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The Synthesis and Chemistry

of Macrolactones



-by-

Lawrence D. Cook

A thesis submitted to the University of Dublin

for the degree of Doctor of Philosophy

Trinity College Dublin

January 2014

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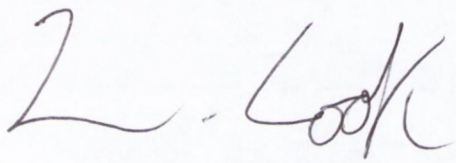
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Summary

The work herein presented is an investigation into the methodology of macrolactonisation *via* an intramolecular acylative cleavage of a tetrahydrofuran ring. The thesis is divided into three Chapters: an introduction outlining the history and biological role of macrolactones, and the techniques currently being exploited in their synthesis; an improvement upon the technique of macrolactonisation *via* intramolecular acylative cleavage of tetrahydrofuran rings; and progress towards the total synthesis of the naturally occurring macrolactone curvularin.

9-(Tetrahydrofuran-2-yl)nonanoic acid was synthesised and converted into several differingly substituted oxacyclotetradecan-2-ones in good yield (72-91%). A new procedure for the selective synthesis of diolides was developed and used to prepare 11,25-dichloro-1,15-dioxacyclooctacosane-2,16-dione. The modifications to the reaction were also applied in the syntheses of several oxecan-2-ones and oxacycloundecan-2-ones substituted with acetoxy, chlorine and trifluoroacetoxy groups as well as a series of alkenyl lactones. A new methodology for the synthesis of long chain 1,4-diols was also discovered.

Several divergent routes towards a total synthesis of the naturally occurring fungal metabolite curvularin were explored in preparation for the acylative THF cleaving macrolactonisation. As a result of which new synthetic procedures for substituted furans and tetrahydrofurans were developed.

Acknowledgements

I would first and foremost like to thank my long suffering supervisor Prof. David Grayson for all of his support and encouragement and patience throughout my time at Trinity College.

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I owe a huge debt of gratitude to all of the technical staff here at Trinity; to John O'Brien and Manuel for putting up with all the dirty samples and to Martin and Gary for looking for the same monomer in so many samples where it just wasn't there.

Thanks too to all of the members of the Scanlon group too; Aoife, Claire, Jean, Lyn, and Robin, it wouldn't have been the same without you.

Finally, I'd like to thank my family; Mum, Dad, Carol, and Chico for putting up with me for so long and for continuing to be as supportive as anyone could ever want you to be.

Abbreviations

OAc	Acetate
Ar	Aromatic
b.p.	Boiling point
BMS	Borane-methyl sulfide complex
br	Broad
n-BuLi	*n*-butyl lithium
j	Coupling constant measured in Hertz
^{o}C	Degrees Celsius
DCM	Dichloromethane
DCC	Dicyclohexylcarbodiimide
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
d	Doublet
EVE	Ethoxy vinyl ester

HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	Infrared
m/z	Mass per unit charge
m. p.	Melting point
Me	Methyl
m	Multiplet
NMR	Nuclear magnetic resonance
Pd/C	Palladium on activated charcoal
ppm	Parts per million
Ph	Phenyl
PCC	Pyridinium chlorochromate
PPTS	Pyridinium *para*-toluenesulfonate
q	Quartet
R_f	Retention factor
RCM	Ring closing metathesis

Rt	Room Temperature
S	Singlet
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
PTSA	*para*-toluenesulfonic acid
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
T	Triplet

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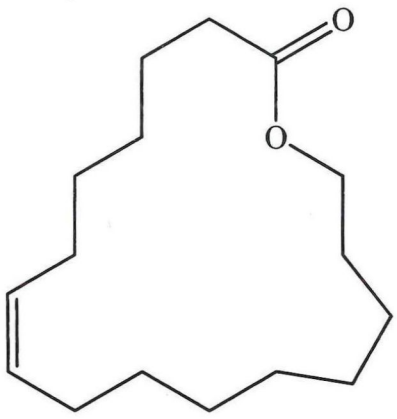
Chapter 1 : Introduction

1. Review of Macrolactones

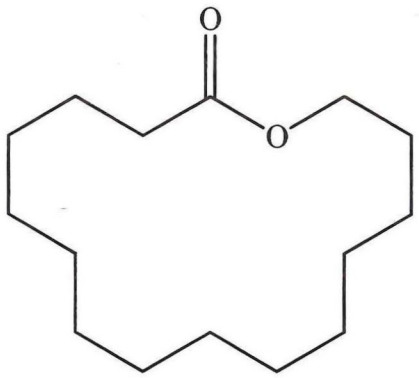
Cyclic compounds, whether aliphatic, aromatic, or heterocyclic form an integral cornerstone of organic chemistry and have driven much of the academic research of the last hundred years.

The relative strain that arises as a result of the conformation of organic molecules into cyclic structures was first postulated in 1885 by Alfred Von Baeyer,[1] his work suggested that the necessary deviation from the optimal tetrahedral angle of 109°28' would preclude the formation of any ring with more or less than 6 atoms.

Whilst this was repudiated by Sachse[2] as early as 1890 and expanded to allow for the synthesis of both smaller rings and 7 and 8-membered rings by the work of Perkin,[3] it was not until 1926 that the first practical examples of macrocyclic rings were found to exist by Ruzicka in the elucidation of the musk macroketones muscone and civetone.[4-6] This field of large ring compounds was extended to the first macrolactones a year later with the elucidation of the structures of ambrettolide **1** and exaltolide **2**.[7]

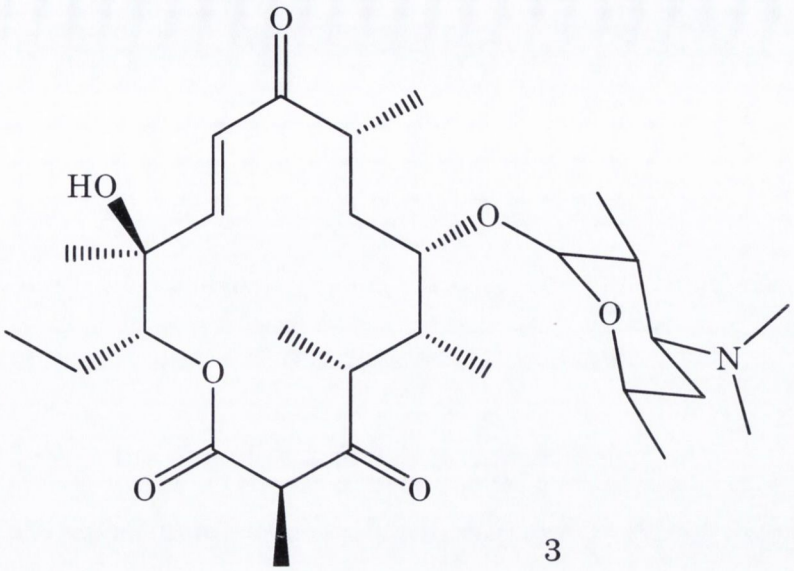


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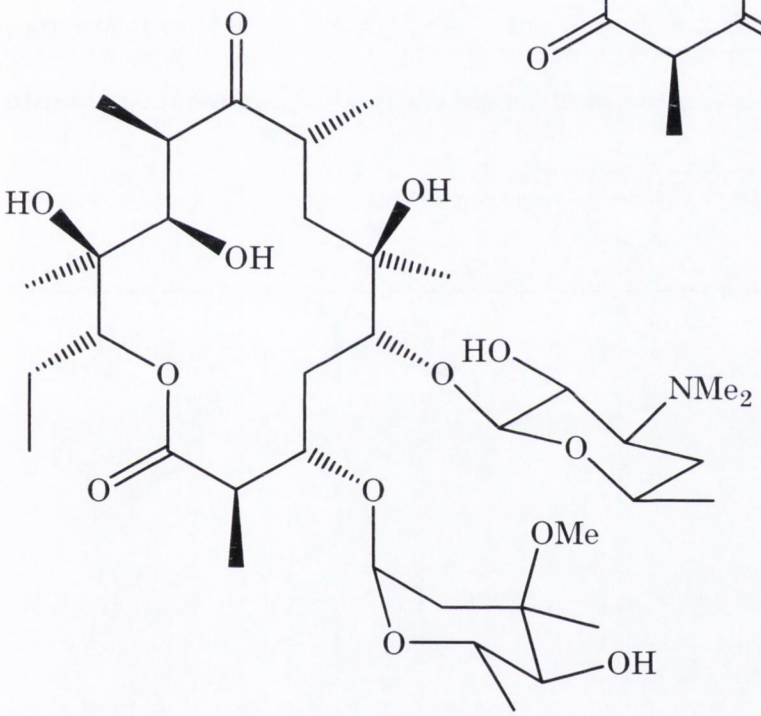


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These were the first confirmed examples of macrolactones, defined as being cyclic esters with a ring size greater than 8 atoms. The field was expanded beyond these simple rings used only in the fragrance industry by Brockmann and Henkel's isolation of pikromycin **3** from a culture of *Actinomycin*, the first of the macrolide series of antiobiotics.[8]



3



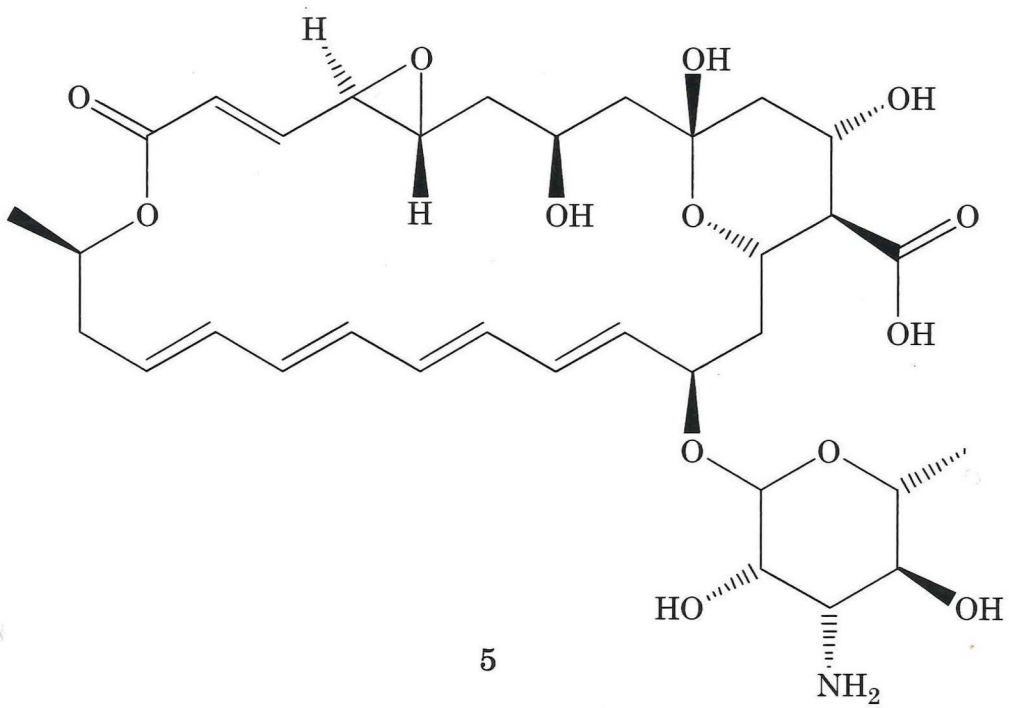
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Other members of this class of macrolactone were soon discovered, including erythromycin[9] **4** and roxithromycin,[10] and are still in frequent use as antibiotics today. They share a common structural motif of a 12-16 membered lactone ring with a large degree of substitution including a deoxy sugar. Their biological functionality against Gram positive bacteria arises *via* selective

binding to the large sub-unit of bacterial ribosomes preventing protein synthesis.[11]

The term macrolide, whilst originally referring only to this series of glycosylated macrolactones, has been frequently appropriated to encompass any biologically active medium to large lactone ring.

The polyene macrolides are a diverse sub-set of these glycosylated macrocycles which commonly display anti-fungal activity,[12] the bacterial fermentation extract natamycin **5** is a typical example.[13]

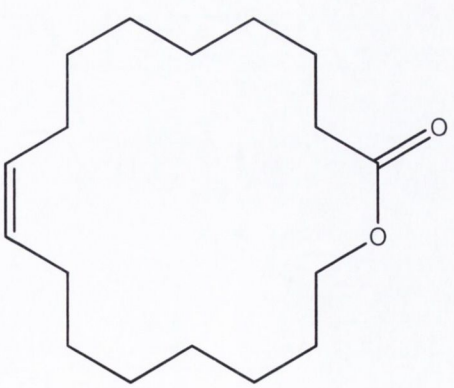


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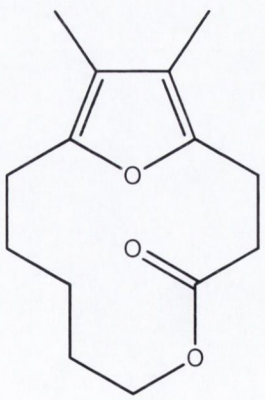
The general structure can be split into two halves, one side containing a series of conjugated *E* double bonds and an amino glycoside, the opposing side is far more hydrophilic typically featuring a large number of hydroxyl and carbonyl groups. This amphiphilic structure plays an important part in its antimicrobial

activity, as it preferentially binds with the fungal sterol ergosterol rather than the eukaryotic cholesterol in cell walls, these binary complexes eventually aggregate into clusters that act as uncontrolled transmembrane channels leading to cell death.[14] The biological role of macrolactones extends far beyond the macrolides though, and over the last fifty years a number of notable examples have been reported.

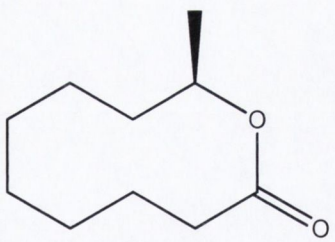
A number of insects use volatile macrolactones as part of their pheromone palette including 9-octadecenolide **6** which is produced by the social wasp,[15] a dimethylfuryl lactone **7** secreted by the black-margined loosestrife beetle,[16] and the phoracantholides I **8** and J **9**, which are pheromones of several longhorn beetles.[17] These play vital roles in the signalling, sexual and territorial behavioural patterns of these insects and can be used as part of biological pest control methods to protect crops.



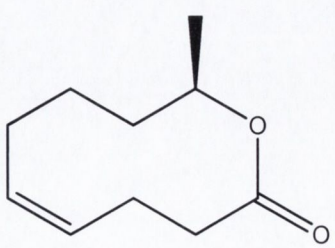
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7

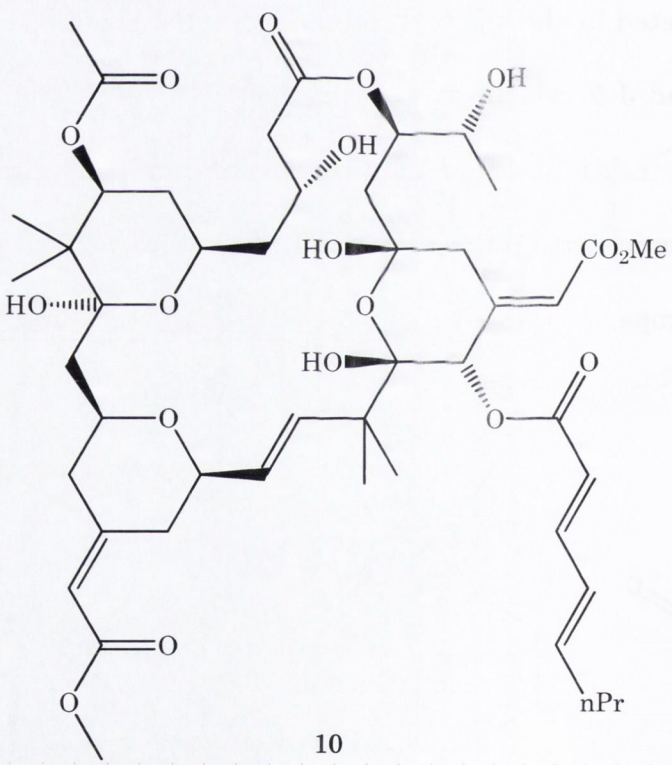


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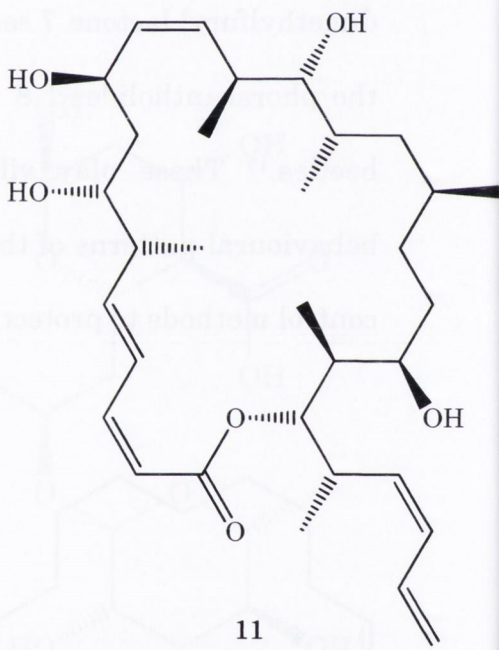


9

Marine life forms, predominantly sponges, have revealed an expansive cache of complex and useful macrocyclic esters frequently possessing antineoplastic properties with unique models of action. These include the bryostatins **10** isolated from *Bugula neritina*[18] whose anticancer activity arises *via* interaction with the protein kinase C pathway of cell signalling,[19] and (-)-dictyostatin[20] **11** a macrolactone isolated from a marine sponge whose stabilisation of cellular microtubules prevents cancerous cells from moving out of the G2-M stage and proliferating.[21]



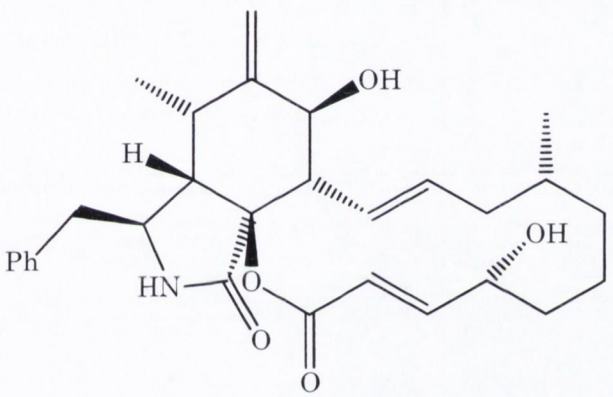
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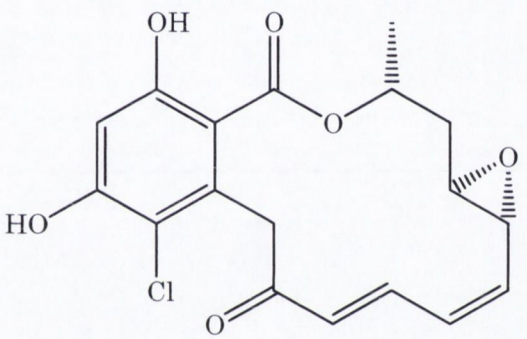
11

Fungal metabolites also present a rich seam of highly biologically active macrolactones, including the cytochalasin series, of which cytochalasin B **12** is typical.[22] Their biological effects though are widely diverse, including

inhibition of angiogenesis[23] and modulating glucose transport[24] but the primary interest in them is as a result of their inhibition of cell division by binding irreversibly to the growing ends of actin filaments, making them powerful potential targets for anti-cancer research.[25] The resorcylic acid lactones are another grouping of fungal metabolites, such as radicicol **13**, their shared structural architecture centring around a semi-substituted ß-resorcylic acid as a fused component of their 12-14 membered lactone rings.[26]

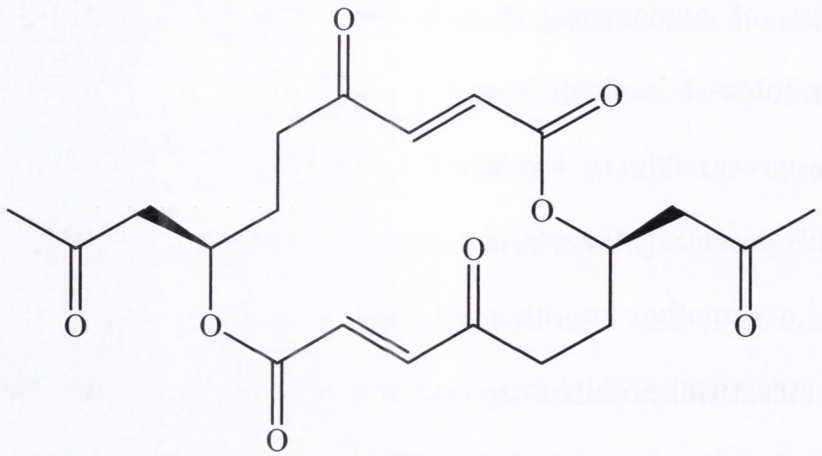


12



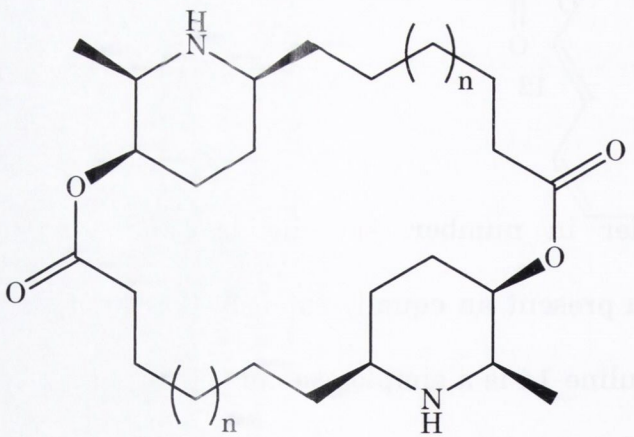
13

Whilst smaller in number, the diolides and tetralides as a structural categorisation present an equally extensive range of structures and biological roles. Vermiculine **14** is a simple example of this set, a cytotoxic antibacterial compound isolated from a strain of *Penicillium,*[27] it has recently been shown to have immunomodulatory effects.[28]



14

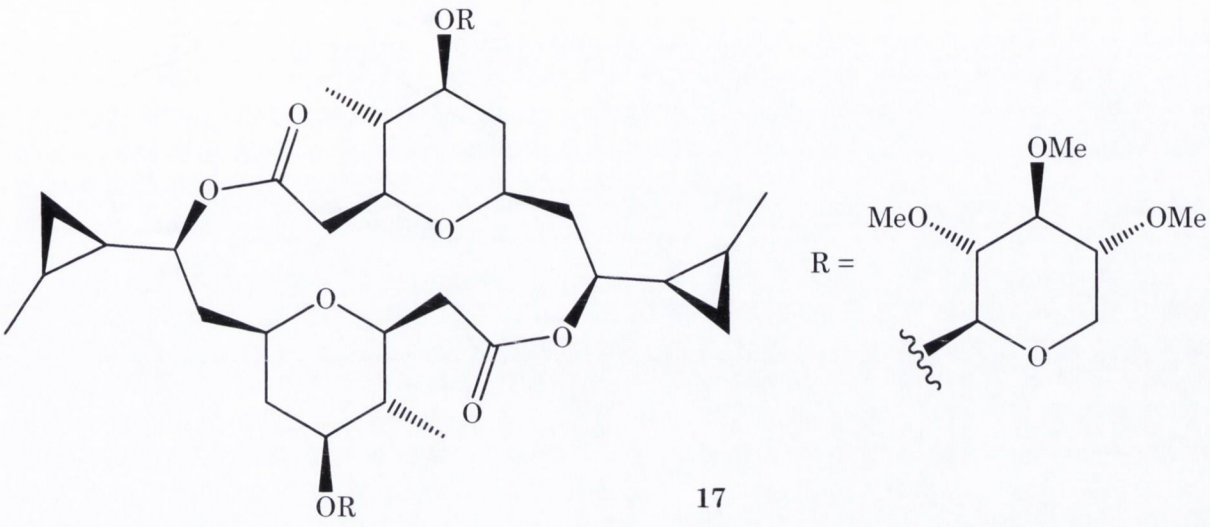
Azimine **15** and carpaine **16** are a pair of diolide alkaloids extracted from the crushed leaves of the papaya plant that have received a good deal of scientific interest owing to their role in folk medicine.[29] Carpaine has been shown to significantly lower systolic and diastolic blood pressure in rat models.[30]



15 n = 1
16 n = 3

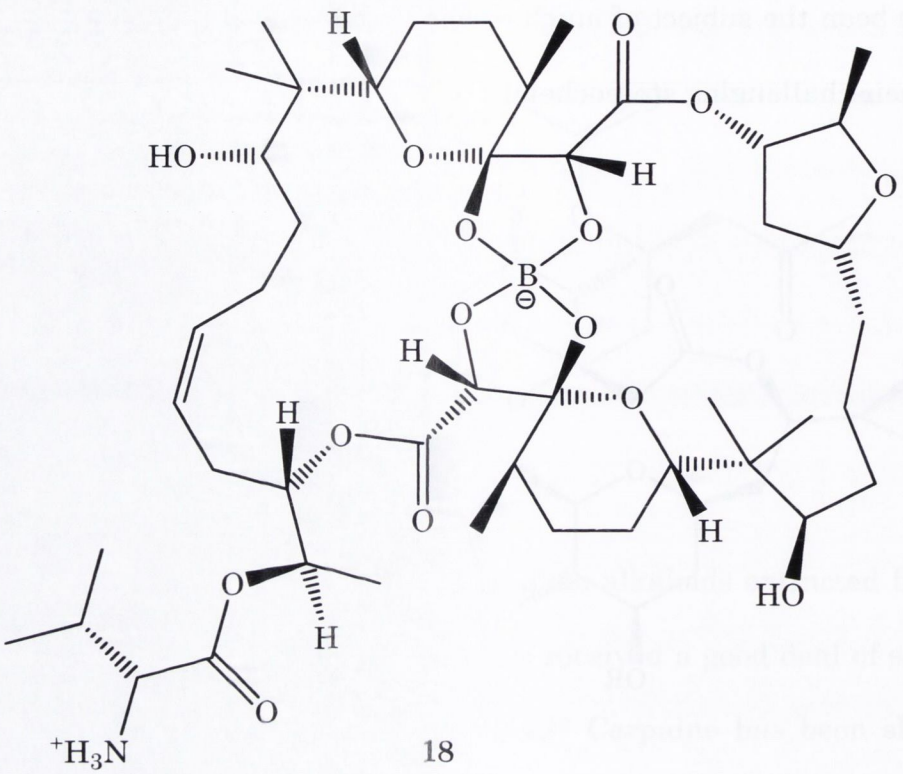
Marine sponges are also capable of producing complex and intriguing diolides, of which the clavosolides, such as clavosolide A **17**, are a fine example. They

have been the subject of much research and several total syntheses as a result of their challenging stereochemistry.[31-33]



17

One of the few boron-containing natural products boromycin **18** is a complex antibiotic extracted from a strain of *Streoptomyces*[34] that has recently been shown to possess potent anti-HIV activity.[35]



18

The fraction of all known macrolides that are documented here give only a small demonstration of their potential importance. Some of the compounds though are, however, only present in nature in minutely small amounts, and so it is unsurprising that a great deal of research has been carried out in developing new methodologies for the synthesis of medium and large ring lactones.

2. Current methodologies in macrolactonisation

Whilst there are a large number of diverse reactions in use and in the literature archives they can be broadly divided into six classes of reactions;

- Macrolactonisation of ω-hydroxycarboxylic acids *via* an activated carboxylic acid group
- Macrolactonisation of ω-hydroxycarbonyls *via* an activated carbonyl group
- Macrolactonisation of ω-hydroxycarboxylic acids *via* an activated hydroxyl group
- Annulation by carbon-carbon bond formation
- Ring expansion by cleavage of fused ring systems
- Miscellaneous reactions

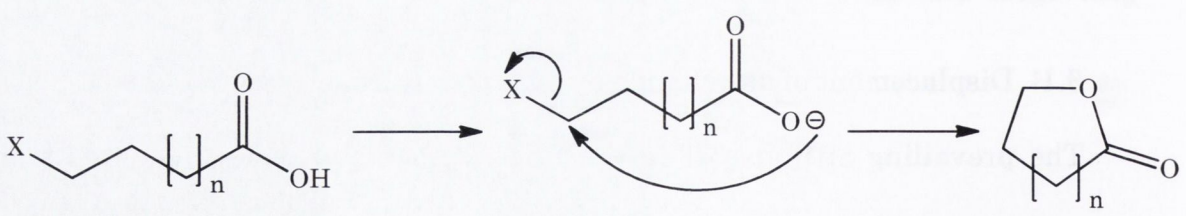
3. Macrolactonisation of ω-hydroxycarboxylic acids *via* an activated carboxylic acid

3.1: Displacement of an ω-halide by carboxylate anion

The prevailing attitude before the first syntheses of macrolactones was that such a transformation of a linear compound would prove to be impossible, inherently resulting in oligomers and polymers as a result of more favourable intermolecular reactions.[36]

A key result of the accumulative strains present within ring systems is that the longer homologues of any linear macrolactone precursors are prone to cyclodimerization, rather than forming monolactones, producing more flexible and hence less strained rings. This has consequently led many researchers to resort to reactions using extremely low concentrations over long times to minimise intermolecular reactions.

It was only with the development of high dilution techniques that the first syntheses of medium (8-10 carbon chain) and large (11 carbon chain upwards) lactones **19** were achieved, *via* the intramolecular displacement of bromide by a carboxylate anion.[37] Previously, these were typically formed either by formation of the silver carboxylate and subsequent deposition of the insoluble silver halide. Utilising high dilution techniques by slowly adding the ω-haloacid **20** to a solution of potassium carbonate achieved reasonable success for some of the longer chain lengths but struggled to form medium sized rings.[38]



20 X=Br, I **19**

n= 4-24, yields = 49-96%

Scheme 1-1 Lactonisation *via* carboxylate displacement of halide

Using this reaction, a set of systematic kinetic studies were undertaken by Illuminati *et al.*[39] using a series of sodium ω-bromocarboxylate salts in a 99:1 DMSO:H_2O solvent system at 50 °C.

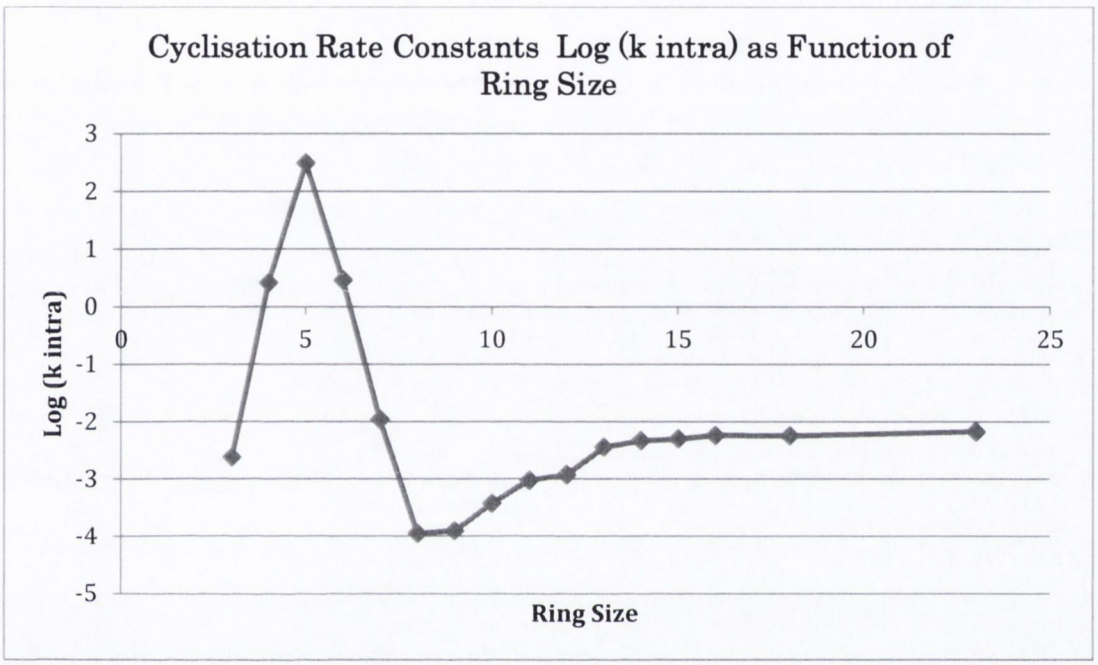


Figure 1.1: Cyclisation rate of sodium ω-bromocarboxylate salts as a function of ring size

The recovered yields of lactones were reasonable to excellent throughout the series (49-96%). However these authors found that whilst it was relatively easy to form rings in the 5 to 7 membered range the reaction rate dropped sharply and significantly when trying to form 8 membered rings, then slowly rose again until reaching a plateau for ring sizes greater than 15.

Ultimately, it is the activation energy of the cyclisation that will determine the extent to which it occurs, this is dependent on the energy and stability of the

transition state which, following the Hammond-Leffler postulate, will closely resemble the product. Thus, the likelihood of successful cyclisation to yield medium-sized macrolactones is greatly reduced both by the rapidly decreasing likelihood of the two reactive terminals coming into close enough proximity to react and overcoming the ring strains present in the product and the loss in entropy.

This loss of entropy can be somewhat abated by the addition of bulky or restricting groups on the linker chain, such as gem-dimethyl groups or heteroatoms[40,41] by both limiting rotation in the open chain form resulting in a smaller drop in entropy and forcing the two ends into a greater probability of meeting.

The difficulties associated with ring formation is a complex subject but can be broadly divided into three main factors:

- Baeyer strain – created due to the contortion of bond angles from their preferred orientation, this is minimised in larger rings due to the inherently greater flexibility of the chain.
- Pitzer strain – Torsional strain across a single bond as a result of a more staggered conformation being forced onto it.
- Transannular strain – Arising from interactions with a separate section of the ring when conformed into a close proximity.

These cumulative strains manifest themselves in a higher internal energy which may be quantified by the strain energy, a measurement of the molar heat of combustion per methylene group in the ring.

Table 1 - Strain energy as a function of ring size[42]

Ring size (CH_2 units)	Ring strain energy (kcal/mol)
3	27.5
4	26.3
5	6.2
6	0.1
7	6.2
8	9.7
9	12.6
10	12.4
11	11.3
12	4.1
13	5.2
14	1.9

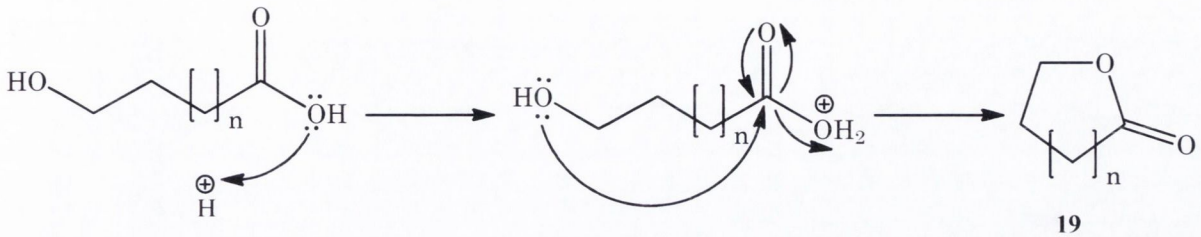
As can be seen from the figures in the table, strain energy decreases as the bond angle between carbons becomes closer to the more stable free-chain arrangement. This strain then begins to rise again following cyclohexane as bond angles begin to deviate once more, necessarily becoming more obtuse. After reaching a maximum at a ring size of 9 carbons the strain energy then falls again as the greater chain length allows for a greater degree of flexibility, meaning that the ring can bend and pucker to a greater extent permitting bond angles closer to those present in the straight chain analogue.

It follows from this that the difficulties in synthesising cyclic organic compounds with a ring size of 12 or greater arise more as a result of the reactive terminals not coming into close enough proximity than as a result of the accumulative ring strain energies.

3.2: Lactonisation *via* intramolecular ring-closure of ω-hydroxycarboxylic acids

Perhaps the most obvious retrosynthetic choice for construction of macrolactones, acid catalysed intramolecular Fischer esterification was first developed by Stoll and Rouve in 1934.[43,44] Whilst capable of producing lactones with up to 24-membered rings by refluxing ω-hydroxycarboxylic acids **21** in benzene with a catalytic amount of acid, it is limited by slow reaction times

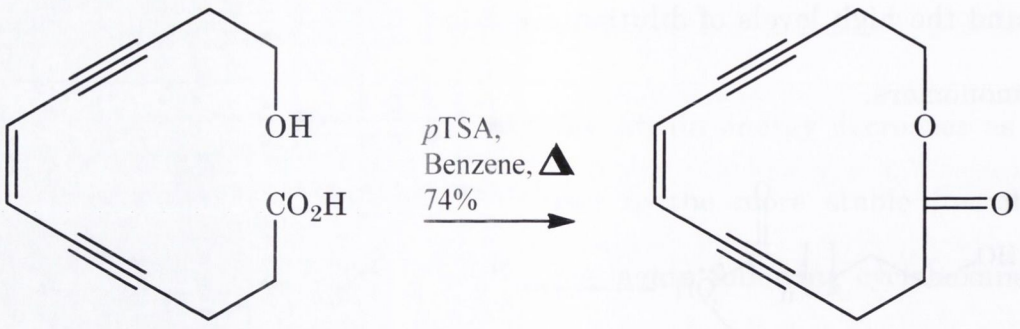
and the high levels of dilution needed to control the preferential formation of monomers.



21 n = up to 23 **19**

Scheme 1-2: Lactonisation *via* Fischer esterification

Nevertheless the reaction does have some scope within synthetic methodologies as demonstrated by Guillerm and Linstrumelle[45] who synthesised the extremely structurally constrained lactone **22** in good yield (74%), the ease of the reaction coming about as a result of the ene-diyne architecture in the starting acid **23** holding the two reactive terminals in close proximity.



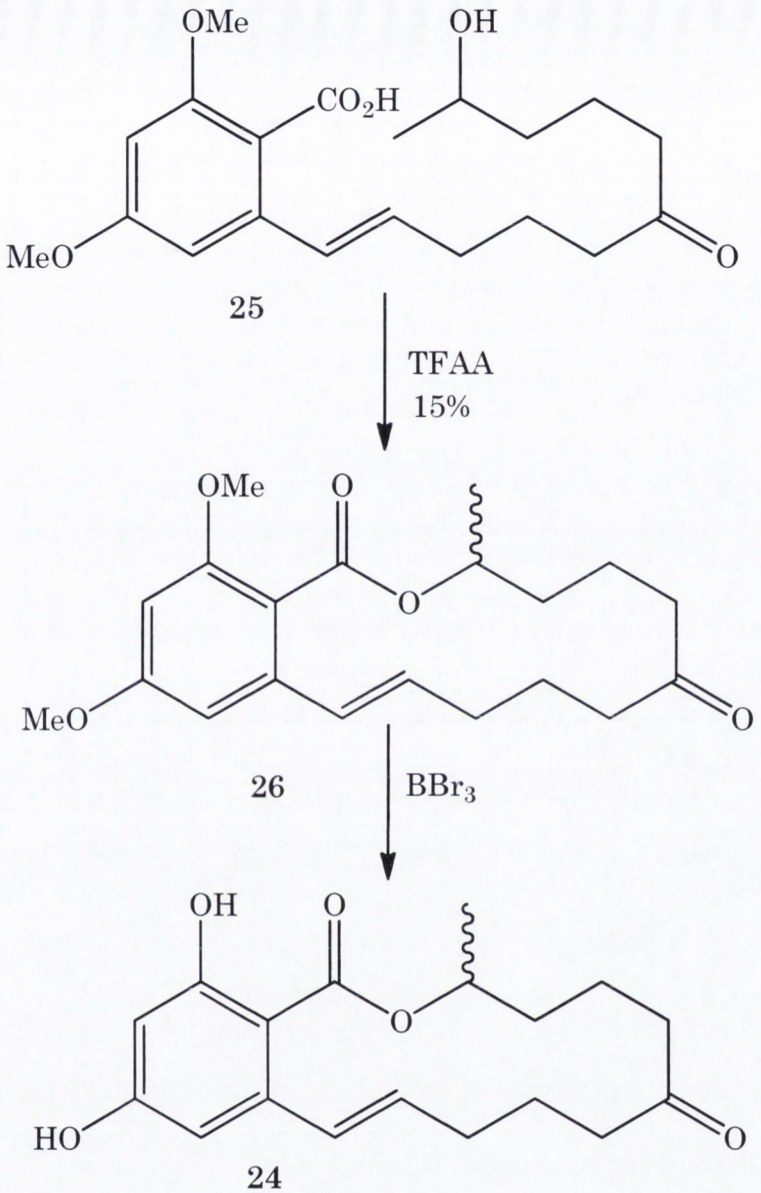
23 **22**

Scheme 1-3: Acid catalysed lactonisation of an structurally constrained ω-hydroxycarboxylic acid

More commonly though, the carboxylic acid is converted to include a more facile leaving group, as discussed below.

3.3: Lactonisation *via* mixed anhydrides

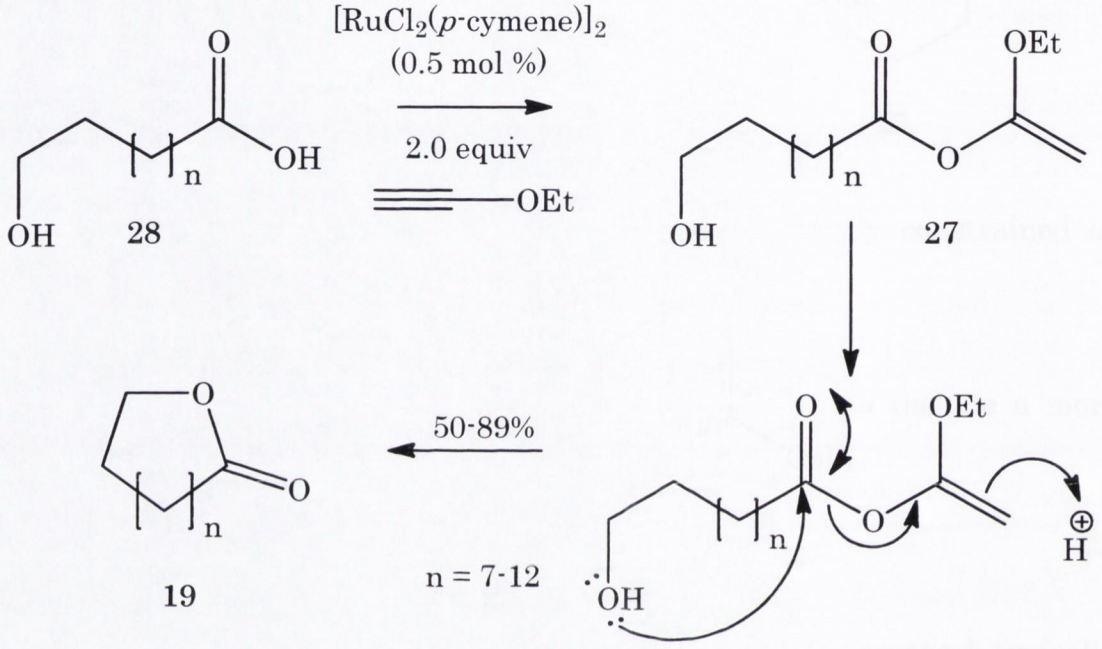
In one of the earliest reports of the carboxylic acid activation protocol, typically a mixed anhydride was formed using trifluoroacetic anhydride as the reagent. The technique was developed by a group at Merck and used as part of a successful total synthesis of the resorcyclic acid lactone zearalenone **24** from an ω-hydroxycarboxylic acid **25**, albeit in a poor yield (15%).[46] The dimethoxy protecting groups on the resorcinol moiety of the initially formed lactone **26** were then subsequently removed using BBr_3 to give the final product.



Scheme 1-4: Synthesis of zearalenone **24** *via* mixed anhydride

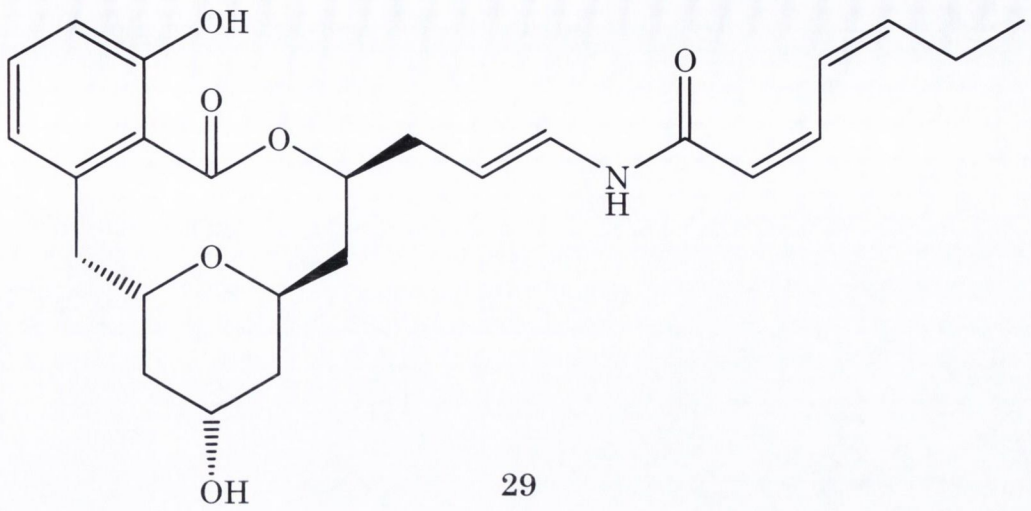
More recently, highly active esters have also been used as intermediates in lactonisation, the ethoxy vinyl esters **27** are pre-formed in a separate step from an ω-hydroxycarboxylic acid **28** using a ruthenium based catalyst and ethoxy acetylene without the need for further purification. Addition of the ester to a dilute solution (≈10%) of PTSA in dichloroethane promotes the cyclisation and

expulsion of ethyl acetate as a byproduct. The reaction is capable of forming substituted medium and large lactones **19** under mild conditions in reasonable to excellent yields (50-89%).[47]



Scheme 1-5: Lactonisaton *via* ethoxy vinyl ester

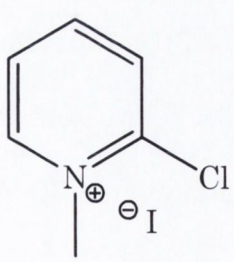
The technique has been used in several total syntheses including one of the anti-cancer sponge extract apicularen A **29**.[48]



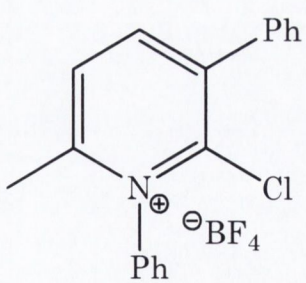
29

3.4: The Mukaiyama reaction

ω-Hydroxycarboxylic acids **21** are also the starting structural framework used in what has come to be known as the Mukaiyama reaction, wherein the reagent is 1-methyl-2-chloropyridinium iodide **30**[49] or, better, the modified reactant 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate **31**, which is designed not to be broken down to form 2-chloropyridine in the presence of TEA under the standard reaction conditions.[50]



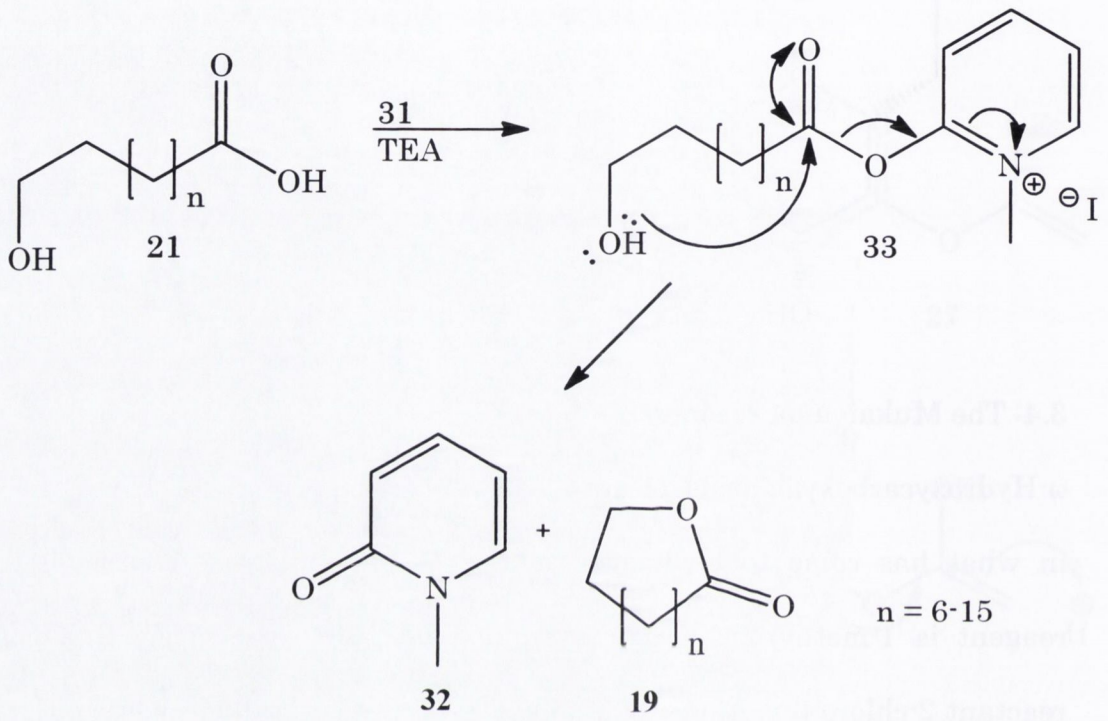
30



31

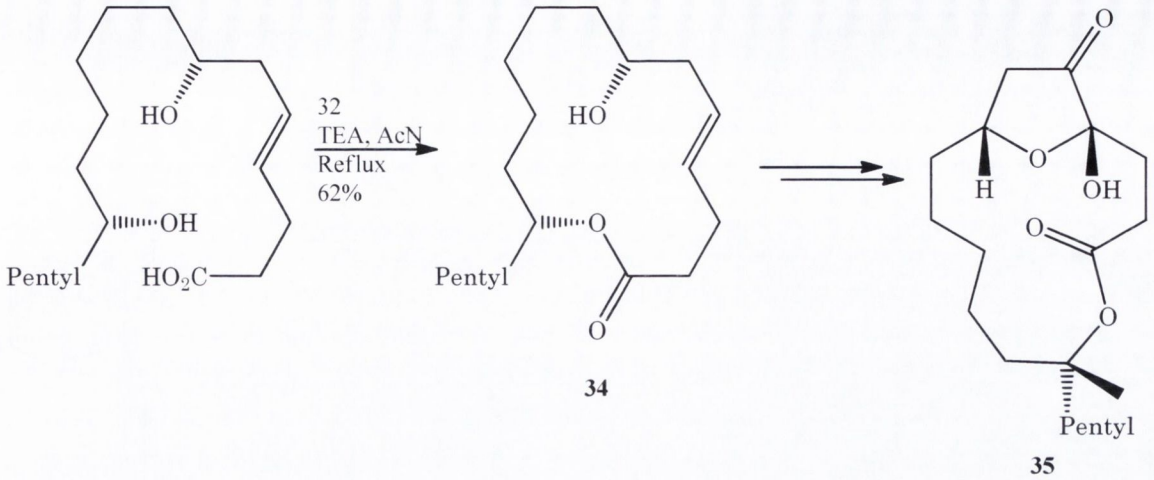
These reagents undergo substitution of the 2-chloro substituent in the presence of a suitable carboxylic acid to form a short lived acyloxypyridinium species **33**,

which quickly undergoes intramolecular attack forming the desired macrolactone and 1-methyl-2-pyridone **32** as a side product.

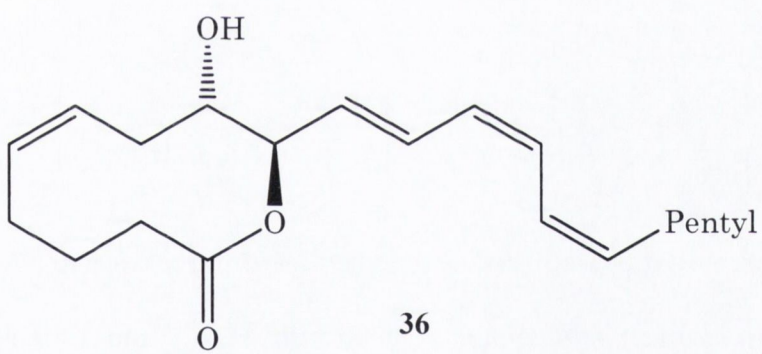


Scheme 1-6: Lactonisation *via* the Mukaiyama reaction

Whilst still dependent on dilution factors to prioritise formation of a monomer over a dimer, the reaction is nonetheless useful, producing yields of up to 85-99% for ring sizes of 12-14 atoms, and has been used in a number of total syntheses including boromycin **18**,[51] ascidiatrienolide **36**,[52] and a precursor **34** to gloeosporin **35**.[53]



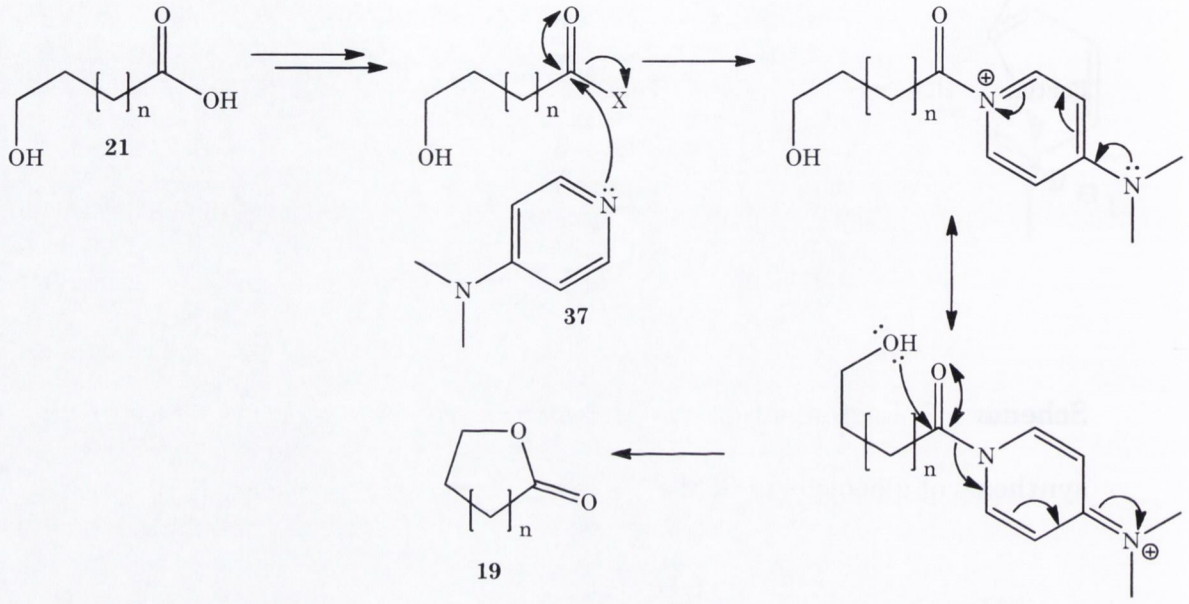
Scheme 1-7: Lactonisation *via* Mukaiyama reaction as a key stage in the total synthesis of gloeosporin 35[53]



3.5: Carboxylic acid activation with 4-dimethylaminopyridine

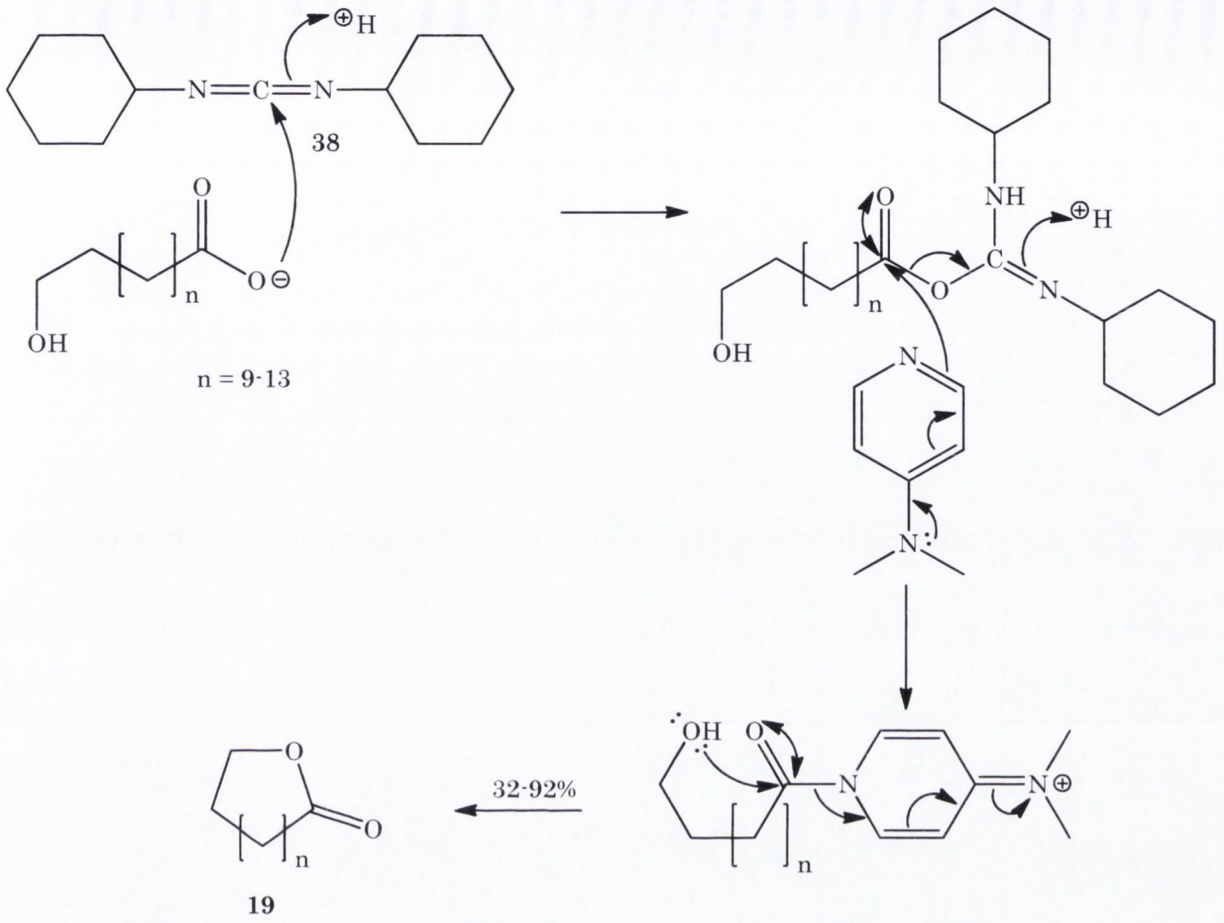
This is a broad grouping of macrolactonisation methodologies many of which remain popular choices for total syntheses, their uniting factor being the installation of a carboxyl leaving group which is displaced by a catalytic amount of DMAP **37** prior to a second displacement leading to intramolecular cyclisation. DMAP may also act as a base in the reaction by deprotonating the

carboxylic acid, thereby making it nucleophilic enough to engage with the carboxylate activating agent.



Scheme 1-8: Role of DMAP **37** in activated carboxylic acid lactonisations

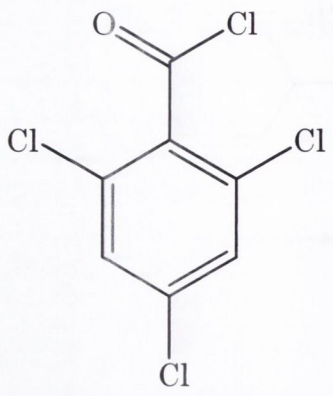
Whilst normally only applied to intermolecular reactions there has been some interest in using a dicyclohexylcarbodiimide **38** and 4-DMAP **37** Steglich esterification system in macrolactonisation.[54] This protocol, commonly referred to as the Keck reaction,[55] though it often gives extremely disappointing yields (<40%), has been used in total syntheses.[56]



Scheme 1-9: Mechanism of Keck lactonisation[55]

The Keck reaction though has largely been superseded by the Yamaguchi reaction which, with over 340 published examples, may be considered the most widely used macrolactonisation technique today.[57]

The reaction, which may also be classified under the mixed anhydride label, utilises 2,4,6-trichlorobenzoyl chloride **39** to activate the carboxyl terminus.

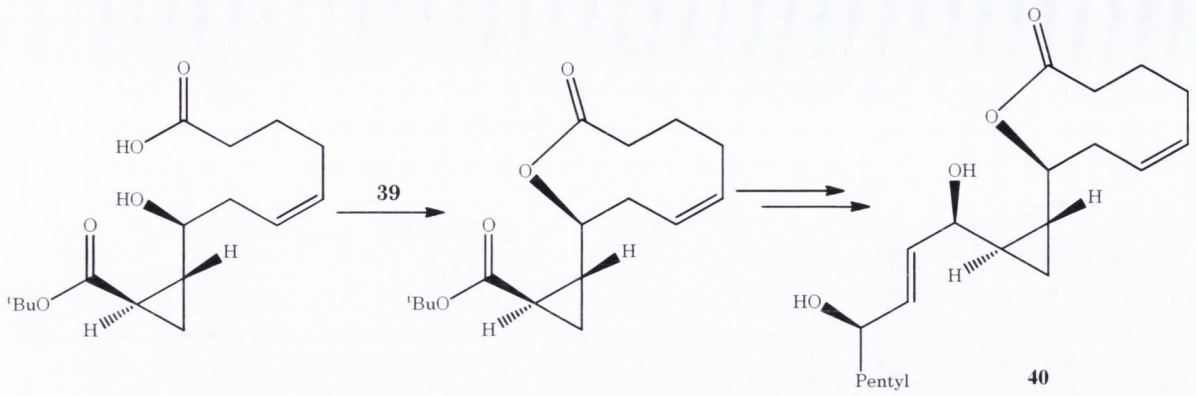


39

This is typically done under basic conditions using TEA to deprotonate the carboxylic acid and remove the HCl formed by anhydride formation, prior to slow addition of the mixed anhydride to a dilute solution of DMAP,[58] although under what are known as the Yonemitsu conditions the lactonisation is performed as a one step process, often with excellent results.[59]

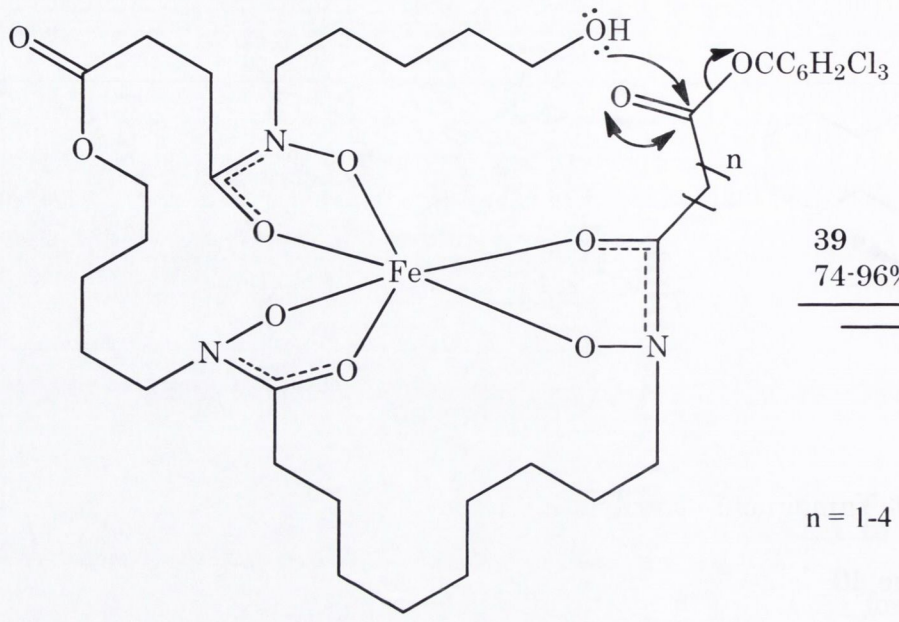
In spite of its widespread use and superior results there are still drawbacks to the use of the Yamaguchi reagent, namely the use of the strongly basic DMAP **37**, high temperatures and high dilution. The reaction is also prone to side effects including epimerisation of chiral centres[60] and isomerisation of *E/Z* double bonds.[61]

These objections aside, the reaction remains profoundly useful in the total synthesis of some very complex and sensitive natural products, for example the marine sponge metabolite halicholactone **40**.



Scheme 1-10: Yamaguchi esterification as a key step in the total synthesis of halicholactone **40**

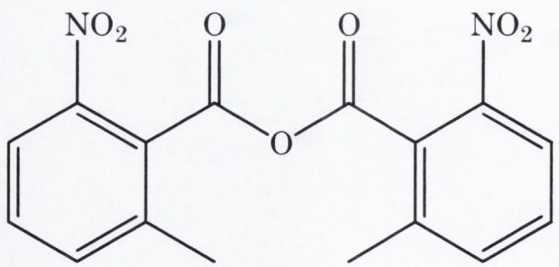
A recent novel application of the Yamaguchi reaction has been demonstrated by Wencewicz *et al.*[62] wherein the intrinsic ability of the natural product target to complex iron (III) ions to pre-form a template **41** for the esterification allowed for the formation of the very large 35-membered ring in excellent yields (74-96%).



41

Scheme 1-11: Iron templated Yamaguchi esterification

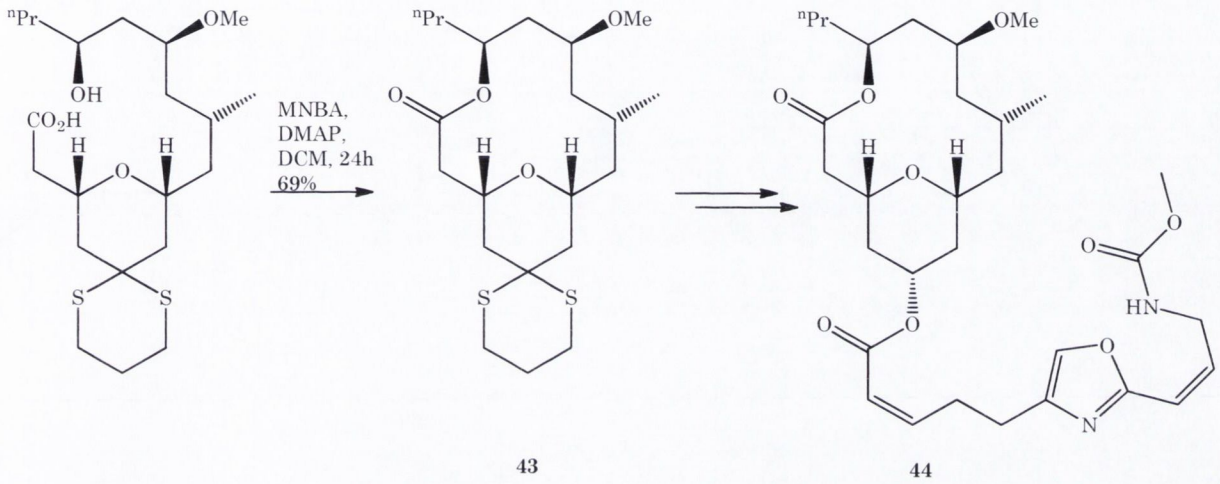
A recently developed analogue of the Yamaguchi reaction, the Shiina reaction, uses 2-methyl-6-nitrobenzoic anhydride (MNBA) **42** as the carboxylate activating agent.[63]



42

Though it also suffers from the same potential *Z/E* isomerisation issues as the Yamaguchi reaction,[64] and the only control over monomer/dimer formation is molar concentration. the Shiina reaction is still capable of macrolactonisations

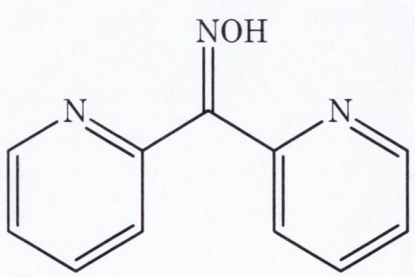
at room temperature in excellent yield (84-93%) and is a powerful new tool which has already been utilised in several total syntheses, for example as a key step in the synthesis of a precursor **43** of the marine sponge macrolactone neopeltolide **44** by Kim *et al.*[65]



43 **44**

Scheme 1-12: Shiina lactonisation in the synthesis of neopeltolide **44**

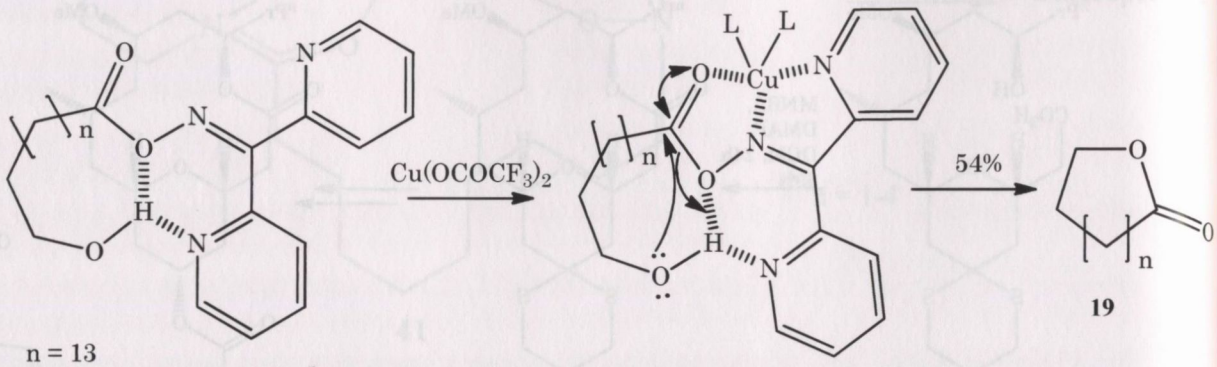
A final notable example is the use of the peptide coupling agent di-2-pyridyl ketone oxime **45** as demonstrated in a synthesis of hapalosin by Palomo *et al.*[66]



45

The oxime ester **46** that this reagent forms with an ω-hydroxycarboxylic acid in the presence of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride

(EDC) and catalytic DMAP is relatively stable until the addition of a copper(II) salt causes cyclisation to proceed smoothly and in reasonable yield (54%). It is conjectured that this was aided *via* the formation of a dual activating template **47**.



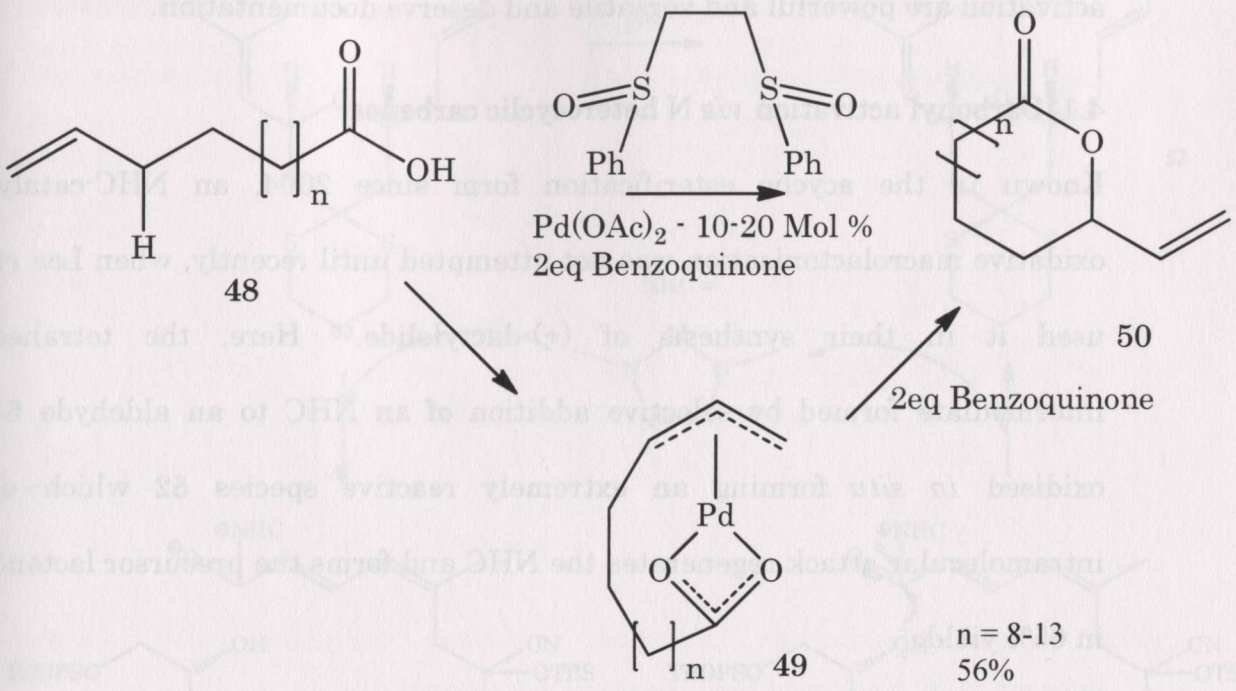
46 **47** **19**

Scheme 1-13: Copper template macrolactonisation with di-2-pyridyl ketone oxime

3.6: Palladium-catalysed activation of carboxylic acids

It is surprising how relatively few documented uses of transition metal catalysed macrolactonisations there are in the literature given the potential for pre-forming a template to selectively produce monomers. There has been some initial research into ruthenium-catalysed reactions,[67] but the only recent notable publication is an allylic oxidation protocol described by Fraunhoffer *et al.*[68] The reaction is understood to proceed *via* complexation of the ω-alkenoic

acid **48** on to the palladium and formation of a π-allylPd species **49**, followed by benzoquinone promoted reductive elimination and esterification.



Scheme 1-14: Palladium catalysed lactonisation of ω-alkenoic acids

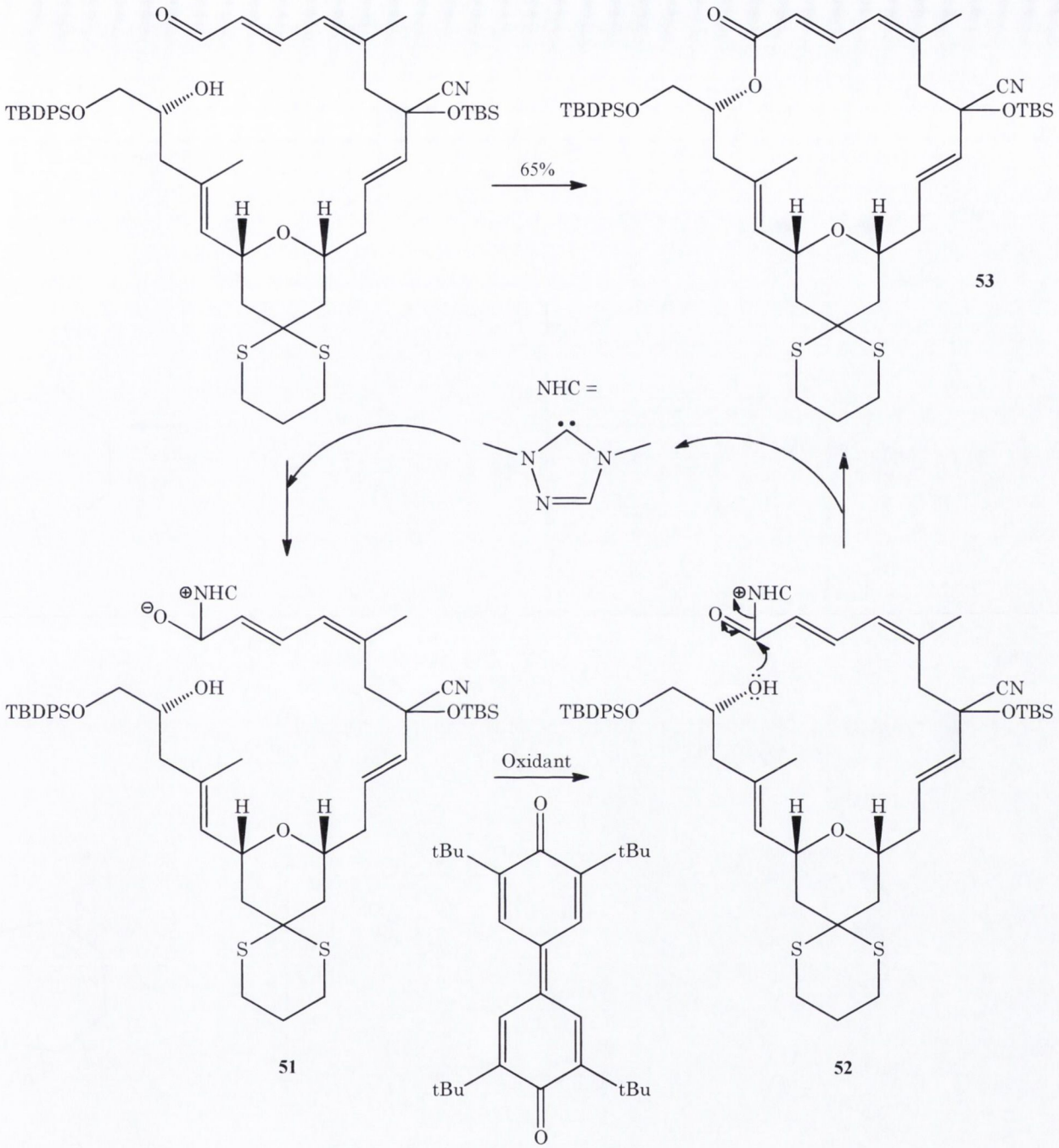
Whilst it is inherently limited by the necessity to have an allyl group α to the annular oxygen atom of the lactone **50**, the reaction employs gentle conditions, and delivers scalability and reasonable yields (56%).

