Loughborough University

A Biosynthetically Inspired Synthetic Route to Substituted Furans, and its Application to the Total Synthesis of the Furan Fatty Acid F_5

A thesis submitted in partial fulfilment of the requirements of the degree Doctor of Philosophy

Robert Jack Lee

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

Thesis Abstract

Dietary fish oil supplementation has long been shown to have significant health benefits, largely stemming from the anti-inflammatory activity of the ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) present in fish oils. The anti-inflammatory properties of these fatty acids has been linked to beneficial health effects, such as protecting the heart, in individuals consuming diets rich in fish, or supplemented with fish oils.[1]

These effects are highly notable in the Māori people native to coastal regions of New Zealand; the significantly lower rates of heart problems compared to the inland populous has been attributed to the consumption of the green lipped mussel *Perna Canaliculus*. Commercially available health supplements based on the New Zealand green lipped mussel include a freeze-dried powder and a lipid extract (Lyprinol®), the latter of which has shown anti-inflammatory properties comparable to classical non-steroidal anti-inflammatory drugs (NSAIDs) such as Naproxen.[2] GCMS analysis of Lyprinol by Murphy *et al.* showed the presence of a class of ω-4 and ω-6 PUFAs bearing a highly electron rich tri- or tetra-alkyl furan ring, which were designated furan fatty acids (F-acids).[3] Due to their instability, isolation of F-acids from natural sources cannot be carried out and a general synthetic route toward this class of natural products was required.

To accomplish this, the biosynthesis of F-acids was mimicked by utilising an oxidation of 1,3-dienes, followed by a dehydration/aromatisation to generate the heterocyclic furan ring. Singlet oxygen was chosen as the means of oxidising the conjugated dienes giving endoperoxides. To mimic the biological aromatisation of the peroxide intermediates the Appel reagent was chosen and, in a novel application of the reagent, was exploited as a mild, metal free method of dehydrating the cyclic peroxides to their corresponding furans.

The biomimetic furan synthesis was applied toward a selection of 1,3-diene substrates bearing a range of pre-installed functionalities and substitution patterns including alkyl, aryl, alkenes, cyclopropyl rings, silyl ethers, and esters, alongside being applied to the total synthesis of the furan fatty acid F_5.

A brief exploration of the possibility of performing the aromatisation reaction under catalytic conditions was carried out, to determine whether endoperoxides could be converted to furans without needing a stoichiometric quantity of Appel reagent, by harnessing a catalytic quantity of triphenylphosphine oxide and regenerating the active P(V) species *via* reaction with oxalyl chloride.

Furthermore, an optimisation study was carried out using a simple design of experiments procedure to ascertain the ideal conditions for carrying out the Appel-type dehydration of endoperoxides.

Finally, the scope of the reaction sequence was expanded to be performed in a continuous flow reactor, with telescoping of the singlet oxygen diene oxidation and Appel-type aromatisation to increase oxidation yields and to omit the requirement for isolation of peroxide intermediates, and was applied to the synthesis of a selection of 2,5-diaryl furan motifs.

Acknowledgements

Firstly, I would like to thank my two fantastic supervisors, Dr Marc Kimber and Dr Gareth Pritchard for giving me the opportunity to work on this project, and for your continued advice, support, and encouragement you've provided over the past years. From undergrad labs and projects, you've constantly been teaching me new skills, tricks of the trade, and making me think and get excited about chemistry, and that's only continued throughout my PhD. Your patience has been unfaltering, and you've both been great supervisors, but also great friends and drinking partners for the past few years (although I'm not sure I'll ever be able to hold my drink like Gaz…or pretend to like Marc!).

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Table of Contents

Abbreviations

AA	Arachidonic acid
BOC	*tert*-Butyloxycarbonyl
br	Broad
BuLi	Butyllithium
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
d	Doublet
DHA	Docosahexaenoic acid
DIBAL-H	Diisobutylaluminium hydride
DIEA	*N,N*-Diisopropylethylamine (Hünig's base)
DMAP	Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DPA	Docosapentaenoic Acid
EPA	Eicosapentaenoic Acid
Eq.	Equivalents
ESI	Electrospray ionisation
F-Acid	Furan fatty acid
FAME	Fatty acid methyl ester
GC-MS	Gas chromatography-mass spectrometry
GI	Gastrointestinal
h	Hours
Hz	Hertz
IR	Infrared
J	Coupling constant
KHMDS	Potassium hexamethyldisilazide (Potassium bis(trimethylsilyl)amide)

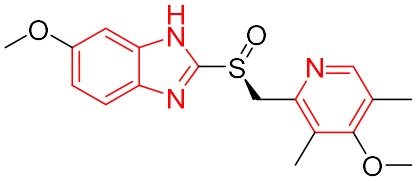
MS	Mass spectrometry
m/z	Mass to charge ratio
NaHMDS	Sodium hexamethyldisilazide (Sodium bis(trimethylsilyl)amide)
NMR	Nuclear magnetic resonance
NSAID	Non-steroidal anti-inflammatory drug
PC	Principal Component
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichoromate
PLA_2	Phospholipase A_2
PUFA	Polyunsaturated fatty acid
q	Quartet
s	Singlet
SPE	Solid Phase Extraction
t	Triplet
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
r.t	Room temperature
UV	Ultraviolet

1. Introduction

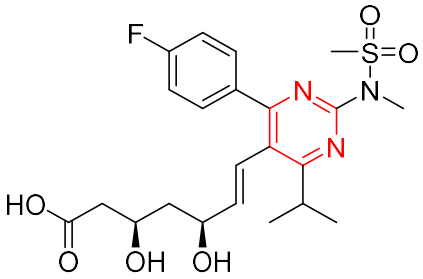
1.1 Heterocyclic Compounds

Heterocycles are a family of compounds which contain a cyclic system bearing one or more non-carbon or hydrogen elements (such as oxygen, nitrogen, or sulfur) in the ring.[4] Heterocyclic compounds have wide variations in ring size, type of heteroatom(s) present, the number of heteroatoms in the ring, and the degree of unsaturation. Fused heterocyclic ring systems are also known, where one or more of the rings contain a heteroatom. Heterocyclic rings are a common feature in a plethora of organic molecules, ranging from natural products to synthetic structures. They are present in almost every aspect of modern life, including pharmaceuticals, agrochemicals, polymers, cosmetics, dyes, electronics, and food additives.[5, 6] As a result, compounds containing heterocyclic units hold the focus of huge research efforts into novel methods for their synthesis; over the past century, heterocyclic chemistry has grown to be one of the largest subdivisions of synthetic organic chemistry.[5]

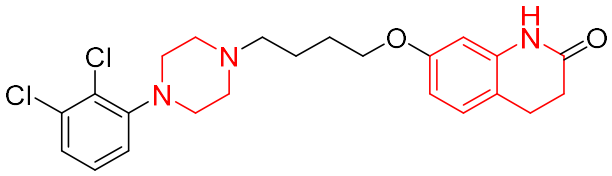
Many heterocyclic compounds possess interesting biological properties, a feature which owes to the unique geometric properties of the cyclic systems and the electron distributions which are influenced by the presence of heteroatoms.[5] These features allow for the effective binding of heterocyclic molecules to biological targets such as ligand receptors and enzymes, making them highly attractive candidates for drug molecules. This is perhaps best expressed in the sales of pharmaceuticals, in which eight of the ten highest selling small molecule drugs in 2013 contained one or more heterocyclic components, netting over $33 billion in sales.[7]



Esomeprazole (Proton Pump Inhibitor) (1)



Rosuvastatin (Statin) (2)



Aripiprazole (Antipsychotic) (3)

Figure 1. The three highest selling small molecule drugs in 2013, with heterocyclic components highlighted in red.[7]

Heterocyclic compounds may be divided into two general classes; those that exhibit aromaticity, and those that do not. Non-aromatic heterocycles typically exhibit chemical properties similar to their acyclic analogues, although it should be noted that physical properties such as melting point, boiling point, and density may differ significantly. Three- and four-membered non-aromatic heterocyclic rings show chemical properties unlike acyclic analogues, however, this can be attributed to the high degree of ring strain, and the thermodynamic drive to become lower in energy.[8] Such properties are not representative of the majority of non-aromatic heterocyclic compounds. An example of the chemical similarities between conventional non-aromatic heterocycles and their acyclic counterparts are pyrrolidine and diethylamine **(Table 1).** Both compounds contain the same numbers of non-hydrogen atoms and their basicities, arguably the primary chemical property of such compounds, are remarkably similar.

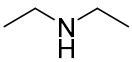
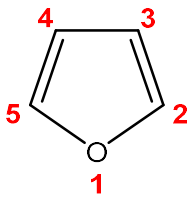
Name	**Pyrrolidine**	**Diethylamine**
Structure	 **(4)**	 **(5)**
Formula	C_4H_9N	$C_4H_{11}N$
pKa (Conjugate Acid)[9]	11.27	10.98

Table 1. Structural and pKa data for a cyclic and an acyclic secondary amine.

Aromatic heterocycles exhibit some unique chemical properties, which can be attributed to the delocalised system of electrons, alongside the presence of one or more heteroatoms whose lone electron pairs and electronegativities further add to the variation seen among heterocyclic motifs. Aromatic molecules are defined as “cyclically conjugated molecular entities with a stability significantly greater than that of a hypothetical localized structure” and to bear aromatic character, such compounds must obey the Hückel (4n + 2) rule. This rule states that “Monocyclic planar (or almost planar) systems of trigonally hybridized atoms that contain (4n + 2) π-electrons (where n is a positive integer) will exhibit aromatic character”.[10] Most commonly for non-fused ring systems, aromatic molecules contain six π-electrons (i.e. when n = 1). These six electrons may all originate from unsaturation in the ring system (as for benzene and pyridine), or from a combination of unsaturation and lone pair of electrons on a heteroatom; the latter case is most common in five-membered heterocycles such as pyrrole, furan, and thiophene. Some ions, such as the cyclopentadienyl anion and the cyclopropenyl cation also exhibit aromatic behaviour.[10]

1.2 Furans

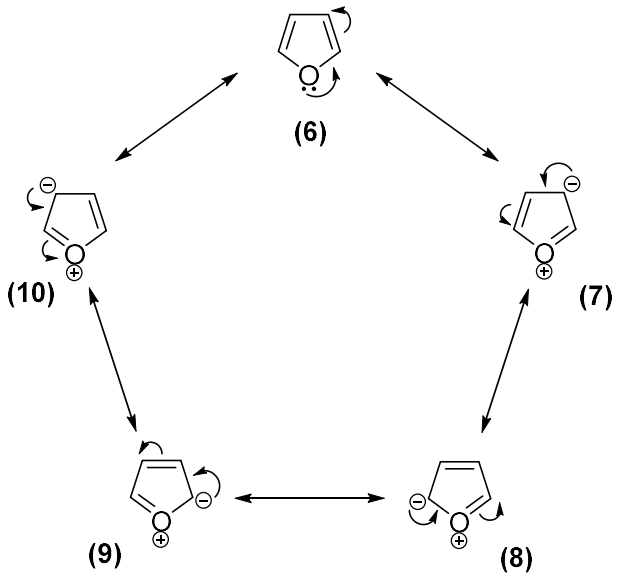
Furans are a class of five-membered, oxygen-containing heteroaromatic compounds. Four π-electrons originate from unsaturation in the carbon skeleton of the molecule, with the additional two electrons (required to fulfil Hückel's 4n + 2 rule) coming from one lone pair on the oxygen atom. A consequence of the six π-electrons being spread across five atoms, compared to six atoms in benzene (a feature also true of pyrrole and thiophene, with such compounds being described as π-electron rich) is a heightened reactivity towards electrophiles. Furan rings readily partake in Friedel-Crafts reactions, requiring weaker Lewis acids and less reactive acid anhydrides as acyl donors than the $AlCl_3$ and acid chlorides required when carrying out the reaction on typical carbocyclic aromatics such as benzene, toluene, or phenol. Electrophilic substitution is preferred at the 2- and 5-positions (α-carbons) of the ring system, although the 3- and 4-positions (β-carbons) will react if both α-positions are blocked **(Figure 2)**.[11]



Furan (6)

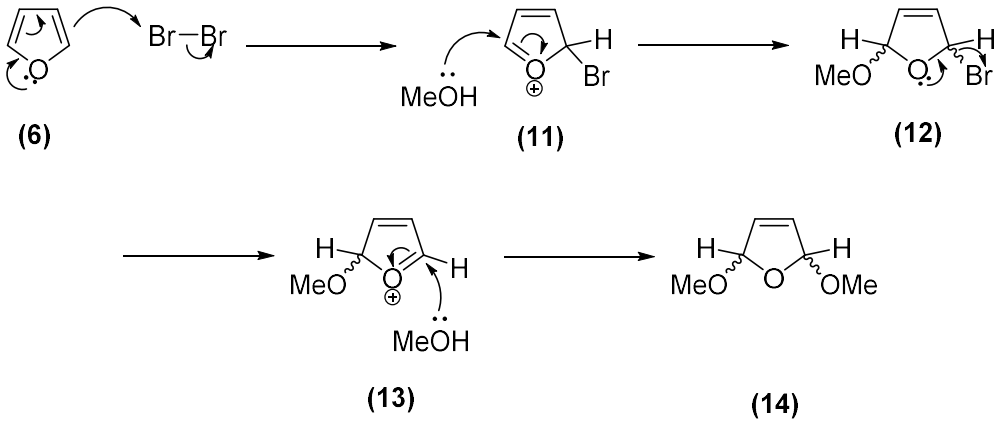
Figure 2. The structure and atom numbering of furan.

The resonance structures of furan involve the delocalisation of one of the oxygen atom's lone pairs into the two double bonds of the cyclopentadiene system as can be seen in **Scheme 1**.[12]



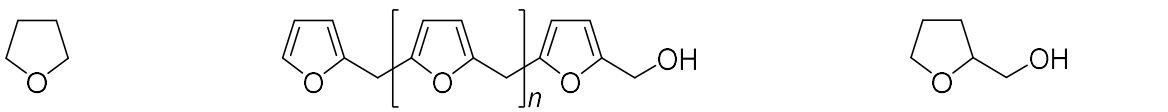
Scheme 1. The five main resonance forms of furan.

Furan is substantially less aromatic than benzene, with structures **7 – 10** contributing little to the overall electronic properties of the heterocycle. One feature of this, is furan's tendency to partake in electrophilic addition reactions over electrophilic substitution; a famous example being the reaction of furan and bromine with methanol as the solvent **(Scheme 2)**.[11]



Scheme 2. Electrophilic addition of methanol to furan in the presence of bromine.

Furan nuclei, alongside their partially hydrogenated (dihydrofurans) and fully hydrogenated analogues (tetrahydrofurans) are widely distributed throughout nature and synthetic materials alike. Simple furanose compounds, such as tetrahydrofuran **15** are used industrially as solvents; polymers, such as poly(furfuryl alcohol) **16** are furan containing and attractive due to the availability from renewable saccharidic sources;[13] furans are also important agrochemicals, one example being the use of tetrahydrofurfuryl alcohol **17** to aid herbicides penetrate the leaves of unwanted flora.[14] In addition, furan ring systems may be employed as synthetic precursors to more complex and/or useful compounds such as pyrroles or Diels-Alder cycloadducts.



Tetrahydrofuran (15) **Poly(furfuryl alcohol) (16)** **Tetrahydrofurfuryl alcohol (17)**

Figure 3. Simple compounds containing the furan or tetrahydrofuran nucleus.

Many natural products bear furan ring systems; simple furan natural products like 2-furfurylmercaptan **18** and 2,2'-difurylmethane **19** are present in roasted coffee beans and are a component of their distinctive aroma,[15] whilst more complex natural products such as xylogranatin F **20** have been show to prevent larvae of the Northern Armyworm, *Mythimna separate*, feeding on the seeds of the Cedar Mangrove, *Xylocarpus granatum*.[16] The furan-containing Limonin **21** is the primary compound responsible for the bitter taste of citrus fruit seeds.[17]

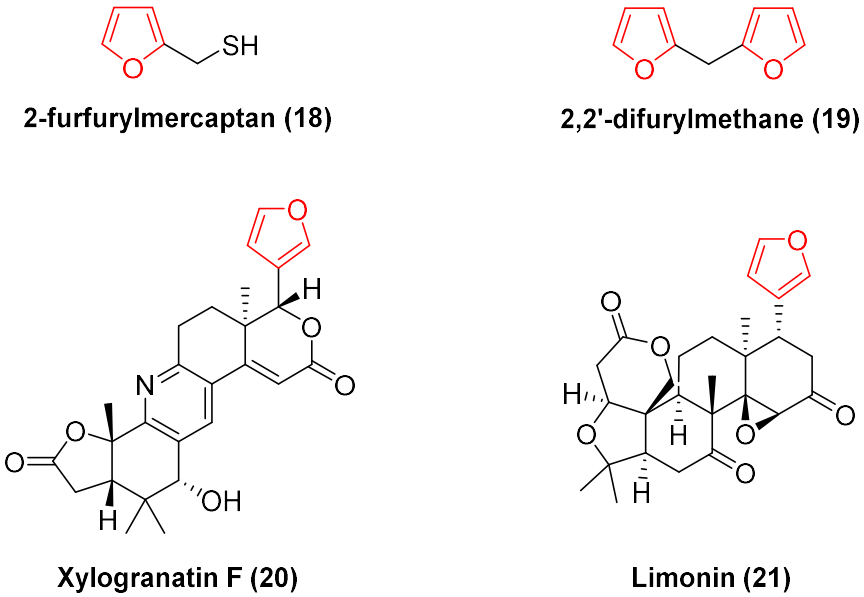
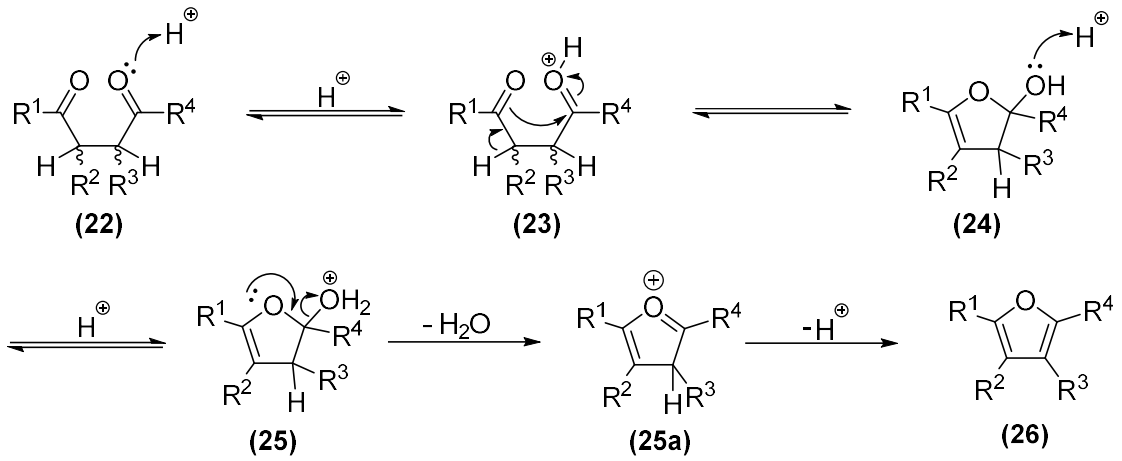


Figure 4. The sturctures of some natural products containing the furan nucleus.

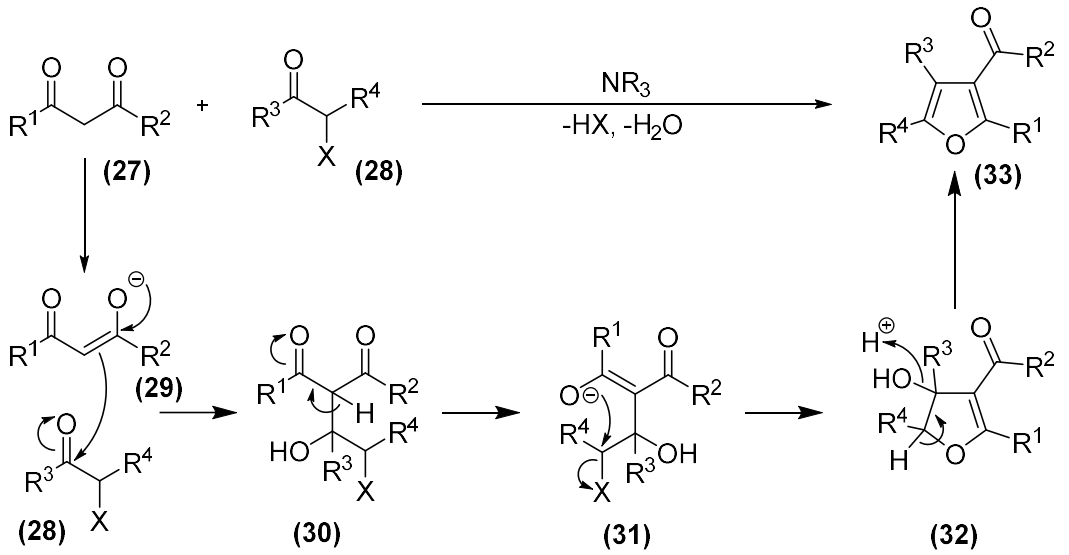
Furans are classically prepared by a method known as the Paal-Knorr synthesis, which sees the cyclisation of 1,4-diketones in the presence of a strong mineral acid **(Scheme 3)**.[18, 19] Recent literature has shown the use of strong organic acids such as trifluoroacetic acid being able to effect the transformation,[20] alongside microwave assisted techniques.[21] This synthetic route to furans, whilst very effective, has two main drawbacks. The requirement for a strong acid to promote cyclisation and dehydration of the 1,4-diketone substrate leads to an inconvenient and often problematic synthetic challenge when acid sensitive functionalities such as acetals, epoxides, or BOC protecting groups are present in the substrate and/or target furan. The second limitation of the Paal-Knorr synthesis is one of substrate availability; 1,4-diketones are a functionality which, until recently, have had a limited number of preparative routes leading to a substantially diminished scope of the furan synthesis.[18]



Scheme 3. A generalised Paal-Knorr synthesis of furans.[19]

An alternative classical route to substituted furans sees the construction of the oxygen heterocycle from a more readily available β-ketoester or 1,3-diketone, and an α-haloketone (**Scheme 4**).[22,23] This reaction, known as the Feist-Benary furan synthesis sees substitution at the α-position of the 1,3-dicarbonyl compound *via* enolate attack at the carbonyl of the α-haloketone; a process similar to the Knoevenagel condensation. The condensation step characteristic of the Knoevenagel reaction is interrupted in the Feist-Benary furan synthesis, as the intermediate enolate then undergoes a *5-exo-tet* cyclisation to a 3-hydroxy-2,3-dihydrofuran **32**.

A final condensation step then takes place to aromatise the system, with the loss of water. This route to furans harnesses milder conditions than the Paal-Knorr synthesis, requiring a nitrogenous base such as triethylamine or ammonia, instead of a strong mineral acid, to catalyse the transformation. However, with the requirement for a 1,3-dicarbonyl substrate, the Feist-Benary synthesis is limited to the preparation of furans bearing carbonyl functionality at the 3-position of the heterocyclic ring.



Scheme 4. Feist-Benary synthesis of Furans. [22,23]

The Paal-Knorr and Feist-Benary furan syntheses are examples of one of the two general strategies for the synthesis of compounds bearing a furan ring system; in this first approach, the furan ring is constructed during the reaction. The second general approach involves the modification of existing furan ring systems to give a diverse range of furans, often from simple precursor compounds.[18]

Many simple furan-containing compounds are available commercially, with a large number being obtained by the acid-mediated hydrolysis and dehydration of cellulose based materials that contain five carbon sugar units. One such example is furan-2-carbaldehyde, more commonly known as furfural, which is obtained by the chemical decomposition of corn cobs, sawdust, and grain husks (bran).[24] Consequently, the name 'furfural', and in turn 'furan', is derived from the latin word for bran, *furfur*.[25]

Furan ring systems are present in a huge number of natural products, many of which are obtained from marine sources. Some notable examples of marine natural products bearing a furan motif include simple compounds such as sarcotin K **34**,[26] furodysin **35**,[27] and nakafuran-8 **36**,[28] through to complex molecules such as (-)-nakadomarin A **37**,[29] and (±)-bipinnatin J **38**.[30] Many possess interesting and varied biological activities;[26,30] as a result, they have grown to become attractive pharmaceutical candidates.

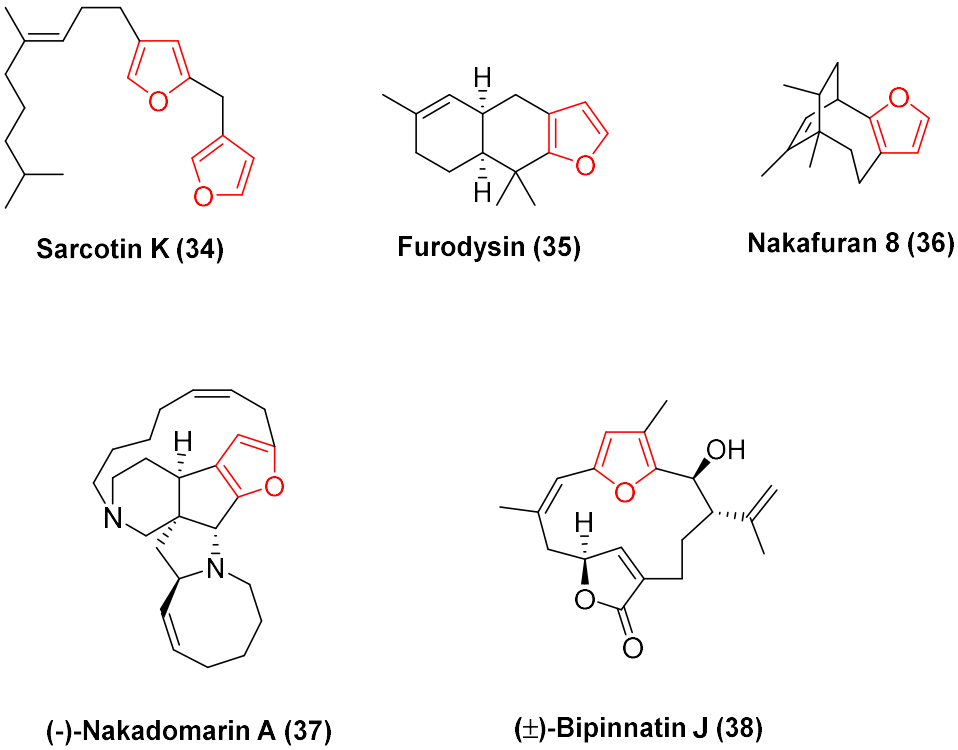


Figure 5. A selection of furan containing marine natural products.

1.3 Inflammation

Inflammation is a condition which contributes to a range of human diseases;[31] and is the defence reaction of biological tissues to injury, infection or irritation by chemicals or physical agents.[32] Inflammation involves pain, heat, redness, swelling, and can result in loss of function of the affected part. Blood vessels near the site of injury are dilated so that the blood flow is locally increased.[33] Leukocytes migrate from the blood stream into the surrounding tissue, a process promoted by the release of chemo-attractants from the site of inflammation and by the up regulation of adhesion molecules on the endothelium. The cellular activities involved in the inflammatory response and the chemical mediators produced, although designed to be damaging to pathogens, can also cause damage to host tissues if left unchecked. Inflammation is normally self-limiting and resolves of its own accord, however loss of these regulatory processes can result in excessive, inappropriate or on-going inflammation that can lead to irreparable damage to host tissues.[31] Chronic inflammation has been suggested to be a common factor in susceptibility to many chronic diseases, including asthma, Alzheimer's disease, cardiovascular disease, cancer and type 2 diabetes.[34] Many other diseases and chronic conditions, however, possess an inflammatory component; a number are summarised in **Table 2**.

Disease/Condition with Inflammatory Component
Asthma
Allergies
Atherosclerosis
Acute Cardiovascular Events
Alzheimer's Disease
Crohn's Disease
Cystic Fibrosis
Chronic Obstructive Pulmonary Disease (COPD)
Cancer
Cachexia
Lupus
Multiple Sclerosis
Non-Alcoholic Fatty Liver Disease
Neurodegenerative Diseases of Ageing
Obesity
Psoriasis
Rheumatoid Arthritis
Response to Surgery/Injury/Trauma/Critical Illness
Type-1 Diabetes
Tuberculosis
Ulcerative Colitis

Table 2. A selection of diseases and conditions with an inflammatory component, and some causes of inflammatory responses.[31,34]

Inflammatory diseases are currently treated using either steroidal based drugs such as hydrocortisone and prednisone, or by administration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen; both of these classes of drugs have side effects. Steroids are powerful anti-inflammatory agents arising from their ability to prevent the release of phospholipids after tissue damage;[35] it has been suggested that steroids accomplish this by stimulating the synthesis of an inhibitor of phospholipase A_2 (PLA_2),[36] the enzyme responsible for releasing arachidonic acid (AA) from storage in membrane phospholipids.[37] By preventing the release of phospholipids, the liberation of arachidonic acid is interrupted with the overall effect of decreasing the concentration of substrate for the formation of inflammatory prostaglandins by the cyclooxygenase metabolic pathways.[38] NSAIDs act by inhibiting the cyclooxygenase enzymes, which prevents the formation of prostaglandins (and other metabolites of arachidonic acid) which are responsible for mediating the inflammatory response. The pathways which steroids and NSAIDs act on to prevent inflammation are shown in **Figure 6**.

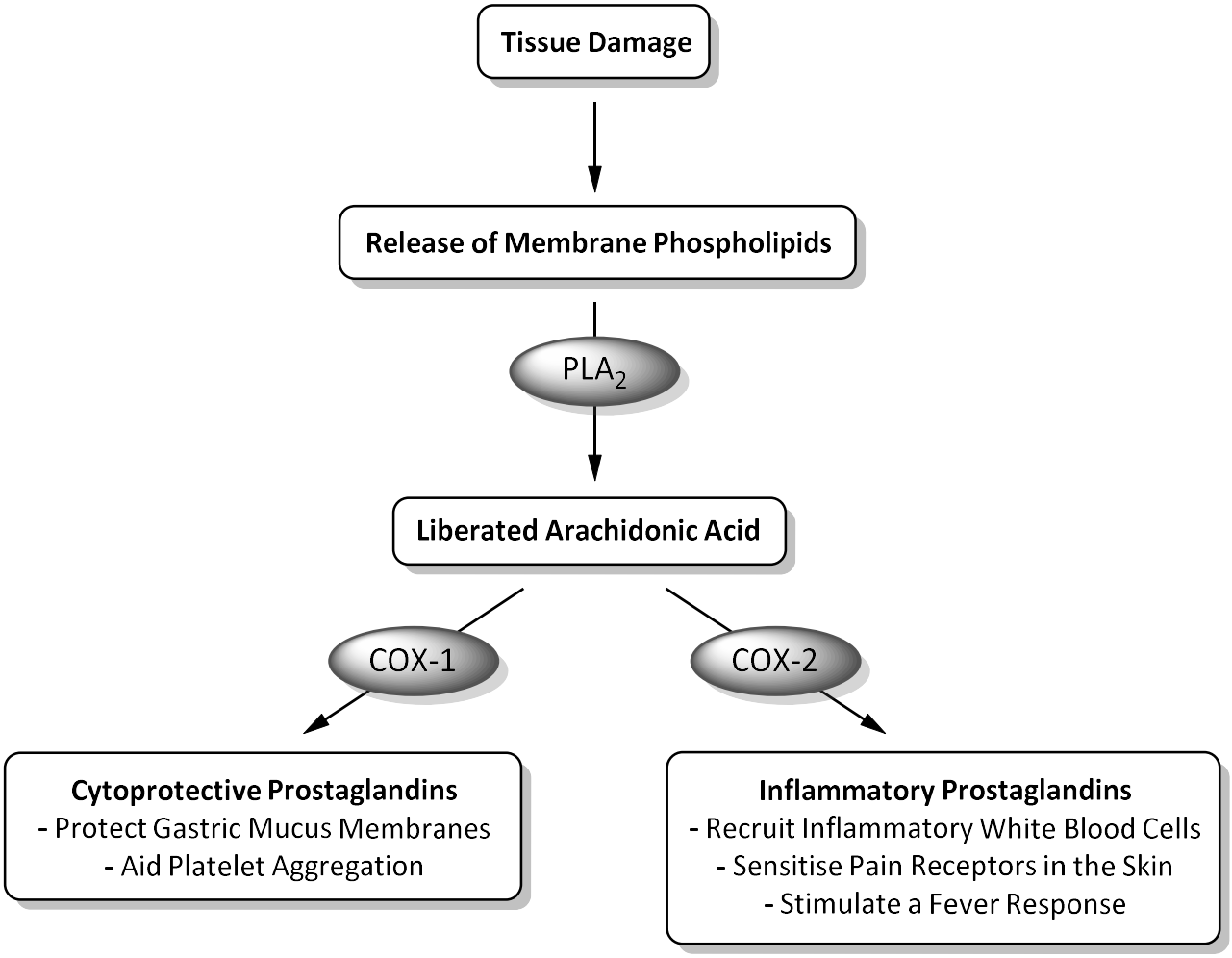
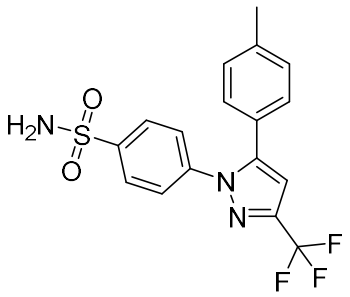


Figure 6. A general schematic for the biosynthesis of inflammatory prostaglandins from arachidonic acid by cyclooxygenase pathways.[39,40]

There are a wide range of side effects attributed to the use of conventional anti-inflammatory medications. The largest number and the biggest range of side effects are associated with steroidal anti-inflammatories. Side effects may include increased appetite and weight gain; neurological disorders such as depression, anxiety, rapid mood swings including irritability and aggression, and hallucinations; be damaging to the kidneys; promote the growth of malignant cancers; hypertension; osteoporosis; diabetes; acne; muscle weakness; and many others.[41, 42] In spite of the abundant adverse effects, the potency of steroids as inhibitors of a diverse range of inflammatory disorders currently ensures their continued use as therapeutic agents.[41]

NSAIDs have comparatively few side effects, however due to their high rate of prescription (being among the most widely prescribed medications in clinical practice)[39] and the nature of the associated adverse effects, NSAIDs do still pose a risk. The major drawback to the use of NSAIDs is damage to the upper gastrointestinal (GI) tract.[43] Conventional NSAIDs such as aspirin and naproxen lead to high incidences of GI irritation; in serious cases, the development of peptic ulcers and GI bleeding may be observed which can prove life threatening.[39] These problems are attributed to the non-selective nature of the drugs. NSAIDs interact with both the cyclooxygenase isozymes (COX-1 and COX-2), with the inhibition of COX-1 pathways being responsible for the GI complications. Whilst inhibition of COX-2 leads to the desirable anti-inflammatory properties, the undesirable inhibition of COX-1 leads to a decrease in cytoprotective prostaglandins that help maintain gastric mucus membranes.[40]

The comparatively recent developments in selective COX-2 inhibitors, an effort to produce NSAIDs which do not exhibit adverse gastrointestinal effects, have had limited success. Aiming to prevent inhibition of the COX-1 pathway whilst blocking the COX-2 pathway responsible for the production of inflammatory prostaglandins, selective COX-2 inhibitors such as celecoxib **39** have minimal gastrointestinal side effects. An unfortunate downside to this class of NSAIDs is the suppression of the formation of vascular prostacyclins, which leads to a marked increase in the incidences of cardiovascular events such as heart attacks and strokes.[44,45]



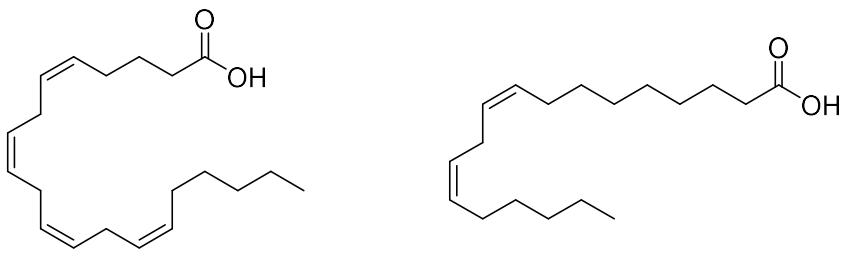
Celecoxib (39)

Figure 7. Celecoxib; a selective COX-2 inhibitor.

1.4 The Effect of Fatty Acids on Inflammation

Fatty acids are a family of terminal carboxylic acids which possess a long hydrocarbon chain. The hydrocarbon chain may be fully saturated or bear varying degrees of unsaturation. When unsaturation is present, the first double bond typically starts at either the ω-3 or ω-6 carbon (the carbon atom furthest from the carboxylic acid functionality being denoted ω-1, with the number increasing sequentially with each carbon atom. This follows from conventional molecular numbering where the carbon atom adjacent to a carbonyl functionality is denoted the α-carbon) and as a result, unsaturated fatty acids are commonly known as omega-3 or omega-6 unsaturated fatty acids.[46] Fatty acid molecules are most often encountered in nature as oils and fats, where they are bound to glycerol by ester linkages, and are commonly known as triglycerides.

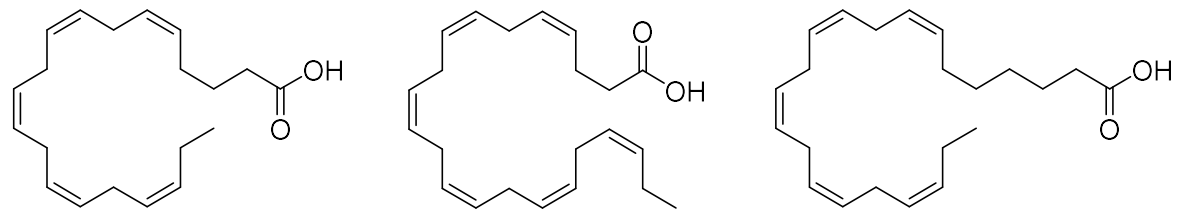
The major fatty acid involved in the inflammatory response is arachidonic acid (AA) **40**, an omega-6 polyunsaturated fatty acid (PUFA) consisting of a twenty carbon chain with four cis-conformed double bonds. As previously mentioned, AA is the substrate for the cyclooxygenase enzymes which leads to the formation of inflammatory prostaglandins. Arachidonic acid is biosynthesised from linoleic acid **41**,[47] an 18-carbon fatty acid found in a wide range of foodstuffs which comprises 84-89% of the total PUFA consumption in the United States.[48]



Arachidonic Acid (40) Linoleic Acid (41)

Figure 8. The structures of arachidonic acid and its biosynthetic precursor, linoleic acid.

Omega-3 polyunsaturated fatty acids are a subset of PUFAs which contribute to human health and well-being. The most important ω-3 PUFAs appear to be eicosapentaenoic acid (EPA) **42** and docosahexaenoic acid (DHA) **43**, however roles for docosapentaenoic acid (DPA) **44** are emerging.[47] Although EPA, DPA, and DHA can be synthesised from simpler plant-derived ω-3 fatty acids, primarily α-linolenic acid, the metabolic pathway does not appear to be particularly efficient in humans and competes with the enzymes responsible for the biosynthesis of arachidonic acid from linoleic acid.[31]

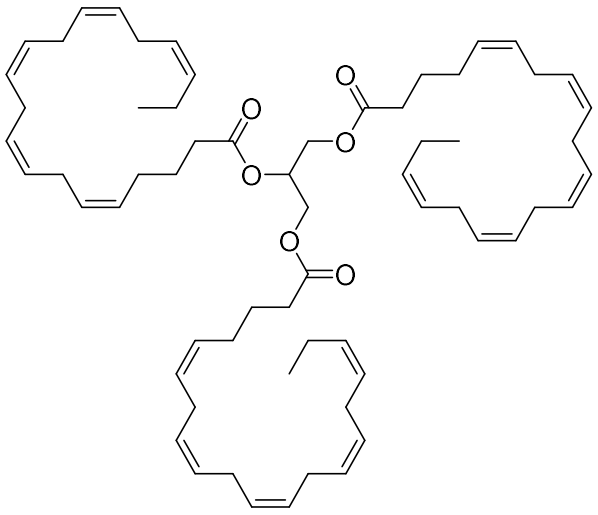


Eicosapentaenoic Acid (EPA) (42) **Docosahexaenoic Acid (DHA) (43)** **Docosapentaenoic Acid (DPA) (44)**

Figure 9. The three most important omega-3 polyunsaturated fatty acids; EPA, DHA, and DPA.

Due to the limited availability of EPA, DHA, and DPA from biosynthesis in the human body, these essential fatty acids must be obtained from dietary sources or fish oil supplements. As a result of their high prevalence in seafood sources, these fatty acids are often referred to as marine omega-3 fatty acids. The three PUFAs are found in high concentrations in fish and seafood, most notably in the flesh of oily fish such as salmon or mackerel where amounts of marine ω-3 fatty acids ranging from 1.5 – 3.0 g per portion of fish (approximately 100 g) are to be expected.[31]

Although the flesh of lean fish does contain notable amounts of the fatty acids (ca. 0.2 – 0.3 g per fish portion), the livers of certain lean fish such as cod contain notably higher concentrations; as such, lipid extracts from cod livers are widely used as dietary supplements. In a typical 1g fish oil supplement capsule, such as cod liver oil, approximately 0.3 g (30%) will be comprised of EPA and DHA. Marine ω-3 PUFAs are rarely encountered as free fatty acids; in fish and conventional fish oil supplements, the fatty acids are bound in the form of triglycerides. Other sources of marine ω-3 PUFAs such as krill oil and concentrated pharmaceutical grade preparations see the fatty acids in the form of phospholipids and ethyl esters respectively.[31]



(45)

Figure 10. A triglyceride containing three EPA subunits.

It is generally considered that incorporation of fatty acids into cell membrane phospholipids is the primary method by which fatty acids influence inflammatory responses,[49] as a result there has been a huge interest into the effects of elevated consumption of marine omega-3 fatty acids and how their increased incorporation into membrane phospholipids influences cellular inflammatory responses, and in turn the overall inflammatory process.[50]

The incorporation of EPA and DHA into membrane phospholipids of cells involved in inflammation occurs mainly at the expense of arachidonic acid, decreasing the concentration in the membranes of the cells involved. Due to the inflammatory response being prompted by the release of AA from membrane phospholipids, incorporation of EPA and DHA (having the knock-on effect of decreasing phospholipid-bound AA) leads to a reduction in the amount of AA liberated when an inflammatory stimulus is present.[31]

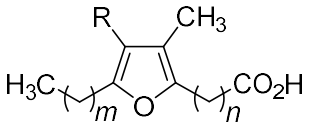
1.5 Lyprinol® and Furan Fatty Acids

One class of naturally occurring fatty acids the furan fatty acids (F-Acids). F-Acids are a family of fatty acids which contain a furan nucleus within the long fatty acid hydrocarbon chain. These compounds are known to be potent free radical scavengers,[2] and have been hypothesised to have antioxidant properties. The ability of F-Acids to quench reactive oxygen species such as hydroxyl and peroxyl radicals, singlet oxygen, and hydrogen peroxide, which are known to lead to tissue damage and appear in tissues undergoing oxidative stress, may contribute to the beneficial properties of diets rich in marine fatty acids.

Whilst present in a plethora of sources such as plants,[51, 52] algae,[53] butter,[54] and olive oil,[55] furan fatty acids are heavily bioaccumulated in marine environments are can be detected in appreciable quantities in lipid extracts from fish and shellfish. Perhaps the most widely recognised source of F-Acids is the New Zealand green-lipped mussel *Perna canaliculus*, from which the commercially available lipid extract Lyprinol® is obtained by means of supercritical CO_2 extraction from a stabilised freeze-dried powder of the green-lipped mussel.[2]

Variation between individual furan fatty acids arise from differences in chain length and degree of substitution about the furan ring. Unlike classical fatty acids such as eicosapentaenoic acid **42** and docosohexaenoic acid **43**, which possess a number of skipped cis-configured double bonds (i.e. those with bridging methylene units between each cis-conformed carbon-carbon double bond), furan fatty acids bear their unsaturation in the form of an aromatic furan ring. Carbon chains at the two alpha positions of the five-membered heterocycle provide the fatty acid character, with one α-carbon bearing either a propyl or pentyl side chain; the other α-carbon bears a longer hydrocarbon chain with a carboxylic acid functionality at its terminus.

At the two β-carbon positions on the furan motif, methyl substituents at either both β-carbons or solely at the β-carbon adjacent to the side chain bearing the carboxylic acid functionality may be present, and lead to an increase in the number of furan fatty acids which occur in nature. **Table 3** summarises the structures of the eight most abundant, naturally occurring furan fatty acids.[56]

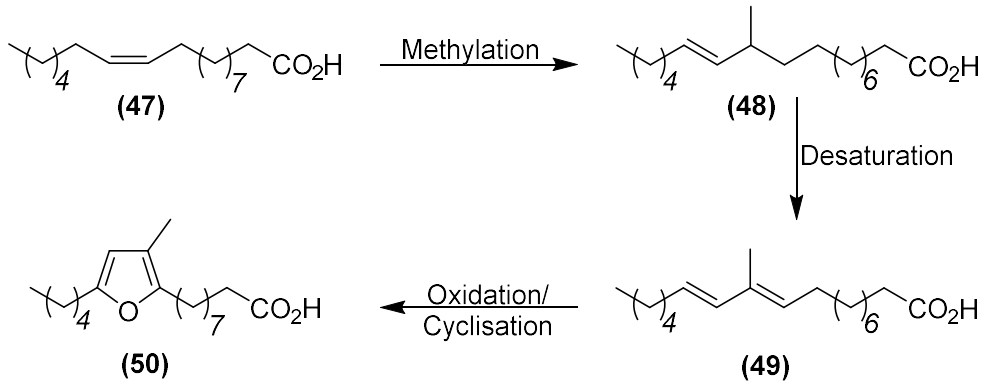


(46)

Structure	m	n	R
F_1	2	8	CH_3
F_2	4	8	H
F_3	4	8	CH_3
F_4	2	10	CH_3
F_5	4	10	H
F_6	4	10	CH_3
F_7	4	12	H
F_8	4	12	CH_3

Table 3. Structures of the most abundant furan fatty acids.[56]

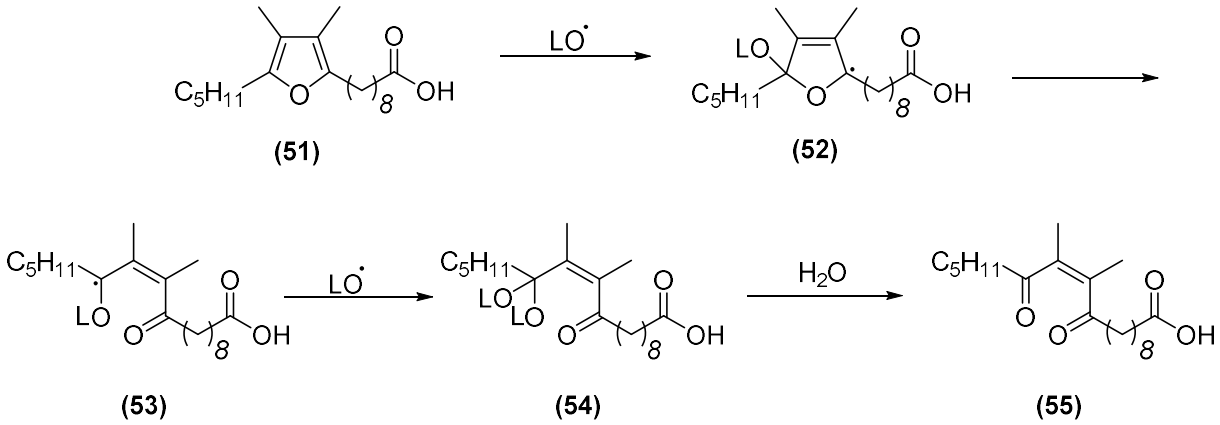
In marine bacteria, F-acids are produced in a biosynthetic pathway starting with *cis*-vaccenic acid **47 (Scheme 5)** a methylation step presumably harnessing S-adenosyl methionine (nature's equivalent to methyl iodide), followed by a desaturation to afford a conjugated 1,3-diene provides a suitable substrate for an enzymatic oxidation. The utilisation of a lipoxygenase enzyme leads to a lipid peroxide which subsequently affords the F-acid *via* a cyclisation sequence.[57] The generation of dimethyl F-Acids in marine bacteria is thought to proceed *via* direct methylation of the heterocycle.



