 9 and 10). When the reaction temperature was increased to 100 °C neither starting material nor the desired product was isolated (Entry 11).

The last modification to the method was a change in reaction time. With the knowledge gained from previous experiments, the reaction proceeded with low amounts of the catalyst (1-3 mol %) and low solvent concentration (1-3 mL/mol) (Entries 12-15). Finally, in an experiment using 3 mol % of gold(I) catalyst at r.t. (48 h), product 158 was obtained in 58% yield as a 25:75 Z/E mixture (Entry 15). Subsequent isomerization gave the desired compound 157 as a yellow oil.

The opposite E/Z-selectivity is not caused by a change in mechanism. Rather, it is likely that the primary products are in fact Z-configured but undergo isomerisation to the E-form under the reaction conditions. This was supported by the observation that the E/Z ratio of product 158 changed from 66:34 to 75:25 upon subjecting the isolated product mixture to the increased reaction time 36-48 h (Entries 14 and 15).

Pure product 157 and its E-isomer 158 were isolated after very careful purification via column chromatography. This was confirmed via $^1$H, and $^{13}$C NMR spectroscopy and mass spectrometry. However, it was much easier to collect the Z/E mixture directly. Pure product 157 was then obtained, without any difficulties and resulted in quantitative yields, by using iodine in CH$_2$Cl$_2$. The reaction process was monitored by $^1$H NMR spectroscopy. Doublet peaks at $\delta$ 6.52 ppm and 5.71 ppm representing the two protons of the carbon-carbon double bond of 158 were absent after a reaction time of 3 hours.
Scheme 47. Reagents: (a) 155, Au(MeCN)SbF$_6$, CH$_3$NO$_2$, r.t., 48 h, (58%); (b) I$_2$, CDCl$_3$, r.t., 3 h, (99%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au cat. [mol%]</th>
<th>Equiv. of 155</th>
<th>Temp. [°C]</th>
<th>Time [h]</th>
<th>Conc. [mL/mmol]</th>
<th>Yield (%) 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>10</td>
<td>r.t.</td>
<td>24</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>10</td>
<td>40</td>
<td>4</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
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<td>3</td>
<td>10</td>
<td>40</td>
<td>24</td>
<td>3</td>
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<td>100</td>
<td>4</td>
<td>3</td>
<td>-</td>
</tr>
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</table>
Table 6. Optimisation of conditions for preparation of 157.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp</th>
<th>Time</th>
<th>H</th>
<th>t</th>
<th>24</th>
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<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td>2</td>
<td>5</td>
<td>r.t.</td>
<td>2</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>5</td>
<td>r.t.</td>
<td>24</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>5</td>
<td>r.t.</td>
<td>36</td>
<td>1</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>5</td>
<td>r.t.</td>
<td>48</td>
<td>1</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

With iodo furan 157 in hand, work could begin on the methylation of the aryl halide. Scheme 48 shows the methylation of iodo furan 157 to give product 160 by the Suzuki-Miyaura coupling. The reaction was carried out in refluxing dioxane, employing potassium carbonate as base, Pd(PPh3)4 as a catalyst, and trimethylboroxine as the coupling partner and source of the methyl group. TLC analysis showed that a new product was present in the mixture. Column chromatography was used to separate the mixture and the new product was confirmed to be the desired product 160 (9%) by 1H NMR and MS analysis. A singlet at δ 1.84 ppm corresponding to the protons of the new methyl group was observed.

![Scheme 48](image)

Scheme 48. Reagents: (a) Pd(PPh3)4, trimethylboroxine, K2CO3, dioxane, reflux, 28 h, (9%).

In order to develop the optimum conditions for this reaction as shown in Table 7, three experiments were carried out by increasing the reaction time from 8 h to 28 h (Entries 1-3). However, the Suzuki-Miyaura coupling only gave a disappointing 9% yield and
trace of starting material was recovered from each case.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time [h]</th>
<th>Yield of 160 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 7. Optimisation of conditions for preparation of 160.

The inefficient methylation step proved problematic due to the precursor iodofuran being a valuable, and difficult to prepare, starting material. In addition, due to the presence of olefinic bonds and ester groups, harsh reagents and conditions (e.g. organolithium reagents) could not be employed. Due to a large mass of product being required to support the further synthetic route, alternative synthetic routes and methods were then considered to form desired product 160 instead of using Suzuki-Miyaura coupling. Herein a seconded synthetic route was developed and followed (Figure 14). An obvious advantage is that the direct methylation of iodofuran 150 allows the application of multiple methylation methods.
It was decided that a halogen-metal exchange could be used to convert iodofuran 150 into dimethylfuran 161 prior to the hydroarylation step. A standard procedure developed by Knight group, $n$-BuLi at low temperature followed by iodomethane, was used to generate dimethylfuran 161 (Scheme 49). After aqueous work-up, TLC analysis indicated that both a new compound and starting material were present in the mixture. After careful purification via column chromatography, dimethylfuran 161 was obtained in an acceptable yield of 67%. $^1$H NMR spectra confirmed this by the presence of singlet peak at $\delta$ 1.84 ppm corresponding to the protons of the newly introduced methyl group.
Dimethyl furan 161 was also obtained in excellent yield of 88% when methyl lithium was used for the iodine-methyl exchange step (Scheme 55). A solution of methyl lithium in diethyl ether, complexed with LiBr was added to a stirred solution of 150 in THF at -78 °C. This was allowed to stir for 3 hours before warming to r.t and stirring for a further 1 hour. After aqueous work-up, pure 161 was isolated by column chromatography. This was confirmed by $^1$H and $^{13}$C NMR.

Of course, it could be possible to introduce a newly methyl group using Suzuki-Miyaura coupling as well (Scheme 51). Under the same conditions used before (Table 7, entry 3), it produced a yield of 52% in this case. However, compared to the other two methods (using $^n$BuLi/MeI and MeLi), there were no obvious advantages to using this method.
The next step was to introduce the unsaturated ester side chain to 161; a series of experiments trialing different conditions is shown in Table 8. As expected the reaction proceeded smoothly and resulted in a good yield of 85%. At the end of the reaction, a mixture of Z/E isomers of 160 was collected directly by column chromatography.

The isomerisation was carried out under the same conditions (I₂, CH₂Cl₂). Surprisingly, signals for the olefinic bond were notably absent in the ¹H NMR spectrum in the first attempt (200 mg scale). TLC analysis showed that many compounds was showed in the mixture. It was hypothesised that the unsuccessful reaction was due to the iodine being present in visible light as well as an excess amount was used, leading to the decomposition of olefinic bond.

After modification, pure 160 was generated after isomerisation by using a catalytic amount iodine in the dark. ¹H NMR spectroscopy can be used to confirm the completion of the isomerisation. Two doublets at 6.46 ppm and 5.57 ppm are observed and only doublets at 6.13 ppm remained confirming that all Z-isomer had been converted to the corresponding E-isomer after 4 hours reaction (Scheme 52). Remarkably, a good yield of 85% was achieved by using a small volume of nitromethane (Table 8, Entry 4, 1 mL/mm). Spectral data was the same as that obtained from the Suzuki-Miyaura coupling reaction of 157.
Scheme 52. Reagents: (a) 155, Au(MeCN)SbF₆, CH₃NO₂, r.t.; then I₂, CH₂Cl₂, r.t., 4 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au cat. [mol%]</th>
<th>Equiv. of 155</th>
<th>Temp. [°C]</th>
<th>Time [h]</th>
<th>Conc. [mL/mmol]</th>
<th>Yield 160 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10</td>
<td>r.t.</td>
<td>48</td>
<td>3.3</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>10</td>
<td>r.t.</td>
<td>64</td>
<td>3</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>10</td>
<td>r.t.</td>
<td>64</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>5</td>
<td>r.t.</td>
<td>64</td>
<td>1</td>
<td>85</td>
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</tbody>
</table>

Table 8. Optimisation of conditions.

5.4 Synthesis of the F-acids Metabolite

Alcohol 162 was subsequently prepared by selective removal of TBDPS ether with tetrabutylammonium fluoride (TBAF) (Scheme 53). A solution of TBAF in THF was added to a stirred solution of 160 in THF at 0 °C and allowed to stir for 5 minutes before warming to r.t. over 4 hours. At the end of reaction, two new spots were observed by TLC. Pure compound 162 (99%) was obtained after purification via column chromatography. This was confirmed via ¹H NMR spectroscopy, as all the peaks representing the protons of TBDPS group were absent. IR spectroscopy was also used to help characterise the product and a peak at ν 3431 cm⁻¹ corresponding to the hydroxyl group was present.
With primary alcohol 162 synthesised, a final step to introduce the carboxylic acid functionality was required (Figure 15).

Originally, the reaction was attempted with several common oxidation methods on a small scale. For example, oxidants like Jones reagent, Dess-Martin periodinane, RuCl₃/NaIO₄ and ceric ammonium nitrate were tested in each experiment, however these all proved to be ineffective for the desired product, however no starting material was also observed from these reactions. This might be due to the harsh reaction conditions decomposing the olefinic bond of alcohol 162.

Pyridinium dichromate (PDC) was then used and investigated as an alternative oxidising agent to form the desired product. The addition of PDC to alcohol 162 dissolved in DMF result in the formation of the corresponding carboxylic acid 163. TLC analysis showed that a different product was present in the mixture with a higher polarity compared with starting material. ¹³C NMR spectroscopy confirmed this by the presence of peak at δ 178.74 ppm representing the carbon of the newly carboxylic
acid. This was also be confirmed by $^{1}$H NMR spectroscopy as the multiplet at $\delta$ 1.34-1.44 ppm representing the two protons of the terminal alcohol carbon shown in the starting material was absent.

In order to develop the optimum conditions, a series of experiments was carried out as shown in Table 9. The initial conditions used (Entry 1) were taken from a similar reaction in the literature but only gave trace yield after purification. Several modified procedures have been employed to enhance the rate and the efficacy of PDC. As is shown in the table, the only improvement in yield came when the solvent system was changed to DMF/MeOH opposed to DMF, and this only increased the yield to 6% (Entry 5).

Scheme 54. Reagents: (a) PDC, DMF/MeOH, r.t., (6%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of PDC</th>
<th>Time [h]</th>
<th>Solvent</th>
<th>Conc. [mL/mmol]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>8</td>
<td>DMF</td>
<td>15</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>16</td>
<td>DMF</td>
<td>15</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>8</td>
<td>DMF/MeOH</td>
<td>2</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>8</td>
<td>DMF/H$_2$O</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>16</td>
<td>DMF/MeOH</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 9. Optimisation of conditions for preparation of carboxylic acid 163.
Due to the lack of success and low yields from the initial methods, an alternative was found. Tetrapropylammonium perruthenate (TPAP)-catalysed oxidation\textsuperscript{86} was then employed to produce desired product. TPAP serves as the oxidation catalyst, and NMO-H\textsubscript{2}O is acting as the co-oxidant in the reaction.\textsuperscript{86} Unlike PDC oxidation, the reaction proceeded smoothly, and after work-up the carboxylic acid 163 was formed in a moderate yield of 20%. An increase in reaction time from one hour to 16 hours led to an improved yield of 50% (Scheme 55). Spectral data is the same as that obtained previously.

Scheme 55. Reagents: (a) TPAP, NMO-H\textsubscript{2}O, MeCN, r.t., 16 h, (50%).

In comparison with PDC oxidation, TPAP/NMO.H\textsubscript{2}O proved to be a simple, clean, mild and effective method for the formation of 163. This is not only because of the higher yield of the reaction, but also due to the low catalyst loadings and a much easier work-up involved.

With carboxylic acid 163 in hand, the next step was to convert the carboxylic acid group to its corresponding methyl ester.\textsuperscript{87} It was mainly considered in order to be convenient for the purification in further synthesis. To a solution of acid 163 in MeOH, thionyl chloride (SOCl\textsubscript{2}) was added slowly at 0 °C over a period of 30 minutes and allowed to stir a further 16 hours at r.t. (Scheme 56). However a lot of new spots were visible on the TLC plate and purification by column chromatography was unsuccessful. \textsuperscript{1}H NMR confirmed neither starting material nor desired product was present in the mixture.
An alternative reaction also proved incapable of generating product 164. The acid chloride was supposed to be generated by using SOCl₂ reacted with 163 in CH₂Cl₂ overnight, then it was isolated after solvent removal. Acid chloride was then stirred with excess MeOH overnight to produce 164. Crude ¹H NMR confirmed this procedure also failed to yield the desired product.

After two failed esterification experiments, it was decided to deprotect the ethyl group directly to gain finally product 95 (Scheme 57). Ester 163 was hydrolysed under mild conditions with lithium hydroxide (LiOH) in 2:1:2 THF:H₂O:MeOH mixture at r.t. for 32 h. TLC analysis indicated a new product was made with higher polarity than the starting material. Pure product 95 was isolated after careful purification via column chromatography in a yield of 45%. ¹H NMR spectra confirmed this by the absence of the triplet and quartet at δ 1.30 ppm and 4.20 ppm representing the protons of the ethyl group of 163.

Consequently, natural product 95 was prepared from 3-alkyne-1,2-diols 149 in 7 steps (7.5% overall yield) (Scheme 58).
Scheme 58. Reagents: (a) I$_2$, NaHCO$_3$, MeCN, 0 °C, 40 h, (45%); (b) MeLi·LiBr, THF, -78 °C, 3 h, then r.t., 1 h, (88%); (c) 155, Au(MeCN)SbF$_6$, CH$_3$NO$_2$, r.t., 48 h; (d) I$_2$, CH$_2$Cl$_2$, r.t., 4 h, (85%, 2 steps); (e) TBAF, THF, 0 °C, 5 min, then r.t., 4 h, (99%); (f) TPAP, NMO·H$_2$O, MeCN, r.t., 16 h, (50%); (g) LiOH, THF:H$_2$O:MeOH, r.t., 32 h (45%).
6.0 Synthesis of F-acids and Their Analogues

Naturally occurring F-acids have received significant attention among organic chemists, resulting in extensive studies being devoted towards developing synthetic routes to these highly substituted furans.\textsuperscript{19,27,69,70} Whilst various approaches exist, such as those documented in the introduction to chapter 3.0, synthesis of F-acids remains challenging in terms of synthetic efficiency.

For this reason, a versatile and flexible approach to the chemical synthesis of F-acids was the focus of this research. Research began by studying and developing the palladium catalysed cyclisation to functionalised furans, and then utilised the cyclisation to construct the furan nuclei of F-acids and their modified analogues.

6.1 Palladium Catalysed Cyclisation to Furans

There have been various methods for the synthesis of functionalised furans. The method used in the research to achieve functionalised furans involves the modification of a approach reported by Tsuji \textit{et al.}\textsuperscript{56}

In their work on the palladium-catalysed reaction of propargylic carbonates with $\beta$-keto esters, a series of simple exomethylene furans have been synthesised in moderate to good yields by the catalysis of Pd(0)-phosphine complexes. In this reaction, propargylic carbonate reacts with palladium catalyst to generate the $\pi$-allylpalladium complex, which is attacked by the soft nucleophile on the central $sp$-carbon. Subsequent nucleophilic attack on the resulting species by the second nucleophilic moiety of the $\beta$-keto ester led to the formation of the exomethylene (Scheme 59).\textsuperscript{57}

The work also produced several functionalised furans from the corresponding exomethylene furans through isomerisation. For example, isomerisation of methylene furan 167 yielded the trisubstituted furan 168 quantitatively under slightly acidic conditions (Scheme 59).\textsuperscript{56}
More recently, similar palladium-catalysed reaction of propargylic carbonates with bisnucleophiles to highly substituted heterocyclic compounds have been extensively studied by Yoshida et al.\textsuperscript{57-59,89} For example, the substituted pyrrole 171 is regioselectively generated in excellent yield of 96\% through the nucleophilic cyclisation of the carbonate 169 with the $\beta$-enamino ester 170 (Scheme 60).\textsuperscript{57}

Unlike methods for furan formation starting from complex molecules, such as 3-alkyne-1,2-diols used in iodine or silver catalysed cyclisation, the palladium catalysed cyclisation allows the formation of the furan nuclei of F-acids and their analogues from two relatively simple and easier prepared compounds, propargylic carbonates and $\beta$-keto esters. As a further advantage in versatility, by modifying the carbon chain length of either propargylic carbonates or $\beta$-keto esters could achieve corresponding F-acids framework.

In order to verify the feasibility and versatility of the palladium catalysed cyclisation, the reaction was pursued, practiced and tested using commercially available or easily prepared propargylic carbonates and $\beta$-keto esters prior to the application to the total

\begin{align*}
\text{Scheme 59. Reagents:} \quad & (a) \text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3, \text{DPPE}, \text{THF}, 20-25 \degree \text{C}, 4 \text{ h}, (88\%); \quad (b) \text{HCl, THF, r.t., 10 min}, (100\%).^{56}
\end{align*}

\begin{align*}
\text{Scheme 60. Reagents:} \quad & (a) \text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3, \text{DPPE}, \text{THF}, 50 \degree \text{C}, 3 \text{ h}; \quad (b) \text{HCl, r.t., 1 h, (96\%, 2 steps).}^{92}
\end{align*}
synthesis of F-acids and their analogues.