4. Macrolactonisation of ω-hydroxycarbonyls *via* activated carbonyl

Though fewer in number, the techniques for lactonisation *via* carbonyl activation are powerful and versatile and deserve documentation.

4.1: Carbonyl activation *via* N heterocyclic carbenes

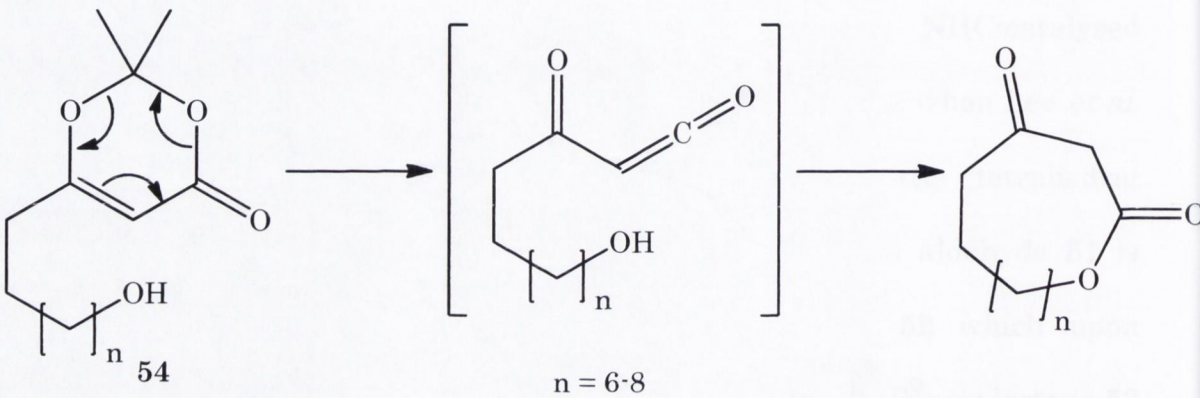
Known in the acyclic esterification form since 2004, an NHC-catalysed oxidative macrolactonisation was not attempted until recently, when Lee *et al.* used it in their synthesis of (+)-dactylolide.[69] Here, the tetrahedral intermediate formed by selective addition of an NHC to an aldehyde **51** is oxidised *in situ* forming an extremely reactive species **52** which upon intramolecular attack regenerates the NHC and forms the precursor lactone **53** in 65% yield.



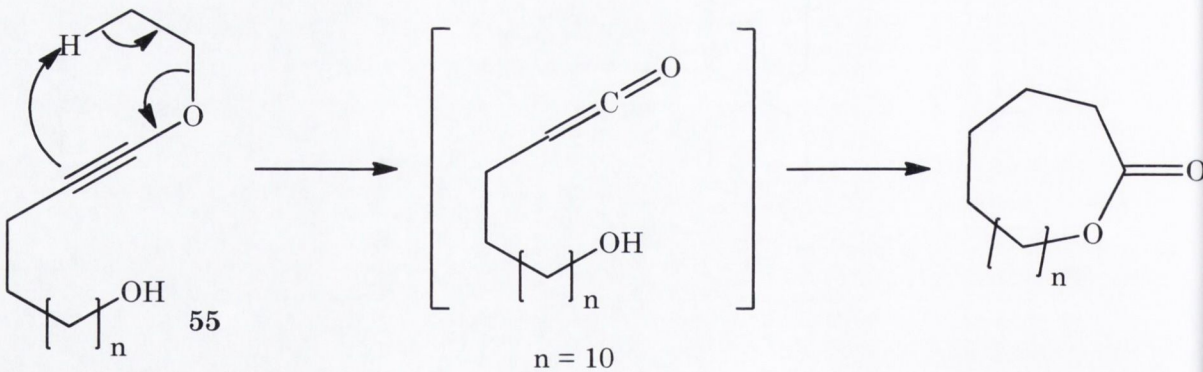
Scheme 1-15: NHC catalysed lactonisation of a precursor to (+) dactylolide **53**

A far more generalised lactonisation strategy by activated carbonyls is with the trapping of *in situ* generated ketenes. The two most flexible examples of these

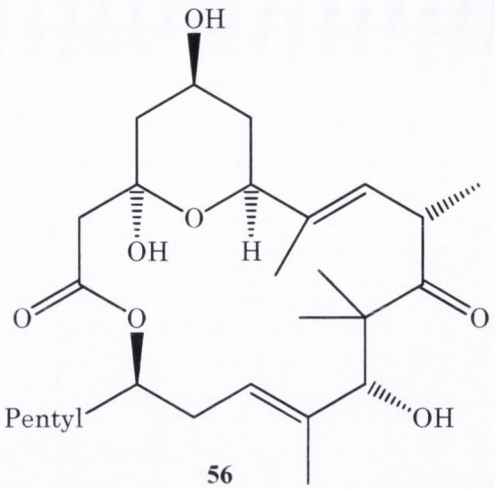
are those using Boeckman's method of thermolytically degrading a 2,2-dimethyl-1,3-dioxinone **54**,[70] and by the *in situ* formation and thermal degradation of an alkynyl ethyl ether **55**, a strategy which has been used in the total synthesis of (+)-acutiphycin **56**.[71]



Scheme 1-16: Boekman lactonisation *via* ketene



Scheme 1-17: Alkynyl ethyl ether degradation route to ketene precursor



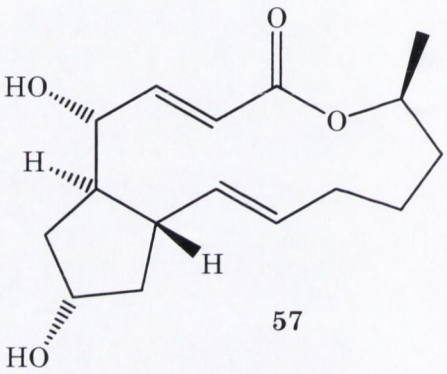
56

5. Macrolactonisation of ω-hydroxycarboxylic acids *via* an activated hydroxyl

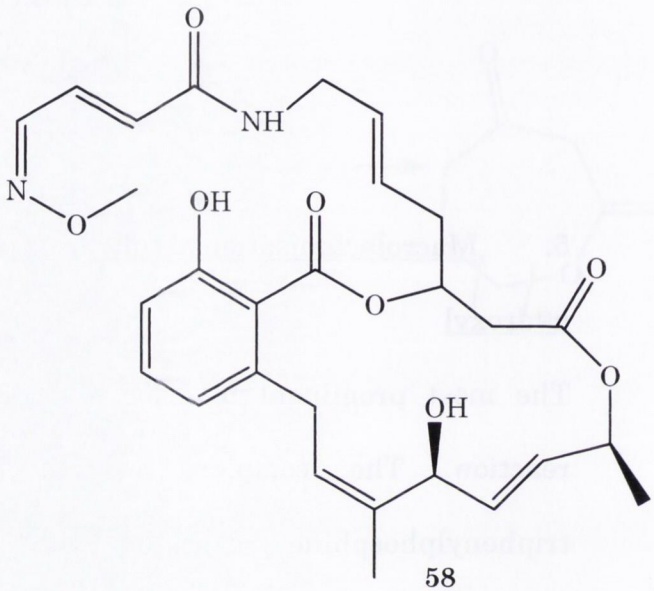
The most prominent member of this class of reactions is the Mitsunobu reaction. The complex reaction pathway mechanism begins with triphenylphosphine attacking the nitrogen-nitrogen bond of diethyl azodicarboxylate to form a new species with a more electrophilic phosphorous atom, this is then attacked by the alcohol oxygen to form an oxyphosphonium species which is subsequently attacked by the carboxylate anion in an S_N2 fashion, inverting the stereochemistry, to complete the cyclisation and deliver triphenylphosphine oxide as a by-product.[72]

The reaction does suffer from several notable drawbacks; it is often difficult to predict or control formation of diolides, hydrazide by-products frequently form,[73] and the triphenylphosphine oxide is notoriously persistent, often requiring multiple sets of column chromatography to fully remove it.

In spite of this, the Mitsunobu reaction continues to be popular as a macrolactonisation technique and has been applied to numerous total syntheses total syntheses such as those of (+)-brefeldin **57**,[74] lobotamide C **58**,[75] and zearalenone **24**.[76]

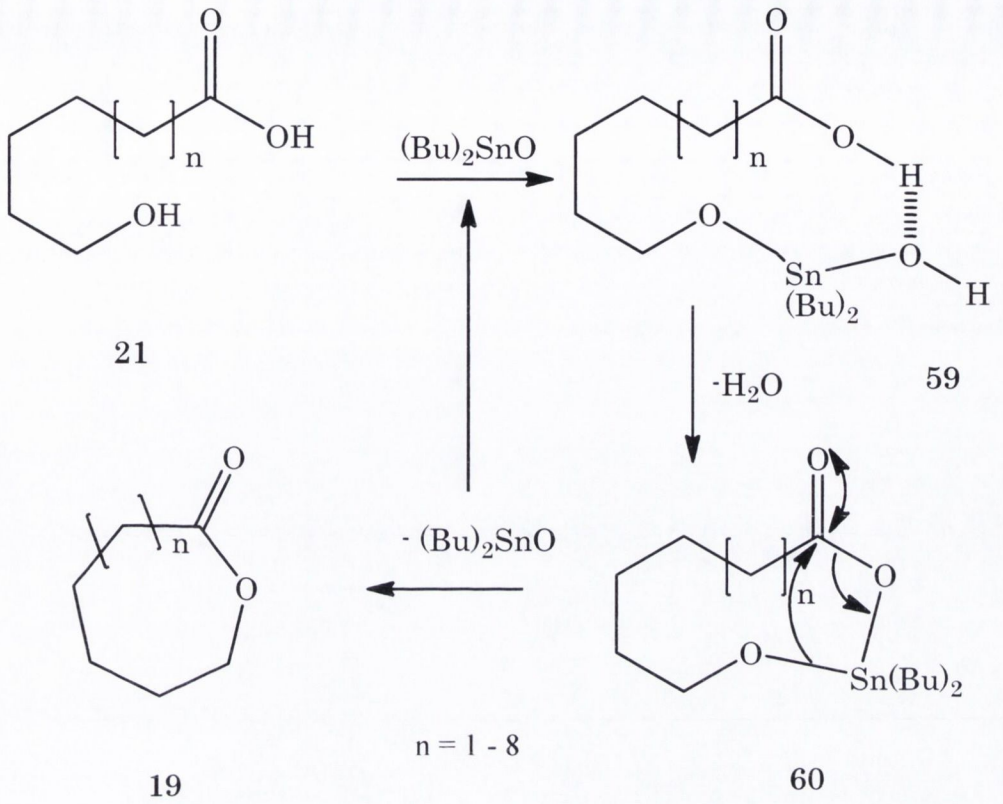


57



58

Although it performs poorly with the more difficult to form 8-12 membered rings, the technique of Steliou *et al* is still worth documenting.[77] Using ω-hydroxy carboxylic acids **21** as the starting materials, the initial reaction is between the hydroxyl group and di-^{n}butyl tin oxide, forming a templated intermediate **59** such that the loss of water and breakdown of the ensuing stannyl carboxylate **60** occurs intramolecularly.



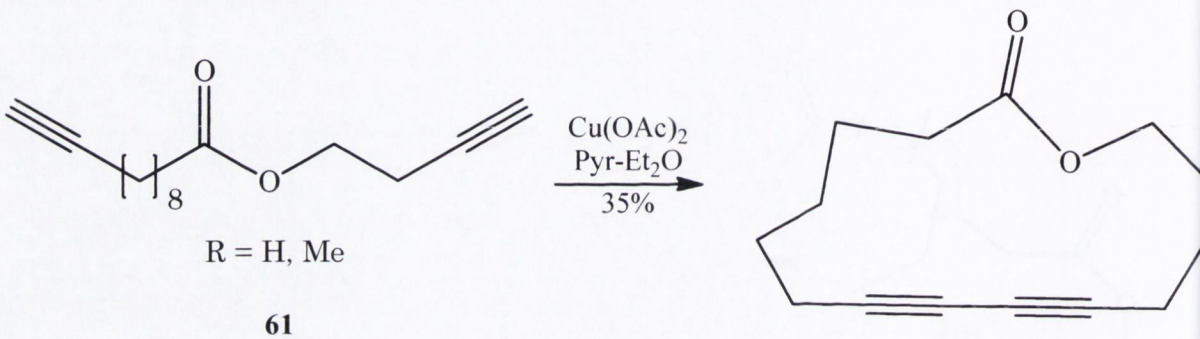
Scheme 1-18: Steliou di-^{n}butyl tin oxide catalysed lactonisation

6. Annulation by carbon-carbon bond formation

Whilst the majority of macrolactone syntheses opt to form the ester bond as the ring closing reaction, an equally valid approach is to form a carbon-carbon bond between the two terminals of a suitable linear ester, the only requirement being that the reaction conditions are not such that hydrolysis of the acyclic ester occurs prior to cyclisation.

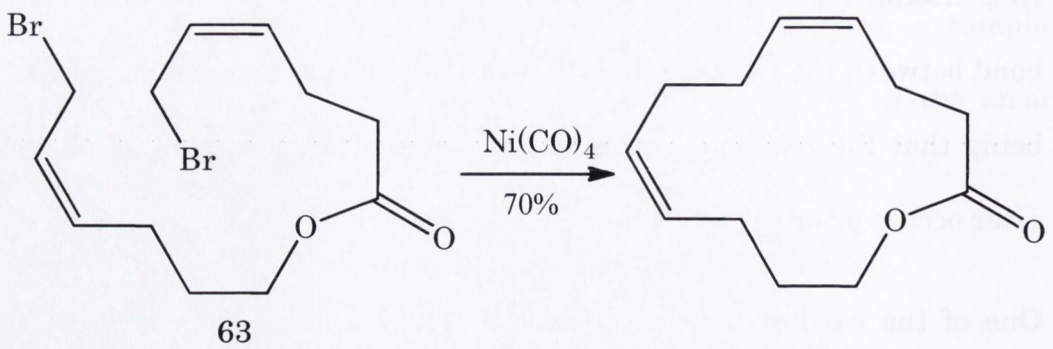
One of the earliest demonstrations of this was the copper acetate mediated oxidative coupling of a di-terminal acetylene ester **61**. Whilst limited in scope

for synthesis of the harder to form medium-sized rings due to the inherently inflexible linear di-yne arrangement in the product increasing the Baeyer strain beyond what is tolerable, the reaction has been used to produce the simple lactone exaltolide **2** in acceptable yield (35%) after hydrogenation of the di-yne **62** to give the cycloalkane.[78]



Scheme 1-19: Copper mediated synthesis of an exaltolide precursor **62**

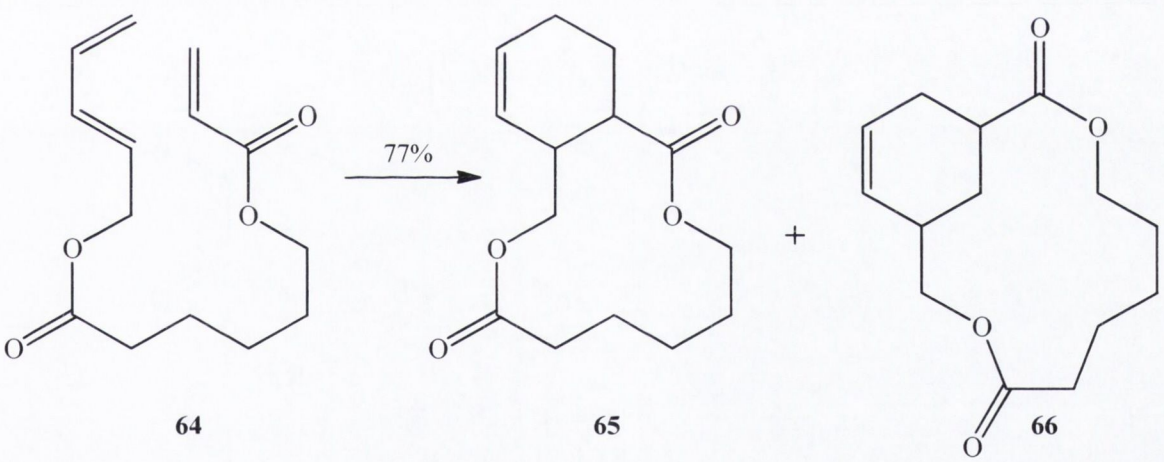
The restrictions imposed by the necessity of utilising a di-yne were somewhat abated in 1972 when Corey *et al.* reported the cyclisation of an allylic dibromide **63** using nickel carbonyl.[79]



Scheme 1-20: Nickel carbonyl mediated lactonisation

Whilst this reaction proceeded in reasonable to good yields (70%) the harsh conditions (refluxing N-methyl-pyrrolidone) mean that it is unlikely to see a great deal of application.

A less demanding set of reaction conditions is the use of an intramolecular Diels-Alder cyclisation as also developed by Corey with an ester linked diene and dienephile **64**,[80] capable of giving moderate to good yields (77%) with a short reaction time. The procedure is nonetheless limited because of the formation of structurally isomers **65** and **66** as products in a roughly 1 to 1 ratio.

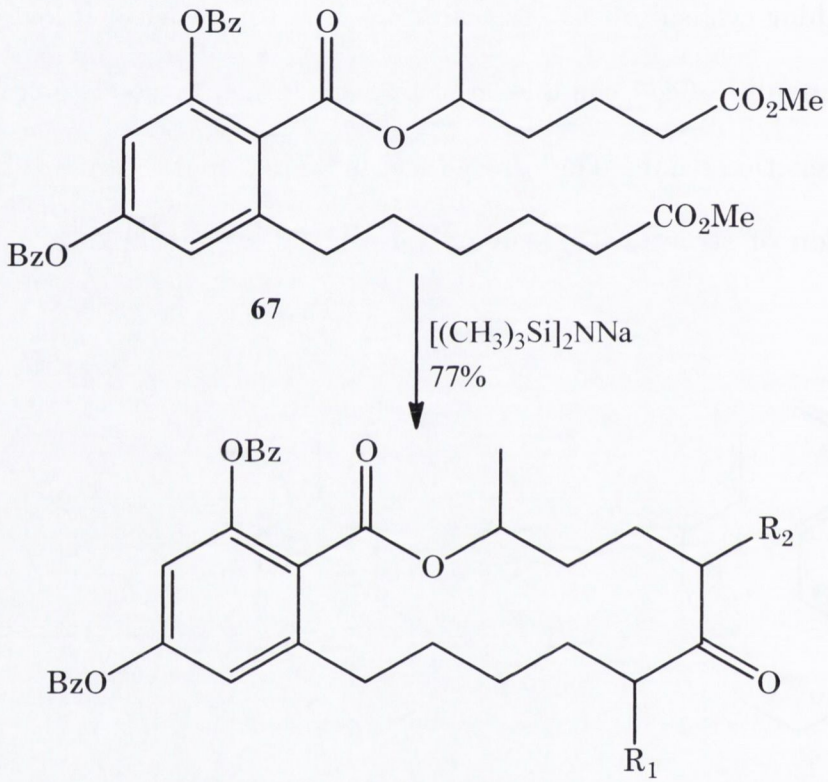


64 **65** **66**

Scheme 1-21: Lactonisation *via* intramolecular Diels-Alder reaction

Under the correct conditions it has also been found possible to utilise the Dieckmann cyclisation reaction in order to form macrolactone rings. Whilst necessitating construction of a lactone pro-ester with easily abstractable α-protons the reaction of **67**, as developed by Hurd and Shah in pursuit of a total

synthesis of zearalenone **24**,[81] performs remarkably well using sodium bis(trimethylsilyl)amide as the strong base. Very dilute conditions are necessitated however and the intrinsic formation of multiple products **68** and **69** does limit its scope.

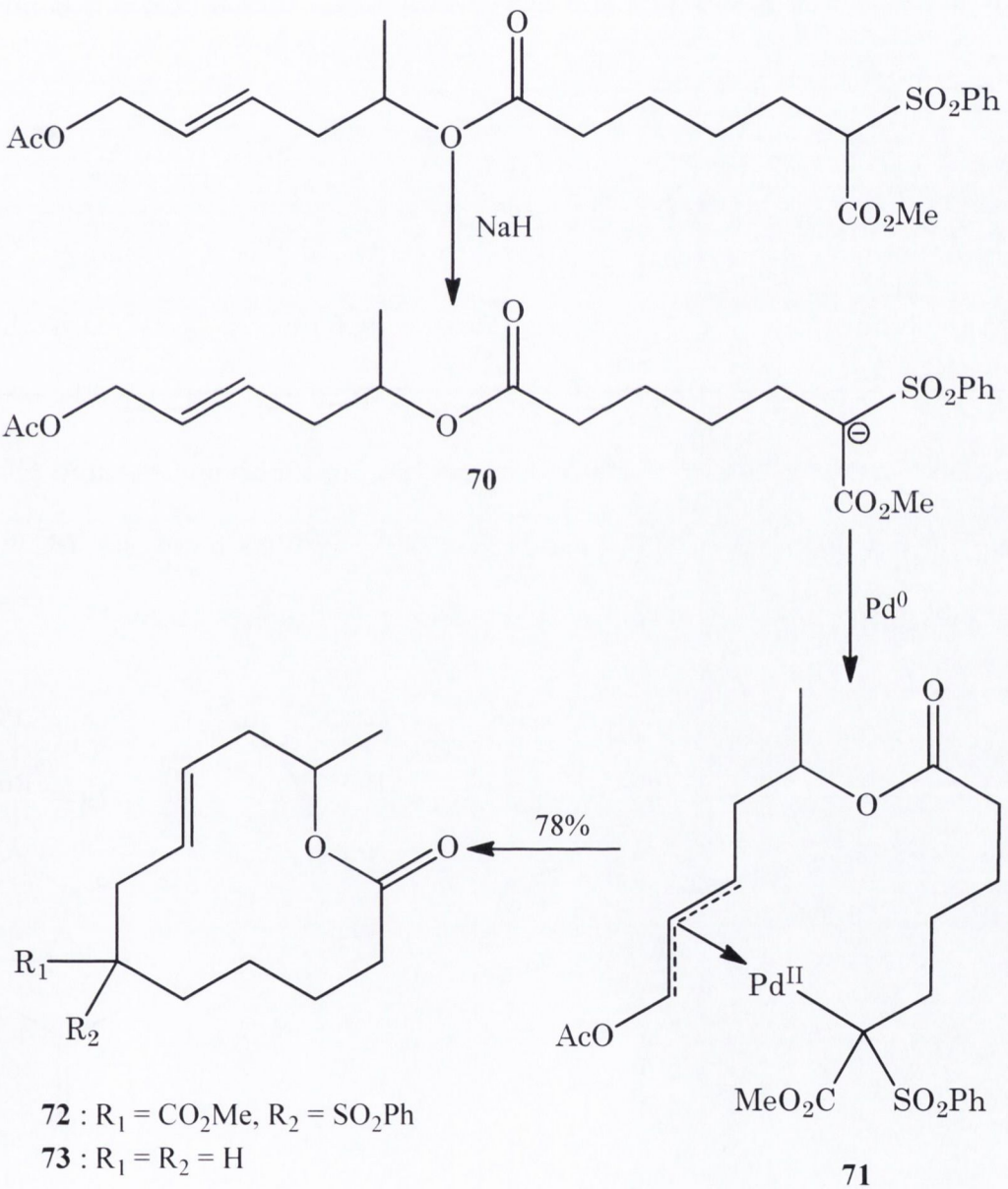


68 $R_1 = H$, $R_2 = CO_2Me$
69 $R_1 = CO_2Me$, $R_2 = H$

Scheme 1-22: Dieckmann cyclisation of a zearalenone precursor **69**

In 1979 Trost and Verhoeven reported the first palladium(0) catalysed macrolactonisation. Using tetrakis(triphenylphosphine)palladium as the catalyst the reaction proceeds *via* initial formation of a stabilised carbanion **70** using sodium hydride prior to addition of the catalyst. Reductive elimination from the templated complex thus formed **71**, and elimination of acetate anion

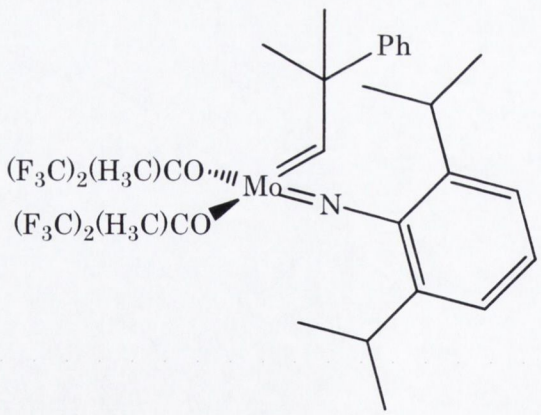
led to formation of a 12-membered lactone **72** in yields of up to 78%.[82] Decarboxylation and desulfonylation, albeit under forcing conditions which limit the application of this pathway, resulted in the formation of the fungal metabolite recifeiolide **73**.



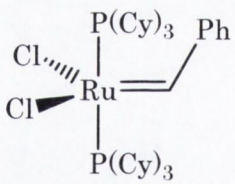
Scheme 1-23: Palladium catalysed coupling in a recifeiolide **73** synthesis

All of these techniques, however, have been somewhat superseded by the development of the ring-closing metathesis methodology, RCM.[83] Capable of good to excellent yields (>90%) for ring sizes between 5 and 35 atoms, and extremely tolerant of other functional groups, the metathesis of terminal *bis*-alkenes **77** has developed into the most utilised carbon-carbon bond-forming macrolactonisation technique.

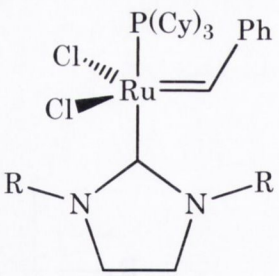
The choice of catalyst itself has developed since the reaction was first documented. The reaction was initially developed using Schrocks's molybdenum catalyst **74**,[84] though this was found to be too unstable in its alkylidene form, leading to the development of the first Grubbs ruthenium based catalyst series **75**.[85] Difficulties with more highly-substituted alkenes led to the development of the second generation Grubbs catalysts **76**, which are stable in the presence of air, moisture and raised temperatures.[86]



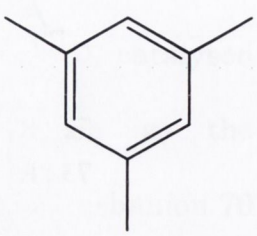
74



75



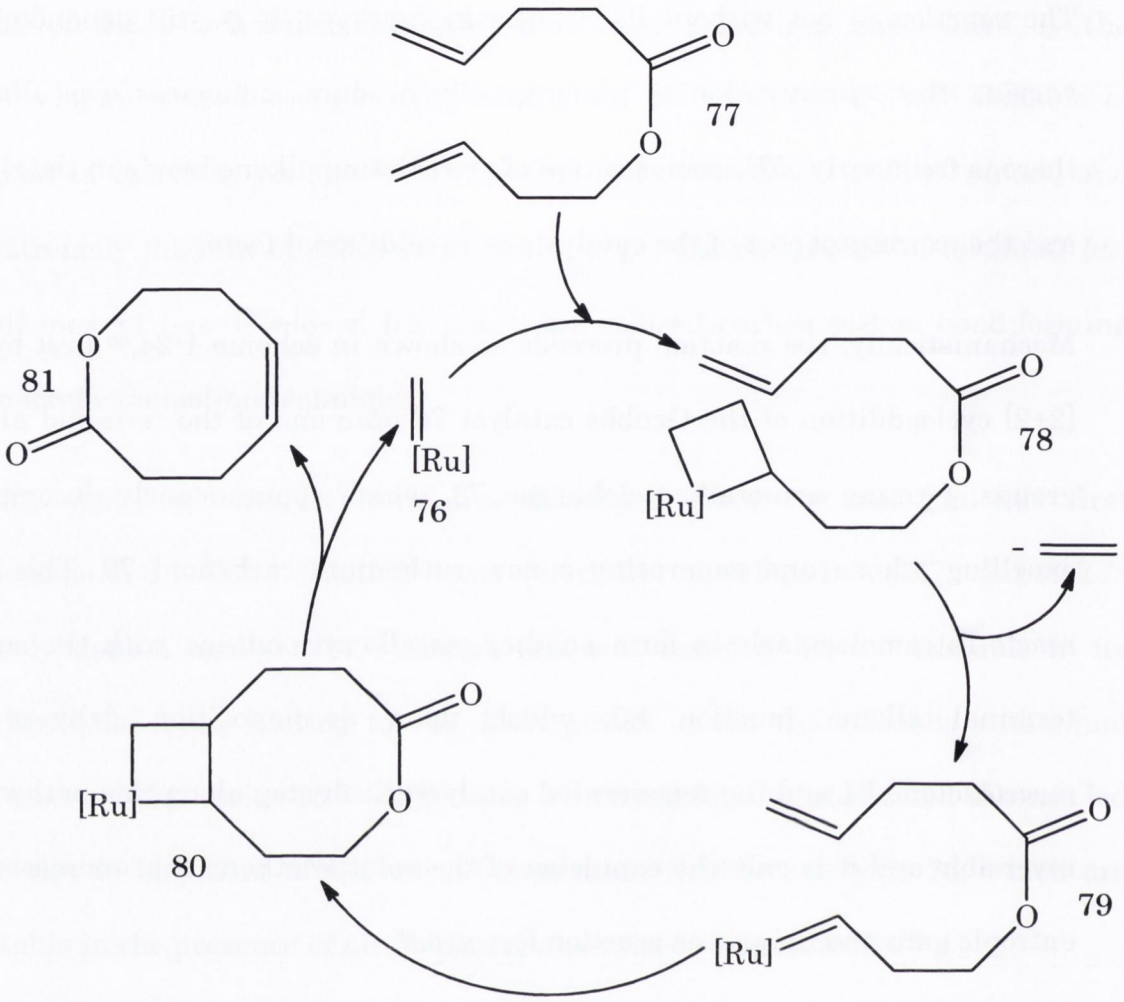
R =



76

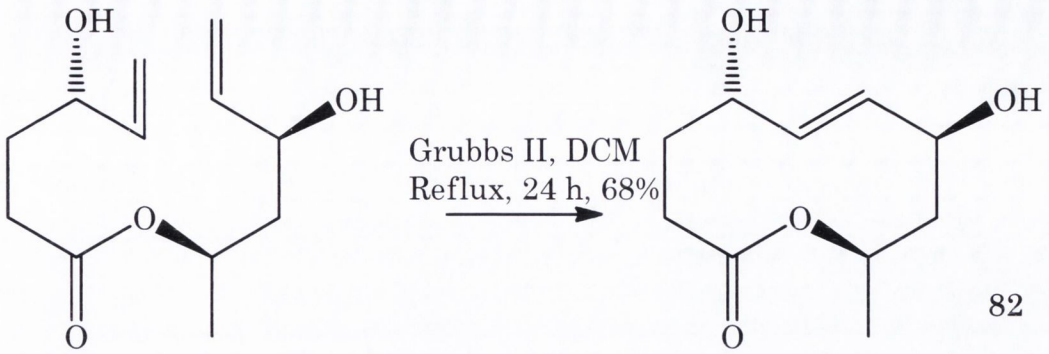
The reaction is not without its drawbacks however; it is still dependent on varying the concentration to preferentially produce monomers over dimers, there is frequently *Z/E* isomerisation of pre-existing alkene bonds in the ring,[87] and the exorbitant cost of the catalysts is an additional factor.

Mechanistically, the reaction proceeds as shown in **scheme 1-24**,[88] first by the [2+2] cycloaddition of the Grubbs catalyst **76** onto one of the terminal alkene groups, forming a metallo-cyclobutane **78**, which spontaneously decomposes expelling ethene and generating a new ruthenium carbenoid **79**. This then reacts intramolecularly to form another metallo-cyclobutane with the second terminal alkene function **80**, which upon decomposition delivers the macrolactone **81** and the regenerated catalyst. Each step along this pathway is reversible and it is only the expulsion of the volatile ethene that increases the entropic gain and drives the reaction forward.[89]

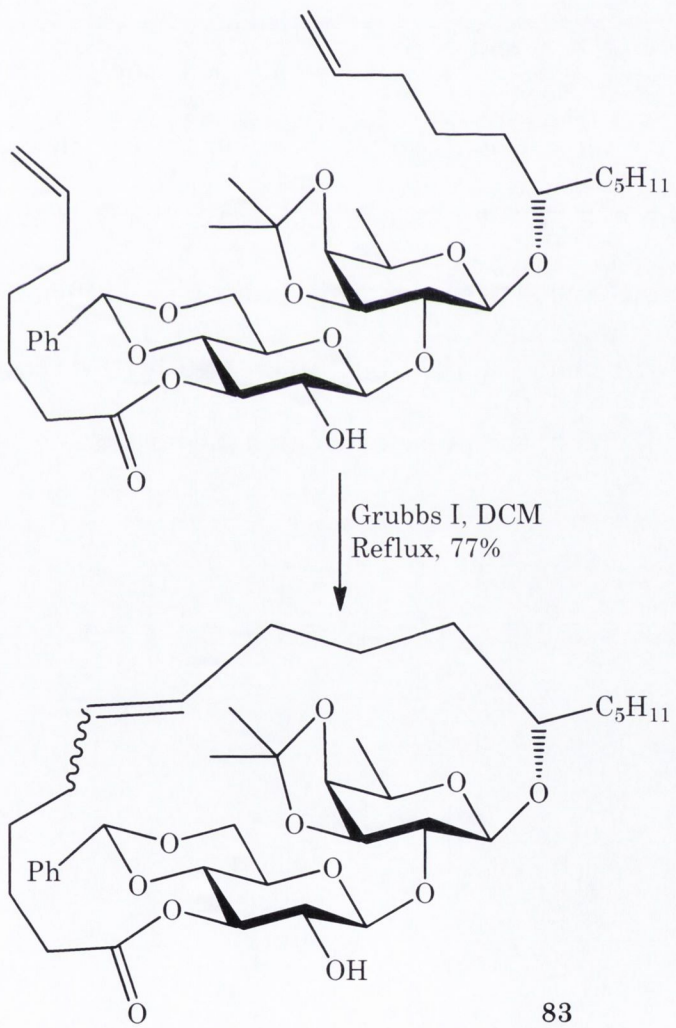


Scheme 1-24: Catalytic cycle of RCM in macrolactone synthesis

As the final ring-closing step in many reaction schemes RCM has found much success in the total syntheses of natural products such as stagonolide C **82**[90] and triclorin A **83**.[91]



Scheme 1-25: RCM in the total synthesis of stagonolide C **82**

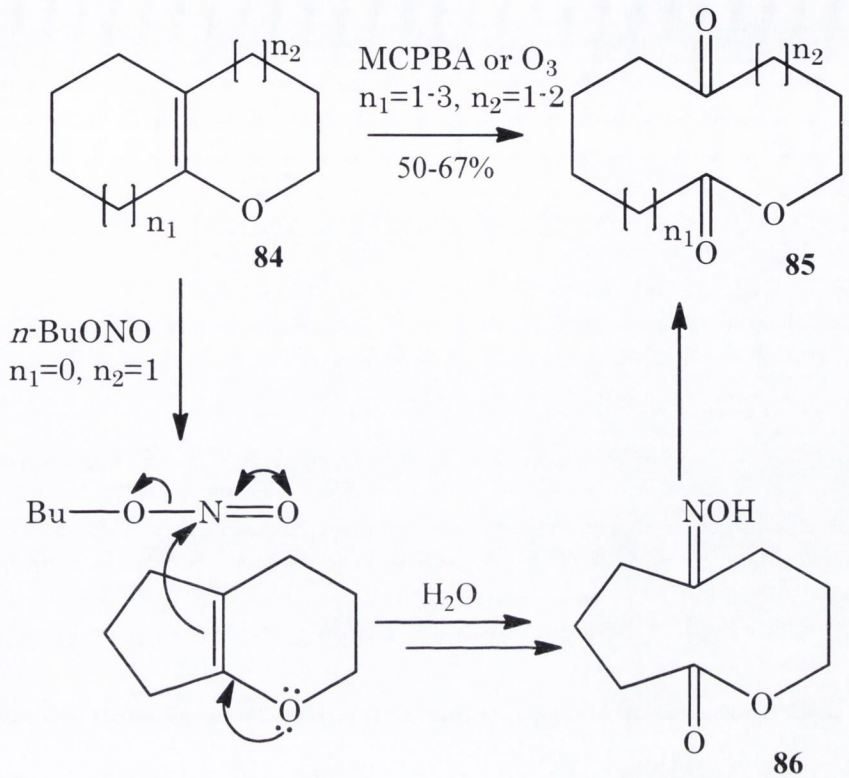


Scheme 1-26: RCM in the total synthesis of triclorin A **83**

7. Macrolactonisation by cleavage of bicyclic compounds

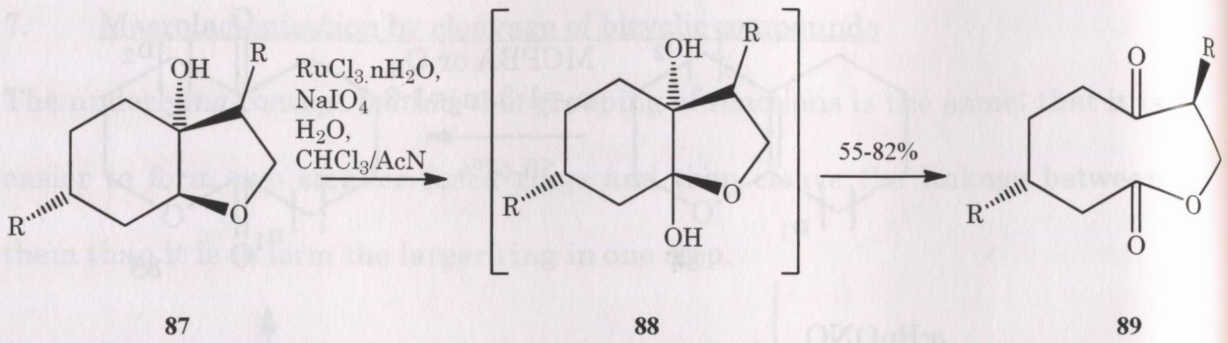
The underlying concept behind this grouping of reactions is the same; that it is easier to form two smaller fused rings and then cleave the linkage between them than it is to form the larger ring in one step.

The oxidative cleavage of fused enol ethers **84** in the pursuit of macrolactones **85** was first documented by Borowitz in 1964[92] and has now expanded to include rings from 10 to 16 members in size.[93,94] Several reaction conditions are documented, and choosing an appropriate methodology depends highly on the size of ring being formed, larger ring sizes are cleaved using either *m*-chloroperbenzoic aid or by the action of ozone followed by a work up with zinc and acetic acid whilst smaller rings are more efficiently formed through hydrolysis of an oxime intermediate **86** created by the actions of *n*-butyl nitrite on the fused alkene in the presence of an aqueous acid.[95]



Scheme 1-27: Lactonisation *via* oxidativce cleavage of fused bicyclics

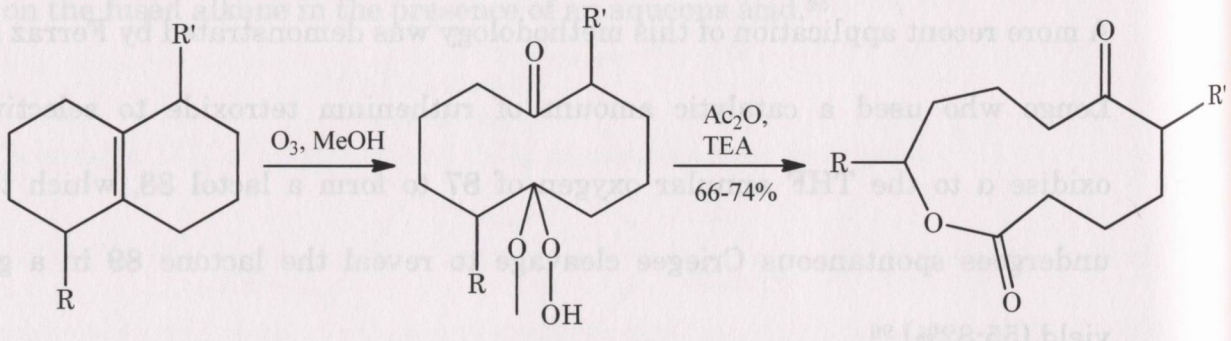
A more recent application of this methodology was demonstrated by Ferraz and Longo who used a catalytic amount of ruthenium tetroxide to selectively oxidise α to the THF annular oxygen of **87** to form a lactol **88**, which then undergoes spontaneous Criegee cleavage to reveal the lactone **89** in a good yield (55-82%).[96]



87 88 89

Scheme 1-28: Lactonisation *via* selective oxidative bond cleavage

A Criegee rearrangement also plays a key part in Schreiber *et al*'s ketolactone synthesis wherein an α-methoxyperoxides **91**, formed as the product of ozonlysis of an alkene group within a fused ring system **90**, is treated with acetic anhydride and a base to form an 11-membered lactone **92**, although in this case there is little regioselective control over which lactone is formed.[97]

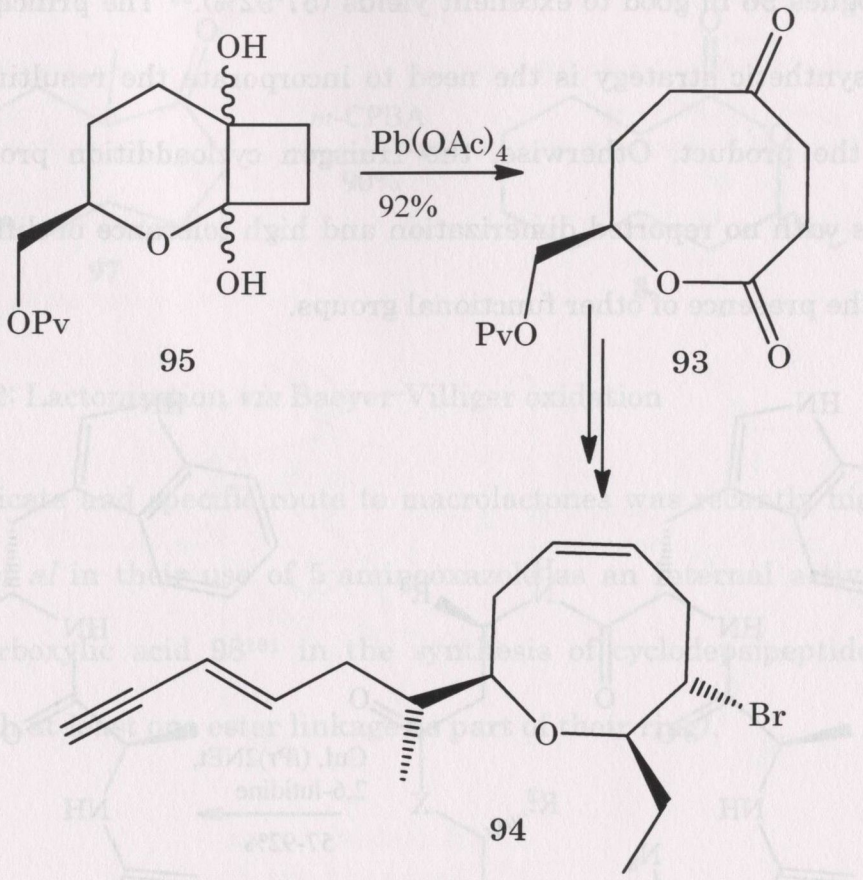


90 91 92

Scheme 1-29: Lactonisation *via* ozonolytic cleavage of an alkene

Finally a cleavage reaction leading to formation of a lactone **93** was used in the formation of a precursor of the algal metabolite laurencin **94**, which itself is not a lactone but does feature an extremely challenging 8-membered ether

function. The oxidative cleavage of an extremely strained fused cyclobutandiol **95** was carried out using lead tetracetate.[98]

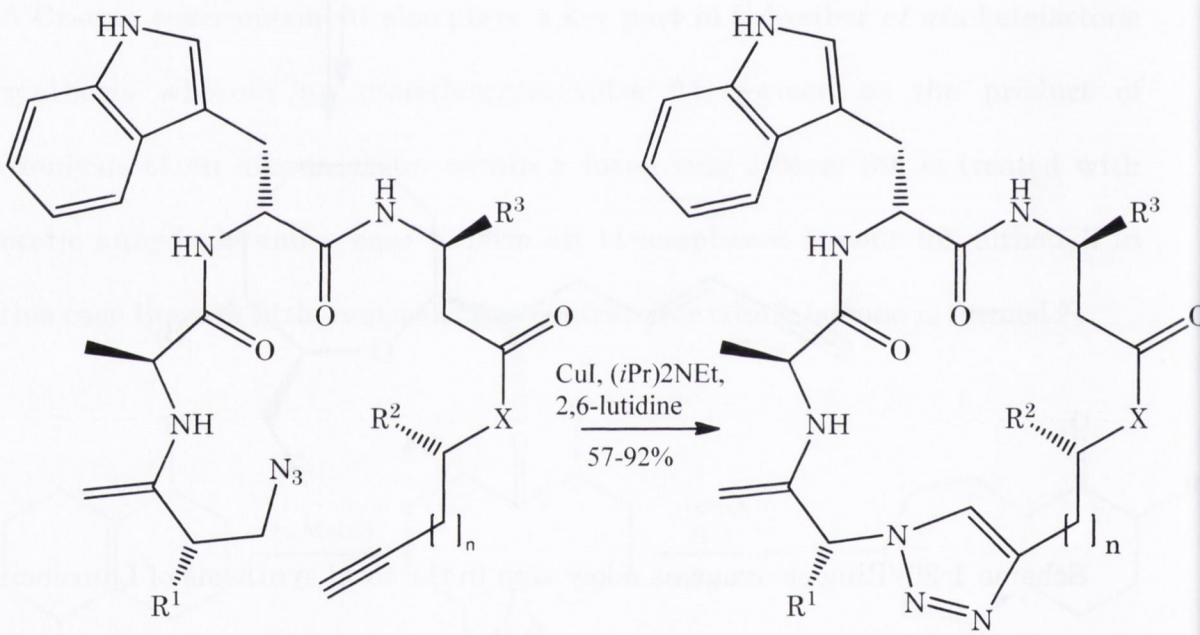


Scheme 1-30: Ring cleavage as a key step in the total synthesis of Laurencin

8. Lactonisation by miscellaneous methods

A number of reactions do not fit easily into any of the categories outlined above but they are useful and enlightening strategies which often reflect the state of organic chemistry at the time of their discovery.

For example the copper catalysed click reaction (azide-alkyne cycloaddition) has recently been used to form the final ring structure in a set of jasplakinolide analogues **96** in good to excellent yields (57-92%).[99] The principle drawback to this synthetic strategy is the need to incorporate the resulting 1,2,3-triazole into the product. Otherwise, the Huisgen cycloaddition produced excellent yields with no reported dimerization and high tolerance of differing ring sizes and the presence of other functional groups.

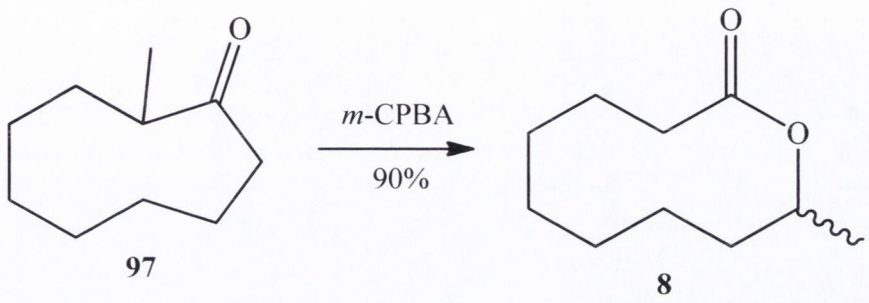


96

Scheme 1-31: Lactonisation *via* the Huisgen cycloaddition

An alternative strategy for medium and large lactone formation is the enlargement of a pre-existing cyclic ketone, the simplest of which is the Baeyer-Villiger oxidation of cyclic ketones as demonstrated by Baldwin in a

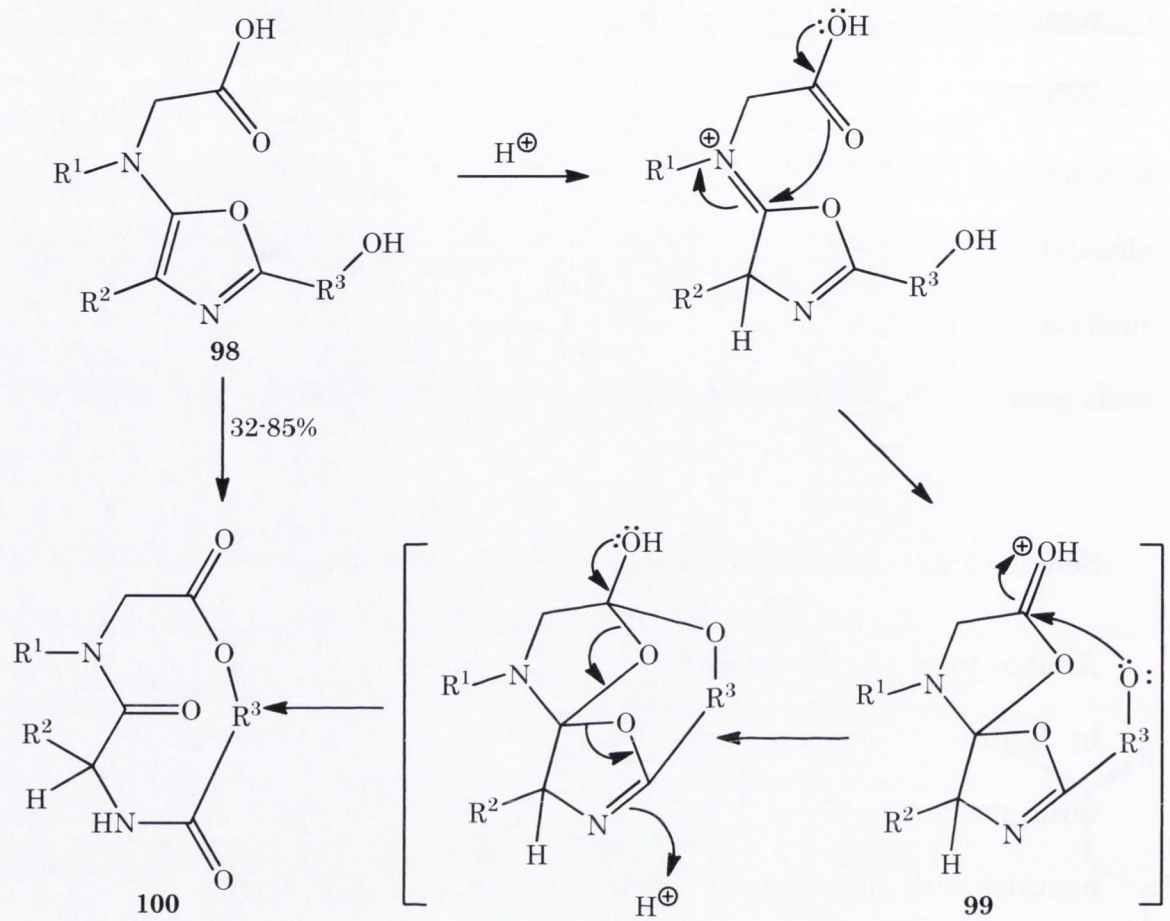
total synthesis of (±)-phoracantholide **8** from a cyclic ketone **97** in yields of over 90%.[100]



97 **8**

Scheme 1-32: Lactonisation *via* Baeyer-Villiger oxidation

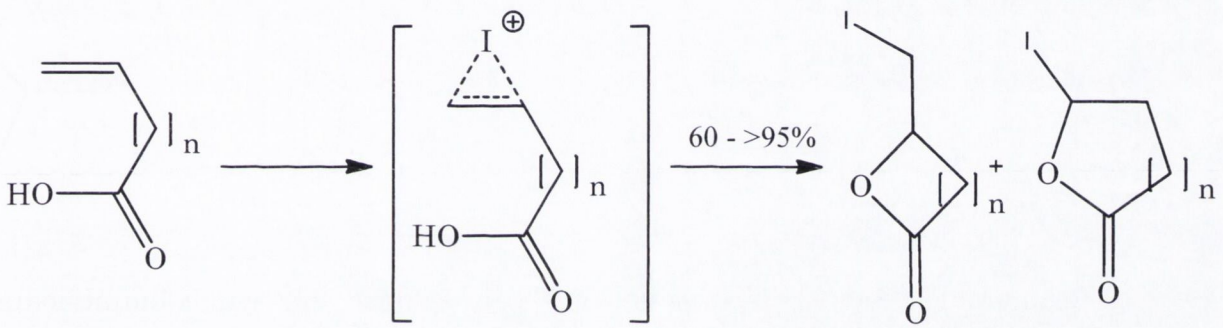
A more intricate and specific route to macrolactones was recently highlighted by Bighin *et al* in their use of 5-aminooxazole as an internal activator of a terminal carboxylic acid **98**[101] in the synthesis of cyclodepsipeptides (cyclic peptides with at least one ester linkage as part of their ring).



Scheme 1-33: Use of 5-aminooxazole in the synthesis of cyclodepsipeptides

The cyclisation is believed to take place *via* a spirolactone intermediate **99** which, upon breakdown, forms a lactone ring **100** and converts the aminooxazole into a peptide bond. The reaction proceeds smoothly and with typically excellent yields (>85%) under very mild conditions (RT, cat. TFA) but requires that there should be a peptide bond in the final product.

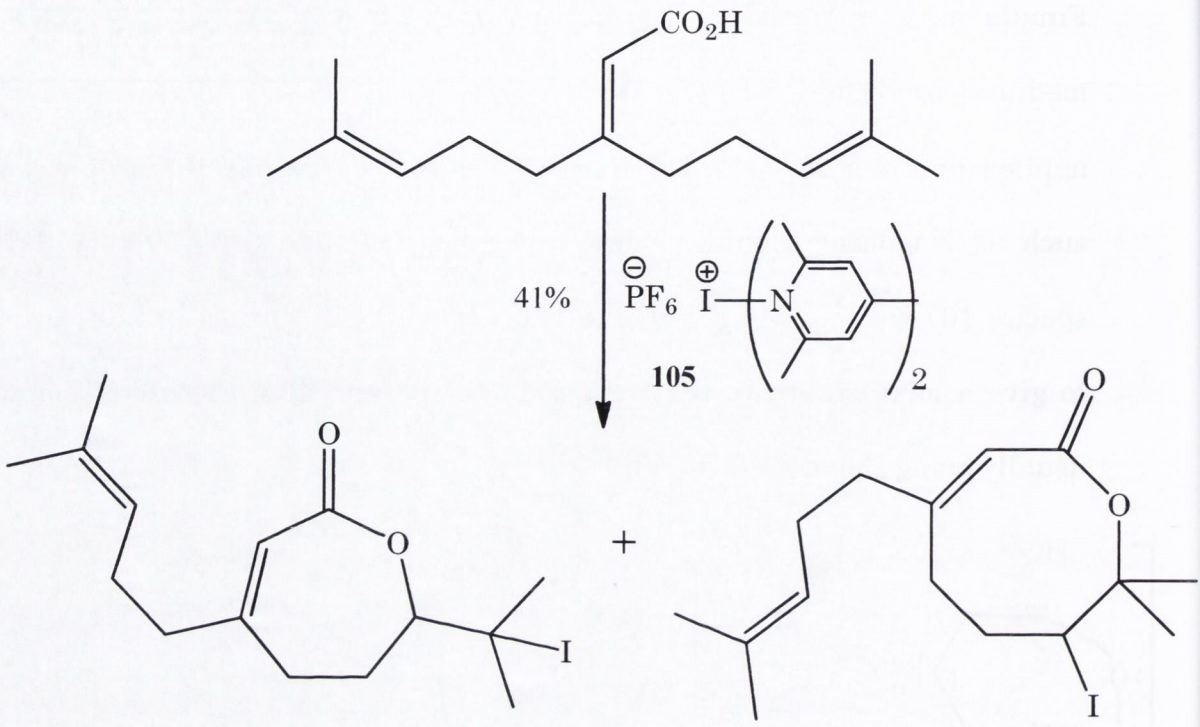
Finally as a methodology for formation of some of the more challenging medium sized rings, iodolactonisation is well known and has occasionally been applied to larger rings.[102] The reaction utilises sources of electrophilic iodine such as N-iodosuccinimide, iodine or cyanogen iodide to form an halonium species **101** with a terminal alkene **102**, this is then attacked intramolecularly to give a mixture of two possible products **103** and **104**, the exo-trig product usually being the more favoured.[103]



102 **101** **103** **104**

Scheme 1-34: Lactonisation *via* an halonium intermediate

Whilst typically only used for smaller rings, the use of bis(sym-collidine)iodine(I) hexafluorophosphate **105** has been noted as being capable of effecting larger cyclisations.[104]



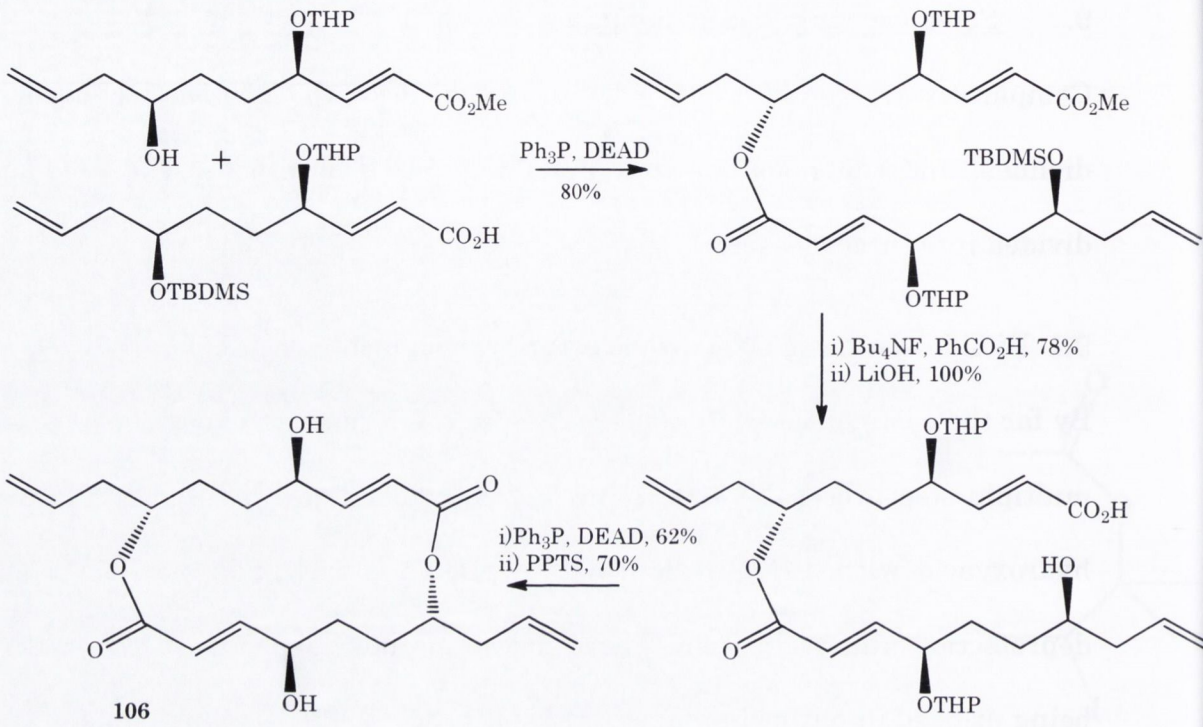
Scheme 1-35: Macrolactonisation using bis(sym-collidine)iodine(I) hexafluorophosphate

9. Selective synthesis of diolides

Comparatively, there are far fewer reported methodologies for producing diolides, and the reactions that are found in the literature can be broadly divided into three classes.

9.1: Diolide synthesis by stepwise esterification/lactonisation

By far the commonest route undertaken for the formation of diolides is to use a multiple step process of esterifying one equivalent of a hydroxyl-protected ω-hydroxyacid with an equivalent of the protected carboxylic acid followed by deprotection and cyclisation. There are numerous examples of this pathway being utilised in natural product total synthesis,[105-108] an example being Noda's synthesis of the cytotoxic bacterial metabolite (-)-vermiculine **106**.[109]



Scheme 1-36: Stepwise macrolactonisation in the total synthesis of vermiculine

This route is clearly flawed in terms of atom economy though and prevention of the formation of higher oligomers in the second esterification step is possible only with the use of high dilution techniques.

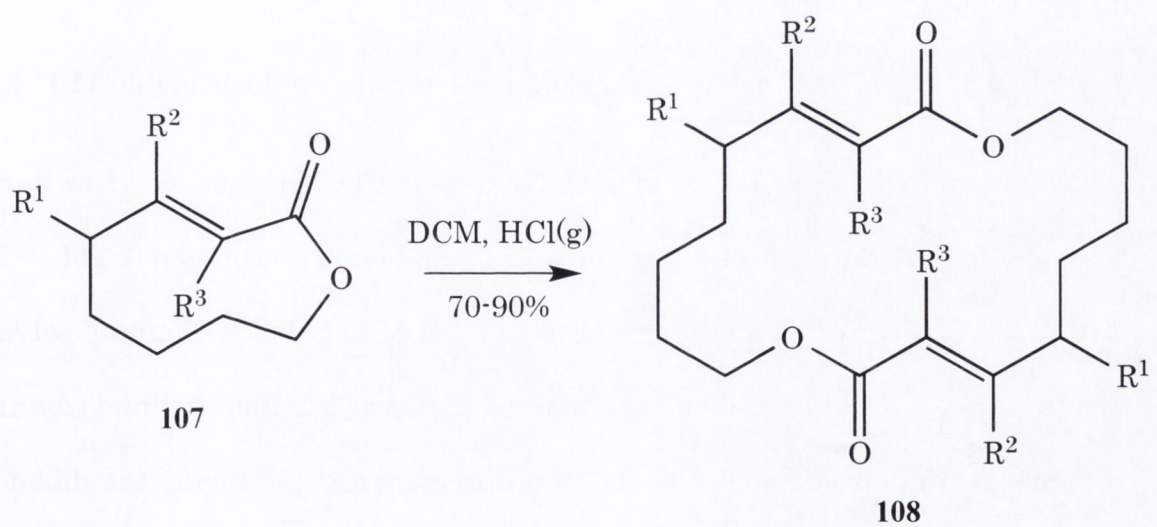
9.2: Preferentially controlled formation of diolides by reaction conditions

Many of the reactions presented as forming monomers in Sections 2.1 to 2.7 can also be applied to the formation of diolides by varying reagent and reactant concentration. This was how the Mitsunobu reaction was first introduced as a method for preferentially forming diolides over monomers,[110] and it has been used in the pursuit of natural products.[111] There are also numerous examples of diolide synthesis using the Yamaguchi[112] protocol and the Shiina reaction.[113]

9.3: Selective formation of diolides

A handful of selective diolide-forming reactions are present in the literature though none of them are generalised in their application.

The first documented case was the discovery by Fouque *et al.* in 1989 that nine- and ten-membered lactone monomers possessing a *trans*-alkene function conjugated to the ester carbonyl group **107** could be dimerised **108** by the action of gaseous HCl in DCM. Little work has been done on developing an understanding an understanding of the mechanism or scope of this reaction, but it would likely be relatively limited due to the strongly acidic reaction conditions.[114]

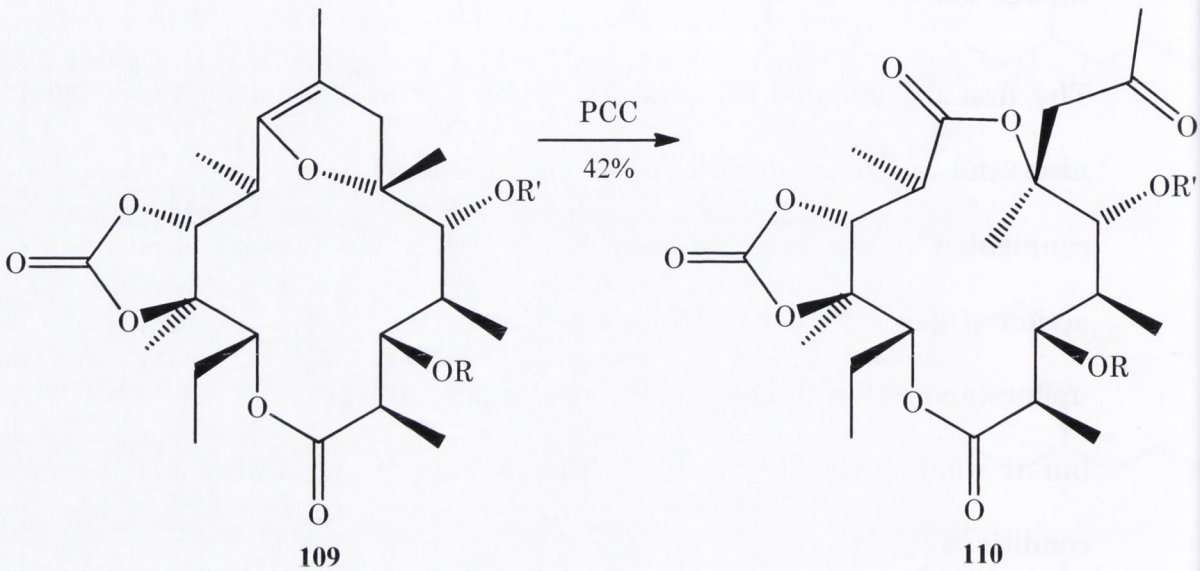


107 **108**

Scheme 1-37: Dimerisation of α,ß-unsaturated macrolactones

A variation on the oxidative enol ether cleavage reaction detailed in Section 7 above on cleavage of bicyclic structures was used to expand the ring size of a series of existing natural macrolactones **109** by Ohara *et al.*,[115] forming a set of

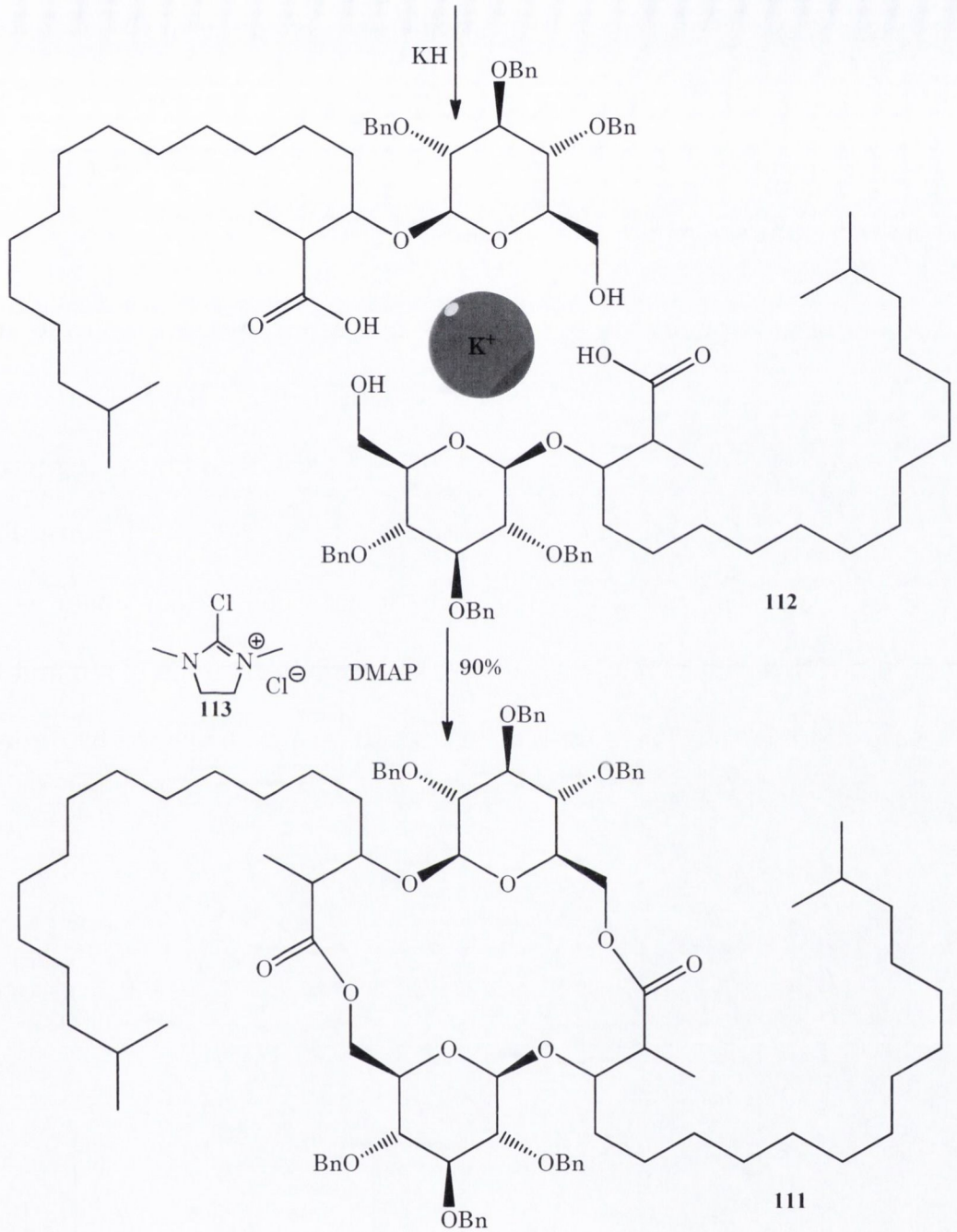
novel diolides **110** in reasonable yield (42%), though the reaction is limited by the need to isolate the pre-existing macrolactone ring system.



109 **110**

Scheme 1-38: Oxidative ring expansion to selectively produce diolide **110**

Finally, a creative solution was recently reported by Fürstner *et al.* as part of their total synthesis of the *Streptomyces* macrodiolide glucolipsin A **111**.[116] The two identical ω-hydroxycarboxylic acids **112** were templated around a solvated potassium ion prior to the addition of 2-chloro-1,3-dimethylimidazolinium chloride **113** and DMAP **37** as the coupling reagents, producing the diolide in yields of 90%.



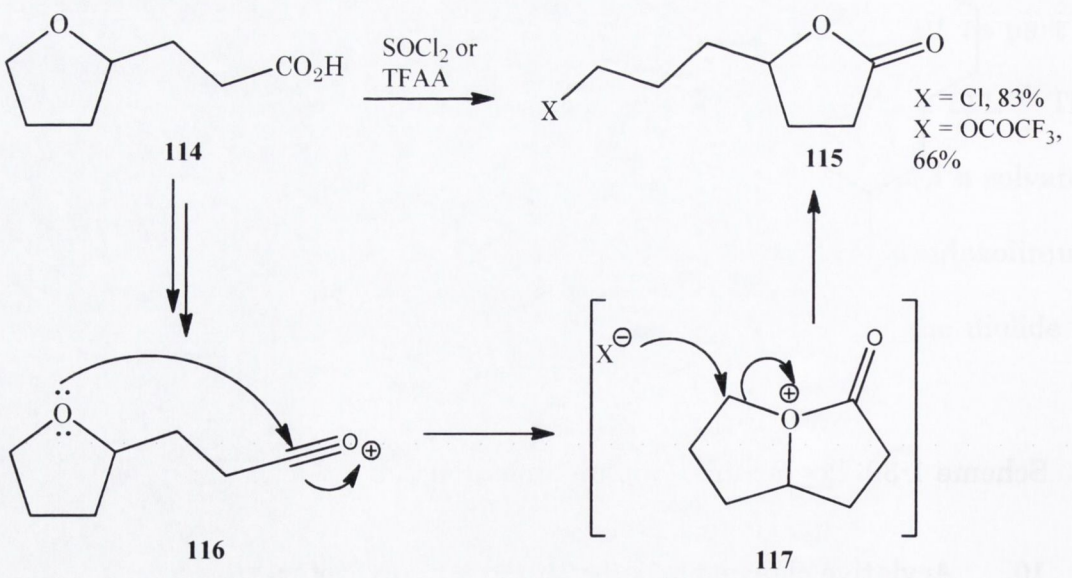
Scheme 1-39: Potassium template macrolactonisation

10. Acylative cleavage of substituted tetrahydrofurans

The cleavage of tetrahydrofurans to give acyclic products has long been documented,[117,118] and historically this has involved quite forcing conditions

such as refluxing with acids over long periods, resulting in the formation of δ-halobutanols,[119] although less restricted methods have also been developed typically including insertion of a metal into the C-O bond allowing for variable terminal groups to be produced.[120]

Acylative cleavage of THF to form a δ-chloroester has been reported since the 1930's[121] but it was not until 1992 that Grayson and Roycroft attempted an intramolecular version of the reaction using a tetrahydrofuran ring tethered to a carboxylic acid **114**. The 5-substituted dihydro-2(3*H*)-furanones **115** thus formed in excellent yields (66-83%) were found to have come about as a result of the tetrahydrofuryl oxygen trapping a tethered acylium ion **116** and forming a butterfly-like fused ring system **117** which was then opened by an available nucleophile.

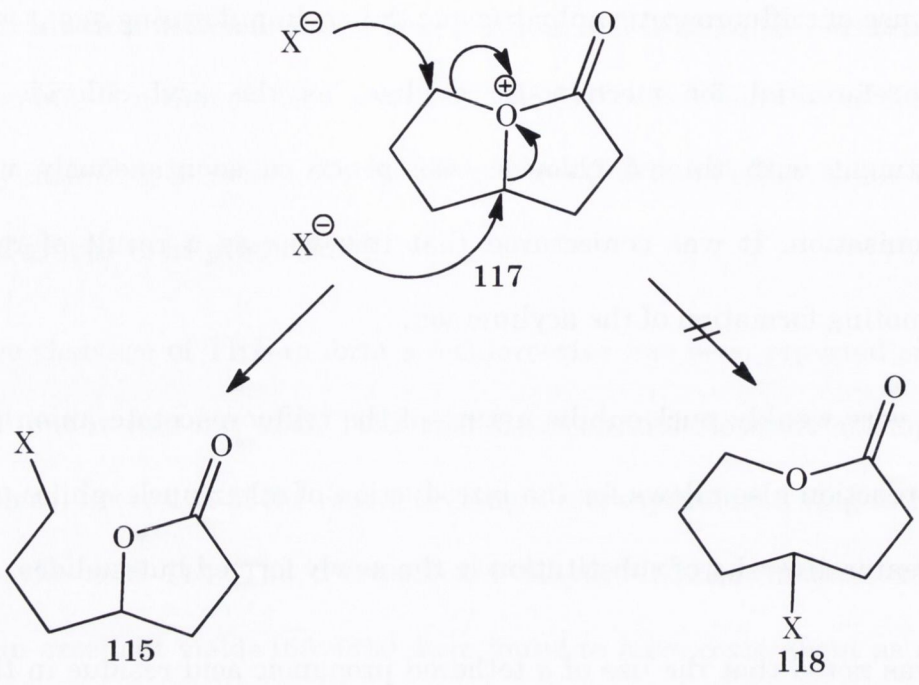


Scheme 1-40: Intramolecular acylative cleavage of 3-(tetrahydrofuran-2-yl)propanoic acid **114**

The use of trifluoroacetic anhydride as the acylium-forming agent was found to be preferential for mechanistic studies as the acyl chloride formed by treatment with thionyl chloride was prone to spontaneously undergo the lactonisation. It was conjectured that this was as a result of residual HCl promoting formation of the acylium ion.

The very weakly nucleophilic nature of the trifluoroacetate anion produced in the reaction also allows for the introduction of other nucleophiles, resulting in a greater diversity of substitution in the newly formed butanolides.

