On the Synthesis of Furans and Furan Fatty Acids

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Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted for candidature for any degree.

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"*It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity…*"

Charles Dickens – *A Tale of Two Cities*

"*We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium a benefit for humanity.*"

Marie Curie

"*The product of mental labour - science - always stands far below its value, because the labour-time necessary to reproduce it has no relation at all to the labour-time required for its original production.*"

Karl Marx

Abstract

This thesis describes the use of silver nitrate and iodine to promote 5-*endo*-dig cyclisations in the synthesis of furans. The oxidation of furylethanols will be discussed as will methods to synthesise furylacetic acids. The total synthesis of a natural product, Plakorsin B will be described along with the total synthesis of the furan fatty acids F_5 and F_6 as well as giving an overview of their proposed role in Nature. Finally, a new methodology for methylation of halogenated heterocycles will be discussed.

Acknowledgements

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My biggest thanks go to my two amazing children, Poppy and Liam. Without their joy and love I could not have completed this thesis. I love you more than words can ever express.

This thesis is dedicated to my two amazing children,

Poppy and Liam.

Detailed Table of Contents

Abbreviations and acronyms

Several abbreviations and acronyms have been used throughout this thesis that may not be familiar to the reader. They are listed below:

Ac	acetyl
ACP	acyl carrier protein
app.	apparent
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aromatic
ATP	adenosine triphosphate
Bn	benzyl
b.p.	boiling point
br.	broad
Bu	butyl
Bz	benzoyl
cat.	catalytic
CI	chemical ionisation
CM	cross metathesis
CoA	coenzyme A
column chromatography	flash column chromatography
COSY	correlation spectroscopy
Cy	cyclohexane
d	day(s)
d	doublet
DCM	dichloromethane
dd	double doublet
dt	double triplet
DEPT	distortionless Enhancement by Polarization Transfer
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio

e.g.	*exempli gratia*
EI	electron ionisation
EPSRC	Engineering and Physical Sciences Research Council
eq.	equivalent(s)
ES	electrospray
ether	diethyl ether
Et	ethyl
EWG	electron withdrawing group
F-acid	furan fatty acid
g	gram
G-II	Grubbs Mark II catalyst
GC	gas chromatography
G-H II	Grubbs-Hoveyda Mark II catalyst
Δ	heat
h	hour(s)
HMBC	heteronuclear multiple quantum coherence
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	iodoxybenzoic acid
IR	infra-red
J	coupling constant
k	kilo
kg	kilogram
LA	linoleic acid
LAEDA	lithium acetylide-ethylenediamine complex
lit.	literature
LOX	lipoxygenase
m	*meta*
m	multiplet
M	molar
mCPBA	3-chloroperoxybenzoic acid
Me	methyl

MHz	megahertz
μmol	micromole(s)
min.	minute(s)
ml	millilitre(s)
mmol	millimole(s)
MMPP	magnesium monoperoxyphthalate hexahydrate
m.p.	melting point
MRSA	methicillin-resistant staphylococcus aureus
MS	mass spectroscopy
n	*normal*
NAD^+	Nicotinamide adenine dinucleotide
NMR	nuclear magnetic resonance
NOSEY	nuclear Overhauser enhancement spectroscopy
o	*ortho*
p	page
P	product
p	*para*
Ph	phenyl
Pr	propyl
ppm	parts per million
PUFA	polyunsaturated fatty acid
q	quartet
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerisation
r.t.	room temperature
σ	sigma
s	singlet
SAM	*S*-adenosyl methionine
SM	starting material
t	triplet
TBAF	tetra *n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl

td	triple doublet
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl
UV	ultra-violet
w/w	weight for weight

Chapter 1: Introduction

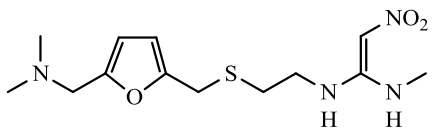
1.1 Heterocycles

Heterocycles constitute the largest group of organic compounds. Of the more than 60 million chemical compounds registered, about one half contain heterocyclic systems. Heterocycles are important, not only because of their abundance, but also because of their chemical, biological and commercial significance. They are found amongst many natural products including vitamins, hormones, antibiotics and alkaloids as well as pharmaceuticals, herbicides, dyes and other commercial products such as corrosion inhibitors, anti-aging drugs and stabilizing agents *etc*.[1]

One of the prevalent features in a heterocycle is the presence of at least one lone pair of electrons (*e.g*. positioned on O, N, S *etc*), which provides a basis for electronic co-ordination, hydrogen bonding, reactivity and resonance. Such electronic properties are crucial to the heterocycle's ability to exhibit biological activity.[2] Traditional synthetic approaches to heterocyclic targets often feature ring closure of a complex acyclic system through the nucleophilic addition of a heteroatom to an electron deficient carbon atom. These electron deficient centres can be found abundantly in compounds such as carbonyls, nitriles and alky halides. An alternative approach is to introduce multiple functionalisation onto a simple or parent heteroaromatic using electrophilic aromatic substitution or by using organometallic methodology.

1.2 Furan

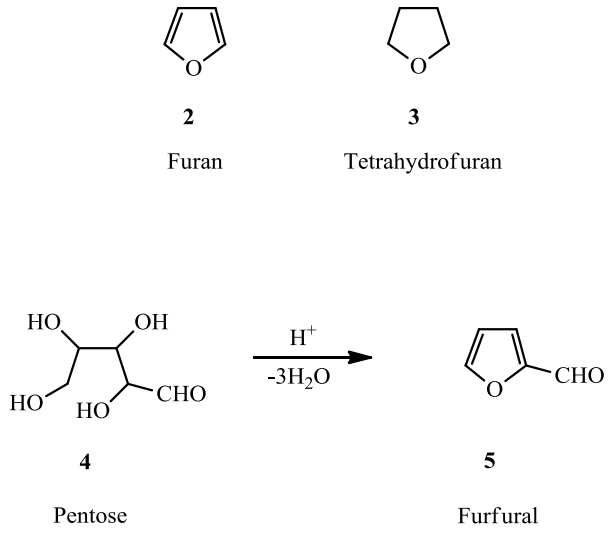
The importance of furans as synthetic intermediates and final products cannot be overstated. An efficient method for their synthesis is therefore of great interest since they are also found in many pharmaceuticals. One such furan-containing pharmaceutical is ranitidine **1**, marketed by GlaxoSmithKline under the trade name Zantac (Scheme **1.1**). One of the best-selling drugs in history, it is used in the treatment of peptic ulcer disease and gastroesophageal reflux disease.[3,4] Acting as a histamine H_2-receptor antagonist, it blocks the action of histamine on acid-producing parietal cells in the stomach, thereby reducing the production of gastric acid and so reduces bleeding from any ulcers which are present.



1

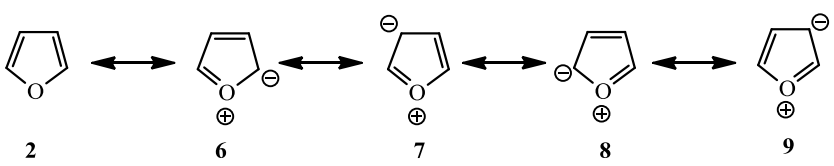
Scheme Error! No text of specified style in document.**1.1: Ranitidine.**

Furan **2** itself is prepared industrially by the catalytic decarbonylation of 2-furaldehyde (furfural) **5** which, in turn, is obtained by treating plant residues such as bran, which are rich in pentoses **4**, with dilute sulphuric acid followed by steam distillation. Furfural **5** was first prepared in this manner in 1831 and its name is derived from *furfur*, the Latin word for bran. In 1870, the word furan was coined from the same root. The commercial importance of furan **2** is mainly due to its role as the precursor of the very widely used solvent tetrahydrofuran (THF) **3** (Scheme **1.2**).



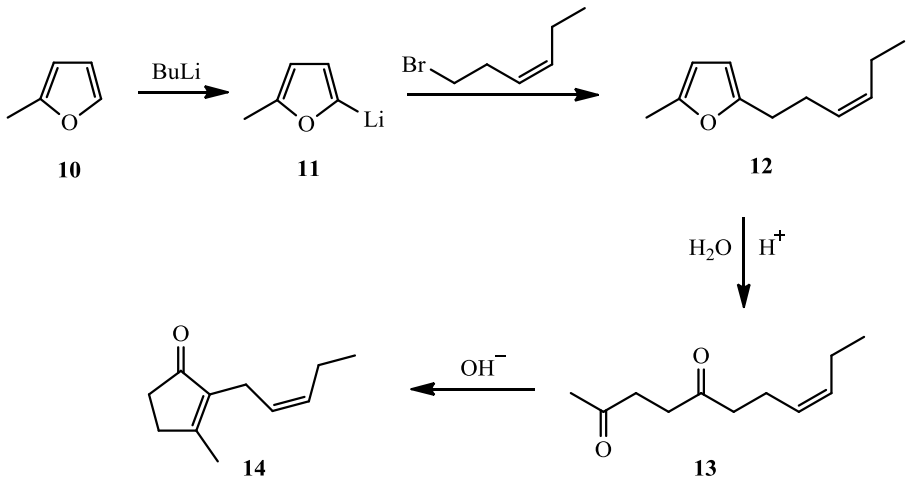
Scheme 1.2: Furan, tetrahydrofuran and the synthesis of furfural.

Furan is a five-membered heteroarene. It has a relatively small dipole moment of 0.71 D, with the negative end situated on the O-atom. This contrasts with the much larger dipole moment of tetrahydrofuran (1.75 D) and confirms that one electron pair of the O-atom is included in the conjugated system and is therefore delocalised. Signals in the region typical for benzenoid compounds in both ^{1}H-NMR and ^{13}C-NMR indicate that a diamagnetic ring current is induced in the furan molecule, thereby fulfilling important experimental criterion for aromaticity in cyclic conjugated systems.[1] However, owing to the high electronegativity of oxygen, furan is less aromatic than its nitrogen and sulphur analogues. The mesomeric forms **6-9** make relatively less of a contribution to its electronic structure (Scheme **1.3**).



Scheme 1. 3: Resonance structures of furan.

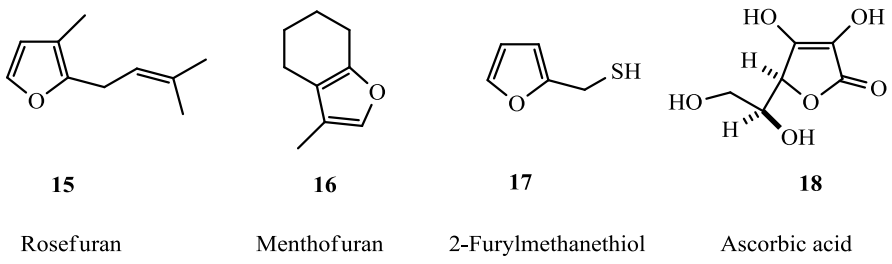
The acid catalysed hydrolysis of furans, along with their ability to undergo cycloadditions can be utilised synthetically. To give one example; the unsaturated furan **12**, generated by metallation of methylfuran **10** followed by alkylation using (*Z*)-1-bromohex-3-ene, is cleaved under aqueous acidic conditions to give the 1,4-diketone **13**. A base catalysed intramolecular aldol condensation then gives (*Z*)-jasmone **14**, a naturally occurring fragrance[1] (Scheme **1.4**).



Scheme 1.4: (Z)-Jasmone synthesis.

1.3 Furans in Nature

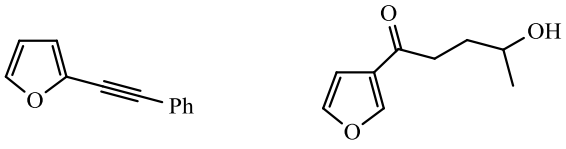
The aromatic furan ring system, whilst absent in animal metabolism, occurs widely in secondary plant metabolites, especially as terpenoids. Some naturally occurring furans have an intense odour: rosefuran **15**, is found in rose oil, and menthofuran **16** is present in peppermint oil. Although thiols are often associated with having an unpleasant odour, 2-furylmethanethiol **17** is a component of roasted coffee aroma. Ascorbic acid **18**, vitamin C, is at the oxidation level of a trihydroxyfuran but in an unsaturated lactone tautomeric form (Scheme **1.5**).



Scheme 1.5: Rosefuran, menthofuran, furfuryl thiol and ascorbic acid.

Like many natural products, naturally occurring furans may have potential health benefits or may prove to be highly active against pathogens or carcinomas. One such naturally occurring furan,

carlina oxide **19**, is obtained by steam distillation from the roots of the carline thistle (*Carlina acaulis*). *Carlina acaulis* has a long history of medicinal use in Europe due to its antimicrobial properties and carlina oxide **19** has been confirmed to be highly active against two MRSA strains as well as displaying strong and selective activity against *Trypanosoma brucei brucei*, the parasite responsible for African trypanosomiasis (sleeping sickness).[5] Another example, (±)-4-ipomeanol **20**, is a well known cytotoxic metabolite of microbially infected sweet potatoes, *Ipomoea batata*. It behaves as a specific lung toxic agent and it is this specificity that has led to it being tested as a potential new drug for the treatment of lung carcinoma[6] (Scheme **1.6**).



19 **20**

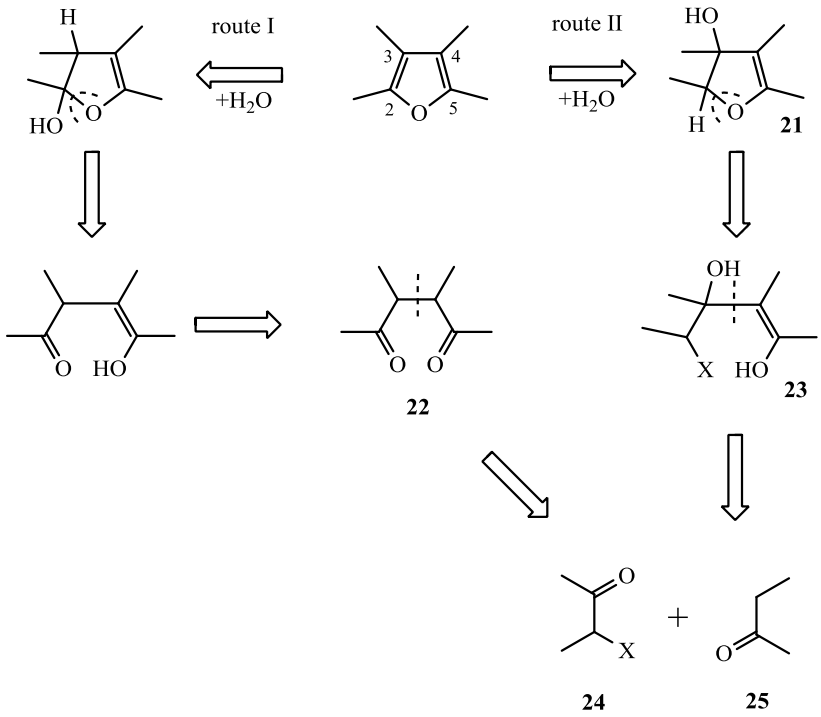
Carlina oxide (±)-4-ipomeanol

Scheme 1.6: Carlina oxide and 4-ipomeanol.

Furan fatty acids were discovered in 1961[7] and have been detected in all organisms that have been investigated since their discovery.[8] Their precise role in Nature is uncertain but they are believed to be potent radical scavengers and may help protect humans against atherosclerosis and cardiovascular disease.[7] They will be discussed in more detail in Chapter **4**.

1.4 Traditional Furan Syntheses

There are many methods available to the modern chemist to synthesise furans. Using retrosynthetic analysis, it can be shown that furan can be viewed as a double enol ether and so can be dissected retrosynthetically in two ways (Scheme **1.7**).



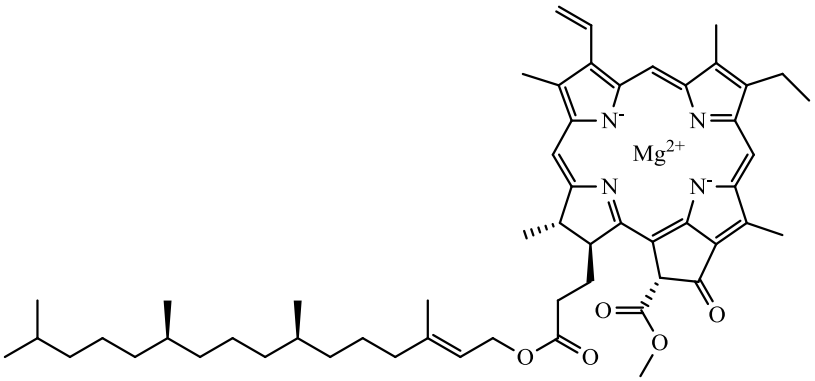
Scheme 1.7: Retrosynthetic analysis of furan.

Route I sees the addition of water across the furan C2/C3 bond, with the hydroxyl group adding at the α-position, followed by cleavage of the O/C2 bond to give the 1,4-dicarbonyl precursor **22**. 1,4-Dicarbonyl compound **22** can then be further disconnected to give α-halocarbonyl **24** and the enolate of carbonyl **25**. In the forward reaction, the enolate of carbonyl **25** can be converted to the 1,4-dicarbonyl **22** by alkylation with α-halocarbonyl **24**. Treatment of 1,4-dicarbonyl **22** with phosphoric acid, or a similar acid, resulting in an intramolecular cyclocondensation reaction to yield the corresponding furan is known as the Paal-Knorr synthesis.[9]

Following route II, addition of water across the furan C2/C3 bond but with the hydroxyl adding to the β-position gives intermediate **21**. Cleavage of O/C2 bond leads to the γ-halo-β-hydroxycarbonyl system **23**. A retroaldol operation then leads to the same starting materials as route I. The forward reaction is known as the Feist-Benary synthesis and involves an aldol-type addition of α-halocarbonyl **24** and carbonyl **25** to give γ-halo-β-hydroxycarbonyl **23** followed by ring-closure to give dihydrofuran **21** and finally dehydration to yield the furan.[10]

1.5 Baldwin's Rules

Approximately 90% of chemically individual molecules discovered in nature contain either a carbocyclic or a heterocyclic subunit,[11] such features also being abundant in synthetic products. Clearly, having the ability to control the key bond-forming step that converts an acyclic precursor into a cyclic structure in both a regio- and stereocontrolled manner is therefore vitally important in the synthesis of complex molecules and a set of rules for predicting the outcome of such reactions would be most beneficial. One such complex, naturally occurring molecule is chlorophyll *a* **26**, which contains a magnesium ion coordinated to a chlorin ring (Scheme **1.8**). The chlorin ring itself is comprised of 3 pyrroles and a pyrroline coupled through four methine linkages. Despite its relatively complex structure, chlorophyll *a* **26** was first synthesised in 1960 by Robert B. Woodward[12] who was awarded the Nobel prize in chemistry in 1965 for "*outstanding achievements in the art of organic chemistry*". Unfortunately, he was not eligible for what would have been his second Nobel Prize when Roald Hoffman shared the 1981 Nobel Prize with Kenichi Fukui (who devised a similar model) for the development of the Woodward-Hoffman rules as he had died two years previously.

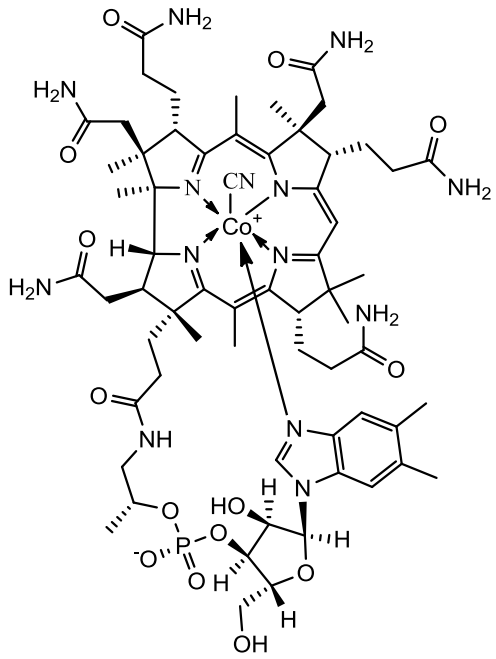


26

Chlorophyll a

Scheme 1.8: Chlorophyll a.

Woodward went on to synthesise another highly complex natural product, vitamin B_{12} **27**, a cobalt containing vitamin which is only biosynthesised by bacteria.[13] Its synthesis in 1973 was a milestone in organic chemistry, taking eleven years and involving more than ninety separate reactions performed by over a hundred co-workers. Vitamin B_{12} contains no less than eight cyclic sub-units and nine chiral centres within the corrin ring frame (Scheme **1.9**).



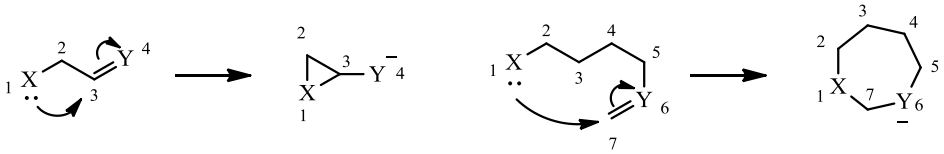
27

Vitamin B_{12}

Scheme 1.9: Vitamin B_{12}.

The sheer number of cyclic systems in nature and in synthetic chemistry dictates that a set of rules to ascertain the likelihood of a particular cyclisation reaction succeeding would be extremely beneficial to the synthetic chemist. In 1976, Jack E. Baldwin published a series of papers where he introduced a set of rules based on transition-state geometry to explain the relative ease and fast rate of some ring closing reactions compared to the slow rate of reaction of others.[14]

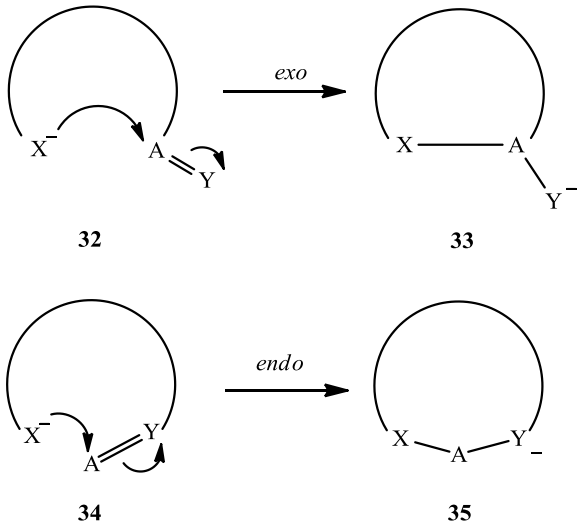
Baldwin introduced a nomenclature for ring closure based on a unified classification of cyclisation processes based on three factors.[15] The nomenclature contains three terms to describe these factors, the first prefix being an integer ≥ 3 and relates to the number of atoms that constitute the skeleton of the cycle. The rules are applicable for ring sizes up to seven atoms (Scheme **1.10**).



28 **29** **30** **31**

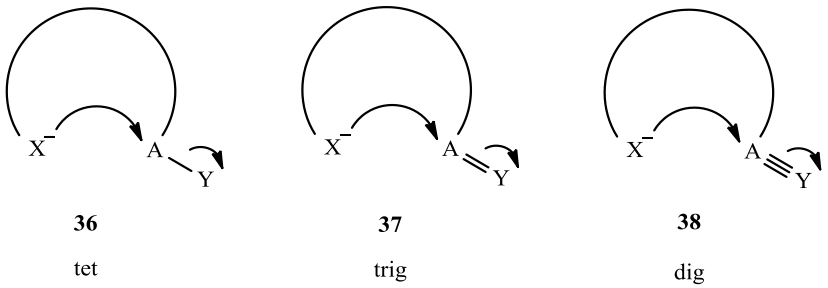
Scheme 1.10

The second prefix, is a term, either "*endo*" or "*exo*", that describes the ring forming process and the position of the bond that is broken in the cyclisation relative to the forming ring. *Exo* indicates the breaking bond is outside of (*exocyclic* to) the newly formed ring whilst *endo* indicates that the breaking bond is inside (*endocyclic* to) the forming ring (Scheme **1.11**).



Scheme 1.11

The third term, the suffixes *Tet*, *Trig* and *Dig*, describe the geometry, and thus the hybridisation, of the carbon atom undergoing the ring-closure reaction. They refer to tetrahedral (sp^3), trigonal (sp^2) and digonal (sp) carbon atoms respectively (Scheme .**1.12**).



Scheme 1.12

The physical bases of Baldwin's rules lies in the stereochemical requirements of the transition states for the various ring-closure processes. The nature and length of the linking chain determines whether the terminal atoms can attain the required transition state geometry and thus achieve the required trajectories for bond formation. For bond formation to occur there must be sufficient overlap of appropriate orbitals. The optimal trajectory for tetrahedral cyclisations is based upon the classic backside attack of S_N2 reactions and yields an attack angle of 180°. For trigonal cyclisations, the attack angle is based upon the Burgi-Dunitz[16] angle of attack on sp^2

carbon atoms of ~ 105–109° while for digonal systems the angle between the three interacting atoms is 120°, an angle that is maintained during the reaction pathway and becomes the angle between these atoms in the final sp^2 hybridised product.

The rules are as follows:

Rule 1: Tetrahedral Systems

a) 3 to 7-*exo*-tet favoured
b) 5 to 6-*endo*-tet disfavoured

Rule 2: Trigonal Systems

a) 3 to 7-*exo*-trig favoured
b) 3 to 5-*endo*-trig disfavoured
c) 6 to 7-*endo*-trig favoured

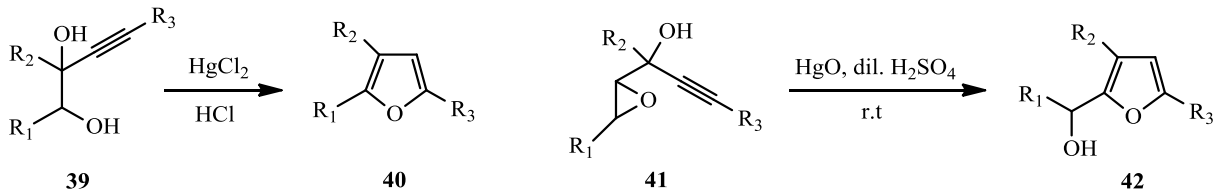
Rule 3: Digonal Systems

a) 3 to 4-*exo*-dig disfavoured
b) 5 to 7-*exo*-dig favoured
c) 3 to 7-*endo*-dig favoured

Baldwin's rules give a good indication as to whether a cyclisation is likely to be successful or not however one stipulation is that in schemes **1.10**, **1.11** and **1.12**, X must be a first row element. This is due to the larger atomic radii and bond lengths of heavier elements as well as the availability of their *d* orbitals.

1.6 Early Catalytic Synthesis of Furans

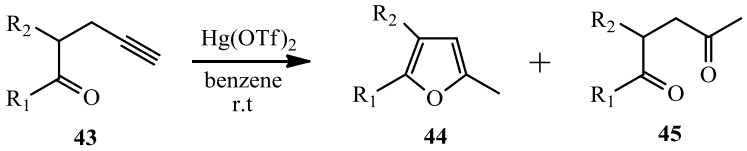
There are many examples of furan synthesis using catalytic amounts of transition metal salts in the literature with varying yields and sometimes harsh conditions. Some of the earliest examples used mercury salts, which can be used to cyclise 3-alkyne-1,2-diols **39**[17] and 1-alkynyl-2,3-epoxyalcohols **41**[18] to give the corresponding furans **40** and **42** in good yields (55-85%) (Scheme **1.13**).



39 40 41 42

Scheme 1.13: Mercury-catalysed furan synthesis.

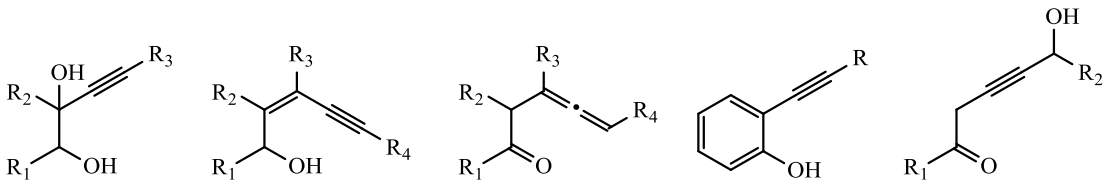
One notable example of a mercury-catalysed cyclisation is that of Nishizawa who employed mercuric-triflate to effect the cyclisation of 1-alkyn-5-ones **43**[19] (Scheme **1.14)**. He demonstrated that furans **44** could be formed under very mild conditions and in excellent yields (70-100%). However, this method does have its limitations: side products, the diones **45**, are often observed and the reaction gives poor yields with aldehydes and non-terminal alkynes (21% and 12-52% respectively). There was also the requirement of benzene as solvent in order to obtain good yields although toluene was only slightly less effective.



43 44 45

Scheme 1.14: Nishizawa's mercuric triflate-catalysed 2-methylfuran synthesis.

There is one problem common to all mercury-catalysed procedures: the toxicity of the mercury salts. Clearly this makes their use undesirable. With this in mind it was of great interest to pursue progress with other, less toxic catalysts. The mid 1980s saw the introduction of palladium to catalyse cyclisation of 3-alkyn-1,2-diols **39**.[20] Palladium has since been shown to effect the cyclisation of (*Z*)-2-en-4-yn-1-ols **47**,[21-23] allenyl ketones **48**,[24-26] *o*-alkynylphenols **49**[27] and alkynones **50,**[28] all to furans with various substitution patterns (Scheme **1.15**).



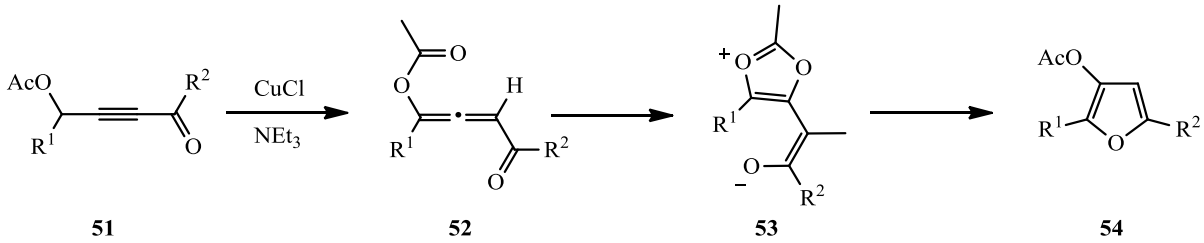
39 47 48 49 50

Scheme 1.15: Substrates for palladium-catalysed furan syntheses.

These palladium-catalysed reactions often give good to high, albeit inconsistent, yields and are capable of producing tetrasubstituted furans with a wide range of substitution patterns. Whilst being much less toxic than their mercury-catalysed counterparts, the palladium-catalysed

reactions often required elevated temperatures as well as extended reaction times. Consideration must also be given to the high cost of palladium itself although it is only required in catalytic amounts.

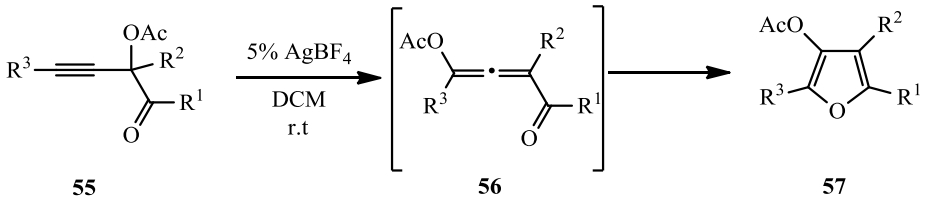
A cheaper alternative to palladium was developed by Gevorgyan. His method involved the synthesis of trisubstituted furans from α-acyloxyalkynones **51** in the presence of copper(I) chloride.[29] Good to excellent yields were obtained (69-90%) but the method suffered from extended reaction times. The mechanism put forward by Gevorgyan involves a base-assisted isomerisation to allenes **52**. There then follows an intramolecular nucleophilic attack to form zwitterions **53**, which are the converted to furans **54** by an intramolecular Ad_N-E process (Scheme **1.16**).



Scheme 1.16: Gevorgyan's copper-catalysed furan synthesis.

1.7 Silver Catalysed Furan Synthesis

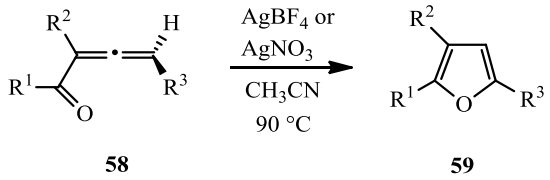
Gevorgyan also developed a route to tetra-substituted furans using a silver(I) catalyst.[29] In the presence of silver(I) tetraborofluorate, α-acyloxy-β-ketoalkynes **55** underwent a [3,3] shift/1,2-migration and cyclo-isomerisation sequence to directly afford tetrasubstituted furans **57** (Scheme **1.17**).



Scheme 1.17: Gevorgyan's silver-catalysed furan synthesis.

In 1990, some 14 years previous to Gevorgyan, Marshall had shown that it was possible to cyclise α-allenones **58** to yield trisubstituted furans **59** in good to excellent yields (72-99%) using

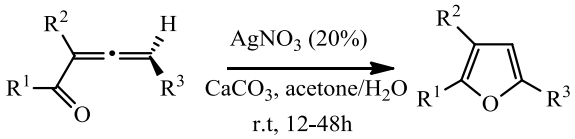
either silver tetrafluoroborate or silver nitrate upon heating in acetonitrile for up to one hour[30] (Scheme **1.18**).



58 **59**

Scheme 1.18: Marshall's early silver-catalysed furan synthesis.

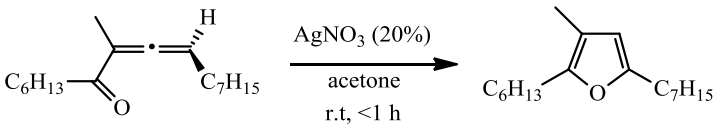
After investing some time optimising this synthesis, Marshall demonstrated that the cyclisation was possible under much milder conditions using a mixture of silver nitrate and calcium carbonate in acetone and water at room temperature[31] (Scheme **1.19**). Yields of 65-95% were reported.



58 **59**

Scheme 1.19:Marshall's silver-catalysed cyclisation utilising calcium carbonate.

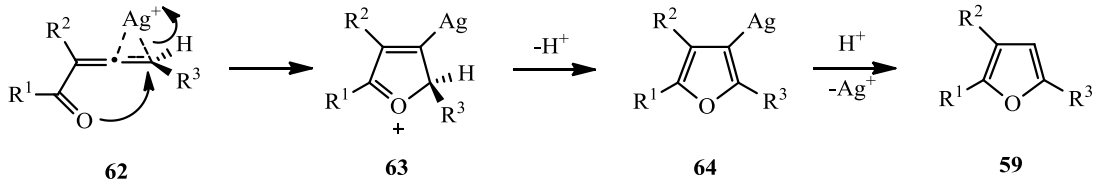
In an attempt to explain the role of water and calcium carbonate in this conversion, Marshall undertook a series of additional studies to clarify their roles, to determine possible reaction pathways and, if possible, to develop a more convenient and efficient procedure.[32] It was found that the reaction proceeded even more efficiently in the absence of calcium carbonate and a significant rate acceleration was observed with decreasing water content. In neat acetone the reaction took less than one hour (Scheme **1.20**).



60 **61**

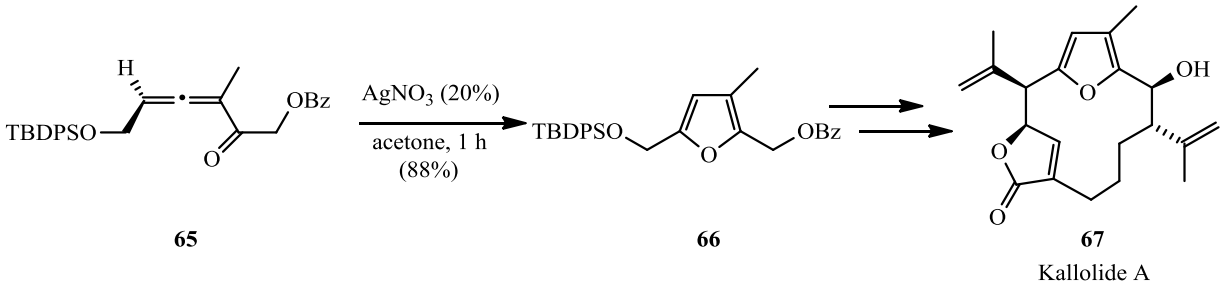
Scheme 1.20: Marshall's optimised silver-catalysed furan synthesis.

Deuterium labelling experiments on α-allenone **62** allowed Marshall to rule out other possible mechanisms in favour of one involving Ag^{+}/H^{+} exchange on Ag(I)-furan intermediate **64** (Scheme **1.21**).[32]



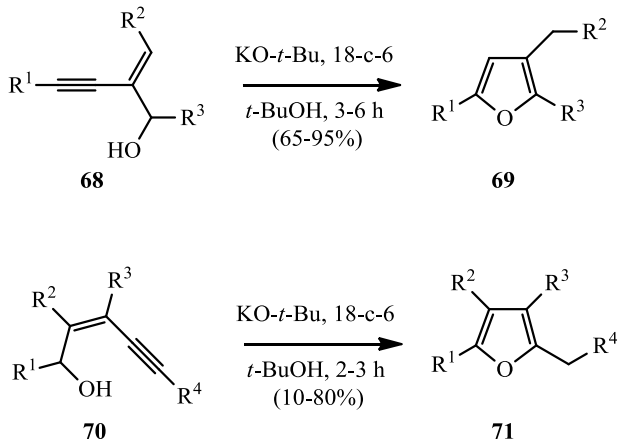
Scheme 1.21: Marshall's proposed mechanism for silver-catalysed cyclisation of α-allenones.

The silver-catalysed cyclisation of α-allenones has been utilised in the total synthesis of natural products. One example is Marshall's total synthesis of kallolide A **67** where α-allenone **65** was treated with silver nitrate in refluxing acetone for one hour[33] (Scheme **1.22**).



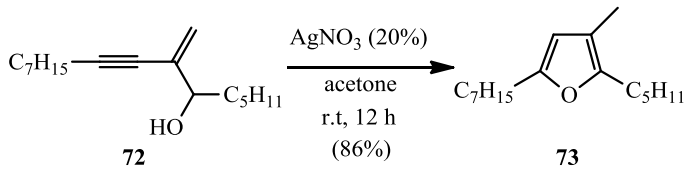
Scheme 1.22: Marshall's kallolide A synthesis.

Although Marshall's allene methodology was highly efficient and exceptionally mild, the starting materials are not particularly readily available. However, alkynyl allylic alcohols such as **68** and **70** are readily accessible through palladium(0)-catalysed Sonogashira coupling of appropriate vinylic halides and terminal alkynes.[34] These alcohols can be used to generate furans **69** and **71** *via* a base-catalysed cyclisation-isomerisation (Scheme **1.23**).[35, 36]



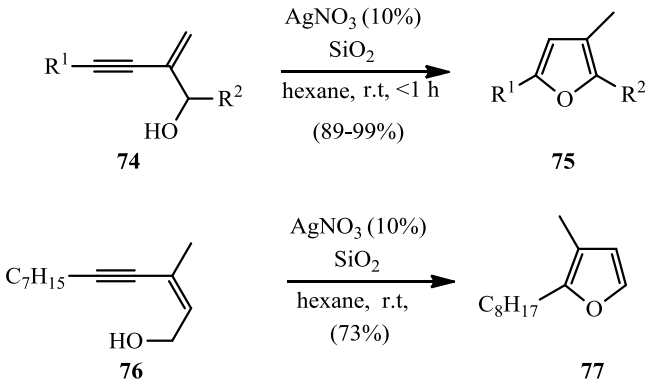
Scheme 1.23: Base-catalysed cyclisation-isomerisation of alkynyl allylic alcohols.

Marshall investigated whether cyclisation of these alcohols could be induced with silver salts. It transpired that silver nitrate in anhydrous acetone effected the cyclisation of alcohol **72** in 86% yield but was relatively slow (12 h) Scheme (**1.24**).[37]



Scheme 1.24: Silver-catalysed cyclisation of alcohol 72.

Comparable results were observed using silver triflate as catalyst whilst both silver tetrafluoroborate and silver trifluoroacetate proved to be more effective giving 97% and 93% yields respectively after just two hours. What interested Marshall most however, was that commercially available 10% w/w silver nitrate on silica gel (henceforth referred to as 10% $AgNO_3.SiO_2$) resulted in a yield of 92% with overnight stirring. After assessing various solvents in an attempt to shorten the reaction times, it was found that using hexane resulted in a yield of 96% in under an hour. Furthermore, the catalyst could be reused with little change in effectiveness. This conversion could also be carried out repeatedly by using a HPLC apparatus for elution of alcohol **72** through a stainless steel column loaded with the 10% $AgNO_3.SiO_2$ catalyst. This procedure was also found to be effective for both β-alkynyl allylic alcohols **74** and γ-alkynyl allylic alcohols **76** (Scheme **1.25**).[37]

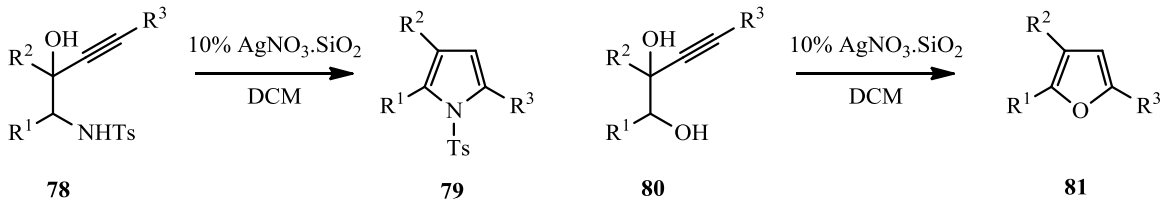


Scheme 1.25: $AgNO_3.SiO_2$-catalysed cyclisation of β- and γ-alkynyl allylic alcohols.

1.8 Silver-catalysed Cyclisation of 3-alkyne-1,2-diols

The Knight group had found success using copper and protons in the synthesis of pyrroles **79** and, to a lesser extent, furans **81** (Scheme **1.26**). After Marshall's publications on the use of silver, Knight chose to investigate whether 10% $AgNO_3.SiO_2$ would also give favourable results

with the synthesis of pyrroles **79**. Sharland, a previous member of the Knight group, demonstrated that, upon exposure to 10% $AgNO_3.SiO_2$, 3-alkyne-2-hydroxy-1-sulfonamides **78** did indeed cyclise to give pyrroles **79** in excellent yields (>95%) and in high purity when screened from daylight.[38] Building on this work, Menzies attempted to cyclise 3-alkyne-1,2-diols **80** with 10% $AgNO_3.SiO_2$ and also found that cyclisation occurred resulting in excellent yields (>95%) of furans **81** and, once again, in very high purity.[39] Following these initial, exciting results, a comprehensive range of furans, as well as pyrroles and pyrazoles, were synthesised by Hayes, another former member of the Knight group. The results of this investigation will be discussed in depth in Chapter **2**.

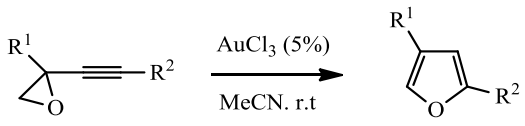


78 **79** **80** **81**

Scheme 1.26: Silver-catalysed synthesis of pyrroles and furans.

1.9 Gold Catalysed Synthesis of Furans

Unsurprisingly, one of silver's main competitors as a catalyst for heterocycles is gold. Gold(III) salts and also gold(I) complexes have been subjected to much investigation into their catalytic activity. Hashmi showed that it is possible to transform alkynyl epoxides **82** to the corresponding furans **83** using a catalytic amount of gold(III) chloride in acetonitrile at room temperature. They did, however, suffer from extended reaction times of between 9 and 28 hours (Scheme **1.27**).[40] Literature searches show that such low catalyst loadings, mild conditions and the toleration of a wide range of functional groups are key features of gold-catalysed cyclisations in furan syntheses.[40-46]

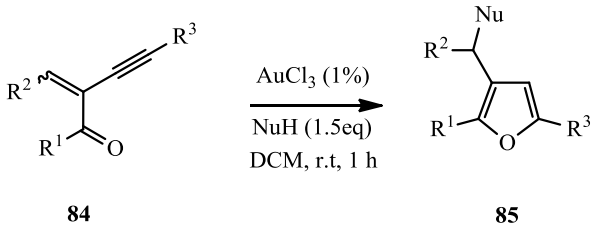


82 **83**

Scheme 1.27: Hashmi's 2004 gold(III)-catalysed furan synthesis.

At around the same time, Larock reported the use of gold(III) chloride as a catalyst in the synthesis of trisubstituted furans **83**.[41] He demonstrated that 2-(1-alkynyl)-2-alken-1-ones **84** react with nucleophiles in the presence of gold(III) chloride to give the corresponding furans **85**

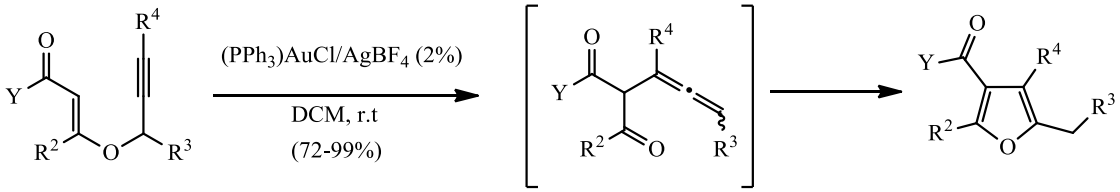
in good to excellent yield (52-90%). Moreover, the regioselective introduction of substituents around the furan ring is determined by the appropriate choice of 2-(1-alkynyl)-2-alken-1-one **84** and nucleophile, thereby allowing for considerable versatility (Scheme **1.28**).



84 **85**

Scheme 1.28: Larock's 2004 gold(III)-catalysed furan synthesis.

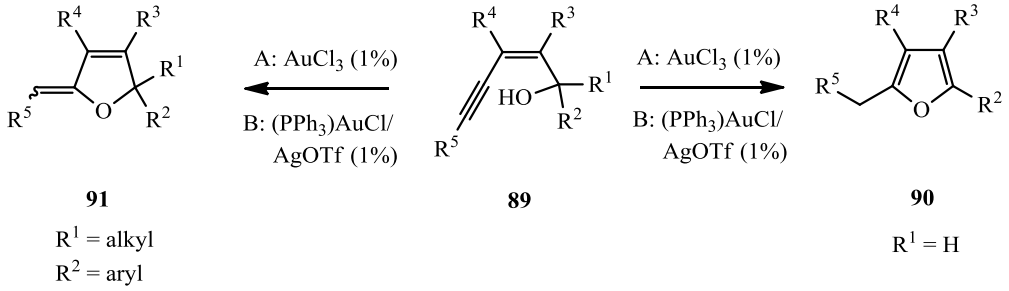
In the following year, Reif published results detailing the synthesis of tetrasubstituted furans **88**.[43] Highly substituted furans **88** were obtained from allenylcarbonyl compounds **87** which in turn were accessed *via* a catalytic version of a propargyl-Claisen rearrangement[47] of propargyl vinyl ethers **86**. The results were most interesting. Several catalysts were tested for activity including triphenylphosphinegold(I) chloride and silver tetraborofluorate but both catalysts failed to yield even a trace of furans **88**. It was noted however that silver tetrafluoroborate did give 100% conversion of propargyl vinyl ethers **86** to allenes **87**. The next logical step was to attempt the reaction using both catalysts combined. This gave excellent yields (72-97%) of furans **88** (Scheme **1.29**).



86 **87** **88**

Scheme 1.29: Kirsch's gold(I)/silver-catalysed furan synthesis.