Work began on the preparation of propargylic substrates by esterification of propargylic alcohol 172 with chloroformate 173 in the presence of pyridine in dichloromethane at 0 °C for 3 hours, as described by Yoshida et al. The desired propargylic carbonate 169 was obtained in good yields of 80% after purification by column chromatography (Scheme 61).

![Scheme 61. Reagents: (a) Pyridine, CH₂Cl₂, 0 °C, 3 h, (80%).](image)

Subsequent cyclisation of 169 and methyl acetoacetate 166 was carried out by treatment with 5 mol% Pd₂(dba)₃·CHCl₃ and 10 mol% DPPE in THF (Scheme 62). As expected the reaction proceeded smoothly and the desired product was obtained in a 72% yield as a yellow oil after purification by column chromatography.

![Scheme 62. Reagents: (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50 °C, 3 h; (b) HCl, r.t., 1 h, (72%, 2 steps).](image)

A simple optimisation of conditions for preparation of 174 was carried out. The reaction was trialled by stirring the resulting mixture at room temperature (Tsuji’s conditions), but this gave a very disappointing 35% yield. The reaction was also repeated by doubling the catalyst loading to 10 mol% Pd₂(dba)₃·CHCl₃ and 20 mol% DPPE,
however higher catalyst loadings inhibited product formation, with the isolated yield dropping to 54% after purification.

Alternative methyl carbonate 176 was trialled and proved to be a more efficient propargylic carbonate substrate for the cyclisation. The methyl carbonate 176 was prepared under the same conditions as the preparation of 169 (Scheme 63). Treatment of 172 with methyl chloroformate and pyridine gave propargylic methyl carbonate 176 as a colourless oil in an 85% yield after purification by column chromatography.

![Scheme 63](image)

Scheme 63. Reagents: (a) Pyridine, dichloromethane, 0 °C, 3 h, (85%).

The preparation of desired furan 174 from 176 and 166 proceeded smoothly and resulted in an 85% isolated yield (Scheme 64).

![Scheme 64](image)

Scheme 64. Reagents: (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50 °C, 3 h; (b) HCl, r.t., 1 h, (85%, 2 steps).

The cyclisation of alternative carbonucleophile 177 with propargylic carbonate was also found to be successful. Formation of furan 178 was carried out using the same conditions employed for the preparation of 174 (Scheme 65). After treatment with mild acid for one hour, TLC and ¹H NMR analysis of the crude reaction mixture indicated furan 178 to be the only detected product. Three singlet peaks at δ 2.61 ppm, 2.47 ppm
and 2.38 ppm were found on the $^1$H NMR spectrum of 178, corresponding to the protons of three different methyl groups.

![Chemical structure](image)

**Scheme 65.** Reagents: (a) Pd$_2$(dba)$_3$·CHCl$_3$, DPPE, THF, 50 °C, 4 h; (b) HCl, r.t., 1 h, (81%, 2 steps).

In an attempt to improve the scope of the reaction as well as to test the feasibility of palladium catalysed cyclisation, an aliphatic propargylic carbonate was required. Carbonate 180 was chosen, and it would be able to introduce the pentyl side chain to expected furan products. Propargylic alcohol 179 is commercially available, but is too expensive for a cost-effective synthesis.

For this reason, as well as a practice for further attempts to synthesise F-acids, a synthetic route was developed and followed starting from commercial hexanal 120 to carbonate 180. Initial attempts in the addition of acetylene to hexanal 120 used lithium acetylide or lithium (trimethylsilyl)acetylide however these both proved inefficient and the presence of many by-products made it impossible to purify.

Finally, commercial ethynylmagnesium bromide was employed and gave the clean product with much improved yield. Propargylic alcohol 179 was prepared via the Grignard addition of commercial ethynylmagnesium bromide to a solution of hexanal 120 in THF at 0 °C. After aqueous work-up and purification by column chromatography, 179 was obtained as a colourless oil (89%). Preparation of 180 was carried out by the esterification of 179 with methyl chloroformate in the presence of pyridine in THF (88%) (Scheme 66).
Scheme 66. Reagents: (a) HCCMgBr, THF, 0 °C, 3.5 h, (89%); (b) methyl chloroformate, pyridine, CH₂Cl₂, 0 °C, 3 h, (88%).

The palladium catalysed cyclisation of 180 and 166 proceeded smoothly as expected, and after work-up the tetrasubstituted furan 181 was isolated in an 81% yield (Scheme 67).

![Chemical structure](image)

Scheme 67. Reagents: (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50 °C, 4 h; (b) HCl, r.t., 1 h, (81%, 2 steps).

Subsequent coupling of carbonate 180 and commercial ethyl 3-oxohexanoate 182 was carried out following the same procedure illustrated previously. The reaction proceeded smoothly, and resulted in an 87% isolated yield of 183 after purification by column chromatography (Scheme 68). ¹H NMR confirmed this by the presence of three triplet peaks at δ 1.31 ppm, 0.92 ppm and 0.85 ppm, and one singlet peak at δ 2.04 ppm representing the protons of four different methyl groups. It was a pleasing to introduce propyl and pentyl side chains to the furan product, and proved it possible for the application of palladium catalysed reaction to the total synthesis of F-acids.
6.2 Initial Synthetic Route to F-acids F₄ and F₆

With successful conditions for furan formation to hand, it was reasoned that the palladium catalysed cyclisation methodology would be able to generate the furan nuclei of F-acids. Several total syntheses of F-acids demonstrated in the introduction to chapter 3.6 and the previous work on F-acid metabolite were considered in the development of a novel retrosynthetic plan for the total synthesis of F-acids.

With these in mind, an initial retrosynthetic plan was developed and followed (Scheme 69). The initial approach to the synthesis of F₆ 8 involved the coupling of β-keto ester 188 and propargylic carbonate 189, leading to the generation of tetrasubstituted furan 187 bearing a β-ester functionality. Subsequent reduction of the β-ester group would deliver furan 186 possessing a hydroxyl group, then a second reduction of the hydroxyl would yield dimethyl furan 185. Finally, F₆ 8 would be prepared by introduction of the terminal carboxylic acid group in the synthesis through deprotection followed by oxidation.
Scheme 69. Proposed initial retrosynthetic plan for the synthesis of F$_6$ 8.

The retrosynthetic plan splits the F-acid molecule into two key substrates, a propargylic carbonate, and a $\beta$-keto ester. These can be modified to yield corresponding F-acids. Due to the fact that there is a propyl or pentyl side chain in most F-acids, ethyl 3-oxohexanoate 182 and ester 188 were used in the synthesis of F-acids (Figure 16).

Figure 16. Two $\beta$-keto esters used in the synthesis of F-acids.

Ester 188 was prepared following the procedure published by Thomson et al.$^{90}$ Commercial hexanoyl chloride 191 was added dropwise to a cool solution of Meldrum’s acid 190 and pyridine in dichloromethane (Scheme 70). After complete acylation, an acid work-up afforded a crude mixture as an orange oil. Heating the crude
mixture in methanol leaded to ester exchange and decarboxylation. After purification by column chromatography, ester 188 was isolated as a colourless oil (93%).

Scheme 70. Reagents (a) Pyridine, CH$_2$Cl$_2$, 0 °C, 1 h; (b) MeOH, reflux, 2 h (93%, 2 steps).

6.2.1 Preparation of the Propargylic Carbonate

With the knowledge gained from the preparation of propargylic carbonate 180, the retrosynthetic plan of compound 189 was developed and followed (Scheme 71). This involved the conversion of commercial cyclododecanone 196 to lactone 195, using Bayer-Villiger oxidation conditions. Subsequent selective reduction of lactone 195 to afford 194, which after protection of the alcohol functionality followed by addition of an acetylenic Grignard reagent to the aldehyde, will deliver the desired propargylic alcohol 207. Eventually, esterification of the hydroxyl group of propargylic alcohol 192 would yield propargylic carbonate 189.

Scheme 71. Retrosynthetic plan for the synthesis of carbonate substrate 189.
The first step in the synthesis of this propargylic carbonate substrate is shown in Scheme 79. Follow a similar procedure reported by Luu et al.\textsuperscript{91} The Bayer-Villiger oxidation of cyclic ketone 196 with mCPBA and trifluoroacetic acid (TFA) in dichloromethane to afford lactone 195 proceeded smoothly and resulted in a good yield of 87\% (Scheme 72).

\textbf{Scheme 72.} Reagents (a) mCPBA, TFA, CH\textsubscript{2}Cl\textsubscript{2}, reflux at dark, 72 h, (87\%).

Subsequent conversion of lactone 195 to the aldehyde 194 was carried out by a selectively reduction. Reaction with diisobutylaluminium hydride (DIBAL-H) at -78 °C for 2 h, followed by an acidic work-up and column chromatography afforded 194 as a colourless solid in good yield (82\%) (Scheme 73). Initially, purification proved difficult as a result of both the lactone and the reduced product displaying similar polarities, as seen by overlapping spots when conducting TLC; and several impurities were always found in the product after purification. Eventually, by switching the elution solvents from light petroleum/ethyl acetate to dichloromethane/ethyl acetate, pure 194 was obtained. \textsuperscript{1}H NMR confirmed this by the presence of triplet peaks at δ 9.78 ppm corresponding to the adjacent proton of the aldehyde group. IR spectroscopy was used to help characterise the product and a peak at ν 3425 cm\textsuperscript{-1} corresponding to the hydroxyl group.
Following the same procedure as for the preparation of 148, the terminal primary alcohol group of aldehyde 194 was protected with a bulky silyl ether to generate aldehyde 197 in an excellent yield of 94% as a yellow liquid. Subsequent Grignard addition of the aldehyde group using ethynylmagnesium bromide, followed by an aqueous work-up and purification by column chromatography afforded the desired propargylic alcohol 198 as a colourless oil in a good yield of 83% (Scheme 74).

Consequently, the preparation of desired compound 199 from propargylic alcohol 198 proceeded smoothly as expected and resulted in a good yield of 81% (Scheme 75).
6.2.2 Synthesis towards to F₆

Due to the successful synthesis of required β-keto ester 188 and propargylic carbonate 199, work began on the construction of the furan nucleus of F₆. Generation of furan 200 was carried out using the conditions employed for the preparation of 183. After aqueous work-up and purification by column chromatography, pure furan 200 was obtained as a yellow oil in an 87% yield (Scheme 76).

![Scheme 76](image)

**Scheme 76.** Reagents: (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50 °C, 4 h; (b) HCl, r.t., 1 h, (87%, 2 steps).

With the desired furan 200 in hand, an unavoidable synthetic challenge in the total synthesis of F₆ was encountered, which is the transformation from β-ester group to a methyl group. Furthermore, problems were likely to be encountered in future work on the synthesis of F-acids bearing only one β-methyl substituent, as transformation of the β-ester group to a proton would be required.

In order to accomplish the target dimethyl furan, a three-step approach was developed. First by the reducing the β-ester group to the corresponding hydroxyl functionality, subsequent undergoing tosylation of the functional group to the formation of tosylate ester. Finally, with a good leaving group in position, the resulting tosylate would yield the desired dimethyl furan through nucleophilic attack by metal hydrides.

Formation of 201 was achieved using the commercial lithium aluminium hydride (LiAlH₄) solution as reducing agent. The reaction proceeded well and gave the desired compound as colourless liquid in a yield of 92% after work-up and purification by column chromatography (Scheme 77).
Initially the preparation of 202 was attempted using a method reported by Kabalka et al.\textsuperscript{92} Furan 201 in dichloromethane was cooled to 0 °C, pyridine was then added, followed by the careful addition of \textit{p}-toluenesulfonyl chloride (TsCl) (Scheme 78). The reaction was monitored by TLC, and gave a crude mixture as a brown oil after work-up. Neither desired product nor starting material were isolated after purification by column chromatography. It was hypothesised that the tosylate-bearing furan product was thermally and/or air sensitive, leading to decomposition.

In order to overcome this problem and test the hypothesis, the reaction was repeated, and the crude reaction mixture was diluted with THF and immediately treated with LiAlH\textsubscript{4} at 0 °C. After work-up and careful purification by column chromatography, pure dimethyl furan 203 was isolated as a colourless oil in a disappointing yield of 4% (Scheme 79). The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra both show the furan to be pure after purification by column chromatography.
Scheme 79. Reagents: (a) TsCl, pyridine, CH$_2$Cl$_2$, 0 °C, 3 h; (b) LiAlH$_4$, THF, 0 °C, 2 h, (4%)

Work was then undertaken to optimise the preparation of dimethyl furan 203 via tosylation (Table 10).

Scheme 80. Reagents: (a) CH$_2$Cl$_2$; (b) LiAlH$_4$, THF, 0 °C, 2 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (a)</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield of 203</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsCl/pyridine</td>
<td>0 °C</td>
<td>16 h</td>
<td>11%</td>
</tr>
<tr>
<td>2</td>
<td>TsCl/pyridine</td>
<td>r.t.</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TsCl/ pyridine/DMAP</td>
<td>0 °C</td>
<td>24 h</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>TsCl/ TEA</td>
<td>0 °C</td>
<td>24 h</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>TsCl/ TEA/DMAP</td>
<td>0 °C</td>
<td>24 h</td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>MsCl/TEA/DMAP</td>
<td>0 °C</td>
<td>24 h</td>
<td>28%</td>
</tr>
<tr>
<td>7</td>
<td>Ts$_2$O/ Yb(III)(OTf)$_3$</td>
<td>r.t.</td>
<td>3 h</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 10. Optimisation of conditions for preparation of 203, all reactions carried out on a 50 mg (0.085 mmol) scale in CH$_2$Cl$_2$. 
Initially, prolonging the reaction time from 3 to 16 hours was attempted, and it was found to provide positive results with a higher yield (11%) isolated (entry 1, Table 10). A subsequent attempt, carried out at room temperature, failed to yield any desired products despite the observation that starting materials had been consumed. This confirmed the previous suspicion that increasing the temperature had a detrimental effect on the yield (entry 2, Table 10).

In order to enhance the stability of the sulfonate intermediate, mesylate was attempted to form instead of tosylate. Treatment of 201 in dicholomethane with methanesulfonyl chloride, and triethylamine (TEA) in the presence of a catalytic amount of DMAP, followed by a work-up and subsequent reduction with LiAlH₄ gave the desired product as colourless oil in a disappointing yield of 28% (entry 6, Table 10).

To avoid the use of TsCl in the tosylation step, another set of conditions were explored. The reaction was attempted using the ytterbium-catalysed conditions reported by Schirrmacher, through the use of p-toluenesulfonic anhydride (Ts₂O), and a catalytic amount of ytterbium trifluoro-methansulfonate (Yb(III)(OTf)₃), with the alcohol suspended in dichloromethane. After work-up, the crude product was used immediately by reducing with LiAlH₄ in THF. Unfortunately, most of the starting material furan 201 was recovered after purification via column chromatography (entry 7, Table 10).

The two-step method proved difficult and inefficient in forming the target dimethyl furan by tosylation and reduction, but it did give the compound, even in a very disappointing yield of 30%. With only two steps remaining to form the final natural product, it was then decided to continue to the next step work and resolve this problem in the future.

After treatment of 203 with TBAF in THF, 184 was obtained after the smooth deprotection of the terminal silyl ether, with the desired product being obtained in an excellent 95% yield, the deprotection of the terminal bulky silyl group proceeded smoothly and resulted in excellent yields (95%) (Scheme 81).
With furan 184 in hand, work moved to the oxidation of the primary hydroxyl group to the corresponding carboxylic acid. Actually, compound 184 was exactly the same substrate used in Knight’s total synthesis of F₆, which was oxidised to F₆ by using PDC (85%) (Scheme 82).³³

Treatment of 184 with PDC in DMF at room temperature on a 15 mg (0.044 mmol) scale, to form the desired furan fatty acid 8 was attempted. Unfortunately, signals for the desired product were not observed in the ¹H and ¹³C NMR spectra of the crude product. Moreover, the starting material was absent in the NMR spectra.

The reaction was attempted again in the same scale by employing the TPAP/NMO-H₂O oxidation conditions. After stirring overnight at room temperature, TLC monitoring indicated the formation of a new polar compound. The ¹³C NMR spectrum of the crude product also gave a positive signal by the presence of a peak at δ 179.9 ppm. Disappointingly, approximately 90% starting material was recovered after purification by column chromatography, with no F-acid obtained.