It was noted that the use of a tethered propanoic acid residue in this reaction always resulted in the opening of the bicyclic system α to the annular oxygen atom rather than at the carbon bridgehead to form an 8-membered lactone **118**.[122]



Scheme 1-41: Possible cleavages of butterfly-like fused intermediate **117**

By lengthening the carboxylic acid-bearing side-chain by two carbon atoms a more flexible acyloxonium intermediate **119** was generated, resulting in a mixture of products. Although nucleophilic attack by the trifluoroacetate ion now only occurred at the bridgehead carbon atom, to yield **120**, a secondary product was an unsaturated alkene, **121**, formed as a result of competing ß-elimination of a proton.

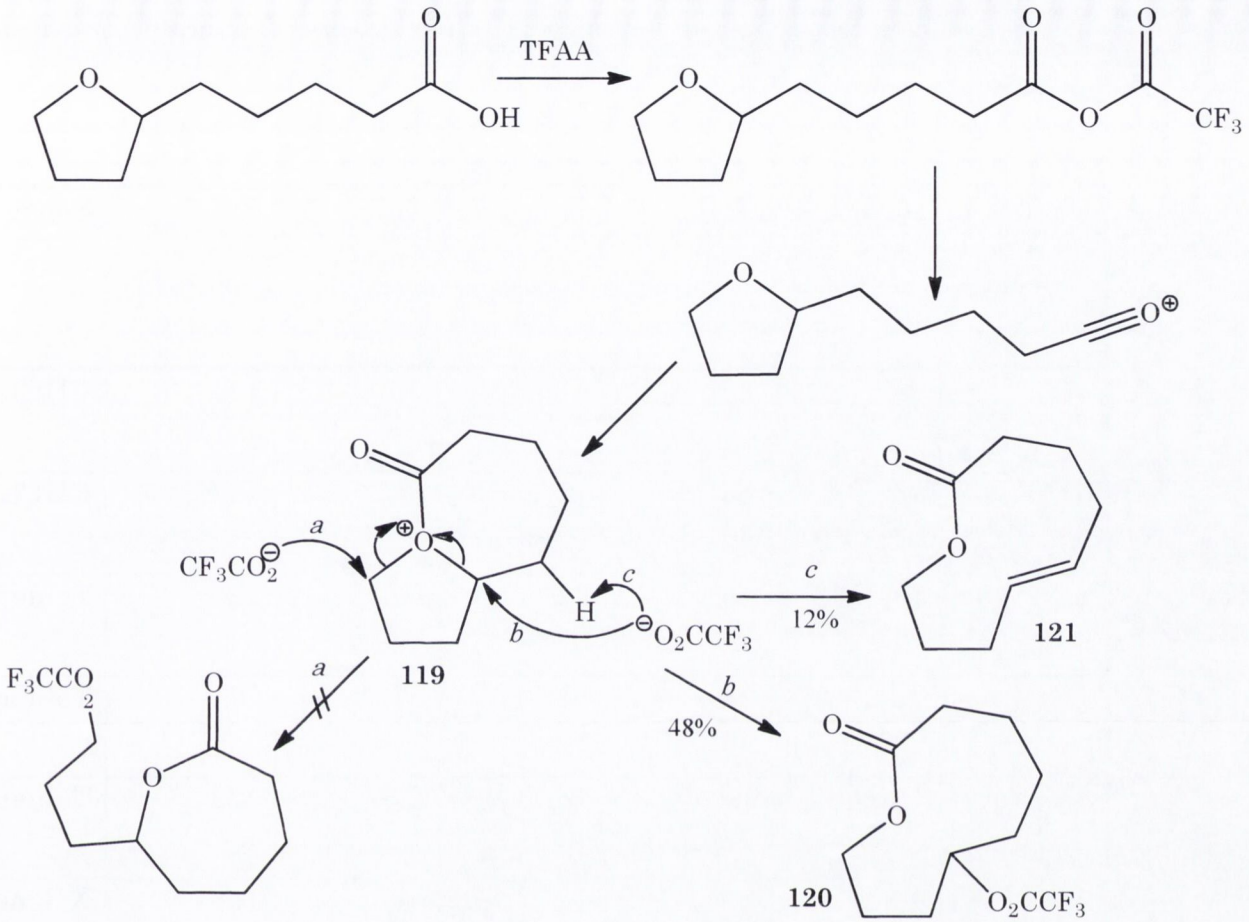
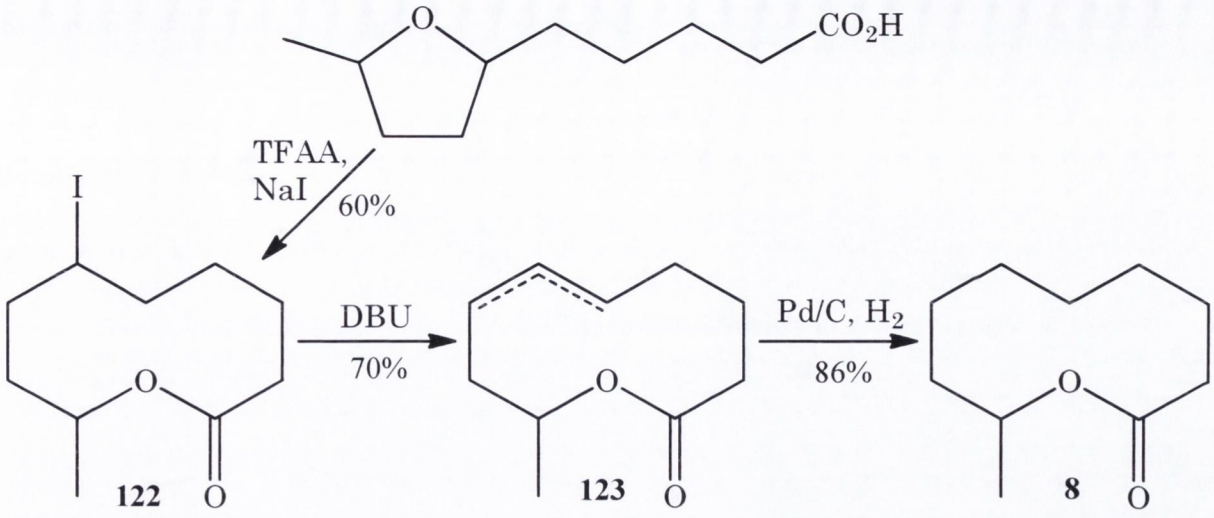

TFAA
OH
CF3
O
O
O

Table 2 - The effects of linker chain length on the rate of macrolactonisation of THF tethered acylium ions.

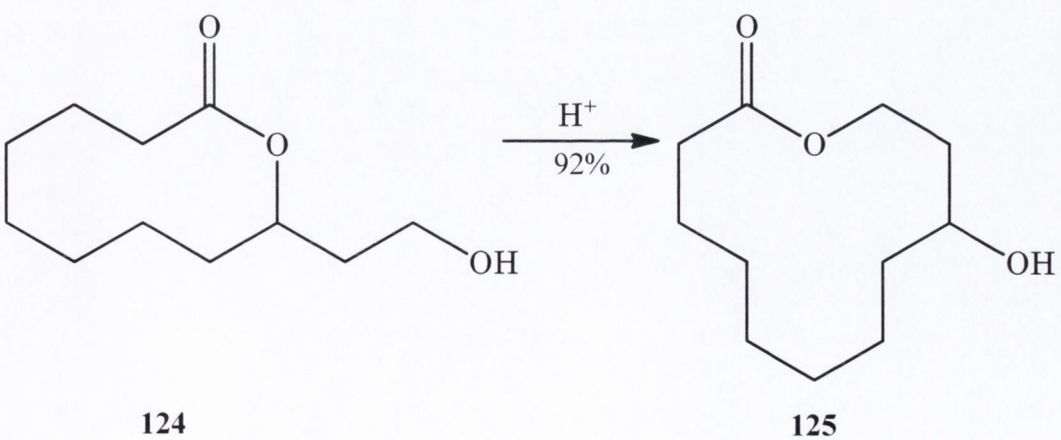
Chain length	Ring size formed	Route *b* % yield	Route *c* % yield	Total % yield	Time (hours)	Solvent
4	9	60	-	60	1	$CHCl_3$
5	10	48	12	60	1	$CHCl_3$
6	11	26	34	60	72	Toluene
7	12	38	13	51	72	Toluene
8	13	1.5	1	2.5	132	Toluene
9	14	3	1	4	168	Xylene

Whilst reasonable yields were achieved for the 9- to 12-membered rings, there was subsequently a dramatic drop-off in isolated product even with greatly extended reaction times and a higher boiling solvent. Nevertheless, the technique was applied successfully as part of a total synthesis of racemic phoracantholide **8**, using sodium iodide as an opportunistic nucleophile to produce an iodolactone **122** and sequential E2 elimination of HI and hydrogenation of the resulting alkene **123**. [123]



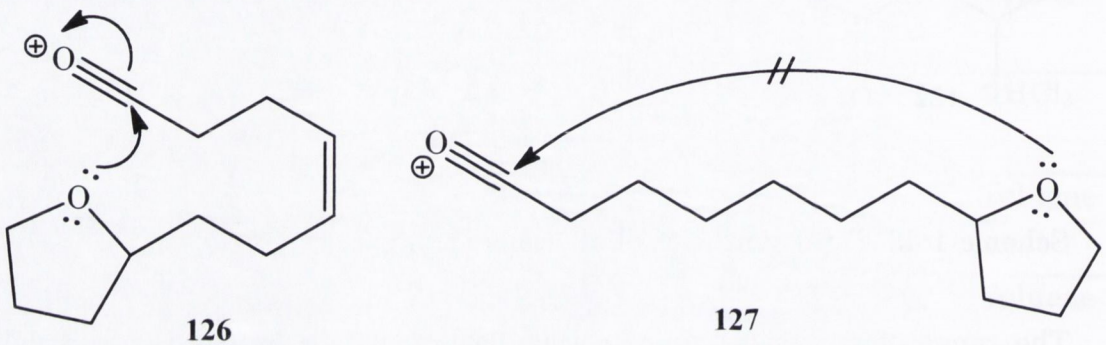
Scheme 1-43: Total synthesis of phoracantholide **8**[123]

The range of ring sizes open to the reaction was subsequently expanded by synthesising a series of hydroxyalkyl substituted lactones capable of undergoing translactonisation reactions, the most efficient of which was the conversion of the 10-membered hydroxyethyl lactone **124** to the 12-membered lactone **125** in 92% yield.[124]



Scheme 1-44: Translactonisation of a hydroxyethyl lactone

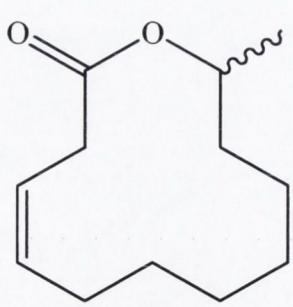
The yields and rates of this lactonisation protocol were also found to be improved by the introduction of *Z*-alkene groups into the chain linking the tetrahydrofuran ring and the carboxylic acid **126**, thereby forcing the acylium ion and the THF ring into closer proximity than they are in the analogous saturated straight chain reaction **127**.



126 **127**

Scheme 1-45: Improving rate of lactonisation by restricting conformational flexibility in linker chain

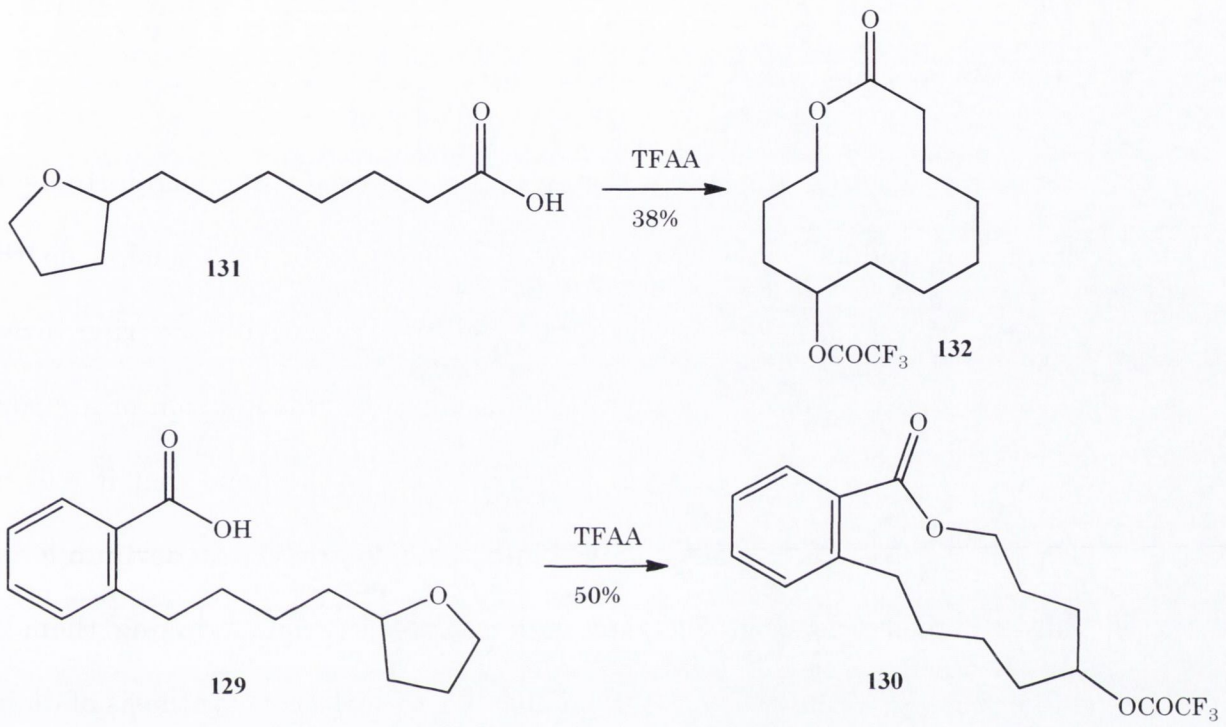
This observation led directly to a total synthesis of the important insect pheromone ferulolactone **128**.[125]



128

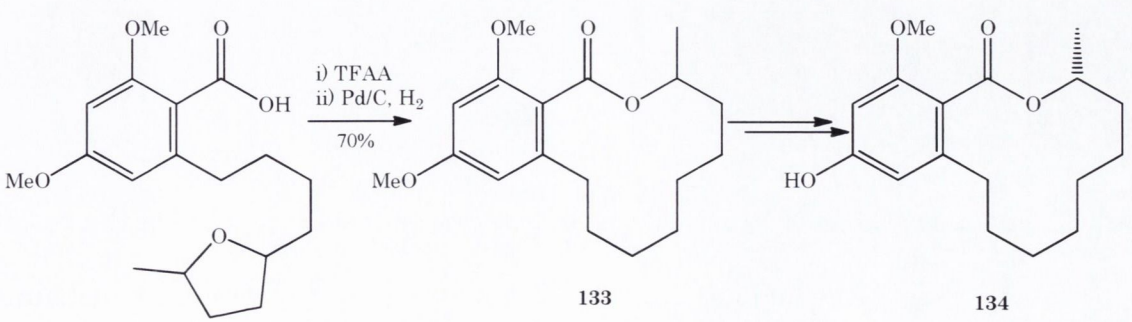
An extension of this was research into the introduction of a 1,2-disubstituted benzene ring into the alkyl chain tethering the tetrahydrofuran ring to the

carboxylic acid **129**, resulting in more facilely synthesised benzo-fused lactones **130** by comparison with the saturated analogues **131** and **132**.



Scheme 1-46: Improvement in yield with conformationally restricted 1,2-benzofused starting material

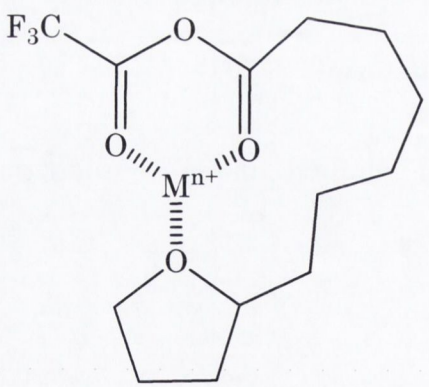
This technique was applied in the production of a precursor **133** to lasiodiplodin **134**.[126]



11. Strategy

The work presented in this thesis forms part of a continuation of the research described in Section 10 above on macrolactonisation *via* acylative cleavage of tetrahydrofurans.

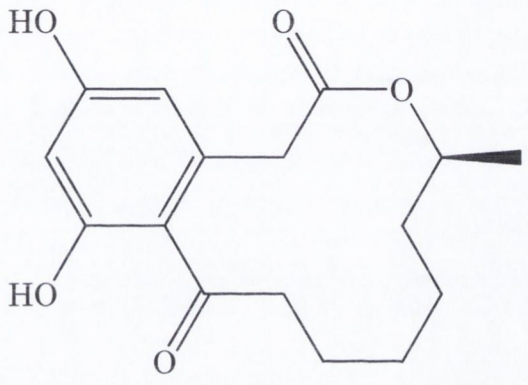
Chapter 2 concerns attempts to improve the yields of the macrolactonisation *via* intramolecular acylative cleavage reaction, specifically focusing on those lactones having larger rings and potentially extending beyond ring sizes of fourteen atoms. This will be investigated using the introduction of a strongly coordinating Lewis acid to the reaction mixture in the hope that it will both promote the degradation of the mixed anhydride to produce an acylium ion and that it may form a complex with both reactive termals bringing them into closer proximity **135**. A novel methodology for the selective synthesis of diolides is also presented.



135

The primary focus of Chapter 3 is an attempted total synthesis of the resorcylic fungal metabolite lactone curvularin **136** with the intention of utilising the

acylative cleavage of a tetrahydrofuran ring reaction as the lactonisation step. Novel methodologies for the synthesis of substituted furans and tetrahydrofurans are also presented.

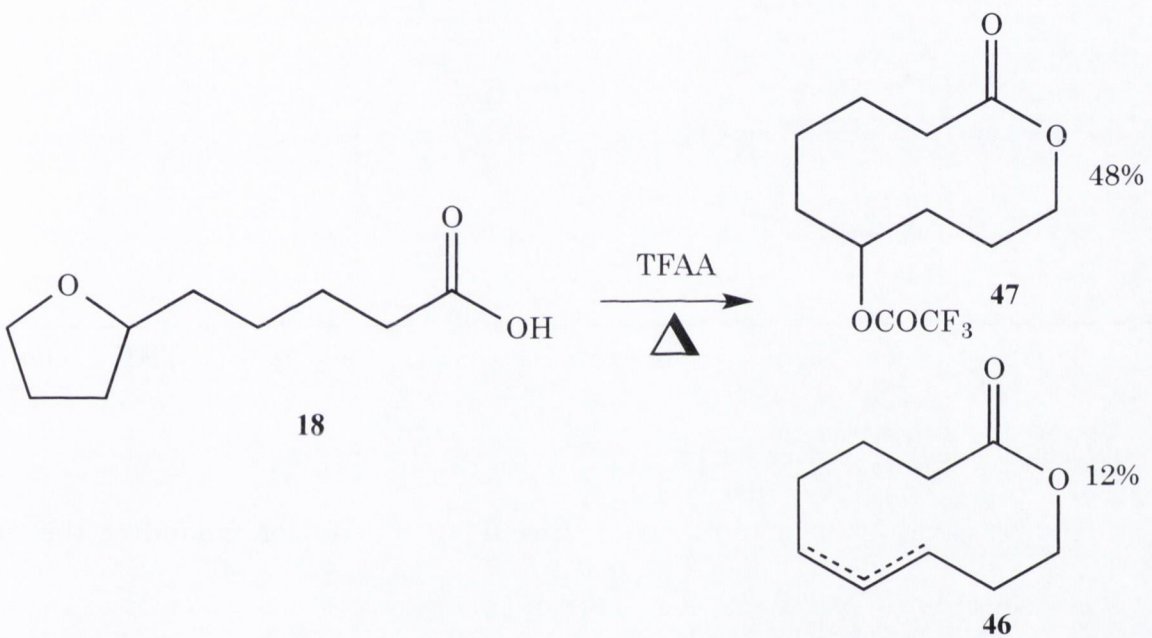


136

Chapter 2 - Macrolactonisation *via* acylative cleavage of tetrahydrofurans with Lewis acids

1. Strategy

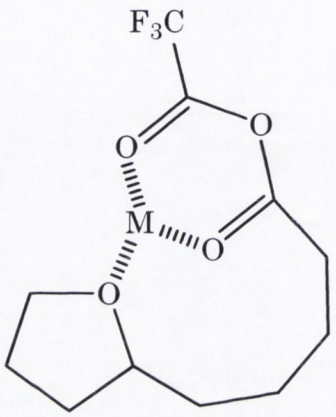
The aim of this body of work is to examine and expand the intramolecular acylative lactonisation reaction in development by the Grayson group to include efficient syntheses of macrocyclic rings larger than ten members in size.



Scheme 2-1: Current methodology in macrolactonisation by acylative THF cleavage

It was hoped that if an appropriate multivalent metallic Lewis acid were introduced to the reaction mixture formation of the mixed anhydride, that simultaneous co-ordination of the oxygen atoms of both the tetrahydrofuran ring and the anhydride function to the metal ion would result in formation of an acylium ion in close proximity to the ether oxygen of the THF ring, leading to a successful intramolecular reaction. Clearly, it would be desirable that

coordination of the tetrahydrofuryl ether oxygen atom to a templating metal ion should not be so strong as to prevent it from acting as a nucleophile towards the powerfully electrophilic acylium species.

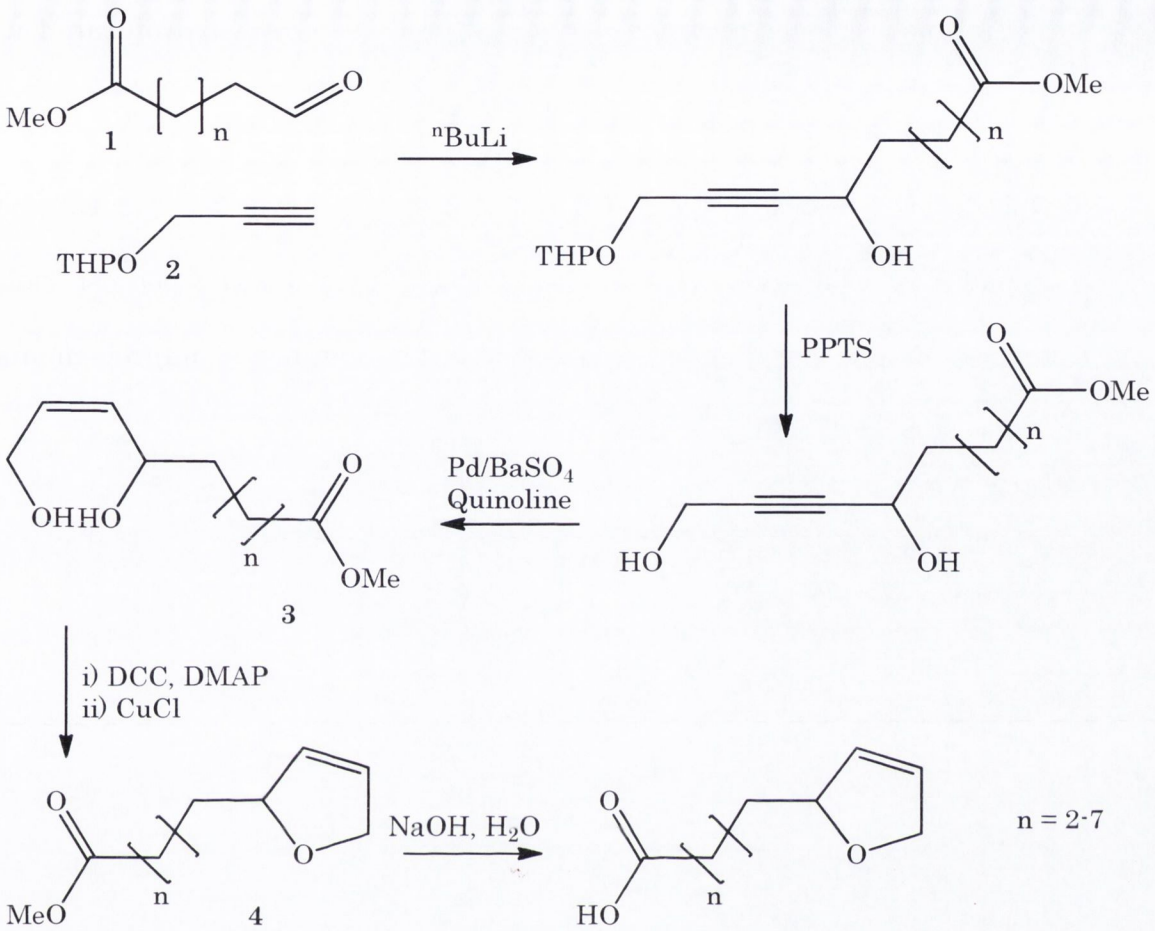


Scheme 2-2: Generic intermediate for acylative THF cleavage macrolactonisation

The choice of Lewis acid in question would also allow for expanding the range of nucleophiles by altering the choice of ligand.

2. Synthesis of 9-(tetrahydrofuran-2-yl)nonanoic acid

To investigate the potential for new reaction conditions as suggested above, a plentiful stock of a carboxylic acid linked by a suitably long tether to a THF moiety was required. To this end, it was decided that a previously established route[123] to dihydrofurans should be modified.



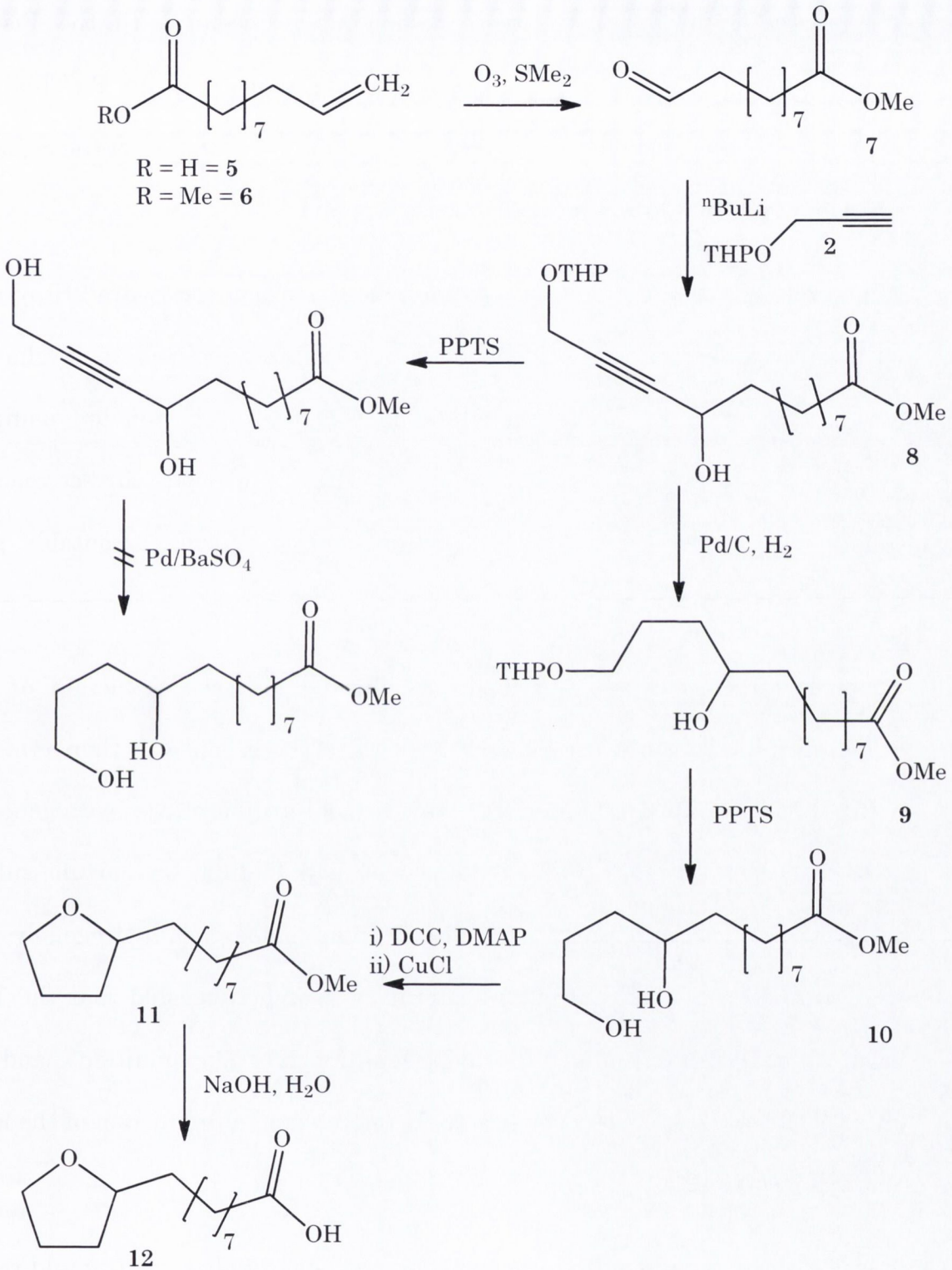
Scheme 2-3: Previous route to tethered dihydrofurans

The overall initial strategy was to selectively attack aldehydoesters **1** of differeing chain-lengths with the carbanion derived from tetrahydropyranyl-protected propargyl alcohol **2**.

This protecting group could then be removed by treatment with pyridinium *para*-toluenesulfonate (PPTS), and the alkyne function then reduced under standard hydrogenation conditions to give a 1,4-diol **3**. This would then be

subjected to a cyclodehydration reaction to produce a tetrahydrofuran **4** using dicyclohexylcarbodiimide and catalytic copper(I) chloride.[123]

It was decided to begin work with the longest carboxylic acid-bearing chain that had previously been tested,[123] and that had given the poorest yield of lactone (8 CH_2 chain), in order to search for significant improvements in lactonisation reaction procedures.



Scheme 2-4: Synthetic route to 9-(tetrahydrofuran-2-yl)nonanoic acid **13**

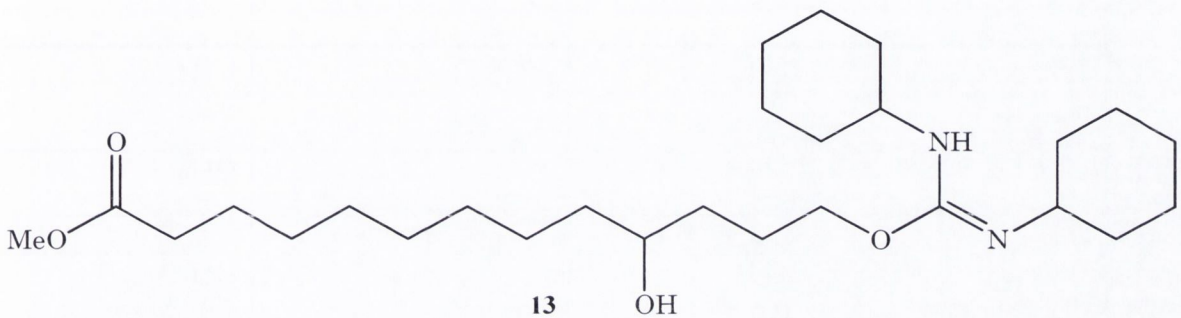
The synthetic procedure to access compound **12** began with the Fischer esterification of undecylenic acid **5** to methyl undecylenoate **6**. This was subjected to ozonolytic cleavage which, after some modification of the reported experimental procedure, produced **7** in good yield (87%).

Propargyl alcohol was protected as 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran **2** with tetrahydropyran in a solvent-free reaction using phosphorus oxychloride as the acid catalyst. Its terminal alkyne was then deprotonated using *n*-butyllithium to give the derived carbanion which, under the correct reaction conditions, attacks the aldehyde function of **7**, producing acceptably pure alkynyl alcohol **8**.

Following the previously-described procedure[123] for the production of 2,5-dihydrofurans from precursors such as **8** the THP group was then removed using PPTS in refluxing ethanol. However, modification of the hydrogenation step proved to be more problematic. Using a palladium on barium sulfate catalyst at atmospheric pressure resulted in a large degree of hydrogenolysis of the terminal alcohol. Eventually, a literature search suggested that the THP group would be stable under the hydrogenation reaction conditions, and the order of the two steps was reversed, resulting in smooth production of the long-chain diol ester **10**.

It was fully expected that the cyclodehydration step applied to **10** would result in slightly lower yields than with the corresponding (*Z*)-olefinic diol as a result of the inherently greater degree of flexibility in the chain, and this was indeed

the case (30% compared with 58% with the unsaturated analogue), with a correspondingly higher percentage of the unreacted intermediate methyl 13-((N,N'-dicyclohexylcarbamimidoyl)oxy)-10-hydroxytridecanoate **13** being produced (20%).



13

However, increasing the reaction time and temperature resulted in a fully acceptable yield of an eight-methylene linked tetrahydrofuranyl ester (60%). Basic hydrolysis of the ester **11** produced **12** in good yield (82%), with no detectable degradation of the THF ring.

Table 3: ^{1}H NMR spectroscopic details for of 9-(tetrahydrofuran-2-yl)nonanoic acid **12**

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.28	10H	m	CH_2
1.41	3H	m	CH_2
1.56	3H	m	CH_2
1.87	2H	m	CH_2
2.31	2H	t J7.3	CH_2CO
3.71	1H	q J7.6	$C\underline{H}_{2a}O$
3.79	1H	quin J6.8	$C\underline{H}O$
3.84	1H	q J7.2	$C\underline{H}_{2b}O$
8.28	1H	S	$CO_2\underline{H}$

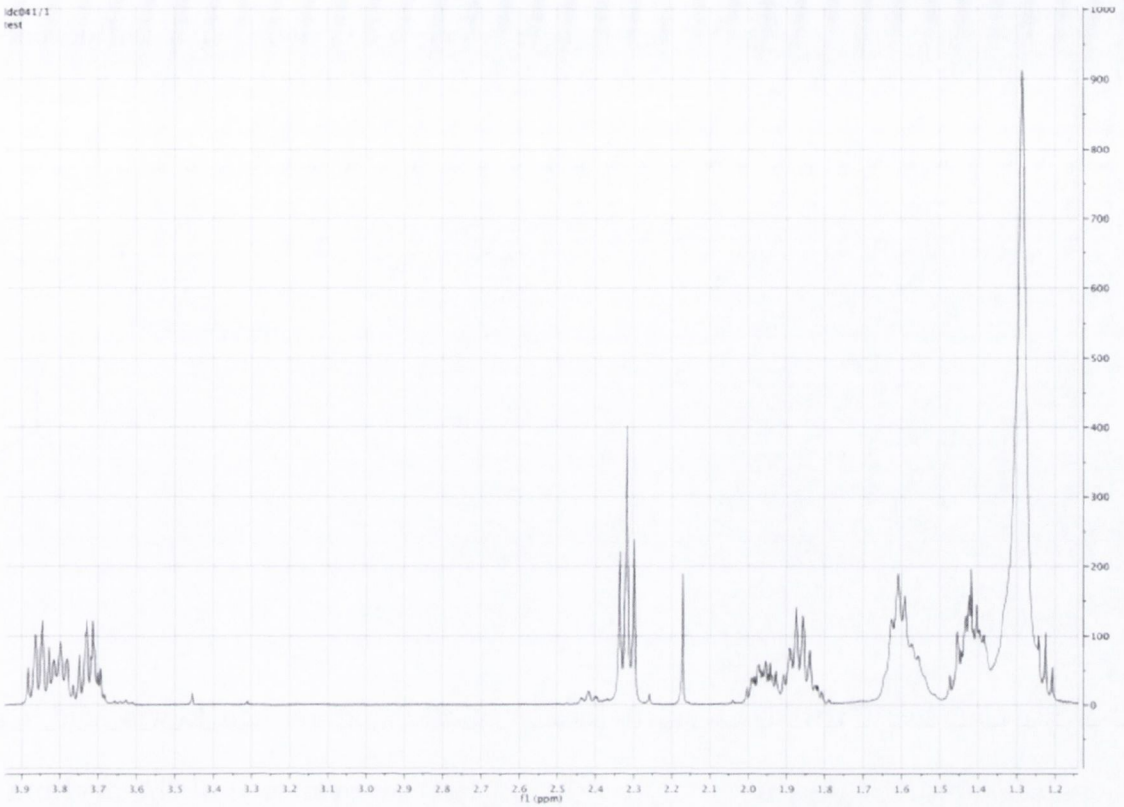


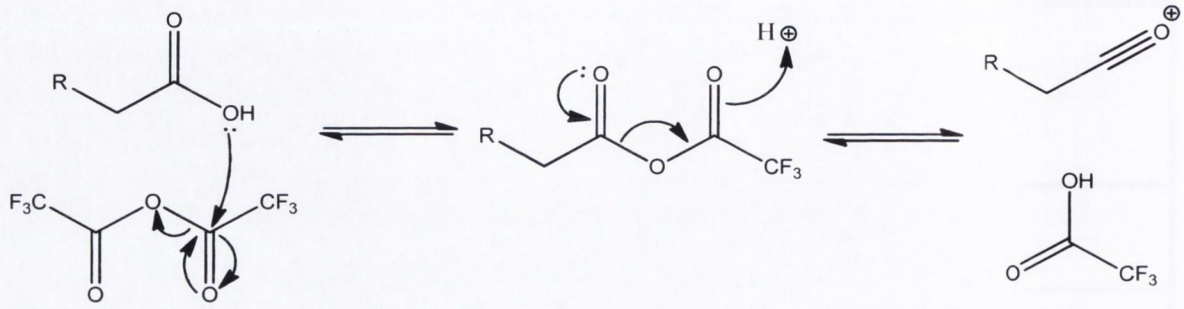
Figure 2-1: ^{1}H NMR spectrum of 9-(tetrahydrofuran-2-yl)nonanoic acid **12**

3. Initial attempts at lactone-forming cyclisation of 12

Our initial approach to a more efficient cyclisation reaction focused on improving two aspects; a more aggressive approach to forming the necessary acylium ion intermediate, and attempting to form a template structure which would place the two reactive ends of the chain in closer proximity than would otherwise be the case.

The method by which acylium ions have been produced by the group has been *via* the acid-catalysed breakdown of a mixed alkanoic-trifluoroacetic anhydride,

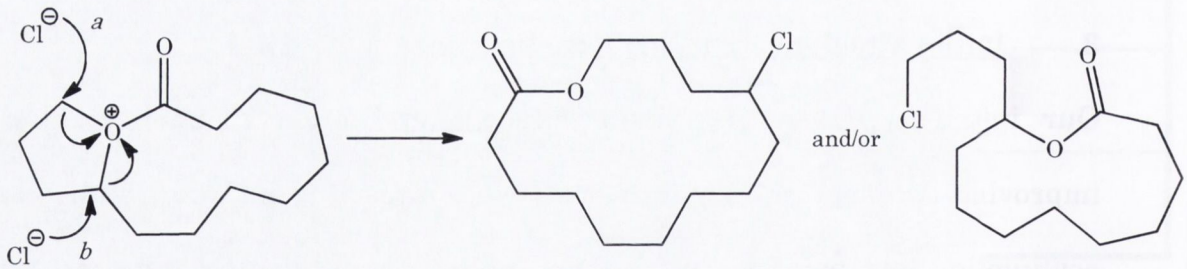
itself formed *in situ* by the reaction of a carboxylic acid with trifluoroacetic anhydride, TFAA.



Scheme 2-5: Formation of acylium ions with TFAA

It was hoped that with the introduction of a strong enough Lewis acid, e.g. a metal chloride, that this would both promote the formation of the acylium ion and co-ordinate both the acylium and the THF oxygen atom in close proximity.

The intermediate thus formed could potentially break down in one of two ways.

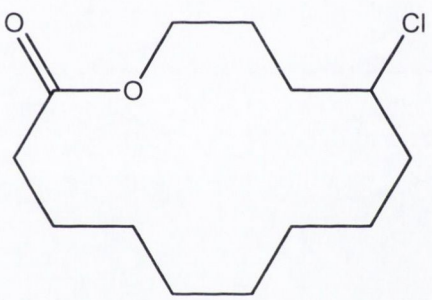


Scheme 2-6: Possible breakdown routes of the bicyclic intermediate

The first Lewis acid chosen to be tested was titanium tetrachloride as a result of its known propensity to promote the formation of acylium ions from mixed anhydrides and to form complexes with tetrahydrofuran. The shape of the

complex formed between titanium tetrachloride and organic compounds is a complex issue and the *cis/trans* geometry is heavily dependent on the size and shape of the ligand in question.[127]

The initial results obtained from these reactions appeared to be extremely encouraging. A large percentage yield (81.5%) of a solid, waxy, neutral product was extracted from the reaction mixture and the NMR spectra of the crude product showed roughly what would be expected from a δ-chlorolactone **14** as the sole product.



14

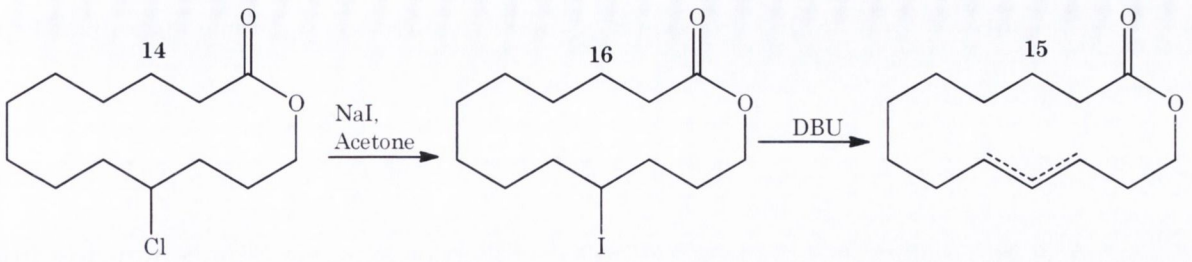
A triplet at δ_H 4.10 ppm was tentatively assigned to the CH_2 group alpha to the ring oxygen, its multiplicity and integration confirmed to us that pathway *a* was the preferred mechanism for breakdown. A 1H multiplet at δ_H 3.90 ppm was similarly assigned to the C-4 proton, and a 2H triplet at δ_H 2.31 ppm could be assigned to the methylene group adjacent to the carbonyl group. At first the lack of any diastereotopic splitting was off-putting but it was reasoned that this was due to the much greater flexibility of the fourteen-membered ring of **14** compared to the smaller rings that had been previously examined.

The IR spectra too confirmed this analysis of the isolated neutral fraction, showing a strong, characteristic absorption at 1732 cm^{-1} for a lactonic carbonyl and a peak at 724 cm^{-1} corresponding to a carbon-chlorine bond.

A series of minor modifications were then made to this new experimental methodology to try and improve the yield even further; a greater excess of reagents, lowering the temperature at which TFAA was added, in order to discourage disproportionation, and switching the solvent to dichloromethane to eliminate the potential for formation of ethyl trifluoroacetate due to trace EtOH present in commercially available $CHCl_3$.

However mass spectrometric analysis of each of these reaction–products continually showed no traces of the monomer or any subsequent degradation products of a monochlorolactone, even with concentrations raised to the practical limits of the instruments.

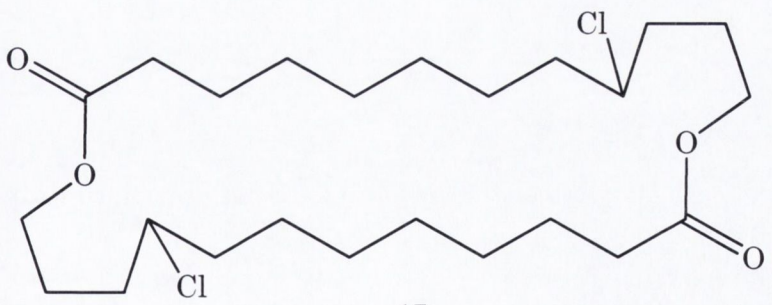
It was thought at first that the newly formed chlorolactones were simply too fragile to withstand the conditions imposed by the available MS techniques. As such, an attempt was made to convert **14** into unsaturated lactone **15**, both *via* simple E_2 elimination reactions and through conversion by the Finkelstein reaction to an iodolactone **16** and subsequent DBU-mediated elimination.



Scheme 2-7: Proposed synthesis of alkenyl lactone **15**

Neither of these approaches gave any detectable results other than return of the starting materials.

It was then considered that it may not have been the monomeric lactones that had been produced, and instead that there had been some polymerisation, or production of higher oligomers. A series of samples were then analysed specifically to look for the dimeric dichlorolactone **17**: a HRMS peak at 515.2695 (calculated for $C_{26}H_{46}O_4NaCl_2$ 515.2671) was found to be the major component of the neutral extract.



17

The NMR spectroscopic data obtained for **17** are summarised in the table below. Key resonances in the ^1H NMR include a triplet centered at δ_H 2.30 ppm with a coupling constant of 7.5 Hz that is assigned to the methylene unit

adjacent to the lactonic carbonyl. A quintet with a coupling constant of 6.9 Hz centered at 3.90 ppm correlates to a proton α to a chlorine atom, and a triplet at 4.09 ppm with a coupling constant of 6.0 Hz which is assignable to the methylene unit adjacent to the annular lactone oxygen. The remaining proton signals are all presented as indistinguishable multiplets.



Figure 2-2: ^{1}H NMR spectrum of 11,25-dichloro-1,15-dioxacyclooctacosane-2,16-dione **17**

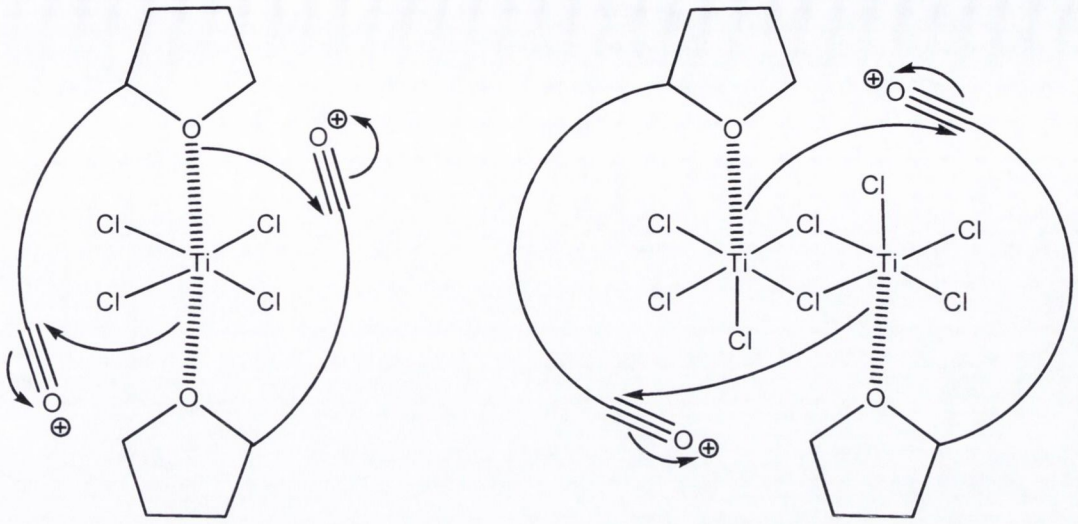
Table 4: ^{1}H NMR spectroscopic details for of 11,25-dichloro-1,15-dioxacyclooctacosane-2,16-dione **17**

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.30	12H	m	CH_2
1.51	1H	m	CH_2
1.63	4H	m	CH_2
1.72	4H	m	CH_2
1.91	1H	m	CH_2
2.30	2H	t J7.5	CH_2CO
3.90	1H	quintet J6.9	CHCl
4.09	2H	t J6.0	CH_2O

It was hoped at first that this was simply a result of reactant concentration, i.e. that the acylium ion was able to react with a second, unconnected THF moiety before it had an opportunity to come into contact with the titanium-bound ring. It was expected that this could be controlled with greater dilution; however, reactions run with 2 times and then 16 times the ratio of solvent still resulted in no detectable levels of the monomer and significant levels of the dimer. Various MS variations were employed (ESI+, ESI-, EI, CI) in the hope that, if the monomer were present, conditions would be such that it would survive to reach the detector in one of them but the dimer continued to be the sole product detected.

No traces of trimers, tetramers or other higher oligomers were noted in any of the samples that had thus far been sent for analysis. This suggested that dimerization was occurring as a result of a mechanistic limitation of the reaction.

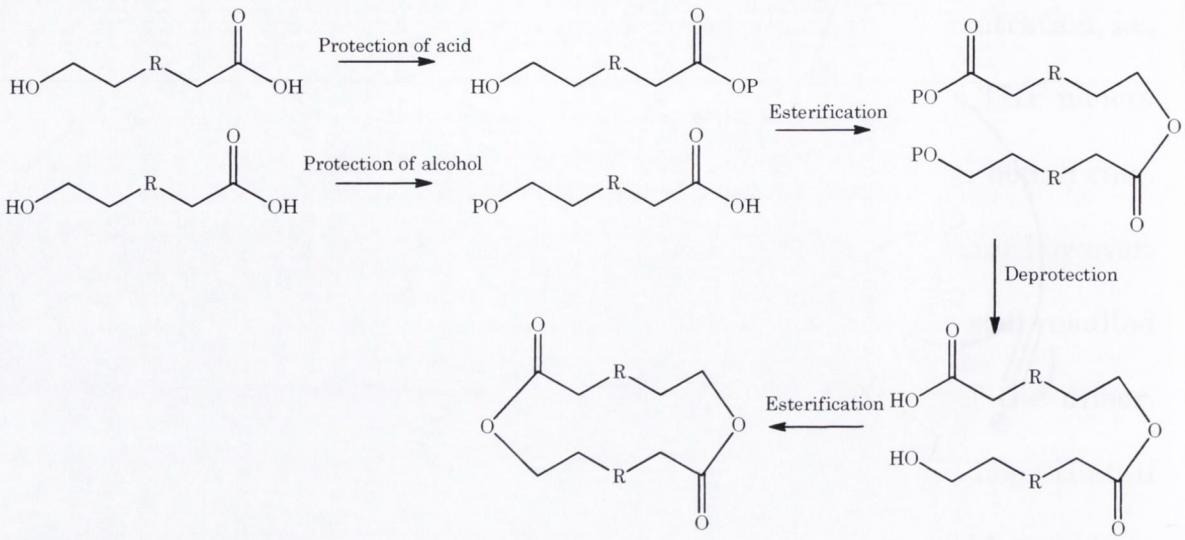
Such a scenario may be explicable as a consequence of "double" coordination to $TiCl_4$ and the length of the methylene chain resulting in the newly formed acylium ion being closer to the "top" THF ring than to the bottom.



Scheme 2-8: Proposed structural mechanism of dimerisation

Whilst at first this dimerization was interpreted as an inherently negative aspect of the reaction mechanism a literature search made it clear that there was no other currently available single reaction capable of producing these dimers, of which several have been mentioned in Chapter 1.

Current methodology to preferentially produce dimers hinges upon multiple step processes of protection, addition, deprotection, and addition.



Scheme 2-9: Generic scheme for stepwise synthesis of diolides

This route is also an imperfect process, as the second addition step is still dependent upon reaction conditions such as concentration to avoid production of higher oligomers or polymers.

4. Investigation of smaller rings

In spite of these results it was still hoped that monolactones with smaller ring sizes that 14 memberes could be produced *via* the same method as a result of acylium ions on the shorter chains of the precursor not being able to reach the "bottom" THF ring of a second molecule of the starting acid.

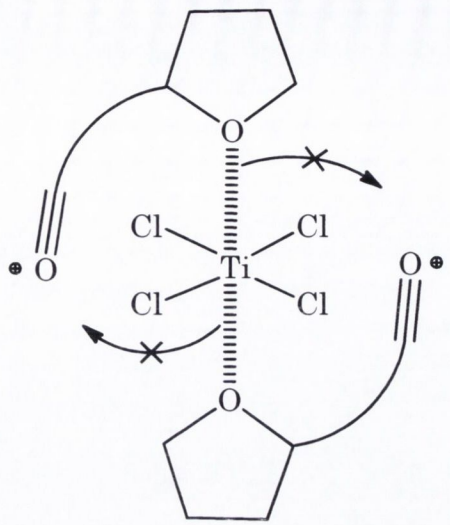
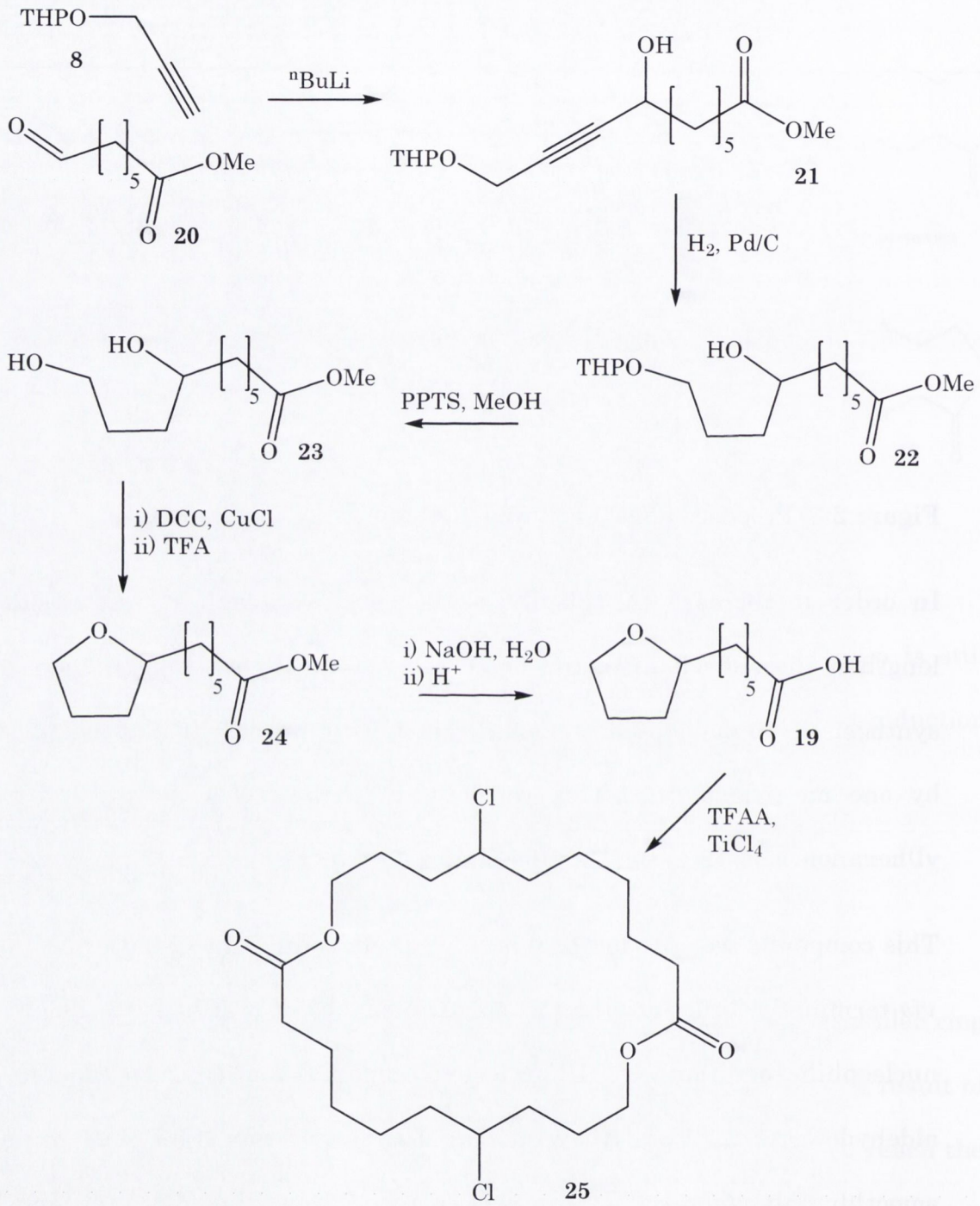


Figure 2-3: Proposed effect of chain length on formation of diolides

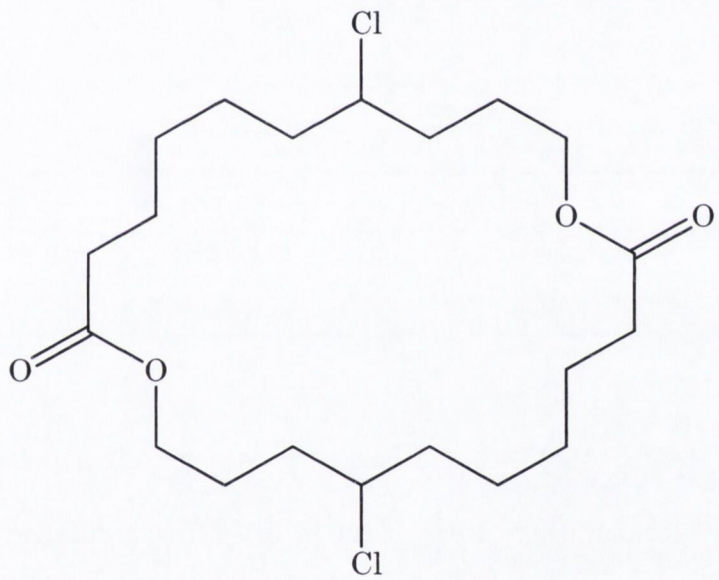
In order to increase the likelihood of a positive result it was decided to lengthen the side-chain of the precursor for the largest known successfully synthesised 10-membered lactone, 5-(tetrahydrofuran-2-yl)pentanoic acid **18**, by one methylene unit. This resulted in the use of 6-(tetrahydrofuran-2-yl)hexanoic acid **19** as the starting material.

This compound was produced in an analogous manner to **12**, described above, *via* terminally differentiating ozonolytic cleavage of cycloheptene followed by nucleophilic addition of THP-protected propargyl alcohol **2** to the resulting aldehyde ester **20**. Catalytic reduction of the alkyne function of **21** proceeded smoothly only when the solvent was switched from ethanol to methanol, this was then followed by sequential deprotection, cyclisation, and saponification to yield the desired acid **19**.



Scheme 2-10: Synthesis of 6-(tetrahydrofuran-2-yl)hexanoic acid **19** and conversion to 8,19-dichloro-1,12-dioxacyclodocosane-2,13-dione **25**

Again, this acid **19** was tested under the same conditions (TFAA @ -10 °C, $TiCl_4$ @ -40 °C), and once again a waxy neutral product was isolated (66%) which showed no significant diastereotopic splitting of proton resonances in the ^1H NMR spectra of the crude product. Mass spectrometric analysis confirmed that the diolide **25** had been produced as the only product (m/z; (HRMS(ES)) calculated for $C_{10}H_{17}ClO_2$ expected 204.0917, not found. Calculated for $C_{20}H_{34}Cl_2O_4$ expected 408.1834, found 431.1742 (M+Na)).



25

Table 5: ^{1}H NMR spectroscopic details for 8,19-dichloro-1,12-dioxacyclodocosane-2,13-dione **25**

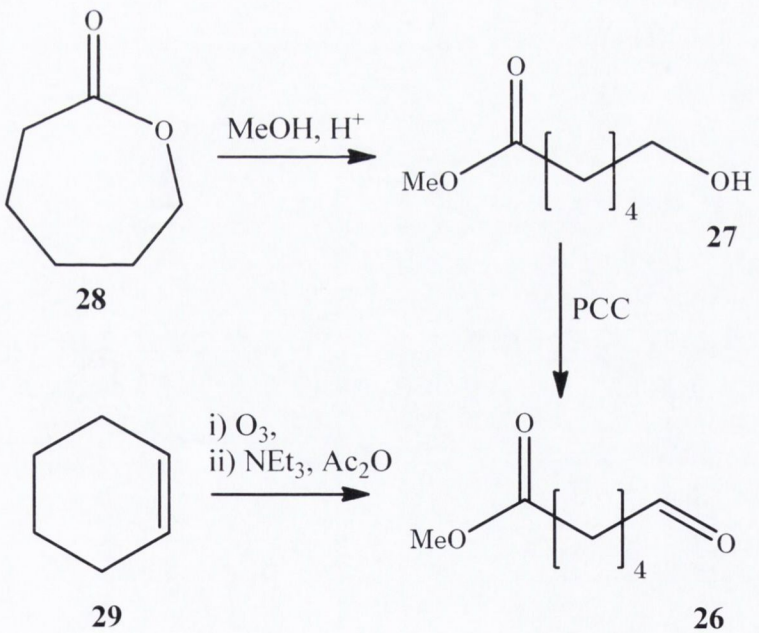
^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.28-1.50	8H	m	CH_2
1.54-2.82	16H	m	CH_2
2.36	4H	t J7.9	CH_2CO_2
3.92	2H	m	CHCl
4.12	4H	t J6.96	CH_2O

The lack of diastereotopicity is significant as it is indicative of a larger ring size resulting in greater flexibility. This is as a result of the greater flexibility leading to fewer transannular interactions and a lessening of Pitzer strains that would force protons attached to the same carbon into differing chemical environments leading to different chemical shifts in a ^{1}H NMR spectrum.

During the course of this research the previous work on large ring cyclisations was combed for mass spectral data and it was found that none had been reported[123] for rings of any size. Consequently, it was deemed appropriate to

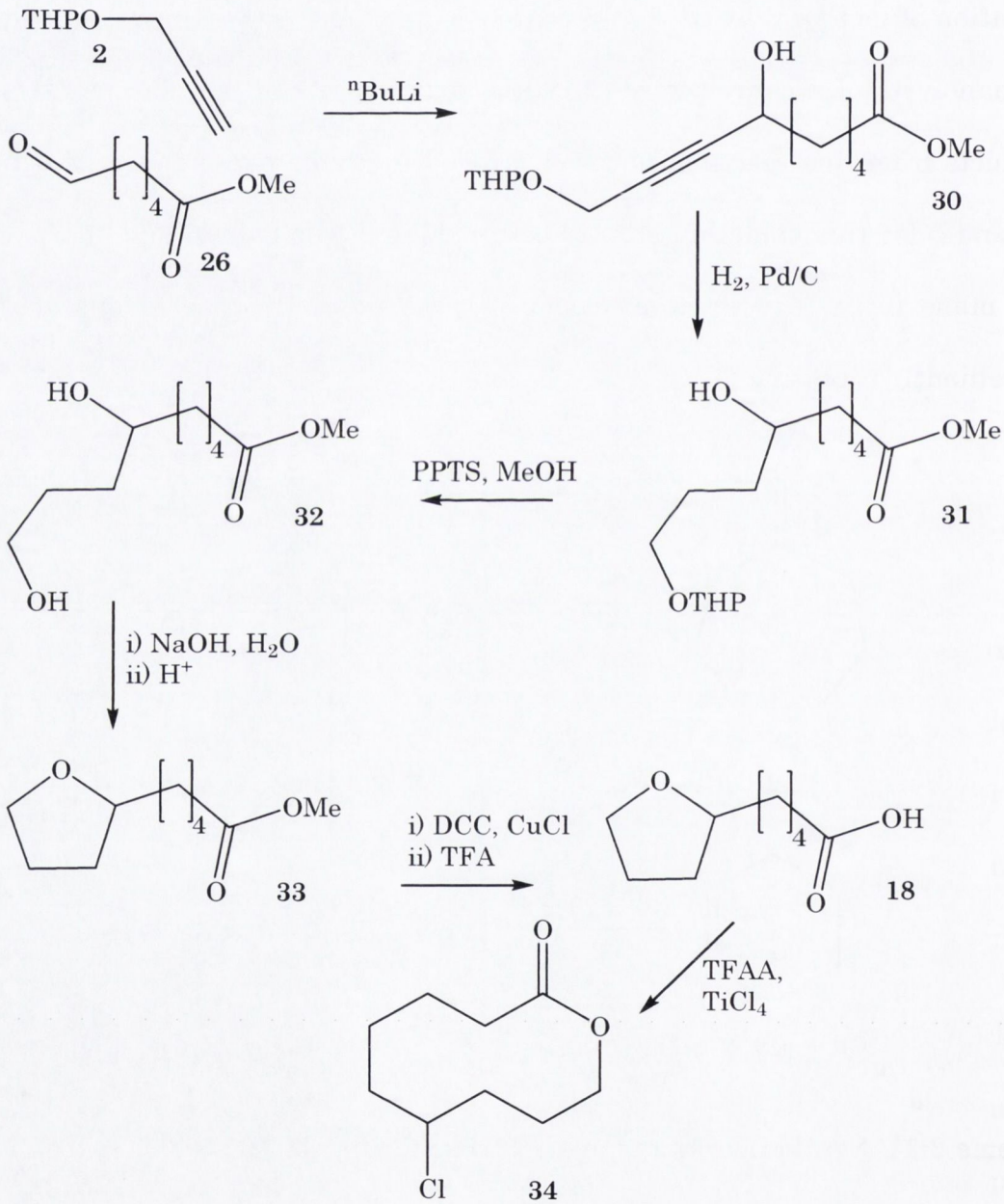
examine whether or not the previously-reported smaller rings had indeed been produced as monomeric lactones, rather than as diolides.

The starting aldehydo-ester **26** necessary for the synthesis of 5-(tetrahydrofuran-2-yl)pentanoic acid **18** was initially produced *via* PCC oxidation of methyl 6-hydroxyhexanoate **27**, itself formed by the acid-catalysed methanolysis of ε-caprolactone **28**. The toxic, insoluble chromium(VI) side-products from this reaction, however, proved to be too persistent and difficult to handle for this oxidation step to be considered worthwhile and so a switch was made to the ozonolytic cleavage of cyclohexene **29** as a means of more conveniently accessing **26**.



Scheme 2-11: Synthetic route to methyl 6-oxohexanoate **26**

The now established synthetic procedural route to chain-linked THF-acids of alkynyl carbanion addition, reduction, deprotection, cyclisation and hydrolysis was then applied with no significant problems noted, giving **18** in acceptable yield (68%).



Scheme 2-12: Synthetic route to 5-(tetrahydrofuran-2-yl)pentanoic acid **18**

When this shorter link-chain acid was subjected to the cyclisation conditions previously used (TFAA @ -10 °C, $TiCl_4$ @ -40 °C) an orange, fragrant product was isolated, which could be distilled to *in vacuo* to give fine white crystals of what had been previously reported as being the chloro-lactone **34** in good yield (74%). Unfortunately the extremely low melting point of these crystals (~30°C) prevented any crystallographic determination of their structure.

Mass spectrometric analysis again showed no molecular ion for the monomeric lactone **34**, but significantly there was also no evidence for the alternative diolide product, which might otherwise have been expected to be formed.

The NMR spectra of both the crude and the purified lactone formed in this reaction showed extremely significant levels of diastereotopic splitting which, in addition its boiling point being low enough to allow it to be distilled, strongly suggested that there had been production of the monomer **34**, as previously claimed.[123]

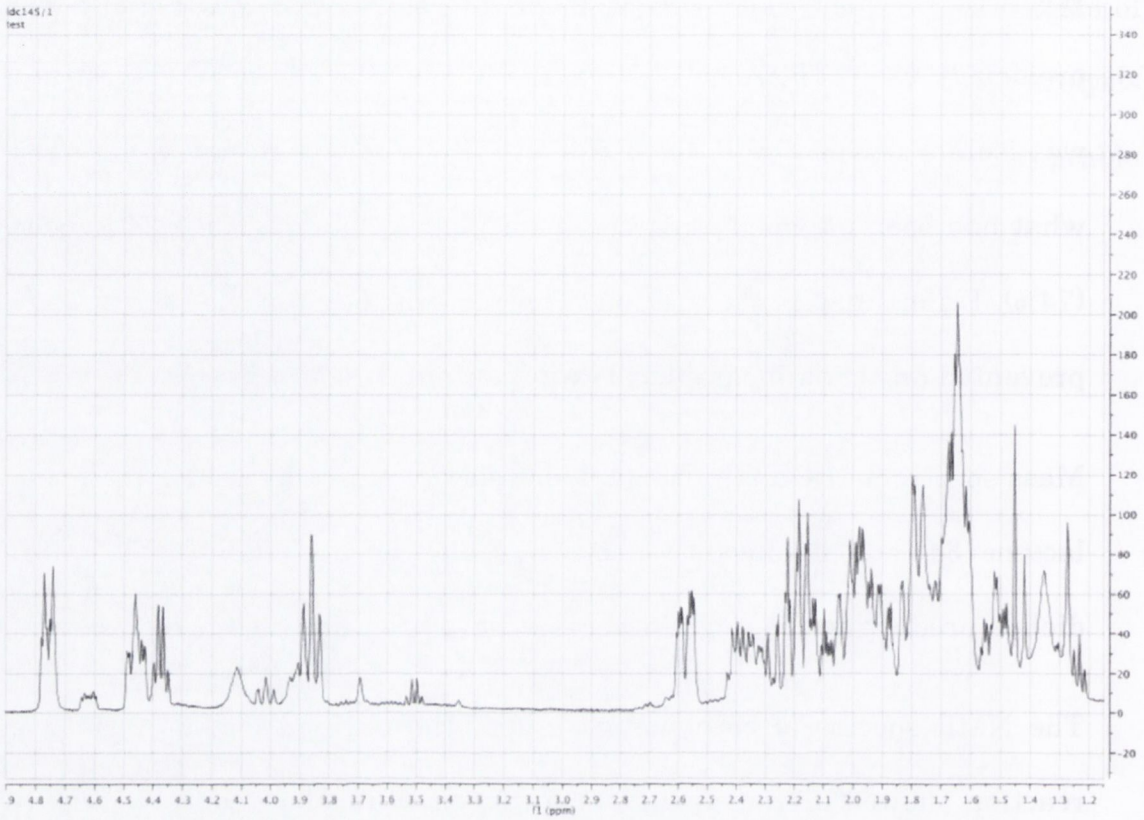


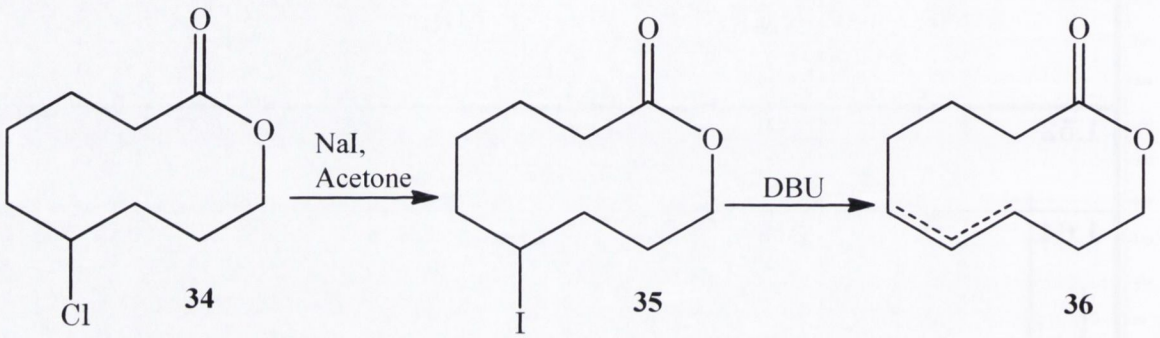
Figure 2-4: ^{1}H NMR spectrum of monomer chlorolactone 7-chlorooxecan-2-one **34**

Table 6: ^{1}H NMR spectroscopic details for chlorolactone 7-chlorooxecan-2-one **34**

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignments
1.52	1H	m	C4 CH_a
1.64	3H	m	C3 CH_a, C5 CH_a, C8 CH_a
1.80	1H	m	C5 CH_b
1.96-2.22	6H	m	C2 CH_a C3 CH_b C4 CH_b C7 CH_{ab} C8 CH_b
2.57	1H	m	C2 CH_b
3.87	1H	m	C9 CH_a
4.46	1H	m	CClH
4.76	1H	m	C9 CH_b

To further confirm the production of the monomeric chlorolactone **34** a Finkelstein reaction was undertaken to produce 11-iodooxacyclotetradecan-2-one **35**, and this was followed by DBU-mediated elimination of HI to produce a

mixture of structural isomers of more stable [towards mass spectrometry] unsaturated lactones **36**. It follows that the precursor chloro-lactone **34** must be unstable under the conditions used for ESI mass spectrometry.



Scheme 2-13: Synthesis of a mixture of isomers of (*E*)-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one

Such a sharp distinction in cut-off point between the formation of of monomeric and dimeric lactones seems unlikely to arise solely as a result of the acylium ion at the terminus of the side-chain being too short to reach a second THF ring in a metal-complexed intermediate.

5. Further modifications

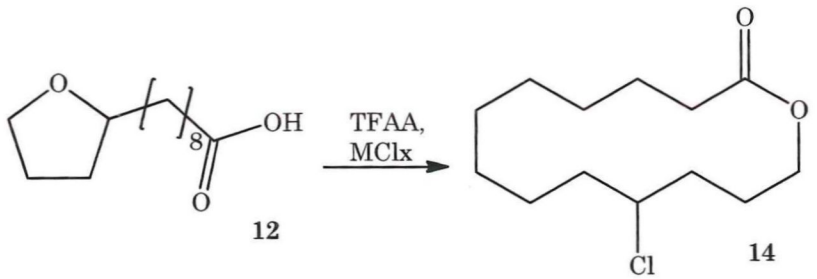
A series of further modifications to the synthetic procedure were then undertaken to try and selectively produce monomeric chlorolactones of sizes greater than 10-membered rings. The compound 9-(tetrahydrofuran-2-yl)nonanoic acid **12** continued to be used as the standard starting material as a

more universal solution was sought, rather than iterating the process from the pentanoic acid species **18** by one methylene unit at a time.

It was hoped that, by altering the Lewis acid used that both the rate of breakdown of the mixed anhydride to the acylium ion would be slowed, and that coordination of the tetrahydrofuran ether oxygen atom to the central metal atom would be modified, such that either the structure of the complex thus formed would deter the intermolecular reaction, or that only mono-coordination would result.

An array of weaker Lewis acids were therefore examined using the mixed anhydride derived from carboxylic acid **12** and TFAA.

Table 7: The use of alternative Lewis acids in lactonisation *via* acylative cleavage of tetrahydrofurans



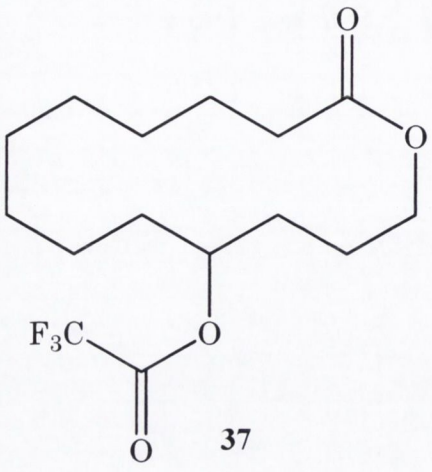
12 14

Lewis Acid (MCl_x)	Appear-ance of neutral product	Characteristic NMR Signals	Dimer/ Monomer appearance in MS	THF complex reference	Mixed anhydride breakdown reference
$SnCl_4$	Orange waxy solid	3.92 (1H, m, CHCl) 4.10 (2H, m, CH_2O)	Dimer only; Calculated for $C_{26}H_{46}O_4Cl_2Na$ expected 515.2671, found 515.2666 ESI+	128	129
$FeCl_3$	Yellow waxy solid	3.90 (1H, m, CHCl) 4.07 (2H, m, CH_2O)	Calculated for $C_{26}H_{46}O_4Cl_2Na$ expected 515.2671, found 515.2687 ESI+	130	131

$AlCl_3$	Viscous dark orange oil	3.91 (1H, m, CHCl) 4.09 (2H, m, CH_2O)	Dimer only; Calculated for $C_{26}H_{46}O_4Cl_2Na$ expected 515.2671, found 515.2658 ESI+	132	133
$ZnCl_2$	Orange brown waxy solid	3.92 (1H, m, CHCl) 4.10 (2H, m, CH_2O)	Dimer only; Calculated for $C_{26}H_{46}O_4Cl_2Na$ expected 515.2671, found 515.2687 ESI+	134	135

The slight variations in the physical appearance for the chlorolactone dimer between reactions may be ascribed to complexation with residual metal cations, as their NMR, MS and IR spectra appeared effectively indistinguishable, and were consistent with production of the dimeric lactone **17**.