The same year, Liu also reported the use of a gold(I)/silver salt complex in a furan synthesis. He showed that a combination of triphenylphosphinegold(I) chloride and silver triflate can be used to cyclise (*Z*)-enynols **89** to give furans **90**, or dihydrofurans **91** when terminal enynols are used, in excellent yield (>83%).[45] Gold(III) chloride can also be used to affect the same result (Scheme **1.30**).

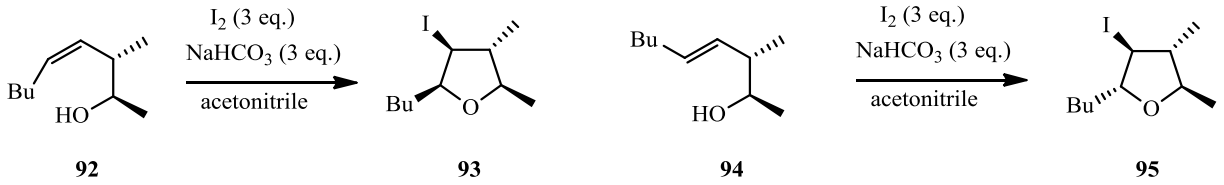


Scheme 1.30: Liu's gold-catalysed furan synthesis.

1.10 Iodocyclisation

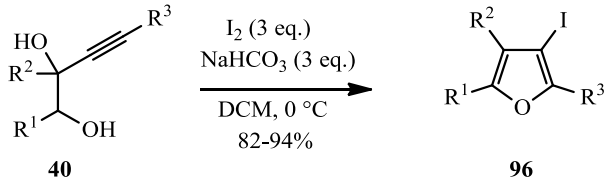
Reactions performed using iodine electrophiles have been known for a long time;[48] Bougalt described the first iodolactonisation over a century ago in 1904.[49] The reaction conditions described by Bougault were very simple; the substrates were treated in an aqueous solution of sodium carbonate with elemental iodine and potassium iodide. Although such reaction conditions still find use today, more advanced iodine-mediated procedures have been added to the repertoire of the synthetic organic chemist. The interaction of iodine electrophiles with double and triple bonds leads to their activation and the addition of a nucleophile to the activated olefin, in either an inter- or intramolecular fashion, resulting in *trans* addition products whilst intramolecular addition to triple bonds results in functionalised alkenes. Some of the key advantages of using elemental iodine in syntheses are that it is inexpensive, non-toxic and readily available.

In the latter part of the last century there was much work conducted in the Knight group on iodine-promoted 5-*endo*-trig cyclisations to form tetrahydrofurans.[50-54] Excellent yields of 81-95% were obtained but a crucial feature of these cyclisations that came to light as a result of Knight's work in this area was the use of anhydrous acetonitrile as solvent.[52, 53] It has been shown that a wide range of tetrasubstituted tetrahydrofurans **93** and **95** can be prepared in a highly stereocontrolled manner from homoallylic alcohols **92** and **94** respectively (Scheme **1.31**).[54]



Scheme 1.31: Knight's iodine-promoted tetrahydrofuran syntheses.

In 1996 Knight reported that 3-alkyne-1,2-diols **39** can be cyclised by exposure to iodine and will undergo a 5-*endo*-dig cyclisation to give β-iodofurans **96** in excellent yields.[55] The method has since been optimised such that β-iodofurans can be formed in yields of 82-94% in dichloromethane using three equivalents of iodine and sodium hydrogen carbonate at 0 °C (Scheme **1.32**).



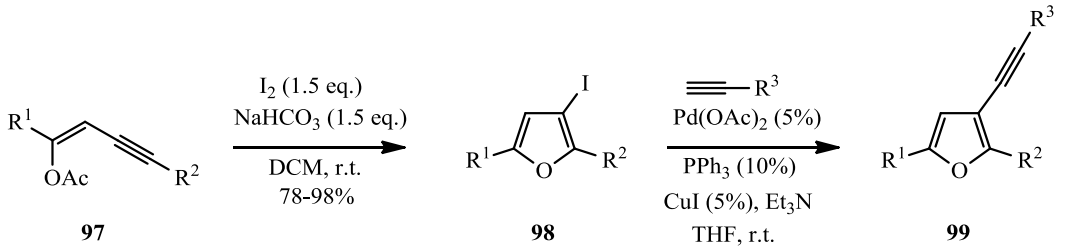
Scheme 1.32: Knight's iodofuran synthesis.

Although very successful procedures, these iodocyclisations suffer from the requirement of an excess of iodine alongside the drawback of occasional side product formation *e.g.* bis-iodination of the alkyne. One clear advantage of iodocyclisation is the presence of the halogen in the final product; a very useful synthetic handle for further modification to the structure *e.g. via* halogen-metal exchange. This feature that will be exploited in the synthesis of F_6 furan fatty acid (Chapter **4**). The development of a wide range of palladium-catalysed coupling reactions utilising halogen-aryl bonds has also made this moiety extremely useful.[56]

The very nature by which furans react makes the synthesis of α-halo derivatives relatively simple whist attempting to selectively halogenate at the β position is no easy feat without suitable directing substituents at the α position. Therefore a synthetic route to β-iodofurans using mild conditions is a valuable transformation.

Recently, Jiang has published details of the iodocyclisation of a wide range of enyne acetates **97** to give the corresponding 2,5-disubstituted 3-iodofurans **98** in excellent yields.[57] To effect the cyclisation, enyne acetates **97** were exposed to 1.5 equivalents of iodine and sodium hydrogen carbonate in dichloromethane at room temperature for eight hours. The resulting iodofurans **98**

were then further functionalised by a Sonogashira coupling[34] to give 2,3,5-trisubstituted furans **99** in excellent yield after six hours in tetrahydrofuran (Scheme **1.33**).



Scheme 1.33: Jiang's 2,3,5-trisubstituted furan synthesis.

1.11 Aims of the Project

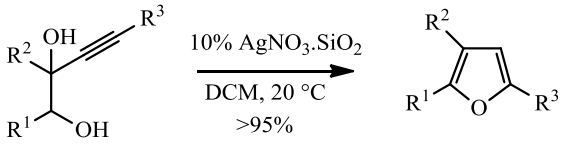
Now that the background of furan **2** syntheses have been covered, the focus of this thesis now turns towards a more in-depth discussion of the work of Hayes followed by the continuation of that work including the synthesis of furylethanols and their curious oxidation products. The attempt to overcome this obstacle towards the synthesis of furylacetic acids will then be described along with the total synthesis of a natural product, plakorsin B. Finally, a chapter devoted to the occurrence and role in Nature of an interesting class of naturally occurring furans, the furan fatty acids, including a total synthesis of two of the more abundant furan fatty acids, F_5 and F_6 completes the narrative section.

Chapter 2: Results and Discussion

Furan Synthesis and 2-Furylethanol Oxidation

2.1 Introduction

There is a continuing need for ever more efficient, mild and environmentally friendly synthetic processes to drive the development of heteroaromatic syntheses.[58] As mentioned in the previous chapter, the Knight group has recently discovered that 10% $AgNO_3.SiO_2$, more often associated with its role as the stationary phase for the chromatographic separation of alkene stereoisomers, is an extremely efficient heterogeneous catalyst for the conversion of 3-alkyne-1,2-diols **80** into the corresponding furans **81**, with the only by-product being an equivalent of water (Scheme **2.1**).[39]

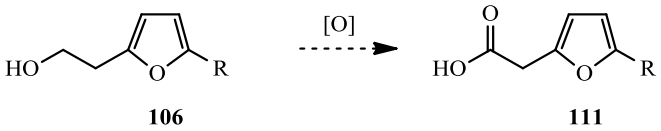


80 **81**

Scheme 2.1: Knight's silver-catalysed furan synthesis.

This discovery made silver catalysts a viable competitor to gold catalysts. Gold catalysts however, have one major drawback: they act in a homogeneous fashion and so make their use in continuous synthetic production rather challenging, since product contamination was unavoidable and purification and catalyst recovery quite difficult. The great advantage that the silver nitrate system has over gold catalysts is its heterogeneous nature and so is much more easily removed. However, leaching of the silver(I) species into the products was a problem in all systems but the heterogeneous nature of the silver catalyst can be utilised and leaching prevented by incorporating the catalyst onto a sulphonated ion exchange resin. This resin can then be incorporated into a flow system which does not leach.[59]

A range of 3-alkyne-1,2-diols **80** were prepared following the work of Hayes and cyclised using 10% $AgNO_3.SiO_2$ to yield the corresponding furans **81**. Furylacetic acids are not well represented in the literature but are an important class of natural products. The silver(I) catalysed synthesis of furans appeared to be an excellent way of preparing furylethanols which could then, in theory, be oxidised to furylacetic acids (Scheme **2.2**).

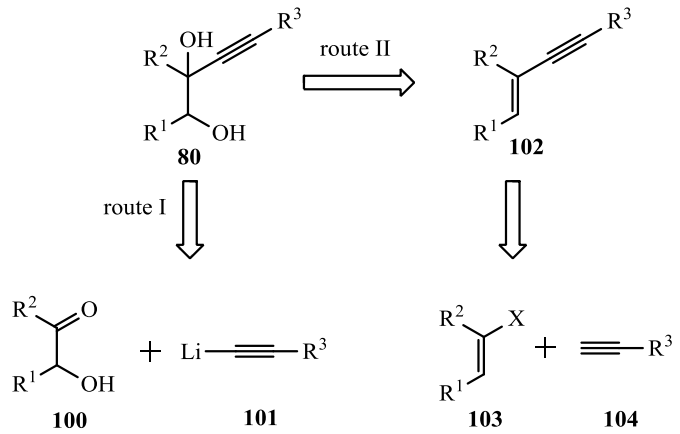


Scheme 2.2: Oxidation of furylethanols

Jones reagent[60, 61] oxidation of these 2-furylethanols however, gave some surprising results which will be discussed later in this chapter.

2.2 Retrosynthesis of 3-alkyne-1,2-diols

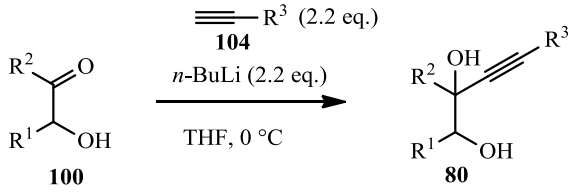
Clearly there are a variety of different approaches to the precursor 3-alkyne-1,2-diols **80**. Continuing the work of both Menzies[39] and Hayes[59], two approaches were chosen in this study: route I comprised condensations between α-hydroxycarbonyls **100** and lithio acetylides **101** in tetrahydrofuran at 0 °C. Route II involved a Sonogashira coupling[34] between the corresponding 1-haloalkene **103** and 1-alkyne **104** followed by regioselective *bis*-hydroxylation of the resulting conjugated enyne **102** (Scheme **2.3**).



Scheme 2.3: Retrosynthesis of 3-alkyne-1,2-diols.

2.3 α-Hydroxycarbonyl Pathway

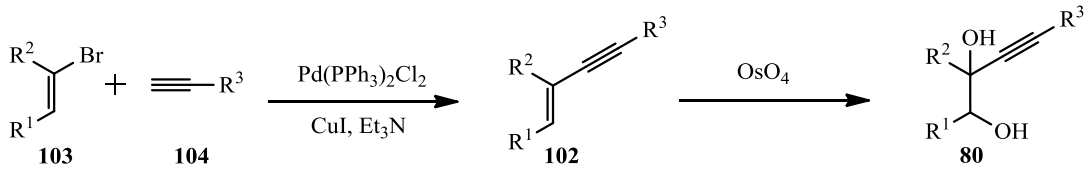
Addition of excess alkyne **104** (2.2 eq) was used to prepare diol **80** on the basis that it is arguably more atom efficient in view of the time and costs involved with standard protection strategies (see later; Chapter **4.8**). This was particularly useful when the alkyne in question was of a volatile nature (Scheme **2.4**).



Scheme 2.4: α-Hydroxycarbonyl pathway to 3-alkyne-1,2-diols.

2.4 Sonogashira Approach

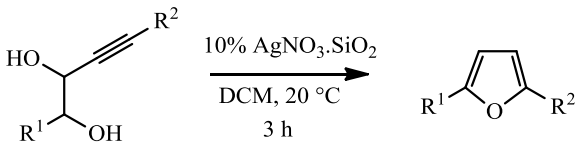
The alternative approach to the diols **80** involved the use of a palladium-catalysed Sonogashira coupling reaction[34] between 1-alkynes **104** and vinyl halides **103**. The resulting conjugated enyne **102** was then subjected to a regioselective *bis*-hydroxylation with catalytic potassium osmate using Sharpless' dihydroxylation protocol,[62] to yield the desired 3-alkyne-1,2-diols **80** (Scheme **2.5**). The main advantage of this method over the α-hydroxycarbonyl pathway is the requirement of just a single equivalent of alkyne without the need for protection although the trade-off for this advantage is the toxicity of the osmium salts



Scheme 2.5: Sonogashira approach to 3-alkyne-1,2-diols.

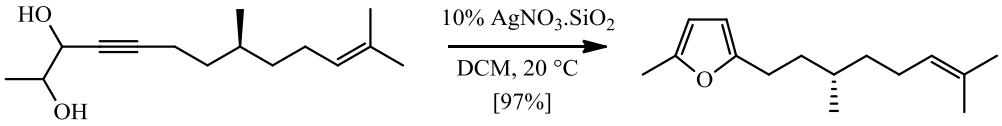
2.5 Silver-catalysed Cyclisation

A wide range of 2,5-disubstituted **106**, 2,4-disubstitued **110** and 2,3,5-trisubstituted furans **81** were synthesised by the Knight group in an attempt to discover the full scope and limitations of this methodology. The results leading to 2,5-disubstituted furans **106** are displayed in Scheme **2.6**. The completely clean conversion of the citronellol-derived diol **107** to furan **108** in quantitative yield is a great indication of the mildness of this procedure.



105 **106**

a) R^1 = Ph; R^2 = Bu [96%][59]
b) R^1 = Me; R^2 = Bu [>95%, by NMR/GC][59]
c) R^1 = Me; R^2 = Ph [98%][59]
d) R^1 = Ph; R^2 = $(CH_2)_2OH$ [97%]
e) R^1 = Bu; R^2 = $(CH_2)_2OH$ [98%]
f) R^1 = Me; R^2 = $(CH_2)_2OTBDMS$ [99%][59]
g) R^1 = Citronellyl; R^2 = $(CH_2)_2OH$ [97%]

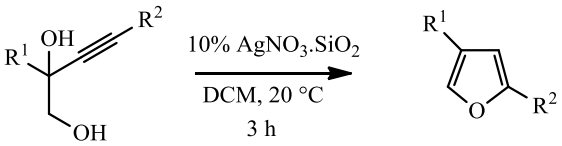


107 **108**

Scheme 2.6: 2,5-disubstuted furan synthesis.

It appeared that these conversions were quantitative and any losses were mechanical or down to product volatility; no by-products were detected. All the transformations were carried out in dry dichloromethane but the reactions proved equally successful in hexane and in some instances, cyclisations were actually faster in this solvent.[39]

Essentially quantitative conversions of 3-alkyne-1,2-diols **109** to the corresponding 2,4-disubstituted furans **110** was also observed (Scheme **2.7**).

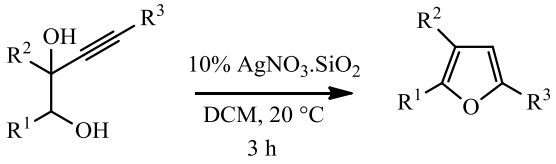


109 **110**

a) R^1 = Ph; R^2 = Bu [98%]
b) R^1 = Ph; R^2 = Bu [97%]
c) R^1 = Me; R^2 = Ph [99%]
d) R^1 = Me; R^2 = Bu [97%; by NMR/GC]

Scheme 2.7: 2,4-disubstituted furan synthesis.

Finally, the cyclisation of 3-alkyne-1,2-diols **80** again produced essentially quantitative yields of the corresponding 2,3,5-trisubstituted furans **81** (Scheme **2.8**).



80 **81**

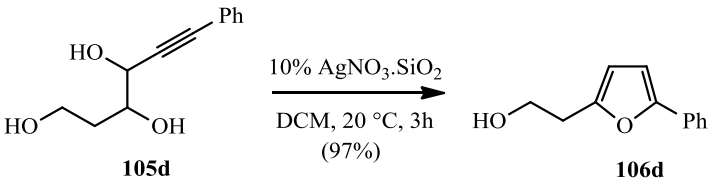
a) $R^1 = R^2 = Ph$; $R^3 = Bu$ [98%]
b) $R^1 = R^2 = Me$; $R^3 = Bu$ [>95%, by NMR/GC]
c) R^1, $R^2 = (CH_2)_4$; $R^3 = Bu$ [99%)
d) $R^1 = R^2 = Ph$; $R^3 = CH_2OTBS$ [94%]
e) $R^1 = Me$; $R^2 = CCBu$; $R^3 = Bu$ [93%]
f) $R^1 = R^2 = Me$; $R^3 = Ph$ [99%]
g) $R^1 = R^2 = Ph$; $R^3 = {}^tBu$ [98%]
h) R^1, $R^2 = (CH_2)_4$; $R^3 = Ph$ [97%]
i) $R^1 = R^2 = Me$; $R^3 = (CH_2)_3OBn$ [99%]
j) $R^1 = R^2 = Ph$; $R^3 = (CH_2)_3OBn$ [99%]
k) $R^1 = R^2 = R^3 = Ph$ [98%]

Scheme 2.8: 2,3,5-trisubstituted furan synthesis.

Once again, all yields were essentially quantitative irrespective of whether the substituents were alkyl groups, aryl groups or bulky *t*-butyl groups (**81g**). The only complication encountered was the partial deprotection during cyclisation of the propargyl alcohol derivative **80d**. However, the combined yield, after chromatographic separation of the *O*-silyl derivative and the corresponding free alcohol, was still 94%. Also, there was no interference from competing 5-*exo*-dig cyclisation involving the *O*-benzyl functions in the reactions of **80i,j**.

2.6 Oxidation of Furylethanol

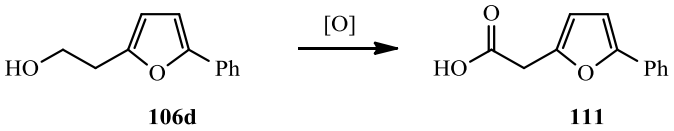
Despite the presence of an unprotected primary hydroxy group, phenyl-substituted alkyne-1,2-diol **105d** underwent smooth silver-catalysed cyclisation to give a virtually quantitative yield of 2-furylethanol **106d** with no interference from the primary hydroxyl group (Scheme **2.9**).



105d **106d**

Scheme 2.9: Furylethanol synthesis.

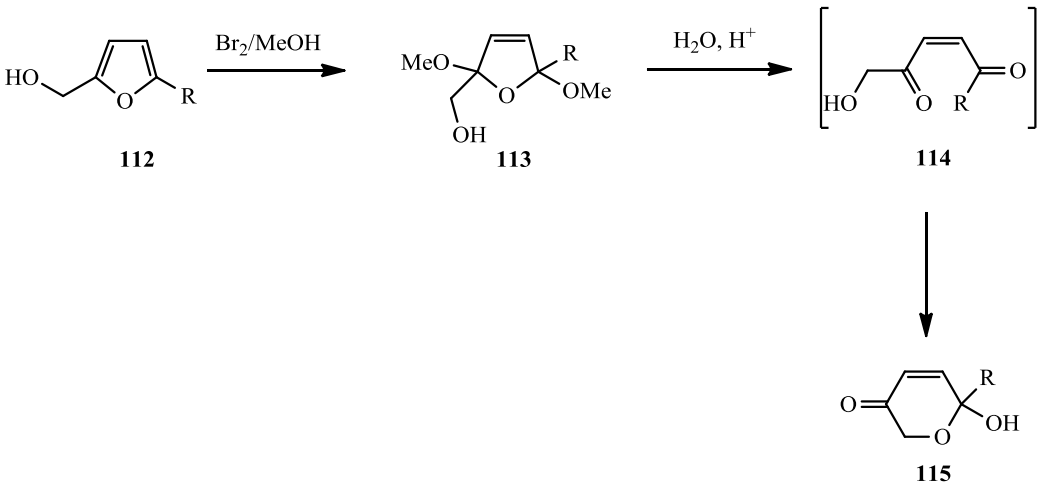
It was hoped that oxidation of 2-furylethanol **106d** would lead to a viable route to furylacetic acid **111** as such acids are not well represented in the literature but are known in the form of furan-containing natural products and are also bioactive (Scheme **2.10**).



106d **111**

Scheme 2.10: Anticipated oxidation product of furylethanols.

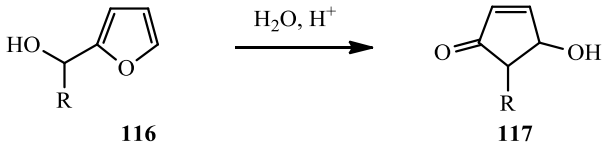
Oddly, at the outset of this project, there were no literature reports of a successful example of the oxidation shown in Scheme **2.9**. However, it has been known for many years that oxidation of 2-furylmethanols **112** do not always follow the expected pathway to the corresponding aldehydes or ketones. Rather, they can induce deep-seated rearrangements, one of the best known being the Achmatowicz oxidation, which originally used bromine in methanol to give pyranones[63-65] **115** (Scheme **2.11**).



112 **113** **114** **115**

Scheme 2.11: Achmatowicz oxidation.

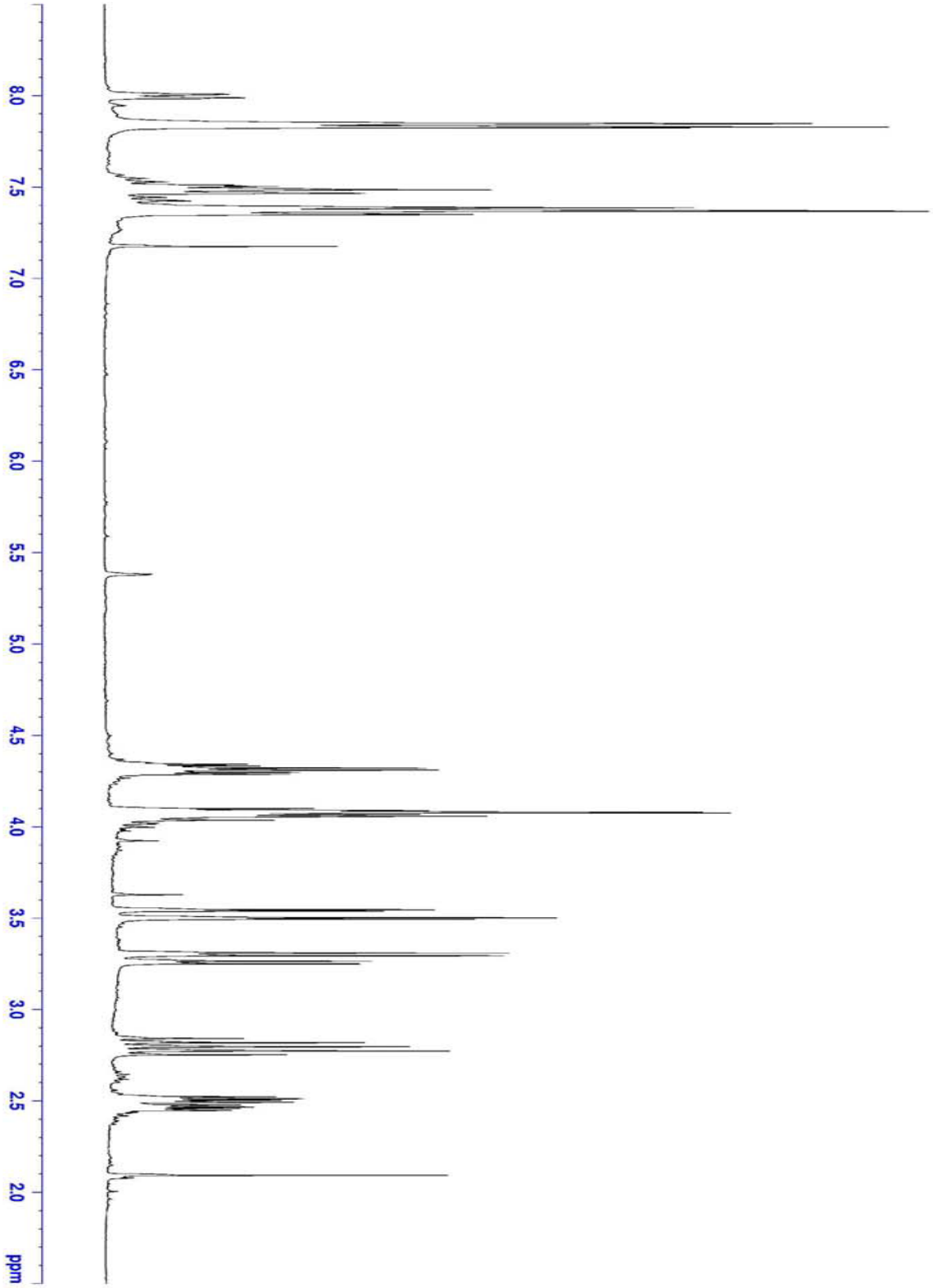
Exposure of these sensitive furyl alcohols **116** to acidic conditions and hence to acidic oxidising agents such as the Jones reagent results in the formation of 4-hydroxy-2-cyclopentenones **117** *via* alcohol protonation, water loss assisted by the furyl ring oxygen, re-addition of water but at the distal 5-position of the furan followed by ring opening and aldol cyclisation (Scheme **2.12**).



116 **117**

Scheme 2.12: Acid-catalysed cyclopentenone formation.

It was therefore far from clear what would happen when an attempt was made to oxidise 2-furylethanol **106d**, especially as there were no precedents in the literature. After cyclisation of alkyne-1,2-diol **100d**, 2-furylethanol **106d** was exposed to Jones reagent for one hour at 0 °C. It was clear that an oxidation had occurred as green chromium(III) salts became apparent. However, quenching with aqueous carbonate followed by a simple solvent extraction gave an excellent yield of a product with a most interesting ^{1}H NMR spectrum (Spectrum **1.1**). Most surprisingly, the spectrum obtained showed that the product clearly did not contain a furan residue and it was equally clear that the product was neither an aldehyde nor a carboxylic acid! Also, the richly detailed spectrum contained strong evidence that the product was aliphatic as it showed the complete absence of alkenyl protons. By analysing the coupling constants and using COSY (Figure **1.1**), HSQC and HMBC we determined that there were two separate groups of protons: a three-proton ABX system and a four-proton AA′BB′ pattern.



Spectrum 1.1: ^{1}H NMR Spectrum of oxidation product.

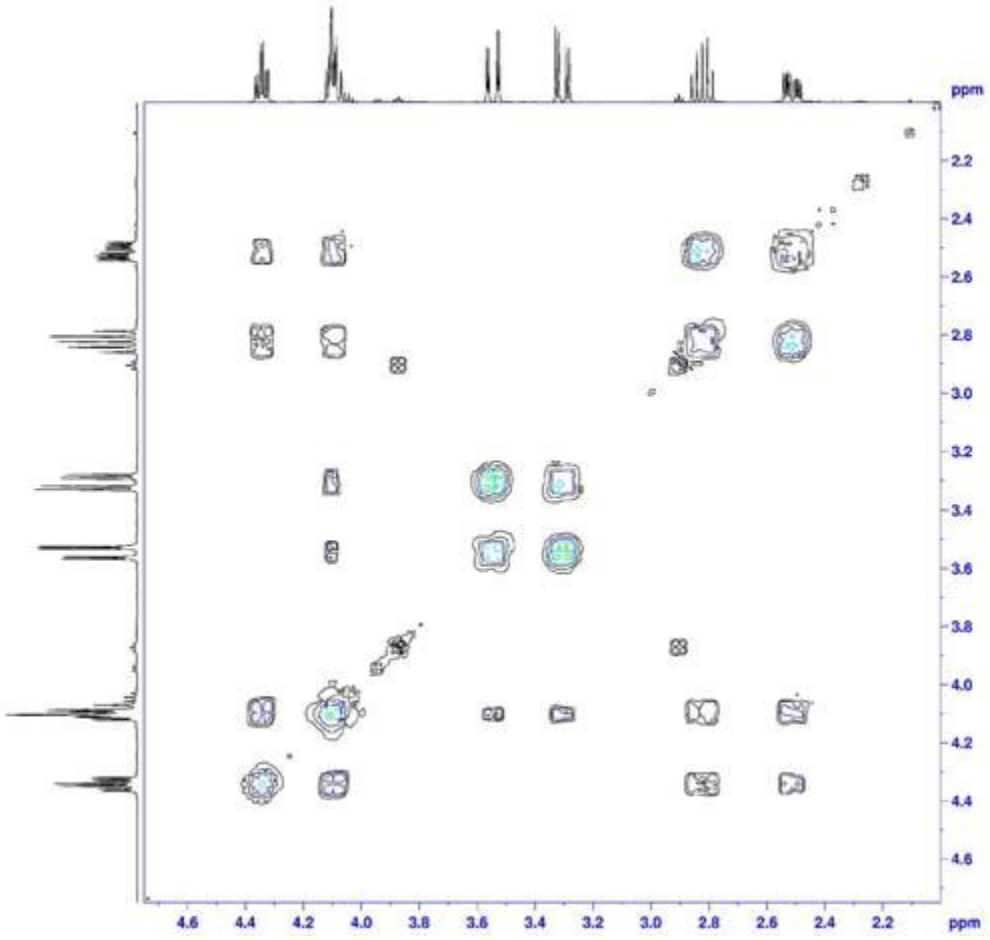
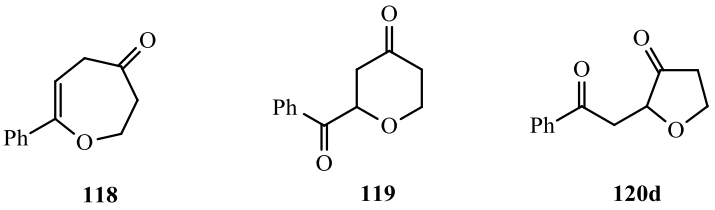


Figure 1.1: COSY analysis of oxidation product.

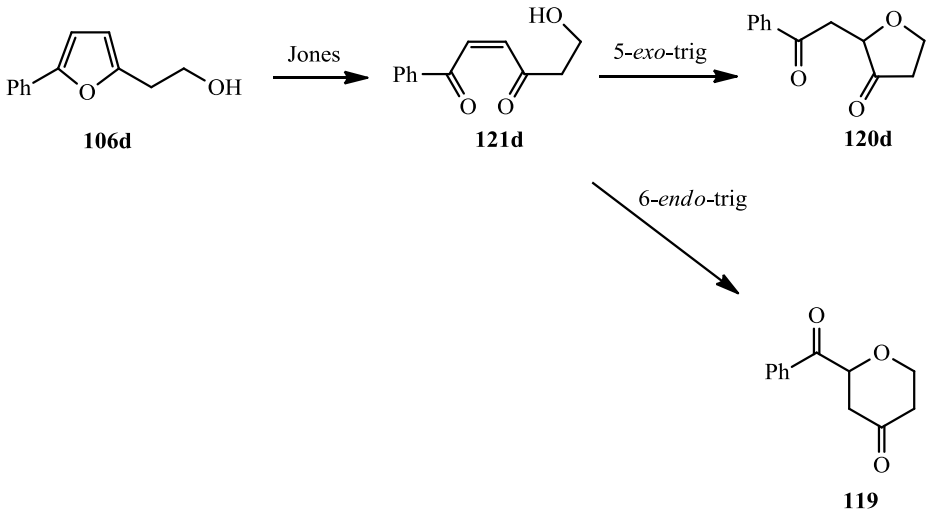
The possible structures that were suggested prior to the commencement of this thesis were an oxepin-4-one **118** and a pyranone **119.** However, during the course of this project further investigations led to a new structure, keto-tetrahydrofuran **120d**, becoming the leading candidate (Scheme **2.13**). The observation of green chromium(III) salts suggested that an oxidation had occurred, a suggestion that was confirmed by molecular weight determination: while the initial furylethanol **106d** ($C_{12}H_{12}O_2$) had a molecular weight of 188, the new product showed *m/z* = 227 for $[M+Na]^+$, equivalent to a molecular weight of 204 and therefore contained an additional oxygen ($C_{12}H_{12}O_2$). This was confirmed by high resolution measurements and so ruled out oxepin-4-one **118**.



Scheme 2.13: Initially proposed structures for oxidation of 2-furylethanol.

Also, infrared and ^{13}C NMR data showed the presence of two ketone groups [δ_C 215.8 and 196.1] with the peak at 196.1 likely to be due to the presence of a benzoyl group, PhCO. The coupling constant values displayed by the four-proton group strongly suggested they were attached to a cyclic system.

It therefore appeared that the furan ring had undergone an initial oxidative ring opening, similar perhaps to the Achmatowicz reaction, to give an intermediate enedione **121d**. Under the acidic conditions of the Jones oxidation, this enedione **121d** could then undergo ring closure *via* an intramolecular Michael addition of the hydroxy group to the enedione acceptor giving either a five- or a six-membered cyclic ether **120d** or **122** (Scheme **2.14**).

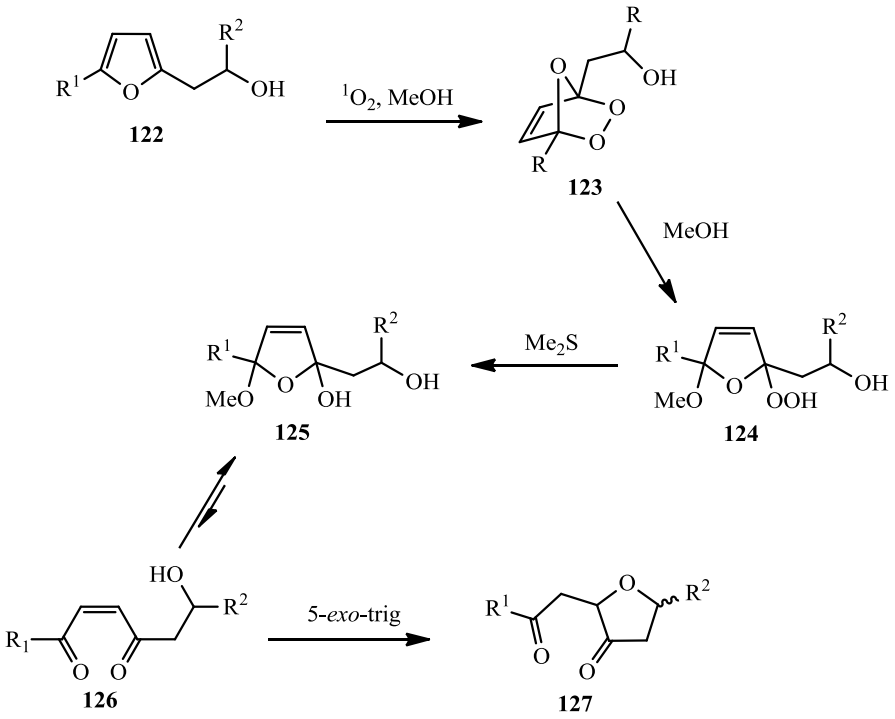


Scheme 2.14: Proposed oxidation pathway.

Baldwin's rules predict that 5-*exo*-trig processes are generally very preferred to 6-*endo*-trig competitors, although both are favoured. With this in mind it would seem that the keto-tetrahydrofuran **120d** would be the most likely candidate for the unexpected product.

During our investigations into the structure of the curious oxidation product, Tofi *et al* published their method of generating a similar keto-tetrahydrofuran using photo-oxidation.[66] They describe

the addition of singlet oxygen to the furan nucleus **122** in a Diels-Alder-like reaction to give an endoperoxide **123**. This endoperoxide **123** is then opened up by nucleophilic attack of the methanol used as the solvent to give a hydroperoxide **124** which is then reduced *in situ* by the addition of dimethyl sulphide to give the hemiacetal **125**. Hemiacetal **125**, in equilibrium with the open chain dione **126**, is the same type of species as the proposed intermediate in the Jones oxidation method (Scheme **2.14**). A Michael addition then completes the transformation in the same manner (Scheme **2.15**).

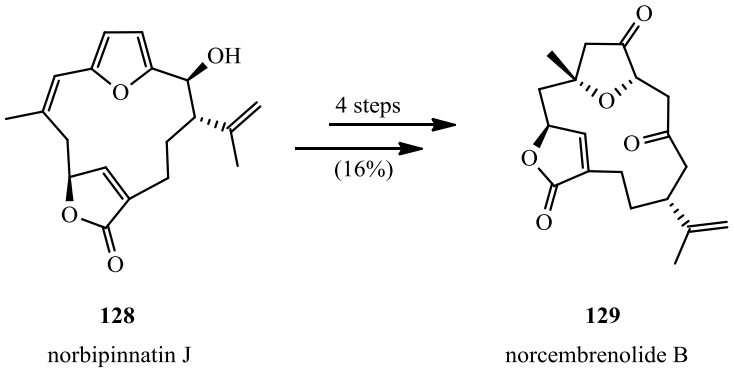


Scheme 2.15: Tofi's photo-oxidation of furylethanol.

All of the spectroscopic and analytical data relating to the structure of keto-tetrahydrofuran **127** in Tofi's report support the related keto-tetrahydrofuran **120d** structure suggested for Jones oxidation of furyleythanol **106d**. The alternative structure, pyranone **119,** formed by the less favoured 6-*endo*-trig mechanism, was ruled out on the basis of this mechanism and also by comparative spectroscopic data. Infrared data suggests a five-membered ring: the carbonyl observed stretch at 1756 cm^{-1} would support a five-membered ring ketone whilst a stretch in the region of 1715 cm^{-1} would be more typical of a ketone on a six-membered ring.[67]

Confirmation of the keto-tetrahydrofuran structure was established when Theodorakis cited our work in his report on the synthesis of norcembrenolide B **129**.[68] In his very recent report he describes the synthesis of norcembrenolide B **129**, a natural product found in gorgonian

octocorals and soft corals of the genus *Simularia* containing a 14-membered cembrane skeleton, *via* norbipinnatin J **128** (Scheme **2.16**).

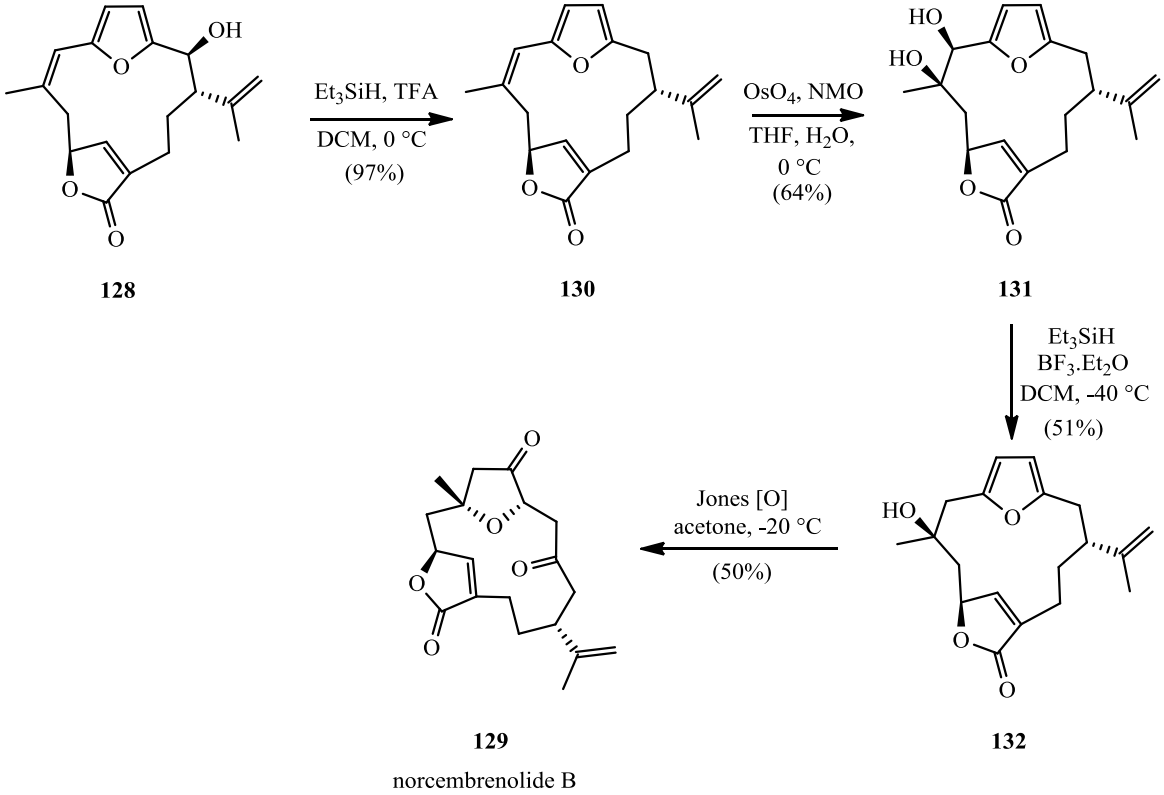


128
norbipinnatin J

129
norcembrenolide B

Scheme 2.16:Theodorakis' synthesis of norcembrenolide B.

After the construction of norbipinnatin J **128**, deoxygenation to afford norrubifolide **130** was followed by dihydroxylation of the double bond conjugated with the furan ring under Upjohn conditions[69] to give diol **131**. Deoxygenation then afforded furan **132** in 51% yield. Conversion to the keto-tetrahydrofuran was then accomplished using Jones reagent with a yield of 50% (Scheme **2.17**). This structure was confirmed *via* crystallographic studies.



128 **130** **131**

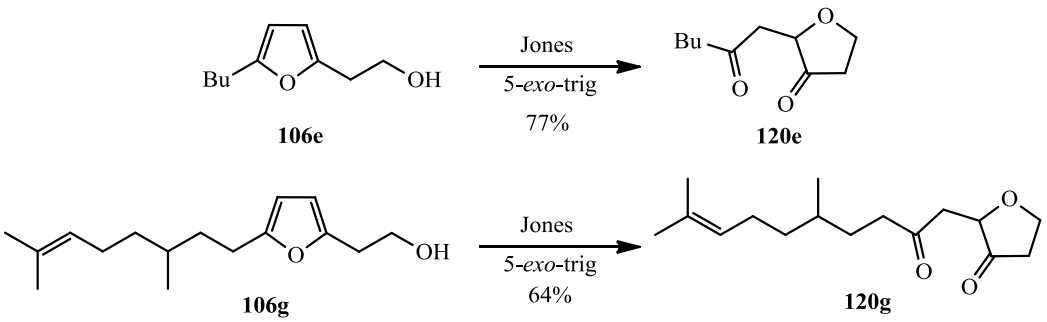
132

129
norcembrenolide B

Scheme 2.17:Theodorakis' synthesis of norcembrenolide B

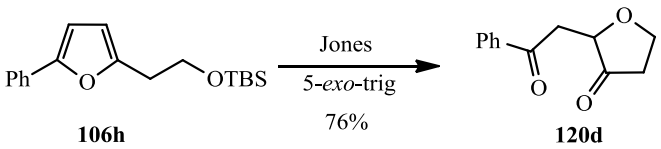
2.7 Further Investigations into the Oxidation of Furylethanols

To determine whether or not this Jones oxidation was a special case that depended upon the phenyl group, related 5-alkyl-substituted 2-furylethanols were exposed to Jones reagent, using the same conditions as for 5-phenylfurylethanol **106d**. The results show that both the 5-butyl derivative **106e** and the citronellol-derived furylethanol **106g** gave the corresponding keto-tetrahydrofurans in 77% and 64% yields respectively (Scheme **2.18**).



Scheme 2.18: Jones oxidation of furylethanols.

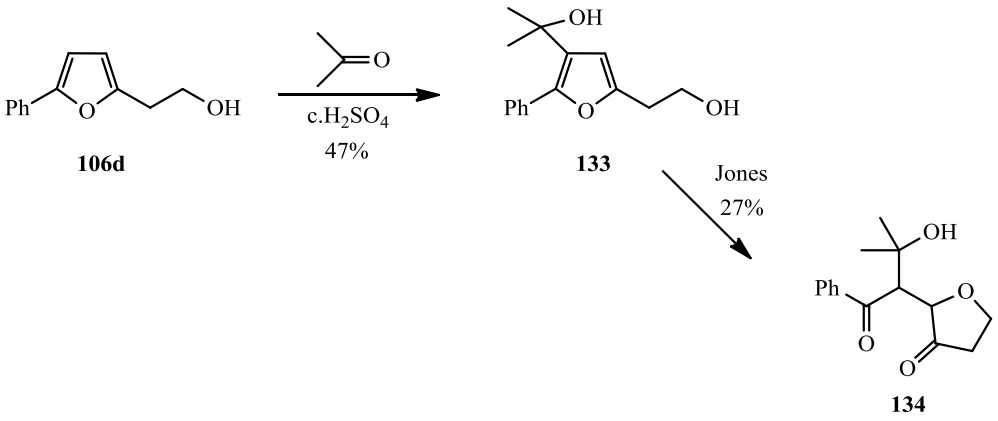
Jones reagent can be used to directly transform *O*-silyl ethers into the corresponding carbonyl compounds by sequential deprotection and oxidation.[70] Similarly, exposing *t*-butyldimethylsilyl ether **106h** to the Jones reagent led to a similar yield of the keto-tetrahydrofuran **120d** as that obtained from the parent alcohol (Scheme **2.19**).



Scheme 2.19: Jones oxidation of silyl-protected furylethanol.

Whilst attempting to determine the origin of the keto-tetrahydrofurans, Hayes had treated 5-phenylfurylethanol **106d** with acidic acetone, essentially Jones reagent without the chromium salts. Addition of 25% sulphuric acid to a solution of 5-phenylfurylethanol **106d** in acetone failed to induce any transformation and surprisingly had no effect at all on furan **106d** even after exposure to the acidic solution for one hour. However, concentrated sulphuric acid did have an effect but did not produce the keto-tetrahydrofuran **120d**. Instead, the acid sensitive furan **106d** had undergone a Friedel-Crafts alkylation at its β-position to give a moderate yield of the trisubstitued furan **133** (Scheme **2.20**). When this compound was then treated with the 'normal'

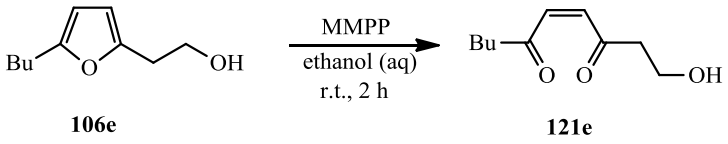
Jones reagent, a poor yield of 27% of keto-tetrahydrofuran **134** was obtained as a 1.5:1 mixture of diastereoisomers.



Scheme 2.20:Friedel-Crafts alkylation and subsequent Jones oxidation of 5-phenylfurylethanol.

Several other alternative oxidation methods were examined in an attempt to obtain 'simple' alcohol oxidation products from the model substrate 5-phenylfurylethanol **106d**. Omitting the acidic component in a Jones oxidation resulted in the formation of a *circa* 1:1 mixture of the starting material and the keto-tetrahydrofuran **120d**. Pyridinium dichromate (PDC) in dimethylformamide (DMF) at ambient temperature[71] did give the keto-tetrahydrofuran **120d** and no other side products but formation was very slow with only a trace amount after overnight stirring. The relatively mild Swern oxidation method[72] delivered a similarly low yield of the keto-tetrahydrofuran **120d**, whilst tetrapropylammonium perrhuthenate (TPAP)[73, 74] and various methods using potassium permanganate[75, 76] all proved unsuccessful.

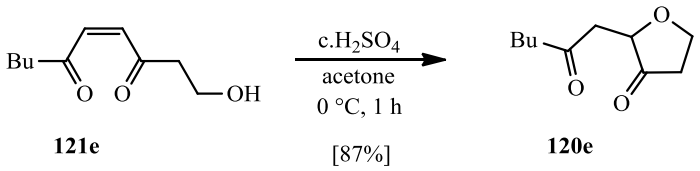
Treatment of alcohol **106e** with magnesium monoperoxyphthalate hexahydrate (MMPP)[77] in aqueous ethanol at ambient temperature for two hours gave a second product type which were identified as (*Z*)-enedione **121e** (Scheme **2.21**).