As a result of the unsuccessful oxidation of 184 and poor yield of dimethyl furan 203, the route to the total synthesis of F-acids was reconsidered. It was really disappointing...
that two key steps limited the development of the synthetic approach and made it completely inefficient. Consequently, the last two steps of initial approach were not pursued further due to the lack of success.

In conclusion, the formal synthesis to F_6 ended with the isolation of furan 184 in 10 steps from commercial cyclododecanone 196 (10% overall yield) (Scheme 83).

Scheme 83. Reagents: (a) mCPBA, TFA, CH_2Cl_2, reflux at dark, 72 h, (87%); (b) DIBAL-H, THF, -78 °C, 2 h, (82%); (c) TBDPSCl, imidazole, CH_2Cl_2, r.t., 16 h, (94%); (d) HCCMgBr, THF, 0 °C, 3 h, (83%); (e) methyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 3 h, (81%); (f) 188, Pd_2(dba)_3·CHCl_3, DPPE, THF, 50 °C, 4 h, then HCl, r.t., 1 h, (87%); (g) LiAlH_4, THF, 0 °C, 2 h, (92%); (h) TsCl, TEA, DMAP, CH_2Cl_2, 0 °C, 24 h; (i) LiAlH_4, THF, 0 °C, 2 h, (30%); (j) TBAF, THF, r.t., 3 h, (95%).

In the course of the initial work towards the synthesis of F_6 8, work was also undertaken alongside this on the total synthesis towards F_4 94. Due to the fact that both F-acids have similar structures (Figure 17), the synthesis of F_4 underwent the same procedures and conditions as outlined above.

Figure 17. F-acids F_4 and F_6.
The construction of the furan framework of F₄ 94 was carried out following a general procedure for the preparation of furans above, from commercial ethyl 3-oxohexanoate 182 and propargylic carbonate 199. Furan 204 was isolated as a yellow oil (93%) after purification by column chromatography, subsequent reduction delivered compound 205 as a pale yellow oil (75%) (Scheme 84).

Scheme 84. (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50 °C, 4 h; (b) HCl, r.t., 1 h, (93%, 2 steps); (c) LiAlH₄, THF, 0 °C, 2 h, (75%).

6.3 Second Synthetic Route of F-acids F₄ and F₆

Looking back to the previous synthesis of F-acids metabolite 95 and F₆ 8, it was found that the conversion of the terminal hydroxyl functionality to a carboxylic acid functionality is an obvious shortcoming in both synthetic routes. Problems in the step became apparent when the oxidations were attempted, such as the instability of the furans, low average yields and unpleasant work-up. These negative factors have greatly limited the efficiency and versatility of synthesis approaches.

As outlined in the introduction to chapter 3.6, a literature report by the Knight group
proposed a perfect solution to address this problem by using alkene cross metathesis with benzyl acrylate and hydrogenation to introduce the terminal carboxylic acid functionality (Scheme 85). The cross metathesis method was capable of avoiding the oxidation step in the synthesis.

Scheme 85. (a) benzyl acrylate, Hoveyda-Grubbs MK II, CH₂Cl₂, reflux, 2 h (87%); (b) H₂, Pd/C, MeOH, 1 h, (91%).

It was therefore considered in the development of a new retrosynthetic plan for target F-acids. With this in mind, the second retrosynthetic plan was developed and followed (Scheme 86).

Scheme 86. Second retrosynthetic plan for the synthesis of F₆.

Unlike the preparation of propargylic carbonate 199, the corresponding aldehyde precursor 110 for the required carbonate is commercially available. Treatment of 10-undecenal 110 with commercial ethynylmagnesium bromide gave an 95% yield of
propargylic alcohol 208 as colourless oil. Subsequent esterification with methyl chloroformate afforded the carbonate 207 in an 87% yield as a pale yellow liquid (Scheme 87).

![Scheme 87](image)

Following the same procedures and conditions as before, starting from ester 188 and carbonate 207, furan 206 was afforded in an 89% yield as a yellow oil. Subsequent reduction of the ester functionality using LiAlH₄, gave alcohol 209 in a 90% yield as pale yellow oil.

![Scheme 88](image)

Originally, formation of dimethyl furan 118 was carried out using the same conditions
employed for the preparation of 203. As expected, an unsatisfactory yield (24%) of the dimethyl furan was isolated (Scheme 89).

![Scheme 89](image)

Scheme 89. (a) TsCl, TEA, DMAP, CH₂Cl₂, 0 °C, 24 h; (b) LiAlH₄, THF, 0 °C, 3 h, (24%).

Fortunately, the breakthrough came when the reaction was attempted following the procedure published by MaGee et al, via the conversion of the hydroxyl functionality to the corresponding iodide; with the desired methyl group being generated after reduction with a metal hydride reagent. Portionwise addition of iodine to a solution of alcohol 209 in the presence of PPh₃ and imidazole gave the iodide, which after an aqueous work-up followed by reduction by LiAlH₄, gave pure 118 was isolated in a much more acceptable yield of 85% (Scheme 90).

![Scheme 90](image)

Scheme 90. (a) PPh₃, I₂, imidazole, CH₃CN, Et₂O, 0 °C, 1 h; (b) LiAlH₄, THF, 0 °C, 4 h, (85%, 2 steps).

With alkene 118 in hand, the final step in the synthesis approach was to introduce the carboxylic acid group. By using Knight group’s method, the reaction was repeated and resulted in an 86% yield (Scheme 91). The required carboxylate group and additional carbon atom were introduced to the molecule by treating 118 with benzyl acrylate, and a catalytic amount of Hoveyda-Grubbs 2nd generation catalyst in dichloromethane at reflux, subsequent hydrogenation to deprotect the carboxylic acid
functionality and saturate the olefinic bond gave the natural product F₆ as a colourless oil.

Scheme 91. (a) benzyl acrylate, Hoveyda-Grubbs MK II, CH₂Cl₂, reflux, 2 h; (b) H₂, Pd/C, MeOH, 2h, (86%, 2 steps).

Consequently, natural product F₆ 8 (Figure 18 and 19) was prepared from commercial 10-undecenal 110 in 7 steps (55% overall yield)
Figure 18. $^1$H NMR of F₆ 8.
Figure 19. $^{13}$C NMR of F$_6$.8.
Preparation of F₄ was carried out under the same conditions as for the preparation of F₆ (Scheme 92). These reactions proceeded smoothly without any difficult and finally provided natural product F₄ 94 (Figure 20 and 21) as a colourless oil in an overall 46% yield.

Scheme 92: (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50 °C, 4 h; HCl, r.t., 1 h, (82%, 2 steps); (b) LiAlH₄, THF, 0 °C, 2 h, (78%); (c) PPh₃, I₂, imidazole, CH₃CN, Et₂O, 0 °C, 1 h; (d) LiAlH₄, THF, 0 °C, 4 h, (80%, 2 steps); (e) benzyl acrylate, Hoveyda-Grubbs MK II, CH₂Cl₂, reflux, 2 h; (f) H₂, Pd/C, MeOH, 2h, (90%, 2 steps), (46% overall yield).

It was found that both F₄ and F₆ are unstable when exposed to silica gel or air at room temperature for a long time during work-up and purification. Hence a rapid processing was required, and they were stored at very low temperature under argon atmosphere. However, there were some impurities observed in later biological testing.
Figure 20. $^1$H NMR of $F_4$ 94.
Figure 21. 1H NMR of F94.
6.4 Synthesis of F-acids Modified Analogues

A range of furans prepared in the Pritchard Group were subjected to biological testing to examine their anti-inflammatory activity. Furan 183 was found to exhibit more potent anti-inflammatory activity than other furans.

![Figure 20. Furan 183.](image)

Originally, it was hypothesised that the $\beta$-ester functionality contributes to its anti-inflammatory activity. Yet other furans containing same $\beta$-ester group were not performing similar anti-inflammatory activity. It was then proposed that the aliphatic side chains might have a positive effect to increase its anti-inflammatory activity.

In order to confirm the hypothesis, F$_4$ and F$_6$ analogues (Figure 21) were required to be prepared and subjected to biological testing. Eventually, it was hoped to determine which aspects of the chemical structure of F-acids are integral to its anti-inflammatory activity, through testing a series of furans formed from each step in the total synthesis of 213 and 214.

![Figure 21. F$_4$ and F$_6$ analogues.](image)
Starting from commercial dodecanal 215, propargylic alcohol 216 was obtained as a colourless oil in a yield of 91%. The desired carbonate substrate 217 was successful formed by esterification, and resulted in a good yield of 83% (Scheme 93).

![Chemical structure](image)

**Scheme 93.** (a) HCCMgBr, THF, 0°C, 3 h, (91%); (b) methyl chloroformate, pyridine, CH₂Cl₂, 0°C, 3 h, (83%).

Preparation of F₄ analogue 213 was carried out by using standard procedure from ester 182 and carbonate 217 (Scheme 94). Due to its non-polar nature, it was very easy to purify by column chromatography. Pure 213 was isolated as a colourless oil in an overall 55% yield.

![Chemical structure](image)

**Scheme 94.** (a) Pd₂(dba)₃·CHCl₃, DPPE, THF, 50°C, 4 h; HCl, r.t., 1 h, (85%, 2 steps); (b) LiAlH₄, THF, 0°C, 2 h, (80%); (c) PPh₃, I₂, imidazole, CH₂CN, Et₂O, 0°C, 1 h; (d) LiAlH₄, THF, 0°C, 4 h, (81%, 2 steps) (55% overall yield).
In conclusion, following the same procedure as above, pure 214 was obtained as a colourless oil starting from ester 188 and carbonate 217 (44% overall yield) (Scheme 95).

\[
\begin{align*}
\text{ester 188} & \quad + \quad \text{carbonate 217} \\
& \quad \xrightarrow{a,b} \quad \text{product 220} \\
& \quad \xrightarrow{c,d} \quad \text{product 214}
\end{align*}
\]

Scheme 95. (a) Pd\(_2\)(dba)\(_3\)·CHCl\(_3\), DPPE, THF, 50°C, 4 h; HCl, r.t., 1 h; (b) LiAlH\(_4\), THF, 0°C, 2 h, (55%, 2 steps); (c) PPH\(_3\), I\(_2\), imidazole, CH\(_2\)CN, Et\(_2\)O, 0°C, 1 h; (d) LiAlH\(_4\), THF, 0°C, 4 h, (80%, 2 steps) (44% overall yield).
7.0 Conclusions and Future Work

The first total synthesis of a natural product, F-acids metabolite 95, has been achieved (12 steps, 3.5% overall yield) in this thesis. However, it was found that the final step, the conversion of the terminal hydroxyl functionality to a carboxylic acid functionality, is an obvious shortcoming in this synthetic route.

Using palladium catalysed cyclisation methodology, a novel synthetic route has been developed and applied to the total syntheses of F-acids F₄, F₆ and their analogues. It has been proved to be a versatile and flexible approach to the chemical synthesis of different F-acids.

Due to the success of this novel synthetic route, a number of different avenues of research could be continued in the future.

The most important aspect of future work associated with this synthetic could be focussed on expanding the scope of the novel synthetic approach to form tri-substituted F-acids precursor 224 (Scheme 96). The transformation is proposed to be produced by an approach involving reduction followed by decarboxylation of the ester group of 223.

Scheme 96. Proposed synthesis route to 224.

A variety of important compounds such as fluorinated F-acids and aromatic substituted F-acids could also be generated by modifications of the β-ester functionality of 223 (Scheme 97). In term of the ability to enhance the metabolic stability, binding selectively, and lipophilicity of F-acids by the presence of the trifluoromethylated
moiety,\textsuperscript{95,96} the formation of fluorinated F-acids is a valuable area to investigate.

\textbf{Scheme 97.} Different avenues of future work.

Instead of the reaction of the $\beta$-ester functionality, another area of future work could be focussed on the development of novel methodology for the direct preparation of fluorinated F-acids (\textbf{Scheme 98}).

\textbf{Scheme 98.} Second proposed synthetic plan for the preparation of trifluoromethylated F-acids.

The trifluoromethyl moiety is intended to be introduced by palladium catalysed cyclisation of propargylic carbonate \textit{222} and $\alpha$-trifluoromethyl ketone \textit{227}. Due to the high electronegativity of fluorine, and the consequently the powerful electron withdrawing nature of the trifluoromethyl group,\textsuperscript{96} it was proposed to stabilise the generation of enolate intermediate \textit{230} and promote the palladium catalysed cyclisation process (\textbf{Scheme 99}).
Experimental
8.0 Experimental

8.1 General experimental

Anhydrous conditions were obtained by performing reactions under a nitrogen or argon atmosphere in oven-dried or flame-dried glassware.

All commercially available reagents were used without further purification. The gold catalysts and palladium catalysts were obtained from Sigma-Aldrich® and were handled under argon.

All the solvents used were obtained commercially except tetrahydrofuran (THF), acetonitrile (MeCN) and dichloromethane. THF was freshly distilled as required from sodium and benzophenone prior to use; MeCN and dichloromethane were both distilled from calcium hydride. Petroleum ether refers to the fractions with a boiling point between 40-60 °C.

$^1$H and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz respectively using either a Bruker Avance 400 MHz NMR spectrometer or a JEOL ECS-400 400 MHz NMR spectrometer as solutions in deuterated CDCl$_3$. Coupling constants are measured in hertz (Hz) and chemical shifts are quoted as parts per million (ppm).

High resolution mass spectra were recorded using a Thermo Fisher Exactive mass spectrometer, with ESI as the ionisation mode.

Flash column chromatography was carried out using Apollo Scientific ZEOprep-60 silica under pressure. The eluent is specified with the applicable methods.

TLC analysis was performed on pre-coated aluminium backed silica plates and were visualised under Ultra Violet light, or with vanillin stain and heating.
8.2 Synthetic Procedures

8.2.1 First Total Synthesis of F-acid metabolite (Chapter 5.0)

Preparation of $(\pm)$-1-((tetrahydro-2$H$-pyran-2-yl)oxy)propan-2-one$^{97}$

$$
\text{O} \quad \text{O} \quad \text{O}
$$

(9)

A solution of hydroxyacetone (0.574 g, 7.36 mmol), 3,4-dihydro-2$H$-pyran (1.243 g, 14.80 mmol), PPTS (180 mg, 0.74 mmol) and anhydrous CH$_2$Cl$_2$ (20 mL) were stirred together at reflux for 20 h. The excess CH$_2$Cl$_2$ was removed by evaporation under reduced pressure yielding a yellow liquid. The title compound was isolated by column chromatography (10:1, light petroleum: ethyl acetate) yielding a colourless liquid (985 mg, 6.47 mmol, 88%). $\nu$$_{\text{max}}$(neat)/cm$^{-1}$: 2927, 2855, 1730, 1428. NMR $\delta$$_H$ (400 MHz, CDCl$_3$): 4.66 (1H, bt, $J$ = 3.6 Hz), 4.27 and 4.13 (2H, ABq, $J$ = 15.6 Hz), 3.85-3.82 (1H, m), 3.54-3.51 (1H, m), 2.20 (3H, s), 1.78-1.69 (2H, m), 1.61-1.54 (4H, m). NMR $\delta$$_C$ (100MHz, CDCl$_3$): 206.8, 98.7, 72.3, 62.3, 30.2, 26.5, 25.2, 19.1. HRMS, $m/z$ found (159.1015, C$_8$H$_{15}$O$_3$$^+$ requires 159.1016). Data was in agreement with that reported in the literature.$^{97}$
Preparation of 6-heptynoic acid methyl ester\textsuperscript{41}

\[
\text{\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{O}};
\node (b) at (-1.5,0) {\text{\begin{center}6-heptynoic acid methyl ester\end{center}}};
\end{tikzpicture}
\end{center}
}\]

(136)

To a stirred solution of 6-heptynoic acid (3.60 g, 28.5 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (30 mL) was added methanol (5.2 mL, 114 mmol) and DMAP (0.35 g, 2.9 mmol) at room temperature. Then DCC (7.20 g, 34.3 mmol) was added to the reaction mixture at 0\textdegree C, which was then stirred for 5 min at 0 \textdegree C and then 3 h at room temperature. The precipitated urea was then filtered off and the filtrate evaporated down in \textit{vacuo}. The residue was taken in dichloromethane (30 mL) which was washed with 0.5 M HCl (30 mL) and then with saturated NaHCO\textsubscript{3} solution (30 mL), and dried over MgSO\textsubscript{4}. The organics were concentrated in \textit{vacuo} to give a light yellow oil which was further purified \textit{via} column chromatography (4:1, light petroleum: ethyl acetate) to isolate the title compound as a pale yellow oil (4.04 g, 24.7 mmol, 87\%). \textit{v}\textsubscript{max}(neat) /\text{cm}\textsuperscript{-1}: 3293, 2117, 1738, 1149. NMR \textit{\delta}_{H} (400 MHz, CDCl\textsubscript{3}): 3.68 (3H, s), 2.35 (2H, t, J = 7.6 Hz), 2.24-2.20 (2H, m), 1.96 (1H, t, J = 2.8 Hz), 1.80-1.72 (2H, m), 1.61-1.55 (2H, m). NMR \textit{\delta}_{C} (100 MHz, CDCl\textsubscript{3}): 172.8, 82.9, 67.5, 50.5, 32.5, 26.8, 22.9, 17.1. HRMS, m/z found (163.0732, C\textsubscript{8}H\textsubscript{12}O\textsubscript{2}Na\textsuperscript{+} requires 163.0730). Data was in agreement with that reported in the literature.\textsuperscript{41}
Preparation of 6-heptyl-1-ol\textsuperscript{98}

\[
\text{\begin{tikzpicture}
\path (0,0) edge[->] (1,0) edge[->] (2,0) edge[->] (3,0);
\end{tikzpicture}}
\]