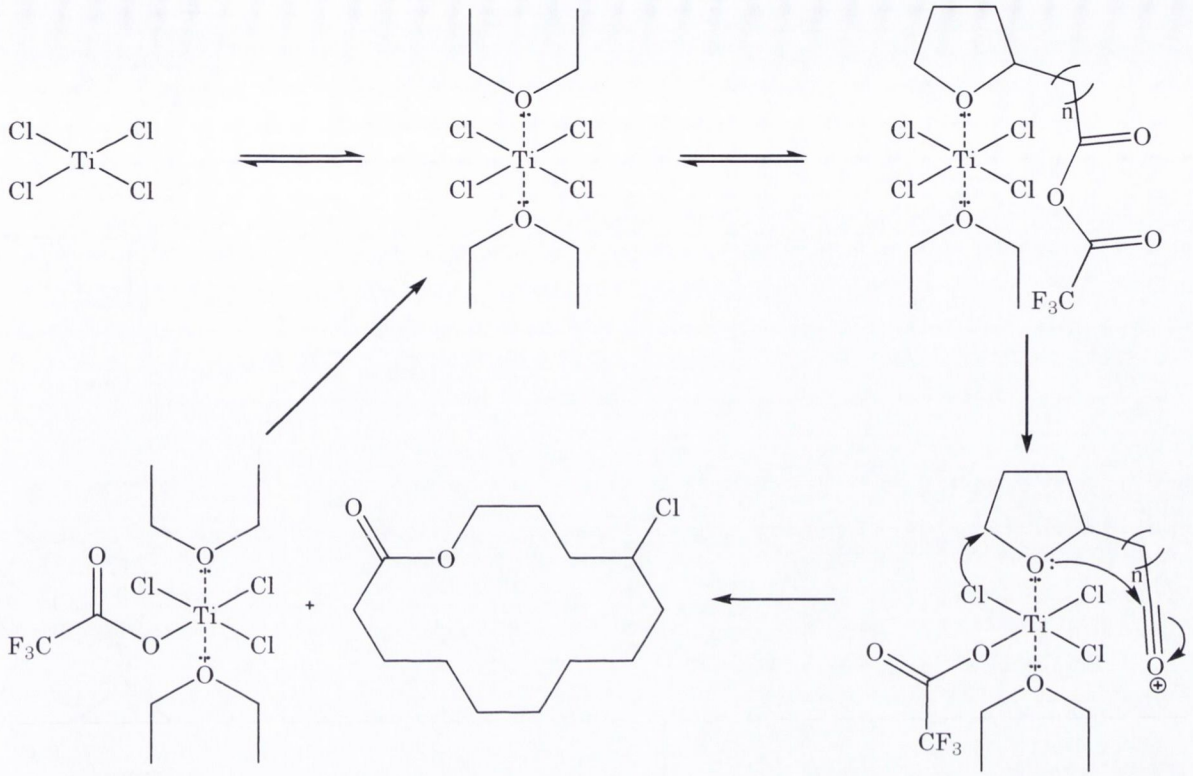
Following reports[136] that ultrasonication could be utilised in conjunction with TFAA to promote the analogous intermolecular acylative cleavage of tetrahydrofuran, the technique was applied to acid **12** in the hopes of deterring dual aggregation of THF rings with the central metal atom, leading to production of a monomeric trifluoroacetoxy lactone **37**.



37

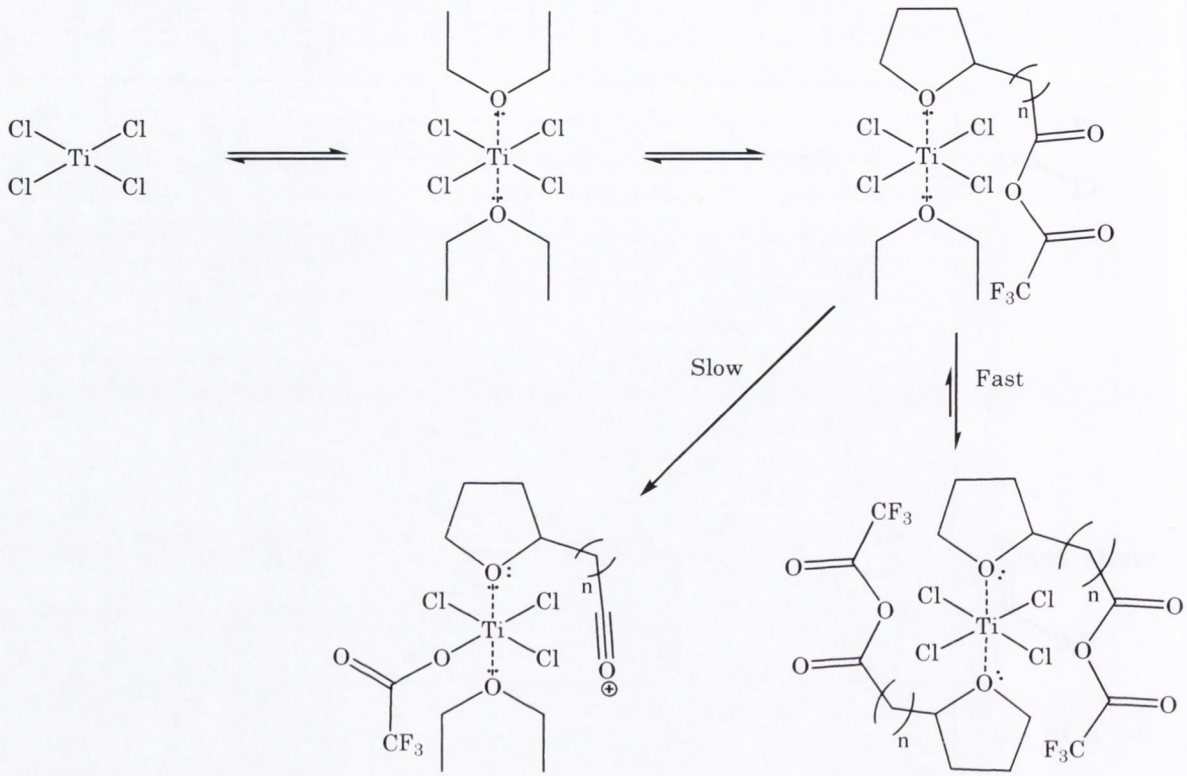
However, whilst a lactonic product was recovered, MS analysis did not show any trace of the desired monomer.

The next approach was to consider the solvent and whether the use of a co-ordinating solvent such as diethyl ether or dimethyl formamide could "block off" one of the co-ordinating sites on the metal atom of a Lewis acid catalyst, allowing for mono-coordination of the substituted THF ring. This also necessitated a change in the order of addition, with the mixed anhydride being formed in one pot followed by slow addition *via* cannula to a second flask containing the $TiCl_4.Et_2O$ complex.



Scheme 2-14: Proposed equilibria of $TiCl_4$:Et_2O/THF

Whilst some lactonic product was recovered from the reaction vessel when diethyl ether was used, there was also significant recovery of the starting material **12**, and MS analysis showed only the presence of the diolide. This may have been as a result of the greater co-ordinating capabilities of the THF oxygen over that of diethyl ether resulting in an unfavourable reacting species.



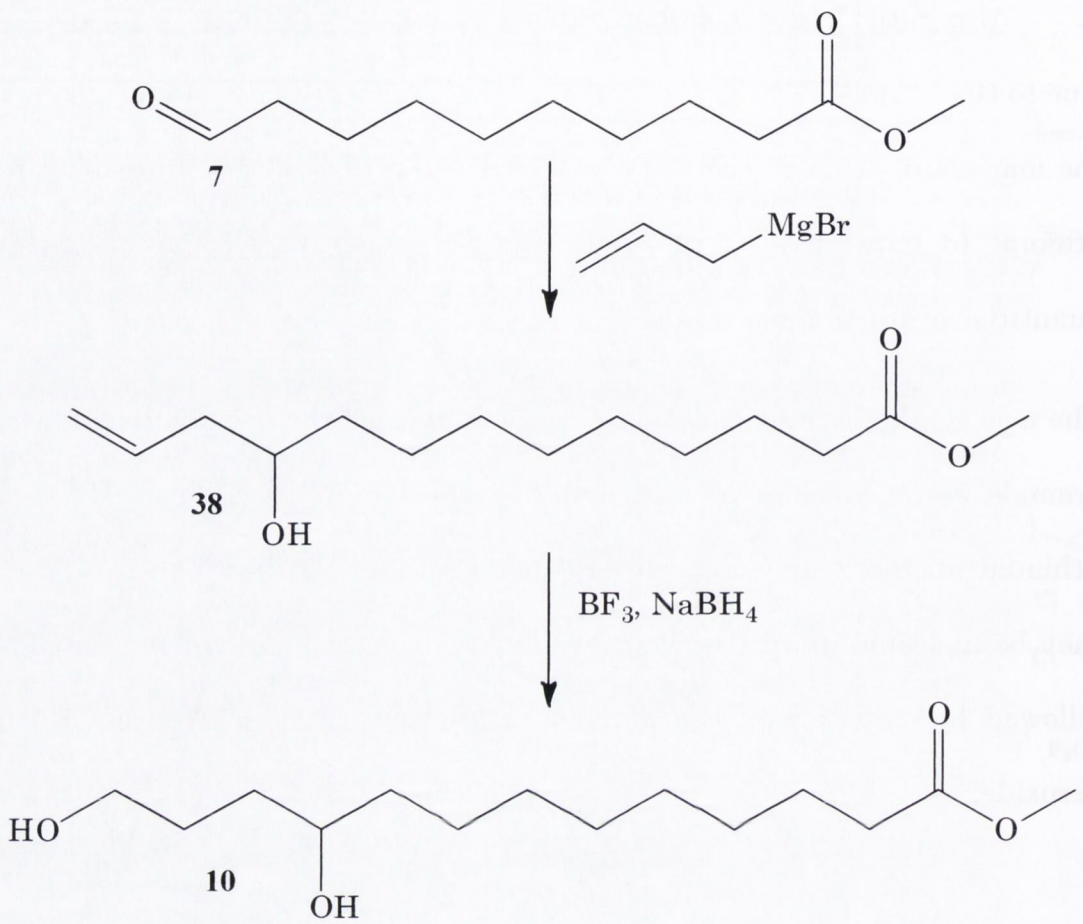
Scheme 2-15: Revised scheme for the equilibria of $TiCl_4$:Et_2O/THF

A further attempt at employing this strategy was undertaken using dimethyl formamide as the solvent in the hope that the strength of its coordination to the metal ion would be somewhere between that of diethyl ether and the substituted THF rings. The reaction was monitored by TLC and when no neutral product was observed after the standard reaction time the flask was heated to reflux overnight but only starting materials were isolated in the work-up.

6. Alternative route to diol precursors for tetrahydrofuran synthesis

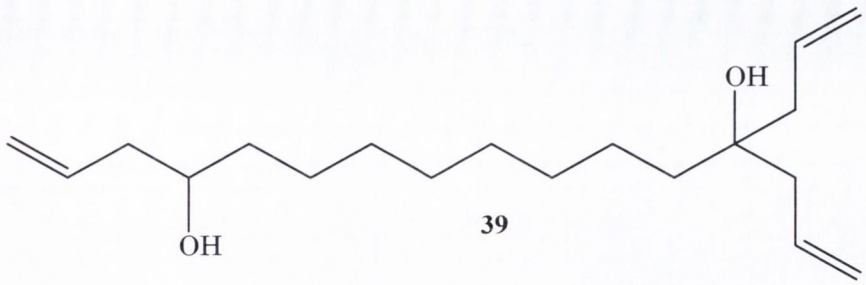
Due to the increasingly large number of tests that were being undertaken with the long-chain acids a secondary synthetic methodology was sought out in an attempt to improve both the yield and the safety of working with larger quantities of starting materials.

The new synthetic route that was proposed involved the use of allylmagnesium bromide as an alternative nucleophile, rather than the far more dangerous lithiated alkyne **2** previously used. The resulting ß-hydroxy alkene **38** could then be hydrated in an anti-Markovnikov fashion with *in-situ* generated BH_3, followed by oxidation of the derived organoborane using alkaline hydrogen peroxide.



Scheme 2-16: Alternative synthetic route to **10** methyl 10,13-dihydroxytridecanoate

The first step worked gratifyingly well with the longer chain aldehydoester methyl 10-oxodecanoate **6**, the only observable by-products being a minor amount of 4-allylhexadeca-1,15-diene-4,13-diol **39**, formed by the sequential addition of allylmagnesium bromide to first the ester and then the resulting ketone.



39

The same reaction conditions did, however, give lower yields and reduced purity for the products isolated from treatment of the shorter chain aldehydes, potentially due to the less lipophilic nature of their methylene chains resulting in a more readily accessible ester group.

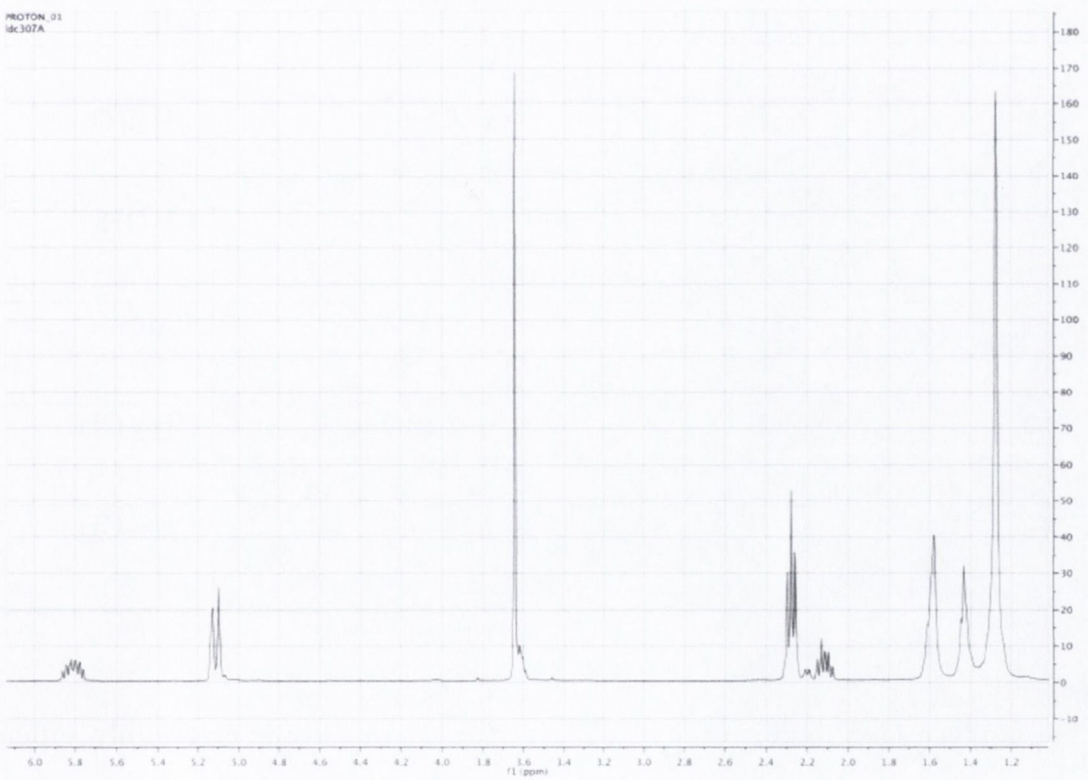


Figure 2-5: ^{1}H NMR spectrum of methyl 10-hydroxytridec-12-enoate **38**

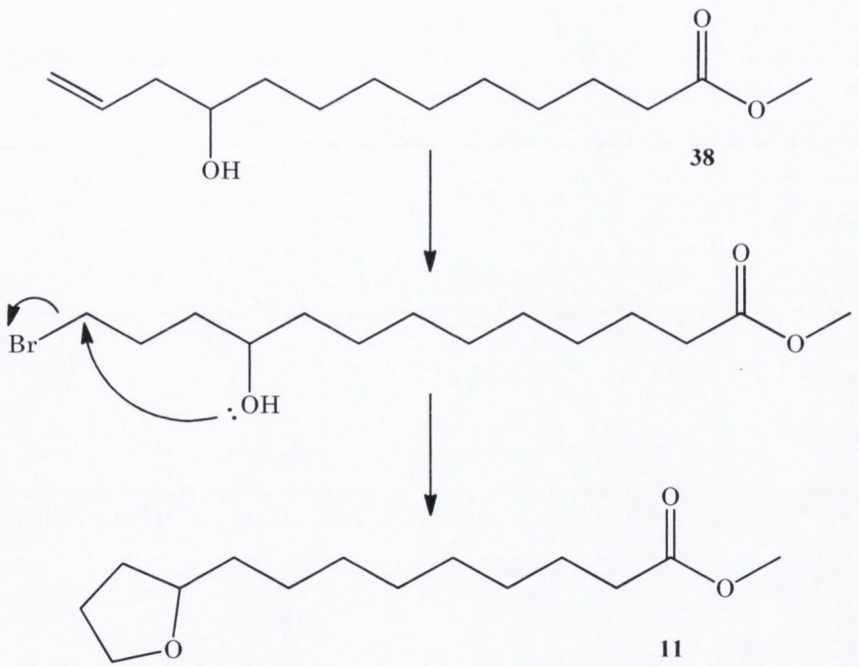
Table 8: ^{1}H NMR spectroscopic details for methyl 10-hydroxytridec-12-enoate **38**

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.26	12H	m	CH_2
1.44	2H	m	$C\underline{H_2}CHOH$
1.57	2H	m	$C\underline{H_2}CHOH$
1.92	1H	bs	$O\underline{H}$
2.27	2H	t J 7.2	CH_2CO
3.62	1H	m	$C\underline{H}OH$
3.64	3H	s	OMe
5.12	2H	d J 12.7	$C\underline{H_2}$=CH
5.81	1H	m	CH_2=$C\underline{H}$

The subsequent oxidative hydroboration also proceeded agreeably efficiently and cleanly, to afford a good yield (77%) of methyl 10,13-dihydroxytridecanoate **10** which was then subjected to the same cyclodehydration reaction as previously described[123]. A small portion of the ester was hydrolysed to 10,13-

dihydroxydecanoic acid during the work up but was easily re-converted by Fischer esterification.

There is also the potential to adapt this reaction procedure to the radical anti-Markovnikov hydrobromination reaction using HBr: it can easily be envisaged that with the application of an appropriate base during workup the resulting *5-exo-tet* cyclisation would produce the tethered THF ring directly, removing another reaction step.



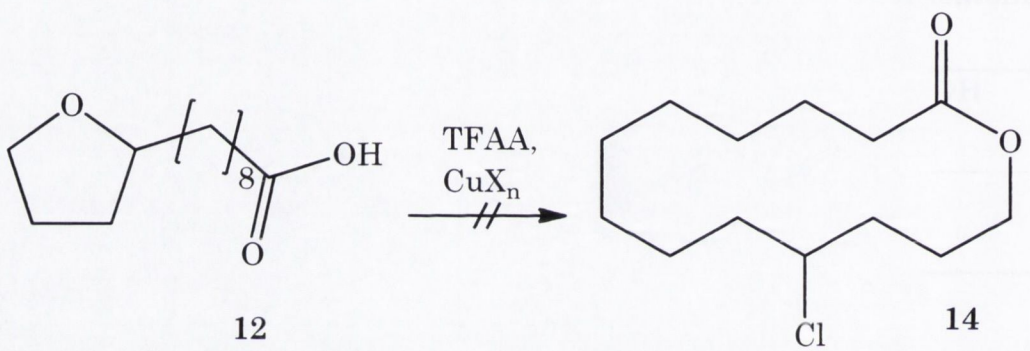
Scheme 2-17: Proposed hydrobromination route to **11**

7. Copper Reagents

It was noted at this point that in the array of Lewis acids tested against both mixed anhydrides and acyl chlorides, none had been copper based reagents. As

copper based reagents have the potential to undertake a plethora of reactions which other transition metals are incapable of, it was deemed important to investigate them. It was also hoped that copper halides are such weak Lewis acids that bis-coordination of THF oxygen atoms would be less likely, suppressing the formation of diolides.

Table 9: Effects of copper halides on the acylative cleavage of tetrahydrofurans



12 **14**

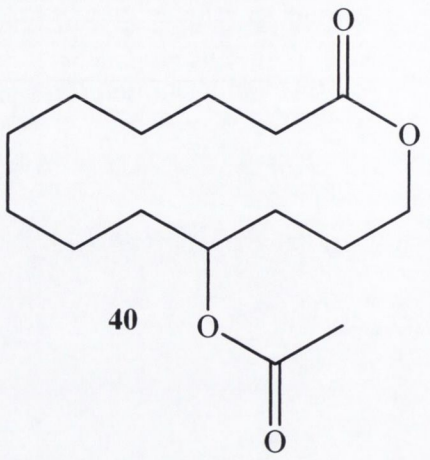
Copper Lewis Acid	Significant ^{1}H NMR Signals	Monomer **14** / Dimer **17** appearance in MS
Copper(I) chloride	4.05 (CHCl), 3.62 (CH_2O lactone)	Dimer/Starting acid
Copper(II) chloride	-	Starting acid
Copper(I) iodide	-	Starting acid

Unfortunately, even with extended periods of refluxing there was no detectable trace of either the monochlorolactone **14**, or the corresponding monoiodolactone

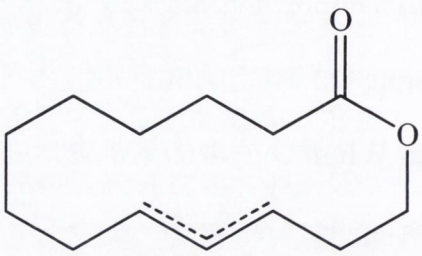
when copper iodide was used. This is shown in the table above; with no presence of any lactone detected when copper(II) chloride or copper(I) iodide is used. When copper(I) chloride is used the only lactonic product detected in the mass spectrum is the diolide and neither of the indicative peaks in the ^{1}H NMR spectrum show any deviation from the spectra for the previously obtained diolide.

It was whilst repeating the testing of these copper reagents that the decision was made to test the reaction of a sample of the acid **12** with TFAA and copper(II) acetate. As with the copper halides no reaction was initially noted by TLC, but after heating to reflux a slight colour change was noted and after 48 hours a lactonic product was isolated.

A mass spectral assay confirmed the presence of the acetoxy monolactone **40** in addition to a mixture of structural isomers of (*E*)-oxacyclotetradec-10-en-2-one **15.** The two products were in roughly the same ratio as reported for the analogous reaction of refluxing the acid **12** with trifluoroacetic anhydride (60 acetoxy:40 alkenyl)[123] but with the acetate as an alternative ligand and at a much improved yield (89% compared to 4% without the Lewis acid).



40



15

The NMR spectroscopic data obtained for the mixture of **40** and **15** are summarised in the table below. Key resonances in the ^{1}H NMR that indicate the synthesis of **40** are the appearance of a singlet integrating for three protons at 2.06 ppm which corresponds to an acetoxy methyl group, and a quintet with a coupling constant of 5.7 Hz centred at 5.1 ppm which is assigned to the proton α to a acetoxy etheric oxygen.

The successful synthesis of **15** is indicated by the presence of the multiplet spread between 5.29-5.54 ppm; this corresponds to the two olefinic protons. The presence of their ^{1}H NMR signal as a multiplet is as a result both of the complex splitting patterns involved and the presence of multiple structural isomers.

The signals for the methylene unit adjacent to the etheric oxygen of the lactone group for both compounds overlap each other resulting in a distorted apparent quartet centred at 4.08 with a coupling constant of 6.48 Hz. The signals for the methylene units adjacent to the carbonyl however lie on top of each other at

2.36 ppm. The remaining proton signals are all presented as indistinguishable multiplets.

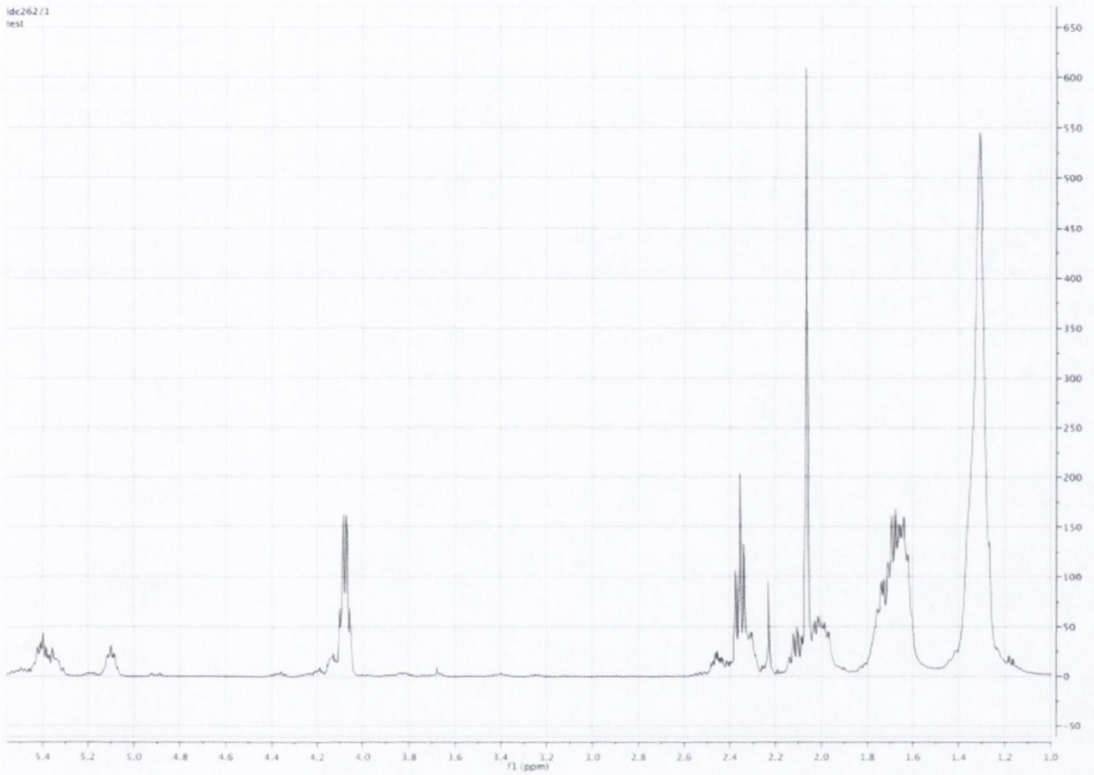


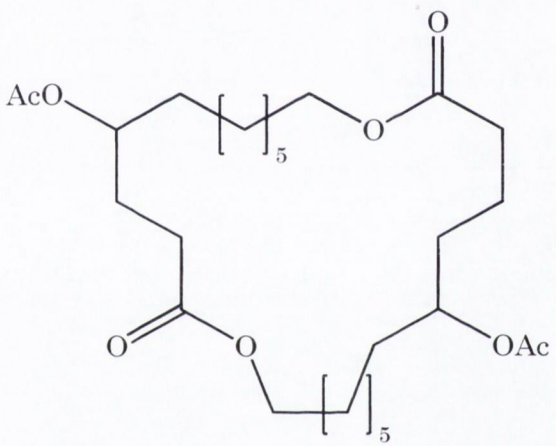
Figure 2-6: ^{1}H NMR spectra of the products **15** and **40** formed by treatment of **12** with TFAA and $CuOAc_2$

Table 10: ^{1}H NMR spectroscopic details for products **15** and **40** formed by treatment of **12** with TFAA and $CuOAc_2$

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.31	8H	m	CH_2
1.66	6H	m	CH_2
2.06	3H	s	OMe
1.93-2.16	2H	m	CH_2CX
2.36	2H	t *J* 7.6	CH_2CO
4.08	2H	Apparent q *J* 6.48	OCH_2
5.10	1H	Quintet *J* 5.73	C<u>H</u>OAc
5.29-5.54	2H	m	CH=CH

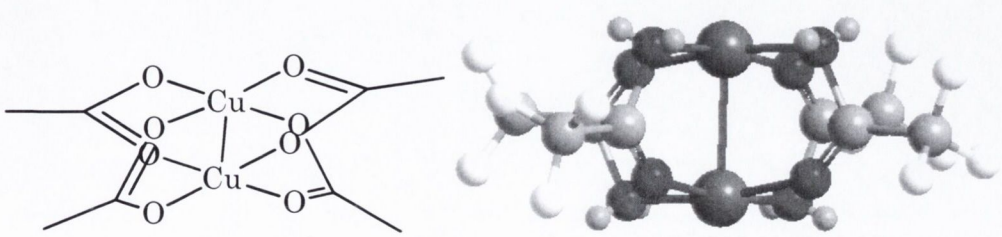
The reaction, however, remained somewhat capricious in its capability to produce the monomer in a selective fashion, as during the course of several repetitions MS analysis also detected the presence of the dimeric compound **41**

(calculated for $C_{28}H_{47}O_6$, expected 479.3373, found 479.3367, ESI-). However, as the crude product was distillable in good yield (>85%) at a temperature and pressure consistent with the boiling points of other similarly sized mono-lactone rings[137-139] (0.5 mmHg, >100 °C) it is reasonable to assume that the monolactone **40** is the major product. Further attempts at purification *via* column chromatography proved impossible due to breakdown of the lactone ring on the column.



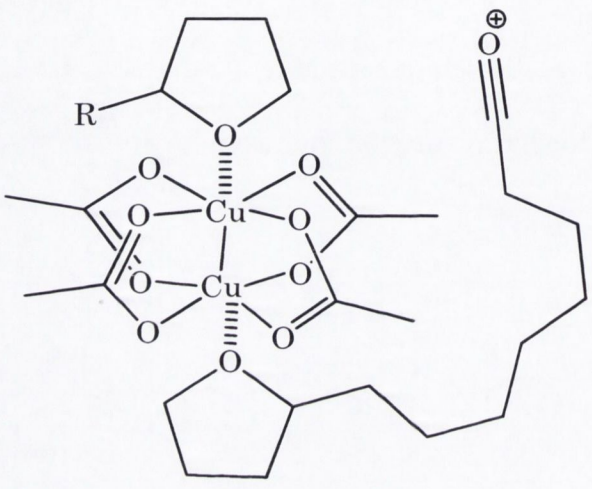
41

It seems feasible that copper acetate is capable of producing monolactones simply as a result of its greater size as it adopts a "paddle-wheel" type structure.



Scheme 2-18: Paddle wheel structure of copper(II) acetate

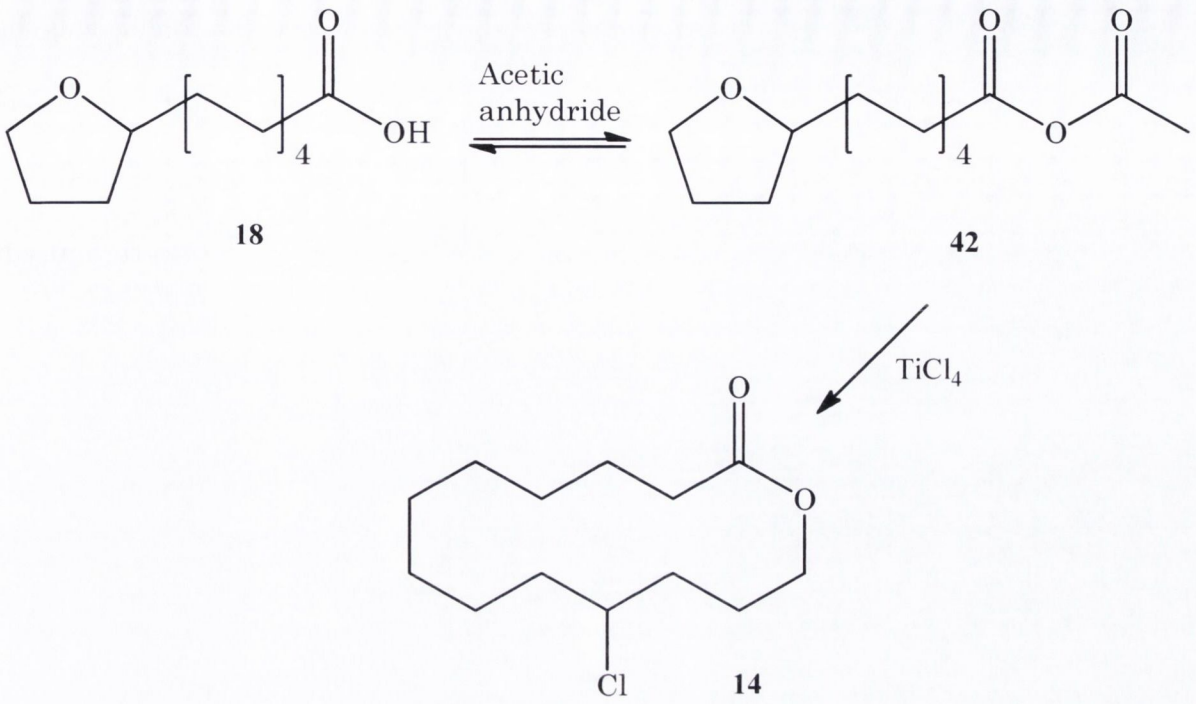
The resulting steric crowding may be enough to largely prevent the tethered acylium ion in the reacting species from being able to reach around to a close enough proximity to a second coordinated THF ring to be able to react with it.



Scheme 2-19: Proposed steric blocking of dimerisation

8. Alternative Mixed Anhydrides

Alternative mixed anhydrides were next investigated. At first, a rather quixotic attempt at forming an acetic-nonanoic anhydride was undertaken using acetic anhydride in an analogous manner to that of trifluoroacetic anhydride.



Scheme 2-20: Synthesis of acetic 9-(tetrahydrofuran-2-yl)nonanoic anhydride **24**

Surprisingly, treatment of the resulting mixture with stoichiometric titanium tetrachloride produced a lactonic product in good yield (72%). Whilst no monomeric lactone was detected by any of the MS techniques employed (ESI+, ESI-, EI) there was also a significant absence of any trace of dimer. The product of the reaction was also isolated as an oil that was distillable *in vacuo* (0.5 mmHg, >100 °C), in comparison to the thick waxy product that is characteristic of the dimer suggesting the possibility that the monomer 11-chlorooxacyclotetradecan-2-one **14** was being synthesised. Unfortunately, there was insufficient material available to permit meaningful recording of the boiling point

Further credence was given to the argument that the monomer was being produced by the findings of Torra and Urpi,[140] who reported a 0.1 ppm shift in the ^1H proton NMR signal of the CH_2OCO protons of monolactones in comparison with diolides, a feature that was observed in the acetic anhydride reactions.

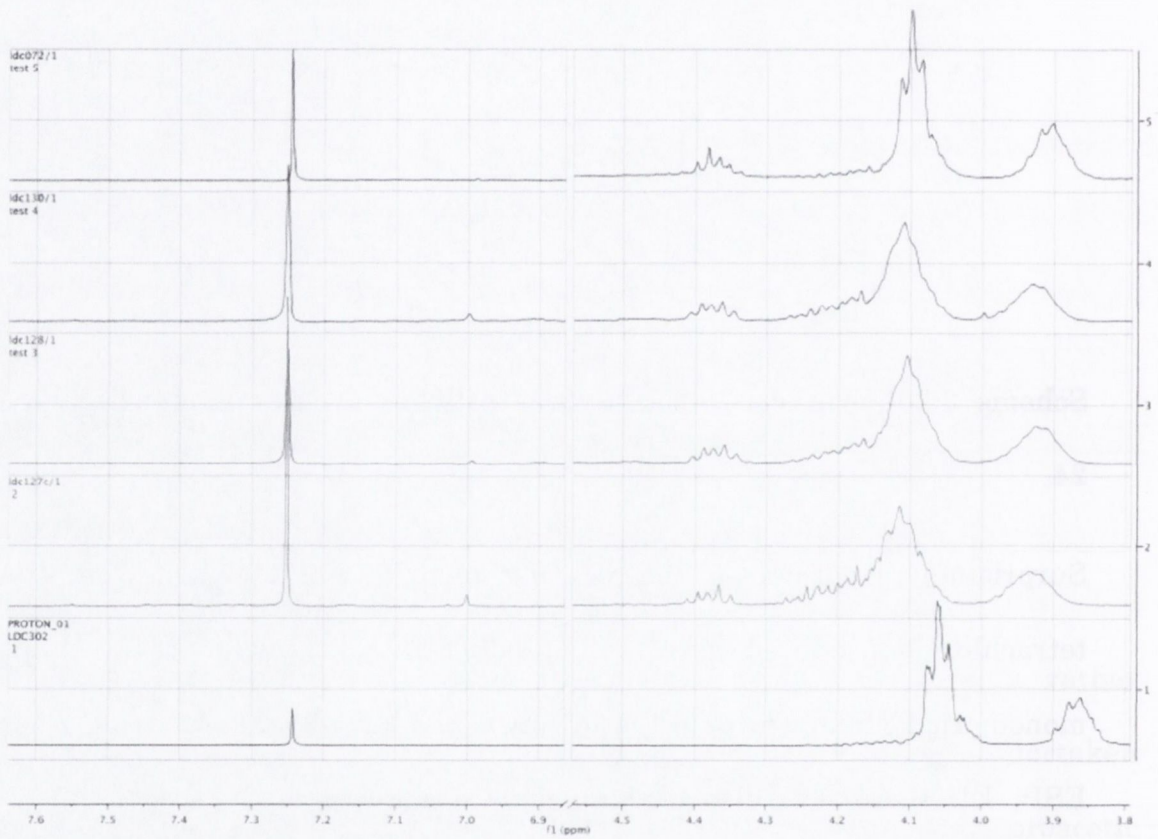
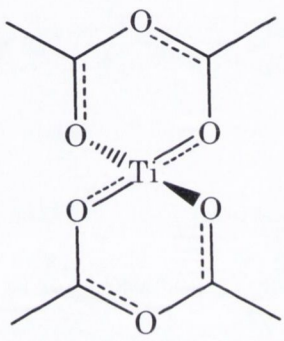


Figure 2-7: Comparison of ^1H NMR spectra of diolide **17** (top 4 spectra) with monomer **14** (bottom spectrum)

The suspected monomeric chlorolactone **14** was subjected to Finkelstein conditions to produce the analogous iodolactone **16** which was subsequently treated with 1,8-diazabicycloundec-7-ene in order to eliminate HI and produce

a monomeric alkene lactone **15**. This was stable enough to withstand mass spectrometric conditions and retrospectively confirm the selective synthesis of the monochlorolactone.

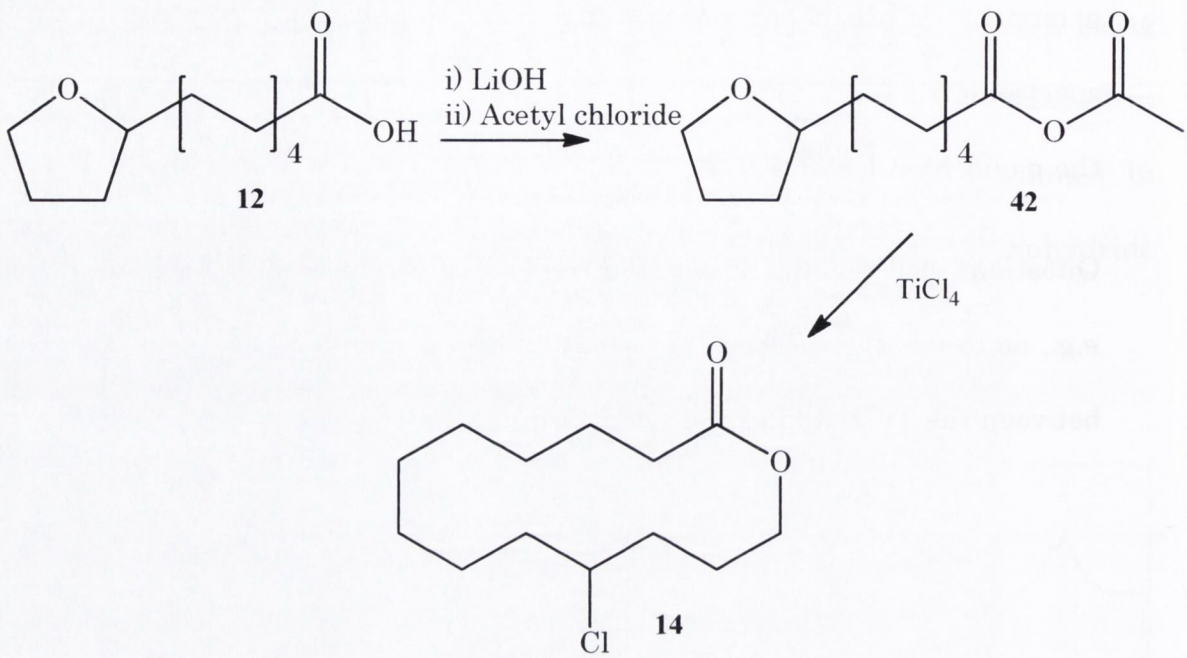
Questions still remained, however, regarding the mechanism for this reaction, *e.g.,* as to whether there was formation of a secondary Lewis acid by reaction between the $TiCl_4$ and excess acetic anhydride.



Scheme 2-21: Proposed structure of acetic anhydride/$TiCl_4$ complex

To test these issues the mixed nonanoic-acetic anhydride **42** was produced and isolated by treating the lithium salt of the acid **12** with acetyl chloride.

Treatment of this mixed anhydride with $TiCl_4$ in DCM resulted in the formation of a compound with identical spectra and physical characteristics to the chloromonolactone **14**.



12 42 14

Scheme 2-22: Synthesis of 11-chlorooxacyclotetradecan-2-one **14**

Testing analogous reactions with alternative Lewis acids, it was discovered that anhydrous iron(III) chloride was strong enough to provoke the reaction, whereas copper(II) acetate was not.

It is not known for certain why monolactones are being specifically produced under these conditions. It is conjectured that as the same degree of THF complexation is present as with the original TFAA/$TiCl_4$ reaction, but less aggressive acylium formation necessitates a two-step process wherein co-ordination of the THF ring occurs first, followed by activation of the mixed anhydride by a second equivalent of Lewis acid.

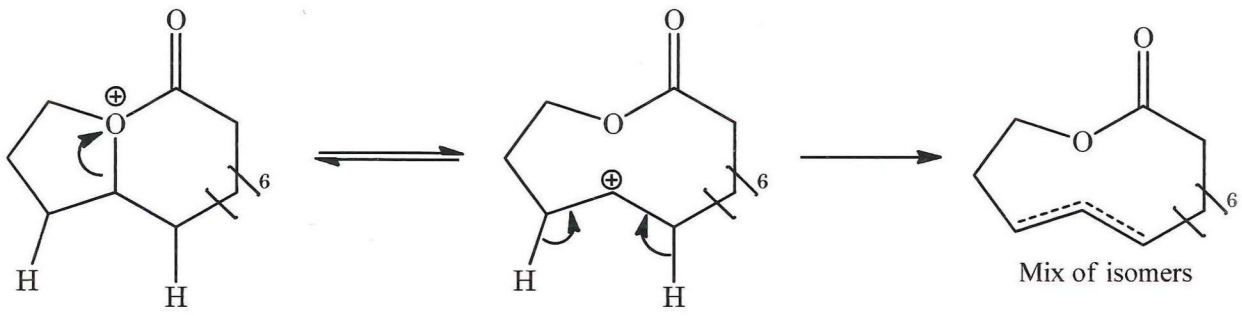
It was considered important to explore the range of this reaction protocol and examine the fate of the bicyclic oxonium intermediate were no nucleophile to

be present. This was achieved by the treatment of 9-(tetrahydrofuran-2-yl)nonanoyl chloride with silver tetrafluoroborate in order to promote formation of the acylium species whilst removing the chlorine nucleophile from the reaction mixture as silver chloride.

It was also decided that the acyl chloride needed to be prepared and isolated separately rather than being synthesised *in situ,* both to minimise the formation of side-products and to confirm the successful transformation of the acid into the acyl chloride. To this end a technique established by the group[141] for prior work was used, wherein the dry lithium salt of the acid was treated with phosphorus trichloride overnight followed by filtration of the insoluble inorganic phosphorus compounds and evaporation of solvent at reduced pressure to reveal the acyl chloride **43**.

In order to promote the formation of the acylium ion silver tetrafluoroborate was added to the reaction mixture.

The ensuing reaction proved to be a very direct route to the unsaturated monolactone **15**, which, in the absence of any strongly basic co-reactant, presumably occurs along E1 pathways.



15

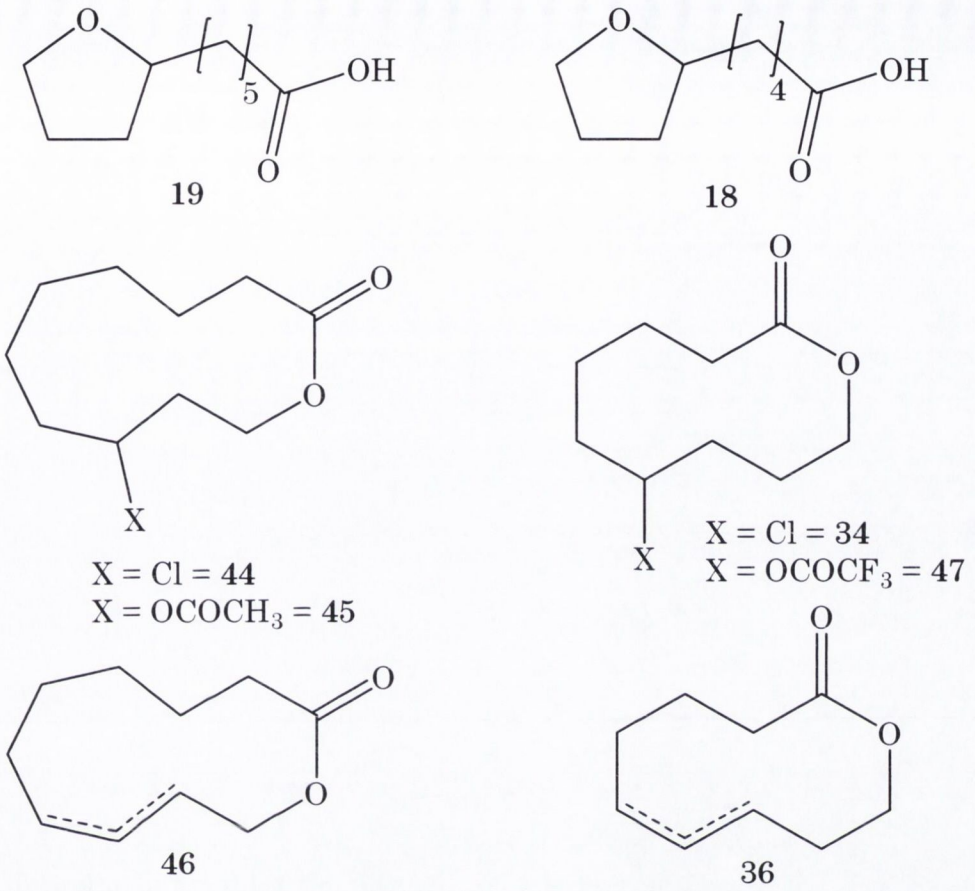
Scheme 2-23: Proposed mechanism of alkenyl lactone formation

9. Investigation of new techniques with smaller rings

It was considered necessary to then extend these new methodologies of using the reagent combinations TFAA/$Cu(OAc)_2$ and $Ac_2O/TiCl_4$ to production of the smaller ring sized lactones to examine the scope of their applicability.

The oxacycloundecanone series was examined first, using 6-(tetrahydrofuran-2-yl)hexanoic acid **19** as the starting material, and the derived δ-chloro **44**, acetoxy- **45** and alkenyl **46** monomer lactones were successfully formed in analogous reactions using reagent combinations of $Ac_2O/TiCl_4$, TFAA/$CuOAc_2$ and oxalyl chloride/$AgBF_4$ respectively.

The oxecan-2-one series was also successfully synthesised, producing the respective chlorolactone **34** and the alkenyl **36** lactone. Curiously however when the acid **18** is treated with trifluoroacetic anhydride and copper(II) acetate under the same conditions as the larger rings it is the trifluoroacetyl lactone **47** 10-oxooxecan-5-yl 2,2,2-trifluoroacetate which is synthesised.



Scheme 2-24: Range of 11 & 10 membered lactone rings synthesisable by the newly developed reaction from their respective starting acids **19** and **18**

In both cases, however, the δ-chloro compounds **34** and **44** remained undetected by MS (see above), and so in order to confirm that the monomer was indeed being formed a sample was taken through the standard route of the Finkelstein reaction-elimination reaction sequence. Due to a shortage of the previously used reagent 1,8-diazabicycloundec-7-ene, bicyclo[2.2.2]octane was employed instead. Upon work-up in addition to the expected alkenyl lactone **36** there was also a significant amount of the starting acid **18**.

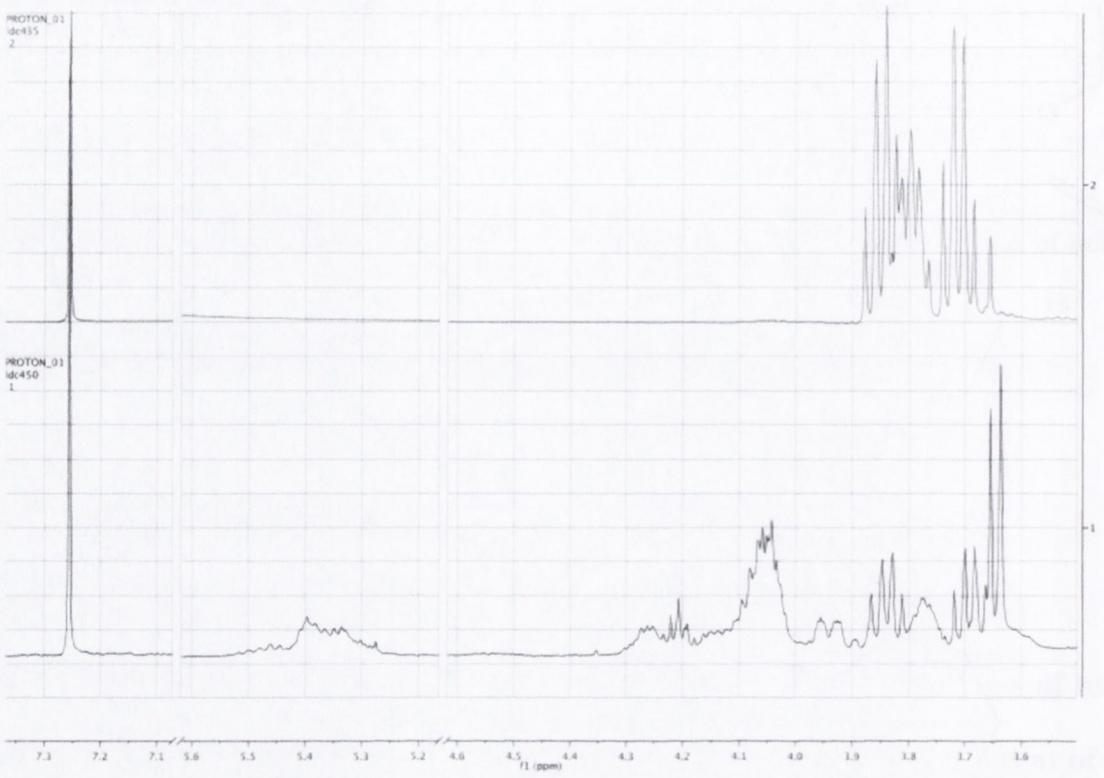
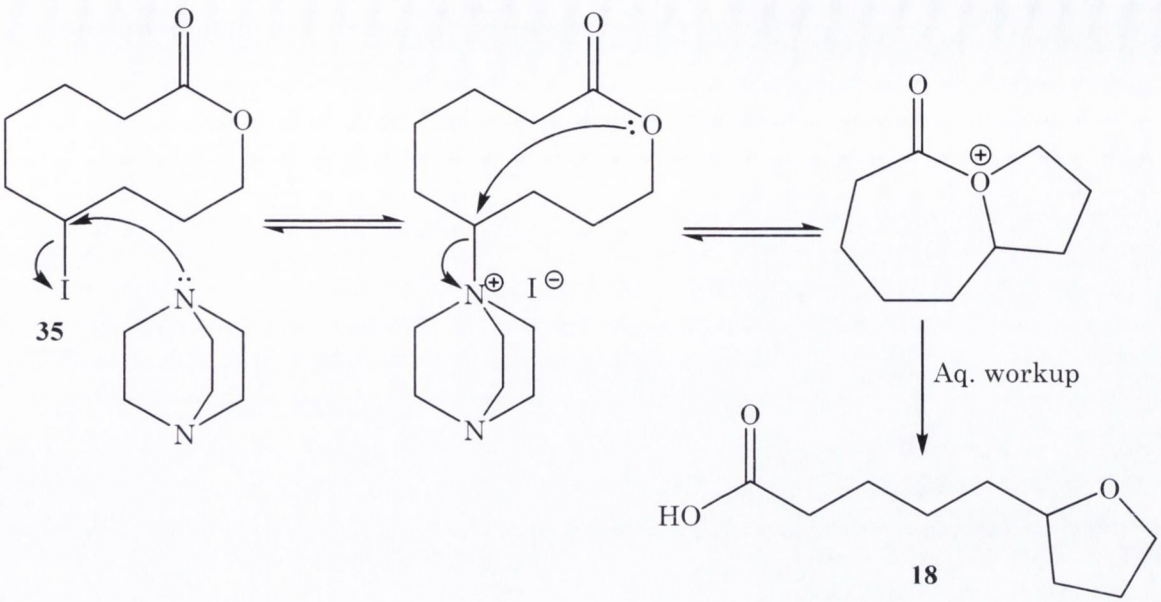


Figure 2-8: ^{1}H NMR spectra of acid **18** (top spectrum) and alkenyl lactone **36** containing re-formed acid **18** (bottom spectrum)

The figure above shows the re-formation of the starting acid **18** by the treatment of the iodolactone **35** with DBU as evidenced by the return of the characteristic quartet-quintet-quartet pattern sequence of the ^{1}H NMR signals of the protons α to the tetrahydrofuryl oxygen. The quartet-quintet-quartet signals, centered at 3.74, 3.80 and 3.88 ppm respectively and are characteristic of all of the substituted tetrahydrofuryl carboxylic acids synthesised in this chapter.

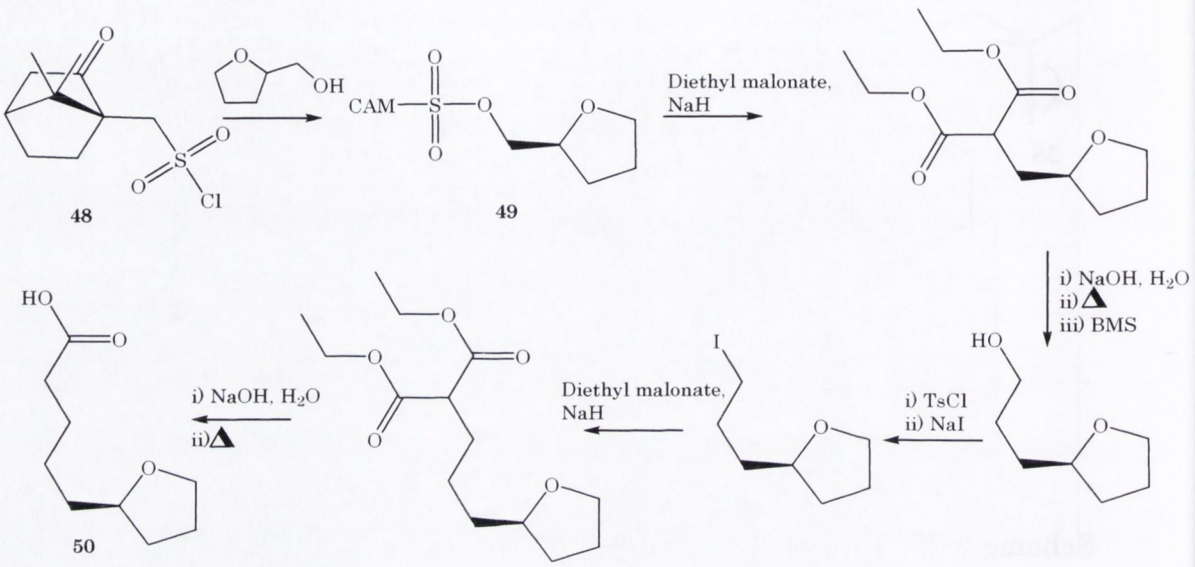


Scheme 2-25: Proposed mechanism for the conversion of 7-iodooxecan-2-one **35** to 5-(tetrahydrofuran-2-yl)pentanoic acid **18**

It has been proposed that the mechanism *via* which there is a reversion to 5-(tetrahydrofuran-2-yl)pentanoic acid **18** proceeds *via* displacement of iodine to form an amine iodide salt. This salt is a good enough leaving group that it can then be displaced by the annular oxygen re-forming the bicyclic intermediate which would break down upon aqueous work-up or with trace amounts of water to regenerate the starting acid.

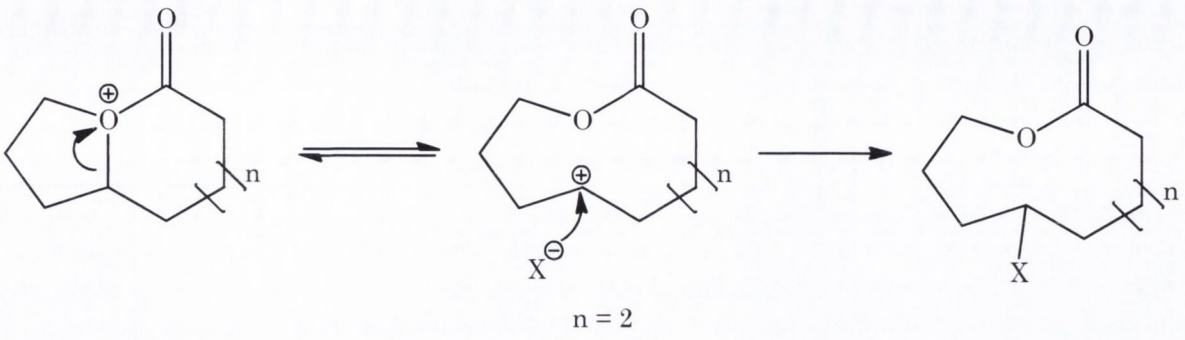
A previous set of work in the group synthesised an optically pure form of (S)-5-(tetrahydrofuran-2-yl)pentanoic acid **50** in small quantities *via* a somewhat convoluted route of using camphorsulfonyl chloride **48** to form the separable diastereomisomers of the camphorsulfonate of tetrahydrofurfuryl alcohol **49**,

and then using this as a leaving group to permit extension of the carbon chain.[142]



Scheme 2-26: Synthetic route to optically active THF-tethered acid **24**

When these optically pure acids have been subjected to the previous standard reaction conditions of refluxing TFAA in DCM the resulting lactones have not shown any optical rotation.[142] It now seems entirely possible that there is a significant degree of S_N1 character to the reaction.



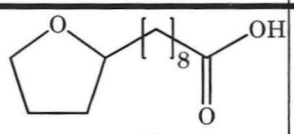
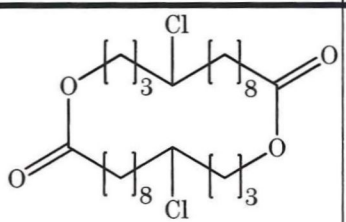
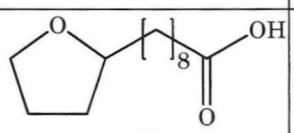
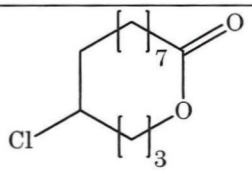
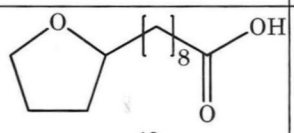
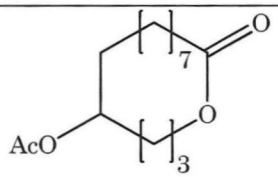
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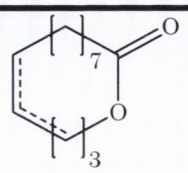
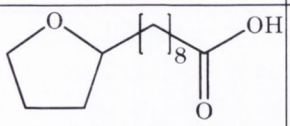
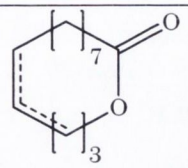
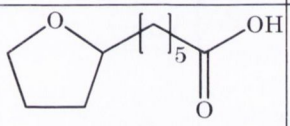
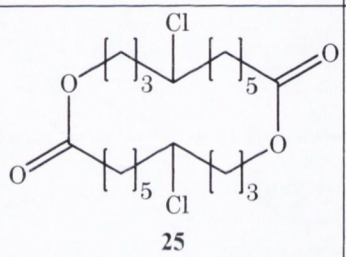
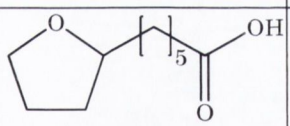
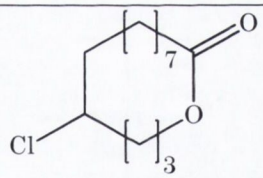
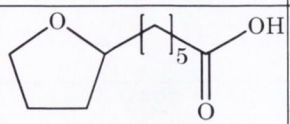
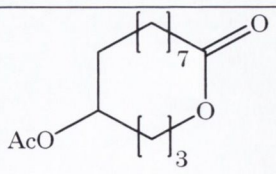
Scheme 2-27: Proposed S_N1 nature of bicyclic ring opening step in the intramolecular acylative cleavage of tetrahydrofuran

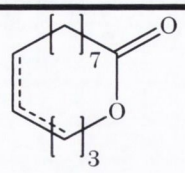
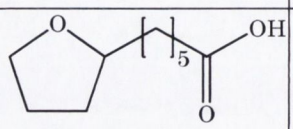
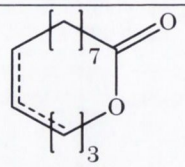
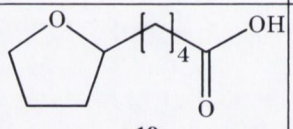
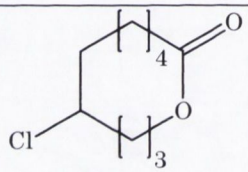
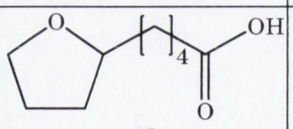
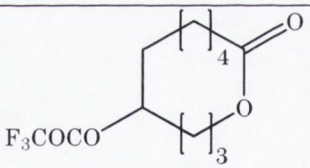
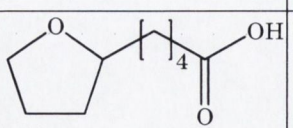
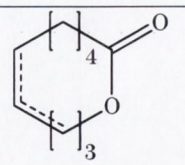
10. Future work

This Chapter has dealt with new and efficient pathways to the synthesis of medium- to large-ring macrolactones, differingly substituted δ to the annular oxygen atom. For the first time diolides have been successfully synthesised in a chemoselective fashion rather than relying on uncertain sets of reaction conditions.

Table 11: Summary of novel macrolactonisations performed *via* the acylative cleavage of THF rings

Starting material	Reaction conditions	Product	Yield	Yield of ring size using previous methodology
 **12**	TFAA, $TiCl_4$, DCM, -10 °C → -40 °C → RT	 **17**	81.5%	Not previously synthesised
 **12**	Ac_2O, $TiCl_4$, DCM, -10 °C → Reflux, 24 hours	 **14**	72%	4%
 **12**	TFAA, $ZnOAc_2$, $CHCl_3$, -10 °C → Reflux, 24 hours	 **40**	89%. 60:40 ratio of acetoxy: alkene	4%

		 **15** Mix of isomers		
 **12**	$AgBF_4$, DCM, RT, 12 hours,	 **15** Mix of isomers	91%	4%
 **19**	TFAA, $TiCl_4$, DCM, -10 °C → -40 °C → RT	 **25**	66%	Not previously synthesised
 **19**	Ac_2O, $TiCl_4$, DCM, -10 oC → Reflux, 24 hours	 **44**	93%	60%
 **19**	TFAA, $CuOAc_2$, $CHCl_3$, -10 °C → Reflux, 24 hours	 **45**	57%	60%

		 **46** Mix of isomers		
 **19**	$AgBF_4$, DCM, RT, 12 hours,	 **46** Mix of isomers	35%	60%
 **18**	TFAA, $TiCl_4$, DCM, -10 °C → -40 °C → RT	 **34**	74%	72%
 **18**	TFAA, $ZnOAc_2$, $CHCl_3$, -10 °C → Reflux, 24 hours	 **47**	40%	72%
 **18**	$AgBF_4$, DCM, RT, 12 hours,	 **46** Mix of isomers	46%	72%

As with essentially all functional group transformation reactions, there are scenarios wherein one particular methodology performs extremely well and another gives a poorer result in terms of either purity, yield, cost, scalability, or safety.

When considered in comparison with the more notable techniques currently used in the total synthesis of macrolactones such as ring closing metathesis the methodologies developed in this chapter possess several advantages; the reagents are less expensive and the yields are often comparable (typically >75%).

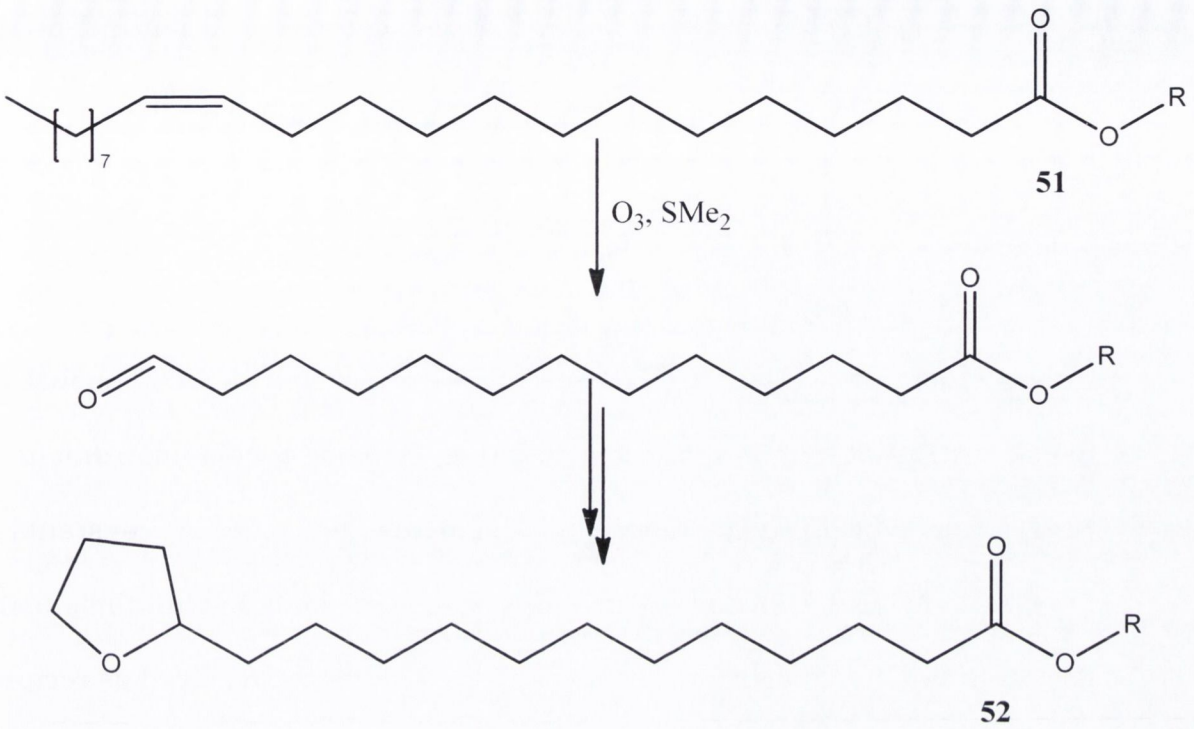
There are drawbacks when compared to RCM though; the reaction is less tolerant of other functional groups, the reagents are stoichiometric, and, depending on the exact methodology used, there may be an unwanted additional functional group on the product.

Compared to the most widely applied macrolactonisation *via* ester bond formation, the Yamaguchi reagent, the reactions developed in this chapter typically delivered similar yields and, depending on which specific methodology is used, uses less aggressive reagents. The Yamaguchi reaction does however require a simpler substrate as the starting material; an ω-hydroxycarboxylic acid rather than an ω-tetrahydrofurylcarboxylic acid.

As has been previously mentioned the newly developed reaction is capable of selectively synthesising diolides which neither of the aforementioned techniques are capable of.

Important steps have also been taken in understanding the underlying mechanism of the cyclisation reaction, with regards to its racemisation, which may play an important role in any potential synthetic applications.

A logical extension of this research would be to lengthen the linker chain within the starting ω-(2-tetrahydrofuryl)carboxylic acid and probe just how large a ring can be usefully synthesised. One potential route to an example of this would be *via* ozonolysis of an ester of erucic acid **51** followed by conversion of the derived aldehydo-ester into the novel starting material **52**.



Scheme 2-28: Proposed scheme for the synthesis of longer chain THF-tethered carboxylic acid **52**

Questions do still remain regarding the mechanism, as to whether the break-down of the bicyclic oxonium ion intermediate is a concerted or a two-step process, and whether this is dependent upon reaction conditions and, as such, whether the chirality at the δ-carbon may be preserved.

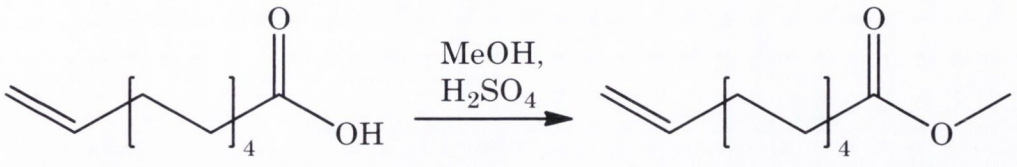
A further proposed aspect by which the dimer/monomer ratio might be controlled could be to exploit the Thorpe-Ingold effect, by placing bulky enough groups on the linker chain to compel a "kink" in the chain and force the two ends together in closer proximity. It was decided that it would be advantageous

to examine such a route in the pursuit of the synthesis of a natural product, and this of research is explored in more depth in the following Chapter.

11. Experimental

Unless otherwise stated all NMR spectra were recorded in $CDCl_3$ using on a Bruker ADVANCE-DPX-400 instrument or Agilent 400/54 instrument. All NMR chemical shifts are reported in ppm and all coupling constants are recorded in Hertz. Infrared spectroscopy was carried out on thin films using a Perkin-Elmer 100 Spectrophotometer and the results are reported as reciprocal centimetres (cm^{-1}). Mass spectra were recorded on a Micromass LCT electron spray mass spectrometer. TLCs were carried out using silica gel (60 F_{254} 0.2mm) pre-coated on aluminium sheets. Column chromatography was performed under gravity using Merck Kieselgel 60 (mesh 230-400 ASTM silica. Ozone was generated by an A2ZS-10GLAB ozone generator using an oxygen cylinder at a flow of 1L/Min. Where use of dry solvents is stated they were prepared as such; THF and diethyl ether were refluxed and subsequently distilled over sodium wire and benzophenone, DCM and chloroform were distilled over $CaCl_2$, and acetone over K_2CO_3.

Methyl undec-10-enoate 6



5 **6**

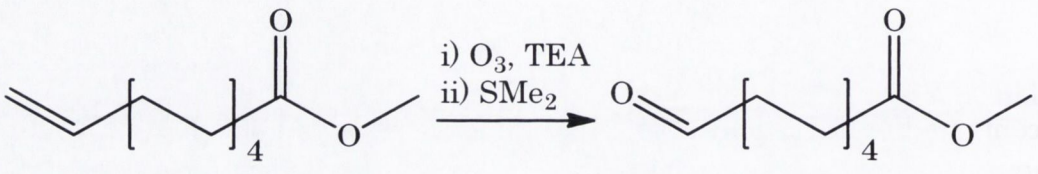
Concentrated sulfuric acid (4 ml; 73.6 mmol) was added slowly to a solution of undecylenic acid **5** (31.1 g; 0.16 mol) in methanol (300 ml) which was then heated to reflux overnight. Approximately 80% of the solvent removed at reduced pressure. The residue remaining in the flask was taken up in ethyl acetate (200 ml) and washed sequentially with water (100 ml x2), 5% aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml). This was then dried over magnesium sulfate and the solvent evaporated *in vacuo* to give methyl undec-10-enoate **6** as an orange oil (29.36 g; 87%) which was analysed and used without any further purification.[143]

υ_{max} (L) 2925 (C=C-H), 2854 (C=C-H), 1739 (C=O), 1168 (C-O), 908 (C=C-H) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.30 (8H, m, CH_2), 1.38 (2H, m, CH_2), 1.63 (2H, quintet, *J* 7.6, CH_2CH_2CO), 2.06 (2H, apparent q, *J* 7.47 $\underline{CH_2}CH=CH_2$), 2.31 (2H, t, *J* 7.9, CH_2CO), 3.68 (3H, s, CO_2Me), 4.96 (2H, m, $CH=CH_2$), 5.82 (1H, m, $CH=CH_2$, J_a = 6.9Hz, J_b = 3.5Hz) ppm.

δ_C (400 MHz; $CDCl_3$) 24.48, 28.42, 28.59, 28.66, 28.74, 28.82, 33.33, 33.64, 51.00, 113.68 ($CH=CH_2$), 138.2 ($CH=CH_2$), 173.89 (C=O) ppm.