Scheme 2.21: MMPP oxidation of 2-furylethanols.

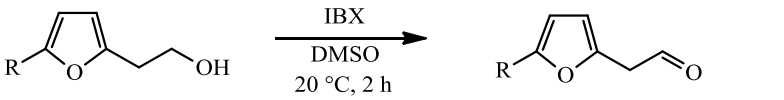
This known reaction gave us a definitive insight into the mechanism of the Jones oxidation reaction. Treating the (*Z*)-enedione **121e** to the same conditions as the Jones reaction minus the chromium salts, stirring in acidic acetone at 0 °C for one hour, led to smooth formation of the corresponding keto-tetrahydrofuran **120e** *via* an acid-induced 5-*exo*-trig Michael addition

(Scheme **2.22**). With this finding there was very strong evidence to support the supposition that these enediones are intermediates in the unexpected oxidation chemistry of 2-furylethanols.



Scheme 2.22: Acid-induced cyclisation of (*Z*)-enediones.

Finally, oxidation of 2-furylethanols **106e** using the hypervalent IBX compound in dimethyl sulphoxide (DMSO) at ambient temperature for two hours gave an excellent yield of the corresponding aldehyde **135e** (Scheme **2.23**), however this could not be repeated with the other furylethanols that were tested, namely **106d** and **106g**. This transformation for furylethanol **106e** was in stark contrast to all the other oxidising agents that were tried.



106d R = Ph
106e R = Bu
106g R = Citronellyl

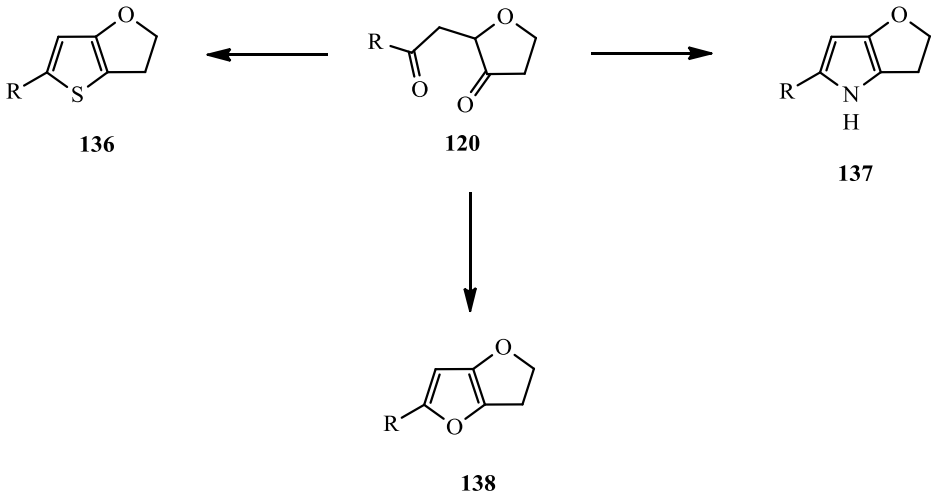
135d R = Ph [0%]
135e R = Bu [72%]
136g R = Citronellyl [0%]

Scheme 2.23: IBX oxidation of 2-furylethanols.

It remains to be seen if aldehyde **135e** can be oxidised to the corresponding carboxylic acid. In our hands, using sodium hypochlorite, this was not possible although a more thorough investigation should be attempted. As stated at the beginning of this chapter, the primary aim of this investigation was to attempt to oxidise 2-furylethanols to their corresponding carboxylic acids. Although this was not achieved, this chemistry has proven to be synthetically useful in the sense that, by carefully choosing the oxidising agent, three separate product types can be obtained from 2-furylethanols. The keto-tetrahydrofurans **120** in particular may yet turn out to be especially useful as this is a structural type that is poorly represented in the current literature.

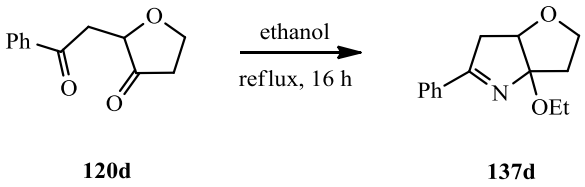
Attempts were made to exploit the synthesis of these keto-tetrahydrofurans **120**. If the structure of the keto-tetrahydrofurans **120** is as has been proposed then it could be possible that the 1,4-dicarbonyl system of the keto-tetrahydrofuran could undergo cyclisation to produce dihydro-thienofuran **136**, dihydro-furopyrrole **137** and dihydro-furofuran **138** derivatives (Scheme **2.24**). This would also provide further evidence for the proposed structure since the alternative

structure, the pyranone **119**, should be precluded from cyclisation due to the rigidity of the 1,4-dicarbonyl system within its structure.



Scheme 2.24: Potential cyclisation products of keto-tetrahydrofurans.

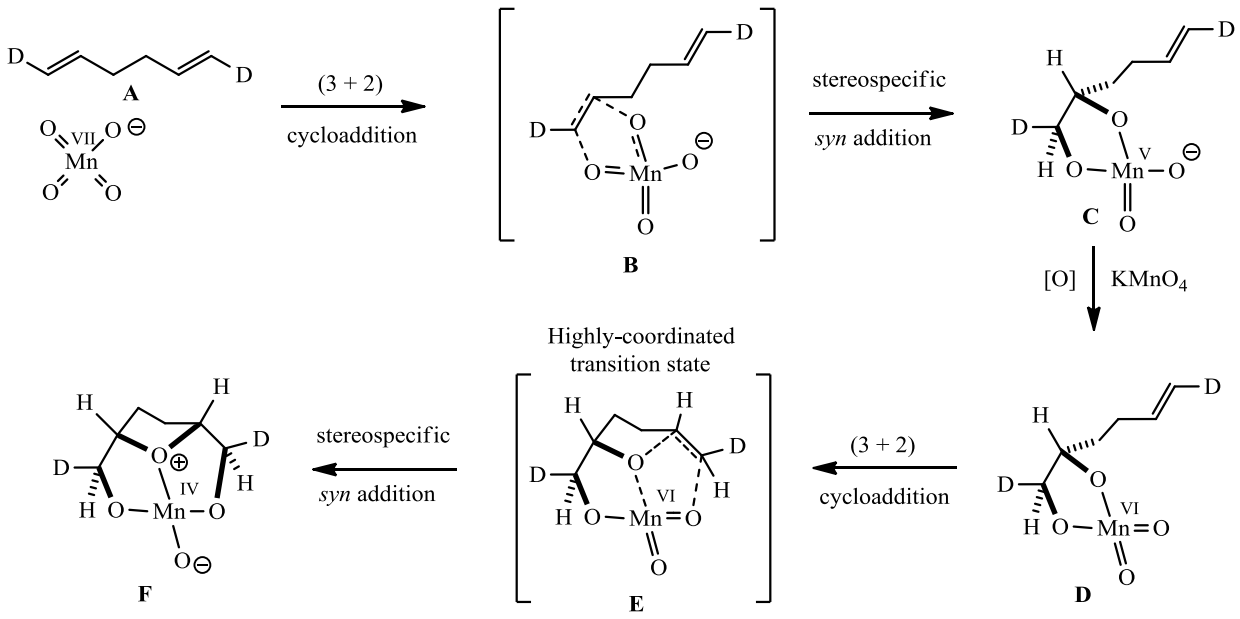
In practice, however, successful cyclisations were achieved using Lawesson's reagent[78] to generate the dihydro-thienofuran **136d** (R = Ph) and ammonium carbonate to give the pyrroline **137d** (Scheme **2.25**). It is not altogether too surprising that the furanofuran **138** could not be obtained since they are not generated under the acidic conditions of the Jones oxidation.



Scheme 2.25

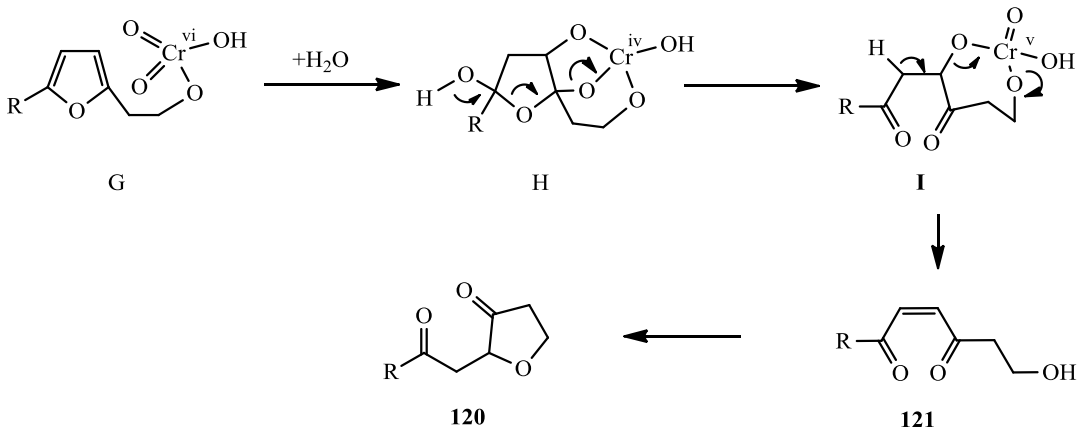
2.8 Possible Mechanisms of Jones Oxidation of 2-Furylethanols

It has long been known that oxidative cyclisation of dienes can be effected using metal-oxo species. First disclosed by Klein and Rojahn in 1965, it was found that treatment of 1,4-hexadiene with potassium permanganate led to the formation of a *cis*-fused tetrahydrofuran in 20% yield.[79] Baldwin then went on to determine the mechanism of the reaction using diastereomeric deuterium-labelled diene **A**.[80] This investigation showed that the addition of the two oxygen atoms was *syn* stereospecific across both double bonds (Scheme **2.26**).



Scheme 2.26: Baldwin's deuterium labelled mechanistic experiments.

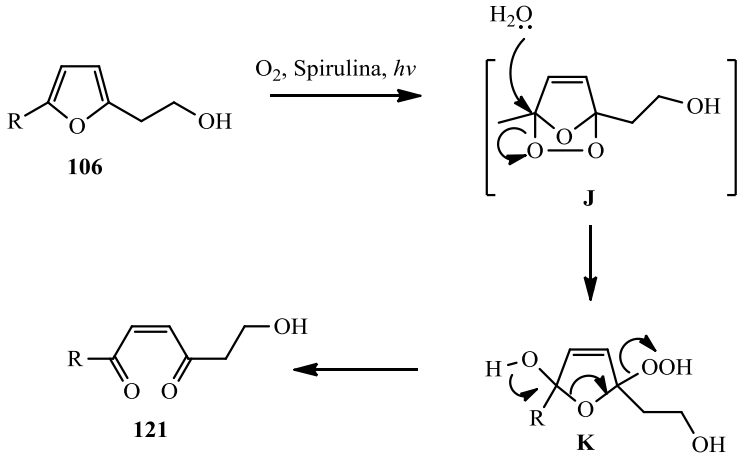
It therefore seemed a possibility that the β-hydroxy group of 2-furylethanols **106** could form complexes with the chromium based oxidation moieties **G**, thereby strongly encouraging such reactive species to interact directly with the furan ring, aided by the oxygen atom of the furan to produce intermediate enediones such as **121**. It is this induced proximity that could cause such reactions to be faster than proton loss α-to the oxygen as in a more conventional oxidation. The highly acidic conditions of the Jones reaction are such that rapid, acid-catalysed cyclisation of this enedione intermediate would then lead to the observed keto-tetrahydrofurans **120** (Scheme **2.27**).



Scheme 2.27

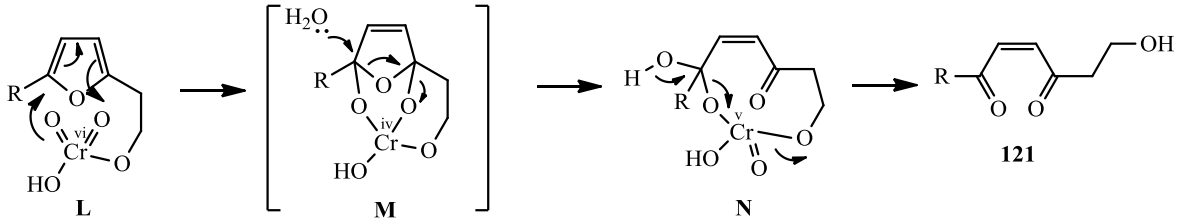
An alternative, but equally plausible mechanism, based upon the findings of Vassilikogiannakis is set out in Scheme **2.28**. A human/animal nutritional supplement named Spirulina was found to effect the same transformation of 2-furylethanols **106** as Jones reagent. Spirulina is made

primarily from two easily cultivated species of cyanobacteria – *Arthrospira plantensis* and *Arthrospira maxima*. It is believed that singlet oxygen forms an ozonide intermediate **J** which can then be opened up by water to yield an intermediate hydroperoxide **K** which then eliminates H_2O_2 to give the 1,4-enedione[81] (Scheme **2.28**).



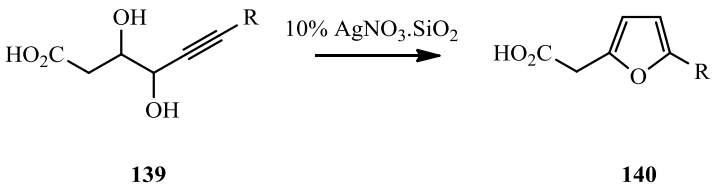
Scheme 2.28: Oxidation of 2-furylethanol in the presence of Spirulina.

Using this mechanism as a template it is proposed that the chromate ester can be directed towards the two α-carbons of the furan and undergo a similar transformation (Scheme **2.29**).



Scheme 2.29

Although furylacetic acids **140** could not be generated by simple oxidation of 2-furylethanols, by altering the starting material we wondered if we could cyclise the dihydroxyalkynoic acids **139** (Scheme **2.30**). The results of this investigation are described in the following chapter.



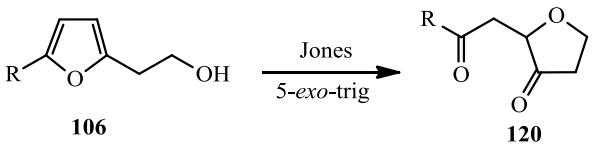
Scheme 2.30: Proposed route to furylacetic acids.

*Chapter **3**: Results and Discussion*

2-Furylacetic Acids and Plakorsin B Syntheses

3.1 Introduction

In the previous chapter, it was shown that 2-furylethanols **106** have a strong tendency to rearrange into the keto-tetrahydrofurans **120** by sequential oxidative ring opening to the corresponding (*Z*)-enediones followed by 5-*exo*-trig Michael-type ring closure, when treated with a variety of oxidising agents, especially the Jones reagent (Scheme **3.1**).



106 **120**

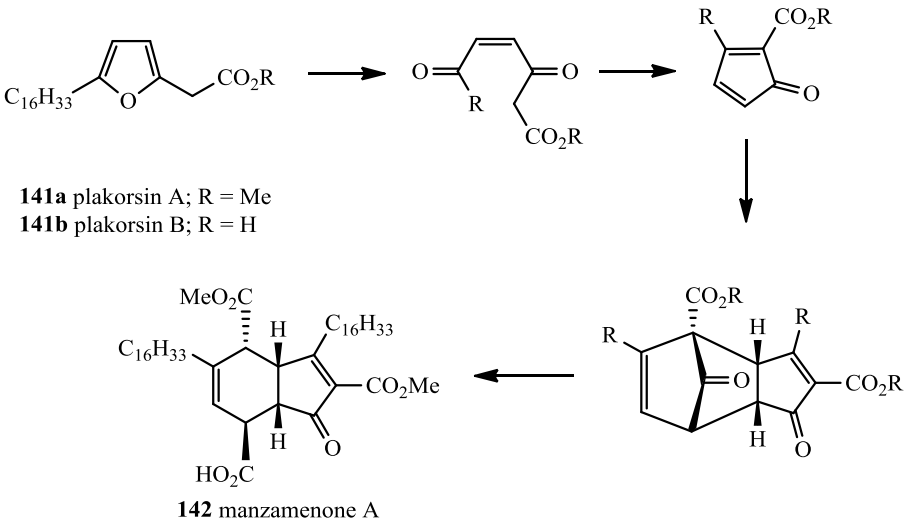
Scheme 3.1: Jones oxidation of 2-furylethanols.

This may account for the fact that the oxidation of 2-furylethanols **106** to the corresponding 2-furylacetic acids **140** is not represented in the current literature. We therefore required a different approach to apply our highly efficient silver-catalysed furan synthesis to transform 3-alkyne-1,2-diols **80** to the synthesis of naturally occurring 2-furylacetic acids **140**.

3.2 Plakorsins A and B: Previous Syntheses

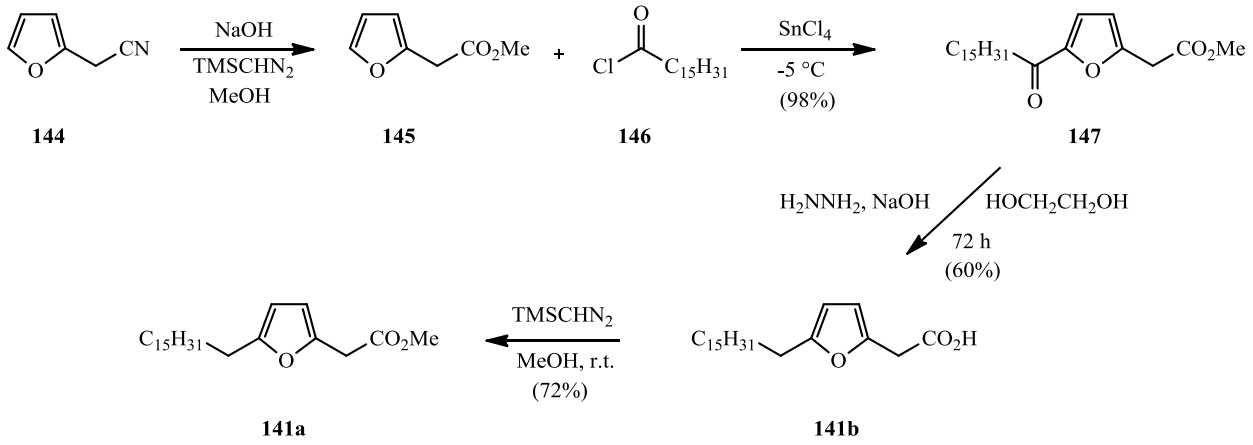
Specific examples of interest were the fatty acid derivatives plakorsins A and B **141** (Scheme **3.2**), isolated from the marine sponge *Plakorsis simplex*.[82] At first sight, these plakorsins **141** would appear to be amongst the easiest of natural products to synthesise, given their simplicity and lack of stereogenic centres. Whilst they are simple enough metabolites, they do display some useful cytotoxic activities against various cancer cell lines[83] and, of greater chemical interest, are the precursors of the much more densely functionalised metabolite manzamenone A **142**,[84-86] a known inhibitor of DNA-polymerase, which makes them a particularly desirable target.

The plakorsins are converted into manzamenone A following sequential oxidative ring opening, aldol condensation, dehydrative dimerisation, and finally a *retro*-Dieckmann ring closure.[86] Additional members of this complex group of metabolites are members of the pyrrolidine alkaloids, the plakordines; by a neat piece of logical deduction, it has been proposed that these compounds are all interrelated biosynthetically.[87]



Scheme 3.2: Plakorsins A and B and manzamenone A.

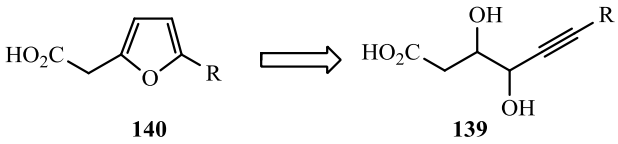
Despite their simplicity, the lack of research around this area uncovers the truth, particularly in the case of plakorsin B **141b**: furylacetic acids are not easy to synthesise. The Whitehead group's synthesis of plakorsins **141** occupied their attention for some time.[85-88] The successful synthesis (Scheme **3.3**) was based on classical steps from 2-(furan-2-yl)acetonitrile **144**, itself generated in two steps from 2-furylmethanol *via* the dangerous 2-furfuryl chloride, which can be highly explosive. Addition of sodium hydroxide then TMS-diazomethane in methanol yielded the corresponding methyl ester **145**. Introduction of the C_{16} fatty side chain was achieved by Friedel-Crafts acylation with palmitoyl chloride **146** to yield furyl ketone **147** (98%) and finally Wolff-Kishner reduction to yield plakorsin B **141b** (60%). Esterification of acid **141b** with TMS-diazomethane yielded plakorsin A **141a** in good yield (72%). Initially, and perhaps unsurprisingly, given the sensitive nature of furans in general, this was a rather inefficient synthesis but the group have subsequently achieved remarkable improvements on this by careful optimisations such that it is now a very effective approach to the plakorsins **141** and, presumably, to many other 5-substituted-2-furylacetic acids in general.



Scheme 3.3: Whitehead's plakorsin A and B synthesis.

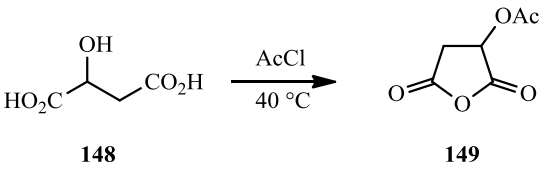
3.3 Furylacetic Acid Synthesis

In spite of these improvements, this is still a challenging synthesis which utilises a large range of reagents and solvents, so with our silver-catalysed method we were hopeful that, in light of the problems associated with the oxidation chemistry (Chapter **2**), a direct approach might be more successful. 2-Furylacetic acids **140** can be disconnected to give the corresponding dihydroxyalkynoic acids **139**. This seemed like a reasonable approach, assuming that there would be no interference from the free carboxylic acid group and further, of course, if such precursors could be synthesised in a general manner (Scheme **3.4**).



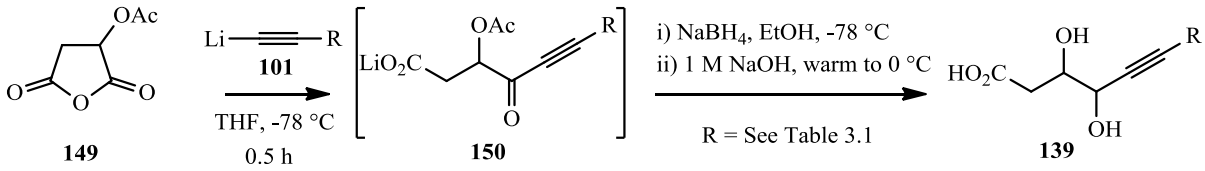
Scheme 3.4

Fortunately, the required precursors **139** are readily available using a literature procedure reported by Lavallée.[89] This one-pot synthesis regioselectively adds a lithio-acetylide **101** to the more reactive ring carbonyl of α-acetoxysuccinic anhydride **149**, itself readily derived from cheap (DL)-malic acid **148** by recyrstallisation from acetyl chloride (Scheme **3.5**).



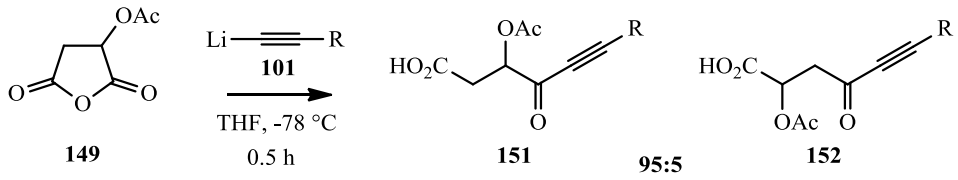
Scheme 3.5

In the present project, the addition of a lithio-acetylide **101** to the anhydride **149** at -78 °C occurs regioselectively at the more electrophilic carbonyl and follows a Bürgi-Dunitz trajectory to give the keto-acetylides **150**. *In situ* sodium borohydride reduction was followed by warming to 0 °C before sodium hydroxide-induced saponification of the acetate group. The reaction mixture was then warmed to ambient temperature, acidified and the products extracted into ethyl acetate (Scheme **3.6**). The resulting polar dihydroxyalkynoic acids **139** were obtained in around 60-80% yields and were essentially a clean mixture of diastereoisomers according to ^{1}H NMR analysis.



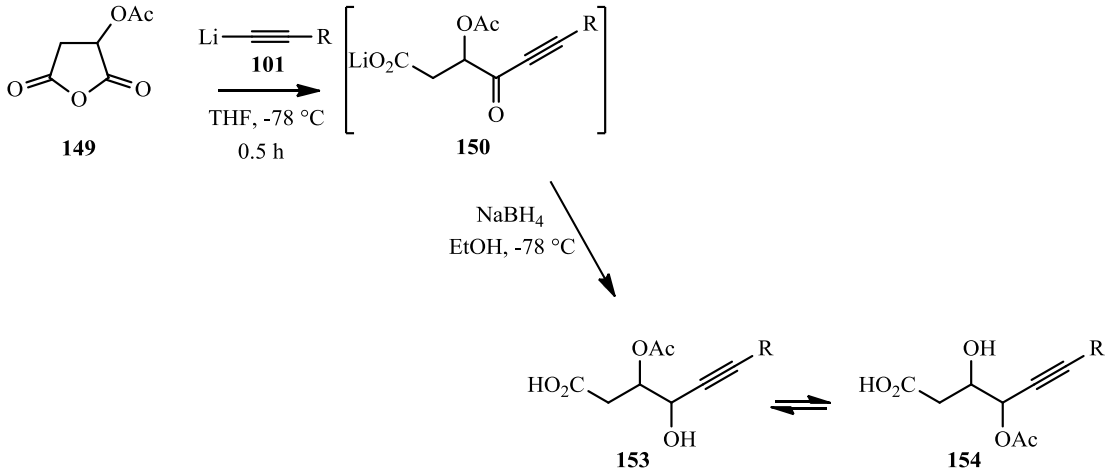
Scheme 3.6: Dihydroxyalkynoic acid symthesis.

In order to determine where the loss was occurring during this one pot synthesis, the reaction was worked up after each addition. After lithio-acetylide addition, the only products were the keto-acids **151** and a trace amount of the isomer **152** in a total amount of 65-85% yield, according to ^{1}H NMR analysis. This indicated that attack of the acetylide is extremely regioselective. Minor constituents of the crude mixture were succinic acid residues and the starting acetylide, which would suggest that a side reaction could be deprotonation of the anhydride by the acetylide. It would seem that the lithio-acetylide **101** is extremely selective with a ratio of 95:5 for attack at the carbonyl adjacent to the acetate group to give the isomeric acids **151** and **152** (Scheme **3.7**), most likely due to the electronic effects of the actetate group rendering the neighbouring carbonyl more electrophilic.



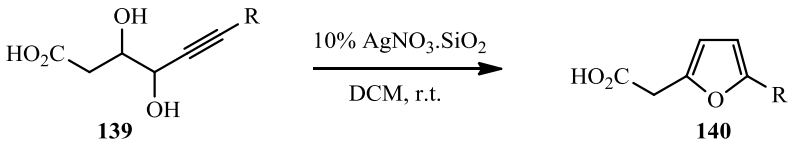
Scheme 3.7: Results of workup prior to sodium borohydride addition.

Workup after sodium borohydride addition resulted in no additional loss with yields in the same area as for workup prior to this addition. The resulting hydroxyl-acids **153** often contained isomers where the acetate group had shifted to give the isomers **154**. As this had no bearing on our one-pot synthesis, this was not investigated further (Scheme **3.8**).



Scheme 3.8: Results of workup after sodium borohydride addition

When the dihydroxy-alkynoic acids **139** were treated with the standard silver-catalysed cyclisation conditions of 10% w/w $AgNO_3.SiO_2$ in dichloromethane, we were delighted to find that cyclisation occurred in excellent yields in excess of 90% (Scheme **3.9**). Any losses in overall yields are almost entirely attributable to the losses incurred in the acetylide addition step (Table **3.1**).



Scheme 3.9: Silver-catalysed 2-furylacetic acid synthesis

Entry	Dihydroxyalkynoic acid	R	2-Furylacetic acid	Overall yield (%) from **149**
1	**139a**	Ph	**140a**	85
2	**139b**	Bu	**140b**	82
3	**139c**	$TBSOCH_2$	**140c**	59
4	**139d**	$TBSO(CH_2)_2$	**140d**	67
5	**139e**	$TBSO(CH_2)_3$	**140e**	68
6	**139f**	Citronellyl	**140f**	71
7	**139g**	$Me(CH_2)_{16}$	**141b**	55

Table 3.1: 2-Furylacetic acid synthesis.

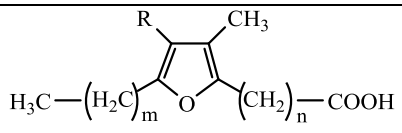
It should be noted that the overall yields quoted are unoptimised. The method was equally effective for aryl- and alkyl-substituted alkynes and both the products (entries 1 and 2) and the *tert*-butyldimethylsilyl groups were completely stable to all conditions used (entries 3-5). The mildness of the procedure is demonstrated by entry 6: the sensitive citronellyl terpene residue survived unmolested. Finally, the method delivered a reasonable yield of plakorsin B **141b** (entry 7) without any need to modify the reaction conditions in view of the presence of the long alkyl chain. The lower yield reported for plakorsin B is mostly due to the fatty nature of the lithio-alkyne **139g**. It is easy to imagine the long fatty chain coiling around on itself and hindering addition to the carbonyl of the anhydride **149**. Results were improved with vigorous stirring and with slightly extended reaction times. The overall yield of 55% is not as bad as it first appears however as the starting material, 1-octadecyne **104g**, can be easily recovered. This route delivers plakorsin B **141** in just two steps using cheap, commercially available starting materials and is a considerable improvement on previous syntheses.

Chapter 4: Results and Discussion

Furan Fatty Acids F_5 and F_6

4.1 What are Furan Fatty Acids?

The most common furan fatty acids (F-acids) are tri or tetrasubstituted furan derivatives[7] with either a propyl or pentyl alkyl side chain in one of the α positions and a long, saturated straight hydrocarbon chain terminating in a carboxylic acid group in the other α position. The β positions are occupied either by one or two methyl groups. Based on work by Glass *et al*, they are numbered according to GC elution times of the corresponding dimethyl esters[90] and the letter F (Table **4.1**).



Number	Compound	m	n	R
155a	F_1	2	8	CH_3
155b	F_2	4	8	H
155c	F_3	4	8	CH_3
155d	F_4	2	10	CH_3
155e	F_5	4	10	H
155f	F_6	4	10	CH_3
155g	F_7	4	12	H
155h	F_8	4	12	CH_3

Table 4.1: Structures of the most abundant furan fatty acids.

An alternative system, proposed by Rahn *et al*, is based on the length of the carboxyalkyl and alkyl chains in the α-positions. These chain lengths are listed, separated by a comma, in parenthesis following the letter F. The prefix 'Me' or 'DiMe' is added prior to the 'F' in the case of methylfuran fatty acids (MFA) or dimethylfuran fatty acids (DFA). Using this system, F-acid 11-(3-methyl-5-pentylfuran-2-yl)-undecanoic acid (furan fatty acid F5 using the Glass nomenclature) is abbreviated to MeF(11,5). More recently, Vetter *et al*, have suggested a modification of the Rahn system.[91] They propose a system where the length of the carboxyalkyl chain is listed first as a number, followed by a letter representing the heterocycle ('D' for dimethylfuran, 'M' for methylfuran or 'F' for furan), followed by the length of the alkyl chain as a number. In this system the example used previously, 11-(3-methyl-5-pentylfuran-2-yl)-

undecanoic acid, is abbreviated to 11M5. Vetter claims that the advantages with this system are that the structure can be directly extracted from the name (unlike the Glass system) and that they can be easily pronounced ('eleven-emm-five'). Also, in recent years, some unsaturated F-acids have been described in the literature, these can be characterised as follows: 9:1M5 and 9M5:1, with the number after the colon dictating the position of the double bond. For the remainder of this thesis however, the older nomenclature system adopted by Glass will be used.

4.2 Isolation and Characterisation

Unlike 2,5-disubstituted furan fatty acids, the F-acids $F_{1\text{-}8}$ are not found in seed oils.[7] F-acids were first detected by Glass *et al*[90] in Northern Pike (*Esox lucius*) in 1974. A year previously Kluytmans and Zandee[92] had published a report on the composition of lipids in the same fish but had overlooked the high content of F-acids. This oversight was most probably due to the fact that they had only determined the GC retention times of the lipids under investigation. Since F-acids and unsaturated fatty acids have similar retention indices[90] they could not distinguish between the two and falsely attributed the peak of F_6 to the unsaturated fatty acid 22:3n-3; an omega-3 fatty acid containing twenty two carbons and three double bonds. Glass[90] however, used EI mass spectrometry in combination with retention indices for compound characterisation. This method allows for clear distinction between F-acids and polyunsaturated fatty acids (PUFA). The use of retention indices alone is the reason why F-acids remained undetected during many lipid and fatty acid investigations.[7]

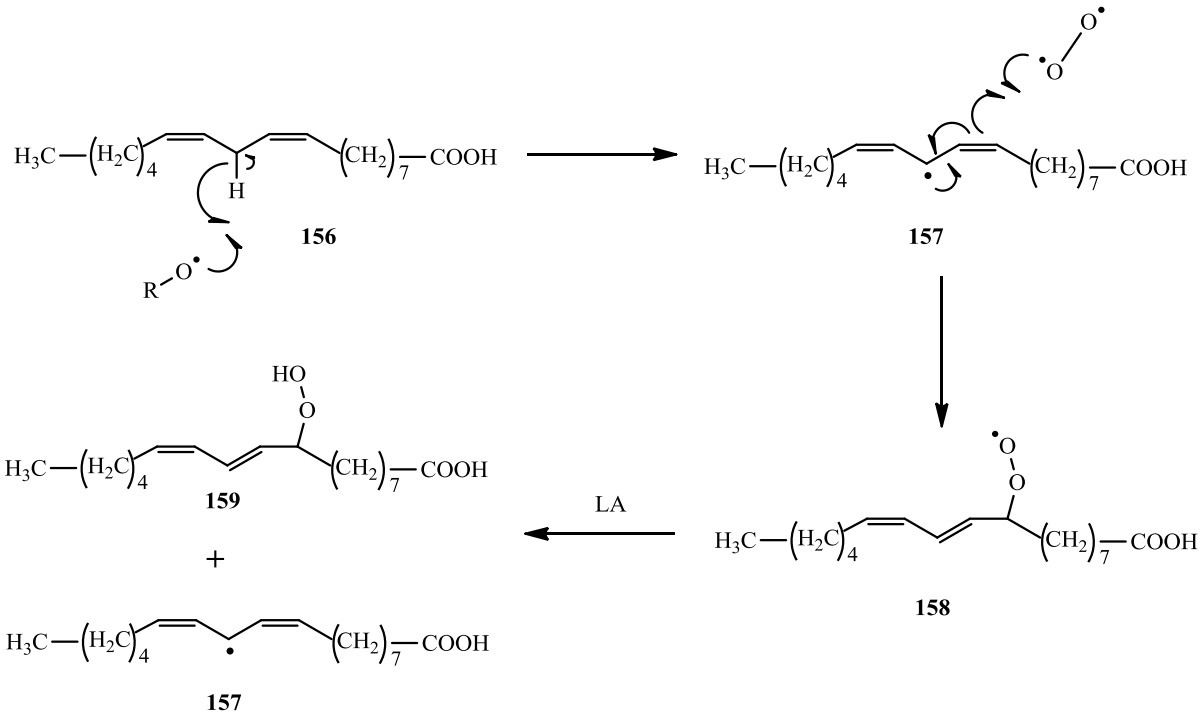
4.3 Distribution in Nature

F-acids are widely distributed in Nature: they have been detected in a huge range of animals from freshwater[93,94] and marine fish[94-100] to mammals,[101] crustaceans,[102-104] amphibians[103] and reptiles.[103] In addition to the common F-acids, F_1-F_8, F-acids with extremely long unsaturated chains of up to twenty carbons at one of the α positions have been isolated from marine sponges.[105] As well as animals, F-acids have also been detected in marine bacteria,[106-108] algae,[109,110] terrestrial plants,[111,114] yeast[113] and fungi.[112] They have also been found in several food fats such as butter[113] and virgin olive oil.[114] They are therefore found in most foods and may play important biological and nutritional roles.

4.4 What is Their Role?

The precise roles of F-acids are uncertain. Glass found that in the Northern Pike, there was a variation in the distribution and accumulation of F-acids throughout the year: an increased accumulation in the testes and liver of male pike during spawning times appeared to show a correlation between the F-acids and the fertilisation process.[92] F-acids have been detected in all types of fish tissue[7] but are most abundant in the liver. This may be due to the unique physiology of fish which, as opposed to mammals, reptiles and birds, do not have reserves of adipose tissue where fats can be stored.[115] Adipose tissue is found in all terrestrially evolved vertebrates and is likely to be a product of Darwinian evolution.[116] Instead, the fat reserves of fish are concentrated either in the liver or, in the case of fast swimming predatory fish such as mackerel, sardines, salmon and tuna, in the muscles. In mammals, F-acids can be found in the liver, where they are esterified to cholesterol or in the blood plasma where they are associated with phospholipids.[7] In plants, they occur mainly bound in phospholipids where they substitute for PUFAs and can account for around 7% of fatty acid content.[7] It was originally believed that F-acids are generated in fish[7] but it has since been shown that all F-acids are generated instead in plants.[7] This will be discussed in more detail in section **4.5**.

The following chemistry (Scheme **4.1**) suggests an antioxidant role, specifically as radical scavengers, for the F-acids. However, this is by no means certain or exclusive. The doubly allylic methylene hydrogens of PUFAs such as linoleic acid (LA) **156** are readily attacked by alkoxy radicals to form relatively stable alkyl radicals **157** which in turn react with singlet oxygen to generate lipid peroxy radicals (LOO•) **158**. These can then readily react with nearby PUFAs to form lipid peroxides (LOOH) **159** and propagate another LOO• radical **157**.



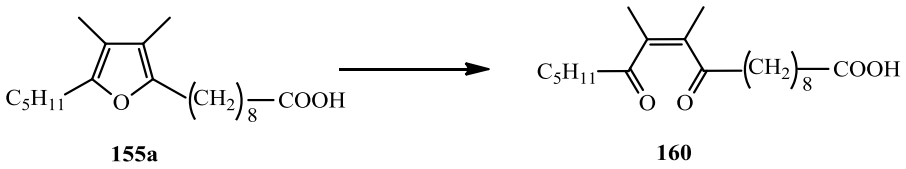
Scheme 4.1 Radical attack on linoleic acid by alkoxy radicals.

An additional route to LOO• is *via* a Fenton-like reaction. The Fenton reaction is an iron-catalysed redox reaction whereby iron(II) is oxidised to iron(III) in the presence of hydrogen peroxide producing a hydroxide ion and a hydroxyl radical. This is then followed by reduction to iron(II) with another molecule of hydrogen peroxide to produce a hydrogen peroxide radical and H^+ (Equation **4.1**). The addition of ferrous ions to a lipid preparation will stimulate lipid peroxidation by peroxide decomposition generating alkoxyl (LO•) and peroxyl (LOO•) radicals.[117]

Equation 4.1: Fenton-like reaction of lipid peroxides.

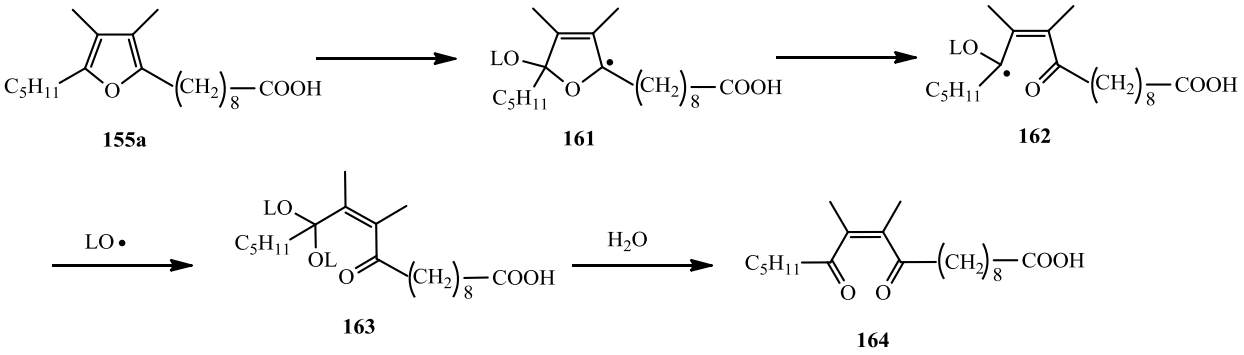
For the Fenton reaction, the rate constant for the reaction of ferrous ions with hydrogen peroxide is 76 mol^{-1} L^{-1} s^{-1}.[118] The rate constant for the reaction of ferrous ions with LOOH is substantially higher at 1.5 x 10^3 mol^{-1} L^{-1} s^{-1}.[119] It is therefore of great biological importance for any ferrous ions to be contained within enzymes so that oxidation can be controlled and regulated in order to avoid unwanted oxidation of LOOH which could then lead to radical-induced oxidation of PUFAs as shown in Scheme **4.1**.

Ferrous ions are used extensively in Nature as catalysts in enzymatic redox reactions.[7] One such enzyme is lipoxygenase (LOX). As previously stated, ferrous ions react easily with LOOH in a Fenton-like reaction. However, in biological systems, ferrous ions are shielded in redox enzymes such as LOX by complexation to avoid the Fenton reaction.[7] In a series of experiments carried out by Spiteller using plant LOX, it was shown that F-acids are radical scavengers.[120] F-acids remained unchanged when soybean LOX-1 was added. Also, when F-acids were incubated with pure LA, no oxidation products were generated from them. However, when LA was added to a solution of F-acid **155a** and soybean LOX-1, dienones **160** were formed (Scheme **4.2**).



Scheme 4.2: Oxidation of F-acids.

Radicals are formed during the Fenton reaction and the only available metal ions in the Spiteller experiment are those in the enzyme LOX. Also, it has been demonstrated that LOX is inactivated if exposed to high amounts of substrate,[121, 122] which is the case if free LA is used as starting material. Therefore LOOH molecules must have been cleaved during the course of the reaction to form alkoxyl radicals (Scheme **4.3**).



Scheme 4.3: F-acids are potent radical scavengers.

Radicals can attack at either the -2 or -5 position of the furan ring of F-acid **155a** to form an intermediate furan radical **161** which undergoes ring opening to give a highly stable mesomeric radical **162** (Scheme **4.3**) This radical is much more stable and therefore less reactive than a peroxyl or alkoxyl radical. It is this prolonged lifetime which allows it to trap a second radical,

such as an alkoxy radical, to form an acetal **163** which undergoes hydrolysis to give the dienone **164**. Thus a single F-acid is able to scavenge two radicals.

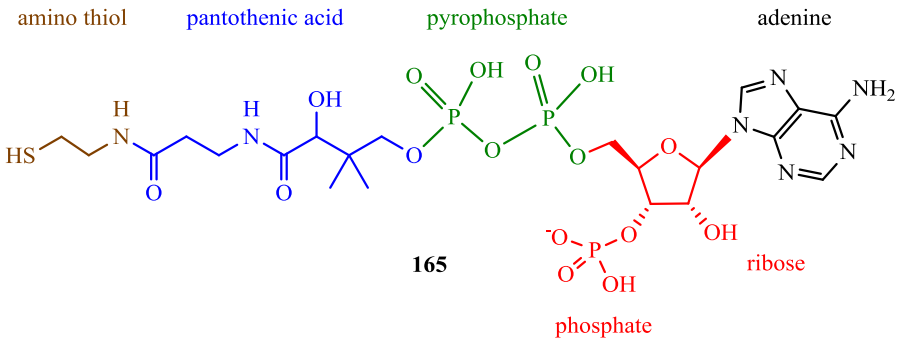
Peroxyl radicals generated either by the Fenton reaction or by the route outlined in Scheme **4.1**, can cause considerable damage to cells. Peroxyl radicals are known to oxidise hydroxy acids,[123] thioethers such as methionine[123] and amino acids with a primary amino group such as lysine.[123] They are also capable of oxidising compounds containing a double bond. Cholesterol,[123] linoleic acid,[123] linolenic acid[124] and oleic acid[126] are also all oxidised to their epoxides. Many of these products are toxic or undergo transformation into toxic products.[7]

It would seem therefore that F-acids play an important role as radical scavengers in biological systems since they are preferentially attacked by peroxyl radicals.[7] Their precise role and importance, however, remains uncertain. Owing to their similarity to PUFAs, they are incorporated into the tissue and blood of mammals where they can partly substitute for PUFA.[7] As a result they are found at sites where lipid peroxidation reactions occur. This may well increase their value as radical scavengers. As mentioned earlier, all F-acids are believed to be generated in plants and algae. This would appear to be the result of natural selection. It is well known that UV radiation can generate radicals and it would appear that plants and algae have evolved a way to protect themselves from the harmful effects of such radiation by synthesising radical scavengers. In terrestrial plants, the F-acid content is found to be enhanced in the green tissues, a further indication of their role as radical scavengers. Where better to place radical scavengers than the place where radicals are generated the most? This observation is further supported by Spiteller's findings that the content of F-acids in plants increases from almost zero at the start of the leaf growing phase to a maximum in July in the Northern Hemisphere and then remains constant until the end of the vegetation period.[7] Radicals can also be generated by invading microorganisms.[7] Phospholipids constitute the outermost layer of a cell. As a consequence they are the first to be exposed to the attack of microorganisms. This mechanical injury can induce a reaction cascade leading to generation of radicals.[7] Once the invader is destroyed, the defence process should cease and as F-acids are present in phospholipids they are ideally placed to halt the progress of lipid peroxidation reactions.[7] Again, this would appear to lend weight to the argument that plants and algae have evolved a biosynthetic pathway to F-acids for defensive purposes. It seems most unlikely that Nature would expend energy on the biosynthesis of a compound that has no function.

4.5 Biosynthesis of F-acids

As mentioned earlier, prior to 1984, it was widely believed that F-acids were biosynthesised by fish. In an interesting series of experiments by Glass in 1984, whereby fish were fed ^{14}C labelled acetate, it was shown that fish incorporated the acetate into the carboxylic side chain through chain elongation but the acetate was not incorporated either into the furan ring or the alkyl side chain,[126] a clear indication that fish do not synthesise either the alkyl side chain or the furan ring. Since feeding experiments are much easier to perform on rats than fish (urine samples are much easier to collect from rats), a further series of experiments were performed once F-acids had been detected in the liver of rats. In an attempt to prove the hypothesis that F-acids are derived from linoleic acid, rats were fed a homolog of linoleic acid but no homologous F-acids were detected in the rats' livers.[127] It was therefore assumed that the F-acids in rats may be derived from their food. This assumption was confirmed by Spiteller in 1989 during an investigation into F-acids in plants.[112] All of the plants and algae investigated were found to contain F-acids. This may explain why fish are more enriched in F-acids compared to mammals, as the marine food chain ultimately depends upon algae and phytoplankton.

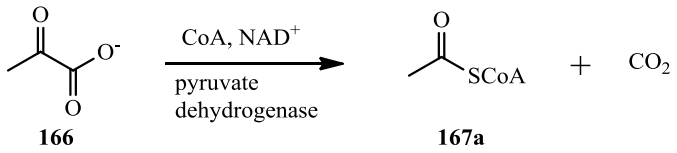
By repeating the labelled feeding experiments on plant cell cultures, it was shown that plants synthesise the basic F-acid skeleton from acetate.[128] However, before describing the biosynthetic route to F-acids from PUFAs, it is worth taking a look at the general biosynthetic pathway of fatty acids. Nature uses a series of enzymatically controlled reactions to build up the carbon chain of fatty acids. One extremely important molecule in the fatty acid biosynthesis is coenzyme A (CoA) **165** which consists of an adenine nucleotide at one end, linked by a 5'-pyrophosphate to pantothenic acid, and then an amino thiol at the other end (Scheme **4.4**).[129]



Scheme 4.4: Structure of coenzyme A.