(145)

To a stirred solution of 6-heptynoic acid methyl ester (3.32 g, 23.7 mmol) in THF (22 mL), finely powdered NaBH$_4$ (5.38 g, 142 mmol) was added. The mixture was heated at reflux, and then methanol (37 mL) was added dropwise over 15 min to the resulting mixture with effervescence being observed. After 3 h at reflux, the resulting mixture was cooled to room temperature, quenched with saturated NH$_4$Cl solution (45 mL) and stirred for a further period of 1.5 h. The organic layer was separated and the aqueous layer phase extracted twice with ethyl acetate (2 $\times$ 30 mL). The combined organic layers were then dried over MgSO$_4$ and concentrated in \textit{vacuo} to give the crude product as light yellow oil. The residue was purified \textit{via} column chromatography (4:1, light petroleum: ethyl acetate) to afford the alcohol as a colourless oil (2.15 g, 17.7 mmol, 75%). $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3583, 3298, 2116, 1050. NMR $\delta_H$ (400 MHz, CDCl$_3$): 3.63 (2H, t, $J$ = 5.6 Hz), 2.19-2.17 (2H, m), 2.02 (1H, OH), 1.93 (1H, t, $J$ = 1.2 Hz), 1.57-1.47 (6H, m). NMR $\delta_C$ (100 MHz, CDCl$_3$): 84.4, 68.3, 62.8, 32.2, 28.2, 24.9, 18.4. HRMS, $m/z$ found (113.0963, C$_7$H$_{13}$O$^+$ requires 113.0961). Data was in agreement with that reported in the literature.\textsuperscript{98}
Preparation of tert-butyl(hept-6-yn-1-yloxy)dimethylsilane

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\begin{align*}
\text{OTBS} \\
\text{(146)}
\end{align*}
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TBSCI (0.746 g, 4.95 mmol) was added portionwise over 1 min to a stirred solution of 6-heptyn-1-ol (0.400 g, 3.38 mmol) and imidazole (0.674 g, 9.90 mmol) in anhydrous CH\(_2\)Cl\(_2\) (20 mL) at 0 °C under nitrogen. The resulting mixture was allowed to stir for a further 16 h at room temperature. The mixture was then diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with H\(_2\)O (3 × 15 mL), brine (15 mL), dried over MgSO\(_4\) and concentrated in vacuo giving a residue which was then purified by column chromatography. Elution with 45:1, light petroleum/ethyl acetate gave the title compound as a light yellow liquid (0.621 g, 2.64 mmol, 78%). \(\nu_{\text{max}}\text{(neat)}/\text{cm}^{-1}: 3314, 2119, 1433, 1361, 1338\). NMR \(\delta_H\) (400 MHz, CDCl\(_3\)): 3.63 (2H, t, \(J = 7.2\) Hz), 2.22-2.19 (2H, m), 1.96 (1H, t, \(J = 2.8\) Hz), 1.60-1.57 (2H, m), 1.57-1.55 (2H, m), 1.55-1.53 (2H, m), 0.91 (9H, s), 0.07 (6H, s). NMR \(\delta_C\) (100 MHz, CDCl\(_3\)): 83.6, 75.6, 67.1, 62.0, 31.2, 27.2, 24.6, 24.0, 17.4, 17.3. HRMS, \(m/z\) found (227.1814, C\(_{13}\)H\(_{27}\)O\(^+\) requires 227.1826). Data was in agreement with that reported in the literature.
Preparation of tert-butyl(hept-6-yn-1-yloxy)diphenylsilane

\[ \text{OTBDPS} \]

(148)

TBDPSCI (1.37 g, 5.00 mmol) was added dropwise over 1 min to a stirred solution of 6-heptyn-1-ol (0.401 g, 3.39 mmol) and imidazole (0.698 g, 9.99 mmol) in anhydrous dichloromethane (25 mL) at 0 °C under nitrogen. The resulting mixture was allowed to stir overnight at room temperature. The mixture was then diluted with dichloromethane (25 mL) and washed with H₂O (3 × 20 mL), brine (20 mL), dried over MgSO₄ and concentrated in vacuo giving a residue as a brown oil. The title compound was isolated by column chromatography (45:1, light petroleum: ethyl acetate) yielding a yellow liquid (1.06 g, 3.02 mmol, 89%). ν\text{max}(\text{neat})/cm⁻¹: 3305, 3030, 2118, 1389, 1361, 702. NMR δH (400 MHz, CDCl₃): 7.69-7.68 (4H, m), 7.45-7.38 (6H, m), 3.69 (2H, t, J = 2.4 Hz), 2.20-2.19 (2H, m), 1.95 (1H, t, J = 2.8 Hz), 1.60-1.58 (2H, m), 1.56-1.54 (2H, m), 1.53-1.51 (2H, m), 1.08 (9H, s). NMR δC (100 MHz, CDCl₃): 134.5, 133.0, 128.5, 126.5, 87.0, 67.1, 62.6, 31.0, 27.7, 25.8, 23.9, 18.2, 17.3. HRMS, m/z found (351.2138, C₂₃H₃₁OSi⁺ requires 351.2139). Data was in agreement with that reported in the literature.
Preparation of (±)-9-((tert-butyl diphenylsilyl)oxy)-2-methylnon-3-yne-1,2-diol

Butyllithium (1.3 mL of a 2.45 M solution in hexanes, 3.25 mmol) was added dropwise to a stirred solution of alkynediol (1.08 g, 2.96 mmol) in anhydrous THF (15 mL) at 0 °C. After 1 h, 1-((tetrahydro-2H-pyran-2-yl)oxy)propan-2-one (0.562 g, 3.55 mmol) was slowly added and the resulting mixture stirred for a further 4 h, then quenched by the careful addition of water (4 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with water (10 mL), brine (15 mL), dried over MgSO₄ and concentrated in vacuo giving a residue as a pale yellow oil. The residue was dissolved in ethanol (28 mL) containing PPTS (0.086 g, 0.34 mmol) and stirred at 55 °C for a further 3 h. The resulting solution was cooled to room temperature and the solvents evaporated. The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate) yielding a colourless liquid (1.02 g, 2.28 mmol, 77%). ν\text{max} (neat) /cm⁻¹: 3583, 3390, 2242, 1389, 1361, 1110, 702. NMR δH (400 MHz, CDCl₃): 7.70-7.68 (4H, m), 7.45-7.38 (6H, m), 3.68 (2H, t, J = 6.4 Hz), 3.61 (1H, d, J = 10.8 Hz), 3.46 (1H, d, J = 10.8 Hz), 2.21 (2H, t, J = 7.2 Hz), 1.59-1.57 (2H, m), 1.52-1.50 (2H, m), 1.49-1.48 (2H, m), 1.45 (3H, s), 1.08 (9H, s). NMR δC (100 MHz, CDCl₃): 135.5, 134.0, 129.5, 127.6, 85.2, 81.7, 70.9, 68.6, 63.7, 32.0, 28.4, 26.9, 25.6, 25.1, 18.6, 18.3. HRMS, m/z found
(447.2326, C_{20}H_{36}OSiNa^+ requires 447.2326).
Preparation of tert-butyl-[5-(3-iodo-4-methylfuran-2-yl)-pentyloxy]-diphenylsilane

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\text{I} \\
\text{O} \\
\text{OTBDPS}
\end{array}
\]

(150)

Sodium hydrogen carbonate (0.065 g, 0.47 mmol) was added to dry acetonitrile (0.4 mL), stirred under dry nitrogen and cooled at 0 °C, followed by the alkynediol 149 (0.200 g, 0.472 mmol). After stirring for 30 min, solid iodine (0.201 g, 0.778 mmol) was added in one portion. The resulting mixture was allowed to stir at 0 °C for a further 40 h. At the end of the reaction, aqueous 10% sodium sulfite solution was then added dropwise until excess iodine colour was completely discharged. The mixture was diluting with ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 × 5 mL). The combined organics were washed with H₂O (10 mL), brine (10 mL), dried over MgSO₄ and concentrated in vacuo to give a yellow oil. The title compound was isolated via column chromatography (50:1, light petroleum: ethyl acetate) yielding a colourless oil (0.11 g, 0.21 mmol, 45%). ν\text{max}(\text{neat}) /cm⁻¹: 2931, 2858, 1589, 1555, 1462, 1388, 1108, 1022, 908, 733. NMR δ_H (400 MHz, CDCl₃): 7.70-7.68 (4H, m), 7.44-7.38 (6H, m), 7.17 (1H, s), 3.67 (2H, t, J = 6.4 Hz), 2.66 (2H, t, J = 7.2 Hz), 1.94 (3H, s), 1.65-1.63 (2H, m), 1.61-1.59 (2H, m), 1.42-1.41 (2H, m), 1.07 (9H, s). NMR δ_C (100 MHz, CDCl₃): 156.2, 137.2, 135.6, 134.1, 129.5, 127.6, 123.3, 69.8, 63.7, 32.2, 27.79, 27.71, 26.8, 25.1, 19.2, 11.3. HRMS, m/z found (533.1373, C₂₆H₃₄O₂Si⁺ requires 533.1367).
Preparation of ethyl (Z)-3-2\([5\text{-methylfuryl}]\)propenoate\(^{66}\)

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\text{\includegraphics[width=0.3\textwidth]{156.png}}
\]

(156)

To a solution of triphenylphosphinegold(I) chloride (0.005 g, 0.01 mmol) in nitromethane (2 mL), AgOTf (1.0 mL of a 0.01 M solution in nitromethane) was added under nitrogen. The mixture was allowed to stir at room temperature for 30 min. 2-Methyl furan (0.822 g, 10.1 mmol) and ethyl propiolate (0.099 g, 1.01 mmol) were added dropwise to the mixture. The resulting mixture was kept stirring at room temperature for 4 h. After which, the solvent was removed in \textit{vacuo} giving a residue which was then purified \textit{via} column chromatography (100:1, light petroleum: ethyl acetate) to afford the title compound as a yellow oil (0.091 g, 0.52 mmol, 52%).

\(\nu_{\text{max}}\text{(neat)} / \text{cm}^{-1}:\) 1715, 1622, 1522, 1175, 1028, 975, 813. NMR \(\delta_H\) (400 MHz, CDCl\(_3\)):

7.64 (1H, d, \(J = 3.6\) Hz), 6.74 (1H, d, \(J = 12.8\) Hz), 6.14 (1H, d, \(J = 0.8\) Hz), 5.65 (2H, d, \(J = 12.8\) Hz), 4.22 (2H, q, \(J = 7.2\) Hz), 2.34 (3H, s), 1.31 (3H, t, \(J = 7.2\) Hz). NMR \(\delta_C\) (100 MHz, CDCl\(_3\)):


HRMS, \(m/z\) found (181.0857, C\(_{10}\)H\(_{15}\)O\(_3\)^+ requires 181.0859). Data was in agreement with that reported in the literature.\(^{66}\)
Preparation of ethyl (E)-3-2[2-(5-methylfuryl)]propenoate

Method 1:

A mixture of palladium(II) acetate (0.01 g, 0.05 mmol), tert-butyl perbenzoate (0.194 g, 1.01 mmol), 2- methylfuran (0.082 g, 1.0 mmol) and ethyl acrylate (0.1 g, 1 mmol) in acetic acid (5 mL) was heated at 100 °C for 3 h. After 3 h, the mixture was poured into cold water (20 mL), and extracted with ethyl acetate (2 × 10 mL). The combined extracts were washed with 10% NaOH solution (15 mL), brine (15 mL), dried over MgSO₄ and solvent removed in vacuo giving crude product as a brown oil. The title compound was isolated by column chromatography (100:1, light petroleum: ethyl acetate) yielding a yellow oil (0.098 g, 0.55 mmol, 55%). νmax(neat)/cm⁻¹: 1709, 1637, 1527, 1159, 1022, 970, 788. NMR δH (400 MHz, CDCl₃): 7.36 (1H, d, J = 15.6 Hz), 6.50 (1H, d, J = 3.2 Hz), 6.23 (1H, d, J = 15.6 Hz), 6.07 (2H, d, J = 3.2 Hz), 4.23 (2H, q, J = 7.2 Hz), 2.33 (3H, s), 1.32 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl₃): 167.3, 155.3, 149.5, 131.0, 116.3, 113.9, 108.7, 60.2, 14.6, 14.3. HRMS, m/z found (181.0848, C₁₀H₁₃O₃⁺ requires 181.0859). Data was in agreement with that reported in the literature.

Method 2:
Ethyl (Z)-3-2[2-(5-methylfuryl)]propenoate (0.020 g, 0.12mmol) was dissolved in deuterated chloroform (0.7 mL) in a NMR tube, one small crystal of iodine was added to the NMR tube. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 5 h, the conversion was completed. Data as above.
Preparation of 3(\textit{Z})-{5-[5-(\textit{tert}-butyldiphenylsilanyloxy)-pentyl]-4-iodo-3-methylfuran-2-yl}-acrylic acid ethyl ester

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

\textit{Method 1:}

Triphenylphosphinegold(I) chloride (0.002 g, 0.004 mmol) was weighed into a flame dried flask, the flask was then evacuated for several minutes and charged with argon. Nitromethane (1.2 mL) and AgOTf (0.4 mL of a 0.01 M solution in nitromethane) were added dropwise to the flask and stirred at room temperature for 30 min. After iodofuran 150 (0.100 g, 0.19 mmol) and ethyl propiolate (0.021 g, 0.19 mmol) were added and the mixture was allowed to stir at room temperature for a further 24 h. After which, the solvent was removed in \textit{vacuo} giving a residue which was then purified \textit{via} column chromatography (100:1, light petroleum: ethyl acetate) to afford the title compound as a yellow oil (0.015 g, 0.025 mmol, 13\%). \textit{\nu}_{\text{max}}(\text{neat}) / \text{cm}^{-1}: 3070, 3049, 2930, 2857, 1707, 1633, 701. NMR $\delta_H$ (400 MHz, CDCl$_3$): 7.69-7.67 (4H, m), 7.44-7.38 (6H, m), 6.52 (1H, d, $J = 12.8$ Hz), 5.71 (1H, d, $J = 12.8$ Hz), 4.25 (2H, q, $J = 7.2$ Hz), 3.68 (2H, t, $J = 6.4$ Hz), 2.69 (2H, t, $J = 7.2$ Hz), 2.02 (3H, s), 1.69-1.60 (4H, m), 1.45-1.43 (2H, m), 1.34 (3H, t, $J = 7.2$ Hz), 1.06 (9H, s). NMR $\delta_C$ (100 MHz, CDCl$_3$): 166.8, 157.6, 145.0, 135.5, 134.0, 129.5, 127.9, 127.6, 123.4, 114.8, 71.9, 63.7, 60.4, 32.2, 30.3, 27.6, 26.8, 25.2, 19.2, 14.2, 12.4. HRMS, $m/z$ found (653.1550, C$_{31}$H$_{39}$O$_4$INaSi$^+$ requires
Method 2:

To a stirred solution of (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (0.01 g, 0.005 mmol) in nitromethane (2.5 mL) was added ethyl propiolate (0.750 g, 7.65 mmol) under argon. The mixture was stirred for 10 min then added iodofuran 150 (0.250 g, 0.476 mmol) and continued stirring for 20 h. The solvent was removed in vacuo to yield a brown oil and purified through column chromatography (95:1, light petroleum: ethyl acetate) to obtain the title compound as a yellow oil (0.172 g, 0.300 mmol, 58%). Data as above.
Preparation of 3(E)-{5-[5-\textit{tert}-butyldiphenylsilanyloxy]pentyl}-4-iodo-3-methylfuran-2-yl\text{-}acrylic acid ethyl ester

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\begin{align*}
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& \quad \text{I} \\
& \quad \text{OTBDPS}
\end{align*}
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(157)