Scheme 5. Biosynthetic pathway for furan fatty acid generation in marine bacteria.[57]

Furan fatty acids are readily oxidised, with a subsequent ring opening to give dioxoenes **(Scheme 6)**; a process which may be effected by reactive oxygen species such as singlet oxygen, and also by radicals such as the alkoxyl radicals (LO•) produced by the enzymatic decomposition of lipid hydroperoxides (LOOH). Radicals oxidise the furan nucleus first by adding to the 2- or 5- position of the F-Acid **51**, affording intermediate **52**. Successive ring opening affords the highly stable mesomeric radical intermediate **53**, which due to its prolonged lifetime, is able to further react with a second radical to form a ketal **54**.[56]

The high reactivity of the tetraalkyl furan core towards radicals, and the ability of intermediate **53** to absorb a second radical species, gives rise to their highly desirable radical scavenging properties. The final dioxoene product **55** is obtained by the hydrolysis of the ketal functionality. F-Acids also have an exceptionally high affinity for peroxyl radicals (a major source of cell damage) of the type LOO•, reacting in a similar manner as for alkoxyl radicals, and likewise affording dioxoenes.[56]



Scheme 6. The oxidative ring opening of furan fatty acids by alkoxyl radicals to form dioxoenes.[56]

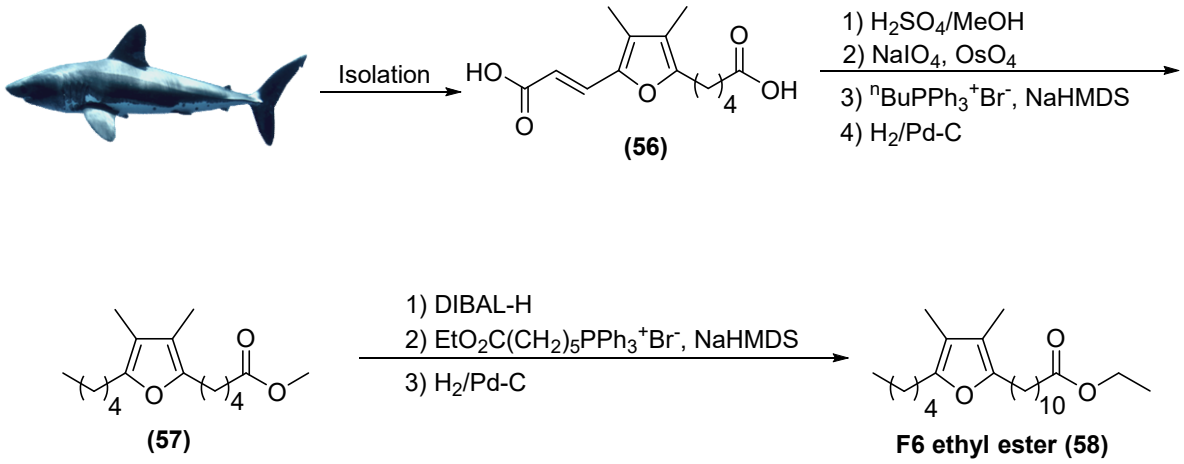
The anti-inflammatory properties of furan fatty acids were hypothesised as a result of a study by Whitehouse *et al.* which showed that Lyprinol® expressed anti-inflammatory activities in rats at concentrations two orders of magnitudes lower than that of fish oils containing abundant EPA.[2, 58] Lyprinol® contains five main lipid classes; sterol esters, triglycerides, free fatty acids, sterols, and polar lipids. A mixture of 90 fatty acids including saturated fatty acids, PUFAs and monounsaturated fatty acids are the primary components of the lipid extract, with EPA and DHA being the primary PUFAs present, on average accounting for 17.9% and 13.5% of the total composition respectively. 7.4% of the lipid extract, reported as 'other', contained a range of molecular entities including fatty acids with branched chains, hydroxyl groups, or conjugated double bonds, fatty aldehydes, and other poly-unsaturated fatty acids for which structures were not known.[3]

Despite the high concentrations of ω-3 PUFAs being likely candidates for the anti-inflammatory properties of Lyprinol®, their prevalence in other dietary sources, and the massive amounts of research carried out into their anti-inflammatory properties, does not account for the high activity of Lyprinol®. It is in the 7.4% of 'other' fatty acids that the presence of unstable FAs were hypothesised to be present, and to be the compounds responsible for the activity of the lipid extract. After esterification to fatty acid methyl esters (FAMEs), gas chromatography – mass spectrometric (GC-MS) analysis of Lyprinol® by Wakimoto *et al.* showed the presence of the methyl esters of furan fatty acids F_4 and F_6 in concentrations of 1.87 mg/g and 2.17 mg/g respectively (corresponding to 1.79 mg/g and 2.09 mg/g respectively of the free fatty acids). After a synthesis of F_6 ethyl ester, the anti-inflammatory properties of the furan fatty acid, compared to a standard NSAID, EPA ethyl ester, and Lyprinol®, were probed. The findings showed that the ethyl ester of F-acid F_6 showed comparable suppression of inflammation in a rat paw swelling model to that of the NSAID naproxen at doses between 5 and 10 mg/kg, alongside Lyprinol® at doses of 200mg/kg. The administration of EPA ethyl ester at a dose of 10 mg/kg did not give rise to significant suppression of the inflamed tissue.[2]

The knowledge that F-acids possess the ability to supress inflammation at doses comparable to those at which conventional non-steroidal anti-inflammatory drugs are effective, yet exhibiting no adverse gastrointestinal effects, is a tremendous leap forwards in the drive to develop a new class of anti-inflammatory agents for the treatment of chronic inflammatory conditions.

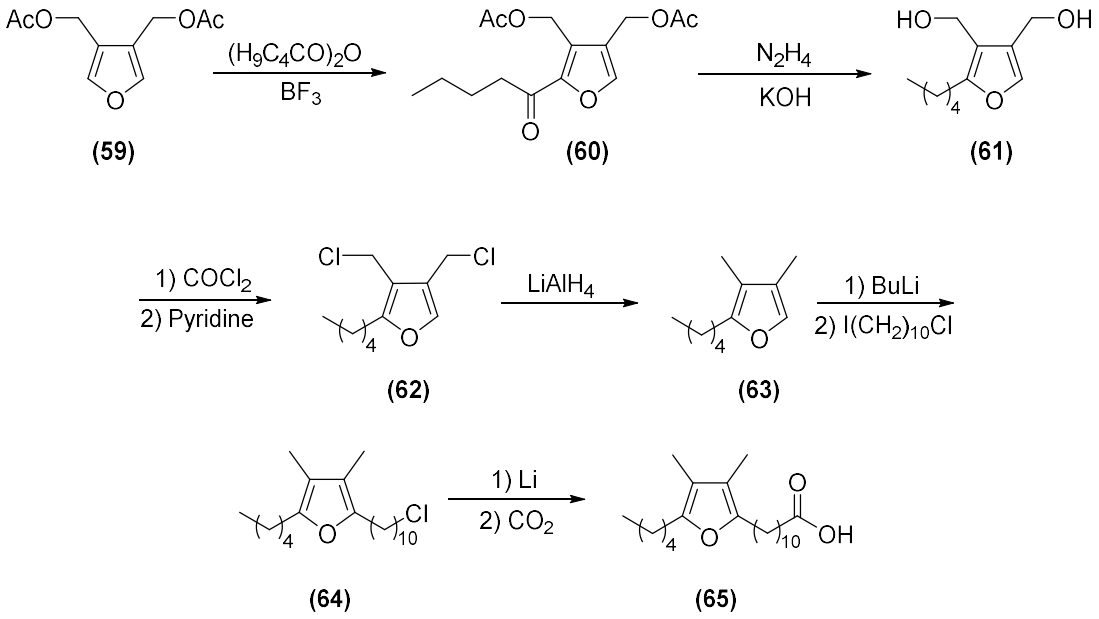
1.6 Previous Synthetic Routes to Furan Fatty Acids

To carry out their bioassay to determine the anti-inflammatory properties of F-Acid F_6, Wakimoto *et al.* required a substantial quantity of pure material for testing. Due to the limited availability of F-Acids from natural sources, being the result of low concentrations and issues surrounding the isolation of the reactive furanoid compounds, a synthetic route was required. The group opted for a semi-synthesis **(Scheme 7)**, starting from the furan fatty acid metabolite **56**, which accounts for ca. 10% of the dry weight of salmon shark (*Lamna ditropis*) bile. After Fischer esterification of the two carboxylic acid functionalities using acidified methanol, the carbon – carbon double bond present at the α-carbon was cleaved using OsO_4 / $NaIO_4$ to give the corresponding furfural derivative; subsequent Wittig olefination with butyltriphenylphosphonium bromide / sodium bis(trimethylsilyl) amide (NaHMDS), followed by hydrogenolysis afforded the pentyl side chain. DIBAL-H reduction of the remaining ester functionality to the corresponding aldehyde, Wittig olefination with (6-ethoxy-6-oxohexyl)triphenylphosphonium bromide / NaHMDS, and finally hydrogenolysis of the resulting carbon – carbon double bond afforded the desired F_6 ethyl ester. Whilst the group reported percentage yields for neither individual steps, nor the overall scheme, it is seen that they obtained 103 mg (0.27 mmol) of the F_6 ethyl ester from 1.6 kg freeze-dried shark bile;[2] quite an inefficient means of producing the desired compound, and at an extremely undesirable environmental cost.



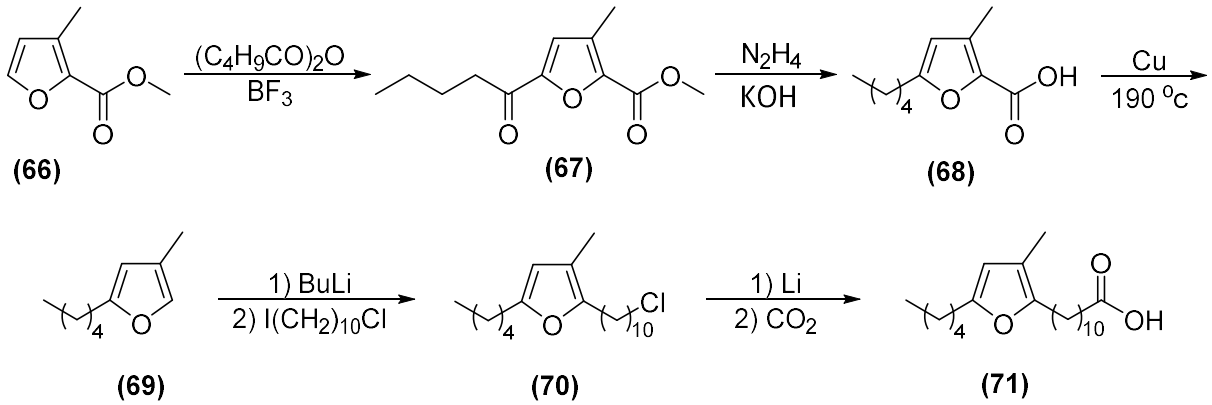
Scheme 7. A semi-synthesis of F_6 ethyl ester.[2]

A different approach to the synthesis of F_6 is seen in **Scheme 8**, and was the first reported total synthesis of the F-Acid.[59] Starting from the readily available bis(acetoxymethyl)furan **59**, Schlenk *et al.* employed a Friedel-Crafts acylation using valeric anhydride and boron trifluoride to functionalise one α-position of the existing furan nucleus. Subsequent treatment with hydrazine and KOH effected a Wolff-Kishner reduction of the ketone functionality, affording the desired pentyl side chain, and also cleaving the acetate esters from the β-positions, leaving terminal hydroxyl groups for further modification. Treatment of the alkylated bis(hydroxymethyl)furan **61** with phosgene, followed by a pyridine quench, afforded the dichoro compound **62** which was reduced in the presence of lithium aluminium hydride to give the 3,4-dimethyl furan derivative **63**. After lithiation of the 2-position of the heterocyclic ring with butyllithium and the addition of 1-chloro-10-iodo-decane to give **64**, the corresponding organolithium compound was prepared and subsequently trapped with CO_2 to give F_6 **65**.[59]



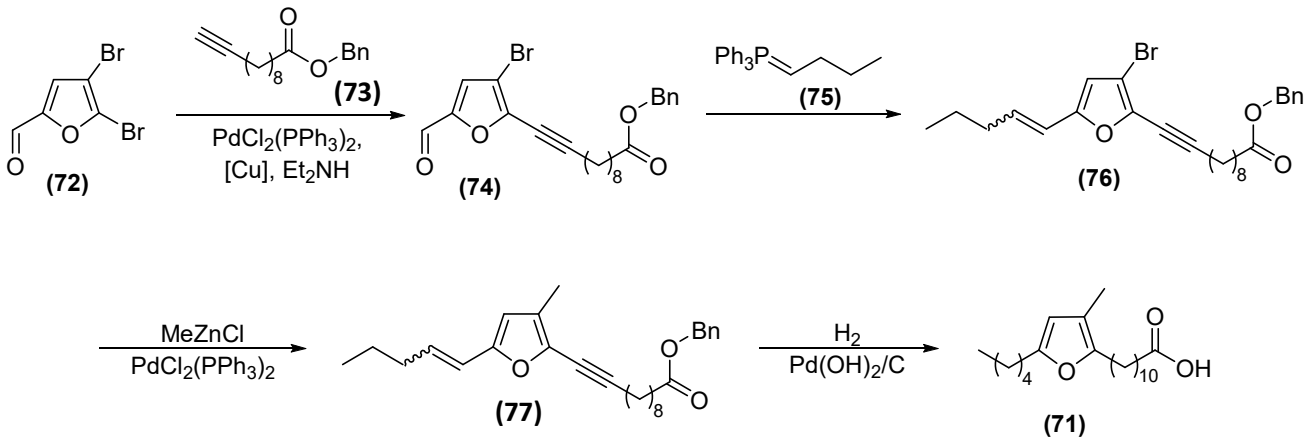
Scheme 8. The first reported synthesis of furan fatty acid F_6.[59]

A synthetic route for the preparation of F_5 **71**, the mono-methylated analogue of F_6 **65**, was shown by the same group **(Scheme 9)**, and follows a similar process as for the synthesis of the 3,4-dimethyl F-Acid. Starting from 3-methyl-2-methylfuroate **66**, Friedel-Crafts acylation functionalised the 5-position of the ring, with a subsequent reduction with hydrazine and KOH removing the ketone functionality and affording the pentyl side chain. The KOH in the Wolff-Kishner also served to cleave the methyl ester at the 2-position of the heterocycle, allowing for decarboxylation to give the dialkylfuran **69**. As for the F_6 synthesis, lithiation and alkylation provided the chlorine-substituted side chain at the remaining α-position, which was converted to F_5 **71** by lithiation and carboxylation.[59]



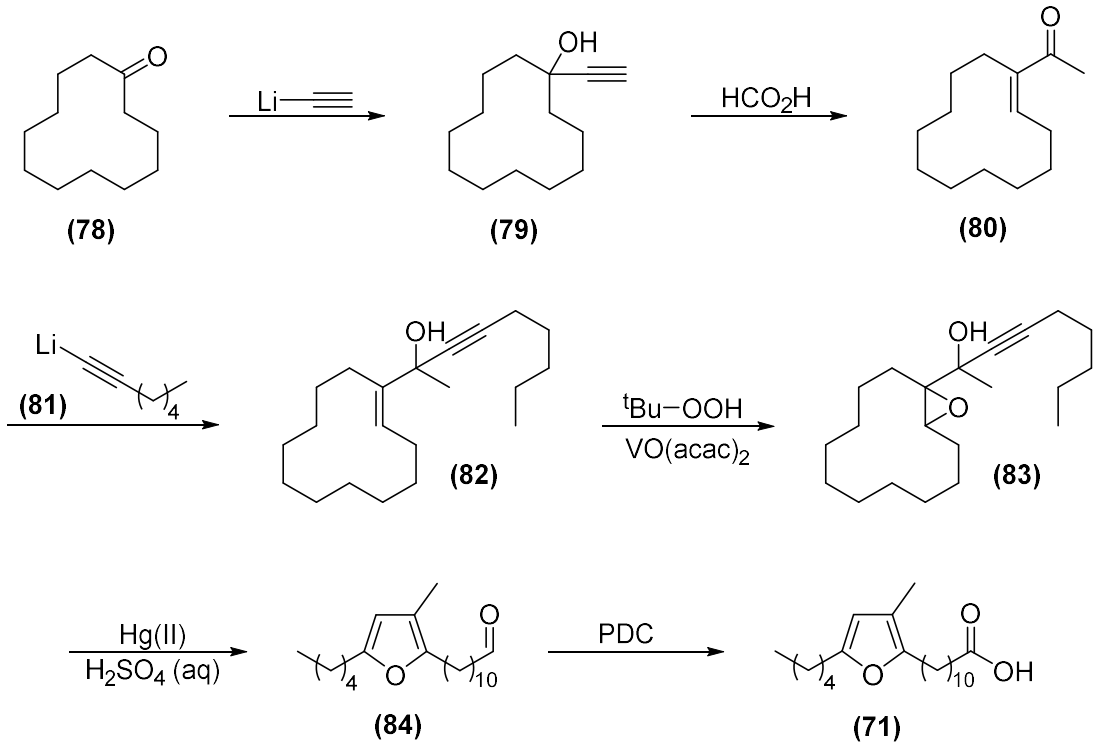
Scheme 9. A synthetic route to furan fatty acid F_5.[59]

An alternative approach to the synthesis of F_5 **63** by Krüger *et al.*,[60] employed palladium cross coupling reactions, alongside a Wittig olefination to modify dibromofurfuraldehyde **72** **(Scheme 10)**. Addition of the long fatty acid chain at the α-position was accomplished by means of a Sonogashira cross coupling. Wittig olefination of the aldehyde component provided the remaining five-carbon chain at the remaining α-position of the heterocycle. A second cross coupling reaction, this time employing methyl zinc chloride afforded intermediate **77** which was converted to F_5 **71** by hydrogenolysis; removing both the double and triple bonds and cleaving the benzyl ester.



Scheme 10. A palladium cross coupling based synthetic route to the furan fatty acid F_5.[60]

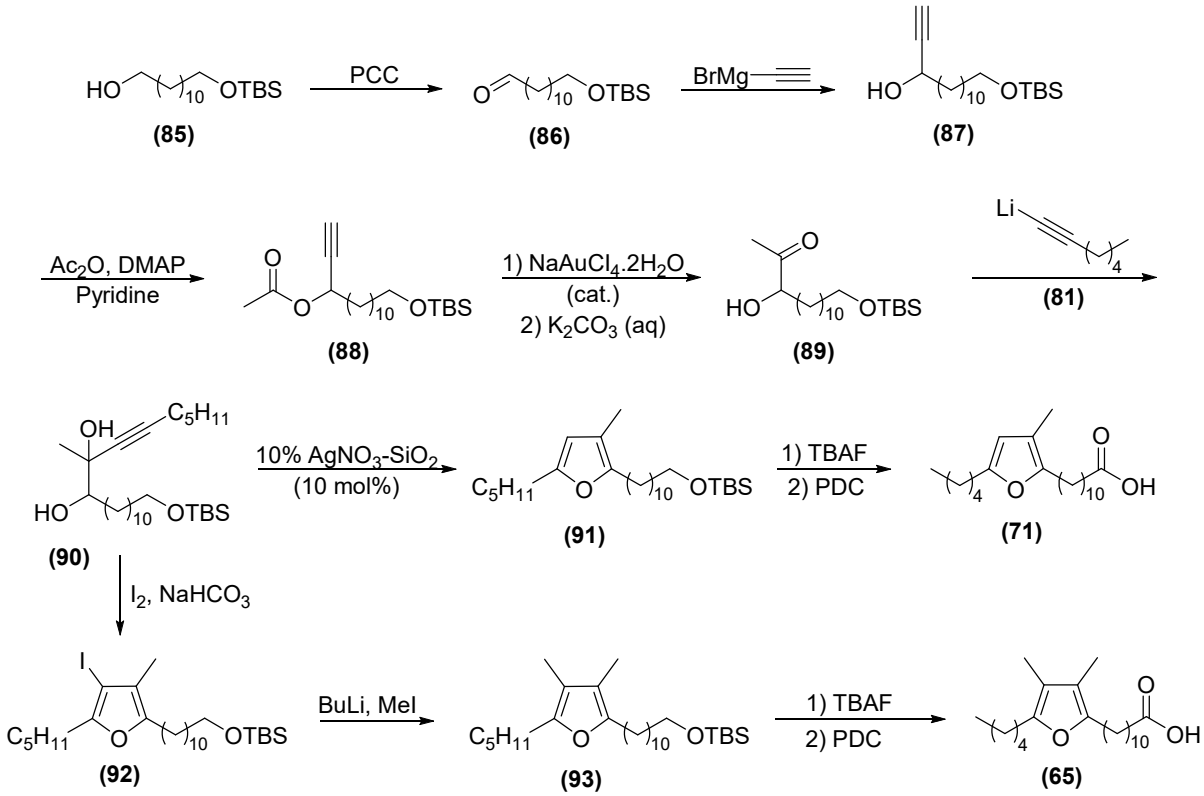
The above syntheses are all of the type where an existing furan nucleus is synthetically modified to afford the desired F-Acid products. As mentioned earlier, this is one of the two primary methods of producing furanoid compounds; the other method being the formation of the furan nucleus from non-heterocyclic starting materials. Several syntheses of F-Acids F_5 **71** and F_6 **65** have been reported, utilising methods which construct the furan core with developed, or partially developed, side chains intact. Starting from the commercially available cyclododecanone **78**, Marson *et al.* prepared the corresponding alkynyl alcohol **79** by addition of lithium acetylide which upon treatment with aqueous formic acid, underwent a Rupe rearrangement to the acetylcyclododecene **80**. Addition of heptynyllithium **81** to the newly formed carbonyl afforded species **82** which was epoxidised to **83** using *tert*-butyl hydroperoxide and catalytic $VO(acac)_2$. The key reaction in this total synthesis was the Hg(II) catalysed formation of the furan nucleus, which formed intermediate **84**; subsequent oxidation of the aldehyde functionality with pyridinium dichromate affords F-Acid F_5 **71 (Scheme 11)**.[61]



Scheme 11. A mercury(II) catalysed furan formation for the fynthesis of the furan fatty acid F_5.[61]

In a mechanistically different approach, Knight *et al.* utilised a 5-*endo*-dig cyclisation of 3-alkyne-1,2-diols to construct the furan nuclei of fatty acids F_5 **71** and F_6 **65 (Scheme 12)**.[62] Starting from the mono-TBS protected 1,12-dodecanediol, oxidation to the aldehyde with PCC followed by addition of ethynylmagnesium bromide to the carbonyl afforded the propargylic alcohol **87**.

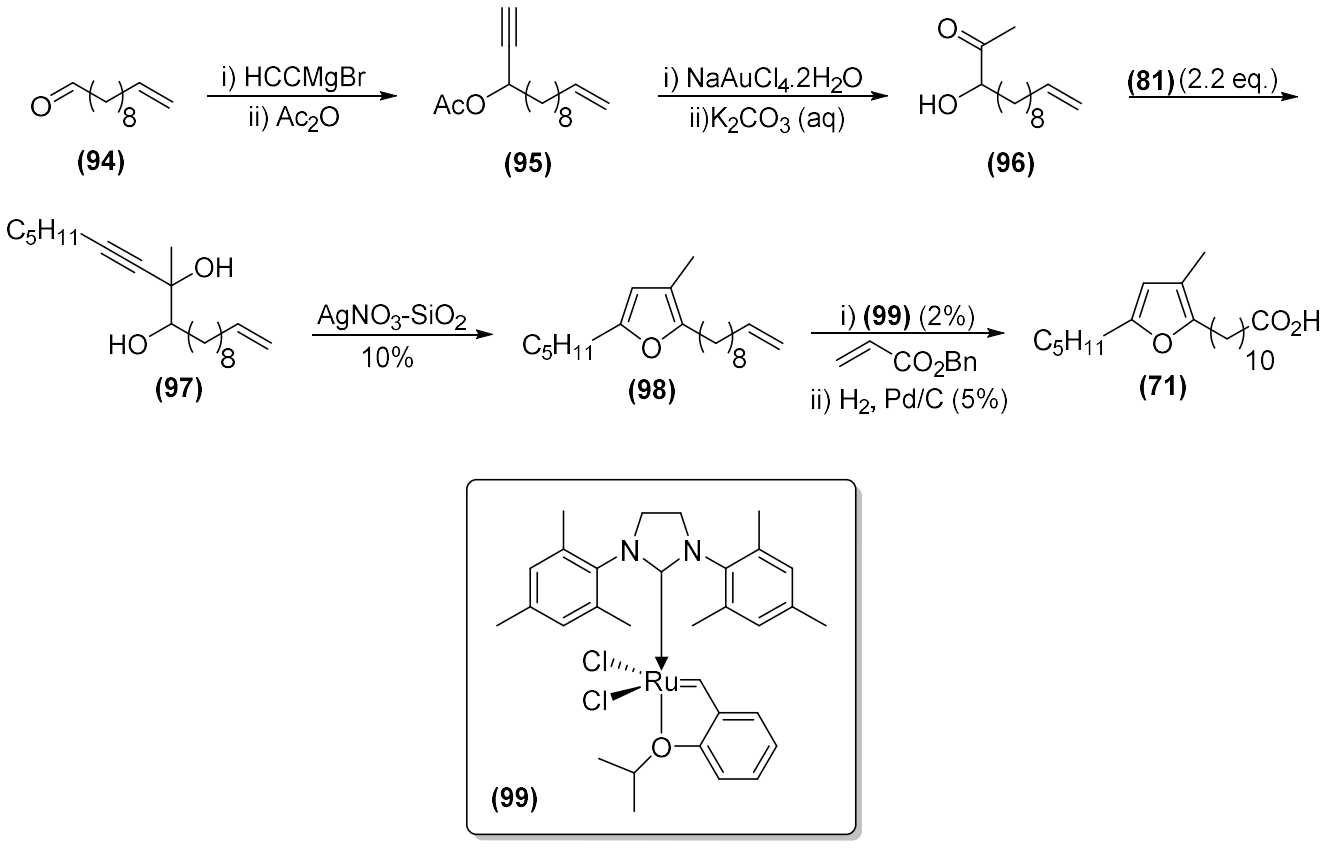
Protection of the alcohol functionality as the acetate ester was followed by an Au(III) catalysed hydration of the triple bond which after work-up provided the α-hydroxyketone **89**. A final reaction with two equivalents of heptynyllithium afforded the key 3-alkyne-1,2-diol intermediate **90** required for the construction of the heterocyclic ring in an overall 53% yield. This key intermediate could then be used to produce precursors to both F_5 **71** and F_6 **65**; the former by means of a Ag(I) catalysed ring closure, and the latter by iodocyclisation. For the synthesis of F_5, a solution of **90** in dichloromethane was treated with 10 mol% of 10% silica-bound silver nitrate. This yielded species **91** which after TBAF deprotection and PDC oxidation, provided F_5 **71** in an overall 40% yield. The iodocyclisation route to F_6 **65** involved the treatment of **90** with iodine under basic conditions, forming iodofuran **92**. Metal-halogen exchange using butyllithium, followed by alkylation with methyl iodide afforded the tetraalkyl furan nucleus, which after the same deprotection/oxidation procedure as for the F_5 synthesis provided F_6 in an overall 35% yield.[62] Whilst being quite efficient overall, the use of toxic chromium reagents for oxidation, reduces the attractiveness of these total syntheses as methods for the preparation of F-acids for biological testing, and ultimately for human consumption.



Scheme 12. Synthetic routes to F-Acids F_5 and F_6 by 5-endo-dig cyclisation from a common precursor.

Knight *et al.* since refined their F-Acid synthetic route **(Scheme 13)**, by utilising an olefin-bearing alkynediol precursor.[63] The low cost of starting material, ease of introduction of carboxylate functionality *via* cross metathesis instead of the oxidation of the terminal hydroxyl group as seen in the original scheme, and tolerance of the alkene functionality to the other steps in the synthesis, all contribute to the modified route's superiority to that of the group's first synthesis.

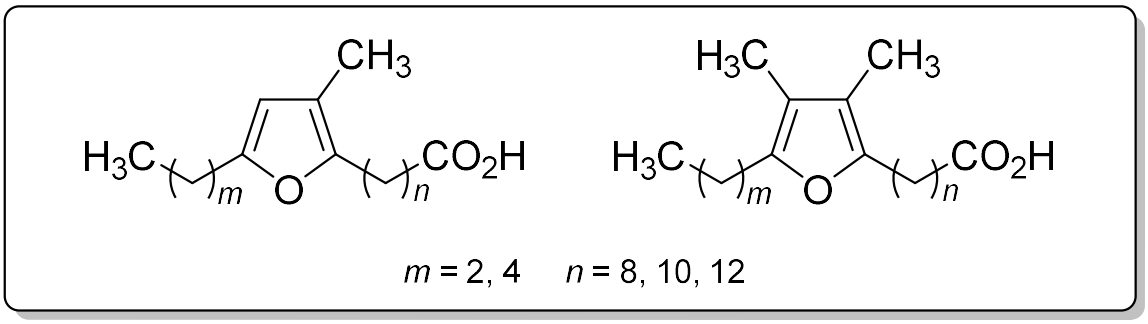
The new route started from aldehyde **94**, which after treatment with ethynylmagnesium bromide followed by acylation of the intermediate alkoxide with acetic anhydride afforded the acetoxy species **95** in excellent yields of >92% after only 1.5 h. In line with the original synthesis, the alkyne functionality was hydrated, utilising the same catalytic $NaAuCl_4$ method as in Utimoto's synthesis, with removal of the acetate protection being accomplished during work-up. Subsequent treatment of the newly formed ketone with excess heptynyllithium afforded the alkynediol **97** in a 90% yield, without requiring prior protection of the existing hydroxyl functionality. The application of the alkynediol-to-furan cyclisation, using silica-adsorbed silver nitrate, quantitatively prepared furan **98**, which after cross metathesis with benzyl acrylate followed by hydrogenation afforded a 74% yield of F_5 **71**. [63]



Scheme 13. Knight et al.'s revised F-Acid synthesis.[63]

2. Aims

Tri- and tetra- substituted furan fatty acids have been shown to have powerful anti-inflammatory properties and are not a source of gastrointestinal complications like traditional NSAIDs. However, they are only present in nature in low concentrations, and are troublesome to isolate due to rapid degradation to biologically inactive molecular entities.



The aim of this research was to develop a new synthetic route towards furan fatty acid F_5, using a biomimetic synthesis to generate F-acid nuclei from alkylated dienes, by means of a sequential $^1O_2$ mediated oxidation/Appel-type dehydrative aromatisation sequence. The application of this general synthesis to dienes bearing chain length variations at the 1 and 4 positions of the diene, and varying methylation patterns at the 2 and 4 positions, was to allow for the preparation of all F-Acids from simple precursor compounds to be possible.

The biomimetic diene oxidation/aromatisation sequence was to be explored as a means of producing a range of furans bearing substitution at all available positions about the heterocycle, being capable of tolerating a range of functional groups, and to expand on the range of generalised furan syntheses by providing a mild and metal-free way of constructing furan nuclei bearing pre-installed functionality.

A further goal was to be able to carry out the biomimetic furan synthesis in a tandem flow reaction sequence to allow for the continuous preparation of substituted furans directly from the corresponding 1,3-dienes. This approach would negate the requirement for isolation of cyclic peroxide intermediates and allow for greater control of oxygen stoichiometry in the photooxidation of dienes so as to minimise overoxidation products (and consequently waste), whilst increasing the overall yields of the furan synthesis to those more acceptable from both an academic and industrial viewpoint.

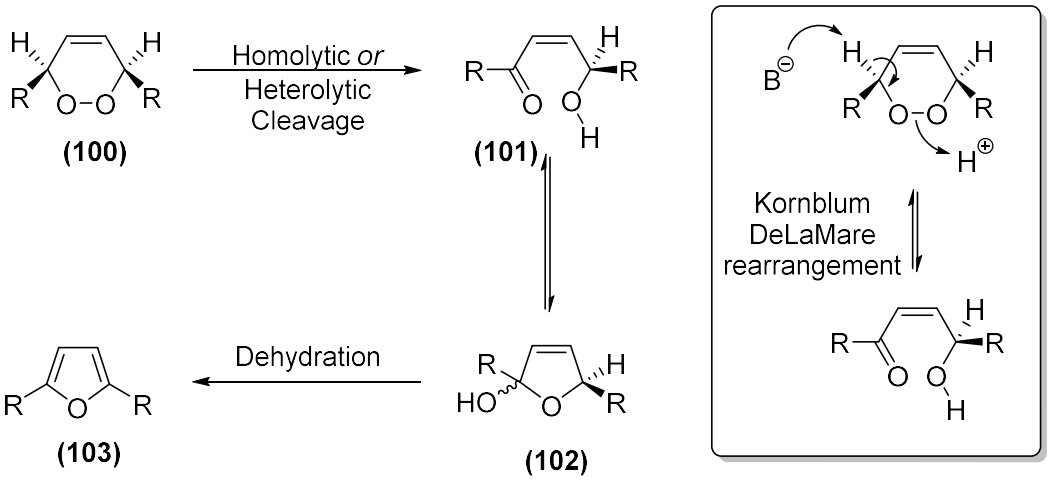
3. Results and Discussion

3.1 The Dehydration of Endoperoxides as a Route to Furans

Whilst the generation of 1,2-dioxines (endoperoxides) *via* the addition of singlet oxygen to 1,3-dienes has been extensively studied and exploited in organic synthesis,[64] a sufficiently mild method of converting the oxidised diene to the corresponding furan, which omits the use of transition metal involvement, is lacking. Methods for the direct conversion of endoperoxides to furans, as seen in the literature, can be grouped into two distinct processes; homolytic and heterolytic cleavages of the peroxide bond.

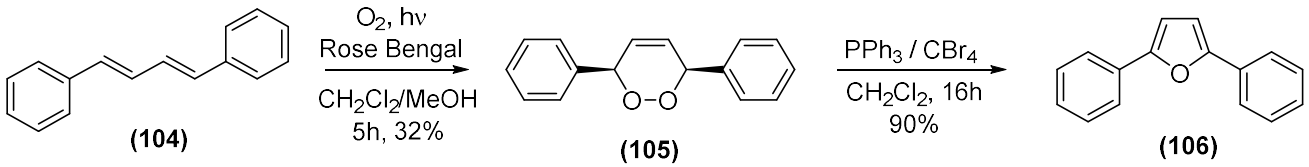
Homolytic processes typically focus on the use of transition metals to mediate the transformation, however examples of thermal homolysis followed by a 1,5-hydrogen shift do exist.[65] The intermediate cis-*γ*-hydroxyenone (**101**) generated by homolysis of the peroxide bond is converted to the target furan *via* cyclisation and dehydration, however the reactions are highly dependent on the substrate and the metal used (Ru(II),[66] Co(II),[67] Sn(II),[68] Fe(II)[69]), and are often associated with the formation of numerous side products. The potential of highly electron rich furans to react further under the reaction conditions is a serious concern, and so limits the scope of these methods.

Heterolytic cleavage of the peroxide bond has primarily been accomplished in a two-step process; an initial base catalysed step sees conversion of the endoperoxide, *via* a Kornblum DeLaMare rearrangement **(Scheme 14)**,[70] to the same *cis*-*γ*-hydroxyenone intermediate seen in homolytic processes; the resultant enone is then dehydrated to the target furan. Direct conversion to the furan under acidic conditions can also be performed (presumably *via* a 1,4-diketone intermediate which then undergoes a Paal-Knorr synthesis),[71] however the substrate scope of such transformations is limited by the requirements for conventionally harsh reaction conditions employing strong mineral acids and significant heating. Whilst the use of alternate reagents including transition metals (e.g. $FeSO_4$)[72] have been shown to facilitate the transformation, these reagents give rise to potential complications when unstable, electron rich, furanoid products such as furan fatty acids are the desired targets.



Scheme 14. Kornblum DeLaMare rearrangement of 1,2-dioxines and dehydration to furans.[70]

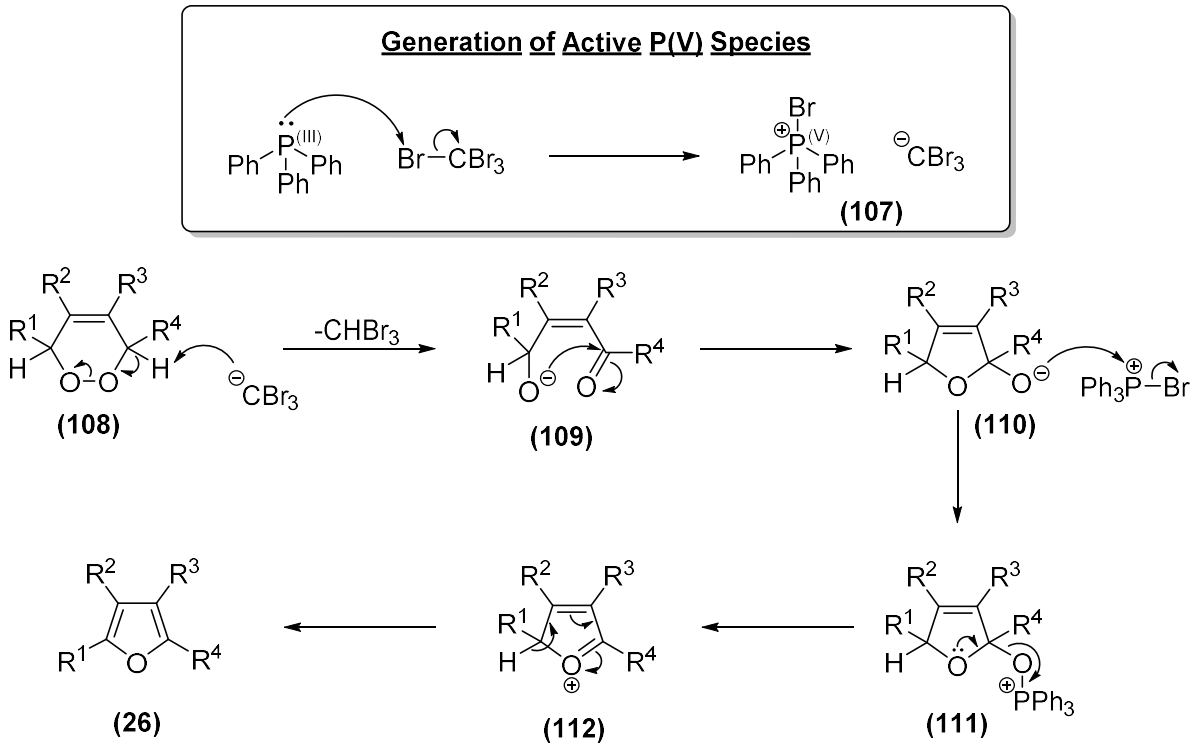
In this work, a new method for the construction of furan ring systems harnessing the reductive power of the Appel reagent to generate the aromatic heterocycle *via* the dehydration of endoperoxides was developed, which enabled the generation of furan rings under mild, metal-free conditions.[73] This reaction is an example of a heterolytic process, with the two components of the Appel reagent facilitating different stages of the reaction in a one-pot process; (i) the heterolytic cleavage of the peroxide bridge and (ii) the dehydration/aromatisation sequence. Initially, a dye sensitised photo-oxidation of 1,3-dienes with singlet oxygen was performed to obtain cyclic peroxides, which were then converted to furans using the newly developed Appel-type dehydration methodology. The reaction was tested using the commercially available *trans,trans*-1,4-diphenyl-1,3-butadiene **104** as the diene precursor; the diphenyl dioxirane **105** obtained by singlet oxygen cycloaddition to the diene occurred readily, albeit in a low yield, however the novel application of Appel conditions employed for dehydration to the corresponding furan **106** were both exceptionally mild, and generally high yielding **(Scheme 15).**



Scheme 15. Formation of 2,5-diphenylfuran from diphenylbutadiene.

Whilst the reaction of singlet oxygen with dienes has been studied extensively,[64] the PPh_3/CBr_4 mediated dehydration of the resulting endoperoxide is a new reaction. Analagous to the Appel reaction which employs an active phosphorus (V) reagent generated by treatment of triphenylphosphine with a tetrahalomethane to convert alcohols to their corresponding halides with inversion of stereochemistry,[74] our dehydration utilises the same reagent combination to promote endoperoxide cleavage and removal of oxygen from the cleaved endoperoxide in the form of the highly stable triphenylphosphine oxide.

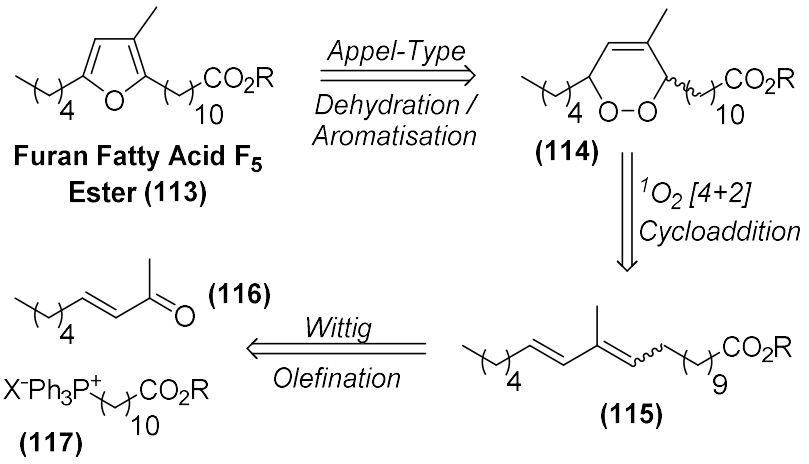
A plausible mechanism for the dehydration reaction is shown below **(Scheme 16)**. Cleavage of the weak oxygen-oxygen bond, formation of the strong phosphorus-oxygen double bond and the formation of an aromatic ring system all lend to the reaction being an effective means of dehydrating endoperoxides due to their high thermodynamic drive.



Scheme 16. Proposed mechanism for the P(V) mediated dehydration of endoperoxides using the Appel reagent.

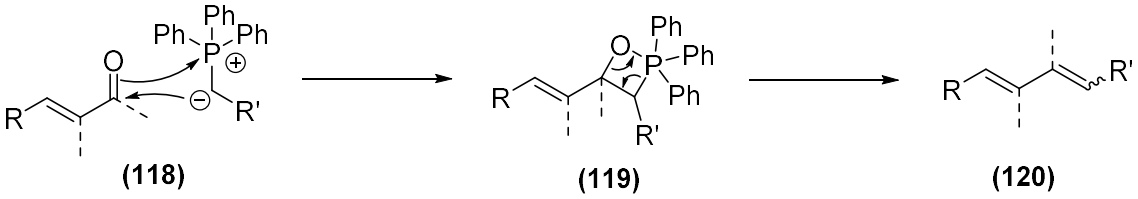
The proposed mechanism begins with the formation of the Appel reagent; an ion pair containing a halophosphonium cation and a trihalomethyl anion. Introduction of an endoperoxide to this reagent is followed by a CX_3^- mediated Kornblum-DeLaMare rearrangement, with the carbanion deprotonating the endoperoxide from one of the carbon atoms adjacent to the peroxide bridge and becoming a haloform species, which does not react further. The newly generated *cis*-γ-alkoxyenone is able to readily undergo a favourable 5-*exo*-trig cyclisation to its ring closed α-alkoxydihydrofuran tautomer, which becomes a viable substrate for aromatisation. Reaction of the alkoxyl functionality with the halophosphonium cation of the Appel reagent forming a strong phosphorus-oxygen bond precedes the elimination of an even more thermodynamically stable phosphine oxide by-product by participation of the neighbouring ring oxygen. The resulting heterocycle then has to lose only a proton in order to aromatise the ring system to the target furan, which the thermodynamic drive toward aromatisation of the ring system aids.

For the synthesis of furan fatty acids using the newly developed furan synthesis, a retrosynthetic plan **(Scheme 17)** was developed and followed. Appropriately substituted 1,3-dienes were prepared *via* Wittig olefination of α,β-unsaturated carbonyl compounds, oxidised to the corresponding endoperoxide by treatment with photogenerated $^1O_2$, and finally dehydrated to the furan ring system using the Appel reagent.

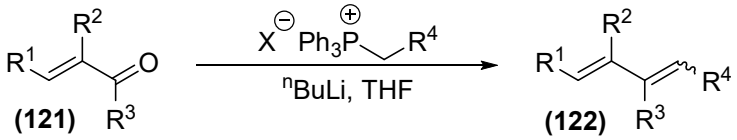


Scheme 17. Proposed retrosynthetic plan for F-Acid preparation via singlet oxygen cycloaddition to a 1,3-diene, and dehydration to the corresponding furan.

Dienes were prepared via Wittig olefination of α,β-unsaturated carbonyl compounds **(Scheme 18 / Table 4)**; those bearing a phenyl substituent were derived from cinnamaldehyde, α-methyl-*trans*-cinnamaldehyde, or benzylideneacetone, whereas those bearing a 1-pentyl substituent were derived from commercially available 3-nonen-2-one. In a similar fashion, F-Acids bearing a propyl α-substituent may be prepared from commercially available 3-hepten-2-one. A mixture of E- and Z- isomers were obtained in the diene products, and subsequent reactions with the dienes were carried out using the mixture.



Scheme 18. Mechanism for the Wittig olefination of unsaturated carbonyl compounds.[75]



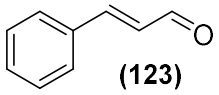
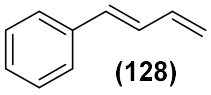
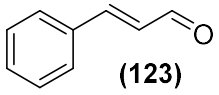
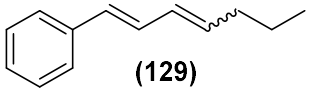
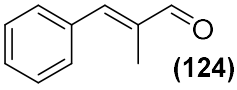
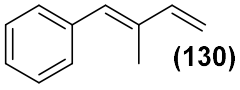
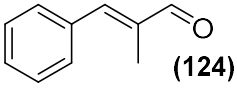
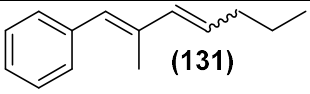
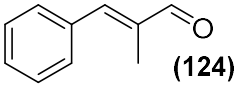
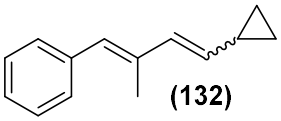
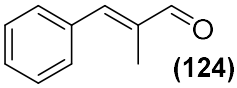
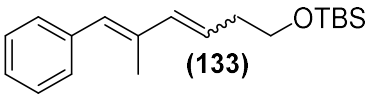
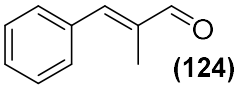
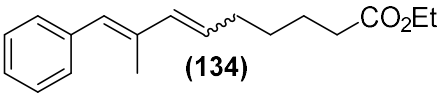
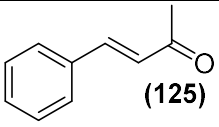
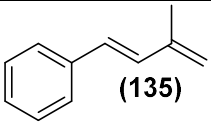
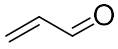
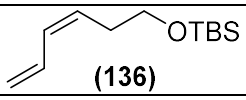
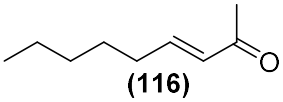
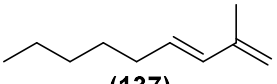
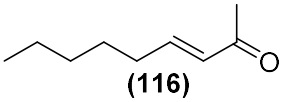
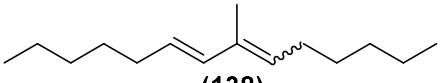
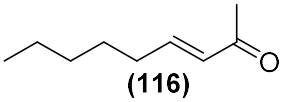
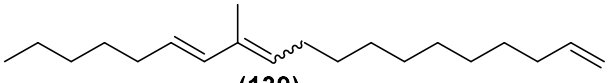
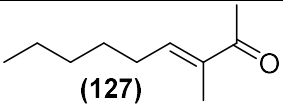
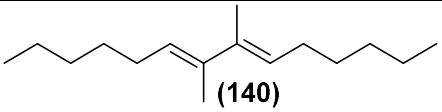
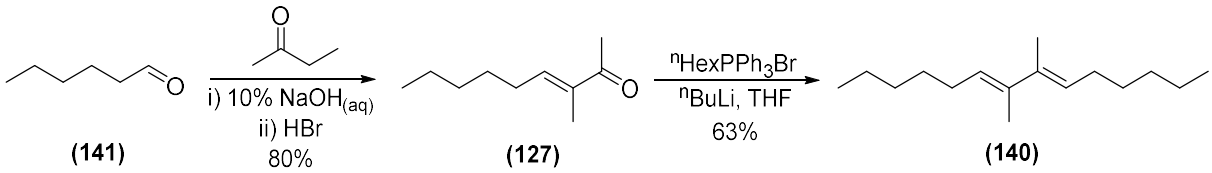
Unsaturated Carbonyl Substrate	Diene Product	Yield (%) [E/Z Ratio]
 (123)	 (128)	61
 (123)	 (129)	82 [1:1.7]
 (124)	 (130)	69
 (124)	 (131)	70 [1.5:1]
 (124)	 (132)	67 [1:1.2]
 (124)	 (133)	78 [2:1]
 (124)	 (134)	80 [1:1.2]
 (125)	 (135)	80
 (126)	 (136)	51
 (116)	 (137)	49
 (116)	 (138)	61 [2.9:1]
 (116)	 (139)	32 [1:2.2]
 (127)	 (140)	63

Table 4: Dienes Prepared via Wittig olefination of unsaturated carbonyl compounds.