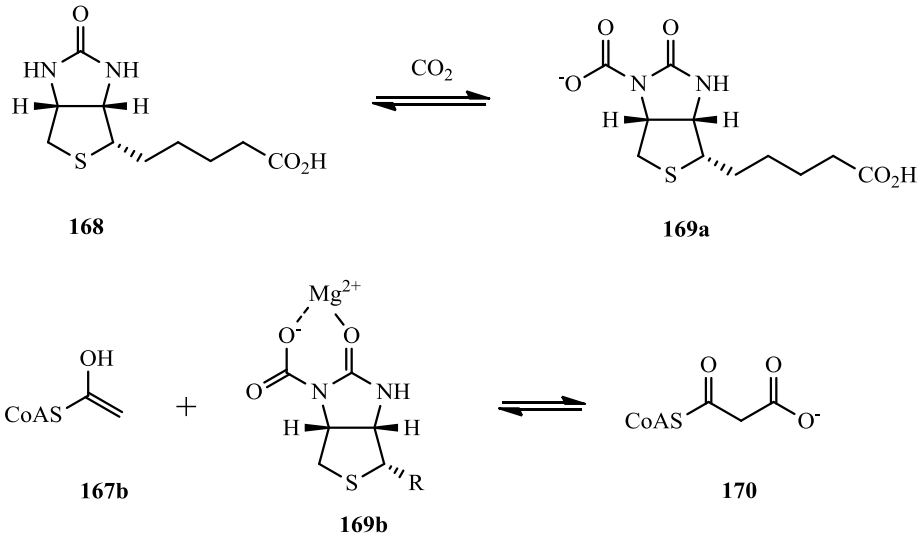
CoA **165** can be converted into acetyl CoA **167a** by the reaction of pyruvate **166** with nicotinamide adenine dinucleotide (NAD^+) and the enzyme, pyruvate dehydrogenase. In this

acetylated form, acetyl CoA **167a** acts as an acetyl transporter in the synthesis of fatty acids (Scheme **4.5**).



Scheme 4.5: Enzyme-controlled formation of acetyl CoA.

It is also required to form malonyl CoA **170** by the addition of CO_2 to acetyl CoA **167a**. CO_2 is carried by another coenzyme, biotin **168**. Biotin **168** contains two fused five-membered heterocyclic rings: a cyclic sulphide with a long chain carboxylic acid for connection to a lysine residue of a protein, and a five-membered cyclic urea. It is the urea moiety that captures and delivers CO_2 to acetyl CoA **167a**. The formation of malonyl CoA **170** can be described as a nucleophilic attack of the enol of acetyl CoA **167b** on the magnesium salt of carboxybiotin **169b** (Scheme **4.6**).

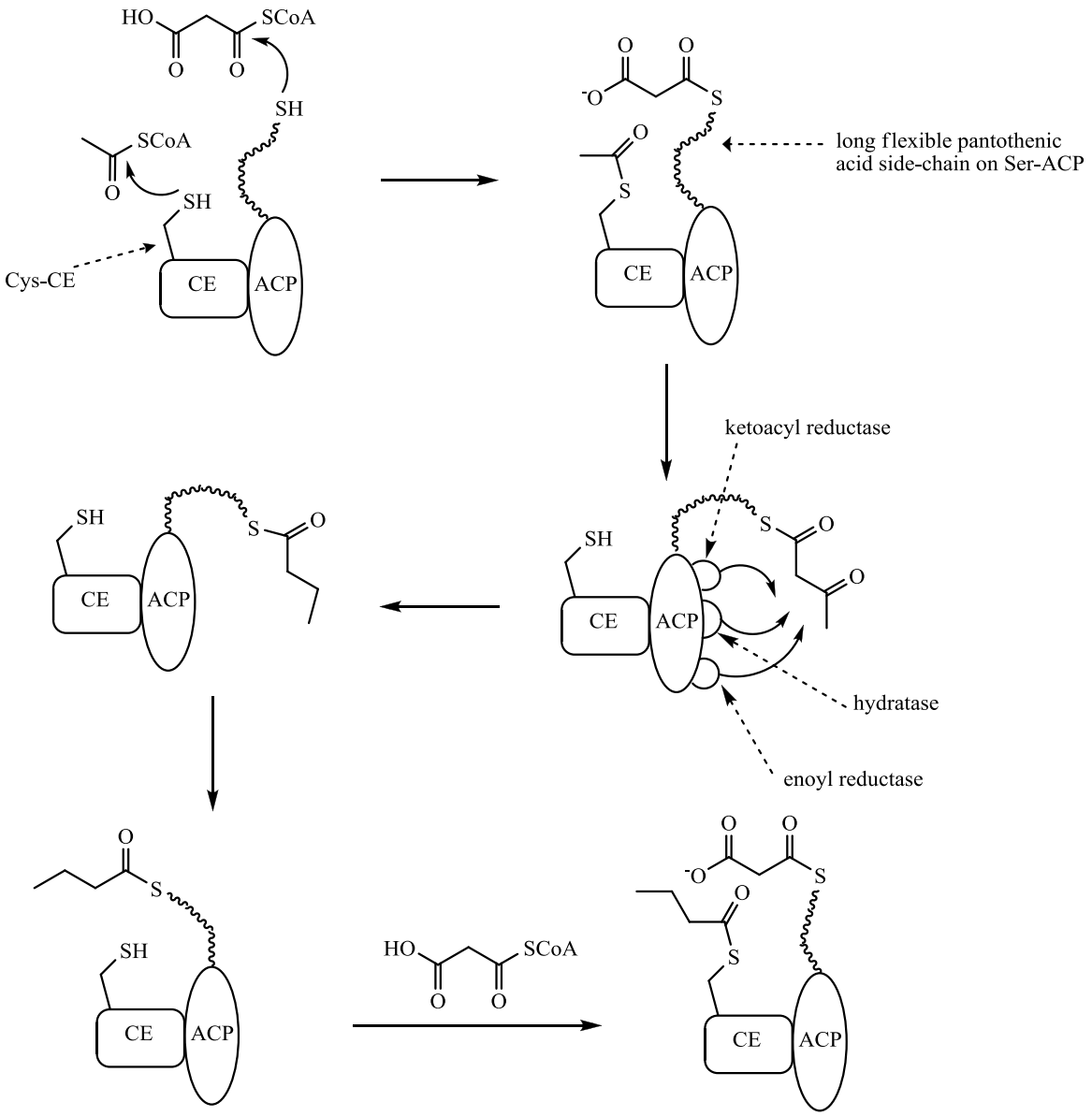


Scheme 4.6: Malonyl CoA generation from acetyl CoA and carboxybiotin.

Fatty acid biosynthesis can be considered as a series of overall Claisen-like condensations between acetyl CoA **167a** and malonyl CoA **170** carried out by a multienzyme dimer. This multienzyme dimer consists of an acyl carrier protein (ACP) and a condensing enzyme (CE). The long side chain of ACP closely resembles CoA **16** and is attached to ACP through a phosphate to a serine residue of ACP. CE contains a cysteine residue for attaching the initial acetyl CoA **167a** in the first step of the synthesis and also for attachment of the growing fatty

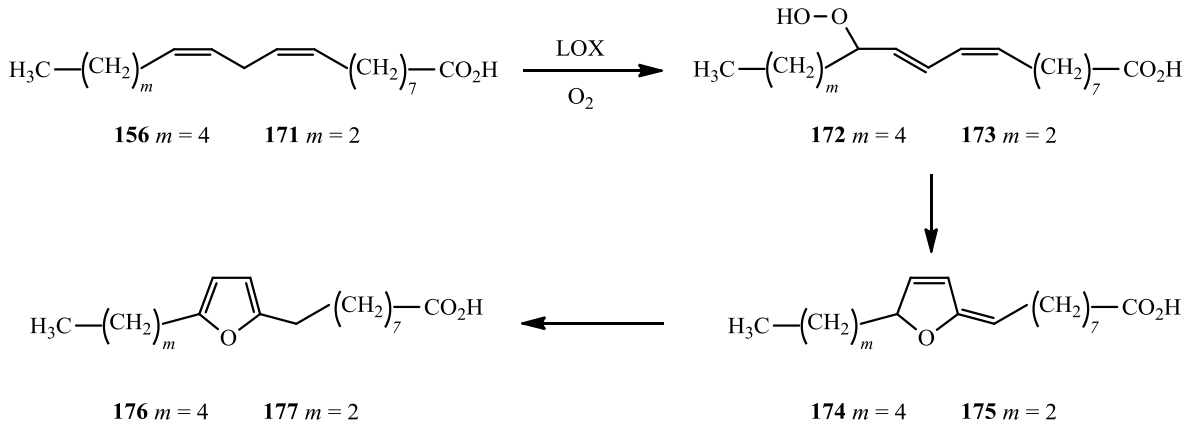
acid chain before hydrolysis of the thioester in the final step to give the completed saturated fatty acid.

The initial step in fatty acid synthesis involves the attachment of acetyl CoA **167a** to the cysteine residue of CE (Cys-CE) along with malonyl CoA **170** attaching to a long pantothenic acid side chain *via* a serine residue of ACP (Ser-ACP). The long flexible side chain of ACP allows the malonyl moiety close enough to react with the acetyl unit on the Cys-CE. There then follows a condensation reaction with release of CO_2 to give a β-diketone. The next step is a series of enzymatically controlled reactions, firstly to reduce the ketone (ketoacyl reductase) followed by dehydration *via* an E1cB mechanism to give the enone (hydratase) and finally reduction of the double bond to generate the saturated side-chain (enoyl reductase). The growing side-chain is then transferred to Cys-CE. Another molecule of malonyl CoA is attached to Ser-ACP and the entire acylation process is ready to be repeated to extend the chain by a further two carbons (Scheme **4.7**).



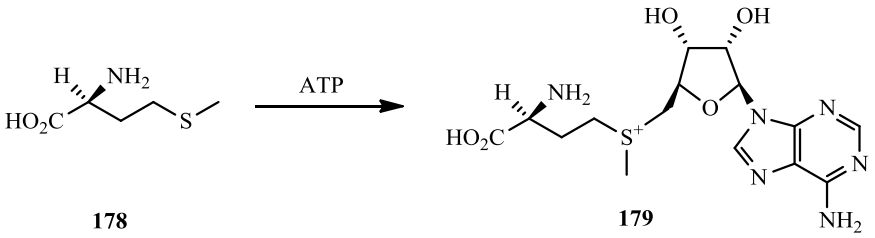
Scheme 4.7: Simplified schematic of fatty acid biosynthesis

It was originally believed that linoleic acid **156** was the precursor of the carbon skeleton of F-acids containing a pentyl side chain, with peroxidation occurring at C-13.[130] F-acids with a propyl side chain were assumed to be derived from linolenic acid with peroxidation at C-12.[130] Using algal cell cultures it was then proven that F-acids containing a pentyl side chain do in fact come from linoleic acid **156** but that F-acids with a propyl side chain originate from 9,12-hexadecadienoic acid **171** and not from linolenic acid.[130] Peroxidation is believed to be initiated from LOX[130] with the singlet oxygen from air[7] (Scheme **4.8**). All other F-acids can be generated by chain elongation using acetate units.



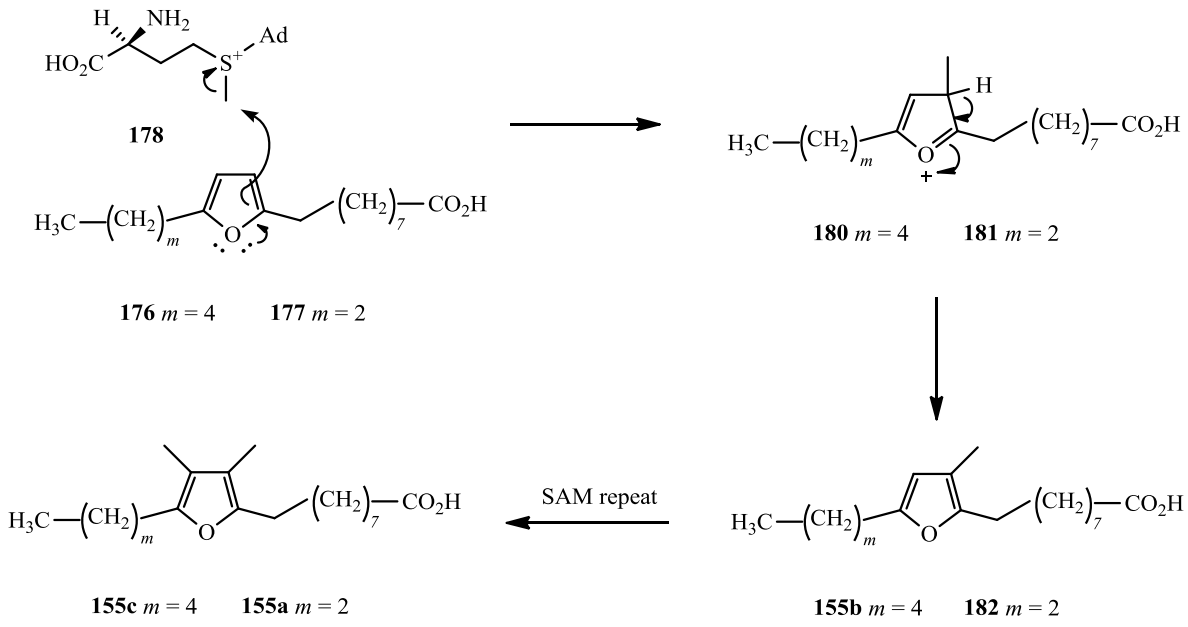
Scheme 4.8: First stage of furan fatty acid biosynthesis

Methyl groups in the β-position of the furan ring are believed to be derived from methionine **178** or, to be more precise, *S*-adenosyl methionine (SAM) **179.**[7] SAM is formed by the reaction of methionine **178** with adenosine triphosphate (ATP). The product, SAM **179**, is a sulfonium salt and is readily attacked by nucleophiles *via* an S_N2 mechanism at the methyl group (Scheme **4.9**).



Scheme 4.9: *S*-adenosyl-methionine (SAM).

Quite how the methyl groups in the β-positions are added is not certain. In Spiteller's excellent review there is no mention of any labelled experiments involving methionine **178** or SAM **179**. However, it would seem quite likely given the well documented role of SAM **179** as a natural methylating agent that electrophilic C-methylation is involved. A proposed mechanism for the addition of a methyl group to the β position is outlined in Scheme **4.10** but it must be stressed that this is purely speculative and does not account for the selectivity shown in the methylation of F-acids.

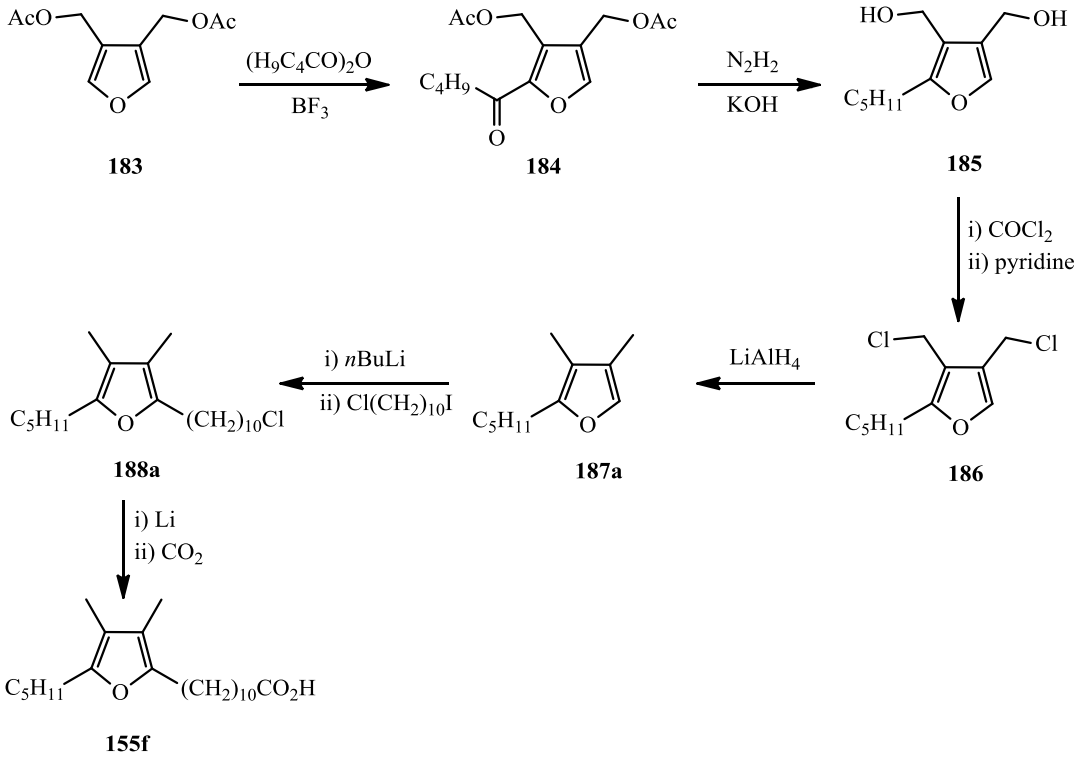


Scheme 4.10: Proposed mechanism for biosynthetic methylation of furan fatty acids.

4.6 Previous Synthetic Routes

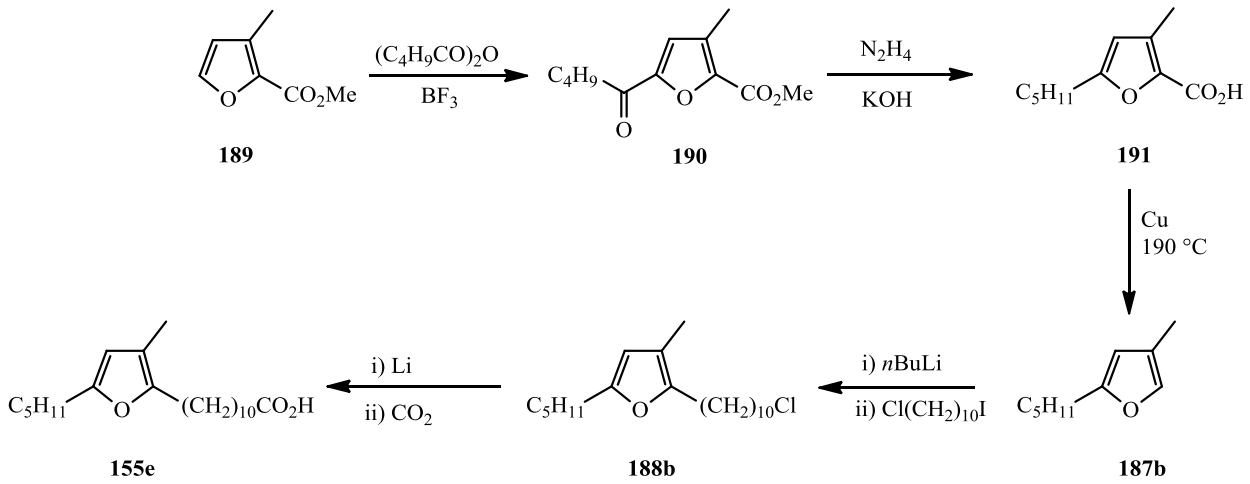
By far the most common F-acid is F_6[7] **155f**, which contains methyl groups at both β positions, a pentyl side chain at one α position and an eleven carbon saturated carboxylic side chain at the other α position. F_6 was first synthesised by Glass *et al* in 1979.[131] In this interesting synthesis, 3,4-bis(acetoxymethyl)furan **183** was chosen as starting material. Friedel-Crafts acylation using valeric acid anhydride and boron trifluoride gave butyl ketone **184**. A Wolff-Kishner reduction with hydrazine followed by simultaneous saponification of the esters at the β positions gave diol **185**. The overall yield for these two combined steps was 60%. This fairly low yield may be due to the acidic conditions of the acylation. Furans are notoriously acid sensitive and will easily ring open in the presence of acids. Boron triflouride has a strong affinity for oxygen and is sold commercially as a complex with tetrahydrofuran so it is easy to imagine how a complex could form with furan itself leading to ring opening. The next step in the Glass synthesis is halogenation of diol **185** followed by lithium aluminium hydride reduction. Glass initially attempted this transformation using both thionyl chloride and oxalyl chloride but without success. However when phosgene was used instead, a satisfactory overall yield of 76% of 3,4-dimethyl-2-pentylfuran **187** (relative to diol **185**) was obtained. It is unclear why halogenation with thionyl chloride and oxalyl chloride failed since these are the standard reagents for such transformations and there are several examples in the literature of halogenation of 3,4-bis(hydroxymethyl)furan.[131-134] The long akyl carboxylic side chain was introduced by lithiation of 3,4-dimethyl-2-pentylfuran **187** at the remaining vacant α-position and subsequent treatment

with 1-chloro-10-iododecane to give homologue **188** with a 58% yield. Finally, metal-halogen exchange of **188** with lithium followed by addition of CO_2 gave the product, F_6 furan fatty acid **155f**, in 32% yield. The overall yield of 8% reflects the difficulty in the synthesis of these natural products (Scheme **4.11**)



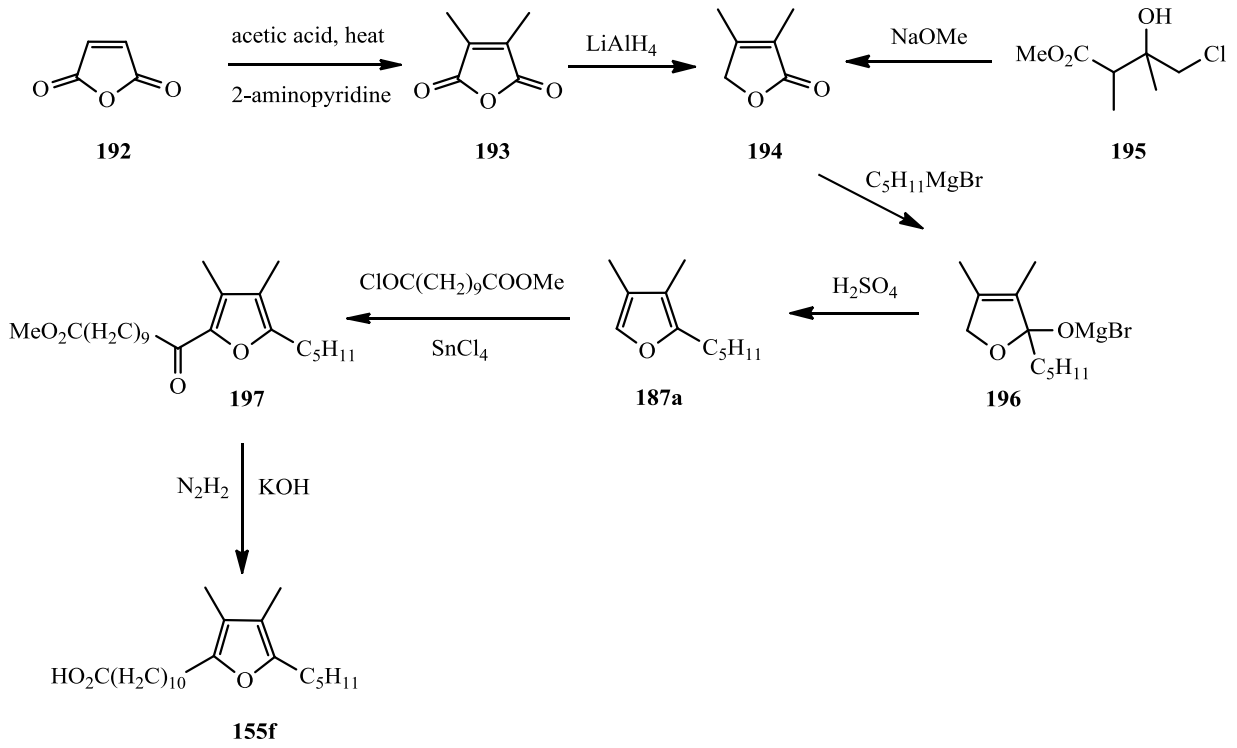
Scheme 4.11: Glass's first synthesis of F_6 furan fatty acid.

A similar synthetic route was taken by Glass to synthesise F_5 but using 3-methyl-2-furoate **189** as starting material in order to provide absolute placement of the methyl group in relation to the alkyl chain when condensing with valeric anhydride to give ketoester **190** with a poor yield of 20%.[131] Ketoester **190** was then reduced and saponified *via* a Wolff-Kishner reduction as in the F_6 synthesis to give the furoic acid **191** in good yield (85%). Glass reported that the presence of quinoline was recommended for the decarboxylation of furanoate but that it did not aid decarboxylation of furoic acid **191** and actually hindered the process by making purification of furan **187b** more difficult. Without quinoline 51% of furan **187b** was distilled from furoic acid **191**. Introduction of the carboxylic alkyl chain was the same as for the synthesis of F_6 with similar yields for the two steps of 51% and 56% respectively, to give an overall yield for F_5 **155e** of just 2% (Scheme **4.12**).



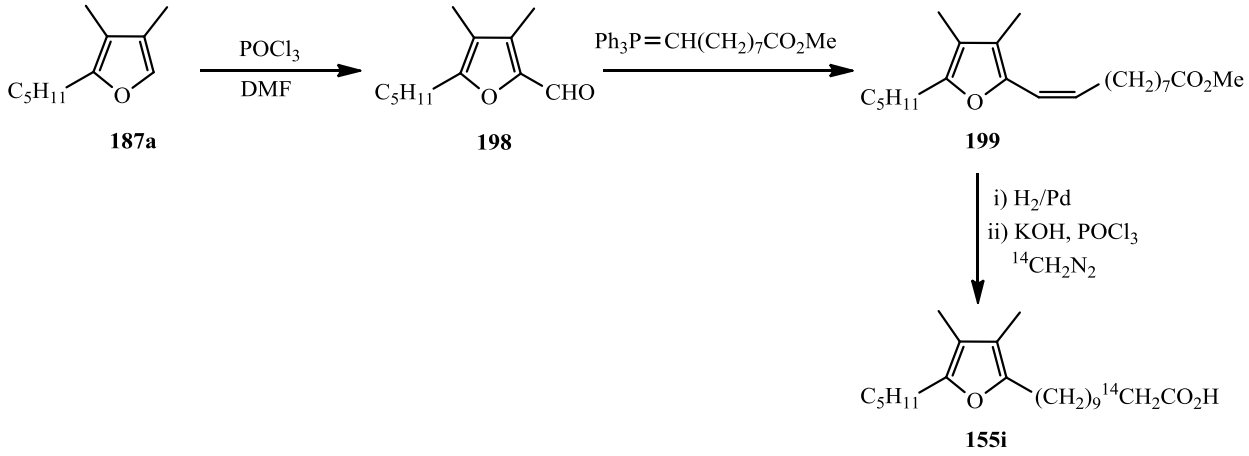
Scheme 4.12: Glass's synthesis of F_5 furan fatty acid.

One of the most difficult aspects of the Glass synthesis was the introduction of the carboxylic side chain. There are limited ways to introduce such a moiety. These days the obvious choices would either be electrophilic aromatic substitution, a metal catalysed coupling reaction or, as in the case of the Glass synthesis, by deprotonation of the furan at the α position followed by addition of an electrophilic analogue of the side chain. In the latter case, the side chain must be introduced as a protected acid. With this in mind, Spiteller developed a slight variation on the Glass synthesis (Scheme **4.11**). Lactone **194** can be generated in two ways: from cyclisation of 4-chloro-3-hydroxy-2,3-dimethylbutanoic acid **195** using sodium methoxide or by lithium aluminium hydride reduction of dimethylmaleic anhydride **193**, itself prepared by heating maleic anhydride **192** in acetic acid. This intriguing transformation was first reported in 1984 by Baumann *et al*[132] but is very poorly represented in the literature and involves decarboxylative dimerization of maleic anhydride **192** to dimethylmaleic anhydride **193** in the presence of 2-aminopyridine. The key intermediate, 3,4-dimethyl-2-pentylfuran **197**, was generated by reaction of the lactone **194** with pentylmagnesium bromide to give **196** followed by an acidic workup. The carboxylic side chain was introduced *via* the acid chloride of the monoester derived from undecanedioic acid using tin(IV) chloride as a catalyst of this Friedel-Crafts acylation. Wolff-Kishner reduction then gave F_6 **155f** (Scheme **4.13**).[136]



Scheme 4.13: Spiteller's synthesis of F_6 furan fatty acid.

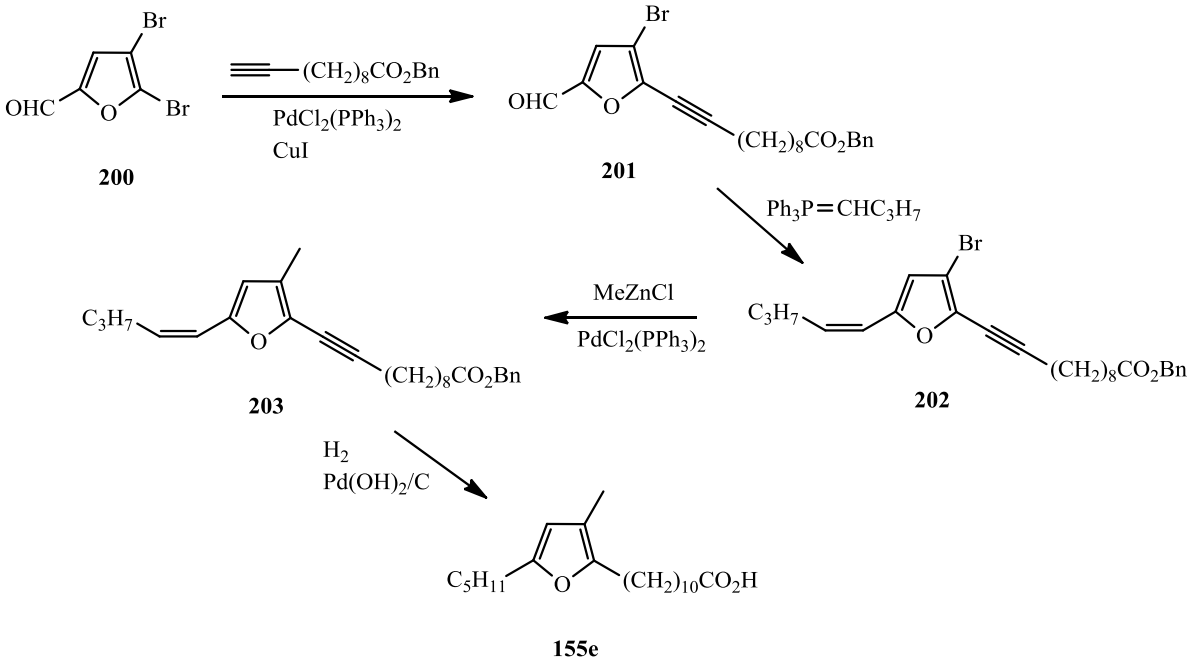
Glass synthesised F_6 labelled with ^{14}C by altering the addition of the carboxylic side chain.[137] An aldehyde moiety was introduced into 3,4-dimethyl-2-pentyl furan **187a** using a Vilsmeier reaction to give aldehyde **198** followed by a Wittig reaction to incorporate the carboxylic side chain (minus one carbon) to give unsaturated ester **199**. Hydrogenation followed by an Arndt-Eistert chain extension using ^{14}C labelled diazomethane gave labelled F_6 **155i** (Scheme **4.14**).



Scheme 4.14: Glass's synthesis of C^{14} labelled F_6 furan fatty acid.

In 1998, Bach published a synthesis that made substantial improvements on Glass's F_5 version. Bach utilised the variation in reactivity of bromine substituents on the furan ring to

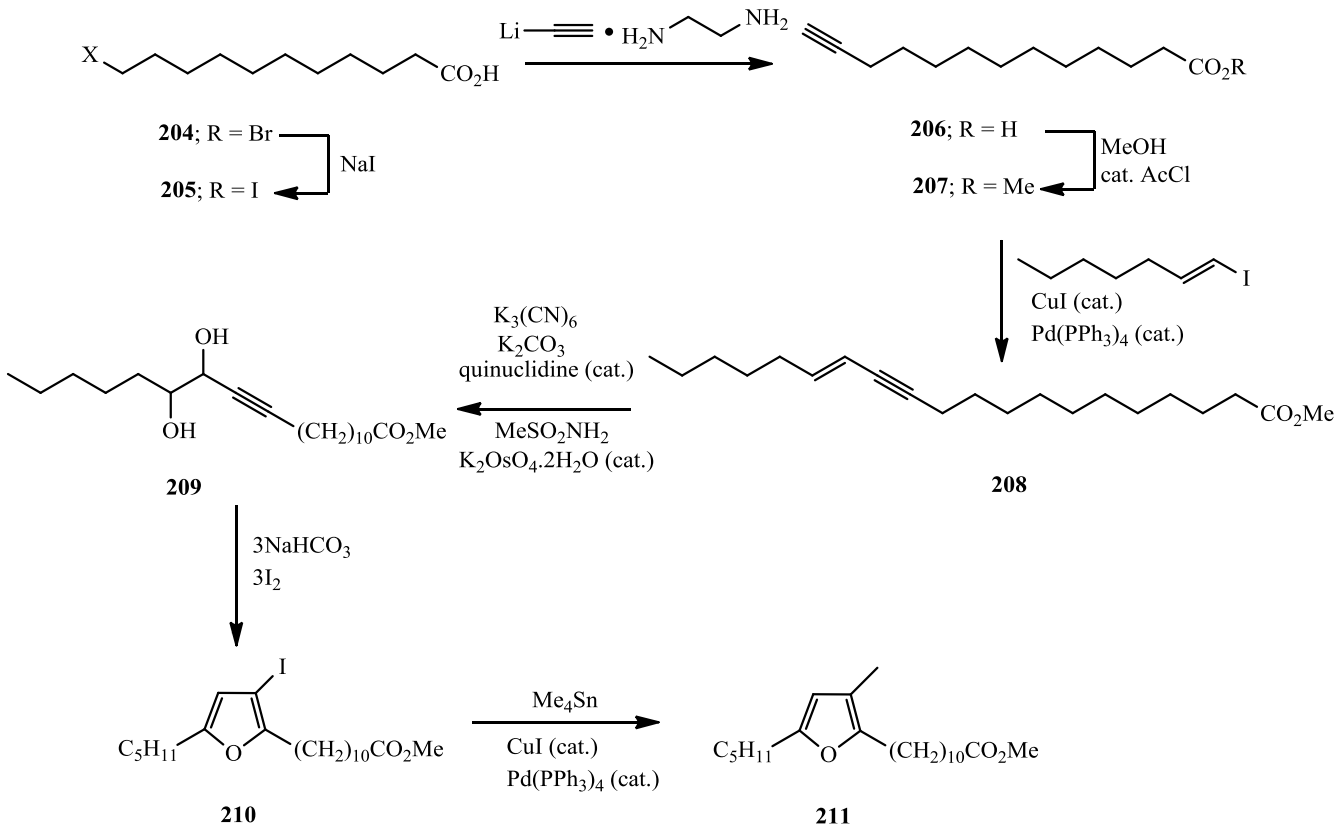
regioselectively couple the carboxylic side chain, with the acid group protected as its benzyl ester, to position 5 of 4,5-dibromofurfural **200** using a palladium(0)-catalysed Sonogashira reaction which gave bromofurfural **201** in 61% yield. This was followed by a Wittig reaction to bring in the pentyl side chain before a second palladium(0)-catalysed reaction using an excess of methylzinc chloride gave the unsaturated furyl benzoate **203** in a combined yield of 64% for the two steps. The real beauty of this sequence lies in the final step: hydrogenation of the unsaturated bonds and simultaneous hydrogenolysis of the benzyl ester in a single operation to give F_5 **155e** in a much improved overall yield of 30% (Scheme **4.15**).[138]



Scheme 4.15: Bach's synthesis of F_6 furan fatty acid.

All of the above syntheses follow a similar pattern. The furan core is either present in the starting material or it is formed very early on in the synthesis and the substituents are added later. An alternative approach is to add the substituents required in the final F-acid before cyclisation to form the furan. With respect to the alkyl and protected carboxylic chains, these are fairly straightforward procedures. However, the degree of substitution of the furan after cyclisation is dependent upon the method of cyclisation. As mentioned previously, the Knight group have been using silver nitrate to effect cyclisation of 3-alkyne-1,2-diols **40**. This methodology is suitable for 2,4- and 2,5-disubstituted and 2,3,5-trisubstituted furans. For tetrasubstituted furans such as F_6, the older iodocyclisation method would be required. This was the route taken in Knight's first total syntheses of F_5 and F_6.[139] This first attempt to synthesise F_5 began by converting commercially available 11-bromoundecanoic acid **204** into the iodide **205** using a Finkelstein

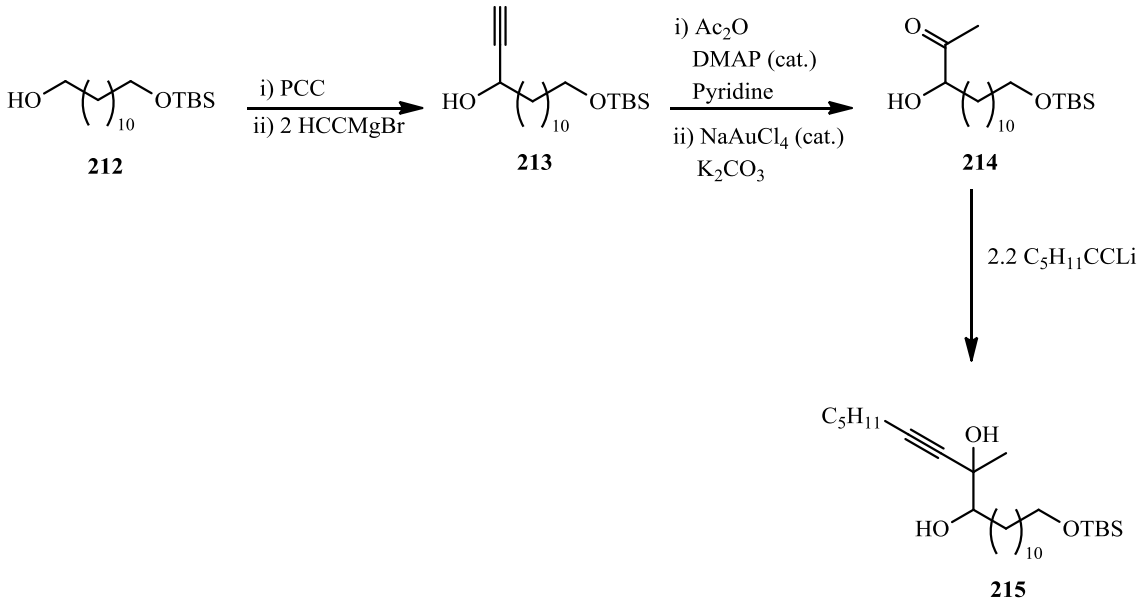
reaction. This step was necessary as the bromide was surprisingly incompatible with the next step in the synthesis, coupling with lithium acetylide-ethylenediamine complex (LAEDA). The alkynoic acid **206** thus generated in 85% yield was then esterified using acidic methanol to give the methyl ester **207.** Sonogashira coupling of this ester **207** with (*E*)-1-iodo-hept-1-ene gave (*E*)-enyne **208** in 74% yield. Chiral diol was not required so a regioselective Sharpless-style *bis*-hydroxylation of the alkene was carried out using the achiral Warren procedure.[140] This gave an excellent 86% yield of alkyne diol **209**. Iodocyclisation of diol **209** did not proceed smoothly however. The standard conditions of three equivalents each of iodine and potassium carbonate in either dry acetonitrile or dichloromethane gave very poor yields of 10% at best of the desired iodofuran **210**. Owing to the fatty nature of the diol **209** it was considered possible that the long, straight hydrocarbon chain was coiling up on itself in solution and thus preventing cyclisation. After a series of solvent studies it was found, perhaps surprisingly, that the reaction in ethyl acetate was both very fast and clean: work up after one hour at ambient temperature gave an excellent 93% yield of iodofuran **210** (Scheme **4.16**).



Scheme 4.16: Knight's first synthesis of F_5 furan fatty acid.

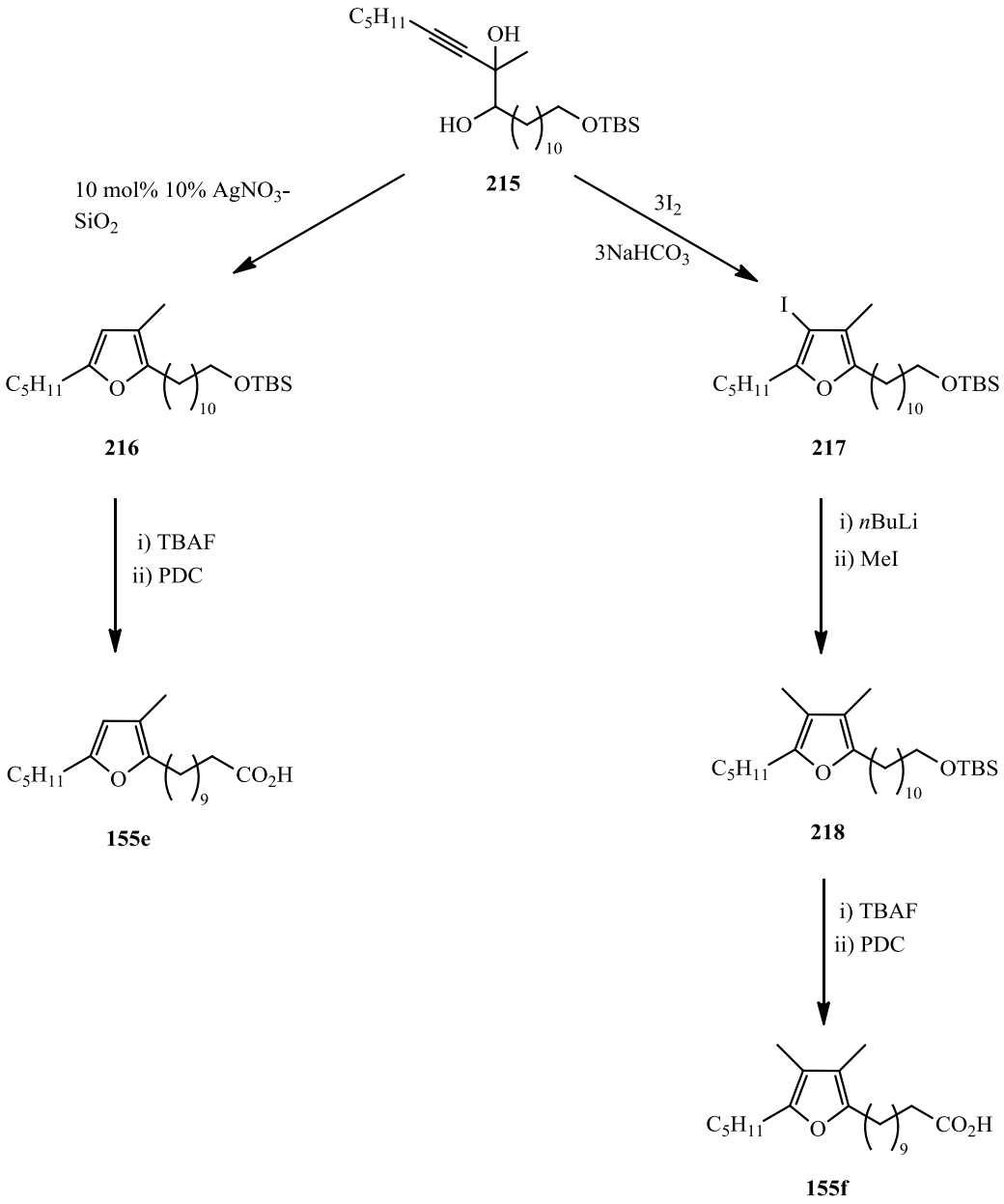
The final step of the synthesis involved a Stille coupling reaction to produce the furyl methyl ester **211**. However this proved to be rather poor yielding. A yield of 57% was recorded but there was also a significant amount of protonated by-product rather than methylated product which was difficult to separate chromatographically. The presence of the ester group prohibited the more efficient way to effect this transformation, namely halogen-metal exchange followed by reaction with iodomethane. With this in mind a modified approach was attempted. Knight also chose to use this opportunity to incorporate the newer silver(I)-catalysed cyclisation methodology. F_5 furan fatty acid is ideally set up for this silver(I) method as it is a 2,3,5-trisubstituted furan and so the methyl group can be incorporated prior to cyclisation and obviates the potentially tricky methylation step. Since F_5 and F_6 are structurally very similar it should be possible to develop a synthetic route to both that deviates only in the cyclisation step: silver(I) catalysed cyclisation for F_5 and iodocyclisation for F_6. Using a substrate bereft of the ester functionality would also permit methylation using halogen-metal exchange at low temperature in the F_6 route.

The routes to the F-acids F_5 and F_6 diverge after the synthesis of diol **215**. The first step in the route to this key precursor was PCC oxidation of the mono-TBS protected 1,12-dodecanediol **212**, followed by condensation with ethynylmagnesium bromide to give alkynol **213**. The alcohol group was temporarily protected as the acetate before treatment with catalytic sodium gold(III) chloride in refluxing methanol to hydrate the triple bond followed by basic work up with potassium carbonate to give hydroxy ketone **214**. Two equivalents of lithio-heptyne were used in the next step on the grounds of atom efficiency. Instead of alcohol protection then deprotection as well as all the solvents required during the reactions and work up, it was deemed more efficient to use an additional equivalent of lithio-heptyne. The equivalent of 1-heptyne present in the final product was easily removed under reduced pressure. The diol **215** was thus generated in excellent overall yield of 53% in five steps (Scheme **4.17**)



Scheme 4.17: First stage of Knight's first synthesis of F_6 furan fatty acid.

The two syntheses diverged after formation of the diol **215**. For the formation of F_5 **155e**, the diol **215** was treated with silver(I) nitrate on silica gel and gave a quantitative yield of TBS-protected furan fatty alcohol **216**. Deprotection followed by oxidation gave F_5 furan fatty acid **155e** in good overall yield of 39% in eight steps. For the synthesis of F_6 **155f**, diol **215** was cyclised using the iodocyclisation methodology mentioned earlier using ethyl acetate as the solvent to give iodofuran **217**. A halogen-metal exchange was followed immediately by reaction with methyl iodide which gave TBS-protected furan fatty alcohol **218**. As in the F_5 route, this was then deprotected and oxidised to give F_6 furan fatty acid **155f** in an overall yield of 34% in nine steps (Scheme **4.18**). With respect to the synthesis of F_6 in particular, this represents a substantial improvement on Glass's and Spiteller's syntheses while the overall yield of F_5 is also an improvement, albeit not as great as for F_6, on the route devised by Bach. The yields of both F-acids, despite being an improvement on previous syntheses, were still deemed unsatisfactory although with hindsight the yields may have actually been higher but due to the instability of the F-acids an accurate measurement can prove difficult. This problem will be mentioned in more detail later.

