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Synthesis of Lactones from Tetrahydrofuran Derivatives and Study of Some Translactonisation Reactions



by

Úna McCarthy

A thesis submitted to the University of Dublin for the degree of

Doctor of Philosophy

December 2002

Trinity College Dublin

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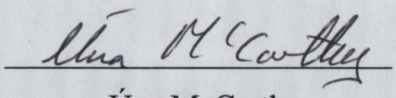

Úna McCarthy

Summary

The research undertaken in the present study focuses on the synthesis of lactones *via* the intramolecular acylative cleavage reactions of tetrahydrofuran derivatives. The thesis is divided into a number of sections: an introduction describing the principle characteristics of, and synthetic routes to medium- and large-ring lactones; studies on intramolecular reactions of 3-(tetrahydro-2'-furyl)propanoic acid; synthesis of some ring-enlarged lactones *via* translactonisation processes; and studies towards the development of a synthetic route to the precursors required for the synthesis of two naturally-occurring lactones.

5-(3'-Iodopropyl)dihydro-3(2*H*)-furanone was prepared in good yield *via* the intramolecular reaction of 3-(tetrahydro-2'-furyl)propanoic acid in the presence of sodium iodide. Subsequent conversion of this iodolactone into [3-(5'-oxo-tetrahydro-2'-furyl)propyl]triphenyl phosphonium iodide was achieved. It was not possible to generate an ylid from this phosphonium salt. The behaviour of 3-(tetrahydro-2'-furyl)propanoic acid was examined in some intramolecular reactions that were conducted in the presence of trifluoroacetic anhydride in a variety of solvents or in the presence of various nucleophiles. Results showed that in most cases dihydro-5-(3'-trifluoroacetoxypropyl)-2(3*H*)-furanone was the predominant product, however, when the reaction was carried out in acetone or tetrahydrofuran, some novel compounds were isolated.

Ten-membered saturated and unsaturated lactones bearing hydroxyalkyl side-chains of varying lengths situated adjacent to the lactone ether oxygen were synthesised *via* the intramolecular acylative cleavage reaction of (tetrahydro-2-furyl)alkanoic acid derivatives The ability of these lactones to undergo tranlactonisation processes was explored. Ring-expanded lactones were obtained from saturated ten-membered lactones. Optimum conversion (92%) was observed in the ring-expansion of two saturated ten-membered lactones bearing hydroxyethyl side-chains which resulted in the formation of derived twelve-membered lactones. The unsaturated ten-membered lactones did not undergo translactonisation.

Various routes were explored for the preparation of two (*Z*)-(5'-methyltetrahydro-2'-furyl)alkenoic acids that were required for the synthesis of two naturally-occurring lactones, Cephalosporolide G and Patulolide C. The most successful routes to these acids involved the employment of Wittig reactions. Isomeric mixtures of both of the requisite acids were obtained in modest yields. Various attempts to form related (*Z*)-configured acids *via* alkynoic acid derivatives were unsuccessful.

Acknowledgements

Firstly, I would like to thank my supervisor, Dr. David Grayson, for all his help and encouragement throughout my time at Trinity.

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Abbreviations

OAc	acetate
CH_3CN	acetonitrile
Ar	aromatic
b.p.	boiling point
BMS	borane-methyl sulfide complex
br	broad
TBDP	*tert*-butyldiphenylsilyl
n-BuLi	*n*-butyl lithium
t-BuLi	*tert*-butyl lithium
cy	cyclohexyl
J	coupling constant measured in Hertz
CW	continuous wave
°C	degrees Celcius
DEPT	Distortionless Enhancement by Polarisation Transfer
DMSO	dimethyl sulfoxide
d	doublet
FAB	Fast Atom Bombardment
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	infrared
LDA	lithium diisopropylamide
MMPP	magnesium monoperoxyphthalate
m/z	mass per unit charge
m. p.	melting point
MOM	methoxymethyl
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
rt	room temperature
s	singlet
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
PTSA	*para*-toluenesulfonic acid
*p*TolSO$_2$Cl	*para*-toluenesulfonylchloride
TFA$_2$O	trifluoroacetic anhydride
TPP	triphenylphosphine
t	triplet
UHP	urea – hydrogen peroxide complex

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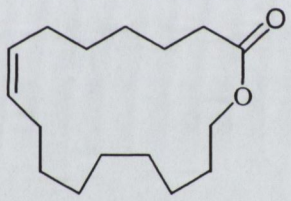
Chapter 1

Introduction

1.1 Macrocyclic Lactones

Macrocyclic lactones are a large class of naturally occurring compounds whose structural diversity is one of the richest in natural product chemistry.