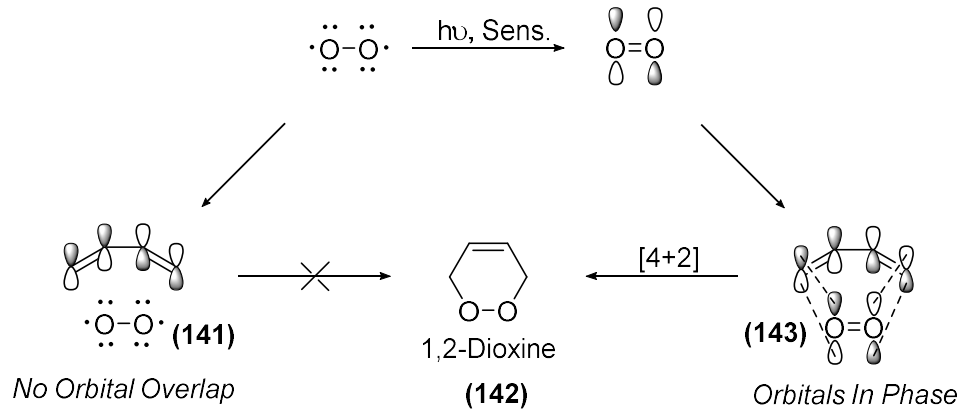
One example of a monosubstituted terminal 1,3-diene **136** was prepared by Wittig olefination of acrolein **126**, and the sole example of a tetra-alkyl diene was generated by the olefination of 3-methyl-3-nonen-2-one (a methylated analogue of the commercially available 3-nonen-2-one). For this diene, the precursor enone **127** had to be prepared prior to formation of the carbon-carbon double bond. A simple aldol reaction between butanone and hexanal in the presence of aqueous sodium hydroxide, followed by distillation over HBr afforded high yields of the desired unsaturated ketone on a multi-gram scale without requiring purification, allowing for the preparation of tetra-alkyl diene **140 (Scheme 19)**.



*Scheme 19. Preparation of diene **140** via dimethyl enone **127**.*

Olefination reactions typically proceeded smoothly in good to excellent yields on gram scales, however, dienes were obtained in all but a few cases as a mixture of *E*- and *Z*- isomers; a common observation made when undertaking Wittig olefination chemistry. With the knowledge that these stereocenters would ultimately be eliminated upon generation of the planar furan ring systems, isomerisation to one isomer was deemed unnecessary. It should be noted however, that a mixture of stereoisomers was observed in the oxidised products after treatment with singlet oxygen, so should be acknowledged by those intending to harness endoperoxides for alternative purposes especially when unsymmetrical 1,3-dienes are employed as substrates for oxidation with $^1O_2$.

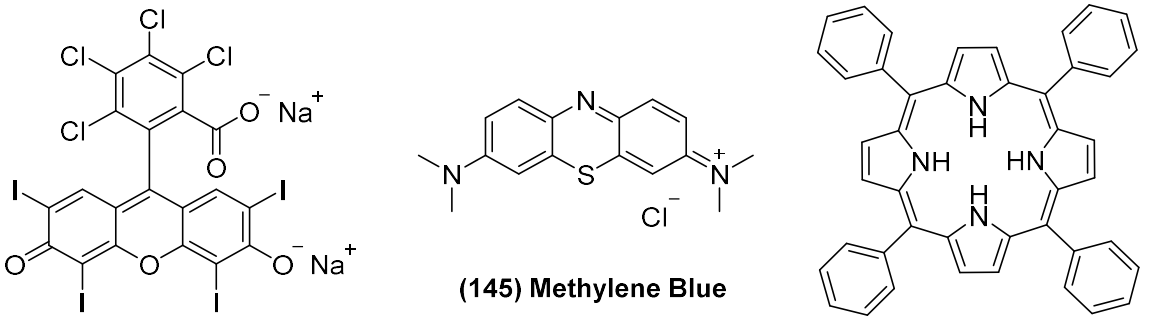
Singlet oxygen ($^1O_2$) is an excited state of molecular oxygen which may be produced by a number of different methods, both naturally and in a laboratory environment. Ground state oxygen ($^3O_2$) exists in a triplet state, having two unpaired electrons, and behaves as a diradical. Ground state oxygen does not possess a formal double bond allowing for participation in pericyclic reactions. Singlet oxygen, however, has the two electrons spin paired, and as a result the molecule can react in a two-electron fashion, behaving similarly to species such as ethylene; with orbital symmetry being such that pericyclic reactions are feasible.[76]



Scheme 20. Orbitals for the [4+2] cycloaddition of 1,3-dienes with dioxygen.

Naturally occurring singlet oxygen is present in the upper atmosphere at a product of the photolysis of ozone and by recombination of oxygen atoms,[77] it is produced in plants when chlorophyll is exposed to more light energy than is required for photosynthesis,[78] and is also utilised for its antibacterial and antimicrobial properties as a defence mechanism against pathogens in both plants and animals.[79]

In laboratory environments, singlet oxygen may be generated by several methods; the most common method by far is photoinduced energy transfer, although direct chemical methods do exist.[80, 81] This method of singlet oxygen generation involves the excitation of a photosensitiser (commonly dye molecules such as disodium Rose Bengal **144**, methylene blue **145**, or tetraphenylporphyrin **146** upon irradiation with light. For the photosensitisers shown below, irradiation wavelengths all fall in the visible region of the electromagnetic spectrum.



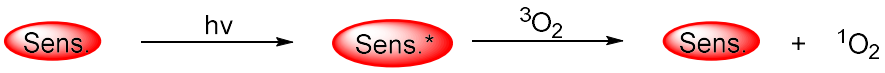
(144) Rose Bengal Disodium Salt

(145) Methylene Blue

(146) Tetraphenylporphyrin

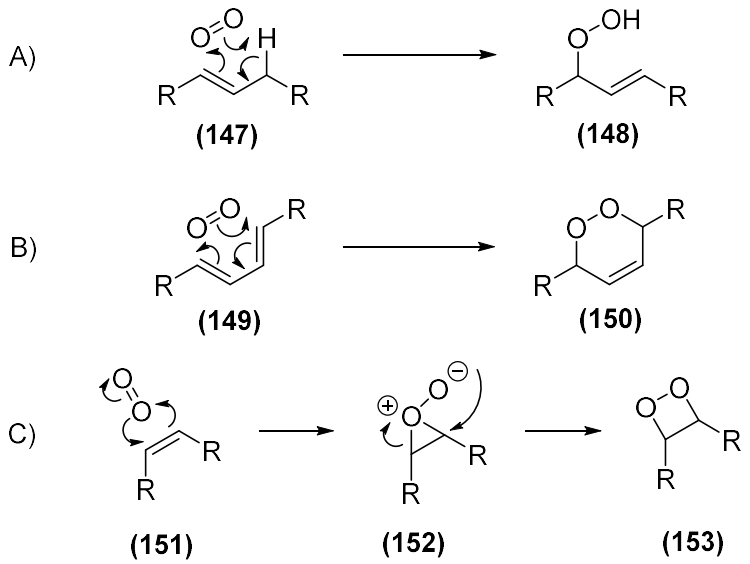
Figure 11. Three common dye photosensitisers for singlet oxygen generation.

For generation of the excited state oxygen species, a solution of the photosensitiser containing dissolved oxygen is irradiated with a visible light source. Absorption of a visible light photon by the photosensitiser leads to an excited molecular entity, which upon collision with a molecule of oxygen transfers its excess energy and generates the singlet oxygen, whilst itself returning to its lower energy state **(Scheme 21)**. To maintain a continuous supply of singlet oxygen, the replacement of the dissolved ground state oxygen can be achieved simply by a continual sparging of the solution with oxygen gas.



Scheme 21. General mechanism for the dye sensitised photogeneration of singlet oxygen.

There are three primary reactions of singlet oxygen with olefin-containing molecules; these are an ene reaction **(Scheme 22 A)** leading to the formation of a hydroperoxide **148**, a [4+2] cycloaddition **(Scheme 22 B)** of the singlet oxygen to conjugated diene systems leading to the formation of endoperoxides **150**, and finally a [2+2] addition of singlet oxygen to activated olefins **(Scheme 22 C)**, leading to the formation of 1,2-dioxetenes **153**,[79] although this latter process proceeds through a stepwise mechanism through a periperoxide **152** instead of a cycloaddition. It is the second type of reaction which was to be utilised for the synthetic preparation of furan nuclei; the addition of singlet oxygen to a range of conjugated dienes, bearing various substitution at each carbon atom of the diene system, was to provide a selection of endoperoxides which were then subsequently converted to furans by means of the Appel-type dehydration reaction.[82]



Scheme 22. The three primary reactions of singlet oxygen with olefinic compounds.[82]

In this work, endoperoxides were prepared by the treatment of analogous 1,3-dienes with singlet oxygen; a process carried out by simultaneously irradiating a solution of the diene either in a dichloromethane/methanol (95:5) mixture containing 10^{-4} M disodium rose bengal in, or in dichloromethane containing 10^{-4} M methylene blue in, with a 400W halogen lamp. Reactions were conducted in a bespoke reaction vessel **(Figure 12)** which allowed for a constant stream of oxygen to pass through the solution in the form of small bubbles. The presence of a dry ice/acetone condensing finger fitted to the gas outlet prevented solvent losses as the reaction was carried out, as continuous gas flow through the solution led to significant solvent losses when the condenser was absent. A constant flow of water through the exterior jacket of the reactor maintained the reaction at a constant temperature, as heat generated from the light source was not insignificant. The apparatus can be seen in **Figure 13** where a cycloaddition reaction was being performed, with disodium rose bengal being used as the photosensitising agent.

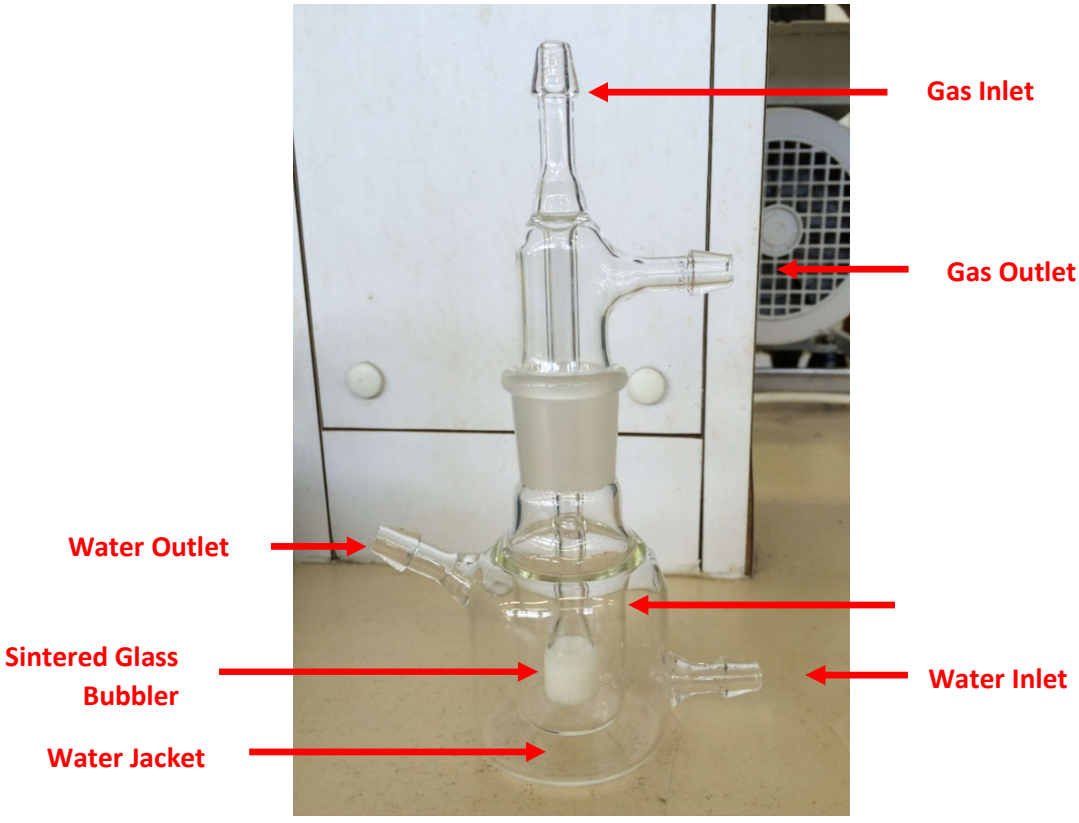


Figure 12. Custom made glassware for small scale photo-oxidations.

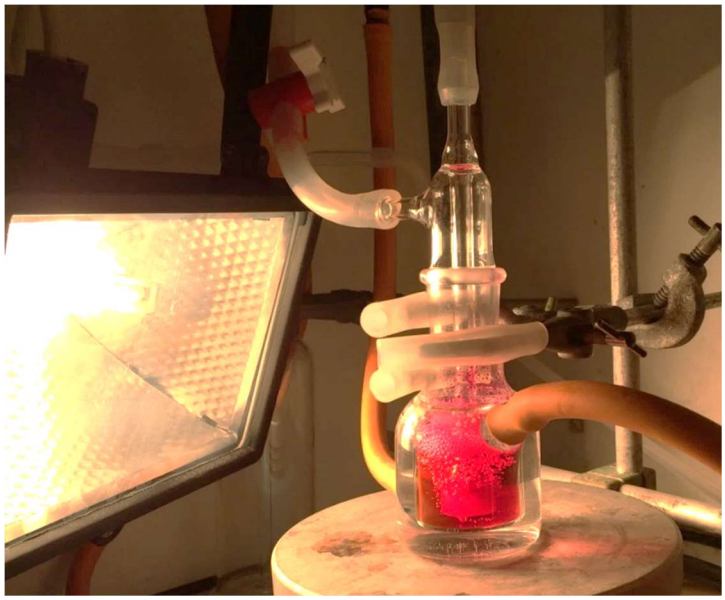
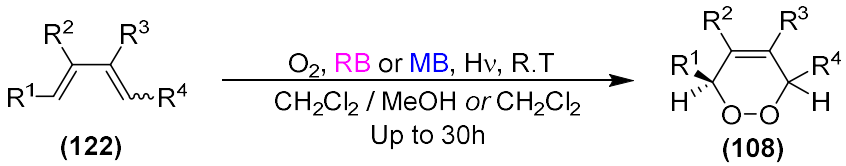
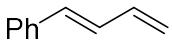
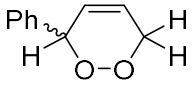
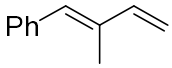
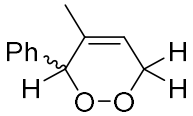
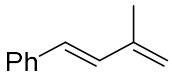
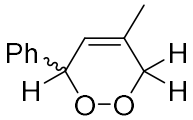
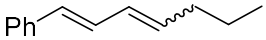
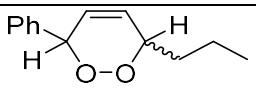
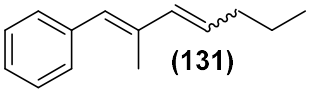
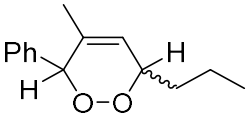
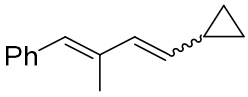
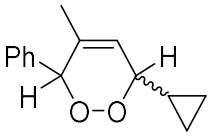
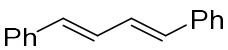
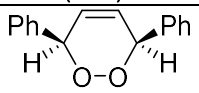
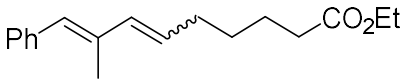
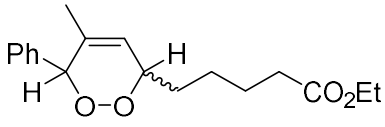
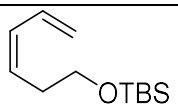
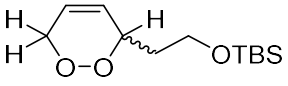
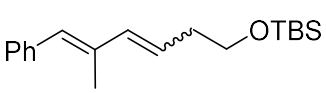
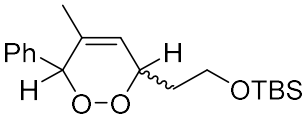


Figure 13. A singlet oxygen [4+2] cycloaddition to a 1,3-diene, employing rose bengal as photosensitiser and a 400W halogen light source.

Dienes obtained *via* the Wittig olefination of unsaturated carbonyl substrates were oxidised to endoperoxides in small-scale batch reactions, with reaction times varying between dienes (as little as 15 minutes, and up to 30h). The reaction was stopped, by removal of irradiation source, when no more diene was observable by TLC. Results of the dye sensitised photo-oxidation are summarised in **Table 5**. Dienes (with a mixture of E- and Z- stereochemistry) were used without prior separation of isomers, and as such a mixture of isomers in the endoperoxide products were obtained. As a consequence of being harnessed for the preparation of planar furans, the endoperoxide stereochemistry was not assessed further.



(122) (108)

1,3-Diene	Endoperoxide Product	Yield (%)
 (128)	 (154)	16
 (130)	 (155)	17
 (135)	 (156)	26
 (129)	 (157)	28
 (131)	 (158)	47
 (132)	 (159)	28
 (104)	 (105)	56
 (134)	 (160)	39
 (136)	 (161)	31
 (133)	 (162)	38

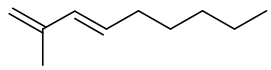
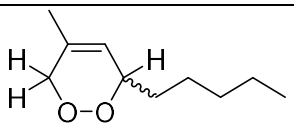
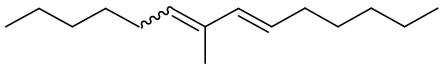
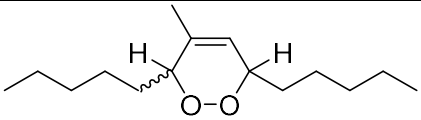
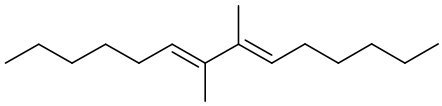
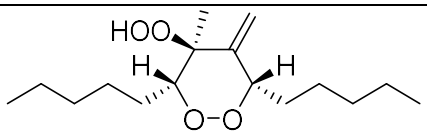
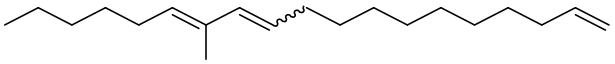
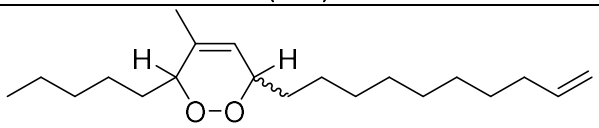
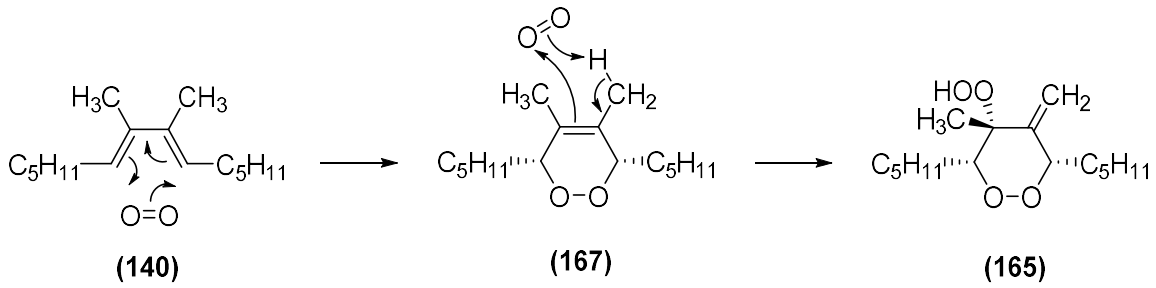
 (137)	 (163)	51
 (138)	 (164)	50
 (140)	 (165)	86
 (139)	 (166)	49

Table 5. Cyclic peroxide products obtained from the photo-oxidation of their parent dienes.

Whilst exploring the photooxidation of various substrates, it was discovered that the treatment of heavily electron-rich tri- and tetra-alkyl dienes led to significant quantities of over-oxidation products which were unsuitable for further treatment with the Appel reagent to effect aromatisation to the desired furan products. A notable example was that of 1,4-dipentyl-2,3-dimethylbutadiene **140**, with the primary product of the photooxidation corresponding to a bisperoxide system **165**. It is thought that the diene underwent the desired [4+2] cycloaddition reaction, giving rise to the desired 1,2-dioxine, however, the endoperoxide product proved more reactive toward singlet oxygen than its precursor; likely due to the locked configuration of the newly formed olefin moiety of the cyclic peroxide, and the adjacent methyl groups.

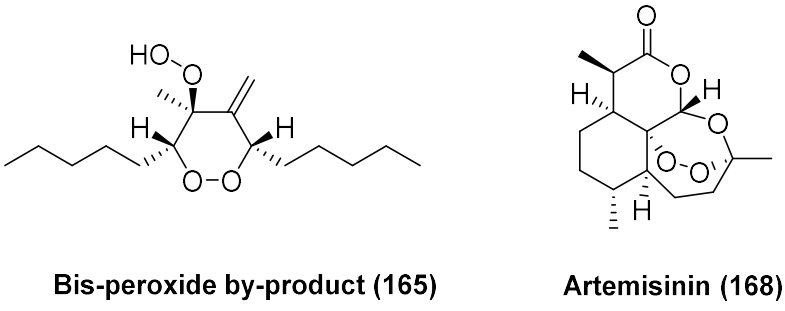
Rapid conversion, *via* an ene reaction **(Scheme 23)** led to the formation of the aforementioned bis peroxide system which has been noted only once in the literature by the photooxidation of hexamethylbenzene,[83] and analogous methylated aromatics (naphthalene, anthracene, etc.). Stereochemistry and structure were confirmed by NoE and TOCSY NMR experiments.



Scheme 23. Proposed mechanism for the over oxidation of electron rich, heavily alkylated dienes.

Despite being a synthetically interesting scaffold, with significant scope for modification stemming from the presence of two different peroxide functionalities and an olefinic moiety, all in close proximity to one another, the bis-peroxide could also be investigated as a potential antimalarial agent. The cyclic peroxide artemisinin **168** is currently in use as a potent antimalarial, with the high activity being attributed to the presence of the peroxide bridge functionality.[84]

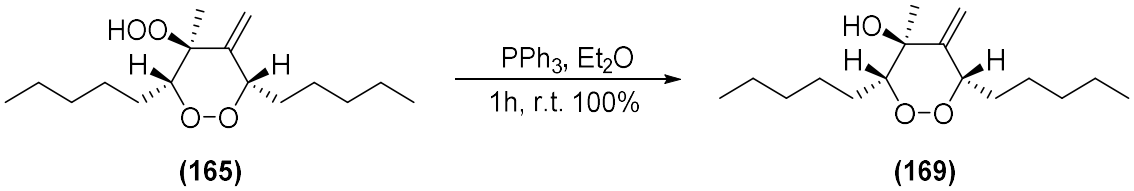
The development of novel peroxide-based compounds could aid in limiting disease resistance. Interestingly, the bis-peroxide **165** formed by the overoxidation of diene **140**, bears distinct structural similarities to artemisinin (**Figure 14)**. Consequently, this chemistry may be applied to the development of a synthetic route to artemisinin derivatives, where currently semi-syntheses are employed.



Bis-peroxide by-product (165) **Artemisinin (168)**

Figure 14. Structural similarities between the over oxidation product of diene 140, and the antimalarial Artemisinin.

The potential of the easily obtained bis-peroxide scaffolds was explored briefly, with the discovery that the potentially explosive bis-peroxiode system can be converted to a 4-hydroxy 1,2-dioxine **169** *via* a chemoselective reduction of the hydroperoxide functionality to the corresponding alcohol by simple treatment with triphenylphosphine in diethyl ether **(Scheme 24)**. This conversion allowed for a rapid and selective reduction of the hydroperoxide functionality without cleavage of the cyclic peroxide, which allows for easy, rapid access to artemisinin-type frameworks from simple diene precursors, with appropriate stereochemistry being transferred from diene geometry.



(165) **(169)**

Scheme 24. Chemoselective hydroperoxide reduction.

^{1}H NMR spectroscopic analysis of the crude reaction mixture (hence the presence of aromatic signals corresponding to the oxidised phosphine) clearly shows suppression of the hydroperoxide signal at approximately 8 ppm whilst leaving the endoperoxide functionality intact **(Figure 15)**.

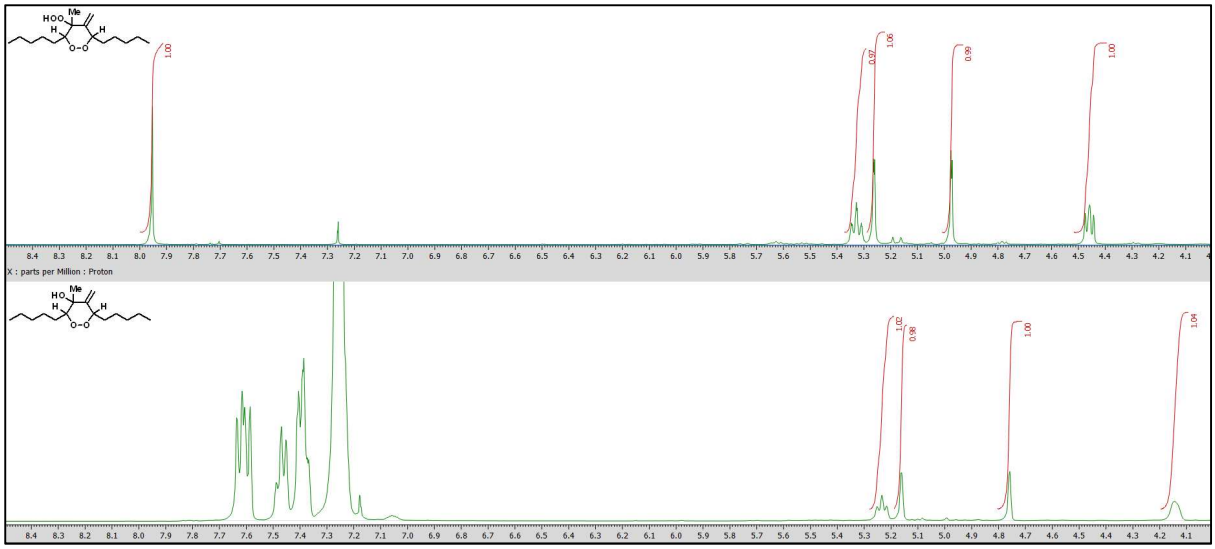
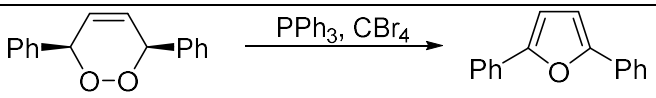


Figure 15. Stacked ^{1}H NMR spectra showing supression of the hydroperoxide proton signal at ~8ppm after treatment with triphenylphosphine.

After an initial test of the reaction to dehydrate endoperoxides using the Appel reagent, with the endoperoxide **105** being generated from commercially available *trans, trans*-1,4-diphenyl-1,3-butadiene **104**, a moderate 55% yield of the desired 2,5-diphenyl furan **106** was obtained; a brief screen was carried out to ascertain suitable conditions to perform the dehydration reaction on alternative substrates for which dienes were not commercially available; variants of the reaction are summarised in **Table 6**.



(105) **(106)**

Entry	Solvent	Temperature	Yield (%)
1	CH_2Cl_2	R.T.	55
2	CH_2Cl_2	R.T.	96*
3	CH_2Cl_2	0 °C	74
4	CH_2Cl_2	10 °C	88
5	CH_2Cl_2	R.T.	-
6	CH_2Cl_2	R.T.	-
7	THF	R.T.	58

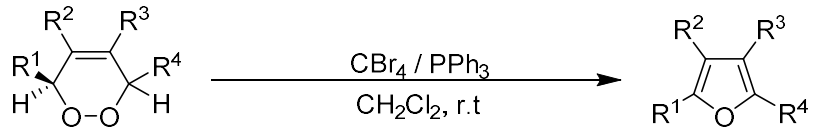
*Table 6. Results of a brief screening of endoperoxide dehydration using the Appel reagent. *Reaction performed with freshly sublimed CBr_4.*

It was found that by carrying out the reaction with freshly sublimed tetrabromomethane led to a marked increase in the overall reaction yield, with an additional 41% yield of furan product being generated with a purer reagent (entry 2). Entries 3 and 4 were performed at lower temperatures (0 °C and 10 °C respectively) which afforded lower conversions to the aromatic heterocycle; the reaction yield being proportional to the temperature at which the reaction was carried out within the small scope of this screen.

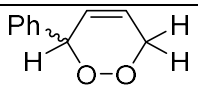
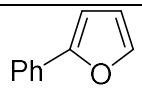
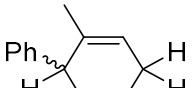
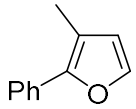
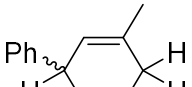
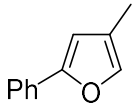
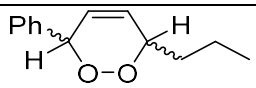
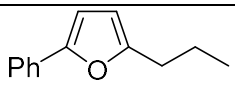
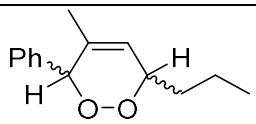
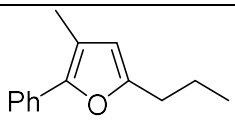
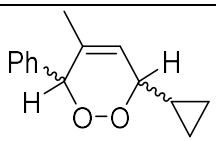
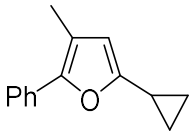
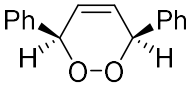
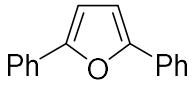
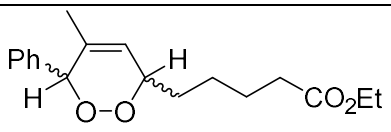
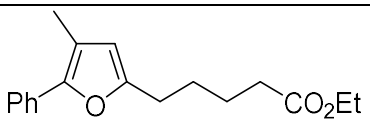
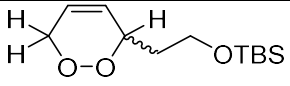
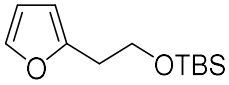
Performing the reaction in the absence of either triphenylphosphine (entry 5) or tetrabromomethane (entry 6) afforded no conversion of the endoperoxide, indicating the necessity for the Appel reagent to be present for the transformation to proceed, and that the reaction was not proceeding *via* degradation of the carbontetrabromide or by a classical phosphine mediated peroxide reduction.[85]

Finally, carrying out the reaction in tetrahydrofuran (entry 7), as a potential greener alternative to dichloromethane, led to a significantly supressed yield and less clean reaction of the furan compared to that of entry 2, making isolation of the pure product significantly more difficult.

With a set of conditions to hand that provided high furan yields and clean reactions for the test endoperoxide, an expansion to a range of substrates was carried out; results are highlighted in **Table 7**. The chosen substrates possessed one, two, or three substituents about the endoperoxide, with alkyl and aryl substituents, cyclopropane rings, esters, alkenes, and silyl ethers all being well tolerated by the reaction. The Appel-type endoperoxide dehydration afforded generally excellent yields of the desired furan products after 16 hours at r.t., with the desired electron rich trialkyl furans common to furan fatty acids being produced in good yields, albeit after a slight extension of reaction time.



(108) (26)

Endoperoxide Substrate	Furan Product	Yield (%)
 (154)	 (170)	82
 (155)	 (171)	91
 (156)	 (172)	87
 (157)	 (173)	76
 (158)	 (174)	50
 (159)	 (175)	93
 (105)	 (106)	95
 (160)	 (176)	98
 (161)	 (177)	94

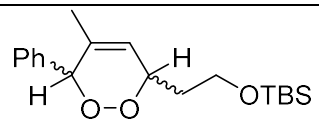
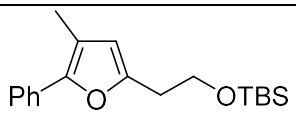
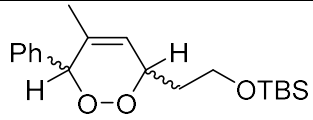
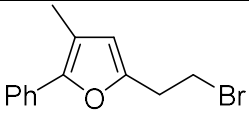
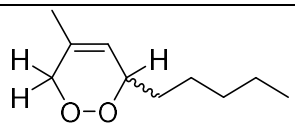
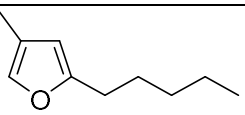
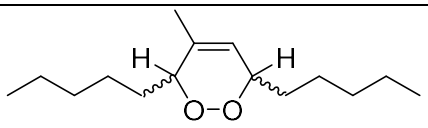
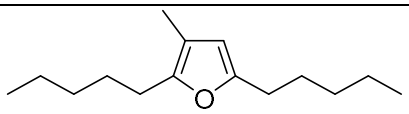
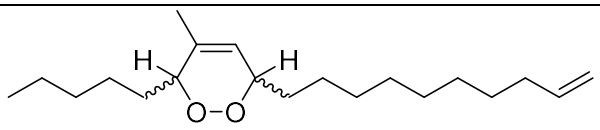
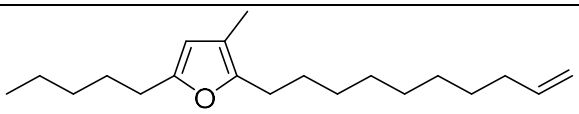
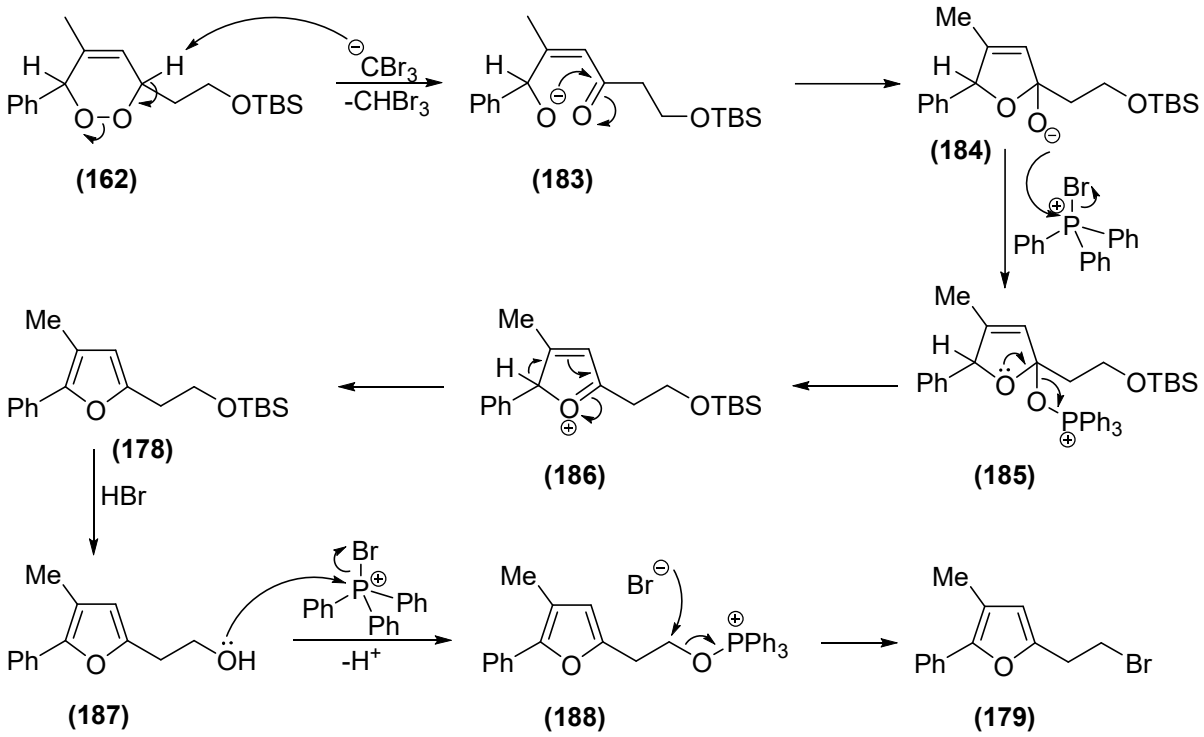
 **(162)**	 **(178)**	63*
 **(162)**	 **(179)**	91**
 **(163)**	 **(180)**	83
 **(164)**	 **(181)**	72
 **(166)**	 **(182)**	54

*Table 7. Furans and their respective yields from Appel-type dehydration of parent endoperoxides. *Reaction performed with standard conditions (1.1eq. Appel reagent at room temperature). **Reaction performed with 2.2 eq. Appel reagent and heated to reflux.*

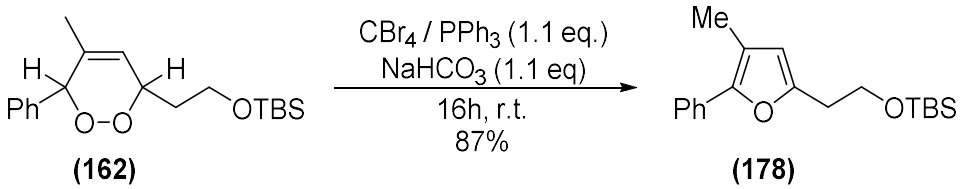
As is most often the case when performing novel chemical reactions, it tends to be the unexpected products of a reaction that prove to be some of the most interesting. This was definitely true of furan entries **178** and **179** in **Table 7**, where a trace quantity of furan **17** was observed when performing the Appel type dehydration of the silyl ether containing endoperoxide **162** under the standard reaction conditions (1.1 eq. of Appel reagent). It was postulated that HBr liberated during the endoperoxide dehydration was slowly facilitating cleavage of the terminal silyl ether, affording a furan bearing a primary alcohol tethered to the heterocycle. This alcohol would then be susceptible to a classical Appel reaction, in which the hydroxyl group is transformed to the corresponding primary bromide by reaction with the active phosphorus (V) species present in the reaction mixture, followed by substitution with a free bromide ion in the reaction mixture **Scheme 25**.



*Scheme 25.Proposed mechanism for the one-pot conversion of silyl ether containing endoperoxide **162** to the alkyl bromide bearing furan **179** via expected product **178**.*

To test this theory, the dehydration was performed using 2.2 equivalents of triphenylphosphine and carbon tetrabromide to facilitate alcohol to bromide conversion without hindering the dehydration of the endoperoxide by consuming the active P(V) reagent before it was able to undergo the aromatisation sequence. To combat the slow cleavage of the silyl ether, the reaction was heated to reflux to accelerate alcohol formation. By modifying the reaction conditions, a successful one-pot, three-reaction sequence (endoperoxide dehydration / silyl ether cleavage / Appel reaction) was achieved, affording an excellent 91% yield of furan **179**.

Acid liberated from the endoperoxide dehydration cleaving the silyl ether was responsible for the supressed yields of furan **178**, by allowing for the consumption of the bromotriphenylphosphonium cation by the in-situ generated primary alcohol. It was thought that the addition of a base to the reaction mixture, to 'mop up' the acid generated during the furan formation, would allow for an increase in the yield of the desired furan **178**. With the knowledge that bases can promote Kornblum-DeLaMare rearrangement of endoperoxides, the choice of a mild base was required so as to remove acid from the reaction system but weak enough not to interfere with the Appel-type endoperoxide dehydration. The addition of solid sodium hydrogen carbonate to the reaction was successful in preventing silyl ether cleavage, with the yield of the target furan being increased from 63% in the absence of sodium bicarbonate to a far more acceptable 87% when the base was present.



Scheme 26. Increased reaction yield of Appel-type dehydration reaction to desired silyl ether containing furan in the presence of $NaHCO_3$.

It is likely that the reason for the low yield of furan **182** was due to acid mediated degradation of the electron rich trialkylfuran core, and that the addition of solid sodium bicarbonate to this, and other low yielding dehydrations, may aid in increasing the overall yield of the reactions, in a similar manner as for the suppression of silyl ether cleavage seen in the preparation of furans **178** and **179**.

3.2 Reaction Optimisation by Design of Experiments

In order to ascertain the most favourable conditions for the dehydrative aromatisation of 1,2-dioxines, using the Appel-type PPh_3 / CBr_4 system, a 3-factor design of experiments (DoE) optimisation study was performed, using a full factorial model. While chemists have long described solvents as polar or non-polar, among attributing descriptions based on their features such as those containing halogens or hydroxyl groups, these descriptors remain rather crude and rely on oversimplified observations such as “like dissolves like”. In reality, individual solvents possess too many independent variables (melting point, boiling point, dipole moment, molecular weight, density, lipophilicity, dielectric constant etc.) to practically compare the properties of one solvent versus another in this manner, and organic chemists generally rely on experience to choose solvents appropriate to the reactions they are performing. By utilising a statistical approach however, multiple solvent parameters may be condensed into fewer variables (Principal Components) which become more representative of a solvent’s properties as a whole.[86]

By plotting these principal components in a solvent space descriptor plot (**Figure 16**)[87], it becomes far easier to see the full picture; solvents that chemists class as similar to one another become grouped into regions of the plot, and the ability to select an appropriate solvent for a given reaction is made easier. By utilising principal components as factors, alongside a third variable (for which temperature was chosen), a design of experiments approach to the optimisation of the furan synthesis from endoperoxides using the Appel reagent was able to be undertaken, allowing for the best conditions for the reaction within the given space (as constrained by the selected factors of the DoE) to be ascertained.

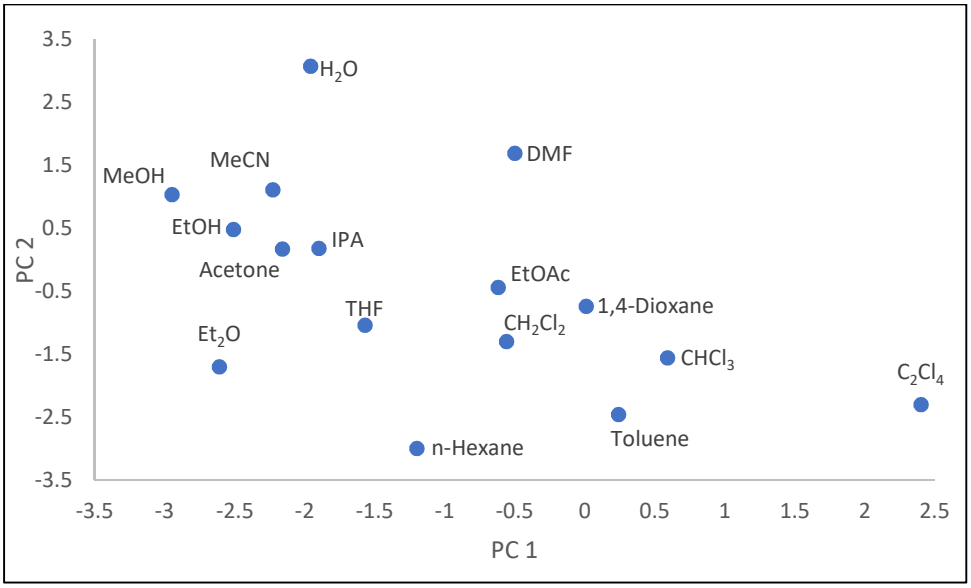
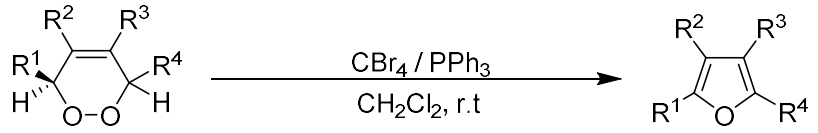


Figure 16. Simplified solvent compatibility plot used for solvent selection in a DoE optimisation study.

Using diphenyldioxine **105** as a test substrate, due to its ease of preparation on a large scale from a cheap and commercially available starting material, a series of reactions were carried out which covered the solvent compatibility plot between 0°C and 20°C **(Table 8)**. While only a small temperature window, significantly lower temperatures would result in the freezing of some of the selected solvents (with the knock-on effect of the immobilisation of reagents), whilst more elevated temperatures were ruled somewhat unnecessary due to the high yields already observed in previously conducted reactions at room temperature. Crude reaction mixtures were spiked with a known concentration of 1,3,5-trimethoxybenzene (acting as an internal standard) prior to ^{1}H NMR analysis, and furan yields were determined by comparison of furanoid βC-H peaks to that of the internal standard.



(108) (26)

Solvent	Temperature (°C)	Yield (%)
Acetonitrile	0	96
Acetonitrile	20	95
Diethyl Ether	0	93
Diethyl Ether	20	95
Dichloromethane	10	94*
1,4-Dioxane	0	91
1,4-Dioxane	20	95
Perchloroethylene	0	82
Perchloroethylene	20	88

*Table 8. Yields obtained for the dehydration of diphenyldioxine **105** in various solvents and at various temperatures. *Value was the average taken from three reactions.*

After carrying out a statistical analysis of the reaction results using a design of experiments software package (Modde), heat maps were generated which provide a visual means of observing the data (**Figure 17**). Highest yields of the 2,5-diphenylfuran **106** product were obtained at higher temperatures, low PC1 values, and high PC2 values. As can be seen from the solvent compatibility plot, the latter two variables correspond to what are often designated highly polar solvents; due to the Appel conditions originally being utilised for the conversion of alcohols to halides,[74] polar protic solvents are unsuitable for the dehydration reaction. Consequently, acetonitrile proves to be the optimum solvent for the reaction, with the highest yields being observed at room temperature. Further elevation of the temperature of the reaction would likely lead to increased, and possibly quantitative, yields however this was not pursued due to a percentage conversion of up to 96% at room temperature being deemed acceptable.

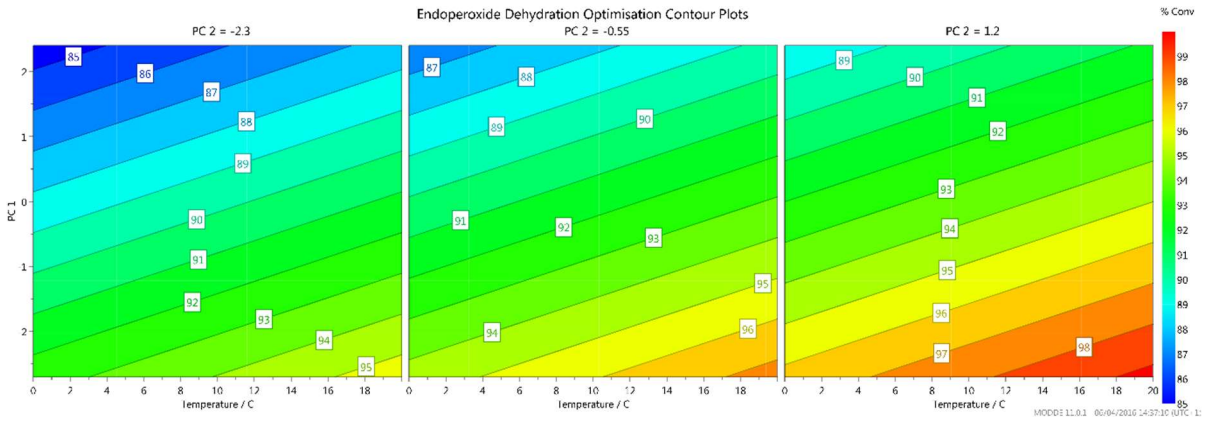
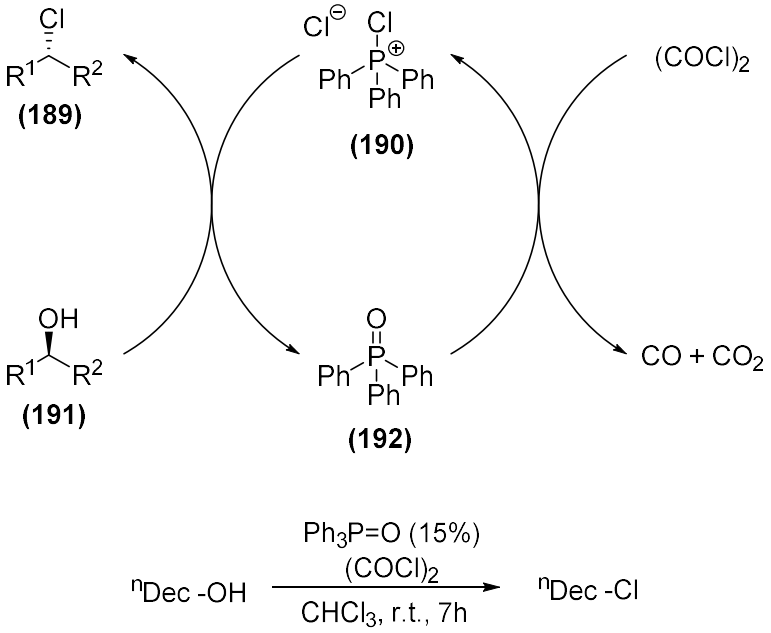


*Figure 17. Reaction yield optimisation contour plots for the dehydration of **105**.*

3.3 Catalytic dehydration of 1,2-dioxines using a modified Appel approach

With successful conditions for an efficient endoperoxide dehydration route in hand, both from the DoE optimisation study and through experimental testing on multiple substrates, it was then postulated that modifications to the route were possible. Drawing on the knowledge of Denton group's work on making the Appel reaction catalytic with regards to the phosphorus reagent **(Scheme 27)**,[88] it was thought that a similar approach would be applicable to the dehydration of endoperoxides. The catalytic Appel reaction proceeds *via* the activation of triphenylphosphine oxide **192** with oxalyl chloride. The entropically favourable reaction generates an *in-situ* source of triphenylphosphine dichloride **190**, which carries out the alcohol-to-chloride conversion, with the regeneration of the triphenylphosphine oxide catalyst. Upon reaction with another molecule of oxalyl chloride, the active P(V) reagent is regenerated, and the cycle continues.