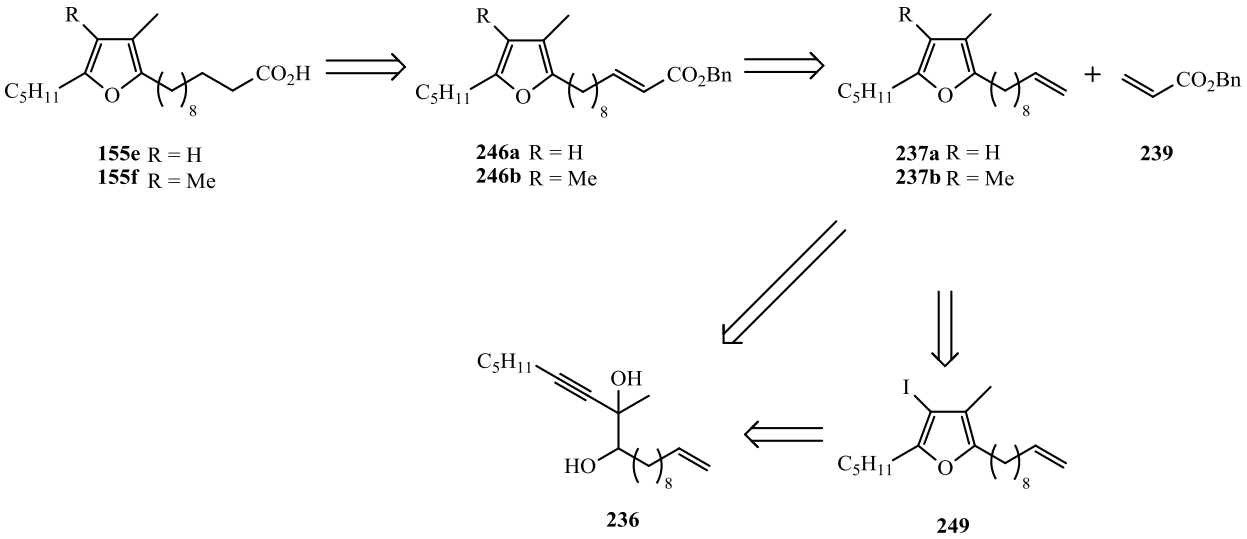


Scheme 4.18: Second stage of Knights synthesis of F_5 and F_6 furan fatty acids.

4.7 Retrosynthesis of the Furan Fatty Acids F_5 and F_6

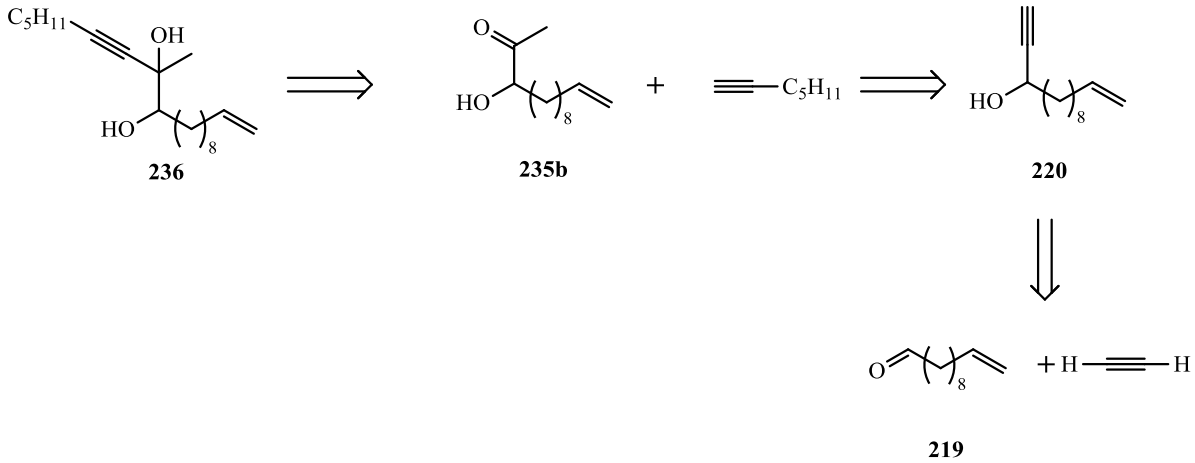
With the knowledge gained from previous syntheses by Knight and also incorporating some of the methodology used by Bach, a retrosynthetic analysis was undertaken for both F_5 **155e** and F_6 **155f** fatty acids. A similar approach was taken to the previous Knight synthesis whereby the two furan fatty acids would have identical synthetic pathways prior to the cyclisation step. As mentioned earlier, one of the key difficulties in previous attempts to synthesise furan fatty acids has been the introduction of the carboxylic side chain. It is clear that this acidic side chain needs to be introduced as a protected derivative. The carboxylic acid functionality can be introduced

very late in the synthesis *via* cross metathesis of furyl alkenes **237a** and **237b** with benzyl acrylate **239** thereby allowing generation of the acids **155e** and **155f** by simultaneous alkene hydrogenation and ester hydrogenolysis of the benzyl esters **246a** and **246b**. Furyl alkene **237a** can be disconnected to 3-alkyne-1,2-diol **236** while furyl alkene **237b** needs to be disconnected to iodofuran **249** before disconnection to the same 3-alkyne-1,2-diol **236** (Scheme **4.19**).



Scheme 4.19: Retrosynthetic analysis of F_5 and F_6 furan fatty acids.

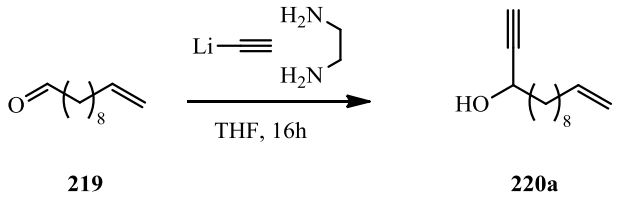
3-Alkyne-1,2-diol **236** can then be disconnected to hydroxy ketone **235b** and 1-heptyne. Functional group interconversion of the methyl ketone function to a terminal alkyne gives alkynol **220**. Finally, disconnecting the alkyne moiety from the bulk of the molecule gives the convenient and cheap commercially available starting material undecylenic aldehyde **219** and acetylene (Scheme **4.20**).



Scheme 4.20: Retrosynthetic analysis of diol precursor to F_5 and F_6 furan fatty acids.

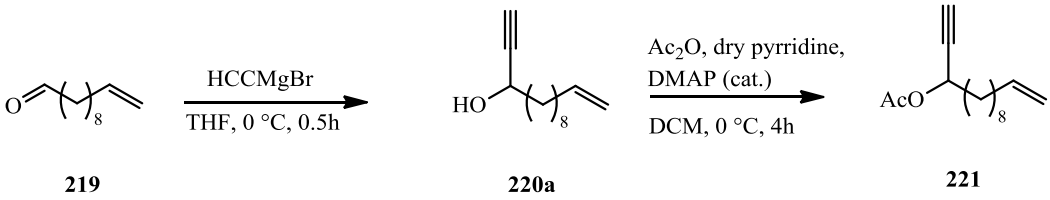
4.8 Synthesis of 3-Alkyne-1,2-diol Precursor to F_5 and F_6 Furan Fatty Acids

The first step in the forward synthesis towards the common precursor to both F-acids, 3-alkyne-1,2-diol **223**, is the addition of acetylene to undecylenic aldehyde **219**. Initial attempts to effect this transformation were attempted using LAEDA however this proved to be inefficient with yields often less than 60% and containing many unidentified by-products (Scheme **4.21**).



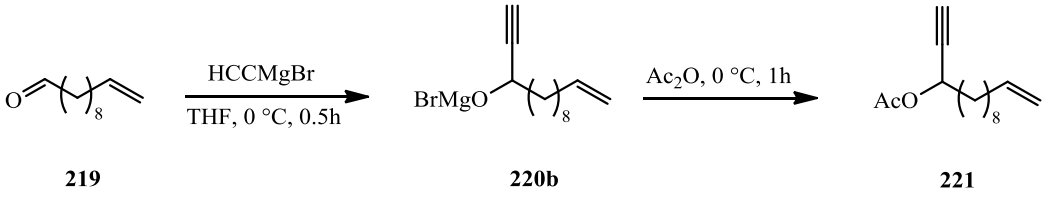
Scheme 4.21: LAEDA acetylation of undecylenic aldehyde.

Switching to commercial ethynylmagnesium bromide gave much improved yields with little, if any, by-products. After optimisation, a 98% yield of alkynol **220a** was recorded. After an aqueous workup, alkynol **220a** was then acetylated using a standard 4-dimethylaminopyridine (DMAP)-catalysed method to give acetate **221** in an 84% yield (Scheme **4.22**).



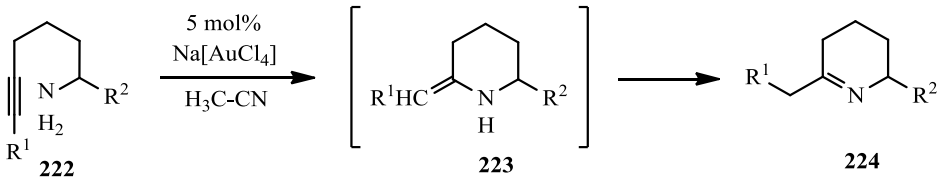
Scheme 4.22: Acetylation of undecylenic aldehyde.

Initially, the reaction was subjected to an aqueous work-up after the Grignard addition, followed by formation of the acetate as described above. However, in order to improve efficiency, on the grounds that less compound handling generally helps to minimise losses, it seemed prudent to carry out the acetylation by direct addition of acetic anhydride to the propargylic alcohol salt **220b**. Happily, this gave the acetate **221** routinely in 92% yield for the two combined steps (Scheme **4.23**).



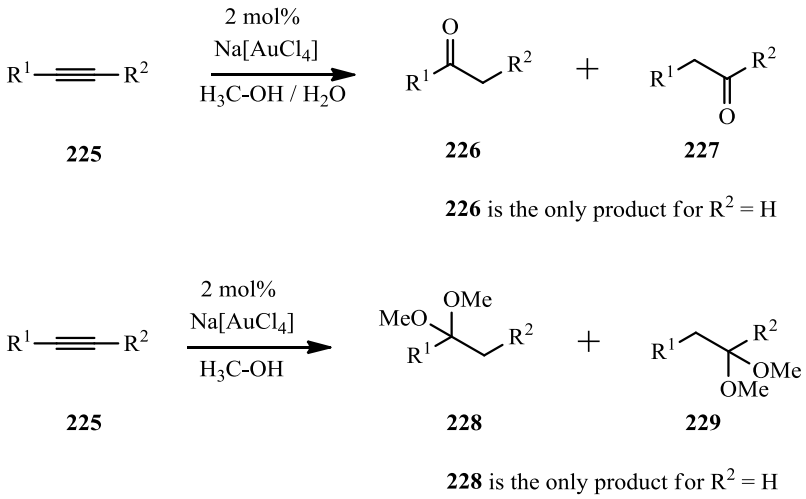
Scheme 4.23: Optimised acetylation of undecylenic aldehyde.

Hydration of the alkyne function can be achieved using several transition metal catalysts.[141] The classic approach utilises mercury(II) salts but also requires strongly acidic conditions which might well be incompatible with the terminal alkene moiety of acetate **221**. In 1982 however, Regen[142] reported that phenylmercuric hydroxide was highly selective for the hydration of non-conjugated terminal alkynes. Reasonable yields of up to 65% of the corresponding methyl ketone were recorded with the advantage that the reaction does not require acidic conditions although it does require stoichiometric amounts of mercury. Palladium(II) salts have also been used with varying degrees of success[143-145] whilst Zeise-type platinum compounds have also been utilised.[146] In 1987, Utimoto compared the effectiveness of palladium(II) and gold(III) catalysts for the intramolecular nucleophilic addition of the amino group in **222** to the alkyne function in **222**.[147] Utimoto's group found that 5 mol% palladium(II)-complexes at 97 °C gave a 70% yield after 20 hours while 5 mol% sodium gold chloride ($NaAuCl_4$) delivered a quantitative yield after just 12 hours at ambient temperature (Scheme **4.24**)



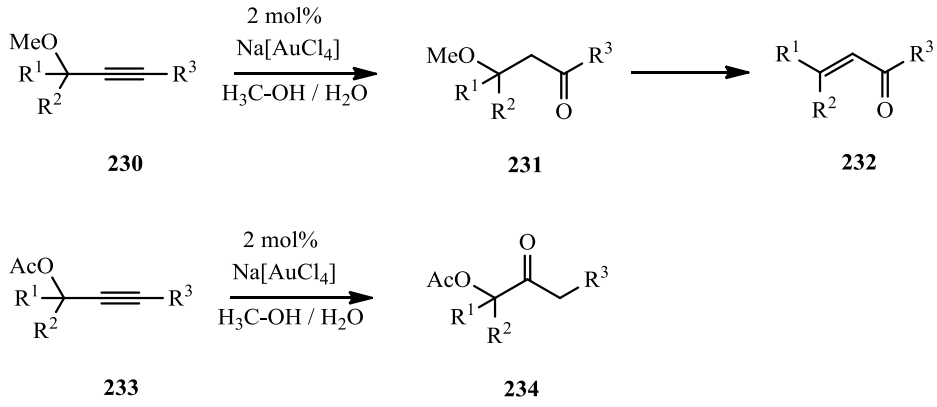
Scheme 4.24: Utimoto's gold(III)-catalysed intramolecular addition of an amino group to an alkyne.

With this in mind, Utimoto investigated whether weaker nucleophiles would add to alkynes in the presence of gold catalysts. Using 2 mol% $NaAuCl_4$ and aqueous methanol, he found that simple terminal alkynes were converted into the corresponding methyl ketone in just one hour in excess of 90% yield. Internal alkynes reacted slowly and delivered a mixture of isomers. Changing the solvent to pure methanol resulted in the formation of the methylketal in >80% yield after one hour whilst internal acetylenes again reacted slowly and gave a mixture of isomers This excellent reaction is an interesting and useful synthetic equivalent to the Wacker oxidation of olefins to produce ketones[148] since *in situ* reoxidation of the catalyst is not necessary[149] (Scheme **4.25**).



Scheme 4.25: Gold(III)-catalysed addition of oxygen nucleophiles to alkynes.

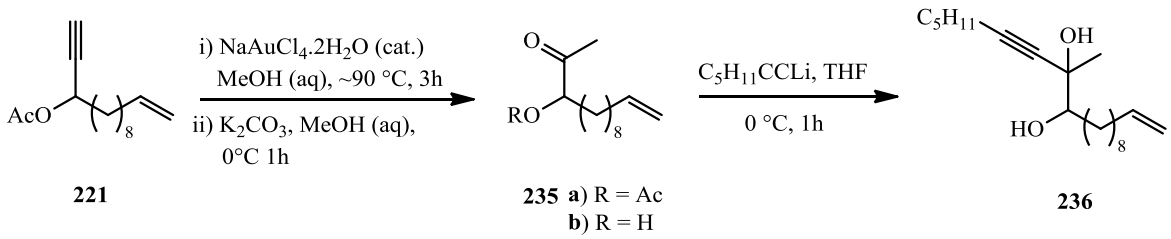
The reaction is not without its drawbacks. Utimoto stated that while a terminal alkyne with a remote hydroxyl group underwent smooth transition to the corresponding ketone, the reaction of a terminal alkyne bearing a propargylic hydroxyl group proceeded sluggishly. Fortunately, protection of the hydroxyl group solved this problem. Furthermore, the choice of protecting group also directs selectivity. Ether protecting groups direct the nucleophile to the remote carbon with the alcohol eliminating to give the enone **232** while ester protecting groups direct the nucleophile to the adjacent carbon to form the *O*-acetyl acyloin **234**. Formation of enone **232** can be considered a non-acidic equivalent of the Meyer-Schuster[150] rearrangement of propargylic alcohols[151] (Scheme **4.26**).



Scheme 4.26: Gold(III)-catalysed hydration of protected propargylic alcohols.

Hydration of acetate **221** using Utimoto's procedure proved to be rather sensitive to the precise conditions used. Initial attempts using gold(III) chloride, rather than the sodium gold chloride used by Utimoto, gave disappointing yields of 42%. Results improved after switching to the catalyst used by Utimoto but still did not equal those reported. It became apparent after several

attempts that it was vital to use distilled water when preparing the aqueous methanol solvent as well as stopping the gold-catalysed hydration after three hours. Aqueous work up followed by hydrolysis of the acetoxy-ketone **235a** delivered excellent yields of the acyloin **235b**. In an attempt to make the reaction 'greener', hydrolysis of the acetoxy-ketone was attempted without aqueous workup of the gold-catalysed hydration. Disappointingly, this proved unsuccessful. After the addition of potassium carbonate to the reaction mixture a strong reddish-purple colour was observed, which bore a resemblance to Faraday's gold colloids, but gave poor yields that, although often containing large quantities of acetoxy-ketone also were contaminated with unknown by-products. For optimum yields, the hydrolysis of the acetoxy-ketone **235a** needs to be carried out at 0 °C rather than at ambient temperature following aqueous work up of the gold-catalysed hydration. The final step in the synthesis of the alkyne-1,2-diol **236** precursor was the addition of just over two equivalents of heptynyl lithium to acyloin **235b** (Scheme **4.27**).



221 **235** **a**) R = Ac **b**) R = H **236**

Scheme 4.27: Optimised route to 3-alkyne-1,2-diol from acetyl-protected propargylic alcohol.

The use of 2.2 equivalents of heptynyl lithium was deemed to be greener and more efficient in all aspects than alcohol protection (for example using TBDMS), condensation and finally deprotection. To illustrate the effectiveness and efficiency of such an approach, consider the following breakdown of costs. Although financially the 'green' cost of such an approach cannot be easily quantified, the impact on the environment must be considered. In the comparison below the cost per unit is based upon prices provided by Sigma Aldrich in 2011/2012. Solvent prices are approximate. Cost for saturated ammonium chloride is based on the solubility of ammonium chloride in water at 20 °C to be 372 g L^{-1}.

For a reaction on a scale of 10.0 mmol acyloin **235b**:

Reagent/Solvent	Number of equivalents	Amount	Cost per unit	Total
1-Heptyne	2.2	2.88 ml	£1.59/ml	£4.59
n-BuLi	2.25	9.00 ml	£0.18/ml	£1.62
THF		100 ml	£0.03/ml	£3.00
Ethyl acetate		75 ml	£0.02/ml	£1.50
Ammonium chloride solution		25 ml	£0.01/ml	£0.25
				£10.96

Table 4.2: Approximate cost for preparation of 3-alkyne-1,2-diol from acetate 221 using 2.2 eq lithioheptyne.

To perform the same conversion but using the protection, condensation and deprotection protocol, the alcohol first needs to be protected using a suitable protecting group. An example would be the commonly used silyl chloride, *tert*-butyldimethylsilyl chloride, to protect the alcohol as a silyl ether.

Reagent/Solvent	Number of equivalents	Amount	Cost per unit	Total
TBDMS-Cl	1.05	1.58 g	£1.72/g	£2.71
Imidazole	1.10	0.75 g	£0.25/g	£0.18
DCM		200 ml	£0.03/ml	£6.00
Ammonium chloride solution		600 ml	£0.01/ml	£6.00
				£14.89

Table 4.3: Approximate cost for silyl-protecting acyloin 235b.

This would then be followed by the reaction in scheme **4.27** using just one equivalent of lithioheptyne.

Reagent/Solvent	Number of equivalents	Amount	Cost per unit	Total
1-Heptyne	1.0	1.30 ml	£1.59/ml	£2.09
n-BuLi	1.05	4.20 ml	£0.18/ml	£0.76
THF		100 ml	£0.03/ml	£3.00
Ethyl acetate		75 ml	£0.02/ml	£1.50
Ammonium chloride solution		25 ml	£0.01/ml	£0.25
				£7.60

Table 4.4: Approximate cost for addition of lithioheptyne to a silyl-protected alcohol to form 3-alkyne-1,2-diol.

Finally, to form 3-alkyne-1,2-diol **236**, the silyl protecting group would need to be removed using a standard tetra *n*-butylammonium fluoride (TBAF) method.

Reagent/Solvent	Number of equivalents	Amount	Cost per unit	Total
TBAF	1.2	12 ml	£0.37/ml	£4.44
THF	2.25	100 ml	£0.03/ml	£3.00
				£7.44

Table 4.5:Approximate cost for silyl deprotection.

The total approximate cost of following a protection, condensation and deprotection route would be £14.89 + £7.60 + £7.44 = £29.93. This is in stark contrast to the approximate total when using an excess of lithioheptyne of £10.96. Obviously this is a simple approximation but it clearly illustrates the financial value to such a methodology. On top of the financial economy and time efficiency of this route are the benefits of a greater yield than can be expected if using the protection/deprotection method and also the impact upon the environment by using far less solvent. The use of "atom efficiency" or "atom economy" is one way of attempting to quantify the green benefits of such an approach.

Atom economy can be expressed as:

$$\text{Atom economy} = \frac{\text{molecular weight of desired product}}{\text{molecular weight of all reactants}} \times 100$$

Equation 4.2: Calculation of atom economy.

For the condensation reaction in scheme **4.27** using 2.2 equivalents of lithioheptyne, the atom economy is:

$$\text{Atom economy} = \frac{MW_{\text{product}}}{MW_{\text{acyloin xx}} + 2.2 \times MW_{\text{lithioheptyne}}} \times 100$$

Equation 4.3: Calculation of atom economy for condensation reaction of acyloin xx with 2.2 equivalents of lithioheptyne.

This compares extremely favourably with the atom economy of the protection/condensation/deprotection methodology.

$$\text{Atom economy} = \frac{MW_{\text{product}}}{MW_{\text{acyloin xx}} + 2.2 \times MW_{\text{lithioheptyne}} + 2.2 \times MW_{\text{TBDMS-Cl}}} \times 100$$

Equation 4.4: Calculation of atom economy for protection/condensation/deprotection methodology using TBDMS-Cl as protecting group.

Of course, in the research laboratory and on such a small scale, the excess heptyne generated as a by-product was allowed to escape. However, on an industrial scale, excess heptyne could easily be captured and recycled thereby further enhancing the green aspect of this, at first glance, seemingly wasteful method The atom economy would be considerably improved if an equivalent of heptyne could be recycled.

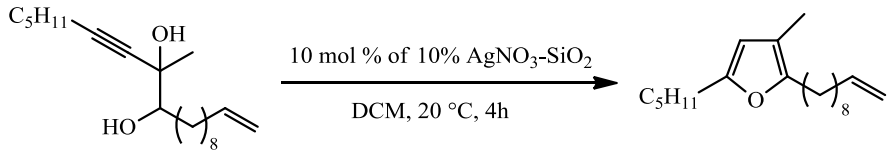
$$\text{Atom economy} = \frac{MW_{\text{product}}}{MW_{\text{acyloin xx}} + 1.2 \times MW_{\text{lithioheptyne}} + 2.2 \times MW_{\text{TBDMS-Cl}}} \times 100$$

Equation 4.5: Calculation of atom economy including capture of excess heptyne.

4.9 Synthesis of F_5 Furan Fatty Acid

At this stage, the synthetic routes to F_5 **155e** and F_6 **155f** diverge: for the former, a silver(I) catalysed cyclisation of diol **236**, and for the latter, an iodocyclisation to form the furan core of F_6. The synthesis of F_5 furan fatty acid **155e** will be discussed in the forthcoming section followed by the iodocylisation and subsequent steps in the synthesis of F_6 furan fatty acid **155f**.

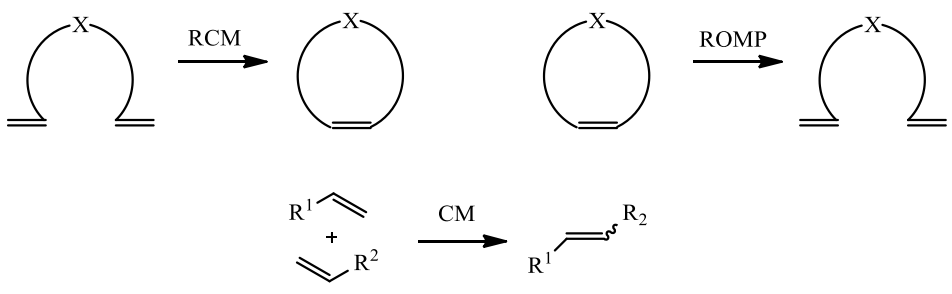
As has been mentioned previously, the silver(I) catalysed method gives excellent, usually quantitative yields when cyclising 3-alkyne-1,2-diols so it was with no great surprise that the F_5 furan precursor **237a** was formed in quantitative yield upon treatment with the standard silver(I) cyclisation conditions (Scheme **4.28**). As can be seen from Spectrum **4.1** this reaction is exceptionally clean with no purification required.



236 **237a**

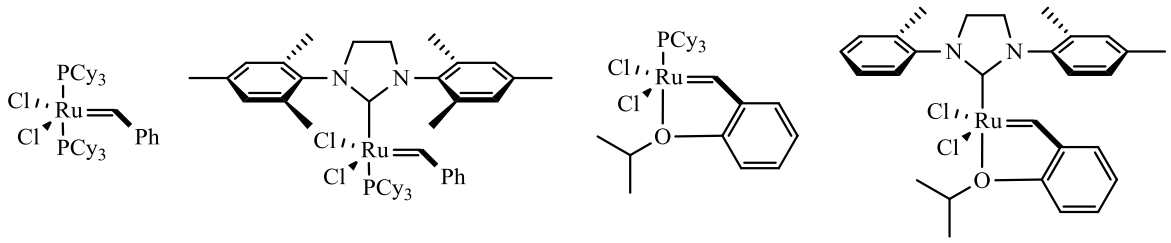
Scheme 4.28: Silver(I)-catalysed cyclisation of 3-alkyne-1,2-diol.

The final step in the synthesis of F_5 was the introduction of the carboxylic acid function. This was originally intended to be introduced in a protected form as benzyl acrylate *via* a cross metathesis (CM) reaction using Grubbs Mark II catalyst (G-II),[152] with the intention of subjecting the metathesis product to a hydrogenation to simultaneously saturate the double bond and deprotect the acid in one step to yield the F-acid. There are, in fact, several types of metathesis reaction with cross metathesis being just one example. The three most important sub types of olefin metathesis are ring-opening metathesis polymerisation (ROMP), ring-closing metathesis (RCM) and cross metathesis (Scheme **4.29**).



Scheme 4.29: Example of olefin metathesis.

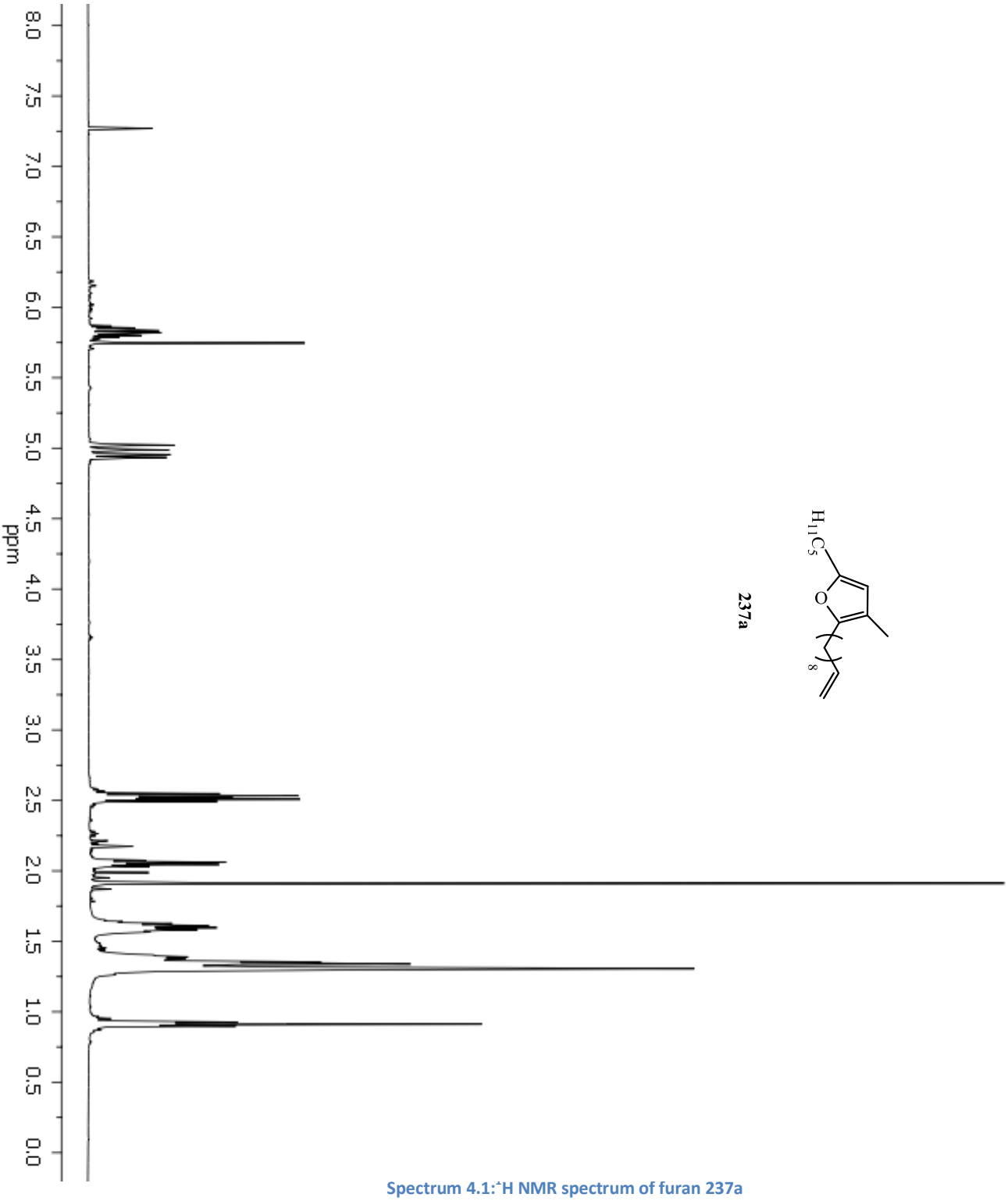
The driving force behind RCM is mostly entropic since one substrate molecule gives rise to two product molecules and since the small molecules released are volatile, if not gaseous, RCM is virtually irreversible and can be driven to completion. ROMP, on the other hand is driven by the ring-strain release upon forming the polymerised products. This ring-strain release also determines the irreversible nature of such a reaction as the pathway back to the cyclic compound has to overcome a large thermodynamic barrier. Cross metathesis is the more difficult of the common metathesis type reactions due to the fact that there are no such driving forces as in RCM and ROMP. There are many variations of Grubbs catalyst, four of the more common are shown in Scheme **4.30**. For more information see the excellent review by Vougioukalakis and Grubbs.[153b]



Grubbs Mk I (G-I) | Grubbs Mk II (G-II) | Grubbs-Hovayda Mk I (G-H I) | Grubbs-Hovayda Mk II (G-H II)

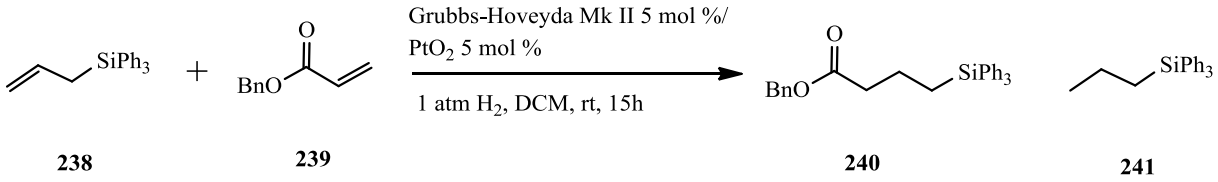
Scheme 4.30: 1st and 2nd generation of Grubbs and Grubbs-Hovayda catalysts.

Surprisingly, the first attempts to perform the metathesis using benzyl acrylate and G-II proved to be completely unsuccessful, with no trace of any metathesis product being observed. After this initial disappointment and in order to conserve the supply of F_5 precursor **237a**, a series of trials were attempted using benzyl acrylate and a substitute long chain alkene, oct-1-ene. The initial attempt was repeated using oct-1-ene but with the same result, no trace of metathesis product. Elevated temperatures and extended reaction times had no effect.



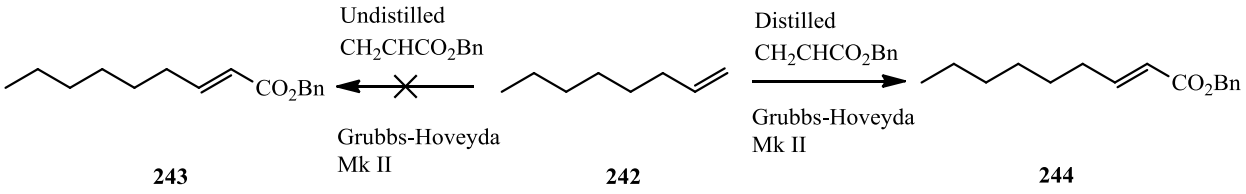
Spectrum 4.1: ^{1}H NMR spectrum of furan 237a

Upon searching the literature for similar metathesis reactions, it was discovered that very few metatheses have been performed using benzyl acrylate and no examples were found using the G-II catalyst. However, an interesting report was found of a tandem cross-metathesis and hydrogenation reaction using benzyl acrylate **239**, an allyltriphenylsilane **238** and Grubbs-Hoveyda Mark II catalyst (G-H II) (Scheme **4.31**).[153, 154]



Scheme 4.31: Tandem cross-metathesis and hydrogenation using Grubbs-Hoveyda mark II catalyst.

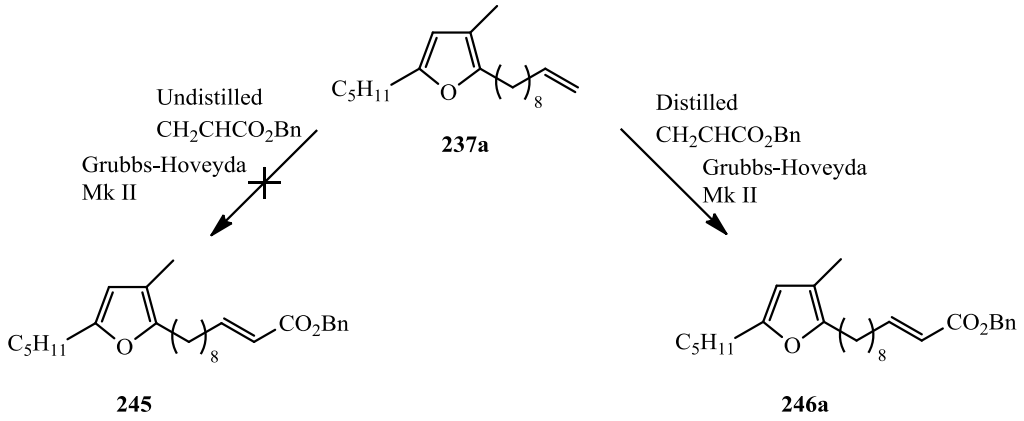
Cossy *et al* reported a yield of 63% for the saturated benzyl ester **240** and 17% alkyltriphenylsilane **241**. Cossy's conditions were tested using benzyl acrylate **239** and oct-1-ene. Disappointingly, no metathesis product was observed at either ambient temperature or refluxing dichloromethane. At this point an observation was made that commercial benzyl acrylate **239** contains 150 ppm *para*-methoxyphenol as a stabilizer and that this may be poisoning the catalyst or otherwise inhibiting the reaction.[155] The procedure was repeated using freshly distilled benzyl acrylate **239** at ambient temperature to give α,β-unsaturated benzyl ester **244** in 92% yield (Scheme **4.32**).



Scheme 4.32: Grubbs-Hoveyda mk II-catalysed metathesis of oct-1-ene and benzyl acrylate.

The G-H II catalysed metathesis was re-attempted using freshly distilled benzyl arcylate **239** and F_5 precursor **237a** at ambient temperature but again, disappointingly, there was no trace of metathesis product. Success was finally achieved with refluxing dichloromethane and gave an excellent yield of 85% (Scheme **4.33**). Quite why metathesis is only possible using freshly distilled benzyl acrylate is uncertain. The amount of *para*-methoxyphenol present in commercial benzyl acrylate does not appear to be sufficient to poison the catalyst: 6.17 mmol benzyl acrylate contains approximately 0.0012 mmol *para*-methoxyphenol; a reaction on this scale would

require 0.103 mmol G-H Mark II . What is certain however, is that commercial benzyl acrylate, in our hands at least, will not undergo cross metathesis prior to distillation.



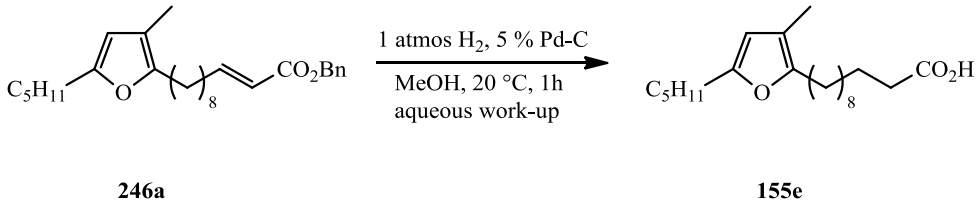
Scheme 4.33: Cross-metathesis of F_5 precursor 237a using benzyl acrylate.

Before optimisation, using the conditions outlined by Cossy's group of three equivalents of benzyl acrylate **239**, benzyl ester **246a** was substantially contaminated with varying amounts of dibenzyl fumarate, a homo-coupled product, as well as excess benzyl acrylate **239.** Separation of the ester **246a** from the contaminants using column chromatography was possible but, owing to the notorious acid-sensitivity of furans, this was undesirable. Fortunately, an excess of acrylate **239** was not required. The metathesis was still highly efficient using just 1.3 equivalents acrylate **239** in refluxing dichloromethane for one hour. A summary of the conditions that were tested are listed in Table **4.6**.

Alkene	Equivalents of Benzyl Acrylate	Catalyst	Temp (°C)	Time (h)	Yield (%)
237a	3	G-II	20	4	0
Oct-1-ene	3	G-II	20	4	0
Oct-1-ene	3	G-II	20	16	0
Oct-1-ene	3	G-II	40	4	0
Oct-1-ene	3	G-II	40	16	0
Oct-1-ene	3	G-H II	20	4	92
237a	3	G-H II	20	4	0
237a	3	G-H II	20	16	0
237a	3	G-H II	40	4	85
237a	1.3	G-H II	40	4	89
237a	1.3	G-H II	40	2	89

Table 4.6: Cross metathesis using benzyl acrylate.

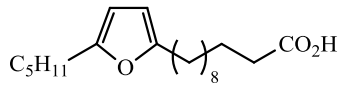
The resulting ester **246a** was now only contaminated with the slight excess of acrylate **239** which was converted into water-soluble propanoic acid during the final hydrogenation-hydrogenolysis step and was removed easily with a water wash to give furan fatty acid F_5 in 93% yield (Scheme **4.34**).



246a **155e**

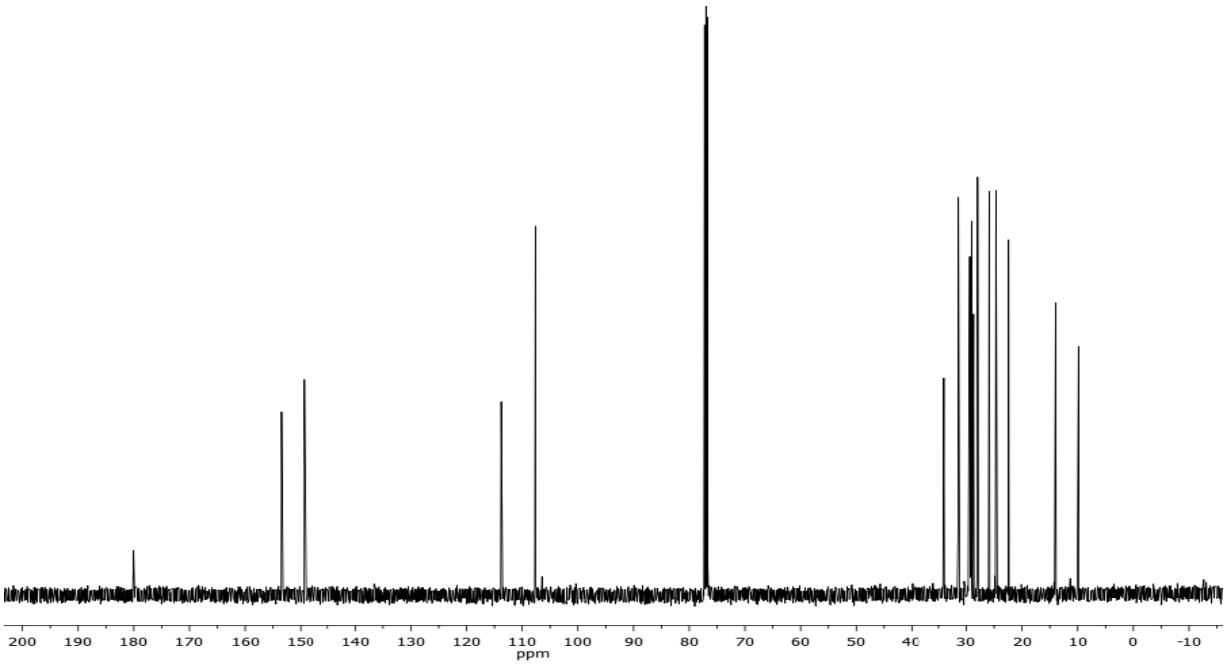
Scheme 4.34: Simultaneous hydrogenation-hydrogenolysis of benzyl ester to form F_5 furan fatty acid.

The resulting furan F_5 **155e** showed identical spectroscopic and analytical data to those previously reported.[156-160] F_5 also proved to be very unstable, with decomposition noticeable after just a day even when stored at -20 °C. The penultimate precursor, ester **246a**, was much more stable although still fairly sensitive but the alkene precursor **237a** was even more so when stored in cold, dark and oxygen-free conditions. Both the ester 2**46a** and the alkene **237a** intermediates would make storable late stage precursors of furan F_5 **155e**. Since the final two steps are both triggered by catalysts and are reasonably simple to carry out and to work-up, these should be transformations that could be carried out by the relatively synthetically inexperienced and hence could provide a ready supply of the F-acid **155e** on a regular basis.



155e

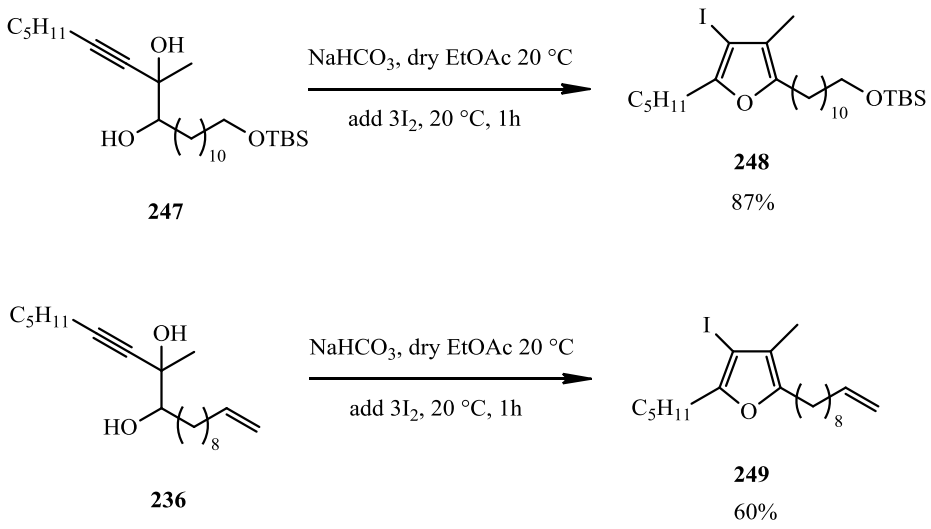
Spectrum 4.2: ^{1}H NMR spectrum of F_5 furan fatty acid



Spectrum 4.3: ^{13}C NMR spectrum of F_5 furan fatty acid

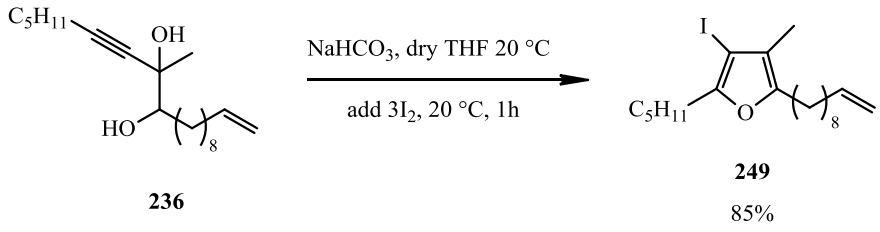
4.10 Synthesis of F_6 Furan Fatty Acid

Iodocyclisation of diol **236** was the first step in the synthesis of furan fatty acid F_6 **155f**. As mentioned in section **4.6**, the Knight group had discovered that various precursors with lengthy fatty chains did not proceed well using the usual solvents for such a transformation (acetonitrile, dichloromethane), but switching to ethyl acetate gave excellent yields of up to 92%. Perhaps surprisingly, given the similarity of substrates, attempts to cyclise diol **236** in ethyl acetate only delivered around 60% of iodofuran **249** and was substantially contaminated with unknown by-products thereby requiring tedious purification of the rather unstable iodofuran (Scheme **4.35**).



Scheme 4.35: Iodocyclisation of 3-alkyne-1,2-diols in ethyl acetate.

With a desire to achieve a higher yield of iodofuran **249,** and also in an attempt to obviate purification by column chromatography for obvious reasons, a different solvent system was investigated. As mentioned previously, it was already known from previous work in the Knight group that acetonitrile and dichloromethane were unsuitable solvents so it was with great fortuity that the first new solvent tested, tetrahydrofuran, gave an excellent yield of 85% in the first trial run and, more importantly, the iodofuran **249** was exceptionally pure after only filtration through a silica plug (Scheme **4.36**).

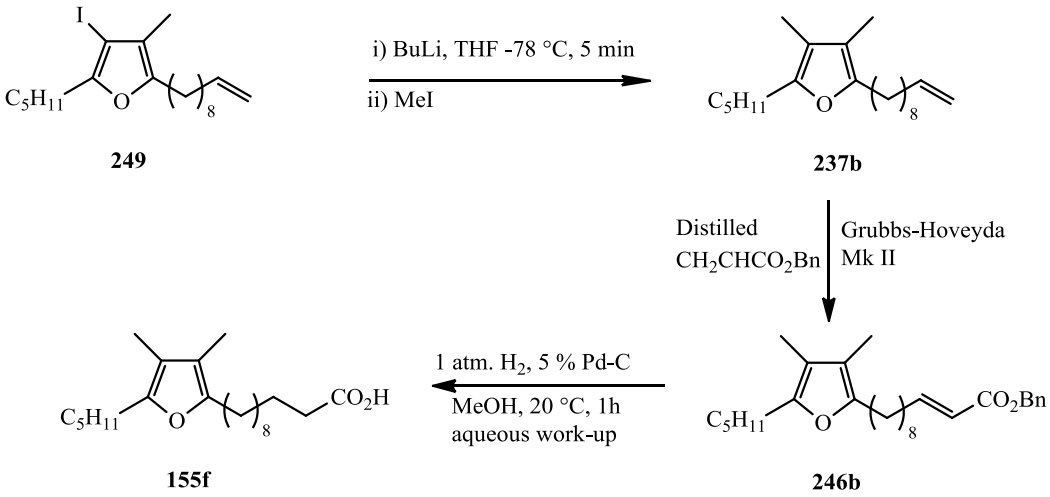


236 **249**

85%

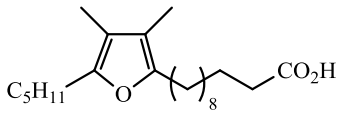
Scheme 4.36: Iodocyclisation of 3-alkyne-1,2-diol in THF.