Methyl 10-oxodecanoate 7



6 **7**

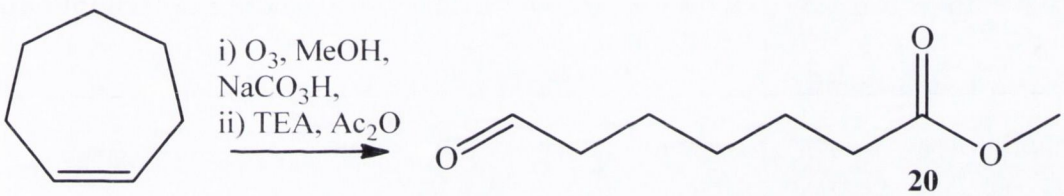
A three necked flask containing methyl undecanoate **6** (10 g; 50 mmol) in a 2:1 DCM/MeOH solvent mixture (200 ml) plus triethylamine (1 ml) was placed in a methanol cold bath at –78 °C. The flask was flushed with nitrogen for 10 minutes at which point ozone was bubbled through until a blue colour appeared (approximately 1.5 hours). The flow of ozone was then halted and the flask flushed with nitrogen until all colour was eliminated. Dimethyl sulfide (15.1 ml; 204 mmol) was then added dropwise and the solution was allowed to warm to room temperature over the course of 4 hours. Removal of the solvent *in vacuo* and subsequent column chromatography (8:2 hexane/ethyl acetate) gave the product methyl 10-oxodecanoate **7** (8.71 g; 87%) as a translucent clear liquid.[144]

υ_{max} (L) 3855 (C<u>H</u>O), 2929, 1734 (CO_2Me and CHO) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.58 (12H, m, CH_2), 2.32 (2H, t, *J* 7.59, $C\underline{H}_2CO_2Me$), 2.44 (2H, dt, *J* 7.4 and 2.4, $C\underline{H}_2CHO$), 3.69 (3H, s, OCH_3), 9.78 (1H, t, *J* 1.8 $C\underline{H}O$) ppm

δ_C (400 MHz; $CDCl_3$) 21.53, 24.40, 28.55, 28.58, 28.66, 33.57 (CH_2CO_2Me), 43.40 (CH_2CHO), 51.01 (OMe), 173.85 ($\underline{C}O_2Me$), 202.52 ($\underline{C}HO$) ppm

Methyl 7-oxoheptanoate 20



20

A 500 ml, 3 necked flask was charged with cycloheptene (7.1 g; 74.4 mmol), DCM (250 ml), methanol (50 ml), and sodium hydrogen carbonate (2 g; 24 mmol) prior to cooling to -78 °C whilst being flushed with N_2. Ozone was bubbled through the solution until a blue colour persisted, nitrogen was then passed through again until all colour had dissipated. The solution was then filtered into a 1 litre flask and the solvent removed by rotary evaporation, acetone (2 x 100 ml) was then added and removed *in vacuo.* The residual oil was taken up in DCM (225 ml) and blanketed in nitrogen whilst it was cooled to 0°C in an ice bath. Triethylamine (16.5 ml) and acetic anhydride (21.24 ml) were then added dropwise. After 15 minutes the ice bath was removed and the

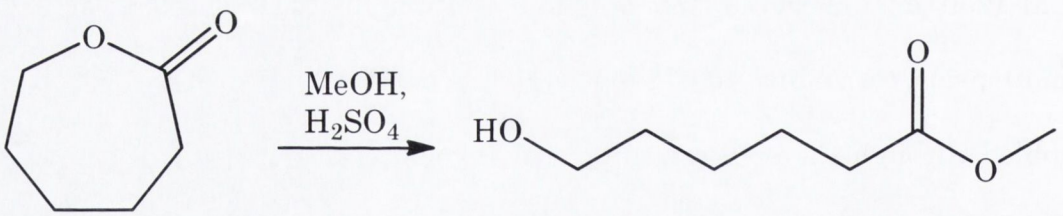
contents of the flask allowed to stir under N_2 for four hours. Distillation (76 °C 0.5 mmHg) gave the aldehyde **20** as a clear oil (7.2 g; 61%).[145]

υ_{max}, 2927, 2855, 1165, 724 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.38 (2H. quintet, *J* 7.1, C3 CH_2), 1.67 (4H, quintet, *J* 7.5, C2 &C4 CH_2), 2.34 (2H, t, *J* 7.3, CH_2CO_2Me), 2.47 (2H, dt, *J* 1.40, 7.4 C6 CH_2), 3.69 (3H, s, OMe), 9.78 (1H, t, *J* 1.45 CHO) ppm

δ_C (400 MHz; $CDCl_3$) 21.22, 24.17, 28.13, 33.33 (CH_2CO_2Me), 43.21 ($\underline{C}H_2CHO$), 51.10 (O$\underline{Me}$), 202.05 ($\underline{C}HO$) ppm, (quaternary ester carbonyl not visible due to low concentrations)

Methyl 6-hydroxyhexanoate 27



28 **27**

Sulfuric acid (2 ml; 55 mmol) was added dropwise to a solution of ε-caprolactone **28** (25.01 g; 0.219 mol) in methanol (250 ml) and the mixture was allowed to stir at room temperature for 48 hours. Approximately 80% of the solvent was then removed *in vacuo* & the solution taken up in water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts

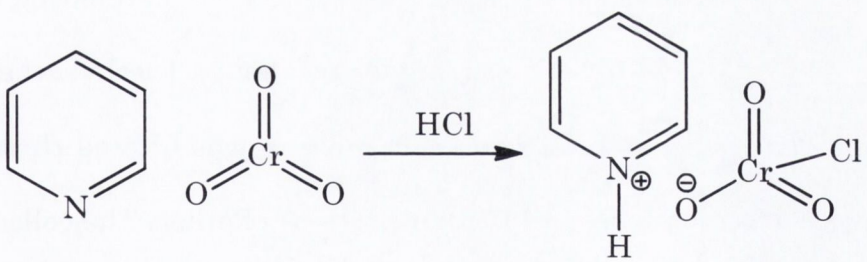
were then washed with further water and saturated Na_2CO_3 (100 ml), dried over $MgSO_4$ and the solvent removed to yield methyl 6-hydroxyhexanoate **27** as a colourless oil (27.8 g; 87%) which was analysed and used without any further purification.[146]

υmax (L) 3416, 1738, 1170 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.36 (2H, m, CH_2), 1.55 (2H, quintet, *J* 7.4, CH_2), 1.62 (2H, quintet, *J* 7.8, CH_2), 2.30 (2H, t, *J* 7.4 CH_2CO_2Me), 2.42 (1H, s, CH_2OH), 3.60 (2H, t, *J* 6.6, CH_2OH), 3.63 (3H, s, CO_2Me) ppm

δ_C (400 MHz; $CDCl_3$) 24.13 (CH_2), 24.79 (CH_2), 31.74 (CH_2), 33.49 (CH_2), 51.06 ($CO_2\underline{Me}$), 61.93 (CH_2OH), 173.83 (C=O) ppm

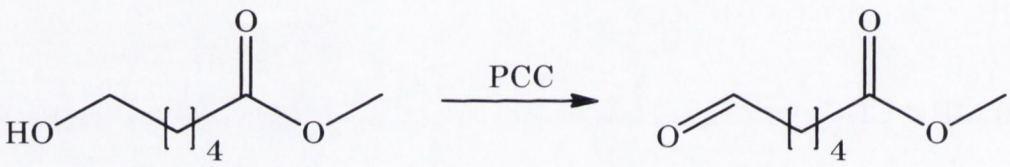
Pyridinium chlorochromate



A solution of chromium trioxide (50 g; 1 mol) in aqueous HCl (92 ml; 6 M, 0.55 mol) was cooled in an ice bath prior to slow addition of pyridine (40 ml, 0.5 mol) over 10 minutes. Upon further cooling a bright orange solid developed that was

filtered and dried to give pyridinium chlorochromate (106 g; 98%) which was used without any further purification.[147]

Methyl 6-oxohexanoate 26



27 **26**

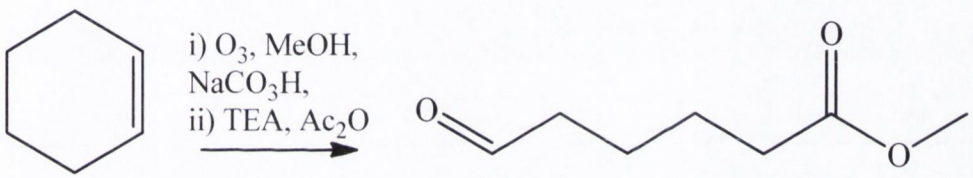
Pyridinium chlorochromate (29.4 g; 0.13 mol) suspended in DCM (136 ml) was cooled in an ice bath, to this a solution of methyl 6-hydroxyhexanoate **27** (13.02 g; 81 mmol) in DCM (30 ml) was slowly added. The ice bath was removed and the solution allowed to stand with rapid stirring for two hours. Diethyl ether (≈ 200 ml) was then added and the diluted reaction mixture was filtered through a plug of silica and washed with several further portions of ether. The collected organic fractions were concentrated *in vacuo* and the crude oil distilled to give methyl 6-oxohexanoate **26** as clear liquid (10.51 g; 81%).[148]

δ_H (400 MHz; $CDCl_3$) 1.66 (4H, quintet, *J* 3.86, C<u>H</u>$_2$), 2.34 (2H, t, *J* 7.5, CH_2), 2.47 (2H, t, *J* 5.6, CH_2), 3.67 (3H, s, OCH_3), 9.76 (1H, t, *J* 1.2, C<u>H</u>O) ppm

δ_C (400 MHz; $CDCl_3$) 21.00 (CH_2), 23.78 (CH_2), 23.86 (CH_2), 33.24 ($\underline{C}H_2CO_2$), 43.03 ($\underline{C}H_2CHO$), 51.14 (OMe), 178.16 ($\underline{C}O_2Me$), 201.74 (CHO) ppm

υmax (L) 2952, 1733, 1170 cm^{-1}

Methyl 6-oxohexanoate 26

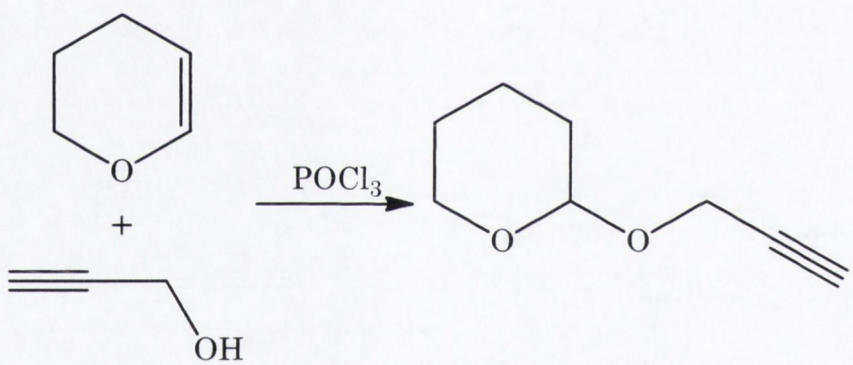


29 **26**

A 500 ml; 3 necked flask was charged with cyclohexene **29** (12.48 g; 82.1 mmol), DCM (250 ml), methanol (50 ml), and sodium hydrogen carbonate (4 g; 48 mmol) prior to cooling to -78 °C whilst being flushed with N_2. Ozone was bubbled through the solution until a blue colour persisted, nitrogen was then passed through again until all colour had dissipated. The solution was then filtered into a 1 litre flask and the solvent removed by rotary evaporation, acetone (2 x 100 ml) was then added and removed *in vacuo.* The residual oil was taken up in DCM (225 ml) and blanketed in nitrogen whilst it was cooled to 0°C in an ice bath, triethylamine (32 ml) and acetic anhydride (42.5 ml) were then added dropwise. After 15 minutes the ice bath was removed and the flask

allowed to stir under N_2 for four hours. Distillation (60 °C 0.5 mmHg) gave the aldehyde **26** as a clear oil (7.9 g; 36%).[149]

2-(prop-2-ynyloxy)tetrahydro-2H-pyran 2



A mixture of propargyl alcohol (14.04 g; 17.85 mmol) and dihydropyran (22.51 g; 26.75 mmol) in a 50 ml flask was cooled on an ice and salt bath. A catalytic amount of phosphorous oxychloride (approximately 20 mg) was then added carefully, the ice bath removed and the flask allowed to stir for 3 hours. Following dilution with diethyl ether (200 ml) the reaction mixture was then washed with brine, dried over $MgSO_4$ and the ether removed under reduced pressure to give of 2-(prop-2-ynyloxy)tetrahydro-2H-pyran **2** as a colourless oil

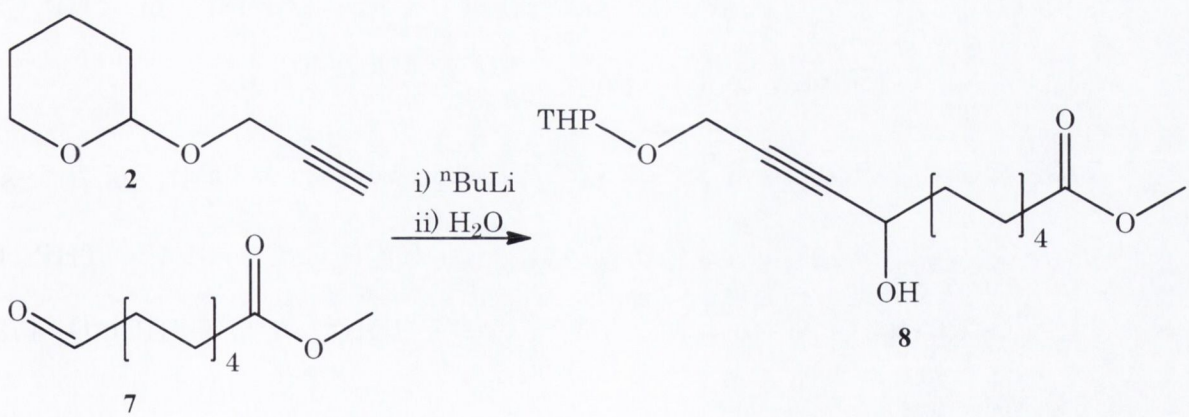
(33.62 g; 95.7%) which was analysed and used without any further purification.[150]

υ_{max} (L) 3290 (C≡C-H), 2942 (C≡C), 1118 (asymm. cyclic ether), 1024 (acyclic ether) cm^{-1}

δ_H ($CDCl_3$) 1.57 (4H, m, C<u>H</u>$_2$), 1.77 (2H, m, C<u>H</u>$_2$), 2.41 (1H, t, *J* 3, C≡C-<u>H</u>), 3.53 (1H, m, THP C<u>H</u>$_2$O), 3.82 (1H, m, THP CH_2O), 4.25 (2H, m, CC<u>H</u>$_2$O), 4.80 (1H, t, *J* 3.3, THP OC<u>H</u>) ppm

δ_C ($CDCl_3$) 18.52 (THP C3), 24.86 (CH_2), 29.74 (CH_2), 53.53 (<u>C</u>H_2C≡C), 61.53 (THP C5), 73.52 (C≡<u>C</u>H), 79.30 (<u>C</u>≡CH), 96.37 (CO_2Me) ppm

Methyl 10-hydroxy-13-(tetrahydro-2H-pyran-2-yloxy)tridec-11-ynoate 8



2-(Prop-2-ynyloxy)tetrahydro-2H-pyran **2** (6.3 g; 44.9 mmol) in dry THF (80 ml) was stirred at –78 °C whilst being flushed with nitrogen. A solution of nbutyl lithium (21.5 ml 2.5 M, 53.7 mmol) was then added dropwise and the resultant

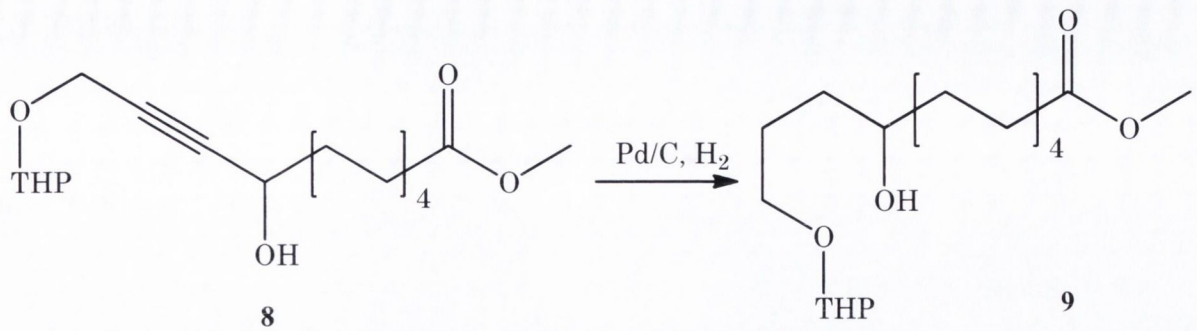
mixture allowed to stir for 10 minutes at which point a solution of methyl 10-oxodecanoate **7** (7.8 g; 38.9 mmol) in dry THF (10 ml) was added dropwise over the course of 5 minutes, the reaction vessel was then held at –78 °C for a further 15 minutes before being allowed to warm to room temperature slowly. This was then quenched over ice water, extracted with ether (3 x 100 ml), washed with brine, dried and the solvent removed *via* rotary evaporation to give methyl 10-hydroxy-13-(tetrahydro-2H-pyran-2-yloxy)tridec-11-ynoate **8** as an orange oil (13.03 g; 98%) which was analysed and used without any further purification.[123]

υ_{max} (L) 3449 (hydroxyl), 3240 (alkyne), 1736 (C=O), 1024 (cyclic ether) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.29 (10H, m, CH_2), 1.43 (2H, m, CH_2), 1.60 (6H, m, THP CH_2), 2.25 (1H, br. s, OH), 2.30 (2H, t *J* 7.54, $C\underline{H}_2CO_2Me$), 3.53 (1H, m, CH) 3.66 (3H, s, $CO_2\underline{Me}$), 3.83 (1H, m, THP C5 CH_2), 4.31 (3H, m, THP C5 & C<u>H</u>OH), 4.81 (1H, m, THP C1) ppm

δ_C (400 MHz; $CDCl_3$) 14.79, 24.44, 24.63, 24.85, 28.62, 28.67, 28.70, 28.84, 29.74, 33.61, 37.17, 51.02 (O<u>Me</u>), 53.81 (O<u>C</u>H_2C≡C), 61.49 (THP C5), 61.91(C≡C<u>C</u>HOH), 80.10 (<u>C</u>≡C), 86.75 (C≡<u>C</u>CHOH), 96.24 (THP C1), 173.90 (<u>C</u>O_2Me) ppm

Methyl 10-hydroxy-13-(tetrahydro-2H-pyran-2-yloxy)tridecanoate 9



8 **9**

A solution of methyl 10-hydroxy-13-(tetrahydro-2H-pyran-2-yloxy)tridec-11-ynoate **8** (5.2 g; 15.27 mmol) and a catalytic amount of Pd/C (100 mg) in ethanol (100 ml) was stirred under a blanket of hydrogen at atmospheric pressure. Once uptake of hydrogen had ceased the solution was washed through a plug of Celite with diethyl ether and the solvent removed to give methyl 10-hydroxy-13-(tetrahydro-2H-pyran-2-yloxy)tridecanoate **9** as a pale yellow oil (5.02 g; 91.7%) which was analysed and used without any further purification.

υ_{max} (L) 3459 (hydroxyl), 1738 (Ester), 1022 (cyclic ether) cm^{-1}

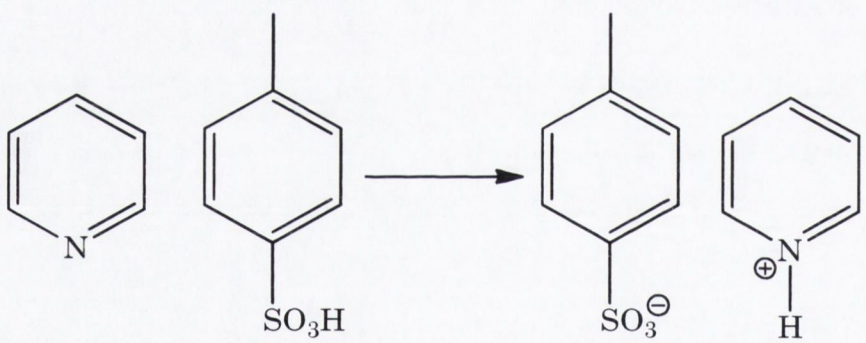
δ_H (400 MHz; $CDCl_3$) 1.27 (10H, m, CH_2), 1.42 (2H, m, CH_2), 1.57 (9H, m, CH_2), 1.70 (2H, m, CH_2), 1.81 (1H, m, CH_2), 2.28 (2H, t, *J* 6.95, CH_2CO), 3.37 (1H, m, $CH_2C\underline{H}_{2a}O$), 3.50 (1H, m, $CH_2C\underline{H}_{2b}O$), 3.60 (1H, bs, OH), 3.65 (3H, s, O<u>Me</u>), 3.72 (1H, m, $OCH_{2a}CH_2$), 3.84 (1H, m, $OCH_{2b}CH_2$), 4.56 (1H, m, OC<u>H</u>O) ppm

δ_C (400 MHz; $CDCl_3$) 19.26 (CH_2), 24.44 (CH_2), 24.90 (CH_2), 24.98 (CH_2), 25.21 (CH_2), 28.62 (CH_2), 28.70 (CH_2), 28.91 (CH_2), 29.14 (CH_2), 30.32 (CH_2), 33.60

(CH_2), 33.94 (CH_2), 37.04 ($\underline{C}H_2CHOH$), 50.99 (O$\underline{Me}$), 61.98 ($\underline{C}H_2OCH$), 62.42 (THP C5), 67.34 (CHOH), 98.24 (CHO_2), 173.94 ($\underline{C}O_2Me$) ppm

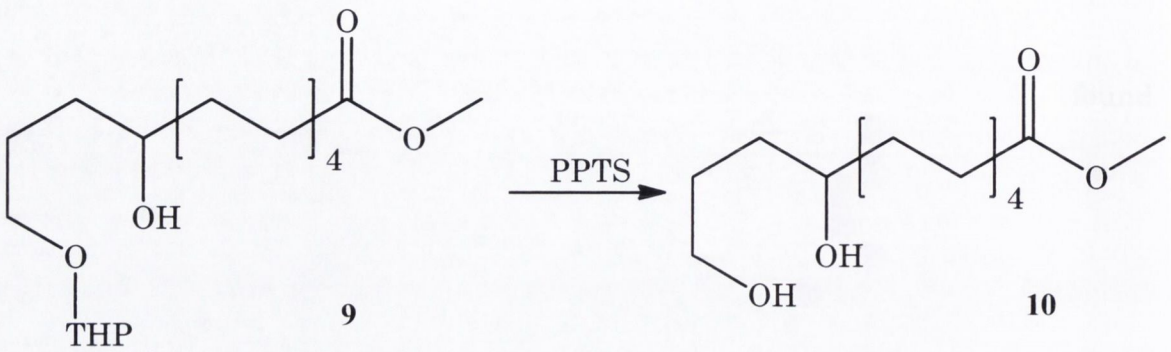
m/z; (HRMS (ES)) calculated. for $C_{19}H_{36}O_5Na$ expected 344.4861, found 344.4921 (M + Na)

Pyridinium *para*-toluene sulfonate



To a flask containing pyridine (12 ml; 150 mmol) was added a magnetic stir-bar and *para*-toluene sulfonic acid (5.7 g; 30 mmol) and the mixture allowed to stir for 20 minutes. The excess of pyridine was then removed *in vacuo* and the remaining solid recrystalised from acetone to give off-white crystals of pyridinium *para*-toluene sulfonate (6.5 g; 86%) which was used without any further purification.[151]

Methyl 10,13-dihydroxytridecanoate 10



Pyridinium *para*-toluenesulfonate (0.35 g; 1.39 mmol) was added to a solution of methyl 10-hydroxy-13-(tetrahydro-2H-pyran-2-yloxy)tridecanoate **9** (4.8789 g; 14.16 mmol) in ethanol (200 ml) and refluxed overnight. At this point approximately two thirds of the ethanol was removed *in vacuo* and the mixture taken up in ethyl acetate. This solution was washed with water and brine before being dried and the solvent removed to give a yellow oil identified as methyl 10,13-dihydroxytridecanoate **10** (2.84 g; 10.93 mmol; 77%) which was analysed and used without any further purification.

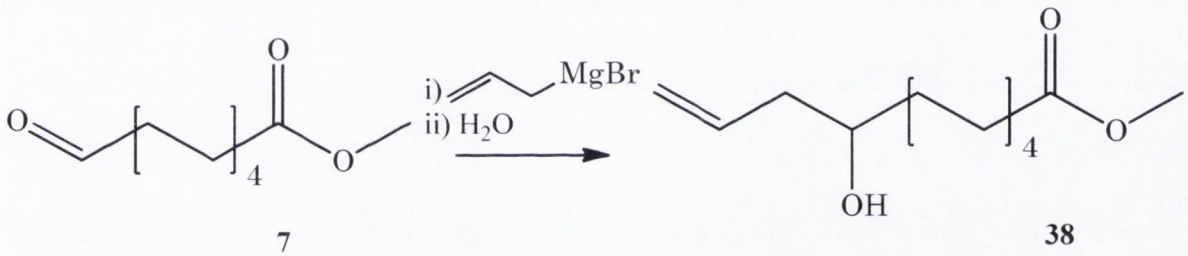
IR υ_{max}, 3356 (OH), 2926, 2854, 1738 (C=O), 1436, 1171, 1050 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.25 (10H, m, CH_2), 1.39 (3H, m, CH_2), 1.57 (5H, m, CH_2), 2.26 (2H, t, *J* 7.4, CH_2CO), 2.99 (2H, s, OH), 3.55 (2H, m, $C\underline{H}_2OH$), 3.60 (1H, m, $C\underline{H}OH$), 3.62 (3H, s, OCH_3) ppm

δ_C (400 MHz; $CDCl_3$) 24.40, 25.23, 28.47, 28.59, 28.68, 28.89, 29.11, 33.58 (CH_2CO), 33.80 ($C\underline{H}_2CHOH$), 36.91($C\underline{H}_2CHOH$), 51.01 (O$\underline{Me}$), 62.05 ($\underline{C}H_2OH$), 71.03 ($\underline{C}HOH$), 174.01 ($\underline{C}O_2OMe$) ppm

m/z; (HRMS (ESI)) calculated for $C_{14}H_{28}O_4Na$ expected 283.3595, found 283.3595 (M + Na)

Methyl 10-hydroxytridec-12-enoate 38



7 **38**

Methyl 10-oxoundecanoate **7** (0.28 g; 1.4 mmol) was taken into sodium dried diethyl ether and the flask placed under nitrogen and cooled with an ice bath. A solution of allylmagnesium bromide (2.6 ml; 0.6 Mol; 1.5 mmol) was slowly added to this flask before being allowed to warm overnight. The reaction mixture was quenched over ice water and extracted with diethyl ether (3 x 100 ml). The collected organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* prior to column chromatography (9:1 DCM/EtOAc) revealing methyl 10-hydroxytridec-12-enoate **38** (0.16 g; 48%) and 4-allylhexadeca-1,15-diene-4,13-diol (8.7 mg; 2%).

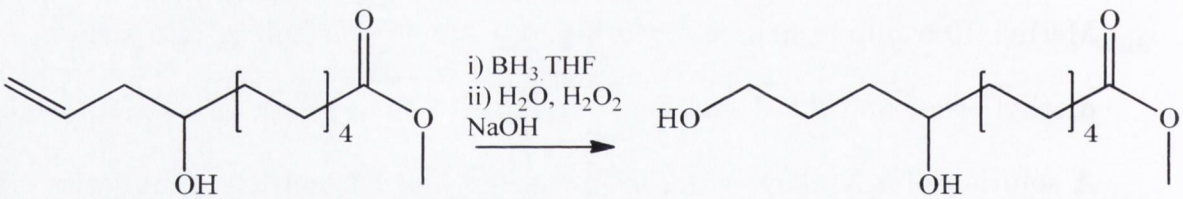
IR υ_{max}, 3400 (C=C), 1735 (C=O) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.26 (12H, m, CH_2) 1.44 (2H, m, $C\underline{H}_2CHOH$) 1.57 (2H, m, $C\underline{H}_2CHOH$) 1.92 (1H, bs, O<u>H</u>), 2.27 (3H, t *J* 7.2, CH_2CO), 3.62 (1H, m C<u>H</u>OH), 3.64 (3H, s, OMe), 5.12 (2H, d *J* 12.7, $C\underline{H}_2$=CH), 5.81 (1H, m, CH_2=C<u>H</u>) ppm

δ_C (400 MHz; $CDCl_3$) 24.90, 25.59, 29.07, 29.13, 29.33, 29.52, 34.06, 36.76 ($\underline{C}H_2CO$), 41.92 ($\underline{C}H_2CHOH$), 51.41 (OMe), 70.62 (<u>C</u>HOH), 118.02 ($\underline{C}H_2$=CH), 134.85 (CH_2=<u>C</u>H), 174.27 (C=O) ppm

m/z; (HRMS (ES)) calculated for $C_{19}H_{34}O_2Na$ expected 317.2457, found 317.2464 (M + Na)

Methyl 10,13-dihydroxytridecanoate 10



38 **10**

Methyl 10-hydroxytridec-12-enoate **38** (0.2074 g; 0.85 mmol) was taken into THF (20 ml) and transferred to a flask equipped with a bubbler base, a gas outlet with bubbler and a gas inlet leading from a 3 necked RBF charged with sodium borohydride (0.1 g; 2.6 mmol), diglyme (10 ml), a magnetic stirring bar and a gas inlet. The entire system was flushed with nitrogen for 10 minutes.

Boron trifluoride diethyl etherate (0.3 ml; 5 mmol) was added dropwise *via* syringe to the three necked flask and the resultant BH_3 bubbled through the THF solution using nitrogen as a courier gas. This was continued for 90 minutes prior to gentle heating of the glyme solution.

After standing for 90 minutes aqueous sodium hydroxide (5 ml; 3 Mol) and hydrogen peroxide (35% solution, 5 ml) were add dropwise to the THF solution and the flask was allowed to stand overnight. The mixture was diluted with water, extracted with diethyl ether (2 x 100 ml) and the combined organic extracts dried over $MgSO_4$ and concentrated to give methyl 10,13-dihydroxytridecanoate as a colourless oil **10** (0.171 g; 77%) which was analysed and used without any further purification.

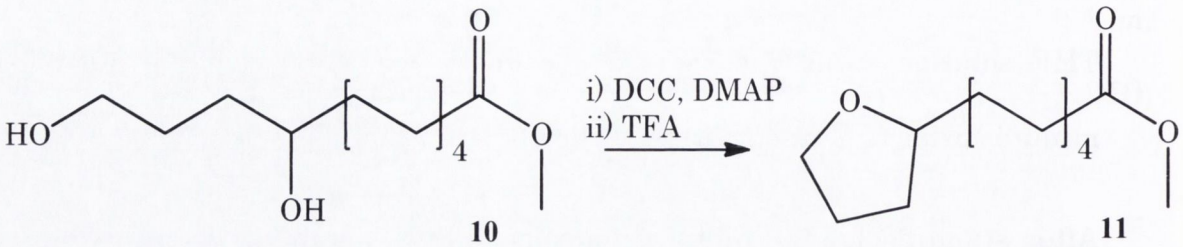
IR υ_{max}, 3352 (OH), 2924, 2852, 1738 (C=O), 1432, 1171, 1051 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.25 (10H, m, CH_2), 1.39 (3H, m, CH_2), 1.57 (5H, m, CH_2), 2.26 (2H, t, *J* 7.5, CH_2CO), 2.99 (2H, s, OH), 3.55 (2H, m, CH_2OH), 3.60 (1H, m, CHOH), 3.62 (3H, s, OCH_3) ppm

δ_C (400 MHz; $CDCl_3$) 24.40, 25.23, 28.47, 28.59, 28.68, 28.89, 29.11, 33.58 ($\underline{C}H_2CO$), 33.80 ($\underline{C}H_2CHOH$), 36.91($\underline{C}H_2CHOH$), 51.01 (OMe), 62.05 (CH_2OH), 71.03 (CHOH), 174.01 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated for $C_{14}H_{28}O_4Na$ expected 283.3595, found 283.3587 (M + Na)

Methyl 9-(tetrahydrofuran-2-yl)nonanoate 11



A solution of methyl 10,13-dihydroxytridecanoate **10** (5.214 g. 21.1 mmol) in dry chloroform (60 ml) was prepared in a 250 ml round bottomed flask, to this was added dicyclohexylcarbodiimide (6.4 g; 31 mmol) and a catalytic amount of copper (I) chloride (≈ 400 mg). The flask was then blanketed with nitrogen and stirred overnight at room temperature. A solution of trifluoroacetic acid (5.2 ml; 0.5 mol; 0.13 molar eq.) in dry $CHCl_3$ was then added and the flask heated to 40 °C for 6 hours. Hexane (10 ml) was then added to precipitate the urea waste and the solution filtered prior to removal of the solvent. The resulting oil was then chromatographed on silica using 5:1 hexane/ethyl acetate giving methyl 9-(tetrahydrofuran-2-yl)nonanoate **11** as a yellow oil (2.91 g; 60.4%).

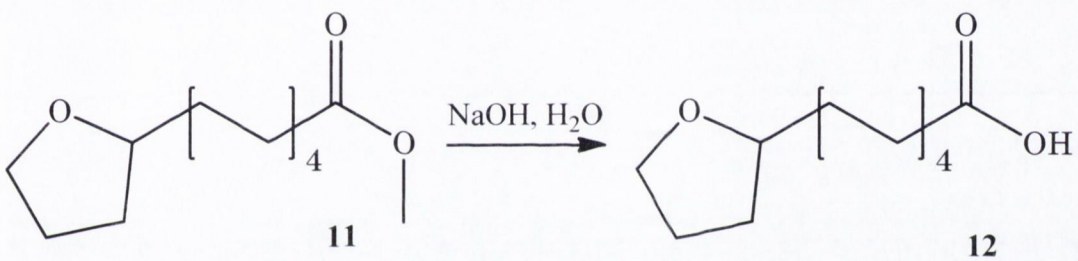
υ_{max} (L) 2928, 2854, 1739 (C=O), 1045 (THF, asymm.) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.24 (10H, m, CH_2), 1.37 (2H, m, CH_2), 1.56 (4H, m CH_2), 1.82 (2H, m, CH_2), 2.25 (2H, t, *J* 7.48, CH_2CO), 3.61 (3H, s, OMe), 3.66 (1H, dd, *J* 7.5 and 6.5, $CH_{2a}O$), 3.72 (1H, apparent quintet, *J* 6.8, CHO), 3.79 (1H, dd, *J* 6.8 and 14, $CH_{2b}O$) ppm

δ_C (400 MHz; $CDCl_3$) 24.40 (CH_2), 25.19 (CH_2), 28.59 (CH_2), 28.66 (CH_2), 28.87 (CH_2), 29.13 (CH_2), 30.87 (CH_2), 33.54 ($\underline{C}H_2CHO$), 35.20 ($\underline{C}H_2CO_2$), 50.89 (O$\underline{Me}$), 67.05 ($\underline{C}H_2O$), 78.89 ($\underline{C}HO$), 173.75 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated for $C_{14}H_{26}O_3Na$, expected 265.1780, found 265.1791 (M + Na)

9-(Tetrahydrofuran-2-yl)nonanoic acid 12



11 **12**

Methyl 9-(tetrahydrofuran-2-yl)nonanoate **11** (0.1998 g; 0.82 mmol) was dissolved in a mixture of ethanol (41 ml) and an aqueous solution of 10% w/w NaOH (0.49 ml) and then refluxed for 3 hours. The cooled solution was then diluted with water (40 ml) & washed with ether (40 ml), the aqueous layer was acidified with dil. HCl and extracted with ether (3 x 10 ml). The organic layer was then dried with $MgSO_4$ and the solvent removed to give the acid 9-(tetrahydrofuran-2-yl)nonanoic acid **12** as a waxy orange solid (0.1557 g; 82%) which was analysed and used without any further purification.

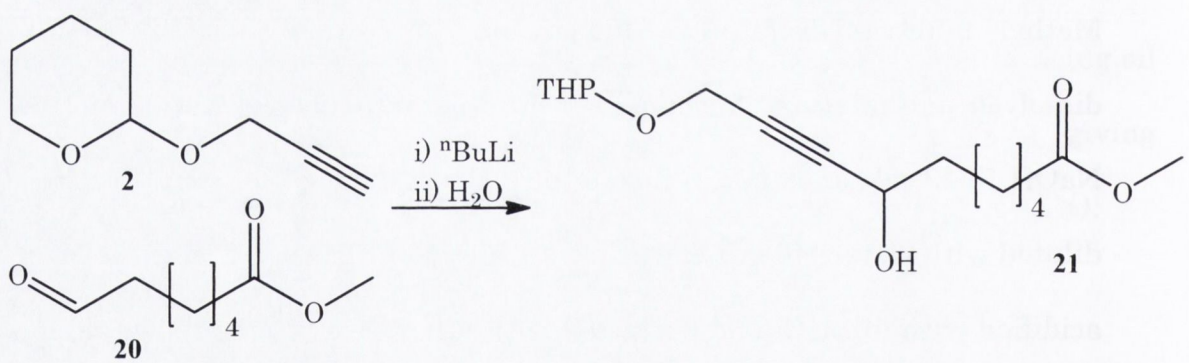
υ_{max} (L) 2926, 2854, 2619 (br, acid OH), 1706, 1180, 720 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.28 (10H, m, CH_2), 1.41 (3H, m, CH_2), 1.56 (3H, m, CH_2), 1.87 (2H, m, CH_2), 2.31 (2H, t *J* 7.3, CH_2CO), 3.71 (1H, q *J* 7.6, $C\underline{H}_{2a}O$), 3.79 (1H, quintet, *J* 6.8, CHO), 3.84 (1H, q *J* 7.2, $C\underline{H}_{2b}O$), 8.28 (1H, s broad, $CO_2\underline{H}$) ppm

δ_C (400 MHz; $CDCl_3$) 24.23 (CH_2), 25.18 (CH_2), 25.80 (CH_2), 28.56 (CH_2), 28.68 (CH_2), 28.87 (CH_2), 29.14 (CH_2), 30.85 (CH_2), 33.60 (CH_2CHO), 35.10 ($\underline{C}H_2CO_2$), 67.04 (CH_2O), 79.07 (CHO), 178.79 ($\underline{C}O_2H$) ppm

m/z; (HRMS (ES)) calculated for $C_{13}H_{24}O_3$ expected 228.1725, found 251.3182 (M+Na)

Methyl 7-hydroxy-10-(tetrahydro-2H-pyran-2-yloxy)dec-8-ynoate 21



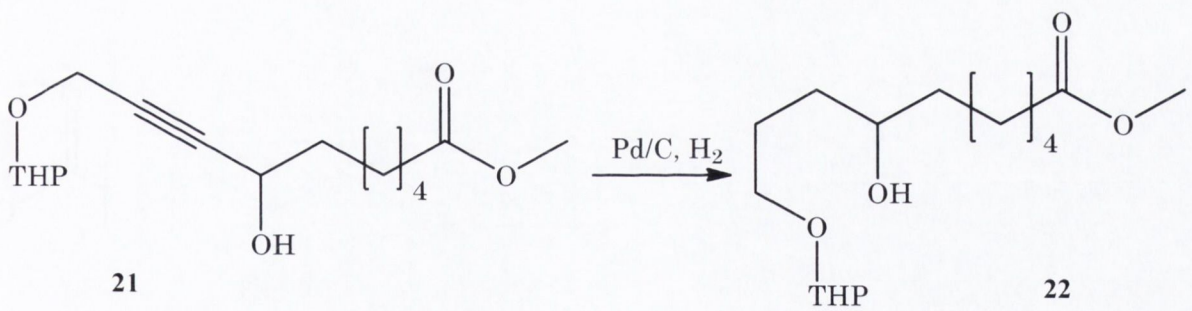
This reaction was carried out in the same way as for the synthesis of **8** above. Methyl 7-oxoheptanoate **20** (3.59 g; 22.7 mmol) produced methyl 7-hydroxy-10-(tetrahydro-2H-pyran-2-yloxy)dec-8-ynoate **21** (5.9 g; 87%) as a pale yellow oil which was analysed and used without any further purification.[123]

δ_H (400 MHz; $CDCl_3$) 1.38 (6H, m, CH_2), 1.56 (12H, m, CH_2), 1.75 (4H, m, CH_2), 1.83 (2H, m, CH_2), 2.33 (2H, t *J* 6.76, CH_2CO_2), 3.54 (2H, m, CH_2) 3.68 (3H, s, OMe), 3.85 (2H, m, $C{\equiv}CCH_2O$), 4.42 (3H, m, CH_2O & $CH_{2a}O$), 4.44 (1H, m, $CH_{2b}O$), 4.82 (1H, m, CHO_2) ppm

δ_C (400 MHz; $CDCl_3$) 24.42 (CH_2), 25.23 (CH_2), 25.58 (CH_2), 28.74 (CH_2), 30.90 (CH_2), 33.53 (CH_2), 35.04 ($\underline{C}H_2CO_2$), 50.98 (OMe), 67.13 (OCH_2), 78.79 (OCH), 173.77 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated for $C_{16}H_{26}O_6$ expected 228.1725, found 251.3182 (M+Na)

Methyl 7-hydroxy-10-(tetrahydro-2H-pyran-2-yloxy)decanoate 22



21 **22**

Run as per synthesis of **9**, solvent changed to methanol. Methyl 7-hydroxy-10-(tetrahydro-2H-pyran-2-yloxy)dec-8-ynoate **21** (255.7 mg; 0.86 mmol) produced methyl 7-hydroxy-10-((tetrahydro-2H-pyran-2-yl)oxy)decanoate **22** (0.185 g; 71%) as a yellow oil which was analysed and used without any further purification.

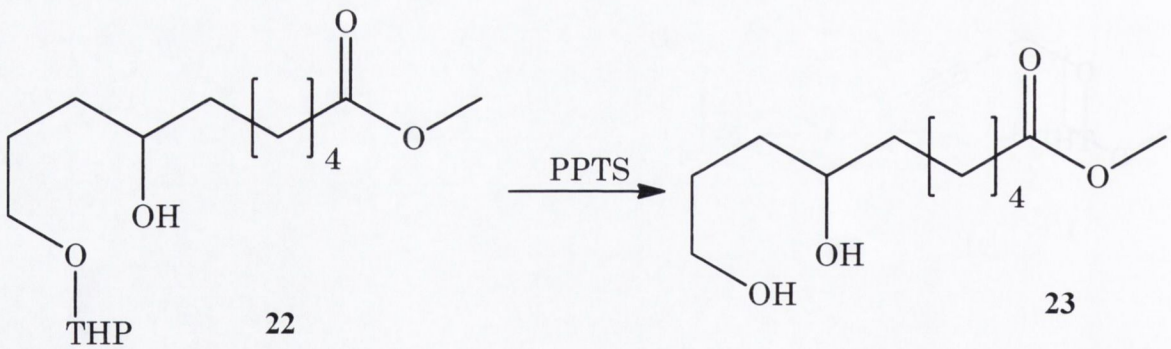
υ_{max} (L) 3456 (OH), 2933, 1736 (C=O), 1022 (cyclic ether) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.35-1.55 (20H, m, CH_2), 1.71 (2H, m, CH_2), 1.83 (2H, m, CH_2), 2.32 (2H, t *J* 7.53, CH_2), 3.41 (1H, m, $CH_{2a}CHO_2$), 3.43 (1H, m, $CH_{2b}CHO_2$), 3.64 (1H, bs, OH), 3.67 (3H, s, OMe), 3.72 (1H, m, $CH_{2a}O$), 3.86 (1H, m, $CH_{2a}O$), 4.60 (1H, m, CHO_2) ppm

δC (400 MHz; CDCl3) 22.87, 24.42, 24.92, 25.02, 28.72, 30.21, 33.55 (CH_2CO_2), 51.01 (OMe), 61.85 (CHOH), 67.32 (CH_2O), 98.42 (CHO_2), 173.64 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated. for $C_{16}H_{30}O_5$ expected 302.4064, found 325.3890 (M + Na)

Methyl 7,10-dihydroxydecanoate 23



Run as per synthesis of **10**. Methyl 7-hydroxy-10-((tetrahydro-2H-pyran-2-yl)oxy)decanoate **22** (3.329 g; 11 mmol) produced methyl 7,10-dihydroxydecanoate **23** (2.16 g; 90%) as an orange oil which was analysed and used without any further purification.

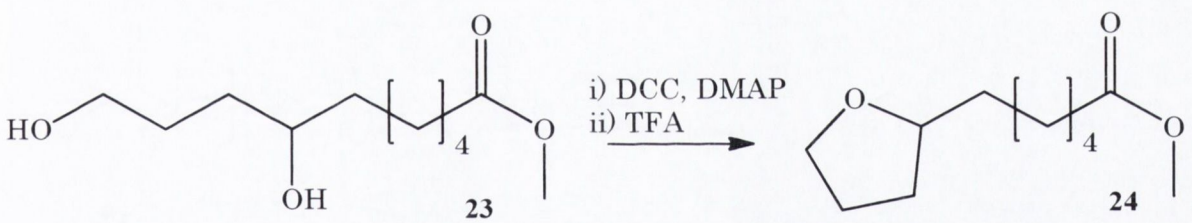
υ_{max} (L) 3379 (OH), 2931, 1709 (C=O), 1172 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.31-1.48 (12H, m, CH_2), 1.63 (6H, m, CH_2), 2.31 (2H, t *J* 6.4, CH_2CO_2), 2.56 (2H, bs, OH), 3.68 (3H, s, OMe) ppm

δ_C (400 MHz; CDCl3) 22.82 (CH_2), 24.90 (CH_2), 25.24 (CH_2), 28.64 ($2CH_2$), 33.52 (CH_2), 33.99 ($\underline{C}H_2CO_2$), 51.07 (OMe), 59.97 (CHOH), 63.74 (CH_2OH), 171.18 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated for $C_{11}H_{22}O_4$ expected 218.2900, found 241.2890 (M + Na)

Methyl 6-(tetrahydrofuran-2-yl)hexanoate 24



Run as per synthesis of **11**. Methyl 7,10-dihydroxydecanoate **23** (5.9472 g; 27.2 mmol) produced methyl 6-(tetrahydrofuran-2-yl)hexanoate **23** (3.285 g; 60%) as an orange oil which was analysed and used without any further purification.

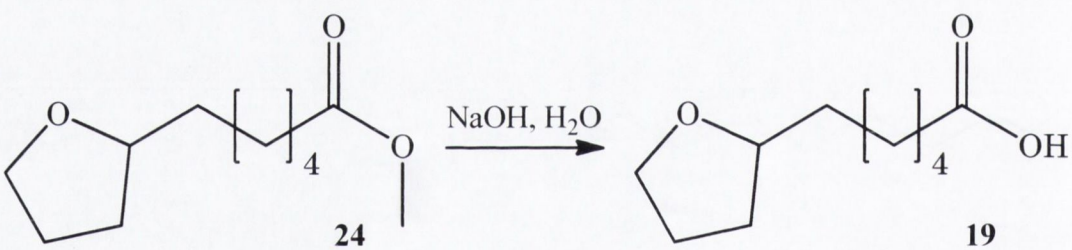
υ_{max} (L) 2911, 2824, 1741 (C=O), 1052 (THF, asymm.) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.28 (15H, m, CH_2), 1.60 (4H, m, CH_2), 1.84 (2H, m, CH_2), 1.94 (1H, m, CH_2), 2.29 (2H, t *J* 7.74, CH_2CO_2), 3.65 (3H, s, OMe), 3.69 (1H, q J 7.31, $CH_{2a}O$), 3.75 (1H, quintet *J* 5.3, CHO), 3.82 (1H, q *J* 7.19, $CH_{2b}O$) ppm

δ_C (400 MHz; $CDCl_3$) 24.42 (CH_2), 25.30 (CH_2), 25.58 (CH_2), 28.74 (CH_2), 30.90 (CH_2), 33.52 ($\underline{C}H_2CHO$), 35.04 ($\underline{C}H_2CO_2$), 50.98 (OMe), 67.13 (CH_2O), 78.79 (OCH), 173.77 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated for $C_{11}H_{20}O_3$, expected 200.1412, found 223.1299 (M + Na)

6-(Tetrahydrofuran-2-yl)hexanoic acid 19



24 **19**

Run as per synthesis of **12**. Methyl 6-(tetrahydrofuran-2-yl)hexanoate **24** (1.397 g; 7 mmol) produced 6-(tetrahydrofuran-2-yl)hexanoic acid **19** (0.7554 g; 58%) as a waxy orange solid which was analysed and used without any further purification.

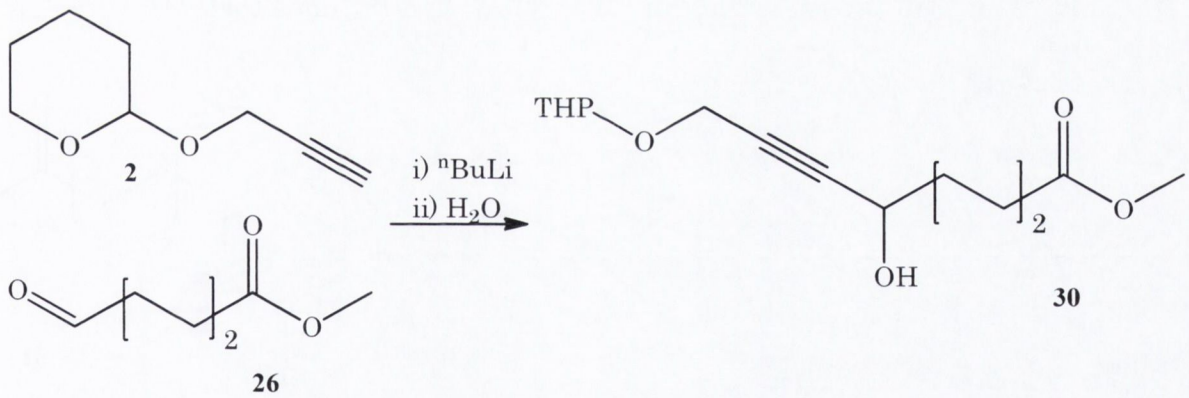
υ_{max} (L) 3412 (CO_2H), 2933, 1733 (C=O), 1171 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.45 (7H, m, CH_2), 1.67 (4H, m, CH_2), 1.90 (2H, m, CH_2), 1.98 (1H, m, CH_2), 2.37 (2H, t J 7.6, CH_2CO_2), 3.75 (1H, q J 7.98, $CH_{2a}O$), 3.81 (1H, quintet J 5.86, CHO), 3.87 (1H, q J 6.94, $CH_{2b}O$) ppm

δ_C (400 MHz; $CDCl_3$) 24.66 (CH_2), 25.70 (CH_2), 26.02 (CH_2), 29.13 (CH_2), 31.38 (CH_2), 33.92 (CH_2), 35.46 (CH_2CO_2), 67.62 (CH_2O), 79.34 (CHO), 179.27 (CO_2H) ppm

m/z; (HRMS (ESI)) calculated for $C_{10}H_{18}O_3$ expected 186.1256, found 185.1175 (M - H)

Methyl 6-hydroxy-9-((tetrahydro-2H-pyran-2-yl)oxy)non-7-ynoate 30



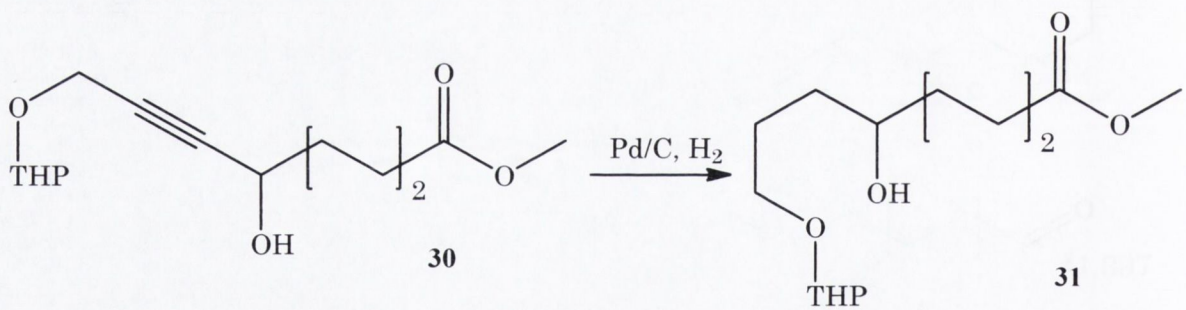
Run as per synthesis of **8**. Methyl 6-oxohexanoate **26** (7.9 g; 54 mmol) produced methyl 6-hydroxy-9-((tetrahydro-2H-pyran-2-yl)oxy)non-7-ynoate **30** (12.5 g; 80%) as an orange oil which was analysed and used without any further purification.[123]

υ_{max} (L) 3431 (OH), 3265 (alkyne), 2942, 2867, 1735 (C=O), 1021 (cyclic ether) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.54-1.78 (m, 16H), 2.33 (2H, t *J* 6.9, CH_2CO_2), 2.42 (1H, bs, OH), 3.54 (1H, m, $C\underline{H}_{2a}OCH$), 3.66 (3H, s, OMe), 3.83 (1H, m, $C\underline{H}_{2b}OCH$), 4.40 (3H, m, $C\underline{H}_2C{\equiv}C$ & $C{\equiv}CC\underline{H}$), 4.80 (1H, m, $C\underline{H}O_2$) ppm

δ_C (400 MHz; $CDCl_3$) 24.07 (CH_2), 24.23 (CH_2), 24.84 (CH_2), 25.13 (CH_2), 29.72 (CH_2CHO_2), 33.46 $CHOHC\underline{H}_2$), 36.74 (CH_2CO), 51.08 (OMe), 53.52, ($\underline{C}H_2C{\equiv}C$), 53.78 ($\underline{C}HOH$), 61.50 ($CH_2\underline{C}H_2O$), 67.49 ($\underline{C}{\equiv}CCHOH$), 73.58 ($C{\equiv}\underline{C}CHOH$), 96.28 (OCHO), 173.62 ($\underline{C}O_2Me$) ppm

Methyl 6-hydroxy-9-((tetrahydro-2H-pyran-2-yl)oxy)nonanoate 31



Run as per synthesis of **9**. Methyl 6-hydroxy-9-((tetrahydro-2H-pyran-2-yl)oxy)non-7-ynoate **30** (12.5 g; 44 mmol) produced methyl 6-hydroxy-9-((tetrahydro-2H-pyran-2-yl)oxy)nonanoate **31** (9.6 g; 76%) as an orange oil which was analysed and used without any further purification.

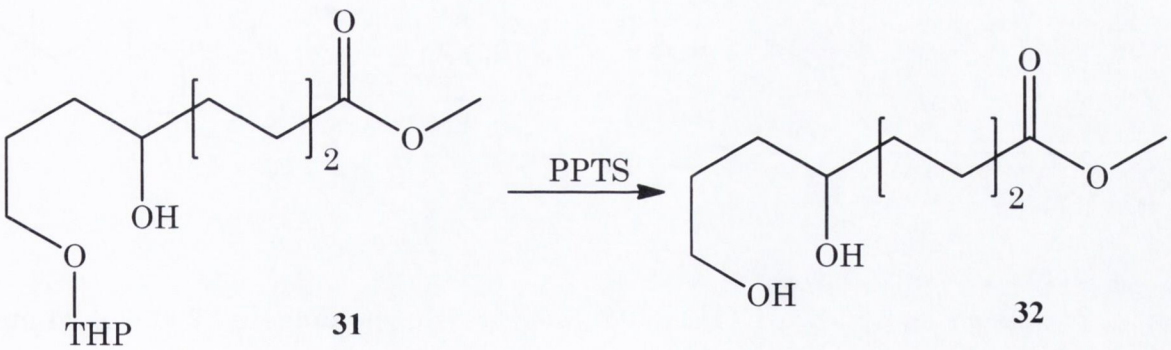
υ_{max} (L) 3473 (OH), 2938, 2866, 1735 (C=O), 1021 (cyclic ether) cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.65 (19H, m, CH_2), 1.83 (2H, m, CH_2), 2.34 (2H, t, *J* 6.99, CH_2CO_2), 3.45 (1H, m, CH_{2a},CHO), 3.53 (1H m, CH_{2b},CHO), 3.66 (1H, bs, OH), 3.68 (3H, s, OMe), 3.87 (2H, m, CH_2O), 4.61 (1H, m, CHO_2) ppm

δ_C (400 MHz; $CDCl_3$) – 19.09, 19.25, 24.48, 24.92, 25.55, 30.14, 33.58, 34.52, 36.57 (CH_2CO), 51.06 (OMe), 61.97 (CHOH), 67.40 (CH_2O), 70.94 (CH_2O), 98.44 (CHO_2), 173.75 (C=O) ppm.

m/z; (HRMS (ES)) calculated for $C_{15}H_{28}O_5$ expected 288.3798, found 311.3720 (M + Na)

Methyl 6,9-dihydroxynonanoate 32



Run as per synthesis of **10**. Methyl 6-hydroxy-9-((tetrahydro-2H-pyran-2-yl)oxy)nonanoate **31** (9.6 g; 33 mmol) produced methyl 6,9-dihydroxynonanoate **32** (4.9 g; 72%) as a yellow oil which was analysed and used without any further purification.

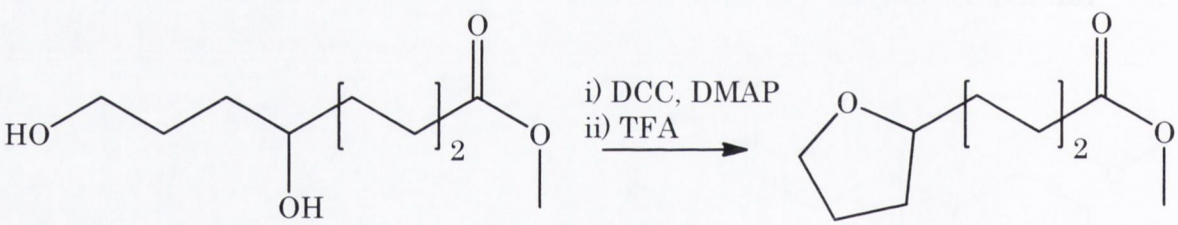
υ_{max} (L) 3443 (OH), 2934, 2862, 1733 (C=O), cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.25-1.66 (12H, m, CH_2), 2.33 (2H, t *J* 7.06, CH_2CO_2), 2.55 (1H, bs, OH), 3.66 (1H, bs, OH), 3.68 (3H, s, OMe) ppm

δ_C (400 MHz; $CDCl_3$) – 23.92 (CH_2), 24.08 (CH_2), 24.32 (CH_2), 25.05 (CH_2), 27.84 (CH_2), 28.72 (CH_2), 33.43 (CH_2CO_2), 51.09 (OMe), 62.51 (CHOH), 63.71 (CH_2OH), 174.30 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ES)) calculated for $C_{10}H_{20}O_4$ expected 204.2634, found 227.2645 (M + Na)

Methyl 5-(tetrahydrofuran-2-yl)pentanoate 33



32 **33**

Run as per synthesis of **11**. Methyl 6,9-dihydroxynonanoate **32** (4.9 g; 24 mmol) produced methyl 5-(tetrahydrofuran-2-yl)pentanoate **33** (1.7 g; 40%) as an orange oil.

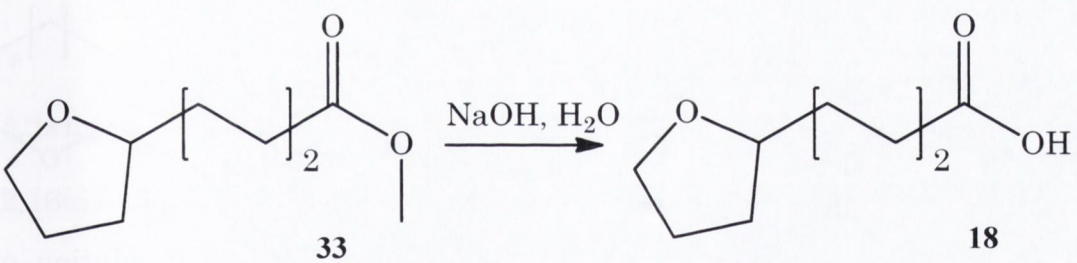
υ_{max} (L) 2921, 2823, 1741 (C=O), 1053 (THF, asymm.) cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.46 (4H, m, CH_2), 1.67 (5H, m, CH_2), 1.88 (2H, m, CH_2), 1.96 (1H, m, CH_2), 2.34 (2H, t *J* 7.6, $C\underline{H}_2CO_2$), 3.68 (3H, s, OMe), 3.73 (1H, q *J* 7.32, $CH_{2a}O$), 3.80 (1H, quintet *J* 6.3, CHO), 3.86 (1H, q *J* 7.11, $CH_{2b}O$) ppm

δ_C (400 MHz; $CDCl_3$) – 24.54 (CH_2), 24.56 (CH_2), 25.50 (CH_2), 30.90 (CH_2), 33.57 (CH_2), 34.85 ($\underline{C}H_2CO_2$), 51.03 (O$\underline{Me}$), 67.16 (CHO$\underline{C}H_2$), 78.67 ($\underline{C}$HOCH$_2$), 173.73 ($\underline{C}O_2Me$) ppm

m/z; (HRMS (ESI)) calculated for $C_{10}H_{18}O_3$ expected 186.1256, found 209.1147 (M + Na)

5-(Tetrahydrofuran-2-yl)pentanoic acid 18



33 **18**

Run as per synthesis of **12**. Methyl 5-(tetrahydrofuran-2-yl)pentanoate **33** (0.28 g; 1.3 mmol) produced 5-(tetrahydrofuran-2-yl)pentanoic acid **18** (0.15 g; 58%) as an orange oil which was analysed and used without any further purification.

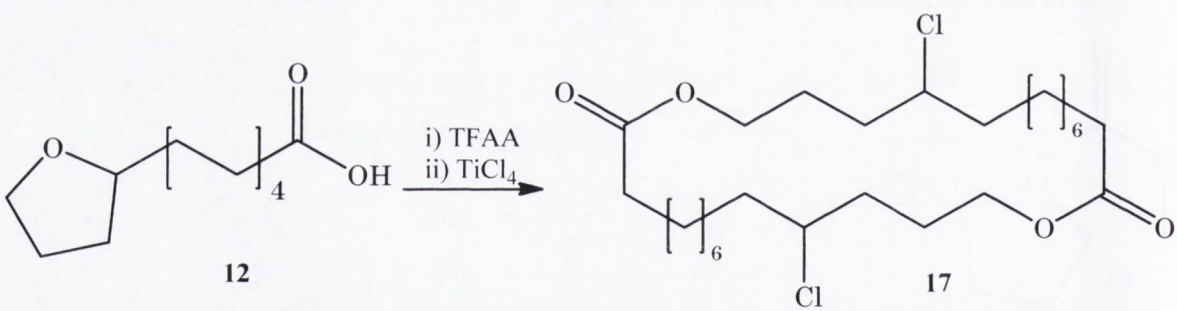
υ_{max} (L) 2934, 2858, 2640 (br, acid OH), 1707 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.48 (4H, m, CH_2), 1.67 (3H, m, CH_2), 1.90 (2H, m, CH_2), 1.98 (1H, m, CH_2), 2.37 (2H, t *J* 7.25, CH_2CO_2), 3.74 (1H, q *J* 7.3, $CH_{2a}O$), 3.83 (1H, quintet *J* 6.12, CHO), 3.88 (1H, q *J* 7.55, $CH_{2b}O$), 8.73 (1H, b, $CO_2\underline{H}$) ppm

δ_C (400 MHz; $CDCl_3$) 24.27 (CH_2), 25.21 (CH_2), 25.38 (CH_2), 30.90 (CH_2), 33.54 (CH_2), 34.77 ($\underline{C}H_2CO_2H$), 67.15 ($CHO\underline{C}H_2$), 78.72 ($\underline{C}HOCH_2$), 179.01 ($\underline{C}O_2H$) ppm

m/z; (HRMS (ESI^+)) calculated for $C_9H_{17}O_3$, expected 173.1178, found 173.1174 (M + H)

11,25-dichloro-1,15-dioxacyclooctacosane-2,16-dione 17



12 **17**

Trifluoroacetic anhydride (90 µl; 1.1 mmol) was added to a solution of 9-(tetrahydrofuran-2-yl)nonanoic acid **12** (0.1486 g; 0.65 mmol) in dry DCM (6.19 ml) under nitrogen at 0 °C, after being stirred for 30 minutes the flask was then cooled to –10 °C and titanium tetrachloride (90 µl; 0.8 mmol) was added dropwise and the flask allowed to warm to room temperature over the course of 2 hours. After quenching over ice/water the mixture was extracted with ether (3 x 20 ml) and then washed sequentially with water, 5% w/w Na_2CO_3 and

brine, dried with $MgSO_4$ and the solvent evaporated to give 11,25-dichloro-1,15-dioxacyclooctacosane-2,16-dione **17** as a yellowy orange solid (0.114 g; 81.5%) which was not subjected to further purification.

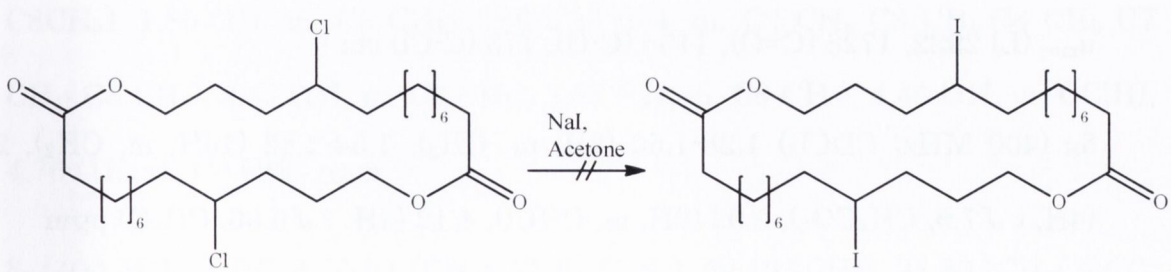
υ_{max} (L) 2927, 2855, 1732 (C=O), 1165, 724 (C-Cl) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.30 (12H, m, CH_2), 1.51 (1H, m), 1.63 (4H, m, CH_2), 1.72 (4H, m, CH_2), 1.91 (1H, m, CH_2), 2.30 (2H, t *J* 7.46, $C\underline{H}_2CO$), 3.90 (1H, q *J* 7.4, $C\underline{H}Cl$), 4.09 (2H, t *J* 5.57, CH_2O) ppm

δ_C (400 MHz; $CDCl_3$) 24.47, 25.34, 26.00, 28.61, 28.64, 28.72, 28.84, 33.82, 34.48, 38.06, 63.03 (CHCl), 63.24 (CH_2O), 173.44 (C=O) ppm

m/z; (HRMS(ES)) calculated for $C_{13}H_{23}ClO_2$ expected 246.7735, not found. Calculated for $C_{26}H_{46}Cl_2O_4$ expected 492.2773, found 515.2665 (M+Na).

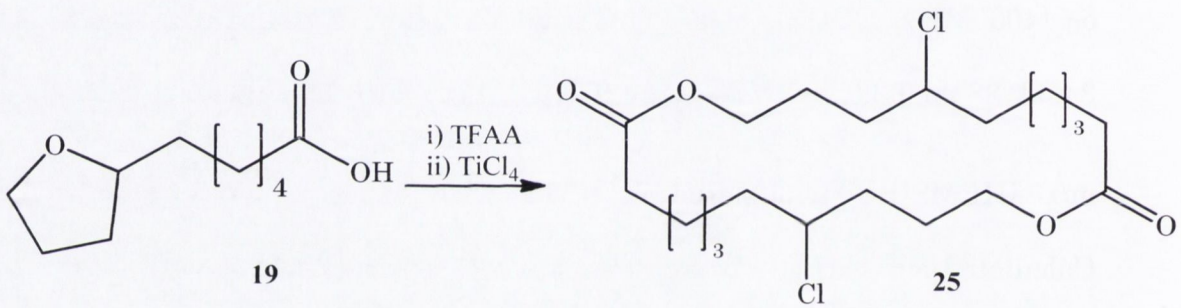
Attempted Finkelstein reaction of 11,25-dichloro-1,15-dioxacyclooctacosane-2,16-dione



Into a flask containing acetone distilled over K_2CO_3 (14 ml) were added 11,25-Dichloro-1,15-dioxacyclooctacosane-2,16-dione **17** (0.49 g; 1 mmol) and sodium

iodide (1.6 g; 10 mmol). The flask was heated to reflux under nitrogen for 24 hours before being cooled and the contents diluted with DCM (30 ml) and washed with water and brine and dried over $MgSO_4$. The solvent was removerd *in vacuo* to reveal a dark brown solid which was shown by ^1H NMR analysis to be identical to the starting diolide.

8,19-Dichloro-1,12-dioxacyclodocosane-2,13-dione 25



19 **25**

Run as per synthesis of **17**. 6-(tetrahydrofuran-2-yl)hexanoic acid **19** (0.1369 g; 0.7 mmol) produced 8,19-dichloro-1,12-dioxacyclodocosane-2,13-dione **25** (0.10 g; 66%) as an orange waxy solid which was analysed and used without any further purification.

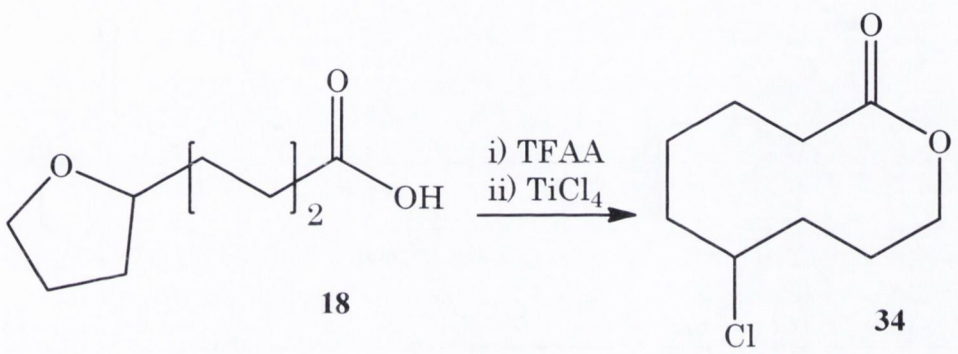
υ_{max} (L) 2932, 1728 (C=O), 1155 (C-O), 775 (C-Cl) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.28-1.50 (8H, m, CH_2), 1.54-2.82 (16H, m, CH_2), 2.36 (4H, t *J* 7.9, CH_2CO_2), 3.92 (2H, m, CHCl), 4.12 (4H, t *J* 6.96, CH_2O) ppm

δC (400 MHz; CDCl3) 17.86, 20.02, 20.49, 22.17, 22.40, 23.32, 24.37, 24.46, 25.57, 30.51, 31.47, 33.76, 34.23, 34.66, 34.73, 34.75, 35.21, 57.77 (CH_2CO), 58.09 (CH_2CO), 60.18 (CHCl), 63.90 (CH_2O), 64.35 (CH_2O), 173.42 (CO) ppm

m/z; (HRMS(ES)) calculated for $C_{10}H_{17}ClO_2$ expected 204.0917, not found. Calculated for $C_{20}H_{34}Cl_2O_4$ expected 408.1834, found 431.1742 (M+Na)

7-Chlorooxecan-2-one 34



Run as per synthesis of **17**. 5-(Tetrahydrofuran-2-yl)pentanoic acid **18** (0.3361 g; 1.95 mmol) produced 7-chlorooxecan-2-one **34** (0.2757 g; 74%) which distilled to purity (b.p. 62-64 °C/0.5 mmHg) as a waxy off-white solid.

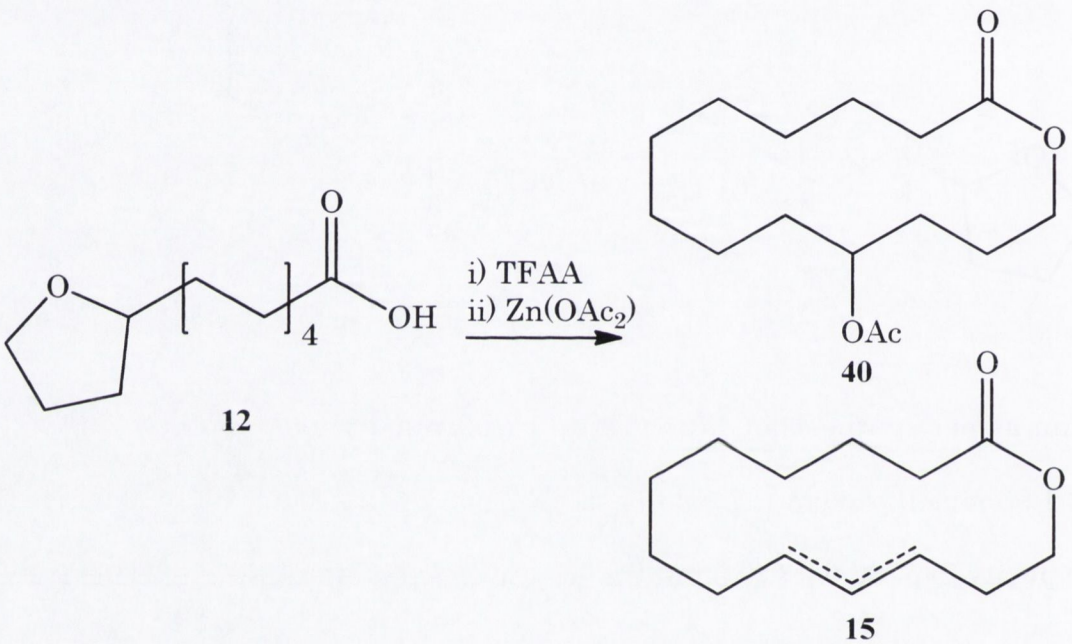
υ_{max} (L) 2931, 1729, 1234, 1163 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.52 (1H, m, C4 CH_a), 1.64 (3H, m, C3 CH_a, C5CH_a, C8CH_a), 1.80 (1H, m, C5 CH_b) 1.96-2.22 (6H, m, C2 CH_a C3 CH_b C4 CH_b C7 CH_{ab} C8 CH_b), 2.57 (1H, m, C2 CH_b), 3.87 (1H, m, C9 CH_a), 4.46 (1H, m, CClH), 4.76 (1H, m, C9 CH_b) ppm

δ_C (400 MHz; $CDCl_3$) 20.01 (CH_2), 23.81 (CH_2), 24.16 (CH_2), 31.89 (CH_2CHCl), 34.13 (CH_2CHCl), 36.39 (CH_2CO), 58.66 ($\underline{C}HCl$), 64.73 ($\underline{C}H_2OCO$), 172.84 (C=O) ppm

m/z; (HRMS (ESI)) calculated for $C_9H_{15}ClO_2$ expected 190.0761, not found. Calculated for $C_{18}H_{30}Cl_2O_4$, expected 380.1521, not found.

Treatment of 9-(tetrahydrofuran-2-yl)nonanoic acid with TFAA and $Cu(OAc)_2$



A solution of 9-(tetrahydrofuran-2-yl)nonanoic acid **12** (41.8 mg; 0.18 mmol) in $CHCl_3$ (30 ml) was flushed with nitrogen prior to cooling in an ice bath. Trifluoroacetic anhydride (0.2 ml; 1.4 mmol) was then added and the flask allowed to stir for ten minutes. Zinc(II) acetate (0.1 g; 0.5 mmol) was then added, a reflux condenser was attached and the contents of the flask were heated to reflux for 24 hours. After cooling the reaction mixture was diluted with diethyl ether (100 ml) and washed with water, 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to give a mixture of 14-

oxooxacyclotetradecan-5-yl acetate **40** and a mixture of structural isomers of (*E*)-oxacyclotetradec-11-en-2-one **15** in a 40:60 ratio as a fragrant orange oil (44 mg; 89%) which could not be further purified.

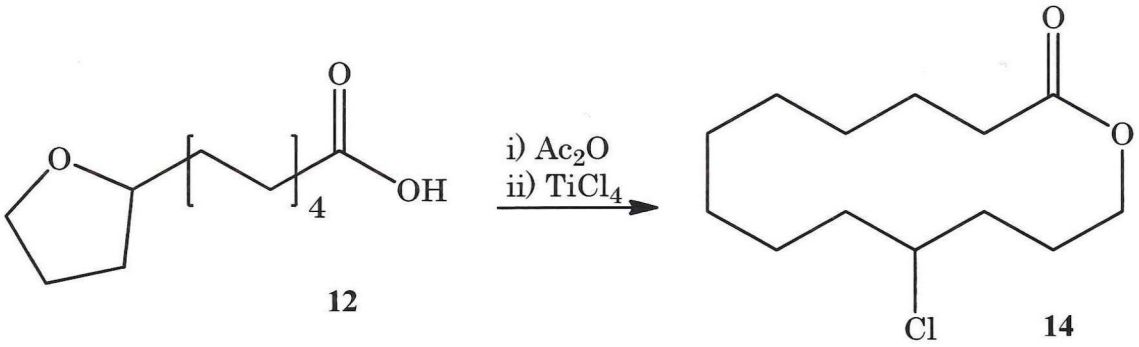
υ_{max} (L) 2928, 2855, 1761, 1737, 1236, 1164, 1036 cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.31 (8H, m, CH_2), 1.66 (6H, m, CH_2), 2.06 (3H, s, OMe), 1.93-2.16 (2H, m, CH_2CX), 2.36 (2H, apparent t *J* 7.67, CH_2CO), 4.08 (2H, apparent q *J* 6.07, OCH_2), 5.10 (1H, quintet *J* 6.19, C<u>H</u>OAc), 5.29-5.54 (2H, m, C<u>H</u>=C<u>H</u>) ppm

δ_C (400 MHz; $CDCl_3$) – 24.6, 25.6, 26.4, 28.9, 29.1, 29.2, 29.5, 31.2 (CH_2), 33.9 (<u>C</u>H_2CH=CH), 36.61 (CH=CHCH_2), 38.69 (<u>C</u>H_2CO), 67.52 (OCH_2), 68.13 (<u>C</u>HOAc), 128.7, 130.8, 130.9, 132.4 (<u>C</u>H=<u>C</u>H isomers), 167.7 (<u>C</u>OOMe), 179.4 (<u>C</u>=O lactone) ppm

m/z; (HRMS (ESI)) calculated for $C_{15}H_{26}O_4Na$, expected 293.1729, found 293.1741 (M+Na)

11-Chlorooxacyclotetradecan-2-one 14



12 **14**

A round-bottomed flask was charged with 9-(tetrahydrofuran-2-yl)nonanoic acid **12** (0.18 g; 0.83 mmol) and DCM (50 ml) and flushed with nitrogen prior to cooling to -10 °C. Acetic anhydride (0.18 ml; 1.9 mmol) was added *via* syringe and the flask was allowed to stir for 5 minutes, titanium tetrachloride (0.2 ml; 1.9 mmol) was added dropwise and the flask was heated to reflux under nitrogen for 24 hours. After cooling the reaction mixture was diluted with diethyl ether (50 ml) and washed with water, 5% NaHCO3 and brine, dried over MgSO4 and the solvent removed *in vacuo* to give 11-chlorooxacyclotetradecan-2-one **14** as a fragrant orange oil (0.14 g; 72%) which was analysed and used without any further purification.

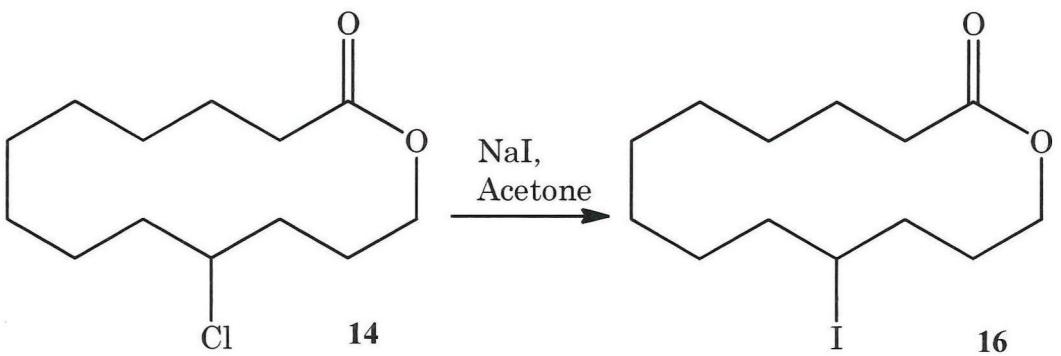
υ_{max} (L) 2928, 2856, 1738, 1709, 1238, 1032, 720 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.30 (12H, m, CH_2), 1.51 (1H, m), 1.63 (4H, m, CH_2), 1.72 (4H, m, CH_2), 1.91 (1H, m, CH_2), 2.42 (2H, t *J* 7.26, $C\underline{H}_2CO$), 3.90 (1H, q *J* 7.38, $C\underline{H}Cl$), 4.09 (2H, t *J* 5.59, CH_2O) ppm

δ_C (400 MHz; $CDCl_3$) 24.47, 25.34, 26.00, 28.61, 28.64, 28.72, 28.84, 33.82, 34.48, 38.06, 63.03 (CHCl), 63.24 (CH_2O), 173.44 (C=O) ppm

m/z; (HRMS (ESI)) calculated. for $C_{13}H_{23}ClO_2Na$, expected 269.1284, not found. Calculated for $C_{26}H_{46}Cl_2NaO_4$, expected 492.2273, not found.