To a solution of tetrasubstituted furan 158 (0.098 g, 0.15 mmol) in dichloromethane (10 mL) in a flask surrounded with aluminium foil. A solution of I\textsubscript{2} (0.1 mL of a 0.04 M solution in CH\textsubscript{2}Cl\textsubscript{2}) was added dropwise to the solution. After 5 h, aqueous 10\% sodium sulphite (0.5 mL) was then added dropwise until excess iodine colour was completely discharged. The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 \times 5 mL). The combined organics were washed with H\textsubscript{2}O (15 mL), brine (15 mL), dried over MgSO\textsubscript{4} and concentrated in vacuo to yield the title compound as a yellow oil (0.097 g, 0.16 mmol, 99\%). \(\text{\nu}_{\text{max}}\)\textsubscript{\text{neat}}/\text{cm}^{-1}: 3070, 3049, 2930, 2857, 1707, 1633, 701. NMR \(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 7.69-7.67 (4H, m), 7.47-7.38 (7H, m), 6.21 (1H, d, J = 15.6 Hz), 4.26 (2H, q, J = 7.2 Hz), 3.68 (2H, t, J = 6.4 Hz), 2.70 (2H, t, J = 7.2 Hz), 2.08 (3H, s), 1.69-1.60 (4H, m), 1.45-1.43 (2H, m), 1.34 (3H, t, J = 7.2 Hz), 1.06 (9H, s). NMR \(\delta\)\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 167.4, 158.5, 145.8, 135.5, 134.0, 129.5, 128.9, 128.8, 127.6, 113.6, 72.6, 63.6, 60.3, 32.1, 28.0, 27.5, 26.8, 25.2, 19.2, 14.3, 12.0. HRMS, \textit{m}/z found (653.1545, C\textsubscript{31}H\textsubscript{39}O\textsubscript{4}INa\textsuperscript{+} requires 653.1555).
Preparation of tert-butyl((5-(3,4-dimethylfuran-2-yl)pentyl)oxy)diphenylsilane

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\text{OTBDPS}
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\[161\]

**Method 1:**

Potassium carbonate (0.036 g, 0.20 mmol), trimethylboroxine (0.027 g, 0.12 mmol), iodofuran 150 (0.047 g, 0.089 mmol), Pd(PPh\(_3\))\(_4\) (0.010 g, 0.090 mmol) and 10% aq. 1,4-dioxane (0.5 mL) were charged to a flask and the contents heated to 105 °C under nitrogen for 28 h. The reaction mixture was filtered through a pad of Celite®, washed with THF and concentrated in vacuo. The residue was purified via column chromatography (100:1, light petroleum: ethyl acetate) to afford the title compound as a colourless oil (0.019 g, 0.045 mmol, 52%). \(\nu_{\text{max}}\) (neat) /cm\(^{-1}\): 1642, 1472, 1428, 1383, 1110, 908, 735. NMR \(\delta_H\) (400 MHz, CDCl\(_3\)): 7.66-7.64 (4H, m), 7.46-7.38 (6H, m), 7.07 (1H, s), 3.63 (2H, t, J = 6.4 Hz), 2.52 (2H, t, J = 7.2Hz), 1.90 (3H, s), 1.84 (3H, s), 1.59-1.52 (4H, m), 1.41-1.31 (2H, m), 1.00 (9H, s). NMR \(\delta_C\) (100 MHz, CDCl\(_3\)): 151.3, 136.3, 135.6, 134.2, 129.5, 127.6, 120.9, 115.5, 63.3, 32.4, 28.3, 26.9, 26.2, 25.4, 19.2, 8.4, 8.0. HRMS, \(m/z\) found (421.2584, \(C_{27}H_{37}O_2Si^+\) requires 421.2557).

**Method 2:**

A solution of iodofuran 150 (0.050 g, 0.095 mmol) dissolved in THF (2 mL) was cooled to -78 °C and stirred for 10 min. \(^{n}\)BuLi (0.1 mL of a 1 M solution in THF, 0.1 mmol)
was added dropwise and stirred for 10 min before iodomethane (0.020 g, 0.14 mmol) was added in one portion. The resulting mixture was allowed to stir for a further 10 min before warming to room temperature and stirring for an additional 10 min. The reaction mixture was quenched by the addition of aqueous ammonium chloride (2 mL). THF was removed under reduced pressure and the product extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried, filtered and evaporated and the product purified by column chromatography (100:1, light petroleum: ethyl acetate) to yield the title compound as a colourless oil (0.026 g, 0.063, 67%). Data as above.

**Method 3:**

A solution of iodofuran 150 (0.51 g, 0.97 mmol) in THF (3.2 mL) was cooled to -78 °C. Methyl lithium (2.3 mL of a 1.4 M solution in diethyl ether complex with LiBr, 3.2 mmol) was added dropwise to the stirred solution and stirred for 3 h. Then the resulting mixture was allowed to warm to room temperature and stir for a further 1 h. The reaction mixture was quenched by the addition of aqueous ammonium chloride (2 mL). THF was carefully removed under reduced pressure and the residue extracted into ethyl acetate (3 × 5 mL). The combined organics were dried over MgSO₄, filtered and evaporated. The residue was purified via column chromatography (100:1, light petroleum: ethyl acetate) to afford the dimethyl furan as a colourless oil (0.358 g, 0.854 mmol, 88%). Data as above.
Preparation of \((E)-\text{ethyl}-3-(5-(5-((\text{tert-butyldiphenylsilyl})\text{oxy})\text{pentyl})-3,4-\text{dimethylfuran-2-yl})\text{acrylate}

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\text{OTBDPS}
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(160)

**Method 1:**

Potassium carbonate (0.018 g, 0.13 mmol), trimethylboroxine (0.011 g, 0.091 mmol), iodofuran 157 (0.028 g, 0.045 mmol), Pd(PPh\(_3\))\(_4\) (0.005 g, 0.004 mmol) and 10% aq. 1,4-dioxane (0.2 mL) were charged to a flask and the contents heated to 105 °C under nitrogen for 28 hours. The reaction mixture was filtered through a pad of Celite\(^\text{®}\), washed with THF and concentrated in vacuo. The residue was purified via column chromatography (110:1, light petroleum: ethyl acetate) to afford the title compound as a pale yellow oil (0.002 g, 0.004 mmol, 9%). \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3434, 3055, 2987, 2685, 1637, 1265, 734. NMR \(\delta\)\(_{\text{H}}\) (400 MHz, CDCl\(_3\)): 7.65-7.63 (4H, m), 7.43-7.34 (7H, m), 6.13 (1H, d, \(J = 15.6\) Hz), 4.20 (2H, q, \(J = 7.2\) Hz), 3.63 (2H, t, \(J = 8.4\) Hz), 2.53 (2H, t, \(J = 7.2\) Hz), 2.01 (3H, s), 1.84 (3H, s), 1.62-1.53 (4H, m), 1.41-1.31 (2H, m), 1.29 (3H, t, \(J = 7.2\) Hz), 1.02 (9H, s). NMR \(\delta\)\(_{\text{C}}\) (100 MHz, CDCl\(_3\)): 168.0, 154.4, 144.8, 135.6, 134.1, 129.5, 129.3, 127.7, 127.6, 117.7, 111.6, 63.8, 60.1, 32.3, 28.0, 26.9, 26.4, 25.5, 19.2, 14.4, 8.9, 8.1. HRMS, \(m/z\) found (519.2915, C\(_{32}\)H\(_{42}\)O\(_4\)Si\(^+\) requires 519.2925).
Method 2:

Dimethyl furan 161 (0.330 g, 0.797 mmol), Au(MeCN)SbF₆ (0.017 g, 0.024 mmol) and nitromethane (0.8 mL) were added to a flask. The flask was charged with argon for several minutes. Ethyl propiolate (0.392 g, 4.00 mmol) was added dropwise to the stirred solution during 10 min. The mixture was stirred for a further 64 h at room temperature under argon. After this period, the solvent was removed in vacuo to yield a brown oil and purified via column chromatography (95:1, light petroleum: ethyl acetate) to yield a crude oil (0.291 g, 0.678 mmol, 85%). The mixture was then dissolved in CH₂Cl₂ (9 mL) in a flask surrounded with aluminium foil. I₂ (0.1 mL of a 0.04 M solution in CH₂Cl₂) was added dropwise to the solution. After 5 h, aqueous 10% sodium sulphite (0.4 mL) was added dropwise until excess iodine colour was completely discharged. The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 × 5 mL), the combined organics were then washed with H₂O (15 mL), brine (15 mL), dried over MgSO₄ and concentrated in vacuo yielding the title compound as a pale yellow oil (0.291 g, 0.677 mmol, 80%). Data as above.
Preparation of (E)-ethyl 3-(5-(5-hydroxypentyl)-3,4-dimethylfuran-2-yl)acrylate

To a solution of silyl ester 160 (0.085 g, 0.17 mmol) in THF (3 mL) was slowly added TBAF (0.33 mL of a 1 M solution in THF, 0.33 mmol) at 0 °C. After 5 min stirring, the resultant mixture was warmed to room temperature and left to stir for a further 4 h. After this period, the mixture was diluted with ethyl acetate (10 mL) and washed with brine (2 × 10 mL), dried with MgSO₄, filtered and the solvent removed under reduced pressure yielding a yellow oil. The mixture was purified by column chromatography (1:1 light petroleum: ethyl acetate) yielding the title compound as a colourless oil (0.046 g, 0.17 mmol, 99%). νmax(neat) /cm⁻¹: 3431, 2977, 2685, 1702, 1604. NMR δH (400 MHz, CDCl₃): 7.40 (1H, d, J = 15.6 Hz), 6.12 (1H, d, J = 15.6 Hz), 4.19 (2H, q, J = 7.2 Hz), 3.62 (2H, t, J = 8.4 Hz), 2.55 (2H, t, J = 7.2 Hz), 2.00 (3H, s), 1.84 (3H, s), 1.68-1.53 (4H, m), 1.44-1.34 (2H, m), 1.31 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl₃): 168.0, 154.2, 144.8, 129.3, 127.8, 117.7, 111.6, 62.8, 60.2, 32.5, 28.0, 26.3, 25.4, 14.4, 8.9, 8.1. HRMS, m/z found (281.1743, C₁₆H₂₅O₄⁺ requires 281.1747; 303.1562, C₁₆H₂₄O₄Na⁺ requires 303.1567).
Preparation of \((E)-5-(5-(3\text{-}ethoxy\text{-}3\text{-}oxoprop\text{-}1\text{-}en\text{-}1\text{-}yl})\text{-}3,4\text{-}dimethylfuran\text{-}2\text{-}yl)\text{pentanoic acid}

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\text{HO}
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\text{O} \\
\text{O}
\end{array}
\text{O} \\
\text{OH}

(163)

To a solution of alcohol 162 (0.042 g, 0.15 mmol) and NMO.H_2O (0.208 g, 1.50 mmol) in acetonitrile (0.6 mL) was added TPAP (0.005g, 0.02 mmol) at 0 °C. After stirring for 5 min, the resultant mixture was warmed to room temperature and then allowed to stir a further 4 h. The reaction mixture was diluted with ethyl acetate (5 mL) and washed with distilled water (5 mL). The aqueous layer was further extracted with ethyl acetate (3 \times 5 mL). The combined organic layers were washed with brine (15 mL), dried with MgSO_4, filtered and the solvent removed under reduced pressure yielding a crude oil. The mixture purified via column chromatography (8:2, 7:3, 6:4, 1:1, light petroleum: ethyl acetate) yielding the title compound as a yellow oil (0.022 g, 0.074 mmol, 50%).

\(\nu_{\text{max}}\text{(neat)}/\text{cm}^{-1}: 3583, 3054, 2986, 2685, 1708, 1637, 1605, 1265.\) NMR \(\delta_H\) (400 MHz, CDCl_3): 7.40 (1H, d, \(J = 15.6\) Hz), 6.12 (1H, d, \(J = 15.6\) Hz), 4.20 (2H, q, \(J = 7.2\) Hz), 2.57-2.55 (2H, m), 2.37-2.36 (2H, m), 2.00 (3H, s), 1.84 (3H, s), 1.66-1.64 (4H, m), 1.30 (3H, t, \(J=3.6\) Hz). NMR \(\delta_C\) (100 MHz, CDCl_3): 178.7, 168.0, 153.6, 144.9, 129.3, 127.7, 117.9, 111.8, 60.2, 33.6, 27.6, 26.0, 24.2, 14.4, 8.9, 8.1. HRMS, \(m/z\) found (295.1537, C_{16}H_{23}O_5$^+$ requires 295.1540).
**Preparation of (E)-5-(5-(2-carboxyvinyl)-3,4-dimethylfuran-2-yl)pentanoic acid**

(95)

To a solution of furan acid ester 163 (0.014 g, 0.048 mmol) in THF: methanol: water (1.4 mL, 2:2:1) was added LiOH (0.004 g, 0.2 mmol) and the resultant mixture stirred at room temperature for 32 h. After this period the reaction was diluted with ethyl acetate (5 mL) and washed with hydrochloric acid (1 M; 5 mL). The aqueous layer was further extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and the solvent removed under reduced pressure yielding the crude acid as yellow oil. The mixture was then purified via column chromatography (1:1, light petroleum: ethyl acetate) yielding the title compound as a white solid (0.005 g, 0.02 mmol, 40%). $\nu_{\text{max}}$ (neat) / cm$^{-1}$: 3583, 3400, 3054, 2987, 1603, 1265. NMR $\delta_H$ (400 MHz, CDCl₃): 7.41 (1H, d, $J = 15.2$ Hz), 6.12 (1H, d, $J = 15.2$ Hz), 2.56-2.58 (2H, m), 2.38-2.37 (2H, m), 2.01 (3H, s), 1.85 (3H, s), 1.67-1.65 (4H, m). NMR $\delta_C$ (100 MHz, CDCl₃): 177.4, 168.4, 153.7, 144.9, 129.5, 127.9, 118.0, 111.3, 33.3, 27.6, 26.0, 24.2, 8.9, 8.1. HRMS, $m/z$ found (267.1201, C₁₄H₁₉O₅$^+$ requires 267.1227; 289.1043, C₁₄H₁₈O₅Na$^+$ requires 289.1046).
To a solution of ethynylmagnesium bromide (7.8 mL, 3.9 mmol, 0.5 M in THF) was added hexanal (0.3 g, 3.0 mmol) at 0 °C. Then the resulting mixture was allowed to stir at room temperature for 3.5 h. The reaction mixture was quenched with saturated aq. NH₄Cl (10 mL), extracted with diethyl ether (3 × 10 mL). The combined organics were washed with brine (30 mL), dried over MgSO₄, filtered and the solvent removed by evaporation under reduced pressure. The residue was purified by column chromatography on silica gel (20:1, pentane: ethyl acetate) to afford propargylic alcohol 179 as a colourless oil (0.336 g, 2.67 mmol, 89%). ν\text{max} /cm⁻¹: 3583, 3309, 2930, 2861, 2249. NMR δ\text{H} (400 MHz, CDCl₃): 4.35 (1H, d, J = 4.8 Hz), 2.44 (1H, d, J = 2.0 Hz), 2.02 (1 H, OH), 1.72-1.67 (2H, m), 1.47-1.40 (2H, m), 1.33-1.27 (4H, m), 0.87 (3H, t, J = 7.2 Hz). NMR δ\text{C} (100 MHz, CDCl₃): 85.1, 72.8, 62.4, 37.6, 31.4, 24.7, 22.6, 14.2. HRMS, m/z found (127.1116, C₆H₁₅O⁺ requires 127.1115). Data was in agreement with that reported in the literature.¹⁰²
Preparation of (±)-benzyl (1-phenylprop-2-yn-1-yl) carbonate

To a stirred solution of 1-phenyl-2-propyn-1-ol (0.520 g, 3.95 mmol) and pyridine (2.5 mL, 32 mmol) in dichloromethane (50 mL) was added dropwise benzyl chloroformate (2.0 g, 12 mmol) at 0 °C, and stirring was continued for 2.5 h at the same temperature. The reaction mixture was diluted with saturated aq NH₄Cl (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over MgSO₄ and the solvent removed by reduced pressure. The title compound was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding a colourless liquid (0.841 g, 3.16 mmol, 80%). νₘₕₐₓ(neat)/cm⁻¹: 3289, 3090, 3066, 3035, 2127, 1748, 1650. NMR δH (400 MHz, CDCl₃): 7.57-7.24 (10H, m), 6.31 (1H, d, J = 2.0 Hz), 5.21 (1H, d, J = 11.6 Hz), 5.18 (1H, d, J = 11.6 Hz), 2.73 (1H, d, J = 2.0 Hz). NMR δC (100 MHz, CDCl₃): 154.2, 135.8, 134.9, 129.4, 128.8, 128.7, 128.4, 128.4, 127.8, 79.6, 76.6, 70.2, 69.5. HRMS, m/z found (289.0829, C₁₇H₁₄O₃Na⁺ requires 289.0835). Data was in agreement with that reported in the literature.
Preparation of (±)-methyl (1-phenylprop-2-yn-1-yl) carbonate