The iodine atom was then exchanged for a methyl group using the well-established method of halogen-metal exchange using a slight excess of butyl lithium at low temperature followed by rapid quenching of the resulting β-lithio furan with iodomethane. The tetrasubstituted furan **246a** was isolated in excellent yields of around 90% and when treated to the same metathesis and hydrogenation-hydrogenolysis reactions outlined in section **3.9** for the synthesis of F_5 **155e**, gave furan fatty acid F_6 **155f** also in excellent yield, which also displayed identical spectroscopic data to those previously reported (Scheme **4.37**).[156,159]



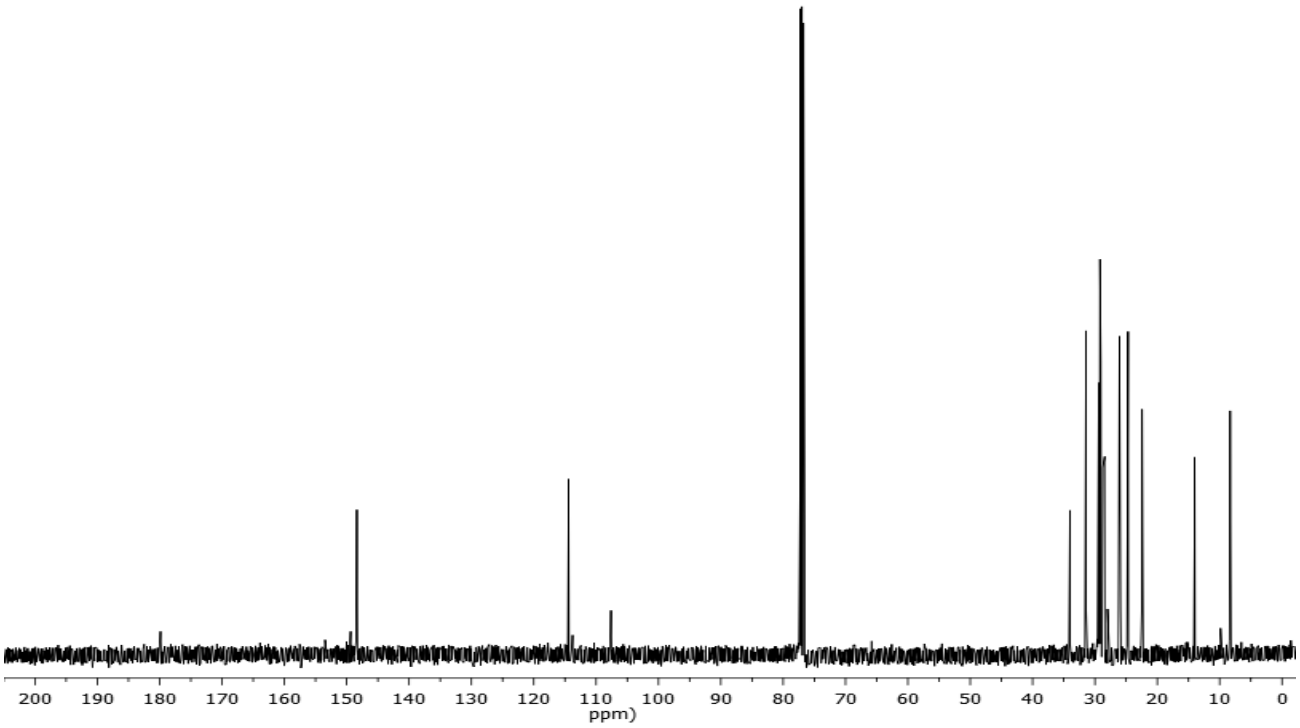
249 **237b** **155f** **246b**

Scheme 4.37: Synthesis of F_6 furan fatty acid from iodofuran 249.



155f

Spectrum 4.4: ^{1}H NMR spectrum of F_6 furan fatty acid

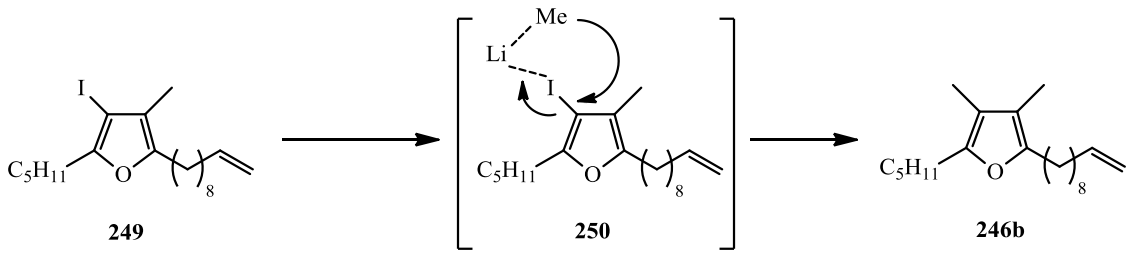


Spectrum 4.5: ^{13}C NMR spectrum of F_6 furan fatty acid

4.11 Halogen-Metal Exchange Using Methyllithium

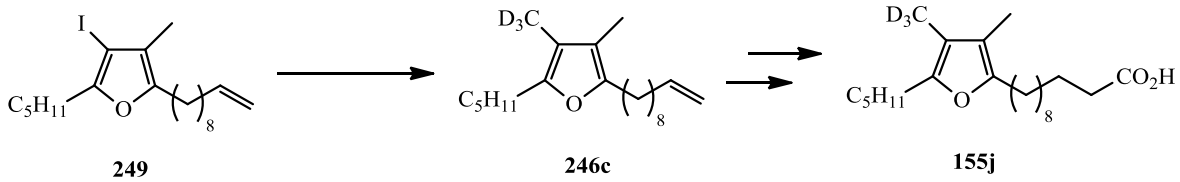
Despite the excellent yields recorded, the iodine-methyl exchange step was particularly demanding and also prone to give products contaminated with the F_5 equivalent species, alkene **237a**. Preventing this protonation proved to be extremely difficult. Performing the reaction using freshly distilled iodomethane and ensuring all glassware was exceptionally dry helped, but a small amount, around 10-15%, of the protonated species was always present. Attempts to separate the two species using column chromatography proved futile, as were attempts to separate the two final products, F_5 **155e** and F_6 **155f**, by reverse phase HPLC. The origin of the proton source was unknown but was assumed to be trace amounts of moisture present in the starting iodofuran **249**. The other product of the halogen-metal exchange step, iodobutane, is sufficiently unreactive to interfere in the alkylation step, at least at low temperature. However, if *methyl*lithium was used instead, would it be possible to generate the much more reactive iodomethane *in situ* by a similar exchange, thereby removing the necessity of handling and purifying this toxic material, whilst also eliminating a potential proton source? No examples of such a transformation could be found in the literature, however, there were a very small number of examples where methyllithium had been used for halogen metal exchange but not for methylation.[160]

With some pessimism, a slight excess of 1.6M ethereal methyllithium-lithium bromide was added to a solution of iodofuran at -78 °C in THF and allowed to stir for 5 minutes before warming to room temperature over one hour. We were delighted to find that the result was F_6 precursor **246b** in 95% yield with less than 3% of the F_5 precursor **246a**! The exact mechanism of this transformation is uncertain but it presumably involves the formation of a complex **250** between the lithium and iodine atoms prior to C-C bond formation. Therefore, the intermediate iodomethane is never really 'free' and hence is available to couple immediately (Scheme **4.38**).



Scheme 4.38: Proposed mechanism for methylation using methyllithium.

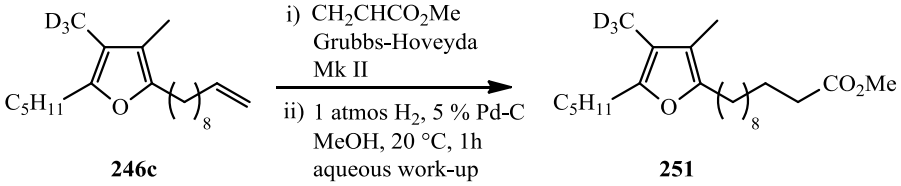
This reaction can be modified to introduce a deuterium labelled methyl group. Addition of deuteriomethyl lithium-lithium iodide complex (0.5M in ether) under otherwise identical conditions gave > 90% yields of the trideuterated F_6 precursor **247c**, which was then converted to trideuterated furan fatty acid F_6 **155j**, typically contaminated with < 3% of the corresponding F_5 precursor **246a**, after cross metathesis and hydrogenation-hydrogenolysis (Scheme **4.39**).



Scheme 4.39: Synthesis of trideuterated F_6.

Of course, it would also be possible to introduce a ^{13}C or ^{14}C labelled methyl group using this method as the choice of labelled methyl group is only restricted to the availability of labelled methyllithium. An alternative and perhaps more conventional method towards generating labelled F_6 **115j** would be to use the standard procedure for halogen-metal exchange *i.e. n*-BuLi at -78 °C followed by labelled iodomethane.

One of the principle purposes of preparing synthetic samples of the F-acids is to establish their role in Nature. Due to their instability and fatty nature they are extremely difficult to isolate from natural sources and, once isolated, will readily decompose. Thus a synthetic sample is quite valuable for performing assays and a deuterated sample even more so. When performing analysis in food laboratories it is common practice to esterify fatty acids. A sample of deuterated methyl ester of F_6 was prepared using methyl acrylate in the metathesis step followed by hydrogenation to give the unsaturated methyl ester **251** (Scheme **4.40**). Almost 100 mg of methyl ester **251** was synthesised and sent to Walter Vetter in Hohenheim for use in his studies.



Scheme 4.40: Synthesis of deuterated-F_6 methyl ester.

Recently Vetter has published a report detailing the levels of saturated F-acids found in various foods.[91] This was achieved by transesterification of the furan fatty acids to their methyl esters followed by silver ion chromatography (20% $AgNO_3$ on silica, 1% deactivated) and subsequent

GC/EI-MS analysis. Vetter confirmed that F-acids are widespread in food but that concentrations may vary, depending upon a variety of parameters. The unstable nature of the F-acids leads to their oxidative breakdown which can have an impact on the uptake by the consumer. Food samples stored for long periods after harvest or have been extensively processed may well be depleted in F-acids which in turn will cause a decrease in the nutritional value of the food. Organic milk and butter however, might have a higher content of F-acids due to higher proportions of F-acids in pasture compared to dried feedstock given to 'non-organic' dairy cows. Vetter's investigations also confirmed that the levels of F-acids are at least one order of magnitude higher in fish and fish oils than in other food sources, with unprocessed fish containing the highest levels. A diet rich in fresh fish is therefore highly recommended!

4.12 Conclusions

Although relatively little is known about the exact role that furan fatty acids play in nature, there is no doubt at all that a diet rich in marine food, which is also relatively enriched in furan fatty acids as well as omega 3 fatty acids, helps to prevent cardiovascular disease and atherosclerosis. It has been proposed that it is the furan fatty acids that may well be responsible for the cardioprotective effects of a fish diet. F-acids are widespread in nature but can only be biosynthesised by plants. As highly efficient radical scavengers, they may play a vital role in protecting plants from the harmful effects of uv radiation, since their levels have been shown to be higher during the vegetative stage, when sunlight and the damage caused by ultra-violet light is at a peak.

The synthetic route to F-acids F_5 and F_6 that has been described could quite feasibly be carried out on a reasonably large scale. The unstable nature of the F-acids dictates that they should be synthesised up to the metathesis step and then held in storage until required. The final steps, metathesis and hydrogenation, can be carried out when fresh samples are required and are suitable for the relatively synthetically inexperienced.

*Chapter **5**: Experimental*

5.1 General Experimental Details

Reagents were obtained from Aldrich, Alfa Aesar, Lancaster, Fluka and Strem chemical suppliers and used as received unless otherwise specified. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[161]

All non-aqueous reactions, unless otherwise stated, were conducted in oven- or flame-dried glassware under an atmosphere of dry nitrogen with magnetic stirring. Solid carbon dioxide and an acetone bath (-78 °C) or an ice-water bath (0 °C) were used to obtain low temperatures. Heated reactions were conducted in a magnetically stirred oil bath heated on a hotplate.

Dried: Refers to addition of dried magnesium sulphate ($MgSO_4$) to remove trace amounts of water.

Filtered: Refers to removal of $MgSO_4$ by filtration of organic solutions through fluted filter paper.

Evaporated: Refers to the distillation of solvent using a Büchi rotary evaporator, attached to a 20 L Charles Austen pump at approx. 8 mbar, heated with a water bath typically between 20 and 40 °C.

Degassed: Refers to bubbling N_2 through the solvent for 30 minutes.

Overnight: 18-24 hours.

When required, solvents were dried and purified prior to use. Anhydrous diethyl ether and anhydrous tetrahydrofuran were obtained by refluxing over sodium with sodium benzophenone ketyl as indicator, followed by distillation. Dichloromethane and toluene were distilled from calcium hydride. Triethylamine, diisopropylamine and pyridine were distilled over sodium hydroxide containing 4Å molecular sieves. “Petrol” refers to petroleum ether b.p. 40-60 °C, “ether” refers to diethyl ether. All aqueous solutions were saturated unless otherwise stated.

All solutions of crude products were dried by brief exposure to dried magnesium sulphate ($MgSO_4$), unless otherwise stated, then filtered and evaporated under reduced pressure. Column chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,[162] and using Merck Kieselgel 60 H silica or Matrix silica 60 as the stationary phase.

All reactions, where appropriate, were monitored by TLC using Merck silica gel 60 F_{254} precoated aluminium backed plates, which were visualised with ultraviolet light or by staining with 2% aqueous potassium permanganate solution. Retention factor values (R_f) are reported in the appropriate solvent system.

All melting points (mp °C) were determined using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected. Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series Fourier Transform Infrared Spectrmometer, as liquid films between sodium chloride plates [film], unless otherwise stated, in which case samples were run as nujol mulls on sodium chloride plates [nujol] or as a solution in dichloromethane [DCM] between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}).

Proton (^1H) NMR spectra were recorded using an Avance Bruker DPX 500 (500 MHz) instrument, with carbon (^{13}C) NMR spectra recorded at 125 MHz unless otherwise stated, in which case ^1H NMR spectra were recorded using an Avance Bruker DPX 400 instrument (400 MHz). Spectra were obtained as dilute solutions in deuterated chloroform, unless otherwise stated, in which case spectra were obtained in dilute solutions of fully deuterated methanol (CD_3OD). The chemical shifts were recorded relative to residual chloroform (7.27 or 77.0 ppm) as an internal standard unless otherwise stated, in which case chemical shifts were recorded relative to partially deuterated methanol (4.78 or 49.15 ppm).[163] Deuterium (^2D) NMR spectra were recorded using a Jeol Eclipse (+) (300 MHz) instrument. Spectra were obtained as dilute solutions of chloroform containing a trace amount of deuterated chloroform. The chemical shifts were recorded relative to deuterated chloroform (7.27 ppm). Abbreviations used for the multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), br. s (broad singlet), br. t (broad triplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), m (unresolved multiplet), app. (apparent) or as a combination of these multiplicities. All coupling constants (*J*) are recorded in Hertz (Hz). Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY, HSQC and HMBC experiments where required.

Mass spectrometric data were determined using a Waters GCT Premier instrument using electron ionisation (EI) unless otherwise stated, in which case such data were obtained using a Waters LCT Premier XE instrument (LRMS) or Agilent 5975C Series GC/MSD (GC-MS) using atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ES). High resolution

mass spectrometric data were determined with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element.

A literature reference associated with title of the compound means it is not a novel compound and any data recorded in this thesis matches well with those reported in the associated references, unless otherwise stated.

5.2 General Procedure for the Synthesis of Furans

TBDMS protection of alkynols[164]

tert-Butyldimethylsilyl chloride (6.5 – 10.5 mmol, l.05 eq) was added to a stirred solution of alkynol (5.9 – 10.0 mmol, 1 eq) and imidazole (7.1 – 10.7 mmol, 1.07 eq) in dichloromethane (20 ml g^{-1}) at ambient temperature and the solution left to stir for 16 h. The solution was then diluted with dichloromethane (20 ml) and washed with aqueous ammonium chloride (3 x 25 ml). The separate organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 49:1) to yield the alkyne.

Addition of 1-alkynes to 2-acetoxysuccinic anhydride[89]

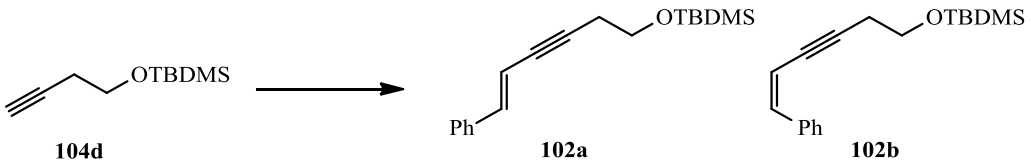
n-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol, 1 eq) was added dropwise to a solution of 1-alkyne (6.32 mmol, 1 eq) in tetrahydrofuran (10 ml) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol, 1 eq) in tetrahydrofuran (10 ml), which was also maintained at -78 °C. After stirring for 0.5 h, a solution of sodium borohydride (0.25 g) in ethanol (5 ml) was added and stirring continued for a further 0.25 h. Aqueous 1M sodium hydroxide (6 ml) was then added and the solution warmed to 0 °C. After stirring for 1 h, sufficient 2M hydrochloric acid was added carefully to acidify the solution to pH 4. The product was extracted with ethyl acetate (3 x 25 ml) and the combined organic extracts washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *diol*

Cyclisation using 10% $AgNO_3.SiO_2$[39]

In a foil-wrapped flask, 10% w/w silver nitrate on silica gel (0.006– 0.132 mmol, 0.1 eq) was added to a stirred solution of a 3-alkyne-1,2-diol (0.06 – 1.32 mmol, 1 eq) in dichloromethane (10 ml g^{-1}). The resulting suspension was stirred for 3-18 h then filtered through celite and the solvent evaporated to yield the furan.

5.3 Experiments and Data

(*E*)- and (*Z*)-1-((*tert*-Butyl))dimethylsilyloxy)-6-phenylhex-5-en-3-yne (102a) and (102b)[168]



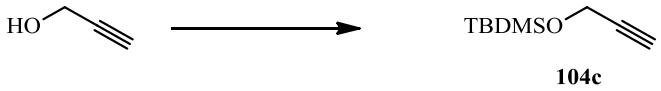
104d **102a** **102b**

(*E/Z*)-β-Bromostyrene (0.72 ml, 5.63 mmol, *E/Z* 9:1), triphenylphosphine (0.30 g, 1.14 mmol), triethylamine (5.78 ml, 77.6 mmol) and copper iodide (0.05 g, 0.26 mmol) were added to a stirred suspension of 10% w/w palladium on carbon (0.23 g, 0.21 mmol) in degassed water (20 ml) and the resulting mixture stirred at ambient temperature for 0.5 h. alkyne **104d** (1.55 g, 8.42 mmol) was added dropwise and the mixture warmed to 80 °C and left to stir overnight. After cooling to ambient temperature the mixture was filtered through celite before the filtrate was washed with ethyl acetate (3 x 25 ml). The separated organic filtrate was dried, filtered and evaporated to yield the *enynes* **102a** and **102b** (0.84 g, 87%) as a yellow oil, containing a ratio of 9:1 of (*E/Z*)-isomers: R_f 0.25 (5 : 95 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 2953, 2856, 2213, 1651, 1492, 1471, 1447, 1388, 1361, 1255, 1105, 1006, 953, 836, 777, 747, 691, 664; δ_H 7.76 (0.2H, d, *J* 7.3, 2 x Ar-H), 7.31-7.18 (4.80H, m, 8 x Ar-H), 6.92 (0.9H, d, *J* 16.3, 6-H), 6.63 (0.1H, d, *J* 12.0, 6-H), 6.16 (0.9H, dt, *J* 16.3 and 2.2, 5-H), 5.71 (0.1H, dt, *J* 12.0 and 2.5, 5-H), 3.68 (1.8H, t, *J* 6.3, 1-CH_2), 3.62 (0.2H, t, *J* 6.3, 1-CH_2), 2.72 (0.2H, td, *J* 6.3 and 2.5, 2-CH_2), 2.67 (1.8H, td, *J* 6.3 and 2.2, 2-CH_2), 0.84 (9H, s, *t*-Bu), 0.00 (6H, s, Si Me); δ_C *major* 140.1 (CH), 136.5 (C), 128.7 (2 x Ar-CH), 128.3 (Ar-CH), 126.1 (2 x Ar-CH), 108.8 (CH), 92.5 (C), 79.9 (C), 61.7 (1-CH_2), 31.8 (2-CH_2), 26.0 (t-Bu Me), 18.4 (C), -5.3 (Si Me); δ_C *minor* 138.1 (CH), 136.4 (C), 128.3 (2 x Ar-CH), 128.1 (Ar-CH), 126.0 (2 x Ar-CH), 107.6 (CH), 93.5 (C), 80.7 (C), 60.9 (1-CH_2), 28.1 (2-CH_2), 26.0 (t-Bu Me), 18.4 (C), -5.3 (Si Me); *m/z* 286 $[M]^+$ 2%, 229 (96), 127 (71), 75 (100) [Found $[M]^+$, 286.1786. $C_{18}H_{26}OSi$ requires *M*, 286.1753].

Source of 1-alkynes(**104**)

Phenylacetylene (**104a**) and 1-hexyne (**104b)** are commercially available.

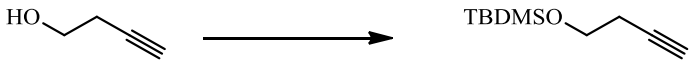
1-((*tert*-Butyl)dimethylsilyloxy)prop-2-yne (104c)[164]



104c

Using the general procedure *tert*-butyldimethylsilyl chloride (1.58 g, 10.5 mmol) was added to propargyl alcohol (0.58 ml, 10.0 mmol) and imidazole (0.73 g, 10.7 mmol) in dichloromethane to yield *alkyne* **104c** as a colourless liquid (1.19 g, 77%): δ_H (400 MHz; $CDCl_3$) 4.33 (2H, d, *J* 2.4, 1-CH_2), 2.41 (1H, t, *J* 2.4, 3-CH), 0.91 (9H, s, *t*-Bu Me), 0.18 (6H, s, Si-Me). All data obtained matched those previously reported in the literature.[164]

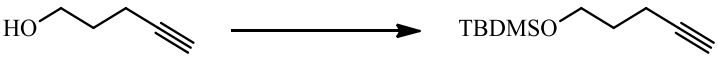
1-((*tert*-Butyl)dimethylsilyloxy)but-3-yne (104d)[164]



104d

Using the general procedure *tert*-butyldimethylsilyl chloride (1.58 g, 10.5 mmol) was added to but-3-yn-1-ol (0.76 ml, 10.0 mmol) and imidazole (0.73 g, 10.7 mmol) in dichloromethane to yield *alkyne* **104d** (1.80 g, 98%), as a colourless oil: δ_H 3.67 (2H, t, *J* 7.2, 1-CH_2), 2.33 (2H, td, *J* 7.2 and 2.8, 2-CH_2), 1.89 (1H, t, *J* 2.8, 4-H), 0.82 (9H, s, t-Bu Me), 0.00 (6H, s, Si-Me). All data obtained matched those previously reported in the literature.[165]

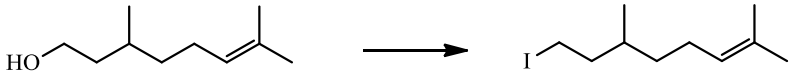
1-((*tert*-Butyl)dimethylsilyloxy)pent-4-yne (104e)[164]



104e

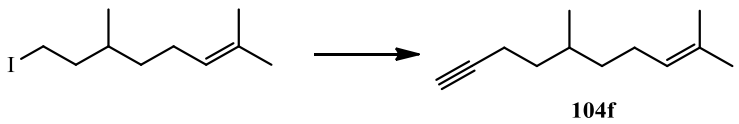
Using the general procedure *tert*-butyldimethylsilyl chloride (0.98 g, 6.5 mmol) was added to pent-4-yn-1-ol (0.50 g, 5.9 mmol) and imidazole (0.49 g, 7.1 mmol) in dichloromethane to yield *alkyne* **104e** (0.91 g, 77%) as a colourless liquid: δ_H 3.70 (2H, t, *J* 6.1, 1-CH_2), 2.27 (2H, td, *J* 7.0, 2.7, 3-CH_2), 1.93 (1H, t, *J* 2.7, CH), 1.75–1.70 (2H, tt, *J* 7.0, 6.1, 2-CH_2), 0.89 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me). All data matched that previously reported in the literature.[166]

1-Iodo-3,7-dimethyloct-6-ene[167]



Iodine (3.35 g, 1.32 mmol,) was added to a stirred solution of triphenylphosphine (3.46 g, 1.32 mmol) and imidazole (0.898 g, 1.32 mmol) in dichloromethane (30 ml). (±)-β-Citronellol (2 ml, 1.10 mmol) was added dropwise after 15 mins, and the resulting mixture stirred at room temperature overnight. The reaction was quenched with water (30 ml) and the product extracted into dichloromethane (3 x 50 ml). The combined organic extracts were washed with water (100 ml) and brine (100 ml), then dried, filtered and evaporated to yield a pale orange oil. Hexane (25 ml) was then added to crystallise the triphenylphosphine oxide, which was then removed by filtration through a sintered funnel. Evaporation of the solvent gave *citronellyl iodide* (2.41g, 82%) as a pale orange oil: υ_{max}/cm^{-1} (film) 3226, 2962, 2923, 1437, 1377, 1180, 1119, 972, 722, 694; δ_H 5.10 (1H, br. t, *J* 7.1, 6-H), 3.26 (1H, ddd, *J* 9.5, 8.6 and 5.6, 1-H_a), 3.17 (1H, ddd, *J* 9.5, 8.2 and 7.1, 1-H_b), 2.06-1.85 (2H, m, 5-CH_2), 1.60 (3H, app. s, 8-Me), 1.60-1.54 (1H, m, 3-H), 1.54 (3H, app. s, 7-Me), 1.50-1.42 (2H, m, 2-CH_2), 1.31-1.04 (2H, m, 4-CH_2), 0.80 (3H, d, *J* 6.5, 3-Me); δ_C 131.9 (7-C), 124.4 (6-CH), 40.9 (CH_2), 36.4 (CH_2), 33.5 (CH), 25.7 (3-Me), 25.3 (CH_2), 18.6 (8-Me), 17.7 (7-Me), 5.2 (CH_2); *m/z* 266 $[M]^+$ 15%, 154 (40), 83 (100) [Found $[M]^+$ 266.0529, $C_{10}H_{19}I$ requires *M*, 266.0532]. All data matched those previously reported in the literature.[167]

2,6-Dimethyldec-2-en-9-yne (104f)[167]

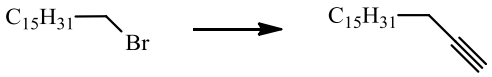


104f

A solution of lithium acetylide ethylene diamine complex (0.955 g, 10.37 mmol) in dimethyl sulfoxide (20 ml) was stirred at 0 °C for 10 mins. Citronellyl iodide (2.3g, 8.64 mmol) was then added dropwise and the reaction mixture allowed to warm to room temperature with stirring for 1 h. Water (10 ml) was added to quench the reaction, the product extracted into hexane (3 x 25 ml) and the combined organic extracts washed with water (100 ml) and brine (100 ml), then dried, filtered and evaporated to yield the *citronellyl acetylene* **104f** as a pale orange oil, (1.13 g, 78%): R_f 0.65 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3304, 3224, 2929, 2358, 1668, 1531, 1436, 1377, 1264, 1079, 895, 739; δ_H 5.10 (1H, br. t, *J* 7.1, 3-H), 2.20 (2H, td, *J* 6.1 and 1.8, 8-CH_2), 2.05 – 1.90 (2H, m, 4-CH_2), 1.85 (1H, t, *J* 1.8, 10-H), 1.61 (3H, d, *J* 0.9, 1-Me),

1.54 (3H, app. s, 2-Me), 1.51 – 1.43 (2H, m), 1.35 – 1.21 (2H, m), 1.13 – 1.03 (1H, m, 6-H), 0.80 (3H, d, *J* 6.6, 6-Me); δ_C 131.2 (2-C), 124.7 (3-CH), 84.5 (9-C), 68.0 (10-CH), 36.7 (CH_2), 35.6 (CH_2), 31.6 (6-CH), 25.7 (1-Me), 25.4 (CH_2), 19.0 (2-Me), 17.6 (6-Me), 16.1 (CH_2). All data matched those previously reported in the literature.[167]

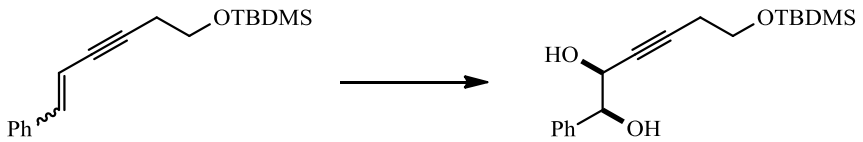
1-Octadecyne (104g)[59]



104g

1-Bromohexadecane (4.72 ml, 15.0 mmol) was added dropwise to a stirred solution of lithium acetylide ethylenediamine complex (2.30 g, 22.5 mmol) in dry dimethyl sulfoxide (15 ml) and maintained at 5 °C for 2 h. The mixture was then allowed to warm to ambient temperature overnight. Water (3.5 ml) was added carefully before the entire mixture was added to water (50 ml) and the resulting mixture extracted with hexane (3 x 100 ml) The combined organic extracts were dried, filtered and evaporated to yield the *alkyne* **104g** (3.58 g, 95%) as a pale yellow wax: δ_H 2.19 (2H, dt, *J* 7.1 and 2.6, 3-CH_2), 1.94 (1H, t, *J* 2.6, 1-H), 1.60 – 1.47 (2H, m, 4-CH_2), 1.43 – 1.34 (2H, m, 5-CH_2), 1.33 – 1.23 (24H, m, 6-CH_2 – 17-CH_2), 0.88 (3H, t, *J* 6.8, 18-Me). All data obtained matched those previously reported in the literature.[59]

(1*RS*, 2*RS*)-6-((*tert*-Butyl)dimethylsilyloxy)-1-phenylhex-3-yne-1,2-diol (105d)

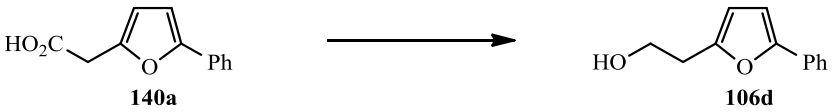


102 **105d**

Potassium ferricyanide (2.30 g, 7.0 mmol), potassium carbonate (0.97 g, 7.0 mmol) and DHQD2-PHAL (0.05 g, 70 μmol) were dissolved in aqueous *t*-butanol (1:1, 10 ml). To this mixture, enynes **102** (0.668 g, 2.33 mmol, as a 9:1(*E/Z*) mixture) were added followed by potassium osmate (VI) dihydrate (2 mg, 5 μmol). The resulting solution was stirred overnight then quenched with sodium sulphite (5 ml), with stirring for 0.5 h. The product was extracted with ethyl acetate (3 x 25 ml), and the combined extracts washed with water (50 ml) and brine (50ml) then dried, filtered and evaporated to yield crude *diols* **105d** as a yellow oil (0.717 g, 96%) containing a ratio of 9:1 of isomers, which was purified by column chromatography (20:80 ethyl acetate – petroleum ether) to give the *syn-diol* **105d** as a pale yellow oil (0.612 g, 82%) and

as a single isomer: R_f 0.26 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3372, 2953, 2896, 5855, 2232, 1672, 1598, 1495, 1471, 1389, 1361, 1326, 1255, 1197, 1102, 1065, 968, 836, 776; δ_H 7.39 (2H, dd, *J* 7.8 and 1.3, 2 x Ar-H), 7.36-7.26 (3H, m, 3 x Ar-H), 5.01 (1H, br. s, OH), 4.63 (1H, d, *J* 7.2, 1-H), 4.34 (1H, td, *J* 7.2 and 1.8, 2-H), 3.59 (2H, t, *J* 7.1, 6-H), 2.21 (2H, td, *J* 7.1 and 1.8, 5-H), 0.86 (9H, s, *t*-Bu), 0.00 (6H, s, Si-Me); δ_C 139.3 (C), 128.2 (Ar-CH), 128.0 (2 x Ar-CH), 127.1 (2 x Ar-CH), 87.3 (C), 77.8 (C), 77.6 (CH), 67.6 (CH), 61.5 (6-CH_2), 31.4 (5-CH_2), 25.9 (*t*-Bu Me), 18.3 (C), -5.3 (Si Me).

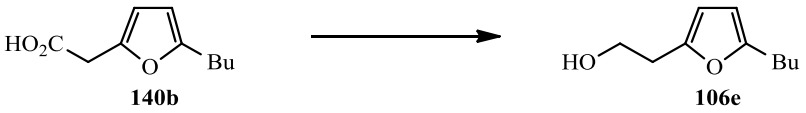
2-(5-Phenylfuran-2-yl)ethanol (106d)



140a **106d**

To a stirred solution of furan **140a** (2.01 g, 9.94 mmol) in tetrahydrofuran (20 ml) in a two-necked flask maintained at 0 °C under an atmosphere of nitrogen was added borane-methyl sulphide (1.24 ml, 12.92 mmol) dropwise and the resulting solution stirred for 1 h. Excess hydride was destroyed by the addition of aqueous tetrahydrofuran (1:1, 20 ml). The aqueous phase was saturated with potassium carbonate and the organic layer separated. The aqueous phase was extracted with diethyl ether (3 x 20 ml) and the combined organic layers were dried, filtered and evaporated to yield the *furylethanol* **106d** as a yellow oil (1.86 g, 98%): δ_H 7.55 – 7.53 (2H, m, Ar-H), 7.29 – 7.25 (2H, m, Ar-H), 7.16 – 7.12 (1H, m, Ar-H), 6.50 (1H, d, *J* 3.2, furan-H), 6.13 (1H, d, *J* 3.2, furan-H), 3.87 (2H, t, *J* 6.3, 2'-CH_2), 2.90 (2H, t, *J* 6.3, 1'-CH_2); δ_C 152.9 (C), 152.5 (C), 130.9 (C), 128.6 (2 x Ar-CH), 127.0 (2 x Ar-CH), 123.4 (Ar-CH), 108.7 (CH), 105.7 (CH), 61.0 (2'-CH_2), 31.7 (1'-CH_2); *m/z* 188 $[M]^+$ 25%, 157 $[M–CH_2OH]^+$, (100) [Found [M] 188.0835. $C_{12}H_{12}O_2$ requires 188.0837]. All data matched that previously reported in the literature.[168]

2-(5-Butylfuran-2-yl)ethanol (106e)

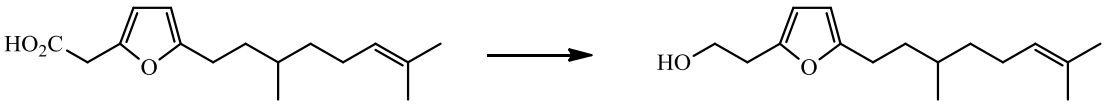


140b **106e**

To a stirred solution of furan **140b** (1.13 g, 6.2 mmol)) in tetrahydrofuran (20 ml) in a two-necked flask maintained at 0 °C under an atmosphere of nitrogen was added borane-methyl sulphide (0.76 ml, 8.06 mmol) dropwise and the solution stirred for 1 h. Excess hydride was destroyed by the addition of aqueous tetrahydrofuran (1:1, 20 ml). The aqueous phase was

saturated with potassium carbonate and the organic layer separated. The aqueous phase was washed with diethyl ether (3 x 20 ml) and the combined organic layers dried, filtered and evaporated to yield the *furylethanol* **106e** as a yellow oil (1.86 g, 98%): δ_H 5.99 (1H, d, *J* 3.0, furan-H), 5.88 (1H, d, *J* 3.0, furan-H), 3.86 (2H, t, *J* 6.2, 2'-CH_2), 2.85 (2H, t, *J* 6.2, 1'-CH_2), 2.58 (2H, t, *J* 7.6, 1''-CH_2), 1.64 – 1.53 (2H, m, 2''-CH_2), 1.43 – 1.31 (2H, m, 3''-CH_2), 0.93 (3H, t, *J* 7.3, 4''-Me); δ_C 155.5 (C), 150.6 (C), 106.8 (CH), 105.1 (CH), 65.0 (2'-CH_2), 37.9 (CH_2), 29.7 (CH_2), 27.5 (CH_2), 22.2 (CH_2), 13.8 (4''-Me); *m/z* 168 $[M]^+$ 50%, 137 (100), [Found [M], 168.1154. $C_{10}H_{16}O_2$ requires *M*, 168.1150].

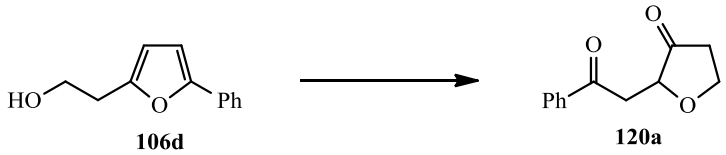
2-(5-(3,7-Dimethyloct-6-en-1-yl)furan-2-yl)ethanol (106g)



140f **106g**

Lithium aluminium hydride (0.38 ml of a 2.0M solution in tetrahydrofuran, 0.76 mmol) was added dropwise to a stirred solution of furan **140f** (0.155 g, 0.586 mmol) in tetrahydrofuran (5ml) maintained at 0 °C under an atmosphere of nitrogen. After 1 h, the reaction was quenched by the addition of sodium hydroxide (1 ml). Sufficient magnesium sulphate was added to dry the mixture before filtering and the solid washed with diethyl ether (3 x 20 ml). The combined organic filtrates were then evaporated to yield the *furylethanol* **106g** as an orange oil (0.082 g, 55%): υ_{max}/cm^{-1} (film) 3425, 3030, 2930, 1617, 1552, 1450, 1214, 947, 884; δ_H 5.92 (1H, d, *J* 2.9, furan-H), 5.80 (1H, d, *J* 2.9, furan-H), 5.10 (1H, br. t, 6''-H), 3.78 (2H, t, *J* 6.2, 2'-CH_2), 2.78 (2H, t, *J* 6.2, 1'-CH_2), 2.60 – 2.42 (2H, m, 1''-CH_2), 1.99 – 1.81 (2H, m, 5''-CH_2), 1.61 (3H, app. s, 8''-Me), 1.53 (3H, app. s, 7''-Me), 1.44 – 1.23 (4H, m, 2''-CH_2 and 4''4CH_2), 1.16 – 1.05 (1H, m, 3''-H), 0.84 (3H, d, *J* 6.2, 3''-Me); δ_C 155.1 (C), 150.8 (C), 131.0 (7''-C), 124.7 (6''-CH), 108.5 (CH), 105.2 (CH), 65.1 (2'-CH_2), 36.8 (CH_2), 35.2 (CH_2), 33.6 (CH_2), 32.1 (3''-CH), 25.7 (CH_2), 25.6 (8''-Me), 25.5 (CH_2), 19.1 (3''-Me), 17.7 (7''-Me); *m/z* 250 $[M]^+$ 25%, 219 (100), [Found [M], 250.1926. $C_{16}H_{26}O_2$ requires *M*, 250.1933].

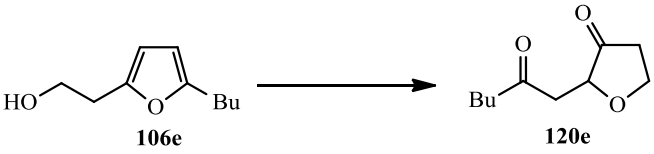
Dihydro-2-(2-phenyl-2-oxoethyl)furyl-3(2*H*)-one (120d)



Jones reagent[170] (0.75 ml of a 2.5 M solution, 1.87 mmol) was added to a stirred solution of furylethanol **106d** (0.271 g, 1.44 mmol) in acetone (10 ml) maintained at 0 °C and stirred for 0.5 h. Sufficient sodium sulphite was added to quench the reaction and the slurry filtered through silica and eluted with ethyl acetate (200 ml). The solvent was removed to yield *keto-tetrahydrofuran* **120d** as an orange oil (0.224 g. 76%): R_f 0.56 (30 : 70 ethyl acetate – petroleum ether); υ_{max}/cm^{-1} (film) 3063, 2945, 1756, 1686, 1597, 1449, 1370, 1268, 1219, 1150, 1092, 736, 689; δ_H 7.86 (2H, app. d, *J* 7.2, 2 x Ar-H), 7.51 (1H, app. t, *J* 7.2, Ar-H), 7.42-7.38 (2H, m, 2 x Ar-H), 4.34 (1H, app. td, *J* 9.1 and 4.2, 5-H_a), 4.13-4.05 (2H, m, 2-H and 5-H_b), 3.55 (1H, dd, *J* 18.0 and 3.4, 1'-H_a), 3.31 (1H, dd, *J* 18.0 and 5.5, 1'-H_b), 2.82 (1H, dt, *J* 18.0 and 9.0, 4-H_a), 2.51 (1H, ddd, *J* 18.0, 7.5 and 4.2, 4-H_b); δc 215.8 (C=O), 196.1 (C=O), 136.2 (C), 133.6 (Ar-CH), 128.7 (2 x Ar-CH), 128.2 (2 x Ar-CH), 75.5 (2-CH), 65.3 (5-CH_2), 40.6 (1'-CH_2), 36.6 (4-CH_2); *m/z* 204 $[M]^+$ 100% 114 (28) [Found [M], 204.0782. $C_{12}H1_2O_3$ requires *M*, 204.0786].

Dihydro-2-(2-oxohexyl)furyl-3(2*H*)-one (120e)

Method 1

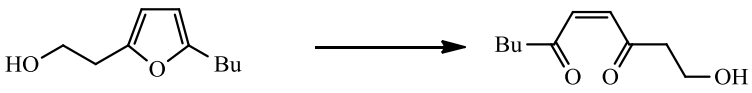


Jones reagent[170] (0.37 ml of a 2.5 M solution, 0.78 mmol) was added to a stirred solution of furylethanol **106e** (0.100 g, 0.60 mmol) in acetone (5 ml) maintained at 0 °C and stirred for 0.5 h. The solution was basified with sufficient aqueous potassium carbonate and extracted into dichloromethane (3 x 10 ml). The solvent was dried. filtered and evaporated to yield *keto-tetrahydrofuran* **120e** as a pale yellow oil (0.085 g. 77%): υ_{max}/cm^{-1} (film) 2930, 1754, 1712, 1445, 1369, 1260, 1219, 1150, 1092; δ_H 4.28 (1H, app. td, *J* 9.1 and 4.1, 5-H_a), 4.05 (1H, app. td, *J* 9.1 and 7.6, 5-H_b), 3.90 (1H, dd, *J* 5.4 and 3.7, 2-H), 2.90 (1H, dd, *J* 17.8 and 3.7, 1'-H_a), 2.78 (1H, dd, *J* 17.8 and 5.4, 1'-H_b), 2.70 (1H, app. dt, *J* 18.0 and 9.0, 4-H_a), 2.45 (1H, ddd, *J* 18.0, 7.6 and 4.1, 4-H_b), 2.35 (2H, t, *J* 7.3, 3'-CH_2), 1.45 (2H, m, 4'-CH_2), 1.10 (2H, m, 5'-CH_2), 0.80

(3H, t, *J* 7.3, 6'-Me); δ_C 215.2 (C=O), 206.8 (C=O), 75.1 (2-CH), 67.1 (5-CH_2), 45.3 (1'-CH_2), 40.9 (3'-CH_2), 36.5 (4-CH_2) 28.6 (CH_2) 22.3 (CH_2), 14.1 (6'-Me); *m/z* 184 $[M]^+$ 100% [Found [M], 184.1097. $C_{10}H_{12}O_3$ requires *M*, 184.1099].

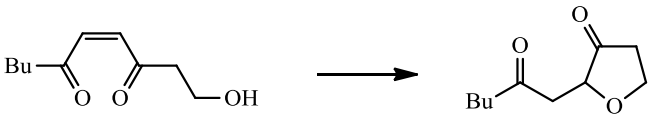
Method 2

(Z)-1-hydroxydec-4-ene-3,6-dione (121e)



106e **121e**

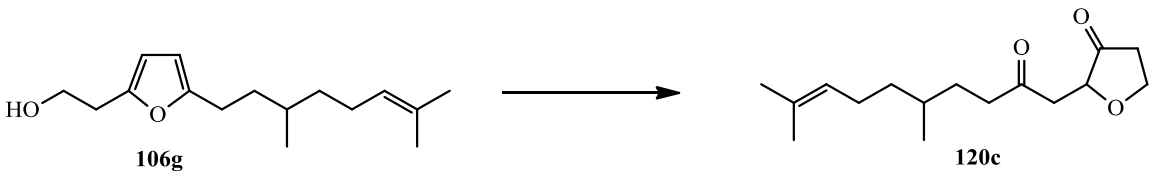
Magnesium monoperoxyphthlate (0.093 g, 0.20 mmol) was dissolved in water (1 ml) and added to a stirred solution of furylethanols **106e** (0.067 g, 0.40 mmol) and stirred at ambient temperature for 1 h. Sufficient aqueous sodium hydrogen carbonate was added to basify the solution and the product extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml) then dried, filtered and the solvent evaporated to yield *enedione* **121e** as a yellow wax (0.070 g, 95%): δ_H 6.37 (1H, d, *J* 11.9, CH), 6.32 (1H, d, *J* 11.9, CH), 3.94 (2H, t, *J* 5.4, 1-H), 2.79 (2H, t, *J* 5.4, 2-H), 2.55 (2H, t, *J* 7.4, 7-H), 1.66 – 1.54 (2H, m, 8-CH_2), 1.41 – 1.27 (2H, m, 9-CH_2), 0.91 (3H, t, *J* 7.3, 10-Me).



121e **120e**

Enedione **121e** (0.070 g, 0.380 mmol) was dissolved in acetone (1 ml) and cooled to 0 °C. Two drops conc. H_2SO_4 were added and the solution stirred for 0.5 h. The solution was basified with sufficient aqueous potassium carbonate and extracted into dichloromethane (3 x 1 ml). The solvent was dried, filtered and evaporated to yield *keto-tetrahydrofuran* **120e** as a pale yellow oil (0.035 g. 75%) with spectroscopic data as listed above.

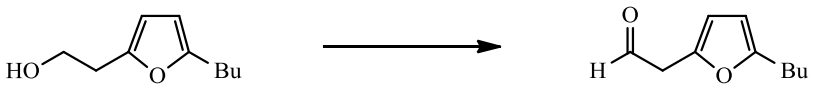
Dihydro-2-(5,9-dimethyl-2-oxodec-8-en-1-yl)furyl-3(2*H*)-one (120g)



106g **120c**

Jones reagent[170] (0.32 ml of a 2.5 M solution, 0.79 mmol) was added to a stirred solution of furylethanol **106e** (0.153 g, 0.61 mmol) in acetone (5 ml) maintained at 0 °C and stirred for 0.5 h. The mixture was then basified by the addition of sufficient aqueous potassium carbonate and the product extracted into ethyl acetate (3 x 25 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *keto-tetrahydrofuran* **120g** as a yellow oil (0.104 g, 64%): ν_{max}/cm^{-1} (film) 3065, 2935, 2886, 2817, 1760, 1715, 1421, 1392, 908, 702; δ_H 5.07 (1H, br. t, *J* 7.1, 8'-H), 4.34 (1H, app. td, *J* 9.1 and 4.1, 5-H_a), 4.10 (1H, app. td, *J* 9.1 and 7.6, 5-H_b), 3.96 (1H, app. t, *J* 4.5, 2-H), 2.99 (1H, ddd, *J* 17.8, 3.6 and 2.4, 1'-H_a), 2.84 (1H, dd, *J* 17.8, 5.5 and 1.4, 1'-H_b), 2.79 (1H, app. dt, *J* 18.0 and 9.0, 4-H_a), 2.51 (1H, ddd, *J* 18.0, 7.5 and 4.2, 4-H_b), 2.47 – 2.34 (2H, m, 3'-CH_2), 2.04 – 1.88 (2H, m, 7'-CH_2), 1.68 (3H, d, *J* 0.9, 10'-Me), 1.64 – 1.57 (1H, m, 4'-H_a), 1.60 (3H, s, 9'-Me), 1.43 – 1.36 (2H, m, 4'-H_b and 5'-H), 1.34 – 1.22 (1H, m, 6'-H_a), 1.19 – 1.10 (1H, m, 6'-H_b), 0.86 (3H, d, *J* 6.3, 5'-Me). δ_C 215.4 (3-C=O), 207.2 (C=O), 131.3 (9'-C), 124.6 (8'-CH), 75.4 (2-CH), 65.1 (5-CH_2), 44.1 (1'-CH_2), 40.7 (3'-CH_2), 36.8 (6'-CH_2), 36.4 (4-CH_2), 32.0 (5'-CH), 30.3 (4'-CH_2), 25.7 (10-Me), 25.4 (7'-CH_2), 19.3 (5'-Me), 17.6 (9'-Me); *m/z* 266 $[M]^+$ 15%, 107 (100), [Found $[M]^+$, 266.1873. $C_{16}H_{26}O_3$ requires *M*, 266.1882].