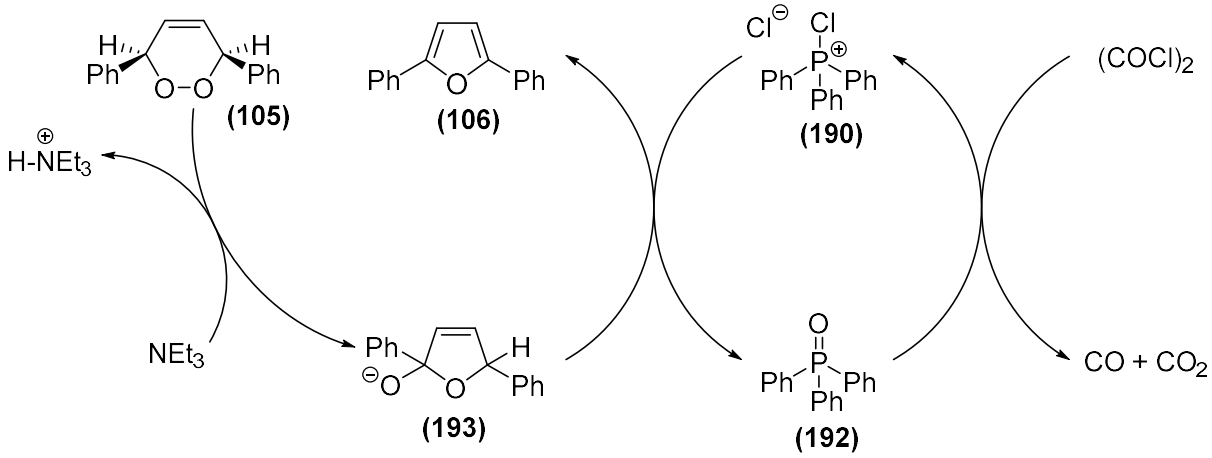


Scheme 27. Catalytic Appel Reaction by Denton et. al.[88]

By substituting the alcohol component of the Appel reaction with an endoperoxide, it was thought that a similar process would occur, leading to furan formation without the requirement for a stoichiometric quantity of halocarbon reagent and triphenylphosphine. An additional attractive feature of making the reaction catalytic would be that the requirement for the often difficult removal of phosphine oxide by-product would be minimal, with a sub-stoichiometric quantity of oxidised phosphine being present in the crude reaction mixture after cessation of the reaction.

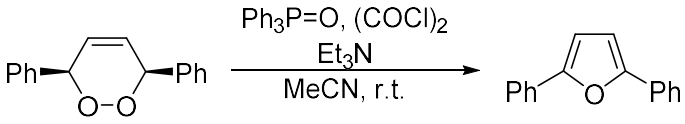
A slight modification to the catalytic Appel reaction, aside from the substitution of alcohol for endoperoxide, would be the likely necessity for the addition of a base. In the non-catalytic approach to furan formation using the Appel reagent, the generation of the active P(V) species was accompanied by the formation of the CX_3^- counterion. This anion served as a base to promote Kornblum DeLaMare rearrangement, cleaving the peroxide bond of the 1,2-dioxine substrate **105**; in the absence of this anion, the addition of a base would be required to facilitate the first step of the reaction **(Scheme 28)**.

Triethylamine was the base of choice for screening the viability of the use of catalytic conditions for the dehydration of endoperoxides to furans, owing to its properties as a strong, non-nucleophilic base. A base of this type was required for two reasons; firstly, the base was required to be strong enough to deprotonate the endoperoxide substrate, promoting Kornblum DeLaMare rearrangement to the active *cis*-γ-hydroxyenone species. Secondly, the presence of oxalyl chloride, a highly reactive species, meant that the use of a nucleophilic base would unlikely be tolerated due to the potential for decomposition of the oxalyl chloride.



Scheme 28. Catalytic dehydration of endoperoxides using a modified Appel sequence.

A series of reactions were carried out to screen conditions for the catalytic endoperoxide dehydration. Reactions were performed in acetonitrile, as determined best from the design of experiments outlined in in chapter 3.2, and spiked with 1 equivalent of trimethoxybenzene to serve as an internal standard for ^{1}H NMR analysis. No conversion was seen when diphenyldioxine **105** was treated with 10% triphenylphosphine oxide **(Table 9, Entry 1)**, nor when treated with 1 equivalent of oxalyl chloride **(Table 9, Entry 2)**. When exposed to a combination of 1 equivalent of oxalyl chloride in the presence of 10% triphenylphosphine oxide **(Table 9, Entries 3 and 4)**, trace quantities of diphenylfuran **106** were observed, but the dioxine remained the primary component of the mixture.



(105) (106)

Entry	Endoperoxide	$OPPh_3$	$(COCl)_2$	Et_3N	Addition	Conversion
1	0.1 mmol	0.01 mmol	0.0 mmol	0.0 mmol	One pot	-
2	0.1 mmol	0.0 mmol	0.15 mmol	0.0 mmol	One pot	-
3	0.1 mmol	0.01 mmol	0.15 mmol	0.0 mmol	One pot	Trace
4	0.1 mmol	0.01 mmol	0.15 mmol	0.0 mmol	Dropwise	Trace
5	0.1 mmol	0.01 mmol	0.15 mmol	0.2 mmol	One pot	7%
6	0.1 mmol	0.01 mmol	0.15 mmol	0.2 mmol	Dropwise	10%
7	0.1 mmol	0.0 mmol	0.0 mmol	1.0 mmol	One pot	-

Table 9. Percentage conversions for catalytic endoperoxide dehydration under different conditions.

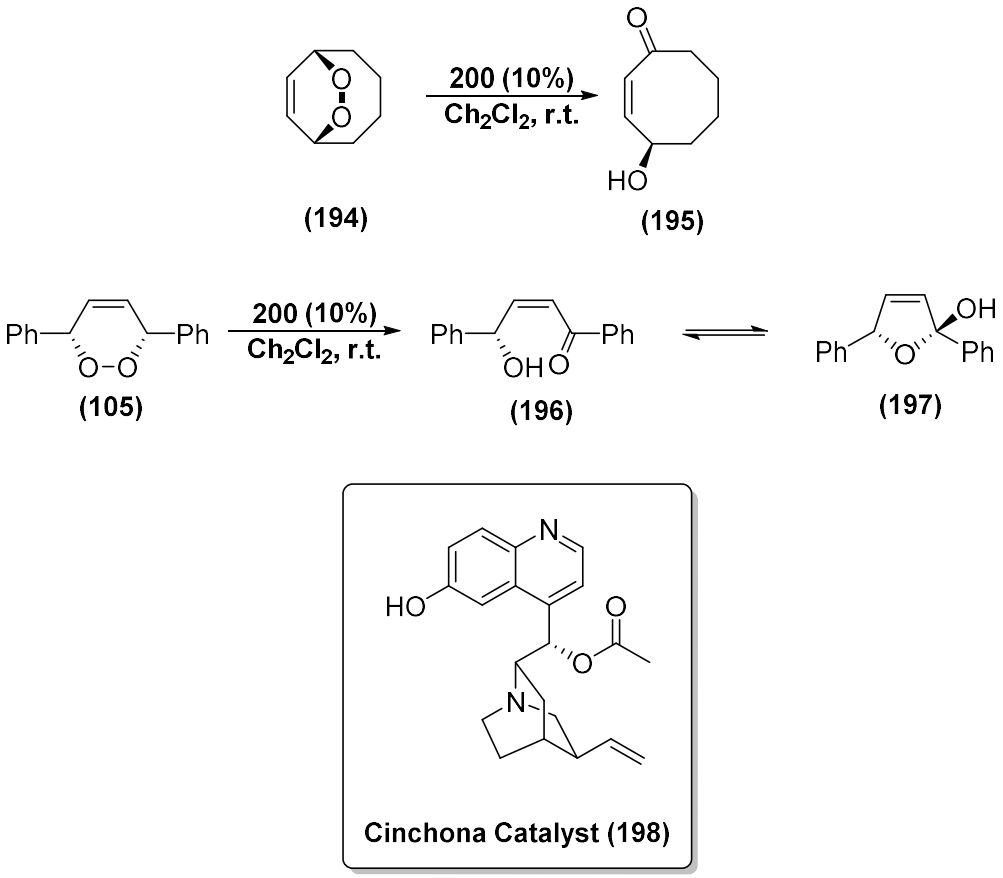
Upon the addition of 2 equivalents of triethylamine to the reaction **(Table 9, Entry 5)**, 1,2-dioxine was completely consumed, and a 7% yield of the furan was obtained; by switching to a dropwise addition of a solution of endoperoxide to a mixture of triphenylphosphine oxide, oxalyl chloride and triethylamine, an increase in yield to 10% was observed. Whilst a low yield, this preliminary study demonstrates the viability of the reaction under catalytic conditions and provides scope for optimisation. To further probe this variant of the Appel-type dehydration of endoperoxides, a ^{31}P NMR study could be carried out to observe the behaviour of the phosphorous species during its inactive and inactivated states, alongside when it interacts with the species being dehydrated.

Treatment of the endoperoxide with just triethylamine **(Table 9, Entry 7)**, led to complete consumption of the endoperoxide, however no furan was produced; the product presumably corresponding to the *cis*-γ-hydroxyenone species **101** formed *via* Kornblum DeLaMare rearrangement.

It should be noted however, that significant decomposition of the oxalyl chloride upon addition of triethylamine to the reaction mixture was observed, with gas evolution being evident immediately after addition of the base. Consequently, this may be a significant factor contributing to the low reaction yields observed during this brief screen of catalytic conditions for the dehydration of endoperoxides to furans. With the base mediated cleavage of the endoperoxide being the initiating factor in the aromatisation sequence, it is likely that formation and isolation of the *cis*-*γ*-hydroxyenone prior to dehydration would be advantageous with respect to the overall yield, whilst reducing the time required to form the furan ring system by eliminating the endoperoxide rearrangement and avoiding unwanted oxalyl chloride consumption by base.

The use of alternative bases such as diisopropylamine, diisopropylethylamine (Hünig's base / DIPEA), N,N-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) all proved unsuccessful, with degradation of the oxalyl chloride being observed. Attempts to use carbonyldiimidazole (CDI) as a milder reagent to activate the phosphine oxide catalyst and to generate a base *in-situ* were also unsuccessful, with no reaction being observed.

As previous work by Toste *et al.* has shown, endoperoxide desymmetrisation can be achieved by treatment of the cyclic peroxide with a modified cinchona catalyst **198 (Scheme 29, top)**.[89] By utilising this chemistry to pre-form the required substrate for the catalytic variant of the furan formation using the Appel reagent **(Scheme 29, centre)**, the omission of a stoichiometric base in the dehydration step could be achieved and significantly increased furan yields obtained whilst supressing the decomposition of the oxalyl chloride reagent. Utilising this approach in future work could lead to a greener method of harnessing the Appel reaction for the dehydration of endoperoxides to furans.

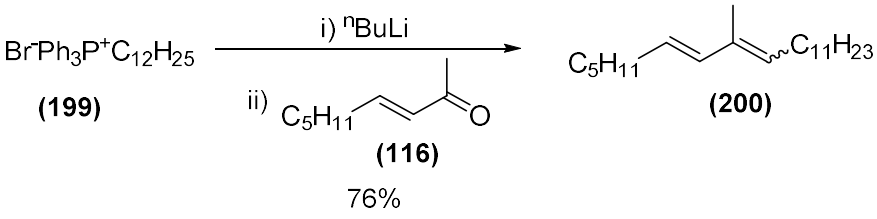


Scheme 29. Endoperoxide desymmetrisation using a Cinchona catalyst (Top),[89] proposed route to rearranged endoperoxide using Cinchona catalyst desymmetrisation (centre), Cinchona alkaloid catalyst used for endoperoxide desymmetrisation (Bottom).

3.4 Total Synthesis of Furan Fatty Acid F_5

With the overall goal of the total synthesis of the furan fatty acid F_5, efforts were then focused on the preparation of the natural product. After the discovery of the increased susceptibility of tetraalkyl dienes to overoxidise to the corresponding bisperoxides, efforts were focused on the synthesis of a trisubstituted F-Acid, of which F_5 was chosen, due to the reduced tendency of trialkyl dienes toward overoxidation compared to their tetraalkyl analogues. While ultimately successful, synthesis of the target F-Acid was non-trivial.

Starting with commercially available 3-nonen-2-one **116**, a Wittig olefination with dodecyltriphenylphosphorane – itself formed by treatment of the corresponding phosphonium salt with ^{n}BuLi – was carried out to test the viability of the enone olefination reaction with a long alkyl chain phosphorus ylide; the product from this reaction would only differ from the diene corresponding to F_5 by the absence of the terminal carboxylate functionality.



Scheme 30. 1,3-diene preparation via Wittig olefination to test the feasibility of enone olefination with long chains.

The reaction proceeded smoothly, affording the desired hydrocarbon in a modest yield of 76% as a 1:2.5 mixture of isomers, yet showing the expected olefinic proton splitting patterns corresponding to the 1,3-diene subunit **(Figure 18)**. With the knowledge that unsaturated ketone substrates could be successfully olefinated with high chain length alkyl phosphoranes, the preparation of the diene for the synthesis of F_5 was then attempted.

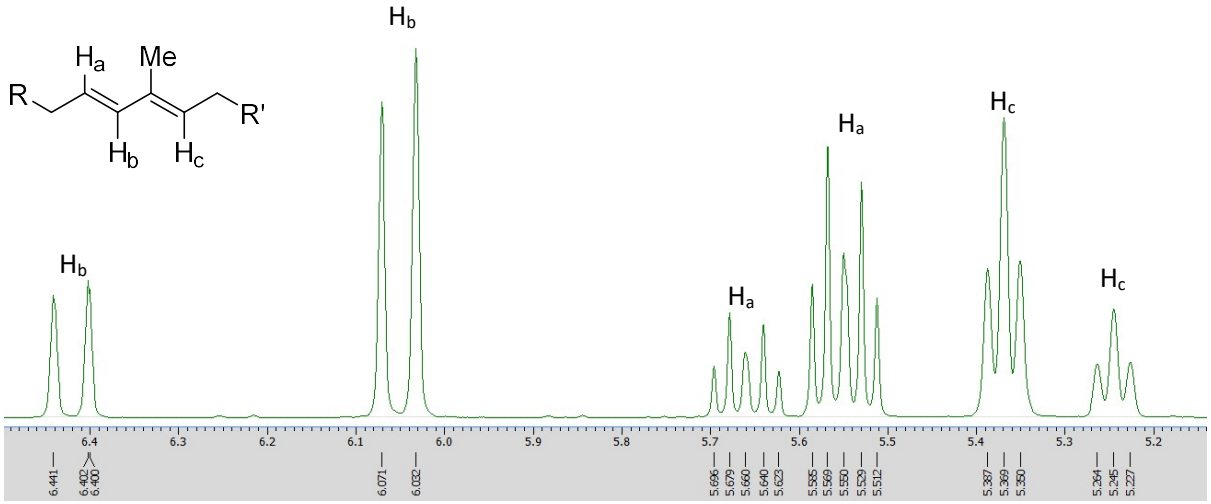
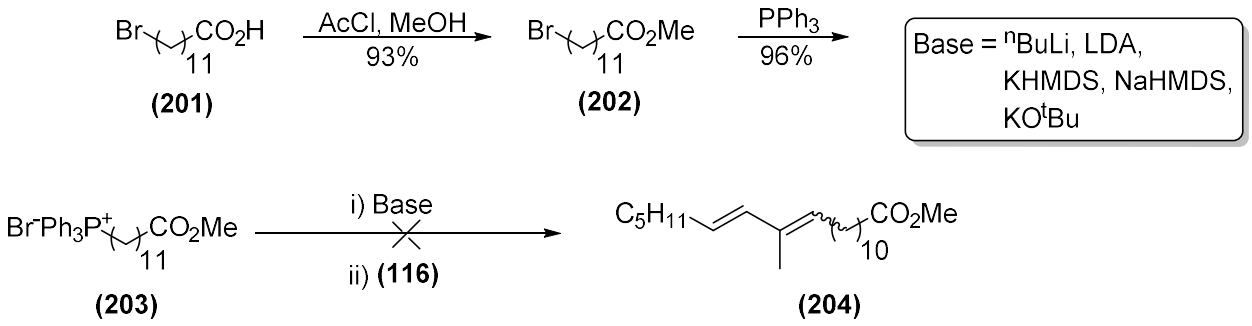


Figure 18. ^{1}H NMR spectrum of olefinic protons for trialkyl 1,3-dienes.

Initial attempts for the preparation of phosphonium salt **205** for the F_5 diene were carried out by esterification of 12-bromododecanoic acid **203** with HCl/MeOH; the addition of acetyl chloride to anhydrous methanol facilitated the formation of an anhydrous source of HCl, which catalysed the esterification of the long chain carboxylic acid in excellent yields and high purity after a simple aqueous work-up with sodium bicarbonate. Subsequent treatment of the esterified species with triphenylphosphine allowed for the formation of the desired phosphonium salt as a viscous tar **(Scheme 31)**.

Unfortunately, when performing olefination reactions with the ester-containing phosphonium salt, under the same conditions as those applied to dodecyltriphenylphosphonium bromide, complete decomposition of the starting materials was observed. No olefinic protons were observed in the ^{1}H NMR spectrum of the crude product, including those of the starting 3-nonen-2-one **116**, and the recovered material being in the form of an uninspiring black tar.



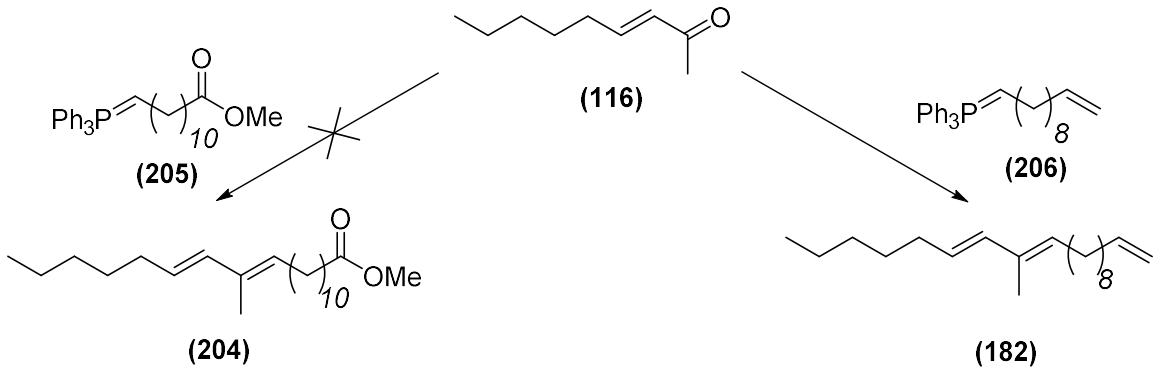
*Scheme 31. Attempted synthesis of F_5 diene precursor **204**.*

At first, this was attributed to the use of butyllithium; the presence of a strong base may have been reacting with the ester functionality of the phosphonium salt rather than forming a stable ylide in high quantities. It should be noted however, that the formation of at least a small quantity of the desired phosphorane was being generated, as the characteristic cherry-red colour of many phosphorus ylides was observed prior to enone addition. The resulting excess of strong base may have led to either deprotonation of the unsaturated carbonyl compound to give an unsaturated enolate, followed by reaction with a second equivalent of enone or a similar reaction. An alternate possibly was the direct addition of the alkyllithium species to the unsaturated ketone, followed by reaction with another species present in the reaction mixture.

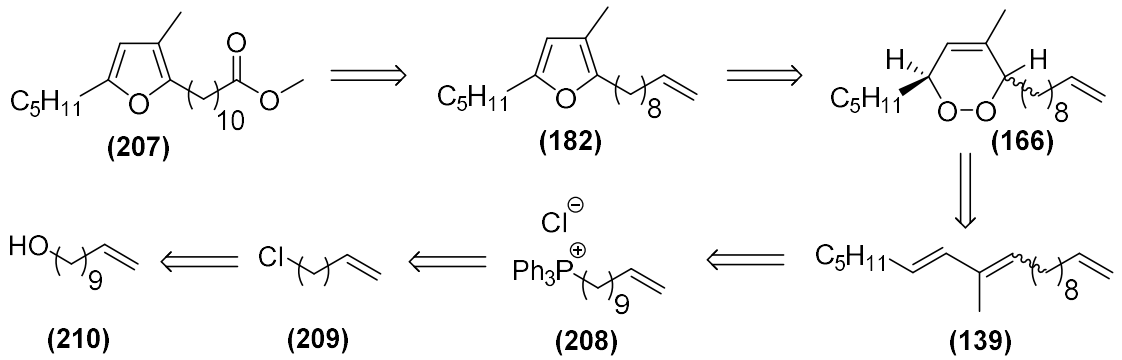
Unfortunately, when alternative (milder and less nucleophilic) bases were employed, the outcome was the same; the use of LDA, KHMDS, NaHMDS, and KOtBu all proved unsuccessful, with no olefinic protons or ester protons being present in the ^{1}H NMR spectra of the crude reactions mixtures. Dilution of the reaction mixture to minimise side reactions also proved unsuccessful, as did a slow addition of enone to the reaction mixture after base was added to the phosphonium salt. Interestingly, it was noticed that the appearance of the strong cherry red colour of the ylide, was present after the addition of base in all cases.

From these observations, it can be assumed that the ylide was indeed forming, however it was unable to participate in the olefination reaction. This may be the result of the two polar head groups (the phosphorus ylide and the methyl ester) tethered by the long hydrocarbon chain effectively coiling up in solution, preventing the further attack at the carbonyl of the unsaturated ketone introduced after deprotonation of the phosphonium salt, allowing for side reactions to dominate and consequently preventing diene formation.

After many failed attempts, it was concluded that the phosphonium salt was unsuitable for the preparation of **204** without significant time and resource expenditure, when an alternative approach could prove more successful. Instead of incorporating the carboxylate functionality prior to furan formation, an alkene functionality was to be present at the terminus of the long alkyl chain **(Scheme 32)**. This terminal olefin could then be subjected to a cross metathesis reaction and a subsequent catalytic hydrogenation to afford the F_5 methyl ester natural product which was desired; adding only two steps to the overall synthesis. A new retrosynthesis was designed and followed **Scheme 33**.

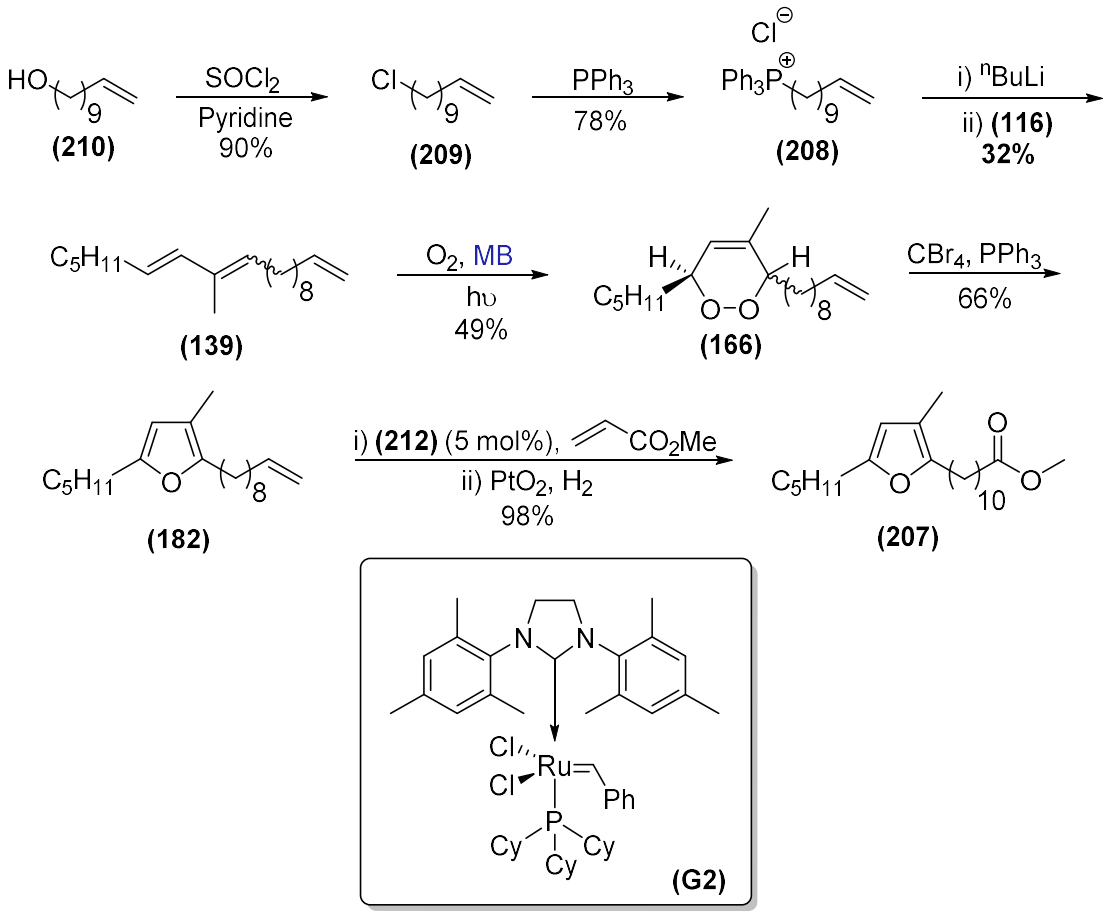


Scheme 32. Initial (left) and modified (right) routes to obtain a 1,3-diene for the synthesis of furan fatty acid F_5.



Scheme 33. Modified retrosynthetic plan for the synthesis of F_5.

The new route for the synthesis of the target natural product, furan fatty acid F_5 **(Scheme 34)**, started from commercially available 10-undecen-1-ol. By conversion of the terminal alcohol to a phosphonium salt, *via* an alkyl halide intermediate, followed by a Wittig olefination as for the previous route (this time with the omission of the polar ester functionality at one end of the hydrocarbon chain) would allow a trialkyl 1,3-diene to be obtained, bearing the aforementioned terminal alkene on the longer of the alkyl chains. After treatment with singlet oxygen to generate an endoperoxide, then an Appel-type dehydration to generate the furan core of the natural product from the cyclic peroxide, the cross metathesis/catalytic hydrogenation sequence would be able to proceed to give the target compound.



Scheme 34. Modified synthetic route to the methyl ester of F-Acid F5.

Conversion of the hydroxyl functionality of 10-undecen-1-ol **210** to an alkyl chloride by treatment with thionyl chloride and pyridine proceeded smoothly, in an excellent 90% yield. The following phosphonium salt formation was performed by reaction of the alkyl chloride with triphenylphosphine under solvent free conditions, simply by heating the two reagents to 250°C for an extended period of time. By employing a solvent in the phosphonium salt formation, it was found that significantly lower yields of product were obtained, which were also notably higher in impurities. Much like phosphonium salt **203**, this phosphonium salt was also obtained as a viscous tar, preventing the ease of purification by trituration. Repeated trituration of the crude products with large volumes of a variety of solvents was required to obtain pure material; upon performing the reaction neat, the necessity for excessive trituration was minimised.

The subsequent Wittig olefination of the phosphonium salt with commercially available 3-nonen-2-one **116** afforded diene **139**, the desired substrate for the biomimetic oxidation, however yields were only moderate at best, with a maximum of 32% conversion being obtained. Possible reasons for this are similar to those of **204**, with a slow rate of reaction permitting side reactions to contribute significantly to the end mixture, resulting in low yields.

Diene oxidation proceeded rapidly, owing to the electron-rich nature of the conjugated diene system, however large quantities of by-products were observed stemming from over-oxidation of the target compound, and a somewhat disappointing yield of 21% of the desired cyclic peroxide was achieved. By reducing the reaction time to only 15 minutes, it was found that the yield of the target endoperoxide increased. Whilst greater quantities of unreacted diene were present, a drastic reduction in the quantities of over-oxidised by-products were seen in the crude reaction mixture.

The unreacted diene was significantly easier to separate from the products of the photo-oxidation than the endoperoxide from the other oxidised species, and was also able to be re-used for a further photo-oxidation upon isolation. The discovery that reduced reaction time was beneficial to the endoperoxide yield also adds weight to the assumption that overoxidised and unwanted side products of the photo-oxidation originated from the *subsequent* oxidation of the desired cyclic peroxide, and not by some other route such as an *initial* ene reaction. Through this shortening of the reaction time, a far more acceptable (although still not as high as would be desirable) 49% yield of endoperoxide **166** was obtained.

A sufficient quantity of 1,2-dioxine was obtained from the altered photo-oxidation time for the key dehydrative aromatisation step to be performed, which proceeded smoothly to afford furan **182** in an acceptable 66% yield. To achieve this yield, an extension of the typical reaction time (from 16 to 40 hours) was required. This is somewhat unsurprising due to the presence of the large alkyl chains bound to the heterocyclic core of the molecule, which may prevent easy access of the Appel reagent to the endoperoxide functionality due to their large and sterically hindering behaviour, thus slowing down the reaction. This dehydration reaction was monitored by thin layer chromatography, with the perceived end of reaction occurring when absence of endoperoxide substrate was observed. Due to the presence of bulky alkyl chains and the slow rate of endoperoxide consumption, an increase in overall yield could possibly be obtained by further extending the reaction time to allow for conversion of intermediates to the desired furan product, without focusing solely on the consumption of endoperoxide after the initial CX_3^- mediated Kornblum-DeLaMare rearrangement.

Finally, a tandem cross metathesis/hydrogenation sequence was utilised to incorporate the terminal carboxylate functionality of the fatty acid product in a quantitative yield. Treatment of furan **182** with an excess of methyl acrylate in the presence of 5 mol% Grubbs 2nd generation catalyst, incorporated a methyl ester functionality at the terminus of the longer of the two carbon chains at the furan α-positions.

After all starting material was consumed (as indicated by TLC), 5 mol% PtO_2 was added to the reaction mixture, and the atmosphere exchanged for hydrogen to facilitate reduction of the double bond of the unsaturated ester system. Both these steps proceeded smoothly to give the esterified furan fatty acid **207**, which required only minimal purification; the reaction was easily monitored by thin layer chromatography using an acidified vanillin stain, which easily discriminated between the unsaturated and hydrogenated products which shared almost identical R_f values.

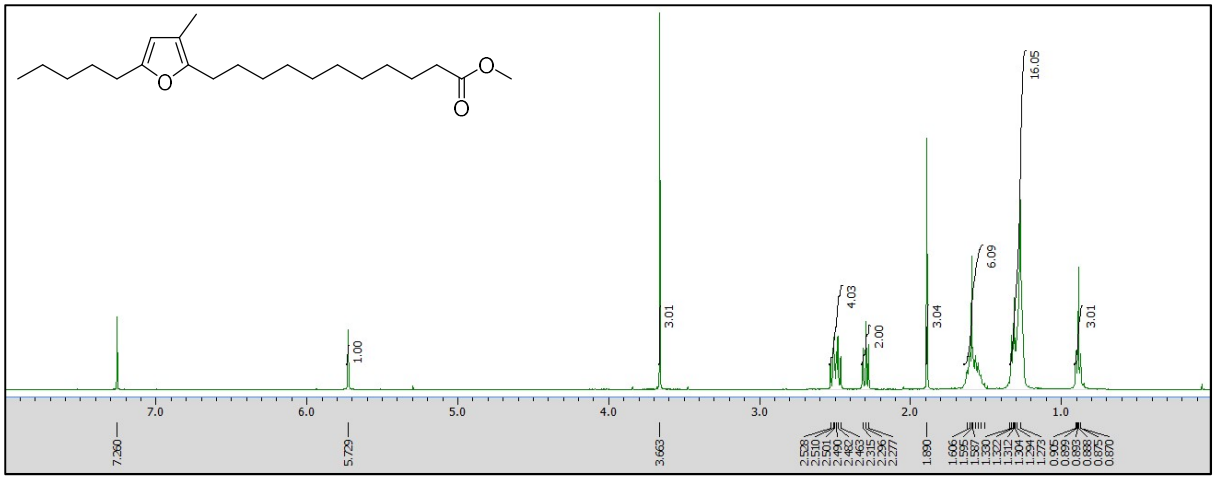
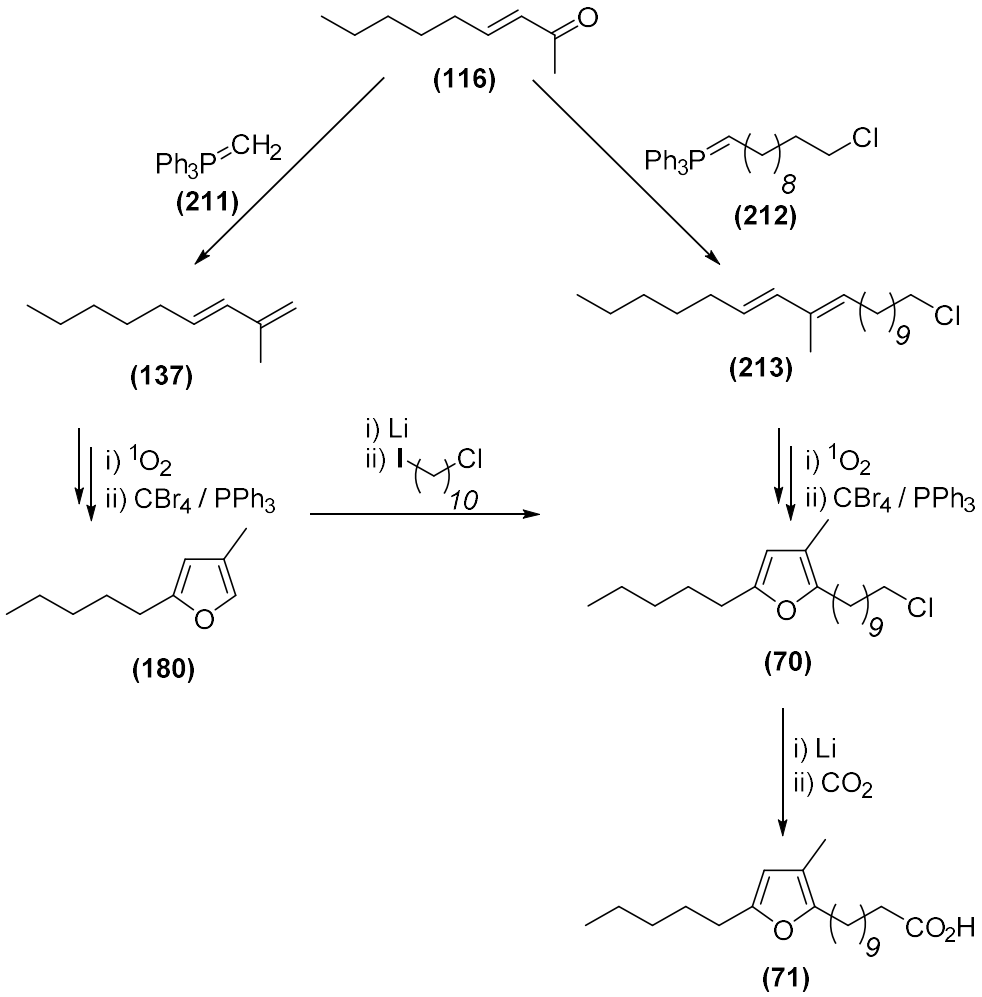


Figure 19. ^{1}H NMR Spectrum of Furan Fatty Acid F_5 Methyl Ester.

To further optimise the total synthesis of the F-Acid F_5, lower concentrations of the diene in the photooxidation step would result likely result in increased yields of the desired product, and fewer over-oxidation products (when increasing the concentration of the diene from 6.7 mg/mL to 16.7 mg/mL a marked decrease in 1,2-dioxine yield was observed – 7% as opposed to the 21% obtained at lower concentrations). The coupling of a more dilute solution with a decreased reaction time should allow for more acceptable yields being obtainable. By substituting alkyl chloride **209** for the corresponding commercially available alkyl bromide, phosphonium salt preparation should be far easier, with lower temperatures and reaction times being required to effect conversion as a result of the weaker carbon-halogen bond.

Incorporation of a section of the synthetic route by Schlenk et al. to F-Acid F_6 could also be applied to the F-Acid synthesis in one of two ways.[59] Either 1,3-dialkylfuran **180** could be prepared *via* the general method outlined in chapter 3.1, and subsequently lithiated at the unsubstituted alpha position of the heterocycle, and an alkyl chain bearing a halogen atom at each terminus added to incorporate the long chain of the F-Acid. A second lithiation followed by a carboxylation would afford the free F-Acid.

Knowing that long-chain phosphoranes may be used to olefinate unsaturated carbonyl compounds (provided they are free of a significantly polar head group), the long α-position chain could also be pre-installed before photo-oxidation. If a halogen was present at the chain end, a lithiation/carboxylation to install the carboxylic acid functionality would allow for an alternate route to access F-Acids **(Scheme 35)**.



Scheme 35. Possible alternative routes to furan fatty acids avoiding late-stage transition metal involvement.

3.5 The application of flow chemistry for the preparation of endoperoxides and furans

Whilst continuous flow processes have been exploited in other industries such as in the production of iron in a blast furnace,[90] oil refining,[91] and ammonia production *via* the Haber-Bosch process[32] for many years **(Figure 20)**, flow chemistry for organic small molecule synthesis is a relatively recent addition to the arsenal of techniques employed by synthetic chemists.[92] Reasons for this are likely due to the availability of increasingly more affordable, flexible, and modular systems for carrying out reactions in flow. Advances in microfluidic technologies, automation of flow reactions, in-line analysis, and a general increase in interest surrounding flow chemistry have all led to a greater number of researchers undertaking reactions in flow.

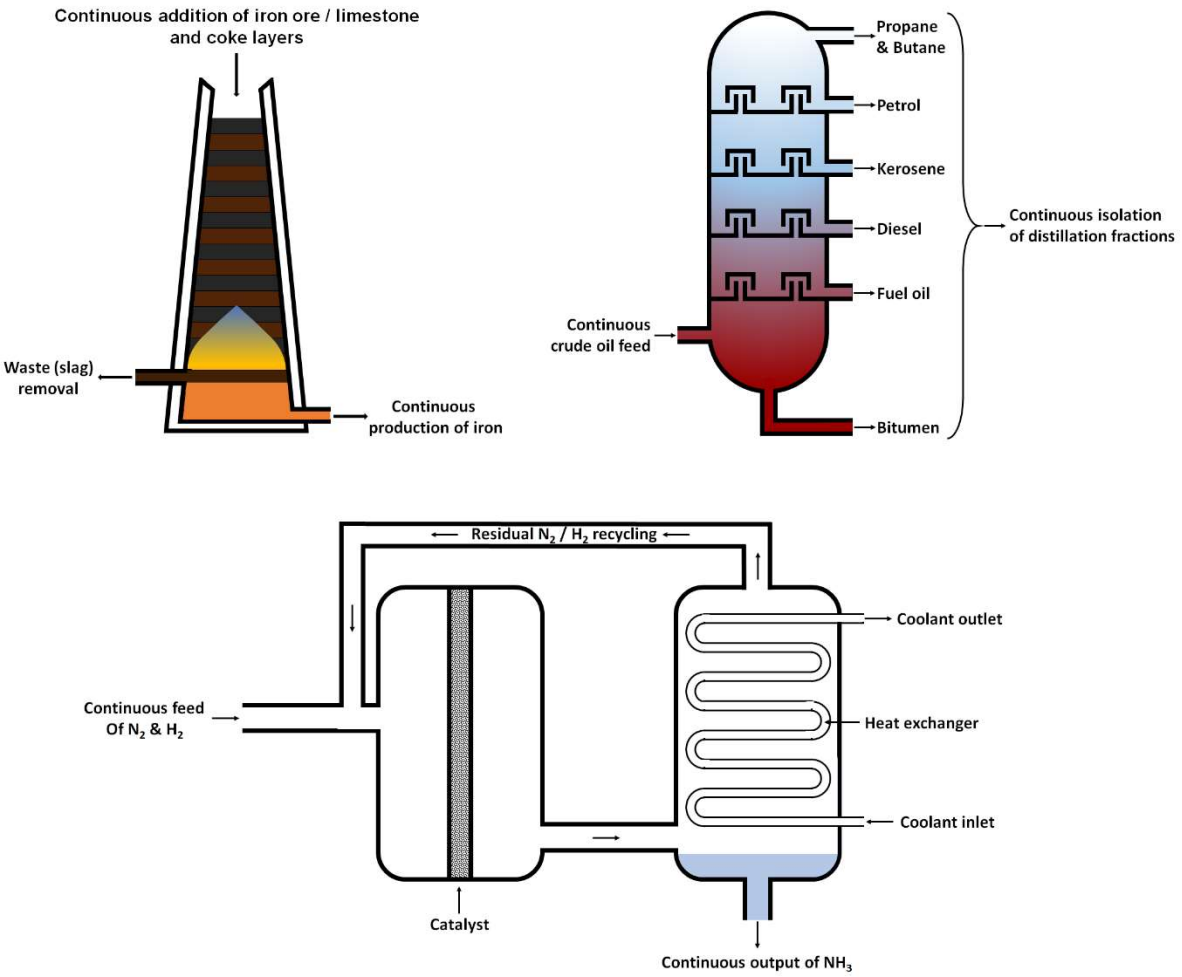


Figure 20. Examples of continuous flow processes in heavy industry.

Performing reactions in continuous flow has several advantages over traditional batch reaction processes. Notable benefits include a high degree of control over the heating and/or cooling of reaction mixtures (as heat transfer is significantly more efficient in a thin tube compared to a bulk liquid, so 'pockets' of heat are avoided) which allows for highly exothermic reactions to be performed without degrading substrates or products; an increased mixing of reagents is also seen as turbulence in the flowing liquid far supersedes that caused by conventional stirring in a flask and consequently the number of molecular collisions per second increases which can lead to shorter reaction times. Finally, the ease of scale up associated with an uninterrupted production of a desired compound, provided a constant supply of reagents is maintained requires less specialist equipment than scale-up of batch reactions.

As a result of innovative reactor designs, the scope of reactions that can be carried out in flow is continuously broadening, and historical limitations (e.g. multi-phase reactions,[93] high-viscosity reactions,[94] and those in which precipitates may be required or may form[95]) are being overcome. Whilst continuous-flow reactions may be carried out using syringe pumps as the driving force, they have several limitations. Most notably, they have a low pressure threshold in comparison to alternative systems; consequently, the use of syringe pumps does not allow for reactions to be performed at significantly elevated pressures, or in a large volume-small diameter tube (due to resistance along the tube supplying pressure). Leaks may also occur where the tubing is connected to the syringe, as these systems are not designed for appreciable back pressures.

As previously mentioned, the availability of specifically designed systems for performing in-flow reactions has hugely expanded the scope of flow chemistry. In this work, the system used was the Vapourtec E-series. This system features three peristaltic pumps, which allows for the introduction of gases into a reaction system, where classical reciprocating piston pumps (colloquially known as HPLC pumps) fail. Peristaltic pumps also have the advantage of a higher tolerance toward particulates in the reaction system than reciprocating piston pumps, which can easily become blocked.

The Vapourtec system also has the option of a photochemical reactor (the UV-150), which consists of a temperature controlled, mirrored chamber containing a 10mL coiled tube reactor encircling either an LED light source, a low pressure, or a medium pressure mercury lamp.

To test and optimise the in-flow reaction conditions, diphenylbutadiene **104** was chosen as it had been used extensively in previously performed batch reactions. Starting with conditions similar to those employed in batch, utilising a 525nm (green) light source, disodium rose Bengal as a photosensitiser at a concentration of 10^{-4}M, and the diene at 0.04M in 5% methanol / dichloromethane, a photo-oxidation was performed. Whilst pure oxygen was used as the oxidant in batch reactions, air was used for in-flow reactions; the reason for this was primarily ease of set-up and the ability to avoid the use of pressurised gas cylinders. The use of air also provides a greener alternative to pure oxygen and avoids the obvious safety hazards associated with introducing pure oxygen into a reaction system. The use of a 'Tee' splitter allowed for the generation of segmented flow **(Figure 21)**, where small plugs of solution were separated by air gaps; this provides an efficient means of enabling oxygen diffusion into the solvent, allowing the cycloaddition to proceed.

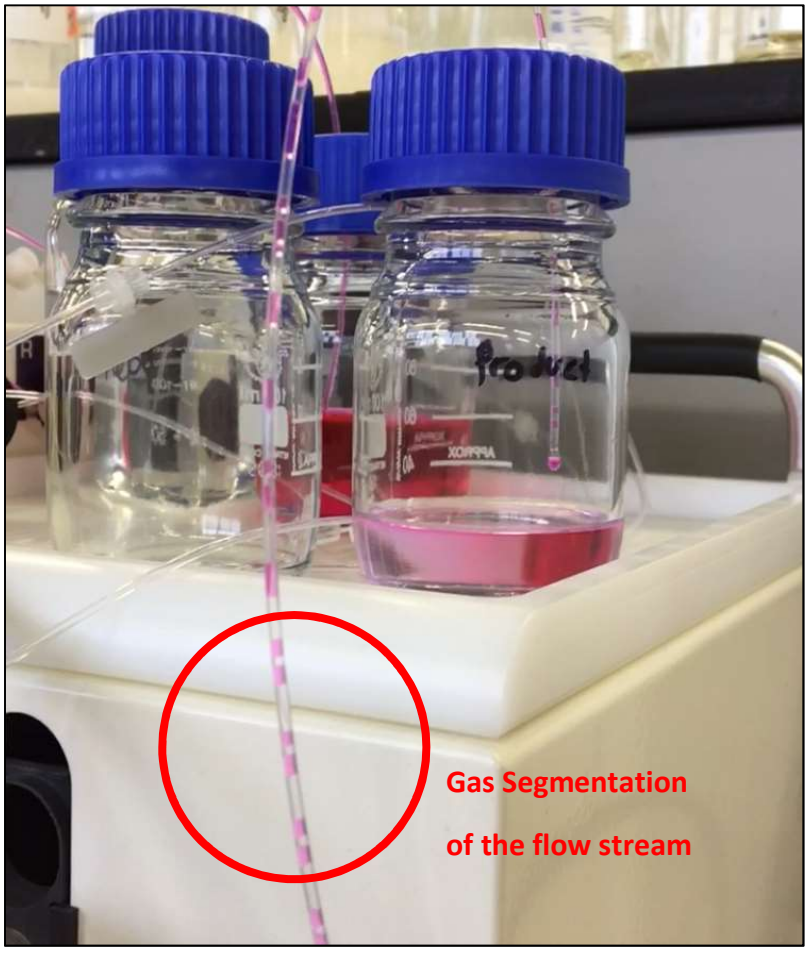


Figure 21. Segmentation of the flow stream by the introduction of air.

The initial reaction was carried out with both the diene/photosensitiser solution and air being fed into the reactor at 0.5 mL/min, leading to a residence time in the reactor of 10 minutes. ^{1}H NMR comparison of the diene and endoperoxide showed a meagre 3.5% conversion. A doubling of the residence time, by the reduction of both the diene/photosensitiser solution and air flow rates to 0.25 mL/min, resulted in a 0.4% increase in yield, while doubling of the air flow rate to 0.5 mL/min and maintaining the reagent flow at 0.25 mL/min, resulted in a satisfying increase in endoperoxide formation, with a 12% conversion being achieved. It was at this point that the reaction stoichiometry was more properly considered; due to the switch from neat oxygen to air, the O_2 concentration had altered drastically.

The reaction requires the incorporation of one O_2 molecule per molecule of diene, so accounting for the oxygen concentration in air being 0.0094 M, and with a diene concentration of 0.04 M, it was calculated that the flow rate of air would need to be approximately 4.3 times greater than that of the substrate solution to provide a stoichiometric quantity of oxygen.