Using the general procedure from 1-phenyl-2-propyn-1-ol (0.270 g, 2.05 mmol), the title compound was isolated by column chromatography (25:1, hexane: ethyl acetate) yielding a colourless liquid (0.331 g, 1.74 mmol, 85%). ν_{max}(neat) / cm^{-1}: 3303, 3036, 2255, 1747, 1322, 1257. NMR δ_H (400 MHz, CDCl₃): 7.55-7.53 (2H, m), 7.40-7.36 (3H, m), 6.28 (1H, d, J = 2.0 Hz), 3.80 (3H, s), 2.71 (1H, d, J = 2.4 Hz). NMR δ_C (100 MHz, CDCl₃): 154.9, 135.8, 129.4, 128.8, 127.7, 79.6, 76.7, 76.5, 55.2. HRMS, m/z found (191.0701, C_{11}H_{11}O_{3}^{+} requires 191.0703). Data was in agreement with that reported in the literature.
Preparation of (±)-methyl oct-1-yn-3-yl carbonate\textsuperscript{104}

\begin{center}
\includegraphics[width=0.2\textwidth]{180}
\end{center}

(180)

Followed general procedure from oct-1-yn-3-ol 179 (0.352 g, 2.79 mmol), the title compound was isolated by column chromatography (25:1, hexane: ethyl acetate) yielding a colourless liquid (0.418 g, 2.46 mmol, 88\%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3295, 2957, 2937, 2862, 2124, 1752, 1443. NMR $\delta$\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 5.18 (1H, td, J = 4.8 Hz and 2.4 Hz), 3.79 (3H, s), 2.50 (1H, d, J = 2.4 Hz), 1.83-1.77 (2H, m), 1.55-1.27 (6H, m), 0.88 (3H, t, J = 6.8 Hz). NMR $\delta$\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 155.5, 80.6, 77.4, 76.2, 55.05, 34.6, 31.2, 24.5, 22.5, 14.02. HRMS, $m/z$ found (185.1171, C\textsubscript{10}H\textsubscript{17}O\textsubscript{3} requires 185.1172). Data was in agreement with that reported in the literature.
Preparation of methyl 2,4-dimethyl-5-phenylfuran-3-carboxylate\textsuperscript{56}

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(174)

To a stirred solution of methyl (1-phenylprop-2-yn-1-yl) carbonate 176 (0.474 g, 1.78 mmol) in THF (10 mL) were added methyl acetoacetate (0.196 g, 1.69 mmol), Pd\(_2\)(dba)\(_3\)⋅CHCl\(_3\) (0.087 g, 0.084 mmol) and DPPE (0.067 g, 0.17 mmol) at room temperature, and stirring was continued for 3 h at 50 °C under argon atmosphere. The reaction mixture was then added 1M HCl (2 mL), and further stirring was continued for 2 h at room temperature. After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel (9:1, light petroleum: ethyl acetate) to give the title compound a yellow oil (0.341 g, 1.44 mmol, 85\%). \( \nu_{\text{max}} \) (neat) / cm\(^{-1}\): 2955, 1740, 1441. NMR \( \delta \)\(_{\text{H}}\) (400 MHz, CDCl\(_3\)): 7.58-7.56 (2H, m), 7.42-7.24 (3H, m), 3.84 (3H, s), 2.59 (3H, s), 2.38 (3H, s). NMR \( \delta \)\(_{\text{C}}\) (100 MHz, CDCl\(_3\)): 165.3, 158.3, 147.8, 131.0, 128.5, 128.4, 127.2, 126.1, 116.9, 115.2, 51.1, 14.5, 10.9. HRMS, \( m/z \) found (231.1014, C\(_{14}\)H\(_{15}\)O\(_3\)\(^+\) requires 231.1016). Data was in agreement with that reported in the literature.
Preparation of 1-(2,4-dimethyl-5-phenylfuran-3-yl)ethan-1-one\textsuperscript{56}

![Chemical Structure](image)

(178)

Starting from propargylic carbonate \textbf{176} (0.074 g, 0.28 mmol) and acetylacetone (0.028 g, 0.28 mmol) in THF (2 mL), the above procedure led to the title compound as a yellow oil (0.049 g, 0.23 mmol, 81%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3058, 2962, 1955, 1666, 1072, 765.

NMR $\delta_H$ (400 MHz, CDCl$_3$): 7.60-7.54 (2H, m), 7.43-7.27 (3H, m), 2.61 (3H, s), 2.47 (3H, s), 2.38 (3H, s). NMR $\delta_C$ (100 MHz, CDCl$_3$): 195.2, 157.3, 148.0, 130.7, 129.0, 128.6, 127.4, 124.5, 116.2, 31.1, 15.4, 11.5. HRMS, $m/z$ found (215.1063, C$_{14}$H$_{15}$O$_2$$^+$ requires 215.1067). Data was in agreement with that reported in the literature.
Preparation of methyl 2,4-dimethyl-5-pentylfuran-3-carboxylate

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\[ \text{O} \]

(181)

Followed general procedure of from methyl oct-1-yn-3-yl carbonate 180 (0.10 g, 0.54 mmol) and methyl acetoacetate (0.063 g, 0.54 mmol), the title compound was isolated by column chromatography (19:1, hexane: ethyl acetate) yielding a pale yellow oil (0.098 g, 0.44 mmol, 81%). \( \nu_{\text{max}} \) (neat) /cm\(^{-1}\): 2954, 2859, 1749, 1583, 1090. NMR \( \delta_H \) (400 MHz, CDCl\(_3\)): 3.78 (3H, s), 2.48 (2H, t, J = 8.0 Hz), 2.04 (3H, s), 1.56-1.52 (2H, m), 1.29-1.23 (4H, m), 0.86 (3H, t, J = 7.2 Hz). NMR \( \delta_C \) (100 MHz, CDCl\(_3\)): 165.8, 157.5, 150.1, 114.4, 113.8, 51.0, 31.3, 28.2, 25.5, 22.4, 14.3, 14.1, 9.9. HRMS, m/z found (225.1484, C\(_{13}\)H\(_{21}\)O\(_3\)\(^+\) requires 225.1485).
Preparation of ethyl 4-methyl-5-pentyl-2-propylfuran-3-carboxylate

Followed general procedure from methyl oct-1-yn-3-yl carbonate 180 (0.092 g, 0.50 mmol) and ethyl 3-oxohexanoate 182 (0.079 g, 0.50 mmol), the title compound was isolated by column chromatography (19:1, hexane: ethyl acetate) yielding a pale yellow oil (0.116 g, 0.435 mmol, 87%). $\nu_{\text{max}}$(neat)/cm$^{-1}$: 2960, 2862, 1712, 1576, 1080. NMR $\delta_H$ (400 MHz, CDCl$_3$): 4.24 (2H, q, $J = 7.2$ Hz), 2.86 (2H, t, $J = 7.6$ Hz), 2.48 (2H, t, $J = 7.6$ Hz), 2.04 (3H, s), 1.65-1.63 (2H, m), 1.60-1.54 (2H, m), 1.31 (3H, t, $J = 7.2$ Hz), 1.30-1.25 (4H, m), 0.92 (3H, t, $J = 7.2$ Hz), 0.85 (3H, t, $J = 7.2$ Hz). NMR $\delta_C$ (100 MHz, CDCl$_3$): 165.1, 161.2, 150.0, 114.3, 113.3, 59.6, 31.2, 30.6, 28.2, 25.5, 22.4, 21.7, 14.3, 14.0, 13.8, 9.9. HRMS, $m/z$ found (267.1952, C$_{16}$H$_{27}$O$_3$ requires 267.1955).
Hexanoyl chloride (1.6 g, 12 mmol) was added dropwise to a solution of Meldrum’s acid (1.4 g, 10 mmol) and pyridine (1.6 mL, 20 mmol) in dichloromethane (20 mL) at 0 °C. The mixture was then allowed to warm to room temperature and left stirring for 1 h. The mixture was washed with 1 M HCl, followed by H2O (20 mL). The organic extract was dried over MgSO4, filtered, and the solvent removed by evaporation under reduced pressure. The residue was refluxed in methanol (30 mL) under nitrogen for 2 h. The solution was cooled to room temperature and the solvent removed under reduced pressure to give the crude product as a brown oil. The title compound was isolated by column chromatography (9:1, light petroleum: ethyl acetate) yielding a colourless liquid (1.60 g, 9.32 mmol, 93%). $\nu_{\text{max}}$ (neat) /cm$^{-1}$: 2956, 2933, 1748, 1716, 1651, 1241. NMR $\delta_H$ (400 MHz, CDCl3): 3.76 (3H, s), 3.47 (2H, s), 2.55 (2H, t, $J = 7.2$ Hz), 1.65-1.57 (2H, m), 1.36-1.25 (4H, m), 0.91 (3H, t, $J = 7.2$ Hz). NMR $\delta_C$ (100 MHz, CDCl3): 202.9, 167.7, 52.3, 49.0, 43.0, 31.1, 23.1, 22.4, 13.9. HRMS, $m/z$ found (173.1175, C$_9$H$_{17}$O$_3^+$ requires 173.1172; 195.0989, C$_9$H$_{16}$O$_3$Na$^+$ requires 195.0992). Data was in agreement with that reported in the literature.
8.2.3 Initial Synthetic Route to F-acids F₄ and F₆ (Chapter 6.2)

**Preparation of oxacyclotridecan-2-one**

![Diagram of oxacyclotridecan-2-one](image)

Cyclododecanone (3.30 g, 16.5 mmol), trifluoroacetic acid (1.39 mL) and m-CPBA (7.67 g, 44.0 mmol) were mixed in dichloromethane (38 mL). The suspension was heated under reflux in the dark for 72 h. After cooling to room temperature, a saturated solution of Na₂CO₃ (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine, dried over MgSO₄ and concentrated in vacuo to give the crude product as light yellow oil. The residue was purified via column chromatography (19:1, light petroleum: ethyl acetate) to afford the lactone 195 as a colourless oil (2.774 g, 14.01 mmol, 85%). ν\text{max}\,(\text{neat}) /\text{cm}^{-1}: 2931, 2862, 2677, 1735, 1458. NMR δ \text{H} (400 MHz, CDCl₃): 4.19-4.16 (2H, m), 2.39-2.36 (2H, m), 1.73-1.65 (4H, m), 1.47-1.44 (2H, m), 1.36-1.33 (12H, m). NMR δ \text{C} (100 MHz, CDCl₃): 174.2, 64.6, 34.7, 27.4, 26.6, 26.4, 26.3, 25.3, 24.9, 24.59, 24.52, 24.1. HRMS, m/z found (199.1692, C₁₂H₂₃O₂⁺ requires 199.1693). Data was in agreement with that reported in the literature.⁹⁵
Preparation of 12-hydroxydodecanal\textsuperscript{105}

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\begin{align*}
\text{O} & \quad \text{H} \\
& \quad \text{OH}
\end{align*}
\]

(194)

Diisobutylaluminium hydride (2.24 mL, 2.24 mmol, 1 M solution in THF) was added dropwise to a solution of the lactone \textbf{195} (0.400 g, 2.02 mmol) in dichloromethane (10 mL) at -78 °C. After stirring at -78 °C for 2 h, methanol (2.8 mL) was added and the mixture poured into 0.5 M HCl (50 mL). After stirring at room temperature for a further 1 h, the organic phase was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organics were washed with brine, dried over MgSO\textsubscript{4} and evaporated. The crude material was purified by column chromatography (3:2, dichloromethane: ethyl acetate) to afford the title compound as a white solid (0.332 mg, 1.66 mmol, 82\%). mp: 76-79 °C. \nu_{\text{max}}^{\text{neat}}/\text{cm}^{-1}: 3425, 3155, 2924, 1797, 1465. NMR \delta_{H} (400 MHz, CDCl\textsubscript{3}): 9.78 (1H, t, J = 2.0 Hz), 3.66 (2H, t, J = 6.8 Hz), 2.46-2.42 (2H, m), 1.68-1.58 (4H, m), 1.55-1.53 (2H, m), 1.50-1.30 (12H, m). NMR \delta_{C} (100 MHz, CDCl\textsubscript{3}): 203.1, 63.1, 43.3, 32.8, 29.5, 29.48, 29.41, 29.3, 29.1, 25.7, 23.2, 22.0. HRMS, \textit{m/z} found (201.1848, C\textsubscript{12}H\textsubscript{25}O\textsubscript{2} \textsuperscript{+} requires 201.1849). Data was in agreement with that reported in the literature.\textsuperscript{105}
Preparation of 12-((tert-butyldiphenylsilyl)oxy)dodecanal

A cooled (0 °C) solution of 12-hydroxydodecanal (1.8 g, 9.0 mmol), TBDPSCl (3.70 g, 13.5 mmol) and imidazole (1.84 g, 27.0 mmol) in dichloromethane (27 mL) was stirred for 16 h. Water (15 mL) was added to the mixture, which was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine, dried over MgSO\(_4\) and concentrated in vacuo giving a residue as a brown oil. The title compound was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding a yellow liquid (3.71 g, 8.46 mmol, 94%). \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3070, 2931, 2854, 2708, 1712, 1589. NMR \(\delta_H\) (400 MHz, CDCl\(_3\)): 9.78 (1H, t, J = 2.0 Hz), 7.70-7.68 (4H, m), 7.44-7.37 (6H, m), 3.67 (2H, t, J = 6.4 Hz), 2.39-2.35 (2H, m), 1.65-1.55 (4H, m), 1.36-1.27 (14H, m), 1.06 (9H, s). NMR \(\delta_C\) (100 MHz, CDCl\(_3\)): 203.1, 135.6, 134.1, 129.4, 127.8, 64.0, 43.9, 33.8, 32.5, 29.58, 29.52, 29.4, 29.3, 29.3, 29.1, 29.0, 26.8, 25.7. HRMS, \(m/z\) found (439.3021, C\(_{28}\)H\(_{43}\)O\(_2\)Si\(^+\) requires 439.3027).
Preparation of $(\pm)$-14-((tert-butyldiphenylsilyl)oxy)tetrade-1-yn-3-ol

![OTBDPS](https://via.placeholder.com/150)

Ethynylmagnesium bromide (3.6 mL, 1.8 mmol, 0.5 M in THF) was added to a solution of aldehyde 197 (0.610 g, 1.39 mmol) in THF (3 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 3 h. After addition of saturated aq. NH$_4$Cl (10 mL), the organic phrase was separated and the aqueous phrase was washed with diethyl ether (3 × 10 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and the solvent removed under reduced pressure. The residue was then purified via column chromatography (15:1, light petroleum: ethyl acetate) yielding the title compound as a colourless oil (0.561 g, 1.15 mmol, 83%). $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3402, 3302, 2931, 2252, 1103. NMR $\delta_H$ (400 MHz, CDCl$_3$): 7.68-7.67 (4H, m), 7.46-7.37 (6H, m), 4.39 (1H, td, $J = 2$ Hz and 6.4 Hz), 3.67 (2H, t, $J = 6.4$ Hz), 2.48 (1H, s), 1.77-1.70 (2H, m), 1.61-1.54 (4H, m), 1.36-1.27 (14H, m), 1.06 (9H, s). NMR $\delta_C$ (100 MHz, CDCl$_3$): 135.6, 134.2, 129.4, 127.5, 85.0, 72.8, 64.0, 62.3, 37.6, 32.6, 29.6, 29.58, 29.55, 29.54, 29.3, 29.2, 26.8, 25.7, 25.0, 19.2. HRMS, $m/z$ found (465.3177, $C_{30}H_{45}O_2Si^+$ requires 465.3183; 487.2994, $C_{30}H_{44}O_2SiNa^+$ requires 487.3003).
Preparation of (±)-14-((tert-butyldiphenylsilyl)oxy)tetradec-1-yn-3-yl methyl carbonate

Methyl chloroformate (0.305 g, 3.23 mmol) was added to a cooled (0 °C) solution of propargylic alcohol 198 (0.500 g, 1.08 mmol) and pyridine (0.8 mL, 8 mmol) in dichloromethane (13 mL). The reaction was allowed to stir at the same temperature for 3 h. The reaction mixture was diluted with saturated aq NH₄Cl (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organics were washed with brine (50 mL), dried over MgSO₄ and the solvent removed by reduced pressure. The title compound was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding a colourless liquid (0.464 g, 0.889 mmol, 81%). ν<sub>max</sub>(neat)/cm⁻¹: 2931, 2854, 2252, 1751, 1273. NMR δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 7.71-7.68 (4H, m), 7.46-7.37 (6H, m), 5.22 (1H, td, J = 2 Hz and 6.8 Hz), 3.83 (3H, s), 3.67 (2H, t, J = 6.4 Hz), 2.53 (1H, s), 1.87-1.81 (2H, m), 1.61-1.47 (4H, m), 1.36-1.27 (14H, m), 1.07 (9H, s). NMR δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 155.0, 135.6, 134.2, 129.4, 127.5, 80.6, 74.4, 67.9, 64.0, 55.0, 34.6, 32.6, 29.6, 29.56, 29.51, 29.4, 29.3, 29.0, 26.8, 25.7, 24.7, 19.2. HRMS, m/z found (523.3232, C₃₂H₄₇O₂Si<sup>+</sup> requires 523.3238; 545.3049, C₃₂H₄₆O₂SiNa<sup>+</sup> requires 545.3058).
Preparation of methyl 5-(11-((tert-butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-pentylfuran-3-carboxylate