2-(5-Butylfuran-2-yl)acetaldehyde (135e)

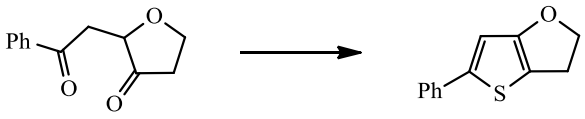


106e **135e**

2-Iodoxybenzoic acid (0.33 g, 1.19 mmol) was carefully added to a stirred solution of 2-furylethanol **106e** (0.100 g, 0.59 mmol) in dimethyl sulfoxide (10 ml) and the solution left to stir overnight. Water (50 ml) was then added and the mixture cooled to 0 °C. The resulting colourless precipitate was filtered off through a plug of celite and the filtrate extracted with ether (5 x 25 ml). The organic fraction was dried, filtered and evaporated to yield the *acetaldehyde* **135e** (0.067 g, 68%) as a colourless oil: δ_H 9.70 (1H, t, *J* 2.3, 1'-H), 6.12 (1H, d, *J* 3.0, furan-H),

5.94 (1H, d, *J* 3.0, furan-H), 3.65 (2H, d, *J* 2.3, 2'-H), 2.59 (2H, t, *J* 7.6, 1''-H), 1.64-1.54 (2H, m, 2''-CH_2), 1.40-1.30 (2H, m, 3''-CH_2), 0.89 (3H, t, *J* 7.3, 4''-Me).

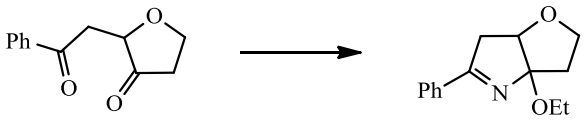
5-Phenyl-2,3-dihydrothieno[3,2-*b*]furan (136d)



120d **136d**

Lawesson's reagent[78] (0.204 g, 0.505 mmol) was added to a stirred solution of keto-tetrahydrofuran **120d** (0.086 g, 0.421 mmol) in toluene (15 ml) and heated to reflux for 2 h. The solution was filtered through silica (diethyl ether, 200 ml) to yield the *thienofuran* **136d** as a yellow oil (0.045 g, 53%): δ_H 7.57 – 7.52 (2H, m, 2 x Ar-H), 7.41 – 7.35 (2H, m, 2 x Ar-H), 7.33 – 7.29 (1H, m, Ar-H), 7.15 (1H, s, 4-H), 4.95 (1H, app. dt, *J* 11.5 and 2.4, O-CH_a), 4.30 (1H, ddd, *J* 11.5, 4.8 and 3.5, O-CH_b), 3.61 (1H, ddd, *J* 15.6, 3.4 and 1.8, O-CH_2-CH_a), 3.27 (1H, app. dt, *J* 15.6 and 2.3, O-CH_2-CH_b); δ_C 163.4 (3-C), 141.8 (C), 141.6 (C), 133.4 (C), 133.4 (CH), 129.0 (CH), 125.6 (CH), 114.0, (4-CH), 64.1 (CH_2), 30.8 (CH_2).

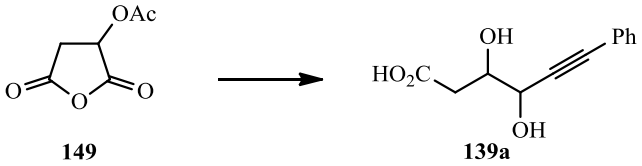
3a-Ethoxy-5-phenyl-3,3a,6,6a-tetrahydro-2*H*-furo[3,2-*b*]pyrrole (137d)



120d **137d**

Ammonium carbonate (0.16 g, 1.65 mmol) and a drop of hydrochloric acid (conc.) was added to a stirred solution of keto-tetrahydrofuran **120d** (0.068 g, 0.33 mmol) in dry ethanol (5 ml). The mixture was heated under reflux overnight before the addition of water (5 ml). Ethanol was removed under reduced pressure and the residue extracted with dichloromethane (3 x 5 ml). The combined organic extracts were washed with water (15 ml) and brine (15 ml) then dried, filtered and evaporated to yield the *pyrroline* **137d** as a brown oil (0.070 g, 92%): δ_H 7.54 – 7.47 (2H, m, 2 x Ar-H), 7.35 – 7.20 (3H, m, 3 x Ar-H), 4.54 (1H, dd, *J*, 6.6 and 1.2, 6a-H), 3.97 (1H, ddd, *J* 9.0, 7.2 and 5.3, 2-H_a), 3.76 (1H, ddd, *J* 9.0, 7.8 and 6.4, 2-H_b), 3.58 (2H, q, *J* 7.0, O-CH_2), 3.27 (1H, dd, *J* 18.5 and 6.6, 6-H_a), 3.06 (1H, dd, *J* 18.5 and 1.2, 6-H_b), 2.44 (1H, app. dt, *J* 12.5 and 7.6, 3-H_a), 2.32 (1H, app. dt, *J* 12.5 and 6.5, 3-H_b); *m/z* (APCI) 232 $[M+H]^+$ 100%, [Found $[M+H]^+$, 232.1335. $C_{14}H_{18}NO_2$ requires $[M+H]^+$, 232.1338].

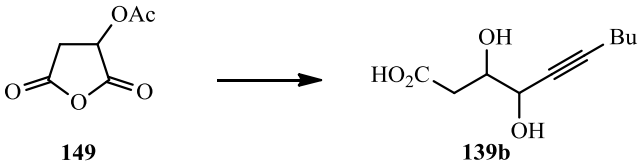
(3*RS*,4*SR*)-3,4-Dihydroxy-6-phenylhex-5-ynoic acid (139a)[89]



149 **139a**

Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of phenylacetylene **104a** (0.70 ml, 6.32 mmol) in tetrahydrofuran before transferring to a second flask containing 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran to yield the *diol* **139a** (1.18 g) as a mixture of diastereomers in a 1:2 ratio. The product could be recrystalised from chloroform to yield the *diol* as a yellow solid (0.209 g, 15%, mp = 103-105 °C), as a single diastereoisomer: R_f 0.10 (40 : 60 ethyl acetate – petroleum ether); δ_H (400 MHz; MeOD) 7.37-7.34 (2H, m, 2 x Ar-H), 7.27-7.20 (3H, m, 3 x Ar-H), 4.41 (1H, d, *J* 4.9, 4-H), 4.05 (1H, ddd, *J* 9.0, 4.9 and 3.8, 3-H), 2.67 (1H, dd, *J* 15.7 and 3.8, 2-H_a) 2.42 (1H, dd, *J* 15.7 and 9.0, 2-H_b); δ_C 174.1 (C), 131.3 (2 x Ar-CH), 128.1 (Ar-CH), 128.0 (2 x Ar-CH), 122.7 (C), 87.3 (C), 85.1 (C), 71.1 (CH), 65.5 (CH), 37.3 (2-CH_2). All data obtained matched that previously reported in the literature.[89]

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-3,4-Dihydroxydec-5-ynoic acid (139b)

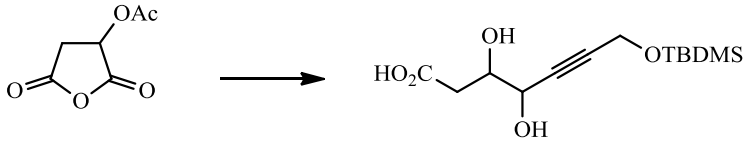


149 **139b**

Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added to a solution of 1-hexyne **104b** (0.72 ml, 6.32 mmol) in tetrahydrofuran. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran to yield a yellow wax, the *diol* **139b** (1.05 g, 83%), which was of suitable quality for all proceeding transformations, contained a mixture of two diastereomers in a 51:49 ratio. Recrystallisation of a small portion (0.1 g) from methanol yielded pure *diol* **139b** as a colourless solid (0.09 g): R_f 0.10 (40 : 60 ethyl acetate – petroleum ether); ν_{max}/cm^{-1} (nujol) 3422, 2962, 2930, 2864, 2234, 1710, 1460, 1420, 1398, 1266, 1156, 1062, 1020, 972, 932, 736, 700; δ_H 4.41 (0.51 H, dt, *J* 3.6 and 2.0, 4-H), 4.22 (0.49H, dt, *J* 6.5 and 1.8, 4-H), 4.05 (0.51H, ddd, *J* 5.7, 3.6 and 1.7, 3-H), 4.01 (0.49H, ddd, *J* 6.5, 5.3, and 2.2, 3-H), 2.82 (0.51H, dd, *J* 17.8 and 5.7, 2-H_a), 2.62 (0.49H, dd, *J* 17.7 and 5.3, 2-

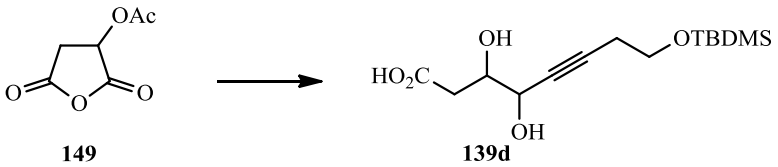
H_a), 2.53 (0.49H, dd, *J* 17.7 and 2.2, 2-H_b), 2.41 (0.51H, dd, *J* 17.8 and 1.7, 2-H_b), 2.20 (0.98H, dt, *J* 7.1 and 2.0, 7-CH_2), 2.10 (1.02H, dt, *J* 7.0 and 1.8, 7-CH_2), 1.50-1.20 (4H, m, 8- and 9-CH_2), 0.85-0.76 (3H, m, 10-Me); δ_C *major* 176.6 (C=O), 90.7 (C), 77.5 (CH), 73.9 (C), 73.5 (CH), 36.9 (CH_2), 30.2 (CH_2), 21.9 (CH_2), 18.4 (CH_2), 13.6 (10-Me); δ_C *minor* 174.6 (C), 93.7 (C), 75.3 (CH), 71.1 (C), 68.5 (CH), 37.2 (CH_2), 30.5 (CH_2), 22.0 (CH_2), 18.4 (CH_2), 13.6 (10-Me); *m/z* 182 [M – H_2O] < 1%, 111 (100) [Found [M – H_2O], 182.0948. $C_{10}H_{14}O_3$ requires *M-H_2O*, 182.0943].

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-7((*tert*-Butyl)dimethylsilyloxy)-3,4-dihydroxyhept-5-ynoic acid (139c)



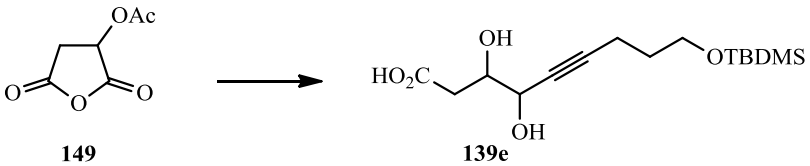
Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of alkyne **104c** (1.08 g, 6.32 mmol) in tetrahydrofuran. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran to yield a yellow oil, the *diol* **139c** (1.18 g, 65%), which was of suitable quality for all proceeding transformations, contained a mixture of 2 diastereomers in a 51:49 ratio: ν_{max}/cm^{-1} (film) 3375, 2928, 2857, 2233, 1710, 1576, 1471, 1362, 1326, 1255, 1154, 1106, 975, 837, 777, 738, 662； δ_H 4.42 (0.51 H, dt, *J* 4.0 and 2.0, 4-H), 4.38 (0.49H, dt, *J* 3.4 and 1.8, 4-H), 4.08 (0.51H, ddd, *J* 5.7, 3.4 and 1.7, 3-H), 4.00 (0.49H, ddd, *J* 5.3, 4.0 and 2.2, 3-H), 3.95 (0.98H, d, *J* 2.0, 7-CH_2), 3.91 (1.02H, d, *J* 1.8, 7-CH_2), 2.82 (0.51H, dd, *J* 17.8 and 5.7, 2-H_a), 2.62 (0.49H, dd, *J* 17.7 and 5.3, 2-H_a), 2.53 (0.49H, dd, *J* 17.7 and 2.2, 2-H_b), 2.41 (0.51H, dd, *J* 17.8 and 1.7, 2-H_b), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_C *major* 176.6 (C), 90.7 (C), 77.5 (CH), 73.9 (C), 73.5 (CH), 71.4 (CH_2), 36.9 (2-CH_2), 25.9 (*t*-Bu Me), 18.3 (C), -5.3(Si-Me); δ_C *minor* 174.6 (C), 93.7 (C), 75.3 (CH), 73.5 (CH_2), 71.1 (C), 68.5 (CH), 37.2 (2-CH_2), 25.9 (*t*-Bu Me), 18.3 (C), -5.3 (Si-Me); *m/z* 156 ([M] - TBDMS - H_2O) 46%, 106 (100).

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-8((*tert*-Butyl)dimethylsilyloxy)-3,4-dihydroxyoct-5-ynoic acid (139d)



Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of alkyne **104d** (1.16 g, 6.32 mmol) in tetrahydrofuran. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxyxuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran to yield a yellow oil, the *diol* **139c** (1.34 g, 70%), which was of suitable quality for all proceeding transformations, contained a mixture of two diastereomers in a 55:45 ratio: ν_{max}/cm^{-1} (film) 3374, 2927, 2855, 2234, 1711, 1577, 1470, 1363, 1326, 1255, 1154, 1110, 975, 837, 777, 740, 660; δ_H 4.45 (0.55 H, dt, *J* 4.0 and 2.0, 4-H), 4.28 (0.45H, dt, *J* 3.4 and 1.8, 4-H), 4.05 (0.55H, ddd, *J* 5.7, 3.4 and 1.7, 3-H), 4.00 (0.45H, ddd, *J* 5.3, 4.0 and 2.2, 3-H), 3.85 (2H, t, *J* 7.3, 8-CH_2), 2.82 (0.55H, dd, *J* 17.8 and 5.7, 2-H_a), 2.62 (0.45H, dd, *J* 17.7 and 5.3, 2-H_a), 2.53 (0.45H, dd, *J* 17.7 and 2.2, 2-H_b), 2.41 (0.55H, dd, *J* 17.8 and 1.7, 2-H_b), 2.36 (0.90H, dt, *J* 7.3 and 2.0, 7-CH_2), 2.30 (1.10H, dt, *J* 7.3 and 1.8, 7-CH_2) 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_C *major* 176.2 (C=O), 91.2 (C), 77.8 (CH), 74.0 (C), 73.7 (CH), 61.4 (8-CH_2), 37.8 (CH_2) 36.9 (CH_2), 25.9 (*t*-Bu Me), 18.3 (C), -5.3(Si-Me); δ_C *minor* 174.5 (C), 93.5 (C), 75.2 (CH), 71.1 (C), 68.5 (CH), 62.4 (8-CH_2), 37.6 (CH_2), 37.2 (CH_2), 25.9 (*t*-Bu Me), 18.3 (C), -5.3 (Si-Me).

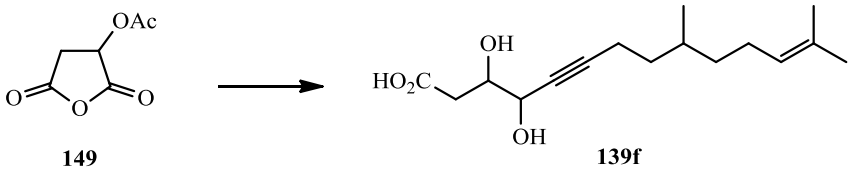
(3*RS*,4*RS*)- and (3*RS*,4*SR*)-9((*tert*-Butyl)dimethylsilyloxy)-3,4-dihydroxynon-5-ynoic acid (139e)



Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of alkyne **104e** (1.25 g, 6.32 mmol) in tetrahydrofuran. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran to yield a yellow oil, the *diol* **139e** (1.40 g, 69%), which was of suitable quality for all proceeding transformations,

contained a mixture of two diastereomers in a 57:43 ratio: ν_{max}/cm^{-1} (film) 3370, 2928, 2860, 2235, 1710, 1576, 1470, 1363, 1326, 1254, 1153, 1110, 975, 837, 777, 740, 660; δ_H 4.45 (0.57 H, dt, *J* 4.0 and 2.0, 4-H), 4.28 (0.43H, dt, *J* 3.4 and 1.8, 4-H), 4.05 (0.57H, ddd, *J* 5.7, 3.4 and 1.7, 3-H), 4.00 (0.43H, ddd, *J* 5.3, 4.0 and 2.2, 3-H), 3.64 (2H, t, *J* 7.3, 9-CH_2), 2.82 (0.57H, dd, *J* 17.8 and 5.7, 2-H_a), 2.62 (0.43H, dd, *J* 17.7 and 5.3, 2-H_a), 2.53 (0.43H, dd, *J* 17.7 and 2.2, 2-H_b), 2.41 (0.57H, dd, *J* 17.8 and 1.7, 2-H_b), 2.36 (0.86H, dt, *J* 7.3 and 2.0, 7-CH_2), 2.30 (1.14H, dt, *J* 7.3 and 1.8, 7-CH_2), 1.65 – 1.55 (2H, m, 8-CH_2), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_C *major* 176.0 (C), 91.1 (C), 77.8 (CH), 74.0 (C), 73.7 (CH), 61.4 (9-CH_2), 36.5 (CH_2) 31.9 (CH_2), 25.9 (*t*-Bu Me), 18.3 (C), 15.4 (CH_2), -5.3(Si-Me); δ_C *minor* 174.5 (C), 93.5 (C), 75.2 (CH), 71.1 (C), 68.5 (CH), 62.4 (9-CH_2), 37.6 (CH_2), 31.2 (CH_2), 25.9 (*t*-Bu Me), 18.3 (C), 15.1 (CH_2), -5.3 (Si-Me).

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-3,4-Dihydroxy-9,13-dimethyltetradec-12-en-5-ynoic acid (139f)

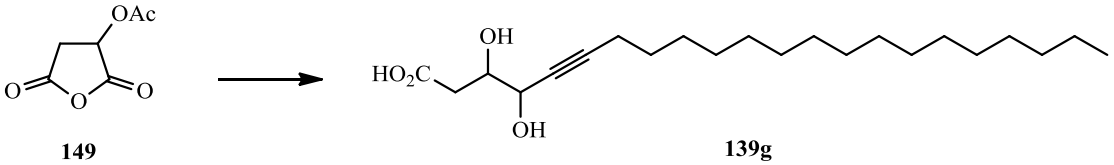


149 **139f**

Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of citronellyl acetylene **104f** (1.04 g, 6.32 mmol) in tetrahydrofuran. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran to yield a yellow oil, the *diol* **139f** (1.32 g, 74%), which was of suitable quality for all proceeding transformations, contained a mixture of 2 diastereomers in a 52:48 ratio: ν_{max}/cm^{-1} (film) 3491, 3224, 2929, 2213, 1714, 1533, 1434, 1377, 1262, 1078, 895, 739; δ_H 5.06 (1H, br. t, *J* 6.5, 12-H), 4.44 (0.52H, dt, *J* 3.6 and 2.0, 4-H), 4.26 (0.48H, dt, *J* 6.6 and 1.8, 4-H), 4.12 (0.52H, app. dt, *J* 5.7, 3.6, 1.8, 3-H), 3.99 (0.48H, ddd, *J* 6.6, 3.1, 2.8, 3-H), 2.88 (0.48H, dd, *J* 16.5 and 2.8, 2-H_a), 2.74 (0.52H, dd, *J* 16.5 and 3.6, 2-H_a), 2.65 (0.48H, dd, *J* 16.5 and 2.2, 2-H_b), 2.41 (0.52H, dd, *J* 16.5 and 1.7, 2-H_b), 2.25 – 2.10 (4H, m, 7-CH_2 and 11-CH_2), 1.68 (3H, app. s, 13-Me), 1.61 (3H, app. s, 14-Me), 1.60 – 1.51 (2H, m), 1.39 – 1.28 (2H, m), 1.18 – 1.12 (1H, m, 9-H), 0.88 (3H, d, *J* 6.4, 9-Me); δ_C *major* 176.6 (C=O), 131.4 (13-C), 124.6 (12-CH), 88.4 (C) 71.6 (CH), 67.9 (C), 65.6 (CH), 36.6 (CH_2), 36.3 (CH_2), 35.5 (CH_2), 31.8 (9-CH), 25.7 (14-Me), 25.4 (CH_2), 19.0 (13-Me), 17.7 (9-Me) 16.4 (CH_2), δ_C *minor* 171.6 (C=O), 131.3 (13-

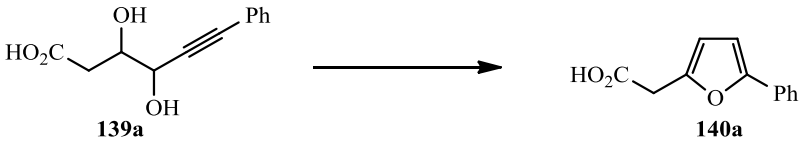
C), 124.7 (12-CH), 88.6 (C), 70.7 (CH), 67.9 (C), 65.4 (CH), 37.3 (CH_2), 36.7 (CH_2), 35.6 (CH_2), 31.6 (9-CH), 25.7 (14-Me), 25.4 (CH_2), 19.0 (13-Me), 17.7 (9-Me), 16.1 (CH_2).

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-3,4-Dihydroxydocos-5-ynoic acid (139g)



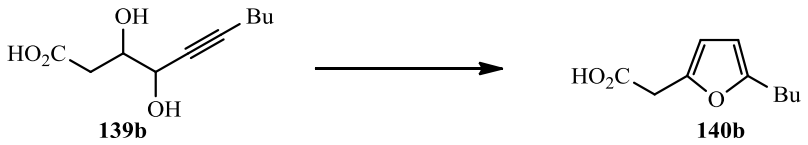
Using the general procedure *n*-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol,) was added dropwise to a solution of 1-octadecyne **104g** (1.58 g, 6.32 mmol,) in tetrahydrofuran. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran. After stirring for 1 h, sodium borohydride (0.25 g) in ethanol (5 ml) was added and stirring continued for a further 0.5 h to yield a yellow wax, the *diol* **139g** (2.00 g, 86%), which was of suitable quality for all proceeding transformations, contained a mixture of two diastereomers in a 55:45 ratio: ν_{max}/cm^{-1} (film) 3481, 2964, 2930, 2220, 1537, 1431, 1354, 1262, 1078, 896, 732; δ_H 4.55 (0.55H, dt, *J* 3.4 and 1.8, 4-H), 4.46 – 4.42 (0.45H, m, 4-H), 4.24 – 3.96 (1H, m, 3-H), 2.88 – 2.50 (2H, m, 2-CH_2), 2.18 – 2.06 (4H, m, 7-CH_2 8-CH_2), 1.50 – 1.40 (2H, m, 9-CH_2), 1.24 (22H, br. s, 10-CH_2 – 21-CH_2), 0.81 (3H, t, *J* 6.8, 22-Me).

2-(5-Phenylfuran-2-yl)acetic acid (140a)[169]



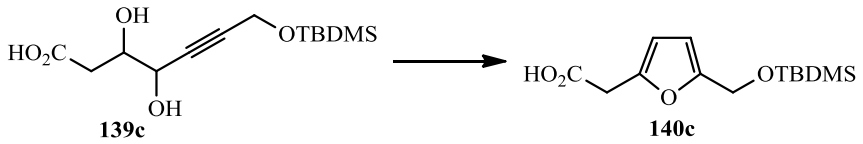
Using the general procedure (18 h), 10% $AgNO_3.SiO_2$ (1.33 g, 0.78 mmol) was stirred with a solution of diol **139a** (1.72 g, 7.80 mmol), as a 2:1 mixture of diastereoisomers, in dichloromethane to yield the *furan* **140a** as a yellow solid (1.40 g, 89%, mp = 78-79 °C): R_f 0.35 (30 : 70 ethyl acetate – petroleum ether); δ_H (MeOD) 7.57 (2H, d, *J* 8.3, 2 x Ar-H), 7.31-7.25 (2H, m, 2 x Ar-H), 7.17 (1H, tt, *J* 7.4 and 1.1, Ar-H), 6.53 (1H, d, *J* 3.3, furan-H), 6.27 (1H, d, *J* 3.3, furan-H), 3.74 (2H, s, 1'-CH_2); δ_C (MeOD) 179.1 (C=O), 153.8 (C), 146.6 (C), 130.7 (C), 128.6 (2 x Ar-CH), 127.3 (2 x Ar-CH), 123.7 (Ar-CH), 110.6 (CH), 105.9 (CH), 30.9 (1'-CH_2); *m/z* (APCI) 203 $[M+H]^+$ 100%, 157 (37), [Found $[M+H]^+$, 203.0714. $C_{12}H_{11}O_3$ requires *M+H*, 203.0708. All data obtained matched those previously reported in the literature.[169]

2-(5-Butylfuran-2-yl)acetic acid (140b)



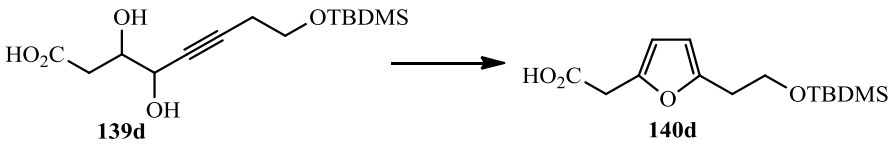
Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.21 g, 0.125 mmol) was stirred with a solution of diol **139b** (0.250 g, 1.25 mmol) in dichloromethane to yield the *furan* **140b** as an orange oil (0.216 g, 95%): ν_{max}/cm^{-1} (film) 3422, 2960, 2873, 1716, 1566, 1466, 1420, 1232, 1015, 906, 733, 650; δ_H 6.06 (1H, d, *J* 3.0, furan-H), 5.85 (1H, d, *J* 3.0, furan-H), 3.62 (2H, s, 1'-CH_2), 2.52 (2H, t, *J* 7.6, 1''-CH_2), 1.58-1.48 (2H, m, 2''-CH_2), 1.36-1.24 (2H, m, 3''-CH_2), 0.85 (3H, t, *J* 7.3, 4''-Me); δ_C 175.6 (C=O), 156.5 (C), 144.8 (C), 108.9 (CH), 105.5 (CH), 33.9 (CH_2), 30.1 (CH_2), 27.7 (CH_2), 22.3 (CH_2), 13.8 (4''-Me); *m/z* 182 [M] 50%, 137 (100), [Found [M], 182.0946. $C_{10}H_{14}O_3$ requires *M*, 182.0943].

2-(5-((*tert*-Butyl)dimethylsilyloxy)methyl)furan-2-yl)acetic acid (140c)



Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.21 g, 0.125 mmol) was stirred with a solution of diol **139c** (0.360 g, 1.25 mmol) in dichloromethane to yield the *furan* **140c** as a yellow oil (0.308 g, 91%): ν_{max}/cm^{-1} (film) 3428, 2960, 2843, 1717, 1564, 1462, 1420, 1391, 1235, 1107, 1015, 906, 777, 735; δ_H 6.05 (1H, d, *J* 3.0, furan-H), 5.91 (1H, d, *J* 3.0, furan-H), 4.05 (2H, s, 1''-CH_2), 3.63 (2H, s, 1'-CH_2), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_C 175.2 (C=O), 155.8 (C), 151.9 (C), 108.7 (CH), 105.5 (CH), 63.4 (1''-CH_2) 33.9 (1'-CH_2), 26.0 (*t*-Bu Me) 18.4 (C), -5.3 (Si-Me).

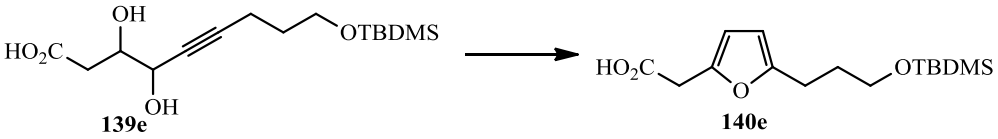
2-(5-((*tert*-Butyl)dimethylsilyloxy)ethyl)furan-2-yl)acetic acid (140d)



Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.21 g, 0.125 mmol) was stirred with a solution of diol **139c** (0.378 g, 1.25 mmol) in dichloromethane to yield the *furan* **140d** as a yellow oil (0.337 g, 95%): ν_{max}/cm^{-1} (film) 3429, 2960, 2845, 1715, 1563, 1460, 1421, 1391,

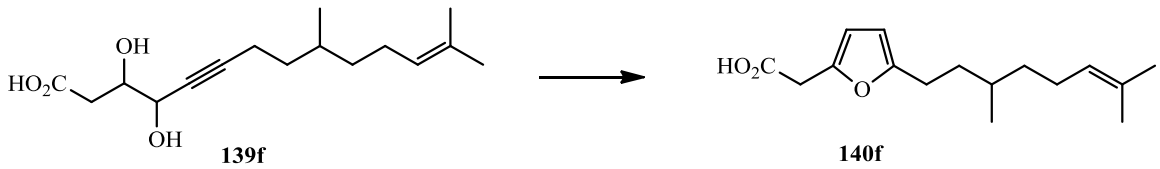
1235, 1107, 1015, 910, 778, 735; δ_H 6.04 (1H, d, *J* 3.0, furan-H), 5.87 (1H, d, *J* 3.0, furan-H), 3.80 (2H, t, *J* 7.3, 2''-CH_2), 3.63 (2H, s, 1'-CH_2), 2.75 (2H, t, *J* 7.3, 1''-CH_2), 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_C 175.1 (C=O), 155.5 (C), 151.7 (C), 108.6 (CH), 105.2 (CH), 60.4 (2''-CH_2) 33.9 (CH_2), 32.4 (CH_2), 26.0 (*t*-Bu Me) 18.4 (C), -5.3 (Si-Me).

2-(5-((*tert*-Butyl)dimethylsilyloxy)propyl)furan-2-yl)acetic acid (140e)



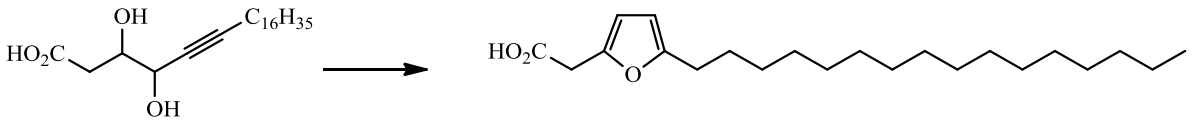
Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.21 g, 0.125 mmol) was stirred with a solution of diol **139c** (0.395 g, 1.25 mmol) in dichloromethane to yield the *furan* **140d** as a yellow oil (0.354 g, 95%): ν_{max}/cm^{-1} (film) 3431, 2962, 2842, 1716, 1563, 1461, 1421, 1391, 1236, 1107, 1015, 912, 778, 730; δ_H 6.02 (1H, d, *J* 3.0, furan-H), 5.85 (1H, d, *J* 3.0, furan-H), 3.80 (2H, t, *J* 7.3, 3''-CH_2), 3.62 (2H, s, 1'-CH_2), 2.75 (2H, t, *J* 7.3, 1''-CH_2), 1.65 – 1.55 (2H, m, 2''-CH_2) 0.84 (9H, s, *t*-Bu Me), 0.00 (6H, s, Si-Me); δ_C 175.2 (C=O), 155.5 (C), 151.7 (C), 108.6 (CH), 105.8 (CH), 62.3 (3''-CH_2) 33.9 (CH_2), 32.4 (CH_2), 26.0 (*t*-Bu Me), 24.4 (CH_2), 18.4 (C), -5.3 (Si-Me).

2-(5-(3,7-Dimethyloct-6-en-1-yl)furan-2-yl)acetic acid (140f)



Using the general procedure (4 h), 10% $AgNO_3.SiO_2$ (0.21 g, 0.125 mmol) was stirred with a solution of diol **139f** (0.353 g, 1.25 mmol) in dichloromethane to yield the *furan* **140f** as a yellow oil (0.311 g, 94%): υ_{max}/cm^{-1} (film) 3465, 3031, 2931, 1716, 1617, 1551, 1453, 1376, 1270, 1121, 947, 884; δ_H 6.13 (1H, d, *J* 3.0, furan-H), 5.92 (1H, d, *J* 3.0, furan-H), 5.10 (1H, br. t, *J* 7.0, 6''-H), 3.69 (2H, s, 1'-CH_2), 2.69- 2.50 (2H, m, 1''-CH_2), 2.06-1.90 (2H, m, 5''-CH_2), 1.69 (3H, app. s, 7''-Me), 1.61 (3H, app. s, 8''-Me), 1.51-1.40 (4H, m, 2''-CH_2 and 4''-CH_2), 1.19-1.09 (1H, m, 3''-H), 0.92 (3H, d, *J* 6.1, 3''-Me); δ_C 175.6 (C=O), 156.5 (C), 144.8 (C), 131.2 (7''-C), 124.9 (6''-CH), 108.9 (CH), 105.5 (H) 36.9 (1'-CH_2), 35.3 (CH_2), 33.9 (CH_2), 32.0 (3''-CH), 25.7 (8''-Me), 25.7 (CH_2), 25.5 (CH_2), 19.4 (3''-Me), 17.7 (7''-Me); *m/z* 264 $[M]^+$ 40%, 219 (100), [Found [M], 264.1723. $C_{16}H_{24}O_3$ requires *M*, 264.1725].

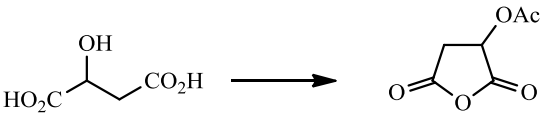
2-(5-hexadecylfuran-2-yl)acetic acid (141b) – Plakorsin B



139g **141b**

Using the general procedure (4 h), 10% $AgNO_3.SiO_2$ (0.40 g, 0.240 mmol) was stirred with a solution of diol **139g** (0.883 g, 2.40 mmol) in dichloromethane to yield the *furan* **141b** as a pale yellow wax (0.563 g, 67%): υ_{max}/cm^{-1} (DCM) 3577, 3035, 1706, 1521, 1444, 1345, 1218, 1010, 952, 771; δ_H 6.13 (1H, d, *J* 3.1, furan-H), 5.92 (1H, d, *J* 3.1, furan-H), 3.69 (2H, s, 1'-CH_2), 2.58 (2H, t, *J* 7.7, 1''-CH_2), 1.58 – 1.48 (2H, m, 2''-CH_2), 1.44 – 1.32 (2H, m, 3''-CH_2), 1.27 (24H, br. s, 4''-CH_2 – 15''-CH_2), 0.89 (3H, t, *J* 6.8, 16''-Me); δ_C 175.4 (C=O), 156.2 (C), 145.4 (C), 108.7 (CH), 105.3 (CH), 33.8 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 28.0 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 22.1 (CH_2), 14.2 (Me); *m/z* 350 $[M]^+$ 17%, 305 (5), 139 (100) [Found $[M]^+$, 350.2808. $C_{22}H_{38}O_3$ requires *M*, 350.2821]. All data obtained matched those previously reported in the literature.[171]

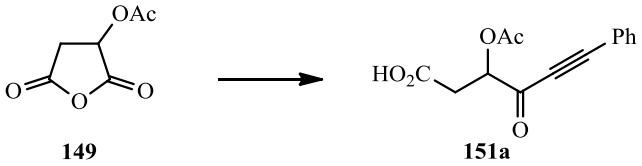
2-Acetoxysuccinic anhydride (149)[89]



148 **149**

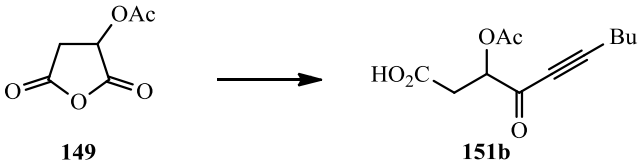
Racemic malic acid **148** (10.0 g, 75 mmol) was added to acetyl chloride (75 ml) in a 250 ml round bottom flask fitted with a reflux condenser and the resulting solution heated to 40 ˚C and stirred vigorously for 2 h. Using a water pump, acetic acid and excess acetyl chloride were removed under reduced pressure. The viscous residue was then recrystallised from hot toluene to yield *2-acetoxysuccinic anhydride* (10.602 g, 89%, mp = 55-57 ˚C (lit. mp. (*S*) = 54-56 ˚C[12]; (*R*) = 56-58 ˚C[12])): δ_H (400 MHz; $CDCl_3$) 5.54 (1H, dd, *J* 9.6 and 6.4, 2-H), 3.39 (1H, dd, *J* 18.9 and 9.6, 3-Ha), 3.05 (1H, dd, *J* 18.9 and 6.4, 3-Hb), 2.21 (3H, s, Me). All data obtained matched those previously reported in the literature.[89]

3-Acetoxy-4-oxo-6-phenylhex-5-ynoic acid (151a)



n-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of phenylacetylene **104a** (0.70 ml, 6.32 mmol) in tetrahydrofuran (10 ml) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran (10 ml), which was also maintained at -78 °C. After stirring for 0.5 h, aqueous ammonium chloride (5 ml) was added. The product was extracted with ethyl acetate (3 x 25 ml), the combined extracts washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *keto-acid* **151a** as a yellow oil (1.41 g, 86%): υ_{max}/cm^{-1} (film) 3488, 3063, 2935, 2593, 2199, 1747, 1710, 1681, 1574, 1490, 1374, 1228, 1078, 1042, 997, 912, 844, 759, 733, 689; δ_H 7.58 (2H, dd, *J* 8.1 and 1.2, 2 x Ar-H), 7.77 (1H, td, *J* 7.7 and 1.2, Ar-H), 7.41 (2H, app. t, *J* 7.7, 2 x Ar-H), 5.65 (1H, dd, *J* 8.1 and 4.0, 3-H), 3.11 (1H, dd, *J* 17.1 and 4.0, 2-H_a), 2.98 (1H, dd, *J* 17.1 and 8.1, 2-H_b), 2.22 (3H, s, Me); δ_C 182.2 (4-C=O), 173.9 (1-C=O), 169.8 (O-C=O), 133.2 (2 x Ar-CH), 131.3 (Ar-CH), 128.8 (2 x Ar-CH), 119.3 (C), 95.6 (C), 85.1 (C), 74.5 (3-CH), 35.2 (2-CH_2), 20.7 (Me).

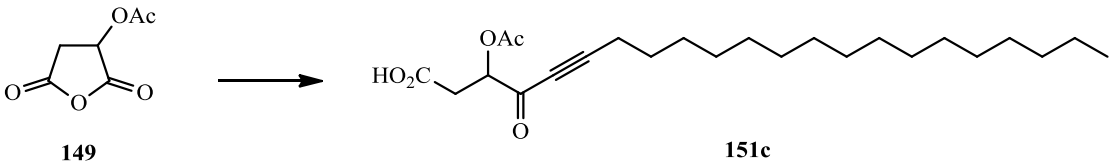
3-Acetoxy-4-oxo-dec-5-ynoic acid (151b)



n-BuLi (2.5 ml of a 2.5M solution in hexanes, 6.32 mmol) was added dropwise to a solution of 1-hexyne **104b** (0.73 ml, 6.32 mmol) in tetrahydrofuran (10 ml) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (1.00 g, 6.32 mmol) in tetrahydrofuran (10 ml), which was also maintained at -78 °C. After stirring for 0.5 h, aqueous ammonium chloride solution (5 ml) was added to quench the reaction. The product was extracted with ethyl acetate (3 x 25 ml), washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *keto-acid* **151b** as a pale yellow oil (1.12 g, 74%): υ_{max}/cm^{-1} (film) 3507, 2960, 2936,

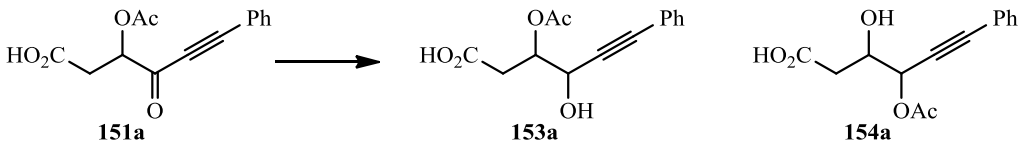
2874, 2211, 1750, 1711, 1689, 1423, 1374, 1230, 1049, 1011, 946, 815, 848, 799; δ_H 5.5 (1H, dd, *J* 8.2 and 3.9, 3-H), 3.05 (1H, dd, *J* 17.1 and 3.9, 2-H_a), 2.91 (1H, dd, *J* 17.1 and 8.2, 2-H_b), 2.41 (2H, t, *J* 7.1, 7-CH_2), 2.18 (3H, s, Me), 1.62 – 1.54 (2H, m, 8-CH_2), 1.48 – 1.38 (2H, m, 9-CH_2), 0.93 (3H, t, *J* 7.3, 10-Me); δ_C 182.3 (4-C=O), 174.4 (1-C=O), 169.9 (O-C=O), 99.9 (C), 78.2 (C), 74.7 (3-CH), 35.1 (2-CH_2), 21.9 (CH_2), 20.6 (Me), 18.9 (CH_2), 13.4 (10-Me).

3-Acetoxy-4-oxodocos-5-ynoic acid (151c)



n-BuLi (0.49 ml of a 2.5M solution in hexanes, 1.21 mmol) was added dropwise to a solution of 1-octadecyne **104g** (0.302 g, 1.21 mmol) in tetrahydrofuran (5 ml) maintained at -78 °C. The solution was stirred for 0.5 h before being transferred to a second flask containing a stirred solution of 2-acetoxysuccinic anhydride **149** (0.190 g, 1.21 mmol) in tetrahydrofuran (5 ml), which was also maintained at -78 °C. After stirring for 0.5 h, aqueous ammonium chloride (2 ml) was added to quench the reaction. The product was extracted with ethyl acetate (3 x 10 ml), washed with water (20 ml) and brine (20 ml) then dried, filtered and evaporated to yield the *keto-acid* **151c** as a pale yellow wax (0.301 g, 61%) υ_{max}/cm^{-1} (DCM) 3465, 2960, 2933, 2210, 1750, 1710, 1690, 1453, 1370, 1235, 1051, 1010, 942, 912, 848; δ_H 5.51 (1H, dd, *J*, 8.3 and 3.8, 3-H), 3.04 (1H, dd, *J* 17.0 and 3.8, 2-H_a), 2.89 (1H, dd, *J* 17.0 and 8.3, 2-H_b), 2.40 (2H, t, *J* 7.2, 7-CH_2), 1.66 – 1.48 (2H, m, 8-CH_2), 1.44 – 1.35 (2H, m, 9-CH_2), 1.25 (24H, br. s, 10-CH_2 – 21-CH_2), 0.88 (3H, t, 6.8, 22-Me).

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-3-Acetoxy-4-hydroxy-6-phenylhex-5-ynoic acid (153a) and (3*RS*,4*RS*)- and (3*RS*,4*SR*)-4-Acetoxy-3-hydroxy-6-phenylhex-5-ynoic acid (154a)



To a stirred solution of keto-acid **151a** (1.41 g, 5.42 mmol) in tetrahydrofuran (20 ml) maintained at -78 °C was added a solution of sodium borohydride (0.21 g) in ethanol (5 ml) and the resulting mixture stirred for 0.25 h. Aqueous ammonium chloride (5 ml) was added and the product extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with

water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *hydroxy-acids* **153a** and **154a** (1.26 g, 87%), in a 55:45 ratio and contained a mixture of 2 diastereomers of each hydroxy-acid in a 2:1 ratio, as a pale yellow oil: υ_{max}/cm^{-1} (film) 3425, 3068, 2930, 2233, 1746, 1730, 1491, 1374, 1230, 1038, 758, 691.

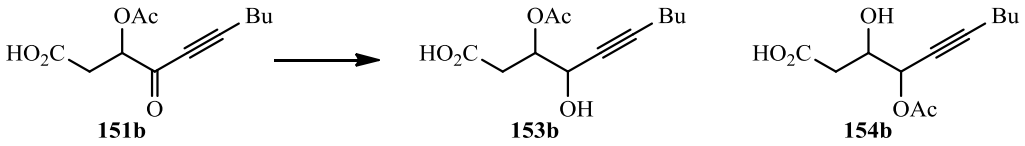
Hydroxy-acid **153a**

δ_H 7.47 – 7.41 (2H, m, 2 x Ar-H), 7.35 – 7.29 (3H, m, 3 x Ar-H), 5.43 (1H, app. dt, *J* 7.7 and 4.1, 3-H), 4.86 (0.67H, d, *J* 3.9, 4-H), 4.77 (0.33H, d, *J* 5.4, 4-H), 3.04 – 2.72 (2H, m, 2-CH_2), 2.17 (2.01H, s, Me), 2.16 (0.99H, s, Me); δ_C *major* 171.3 (C=O), 169.9, (C=O), 131.8 (2 x Ar-H), 129.1 (Ar-H), 128.3 (2 x Ar-H), 121.5 (C), 85.2 (C), 82.5 (C), 72.4 (3-CH), 63.9 (4-CH), 36.6 (2-CH_2), 21.0 (Me); δ_C *minor* 171.3 (C=O), 169.9, (C=O), 131.8 (2 x Ar-H), 129.1 (Ar-H), 128.3 (2 x Ar-H), 121.5 (C), 85.2 (C), 82.5 (C),71.9, (CH), 63.8 (4-CH), 37.02 (2-CH_2), 21.0 (Me).

Hydroxy-acid **154a**

δ_H 7.47 – 7.41 (2H, m, 2 x Ar-H), 7.35 – 7.29 (3H, m, 3 x Ar-H), 5.72 (0.67H, d, *J* 3.7, 4-H), 5.67 (0.33H, d, *J* 6.3, 4-H), 4.39 (0.67H, app. dt, *J* 8.7 and 3.7, 3-H), 4.34 (0.33H, ddd, *J* 9.0, 6.3 and 3.5, 3-H), 3.04 – 2.72 (2H, m, 2-CH_2), 2.13 (2.01H, s, Me), 2.12 (0.99H, s, Me); δ_C *major* 171.3 (C=O), 169.9, (C=O), 132.02 (2 x Ar-H), 128.9 (Ar-H), 128.5 (C), 128.3 (2 x Ar-H), 85.5 (C), 82.5 (C), 69.2 (3-CH_2), 67.0 (CH), 34.5 (2-CH_2), 21.0 (Me); δ_C *minor* 171.3 (C=O), 169.9, (C=O), 132.02 (2 x Ar-H), 128.9 (Ar-H), 128.5 (C), 128.3 (2 x Ar-H), 85.5 (C), 82.5 (C), 69.1 (CH), 63.8 (CH), 34.9 (2-CH_2), 21.0 (Me).

(3*RS*,4*RS*)- and (3*RS*,4*SR*)-3-Acetoxy-4-hydroxy-6-phenylhex-5-ynoic acid (153b) and (3*RS*,4*RS*)- and (3*RS*,4*SR*)-4-Acetoxy-3-hydroxy-6-phenylhex-5-ynoic acid (154b)



To a stirred solution of keto-acid **151b** (1.20 g, 5.01 mmol) in tetrahydrofuran (20 ml) maintained at -78 °C was added a solution of sodium borohydride (0.19 g) in ethanol (5 ml) and stirred for 0.25 h. Aqueous ammonium chloride (5 ml) was added and the product extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *hydroxy-acids* **153b** and **154b** (1.02 g, 84%), in a 53:47 ratio and contained a mixture of two diastereomers of each hydroxy-acid in a

51:49 ratio, as a pale yellow oil: υ_{max}/cm^{-1} (film) 3497, 2955, 2932, 2874, 2220, 1741, 1421, 1370, 1230, 1049, 1001, 951, 814, 847, 799.