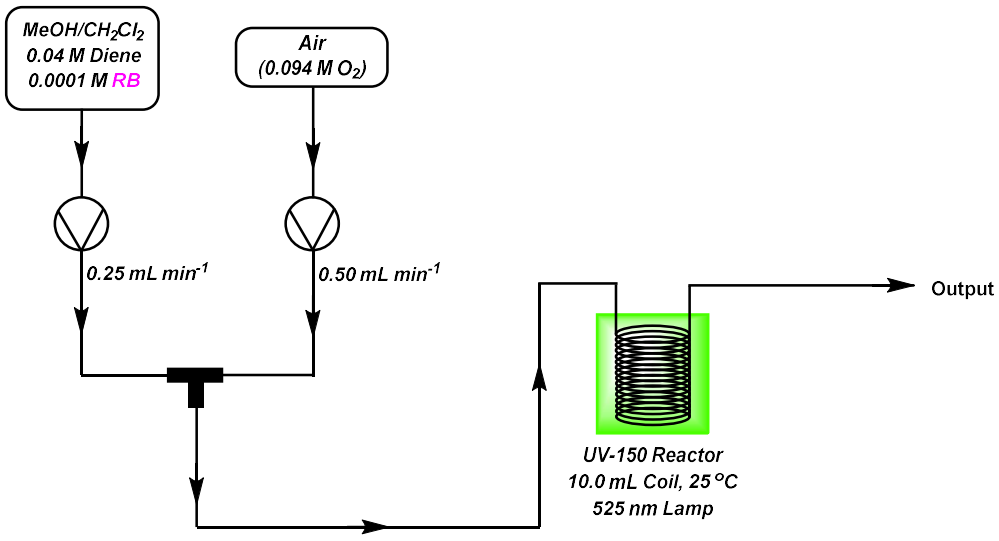


Figure 22. Reactor schematic for continuous-flow endoperoxide formation.

Another consideration was the desire to be able to directly generate the corresponding furan without isolation of the intermediate endoperoxide. It was envisioned that introduction of the Appel reagent into the output stream of the photochemical reactor, then feeding the resulting mixture through a second reactor, would allow for a simple and continuous diene-endoperoxide-furan transformation. With this in mind, it became necessary to address the solvent system in use for the photo-oxidation. The CH_2Cl_2/MeOH mixture was initially chosen as the diene was insoluble in methanol, and the photosensitiser insoluble in dichloromethane; the use of 5% methanol in dichloromethane allowed for the solvation of both components. Due to the nature of the Appel reagent, which was initially developed for the preparation of alkyl halides from the corresponding alcohols,[74] the presence of methanol was unsuitable for the tandem approach that was desired as the solvent would be competing with the endoperoxide.

Knowing from the prior DoE that acetonitrile was the best solvent for the Appel dehydration, and with the knowledge that singlet oxygen photo-oxidations may also be performed in acetonitrile, this was chosen as the solvent of choice for performing the tandem flow reaction sequence. With both the diene and photosensitiser soluble in MeCN at the concentrations used, the pursuit of quantitative endoperoxide formation continued.

Performing the reaction in acetonitrile, with an air flow rate of 1.5 mL/min, a diene/photosensitiser solution flow rate of 0.2 mL/min, and carrying out the reaction under 5 Bar of back pressure (in an effort to force oxygen to dissolve in the reaction medium), afforded a satisfying 37% conversion to the endoperoxide; more than tripling the result of the previous run, and edging closer to the yields obtained in the batch photo-oxidations. It was observed in the output stream however, that the photosensitiser had completely photobleached during the course of the reaction; this bleaching leads to the photocatalyst becoming inactive, and unable to generate singlet oxygen.

This degradation of the catalyst is a known occurrence, however in the sealed photochemical reactor, it is not possible – without stopping the reaction during a run and dismantling the reactor – to see at what point no more catalyst is present. By increasing the dye loading to 2×10^{-4} M, to compensate for the degradation, and increasing the back pressure to 7.5 Bar to further aid O_2 dissolution, an excellent 92% conversion to the endoperoxide was seen. A further increase in dye loading and back pressure, to 3×10^{-4} M and 9.0 Bar respectively, increased the yield by an additional 1%. A subsequent increase in the air flow rate, from 1.5 to 1.75 mL/min, resulted in a 96% conversion to the cyclic peroxide.

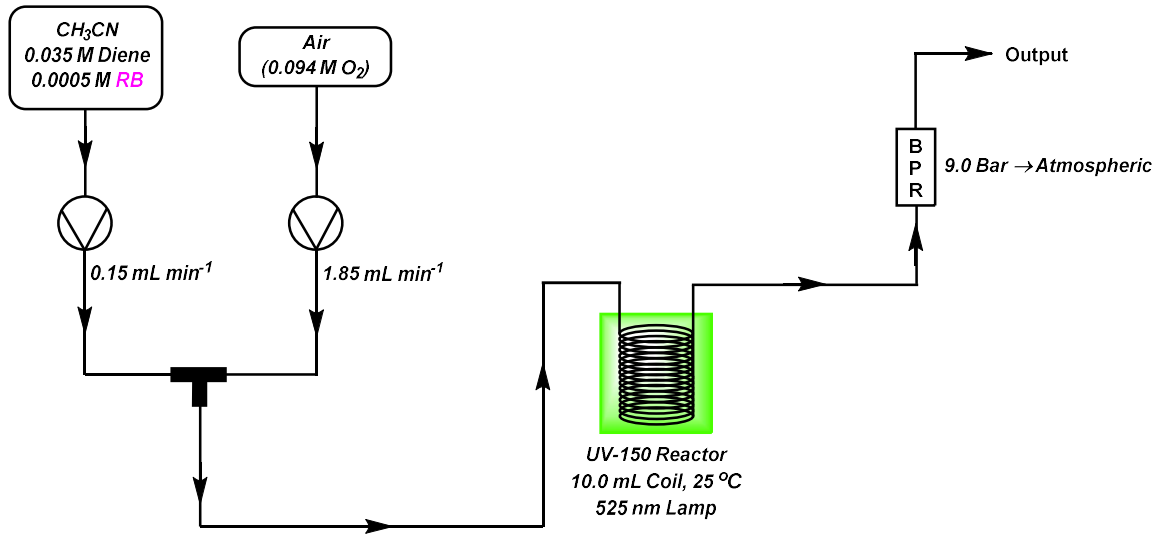
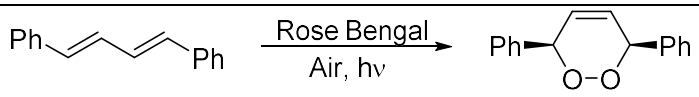


Figure 23. Modified reactor schematic for optimised endoperoxide formation in flow.

At this point, it appeared that the conversion could not be much improved upon. A further increase in dye loading and air flow rate, to 5×10^{-4} M and 1.85 mL/min respectively, alongside a drop in diene concentration from 0.04 to 0.035 M resulted in a 97% conversion appeared to reinforce this notion. Quantitative oxidation of the diene substrate was, however possible; the fabled 100% conversion was achieved by reducing the diene solution flow rate to 0.15 mL/min; increasing the residence time (giving more time for the reaction to proceed) and once again elevating the diene:oxygen stoichiometry.

It is possible that the flow segmentation became more efficient with the larger discrepancy between solution and air flow rates, thus affording better mixing / O_2 dissolution and in turn achieving a quantitative preparation of the endoperoxide. It should also be noted that in comparison to the batch reaction for the preparation of the diphenyl endoperoxide, which afforded only a moderate yield of 56%, the continuous flow reaction proceeded far more cleanly; the only impurity being residual photosensitiser. As disodium rose Bengal is a salt, it is easily removed by column chromatography, where it is immobilised on the silica bed.



(104) **(105)**

#	104 (M)	135 (M)	Solvent	Diene Flow Rate (mL/min)	Air Flow Rate (mL/min)	Back Pressure (Bar)	Conversion (%)
1	0.04	1×10^{-4}	CH_2Cl_2/MeOH	0.50	0.50	0	3.5
2	0.04	1×10^{-4}	CH_2Cl_2/MeOH	0.25	0.25	0	3.9
3	0.04	1×10^{-4}	CH_2Cl_2/MeOH	0.25	0.50	0	12
4	0.04	1×10^{-4}	MeCN	0.20	1.50	5.0	37
5	0.04	2×10^{-4}	MeCN	0.20	1.50	7.5	92
6	0.04	3×10^{-4}	MeCN	0.20	1.50	9.0	93
7	0.04	3×10^{-4}	MeCN	0.20	1.75	9.0	96
8	0.035	5×10^{-4}	MeCN	0.20	1.85	9.0	97
9	0.035	5×10^{-4}	MeCN	0.15	1.85	9.0	100

Table 10. Percentage conversions for the continuous flow generation of endoperoxides.

With optimised conditions in hand for the formation of the endoperoxide, conditions for the Appel-type dehydration for the formation of the corresponding furan were then required; the DoE conditions established in chapter 3.2 were used as a starting point, with the indication that slightly elevated temperatures would be favourable. Separate solutions of endoperoxide, previously made in batch, and Appel reagent (containing equimolar quantities of CBr_4 and PPh_3) at concentrations of 0.035 and 0.039 M respectively (corresponding to 1.1 equivalents of CBr_4/PPh_3) were prepared. With both solutions having a 0.15 mL/min flow rate, the two solutions combined at a 'Tee' junction and passed through a 10 mL reactor coil maintained at 25°C (slightly elevated temperature to aid the reaction, but also to account for and negate local variations in the lab temperature). The reaction was performed at atmospheric pressure as for previous batch reactions and astoundingly, quantitative conversion to the furan was achieved on the first run, with no endoperoxide remaining in the reaction's output stream.

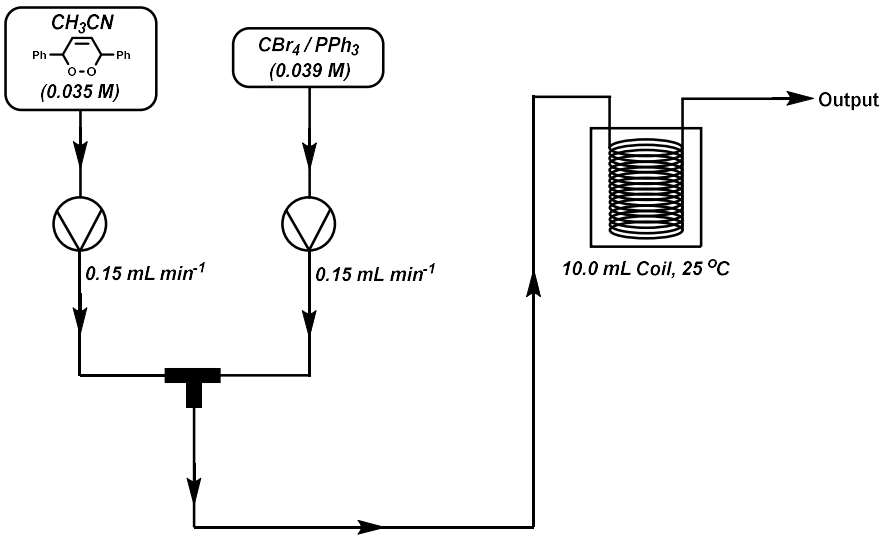


Figure 24. Reactor schematic for furan preparation in continuous flow.

Once both reactions had been optimised independently, the next challenge was to perform the two reactions together in tandem. It was hypothesised that the conditions for the photooxidation of the diene would interfere with the Appel dehydration, as the active P(V) reagent could be prone to quenching in the presence of dissolved oxygen. In an effort to mitigate this, an adjustable pressure regulator was fitted between the two reactors. This allowed for a 'step down' to atmospheric pressure after the first reactor, allowing the compressed gas to expand and hopefully reduce the concentration of oxygen dissolved in the reaction medium. Introduction of the Appel reagent to the freshly generated endoperoxide, under the conditions used previously, resulted in a moderate, yet disappointing yield of 63%; no diene remained after the first reactor, however the efficiency of the dehydration step was drastically lower than anticipated.

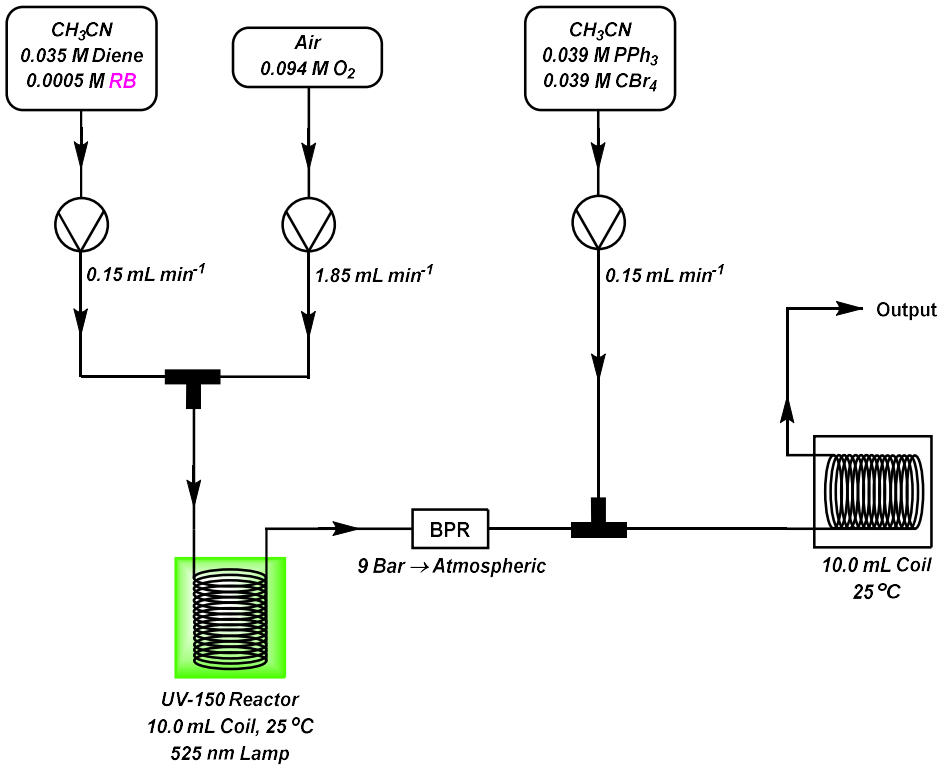


Figure 25. Reactor schematic for telescoped endoperoxide/furan formation in continuous flow.

Whilst previously assuming that the presence of dissolved oxygen may lead to quenching of the P(V) reagent, it was also considered that the re-segmentation of the flow stream after the pressure 'step down' could lead to inefficient mixing between the Appel reagent and the endoperoxide substrate streams. To probe this, the adjustable pressure regulator between the two reactors was removed, and the tandem synthesis performed at a constant back pressure of 9.0 Bar across both reactors. In doing this, a huge spike in reaction efficiency was observed, with a 98% conversion to the furan being observed over two steps, with no isolation of the intermediate endoperoxide being performed; suggesting that inefficient mixing was indeed the cause of the poor yield in the previous attempt. Whilst not achieving a quantitative yield across both steps, a 98% overall conversion from diene to furan was deemed acceptable; the endoperoxide and furan have appreciably different polarities, and so are easily separable by column chromatography. A probable reason for the 2% unconverted endoperoxide would be the aforementioned quenching of the P(V) reagent, which could be overcome by the use of a slightly larger excess of CBr_4/PPh_3.

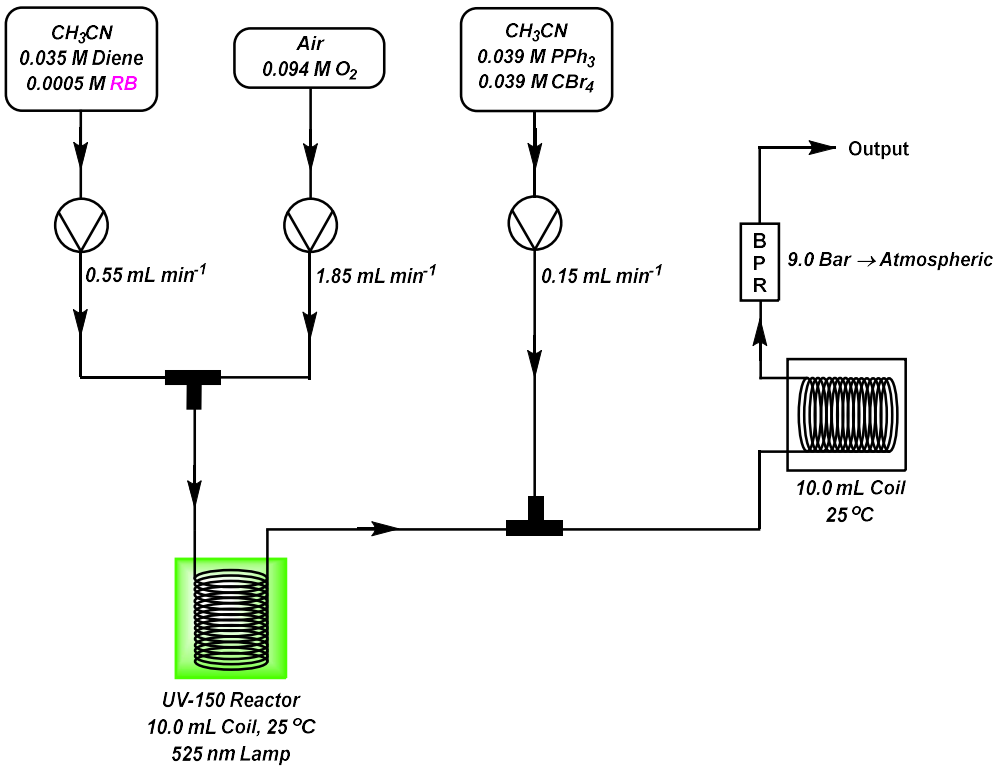
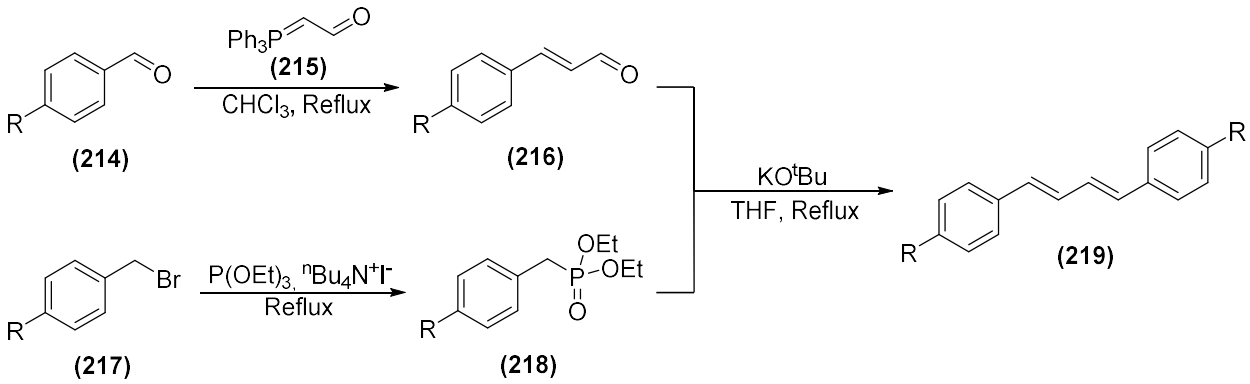


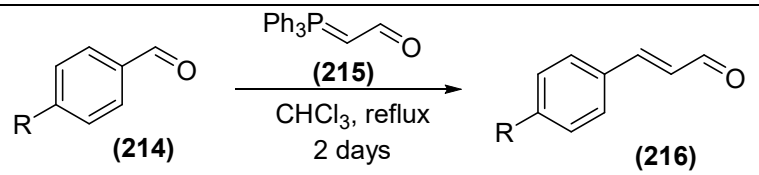
Figure 26. Modified reactor schematic for the telescoped formation of furans from 1,3-dienes in continuous flow.

With a set of optimised conditions for furan formation from substituted conjugated dienes in near-quantitative yields over more than one step, using only air as an oxidant and the Appel reagent as a means of converting the intermediate endoperoxide to the aromatic heterocycle, a range of additional 1,4-diaryl-1,3-butadienes were prepared to subject to the tandem oxidation/dehydration sequence. Diaryl heterocycles are common motifs in applications such as organic light emitting diodes (OLEDs), and so a high yielding and general route for their preparation would be attractive.

Dienes were prepared according to **Scheme 36**; initially, cinnamaldehyde derivatives **216** were prepared from their corresponding benzaldehyde derivatives **214** *via* Wittig olefination with (triphenylphosphoranylidene)acetaldehyde **215** in refluxing chloroform **(Table 11)**.



Scheme 36. Preparation of diaryl 1,3-dienes from simple starting materials.



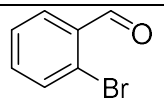
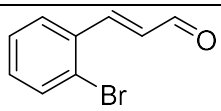
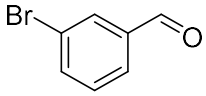
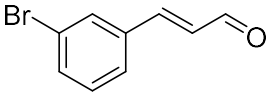
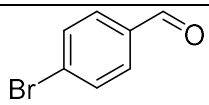
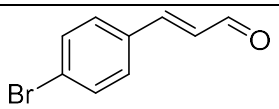
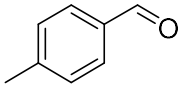
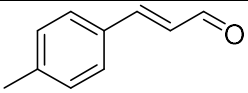
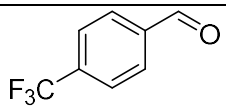
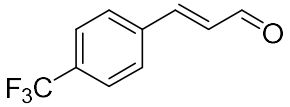
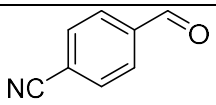
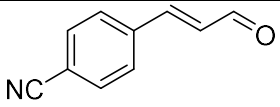
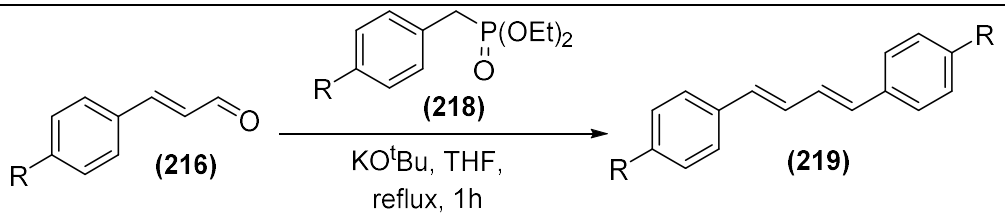
Benzaldehyde Substrate	Cinnamaldehyde Product	Yield (%)
 (220)	 (226)	71
 (221)	 (227)	64
 (222)	 (228)	52
 (223)	 (229)	31*
 (224)	 (230)	74
 (225)	 (231)	82

*Table 11. Cinnamaldehyde derivatives prepared by treatment of corresponding benzaldehydes with (triphenylphosphoranylidene)acetaldehyde. *Prepared via condensation (p-TolCHO, CH_3CHO, NaOH, EtOH, H_20, 0°C, 16h).*

Benzylphosphonate derivatives **218** were prepared from the corresponding benzyl bromide derivatives **217** and triethylphosphite *via* Michaelis-Arbuzov reactions in the presence of tetrabutylammonium iodide; excess phosphite was removed under vacuum, and the phosphonate used without additional purification. Subsequently, the desired diaryl-1,3-diene substrates **219** for carrying out the tandem photo-oxidation/Appel type dehydration sequence in continuous flow were prepared *via* a simple Horner-Wadsworth-Emmons between the cinnamaldehyde and benzylphosphonate derivatives by heating with potassium *tert*-butoxide in anhydrous tetrahydrofuran **(Table 12)**.



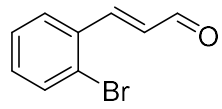
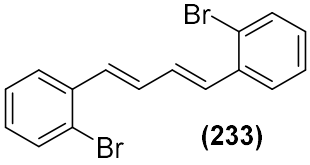
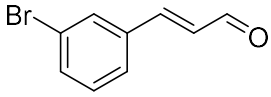
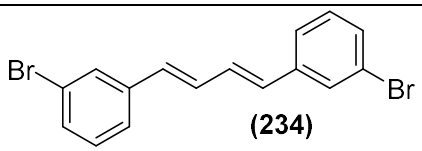
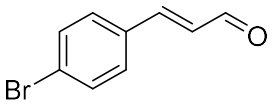
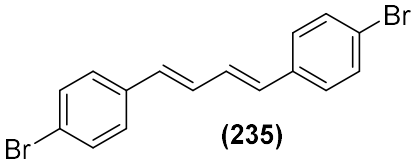
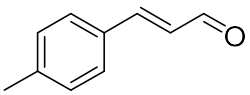
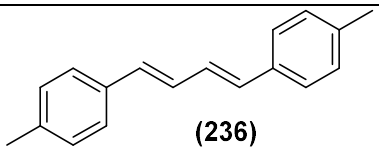
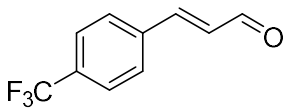
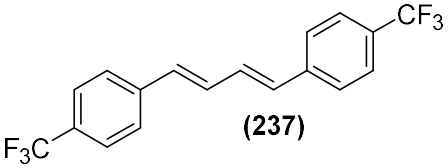
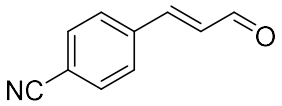
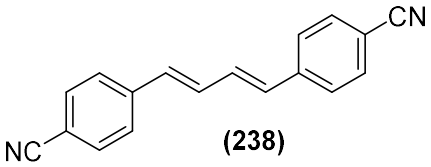
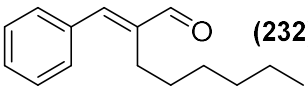
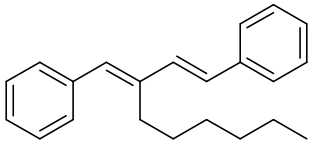
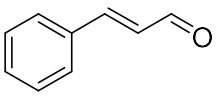
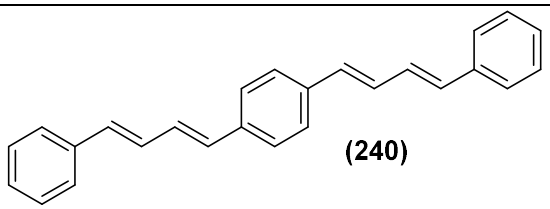
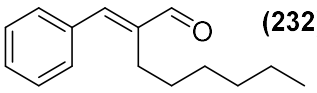
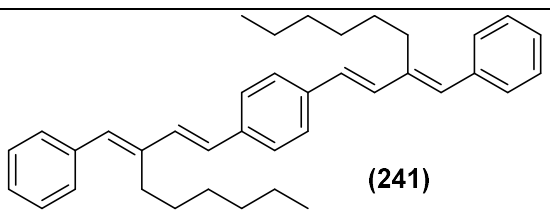
Cinnamaldehyde Substrate	Diene Product	Yield
 (226)	 (233)	38
 (227)	 (234)	43
 (228)	 (235)	55
 (229)	 (236)	71
 (230)	 (237)	58
 (231)	 (238)	69
 (232)	 (239)	88
 (123)	 (240)	69
 (232)	 (241)	84

Table 12. Dienes obtained by Horner-Wadsworth olefination of cinnamaldehyde derivatives.

A selection of substituted analogues of *trans,trans*-1,4-diphenyl-1,3-butadiene were prepared by means of the synthesis outlined in **Scheme 36**, however upon attempted preparation of the required solutions of dienes for tandem flow reaction, it was discovered that the dienes exhibited frustratingly low solubilities in acetonitrile – the solvent for which the optimisation studies using the unfunctionalised diene substrate were performed in. All attempts to aid solvation of the diene into acetonitrile, including heating, sonication, and long periods of agitation all proved unsuccessful in promoting solvation of the diene. Unfortunately, this resulted in the reaction optimisation having to be readdressed, with the use of an alternative solvent being required.

Knowing that deutero-chloroform was sufficiently able to solvate most of the dienes for NMR analysis, coupled with the extended lifetime of singlet oxygen in halogenated solvents compared to in non-halogenated solvents (e.g. 207 μs in chloroform vs 75 μs in acetonitrile) which would allow for a more efficient photo-oxidation, chloroform was chosen for the telescoped oxidation/dehydration reactions with diaryl diene substrates. Due to rose Bengal being in salt form however, the photosensitiser's solubility in chloroform had to be considered, and the reaction conditions once again altered. To facilitate singlet oxygen generation, rose Bengal was exchanged for tetraphenylporphyrin; a dye able to dissolve in non-polar solvents.

In carrying out previous reactions with preformed Appel reagent from carbon tetrabromide and triphenylphosphine, it was observed that the active phosphorus species being introduced to convert the endoperoxide to the aromatic furan ring was gradually deteriorating, likely due to quenching by atmospheric moisture and/or oxygen; this led to reduced yields of furan products on consecutive reactions, where the Appel reagent was made in a large batch and used for several reactions over the course of 1-2 days. To counter this gradual loss of reagent, it was envisioned that an *in-situ* generation of the active dehydrating reagent would be an appropriate means of avoiding P(V) losses.

By spiking the diene substrate solution with carbon tetrachloride (itself being inert toward both singlet oxygen oxidation, and toward photo-oxidation), then introducing a solution of only triphenylphosphine after the generation of the endoperoxide (prior introduction would lead to unwanted formation of triphenylphosphine oxide *via* the reaction of singlet oxygen with the phosphine), the formation of chlorotriphenylphosphonium trichloromethanide could be promoted, allowing for a consistent endoperoxide dehydration sequence. In addition, the use of carbon tetrachloride eliminates the need to remove bromoform from the final reaction mixture, as the CCl_4 is converted to chloroform upon abstraction of a proton from the endoperoxide, a feature which lends elegance to the sequence due to chloroform also being the reaction solvent and could simply be evaporated off once the reaction was complete.

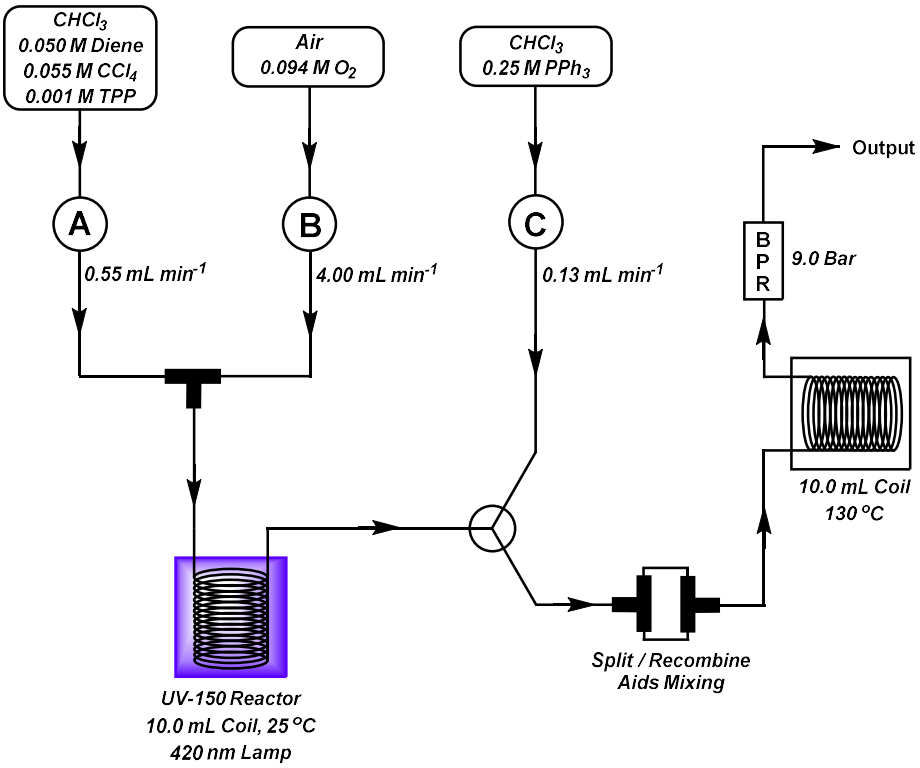
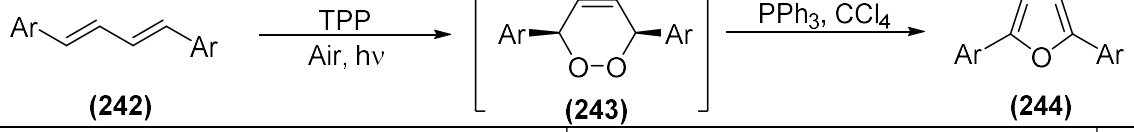


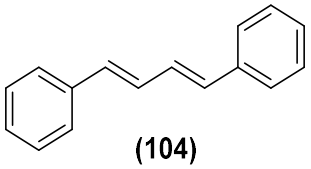
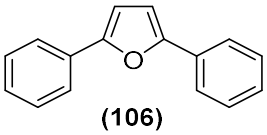
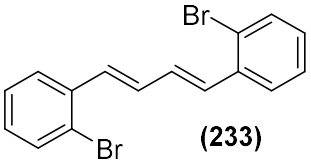
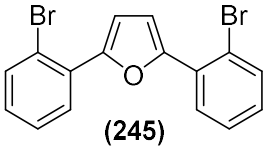
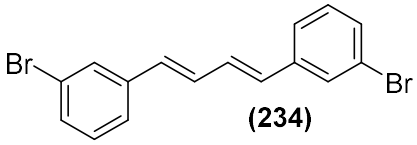
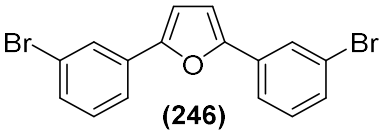
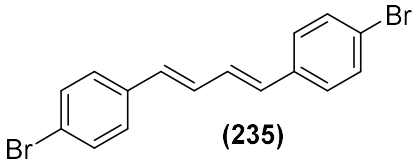
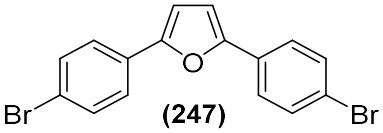
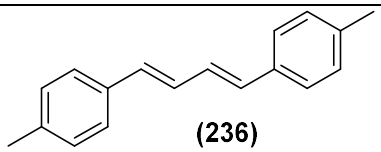
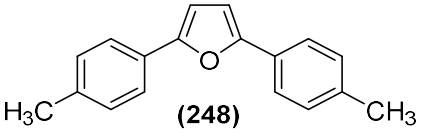
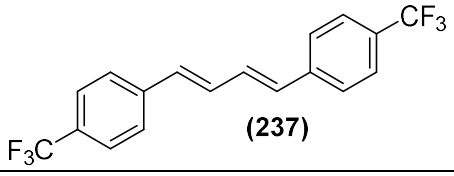
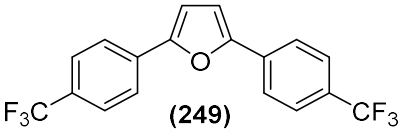
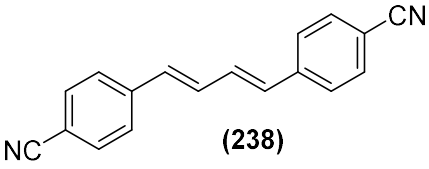
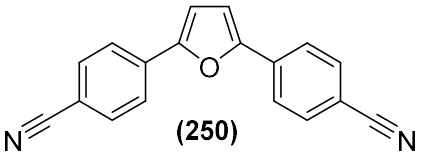
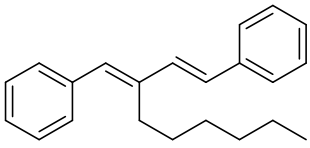
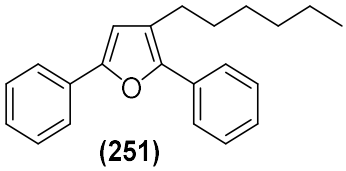
Figure 27. Modified reactor schematic for the telescoped preparation of furans in-flow.

A test reaction on *trans,trans*-1,4-diphenyl-1,3-butadiene **104** with the newly modified conditions exhibited a quantitative conversion of the diene to the corresponding endoperoxide **105**, however only a trace amount of the furan **106** was seen. An assumption based on the increased strength of carbon-chlorine bonds relative to carbon-bromine bonds was that the formation of the phosphorus (V) reagent with CCl_4 was proceeding more slowly than with CBr_4. The obvious method of remedying the sluggish reagent formation would be to heat the solution. One of the benefits of performing reactions in flow, is the ease in which reactions can be carried out under elevated pressures. The 9 bar of back pressure used to accelerate the photo-oxidation step, also allowed for the elevation of the dehydration reaction's temperature far beyond that which would ordinarily be permitted by the solvent's boiling point. It was found that heating the secondary reactor to 130 °C, a quantitative conversion from diene through to furan was achieved.

Once again with a fresh set of conditions that would allow for furan preparation from substrates which proved insoluble in more polar solvents, the selection of diaryl dienes seen in **Table 12** were subjected to the telescoped oxidation/dehydration reactions **(Table 13)**.



(242) (243) (244)

#	Diene	Furan	Yield (%)
1	 (104)	 (106)	100
2	 (233)	 (245)	0
3	 (234)	 (246)	61
4	 (235)	 (247)	96
5	 (236)	 (248)	73
6	 (237)	 (249)	33
7	 (238)	 (250)	27
8	 (239)	 (251)	54

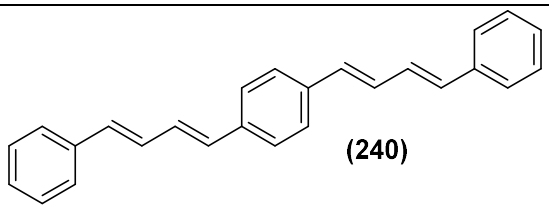
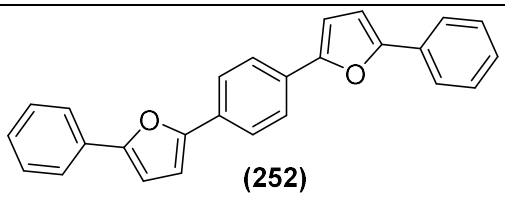
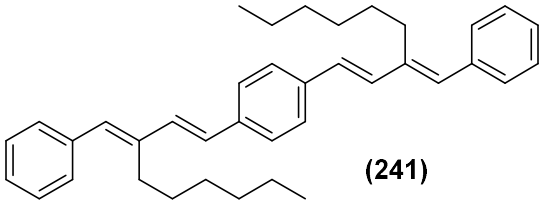
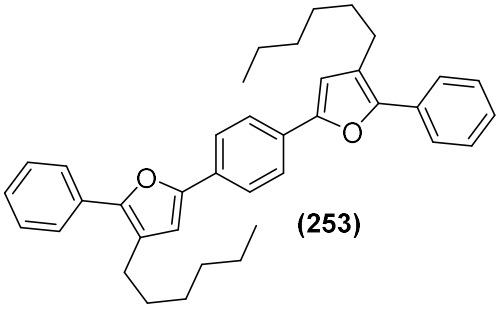
9	 (240)	 (252)	Trace
10	 (241)	 (253)	48

Table 13. Isolated yields from the telescoped continuous flow diene oxidation and furan preparation using the Appel reagent.

Most of the dienes underwent smooth oxidation and dehydration, affording furans in appreciable yields, with the photo-oxidation being the step limiting higher efficiencies of heterocycle preparation; a feature observed by the presence of varying quantities of unreacted diene in the output stream of the reactors, whilst no endoperoxide intermediate was observed in the crude reaction mixtures.

Diene **240** unfortunately remained too insoluble to be a viable substrate; attempts to pump a suspension of fine particles of the diene achieved a trace conversion to the furan by ^{1}H NMR, however isolation of the bis-furan was unsuccessful. When **241 (**the alkylated analogue of **240**) was exposed to the tandem reaction sequence, however a significantly higher yield was observed. This observation lends weight to the hypothesis that the poor solubility of **240** was responsible for the lack of furanoid product.

Whilst only a moderate yield of **251** and **253** were obtained, this can easily be explained by the presence of over- and side-oxidation product, such as those stemming from ene- reactions with the alkyl chain and unsaturation either in the starting material or in the desired product. It is possible that careful control of the photo-oxidation conditions may allow for the desired oxidation product to dominate the photocatalytic reaction, thus increasing the overall yields of the furans.

Many of the diaryl furan products exhibited an impressive fluorescence under irradiation with ultraviolet light **(Figure 28)**. The ability to monitor the generation of furan products as they are generated by means of a continuous monitoring process with UV-Vis spectroscopy would add to the novelty of the continuous flow furan synthesis and allow for a more rapid analysis of the reaction mixtures for furan content.

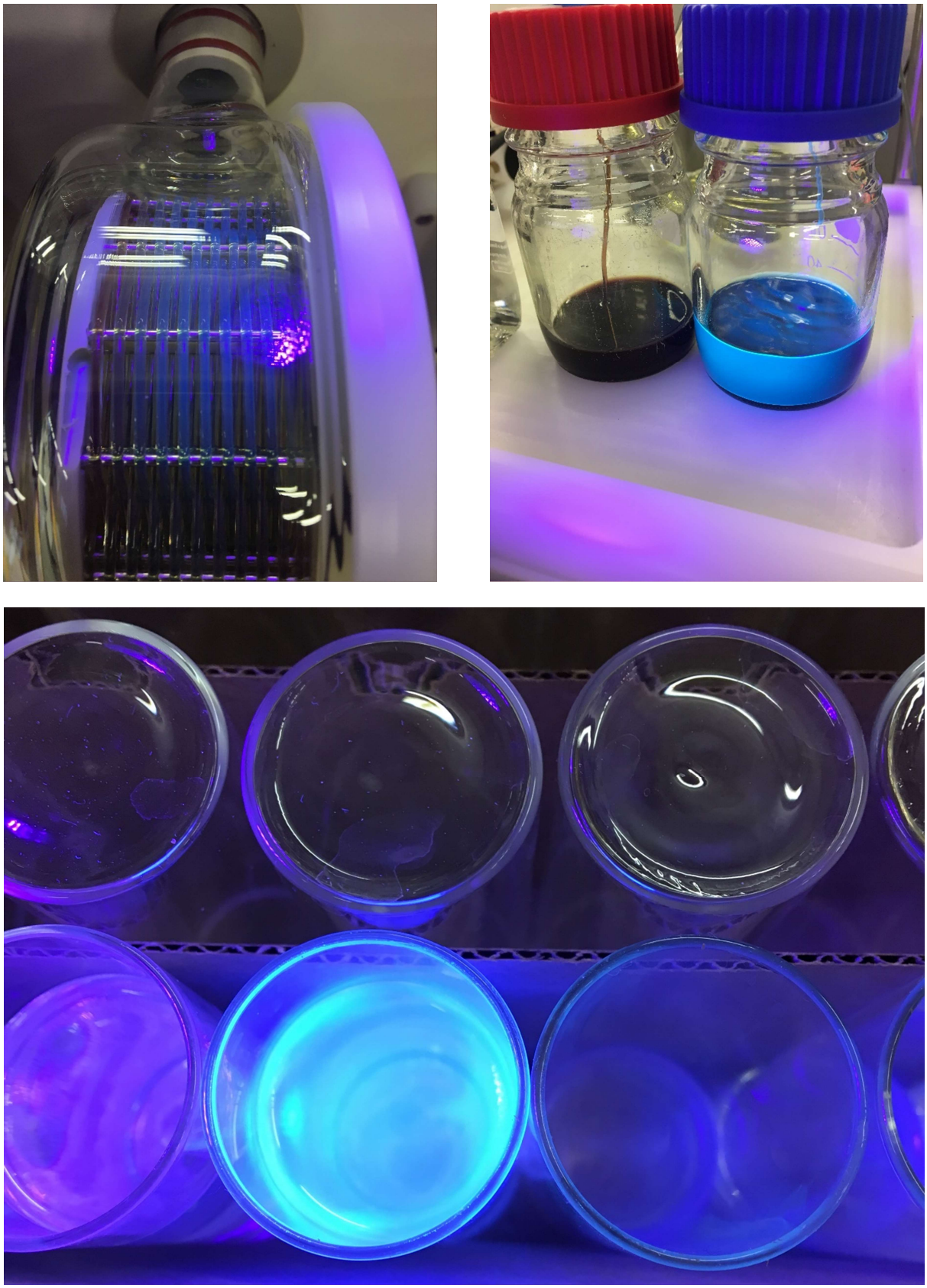


*Figure 28. Fluorescence of bis-furan **253**. Increasing fluorescence through the flow reactor as furan is generated (top left), comparison of diene solution and furan solution after reaction (top right), high fluorescence of pure furan after column chromatography (bottom).*

Furans **237** and **238** also showed disappointing yields, with large quantities of the precursor dienes being recovered from the reaction mixtures, although this can easily be attributed to the electron poor nature of the dienes, which are prone to significantly slower [4+2] cycloaddtion reactions than their more electron rich counterparts. Once again, careful tailoring of the photo-oxidation, perhaps by a significant increase in oxygen concentration or by an increase in residence time, are likely to produce higher conversions in the photoreactor and consequently boosted furan yields. Fortunately for these substrates, the absence of functionalities prone to oxidation with singlet oxygen would allow for treatment with a larger excess of singlet oxygen without giving rise to over-oxidation products.

Whilst the use of the Appel reagent to dehydrate endoperoxides is an elegant method for furan synthesis, and applicable to the synthesis of highly unstable furanoid compounds such as the F-Acids, or those bearing sensitive functional groups, many furans are more tolerant toward slightly harsher reaction conditions. Thoughts then turned to a greener approach of effecting the transformation from endoperoxide to furan. It is well known that heating with acid is an effective means of converting endoperoxides to furans, by means of a classical Paal-Knorr synthesis, and provided the product heterocycles are stable to the reaction conditions, is a far more atom economical means of furan preparation than the use of a greater than stoichiometric quantity of phosphine and tetrahalomethane. With this in mind, a dehydration utilising *p*-toluenesulfonic acid was considered.

Using the previously optimised conditions for $^1O_2$ generation in acetonitrile with disodium rose Bengal as a photosensitiser, a stream of diphenyldioxine **105** was generated. Introduction of a stream of 0.035 M *p*-TSA at 0.15 mL/min, followed by a 20 minute residence time in a second reactor with the back pressure maintained at 9.0 Bar across both reactors, afforded only a trace of the desired 2,5-diphenylfuran product **106**. Whilst disappointing, as a low temperature H^+ mediated dehydration would be elegant, this result was expected as the second reactor was not heated above ambient temperature. A second run, in which reactor two was also heated to 125°C, gave a 100% conversion to the desired product. In addition, the use of a solid supported sulfonic acid catalyst could easily be applicable to this synthesis; further increasing the atom economy and removing the need to extensively purify the end product.

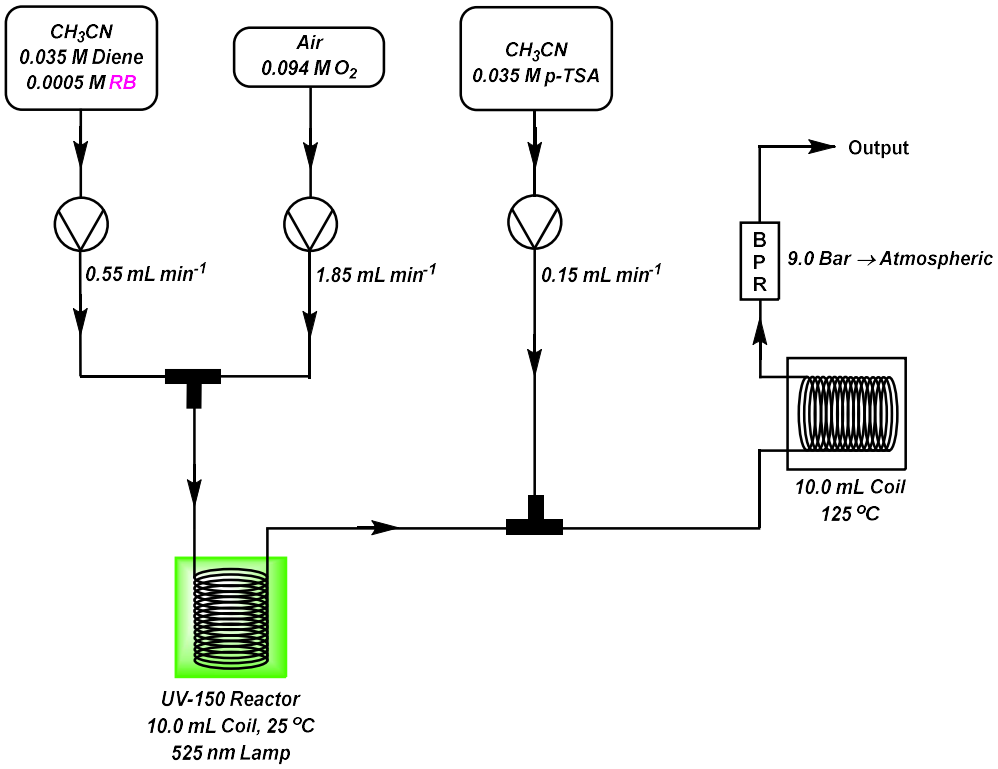


Figure 29. Reactor schematic for the acid mediated dehydration of endoperoxides to furans.

An ideal merging of several concepts laid out in this work would be the telescoping of modified routes to individual components of the furan formation. Provided the solubility of all substrates in a solvent compatible with all steps (with acetonitrile and chlorinated solvents generally being safe choices), the coupling of a diene photo-oxidation, endoperoxide desymmetrisation using a solid supported cinchona catalyst **198**, followed by a catalytic Appel-type dehydration of the resulting *cis*-γ-hydroxyenone on a solid-supported phosphine oxide catalyst, and a final removal of acid by a basic ion exchange resin would result in a clean, simple, atom economical synthesis of furans from conjugated dienes **(Figure 30)**. This type of process could easily be achieved with the use of commercially available reactors and several packed column reactors which enable solid supported reagents to be utilised in a continuous flow reactor.