Following general procedure for the synthesis of tetrasubstituted furans above, from β-keto 188 (0.080 g, 0.47 mmol) and propargylic carbonate 199 (0.238 g, 0.455 mmol) was obtained the title compound by column chromatography (20:1, light petroleum: ethyl acetate) as a yellow oil (0.217 g, 0.350 mmol, 77%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3071, 3049, 2924, 2854, 1715, 1576. NMR $\delta$H (400 MHz, CDCl$_3$): 7.72-7.68 (4H, m), 7.46-7.35 (6H, m), 3.89 (3H, s), 3.66 (2H, t, J = 6.4 Hz), 2.91 (2H, t, J = 6.4 Hz), 2.52 (2H, t, J = 7.6 Hz), 2.07 (3H, s), 1.66-1.53 (6H, m), 1.40-1.27 (18H, m), 1.06 (9H, s), 0.95 (3H, t, J = 6.0 Hz). NMR $\delta$C (100 MHz, CDCl$_3$): 161.6, 150.0, 135.5, 134.1, 129.4, 127.5, 114.2, 64.0, 50.8, 32.6, 31.4, 29.62, 29.60, 29.3, 29.0, 28.5, 27.99, 27.90, 26.8, 25.7, 25.5, 22.3, 19.2, 14.0, 9.9. HRMS, m/z found (641.3985, C$_{39}$H$_{58}$O$_4$SiNa$^+$ requires 641.3997).
Preparation of (5-(11-((tert-butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-
pentylfuran-3-yl)methanol

(201)

To a cooled (0 °C) solution of ester 200 (0.544 g, 0.880 mmol) in THF (3.5 mL) was added LiAlH₄ (1.76 mL, 1.76 mmol, 1 M in THF). After being stirring at the same temperature for 2h, the reaction was quenched by the carefully addition of methanol (0.5 mL) and water (0.5 mL). After 30 min at room temperature, the reaction mixture was then poured into diethyl ether (10 mL), dried over MgSO₄ and filtered. The unfiltered residue was extracted with diethyl ether (4 × 5 mL) and all extracts were combined and evaporated under reduced pressure. The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate) yielding a colourless liquid (0.478 g, 0.810 mmol, 92%). NMR δ_H (400 MHz, CDCl₃): 7.74-7.71 (4H, m), 7.47-7.39 (6H, m), 4.45 (2H, s), 3.70 (2H, t, J = 6.4 Hz), 2.61 (2H, t, J = 7.2 Hz), 2.54 (2H, t, J = 7.2 Hz), 1.99 (3H, s), 1.67-1.55 (6H, m), 1.40-1.27 (18H, m), 1.09 (9H, s), 0.93 (3H, t, J = 7.2 Hz). NMR δ_C (100 MHz, CDCl₃): 151.2, 149.5, 135.6, 134.2, 129.5, 127.5, 119.1, 113.6, 64.0, 55.4, 32.6, 31.4, 29.65, 29.64, 29.46, 29.42, 29.2, 28.75, 28.70, 26.9, 26.0, 25.9, 25.8, 22.4, 19.2, 14.0, 8.1. HRMS, m/z found (591.4221, C₃₈H₅₉O₃Si⁺ requires 591.4228)
Preparation of tert-butyl((11-(3,4-dimethyl-5-pentylfuran-2-yl)undecyl)oxy)diphenylsilane

To a stirred, cooled (0 °C) solution of alcohol 201 (0.04 g, 0.07 mmol), TEA (0.021 g, 0.21 mmol) and DMAP (0.002 g, 0.02 mmol) in dichloromethane (2 mL) was added 4-toluenesulfonyl chloride (0.027 g, 0.14 mmol). The reaction mixture was stirred at 0 °C for 24 h. Water (4 mL) was added, and then the organic phrase was washed with saturated aq. NaHCO₃ (4 mL) followed by brine. The organic phrase was collected and dried over MgSO₄, and the solvent evaporated under reduced pressure. The residue was dissolved in THF (3.5 mL), and then a solution of LiAlH₄ (0.2 mL, 0.2 mmol, 1 M in THF) was added dropwise at 0 °C. After being stirring at the same temperature for 2 h, the reaction was quenched by the careful addition of methanol (0.5 mL) and water (0.5 mL). After 30 min at room temperature, the reaction mixture was then poured into diethyl ether (5 mL), dried over MgSO₄ and filtered. The solid residue was extracted with diethyl ether (4 × 5 mL) and all extracts were combined and evaporated under reduced pressure. The title compound was isolated by column chromatography (90:1, light petroleum: ethyl acetate) yielding a colourless oil (0.012 g, 0.021 mmol, 30%).

NMR δH (400 MHz, CDCl₃): 7.69-7.68 (4H, m), 7.44-7.28 (6H, m), 3.67 (2H, t, J = 6.4 Hz), 2.51 (4H, t, J = 7.2 Hz), 1.86 (6H, s), 1.62-1.54 (6H, m), 1.40-1.27 (18H, m), 1.07
(9H, s), 0.91 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl₃): 148.44, 148.42, 135.7, 134.2, 129.4, 127.8, 114.4, 64.0, 32.6, 31.9, 29.6, 29.5, 29.46, 29.40, 29.2, 28.9, 28.8, 26.8, 26.8, 26.1, 26.0, 25.7, 22.4, 19.2, 14.1, 8.39, 8.38. HRMS, m/z found (575.4286, C₃₈H₅₉O₂Si⁺ requires 575.4284).
Preparation of 11-(3,4-dimethyl-5-pentylfuran-2-yl)undecan-1-ol

To a stirred, cooled (0 °C) solution of the furan 203 (0.030 g, 0.058 mmol) in THF (1.2 mL) was added TBAF (0.12 mL, 0.12 mmol, 1 M in THF). After stirring at room temperature for 3 h, the solvent was evaporated and the residue was taken up in diethyl ether and H₂O (1:1, 5 mL). The organic layer was separated and the aqueous layer was washed with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent evaporated under reduced pressure. The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate) yielding a colourless oil (0.019 g, 0.055 mmol, 95%). NMR δH (400 MHz, CDCl₃): 3.66 (2H, t, J = 6.8 Hz), 2.50 (4H, t, J = 7.2 Hz), 1.80 (6H, s), 1.61-1.54 (6H, m), 1.39-1.28 (18H, m), 0.90 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl₃): 148.4, 114.4, 63.1, 32.8, 31.4, 29.7, 29.5, 29.4, 29.2, 28.8, 28.5, 26.09, 26.07, 25.7, 22.4, 14.1, 8.38, 8.37. HRMS, m/z found (337.3107, C₂₂H₄₁O₂⁺ requires 337.3101). Data was in agreement with that reported in the literature.
Preparation of ethyl 5-(11-((tert-butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-propylfuran-3-carboxylate

Following general procedure for the synthesis of tetrasubstituted furans above, from ethyl 3-oxohexanoate (0.041 g, 0.26 mmol) and propargylic carbonate 199 (0.133 g, 0.254 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as yellow oil (0.142 g, 0.236 mmol, 93%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3050, 2958, 2855, 1712, 1576. NMR $\delta$H (400 MHz, CDCl$_3$): 7.68-7.64 (4H, m), 7.43-7.35 (6H, m), 4.26 (2H, q, J = 7.2 Hz), 3.65 (2H, t, J = 6.4 Hz), 2.88 (2H, t, J = 8.0 Hz), 2.50 (2H, t, J = 7.2 Hz), 2.07 (3H, s), 1.70-1.60 (2H, m), 1.57-1.53 (4H, m), 1.33 (3H, t, J = 7.2 Hz), 1.38-1.27 (14H, m), 1.05 (9H, s), 0.93 (3H, t, J = 7.2 Hz). NMR $\delta$C (100 MHz, CDCl$_3$): 165.1, 161.3, 150.1, 135.6, 134.2, 129.5, 127.6, 114.3, 113.4, 64.1, 59.6, 32.6, 30.1, 29.7, 29.6, 29.4, 29.1, 28.5, 26.9, 25.8, 25.5, 21.7, 19.3, 14.2, 13.9, 10.0. HRMS, $m/z$ found (605.4016, C$_{38}$H$_{57}$O$_4$Si$^+$ requires 605.4021; 627.3833, C$_{38}$H$_{56}$O$_4$SiNa$^+$ requires 627.3840).
Preparation of (5-(11-((tert-butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-propylfuran-3-yl)methanol

Following general procedure for the reduction of ester above, from tetrasubstituted furan 204 (0.225 g, 0.371 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as pale yellow oil (0.118 g, 0.195 mmol, 75%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3425, 3070, 2931, 2854, 2214. NMR $\delta_H$ (400 MHz, CDCl$_3$): 7.71-7.69 (4H, m), 7.45-7.39 (6H, m), 4.44 (2H, s), 3.68 (2H, t, $J = 6.4$ Hz), 2.59 (2H, t, $J = 7.2$ Hz), 2.53 (2H, t, $J = 7.2$ Hz), 1.98 (3H, s), 1.65-1.55 (6H, m), 1.38-1.27 (12H, m), 1.08 (9H, s), 0.94 (3H, t, $J = 7.2$ Hz). NMR $\delta_C$ (100 MHz, CDCl$_3$): 151.0, 149.6, 135.6, 134.2, 129.7, 127.5, 119.3, 113.5, 64.0, 55.4, 32.6, 29.7, 29.64, 29.62, 29.43, 29.41, 29.2, 28.6, 28.0, 26.8, 25.9, 25.8, 22.3, 19.2, 13.7, 8.1. HRMS, $m/z$ found (563.3918, C$_{36}$H$_{55}$O$_3$Si$^+$ requires 563.3915).
8.2.4 Second Synthetic Route to F-acids $F_4$ and $F_6$ (Chapter 6.3)

**Preparation of (±)-tridec-12-en-1-yn-3-ol**

(208)

Following general procedure for the preparation of propargylic alcohol above, from 10-undecenal (1.682 g, 10.00 mmol) was obtained the title compound by column chromatography (5:1, light petroleum: ethyl acetate) as a colourless liquid (1.842 g, 9.494 mmol, 95%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3548, 3309, 3077, 2926, 2854, 1640, 1033, 909. NMR $\delta_H$ (400 MHz, CDCl$_3$): 5.83 (1H, ddt, J = 16.8, 10.4 and 6.8 Hz), 5.03-4.96 (2H, m), 4.39 (1H, td, J = 6.4 and 2.0 Hz), 2.49 (3H, s), 2.08-2.03 (2H, m), 1.74-1.68 (2H, m), 1.41-1.24 (10H, m). NMR $\delta_C$ (100 MHz, CDCl$_3$): 139.2, 114.1, 85.0, 72.8, 62.3, 37.6, 33.8, 29.4, 29.3, 29.2, 29.1, 28.9, 25.0. HRMS, $m/z$ found (195.1762, C$_{13}$H$_{22}$O$^+$ requires 195.1743). Data was in agreement with that reported in the literature.
Preparation of (±)-methyl tridec-12-en-1-yn-3-yl carbonate

Following general procedure for the preparation of propargylic carbonate above, from propargylic alcohol 208 (0.676 g, 3.50 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as a pale yellow liquid (0.634 g, 2.76 mmol, 79%). \( \nu_{\text{max}} \) (neat)/cm\(^{-1} \): 3295, 3077, 2927, 2855, 1753, 1640, 1442, 1265, 910. NMR \( \delta_H \) (400 MHz, CDCl\(_3\)): 5.83 (1H, ddt, J = 17.6, 8.0 and 6.8 Hz), 5.21 (1H, td, J = 6.4 and 2.0 Hz), 5.04-4.93 (2H, m), 3.83 (3H, s), 2.53 (1H, s), 2.08-2.03 (2H, m), 1.89-1.77 (2H, m), 1.48-1.41 (2H, m), 1.41-1.24 (10H, m). NMR \( \delta_C \) (100 MHz, CDCl\(_3\)): 155.0, 139.2, 114.1, 80.1, 74.9, 67.9, 54.9, 34.5, 33.8, 29.3, 29.07, 29.03, 28.9, 24.7. HRMS, m/z found (275.1617, C\(_{15}\)H\(_{24}\)O\(_3\)Na\(^+\) requires 275.1618).
Preparation of ethyl 5-(dec-9-en-1-yl)-4-methyl-2-propylfuran-3-carboxylate

Following general procedure for the synthesis of tetrasubstituted furans above, from ethyl 3-oxohexanoate (0.252 g, 1.43 mmol) and propargylic carbonate 207 (0.360 g, 1.43 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as yellow oil (0.383 g, 1.15 mmol, 82%). NMR δH (400 MHz, CDCl3): 5.83 (1H, ddt, J = 17.6, 8.0 and 4.4 Hz), 4.99-4.90 (2H, m), 4.25 (2H, t, J = 7.2 Hz), 2.86 (2H, t, J = 7.2 Hz), 2.48 (2H, t, J = 7.2 Hz), 2.48 (2H, t, J = 7.2 Hz), 2.04 (3H, s), 2.04-2.01 (2H, m), 1.67-1.52 (2H, m), 1.40-1.22 (13H, m), 0.91 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl3): 165.1, 161.3, 150.0, 139.3, 114.3, 114.1, 59.6, 33.8, 30.8, 29.4, 29.3, 29.1, 29.0, 28.9, 28.5, 25.5, 21.7, 14.4, 13.8, 9.9. HRMS, m/z found (335.2587, C21H35O3+ requires 335.2581).
Preparation of (5-(dec-9-en-1-yl)-4-methyl-2-propylfuran-3-yl)methanol

Following general procedure for the reduction of ester above, from tetrastubstituted furan 210 (0.740 g, 2.22 mmol) was obtained the title compound by column chromatography (8:1, light petroleum: ethyl acetate) as pale yellow oil (0.584 g, 1.86 mmol, 84%). NMR δH (400 MHz, CDCl3): 5.83 (1H, ddt, J = 17.6, 8.0 and 4.4 Hz), 5.04-4.93 (2H, m), 4.43 (2H, s), 2.57 (2H, t, J = 7.2 Hz), 2.51 (2H, t, J = 7.2 Hz), 2.06 (2H, t, J = 7.2 Hz), 1.97 (3H, s), 1.68-1.58 (4H, m), 1.37-1.26 (10H, m), 0.94 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl3): 151.0, 149.6, 139.2, 119.3, 114.1, 113.5, 55.9, 33.8, 29.4, 29.3, 29.2, 29.1, 28.9, 28.6, 28.0, 25.9, 22.3, 13.7, 8.1. HRMS, m/z found (315.2289, C19H33O2+ requires 315.2295).
Preparation of 2-(dec-9-en-1-yl)-3,4-dimethyl-5-propylfuran

To a stirred, cooled (0 ℃) solution of furan alcohol 211 (0.505 g, 1.73 mmol), recrystallized triphenylphosphine (0.590 g, 2.249 mmol), and imidazole (0.153 g, 2.246 mmol) in acetonitrile and diethyl ether (1:1.6, 3.6 mL) was slowly added iodine (0.609 g, 2.422 mmol) resulting a yellow suspension. After stirring at the same temperature for 1 h, the reaction mixture was diluted with diethyl ether (5 mL) and sequentially washed with saturated aqueous Na$_2$S$_2$O$_3$, saturated aqueous CuSO$_4$, and H$_2$O. The organic layer was dried over MgSO$_4$, filtered, and concentrated to afford the crude product as a brown oil. The residue was taken up in THF (3.5 mL) and treated with LiAlH$_4$ (3.5 ml, 3.5 mmol, 1 M in THF) at 0 ℃ for 4 h. The reaction was quenched by the carefully addition of methanol (1 mL) and water (1 mL). After 1 h at room temperature, the reaction mixture was then poured into diethyl ether (20 mL), dried over MgSO$_4$ and filtered. The unfiltered residue was extracted with diethyl ether (4 × 10 mL) and all extracts were combined and evaporated under reduced pressure. The title compound was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding a colourless liquid (0.406 g, 1.47 mmol, 85%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3077, 2926, 2855, 1641, 1455, 1380. NMR $\delta$H (400 MHz, CDCl$_3$): 5.80 (1H, ddt, J = 17.6, 8.0 and 4.4 Hz), 5.00-4.89 (2H, m), 2.48-2.43 (4H, m), 2.04-1.99 (2H, m), 1.81 (6H, s),
1.61-1.51 (4H, m), 1.37-1.26 (10H, m), 0.89 (3H, t, J = 7.2 Hz). NMR δC (100 MHz, CDCl₃): 148.5, 148.3, 139.3, 114.7, 114.5, 114.1, 33.8, 29.5, 29.4, 29.2, 29.1, 29.0, 28.8, 28.1, 26.1, 22.2, 13.8, 8.4. HRMS, m/z found (276.2403, C_{19}H_{32}O requires 276.2448).
Hoveyda-Grubbs Catalyst 2\textsuperscript{nd} (0.04 g, 0.05 mmol) was added to a stirred solution of furan 212 (0.260 g, 0.942 mmol) in dichloromethane (15 mL). Benzyl acrylate (0.210 g, 1.30 mmol) was added and the solution refluxed under argon for 3 h. The solution was filtered through a plug of silica and the solvent evaporated to yield a brown oil. The residue was taken up in methanol (10 mL) and treated with 10% palladium on carbon (0.150 g). The reaction was stirred under an atmosphere of hydrogen for 2 h then the catalyst removed by filtration. The solvent was removed under reduced pressure. The title compound was isolated by column chromatography (8:1, 4:1, 2:1, 1:1, light petroleum: ethyl acetate) yielding a colourless oil (0.272 g, 0.848 mmol, 90%).