11-Iodooxacyclotetradecan-2-one 16



14 **16**

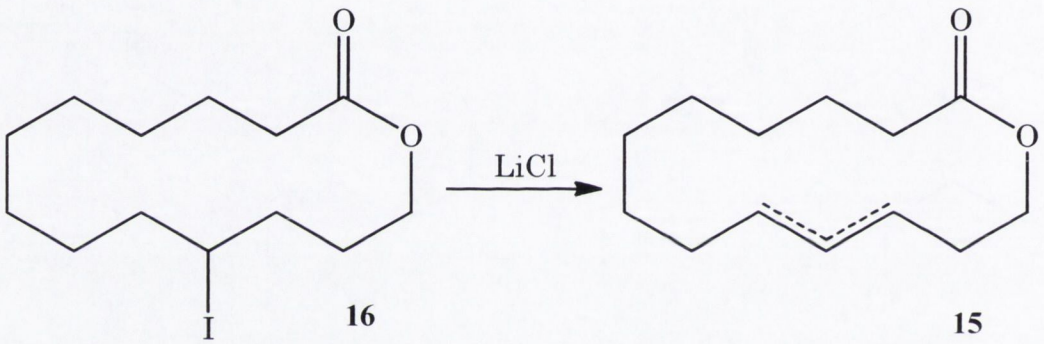
A 50 ml round bottomed flask was charged with 11-chlorooxacyclotetradecan-2-one **14** (436 mg; 1.7 mmol), acetone (25 ml) and a magnetic stir bar. Sodium iodide (3.2 g; 21.3 mmol) was added to the mixture and the flask was heated to reflux for 36 hours. After cooling the acetone was removed on a rotary evaporator and the residue taken into diethyl ether and washed with water and sat. aq. sodium thiosulfate. The organic layer was dried over $MgSO_4$ and the solvent evaporated on a rotary evaporator yielding 11-iodooxacyclotetradecan-2-one **16** as a fragrant translucent oil (355 mg; 60%) which was analysed and used without any further purification.

υ_{max} (L) 2928, 2856, 1738, 1709, 1238, 1032, 650 cm^{-1}

NMR spectroscopy not possible as sample destroyed on contact with solvent.

m/z; (HRMS (ES)) calculated for $C_{13}H_{23}IO_2$, expected 338.0743, not found. Calculated for $C_{26}H_{46}I_2O_4$, expected 648.1172, not found.

Treatment of 11-iodooxacyclotetradecan-2-one with lithium chloride



16 **15**

Finely ground lithium chloride (0.34 g; 8 mmol) was added to a solution of 11-iodooxacyclotetradecan-2-one **16** (0.054 g; 0.16 mmol) in DMF (5 ml) and the flask was heated to reflux overnight. Upon cooling the reaction was quenched with sat. aq. ammonium chloride and extracted with diethyl ether (2 x 25 ml). The combined organic extracts were washed with water (3 x 10 ml) dried over $MgSO_4$ and the solvent removed by rotary evaporation to give a mixture of 10/11 E/Z structural isomers of (*E*)-oxacyclotetradec-11-en-2-one **15** (24.3 mg; 72%) which were analysed without any further purification.

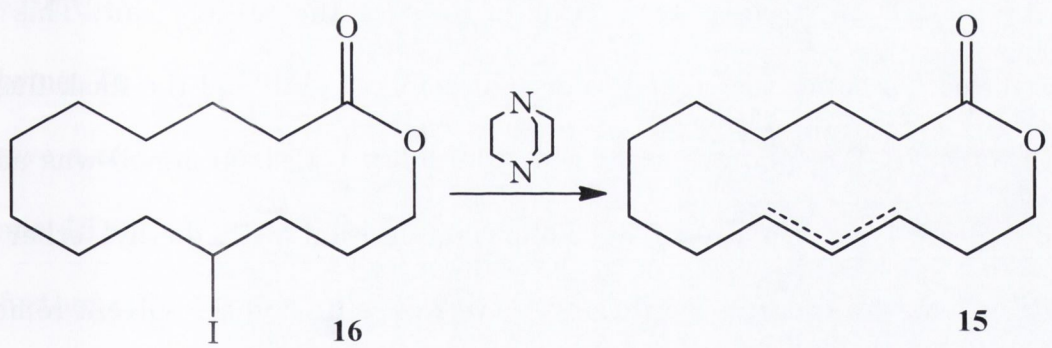
υ_{max} (L) 3324, 2927, 2853, 1733, 1710, 1166, 799 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.26 (8H, m, CH_2), 1.54-1.70 (6H, m, CH_2), 1.85-2.13 (2H, m, CH_2), 2.31 (2H, t *J* 7.26, $CH_2C{=}O$), 4.03, (2H, m, OCH_2), 5.27-5.52 (2H, m, CH=CH) ppm

δ_C (400 MHz; $CDCl_3$) 29.25, 29.2, 29.1, 29.07, 29.0, 28.9, 24.6, 20.9 (CH_2), 33.8 ($\underline{C}H_2C{=}O$), 63.9 (CH_2O), 124.9, 128.5, 131.3, 133.5 (CH=CH), 178.6 (C=O) ppm

m/z; (HRMS (ESI)) calculated for $C_{13}H_{21}O_2$, expected 209.1592 found 209.1534 (M-H). Calculated for $C_{26}H_{42}O_4$, expected 419.6167, not found.

Treatment of 11-iodooxacyclotetradecan-2-one with 1,4-diazabicyclo[2.2.2]octane

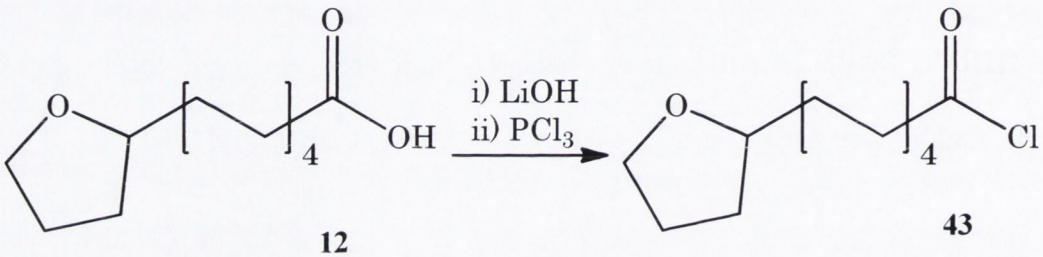


16 **15**

A flask charged with 11-iodooxacyclotetradecan-2-one **16** (51.4 mg; 0.15 mmol) in dimethyl formamide (5 ml) was treated with 1,4-diazabicyclo[2.2.2]octane (20 mg; 0.18 mmol) and the flask heated to reflux overnight. Upon cooling the reaction was diluted with diethyl ether (25 ml) and washed with water (3 x 10 ml), dried over $MgSO_4$ and the solvent removed by rotary evaporation to give a

mixture of 10/11 E/Z structural isomers of (*E*)-oxacyclotetradec-11-en-2-one **15** (24.3 mg; 72%) which were analysed without any further purification.

9-(Tetrahydrofuran-2-yl)nonanoyl chloride 43

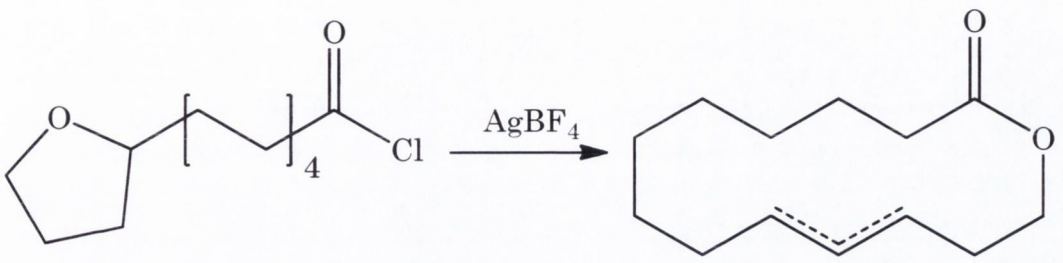


12 **43**

9-(Tetrahydrofuran-2-yl)nonanoic acid **12** (53.7 mg; 23 mmol) was treated with an aqueous solution of lithium hydroxide (10 ml; 1M, 30 mmol). The solvent was removed on a rotary evaporator to produce the lithium salt. This was dried, finely ground, suspended in dry chloroform (5 ml) and the flask flushed with nitrogen. Phosphorous trichloride (0.9 ml; 0.1 M, 0.09 mmol) was added and the flask stirred overnight. Following dilution with diethyl ether the reaction mixture was filtered through a stick of celite and the solvent removed to give 9-(tetrahydrofuran-2-yl)nonanoyl chloride **43** as a light yellow oil (20 mg; 35%) which was analysed and used without any further purification.

υ_{max} (L) 2921, 1790 (C=O), 1459, 1171, 802 cm^{-1}

Treatment of 9-(tetrahydrofuran-2-yl)nonanoyl chloride 43 with silver tetrafluoroborate



43 **15**

9-(Tetrahydrofuran-2-yl)nonanoyl chloride **43** (55 mg; 0.22 mmol) was dissolved in $CHCl_3$ (10 ml) and flushed with nitrogen in a round bottom flask. Sodium tetrafluoroborate (50 mg; 0.25 mmol) was added and the flask was stirred overnight in the dark. The reaction mixture was worked-up by dilution with diethyl ether and sequential washing with water, 2 x 1% $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated to give a mixture of 10/11 E/Z structural isomers of (*E*)-oxacyclotetradec-11-en-2-one **15** (33.1 mg; 70%) as a light yellow oil which was analysed without any further purification.

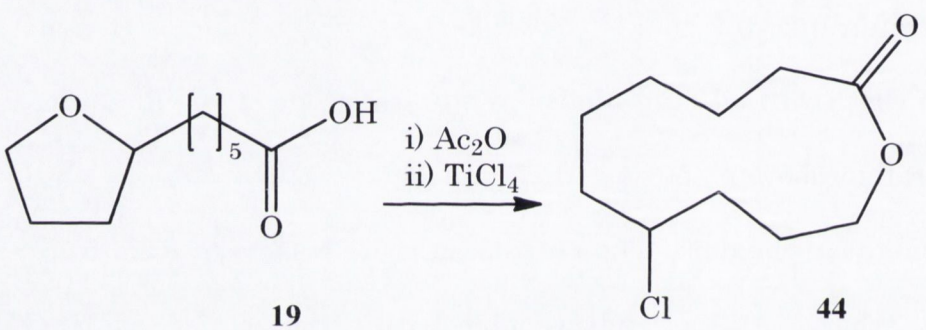
υ_{max} (L) 3324, 2927, 2853, 1733, 1710, 1166, 799 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.26 (8H, m, CH_2), 1.54-1.70 (6H, m, CH_2), 1.85-2.13 (2H, m, CH_2), 2.31 (2H, t *J* 7.6, $CH_2C{=}O$), 4.03, (2H,apparent dt J_a 2.91 J_b 6.89 , OCH_2), 5.27-5.52 (2H, m, CH=CH) ppm

δ_C (400 MHz; $CDCl_3$) 29.25, 29.2, 29.1, 29.07, 29.0, 28.9, 24.6, 20.9 (CH_2), 33.8 ($\underline{C}H_2C=O$), 63.9 (CH_2O), 124.9, 128.5, 131.3, 133.5 (CH=CH), 178.6 (C=O) ppm

m/z; (HRMS (ESI)) calculated for $C_{13}H_{21}O_2$, expected 209.1592 found 209.1534 (M-H). Calculated for $C_{26}H_{42}O_4$, expected 419.6167, not found.

8-Chlorooxacycloundecan-2-one 44



19 **44**

Run as per synthesis of **14**. 6-(tetrahydrofuran-2-yl)hexanoic acid **19** (52.2 mg; 0.3 mmol) produced crude 8-chlorooxacycloundecan-2-one **44** (53.4 mg; 93%) as an orange oil which was analysed and used without any further purification.

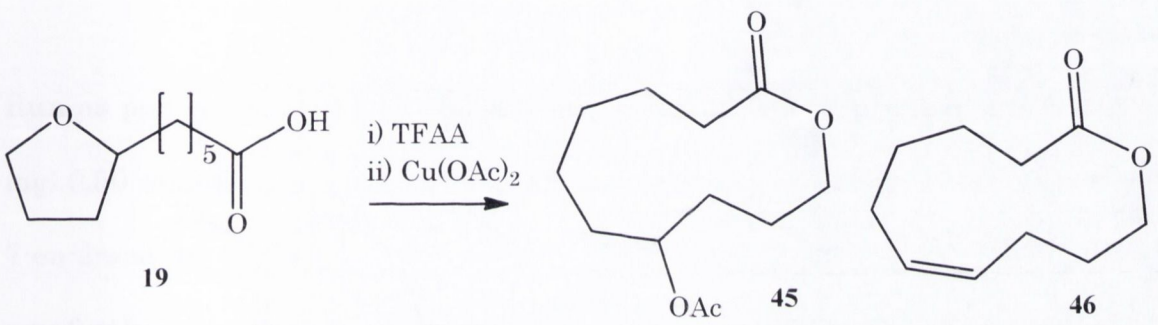
υ_{max} (L) 2932, 1721 (C=O), 1154 (C-O), 772 (C-Cl) cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.28-1.47 (4H, m, CH_2), 1.53-1.82 (8H, m, CH_2), 2.35 (2H, t *J* 7.21, CH_2CO), 3.89 (1H, q *J* 7.1, CHCl), 4.07 (2H, t *J* 6.23, CH_2O) ppm

δ_C (400 MHz; $CDCl_3$) 24.4, 25.7, 26.0, 28.4, 33.7, 34.9 (CH_2), 38.1 ($\underline{C}H_2C=O$), 63.1 (CHCl), 63.9 (CH_2O), 178.6 (C=O) ppm

m/z; (HRMS (ES)) calculated for $C_{10}H_{17}ClO_2$, expected 204.0917, calculated for $C_{20}H_{34}Cl_2O_4$, expected 408.1834, neither found.

Treatment of 6-(tetrahydrofuran-2-yl)hexanoic acid 19 with TFAA and $Cu(OAc)_2$



19 **45** **46**

Run as per synthesis of **40/15.** 6-(Tetrahydrofuran-2-yl)hexanoic acid **19** (56.4 mg; 0.30 mmol) produced a mixture of 11-oxooxacycloundecan-5-yl acetate **45** and a mixture of isomers of (*Z*)-oxacycloundec-7-en-2-one **46** in a roughly 1:1 ratio with a recovery of 32.5 mg total neutral organic product, a 57% recovery of the starting material weight.

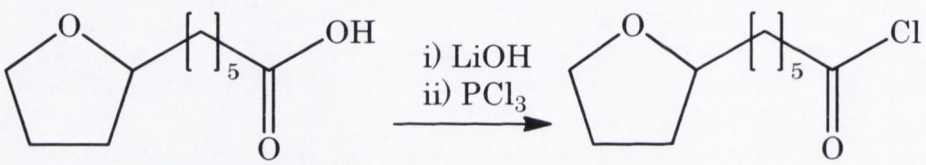
υ_{max} (L) 2948, 2851, 1761, 1741, 1230, 1164, cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.26-1.46 (4H, m, CH_2), 1.54-1.80 (4H, m, CH_2), 1.86-2.01 (4H, m, CH_2), 2.21 (3H, s, OMe), 2.45 (2H, t *J* 7.4, CH_2CO), 4.24 (2H, t *J* 5.4, CH_2O), 5.11-5.18 (1H, m, C<u>H</u>OAc), 5.21-5.30 (1H, m, C<u>H</u>=CH), 5.34-5.43 (1H, m, CH=C<u>H</u>) ppm

δ_C (400 MHz; $CDCl_3$) – 20.9, 21.2, 22.6, 26.4, 27.0, 28.9, 35.0 (CH_2), 64.3 (CH_2O), 64.9 (CH_2O), 78.2 (CHOAc), 129.4 (C=C), 131.6 (C=C), 173.7 (OAc), 203.4 (CO) ppm

m/z; (HRMS (ESI)) calculated for $C_{12}H_{20}O_4$, expected 228.1362, found 227.1276 (M - H)

6-(Tetrahydrofuran-2-yl)hexanoyl chloride 53

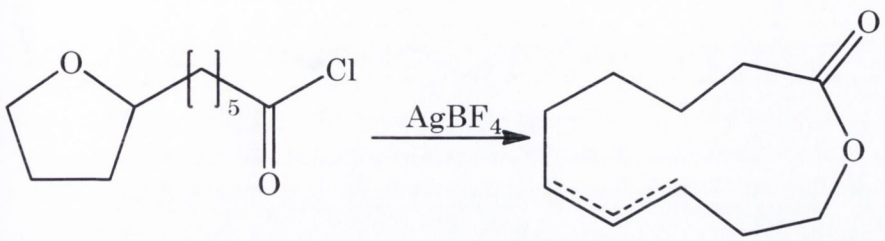


19 **53**

Run as per synthesis of **48**. 6-(Tetrahydrofuran-2-yl)hexanoic acid **19** (101 mg; 0.54 mmol) produced 6-(tetrahydrofuran-2-yl)hexanoyl chloride **51** (106.4 mg; 95%) as an light yellow oil which was analysed without any further purification.

υ_{max} (L) 3321, 2928, 1730, 1713, 1166, 799 cm^{-1}

Treatment of 6-(tetrahydrofuran-2-yl)hexanoyl chloride 53 with silver tetrafluoroborate



53 **46**

Run as per synthesis of **36**. 6-(tetrahydrofuran-2-yl)hexanoyl chloride **53** (101 mg; 0.50 mmol) produced a mixture of structural isomers of (*E*)-oxacycloundec-7-en-2-one **46** (30 mg; 35%) as a light yellow oil which was analysed without any further purification.

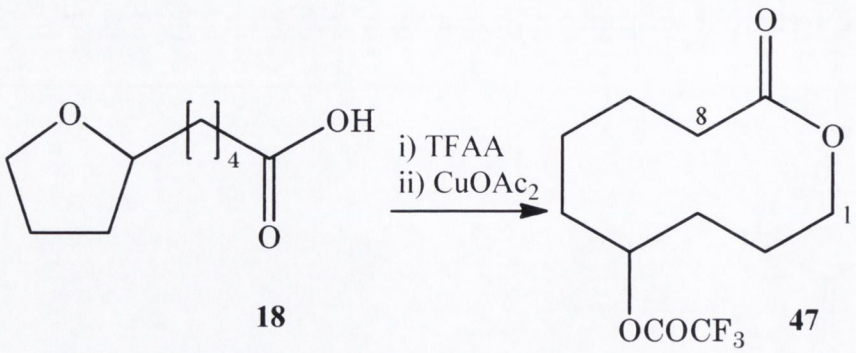
υ_{max} (L) 3321, 2927, 2853, 1710, 1166 cm^{-1}

δ_H (400 MHz; $CDCl_3$) – 1.25 (4H, m, CH_2), 1.51-1.70 (4H, m, CH_2), 1.92-2.08 (2H, m, CH_2), 2.29 (2H, t *J* 7.16, CH_2CO), 4.05 (2H, t *J* 5.90, CH_2O), 5.29-5.53 (2H, m, CH=CH) ppm

δ_C (400 MHz; $CDCl_3$) – 25.6, 26.0, 29.1, 29.6, 31.3 (CH_2), 35.4 ($\underline{C}H_2C$=O), 67.4 (CH_2O), 125.4 ($\underline{C}$H=CH), 133.0 (CH=$\underline{C}$H), 181.5 (C=O) ppm

m/z; (HRMS (ESI)) calculated for $C_{10}H_{16}O_2$ expected 168.1150, found 169.1225 (M+H)

10-oxooxecan-5-yl 2,2,2-trifluoroacetate 47



18 **47**

Run as per synthesis of **40**. 5-(tetrahydrofuran-2-yl)pentanoic acid **18** (29.6 mg; 0.17 mmol) produced crude 10-oxooxecan-5-yl 2,2,2-trifluoroacetate **47** (0.14 mg; 40%) as an orange oil which was analysed without any further purification.

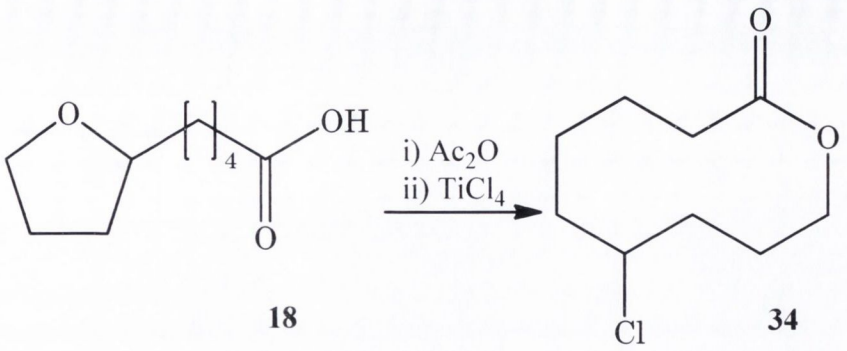
υ_{max} (L) 1777, 1730, 2853, 1216, 1151 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.47-1.55 (1H, m, C6 CH_a), 1.59-1.71 (4H, m, C5 CH_2, C6 CH_b, C7 CH_a), 1.74-1.83 (2H, m, C3 CH_a C2 CH_a) 1.96-2.22 (4H, m, C2 CH_b C3 CH_b C7 CH_b C8 CH_a), 2.58-2.65 (1H, m, C8 CH_b), 3.88-3.95 (1H, m, C1 CH_a), 4.71-4.79 (1H, m, C1 CH_b), 5.32-5.60 (1H, m, $CHOCOCF_3$) ppm

δ_H (400 MHz; $CDCl_3$) 20.4 (C7), 23.7 (C2), 24.3 (C6), 28.6 (C5), 31.5 (C3), 34.3 (C8), 65.0 (C1), 77.6 (C4), 114.6 (CF_3), 157.6 ($\underline{C}OCF_3$), 173.2 ($CH_2\underline{C}$=O) ppm

m/z; (HRMS (ESI)) calculated for $C_{11}H_{15}F_3O_4$ expected 268.0922, not found

7-Chlorooxecan-2-one 34



18 **34**

Run as per synthesis of **14**. 5-(tetrahydrofuran-2-yl)pentanoic acid **18** (213 mg; 1.2 mmol) produced 7-chlorooxecan-2-one **34** (183 mg; 77%) as an orange oil.

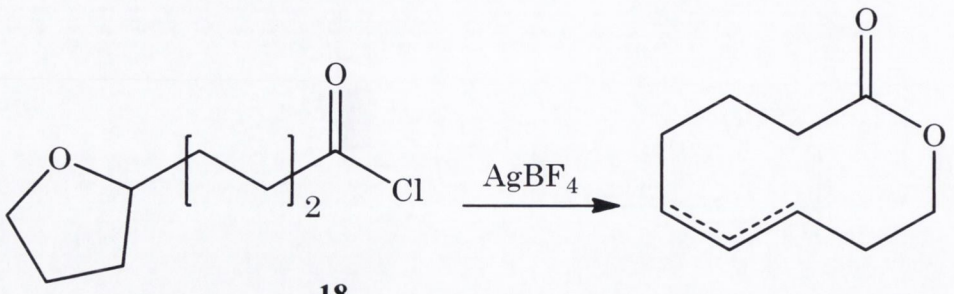
υ_{max} (L) 2931, 1729, 1234, 1163 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.52 (1H, m, C4 CH_a), 1.64 (3H, m, C3 CH_a, C5CH_a, C8CH_a), 1.80 (1H, m, C5 CH_b) 1.96-2.22 (6H, m, C2 CH_a C3 CH_b C4 CH_b C7 CH_{ab} C8 CH_b), 2.57 (1H, m, C2 CH_b), 3.87 (1H, m, C9 CH_a), 4.46 (1H, m, CClH), 4.76 (1H, m, C9 CH_b) ppm

δ_C (400 MHz; $CDCl_3$) 20.01 (CH_2), 23.81 (CH_2), 24.16 (CH_2), 31.89 (CH_2CHCl), 34.13 (CH_2CHCl), 36.39 (CH_2CO), 58.66 ($\underline{C}HCl$), 64.73 ($\underline{C}H_2OCO$), 172.84 (C=O) ppm

m/z; (HRMS (ESI)) calculated for $C_9H_{15}ClO_2$ expected 190.0761, not found. Calculated for $C_{18}H_{30}Cl_2O_4$, expected 380.1521, not found.

Isomers of (*Z*)-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one 36



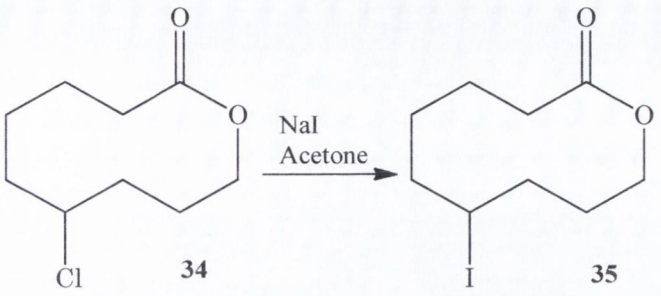
18 **36**

Run as per synthesis of **46**. 5-(Tetrahydrofuran-2-yl)pentanoic acid **18** (0.0191 g; 0.1 mmol) produced a mixture of isomers of (*Z*)-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one **36** (7.9 mg; 46%) which was analysed without further purification, due to the small amount of material available full characterisation was not possible.

δ_H (400 MHz; $CDCl_3$) 1.49 (1H, m, C4 CH_a), 1.56-1.80 (3H, m, C3 CH_a, C5CH_a, C8CH_a), 1.90-2.27 (6H, m, C5 CH_b C2 CH_a C3 CH_b C4 CH_b C7 CH_{ab} C8 CH_b), 2.58 (1H, m, C2 CH_b), 3.88 (1H, t *J* 10.2, C9 CH_a), 5.53 (2H, m, CH=CH) ppm

m/z; (HRMS (ESI)) calculated for $C_9H_{14}O_2$ expected 154.0994, not found.

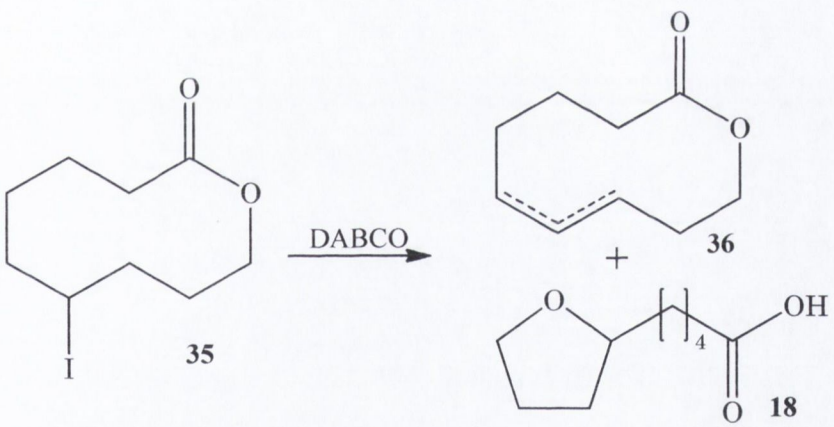
7-Iodooxecan-2-one 35



Ran as per synthesis of **16**. 7-Chlorooxecan-2-one **34** (190 mg; 1 mmol) produced **35** (152 mg; 54%) as a pale yellow oil which was not subjected to further purification prior to analysis or use.

υmax (L) 2999, 1733 (C=O) cm-1

Treatment of 7-iodooxecan-2-one with 1,4-diazabicyclo[2.2.2]octane



Ran as per synthesis of **15**. 7-Iodooxecan-2-one **35** (190 mg; 1 mmol) produced 5-(tetrahydrofuran-2-yl)pentanoic acid **18** and a mixture of structural isomers of (*E*)-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one **36** as a yellow oil.

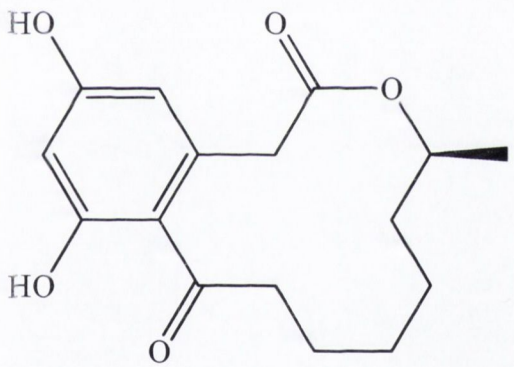
^{1}H NMR analysis indicated that it was a mixture of **18** and **36**.

Chapter 3 - Progress towards a total synthesis of curvularin

1. Curvularin

In Chapter 2 a series of modifications to the Grayson group technique for macrolactonisation were detailed and the yields of larger ring synthesis dramatically improved.

In order to test the limits of this new modification to the acylative THF macrolactonisation reaction and to probe the potential for exploting the Thorpe-Ingolde effect a total synthesis was undertaken with the endgame being the synthesis of a series of analogues of curvularin and of curvularin **1** itself.



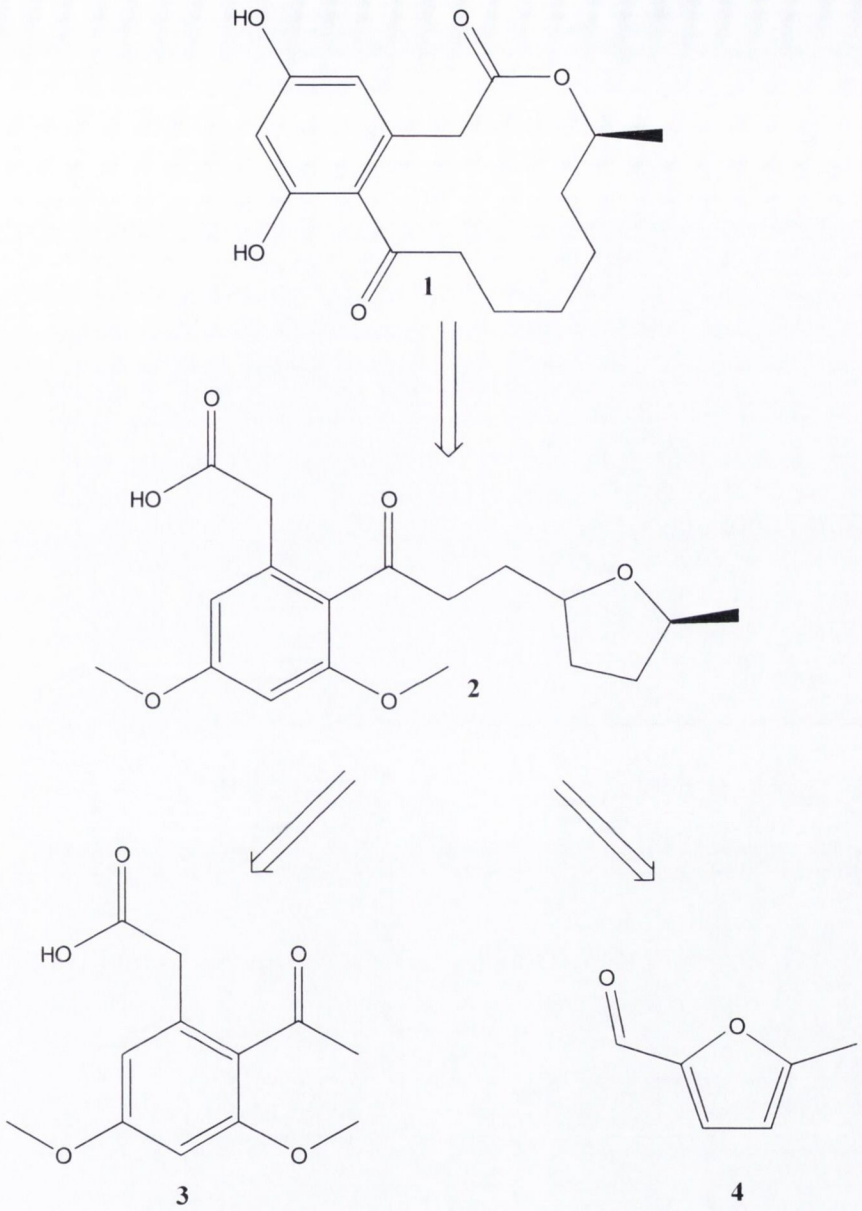
1

Curvularin is a member of the resorcylic lactone family first documented as a metabolite of a strain of *Curvularia*[152] and subsequently found to be present in a number of other species[153-156]. The macrolactone has been reported as possessing a number of extremely potent biological properties including anti-neoplasticity,[157] inhibition of cell signalling[158], and anti-inflammatory activity

in arthritis models.[159] A number of total syntheses of curvularin and its analogues have previously been undertaken[160-162].

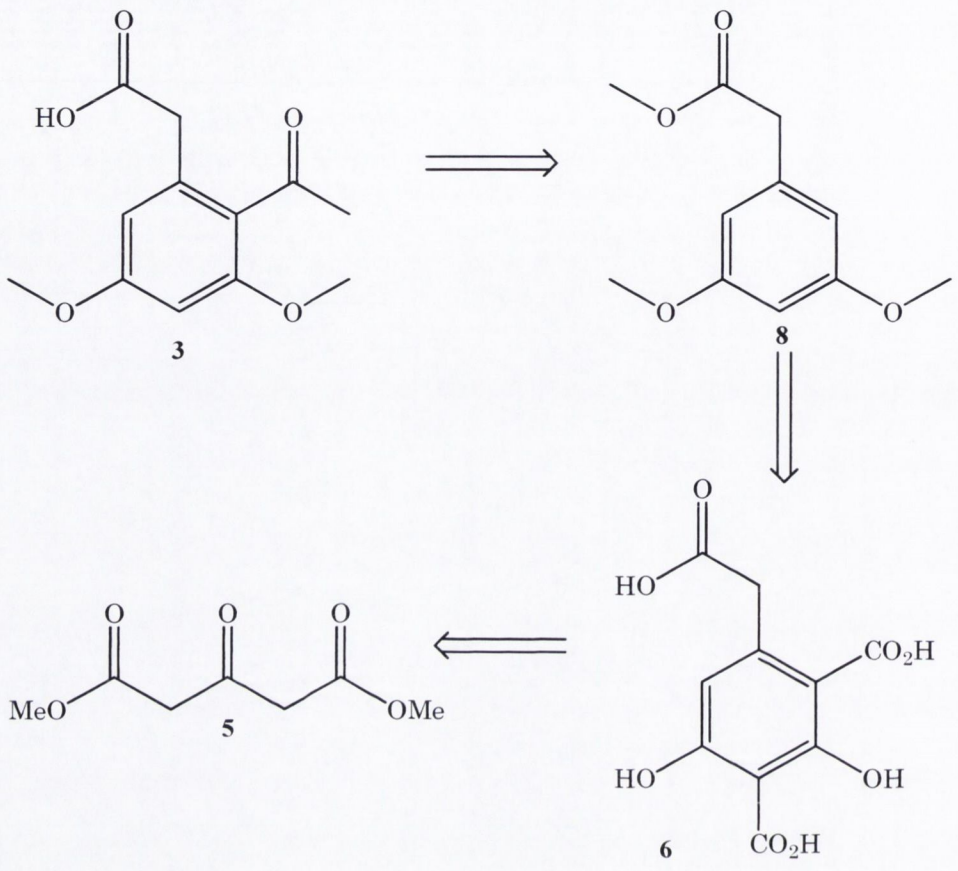
2. Retrosynthetic analysis

Our attempted synthesis of curvularin formed part of a continuation of previous work with the same aim. A retrosynthetic analysis (**scheme 3-1**) of curvularin gave as cyclisation precursor the 5-methyltetrahydrofuran linked to a dimethoxyresorcyl acetic acid **2**.



Scheme 3-1: Retrosynthetic analysis of curvularin **1**

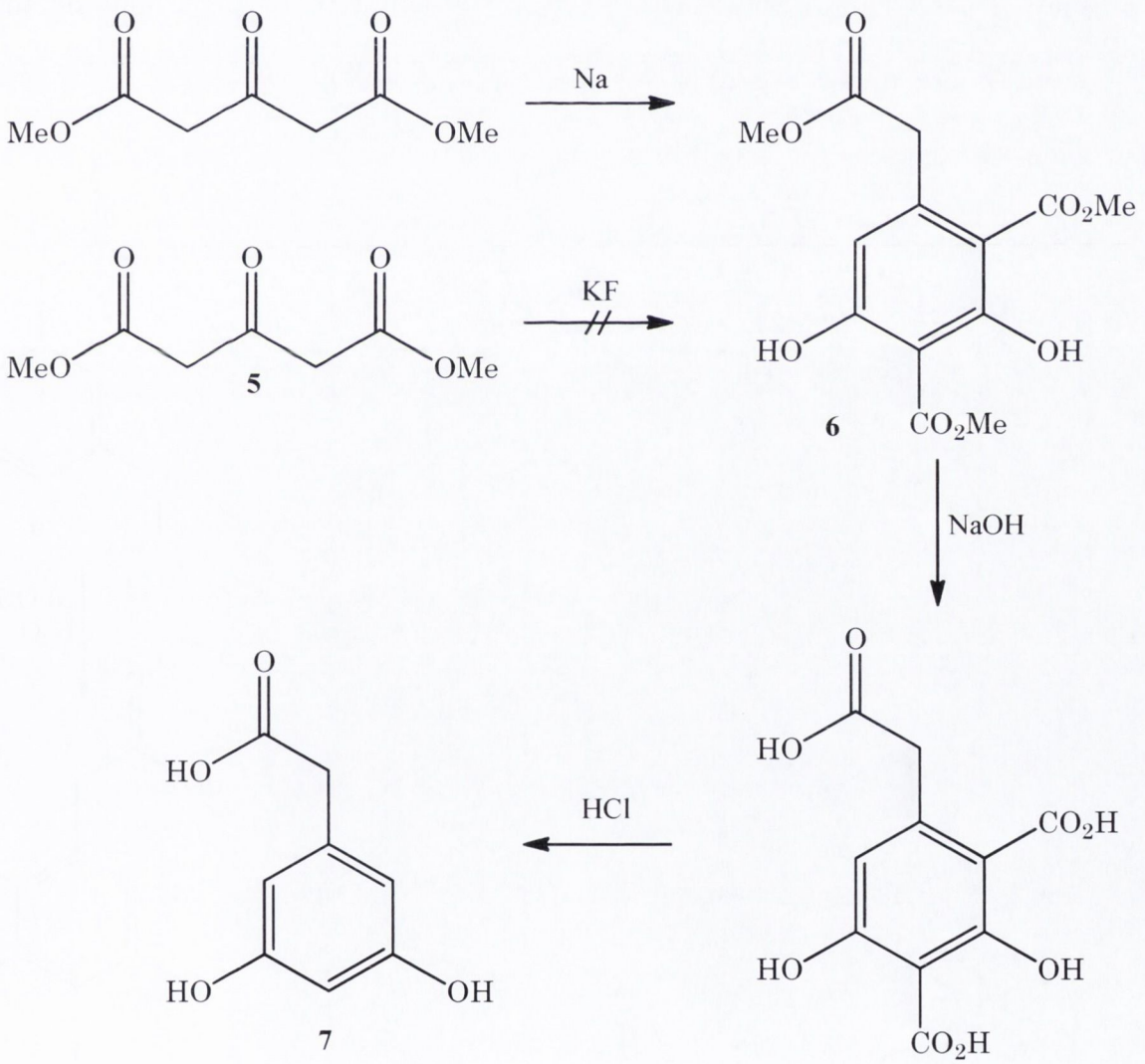
The protected resorcinol fragment **3** in turn can be synthesised from dimethyl 1,3-acetonedicarboxylate **5** (**scheme 3-2**).



Scheme 3-2: Retrosynthetic analysis of protected resorcinol fragment **3**

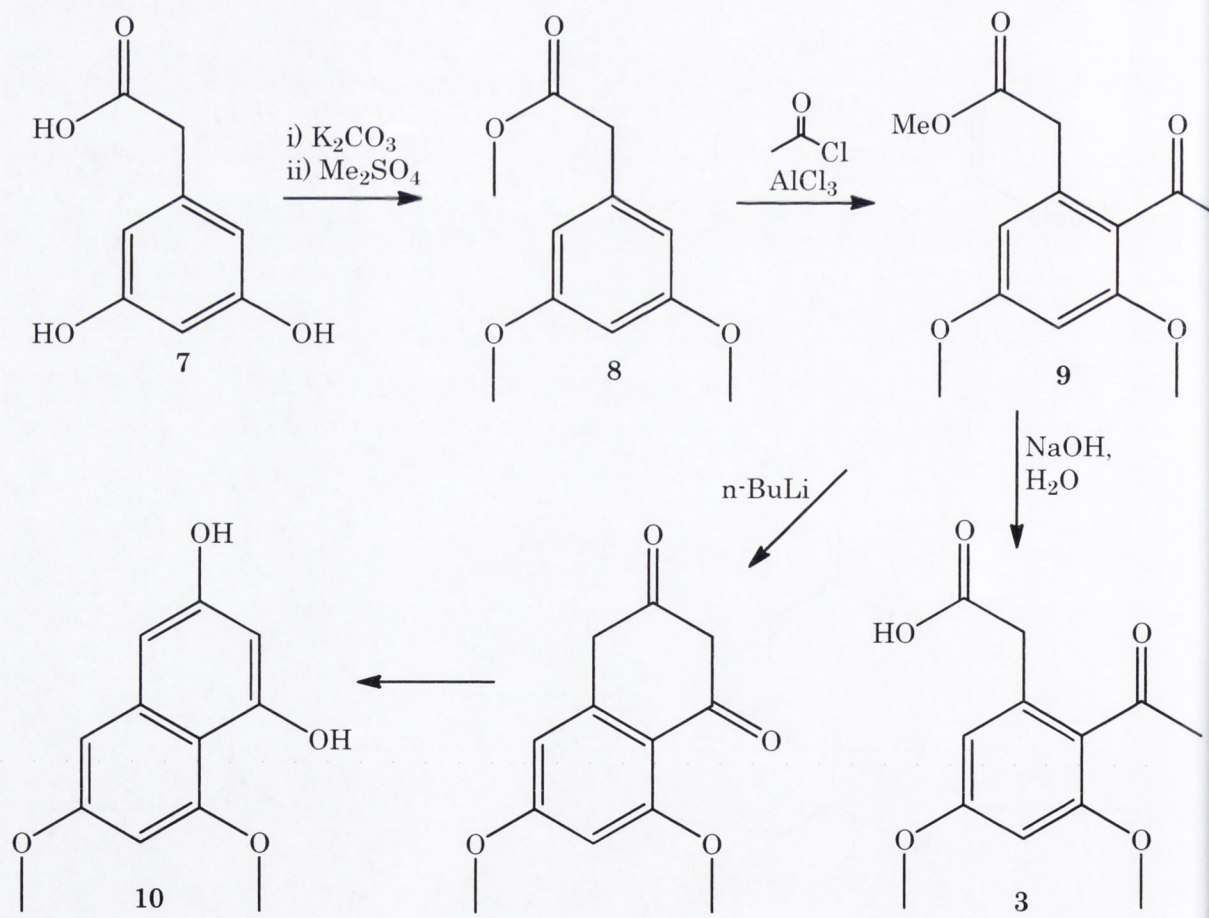
3. Synthesis of 2-acetyl-3,5-dimethoxyphenyl)acetic acid

The base-catalysed self-condensation of dimethoxy 1,3-acetone dicarboxylate **5** proceeds smoothly in refluxing toluene, a modification to the reaction using potassium fluoride as reported by Takeuchi[163] proved unsuccessful. Hydrolysis of the ensuing ester **6** and subsequent decarboxylation was undertaken in one pot producing 2-(3,5-dihydroxyphenyl)acetic acid **7** in 92% yield.



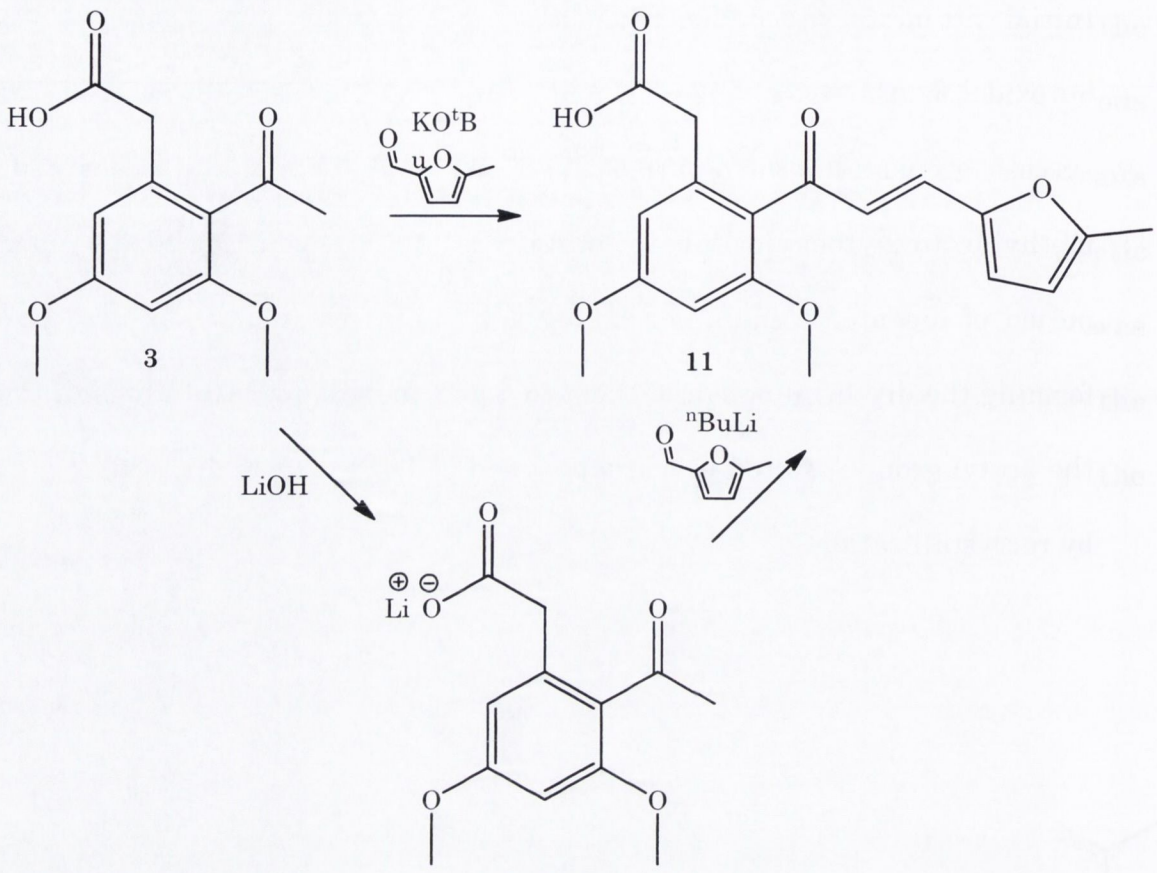
Scheme 3-3: Synthesis of 2-(3,5-dihydroxyphenyl)acetic acid **7**

In order to produce a suitably protected cyclisation precursor of curvularin the phenolic hydroxyl groups of **7** were protected under a somewhat circuitous route of triple methylation with dimethyl sulfate followed by a Friedel-Crafts acylation with acetyl chloride and subsequent re-saponification of the acetic acid to produce the key intermediate **3**. The return to the free acid was necessitated as if the subsequent aldol condensation was carried out on the methyl ester, an intramolecular Claisen reaction takes place leading to the naphthalene derivative **10**.



Scheme 3-4: Synthesis of 2-(2-acetyl-3,5-dimethoxyphenyl)acetic acid **3**

Initial attempts to conduct an aldol condensation using potassium tert-butoxide as the base and elevated temperatures resulted in only partial success, giving a low yield of the target compound (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11** (35%) which needed a laborious period of repeated column chromatography to purify it. It was found that by forming the dry lithium salt of the acid **3** and then using ^{n}-BuLi to deprotonate the acetyl group resulted in a greater yield of **11** (88%) which could be purified by recrystallisation.



Scheme 3-5: Synthesis of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11**

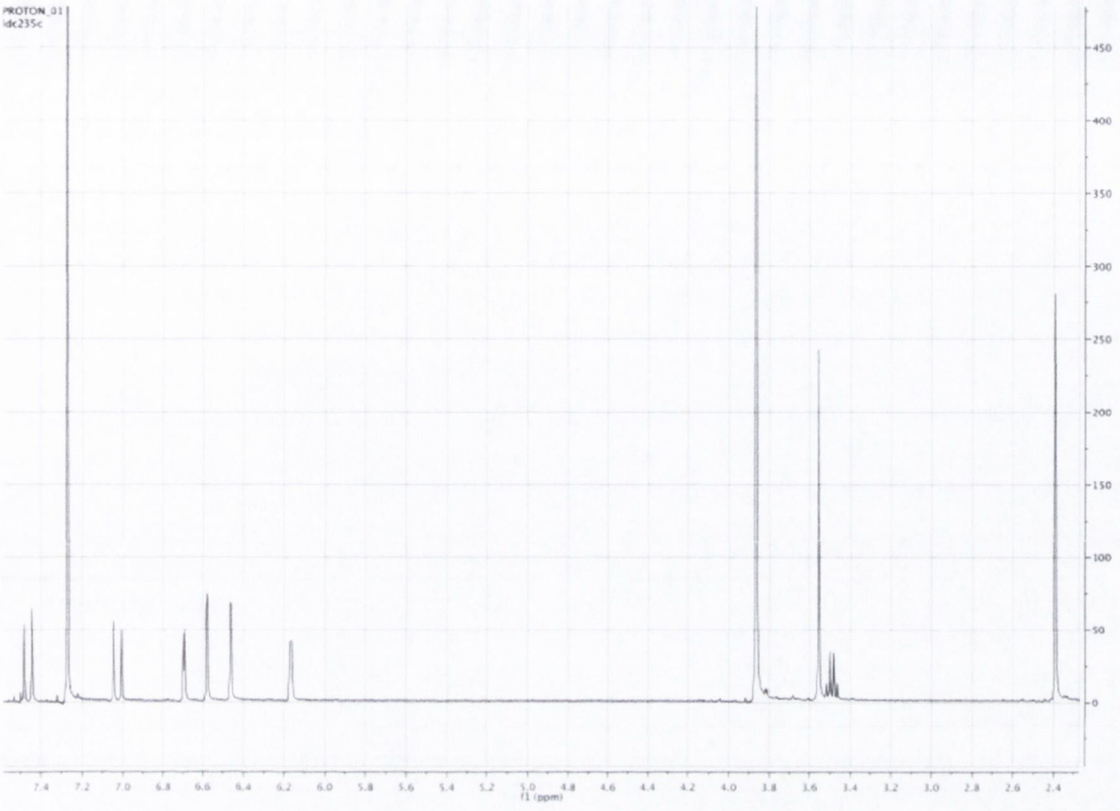
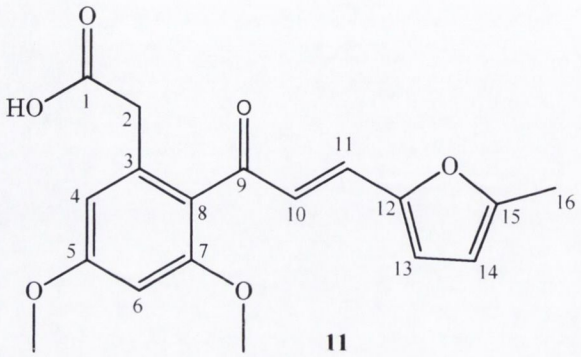


Figure 3-1: ^{1}H NMR spectrum of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11**

Table 12: ^{1}H NMR spectroscopic details of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11**



11

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
2.40	3H	s	CH_3
3.37	2H	s	CH_2CO_2
3.87	6H	s	OMe
6.17	1H	d, *J* 3.0	$CH_{13/14}$
6.47	1H	d, *J* 1.5	$CH_{4/6}$
6.58	1H	d, *J* 2.0	$CH_{4/6}$
6.70	1H	d, *J* 3.1	$CH_{13/14}$
7.01	1H	d, *J* 15.4	$CH_{10/11}$
7.44	1H	d, *J* 15.6	$CH_{10/11}$

4. Attempted hydrogenation of fully unsaturated lactonisation precursor (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid 11

When the unsaturated precursor was subjected to standard hydrogenation conditions it was found that more than the three expected molar equivalents of hydrogen were uptaken. An NMR analysis of the recovered product gave no clear indication as to the fate of the compound, instead what appeared to be a mixture of compounds was shown with no identifiable peaks, a suspicion that was confirmed by TLC showing more than 9 compounds running into one another.

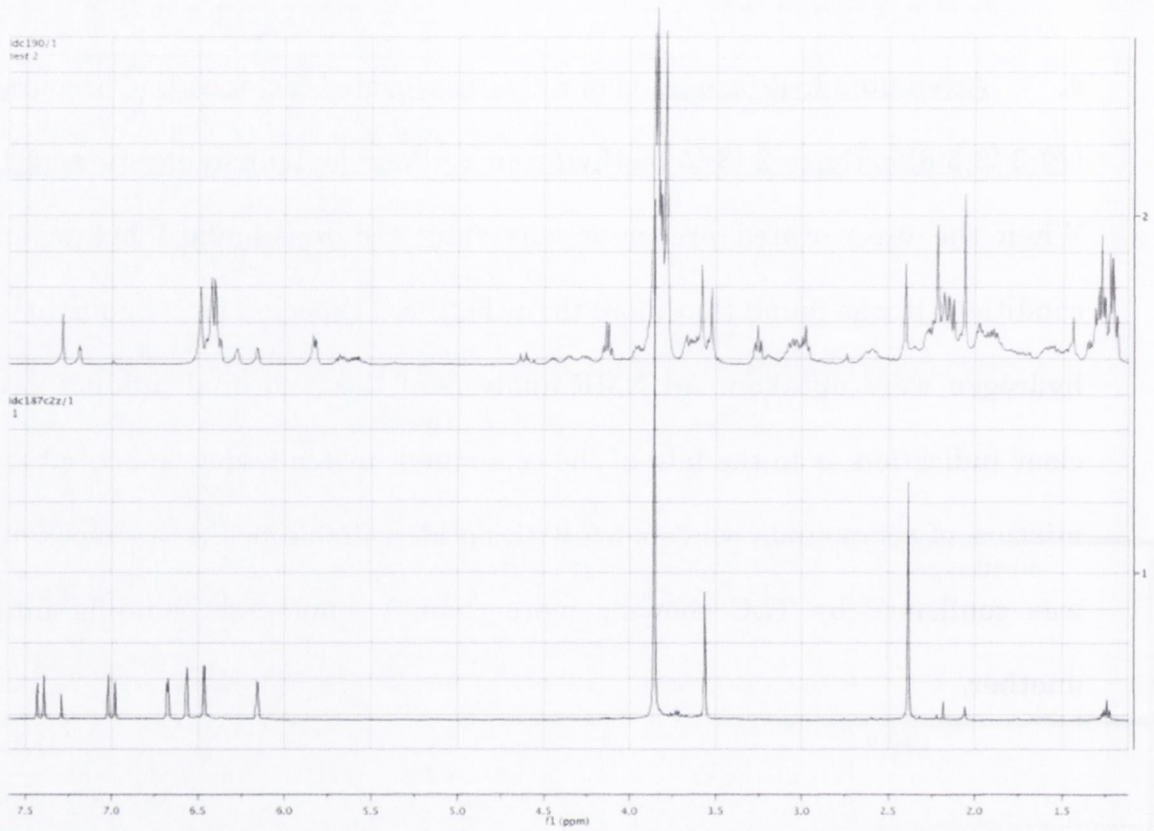


Figure 3-2: ^{1}H NMR spectrum indicating breakdown of **11** (bottom spectrum) upon hydrogenation into multiple indistinguishable products (top spectrum)

Altering the solvent to either ethanol or ethyl acetate, which whilst not a common solvent for hydrogenation has given good results for the group previously[164], resulted in an indecipherable array of peaks with no detectable formation of any one major product observed.

As there was no single clearly identifiable breakdown product present in the ^{1}H NMR spectrum assigning a breakdown pathway for **11** is difficult. It is considered likely though that the breakdown of **11** occurs as a result of

stepwise addition of a hydrogen atom leading to the formation of a cation, this would then act then as a nucleophile resulting in subsequent cyclisations, potentially followed by further breakdown *via* hydrogenolysis etc.

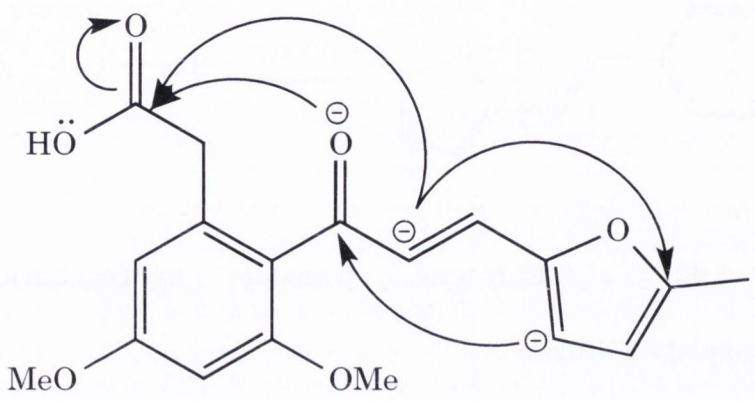


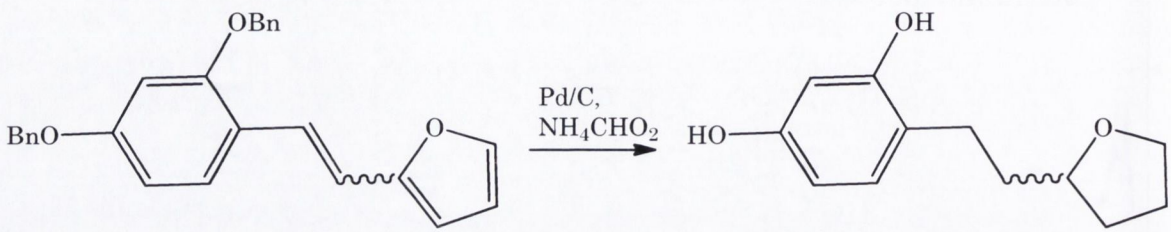
Figure 3-3: Possible routes for breakdown pathway of **11** upon treatment under standard hydrogenation conditions

Possible routes for breakdown pathway of **11** upon treatment under standard hydrogenation conditions

Assuming that the problem was an acid driven hydrogenolysis a series of experiments were then undertaken using increasing percentages of TEA (0.125% → 10%) but to no significant improvement towards production of a single identifiable product was noted, again returning an indecipherable array of multiple peaks.

A literature search highlighted the potential use of catalytic transfer hydrogenation using palladium on activated carbon and ammonium formate as

a hydrogen source to reduce conjugated furyl olefins.[165] A particularly pertinent example is shown below.



Scheme 3-6: – Catalytic transfer hydrogenation of 2-(2,4-bis(benzyloxy)styryl)furan

Again, however, using these conditions there was significant breakdown of the starting material *(E)*-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11** even at reduced temperatures.

5. Hydrogenation of the unsaturated ester

It was thought that the carboxylic acid function of (E)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11** was playing a significant part in its breakdown during hydrogenation.

As such it was hoped that the corresponding methyl ester **12** would prove to be more stable under the reaction conditions. Fischer esterification of **11** however resulted in the total breakdown of the starting material as evidenced by NMR spectroscopy.

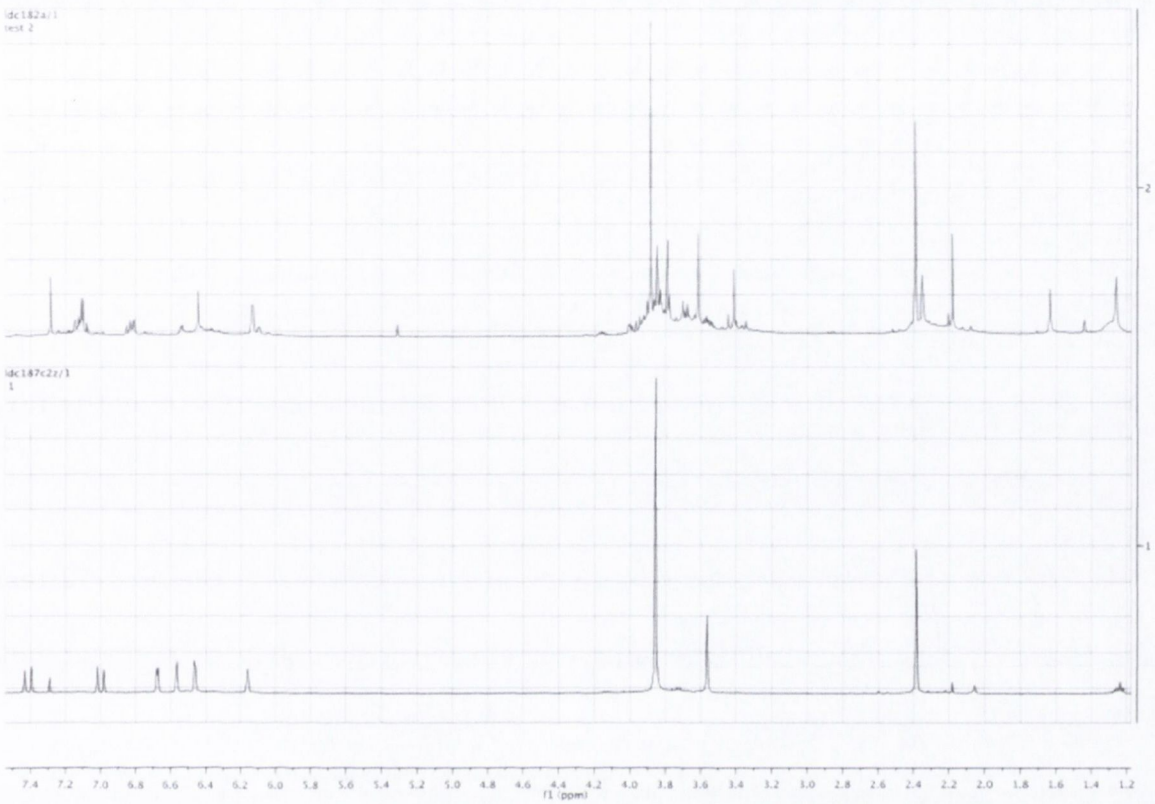
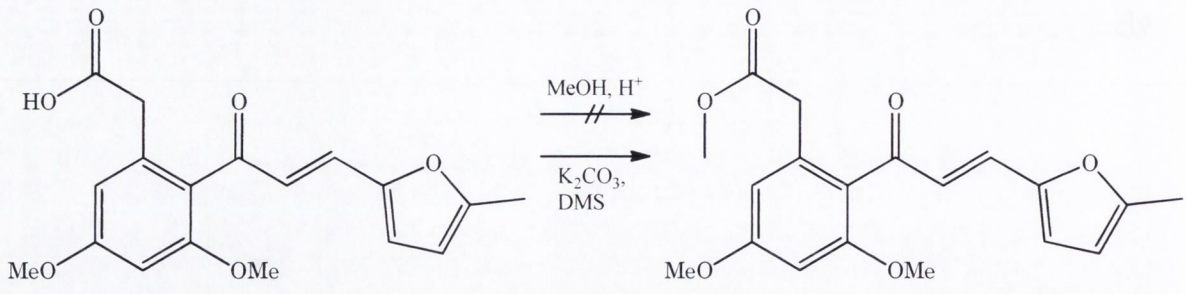


Figure 3-4: ^{1}H NMR spectrum of the breakdown product (top spectrum) of **11** (bottom spectrum) upon Fischer esterification treatment

Accordingly a return was made to the K_2CO_3/DMS methodology originally used to make the ester **8**. This resulted in a good return of product with the only drawback being the presence of a significant amount of residual DMS reagent. This was eventually removed *via* the addition of acetic acid during the work-up, to produce the volatile methyl acetate.



11 12

Scheme 3-7: Synthesis of (*E*)-methyl 2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetate **12**

The use of catalytic transfer hydrogenation as applied to the acid **12** resulted again in a significant degree of hydrogenolysis although some starting material was recovered.

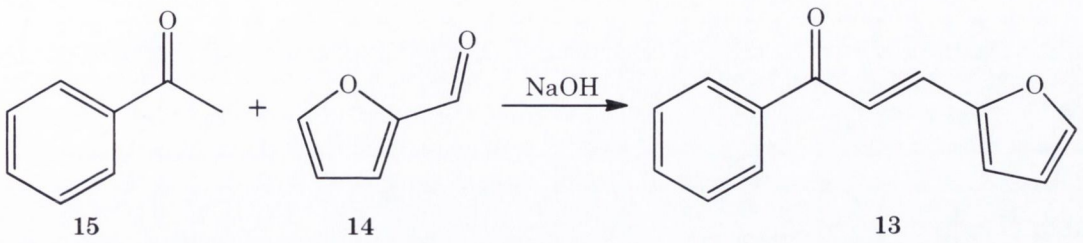
A return to the standard hydrogenation procedure of Pd/C under atmospheric pressure did finally result in the production of some 9% of the desired product **2**.

However the recovered yield of 9% was considered unacceptable for such a late stage in a total synthesis and a new approach was sought.

The source of instability of the precursors **11** and **12** may arise as a result of its benzyl methoxy groups contributing to the electronic density of the system.

Accordingly, a model hydrogenation compound, (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one **13,** was synthesised by the aldol condensation of

furaldehyde **14** with acetophenone **15** in order that alternative reduction techniques could be screened with a less valuable substrate.

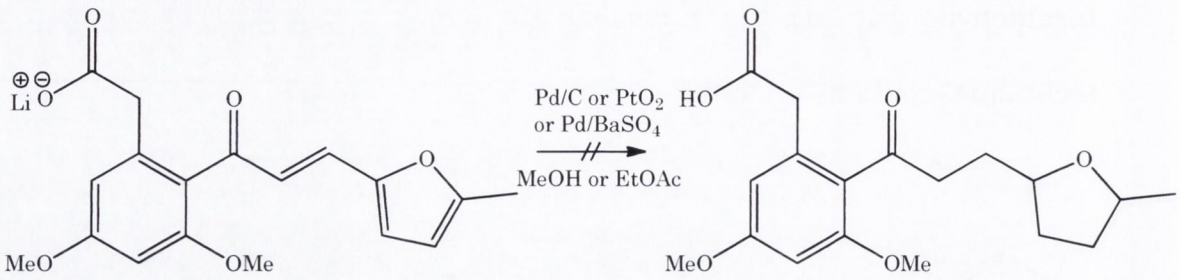


15 14 13

Scheme 3-8: Synthesis of model hydrogenation compound (E)-3-(furan-2-yl)-1-phenylprop-2-en-1-one **13**

However this model compound was not a perfect match as was shown in its clean reduction using platinum oxide as the catalyst whereas the use of the same conditions with the unsaturated precursor led to hydrogenolysis and breakdown yet again.

An alternative strategy that was raised at this time was the potential for hydrogenating the lithium salt of the precursor acid **11** in the hope that this would limit any intervention by the free carboxyl function. However, none of the tests carried out with a series of catalysts and conditions resulted in the formation of a single product instead mixtures of products were obtained.

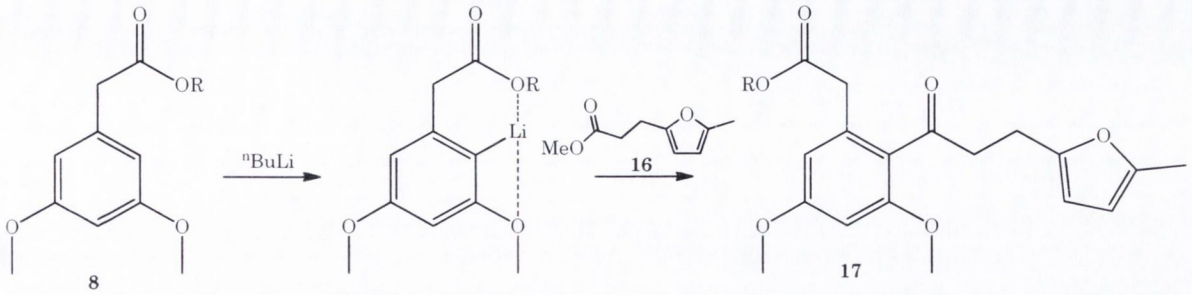


11 2

Scheme 3-9: Treatment of lithium salt of **11** under standard hydrogenation conditions

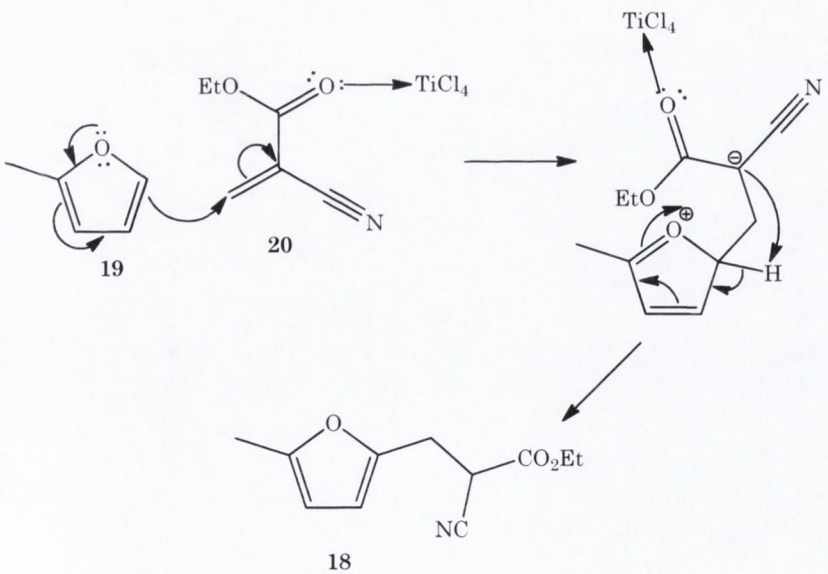
6. Ortho-lithiation route

The first route that was considered as an alternative involved proceeding *via* an ortho-lithiated version of the dimethoxy ester **8**. This could then be used as a nucleophile against a semi-hydrogenated furyl propanoate **16** to produce the semi-saturated precursor **17** which it was hoped would be more stable towards over-hydrogenation. The use of methoxy groups to promote *ortho*-lithiation is well-documented[166,167] as a precedent for this reaction, it was considered likely that the reaction would need to be undertaken using the lithium salt of the free acid of **8** to avoid enolisation.



Scheme 3-10: Proposed *ortho*-lithiation synthetic route to **17**

Attention firstly turned to the second coupling partner, it was hoped that the ester carbonyl of methyl 3-(5-methylfuran-2-yl)propanoate would be electrophilic enough for the reaction to proceed. The intermediate **18** was synthesised by the addition of 2-methyl furan **19** to ethyl cyanoacrylate **20**, the reaction mediated by a catalytic quantity of titanium tetrachloride.



Scheme 3-11: Mechanism for synthesis of methyl 2-cyano-3-(5-methylfuran-2-yl)propanoate **18**

The NMR spectroscopic data obtained for **18** is summarised in the table below. Key resonances in the ^{1}H NMR that indicate the synthesis of **18** are the disappearance of the aromatic proton α to the furyl oxygen and the concomitant appearance of a multiplet integrating for 2 protons centred between 3.14-3.29 ppm which is assigned to the methylene unit connecting the 2-methyl furan and the cyano-ester.

The remaining furyl protons are detected at 5.87 and 6.09 ppm as doublets with a coupling constant of 3.0 Hz. In addition to this, the characteristic triplet-quartet pattern of an ethyl ester is detected centred at 2.27 and 4.29 ppm respectively, with a coupling constant of 7.0 Hz.

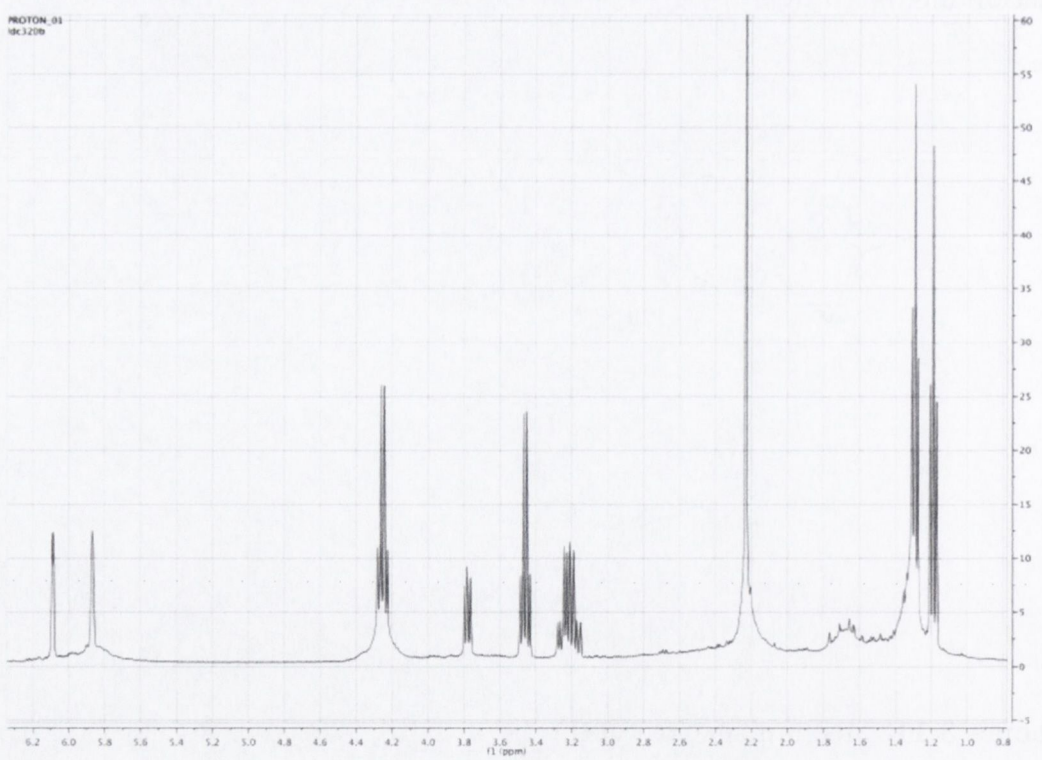


Figure 3-5: ^{1}H NMR spectra of ethyl 2-cyano-2-(5-methylfuran-2-yl)acetate **18**

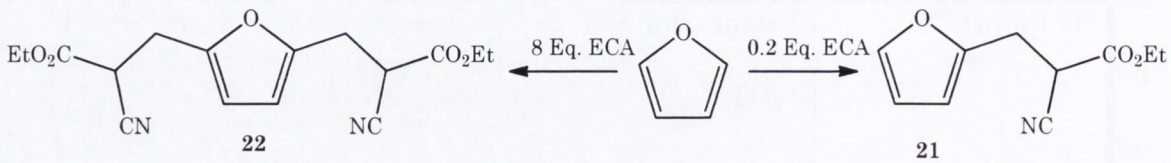
Table 13: ^{1}H NMR spectroscopic details of ethyl 2-cyano-2-(5-methylfuran-2-yl)acetate **18**

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.33	3H	t, *J* 7.0	$CH_2C\underline{H_3}$
2.27	3H	s	$\underline{CH_3}C$
3.14-3.29	2H	m	$\underline{CH_2}CHCN$
3.82	1H	dd, *J* 6.0 and 14.9	$C\underline{H}CN$
4.29	2H	q, J 7.0	OCH_2
5.87	1H	d, *J* 3.0	$CH{=}C\underline{H}{-}CH$
6.09	1H	d, *J* 3.0	$CH_3C\underline{H}{=}CH$

Surprisingly the analogous reaction with furan failed completely under the same conditions. A series of alternative Lewis acids were screened but this still resulted in no improvement.

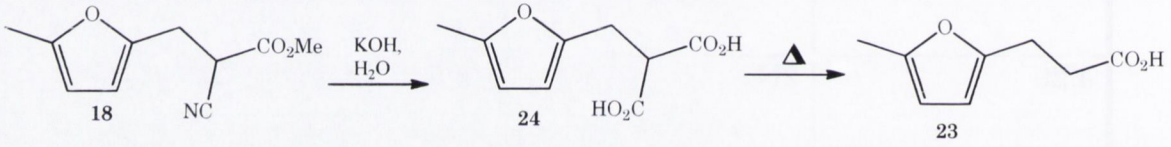
Changing the order of addition however such that $TiCl_4$ was added neat as the final component of the reaction mixture resulted in the formation of ethyl 2-cyano-3-(furan-2-yl)propanoate **21** in good yield (72%). Adjusting the

stoichiometry of the reaction also allowed for the double addition product, diethyl 3,3'-(furan-2,5-diyl)bis(2-cyanopropanoate) **22** to be generated.