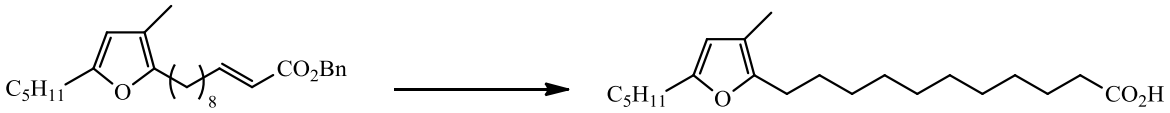
Hydroxy-acid **153b**

δ_H 5.35 – 5.25 (1H, m, 3-H), 4.62 (0.51H, dt, *J* 3.9 and 2.0, 4-H), 4.52 (0.49H, dt, *J* 5.4 and 1.9, 4-H), 2.98 – 2.61 (2H, m, 2-CH_2), 2.23 (2H, dt, *J* 7.0 and 4.9, 2.27 – 2.19 (2H, m, 7-CH_2), 2.13 (1.53H, s, Me), 2.12 (1.47H, s, Me), 1.55 – 1.46 (2H, m, 8-CH_2), 1.45 – 1.34 (2H, m, 9-CH_2), 0.92 (3H, t, *J* 7.3, 10-Me).

Hydroxy-acid **154b**

δ_H 5.47 (0.51H, dt, *J* 3.8 and 2.0, 4-H), 5.42 (0.49H, dt, *J* 4.2 and 2.0, 4-H), 4.27 (0.51H, app. dt, *J* 8.7 and 3.8, 3-H), 4.21 (0.49H, ddd, *J* 9.4, 6.2 and 4.2, 3-H), 2.98 – 2.61 (2H, m, 2-CH_2), 2.27 – 2.19 (2H, m, 7-CH_2), 2.11 (1.53H, s, Me), 2.10 (1.47H, s, Me), 1.55 – 1.46 (2H, m, 8-CH_2), 1.45 – 1.34 (2H, m, 9-CH_2), 0.92 (3H, t, *J* 7.3, 10-Me).

11-(3-methyl-5-pentylfuran-2-yl)undecanoic acid (155e) – F_5 furan fatty acid

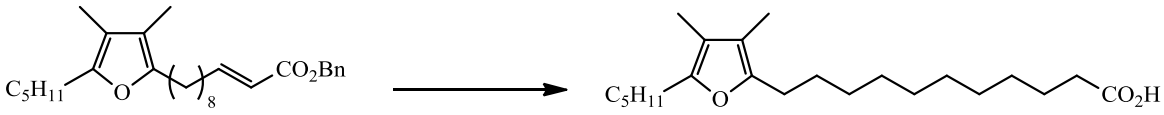


246a **155e**

A 250 ml round-bottomed flask was fitted with a three way tap and charged with 10% w/w palladium on carbon (0.072 g, 0.067 mmol). Methanol (50 ml) was added carefully followed by benzyl ester **246a** (0.573 g, 1.35 mmol). The flask was evacuated, flushed with hydrogen (x 3) and the mixture stirred for 1 h. The mixture was then filtered through a silica plug and the solvent evaporated. The residue was diluted with diethyl ether (30 ml) washed with water (3 x 20 ml), then the solvent was dried, filtered and evaporated and the product purified by column chromatography to yield the *furan fatty acid* **155e** as a colourless oil (pentane/diethyl ether, 95 : 5):υ_{max}/cm^{-1} (film) 3095, 3037, 2927, 2855, 2673, 1710, 1576, 1466, 1432, 1413, 1284, 1235, 949, 795, 722; δ_H 12.0-10.5 (1H, br. s, OH), 5.74 (1H, s, 4-H), 2.53 (2H, t, *J* 6.4, furan-CH_2), 2.50 (2H, t, *J* 6.2, furan-CH_2), 2.36 (2H, t, *J* 7.5, 10'-CH_2), 1.91 (3H, s, 3-Me), 1.69-1.54 (6H, m, 3 x CH_2), 1.37-1.32 (6H, m, 3 x CH_2), 1.29 (10H, br. s, 5 x CH_2), 0.90 (3H, t, *J* 6.9, 5``-Me); δ_C 180.1 (C=O), 153.5 (C), 149.4 (C), 113.8 (C), 107.6 (4-CH), 34.1 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.9 (CH_2),

25.9 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 14.0 (5``-Me), 9.9 (3-Me); *m/z* 336 [M] 50%, 86 (100), [Found [M], 336.2669. $C_{21}H_{36}O_3$ requires *M*, 336.2664].

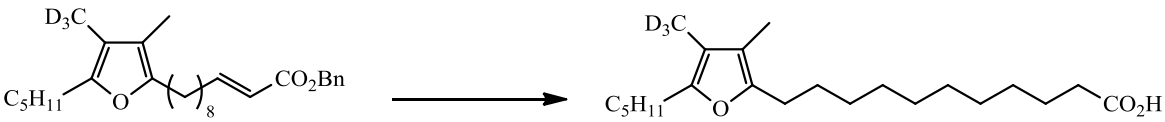
11-(3,4-Dimethyl-5-pentylfuran-2-yl)undecanoic acid (155f) – F_6 furan fatty acid



246b **155f**

A 250 ml round-bottomed flask was fitted with a three way tap and charged with 10% w/w palladium on carbon (0.071 g, 0.067 mmol). Methanol (50 ml) was added carefully followed by benzyl ester **246b** (0.583 g, 1.33 mmol). The flask was evacuated, flushed with hydrogen (x 3) and the mixture stirred for 1 h. The mixture was then filtered through a silica plug and the solvent evaporated. The residue was diluted with diethyl ether (30 ml), washed with water (3 x 20 ml) and the solvent dried, filtered and evaporated before the product was purified by column chromatography to yield the *furan fatty acid* **155f** as a colourless oil (pentane/diethyl ether, 95 : 5):υ_{max}/cm^{-1} (film) 3375, 2926, 2856, 2672, 1710, 1597, 1457, 1413, 1379, 1282, 1260, 1105, 910, 796, 734; δ_H 2.50 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.36 (2H, t, *J* 7.5, 10'-CH_2), 1.85 (6H, app. s, 2 x furan-Me), 1.70-1.60 (4H, m, 2 x CH_2), 1.59 – 1.52 (4H, m, 2 x CH_2), 1.38 – 1.30 (4H, m, 2 x CH_2), 1.29 (10H, br. s, 5 x CH_2), 0.90 (3H, t, *J* 7.0, 5``-Me); $\delta_C$ 179.9 (C=O), 148.4 (C), 148.4 (C), 114.4 (C), 114.4 (C), 34.1 ($CH_2$), 31.4 ($CH_2$), 29.5 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.4 ($CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 28.8 ($CH_2$), 28.4 ($CH_2$), 26.1 ($CH_2$), 26.1 ($CH_2$), 24.7 ($CH_2$), 22.4 ($CH_2$), 14.0 (5``-Me), 8.3 (Me), 8.3 (Me); *m/z* 350 [M] 58%, 86 (100), [Found [M], 350.2819. $C_{22}H_{38}O_3$ requires *M*, 350.2821].

11-(3-Methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undecanoic acid (155j) – *d_3*-F_6 furan fatty acid

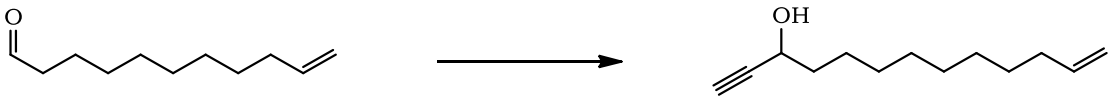


246c **155j**

A 250 ml round-bottomed flask was fitted with a three way tap and charged with 10% w/w palladium on carbon (0.05 g, 0.0482 mmol). Methanol (40 ml) was added carefully followed by benzyl ester **246c** (0.426 g, 0.965 mmol). The flask was evacuated, flushed with hydrogen (x 3) and the mixture stirred for 1 h. The mixture was then filtered through a silica plug and the

solvent evaporated. The residue was diluted with diethyl ether (30 ml) and washed with water (3 x 20 ml) then the solvent was dried, filtered and evaporated and the product purified by column chromatography (pentane/diethyl ether, 95 : 5) to yield the *furan fatty acid* **155j** as a colourless oil (0.314 g, 92%): υ_{max}/cm^{-1} (film) 3375, 2926, 2856, 2672, 1710, 1597, 1457, 1413, 1379, 1282, 1260, 1105, 910, 796, 734; δ_H 2.50 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.36 (2H, t, *J* 7.5, 10'-CH_2), 1.85 (3H, s, 3-Me), 1.70-1.60 (4H, m, 2 x CH_2), 1.59 – 1.52 (4H, m, 2 x CH_2), 1.38 – 1.30 (4H, m, 2 x CH_2), 1.29 (10H, br. s, 5 x CH_2), 0.90 (3H, t, *J* 7.0, 5``-Me); δ_D (46 MHz) ($CHCl_3$) 1.84 (3D, s, 4-CD_3); δ_C 179.9 (C=O), 148.4 (C), 148.4 (C), 114.4 (C), 114.4 (C), 34.1 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 14.0 (5``-Me), 8.3 (Me), 8.3 (Me); *m/z* 350 [M] 58%, 86 (100), [Found [M], 350.2819. $C_{22}H_{38}O_3$ requires *M*, 350.2821].

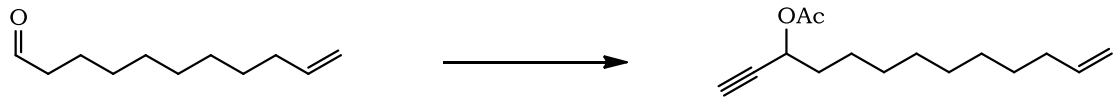
Tridec-12-en-1-yn-3-ol (220)[172]



219 **220**

An oven-dried 250 ml three neck round-bottomed flask fitted with a gas bubbler and under an atmosphere of dry nitrogen was charged with ethynylmagnesium bromide (20.0 ml of a 0.5 M solution in tetrahydrofuran, 10.0 mmol) and tetrahydrofuran (60 ml) and cooled to 0 °C. After ten minutes undecylenic aldehyde was added (1.82 ml, 8.33 mmol) dropwise and the reaction monitored by tlc. After 0.5 h the reaction was quenched by the addition of aqueous ammonium chloride (15 ml) and concentrated under reduced pressure. The residue was extracted into diethyl ether (3 x 15 ml) and the combined organic extracts washed with water (30 ml) and brine (30 ml) then dried, filtered and evaporated to yield the *alkynol* **220** as a yellow oil (1.62 g, 94%) which was of suitable quality for all subsequent transformations: υ_{max}/cm^{-1} (film) 3410, 3309, 3074, 2931, 2855, 2339, 1641, 1466, 1371, 1232, 1021, 910, 630; δ_H (400 MHz)5.82 (1H, ddt, *J* 17.0, 10.2 and 6.8, 12-H), 5.00 (1H, dd, *J* 17.0 and 1.5, 13-H_a), 4.94 (1H, dd, *J* 10.2 and 1.5, 13-H_b), 4.38 (1H, td, *J* 6.7 and 2.1, 3-H), 2.47 (1H, d, *J* 2.1,1-H), 2.08-2.01 (2H, m, CH_2), 1.77-1.63 (2H, m. CH_2), 1.52-1.42 (2H, m, CH_2), 1.41 – 1.31 (2H, m, CH_2), 1.25 (8H, br. s, 4 x CH_2); δ_C (100 MHz) 139.4 (12-CH), 114.3 (13-CH_2), 85.2 (2-C), 73.0 (1-CH), 62.5 (3-CH), 37.8 (CH_2), 33.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.1 (CH_2); *m/z* 193 $[M-H]^+$ 100%. All date obtained matched those previously reported in the literature.[172]

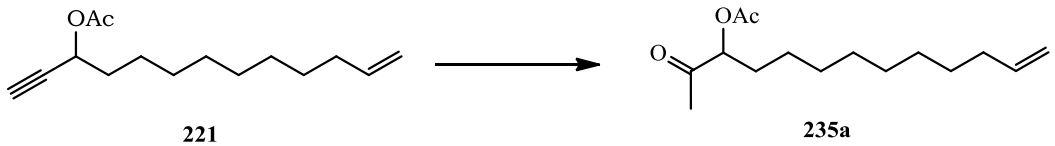
3-Acetyloxytridec-12-en-1-yne (221)



219 **221**

To an oven-dried 250 ml three neck round-bottomed flask fitted with a gas bubbler and under an atmosphere of dry nitrogen were added ethynylmagnesium bromide (50.0 ml of a 0.5M solution in tetrahydrofuran, 25.0 mmol) and tetrahydrofuran (160 ml). The solution was cooled to 0 °C. and allowed to stir for ten minutes. Undecylenic aldehyde (4.55 ml, 20.83 mmol) was added dropwise and the reaction monitored by tlc. After 0.5 h, acetic anhydride (2.75 ml, 29.16 mmol) was added and the reaction again monitored by tlc. After one hour, the reaction mixture was quenched by the addition of aqueous ammonium chloride (30 ml) and concentrated under reduced pressure. The residue was extracted into diethyl ether (3 x 25 ml) and the combined organic extracts washed with water (50 ml) and brine (50 ml) then dried, filtered though a plug of silica with dichloromethane (100 ml) and the solvent evaporated to yield the *acetate* **221** as colourless oil (4.87 g, 99%) which was of sufficient quality for all proceeding transformations: R_f 0.28 (5 :95, ethyl acetate – hexane); ν_{max}/cm^{-1} (film) 3308, 3077, 2927, 2856, 2333, 1744, 1641, 1372, 1234, 1022, 910, 630; δ_H 5.81 (1H, ddt, *J* 17.0, 10.2 and 6.8, 12-H), 5.34 (1H, td, *J* 6.7 and 2.1, 3-H), 5.00 (1H, app. ddd, *J* 17.0, 3.5 and 1.4, 13-H_a), 4.93 (1H, ddt, *J* 10.2, 2.2 and 1.4, 13-H_b), 2.45 (1H, d, *J* 2.1, 1-H), 2.09 (3H, s, Me), 2.07-2.00 (2H, m, CH_2), 1.80-1.70 (2H, m, CH_2), 1.48-1.32 (2H, m, CH_2), 1.26 (10H, br. s, 5 x CH_2); δ_C 169.9 (C=O), 139.1 (12-CH), 114.1 (13-CH_2), 81.4 (2-C), 73.4 (1-CH), 34.6 (CH_2), 33.8 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 21.0 (Me); *m/z* 236 $[M]^+$ 15%, 59 (100)

3-Acetoxytridec-12-en-2-one (235a)

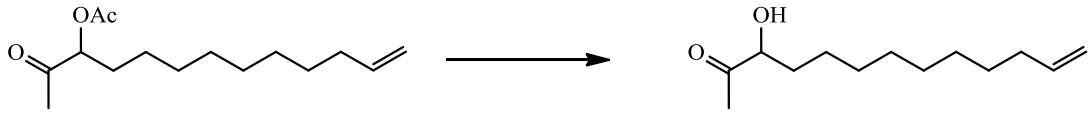


221 **235a**

Sodium gold chloride (0.131 g, 0.33 mmol) was added to a stirred solution of acetate 221 (3.89 g, 16.46 mmol) in aqueous methanol (40 ml, 9:1 methanol/distilled water) and refluxed for 3 h. After 3 h the solution was concentrated and the residue diluted with diethyl ether (50 ml), washed with a brine/ammonia solution (1:1, 2 x 50ml), water (50 ml) and brine (50 ml). The organic layer was then dried, filtered and evaporated to yield the *acetoxy ketone* **235a** as a pale

yellow oil (3.56 g, 85%): ν_{max}/cm^{-1} (film) 3076, 2927, 1745, 1734, 1641, 1435, 1372, 1240, 1044, 994, 909; δ_H 5.82 (1H, ddt, *J* 16.9, 10.2 and 6.7, 12-H), 5.03 – 4.97 (2H, m, 13-H_a and 3-H), 4.94 (1H, ddt, *J* 10.2, 2.1 and 1.0, 13-H_b), 2.17 (3H, s, Me), 2.16 (3H, s, Me), 2.08 – 2.00 (2H, m, CH_2), 1.80 – 1.70 (2H, m, 4-H_a and 4-H_b), 1.42 – 1.32 (2H, m, CH_2), 1.28 (10H, br. s, 5 x CH_2); δ_C 205.5 (2-C=O), 170.8 (C=O), 139.3 (12-CH), 114.3 (13-CH_2), 78.9 (3-CH), 33.9 (CH_2), 30.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.2 (Me), 25.3 (CH_2), 20.8 (Me).

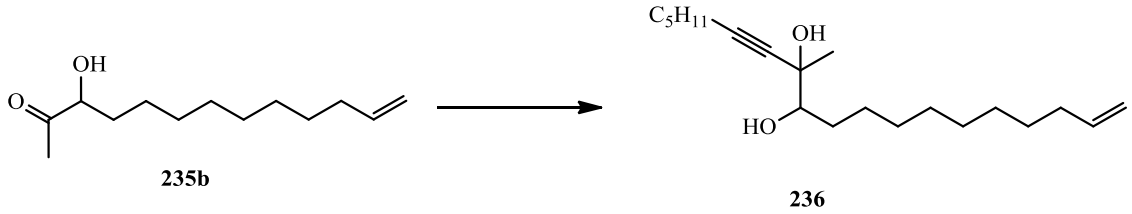
3-Hydroxytridec-12-en-2-one (235b)



235a **235b**

Potassium carbonate (4.55 g, 32.92 mmol) was added to a stirred solution of acetoxy ketone **235a** (3.56 g, 14.00 mmol) in aqueous methanol (40 ml, 9:1 methanol/water) maintained at 0 °C. After 0.5 h the solution was concentrated and then diluted with diethyl ether (25 ml). The product was extracted into diethyl ether (2 x 25 ml) and the combined organic extracts washed with water (50 ml) and brine (50 ml) and the solvent dried, filtered and evaporated and the product purified by column chromatography (15 : 85 ethyl acetate – petroleum ether) to yield the *hydroxy ketone* (2.68 g, 90%) as a colourless oil: R_f 0.65 (15 : 85 ethyl acetate – hexane); ν_{max}/cm^{-1} (film) 3477, 3076, 2925, 2854, 1714, 1640, 1464, 1438, 1358, 1247, 1130, 1087, 994, 909, 722; δ_H 5.82 (1H, ddt, *J* 17.0, 10.2 and 6.7, 12-H), 5.00 (1H, app. ddd, *J* 17.0, 3.7 and 1.6, 13-H_a), 4.94 (1H, ddt, *J* 10.2, 2.2 and 1.2, 13-H_b), 4.19 (1H, dd, *J* 7.3 and 3.7, 3-CH), 2.21 (3H, s, 1-Me), 2.09 – 1.99 (2H, m, CH_2), 1.90 – 1.80 (2H, m, 4-H_a), 1.65 – 1.52 (2H, m , CH_2), 1.51 – 1.43 (1H, m, 4-H_b), 1.43 (4H, m, 2 x CH_2), 1.30 (6H, br. s, 3 x CH_2); δ_C 209.9 (2-C=O), 139.1 (12-CH), 114.1 (13-CH_2), 76.9 (3-CH), 33.7 (CH_2), 33.6 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.1 (1-Me), 24.8(CH_2) *m/z* 212 $[M]^+$ 10 %, 149 (40), 109 (50), 84 (100) [Found $[M]^+$, 212.1781. $C_{13}H_{24}O_2$ requires *M* 212.1776].

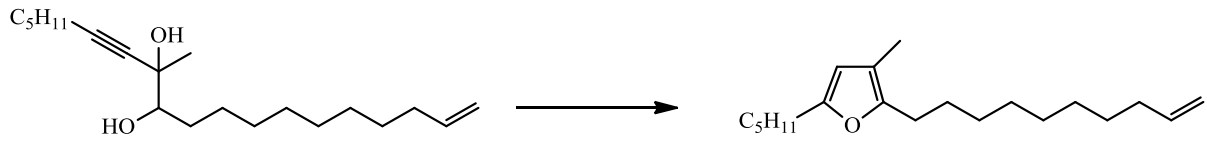
(*RS*, *RS*)- and (*RS*, *SR*)-8-Methylnonadec-18-en-6-yne-8,9-diol (236)



235b **236**

n-BuLi (11.63 ml of a 2.5 M solution in tetrahydrofuran, 29.08 mmol) was added dropwise to a stirred solution of 1-heptyne (3.84 ml, 29.08 mmol) in tetrahydrofuran (50 ml) maintained at 0 °C. After stirring for 0.5 h the contents were transferred to an oven-dried pressure-equalising dropping funnel attached to a second flask containing a stirred solution of hydroxy ketone **235b** (2.058 g, 9.69 mmol) in tetrahydrofuran (50 ml) maintained at -78 °C. The lithiated 1-heptyne was carefully added dropwise and stirred for 1 h. The reaction mixture was quenched by the addition of aqueous ammonium chloride (20 ml) and the solution concentrated under reduced pressure. The product was extracted with ethyl acetate (3 x 25 ml) and the combined organic layers washed with water (50 ml) and brine (50 ml). The solvent was dried, filtered and evaporated and the product purified by column chromatography to yield the *diol* **236** as a pale yellow oil (2.68 g, 89%) containing a mixture of diastereomers in a 4:1 ratio. *major diastereomer* R_f 0.21 (ethyl acetate – hexane, 1:4); *minor diastereomer* R_f 0.29 (ethyl acetate – hexane, 1:4); υ_{max}/cm^{-1} (film) 3407, 3077, 2927, 2856, 2245, 1641, 1466, 1378, 1329, 1207, 1078, 993, 909, 734; δ_H 5.82 (1H, ddt, *J* 17.0, 10.2 and 6.7, 18-H), 5.00 (1H, app. ddd, *J* 17.0, 3.6 and 1.6, 19-H_a), 4.94 (1H, ddt, *J* 10.2, 2.1 and 1.1, 19-H_b), 3.54 (0.80H, dd, *J* 7.8 and 2.0, 9-H), 3.36 (0.20H, dd, *J* 10.0 and 1.8, 9-H), 2.24 – 2.17 (2H, m), 2.05 (2H, m), 1.69 – 1.57 (2H, m), 1.55 – 1.46 (2H, m), 1.40 (3H, s, 8-Me), 1.38 – 1.33 (8H, m, 4 x CH_2), 1.29 (8H, br. s, 4 x CH_2); δ_C *major* 139.2 (18-CH), 119.1 (19-CH_2), 85.6 (C), 77.9 (9-CH), 73.5 (C), 71.2 (C), 33.8 (CH_2), 31.0 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 26.6 (CH_2), 23.6 (8-Me), 22.1 (CH_2), 18.6 (CH_2), 14.0 (1-Me); δ_C *minor* 139.2 (18-CH), 119.1 (19-CH_2),82.4 (C), 78.5 (9-CH), 74.5 (C), 71.9 (C), 38.2 (CH_2), 36.2 (CH_2), 32.4 (CH_2), 31.1 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 26.0 (8-Me), 18.6 (CH_2), 16.0 (1-Me); *m/z* 291 [M – H_2O] 5%, 169 (100) [Found [M – H_2O], 290.2607 $C_{20}H_{34}O$ requires *M-H_2O*, 290.2610].

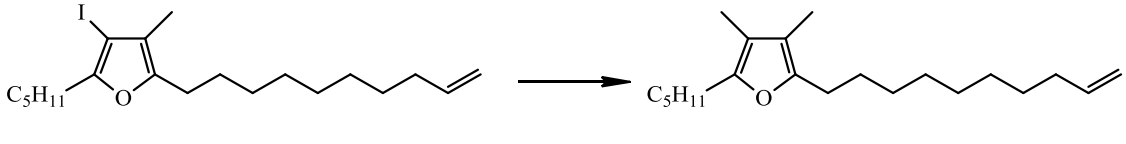
2-(dec-9-en-1-yl)-3-methyl-5-pentylfuran (237a)



236 **237a**

Using the general procedure (3 h), 10% $AgNO_3.SiO_2$ (0.253 g, 0.148 mmol) was stirred with a solution of diol **236** (0.459 g, 1.488 mmol) in dichloromethane (5 ml) to yield the *furan* **237a** as a colourless oil (0.414 g, 96%): ν_{max}/cm^{-1} (film) 3077, 2926, 2855, 1641, 1597, 1463, 1379, 1261, 1157, 1105, 993, 956, 910; δ_H 5.82 (1H, ddt, *J* 17.0, 10.2 and 6.7, 9'-H), 5.75 (1H, s, 4-H), 5.01 (1H, app. ddd, *J* 17.0, 3.5 and 1.6, 10'-H_a), 4.94 (1H, ddt, *J* 10.2, 2.1 and 1.1, 10'-H_b), 2.53 (2H, t, *J* 6.2, furan-CH_2), 2.51 (2H, t, *J* 6.1, furan-CH_2), 2.10 – 2.01 (2H, m, CH_2), 1.91 (3H, s, 3-Me), 1.66 – 1.54 (4H, m, 2 x CH_2), 1.43 – 1.33 (4H, m, 2 x CH_2), 1.31 (10H, br. s, 5 x CH_2), 0.91 (3H, t, *J* 7.0, 5''-Me); δ_C 153.5 (C), 149.4 (C), 139.2 (9'-CH), 114.1 (10'-CH_2), 113.8 (3-C). 107.6 (4-CH), 33.8 (CH_2), 31.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 14.0 (5''-Me), 9.9 (3-Me); *m/z* (APCI) 291 $[M+H]^+$ 100%, 115 (40) [Found $[M+H]^+$, 291.2699. $C_{20}H_{35}O$ requires *M+H* 291.2688].

2-(dec-9-en-1-yl)-3,4-dimethyl-5-pentylfuran (237b)



249 **237b**

Method 1:

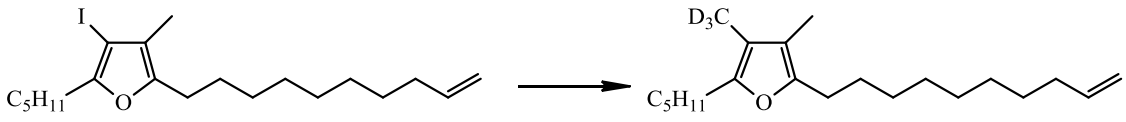
Iodofuran **249** (0.456 g, 1.095 mmol) dissolved in tetrahydrofuran (10 ml) in a 50 ml three-necked round-bottomed flask was cooled to -78 °C and stirred for 10 mins. *n*-BuLi (0.526 ml, 1.314 mmol) was added dropwise and stirred for 3 mins. Freshly distilled iodomethane (0.10 ml, 1.533 mmol) was added in one portion and stirred for a further 10 mins before warming to ambient temperature and stirring for an additional 10 mins. The reaction mixture was quenched by the addition of aqueous ammonium chloride solution (2 ml). Tetrahydrofuran was removed under reduced pressure and the product extracted into diethyl ether (3 x 5 ml). The combined organic extracts were dried, filtered and evaporated and the product purified by column

chromatography (pentane/diethyl ether, 99 : 1) to yield the *furan* **237b** as a yellow oil (0.248 g, 75%): R_f 0.28 (pentane/diethyl ether, 99 : 1); ν_{max}/cm^{-1} (film) 3077, 2926, 2856, 1641, 1597, 1466, 1378, 1256, 1134, 1109, 1054, 993; δ_H 5.82 (1H, ddt, *J* 17.0, 10.2 and 6.7, 9'-CH), 5.00 (1H, app. ddd, *J* 17.0, 3.6 and 1.5, 10'-H_a), 4.94 (1H, ddt, *J* 10.2, 2.3 and 1.2, 10'-H_b), 2.49 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.05 (2H, app. q, *J* 7.0, 8'-CH_2), 1.84 (6H, app. s, 2 x furan-Me), 1.63 – 1.51 (4H, m, 2 x CH_2), 1.42 – 1.33 (4H, m, 2 x CH_2), 1.29 (10H, br. s, 5 x CH_2); δ_C 148.4 (C), 148.4 (C), 139.2 (9'-CH), 114.4 (CH), 114.4 (CH), 114.1 (10'-CH_2), 33.8 (CH_2), 31.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 22.5 (4''-CH_2), 14.0 (5''-Me), 8.3 (Me). 8.3 (Me); *m/z* 305 $[M]^+$ 5%, 247 (50), 179 (100) [Found $[M]^+$, 304.2766. $C_{21}H_{36}O$ requires *M*, 304.2766].

Method 2:

Methyllithium (2.63 ml of a 1.5 M solution in diethyl ether complexed with LiBr, 3.94 mmol) was added dropwise to a stirred solution of iodofuran **249** (0.328 g, 0.787 mmol) in tetrahydrofuran (10 ml) maintained at -78 °C and stirred for 0.5 h. After warming to ambient temperature and stirring for a further 0.5 h the reaction mixture was quenched by the addition of aqueous ammonium chloride (5 ml). Tetrahydrofuran was evaporated and the residue diluted with diethyl ether (10 ml). The product was extracted into diethyl ether (2 x 10 ml) and the combined organic extracts washed with water (30 ml) and brine (30 ml) before the solvent was dried, filtered and evaporated to yield the *furan* as a pale yellow oil (0.210 g, 88%). All data obtained was in accord with that previously obtained from the conventional approach.

2-(dec-9-en-1-yl)-3-methyl-4-trideuteriomethyl-5-pentylfuran (237c)



249 **237c**

Method 1:

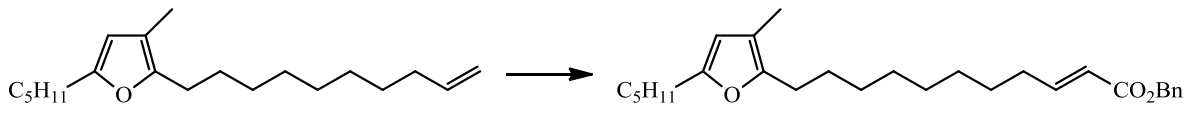
Iodofuran **249** (0.558 g, 1.34 mmol) dissolved in tetrahydrofuran (15 ml) in a 50 ml three-necked round-bottomed flask was cooled to -78 °C and stirred for 10 mins. *n*-BuLi (0.64 ml, 1.61 mmol) was added dropwise and stirred for 3 mins before freshly distilled d_3-iodomethane (0.12 ml, 1.88 mmol) was added in one portion and stirred for a further 10 mins before warming to ambient temperature and stirring for an additional 10 mins. The reaction mixture was quenched by the

addition of aqueous ammonium chloride (2 ml). Tetrahydrofuran was removed under reduced pressure and the product extracted into diethyl ether (3 x 5 ml). The combined organic extracts were dried, filtered and evaporated and the product purified by column chromatography (pentane/diethyl ether, 99 : 1) to yield the *d_3-furan* **237c** as a yellow oil (0.381 g, 92%): R_f 0.28 (pentane/diethyl ether, 99 : 1); ν_{max}/cm^{-1} (film) 3077, 2926, 2855, 1641, 1597, 1463, 1379, 1261, 1156, 1102, 993, 956, 909; δ_H 5.82 (1H, ddt, *J* 17.0, 10.2 and 6.7, 9'-CH), 5.00 (1H, app. ddd, *J* 17.0, 3.7 and 1.6, 10'-H_a), 4.94 (1H, ddt, *J* 10.2, 2.2 and 1.2, 10'-H_b), 2.49 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.05 (2H, app. q, *J* 7.0, 8'-CH_2), 1.84 (3H, s, 3-Me), 1.63 – 1.51 (4H, m, 2 x CH_2), 1.42 – 1.33 (4H, m, 2 x CH_2), 1.29 (10H, br. s, 5 x CH_2); δ_D (46 MHz) ($CHCl_3$) 1.83 (3D, s, 4-CD_3); δ_C 148.4 (C), 148.4 (C), 139.2 (9'-CH), 114.4 (CH), 114.3 (CH), 114.1 (10'-CH_2), 33.8 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 22.4 (4''-CH_2), 14.0 (5''-Me), 8.3 (Me).

Method 2:

Methyl-d_3 lithium (20.0 ml of a 0.5 M solution in diethyl ether complexed with LiI, 10.0 mmol) was added dropwise to a stirred solution of iodofuran **249** (1.23 g, 2.96 mmol) in tetrahydrofuran (10 ml) maintained at -78 °C and stirred for 0.5 h. After warming to ambient temperature and stirring for a further 0.5 h the reaction was quenched by the addition of aqueous ammonium chloride (5 ml). Tetrahydrofuran was evaporated and the residue diluted with diethyl ether (10 ml). The product was extracted into diethyl ether (2 x 10 ml) and the combined organic extracts washed with water (30 ml) and brine (30 ml) before the solvent was dried, filtered and evaporated to yield the *d_3-furan* as a pale yellow oil (0.783 g, 86%). All data obtained was in accord with that previously obtained from the conventional approach.

(*E*)-Benzyl 11-(3-methyl-5-pentylfuran-2-yl)undec-2-enoate (246a)

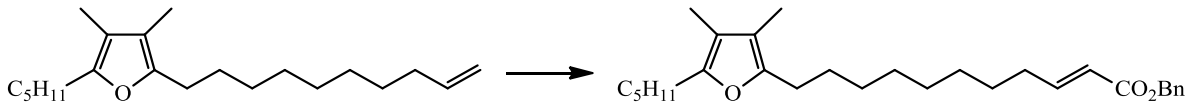


237a **246a**

Grubbs-Hovayda Mk II catalyst (0.042 g, 0.067 mmol) was added to a stirred solution of furan **237a** (0.391 g, 1.35 mmol) in dichloromethane (12 ml). Freshly distilled benzyl acrylate (0.26 ml, 1.76 mmol) was added and the solution refluxed under an atmosphere of dry nitrogen for 2 h. The solution was filtered through a plug of silica and the solvent evaporated to yield the *benzyl*

ester **246a** as a colourless oil (0.510 g, 89%): ν_{max}/cm^{-1} (film) 3065, 3033, 2928, 2856, 1724, 1654, 1597, 1497, 1456, 1406, 1377, 1264, 1172, 1046, 1017, 981, 809, 735, 697; δ_H 7.41 – 7.34 (5H, m, 5 x Ar-H), 7.03 (1H, dt, *J* 14.3 and 7.0, 9'-CH), 5.87 (1H, d, *J* 14.3, 10'-CH), 5.74 (1H, s, 4-H). 5.18 (2H, s, 13'-CH_2), 2.52 (2H, t, *J* 7.5, furan-CH_2), 2.50 (2H, t, *J* 7.5, furan-CH_2), 2.20 (2H, app. q, *J* 7.0, 8'-CH_2), 1.90 (3H, s, 3-Me), 1.65 – 1.53 (2H, m, CH_2), 1.50 – 1.40 (2H, m, CH_2), 1.36 – 1.31 (4H, m, 2 x CH_2), 1.29 (10H, m, 5 x CH_2), 0.90 (3H, t, *J* 6.8, 5''-Me); δ_C 166.6 (C=O), 153.5 (C), 150.2 (9'-CH), 149.4 (3-C), 136.2 (C), 128.6 (2 xAr-CH), 128.3 (Ar-CH), 128.2 (2 x Ar-CH), 120.9 (10'-CH), 107.6 (4-CH), 66.0 (13-CH_2), 32.3 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 14.0 (5''-Me), 9.9 (3-Me); *m/z* 425 $[M]^+$ 15%, 317 (5), 165 (100) [Found $[M]^+$, 424.2975. $C_{28}H_{40}O_3$ requires *M*, 422.2977].

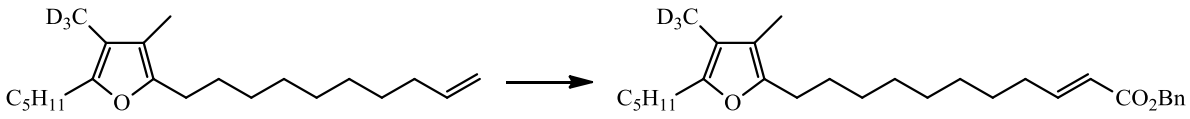
(*E*)-Benzyl 11-(3,4-dimethyl-5-pentylfuran-2-yl)undec-2-enoate (246b)



237b **246b**

Grubbs-Hovayda Mk II catalyst (0.0417 g, 0.066 mmol) was added to a stirred solution of furan **237b** (0.405 g, 1.33 mmol) in dichloromethane (12 ml). Freshly distilled benzyl acrylate (0.60 ml, 4.00 mmol) was added and the solution refluxed under an atmosphere of nitrogen for 2 h. The solution was filtered through a plug of silica and the solvent evaporated to yield the *benzyl ester* **246b** as a colourless oil (0.519 g, 89%): ν_{max}/cm^{-1} (film) 3065, 3033, 2928, 2856, 1724, 1654, 1497, 1377, 1264, 1173, 1046, 1017, 982, 808, 736, 698; δ_H 7.42 – 7.32 (5H, m, 5 x Ar-H), 7.04 (1H, dt, *J* 13.0 and 7.0, 9'-CH), 5.87 (1H, d, *J* 13.0, 10'-CH), 5.18 (2H, s, 13'-CH_2), 2.49 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.20 (2H, app. q, *J* 7.0, 8'-CH_2), 1.90 (6H, app. s, 2 x furan-Me), 1.65 – 1.53 (2H, m, CH_2), 1.50 – 1.40 (2H, m, CH_2), 1.36 – 1.31 (4H, m, 2 x CH_2), 1.29 (10H, m, 5 x CH_2), 0.90 (3H, t, *J* 6.8, 5''-Me); δ_C 166.6 (C=O), 150.2 (9'-CH), 148.4 (C), 148.4 (C), 136.2 (C), 128.6 (2 xAr-CH), 128.3 (Ar-CH), 128.2 (2 x Ar-CH), 120.9 (10'-CH), 114.4 (C), 114.4 (C), 66.0 (13-CH_2), 33.8 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 14.0 (5''-Me), 8.4. (Me), 8.3 (Me); *m/z* 439 $[M]^+$ 15%, 332 (5), 179 (100) [Found $[M]^+$, 438.3133. $C_{29}H_{42}O_3$ requires *M*, 438.3134].

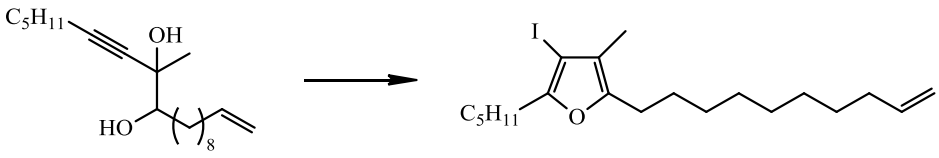
(*E*)-Benzyl 11-(3-methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undec-2-enoate (246c)



237c **246c**

Grubbs-Hovayda Mk II catalyst (0.009 g, 0.015 mmol) was added to a stirred solution of d_3-furan **237c** (0.090 g, 0.290 mmol) in dichloromethane (5 ml). Freshly distilled benzyl acrylate (0.05 ml, 0.38 mmol) was added and the solution refluxed under an atmosphere of nitrogen for 2 h. The solution was filtered through a plug of silica and the solvent evaporated to yield the *benzyl ester* **246c** as a colourless oil (0.111 g, 86%): ν_{max}/cm^{-1} (film) 3033, 2928, 2856, 1724, 1654, 1497, 1455, 1405, 1377, 1294, 1266, 1174, 1047, 982, 809, 736, 697; δ_H 7.42 – 7.32 (5H, m, 5 x Ar-H), 7.04 (1H, dt, *J* 13.0 and 7.0, 9'-CH), 5.87 (1H, d, *J* 13.0, 10'-CH), 5.18 (2H, s, 13'-CH_2), 2.49 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.20 (2H, app. q, *J* 7.0, 8'-CH_2), 1.83 (3H, s, 3-Me), 1.60 – 1.50 (2H, m, CH_2), 1.50 – 1.40 (2H, m, CH_2), 1.36 – 1.31 (4H, m, 2 x CH_2), 1.29 (10H, m, 5 x CH_2), 0.89 (3H, t, *J* 7.0, 5''-Me); δ_D (46 MHz) ($CHCl_3$) 1.82 (3D, s, 4-CD_3); δ_C 166.6 (C=O), 150.1 (9'-CH), 148.4 (C), 148.4 (C), 136.2 (C), 128.6 (2 xAr-CH), 128.3 (Ar-CH), 128.2 (2 x Ar-CH), 120.9 (10'-CH), 114.4 (C), 114.4 (C), 66.0 (13-CH_2), 32.4 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 26.1 (CH_2), 22.4 (CH_2), 14.0 (5''-Me), 8.3 (3-Me); *m/z* 442 $[M]^+$ 15%, 335 (5), 182 (100) [Found $[M]^+$, 441.3321. $C_{29}H_{39}D_3O_3$ requires *M*, 441.3322].

2-(dec-9-en-1-yl)-4-iodo-3-methyl-5-pentylfuran (249)



236 **249**

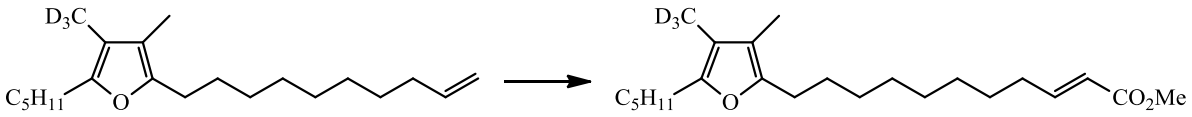
Sodium hydrogen carbonate (0.464 g, 5.52 mmol) was added to a stirred solution of diol **236** (0.568 g, 1.84 mmol) in tetrahydrofuran (50 ml) and maintained at 0 °C for 15 mins. Iodine (1.402 g, 5.52 mmol) was added to the solution, stirred and allowed to warm to ambient temperature for 3 h. Sufficient sodium sulphite was then added to quench the reaction mixture before evaporation of tetrahydrofuran under reduced pressure. The residue was extracted into diethyl ether (3 x 25 ml) and the combined organic extracts washed with water (50 ml) and brine

(50 ml) then dried and filtered through a silica plug using 99 : 1 pentane – diethyl ether as the eluent. The solvent was then evaporated to yield *iodofuran* **249** (0.595 g, 78%) as a colourless oil: ν_{max}/cm^{-1} (film) 3078, 2926, 2855, 1640, 1623, 1573, 1458, 1375, 1024, 989, 909, 720, 708; δ_H 5.82 (1H, ddt, *J* 17.1, 10.2 and 6.7, 9'-H), 5.00 (1H, app. ddd, *J* 17.1, 3.5 and 1.7, 10'-H_a), 4.94 (1H, ddt, *J* 10.2, 2.2 and 1.2, 10'-H_b), 2.62 (2H, t, *J* 7.5, furan-CH_2), 2.56 (2H, t, *J* 7.4, furan-CH_2), 2.08 – 2.01 (2H, m, CH_2), 1.87 (3H, s, 3-Me), 1.65 – 1.53 (4H, m, 2 x CH_2), 1.42 – 1.31 (6H, m, 3 x CH_2), 1.30 (8H, br. s, 4 x CH_2), 0.91 (3H, t, *J* 7.1, 5''-Me); δ_C 153.6 (C), 149.8 (C), 139.2 (9'-CH), 116.7 (3-C), 114.1 (10'-CH_2), 69.8 (4-C), 33.8 (CH_2), 31.2 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 22.4 (CH_2), 14.0 (5''-Me), 11.3 (3-Me);); *m/z* 416 $[M]^+$ 50%, 84 (100), [Found $[M]^+$, 416.1577. $C_{20}H_{33}OI$ requires *M*, 416.1576].

Methyl 11-(3-methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undecanoate (251)

Step 1:

(E)-Methyl 11-(3-methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undec-2-enoate

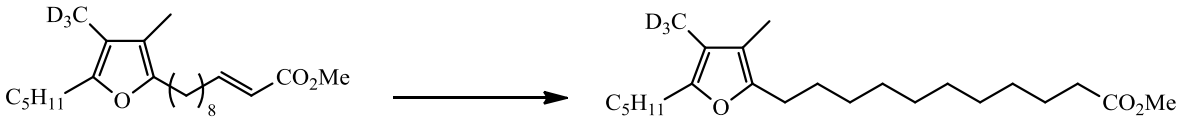


237c

Grubbs-Hovayda Mk II catalyst (0.037 g, 0.060 mmol) was added to a stirred solution of d_3-furan **237c** (0.366 g, 1.190 mmol) in dichloromethane (20 ml). Methyl acrylate (0.16 ml, 1.785 mmol) was added and the solution refluxed under an atmosphere of dry nitrogen for 2 h. The solution was filtered through a plug of silica and the solvent evaporated to yield the *methyll ester* **246d** as a colourless oil (0.378 g, 87%): ν_{max}/cm^{-1} (film) 3030, 2928, 2856, 1728, 1658, 1457, 1435, 1317, 1269, 1196, 1175,, 1042, 979, 920, 851, 799, 703; δ_H 6.98 (1H, dt, *J* 15.6 and 7.0, 9'-CH), 5.82 (1H, dt, *J* 15.6 and 1.5, 10'-CH), 3.73 (3H, s, 13'-Me), 2.49 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.19 (2H, app. qd, *J* 7.0 and 1.5, 8'-CH_2), 1.84 (3H, s, 3-Me), 1.63 – 1.52 (4H, m, 2 x CH_2), 1.49 – 1.41 (2H, m, CH_2), 1.37 – 1.31 (4H, m, 2 x CH_2), 1.29 (8H, br. s, 4 x CH_2), 0.89 (3H, t, *J* 7.1, 5''-Me); δ_D (46 MHz) ($CHCl_3$) 1.82 (3D, s, 4-CD_3); δ_C 167.1 (C=O), 149.7 (9'-CH), 148.4 (C), 148.3 (C), 120.8 (10'-CH), 114.5 (C), 114.3 (C), 51.3 (13-Me), 32.1 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.5

(CH_2), 26.1 (CH_2), 22.4 (CH_2), 14.0 (5''-Me), 8.3 (3-Me); *m/z* 442 $[M]^+$ 15%, 365 (10), 105 (100) [Found $[M]^+$, 365.3008. $C_{23}H_{35}D_3O_3$ requires *M*, 365.3009].

Step 2:



251

A 100 ml round-bottomed flask fitted with a three way tap was charged with 10% w/w palladium on carbon (0.015 g, 0.0142 mmol). Methanol (10 ml) was added carefully followed by methyl ester **246d** (0.104 g, 0.285 mmol). The flask was evacuated, flushed with hydrogen (x 3) and the mixture stirred for 1 h. The mixture was then filtered through a silica plug and the solvent evaporated. The residue was diluted with diethyl ether (10 ml) and washed with water (3 x 10 ml). The solvent was then dried, filtered and evaporated and the product purified by column chromatography (pentane/diethyl ether, 95 : 5) to yield the *d_3-furan fatty acid methyl ester* **251** as a colourless oil (0.095 g, 91%):υ_{max}/cm^{-1} (film) 2926, 2855, 2672, 1741, 1642, 1434, 1170; δ_H 3.67 (3H, s, 13'-Me), 2.49 (4H, app. t, *J* 7.5, 2 x furan-CH_2), 2.31 (2H, t, *J* 7.6, 10'-CH_2), 1.84 (3H, s, 3-Me), 1.67 – 1.59 (4H, m, 2 x CH_2), 1.59 – 1.52 (4H, m, 2 x CH_2), 1.36 – 1.24 (14H, m, 7 x CH_2), 0.89 (3H, t, *J* 7.1, 5``-Me); δ_D (46 MHz) ($CHCl_3$) 1.81 (3D, s, 4-CD_3) δ_C 174.3 (C=O), 148.4 (C), 148.4 (C), 114.4 (C), 114.4 (C), 51.4 (13'-Me) 34.1 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 26.1 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 14.0 (5``-Me), 8.3 (3-Me); *m/z* 367 $[M]^+$ 10%, 105 (100), [Found [M], 367.3165. $C_{23}H_{37}D_3O_3$ requires *M*, 367.3166].

*Chapter **6**: References*

6.1 References

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Chapter 7: Appendix

7.1 Publications

S. J. Hayes, D. W. Knight, A. W. T. Smith and M. J. O'Halloran, *Tetrahedron Lett.*, 2010, **51**, 717.

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