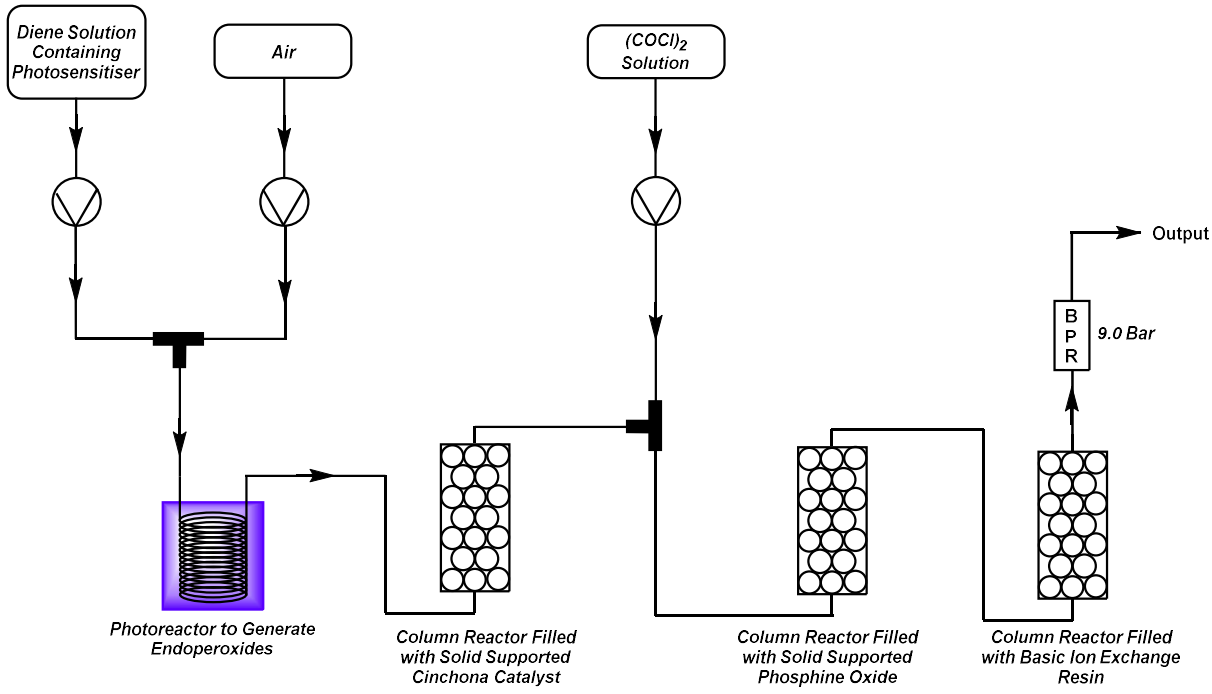


Figure 30. Hypothetical telescoped continuous-flow reactor schematic for atom economical furan generation.

4. General Conclusions

This work has highlighted a mild, metal-free, redox-neutral approach for the construction of multi-substituted furan ring systems from simple 1,3-diene precursors. This was achieved over two steps by means of a simple oxidation, harnessing dye sensitised photogenerated singlet oxygen to generate cyclic peroxide intermediates, followed by conversion to aromatic furan nuclei using a novel application of the Appel reagent.

The newly developed methodology was shown to be tolerant toward a wide range of substituents and functional groups including aromatic rings, alkyl chains, cyclopropane rings, esters, silyl ethers, alkyl bromides, and alkenes. The chemistry allowed for the preparation of mono-, bis-, and tri- substituted furan ring systems including highly electron rich (and reactive) trialkyl furans, as illustrated by the incorporation of the furan synthesis into the total synthesis of the marine natural product, furan fatty acid F_5. This natural product, a potential anti-inflammatory fatty acid, was prepared in a seven-step synthesis in an overall 7% yield starting from commercially available 11-undecen-1-ol.

In the course of investigating the substrate scope of the dehydration of endoperoxides to furans, it was discovered that the treatment of endoperoxides bearing silyl ether functionalities with the Appel reagent resulted in the formation of trace quantities of desilylated products, which were then able to undergo a classical Appel reaction *in-situ* to produce furans containing a bromine atom in place of the silyl ether. By doubling the quantity of Appel reagent and heating the reaction to reflux, it was found that excellent yields of the alkyl bromide product could be obtained with complete suppression of the silyl ether containing furan product. To complement this, a modification to the original reaction was developed; the addition of sodium bicarbonate to the reaction allowed for formation of the desired silyl ether bearing furan at significantly elevated yields, with complete suppression of the alkyl bromide side product.

To optimise the endoperoxide dehydration reaction, a design of experiments study using a 3 factor, full factorial model was chosen. A solvent compatibility plot was used to condense a range of common laboratory solvents into two principal components which afforded two of the three factors of the DoE, with reaction temperature being the third. Using this model, it was determined that optimum furan yields could be obtained when reactions were performed in acetonitrile at (or above) room temperature. Additionally, an attempt to carry out a catalytic variant of the endoperoxide dehydration was made, harnessing oxalyl chloride to regenerate an active P(V) species from a sub-stoichiometric quantity of phosphine oxide. Whilst only a preliminary study, this work showed that it may be possible to prepare furans under a catalytic variant of the Appel-type endoperoxide dehydration.

Finally, it was found that by performing the furan synthesis in a telescoped continuous flow reaction sequence, greater yields of furans than in batch reactions could be obtained directly from their parent dienes (100% vs 53% in batch), omitting the requirement for the isolation of endoperoxide intermediates. This was primarily attributed to a marked increase in the diene oxidation step by employing a pressurised segmented flow set-up, whereby the diene/photosensitiser solution was segmented by pressurised air (the oxygen source), and allowing for greater irradiation of the reaction mixture than in batch as a result of the flow photoreactor design. This telescoped flow synthesis of furans from 1,3-dienes was applied to the preparation of a selection of 2,5-diaryl furan motifs which serve as potential OLED precursor molecules.

5. Future Work

Future work in this field should see the exploration of a catalytic variant of the Appel-type dehydration of endoperoxides to furans in greater depth. The formation of a *cis*-γ-hydroxyenone *via* either a base mediated or cinchona alkaloid catalysed Kornblum-DeLaMare rearrangement prior to treatment with oxalyl chloride and a sub-stoichiometric quantity of triphenylphosphine oxide. By separating the endoperoxide to furan conversion into two discreet steps, the decomposition of the oxalyl chloride in the presence of the base (required to facilitate the heterolytic cleavage of the peroxide bond) should be stopped, and thus allow for regeneration of an active P(V) species from the phosphine oxide catalyst to allow for furan generation. A catalytic variant of the endoperoxide dehydration under Appel reaction conditions would greatly improve the atom economy of the furan synthesis, and make the process a far more attractive means of preparing furans from 1,3-dienes.

Furthermore, the development of a telescoped continuous flow sequence to further expand the scope of the catalytic synthesis by harnessing solid supported reagents should be investigated as a means of increasing the purity of the crude reaction mixture after furan formation. A stream of endoperoxide (which should be generated by the segmented flow photo-oxidation outlined in chapter 3.5) passed through a basic ion exchange resin or solid supported cinchona catalyst to facilitate cleavage of the peroxide bridge, followed by the introduction of oxalyl chloride to the reaction stream and passing the resulting mixture through a reactor containing a solid supported phosphine oxide should allow for the generation of furans. By using this method, minimal waste products would be present after furan formation, and a high purity furan stream able to be generated continuously.

Regarding the application of the Appel-type endoperoxide dehydration to the total synthesis of furan fatty acids, a more efficient and general synthesis should be pursued by harnessing the easy α-alkylation of furan nuclei. After generating 2-pentyl-4-methylfuran by the procedure outlined in chapter 3.1, alkylation to install the fatty acid side chain should be undertaken. Proceeding via this route would omit the requirement for the cross metathesis and hydrogenation steps of the natural product synthesis (making it completely transition metal free), and reducing the number of steps in the synthesis from seven to five. Furan yields could again be improved by the use of flow chemistry to perform the diene oxidation, where diene:oxygen ratios are more easily maintained, overoxidation products minimised, and overall yields vastly improved. The continuous flow photo-oxidation should be applied to the generation of tetra-alkyl dienes to facilitate the generation of tetra-alkyl endoperoxides whilst interrupting the formation of species such as bis-peroxides. Access to 3,4-dimethyl furan fatty acids (such as F_6) was prevented in this work by the lack of access to the precursor cyclic peroxides when performing batch oxidations. With the knowledge that flow processes permit effective control of oxidation conditions, these natural products should once again be targeted as a direct comparison of the anti-inflammatory effects of F-acids bearing varying chain lengths and substitution patterns about the heterocyclic nucleus should be investigated.

6. Experimental

6.1 General Information

Anhydrous conditions were obtained by using oven dried glassware, purged with dry, oxygen free nitrogen and subjected to further flame drying under the nitrogen flow prior to the addition of reagents and/or solvents. All needles were flame dried prior to use, and gas tight syringes were used when handling pyrophoric reagents. Inert atmospheres were maintained, where necessary, by means of a balloon of nitrogen or argon; for cross metathesis reactions, a gentle flow of nitrogen was maintained by use of a mineral oil-filled bubbler.

All solvents and commercially available reagents were purchased from Sigma-Aldrich, Alfa Aesar, TCI, or Fischer Scientific, and were used without prior purification apart from THF, which was distilled as required over benzophenone and sodium. Anhydrous diethyl ether, toluene, and dichloromethane were purchased dry from commercial suppliers. Petroleum ether refers to the fractions with a boiling point range of 40 – 60 °c.

^{1}H and ^{13}C NMR spectra, recorded at 400 MHz and 100 MHz respectively, were obtained using a Bruker Avance 400 MHz spectrometer or JEOL ECS-400 400 MHz spectrometer. The deuterated solvent used for obtaining measurements is specified in brackets. Where a mixture of isomers was obtained, data quoted corresponds to the major isomer.

High resolution mass spectra were obtained using a Thermofischer exactive (orbi) resolution mass spectrometer, with ESI as the ionisation source.

Thin layer chromatography (TLC) analysis was performed on aluminium backed silica plates. Plates were visualised by ultraviolet light (254 nm), or with vanillin or $KMnO_4$ stains and heating.

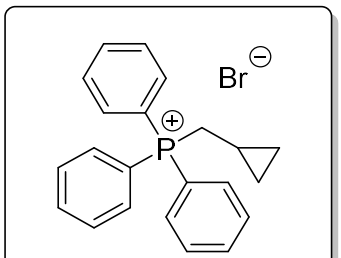
Column chromatography was performed using Apollo Scientific ZEOprep-60 silica, with a particle size of 40-63 microns; eluents are specified in brackets.

All continuous-flow reactions were performed on a Vapourtec “EasyPhotochem” E-series reaction system; photocatalytic oxidation reactions were carried out in a Vapourtec UV-150 reactor module (10mL) equipped with a 525nm or 420nm LED light source. In-flow Appel-type dehydration reactions were carried out in a Vapourtec standard coiled tube reactor (10 mL). The reactor system was primed with the required solvent/air mixture, then brought up to pressure and then temperature and allowed to stabilise for ca. 1 hour prior to initiation of reactions. A Vapourtec standard manual back pressure regulator (BPR) was employed to mediate the reaction pressure.

6.2 Synthetic Procedures

6.2.1 Diene Precursors

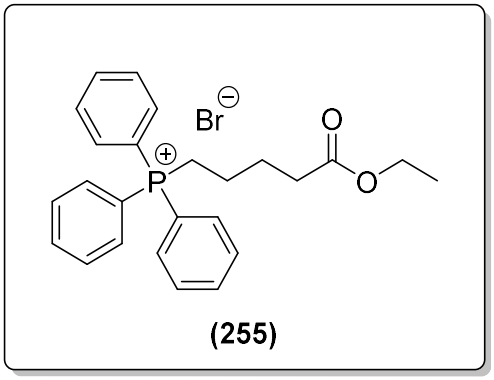
(Cyclopropylmethyl)triphenylphosphonium bromide[96]



(254)

A solution of (bromomethyl)cyclopropane (0.48 mL, 5.00 mmol) and PPh_3 (1.570 g, 6.00 mmol) in toluene (5 mL) was heated to reflux for 16 h. After this period, the mixture was cooled, solvents removed *in vacuo*, and the residue triturated with diethyl ether (3 x 10 mL) affording a white powder (1.160 g, 2.90 mmol, 58 %). **δH** (400 MHz, $CDCl_3$): 7.91 – 7.86 (6H, m), 7.83 – 7.75 (3H, m), 7.71 – 7.64 (6H, m), 3.96 – 3.91 (2H, m), 0.93 – 0.82 (1H, m), 0.61 – 0.53 (4H, m). **δC** (100 MHz, $CDCl_3$):134.9, 134.0, 130.4, 118.9, 28.1, 27.6, 6.4, 4.3. **IR** (v_{max}, cm^{-1}): 1439, 1265, 1114. **MS (**m/z): Found 317.1455 ($C_{22}H_{22}P^+$ requires 317.1454).

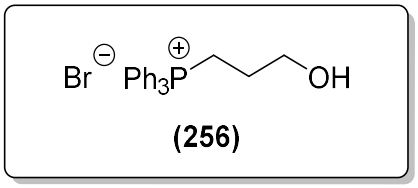
(5-Ethoxy-5-oxopentyl)triphenylphosphonium bromide



(255)

A solution of PPh_3 (3.147 g, 12.00 mmol) and ethyl 6-bromohexanoate (1.8 mL, 10.0 mmol) in MeCN (20 mL) was heated to reflux for 2.5 days. After this period, the mixture was allowed to cool, triturated with diethyl ether (3 x 50 mL), then dried under vacuum to give the phosphonium salt as a white gum (4.330 g, 8.90 mmol, 89%). **δH** (400 MHz, $CDCl_3$): 7.57 – 7.40 (12H, m), 7.10 – 6.94 (3H, m), 3.73 (2H, q, *J* = 7.2Hz), 3.48 – 3.30 (2H, m), 1.91 (2H, t, *J* = 7.6 Hz), 1.42 – 1.28 (6H, m), 0.89 (3H, t, *J* = 7.2Hz). **δC** (100 MHz, $CDCl_3$): 173.2, 133.54, 130.5, 128.4, 60.1, 33.6, 29.6, 24.2, 22.7, 22.2, 14.1. **IR** (v_{max}, cm^{-1}): 1724, 1440, 1379, 1190, 1113. **MS (**m/z): Found 405.1980 ($C_{26}H_{30}O_2P^+$ requires 405.1978).

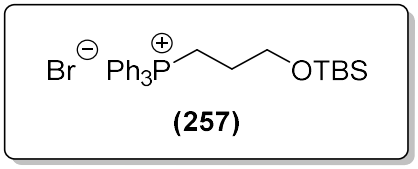
(3-Hydroxypropyl)triphenylphosphonium bromide[97]



(256)

A solution of 3-bromo-1-propanol (2.25 mL, 25.00 mmol) and PPh_3 (7.213 g, 27.50 mmol) in toluene (10 mL) was heated to reflux for 16 hours. After this period the mixture was cooled to room temperature, triturated with diethyl ether (3 x 50 mL), and dried under vacuum affording the phosphonium salt as a white powder (9.887 g, 24.80 mmol, 99%). **MP** = 220.2 – 223.8 °C. **δH** (400 MHz, $CDCl_3$): 7.92 – 7.65 (15H, m), 3.93 – 3.75 (4H, m), 3.35 (1H, s (br)), 1.90 – 1.79 (2H, m). **δC** (100 MHz, $CDCl_3$): 135.1, 133.6, 130.6, 118.5, 60.3, 25.9, 20.2. **IR** (ν_{max}, cm^{-1}): 3314 (br), 2305, 1439, 1264, 1112, 896, 737. **MS (**m/z): Found 321.1397 ($C_{21}H_{22}OP^+$ requires 321.1403).

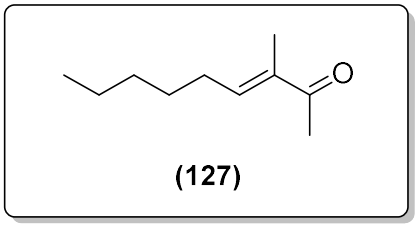
(3-((*tert*-Butyldimethylsilyl)oxy)propyl)triphenylphosphonium bromide[98]



(257)

To a solution of **256** (4.013 g, 10.00 mmol) and imidazole (0.749 g, 11.00 mmol) in CH_2Cl_2 (30 mL) was added a solution of TBSCl (1.658 g, 11.00 mmol) in CH_2Cl_2 (10 mL) dropwise. The resulting mixture was stirred at room temperature for 16 h, solvents removed *in vacuo*, then triturated with Et_2O (3 x 100 mL). Removal of residual solvent *in vacuo* afforded the phosphonium salt as a white powder (4.627 g, 9.00 mmol, 90%). **MP** = 107.5 – 111.8 °C. **δH** (400 MHz, $CDCl_3$): 7.84 – 7.63 (15H, m), 3.83 – 3.69 (4H, m), 1.90 – 1.76 (2H, m), 0.09 (9H, s), 0.04 (6H, s). **δC** (100 MHz, $CDCl_3$): 135.4, 133.7, 133.4, 130.7, 118.7, 60.3, 26.0, 19.7, -3.5, -5.3. **IR** (ν_{max}, cm^{-1}): 2306, 1440, 1265, 1113, 998, 743. **MS (**m/z): Found 435.2260 ($C_{27}H_{36}SiOP^+$ requires 435.2268).

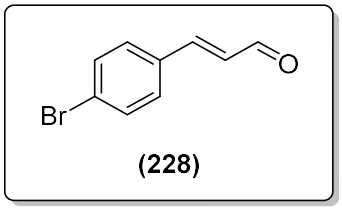
(E)-3-Methylnon-3-en-2-one[99]



(127)

Hexanal (6.0 mL, 50.0 mmol) was added dropwise to a vigorously stirred biphasic mixture of butanone (20 mL, 0.22 mol) and aqueous NaOH (15 mL, 10% w/v) over a 1 h period. After complete addition, the mixture was stirred at room temperature for 60 h, then the layers separated and the aqueous layer extracted into ethyl acetate (2 x 20 mL). Combined organics were dried over $MgSO_4$, filtered, and solvents removed *in vacuo* to give a colourless oil. Aqueous HBr (2 drops, 40% w/v), and the mixture distilled to obtain the crude, wet enone as a colourless oil. The distillate was diluted with ethyl acetate (20 mL), dried over $MgSO_4$, filtered, and solvents removed *in vacuo* affording a colourless oil (5.694 g, 40.10 mmol, 80%). **δH** (400 MHz, $CDCl_3$): 6.65 – 6.61 (1H, t, J = 7.2 Hz), 2.30 (3H, s), 2.23 (2H, dt, J_1 = 7.2 Hz, J_2 = 7.6 Hz), 1.76 (3H, s), 1.50 – 1.43 (2H, m), 1.37 – 1.27 (4H, m), 0.90 (3H, t, J = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 200.1, 144.1, 137.7, 31.7, 29.2, 28.4, 25.5, 22.6, 14.1, 11.2. **IR** (ν_{max}, cm^{-1}): 1669, 1641, 1459, 1366. **MS (**m/z): Found 153.1434 ($C_{10}H_{19}O^+$ requires 155.1430).

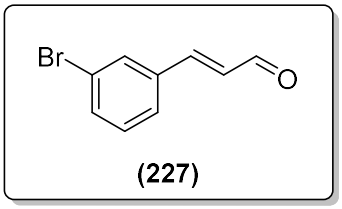
(E)-3-(4-Bromophenyl)acrylaldehyde[100]



(228)

To a solution of 4-bromobenzaldehyde (0.93 g, 5.0 mmol) in $CHCl_3$ (50 mL) under a N_2 atmosphere, was added (triphenylphosphoranylidene)acetaldehyde (1.70 g, 5.6 mmol), and the mixture heated to reflux for 2 days. After this period, solvents were removed in vacuo, ethyl acetate (25 mL) added, and the mixture filtered through a short plug of silica, washing with additional ethyl acetate (50 mL). Solvent was removed in vacuo, and the crude product purified by column chromatography (20% EtOAc in hexane, R_f = 0.36) affording a yellow oil which crystallised on standing (564 mg, 2.6 mmol, 52%). **δH** (400 MHz, $CDCl_3$): 9.71 (1H, d, *J* = 7.6 Hz), 7.59 – 7.56 (2H, m), 7.45 – 7.38 (3H, m), 6.71 (1H, dd, *J* = 16.0 Hz, *J* = 7.6 Hz). **δC** (100 MHz, $CDCl_3$): 193.4, 151.2, 132.9, 132.4, 129.8, 129.0, 125.7. **IR** (ν_{max}, cm^{-1}): 1679, 1626, 1586, 1126, 907, 732.

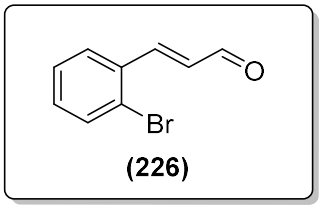
(E)-3-(3-Bromophenyl)acrylaldehyde[101]



(227)

To a solution of 3-bromobenzaldehyde (0.93 g, 5.0 mmol) in $CHCl_3$ (50 mL) under a N_2 atmosphere, was added (triphenylphosphoranylidene)acetaldehyde (1.70 g, 5.6 mmol), and the mixture heated to reflux for 2 days. After this period, solvents were removed in vacuo, ethyl acetate (25 mL) added, and the mixture filtered through a short plug of silica, washing with additional ethyl acetate (50 mL). Solvent was removed in vacuo, and the crude product purified by column chromatography (20% EtOAc in hexane, R_f = 0.34) affording a yellow oil which crystallised on standing (675 mg, 3.2 mmol, 64%). **δH** (400 MHz, $CDCl_3$): 9.71 (1H, d, *J* = 7.6 Hz), 7.71 (1H, t, *J* = 2.0 Hz), 7.58 – 7.55 (1H, m), 7.51 – 7.48 (1H, m), 7.40 (1H, d, *J* = 16.0 Hz), 7.31 (1H, t, *J* = 7.6 Hz), 6.70 (1H, dd, *J* = 16.0 Hz, *J* = 7.6 Hz). **δC** (100 MHz, $CDCl_3$): 193.2, 150.7, 136.1, 134.0, 131.2, 130.6, 129.7, 126.9, 123.2. **IR** (v_{max}, cm^{-1}): 1677, 1626, 1564, 1471, 1121.

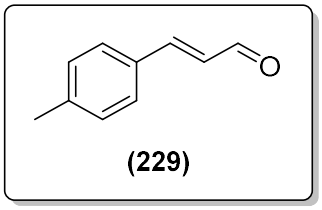
(E)-3-(2-Bromophenyl)acrylaldehyde[102]



(226)

To a solution of 2-bromobenzaldehyde (0.93 g, 5.0 mmol) in $CHCl_3$ (50 mL) under a N_2 atmosphere, was added (triphenylphosphoranylidene)acetaldehyde (1.70 g, 5.6 mmol), and the mixture heated to reflux for 2 days. After this period, solvents were removed in vacuo, ethyl acetate (25 mL) added, and the mixture filtered through a short plug of silica, washing with additional ethyl acetate (50 mL). Solvent was removed in vacuo, and the crude product purified by column chromatography (20% EtOAc in hexane, R_f = 0.35) affording a yellow oil which crystallised on standing (749 mg, 3.55 mmol, 71%). **δH** (400 MHz, $CDCl_3$): 9.77 (1H, d, *J* = 7.6 Hz), 7.91 (1H, d, *J* = 16.0 Hz), 7.67 – 7.65 (2H, m), 7.40 – 7.36 (1H, m), 7.31 – 7.27 (1H, m), 6.67 (1H, dd, *J* = 16.0 Hz, *J* = 7.6 Hz). **δC** (100 MHz, $CDCl_3$): 193.5, 150.6, 133.8, 133.7, 132.2, 130.8, 128.0, 128.0, 125.8. **IR** (ν_{max}, cm^{-1}): 1683, 1619, 1464, 1130, 1107, 976.

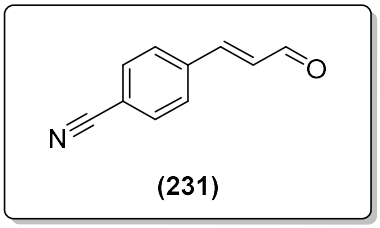
(E)-3-(p-Tolyl)acrylaldehyde[103]



(229)

To a solution of p-tolualdehyde (2.40 mL, 20.0 mmol) and sodium hydroxide (80 mg, 2.0 mmol) in ethanol (50 mL) and water (10 mL) cooled to 0 °C was added a solution of acetaldehyde (2.80 mL, 50.0 mmol) in ethanol (20 mL) dropwise over a 2 h period. The resulting mixture was allowed to stir at 0 °C for 16 h, then the solution was acidified to pH 5 with 1M HCl solution. The mixture was concentrated to ca. 20 mL *in vacuo*, then extracted with ethyl acetate (3 x 50 mL), the combined organics washed with saturated $NaHCO_3$ solution (20 mL), brine (20 mL), then dried over $MgSO_4$, filtered, and solvents removed *in vacuo*. The crude product was purified by column chromatography (20% ethyl acetate in hexanes, Rf = 0.47), affording a yellow oil (0.89 g, 6.1 mmol, 31%). **δH** (400 MHz, $CDCl_3$): 9.68 (1H, d, *J* = 7.6 Hz), 7.48 – 7.44 (3H, m), 7.24 (2H, d, *J* = 8.4 Hz), 6.69 (1H, dd, *J* = 15.6 Hz, *I* = 7.6 Hz), 2.41 (3H, s). **δC** (100 MHz, $CDCl_3$): 193.9, 153.0, 142.1, 131.4, 129.9, 128.6, 127.8, 21.7. **IR** (v_{max}, cm^{-1}): 1681, 1668, 1628, 1616, 1127, 973, 909, 731.

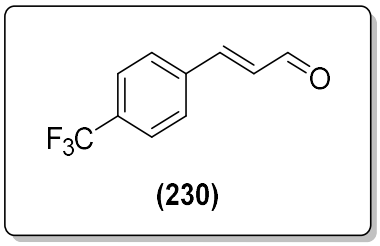
E-4-(3-Oxoprop-1-en-1-yl)benzonitrile[104]



(231)

To a solution of 4-formylbenzonitrile (0.66 g, 5.0 mmol) in chloroform (50 mL) under a nitrogen atmosphere was added (triphenylphosphoranylidene)acetaldehyde (1.70 g, 5.0 mmol) and the mixture heated to reflux for 48 h. After this period, solvents were removed *in vacuo*, ethyl acetate (25 mL) added and the mixture filtered through a short plug of silica, washing with additional ethyl acetate (50 mL). Solvents were removed *in vacuo* and the crude product purified by column chromatography (50% ethyl acetate in hexanes, Rf = 0.38) affording a yellow oil which crystallised on standing (644 mg, 82%). **δH** (400 MHz, $CDCl_3$): 9.75 (1H, d, *J* = 7.6 Hz), 7.72 (2H, d, *J* = 8.0 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 7.48 (1H, d, *J* = 16.0 Hz), 6.77 (1H, dd, *J* = 16.0 Hz, *J* = 7.6 Hz). **δC** (100 MHz, $CDCl_3$): 193.0, 149.6, 138.2, 132.9, 131.2, 128.8, 118.2, 114.3. **IR** (ν_{max}, cm^{-1}): 2224, 1683, 1625, 1417, 1123, 978, 812.

(E)-3-(4-(Trifluoromethyl)phenyl)acrylaldehyde[105]

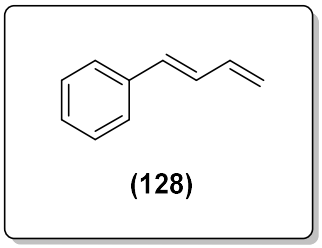


(230)

To a solution of 4-(trifluoromethyl)benzaldehyde (0.87 g, 5.0 mmol) in chloroform (50 mL) under a nitrogen atmosphere was added (triphenylphosphoranylidene)acetaldehyde (1.70 g, 5.0 mmol) and the mixture heated to reflux for 48 h. After this period, solvents were removed *in vacuo*, ethyl acetate (25 mL) added and the mixture filtered through a short plug of silica, washing with additional ethyl acetate (50 mL). Solvents were removed *in vacuo* and the crude product purified by column chromatography (20% ethyl acetate in hexanes, Rf = 0.42) affording a yellow oil (740 mg, 74%). **δH** (400 MHz, $CDCl_3$): 9.75 (1H, d, *J* = 8.0 Hz), 7.71 – 7.67 (4H, m), 7.51 (1H, d, *J* = 16.0 Hz), 6.78 (1H, dd, *J* = 16.0 Hz, *J* = 8.0 Hz). **δC** (100 MHz, $CDCl_3$): 193.3, 150.4, 137.4, 132.9, 130.6, 128.7, 128.6, 126.2. **IR** (ν_{max}, cm^{-1}): 1681, 1627, 1602, 1400, 1321, 1164, 1121, 1101, 1072, 1061, 1010, 972, 828, 799.

6.2.2 Dienes

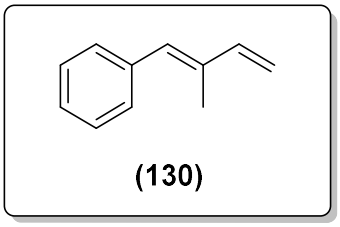
(E)-Buta-1,3-dien-1-ylbenzene[106]



(128)

Methyltriphenylphosphonium iodide (2.02 g, 5.00 mmol) was suspended in anhydrous THF (50 mL) and cooled to -78 °C. ^{n}BuLi (3.0 mL, 2.5 M in hexanes, 7.50 mmol) was added dropwise, and the mixture brought to room temperature and stirred for 30 minutes to give a clear orange-red solution. *Trans*-cinnamaldehyde (0.95 mL, 7.50 mmol) was added in one portion, and the mixture stirred for 18 hours. Removal of solvents *in vacuo* followed by column chromatography (100% hexanes, R_f = 0.35) afforded the title compound as a colourless oil (397 mg, 3.1 mmol, 61%). **δH** (400 MHz, $CDCl_3$): 7.47 – 7.42 (2H, m), 7.38 – 7.35 (2H, m), 7.30 – 7.25 (1H, m), 6.88 – 6.81 (1H, m), 6.63 – 6.52 (2H, m), 5.39 (1H, d, *J* = 16.8 Hz), 5.23 (1H, d, *J* = 10.4 Hz). **δC** (100 MHz, $CDCl_3$): 137.3, 137.3, 133.0, 129.8, 128.8, 127.8, 126.6, 117.8. **IR** (v_{max}, cm^{-1}): 1804, 1602, 1494, 1449. **MS** (m/z): Found 131.0859, ($C_{10}H_{11}^{+}$ requires 131.0855).

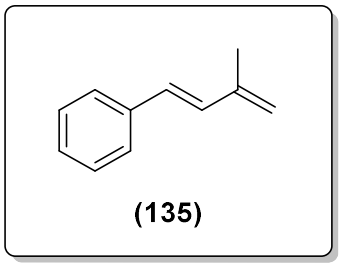
(E)-(2-Methylbuta-1,3-dien-1-yl)benzene[107]



(130)

Methyltriphenylphosphonium iodide (2.021 g, 5.00 mmol) was suspended in anhydrous THF (50 mL) and cooled to -78 °C. ^{n}BuLi (3.0 mL, 2.5 M in hexanes, 7.50 mmol) was added dropwise, and the mixture brought to room temperature and stirred for 30 minutes to give a clear orange-red solution. α-methyl-*trans*-cinnamaldehyde (1.05 mL, 7.50 mmol) was added in one portion, and the mixture stirred for 18 hours. Methanol (5.0 mL) was added, then solvents removed *in vacuo* followed by column chromatography (100% hexanes, R_f = 0.35) affording a colourless oil (0.489 g, 3.50 mmol, 69%). **δH** (400 MHz, $CDCl_3$): 7.49 – 7.33 (5H, m), 6.70 (2H, m), 5.45 (1H, d, *J* = 17.6 Hz), 5.28 (1H, d, *J* = 10.4 Hz), 2.15 (3H, s). **δC** (100 MHz, $CDCl_3$): 142.1, 138.0, 136.2, 131.9, 129.5, 128.4, 126.9, 113.2, 13.4. **IR** (ν_{max}, cm^{-1}): 1804, 1607, 1489, 1444. **MS (**m/z): Found 145.1016, ($C_{11}H_{13}^{+}$ requires 145.1012).

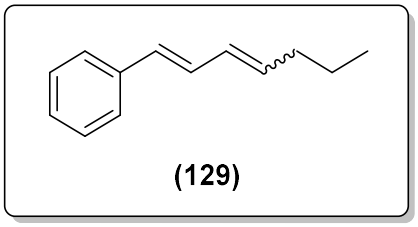
(E)-(3-Methylbuta-1,3-dien-1-yl)benzene[108]



(135)

Methyltriphenylphosphonium iodide (2.02 g, 5.00 mmol) was suspended in anhydrous THF (50 mL) and cooled to -78 °C. ^{n}BuLi (3.0 mL, 2.5 M in hexanes, 7.50 mmol) was added dropwise, and the mixture brought to room temperature and stirred for 30 minutes to give a clear orange-red solution. Benzylideneacetone (0.731 g, 5.50 mmol) was added in one portion, and the mixture stirred for 16 hours, after which point MeOH (5.0 mL) was added, then solvents removed *in vacuo*. Column chromatography (100% hexanes, R_f = 0.42) affording a colourless oil (0.576 g, 4.0 mmol, 80%). **δH** (400 MHz, $CDCl_3$): 7.48 – 7.45 (2H, m), 7.37 – 7.33 (2H, m), 7.28 – 7.23 (1H, m), 6.91 (1H, d, *J* = 16.4 Hz), 6.57 (1H, d, *J* = 16.4 Hz), 5.15 2H, d, *J* = 16.8 Hz), 2.01 (3H, s). **δC** (100 MHz, $CDCl_3$): 142.2, 137.5, 131.8, 128.8, 128.7, 127.5, 126.6, 117.5, 18.7. **IR** (v_{max}, cm^{-1}): 1605, 1493, 1446. **MS (**m/z): Found 145.1014 ($C_{11}H_{13}^{+}$ requires 145.1012).

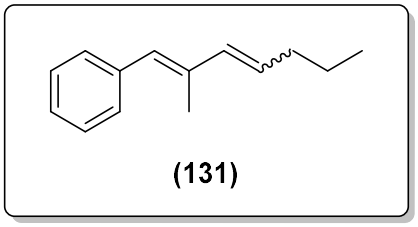
((1E)-Hepta-1,3-dien-1-yl)benzene (E/Z = 1.0 : 1.7)



(129)

^{n}Butyltriphenylphosphonium bromide (2.00g, 5.00 mmol) was suspended in anhydrous THF (50 mL) and cooled to -78 °C. ^{n}BuLi (3.0 mL, 2.5 M in hexanes, 7.50 mmol) was added dropwise, and the mixture brought to room temperature and stirred for 30 minutes to give a clear orange-red solution. *Trans*-cinnamaldehyde (0.95 mL, 7.50 mmol) was added in one portion, and the mixture stirred for 40 hours. Removal of solvents *in vacuo* followed by column chromatography (100% hexanes, R_f = 0.36) affording a colourless oil (0.707 g, 4.1 mmol, 82%, E/Z = 1.0 : 1.7). **δH** (400 MHz, $CDCl_3$): 7.53 – 7.29 (5H, m), 7.20 (1H, dd, J_1 = 15.6 Hz, J_2 = 11.2 Hz), 6.63 (1H, d, J = 15.6 Hz), 6.35 – 6.26 (1H, m), 5.68 – 5.61 (1H, m), 2.37 (2H, dt, J_1 = 7.8 Hz, J_2 = 7.2 Hz), 1.62 – 1.53 (2H, m), 1.07 (3H, t, J = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 137.9, 133.2, 132.2, 129.1, 128.8, 127.5, 126.5, 126.3, 30.2, 23.1, 14.0. **IR** (ν_{max}, cm^{-1}): 1595, 1492, 1449. **MS (**m/z): Found 173.1328 ($C_{13}H_{17}^{+}$ requires 173.1325).

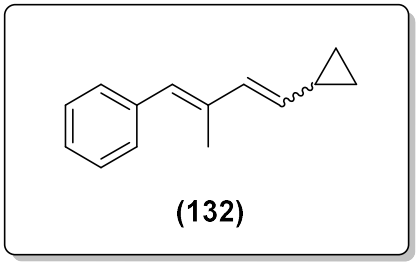
(1E)-2-Methylhepta-1,3-dien-1-yl)benzene (E/Z = 1.5 : 1.0)



(131)

^{n}Butyltriphenylphosphonium bromide (2.000 g, 5.00 mmol) was suspended in anhydrous THF (50 mL) and cooled to -78 °C. ^{n}BuLi (3.0 mL, 2.5 M in hexanes, 7.50 mmol) was added dropwise, and the mixture brought to room temperature and stirred for 30 minutes to give a clear orange-red solution. α-methyl-*trans*-cinnamaldehyde (1.05 mL, 7.50 mmol) was added in one portion, and the mixture stirred for 18 hours. Removal of solvents *in vacuo* followed by column chromatography (100% hexanes, R_f = 0.31) giving a colourless oil (0.654 g, 3.50 mmol, 70%, E/Z = 1.5 : 1.0). **δH** (400 MHz, $CDCl_3$): 7.42 – 7.24 (5H, m), 6.49 (1H, s), 6.31 (1H, d, J = 15.6 Hz), 5.85 (1H, dt, J_1 = 15.6 Hz, J_2 = 6.8 Hz), 2.23 (2H, dt, J_1 = 6.8 Hz, J_2 = 7.2 Hz), 2.06 (3H, s), 1.58 – 1.47 (2H, m), 1.01 (3H, t, J = 7.6 Hz). **δC** (100 MHz, $CDCl_3$): 138.3, 136.0, 135.5, 130.4, 129.3, 129.2, 128.2, 126.4, 35.3, 23.0, 14.1, 14.0. **IR** (ν_{max}, cm^{-1}): 1598, 1492, 1443, 1379. **MS (**m/z): Found 187.1120 ($C_{13}H_{15}O^+$ requires 187.1117).

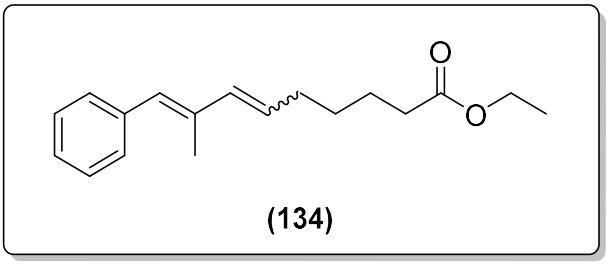
((1E)-4-Cyclopropyl-2-methylbuta-1,3-dien-1-yl)benzene (E/Z = 1.0 : 1.2)



(132)

To a suspension of **254** (0.795 g, 2.00 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added ^{n}BuLi (0.9 mL, 2.5 M in hexanes, 2.20 mmol) dropwise. After complete addition, the resulting mixture was brought to r.t. and allowed to stir for 1 h at room temperature. α-methyl-*trans*-cinnamaldehyde (0.35 mL, 2.50 mmol) added dropwise, and the solution stirred at room temperature for 6 h. After this period, MeOH (2 mL) was added, then solvents were removed *in vacuo*, and the crude product purified by column chromatography (19:1 Hexanes/Ethyl acetate, R_f = 0.58) to give a colourless oil (0.247 g, 1.34 mmol, 67%, E/Z = 1.0 : 1.2). **δH** (400 MHz, $CDCl_3$): 7.34 – 7.20 (5H, m), 6.58 (1H, s), 5.91 (1H, d, J = 11.6 Hz), 4.81 (1H, dd, J_1 = 11.6 Hz, J_2 = 10.8 Hz), 2.12 (3H, m), 1.53 – 1.45 (1H, m), 0.84 – 0.76 (2H, m), 0.48 – 0.41 (2H, m). **δC** (100 MHz, $CDCl_3$): 138.3, 135.7, 134.3, 133.0, 131.9, 129.2, 128.1, 126.3, 18.8, 11.5, 8.3. **IR** (v_{max}, cm^{-1}): 1635, 1596, 1490, 1442, 1265. **MS (**m/z): Found 185.1329 ($C_{14}H_{17}^{+}$ requires 185.1325).

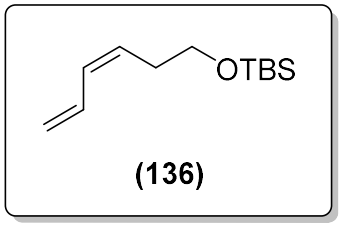
Ethyl (8E)-8-methyl-9-phenylnona-6,8-dienoate (E/Z = 1.0 : 1.2)[109]



(134)

Cs_2CO_3 (6.516 g, 20.00 mmol) was added to a solution of **255** (2.431 g, 5.00 mmol) and α-methyl-*trans*-cinnamaldehyde (0.75 mL, 5.40 mmol) in CH_2Cl_2 (60 mL) and the resulting mixture heated to reflux for 24 h. After this period the mixture was allowed to cool to room temperature, Celite® (c.a. 2.0 g) was added and the mixture stirred for 10 min. The mixture was filtered under vacuum, washing with hexanes (20 mL) and solvents removed *in vacuo*. Purification by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.42) afforded the diene as a colourless oil (1.086 g, 4.02 mmol, 80%, E/Z = 2.7 : 1.0). **δH** (400 MHz, $CDCl_3$): 7.32 – 7.17 (5H, m), 6.42 (1H, s), 6.22 (1H, d, J = 16.0 Hz), 5.75 (1H, dt, J_1 = 16.0 Hz, J_2 = 6.8Hz), 4.12 (2H, q, J = 7.6 Hz), 2.38 – 2.16 (4H, m), 1.97 (3H, s), 1.71 – 1.61 (2H, m), 1.51 – 1.41 (2H, m), 1.25 (3H, t, J = 7.6Hz). **δC** (100 MHz, $CDCl_3$): 173.8, 138.2, 135.8, 135.6, 129.8, 129.5, 129.2, 128.1, 126.3, 60.3, 34.3, 32.7, 29.1, 27.7, 18.7, 14.2. **IR** (ν_{max}, cm^{-1}): 1742, 1611, 1040. **MS (**m/z): Found 295.1677 ($C_{18}H_{24}O_2Na^+$ requires 295.1669).

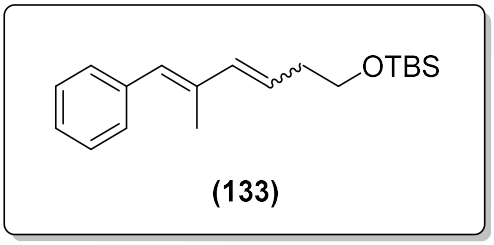
(Z)-*tert*-Butyl(hexa-3,5-dien-1-yloxy)dimethylsilane[110]



(136)

To a suspension of **257** (1.547 g, 3.00 mmol) in anhydrous THF (20 mL) cooled to -78 °C was added KHMDS (6.0 mL, 0.5 M in toluene, 3.00 mmol) dropwise. The mixture was brought to room temperature and stirred for 1 hour, then cooled to -78 °C and acrolein (0.30 mL 4.50 mmol) added. The mixture was stirred for 1h at -78 °C, then brought to room temperature and stirred for a further 2 hours. The mixture was concentrated *in vacuo* (ca. 5 mL), diluted with hexanes (30 mL), washed with water (3 x 25 mL), dried over $MgSO_4$, filtered, and solvents removed *in vacuo.* Column chromatography (9:1 hexanes/ethyl acetate R_f = 0.73) afforded a yellow oil (0.326 g, 1.53 mmol, 51%). **δH** (400 MHz, $CDCl_3$): 6.63 (1H, ddd, J_1 = 17.2 Hz, J_2 = 12.4 Hz, J_3 = 10.0 Hz), 6.06 (1H, dd, J_1 = 12.4 Hz, J_2 = 10.0 Hz), 5.46 (1H, dt, J_1 =10.0 Hz, J_2 = 8.0 Hz), 5.20 (1H, d, J = 17.2Hz), 5.09 (1H, d, J = 10.0Hz), 3.66 (2H, t, J = 5.6 Hz), 2.3 (2H, dt, J_1 = 8.0 Hz, J_2 = 5.6Hz), 0.88 (9H, s), 0.10 (6H, s). **δC** (100 MHz, $CDCl_3$): 132.4, 130.9, 128.7, 117.4, 62.8, 31.6, 26.0, 18.4, -5.2. **IR** (v_{max}, cm^{-1}): 1676, 1590, 1255, 1118. **MS (**m/z): Found 235.1491 ($C_{12}H_{24}SiONa^+$ requires 235.1489).

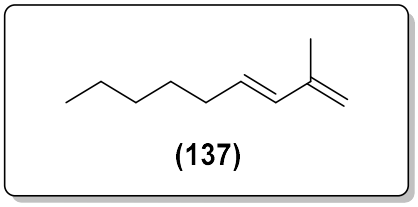
tert-Butyldimethyl(((5E)-5-methyl-6-phenylhexa-3,5-dien-1-yl)oxy)silane (E/Z = 2 : 1)



(133)

To a suspension of **257** (5.150 g, 10.0 mmol) in anhydrous THF (50 mL) cooled to -78 °C was added ^{n}BuLi (6.0 mL, 2.5 M in hexanes, 15.00 mmol) dropwise. After complete addition, the resulting mixture was brought to r.t. and allowed to stir for 1 h, then α-methyl-*trans*-cinnamaldehyde (3.0 mL, 20.0.0 mmol) added dropwise, and the solution stirred for 12h. After this period, MeOH (10 mL) was added, solvents removed *in vacuo*, and the crude product purified by column chromatography (19:1 Hexanes/Ethyl acetate, R_f = 0.38) affording a colourless oil (2.080 g, 7.80 mmol, 78%, E/Z = 2 : 1). **δH** (400 MHz, $CDCl_3$): 7.38 – 7.23 (5H, m), 6.47 (1H, s), 6.29 (1H, d, *J* = 15.6Hz), 5.79 (1H, dt, J_1 = 15.6Hz, J_2 = 6.8 Hz), 3.73 (2H, t, *J* = 7.2Hz), 2.42 (2H, dt, J_1 = 6.8Hz, J_2 = 7.2Hz), 2.01 (3H, s), 0.92 (9H, s), 0.10 (6H, s). **δC** (100 MHz, $CDCl_3$): 138.1, 137.0, 135.8, 134.9, 129.7, 129.2, 128.0, 126.4, 63.2, 36.6, 26.0, 18.4, 13.9, -5.2. **IR** (ν_{max}, cm^{-1}): 1604, 1472, 1387, 1360, 1254, 1100. **MS (**m/z): Found 325.1962 ($C_{19}H_{30}SiONa^+$ requires 325.1958).

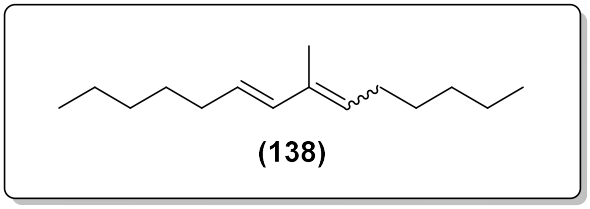
(E)-2-Methylnona-1,3-diene[111]



(137)

To a suspension of methyltriphenylphosphonium bromide (0.720 g, 2.00 mmol) in anhydrous THF (20 mL) cooled to -78 °C was added ^{n}BuLi (1.0 mL, 2.5 M in hexanes, 2.50 mmol) dropwise. After complete addition, the mixture was brought to r.t. and stirred for 1 h, then 3-nonen-2-one (0.41 mL, 2.50 mmol) added dropwise. The resulting mixture was allowed to stir at room temperature for 2h, then MeOH (2 mL) was added, solvents removed *in vacuo*, and the crude product purified by column chromatography (100% hexanes, R_f = 0.70). The pure diene was obtained as a colourless oil (0.133 mg, 0.96 mmol, 49%). **δH** (400 MHz, $CDCl_3$): 6.16 (1H, d, *J* = 15.6 Hz), 5.69 (1H, dt, J_1 = 15.6Hz, J_2 = 6.8 Hz), 4.89 (2H, s), 2.14 (2H, dt, J_1 = 6.8 Hz, J_2 = 8.4 Hz), 1.86 (3H, s), 1.46 – 1.31 (6H, m), 0.92 (3H, t, *J* = 7.6 Hz). **δC** (100 MHz, $CDCl_3$): 142.3, 132.7, 131.2, 114.1, 32.8, 31.5, 29.1, 22.6, 18.7, 14.1, 12.5. **IR** (ν_{max}, cm^{-1}): 1647, 1609, 1455, 1437, 1377. **MS** (m/z): Found 137.1327 ($C_{10}H_{17}^-$ requires 137.1325).