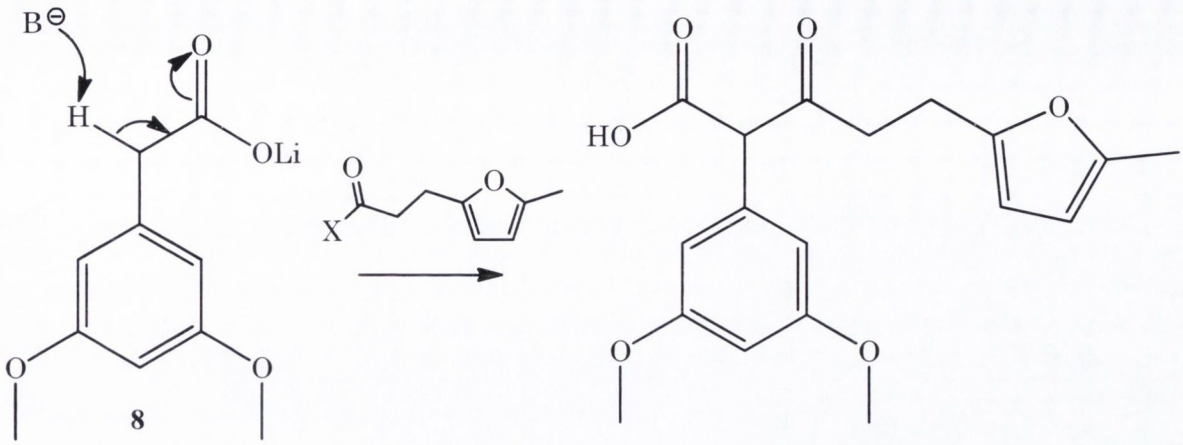
Scheme 3-12: Differential addition of ECA to furan to produce **21** and **22**

The cyano-ester **18** was subsequently converted into the acid **23** by a process of saponification and thermal decarboxylation.



Scheme 3-13: Synthesis of 3-(5-methylfuran-2-yl)propanoic acid **23**

However it was at this point that the directed *ortho*-lithiation route was abandoned, as a literature search highlighted the pKa of lithium carboxylates being low enough for ^{n}Bu-Li to abstract a proton α to the carboxylate[168] in preference over the intended phenyl proton.[169] The enolate ion thus formed would then act as a nucleophile following the addition of the furyl ester.

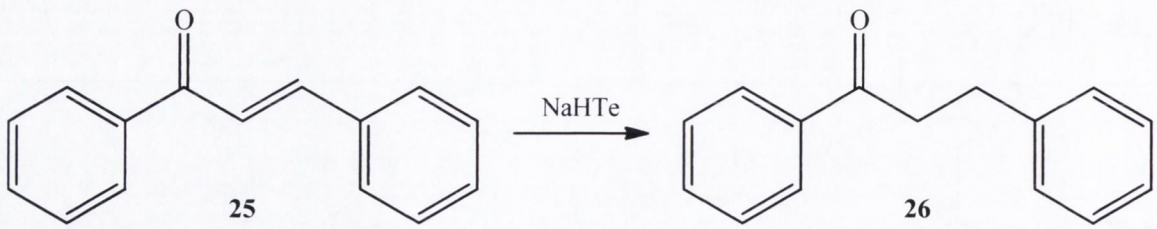


Scheme 3-14: Proposed alternative product of *ortho*-lithiation route to **17**

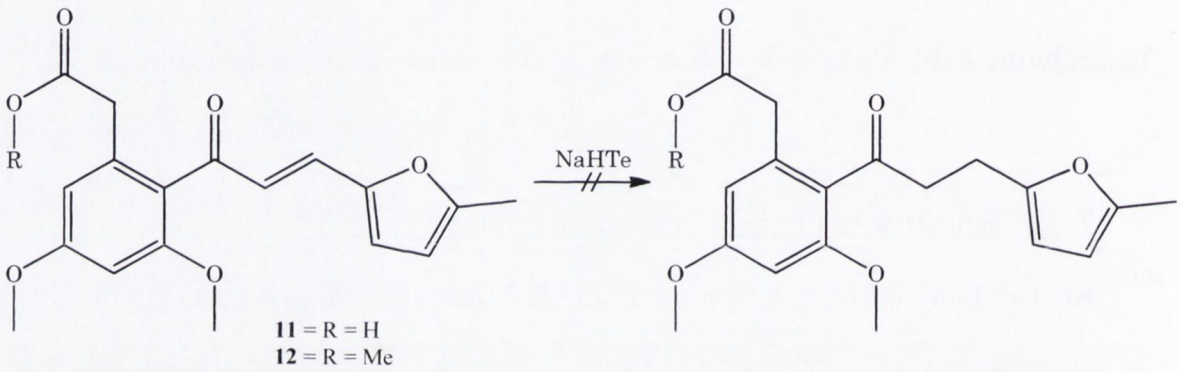
7. <u>Selective reduction of the conjugated enone of 11</u>

In tandem with the directed *ortho*-lithiation research detailed above a concerted series of experiments were being undertaken to determine the possibility of selectively reducing the α,β-unsaturated ketone function.

A literature search highlighted the use of sodium hydrogen telluride for just such a reaction[170]. However, although the reaction had been reported as not interfering with either phenyl or furyl groups neither the acid **11** nor the ester **12** gave any of the expected product **17**. Applying the same reaction conditions to the model compound **13** also failed to give any alkane by NMR analysis. In order to confirm that the NaHTe was successfully being produced by the *in situ* technique[171] and that an excess of the $NaBH_4$ used to produce it was not reducing the ketone a sample of chalcone **25** was subjected to the same conditions and found to have been selectively reduced.

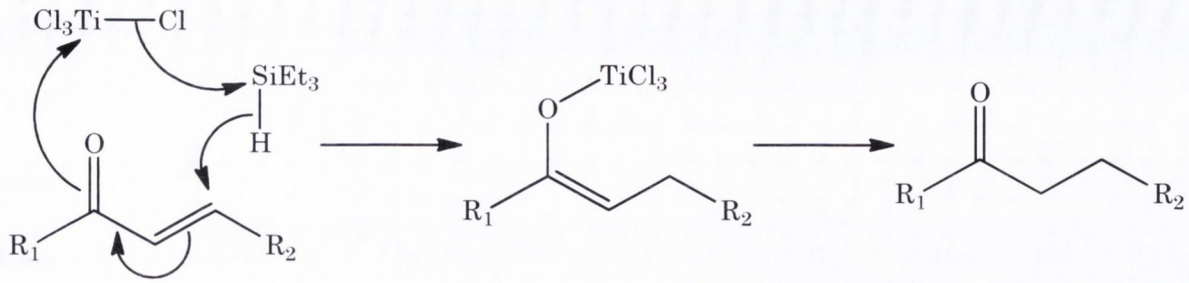


Scheme 3-15: Selective reduction of α,ß-unsaturated ketone of chalcone with sodium hydrogen telluride



Scheme 3-16: Treatment of **11/12** with sodium hydrogen telluride

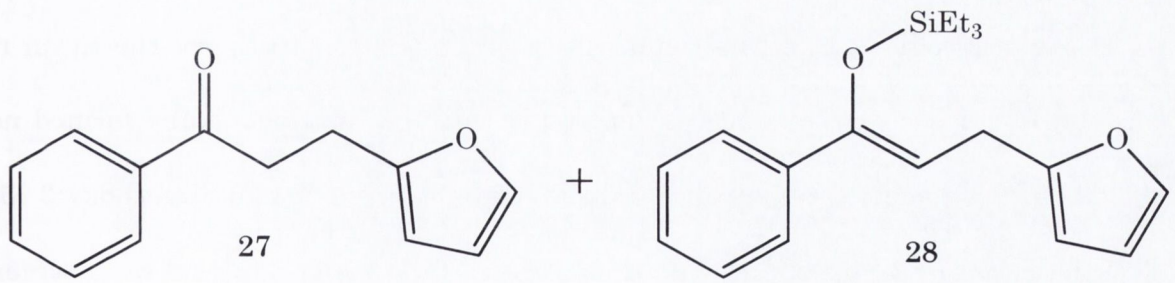
In parallel to this the use of triethyl silane as a selective reductant was being examined. This was initially investigated using titanium tetrachloride to activate the carbonyl bond allowing for hydride addition at the ß-carbon producing a titanium enolate which reverts to the saturated carbonyl compound upon aqueous work-up.



Scheme 3-17: Mechanism of titanium tetrachloride promoted selective reduction of α,β-unsaturated ketones

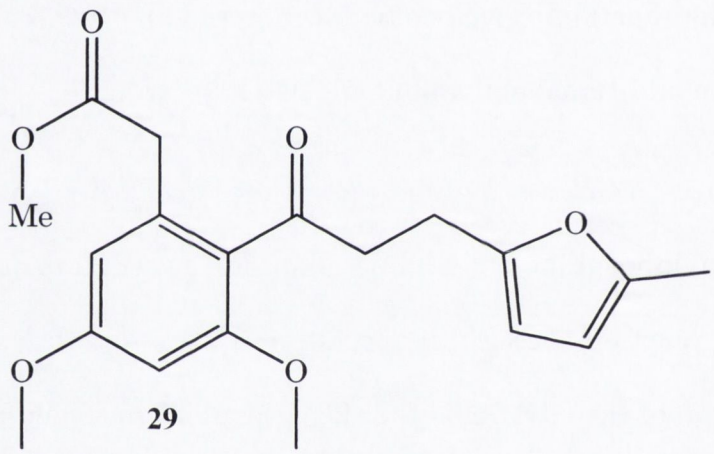
However, the reaction proved to be incompatible with the model compound **13** even with an additional equivalent of $TiCl_4$ to co-ordinate with the furan ring.

A literature search highlighted the use of Wilkinson's catalyst (tris(triphenylphosphine)rhodium(I) chloride) as an alternative to $TiCl_4$. The subsequent reaction successfully produced 3-(furan-2-yl)-1-phenylpropan-1-one **27** in addition to the silyl enol ether **28** equivalent in a roughly 1:2 ratio.



Scheme 3-18: Mixture of products formed by treatment of **13** with Wilkinson's catalyst and triethylsilane

The enol ether **28** was eventually broken down after stirring in aqueous HCl for 1 hour to yield the ketone. The reaction was then successfully applied to the unsaturated precursor ester **12**. The recovered product **29** was contaminated with side-products and required multiple applications of column chromatography during which there was noticeable breakdown into further by-products, to obtain a clean sample of methyl 2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)propanoyl)phenyl)acetate **29**.

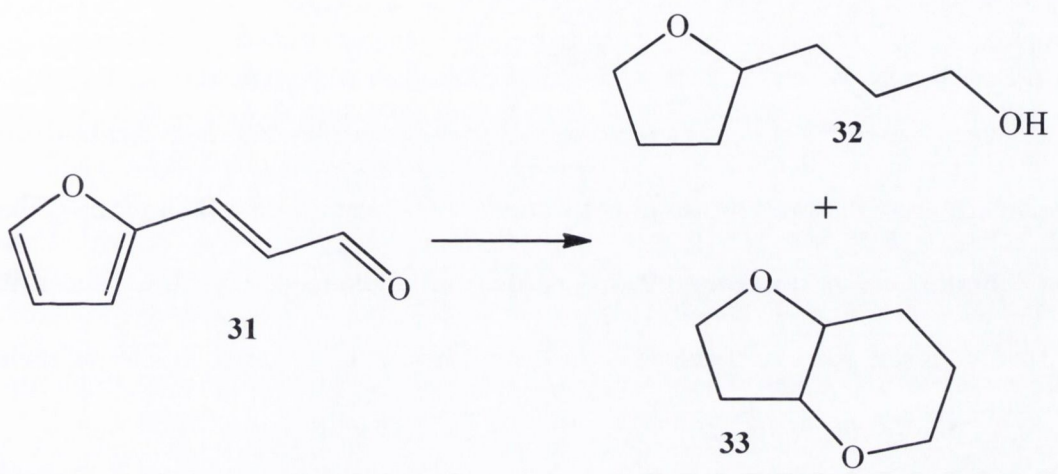


29

Catalytic reduction of this compound with a view to saturating the furan ring continued to be problematic, resulting in multiple products being formed none of which seemed to be the desired ester methyl 2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)propanoyl)phenyl)acetate **30**. Various catalysts were screened including Pd/C, $Pd/CaCO_3$, PtO_2, Wilkinson's catalyst and Rh/Al_2O_3 but with no significant improvement.

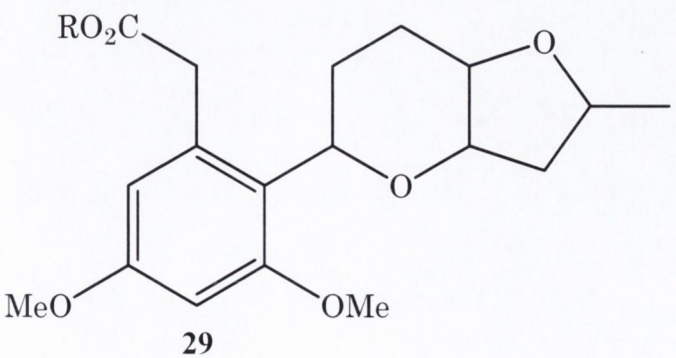
A probable cause for this instability was highlighted in a paper dealing with the hydrogenation of ß-furylacrolein **31**.[172] It was found that in addition to the

expected product 3-(tetrahydrofuran-2-yl)propan-1-ol **32** there was also significant formation of a fused diether identified as hexahydro-2H-furo[3,2-*b*]pyran **33**, often as the major or sole product.



Scheme 3-19: Products of catalytic hydrogenation of ß-furylacrolein

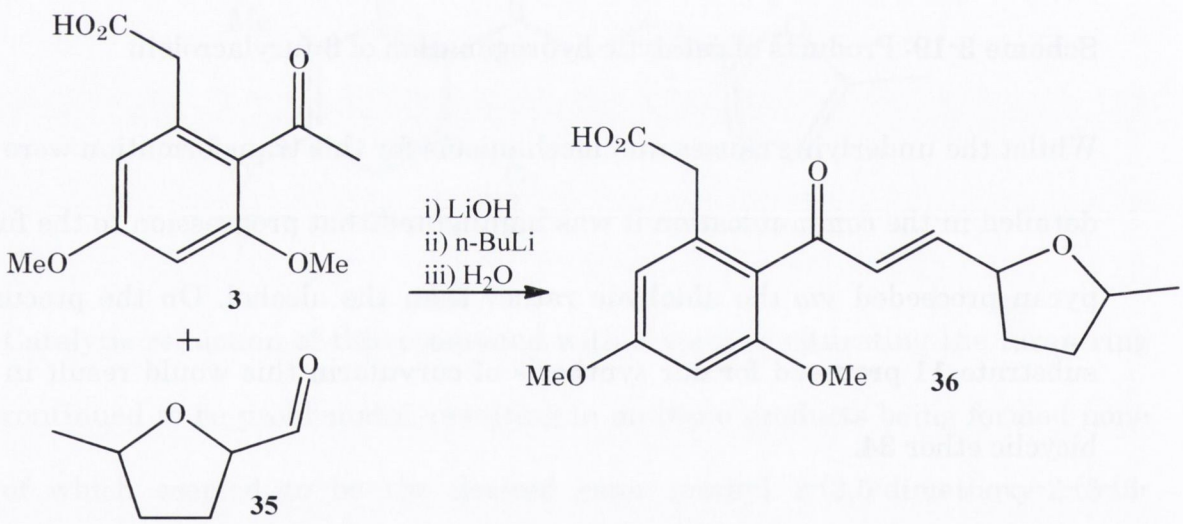
Whilst the underlying causes and mechanisms for this transformation were not detailed in the communication it was highlighted that progression to the furyl-pyran proceeded *via* the aldehyde rather than the alcohol. On the precursor substrate **11** proposed for our synthesis of curvularin this would result in the bicyclic ether **34**.



As a result of these difficulties it became clear that an alternative synthetic strategy was required.

8. Hydrogenation of 5-methylfurfural

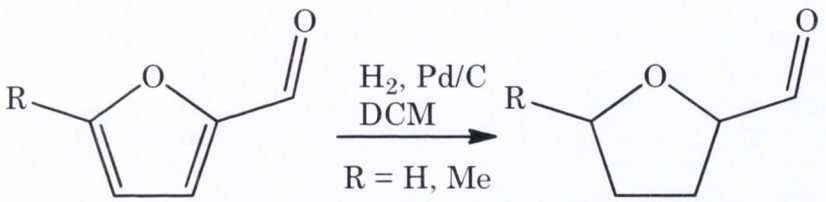
It was hoped that by using the fully saturated 5-methyltetrahydrofuran-2-carbaldehyde **35** in the aldol condensation reaction with **3** that the subsequent problems with hydrogenation could be bypassed as the remaining α,ß-unsaturated ketone function has been shown [see above] to be selectively reducible using Wilkinson's catalyst and triethylsilane.



Scheme 3-20: Proposed synthesis of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methyltetrahydrofuran-2-yl)acryloyl)phenyl)acetic acid **36**

The reduction of furfural by catalytic hydrogenation typically runs to completion, and leads to production of tetrahydrofurfuryl alcohol. A recent

report by Linares and Nudelman[173] indicated that the use of DCM as a solvent and Pd/C as the catalyst could selectively reduce furfural to the saturated aldehyde **37** at slightly elevated pressures.

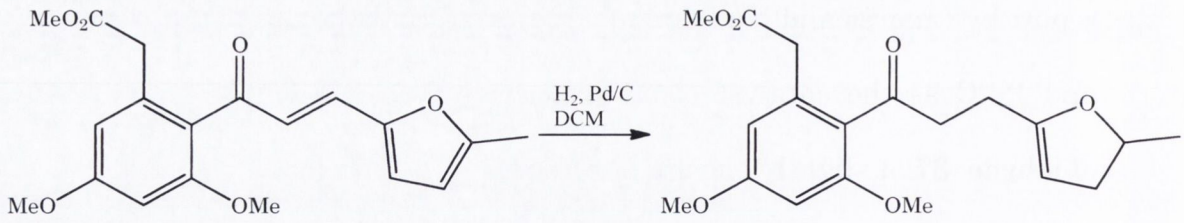


Scheme 3-21: Reported catalytic hydrogenation of furaldehydes

However, this reaction was not found to be reproducible, giving significant degrees of either hydrogenolysis or over reduction. Multiple permutations were examined including altered pressures, solvents and catalysts, but to no avail. The addition of triethylamine to mitigate hydrogenolysis had no effect.

The uptake of hydrogen at atmospheric pressure was monitored and there was found to be significant formation of multiple products, even after less than one molar equivalent of hydrogen had been taken up, necessitating consideration of an alternative strategy for the synthesis of 5-methyltetrahydrofuran-2-carbaldehyde **38**.

During this series of elevated pressure reactions, a set of conditions for the successful partial reduction of the fully unsaturated lithium salt of the precursor acid were found wherein the α,β-unsaturated ketone and the 4-5-double bond on the furan ring were selectively reduced without any significant further breakdown to give the enol ether **39**.



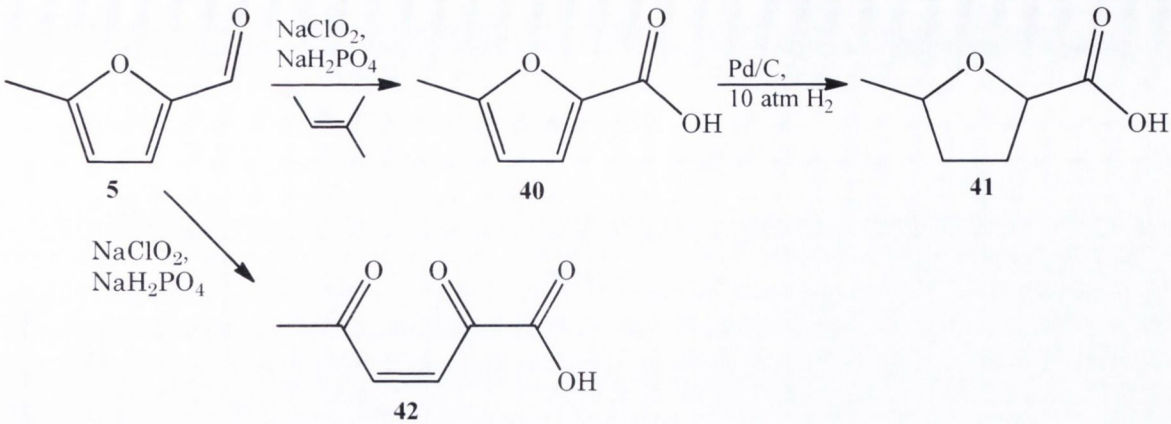
12 39

Scheme 3-22: Synthesis of **39** *via* partial hydrogenation of **12**

9. Alternative strategies for the synthesis of 5-methyltetrahydrofuran-2-carbaldehyde 38

The first approach to this was *via* oxidation of the aldehyde to the more stable acid followed by full hydrogenation of the furan ring and stepwise reduction of the acid to the alcohol and then oxidation to the aldehyde.

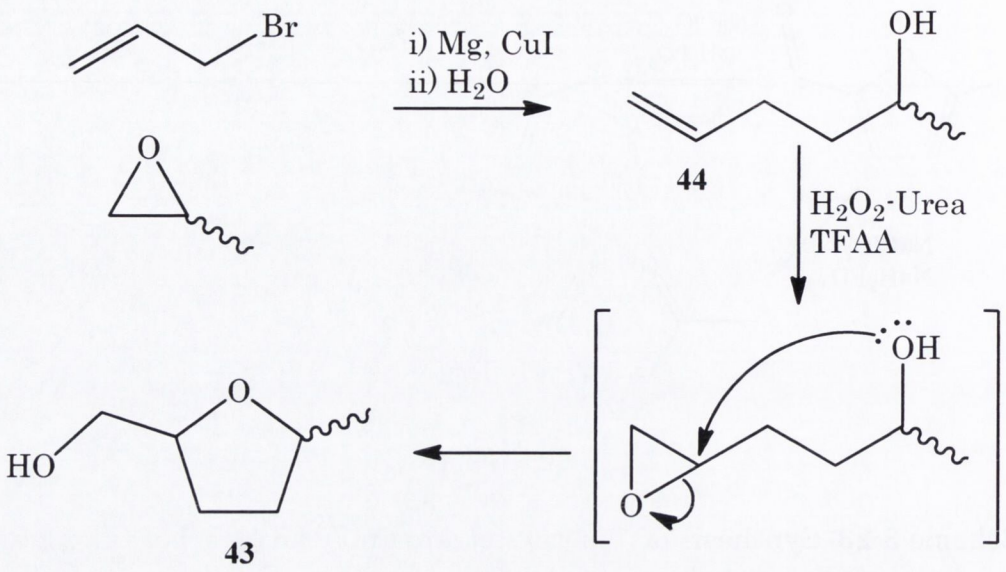
The first oxidation was undertaken using Pinnick conditions of sodium chlorite with 2-methyl-2-butene as a hypochlorite scavenger, the only side-product detected being from oxidative cleavage of the furan ring to give (*Z*)-2,5-dioxohex-3-enoic acid **42**.



Scheme 3-23: Synthesis of 5-methyltetrahydrofuran-2-carboxylic acid **41**

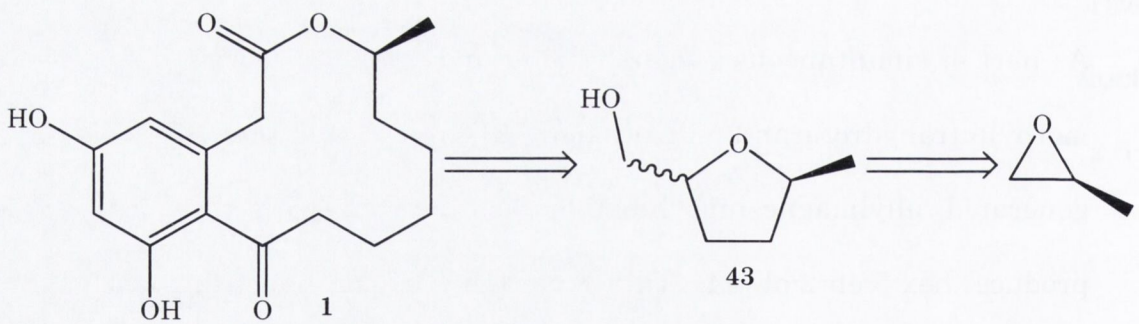
However the subsequent hydrogenation step faltered with either limited or no hydrogen uptake unless the 5-methylfuran-2-carboxylic acid **40** was recrystalised from ether. This did not remove the (*Z*)-2,5-dioxohex-3-enoic acid but the subsequent hydrogenation proceeded smoothly to give the fully saturated acid **41**.

As part of simultaneous research being undertaken a more facile route to (5-methyltetrahydrofuran-2-yl)methanol **43** was established wherein *in situ* generated allylmagnesium bromide was reacted with propylene oxide to produce hex-5-en-2-ol **44**. This was then epoxidised using the hydrogen peroxide adduct of urea and undergoes an *in situ* spontaneous 5-exo-tet cyclisation to form the alcohol **43** in excellent yield (98%).



Scheme 3-24: Synthesis of (5-methyltetrahydrofuran-2-yl)methanol **43**

An additional benefit to this route is the potential for selectively producing one enantiomer of the final lactone using a single enantiomer of the propylene oxide.

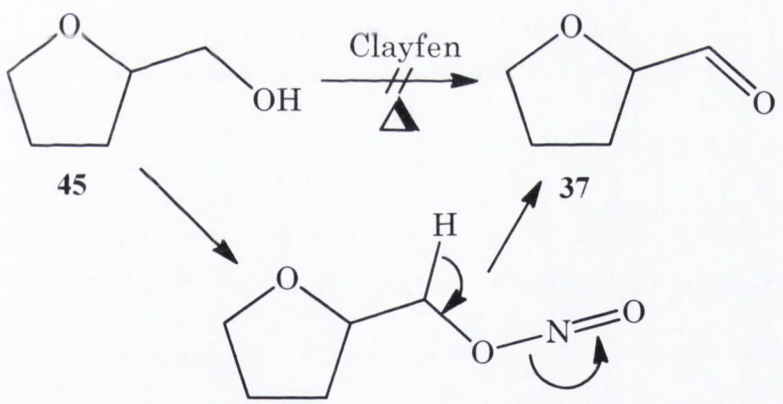


Scheme 3-25: Proposed retrosynthesis of single enantiomer of curvularin **1**

10. Oxidation of (5-methyltetrahydrofuran-2-yl)methanol 43

Attention then turned to the oxidation of the alcohol to the aldehyde **38.** The commercially available tetrahydrofurfuryl alcohol **45** was used as a test substrate, with the intention of synthesising tetrahydrofuran-2-carbaldehyde **37**, until a successful methodology was established.

Initial approaches focused on using montmorillonite clay-supported iron(III) nitrate as the oxidant. This reagent, known as clayfen, had been reported as causing oxidation *via* the nitrite ester to give a range of aldehydes in good yield (>90%) after refluxing overnight.[174] However none of the anticipated aldehyde **37** was recovered even with freshly prepared clayfen.



Scheme 3-26: Proposed oxidation of **45** *via* clayfen formed nitrite ester

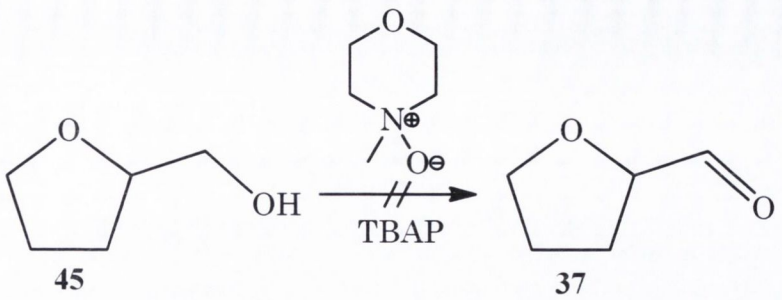
The reaction had, however, been reported as successful under solvent free conditions using microwaves.[175] Due to technical limitations an exact repetition of the reported experimental conditions (900 Watts, 30 seconds) was not possible but adaptations of various times and temperatures at 300 and 650

Watts were attempted. Whilst acidic, red nitrous by-product fumes were observed there was still no aldehyde noted after work-up.

The next technique investigated was an oxidation under Swern conditions using DMSO, oxalyl chloride and TEA, a technique that had been reported as successful for the oxidation of tetrahydrofurfuryl alcohol **45** by Bianchi *et al.*[176] However whilst the characteristic aldehyde proton peak was detected at 9.66 ppm it was by far the minor product of the reaction and formed in too small a quantity to be considered a route worth pursuing.

Pyridinium chlorochromate (PCC) was then investigated as an oxidant, but whilst it had shown promise in the oxidation of structurally similar alcohols[177] the recovered product of the reaction with tetrahydrofurfuryl alcohol showed no trace of any aldehyde.

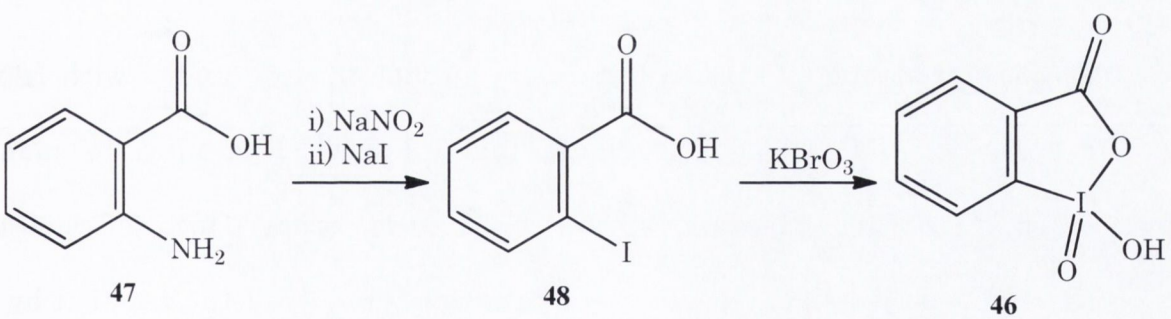
Tetra-n-butylammonium perrutheniate and tetra-n-propylammonium perruthenate have been reported as being excellent catalytic oxidants with sensitive substrates.[178] However, various attempts to synthesis the tetra-n-butylammonium perrutheniate failed, most likely due to a degraded sample of the starting ruthenium trichloride.



45 37

Scheme 3-27: Treatment of **45** with tetra-n-butylammonium perrutheniate and N-Methylmorpholine N-oxide

Finally, *o*-iodoxybenzoic acid (IBX) **46** was examined as an oxidant. This mild oxidiser was synthesised starting from anthranilic acid **47** which, after diazotisation and treatement with sodium iodide, produced 2-iodobenzoic acid **48** in excellent yield (96%).[179] This was then further oxidised to IBX using potassium bromate according to methodology originally laid out by Frigerio and Santagostino.[180]



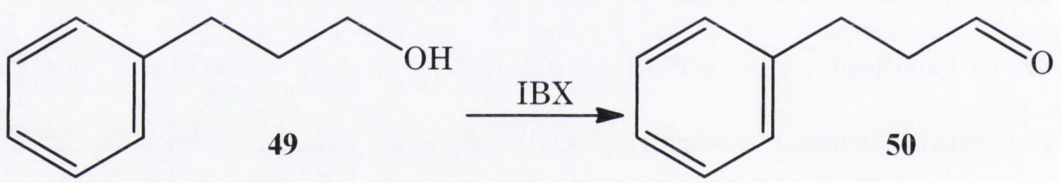
47 48 46

Scheme 3-28: Synthesis of *o*-iodoxybenzoic acid **46**

However, upon treatment of the alcohol with IBX in DMSO for 24 hours no product was recovered at all, either as the alcohol **45**, aldehyde **37**, or a

breakdown product. A literature search highlighted the boiling point of tetrahydrofuran-2-carbaldehyde **37** as being between 41-45 °C at 12-17 Torr[181,182] suggesting the possibility that the aldehyde was being synthesised but was being lost in the work-up.

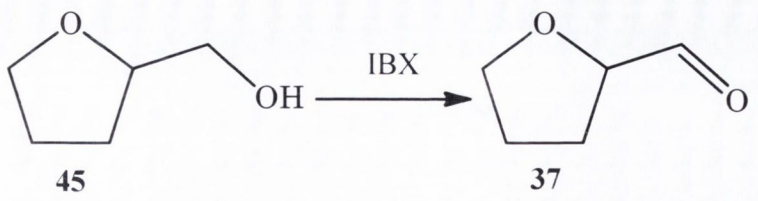
To examine this, two control reactions were carried out. Firstly 3-phenylpropan-1-ol **49** was subjected to identical reaction conditions in the hope that the less volatile aldehyde **50** thus produced would be isolable following evaporation of solvent at reduced pressure. This reaction worked well, as expected.



49 **50**

Scheme 3-29: Oxidation of 3-phenylpropan-1-ol **49** with IBX **46**

Secondly a sample of tetrahydrofurfuryl alcohol **45** was treated with IBX in deuteriated DMSO and an aliquot taken every 30 minutes to monitor progression of the oxidation using ^{1}H NMR spectroscopy. This confirmed that the aldehyde was being generated as the sole product of the reaction by the development of the characteristic aldehyde proton peak at 9.66.



45 37

Scheme 3-30: Oxidation of tetrahydrofurfuryl alcohol **45** with IBX

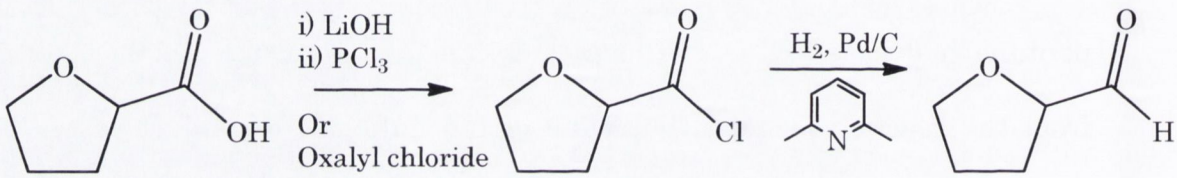
However, all efforts to isolate the aldehyde **37** from the reaction mixture by extraction using ether failed. Attempts to distil off the diethyl ether solvent resulted in high levels of entrainment, and switching the extraction solvent to pentane had no effect. An attempt was made to distil the aldehyde directly from the reaction mixture, but none of the anticipated product came across before decomposition began to occur.

A full literature search indicated that of the reported syntheses of tetrahydrofuran-2-carbaldehyde **37** the majority were inappropriate for our needs; either as a result of an expensive and inaccessible reagent,[183] the generation of multiple products,[184] or the reported method had generated **37** *in situ* in an appropriate solvent and subsequently introduced it as a solution into the next step.

The only reported successful isolation of the compound utilised the Swern oxidation technique and required a lengthy process of bulb-to-bulb distillation, resulting in a very poor yield (42%)[176] which was considered too low to have any application at such a late stage in a total synthesis with as valuable a substrate as (5-methyltetrahydrofuran-2-yl)methanol **43.**

11. Aldehyde synthesis by the Rosenmund reaction

A reaction protocol was thus sought which would allow for synthesis of the aldehyde in a suitable solvent and at an appropriate concentration for the succeeding aldol condensation. Within these parameters the most obvious route was to examine the possibility of converting tetrahydrofuran-2-carboxylic acid **51** into the acyl chloride **52** and performing a Rosenmund reaction to generate the aldehyde **37**.



51 **52** **37**

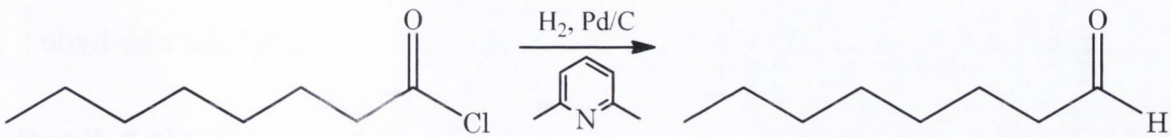
Scheme 3-31: Proposed synthesis of tetrahydrofuran-2-carbaldehyde **37** via Rosenmund reaction

The benefit of using the Rosenmund reaction to generate the aldehyde lies in its use of THF as a solvent, and removal of by-products and reagents by filtration producing a concentrated solution of the aldehyde in a solvent suitable for further transformations, including the all important aldol condensation reaction.

Conversion of the acid into the acyl chloride was initially undertaken by forming the lithium salt followed by treatment with phosphorous trichloride[141]. Inorganic phosphor salt precipitates, however, hindered the use of this route,

being resistant to filtration through a block of Celite and so a switch was made to using oxalyl chloride in DCM to generate the acyl chloride.[185]

Capability to exploit the Rosenmund reduction was first examined using octanoyl chloride **53** as a test compound.

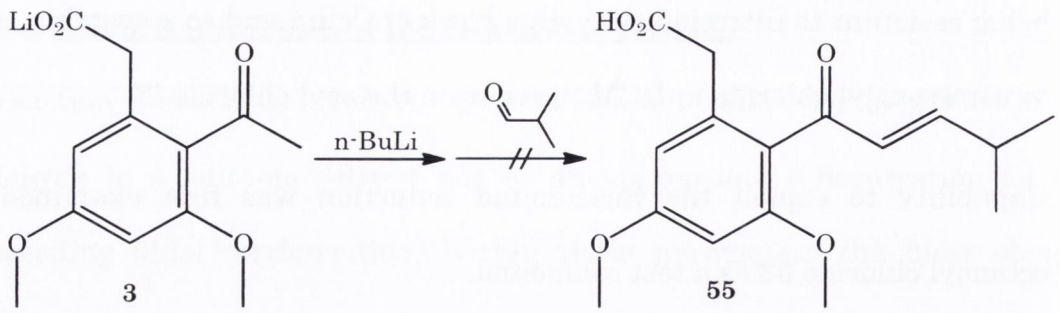


53 **54**

Scheme 3-32: Reduction of octanoyl chloride **53** *via* Rosenmund reaction

Whilst n-octanal **54** was successfully synthesised it was less clear as to whether the expected tetrahydrofurfuryl alcohol **45** had been successfully transformed, as any NMR of the filtered reaction mixture was swamped by the THF solvent signals at 1.35 and 3.76. Attempts to remove this solvent gave NMR spectra identical to that of tetrahydrofuran-2-carboxylic acid **51**, though it is unclear whether this was generated as a result of hydrolysis or of oxidation.

At this point it was considered necessary to test an aldol reaction of the protected precursor ketone **3** with an unsaturated aldehyde as an assurance that the reaction would proceed smoothly with tetrahydrofuryl-2-carbaldehyde **37**.



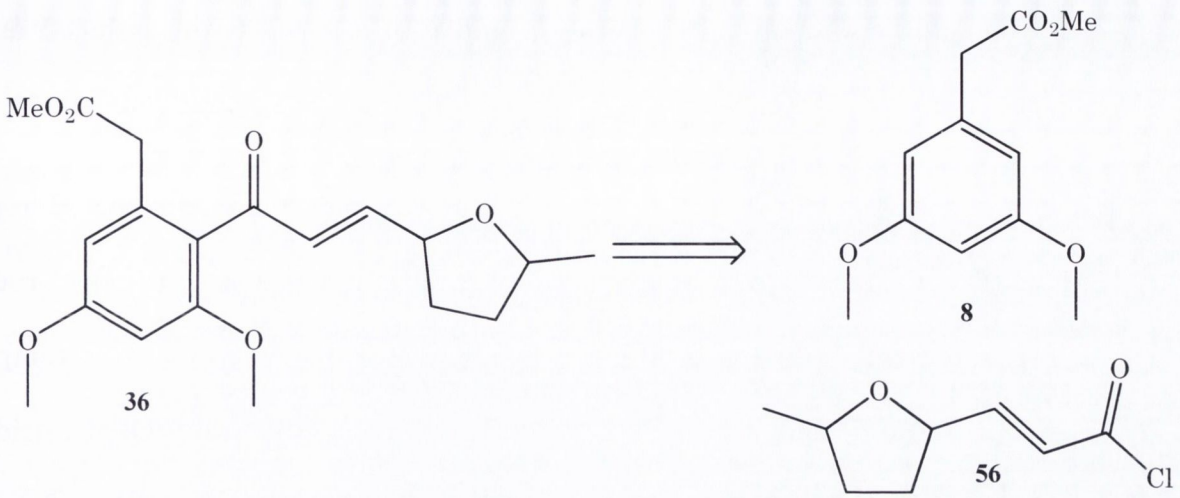
Scheme 3-33: Attempted aldol condensation of **3** with saturated aldehyde

However the reaction did not produce any of the expected (*E*)-2-(3,5-dimethoxy-2-(4-methylpent-2-enoyl)phenyl)acetic acid **55**, instead returning either a complex mixture of unidentifiable breakdown products or a return of starting materials.

As the simple saturated aldehyde did not condense as smoothly as hoped it was decided to give up on the tetrahydrofuran-2-carbaldehyde route and examine yet another alternative strategy.

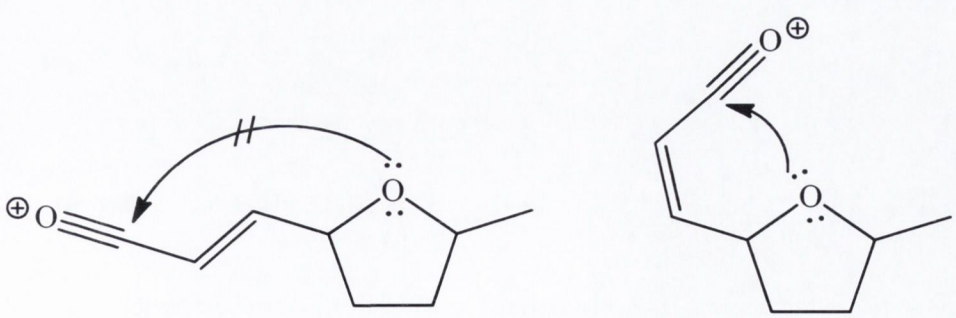
12. Alternative Friedel-Crafts reactions

The final synthetic strategy that was examined was to modify the Friedel-Crafts reaction and try to introduce a fully saturated tetrahydrofuran ring at this stage.



Scheme 3-34: Retrosynthesis of proposed alternative Friedel-Crafts reaction for the synthesis of **36**

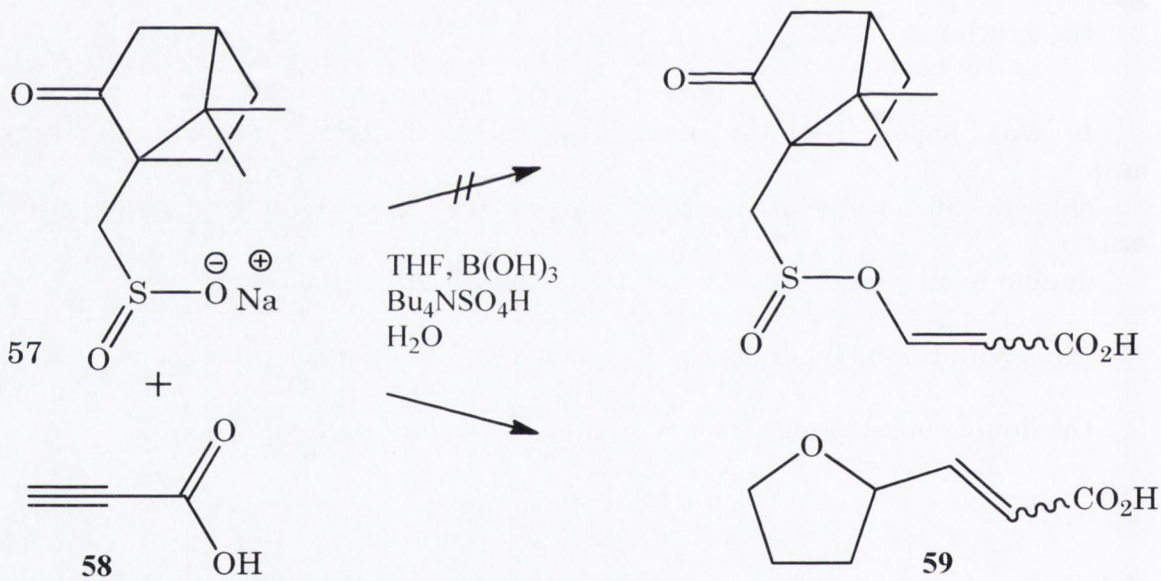
It was hoped that by using (*E*)-3-(5-methyltetrahydrofuran-2-yl)acryloyl chloride **56** as one of the coupling partners that the *E*-configuration of the double bond would prevent any intramolecular lactonisation upon formation of the acylium ion. Whereas the (*Z*) isomer would be more prone to cyclisation as the double bond angles the acylium ion towards the ring-oxygen.



Scheme 3-35: Effect of *E/Z* stereochemistry on the stability of intermediate acylium species formed during a Friedel-Crafts reaction

The resulting α,β-unsaturated ketone could then be selectively reduced using the triethylsilane/Wilkinson's catalyst route outlined in **Section 7** above.

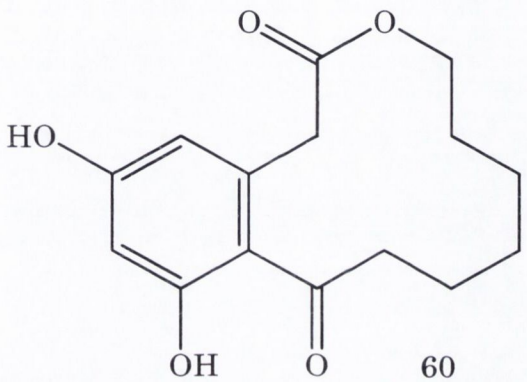
The synthetic route to the (*E*) acid chloride exploited an unexpected result obtained within the group as part of separate investigations into novel routes towards optically pure substituted tetrahydrofurans wherein an attempted nucleophilic addition coupling of camphor sulfinic acid **57** and propiolic acid **58** instead produce a racemic mixture of *E/Z* 3-(tetrahydrofuran-2-yl)acrylic acid **59** was recovered as the principle product.



Scheme 3-36: Synthesis of 3-(tetrahydrofuran-2-yl)acrylic acid **59**

Whilst investigations into the limitations of this novel reaction are still in their preliminary stages, the equivalent 5-methyltetrahydrofuryl analogue has not yet been successfully synthesised, *i.e.* application of similar reaction conditions

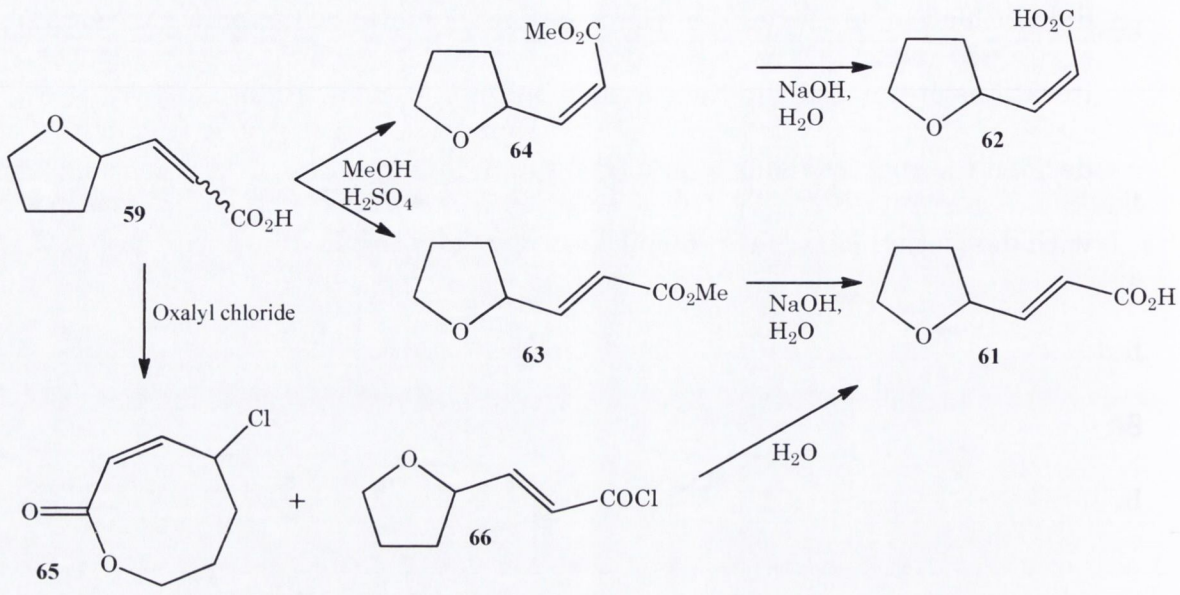
did not lead to any formation of the desired 5-methyl compound. Various iterations of the reaction have been examined to no avail and as such it was decided to progress using as a model the 3-(tetrahydrofuran-2-yl)acrylic acid **59** with desmethyl-curvularin **60** as the target end-product.



60

The mixture of isomeric acrylic acids **61** and **62** was esterified using $MeOH/H_2SO_4$, allowing for an easier separation by column chromatography. Whilst the (*Z*)-acid **62** appears to be the slightly more preferred product of the reaction (*Z*/*E* ratio 6:4) there is also evidence to suggest that extended periods of reflux during esterification may produce greater quantities of the more thermodynamically-preferred (*E*)-alkene.

This was followed by saponification to return pure samples of each of the acids. Treatment of the (*E*)-acid **60** with oxalyl chloride produced the relatively stable acyl chloride **66**, whereas the (*Z*)-acid **62**was handily converted into a neutral product that may be the δ-chloro lactone **65**.



Scheme 3-37: Synthesis and isolation of *E* and *Z* isomers of 3-(tetrahydrofuran-2-yl)acrylic acid **61** and **62**

The NMR spectroscopic data obtained for **61** is summarised in the table below. Key resonances in the ^{1}H NMR that indicate the synthesis of **61** are the pair of signals corresponding to the *E* olefinic protons; a doublet centred at 6.01 ppm with a coupling constant of 15.6 Hz assignable to the hydrogen α to the carboxylic acid and a double doublet centred at 7.00 ppm with coupling constants of 15.4 and 5.3 Hz. The remaining proton's signals present themselves as a series of multiplets due to the large degree of diastereotopicity present in the small ring.

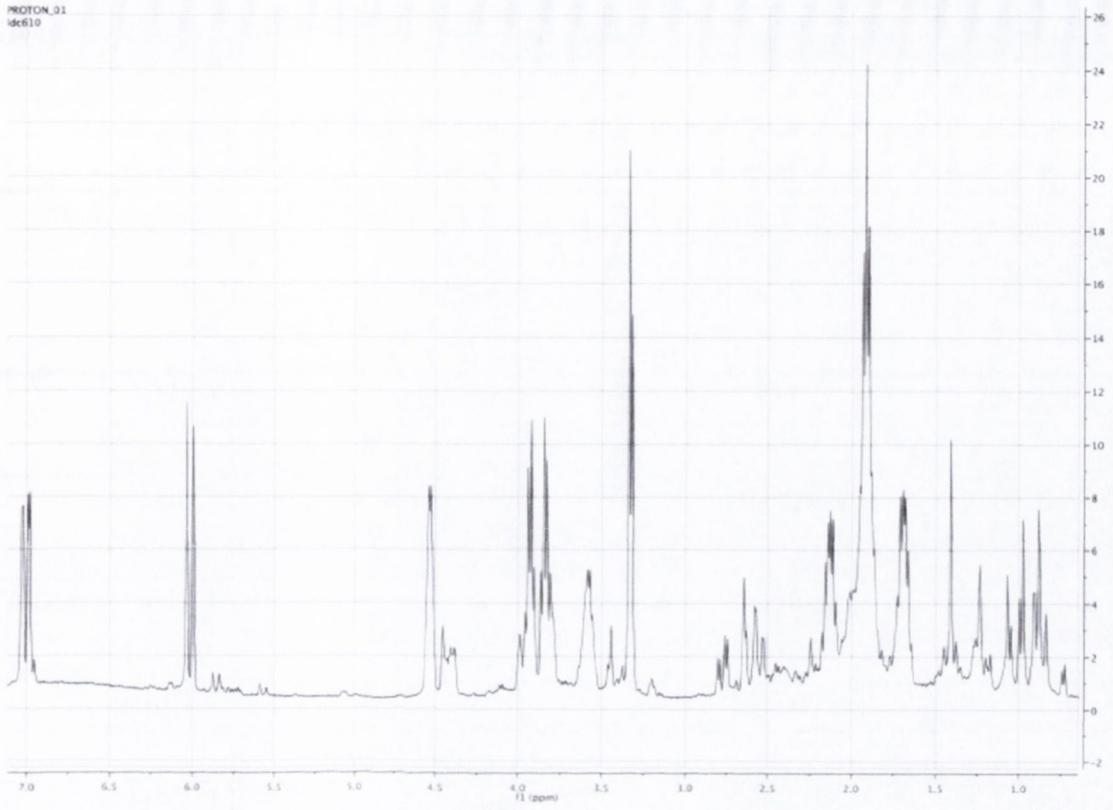


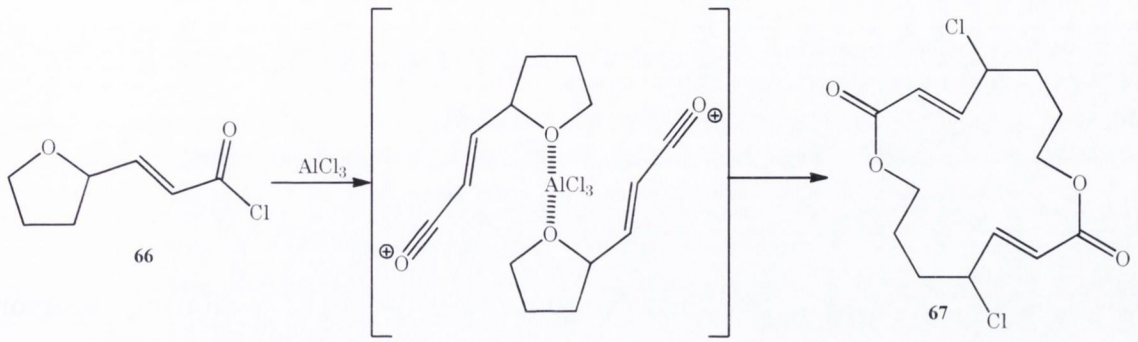
Figure 3-6: ^{1}H NMR spectrum of (*E*)-3-(tetrahydrofuran-2-yl)acrylic acid **61**

Table 14: Analysis of ^{1}H NMR spectrum of (*E*)-3-(tetrahydrofuran-2-yl)acrylic acid **61**

^{1}H (ppm)	Integration (^{1}H NMR)	Multiplicity (^{1}H NMR)	Assignment
1.68	1H	m	$C4H_a$
1.92	2H	m	$C5H_2$
2.32	1H	m	$C4H_b$
3.84	1H	m	$OC6H_b$
3.93	1H	m	$OC6H_a$
4.53	1H	q *J* 7.2	CHO
6.01	1H	d, *J* 15.6	$CHCO_2$
7.00	1H	dd, J_{ab} 5.3 and 15.4	CHC<u>H</u>=

Unfortunately, whilst the (*E*)-acyl chloride **66** was stable enough to handle for brief periods at room temperature, when it was introduced as part of a Friedel-Crafts reaction the only products recovered were the starting dimethoxyester **8** and a lactonic product. This neutral extract is believed to be the diolide lactone

67 derived from the (*E*)-acyl chloride, presumably as a result of co-ordination to a central aluminium atom (*cf.* Chapter 2).



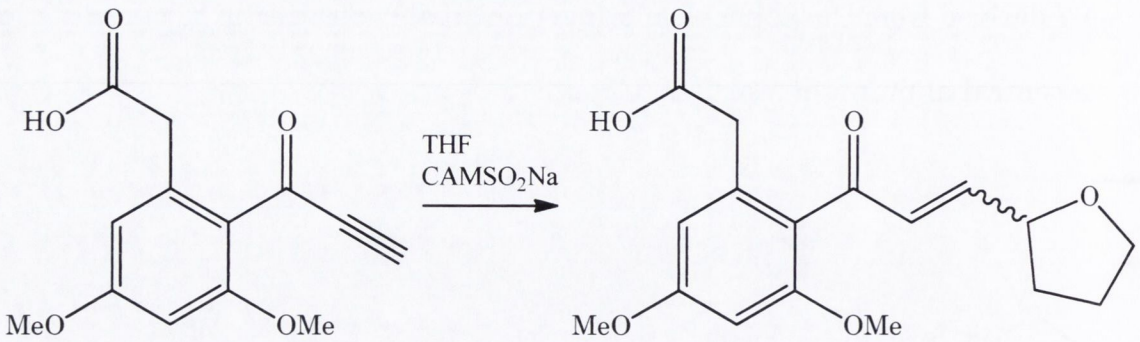
Scheme 3-38: Dimerisation of (*E*)-3-(tetrahydrofuran-2-yl)acryloyl chloride **65** templated on aluminium trichlorde

13. Conclusions and future work

Whilst it is profoundly frustrating not to have completed a total synthesis of curvularin **1**, several options remain open to produce the target compound.

It may be possible that use of a less reactive mixed anhydride of (*E*)-3-(tetrahydrofuran-2-yl)acrylic acid **61** in the Friedel-Crafts acylation step, rather than the acyl chloride **66**, may prevent formation of diolides.

Another route that deserves to be explored would be *via* the synthesis of 2-(3,5-dimethoxy-2-propioloylphenyl)acetic acid **68**, followed by the radical addition of tetrahydrofuran (or, better, 2-methyltetrahydrofuran) to the terminal alkyne function.



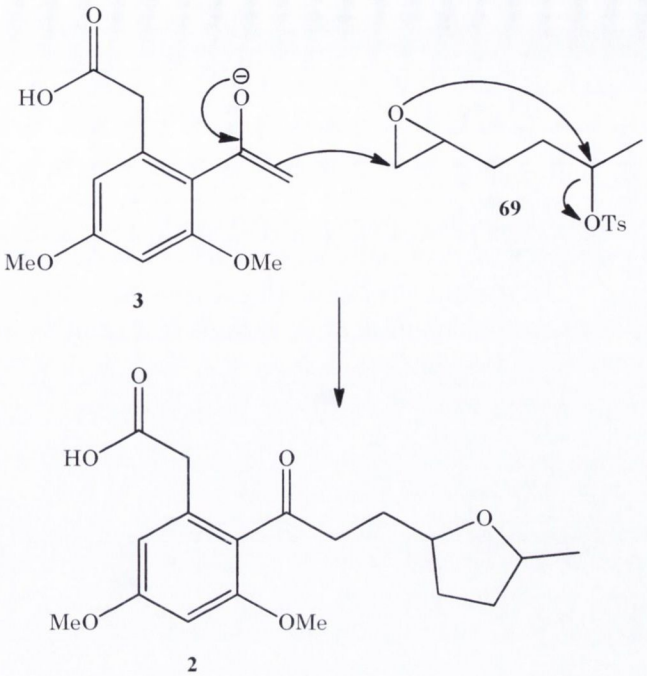
68

Scheme 3-39: Proposed alternative route to desmethyl-curvularin precursor

This route, though, is obviously limited by the difficulty of synthesising the alkyne, as the Friedel-Crafts coupling partner propioloyl chloride is not obtainable by standard flask chemistry and has been reported as being explosive.

It is possible that a number of the breakdown paths that the fully unsaturated precursor **11** undergoes could be limited by an appropriate protection of the ketone function.

Finally, an approach that has been considered is nucleophilic addition of the enolate of the ketone **3** to 4-(oxiran-2-yl)butan-2-yl 4-methylbenzenesulfonate **69**, to give an intermediate that would hopefully then undergo a spontaneous tandem intramolecular cyclisation reaction to generate the saturated precursor **2**.

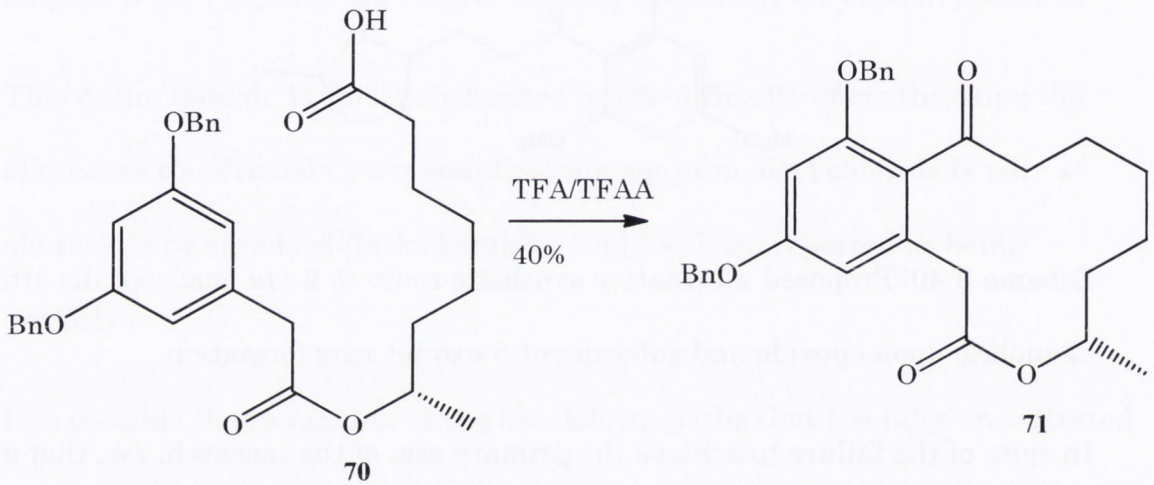


Scheme 3-40: Proposed alternative synthetic route to **2** *via* nucleophilic attack of enolate upon epoxide and subsequent 5-exo-tet ring formation

In spite of the failure to achieve the primary aim of the research, *i.e.*, that of a total synthesis of curvularin **1**, a number of key advances have been made. For example, the additions of ethyl cyanoacrylate to furan, and of tetrahydrofuran to propiolic acid both possess a great deal of synthetic applicability and need to be explored fully in order to understand the limits of the new reactions.

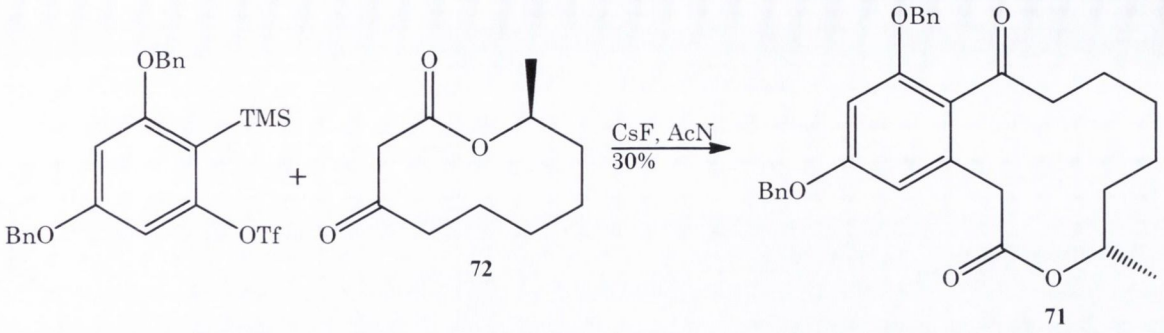
Of the current methodologies reported in the literature for the lactonic ring closure of a total synthesis of curvularin **1** only two target the natural (S) enantiomer. The earlier of the two methods relies on an intramolecular Friedel-Crafts acylation reaction of an ω-carboxylic ester **70** as the final ring closing step to produce a curvularin precursor **71**.

First developed by Bycroft in 1967[186] as part of a total synthesis of di-*O*-curvularin the reaction was modified by Gerlach to produce pure curvularin **1**.[187] The same methodology has been applied several times in the pursuit of total syntheses and structural analogues but consistently delivers a very poor yield of 40% or lower, [188-190] something which the results detailed in chapter 2 of this thesis appear to indicate could be improved upon.



Scheme 3-41: Synthesis of curvularin precursor **71** *via* Bycroft methodology

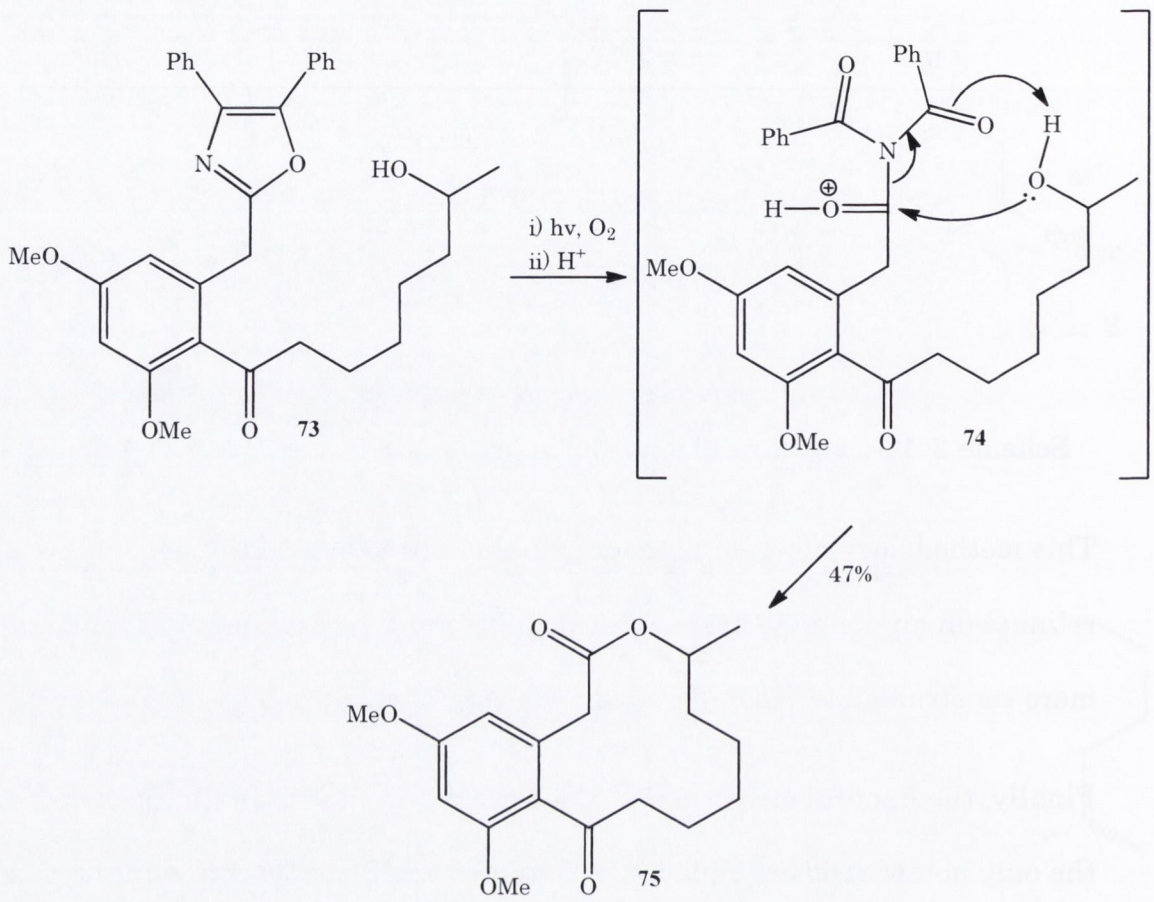
Recently a second methodology has been established for the synthesis of chirally pure curvularin by an aryne acyl alkylation reaction.[162]



Scheme 3-42: Synthesis of curvularin precursor **71** *via* Tadross methodology

This methodology however is severely limited both by its low yield (30%), reliance on an unstable aryne intermediate and the necessity of forming a more constrained ten membered lactone ring **72** in a previous step.

Finally, the handful of syntheses which are reported only in the racemic form the only noteworthy example is Wasserman's methodology wherein the ring closing step forms the ester bond of the lactone.[191] The reaction uses an ω-hydroxycarboxylic acid starting material wherein the acid is protected as an oxazole **73**, in the final step this is converted to a carboximide leaving group **74** promoting lactonisation to a protected curvularin analogue **75**.



Scheme 3-43: Synthesis of curvularin precursor **75** *via* Wasserman methodology

The reaction does however still suffer from low yields (47%) and a lack of any control over which enantiomer is synthesised, depending on which of the future work routes detailed above is successfully exploited one of both of these drawbacks may be overcome.

In summation, macrolactonisation *via* intramolecular acylative cleavage of a tetrahydrofuran ring has been shown to be a useful and creative addition to the library of functional group transformations. Typically delivering yields of

more than 70%, which is roughly comparable to the average yields of most of the more notable techniques in macrolactonisation (c.f. the Yamaguchi reagent typically gives 60-80% yield).

Compared to ring closing metathesis as a methodology for synthesising macrolactones the newly developed technique's primary advantage is the low price and ease of availability of the reagents used. However, this is counteracted by the reagents needing to be used in stoichiometric quantities rather than catalytically.

Depending on the exact reaction conditions used the reagents employed may also be far less harsh in comparison with other more notable techniques (c.f. acid catalysed Fisher esterification or the of ω-hydroxycarboxylic acid with the use of TFAA and copper acetate).

That the reaction is capable of producing a variety of end products from the same starting material may be seen as both a positive and a negative depending both on whether the target molecule is substituted δ to the annular oxygen, and whether the target molecule may be part of an array of organic compounds undergoing screening against a disease target or a single target molecule, for example as part of a natural product synthesis.

Finally, a distinct advantage that the macrolactonisation reactions developed in the work presented here possess above those currently in the literature is

it's capability to selectively produce either the monomer or the dimer depending on the reagents rather than on reaction conditions.

There are however negative aspects to the newly developed reaction. The starting tetrahydrofurylcarboxylic acids are more intricate, requiring a more protracted series of precursor molecules than the ω-hydroxycarboxylic acids used with the Yamaguchi reagent.

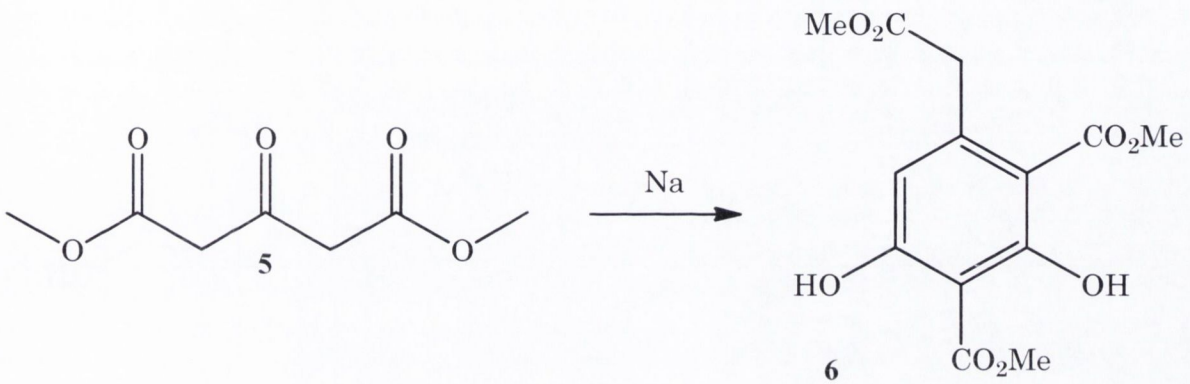
Whilst some of the reaction conditions used are relatively benign some, such as those used to produce monomer chlorolactones (refluxing $CHCl_3$ in the presence of $TiCl_4$ or FeC_3), can be very harsh potentially leading to side-reactions and consequentially lower yields of greater impurity compared to less aggressive reagents such as ring closing metathesis.

Finally, that the reaction mechanism is still not fully understood, specifically the contrivance by which the production of monomers and dimers is delineated, is a negative aspect of the newly developed reaction.

These objections aside however, the reaction remains a useful, interesting addition to the library of organic functional group transformations and deserves to be explored and exploited further.

14. Experimental

Dimethyl 2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)isophthalate 6



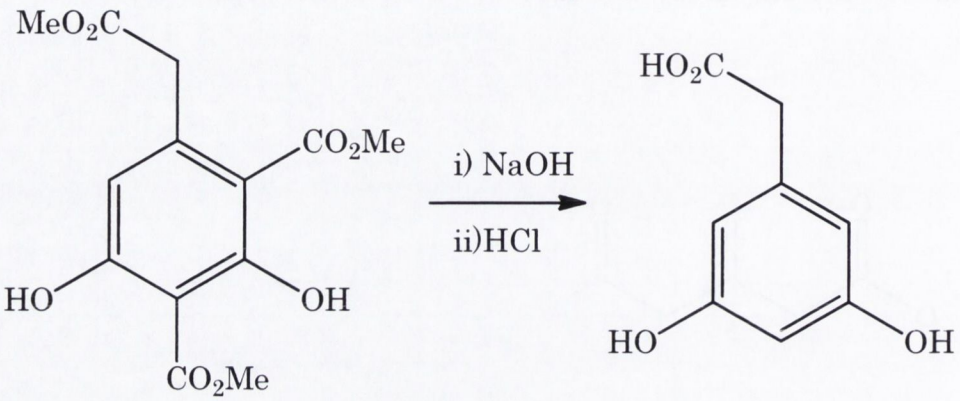
Finely divided sodium (0.25 g, 10.8 mmol) was added slowly to a flask containing dimethyl 1,3-acetonedicarboxylate **5** (20.01 g, 0.11 mol) and the mixture was heated to reflux under nitrogen overnight. The solid that formed upon cooling was recrystallised from methanol (100 ml) to give fine white crystals of dimethyl 2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)isophthalate[192] **6** (6.98 g, 41%).

υ_{max}, 2925, 1731 (C=O), 1670, 1580 cm^{-1}

δ_H (400 MHz; $CDCl_3$) - 3.71(s, 3H, $CO_2\underline{Me}$), 3.83 (2H, s, CH_2), 3.89 (3H, s, OMe), 4.04 (3H, s, OMe), 6.40 (s, 1H, H_{ar}), 12.06 (s, 1H, OH), 13.00 (s, 1H, OH) ppm

m/z; (HRMS (ES)) calculated for $C_{13}H_{14}O_8$ expected 298.0689, found 321.0594 (M + Na)

2-(3,5-Dihydroxyphenyl)acetic acid 7



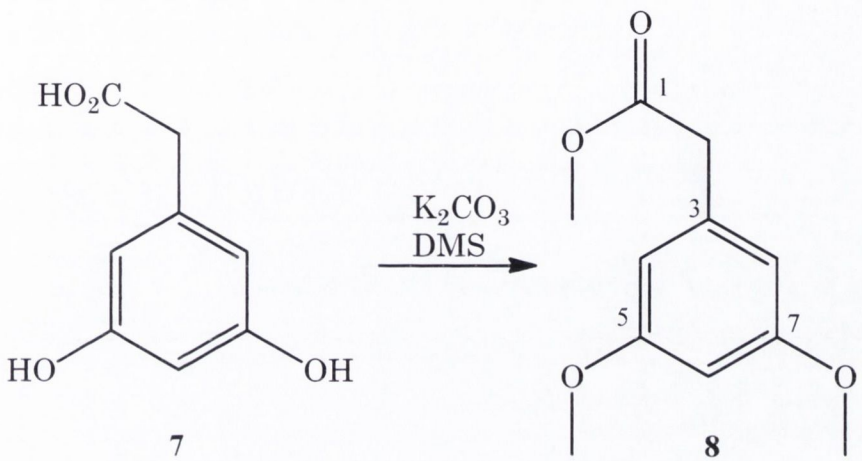
6 **7**

Dimethyl 2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)isophthalate **6** (13.65 g, 46 mmol) was dissolved in aqueous NaOH (14%, 72 ml), a condenser was attached and the mixture was refluxed overnight. Upon cooling the reaction mixture was acidified with conc. HCl, activated charcoal was added and the flask was returned to reflux for 30 minutes. The cooled mixture was then filtered and extracted with ethyl acetate (4 x 50 ml). The combined organic extracts were then washed with brine and dried over MgSO4 and the solvent evaporated to reveal 2-(3,5-dihydroxyphenyl)acetic acid[193] **7** as a clear oil (7.2 g, 92%) which was analysed and used without further purification.