$\nu_{\text{max}}$ (neat) /cm$^{-1}$: 3583, 3400, 2927, 2855, 2087, 1709, 1651. NMR $\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 2.52-2.47 (4H, m), 2.37 (2H, t, J = 7.6 Hz), 1.85 (6H, s), 1.69-1.55 (6H, m), 1.41-1.23 (12H, m), 0.98 (3H, t, J = 6.8 Hz). NMR $\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 179.9, 148.4, 148.2, 114.6, 114.4, 34.0, 30.3, 29.5, 29.4, 29.3, 29.25, 29.24, 29.0, 28.8, 28.1, 26.0, 24.6, 22.1, 13.8, 8.3. HRMS, $m/z$ found (323.2582, C$_{20}$H$_{35}$O$_3$\textsuperscript{+} requires 323.2581). Data was in agreement with that reported in the literature.}\textsuperscript{27}
Preparation of methyl 5-(dec-9-en-1-yl)-4-methyl-2-pentylfuran-3-carboxylate

Following general procedure for the synthesis of tetrasubstituted furans above, from β-keto 188 (0.265 g, 1.54 mmol) and propargylic carbonate 207 (0.581 g, 2.32 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as yellow oil (0.480 g, 1.38 mmol, 89%). NMR δ_H (400 MHz, CDCl₃): 5.83 (1H, ddt, J = 17.6 Hz, 8.0 Hz and 4.4 Hz), 5.32-4.93 (2H, m), 3.82 (3H, s), 2.91 (2H, t, J = 7.2 Hz), 2.52 (2H, t, J = 7.2 Hz), 2.07 (3H, s), 2.06-2.02 (2H, m), 1.68-1.55 (4H, m), 1.49-1.20 (14H, m), 0.89 (3H, t, J = 7.2 Hz). NMR δ_C (100 MHz, CDCl₃): 165.6, 161.6, 150.1, 139.3, 114.2, 114.1, 113.0, 50.9, 33.8, 31.4, 29.4, 29.3, 29.1, 29.0, 28.9, 28.5, 28.0, 27.9, 25.5, 22.4, 14.0, 8.9. HRMS, m/z found (349.2738, C_{22}H_{37}O_{3}^+) requires 349.2737).
Preparation of (5-(dec-9-en-1-yl)-4-methyl-2-pentylfuran-3-yl)methanol

(209)

Following general procedure for the reduction of ester above, from tetrasubstituted furan 206 (0.452 g, 1.29 mmol) was obtained the title compound by column chromatography (9:1, light petroleum: ethyl acetate) as colourless oil (0.347 g, 1.08 mmol, 84%). ν<sub>max</sub>(neat)/cm<sup>-1</sup>: 3325, 3073, 2925, 1641, 1465, 993. NMR δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 5.83 (1H, ddt, J = 17.6 Hz, 8.0 Hz and 4.4 Hz), 4.99-4.90 (2H, m), 4.33 (2H, s), 2.54 (2H, t, J = 7.2 Hz), 2.47 (2H, t, J = 7.2 Hz), 2.01 (2H, t, J = 7.2 Hz), 1.97 (3H, s), 1.57-1.55 (4H, m), 1.49-1.20 (14H, m), 0.87 (3H, t, J = 7.2 Hz). NMR δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 151.3, 149.6, 139.3, 119.2, 114.1, 113.6, 55.5, 33.8, 31.4, 29.5, 29.4, 29.2, 29.1, 28.9, 28.79, 28.71, 26.1, 25.9, 22.4, 14.0, 8.2. HRMS, m/z found (343.2606, C<sub>21</sub>H<sub>36</sub>O<sub>2</sub>Na<sup>+</sup> requires 343.2608).
Preparation of 2-(dec-9-en-1-yl)-3,4-dimethyl-5-pentylfuran$^{69}$

Following general procedure for the preparation of dimethyl furans above, from furan 209 (0.452 g, 1.292 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as colourless oil (0.328 g, 1.08 mmol, 84%).

$\nu_{\text{max}}$(neat)/cm$^{-1}$: 3033, 2928, 2856, 1654, 1428. NMR $\delta_H$ (400 MHz, CDCl$_3$): 5.82 (1H, ddt, J = 17.6 Hz, 8.0 Hz and 4.4 Hz), 4.99-4.89 (2H, m), 2.48-2.44 (4H, m), 2.01 (2H, q, J = 7.2 Hz), 1.97 (3H, s), 1.57-1.55 (4H, m), 1.49-1.20 (14H, m), 0.87 (3H, t, J = 7.2 Hz). NMR $\delta_C$ (100 MHz, CDCl$_3$): 148.49, 148.47, 139.3, 114.5, 114.1, 33.8, 31.5, 29.5, 29.4, 29.37, 29.30, 29.2, 29.0, 28.8, 28.5, 26.1, 22.5, 14.1, 8.4. HRMS, $m/z$ found (305.2836, C$_{21}$H$_{37}$O$^+$ requires 305.2839). Data was in agreement with that reported in the literature.$^{69}$
Preparation of 11-(3,4-dimethyl-5-pentylfuran-2-yl)undecanoic acid

Following general procedure for the preparation of furan fatty acid above, from furan 118 (0.106 g, 0.349 mmol) was obtained the title compound by column chromatography (8:1, 4:1, 2:1, 1:1, light petroleum: ethyl acetate) as colourless oil (0.105 g, 0.300 mmol, 86%). \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3584, 3400, 2926, 2855, 1710, 1456, 1329. NMR \(\delta_H\) (400 MHz, CDCl\(_3\)): 2.52-2.47 (4H, m), 2.37 (2H, t, J = 7.6 Hz), 1.85 (6H, s), 1.69-1.63 (2H, m), 1.58-1.56 (4H, m), 1.36-1.29 (18H, m), 0.90 (3H, t, J = 6.8 Hz). NMR \(\delta_C\) (100 MHz, CDCl\(_3\)): 179.7, 148.43, 148.41, 114.4, 34.2, 31.4, 30.3, 29.5, 29.43, 29.40, 29.25, 29.24, 29.0, 28.8, 28.5, 26.09, 26.07, 24.7, 22.4, 14.0, 8.4, 8.3. HRMS, \(m/z\) found (351.2896, \(\text{C}_{22}\text{H}_{39}\text{O}_3^+\) requires 351.2894). Data was in agreement with that reported in the literature.
8.2.5 Synthesis of F-acids modified analogues (Chapter 6.4)

Preparation of (±)-tetradec-1-yn-3-ol\textsuperscript{106}

Following general procedure for the preparation of propargylic alcohol above, from dodecanal (1.84 g, 10.0 mmol) was obtained the title compound by column chromatography (4:1, light petroleum: ethyl acetate) as colourless liquid (2.317 g, 9.093 mmol, 91\%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3689, 3603, 3302, 3155, 2931, 2677. NMR $\delta_H$ (400 MHz, CDCl$_3$): 4.38-4.32 (1H, m), 2.45 (1H, d, $J = 3.2$ Hz), 1.72-1.65 (2H, m), 1.50-1.40 (2H, m), 1.28-1.24 (16H, m), 0.86 (3H, t, $J = 7.2$Hz). NMR $\delta_C$ (100 MHz, CDCl$_3$): 85.0, 72.9, 62.4, 37.7, 36.9, 29.7, 29.64, 29.60, 29.4, 29.3, 25.0, 22.7, 14.2. HRMS, $m/z$ found (233.1881, C$_{14}$H$_{26}$ONa$^+$ requires 233.1876). Data was in agreement with that reported in the literature.\textsuperscript{106}
Preparation of (±)-methyl tetradec-1-yn-3-yl carbonate

Following general procedure for the preparation of propargylic carbonate above, from propargylic alcohol 216 (1.796 g, 8.323 mmol) was obtained the title compound by column chromatography (19:1, light petroleum: ethyl acetate) as colourless liquid (1.851 g, 6.906 mmol, 83%). \( \nu_{\text{max}}(\text{neat}) / \text{cm}^{-1} \): 3309, 3155, 2924, 2854, 1751, 1273. NMR \( \delta_H \) (400 MHz, CDCl\(_3\)): 5.18 (1H, td, \( J = 6.4 \) and 2 Hz), 3.79 (3H, s), 2.49 (1H, d, \( J = 2.0 \) Hz), 1.81-1.78 (2H, m), 1.50-1.40 (2H, m), 1.28-1.24 (16H, m), 0.86 (3H, t, \( J = 7.2 \) Hz). NMR \( \delta_C \) (100 MHz, CDCl\(_3\)): 155.0, 80.6, 74.4, 68.0, 55.0, 34.6, 31.9, 29.6, 29.6, 29.5, 29.48, 29.42, 29.1, 24.8, 22.7, 14.2. HRMS, \( m/z \) found (269.2110, \( C_{16}H_{28}O_3^+ \) requires 269.2111).
Preparation of ethyl 4-methyl-2-propyl-5-undecylfuran-3-carboxylate

Following general procedure for the synthesis of tetrasubstituted furans above, from ethyl 3-oxohexanoate (0.749 g, 4.74 mmol) and propargylic carbonate 217 (0.847 g, 3.16 mmol) was obtained the title compound by column chromatography (20:1, light petroleum: ethyl acetate) as yellow oil (0.940 g, 2.69 mmol, 85%). \( \nu_{\text{max}}(\text{neat}) /\text{cm}^{-1} \):

3055, 2854, 2685, 1705, 1265. NMR \( \delta_H \) (400 MHz, CDCl\(_3\)): 4.25 (2H, q, J = 7.2 Hz), 2.86 (2H, t, J = 7.6 Hz), 2.48 (2H, t, J = 7.6 Hz), 2.04 (3H, s), 1.69-1.59 (2H, m), 1.56-1.51 (2H, m), 1.32 (3H, t, J = 7.2 Hz), 1.30-1.23 (16H, m), 0.91 (3H, t, J = 7.6 Hz), 0.86 (3H, t, J = 7.6 Hz). NMR \( \delta_C \) (100 MHz, CDCl\(_3\)): 165.1, 161.3, 150.1, 114.3, 113.3, 59.6, 31.9, 30.0, 29.7, 29.6, 29.4, 29.1, 28.5, 25.5, 22.7, 21.7, 14.4, 14.2, 13.8, 9.9. HRMS, \( m/z \) found (351.2893, C\(_{22}\)H\(_{28}\)O\(_3^+\) requires 351.2894).
Preparation of (4-methyl-2-propyl-5-undecylfuran-3-yl)methanol

Following general procedure for the reduction of ester above, from tetrasubstituted furan 218 (0.845 g, 2.414 mmol) was obtained the title compound by column chromatography (10:1, light petroleum: ethyl acetate) as colourless oil (0.595 g, 1.93 mmol, 80%). $\nu_{\text{max}}$(neat) /cm$^{-1}$: 3410, 3155, 2924, 2854, 1465. NMR $\delta$H (400 MHz, CDCl$_3$): 4.40 (2H, s), 2.53 (2H, t, J = 7.6 Hz), 2.47 (2H, t, J = 7.2 Hz), 1.93 (3H, s), 1.62-1.52 (4H, m), 1.30-1.27 (16H, m), 0.89 (3H, t, J = 7.2 Hz), 0.84 (3H, t, J = 7.2 Hz). NMR $\delta$C (100 MHz, CDCl$_3$): 151.1, 149.7, 119.4, 113.6, 55.5, 32.0, 29.7, 29.6, 29.4, 29.3, 28.7, 28.1, 25.9, 22.7, 22.3, 14.2, 13.8, 8.2. HRMS, $m/z$ found (309.2786, C$_{20}$H$_{37}$O$_2$+ requires 309.2788).
Preparation of 3,4-dimethyl-2-propyl-5-undecylfuran

Following general procedure for the preparation of dimethyl furans above, from furan 219 (0.380 g, 1.225 mmol) was obtained the title compound by column chromatography (20:1, light petroleum: ethyl acetate) as colourless oil (0.314 g, 0.992 mmol, 81%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3309, 3155, 2924, 1465. NMR $\delta_H$ (400 MHz, CDCl$_3$): 2.54-2.47 (4H, m), 1.85 (6H, s), 1.69-1.55 (4H, m), 1.30-1.27 (16H, m), 0.94 (3H, t, $J = 7.2$ Hz), 0.85 (3H, t, $J = 7.2$ Hz). NMR $\delta_C$ (100 MHz, CDCl$_3$): 148.4, 148.2, 114.6, 114.4, 31.9, 29.7, 29.67, 29.65, 29.62, 29.4, 29.3, 28.8, 28.0, 26.1, 22.9, 22.1, 14.1, 13.8, 8.3. HRMS, $m/z$ found (293.2853, C$_{20}$H$_{37}$O$^+$ requires 293.2839).
Preparation of (4-methyl-2-pentyl-5-undecylfuran-3-yl)methanol

Following general procedure for the reduction of ester above, from β-keto 188 (0.059 g, 0.341 mmol) and propargylic carbonate 217 (0.092 g, 0.342 mmol) was obtained the title compound by column chromatography (15:1, light petroleum: ethyl acetate) as colourless oil (0.060 g, 0.19 mmol, 55%). $\nu_{\text{max}}$ (neat) /cm$^{-1}$: 3417, 3387, 3305, 3155, 2924, 1465. NMR $\delta$H (400 MHz, CDCl$_3$): 4.43 (2H, s), 2.58 (2H, t, J = 7.2 Hz), 2.51 (2H, t, J = 7.2 Hz), 1.97 (3H, s), 1.62-1.56 (4H, m), 1.33-1.27 (20H, m), 0.92-0.76 (6H, m). NMR $\delta$C (100 MHz, CDCl$_3$): 151.2, 149.5, 119.1, 113.5, 55.5, 31.9, 31.4, 29.68, 29.66, 29.63, 29.4, 29.3, 29.2, 28.7, 28.6, 26.0, 25.9, 22.7, 22.4, 14.1, 14.0, 8.1. HRMS, $m/z$ found (321.3164, C$_{22}$H$_{41}$O$_2^+$ requires 321.3152).
Preparation of 3,4-dimethyl-2-pentyl-5-undecylfuran

Following general procedure for the preparation of dimethyl furans above, from furan 220 (60 mg, 0.19 mmol) was obtained the title compound by column chromatography (25:1, light petroleum: ethyl acetate) as colourless oil (48 mg, 0.152 mmol, 80%).

\[ \text{ν}_{\text{max}}(\text{neat})/\text{cm}^{-1}: 3055, 2931, 2854, 1427. \]

NMR \[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 2.50 (4\text{H}, \text{t, } J = 7.6 \text{ Hz}), 1.85 (6\text{H}, \text{s}), 1.62-1.54 (4\text{H}, \text{m}), 1.33-1.27 (20\text{H}, \text{m}), 0.92-0.88 (6\text{H}, \text{m}). \]

NMR \[ \delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 148.45, 148.43, 114.4, 31.9, 31.4, 29.74, 29.70, 29.6, 29.4, 29.3, 29.2, 28.8, 28.5, 26.1, 26.0, 22.7, 22.5, 14.17, 14.10, 8.4. \]

HRMS, \[ m/z \text{ found 407.3143, } \text{C}_{22}\text{H}_{40}\text{ONa}^+ \text{ requires 407.3132}. \]
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