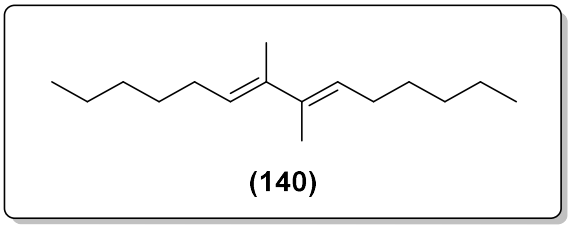
(8E)-7-Methyltetradeca-6,8-diene (E/Z = 2.9 : 1.0)



(138)

To a suspension of ^{n}hexyltriphenylphosphonium bromide (2.140 g, 5.00 mmol) in anhydrous THF (50 mL) cooled to -78 °C was added ^{n}BuLi (2.0 mL, 2.5 M in hexanes, 5.00 mmol) dropwise, the mixture brought to r.t. and stirred for 1 h. After this period, 3-nonen-2-one (0.83 mL, 5.00 mmol) was added dropwise to the ylide solution, and the solution stirred at room temperature for 2 h. MeOH (5 mL) was added, solvents were removed *in vacuo*, and the product purified by column chromatography (100% hexanes, R_f = 0.62). The diene was obtained as a pale yellow oil (0.636 mg, 3.10 mmol, 61%, E/Z = 2.9 : 1.0). **δH** (400 MHz, $CDCl_3$): 6.08 (1H, d, *J* = 15.6 Hz), 5.58 (1H, dt, J_1 = 15.6Hz, J_2 = 6.8 Hz), 5.40 (1H, t, *J* = 7.6 Hz), 2.17 – 2.08 (4H, m), 1.75 (3H, s), 1.47 – 1.29 (12H, m), 0.94 – 0.92 (6H, m). **δC** (100 MHz, $CDCl_3$): 134.7, 133.4, 130.7, 127.6, 32.9, 31.6, 31.6, 29.4, 29.4, 28.1, 22.7, 22.6, 14.1, 14.1, 12.4. **IR** (ν_{max}, cm^{-1}): 1643, 1466, 1379, 1097. **MS (**m/z): Found 209.2265 ($C_{15}H_{29}^{+}$ requires 209.2265).

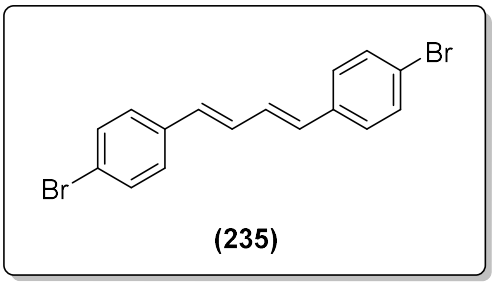
(6E,8E)-7,8-Dimethyltetradeca-6,8-diene



(140)

^{n}BuLi (2.2 mL, 2.3 M in hexanes, 5.00 mmol) was added dropwise to a suspension of ^{n}hexyltriphenylphosphonium bromide (2.141 g, 5.00 mmol) in anhydrous THF (50 mL) cooled to -78 °C. After complete addition, the mixture was brought to r.t. and allowed to stir for 1 h, then **127** (0.770 g, 5.00 mmol) added dropwise and the resulting mixture stirred at room temperature for 2 h. MeOH (5 mL) was added to the solution, solvents were removed *in vacuo*, and the crude product purified by column chromatography (100% hexanes, R_f = 0.60) to give a colourless oil (0.660 g, 3.10 mmol, 63%). **δH** (400 MHz, $CDCl_3$): 5.16 – 5.10 (2H, m), 2.23 – 1.97 (4H, m), 1.76 (3H, s), 1.67 (3H, s), 1.43 – 1.32 (12H, m), 0.92 – 0.85 (6H, m). **δC** (100 MHz, $CDCl_3$): 140.0, 135.2, 127.1, 125.3, 31.6, 31.5, 30.1, 29.4, 28.9, 27.8, 23.4, 22.7, 22.6, 15.6, 14.1, 14.0. **IR** (ν_{max}, cm^{-1}): 1641, 1466, 1377. **MS** (m/z): Found 221.2270 ($C_{16}H_{29}^{+}$ requires 221.2264).

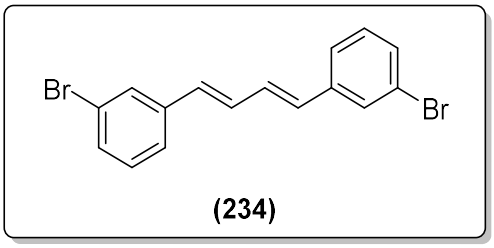
(1E,3E)-1,4-Bis(4-bromophenyl)buta-1,3-diene[112]



(235)

A mixture of triethyl phosphite (1.30 mL, 7.6 mmol), 4-bromobenzyl bromide (1.25 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude 4-bromobenzyl phosphonate (0.85 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). (E)-3-(4-bromophenyl)acrylaldehyde (0.42 g, 2.0 mmol) was added, followed by KO^tBu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a pale yellow solid (394 mg, 1.1 mmol, 55%). **δH** (400 MHz, $CDCl_3$): 7.47 – 7.43 (4H, m), 7.31 – 7.28 (4H, m), 6.95 – 6.87 (2H, m), 6.65 – 6.56 (2H, m). **δC** (100 MHz, $CDCl_3$):136.1, 132.1, 131.8, 129.6, 127.9, 121.4. **IR** (ν_{max}, cm^{-1}): 1602, 1486, 908, 734, 650.

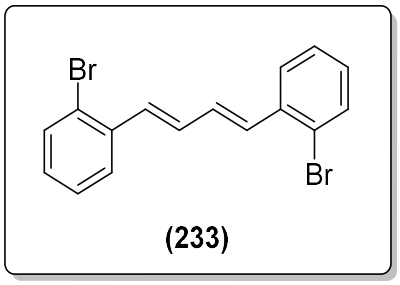
(1E,3E)-1,4-Bis(3-bromophenyl)buta-1,3-diene



(234)

A mixture of triethyl phosphite (1.30 mL, 7.6 mmol), 3-bromobenzyl bromide (1.25 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude 3-bromobenzyl phosphonate (0.85 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). (E)-3-(3-bromophenyl)acrylaldehyde (0.42 g, 2.0 mmol) was added, followed by KO^{t}Bu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a pale yellow solid (311 mg, 0.85 mmol, 43%). **δH** (400 MHz, $CDCl_3$): 7.47 – 7.43 (4H, m), 7.31 – 7.28 (4H, m), 6.95 – 6.87 (2H, m), 6.65 – 6.56 (2H, m). **δC** (100 MHz, $CDCl_3$): 139.3, 132.1, 130.6, 130.2, 130.1, 129.2, 125.1, 122.9. **IR** (v_{max}, cm^{-1}): 1602, 1486, 908, 734, 650.

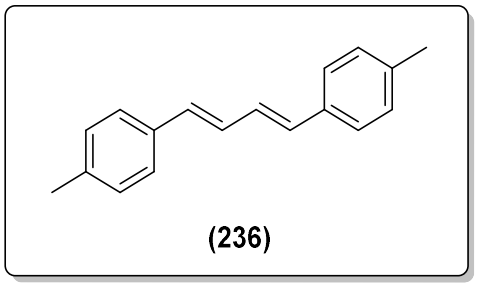
(1E,3E)-1,4-Bis(2-bromophenyl)buta-1,3-diene



(233)

A mixture of triethyl phosphite (1.30 mL, 7.6 mmol), 2-bromobenzyl bromide (1.25 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude 2-bromobenzyl phosphonate (0.85 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). (E)-3-(2-Bromophenyl)acrylaldehyde (0.42 g, 2.0 mmol) was added, followed by KO^tBu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a pale yellow solid (276 mg, 0.76 mmol, 38%). **δH** (400 MHz, $CDCl_3$): 7.65 (2H, dd, *J* = 8.4 Hz, *J* = 1.6 Hz), 7.57 (2H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz), 7.30 (2H, t, *J* = 7.6 Hz), 7.13 – 7.05 (4H, m), 7.01 – 6.94 (2H, m). **δC** (100 MHz, $CDCl_3$): 136.8, 133.3, 132.3, 131.7, 129.0, 127.6, 126.6, 124.1. **IR** (ν_{max}, cm^{-1}): 1603, 1582, 1459, 1434, 1019, 979, 738, 675.

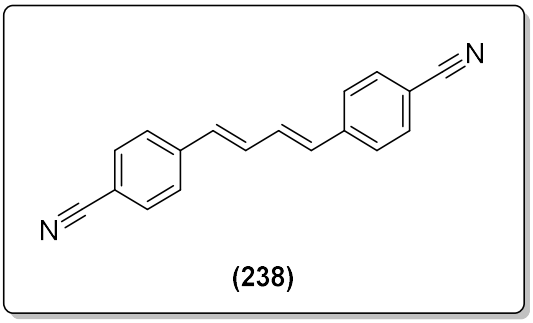
(1E,3E)-1,4-Di-p-tolylbuta-1,3-diene[113]



(236)

A mixture of triethyl phosphite (1.30 mL, 7.6 mmol), 4-methylbenzyl bromide (0.93 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude 4-methylbenzyl phosphonate (0.60 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). (E)-3-(p-Tolyl)acrylaldehyde (0.29 g, 2.0 mmol) was added, followed by KO^tBu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a pale yellow solid (332 mg, 1.42 mmol, 71%). **δH** (400 MHz, $CDCl_3$): 7.34 (4H, d, *J* = 8.0 Hz), 7.14 (4H, d, *J* = 8.0 Hz), 6.95 – 6.87 (2H, m), 6.66 – 6.58 (2H, m), 2.36 (6H, s). **δC** (100 MHz, $CDCl_3$): 137.4, 134.8, 132.3, 129.5, 128.6, 126.3, 21.4. **IR** (ν_{max}, cm^{-1}): 1600, 1509, 1479, 1447, 993, 907, 732.

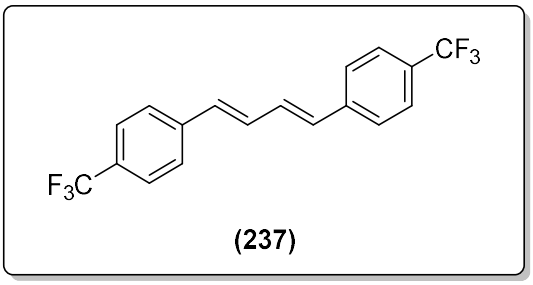
4,4'-((1E,3E)-Buta-1,3-diene-1,4-diyl)dibenzonitrile



(238)

A mixture of triethyl phosphite (1.30 mL, 7.6 mmol), 4-cyanobenzyl bromide (0.98 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude 4-cyanobenzyl phosphonate (0.63 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). (E)-3-(p-tolyl)acrylaldehyde (0.31 g, 2.0 mmol) was added, followed by KO^tBu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a pale yellow solid (353 mg, 1.38 mmol, 69%). **δH** (400 MHz, $CDCl_3$): 7.61 (4H, d, *J* = 8.4 Hz), 7.51 (4H, d, *J* = 8.4 Hz), 7.04 (2H, m), 6.73 (2H, m). **δC** (100 MHz, $CDCl_3$): 133.1, 132.7, 132.6, 130.4, 127.4, 127.0, 119.0. **IR** (ν_{max}, cm^{-1}): 2221, 1600, 1559, 1507, 984, 747.

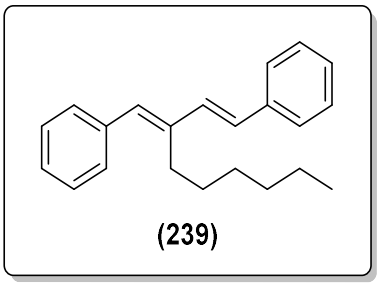
(1E,3E)-1,4-Bis(4-(trifluoromethyl)phenyl)buta-1,3-diene[114]



(237)

A mixture of triethyl phosphite (1.30 mL, 7.6 mmol), 4-(trifluoromethyl)benzyl bromide (1.20 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude 4-(trifluromethyl)benzyl phosphonate (0.74 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). (E)-3-(4-trifluromethylphenyl)acrylaldehyde (0.40 g, 2.0 mmol) was added, followed by KO^tBu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a pale yellow solid (396 mg, 1.16 mmol, 58%). **δH** (400 MHz, $CDCl_3$): 7.58 (4H, d, *J* = 8.4 Hz), 7.52 (4H, d, *J* = 8.4Hz), 7.06 – 6.98 (2H, m), 6.77 – 6.70 (2H, m). **δC** (100 MHz, $CDCl_3$): 140.5, 132.8, 131.0, 126.7, 126.7, 125.8, 125.7. **IR** (ν_{max}, cm^{-1}): 1610, 1411, 1317, 1105, 985, 859, 804, 593, 501.

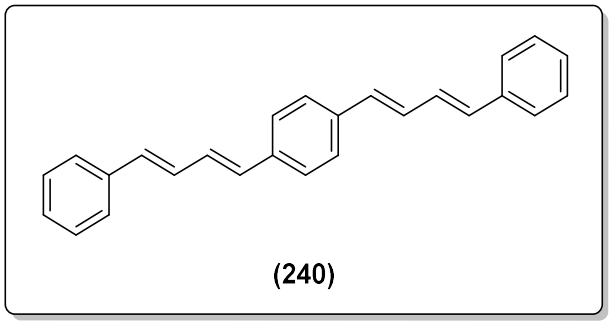
((1E,3E)-2-Hexyl-1,4-diphenylbuta-1,3-diene[115]



(239)

Diethyl benzyl phosphonate (0.57 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). Hexylcinnamaldehyde (0.43 g, 2.0 mmol) was added, followed by KO^tBu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was purified by column chromatography (100% hexanes, Rf = 0.52) affording a colourless oil (0.47 g, 1.76 mmol, 88%). **δH** (400 MHz, $CDCl_3$): 7.47 (2H, d, *J* = 7.2 Hz), 7.39 – 7.31 (6H, m), 7.26 – 7.21 (2H, m), 6.88 (1H, d, *J* = 16.0 Hz), 6.66 (1H, d, *J* = 16.4 Hz), 6.62 (1H, s), 2.56 (2H, t, *J* = 7.6 Hz), 1.68 – 1.60 (2H, m), 1.48 – 1.40 (2H, m), 1.35 – 1.31 (4H, m), 0.91 (3H, t, *J* = 6.8 Hz). **δC** (100 MHz, $CDCl_3$): 141.0, 137.9, 137.8, 133.4, 131.9, 128.9, 128.7, 128.3, 127.7, 127.4, 126.8, 126.5, 31.7, 29.8, 29.3, 27.6, 22.8, 14.2. **IR** (ν_{max}, cm^{-1}): 1594, 1492, 1467, 961, 908, 733.

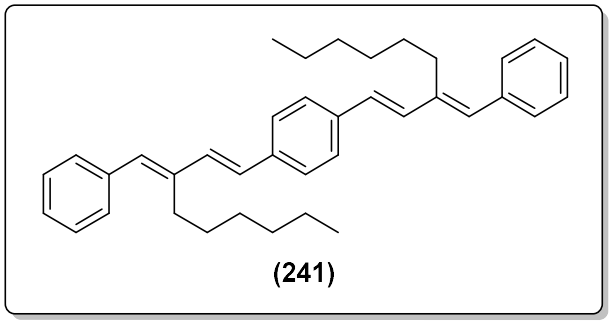
1,4-Bis((1E,3E)-4-phenylbuta-1,3-dien-1-yl)benzene



(240)

A mixture of triethyl phosphite (2.6 mL, 15.2 mmol), p-xylylene dibromide (1.32 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude bis-phosphonate (0.98 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). *Trans*-Cinnamaldehyde (0.94 mL, 7.5 mmol) was added, followed by KO^{t}Bu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was recrystallised from ethanol, affording a yellow solid (576 mg, 1.73 mmol, 69%). **δH** (400 MHz, $CDCl_3$): 7.40 (4H, s), 7.37 – 7.31 (10H, m), 7.01 – 6.92 (4H, m), 6.71 – 6.61 (4H, m). **δC** (100 MHz, $CDCl_3$): 139.8, 137.4, 132.9, 129.3, 129.2, 128.7, 128.3, 127.5, 126.7, 126.6. **IR** ν_{max}, cm^{-1}): 1590, 1487, 1445, 983, 741, 687.

1,4-Bis((E)-3-((E)-benzylidene)non-1-en-1-yl)benzene

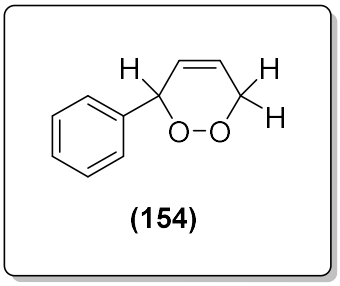


(241)

A mixture of triethyl phosphite (2.6 mL, 15.2 mmol), p-xylylene dibromide (1.32 g, 5.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.5 mmol) was heated to reflux for 16h, after which excess triethyl phosphite was removed in vacuo. A portion of the crude bis-phosphonate (0.98 g, 2.5 mmol) was taken, and dissolved in anhydrous THF (2 mL). Hexyl cinnamaldehyde (1.70 mL, 7.5 mmol) was added, followed by KO^{t}Bu (0.34 g, 3.0 mmol) in one portion. The resulting mixture was heated to reflux for 1 hour, then the mixture cooled and diluted with water (25 mL) and solids collected by suction filtration. The crude product was purified by column chromatography (100% hexanes, Rf = 0.74) affording a pale yellow oil (1.06 g, 2.10 mmol, 84%). **δH** (400 MHz, $CDCl_3$): 7.45 (4H, s), 7.40 – 7.33 (8H, m), 7.27 – 7.23 (2H, m), 6.90 (2H, d, *J* = 16.0 Hz), 6.66 (2H, d, *J* = 16.0 Hz), 6.64 (2H, s), 2.57 (4H, t, *J* = 8.4 Hz), 1.69 – 1.61 (4H, m), 1.47 -1.33 (12H, m), 0.92 (6H, t, *J* = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 141.1, 137.9, 136.8, 133.2, 132.0, 128.9, 128.4, 128.3, 127.4, 126.8, 31.7, 29.8, 29.3, 27.6, 22.8, 14.2. **IR** (v_{max}, cm^{-1}): 1594, 1492, 1469, 1265, 960, 857, 747, 696.

6.2.3 Endoperoxides

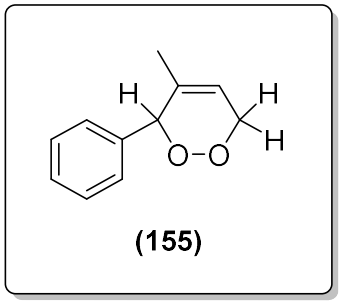
3-Phenyl-3,6-dihydro-1,2-dioxine[106]



(154)

A constant stream of oxygen was passed through a solution of **128** (0.130 g, 1.00 mmol) and 10^{-4} M disodium Rose Bengal in CH_2Cl_2/MeOH (19:1, 30 mL, 3.00 μmol) whilst exposed to a 400 W halogen light source for 30 hours at room temperature. After removal of solvents *in vacuo*, column chromatography (9:1 hexanes/ethyl acetate R_f = 0.45) afforded **154** as an unstable colourless oil (0.026 g, 0.20 mmol, 16%). **δH** (400 MHz, $CDCl_3$): 7.41 – 7.33 (5H, m), 6.21 – 6.16 (1H, m), 6.14 – 6.10 (1H, m), 5.65 – 5.62 (1H, m), 4.80 – 4.74 (1H, m), 4.62 – 4.56 (1H, m). **δC** (100 MHz, $CDCl_3$): 137.1, 129.0, 128.6, 126.9, 124.9, 80.7, 69.9. **IR** (ν_{max}, cm^{-1}): 1493, 1454, 1379, 1260, 1059, 1033. **MS** (m/z): Found 185.0575, ($C_{10}H_{10}O_2Na^+$requires 185.0573).

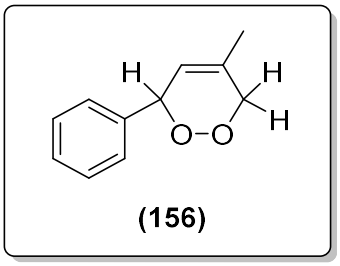
4-Methyl-3-phenyl-3,6-dihydro-1,2-dioxine[116]



(155)

A constant stream of oxygen was passed through a solution of **130** (0.144 g, 1.00 mmol) and 10^{-4} M disodium Rose Bengal in CH_2Cl_2/MeOH (19:1, 30 mL) whilst exposed to a 400W halogen light source for 18 hours at room temperature. After removal of solvents *in vacuo*, column chromatography (9:1 hexanes/ethyl acetate R_f = 0.42) afforded **155** as a colourless oil (0.030 g, 0.17 mmol, 17%). **δH** (400 MHz, $CDCl_3$): 7.40 – 7.35 (5H, m), 5.89 – 5.87 (1H, m), 5.33 (1H, s), 4.74 – 4.68 (1H, m), 4.63 – 4.58 (1H, m), 1.59 (3H, s). **δC** (100 MHz, $CDCl_3$): 136.6, 133.2, 129.4, 129.1, 128.6, 120.0, 84.6, 70.2, 19.0. **IR** (ν_{max}, cm^{-1}): 1677, 1492, 1453, 1380, 1068, 1020. **MS (**m/z): Found 199.0730 ($C_{11}H_{12}O_2Na^+$ requires 199.0730).

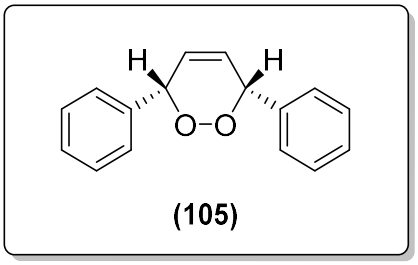
5-Methyl-3-phenyl-3,6-dihydro-1,2-dioxine[116]



(156)

A constant stream of oxygen was passed through a solution of **135** (0.100 g, 0.69 mmol) and 10^{-4} M disodium Rose Bengal in CH_2Cl_2/MeOH (19:1, 30 mL) whilst exposed to a 400W halogen light source for 28 hours at room temperature. After removal of solvents *in vacuo*, column chromatography (9:1 hexanes/ethyl acetate R_f = 0.51) afforded **156** as a colourless oil (0.045 g, 0.26 mmol, 26%). **δH** (400 MHz, $CDCl_3$): 7.42 – 7.36 (5H, m), 5.84 – 5.82 (1H, m), 5.62 – 5.60 (1H, m), 4.64 (1H, d, *J* = 16.0 Hz), 4.45 (1H, d, *J* = 16.0 Hz), 1.86 (3H, s). **δC** (100 MHz, $CDCl_3$): 137.8, 132.5, 128.8, 128.5, 128.5, 120.8, 80.4, 73.0, 18.3. **IR** (v_{max}, cm^{-1}): 1681, 1492, 1453, 1022. **MS (**m/z): Found 199.0730 ($C_{11}H_{12}O_2Na^+$ requires 199.0730).

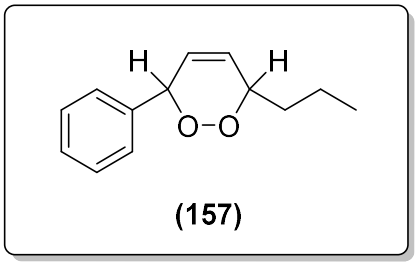
(3R,6S)-3,6-Diphenyl-3,6-dihydro-1,2-dioxine[64]



(105)

A constant stream of oxygen was passed through a solution of *trans,trans*-1,4-diphenyl-1,3-butadiene (2.07 g, 10.00 mmol) in 19:1 CH_2Cl_2/MeOH (80 mL) containing 10^{-4} M methylene blue for 24 h. Solvents were removed *in vacuo*, followed by column chromatography (5:1 hexanes/ethyl acetate R_f = 0.50) afforded the endoperoxide **105** as pale yellow crystals (1.33 g, 5.60 mmol, 56%). **δH** (400 MHz, $CDCl_3$): 7.50 – 7.25 (10H, m), 6.35 (2H, s), 5.68 (2H, s). **δC** (100 MHz, $CDCl_3$): 137.6, 132.9, 128.8, 128.7, 128.5, 80.2. **IR** (v_{max}, cm^{-1}): 1595, 1492, 1454, 1265, 1061. **MP** (°C): 79.1 – 84.2. **MS (**m/z): Found 261.0883 ($C_{16}H_{14}O_2Na^+$ requires 261.0886).

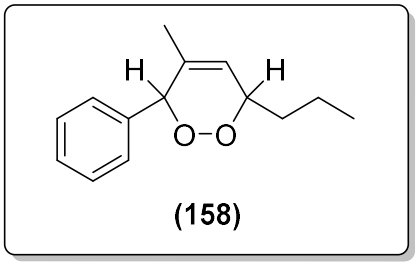
3-Phenyl-6-propyl-3,6-dihydro-1,2-dioxine



(157)

A constant stream of oxygen was passed through a solution of **129** (0.172 g, 1.00 mmol) in CH_2Cl_2/MeOH (19:1, 30 mL) containing 10^{-4} M disodium Rose Bengal whilst exposed to a 400W halogen light source for 13 hours at room temperature. After removal of solvents *in vacuo*, column chromatography (9:1 hexanes/ethyl acetate R_f = 0.43) afforded **157** as a pale yellow oil (0.057 g, 0.30 mmol, 28%). **δH** (400 MHz, $CDCl_3$): 7.46 – 7.38 (5H, m), 6.18 – 6.09 (2H, m), 5.57 – 5.55 (1H, m), 4.64 – 4.62 (1H, m), 1.84 – 1.48 (4H, m), 1.00 (3H, t, *J* = 7.2 Hz) **δC** (100 MHz, $CDCl_3$): 137.7, 128.9, 128.8, 128.7, 128.6, 126.3, 80.2, 78.3, 35.2, 18.8, 14.1. **IR** (ν_{max}, cm^{-1}): 1681, 1492, 1453, 1381, 1257, 1108, 1066. **MS (**m/z): Found 227.1042 ($C_{13}H_{16}O_2Na^+$ requires 227.1043).

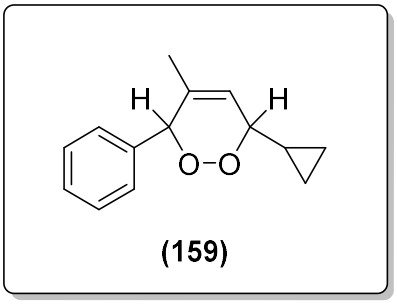
4-Methyl-3-phenyl-6-propyl-3,6-dihydro-1,2-dioxine



(158)

A constant stream of oxygen was passed through a solution of **131** (0.190 g, 1.00 mmol) in CH_2Cl_2/MeOH (19:1, 30 mL) containing 10^{-4} M disodium Rose Bengal whilst exposed to a 400W halogen light source for 3.5 hours at room temperature. After removal of solvents *in vacuo*, column chromatography (9:1 hexanes/ethyl acetate R_f = 0.49) afforded **158** as a yellow oil (0.103 g, 0.50 mmol, 47%). **δH** (400 MHz, $CDCl_3$): 7.42 – 7.37 (5H, m), 5.87 – 5.83 (1H, m), 5.25 (1H, s), 4.77 – 4.65 (1H, m), 1.79 – 1.47 (7H, m), 1.01 (3H, t, *J* = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 137.2, 132.7, 129.3, 128.8, 128.5, 124.2, 83.9, 78.3, 35.4, 19.1, 18.7, 14.1. **IR** (ν_{max}, cm^{-1}): 1602, 1493, 1454, 1380, 1254, 1065, 1025. **MS (**m/z): Found 219.1377 ($C_{14}H_{19}O_2^+$ requires 219.1380).

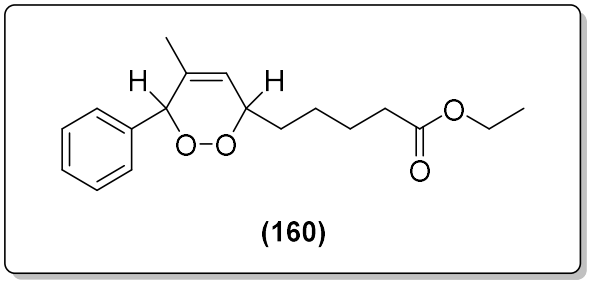
6-Cyclopropyl-4-methyl-3-phenyl-3,6-dihydro-1,2-dioxine



(159)

A solution of **132** (0.184 g, 1.00 mmol) in 19:1 CH_2Cl_2/MeOH (30 mL) containing 10^{-4} M methylene blue was irradiated for 2.5 h at room temperature with a 400W halogen light source, whilst a constant stream of oxygen was passed through the solution. After this period, solvents were removed *in vacuo* and the residue purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.44) to give a colourless oil (0.060 g, 0.28 mmol, 28%). **δH** (400 MHz, $CDCl_3$): 7.42 – 7.31 (5H, m), 5.91 – 5.88 (1H, m), 5.17 (1H, s), 3.90 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 1.65 (3H, s), 1.08 – 0.92 (1H, m), 0.66 – 0.32 (4H, m). **δC** (100 MHz, $CDCl_3$): 135.7, 131.5, 127.8, 127.2, 126.9, 121.5, 82.2, 81.3, 17.5, 11.7, 1.8. **IR** (ν_{max}, cm^{-1}): 1678, 1493, 1454, 1051, 1027. **MS (**m/z): Found 239.1044 ($C_{14}H_{16}O_2Na^+$ requires 239.1043).

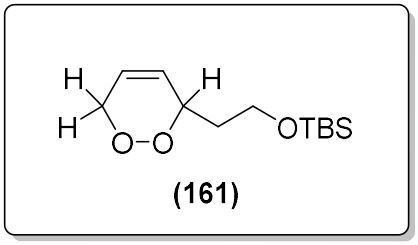
Ethyl 5-(5-methyl-6-phenyl-3,6-dihydro-1,2-dioxin-3-yl)pentanoate



(160)

A solution of **134** (0.273 mg, 1.01 mmol) in 19:1 CH_2Cl_2/MeOH (30 mL) containing 10^{-4} M disodium Rose Bengal was irradiated for 2.5 h at room temperature with a 400W halogen light source, whilst a constant stream of oxygen was passed through the solution. After this period, solvents were removed *in vacuo* and the residue purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.20) to give a colourless oil (0.112 g, 0.39 mmol, 39%). **δH** (400 MHz, $CDCl_3$): 7.36 – 7.30 (5H, m), 5.80 (1H, m), 5.19 (1H, s), 4.58 – 4.55 (1H, m), 4.11 (2H, q, *J* = 7.2Hz), 2.30 (2H, t, *J* = 7.2 Hz), 1.79 – 1.39 (9H, m), 1.24 (3H, t, *J* = 7.2Hz). **δC** (100 MHz, $CDCl_3$): 173.7, 137.0, 133.0, 129.4, 128.9, 128.6, 124.0, 84.0, 78.3, 60.3, 34.3, 33.0, 25.1, 25.0, 19.1, 14.3. **IR** (ν_{max}, cm^{-1}): 1741, 1448, 1374, 1241, 1047. **MS (**m/z): Found 327.1577 ($C_{18}H_{24}O_4Na^+$ requires 327.1567).

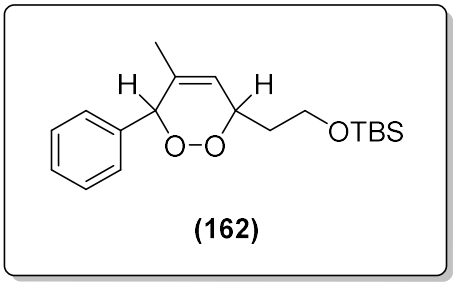
***tert*-Butyl(2-(3,6-dihydro-1,2-dioxin-3-yl)ethoxy)dimethylsilane**



(161)

A constant stream of oxygen was passed through a solution of **136** (0.101 g, 0.47 mmol) in CH_2Cl_2/MeOH (19:1, 30 mL) containing 10^{-4} M disodium Rose Bengal whilst irradiated with a 400W halogen light source for 30 hours. After this period, solvents were removed *in vacuo* and the crude product purified by column chromatography (9:1 hexanes/ethyl acetate R_f = 0.52) affording a colourless oil (0.036 g, 0.15 mmol, 31%). **δH** (400 MHz, $CDCl_3$): 6.00 – 5.95 (2H, m), 4.77 – 4.73 (1H, m), 4.57 – 4.53 (2H, m), 3.82 – 3.71 (2H, m), 1.94 – 1.75 (2H, m), 0.91 (9H, s), 0.03 (6H, s). **δC** (100 MHz, $CDCl_3$): 128.2, 123.9, 75.8, 69.9, 59.1, 35.8, 25.9, 18.3, -5.4. **IR** (ν_{max}, cm^{-1}): 1683, 1471, 1257, 1096. **MS (**m/z): Found 267.1381 ($C_{12}H_{24}SiO_3Na^+$ requires 267.1387).

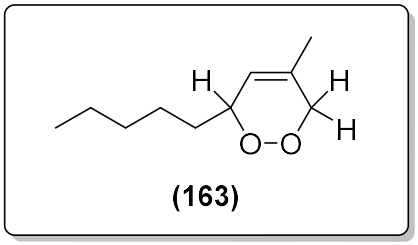
tert-Butyldimethyl(2-(5-methyl-6-phenyl-3,6-dihydro-1,2-dioxin-3-yl)ethoxy)silane



(162)

A constant stream of oxygen was passed through a solution of **133** (0.303 g, 1.00 mmol) in CH_2Cl_2/MeOH (19:1, 30 mL) containing 10^{-4} M methylene blue, under irradiation from a 400W halogen light source for 5 hours. After this period, solvents were removed *in vacuo* and the crude product purified by column chromatography (9:1 hexanes/ethyl acetate R_f = 0.35) affording a colourless oil (0.129 g, 0.38 mmol, 38%). **δH** (400 MHz, $CDCl_3$): 7.40 – 7.38 (5H, m), 5.91 – 5.90 (1H, m), 5.33 (1H, s), 4.90 – 4.78 (1H, m), 3.85 – 3.80 (2H, m), 2.09 – 1.82 (2H, m), 1.62 (3H, s), 0.95 (9H, s), 0.12 (6H, s). **δC** (100 MHz, $CDCl_3$): 136.7, 132.9, 129.3, 128.9, 128.5, 124.2, 84.1, 75.5, 59.3, 36.4, 26.0, 18.9, 18.4, -5.3. **IR** (ν_{max}, cm^{-1}): 1471, 1455, 1387, 1255, 1095. **MS** (m/z): Found 357.1859 ($C_{19}H_{30}SiO_3Na^+$ requires 357.1856).

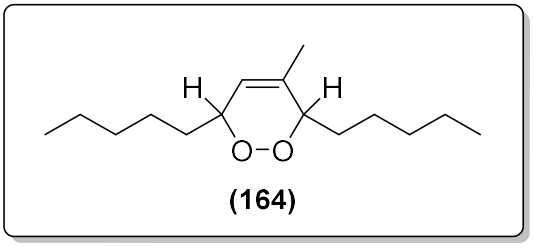
5-Methyl-3-pentyl-3,6-dihydro-1,2-dioxine



(163)

A solution of **137** (0.133 g, 0.96 mmol) in 19:1 CH_2Cl_2/MeOH (30 mL) containing 10^{-4} M disodium Rose Bengal was irradiated for 20 h at room temperature with a 400W halogen light source, whilst a constant stream of oxygen was passed through the solution. After this period, solvents were removed *in vacuo* and the residue purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.44) to give a colourless oil (0.084 g, 0.49 mmol, 51%). **δH** (400 MHz, $CDCl_3$): 5.54 – 5.52 (1H, m), 4.94 – 4.46 (1H, m), 4.41 (1H, d, *J* = 15.6 Hz), 4.21 (1H, d, *J* = 15.6 Hz), 1.67 (3H, s), 1.57 – 1.30 (8H, m), 0.85 (3H, t, *J* = 7.2Hz). **δC** (100 MHz, $CDCl_3$): 131.4, 122.1, 78.3, 72.8, 32.9, 31.8, 24.8, 22.5, 18.0, 14.0. **IR** (v_{max}, cm^{-1}): 1682, 1450, 1380, 1175, 1066, 1021. **MS** (m/z): Found 193.1204 ($C_{10}H_{18}O_2Na^+$ requires 193.1199).

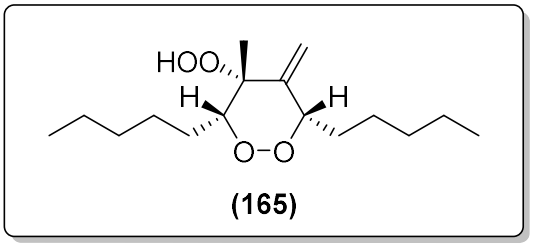
4-Methyl-3,6-dipentyl-3,6-dihydro-1,2-dioxine



(164)

A solution of **138** (0.416 g, 2.00 mmol) in 19:1 CH_2Cl_2/MeOH (30 mL) containing 10^{-4} M disodium Rose Bengal was irradiated for 18 h at room temperature with a 400W halogen light source, whilst a constant stream of oxygen was passed through the solution. After this period, solvents were removed *in vacuo* and the residue purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.52) to give a colourless oil (0.240 g, 1.00 mmol, 50%). **δH** (400 MHz, $CDCl_3$): 5.53 (1H, m), 4.49 (1H, m), 4.25 (1H, m), 1.75 – 1.28 (19H, m), 0.92 (3H, t, *J* = 6.8 Hz), 0.90 (3H, t, *J* = 6.8 Hz). **δC** (100 MHz, $CDCl_3$): 134.5, 122.6, 81.8, 78.2, 33.0, 32.8, 31.8, 31.7, 25.5, 25.1, 22.6, 22.5, 18.9, 14.1, 14.0. **IR** (ν_{max}, cm^{-1}): 1467, 1380, 1056. **MS** (m/z): Found 263.1987 ($C_{15}H_{28}O_2Na^+$ requires 263.1982).

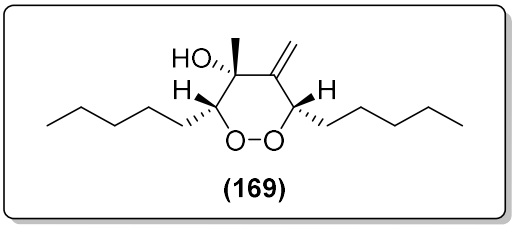
(3R,4R,6S)-4-Hydroperoxy-4-methyl-5-methylene-3,6-dipentyl-1,2-dioxane



(165)

A solution of **140** (0.140 g, 0.63 mmol) in 19:1 CH_2Cl_2/MeOH (30 mL) containing 10^{-4} M disodium Rose Bengal was irradiated for 2.5 h at room temperature with a 400W halogen light source, whilst a constant stream of oxygen was passed through the solution. After this period, solvents were removed *in vacuo* and the residue purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.27) to give a colourless oil (0.155 g, 0.54 mmol, 86%). **δH** (400 MHz, $CDCl_3$): 8.00 (1H, s), 5.32 (1H, t, *J* = 6.8 Hz), 5.26 (1H, s), 4.97 (1H, d, *J* = 2.0 Hz), 4.45 (1H, t, *J* = 6.8 Hz), 2.00 (2H, m), 1.81 (3H, s), 1.55 – 1.21 (14H, m), 0.86 (3H, t, *J* = 7.2 Hz), 0.86 (3H, t, *J* = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 148.5, 134.9, 129.6, 113.6, 87.4, 32.4, 31.8, 31.7, 30.0, 29.2, 25.6, 24.1, 22.7, 22.6, 14.1, 14.0. **IR** (ν_{max}, cm^{-1}): 3402 (br), 1636, 1458, 1373, 1064. **MS (**m/z): Found 309.2036 ($C_{16}H_{30}O_4Na^+$ requires 309.2036).

(3R,4R,6S)-4-Methyl-5-methylene-3,6-dipentyl-1,2-dioxan-4-ol

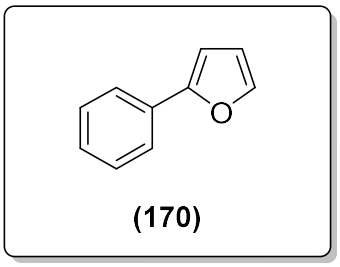


(169)

A solution of **165** (50 mg, 0.16 mmol) and triphenylphosphine (46 mg, 0.18 mmol) in diethyl ether (10 mL) was stirred at room temperature for 16h. After this period, solvents were removed *in vacuo* and the crude product analysed by ^{1}H NMR which showed loss of the hydroperoxide signal and left the cyclic peroxide intact. The absence of observable rotamers added to the evidence that the peroxide bridge had not been cleaved. **δH** (400 MHz, $CDCl_3$): 5.30 (1H, t, *J* = 7.2Hz), 5.23 (1H, s), 4.83 (1H, s), 4.21 (1H, m), 2.09 (1H, s(br)), 2.01 (2H, m), 1.82 (3H, s), 1.50 – 1.25 (14H, m), 0.88 (6H, m).

6.2.4 Furans

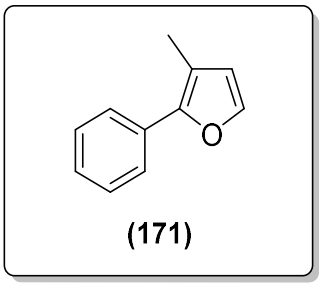
2-Phenylfuran[117]



(170)

To a solution of CBr_4 (0.059 g, 0.18 mmol) in CH_2Cl_2 (1.0 mL) cooled to 0 °C was added PPh_3 (0.047 g, 0.18 mmol) and the mixture stirred for 10 minutes. A solution of **154** (0.026 g, 0.16 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion, brought to r.t. and stirred for 16 hours. Solvents were removed *in vacuo* and the crude product purified by column chromatography (100% hexanes, R_f = 0.48) affording **170** as an unstable colourless oil (0.021 g, 0.15 mmol, 82%). **δH** (400 MHz, $CDCl_3$): 7.72 – 7.69 (2H, m), 7.50 (1H, d, *J* = 2.0 Hz), 7.43 – 7.39 (2H, m), 7.31 – 7.28 (1H, m), 6.69 (1H, d, *J* = 3.2 Hz), 6.51 (1H, dd, J_1 = 3.2 Hz, J_2 = 2.0 Hz). **δC** (100 MHz, $CDCl_3$): 154.0, 142.1, 131.0, 128.7, 127.4, 123.8, 111.7, 105.0. **IR** (ν_{max}, cm^{-1}): 1650, 1577, 1540, 1470, 1202, 1113, 1025. **MS (**m/z): Found 145.0648, ($C_{10}H_9O^+$ requires 145.0648).

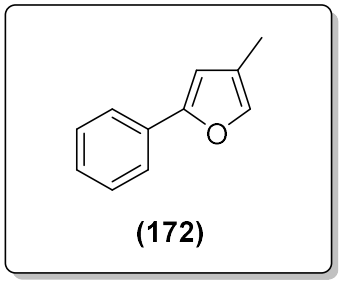
3-Methyl-2-phenylfuran[118]



(171)

To a solution of CBr_4 (0.062 g, 0.19 mmol) in CH_2Cl_2 (1.0 mL) cooled to 0 °C was added PPh_3 (0.049 g, 0.10 mmol) and the mixture stirred for 10 minutes. A solution of **155** (0.030 g, 0.17 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion, the mixture brought to r.t. and stirred for 16 hours. Solvents were removed *in vacuo* and the crude product purified by column chromatography (100% hexanes, R_f = 0.51) affording **171** as a colourless oil (0.027 g, 0.17 mmol, 91%). **δH** (400 MHz, $CDCl_3$): 7.65 – 7.63 (2H, m), 7.44 – 7.38 (3H, m), 7.29 – 7.24 (1H, m), 6.34 (1H, d, *J* = 1.6 Hz), 2.30 (3H, s). **δC** (100 MHz, $CDCl_3$): 148.8, 140.8, 131.9, 128.6, 126.8, 125.4, 116.3, 115.2, 12.0. **IR** (ν_{max}, cm^{-1}): 1682, 1608, 1510, 1485, 1443, 1164. **MS** (m/z): Found 159.0804 ($C_{11}H_{11}O^+$ requires 159.0805).

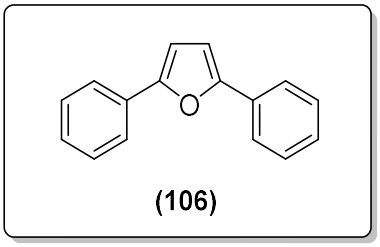
4-Methyl-2-phenylfuran[119]



(172)

To a solution of CBr_4 (0.093 g, 0.28 mmol) in CH_2Cl_2 (2.0 mL) cooled to 0 °C was added PPh_3 (0.074 g, 0.28 mmol) and the mixture stirred for 10 minutes. A solution of **156** (0.045 g, 0.26 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion, the mixture brought to r.t., and stirred for 16 hours. Solvents were removed *in vacuo* and the crude product purified by column chromatography (100% hexanes, R_f = 0.50) affording **172** as a colourless oil (0.036 g, 0.23 mmol, 87%). **δH** (400 MHz, $CDCl_3$): 7.69 – 7.67 (2H, m), 7.43 – 7.39 (2H, m), 7.31 – 7.26 (2H, m), 6.57 (1H, s), 2.12 (3H, s). **δC** (100 MHz, $CDCl_3$): 153.8, 138.9, 131.1, 128.7, 127.2, 123.7, 122.0, 107.7, 9.9. **IR** (v_{max}, cm^{-1}): 1597, 1539, 1479, 1445, 1387, 1185. **MS (**m/z): Found 159.0809 ($C_{11}H_{11}O^+$ requires 159.0804).

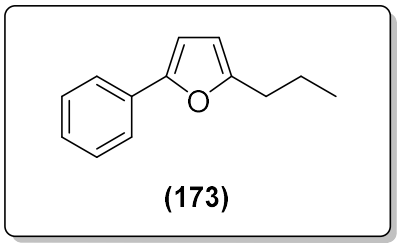
2,5-Diphenylfuran[120]



(106)

To a solution of CBr_4 (0.182 g, 0.55 mmol) in CH_2Cl_2 (3.0 mL) cooled to 0 °C was added PPh_3 (0.144 g, 0.55 mmol) and the mixture stirred for 20 minutes. After this period, a solution of **105** (0.120 g, 0.50 mmol) in CH_2Cl_2 (2.0 mL) was added in one portion, the mixture brought to r.t. and stirred for 16 h. Solvents were removed *in vacuo*, then purified by column chromatography (4:1 hexanes/ethyl acetate R_f = 0.58) affording a pale yellow crystalline solid (0.104 g, 0.48 mmol, 95%). **δH** (400 MHz, $CDCl_3$): 7.77 – 7.25 (10H, m), 6.74 (2H, s). **δC** (100 MHz, $CDCl_3$): 153.4, 130.8, 129.3, 128.7, 123.7, 107.3. **IR** (ν_{max}, cm^{-1}): 1597, 1482, 1443, 1288. **MP** (°C): 86.0 – 90.2. **MS** (m/z): Found 221.0959 ($C_{16}H_{13}O^+$ requires 221.0961).

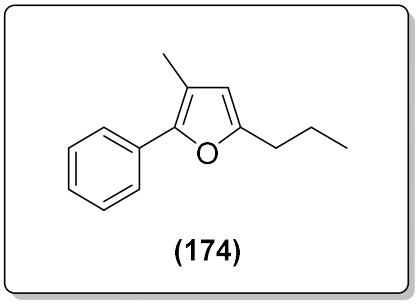
2-Phenyl-5-propylfuran[121]



(173)

To a solution of CBr_4 (0.091 g, 0.27 mmol) in CH_2Cl_2 (2.0 mL) cooled to 0 °C was added PPh_3 (0.072 g, 0.27 mmol) and the mixture stirred for 25 minutes. A solution of **157** (0.051 g, 0.25 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion and stirred for 18 hours. Solvents were removed *in vacuo*, then purified by column chromatography (100% hexanes, R_f = 0.48) affording **173** as a colourless oil (0.036 g, 0.20 mmol, 76%). **δH** (400 MHz, $CDCl_3$): 7.67 – 7.64 (2H, m), 7.39 – 7.35 (2H, m) 7.25 – 7.21 (1H, m), 6.57 (1H, d, *J* = 3.2 Hz), 6.08 (1H, d, *J* = 3.2 Hz), 2.68 (2H, t, *J* = 7.6 Hz) 1.79 – 1.70 (2H, m), 1.02 (3H, t, *J* = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 156.4, 152.2, 131.4, 128.7, 126.8, 123.4, 107.1, 105.7, 30.3, 21.6, 13.9. **IR** (ν_{max}, cm^{-1}): 1594, 1546, 1487, 1448, 1204, 1015. **MS (**m/z): Found 187.1114 ($C_{13}H_{15}O^+$ requires 187.1117).