υ_{max}, 3274 (OH), 2922, 1701 (C=O), 1608 (C=C), 1460 cm^{-1}

δ_H (400 MHz; DMSO-d_6) - 3.32 (2H, s, CH_2), 6.04 (1H, s, CH_{ar}), 6.07 (s, 2H, CH_{ar}), 9.12 (2H, br s, OH) ppm

Methyl 2-(3,5-dimethoxyphenyl)acetate 8



7 **8**

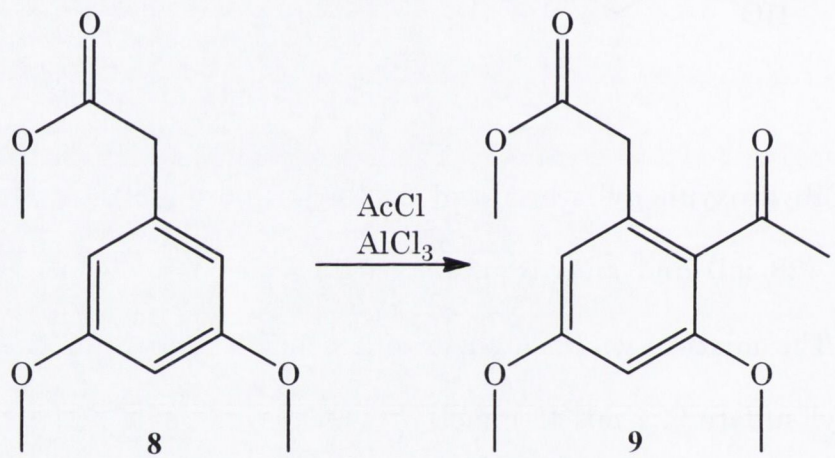
2-(3,5-Dihydroxyphenyl)acetic acid **7** (2.4 g, 14.6 mmol) was dissolved in dry acetone (28 ml) and anhydrous potassium carbonate (6.45 g, 46 mmol) was added. The mixture was heated to reflux for an hour prior to the addition of dimethyl sulfate (4.1 ml, 43 mmol) at which point the reaction was allowed to stir overnight. The reaction was quenched with water (100 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were sequentially washed with 5% KOH (50 ml), water (2 x 50 ml) and brine (50 ml) prior to drying over $MgSO_4$ and removal of the solvent *in vacuo* to give methyl 2-(3,5-dimethoxyphenyl)acetate[194] **8** (2.68 g, 87%) as an orange oil which was analysed and used without further purification.

υ_{max}, 3080, 1738 (C=O), 1598 (C=C), 1105, 1058, 953 cm^{-1}

δ_H (400 MHz; $CDCl_3$) - 3.54 (2H, s, CH_2), 3.68 (3H, s, CO_2Me), 3.76 (6H, s, OMe), 6.36 (1H, s, CH_{ar}), 6.42 (2H, s, CH_{ar}) ppm

δ_C (400 MHz; $CDCl_3$) 41.2 (CH_2), 52.1 (OMe), 99.0 (C6), 107.4 (C2,4), 136.1 (C3), 159.9 (C5,7), 172.3 (CO_2) 160.8 (3', 5'-C), 136.0 (1'-C), 107.3 (2',6'-C) ppm

Methyl 2-(2-acetyl-3,5-dimethoxyphenyl)acetate 9



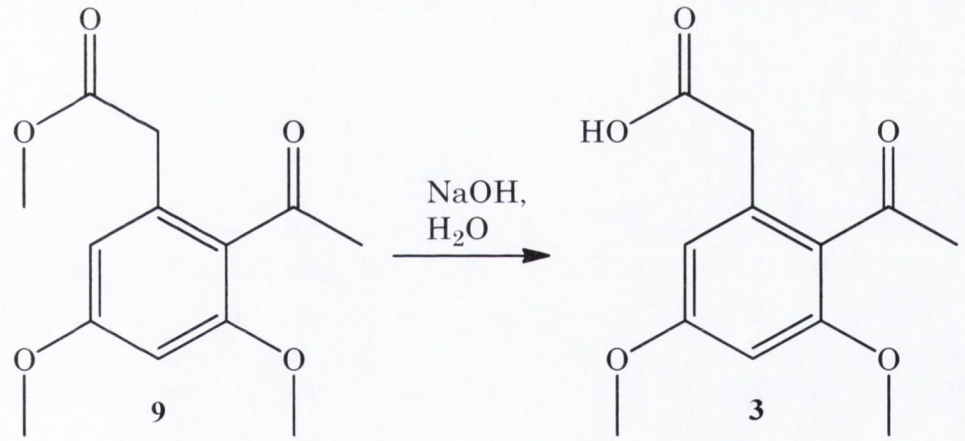
A three-necked flask with a dropping funnel and reflux condenser attached was charged with finely ground aluminium trichloride (1.19 g; 8.9 mmol), DCM (30 ml) and a magnetic stir-bar. The flask was cooled to 0 °C in an ice bath prior to the addition of freshly distilled acetyl chloride (0.48 ml; 6.7 mmol) at which point the contents of the flask were left to stir for 10 minutes. Methyl 2-(3,5-dimethoxyphenyl)acetate **8** (1.21 g, 5.7 mmol) was then slowly added and the flask heated to reflux under nitrogen for four hours. The cooled reaction mixture was quenched over ice water and extracted with DCM (50 ml). The

lower organic layer was washed sequentially with aqueous sodium hydroxide (0.1 M), water and brine before drying over $MgSO_4$. Removal of the solvent *in vacuo* gave methyl 2-(2-acetyl-3,5-dimethoxyphenyl)acetate[195] **9** as an off white solid (0.81 g; 56%) which was analysed and used without further purification.

υ_{max}, 2990, 1718 (C=O), 1594 (C=C), 1050 cm^{-1}

δ_H (400 MHz; $CDCl_3$) - 2.53 (3H, s, $C{=}OCH_3$), 3.71 (3H, s, CO_2Me), 3.73 (2H, s, CH_2CO_2), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 6.37 (1H, d, *J* 2.0, CH_{ar}), 6.44 (1H, d, *J* 2.3, CH_{ar}) ppm

2-(2-Acetyl-3,5-dimethoxyphenyl)acetic acid 3



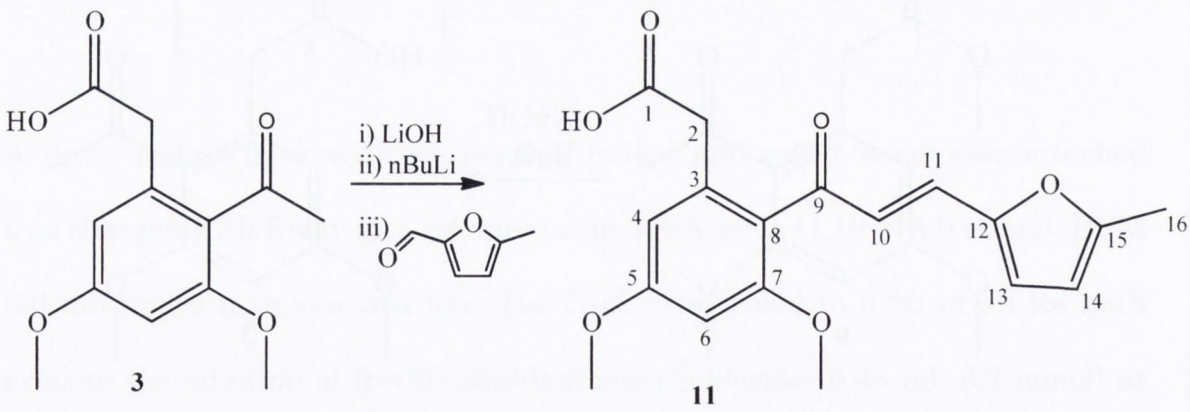
To a solution of methyl 2-(2-acetyl-3,5-dimethoxyphenyl)acetate **9** (1.70 g; 6.7 mmol) in methanol (20 ml) was added an aqueous solution of sodium hydroxide (3.5 M, 2.25 ml). The flask was heated to reflux for 12 hours. Upon cooling the methanol was removed *in vacuo* and the remaining product diluted with water

and washed with ether. The lower aqueous layer was acidified with concentrated HCl and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were dried with $MgSO_4$ and the solvent removed at reduced pressure to give 2-(2-acetyl-3,5-dimethoxyphenyl)acetic acid[196] **10** as a white solid (1.4 g; 89%) which was analysed and used without further purification.

υ_{max}, 3275, 1718 (C=O), 1060 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.65 (3H, t, C=OMe), 3.60 (2H, s, CH_2CO_2), 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 6.45 (1H, d, *J* 2.12, CH_{ar}), 6.53 (1H, d, *J* 2.36, CH_{ar}) ppm

(*E*)-2-(3,5-Dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid 11



2-(2-Acetyl-3,5-dimethoxyphenyl)acetic acid (1.5 g; 6.3 mmol) **3** was treated with an aqueous solution of lithium hydroxide (0.1 M, 70 ml) and the water diligently removed at reduced pressure. The resulting crystals were finely

ground and suspended in a round bottomed flask containing dry THF (120 ml). The flask was flushed with nitrogen and cooled to -40 °C. n-Butyl lithium (6.4 ml; 2.5 M in hexanes; 16 mmol) was added dropwise and the mixture was allowed to stir for 20 minutes. 5-Methylfurfural **4** (0.76 ml; 7.6 mmol) was then added dropwise and the flask allowed to warm to room temperature overnight. The reaction mixture was quenched over ice water (200 ml) and washed with diethyl ether (50 ml). The lower aqueous layer was acidified with concentrated HCl and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were sequentially washed with water and brine prior to drying over $MgSO_4$ and removal of the solvent *in vacuo* to give dark red crystals. Recrystalisation from diethyl ether gave (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid[196] **11** (1.8 g; 88%) as a fine orange powder.

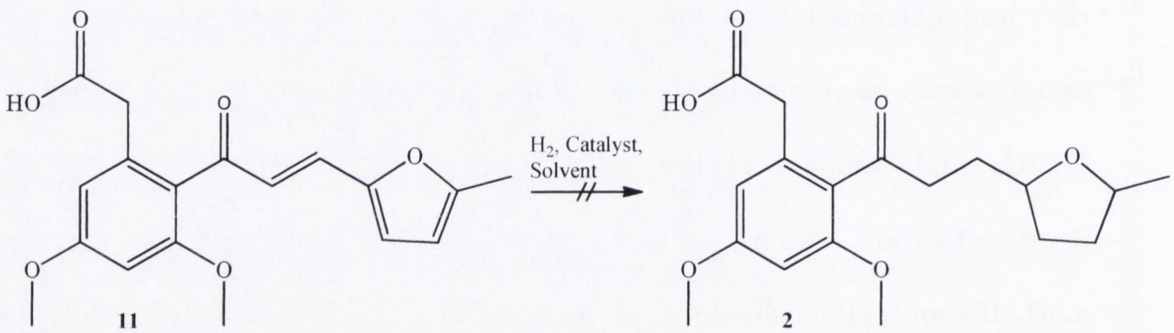
υ_{max}, 2942, 1710 (C=O), 1155 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.40 (3H, s, CH_3), 3.37 (2H, s, CH_2CO_2), 3.87 (6H, s, OMe), 6.17 (1H, d, *J* 3.0, $H_{13/14}$), 6.47 (1H, d, *J* 1.5, $H_{4/6}$), 6.58 (1H, d, *J* 2.0, $H_{4/6}$), 6.70 (1H, d, *J* 3.1, $H_{13/14}$), 7.01 (1H, d, *J* 15.4, $H_{10/11}$), 7.44 (1H, d, *J* 15.6, $H_{10/11}$) ppm

δ_C (400 MHz; $CDCl_3$) 13.6 (C16), 41.4 (C2), 55.2 (OMe), 55.4 (OMe), 97.7 (C4), 106.9 (C6), 109.2 (C14), 119.0 (C13), 122.6 (C11), 130.4 (C10), 135.5, 149.4, 156.2, 159.5, 162.3, 171.5 (C1) ppm

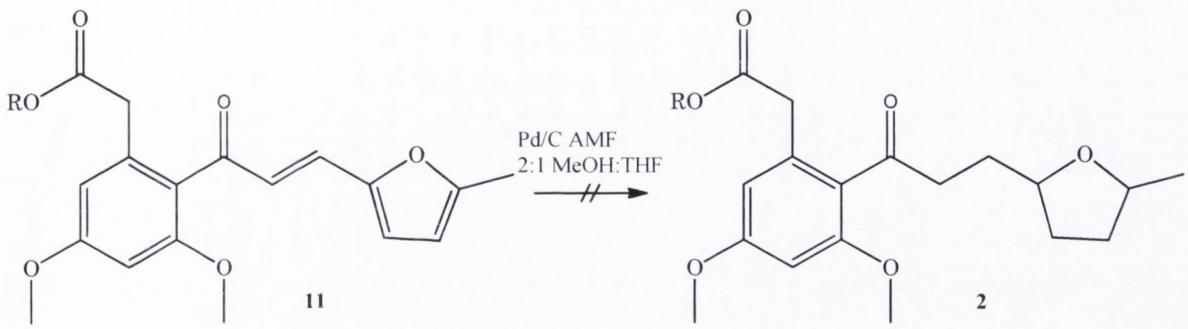
m/z; (HRMS (ESI)) calculated for $C_{18}H_{18}O_6$ expected 330.1103, found 353.1008 (M + Na)

Generalised procedure for treatment of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid 11 under standard hydrogenation conditions



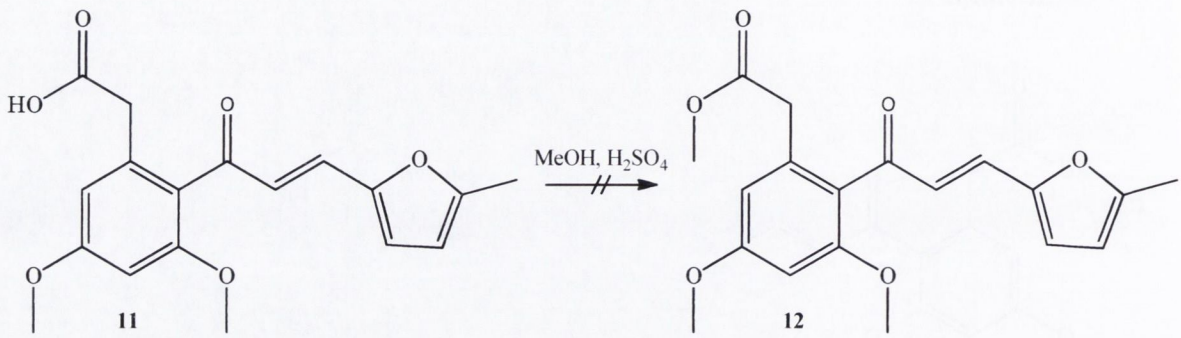
As a representative procedure the use of Pd/C in methanol is described. A solution of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11** (50 mg, 0.21 mmol) and palladium on activated carbon (20 mg) in methanol (20 ml) was stirred under a blanket of hydrogen at atmospheric pressure. Once uptake of hydrogen had appeared to cease the reaction mixture was filtered through a plug of Celite and the solvent removed at reduced pressure. NMR analysis of the crude product showed it to be a complex mixture containing none of the expected tetrahydrofuran alkane.

Treatment of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid 11 under catalytic transfer hydrogenation conditions



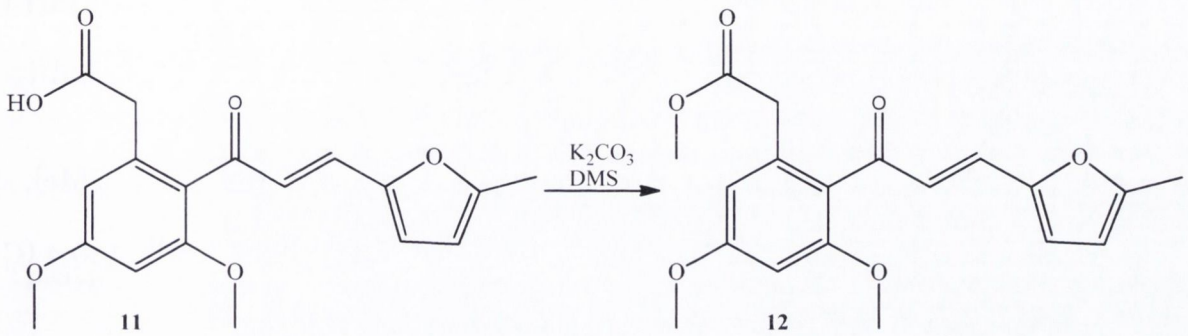
(*E*)-2-(3,5-Dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid (65 mg; 19 mmol) **11** was dissolved in methanol (2 ml) and THF (1 ml) in a round bottom flask with a tap side-arm and a reflux condenser. Palladium on activated carbon (10 mg) was added and the system was flushed with nitrogen. A solution of ammonium formate (148 mg; 2.3 mmol) in methanol (2 ml) and THF (1 ml) was added and the system was heated to reflux for 3 hours. Upon cooling the reaction mixture was filtered through a plug of Celite, washed with water, dried over $MgSO_4$ and the solvent removed at reduced pressure. NMR analysis of the crude product showed it to be a complex mixture containing none of the expected tetrahydrofuran alkane.

Treatment of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid 11 under Fischer esterification conditions



To a solution of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid (25 mg; 0.7 mmol) in methanol (20 ml) was added sulfuric acid (1 ml). The reaction mixture was heated to reflux under nitrogen for 12 hours. After cooling approximately 90% of the methanol was removed at reduced pressure. The remaining residue was diluted with water (50 ml) and extracted with ethyl acetate (3 x 20 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. None of the expected tetrahydrofuran ester was found in the product mixture.

(*E*)-Methyl 2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetate 12



A solution of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid (102 mg; 0.31 mmol) **11** and potassium carbonate (0.54 g) in dry acetone (10 ml) was refluxed under nitrogen for 1 hour. Dimethyl sulfate (0.2 ml; 2.1 mmol) was added and the contents of the flask refluxed overnight. Upon cooling acetic acid (3 ml) was added and the flask re-heated to reflux for 75 minutes. The reaction was then quenched with water (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were sequentially washed with 5% KOH (50 ml), water (2 x 50 ml) and brine (50 ml) prior to drying over $MgSO_4$. Removal of the solvent *in vacuo* yielded methyl (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetate **12** (106 mg; 99%) as an orange solid which was analysed and used without further purification.

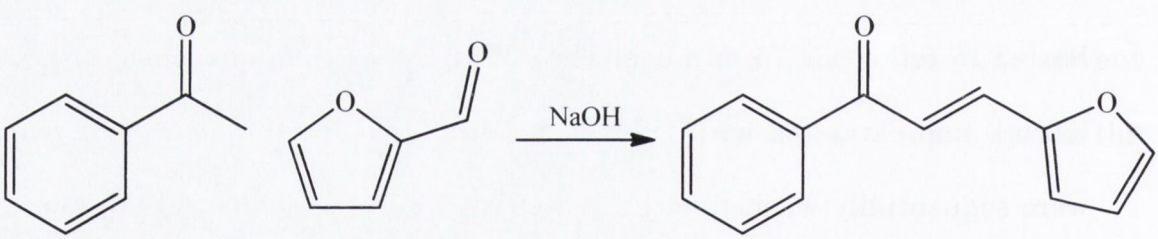
υ_{max}, 2942, 1750 (C=O), 1155 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.40 (3H, s, CH_3), 2.34 (2H, s, CH_2CO_2), 3.61 (3H, s, CO_2Me), 3.78 (3H, s, OMe), 3.83 (3H, s, OMe), 6.17 (1H, d, *J* 3.0, $H_{13/14}$), 6.47 (1H, d, *J* 1.5, $H_{4/6}$), 6.58 (1H, d, *J* 2.0, $H_{4/6}$), 6.70 (1H, d, *J* 3.1, $H_{13/14}$), 7.01 (1H, d, *J* 15.4, $H_{10/11}$), 7.44 (1H, d, *J* 15.6, $H_{10/11}$) ppm

δ_C (400 MHz; $CDCl_3$) 13.6 (C16), 38.6 (C2), 51.96 ($CO_2\underline{Me}$), 55.3 (OMe), 55.8 (OMe), 97.7 (C4), 106.9 (C6), 109.2 (C14), 119.0 (C13), 122.6 (C11), 130.4 (C10), 135.5, 149.4, 156.2, 159.5, 162.3, 171.4 (C1) ppm

m/z; (HRMS (ESI)) calculated for $C_{19}H_{20}O_6$ expected 344.1260, found 367.1162 (M + Na)

(*E*)-3-(Furan-2-yl)-1-phenylprop-2-en-1-one 13

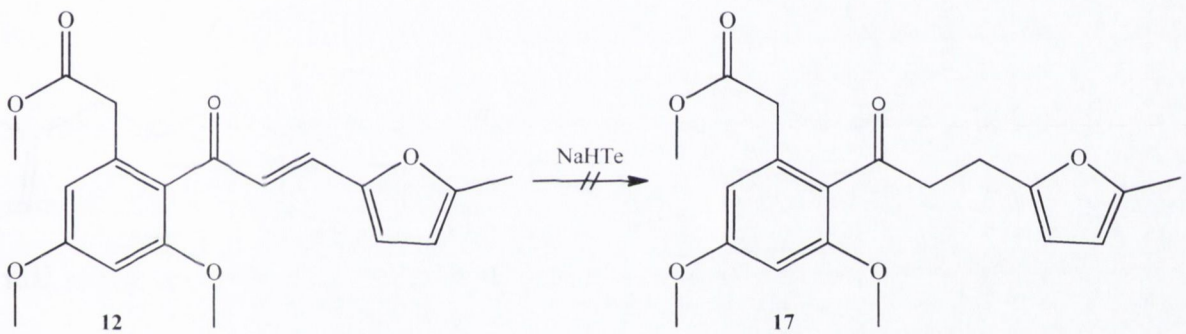


15 **14** **13**

A solution of furfural **14** (5.1 g; 53 mmol) in methanol (200 ml) was cooled on an ice bath prior to the slow addition of an aqueous solution of sodium hydroxide (10%; 50 ml). Acetophenone **15** (5 g; 41 mmol) was then slowly added and the flask allowed to warm to room temperature and stirred for four hours.

The reaction mixture was then diluted with water (100 ml) and extracted with DCM (150 ml) and the solvent removed to give (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one[197] **13** (7.91 g; 96%) as yellow flakes which were analysed and used without further purification.

Treatment of methyl (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetate 12 with sodium hydrogen telluride

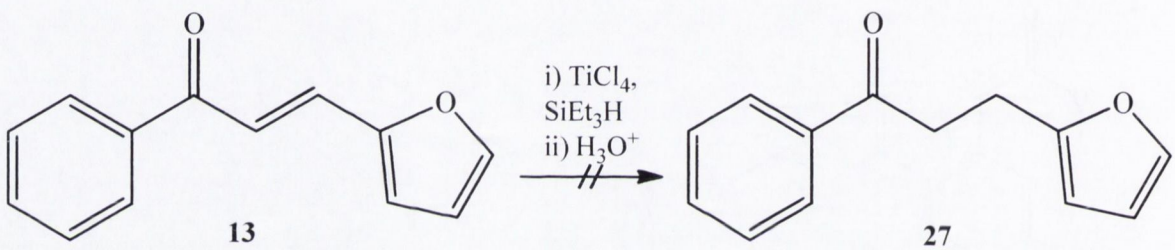


12 17

A 25 ml round bottomed flask with a reflux condenser containing sodium borohydride (46 mg; 1.2 mmol), ethanol (3 ml) and finely divided tellurium (66 mg; 0.5 mmol) was heated and stirred in an atmosphere of nitrogen until effervescence and the development of a purple colour were noted. Reflux was continued for 15 minutes prior cooling and the addition of methyl (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetate (71 mg; 0.2 mmol) **12** in ethanol (0.4 ml). The reaction mixture continued to be stirred at room temperature overnight. The crude reaction mixture was filtered through a plug of Celite and the solvent removed at reduced pressure. None of the expected

product, methyl 2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)propanoyl)phenyl)acetate **17**, was recovered, NMR analysis of the crude product showed it to be a complex mixture containing none of the expected tetrahydrofuran alkane.

Treatment of (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one 13 with titanium tetrachloride/triethylsilane

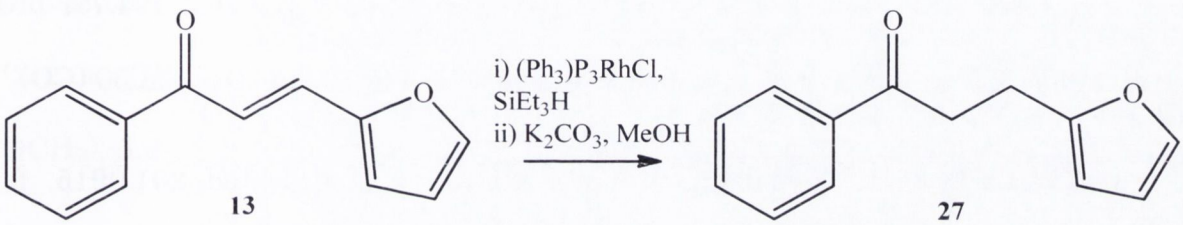


13 **27**

A solution of (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one **13** (199 mg; 1 mmol) in dry DCM (10 ml) was blanketed with nitrogen prior to the addition of a solution of 1 M titanium tetrachloride in DCM (1.2 ml; 1.2 mmol). This mixture was allowed to stir for 10 minutes prior to the addition of a solution 1 M triethylsilane in DCM (1.2 ml; 1.2 mmol). The resulting mixture was allowed to stir for a further hour before being quenched over ice and extracted with further DCM. The lower organic layer was sequentially washed with saturated sodium bicarbonate solution and water, dried over $MgSO_4$ and the solvent removed at reduced pressure. None of the expected product, 3-(furan-2-yl)-1-

phenylpropan-1-one **27**, was recovered, NMR analysis of the crude product showed it to be a complex mixture containing none of the expected product.

3-(Furan-2-yl)-1-phenylpropan-1-one 27



A flask containing (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one **13** (215 mg; 1 mmol) and tris(triphenylphosphine)rhodium(I) chloride (7 mg) in toluene (10 ml) was blanketed with nitrogen. Triethyl silane (0.2 ml; 1.2 mmol) was added and a reflux condenser attached and the solution was heated to 50 °C for 2 hours. Upon cooling a solution of potassium carbonate (10 mg) in methanol (10 ml) was added and the contents of the flask were stirred for 1 hour at room temperature. The reaction mixture was then diluted with water and extracted with ethyl acetate (3 x). The organic extracts were combined and the solvent removed at reduced pressure. The residue in the flask was dissolved in ethanol (50 ml) and diethyl ether (50 ml) and vigorously stirred following the addition of dilute HCl (10 ml; 0.01 M) for 30 minutes. The layers were then separated and the upper organic layer washed with brine, dried over $MgSO_4$ and the solvent removed at reduced pressure to give 3-(furan-2-yl)-1-phenylpropan-1-

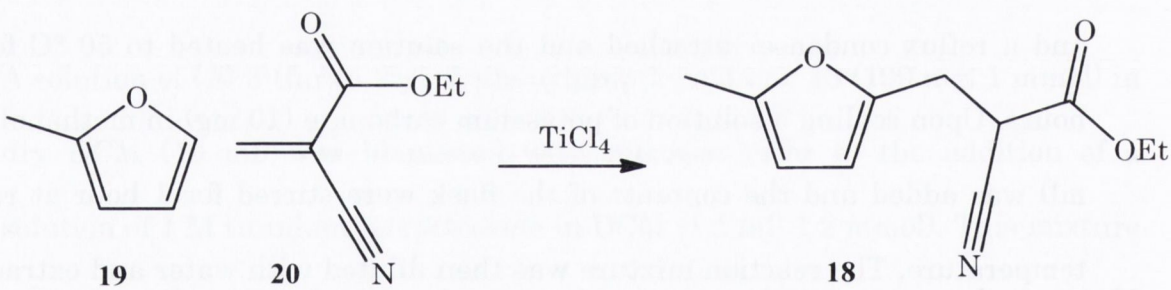
one[198] **27** (195 mg; 96%) as a light yellow oil which was analysed without further purification.

δ_H (400 MHz; $CDCl_3$) 3.09 (2H, t, *J* 7.7, CH_2-Furan), 3.32 (2H, t, *J* 7.8, CH_2CO), 6.3-6.5 (3H, m, Furan-H), 7.87-8.00 (5H, m, Ph-H) ppm

δ_C (400 MHz; $CDCl_3$) 22.44 ($COCH_2\underline{C}H_2$), 36.90 ($CO\underline{C}H_2CH_2$), 104.78, 110.14, 125.73, 127.95, 127.99, 128.56, 133.08, 136.71, 140.89, 154.91, 198.50 (CO)

m/z; (HRMS (ESI)) calculated for $C_{13}H_{12}O_2$ + H expected 201.0915, found 201.0919

Ethyl 2-cyano-3-(5-methylfuran-2-yl)propanoate 18



19 **20** **18**

Ethyl cyanoacrylate **19** (10ml, 84 mmol) was added to a stirred solution of 2-methylfuran **20** (8.2 g; 0.1 mol) and titanium tetrachloride (0.45 ml; 4 mmol) in toluene (21 ml). The contents of the flask were allowed to stir for 24 hours at room temperature. The reaction mixture was quenched with water (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were dried

over $MgSO_4$ and the solvent removed at reduced pressure to give ethyl 2-cyano-3-(5-methylfuran-2-yl)propanoate **18** (16 g; 91%) as a dark red oil which was analysed without further purification.

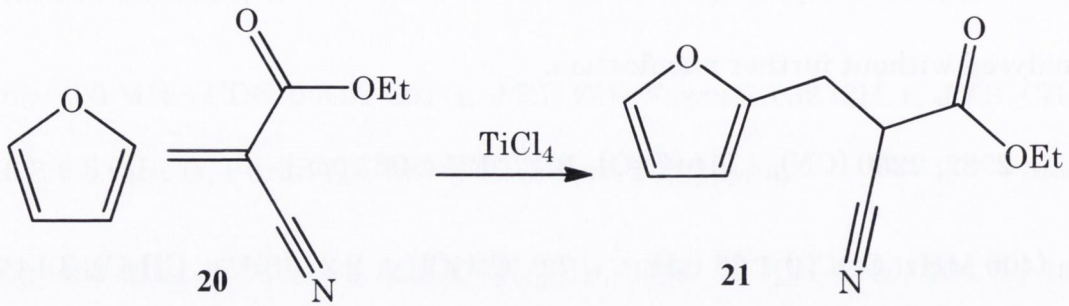
υ_{max}, 2982, 2250 (CN), 1754 (C=O), 1617, 1217, 962 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.33 (3H, t, *J* 7.0, $CH_2C\underline{H}_3$), 2.27 (3H, s, $\underline{CH}_3C$), 3.14-3.29 (2H, m, $\underline{CH}_2CHCN$), 3.82 (1H, dd, *J* 6.0 and 14.9, C<u>H</u>CN), 4.29 (2H, q *J* 7.2, OCH_2), 5.87 (1H, d, *J* 3.0, CH=C<u>H</u>-CH), 6.09 (1H, d, *J* 3.0, $CH_3C\underline{H}$=CH) ppm

δ_C (400 MHz; $CDCl_3$) 13.3 (CH_3), 13.9 (CH_3), 28.6 (Ar-$\underline{C}H_2$), 37.5 (<u>C</u>HCN), 62.9 ($O\underline{C}H_2$), 106.2 ($H\underline{C}$=), 109.2 (HC=), 115.8 (CN), 147 (C_q), 156.2 (C_q), 165.2 ($\underline{C}O_2$) ppm

m/z; (HRMS (ESI)) calculated for $C_{11}H_{13}NO_3$ expected 206.0817, found 206.0815

Ethyl 2-cyano-3-(furan-2-yl)propanoate 21



20 **21**

Titanium tetrachloride (0.2 ml; 1.8 mmol) was added to a flask containing a stirred solution of ethyl cyanoacrylate **20** (2 ml; 17 mmol) and furan (12 ml; 165 mmol) in acetonitrile (5 ml). The flask was heated to reflux for 12 hours. Upon cooling the reaction mixture was quenched with water and and extracted with DCM (2 x 50 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed at reduced pressure to give ethyl 2-cyano-3-(furan-2-yl)propanoate **21** (2.3 g; 72%) as a dark orange oil which was analysed without further purification.

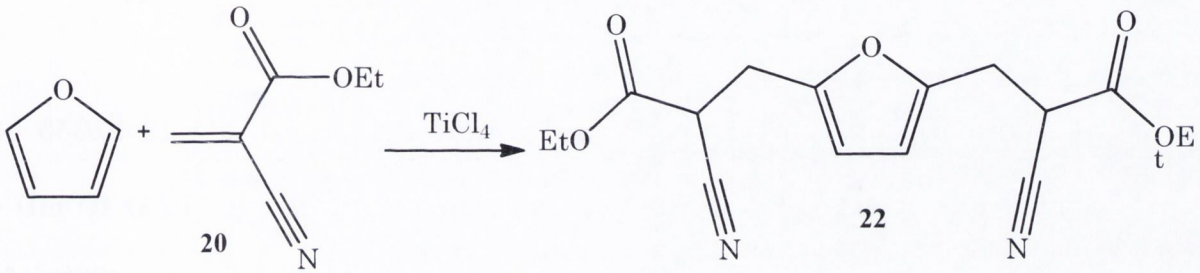
υ_{max}, 2970, 2243 (CN), 1731 (C=O), 1217 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7, $CH_2\underline{CH_3}$), 3.15-3.33 (2H, m, $C\underline{H_2}CH$), 3.78 (1H, m, CHCN), 4.25 (2H, q, *J* 7, $\underline{CH_2}CH_3$), 6.23 (1H, d, *J* 3.3, CH=$\underline{CH}$-C_q), 6.30 (1H, dd, *J* 3 and 1.5, $\underline{CH}$=CH-C_q), 7.34 (1H, d, *J* 1.6, $C\underline{H}$-O) ppm

δ_C (400 MHz; $CDCl_3$) 164.9 (CO_2), 149 (C_q), 142.5 (C_q), 115.6 (CN), 110.5 (CH-O), 109.4 (CH=$\underline{CH}$), 109.3 ($\underline{CH}$=CH), 63.1 (OCH_2), 36.8 ($\underline{C}$HCN), 28.5 (Ar-$\underline{CH_2}$), 13.9 CH_2CH_3) ppm

m/z; (HRMS (ESI)) calculated for $C_{10}H_{11}NO_3$ expected 192.0661, found 192.0658

Diethyl 3,3'-(furan-2,5-diyl)bis(2-cyanopropanoate) 22



This reaction was carried out in the same way as for the synthesis of **21** above, ECA used in excess. Furan (1.5 ml; 20 mmol) produced diethyl 3,3'-(furan-2,5-diyl)bis(2-cyanopropanoate) **22** (5.88 g, 89%) as a viscous dark red oil which was analysed without further purification.

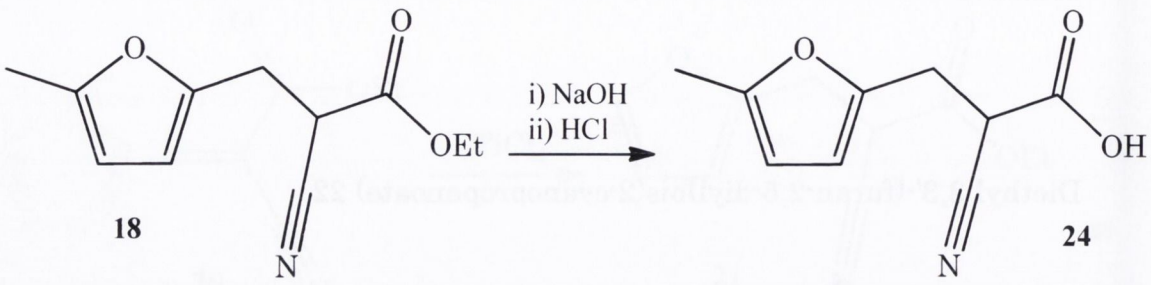
υ_{max}, 2992, 2243 (CN), 1732 (C=O), 1142 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.29 (6H, t, *J* 7, $CH_2\underline{CH_3}$), 3.15-3.30 (4H, m, $C\underline{H_2}CH$), 3.78 (2H, m, CHCN), 4.25 (4H, q, *J* 7.1, $\underline{CH_2}CH_3$), 6.16 (2H, s, $C\underline{H}=C\underline{H}\text{-}C_q$) ppm

δ_C (400 MHz; $CDCl_3$) 13.5 (CH_3), 28.3 ($Ar\text{-}CH_2$), 36.7 ($\underline{C}HCN$), 63.1 (OCH_2), 109.4 (CH=CH), 115.3 (CN), 148.8 (C_q), 165 (CO_2) ppm

m/z; (HRMS (ES)) calculated for $C_{16}H_{18}N_2O_5$ expected 317.1137, found 317.1149

2-cyano-3-(5-methylfuran-2-yl)propanoic acid 24



18 **24**

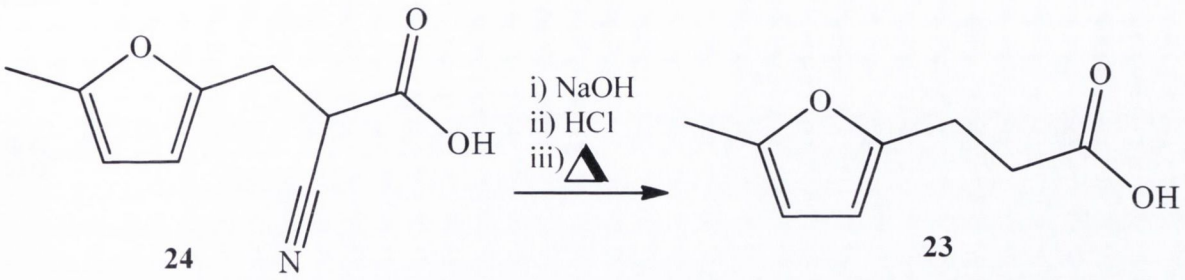
A solution of ethyl 2-cyano-3-(5-methylfuran-2-yl)propanoate **16** (6.055 g; 29 mmol) in ethanol (100 ml) and aqueous sodium hydroxide (10%, 19 ml) was refluxed under nitrogen for 12 hours. Once cooled approximately 80% of the methanol was removed at reduced pressure and the remaining residue was diluted in water, washed with diethyl ether and acidified with HCl prior to extraction with diethyl ether (3 x 50 ml). The combined organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to give 2-cyano-3-(5-methylfuran-2-yl)propanoic acid **24** as a dark brown oil (5.7 g; 97%) as a viscous orange oil which was analysed without further purification.

υ_{max}, 3482 (OH), 2256 (CN), 1740 (C=O), 1270 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.27 (3H, s, CH_3), 3.24 (2H, m, $\underline{CH_2}CHCN$), 3.73 (1H, dd, *J*6 and 8.5, C$\underline{H}$CN), 5.87 (1H, d, *J*3, CH=C$\underline{H}$), 6.12 (1H, d, *J*3, CH=C$\underline{H}$) ppm

m/z; (HRMS (ES)) calculated for $C_9H_8NO_3$ expected 178.0504, found 178.0511

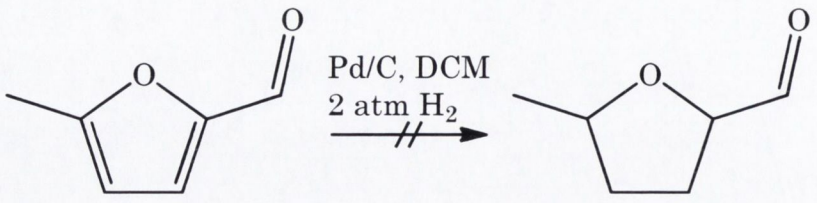
3-(5-Methylfuran-2-yl)propanoic acid 23



24 **23**

A solution of 2-cyano-3-(5-methylfuran-2-yl)propanoic acid **20** (0.375 g; 2 mmol) in water (50 ml) was treated with potassium hydroxide (0.15 g) and the solution heated to reflux overnight. Once cooled the reaction mixture was washed with diethyl ether and acidified with HCl prior to extraction with ethyl acetate (3 x 50 ml). The combined organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* . The viscous brown oil was taken into a flask and heated with a heat gun to evolve CO_2 unfortunately this degraded the compound before confirmation of the structure could take place.

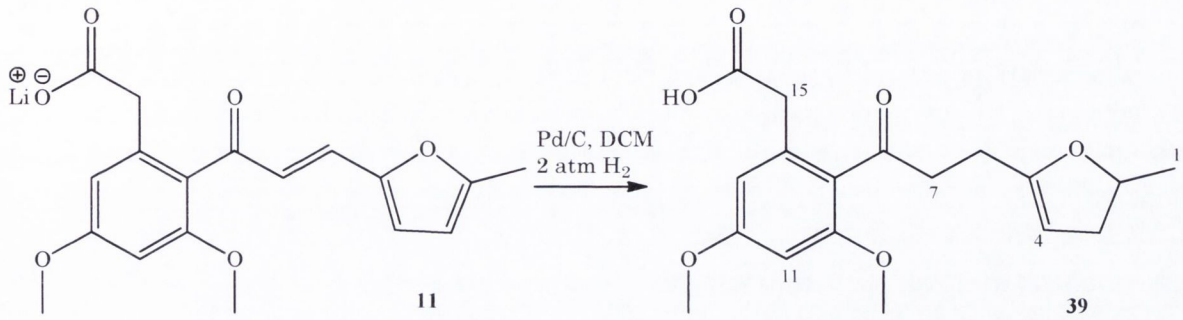
Treatment of 2-methylfurfuraldehyde 4 with Pd/C and hydrogen in DCM



4 **38**

As a representative procedure the use of Pd/C in DCM is described. A 20 ml conical flask was charged with a solution of 2-methylfurfuraldehyde **4** (317mg; 2.88 mmol) and palladium on carbon (20 mg) in DCM (5 ml).The conical flask was placed inside a high-pressure reaction vessel and the whole system was flushed with argon. The high-pressure bomb was then charged with hydrogen up 30 psi and the flask allowed to stir for 5 hours. The system was flushed with argon again and the conical flask removed. The reaction mixture was filtered and the solvent removed at reduced pressure. None of the expected product, 5-methyltetrahydrofuran-2-carbaldehyde[173] **38**, was recovered.

2-(3,5-Dimethoxy-2-(3-(5-methyl-4,5-dihydrofuran-2-yl)propanoyl)phenyl)acetic acid 39

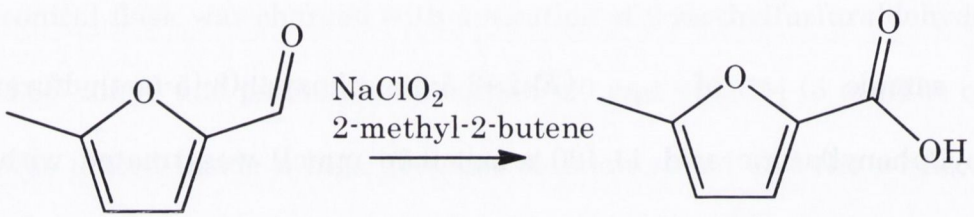


11 39

A sample of (*E*)-2-(3,5-dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11** (20.2 mg; 0.06 mmol) was treated with an aqueous solution of lithium hydroxide (0.02 M; 3.8 ml) and the water thoroughly removed at reduced pressure. The resulting salt was finely ground and suspended with palladium on carbon (5 mg) in DCM (0.5 ml) in a conical flask. The conical flask was placed inside a high-pressure reaction vessel and the whole system was flushed with argon. The high-pressure bomb was then charged with hydrogen up 30 psi and the flask allowed to stir overnight. Following discharge of the hydrogen the reaction mixture was filtered acidified with concentrated HCl and extracted with diethyl ether (3 * 30 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to yield 2-(3,5-dimethoxy-2-(3-(5-methyl-4,5-dihydrofuran-2-yl)propanoyl)phenyl)acetic acid **39** (7 mg; 35%). Due to the small quantities recovered a full spectrographic analysis was not possible.

δ_H (400 MHz; $CDCl_3$) 1.19 (3H, d, *J* 6.5, C1H_3), 1.96 (1H, m, C3H_a), 2.98 (2H, t, *J* 6.5, C6H_2), 3.06 (1H, m, C3H_b), 3.27 (3H, t *J* 7.1, C7H_2), 3.45 (2H, s, CH_2CO_2), 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 3.92 (1H, m, C2H), 5.81 (1H, m, C=C<u>H</u>CH_2), 6.41 (1H, s, ArH), 6.51 (1H, s, ArH) ppm

5-Methylfuran-2-carboxylic acid 4

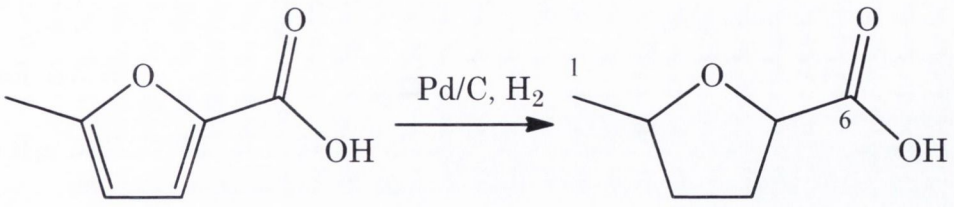


4 **40**

To a stirred solution of 2-methylfurfural **4** (0.5304 g; 4.8 mmol) in water (36 ml) and t-butanol (125 ml) was sequentially added monosodium phosphate (1.02 g; 8.5 mmol), 2-methyl-2-butene (3.8 ml; 36 mmol) and sodium chlorite (1.1 g; 12.1 mmol). The mixture was stirred overnight prior to the volatile materials being removed at reduced pressure. The residue was taken up in 0.5 N HCl (150 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield an orange solid which was recrystallised from diethyl ether to give 5-methylfuran-2-carboxylic acid[199] **40** (262 mg; 43%) as a pale yellow solid.

δ_H (400 MHz; $CDCl_3$) 2.39 (3H, s, Me), 6.16 (1H, d, *J* 3, C<u>H</u>=CH), 7.23 (1H, d, *J* 3, C<u>H</u>=CH), 10.59 (1H, br s, CO_2H) ppm

5-Methyltetrahydrofuran-2-carboxylic acid 41

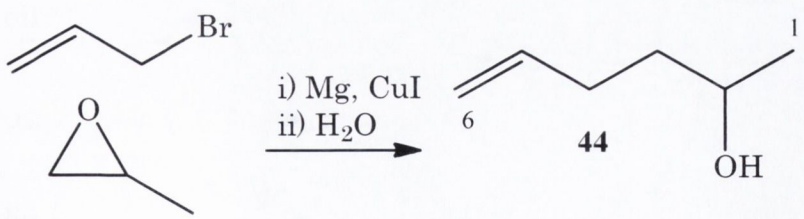


40 **41**

This reaction was carried out in the same way as for the hydrogenation of 2-methylfurfural **4** above. 5-methylfuran-2-carboxylic acid **40** (93.6 mg; 0.74 mmol) gave 5-methyltetrahydrofuran-2-carboxylic acid[200] **41** (49.8 mg; 52%) as a clear oil that was analysed without further purification.

δ_H (400 MHz; $CDCl_3$) 1.35 (3H, d, *J* 5.5, CH_3), 1.51 (1H, m, C2H_a), 2.06(1H, m, C2H_b), 2.17-2.38 (2H, m, C3H_2), 4.18 (1H, m, C2H), 4.46 (1H, dd, *J* 4.6 and 8.9 C5) ppm

Hex-5-en-2-ol 44



44

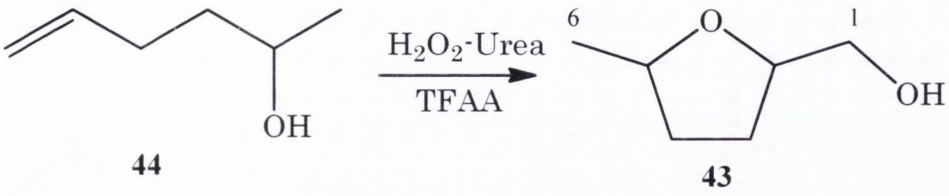
A three-necked 100 ml flask equipped with a dropping funnel and a stirring bar was charged with magnesium powder (1.58 g; 65 mmol) and cooled to 0 °C and flushed with nitrogen. A solution of allyl bromide (5.5 ml, 60 mmol) in dry

THF (80 ml) was slowly added over the course of 1 hour. The flask was then stirred at room temperature for 2 hours before re-cooling to -40 °C. Copper(I) iodide (1.14 g; 6 mmol) was then added and the contents allowed to stir for 30 minutes. A solution of propylene oxide (2.1 ml, 30 mmol) in dry THF (5 ml) was added to the flask over the course of 10 minutes followed by stirring for a further hour at -40 °C. The flask was then warmed to room temperature over the course of 2 hours. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether (2 x 50 ml). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvent removed at reduced pressure to give hex-5-ene-2-ol[201] **44** (2.15 g; 72%) as a clear oil that was analysed without further purification.

υ_{max}, 3358, 3079, 2970, 2931, 1642, 1122, 910 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.19 (3H, d, *J* 6.1, CH_3), 1.53 (2H, m, C3 CH_2), 2.14 (2H, m, C4 CH_2), 3.81 (1H, m, C<u>H</u>OH), 4.96 (dd, 1 H, *J*= 10.1, 1.5, CH=C<u>H</u>$_{2b}$), 5.03 (dd, 1 H, *J*= 17.1, 1.4, CH=C<u>H</u>$_{2a}$), 5.83 (ddt, 1 H, *J*= 16.9, 10.2, 6.6, C<u>H</u>=CH2) ppm

(5-Methyltetrahydrofuran-2-yl)methanol 43



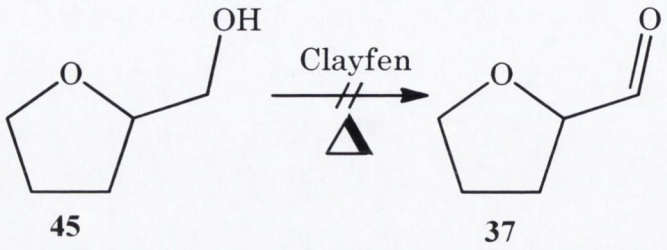
44 **43**

Hex-5-ene-2-ol **44** (976 mg; 9.7 mmol) was dissolved in DCM (50 ml). Urea-hydrogen peroxide (9.2 g; 97 mmol) and disodium hydrogen phosphate were added with vigorous stirring and a reflux condenser attached. Trifluoroacetic anhydride (3.4 ml; 24 mmol) was subsequently added dropwise down the condenser. The mixture was then subjected to sonication at room temperature for four hours and then left stirring overnight. Saturated sodium hydrogen carbonate was slowly added until effervescence had cease and the reaction mixture was neutral. The reaction mixture was then extracted with DCM (2 x 50 ml) and the combined organic layers washed with saturated sodium hydrogen carbonate and brine, dried over $MgSO_4$ and the solvent removed at reduced pressure to give (5-methyltetrahydrofuran-2-yl)methanol **43** as a clear oil[202] (961 mg; 98%) that was analysed without further purification.

υ_{max}, 3425 (OH), 2970, 2900, 1450, 1090 (cyclic ether) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.23 (3H, d, Me), 1.44 (1H, m, $C3H_a$), 1.68 (1H, m, $C3H_b$), 1.97 (2H, m, $C4H_2$), 2.22 (1H, br s, OH), 3.48 (1H, m, C2H), 3.65 (1H, m, C5H), 4.10 (2H, dd J_a 7.1 J_b 14.4, CH_2OH) ppm

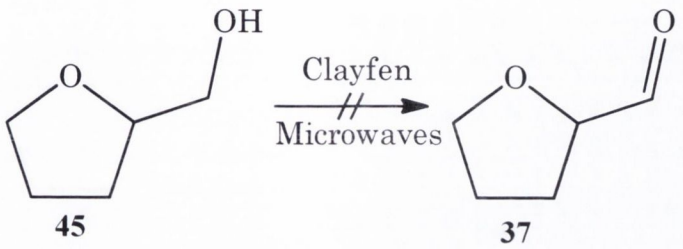
Treatment of (tetrahydrofuran-2-yl)methanol 45 with clayfen



45 **37**

Tetrahydrofurfuryl alcohol **45** (241 mg; 2.3 mmol) was dissolved in hexane (40 ml) in a 100 ml round bottomed flask. Clayfen (5.9 g) was slowly added over the course of 10 minutes. A condenser was attached to the flask and the contents heated to reflux for 24 hours. Once cooled the contents of the flask were filtered and the solvent removed at reduced pressure. None of the expected product, tetrahydrofuran-2-carbaldehyde[175], was detected in the proton NMR spectra, instead there was either a return of the alcohol **45** or a complex mixture of unidentifiable compounds.

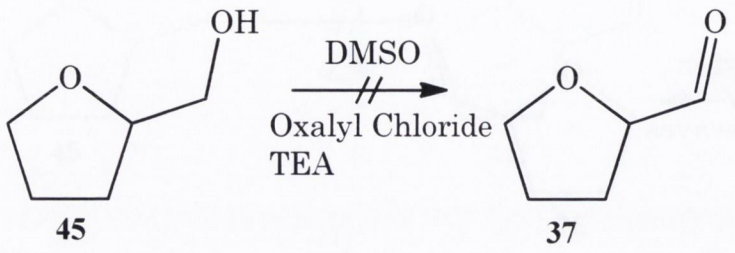
Treatment of (tetrahydrofuran-2-yl)methanol 45 with clayfen under microwave conditions



45 **37**

Tetrahydrofurfuryl alcohol **45** (0.200 g; 2 mmol) was mixed thoroughly with Clayfen (2.78 g) in a 20 ml round bottom flask. A reflux condenser was attached to the flask and the system was subjected to microwave irradiation (650 Watt) for 30 seconds. The contents of the flask were then filtered and washed through with hexane. Solvent was removed at reduced pressure. None of the expected product, tetrahydrofuran-2-carbaldehyde,[175] was detected in the proton NMR spectra, instead there was either a return of the alcohol **45** or a complex mixture of unidentifiable compounds.

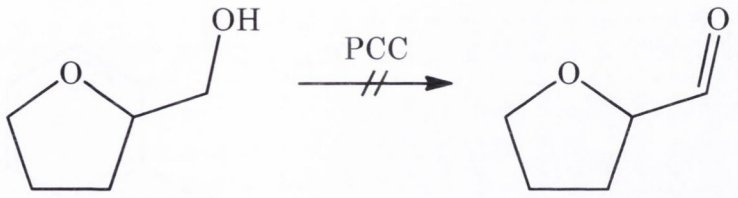
Treatment of (tetrahydrofuran-2-yl)methanol 45 under Swern oxidation conditions



45 **37**

A solution of dimethyl sulfoxide (1.2 ml, 16.8 mmol) in DCM (23 ml) under an atmosphere of nitrogen and cooled to -60 °C was treated dropwise with a solution of oxalyl chloride (5.2 ml; 60 mmol) in DCM (5.2 ml). The contents of the flask were stirred for 20 minutes prior to the dropwise addition of a solution of tetrahydrofurfuryl alcohol **45** (878 mg; 8.6 mmol) in DCM (5 ml). This mixture was allowed to stire for a further 10 minutes prior to the slow addition of TEA (6 ml; 43 mmol). The contents of the flask were then allowed to warm to room temperature followed by an additional period of 30 minutes stirring. The reaction was quenched with water, extracted with DCM (2 x 20 ml) and the solvent removed at reduced pressure. Whilst the NMR showed a characteristic aldehyde proton peak at 9.66 ppm[203] it was by far the minor product.

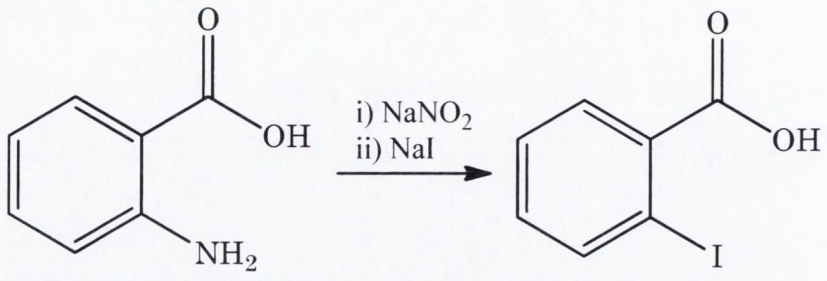
Treatment of (tetrahydrofuran-2-yl)methanol 45 with pyridinium chlorochromate



45 **37**

A solution of tetrahydrofurfuryl alcohol **45** (238 mg; 2.3 mmol) in dry DCM (66 ml) was stirred for 15 minutes in the presence of 3 Å molecular sieves (2 g). Pyridinium chlorochromate (2.54 g; 11.7 mmol) was then added in small portions over 10 minutes. The flask was then subjected to sonication at room temperature for 4 hours. The reaction mixture was then diluted with DCM (100 ml) and filtered through a plug of silica gel, washed through with further portions of DCM. The combined organic extracts were concentrated to an oil at reduced pressure. None of the expected product, tetrahydrofuran-2-carbaldehyde **37**, was detected in the ^{1}H NMR spectra, instead the spectra showed a complex mixture of products.[184]

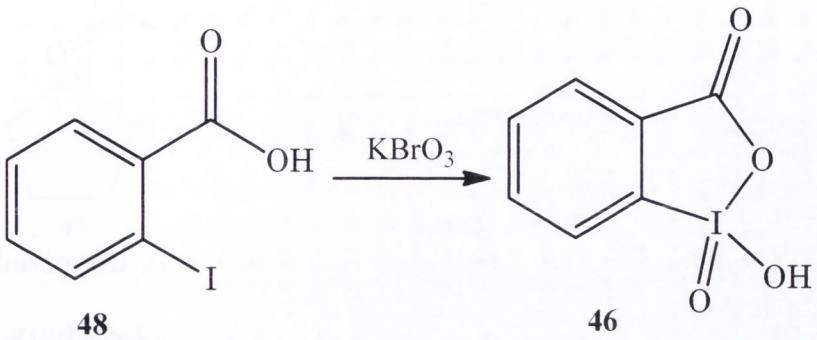
2-Iodobenzoic acid 48



47 **48**

Anthranilic acid **47** (14 g; 101 mmol) was dissolved in 2M sulfuric acid (1.5 L) and the solution cooled to 5 °C in an ice bath. A cold solution of sodium nitrite (7 g; 101 mmol) in water (25 ml) was added slowly, maintaining the temperature below 10 °C. After stirring for 10 minutes a solution of sodium iodide (26 g; 166 mmol) was added. The reaction was then heated to boiling point for 10 minutes and allowed to cool. The solid product was collected by suction filtration and recrystallised from hot water giving 2-iodobenzoic acid **48** (15 g; 60%) as fine brown crystals that were was used in the next step without any further purification.[204]

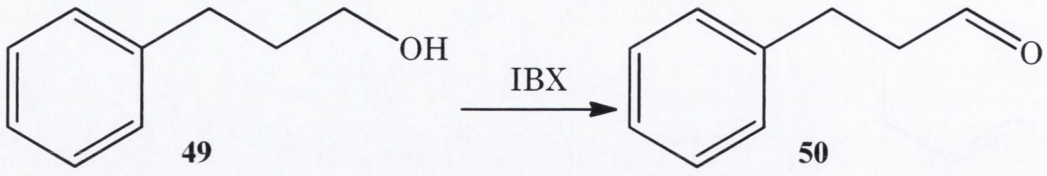
2-Iodoxybenzoic acid 46



48 **46**

A vigorously stirred slurry of 2-iodobenzoic acid **48** (1.0259 g; 4.1 mmol) in dilute sulfuric acid (0.73 M; 10 ml) was warmed to 50 °C prior to the slow addition of potassium bromate (0.89 g; 5.3 mmol) over 30 minutes. The flask was then heated to 70 °C for 4 hours. Upon cooling in an ice-bath a fine light brown precipitate developed which was isolated by filtration and sequential washing with anhydrous acetone and diethyl ether to give 2-iodoxybenzoic acid[176] **46** (985 mg; 96%) as a light brown power which was used without any further purification.

3-Phenylpropanal 50

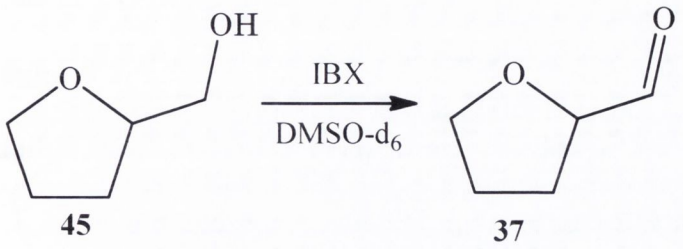


49 50

A portion of 2-iodoxybenzoic acid **46** (480 mg; 1.7 mmol) was dissolved in DMSO (4 ml) over 10 minutes. A solution of 3-phenyl-1-propanol **49** (201 mg; 1.48 mmol) in DMSO (1 ml) was then added and the reaction allowed to stir overnight. The reaction mixture was then diluted with water (20 ml) and filtered, extracted with ether (50 ml). The upper organic layer was then washed with water (3 x 50 ml), dried over $MgSO_4$ and the solvent removed at reduced pressure to give 3-phenylpropanal[205] **50** (174mg; 86%) as a clear oil that was analysed without any further purification.

δ_H (400 MHz; $CDCl_3$) 2.77 (2H, td, *J* 7.8 and 1.0, $ArCH_2$), 2.95 (2H, t, *J* 7.8, CH_2CHO), 7.18-7.22 (3H, m, ArH), 7.27-7.31 (2H, m,ArH), 9.81 (1H, t, *J* 1.4, CHO)

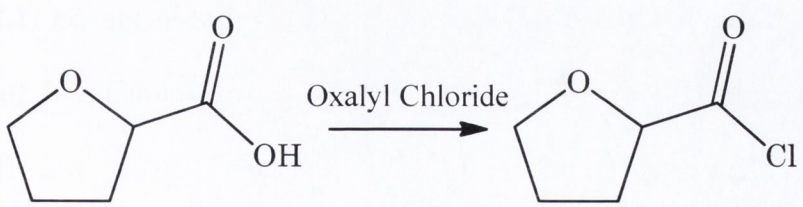
Tetrahydrofuran-2-carbaldehyde 37



45 **37**

A portion of 2-iodoxybenzoic acid **46** (648 mg; 2.31 mmol) was dissolved in deuterated DMSO (4 ml) over 10 minutes. A solution of tetrahydrofurfuryl alcohol **45** (210 mg; 2 mmol) in deuterated DMSO (1 ml) was then added and the flask allowed to stir. A sample taken for NMR analysis after 24 hours showed the presence of tetrahydrofuran-2-carbaldehyde[176] **37** by the characteristic aldehyde proton peak at 9.50, due to the presence of IBX, starting materials and side products a full characterisation was not possible.

Tetrahydrofuran-2-carbonyl chloride 52



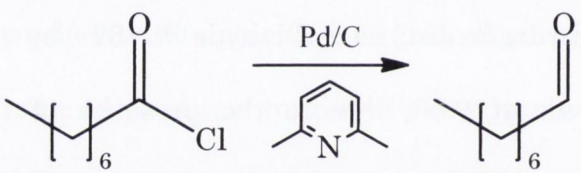
51 **52**

A flask containing tetrahydrofuran-2-carboxylic acid **51** (2.57 g; 22.1 mmol) and a magnetic stirring bar was flushed with nitrogen. Oxalyl chloride (4.4 ml; 51

mmol) was then added *via* syringe and the reaction mixture allowed to stir overnight. Excess oxalyl chloride was then removed at reduced pressure to give tetrahydrofuran-2-carbonyl chloride[206] **52** (2.45 g; 95%) as a light orange oil which was analysed without further purification, due to the inherent instability of the compound a full spectral analysis was not feasible.

υ_{max}, 2958, 1720 (C=O), 1176, 1072 (cyclic ether), 924, cm^{-1}

Octanal 54

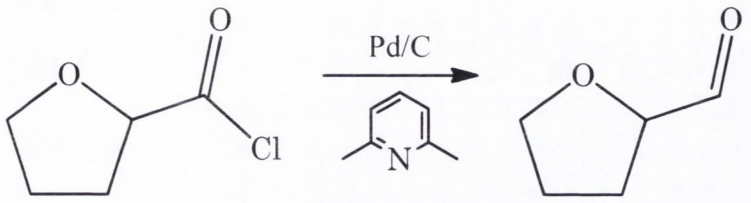


53 **54**

A three-necked flask containing 2,6-dimethylpyridine (830 mg; 7.75 mmol), 10% palladium on carbon (95 mg) and dry THF (30 ml) was stirred under an atmosphere of dry hydrogen until uptake ceased. Octanoyl chloride **53** (1.2 g; 7.4 mmol) was then added *via* syringe, and the flask was continued to be stirred until hydrogen uptake ceased again. The reaction mixture was then filtered and the solvent removed at reduced pressure to yield octanal[207] **54** (730 mg; 61%) as a clear oil which was analysed without any further purification.

δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t *J* 7.8, CH_3), 1.22-1.38 (8H, m, CH_2), 1.52 (2H, m, CH_2), 2.41 (2H, m, CH_2CO), 9.75 (1H, t *J* 1.8, CHO) ppm

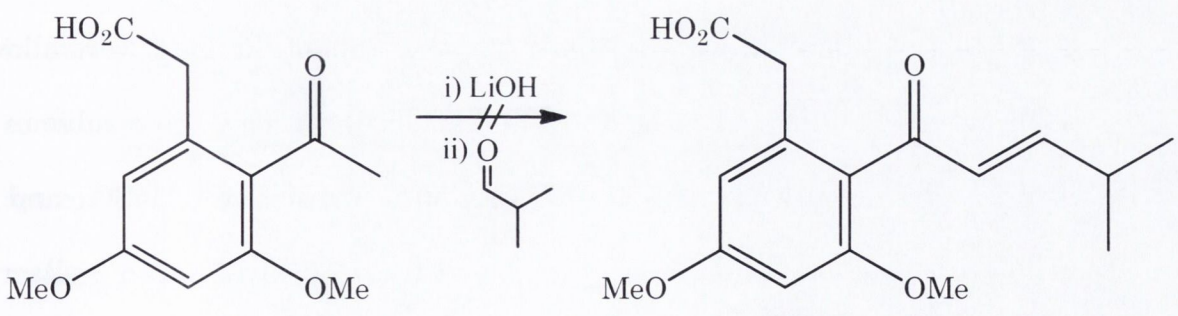
Treatment of tetrahydrofuran-2-carbonyl chloride with Rosenmund reaction conditions



52 **37**

This reaction was carried out in the same way as for the synthesis of octanal **54** above. None of the expected product, tetrahydrofuran-2-carbaldehyde, was detected in the ^{1}H NMR spectra, instead the spectra appeared to indicate reformation of tetrahydrofuran-2-carboxylic acid **51**.

Attempted aldol condensation of 2-(2-acetyl-3,5-dimethoxyphenyl)acetic acid 11 with isobutyraldehyde

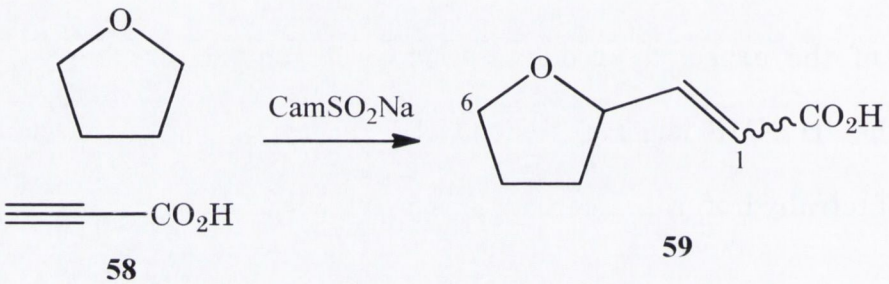


11 **55**

This reaction was carried out in the same way as for the synthesis of (*E*)-2-(3,5-Dimethoxy-2-(3-(5-methylfuran-2-yl)acryloyl)phenyl)acetic acid **11**, above.

Isobutyraldehyde was freshly distilled prior to reaction. None of the expected product, (*E*)-2-(3,5-dimethoxy-2-(4-methylpent-2-enoyl)phenyl)acetic acid **55**, was recovered. Instead a complex mixture of minor compounds and the starting ketone **11** were detected by NMR.

3-(Tetrahydrofuran-2-yl)acrylic acid 59



58 **59**

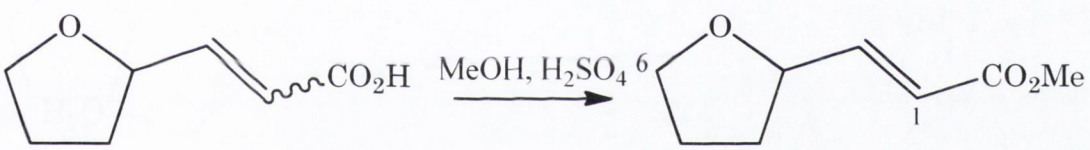
A solution of boric acid (162 mg; 2.6 mmol), Tetrabutylammonium hydrogensulfate (78 mg; 0.22 mmol) and propiolic acid **58** (0.15 g; 2.15 mmol) in THF (30 ml) was added to a stirred solution of sodium (+)-camphorsulfinate **57** (0.51 g; 2.1 mmol) in water (10 ml). The contents of the flask were allowed to stir overnight after which the THF was removed *in vacuo*. The residue in the flask was extracted with diethyl ether (2 x 50 ml), dried over $MgSO_4$, and the solvent removed at reduced pressure to give 3-(tetrahydrofuran-2-yl)acrylic acid[208] **59** (266 mg; 87%) as a clear oil which was analysed and used in the next step without any additional purification.

υ_{max}, 2953, 1720 (C=O), 1193 (C=C), 1052 (cyclic ether), 818 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.68 (1H, m, C4H_a), 1.91 (2H, m, C5H_2), 2.11 (1H, m, C4H_b), 3.70 (3H, s, OMe), 3.80 (1H, m, OC6H_b), 3.90 (1H, m, OC6H_a), 4.53 (1H, q, *J* 5.1, (*E*) CHO), 5.23 (1H, q, *J* 7.6, (*Z*) CHO), 5.70 (1H, d, *J* 11.5, (*Z*) $CHCO_2$), 6.01 (1H, d, *J* 15.6, (*E*) $CHCO_2$), 6.39 (1H, dd, J_{ab} 7.1 and 11.8, (*Z*) CHC<u>H</u>=), 7.00 (1H, dd, J_{ab} 5.3 and 15.4, (*E*) CHC<u>H</u>=) ppm

δ_C (400 MHz; $CDCl_3$) 25.9, 25.4 (C5), 32.1, 31.4 (C4), 68.5, 68.4 (C6), 76.0, 77.3 (C3), 119.2, 118.9 (C2), 152.8, 151.0 (C1), 171.2 (CO_2H) ppm

(*E*)-Methyl 3-(tetrahydrofuran-2-yl)acrylate 63



59 **63**

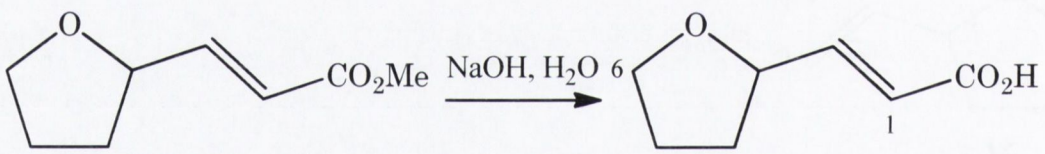
Crude 3-(tetrahydrofuran-2-yl)acrylic acid **59** (3.93 g; 27.7 mmol) was dissolved in methanol (70 ml). Concentrated sulfuric acid (5 ml) was added and a reflux condenser attached and the flask was heated to reflux overnight. Upon cooling approximately 80% of the solvent was removed at reduced pressure, the remaining residue in the flask was diluted with water and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* and the resulting oil purified by column chromatography (8:2 hexane:ether) to yield (*E*)-methyl 3-(tetrahydrofuran-2-yl)acrylate[209] **63** as a clear oil (851 mg; 22%).

υ_{max}, 2952, 1718 (C=O), 1193 (C=C), 1052 (cyclic ether), 816 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.56 (1H, m, C4H_a), 1.91 (2H, m, C5H_2), 2.33 (1H, m, C4H_b), 3.70 (3H, s, OMe), 3.80 (1H, m, OC6H_b), 3.90 (1H, m, OC6H_a), 4.50 (1H, q, *J* 5.8, CHO), 6.01 (1H, d, *J* 15.5, $CHCO_2$), 6.90 (1H, dd, J_{ab} 4.6 and 15.6, CHC<u>H</u>=) ppm

δ_C (400 MHz; $CDCl_3$) 25.9 (C5), 31.9 (C4), 51.4 (OMe), 68.2 (C6), 75.8 (C3), 118.7 (C2), 151.5 (C1), 178.1 (C=O) ppm

(*E*)-3-(Tetrahydrofuran-2-yl)acrylic acid 61



63 **61**

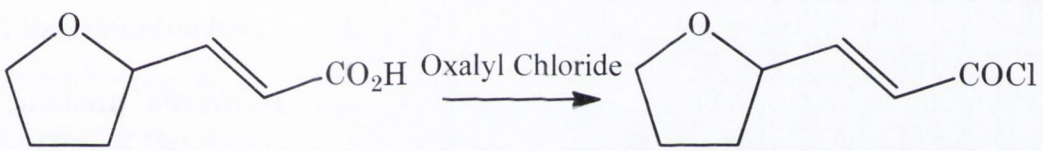
(*E*)-Methyl 3-(tetrahydrofuran-2-yl)acrylate **63** (851 mg; 5.4 mmol) was dissolved in a mixture of ethanol (41 ml) and an aqueous solution of 10% w/w NaOH (0.49 ml) and then refluxed for 3 hours. The cooled solution was then diluted with water (40 ml) & washed with ether (40 ml), the aqueous layer was acidified with dil. HCl and extracted with ether (3 x 10 ml). The organic layer was then dried with $MgSO_4$ and the solvent removed to give the acid (*E*)-3-(tetrahydrofuran-2-yl)acrylic acid[208] **61** (617 mg; 73%) which was analysed and used in the next reaction without any further purification.

υ_{max}, - 2957, 2878, 1698 (C=O), 1658 (C=C) 1176, 1048 (cyclic ether) cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.68 (1H, m, C4H_a), 1.92 (2H, m, C5H_2), 2.32 (1H, m, C4H_b), 3.84 (1H, m, OC6H_b), 3.93 (1H, m, OC6H_a), 4.53 (1H, q, *J* 7.2, CHO), 6.01 (1H, d, *J* 15.6, $CHCO_2$), 7.00 (1H, dd, *Jab* 5.3 and 15.4, CHC<u>H</u>=) ppm

δ_C (400 MHz; $CDCl_3$) 25.9 (C5), 32.1 (C4), 68.5 (C6), 76.0 (C3), 119.2 (C2), 152.8 (C1), 171.2 (CO_2H) ppm

(*E*)-3-(tetrahydrofuran-2-yl)acryloyl chloride 66

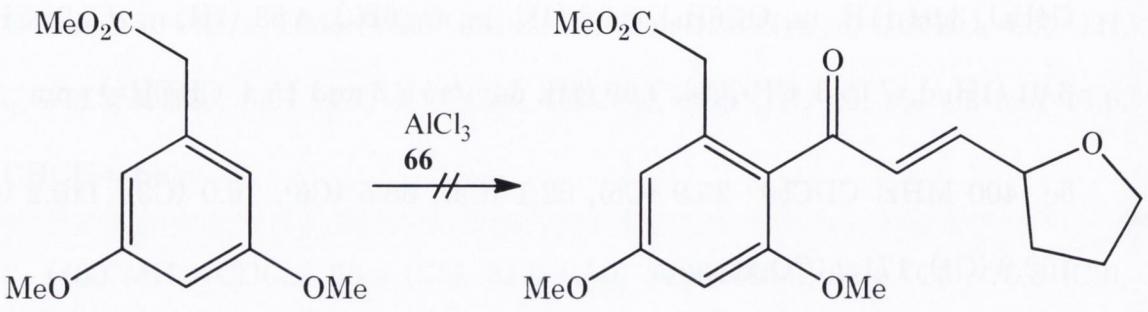


61 **66**

This reaction was carried out in the same way as for the synthesis of **52** above.[206]

υ_{max}, 2932, 1717 (C=O), 1164, 977, 750 (C-Cl) cm^{-1}

Attempted Friedel-Crafts coupling of (*E*)-3-(tetrahydrofuran-2-yl)acryloyl chloride 66 and methyl 2-(3,5-dimethoxyphenyl)acetate 8



8 **70**

This reaction was carried out in the same way as for the synthesis of **9** above. None of the expected product, (*E*)-methyl 2-(3,5-dimethoxy-2-(3-(tetrahydrofuran-2-yl)acryloyl)phenyl)acetate **70**, was recovered. Instead the crude ^{1}H NMR spectra showed a mixture of the starting phenyl ester and a lactonic compound posited as being (3E,11E)-5,13-dichloro-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione **67**.

Due to time constraints and the presence of the starting ester, a full characterisation was not possible but the presence of a persistent neutral compound with ^{1}H NMR (400 MHz; $CDCl_3$) peaks at 3.19 (2H, t *J* 5.9, CH_2O), 6.38 (1H, d J 2.68, C<u>H</u>=CHCHCl), 6.41 (1H, dd J_a 2.14 J_b 17.49, CH=C<u>H</u>CHCl) strongly indicate the formation of the dimer **67.**

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