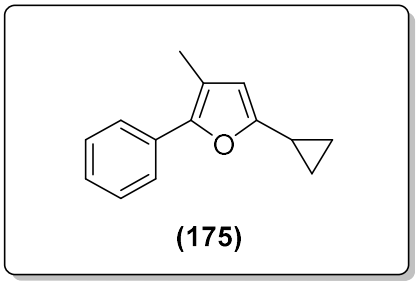
3-Methyl-2-phenyl-5-propylfuran



(174)

To a solution of CBr_4 (0.112 g, 0.34 mmol) in CH_2Cl_2 (2.0 mL) cooled to 0 °C was added PPh_3 (0.089 g, 0.34 mmol) and the mixture stirred for 20 minutes. A solution of **158** (0.067 g, 0.31 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion, the mixture brought to r.t., and stirred for 18 hours. Solvents were removed *in vacuo*, then column chromatography (100% hexanes, R_f = 0.32) afforded **174** as a colourless oil (0.031 g, 0.22 mmol, 72%). **δH** (400 MHz, $CDCl_3$): 7.59 (2H, d, *J* = 7.2Hz), 7.39 (2H, t, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 5.94 (1H, s), 2.62 (2H, t, *J* = 7.6 Hz) 2.25 (3H, s), 1.72 – 1.68 (4H, m), 1.00 (3H, t, *J* = 7.2Hz). **δC** (100 MHz, $CDCl_3$): 154.8, 146.8, 137.3, 128.5, 126.1, 125.0, 117.1, 110.8, 30.2, 21.5, 13.9, 12.1. **IR** (ν_{max}, cm^{-1}): 1675, 1616, 1449, 1238. **MS (**m/z): Found 201.1271 ($C_{14}H_{17}O^+$ requires 201.1274).

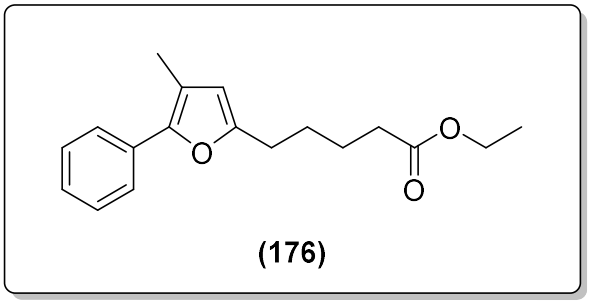
5-Cyclopropyl-3-methyl-2-phenylfuran



(175)

To a solution of CBr_4 (0.074 g, 0.22 mmol) in CH_2Cl_2 (1.0 mL) cooled to 0 °C was added PPh_3 (0.059 g, 0.22 mmol). The resulting mixture was stirred for 10 min, then a solution of **159** (0.044 g, 0.20 mmol in CH_2Cl_2 (1.0 mL) was added. The solution was brought to r.t. and stirred for 16h. After this period, solvents were removed *in vacuo* and the crude product purified by column chromatography (19:1 hexanes/ethyl acetate, R_f = 0.52) to give the furan as a colourless oil (0.037 g, 0.19 mmol, 93%). **δH** (400 MHz, $CDCl_3$): 7.61 – 7.58 (2H, m), 7.42 – 7.38 (2H, m), 7.26 – 7.21 (1H, m), 5.94 (1H, s), 2.25 (3H, s), 1.95 – 1.90 (1H, m), 0.95 – 0.83 (4H, m). **δC** (100 MHz, $CDCl_3$): 155.6, 146.3, 132.1, 128.4, 126.1, 124.8, 117.2, 109.3, 12.0, 8.8, 6.9. **IR** (ν_{max}, cm^{-1}): 1600, 1558, 1444. **MS (**m/z): Found 221.0939 ($C_{14}H_{14}ONa^+$ requires 221.0937).

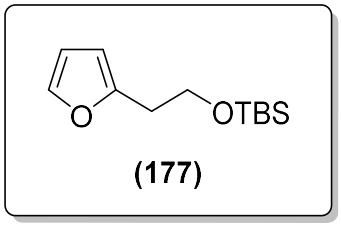
Ethyl 5-(4-methyl-5-phenylfuran-2-yl)pentanoate



(176)

To a solution of CBr_4 (0.092 g, 0.28 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added PPh_3 (0.073 g, 0.28 mmol), and the mixture stirred for 10 min. After this period, a solution of **160** (0.072 g, 0.25 mmol) in CH_2Cl_2 (1.0 mL) was added. The resulting mixture was heated to reflux for 30 h, then the mixture cooled, solvents removed *in vacuo*, and purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.33). The pure furan was obtained as a yellow oil (0.064 g, 0.24 mmol, 94%). **δH** (400 MHz, $CDCl_3$): 7.61 – 7.58 (2H, m), 7.41 – 7.37 (2H, m), 7.25 – 7.20 (1H, m), 5.96 (1H, s), 4.14 (2H, q, *J* = 7.2 Hz), 2.69 – 2.65 (2H, m), 2.38 – 2.33 (2H, m), 2.24 (3H, s), 1.77 – 1.68 (2H, m), 1.26 (3H, t, *J* = 7.6Hz). **δC** (100 MHz, $CDCl_3$): 173.7, 154.2, 147.0, 132.2, 128.5, 126.2, 125.0, 117.1, 111.0, 60.4, 34.2, 27.8, 27.7, 24.6, 14.3, 12.1. **IR** (ν_{max}, cm^{-1}): 1728, 1604, 1558, 1443, 1373, 1180. **MS (**m/z): Found 309.1464 ($C_{18}H_{22}O_3Na^+$ requires 309.1461).

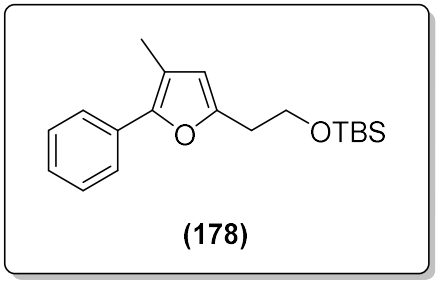
tert-Butyl(2-(furan-2-yl)ethoxy)dimethylsilane[122]



(177)

A solution of CBr_4 (0.060 g, 0.18 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 °C and PPh_3 (0.047 g, 0.18 mmol) added. The mixture was stirred for 20 minutes, then a solution of **161** (0.039 g, 0.16 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion. The solution was brought to room temperature and stirred with TLC monitoring. After 18 h solvents were removed *in vacuo*. Column chromatography (19:1 hexanes/ethyl acetate R_f = 0.54) afforded a colourless oil (0.034 g, 0.15 mmol, 95%). **δH** (400 MHz, $CDCl_3$): 7.31 – 7.30 (1H, m), 6.29 – 6.28 (1H, m), 6.06 – 6.05 (1H, m), 3.85 (2H, t, *J* = 7.2Hz), 2.85 (2H, t, *J* = 7.2Hz), 0.87 (9H, s), 0.01 (6H, s). **δC** (100 MHz, $CDCl_3$): 153.4, 141.0, 110.3, 106.2, 61.7, 32.0, 26.0, 18.4, -5.4. **IR** (ν_{max}, cm^{-1}): 1599, 1507, 1472, 1255, 1105, 1005. **MS (**m/z): Found 249.1285 ($C_{12}H_{22}SiO_2Na^+$ requires 249.1281).

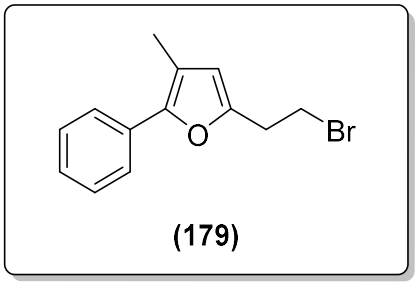
tert-Butyldimethyl(2-(4-methyl-5-phenylfuran-2-yl)ethoxy)silane



(178)

To a solution of CBr_4 (0.054 g, 0.16 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added PPh_3 (0.043 g, 0.16 mmol), and the mixture stirred for 10 min. After this period, a solution of **162** (0.050 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added, and the mixture brought to r.t. The resulting mixture was allowed to stir for 16 h, then solvents removed *in vacuo*, and purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.57). The pure furan was obtained as a pale yellow oil (0.030 g, 0.09 mmol, 63%). **δH** (400 MHz, $CDCl_3$): 7.62 – 7.60 (2H, m), 7.43 – 7.39 (2H, m), 2.28 – 7.25 (1H, m) 6.03 (1H, s), 3.91 (2H, t, *J* = 6.8 Hz), 2.89 (2H, t, *J* = 6.8 Hz), 2.26 (3H, s), 0.91 (9H, s), 0.06 (6H, s) . **δC** (100 MHz, $CDCl_3$): 151.5, 147.1, 132.2, 128.5, 126.2, 125.0, 117.1, 112.1, 61.8, 32.0, 25.9, 18.6, 12.0, -5.4. **IR** (ν_{max}, cm^{-1}): 1471, 1455, 1387, 1256, 1096. **MS** (m/z): Found 339.1757 ($C_{19}H_{28}SiO_2Na^+$ requires 339.1751).

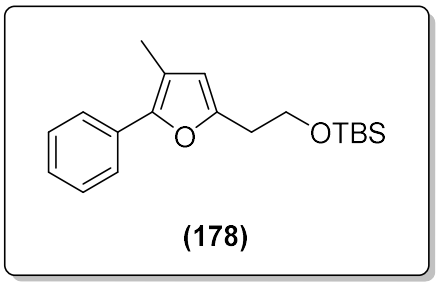
5-(2-Bromoethyl)-3-methyl-2-phenylfuran



(179)

To a solution of CBr_4 (0.292 g, 0.88 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added PPh_3 (0.232 g, 0.88 mmol), and the mixture stirred for 10 min. After this period, a solution of **162** (0.130 g, 0.40 mmol) in CH_2Cl_2 (2.0 mL) was added. The resulting mixture heated to reflux for 16 h, cooled, then solvents removed *in vacuo*, and purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.81). The pure furan was obtained as a pale yellow oil (0.097 g, 0.36 mmol, 91%). **δH** (400 MHz, $CDCl_3$): 7.71 – 7.61 (2H, m), 7.48 – 7.41 (2H, m), 7.31 – 7.26 (1H, m), 6.12 (1H, s), 3.65 (2H, t, *J* = 7.2 Hz), 3.25 (2H, t, *J* = 7.2 Hz), 2.30 (3H, s). **δC** (100 MHz, $CDCl_3$): 150.6, 147.8, 131.8, 128.5, 126.5, 125.1, 117.1, 112.5, 31.9, 29.8, 11.9. **IR** (ν_{max}, cm^{-1}): 1679, 1600, 1551, 1491, 1378, 1071. **MS** (m/z): Found 287.0049 ($C_{13}H_{13}BrONa^+$ requires 287.0042 for ^{79}Br).

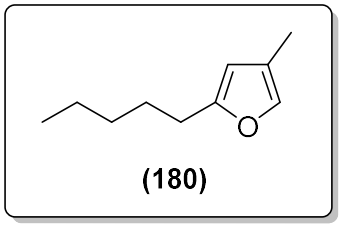
tert-Butyldimethyl(2-(4-methyl-5-phenylfuran-2-yl)ethoxy)silane



(178)

To a solution of CBr_4 (0.054 g, 0.16 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added PPh_3 (0.043 g, 0.16 mmol), and the mixture stirred for 10 min. After this period, solid $NaHCO_3$ (13 mg, 0.16 mmol) and a solution of **162** (0.050 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added, and the mixture brought to r.t. The resulting mixture was allowed to stir for 16 h, then solvents removed *in vacuo*, and purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.57). The pure furan was obtained as a pale yellow oil (0.041 g, 0.13 mmol, 87%). Data was consistent with that for the unmodified reaction.

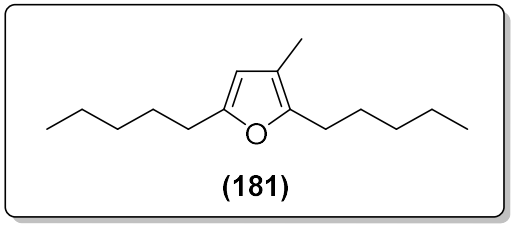
4-Methyl-2-pentylfuran[59]



(180)

To a solution of CBr_4 (0.179 g, 0.54 mmol) in CH_2Cl_2 (3.0 mL) cooled to 0 °C was added PPh_3 (0.141 g, 0.54 mmol) and the mixture stirred for 10 minutes. A solution of **163** (0.084 g, 0.49 mmol) in CH_2Cl_2 (2.0 mL) was added in one portion and stirred for 16 hours. Solvents were removed *in vacuo*, and the crude product purified by column chromatography (100% hexanes, R_f = 0.74) afforded **180** as a colourless oil (0.062 g, 0.41 mmol, 83%). **δH** (400 MHz, $CDCl_3$): 7.08 (1H, s), 5.87 (1H, s), 2.58 (2H, t, *J* = 7.6 Hz), 2.01 (3H, s), 1.67 – 1.59 (2H, m), 1.36 – 1.28 (4H, m), 0.92 (3H, t, *J* = 7.2Hz). **δC** (100 MHz, $CDCl_3$): 156.7, 137.2, 120.4, 107.4, 31.4, 28.1, 27.7, 22.5, 14.0, 9.9. **IR** (ν_{max}, cm^{-1}): 1643, 1553, 1468, 1381, 1167, 1096. **MS** (m/z): Found 153.1278 ($C_{10}H_{17}O^+$ requires 153.1274)

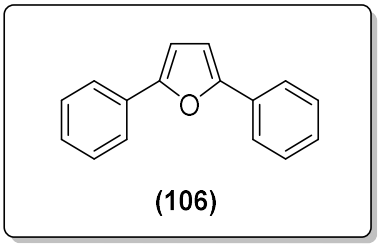
3-Methyl-2,5-dipentylfuran



(181)

To a solution of CBr_4 (0.365 g, 1.10 mmol) in CH_2Cl_2 (7.0 mL) cooled to 0 °C was added PPh_3 (0.289 g, 1.1 mmol) and the resulting mixture stirred for 10 minutes. After this period, a solution of **164** (0.239 g, 1.00 mmol) in CH_2Cl_2 (3.0 mL) was added, the solution brought to r.t., and stirred for 16h. Solvents were removed *in vacuo*, and the crude product purified by column chromatography (9:1 hexanes/ethyl acetate, R_f = 0.70). The furan was obtained as a colourless oil (0.160 g, 0.72 mmol, 72%). **δH** (400 MHz, $CDCl_3$): 5.76 (1H, s), 2.54 (2H, t, *J* = 8.0 Hz), 2.53 (2H, t, *J* = 7.6 Hz), 1.93 (3H, s), 1.66 – 1.56 (4H, m), 1.39 – 1.28 (8H, m), 0.94 – 0.90 (6H, m). **δC** (100 MHz, $CDCl_3$): 153.5, 149.4, 113.8, 107.6, 31.5, 31.4, 28.5, 28.0, 27.9, 25.9, 22.5, 22.5, 14.1, 14.0, 9.9. **IR** (ν_{max}, cm^{-1}): 1637, 1576, 1466, 1379, 1219. **MS** (m/z): Found 223.2062 ($C_{15}H_{27}O^+$ requires 223.2056).

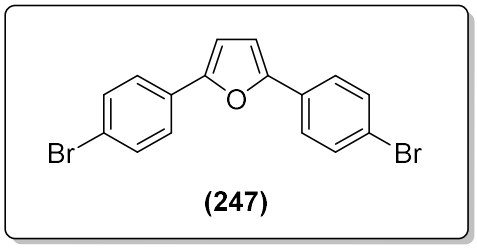
2,5-Diphenylfuran[120]



(106)

A solution of *trans,trans*-1,4-diphenyl-1,3-butadiene (0.26 g, 1.25 mmol, 0.0250 M) in $CHCl_3$ (50 mL) containing tetraphenylporphyrin (31 mg, 0.05 mmol, 10^{-3} M) and CCl_4 (133 µL, 1.38 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. ^1H NMR analysis of the crude reaction mixture showed complete conversion of both diene to endoperoxide, and endoperoxide to furan. Purification of the crude product *via* column chromatography (19:1 hexanes/ethyl acetate, R_f = 0.42) afforded an off-white solid (258 mg, 1.17 mmol, 94%). **δH** (400 MHz, $CDCl_3$): 7.77 – 7.25 (10H, m), 6.74 (2H, s). **δC** (100 MHz, $CDCl_3$): 153.4, 130.8, 129.3, 128.7, 123.7, 107.3. **IR** (ν_{max}, cm^{-1}): 1598, 1482, 1443, 1288.

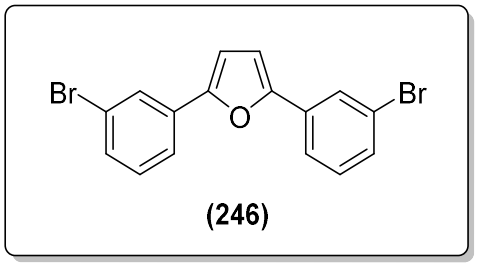
2,5-Bis(4-bromophenyl)furan[123]



(247)

A solution of (1E,3E)-1,4-bis(4-bromophenyl)buta-1,3-diene (364 mg, 1.00 mmol, 0.0250 M) in $CHCl_3$ (40 mL) containing tetraphenylporphyrin (25 mg, 0.05 mmol, 10^{-3} M) and CCl_4 (107 µL, 1.10 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture showed complete conversion of both diene to endoperoxide, and endoperoxide to furan. Purification of the crude product *via* column chromatography (19:1 hexanes/ethyl acetate, R_f = 0.45) afforded a pale yellow solid (362 mg, 0.96 mmol, 96%). **δH** (400 MHz, $CDCl_3$): 7.62 – 7.58 (4H, m), 7.54 – 7.51 (4H, m), 6.74 (2H, s). **δC** (100 MHz, $CDCl_3$): 152.7, 132.0, 129.5, 125.3, 121.4, 108.0. **IR** (ν_{max}, cm^{-1}): 1650, 1482, 1382, 908, 733.

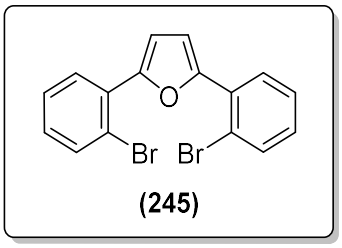
2,5-Bis(3-bromophenyl)furan[124]



(246)

A solution of (1E,3E)-1,4-bis(3-bromophenyl)buta-1,3-diene (182 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (20 mL) containing tetraphenylporphyrin (13 mg, 0.025 mmol, 10^{-3} M) and CCl_4 (54 µL, 0.55 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture showed residual unconverted diene, however all endoperoxide generated had been converted to the furan product. Purification of the crude product *via* column chromatography (19:1 hexanes/ethyl acetate, R_f = 0.47) afforded a pale yellow solid (115 mg, 0.31 mmol, 61%). **δH** (400 MHz, $CDCl_3$): 7.86 (2H, s), 7.64 (2H, d, *J* = 7.6 Hz), 7.39 (2H, d, *J* = 8.4 Hz), 7.27 (2H, dd, *J* = 8.4 Hz, *J* = 7.6 Hz), 6.75 (2H, s). **δC** (100 MHz, $CDCl_3$): 152.4, 132.4, 130.5, 130.4, 126.7, 123.0, 122.4, 108.5. **IR** (ν_{max}, cm^{-1}): 1659, 1607, 1581, 1567, 1473, 909, 735.

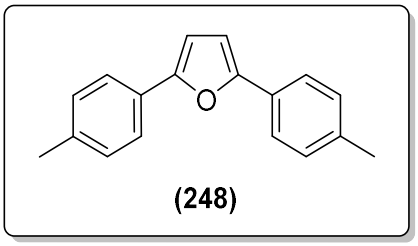
Attempted preparation of 2,5-bis(2-bromophenyl)furan



(245)

A solution of (1E,3E)-1,4-bis(2-bromophenyl)buta-1,3-diene (182 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (20 mL) containing tetraphenylporphyrin (13 mg, 0.025 mmol, 10^{-3} M) and CCl_4 (54 µL, 0.55 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. ^1H NMR analysis of the crude reaction mixture showed no conversion to the desired furan product.

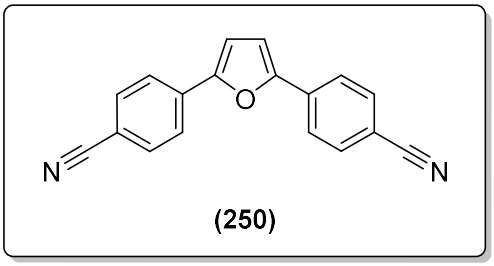
2,5-Di-p-tolylfuran[125]



(248)

A solution of (1E,3E)-1,4-bis(p-tolyl)buta-1,3-diene (117 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (20 mL) containing tetraphenylporphyrin (13 mg, 0.025 mmol, 10^{-3} M) and CCl_4 (54 µL, 0.55 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture showed residual unconverted diene, however all endoperoxide generated had been converted to the furan product. Purification by column chromatography afforded a white solid (91 mg, 0.37 mmol, 73%). **δH** (400 MHz, $CDCl_3$): 7.63 (4H, d, *J* = 8.4 Hz), 7.20 (4H, d, *J* = 8.4Hz), 6.66 (2H, s), 2.37 (6H, s). **δC** (100 MHz, $CDCl_3$): 137.2, 129.5, 128.3, 126.3, 123.7, 106.5, 21.4. **IR** (ν_{max}, cm^{-1}): 1662, 1605, 1502, 1114, 923, 791.

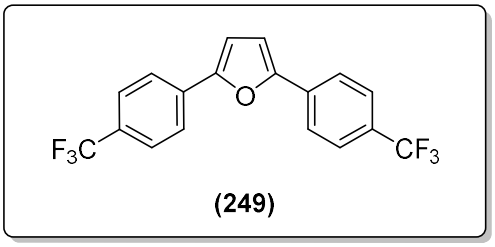
4,4'-(Furan-2,5-diyl)dibenzonitrile[126]



(250)

A solution of (1E,3E)-1,4-bis(4-cyanophenyl)buta-1,3-diene (128 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (20 mL) containing tetraphenylporphyrin (13 mg, 0.025 mmol, 10^{-3} M) and CCl_4 (54 µL, 0.55 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. Purification by column chromatography afforded a pale yellow solid (36 mg, 0.14 mmol, 27%). **δH** (400 MHz, $CDCl_3$): 7.66 (4H, d, *J* = 8.8 Hz), 7.60 (4H, d, *J* = 8.8 Hz), 7.19 (2H, s). **δC** (100 MHz, $CDCl_3$): 145.5, 132.7, 132.6, 127.3, 127.0, 118.2, 111.1. **IR** (ν_{max}, cm^{-1}): 2220, 1653, 1506, 1411, 1174, 837.

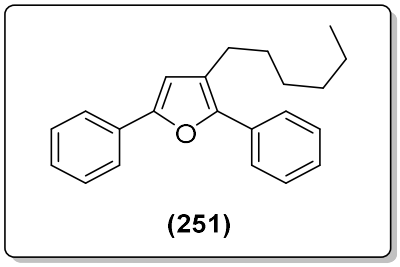
2,5-Bis(4-(trifluoromethyl)phenyl)furan[127]



(249)

A solution of (1E,3E)-1,4-bis(4-(trifluoromethyl)phenyl)buta-1,3-diene (171 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (20 mL) containing tetraphenylporphyrin (13 mg, 0.025 mmol, 10^{-3} M) and CCl_4 (54 µL, 0.55 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. Purification by column chromatography (5% EtOAc in hexanes) afforded a white solid (59 mg, 0.17 mmol, 33%). **δH** (400 MHz, $CDCl_3$): 7.63 – 6.61 (8H, m), 7.20 (2H, s). **δC** (100 MHz, $CDCl_3$): 134.0, 129.7, 129.4, 129.1, 126.9, 125.6, 122.9. **IR** (ν_{max}, cm^{-1}): 1612, 1321, 1176, 1123, 989, 687.

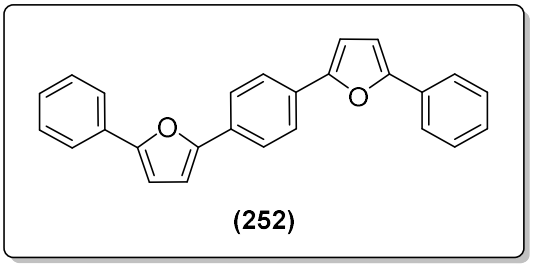
3-Hexyl-2,5-diphenylfuran



(251)

A solution of ((1E,3E)-2-hexyl-1,4-diphenylbuta-1,3-diene (145 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (20 mL) containing tetraphenylporphyrin (13 mg, 0.025 mmol, 10^{-3} M) and CCl_4 (54 µL, 0.55 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. The crude product was purified by column chromatography (100% hexanes, Rf = 0.55) affording a colourless oil (82 mg, 0.27 mmol, 54%). **δH** (400 MHz, $CDCl_3$): 7.76 – 7.71 (4H, m), 7.48 – 7.39 (4H, m), 7.32 – 7.25 (2H, m), 6.69 (1H, s), 2.72 (2H, t, *J* = 8.0 Hz), 1.75 – 1.68 (2H, m), 1.49 – 1.43 (2H, m), 1.40 – 1.33 (4H, m), 0.93 (3H, t, *J* = 6.8 Hz). **δC** (100 MHz, $CDCl_3$): 152.0, 148.0, 131.9, 131.0, 128.8, 128.7, 127.3, 126.9, 125.6, 124.2, 123.8, 109.3, 31.9, 30.1, 29.4, 26.2, 22.8, 14.2. **IR** (ν_{max}, cm^{-1}): 1613, 1595, 1493, 1466, 1445, 933, 762, 692.

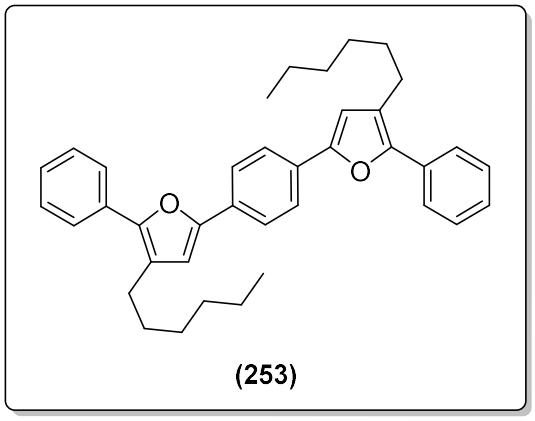
Attempted preparation of 1,4-bis(5-phenylfuran-2-yl)benzene[128]



(252)

A continuously stirred suspension of 1,4-bis((1E,3E)-4-phenylbuta-1,3-dien-1-yl)benzene (167 mg, 0.50 mmol, 0.0125 M) in $CHCl_3$ (40 mL) containing tetraphenylporphyrin (26 mg, 0.05 mmol, 10^{-3} M) and CCl_4 (108 µL, 1.10 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. ^1H NMR analysis of the crude reaction mixture showed only trace conversion to the desired furan product, however isolation by column chromatography proved unsuccessful.

1,4-Bis(4-hexyl-5-phenylfuran-2-yl)benzene

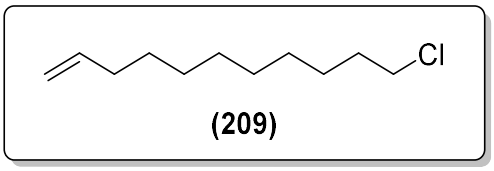


(253)

A solution of 1,4-bis((E)-3-((E)-benzylidene)non-1-en-1-yl)benzene (251 mg, 0.50 mmol, 0.0250 M) in $CHCl_3$ (40 mL) containing tetraphenylporphyrin (26 mg, 0.05 mmol, 10^{-3} M) and CCl_4 (108 µL, 1.10 mmol, 0.0275 M) was pumped at 0.30 mL min^{-1} combining with an air stream at 1.10 mL min^{-1} into a 'Y' junction, under 9.0 Bar back pressure (total 10.0 Bar pressure). The resulting segmented flow steam was passed through a UV-150 reactor coil equipped with a 420 nm LED light source (10 mL, τ = 24.4 min) at 35 °C. The resulting output stream was combined with a stream of PPh_3 (0.03 M in $CHCl_3$) in a 'Y' mixer, after which the stream was split and recombined through two '+' splitters to aid mixing of the two reagent streams which was hindered by the gas segmentation of the flow. The resulting stream was pumped into a second reactor coil (10.0 mL, τ = 14.1 min) heated to 130 °C, the output stream collected, and solvents removed *in vacuo*. The crude product was purified by column chromatography (100% hexanes, Rf = 0.70) afforded a yellow solid (0.13 g, 0.24 mmol, 48%). **δH** (400 MHz, $CDCl_3$): 7.74 – 7.70 (8H, m), 7.47 – 7.43 (4H, m), 7.31 – 7.27 (2H, m), 6.69 (2H, s), 2.71 (4H, t, *J* = 8.0 Hz), 1.71 (4H, m), 1.45 – 1.32 (12H, m), 0.90 (6H, t, *J* = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 151.8, 148.1, 131.8, 129.5, 128.7, 126.9, 125.6, 124.4, 124.0, 109.4, 31.8, 30.0, 29.3, 26.2, 22.7, 14.2. **IR** (ν_{max}, cm^{-1}): 1601, 1496, 908, 733, 692.

6.2.5 Furan Fatty Acid F_5 Total Synthesis

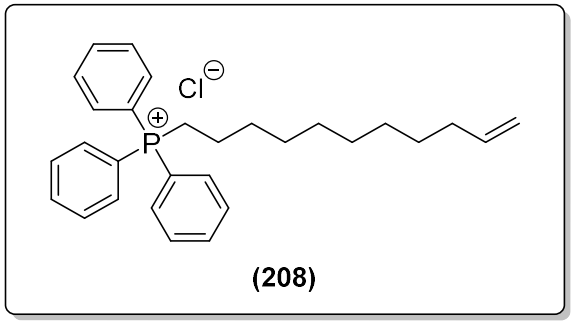
11-Chloroundec-1-ene[129]



(209)

To a mixture of 10-undecen-1-ol (10.0 mL, 49.8 mmol) and pyridine (2.0 mL, 24.8 mmol) under a nitrogen atmosphere was added thionyl chloride (7.2 mL, 99.30 mmol) dropwise over a 1 h period. After complete addition, the resulting mixture was heated to 65°C for 2 h, after which the mixture was cooled and water (25 mL) was added slowly to quench the residual thionyl chloride. The mixture was extracted into ethyl acetate (3 x 25 mL), the combined organics were washed sequentially with 2M HCl solution (10 mL), saturated $NaHCO_3$ (3 x 10mL), and brine (10 mL). The organics were dried over $MgSO_4$, filtered, and solvents removed *in vacuo* to afford a yellow oil. The crude oil was dissolved in hexanes (100 mL), and filtered through a short plug of silica. Removal of solvents *in vacuo* gave the pure compound as a colourless oil (8.51 g, 45.1 mmol, 90%). **δH** (400 MHz, $CDCl_3$): 5.86 – 5.76 (1H, m), 5.02 – 4.91 (2H, m), 3.53 (2H, t, *J* = 6.8Hz), 2.06 – 2.01 (2H, m), 1.80 – 1.74 (2H, m), 1.44 – 1.28 (12H, m). **δC** (100 MHz, $CDCl_3$): 139.3, 114.2, 45.3, 33.9, 32.7, 29.5, 29.5, 29.2, 29.0, 29.0, 27.0. **IR** (ν_{max}, cm^{-1}): 1640, 1465.

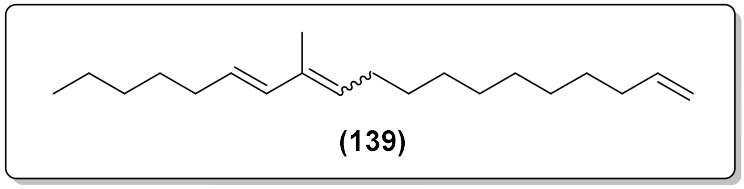
Triphenyl(undec-10-en-1-yl)phosphonium chloride[130]



(208)

PPh_3 (13.088 g, 49.90 mmol) was dissolved in **209** (8.486 g, 45.00 mmol) in a sealed tube under an atmosphere of nitrogen. The solution was heated to 250°C for 3 days, at which point the hot mixture was poured into a beaker and allowed to cool. The crude phosphonium salt was triturated with diethyl ether (3 x 100 mL), then dried under vacuum to afford the phosphonium salt as a pale yellow tar (15.834 g, 35.12 mmol, 78%). **δH** (400 MHz, $CDCl_3$):7.87 – 7.64 (15H, m), 5.77 (1H, d, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_3 = 6.8 Hz), 4.96 (1H, dd, J_1 = 17.2 Hz, J_2 = 1.6 Hz), 4.90 (1H, dd, J_1 = 10.4 Hz, J_2 = 1.6 Hz), 3.97 – 3.81 (2H, m), 2.00 (2H, dt, J_1 = 6.8 Hz, J_2 = 7.2 Hz), 1.66 – 1.59 (4H, m), 1.31 – 1.20 (10H, m). **δC** (100 MHz, $CDCl_3$):139.2, 134.9, 133.9, 130.4, 119.1, 114.1, 33.8, 30.6, 30.4, 29.4, 29.3, 29.2, 29.0, 28.8, 22.8. **IR** (v_{max}, cm^{-1}): 1627, 1588, 1438, 1267, 1114. **MS (**m/z): Found 415.2554 ($C_{29}H_{26}P^+$ requires 415.2549).

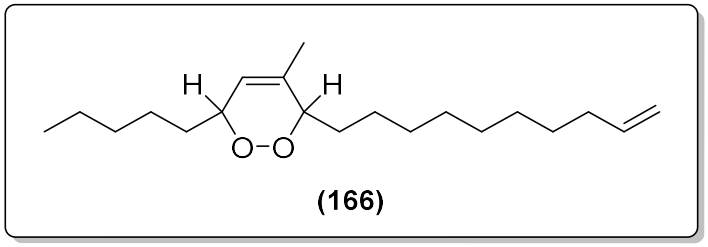
(13E)-12-Methylnonadeca-1,11,13-triene (E/Z = 1.0 : 2.2)



(139)

208 (2.253 g, 5.00 mmol) was dissolved in anhydrous THF (20 mL) under a nitrogen atmosphere and cooled to -78°C, ^{n}BuLi (2.0 mL, 2.5 M in hexanes, 5.00 mmol) added dropwise to produce an orange-red solution of ylide then allowed to warm to room temperature, and stirred for 1 h. After this period, 3-nonen-2-one (0.92 mL, 5.50 mmol) was added dropwise to the ylide, and the resulting mixture stirred 16 h. MeOH (5 mL) was added to quench the reaction, and solvents were removed *in vacuo*. The crude product was purified by column chromatography (100% hexanes, R_f = 0.57) affording the pure compound as a colourless oil (0.448 g, 1.62 mmol, 32 %, E/Z = 1.0 : 2.2). **δH** (400 MHz, $CDCl_3$): 6.04 (1H, d, *J* = 15.6 Hz), 5.80 (1H, m), 5.54 (1H, dt, J_1 = 15.6Hz, J_2 = 6.8 Hz), 5.37 (1H, t, *J* = 7.6Hz), 5.01 – 4.95 (1H, m), 4.94 – 4.90 (1H, m), 2.14 – 2.00 (6H, m), 1.40 – 1.27 (18H, m), 0.90 – 0.84 (3H, m). **δC** (100 MHz, $CDCl_3$): 139.3, 134.8, 133.5, 130.8, 127.7, 114.2, 33.9, 33.0, 31.6, 29.8, 29.6, 29.5, 29.5, 29.5, 29.2, 29.0, 28.2, 22.7, 14.2, 12.5. **IR** (ν_{max}, cm^{-1}): 1640, 1465, 1378. **MS (**m/z): Found 275.2738 ($C_{20}H_{35}^-$ requires 275.2733).

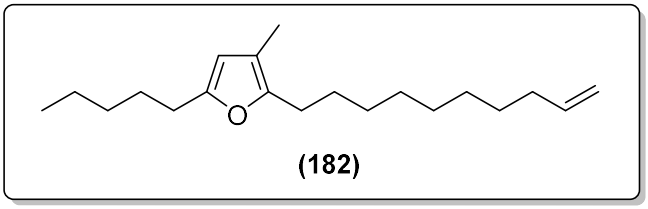
3-(Dec-9-en-1-yl)-4-methyl-6-pentyl-3,6-dihydro-1,2-dioxine



(166)

A stream of oxygen was passed through a solution of **139** (0.200 g, 0.72 mmol) in CH_2Cl_2/MeOH (19:1, 30 mL) containing 10^{-4} M methylene blue whilst irradiated for 15 minutes at room temperature with a 400W halogen light source. After this period, solvents were removed *in vacuo*, and the crude product purified by column chromatography (9:1 peteroleum ether/ethyl acetate, R_f = 0.81) affording a colourless oil (0.108 g, 0.35 mmol, 49%). **δH** (400 MHz, $CDCl_3$): 5.83 (1H, m), 5.53 (1H, d, *J = 10.4 Hz*), 5.03 (1H, dd, J_1 *= 17.2 Hz,* J_2 *= 1.2 Hz*), 4.94 (1H, dd, J_1 = 10.0 Hz, J_2 *= 1.2 Hz*), 4.54 (1H, m), 4.13 (1H, m), 2.07 – 1.98 (2H, m), 1.75 (3H, s), 1.67 – 1.32 (22H, m), 0.91 (3H, t, *J = 6.8 Hz*). **δC** (100 MHz, $CDCl_3$): 134.7, 133.2, 125.8, 122.6, 81.8, 78.3, 33.0, 32.6, 32.0, 31.9, 31.4, 31.1, 29.8, 29.7, 29.4, 29.2, 24.9, 22.6, 19.0, 14.1. **IR** (ν_{max}, cm^{-1}): 1645, 1560, 1466, 1096, 1017. **MS (**m/z): Found 331.2615 ($C_{20}H_{36}O_2Na^+$ requires 331.2608).

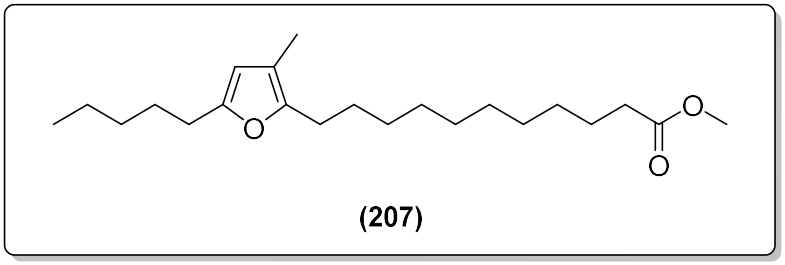
2-(Dec-9-en-1-yl)-3-methyl-5-pentylfuran[63]



(182)

A solution of CBr_4 (0.047 g, 0.14 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0°C and PPh_3 (0.037 g, 0.14 mmol) added. The mixture was stirred for 10 minutes, then a solution of 1,2-dioxine **166** (0.040 g, 0.13 mmol) in CH_2Cl_2 (1.0 mL) added and the solution brought to r.t. The resulting mixture was allowed to stir for 40 h, then solvents removed *in vacuo*. The crude product was purified by column chromatography (99:1 hexanes/ethyl acetate, R_f = 0.42) affording the furan as a colourless oil (0.025 g, 0.09 mmol, 66%). **δH** (400 MHz, $CDCl_3$): 5.85 – 5.75 (1H, m), 5.72 (1H, s), 5.00 – 4.90 (2H, m), 2.51 (2H, t, *J* = 7.6 Hz), 2.48 (2H, t, *J* = 7.6 Hz), 2.06 – 2.01 (2H, m), 1.89 (3H, s), 1.61 – 1.52 (4H, m), 1.37 – 1.25 (14H, m), 0.91 – 0.88 (3H, m). **δC** (100 MHz, $CDCl_3$): 153.6, 149.5, 139.3, 114.2, 113.9, 107.7, 33.9, 33.9, 31.5, 29.8, 29.5, 29.4, 29.3, 29.2, 29.0, 27.1, 26.0, 22.5, 14.1, 10.0. **IR** (ν_{max}, cm^{-1}): 1640, 1576, 1463, 1378. **MS (**m/z): Found 291.2680 ($C_{20}H_{35}O^+$ requires 291.2682).

Methyl 11-(3-methyl-5-pentylfuran-2-yl)undecanoate[62] (F_5 Methyl Ester)



(207)

A solution of **182** (0.020 g, 0.07 mmol) and Grubbs 2nd generation catalyst (0.006 g, 0.01 mmol, 10 mol%) in toluene (5 mL) was degassed with ethylene for 30 min, then maintained under an atmosphere of nitrogen. Methyl acrylate (0.062 mL, 0.75 mmol) was added, and the resulting mixture was heated to 100 °C for 4 hours after which point TLC monitoring showed complete consumption of the starting furan. After this period the mixture was cooled, PtO_2 (0.002 g, 0.01 mmol, 10 mol%) was added and the mixture degassed with hydrogen. The mixture was stirred for 15 h at room temperature under a hydrogen atmosphere, then solvents were removed *in vacuo* and the crude product adsorbed onto silica. Purification by column chromatography (19:1 hexanes/ethyl acetate, R_f = 0.36) afforded the methyl ester of F_5 as a colourless oil (0.024 mg, 0.07 mmol, 98%). **δH** (400 MHz, $CDCl_3$): 5.76 (1H, s), 3.66 (3H, s), 2.54 (2H, t, *J* = 7.6Hz), 2.51 (2H, t, *J* = 7.6 Hz), 2.30 (2H, t, *J* = 8.4 Hz), 1.87 (3H, s), 1.65 – 1.52 (7H, m), 1.35 – 1.24 (15H, m), 0.89 (3H, t, *J* = 7.2 Hz). **δC** (100 MHz, $CDCl_3$): 174.4, 153.5, 149.4, 113.8, 107.6, 51.4, 34.1, 31.4, 29.5, 29.4, 29.4, 29.2, 29.2, 29.2, 28.8, 28.0, 27.9, 25.9, 25.0, 22.4, 14.0, 9.9. **IR** (ν_{max}, cm^{-1}): 1743, 1638, 1576, 1462, 1436. **MS,** m/z Found (373.2712, $C_{22}H_{38}O_3Na^+$ requires 373.2713).

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6.0 Publications

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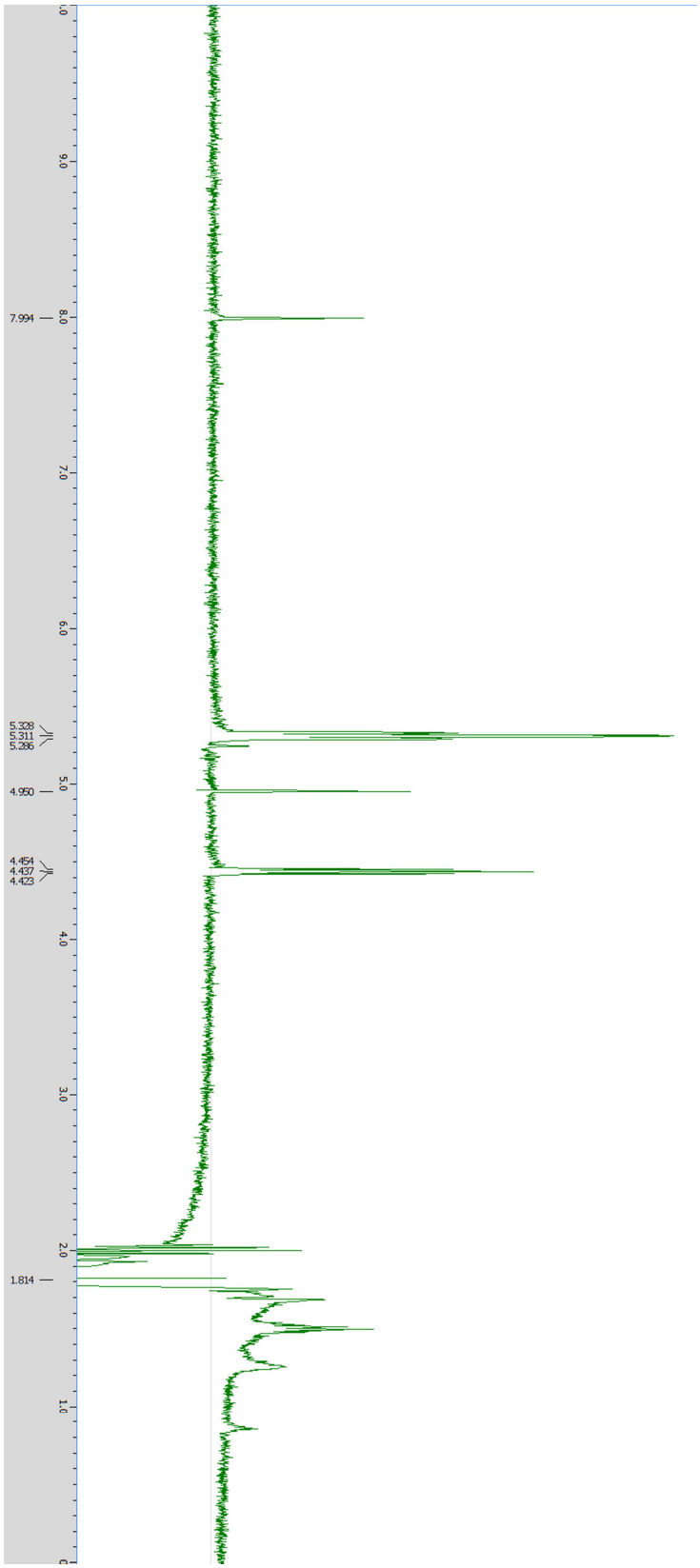
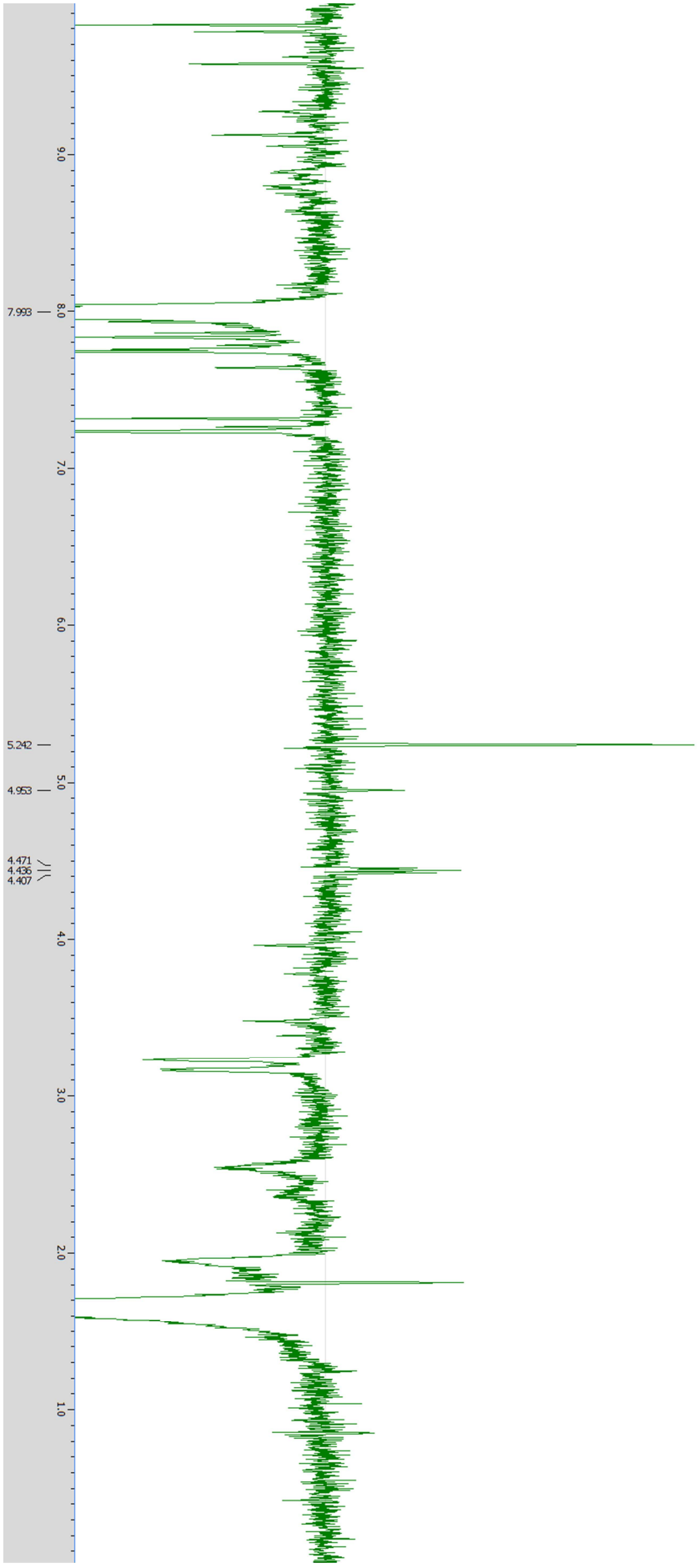
7.0 Appendix 1 – Bis-Peroxide NOE




9.0
7.993
8.0
7.0
6.0
5.242
4.953
5.0
4.471
4.436
4.407
4.0
3.0
2.0
1.0