In 1926, pioneering research by Ruzicka[1] initiated interest in the area of macrocyclic compounds. His work involved the structure elucidation of the musk components, civetone and muscone, and revealed them to be large-ring ketones. This discovery disproved the inaccurate prediction of the von Baeyer strain theory that such compounds would be too unstable to exist. Ruzicka's work prompted the elucidation of the structures of many more large-ring compounds, and in 1927 the first macrocylic lactones were discovered by Kerschbaum.[2] These were ambrettolide **1** and exaltolide **2** which were found in oils from ambrette seeds *Hibiscus abelmochus* and from the roots of *Angelica archangelica officinalis*, respectively.



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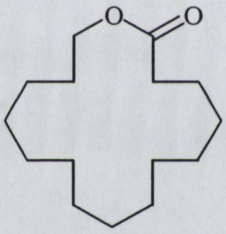

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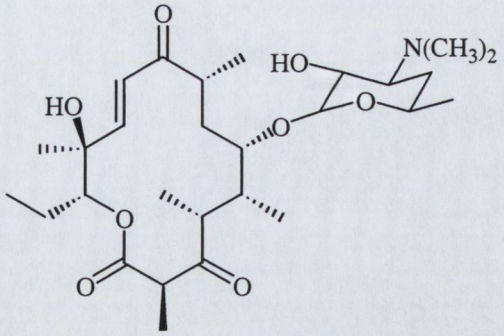
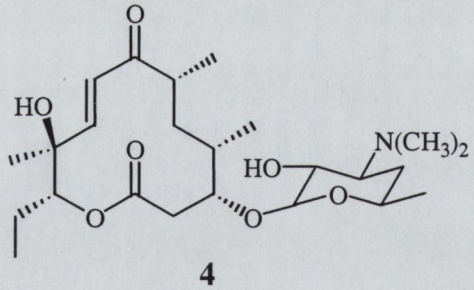
Initially, interest in this area was due to the commercial importance of these macrocyclic compounds in the fragrance industry; however, it was with the isolation of antibiotic lactones during the ensuing years that the biological potential and synthetic challenge of these compounds was genuinely appreciated. Thus, in 1950, the macrolide antibiotic picromycin **3** was isolated from an *Actinomyces* culture by Brockmann and Henkel,[3] although the structure was not elucidated until 1968 when mass spectrometry and NMR techniques became available.[4] Shortly afterwards, discovery of several structurally related antibiotics isolated from a *Streptomyces* culture fuelled research into a synthetic route towards these desirable macrocyclic compounds.



3

All the newly discovered antibiotics had similar structures featuring a twelve- to sixteen-membered lactone ring bearing numerous substituents. The antibiotics isolated from *Streptomyces* cultures included methymycin **4**,[5] carbomycin A **5**[6] and the erythromycins A **6** and B **7**[7] (erythromycins have recently been identified as active elastase inhibitors with the ability to reduce mucus hypersecretion and therefore are being considered as potential drugs in the treatment of conditions such as cystic fibrosis).[8] Over the following decades these lactones were joined by compounds isolated from a whole range of natural sources and possessing diverse biological properties, but all structurally related as medium-ring (eight- to twelve-membered) and macrocyclic (thirteen- to eighteen-membered) lactones.



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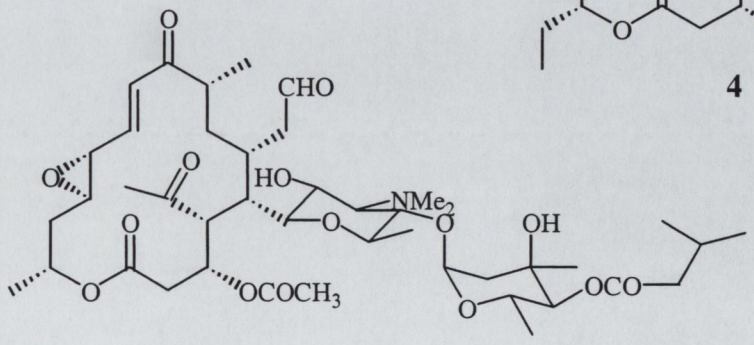

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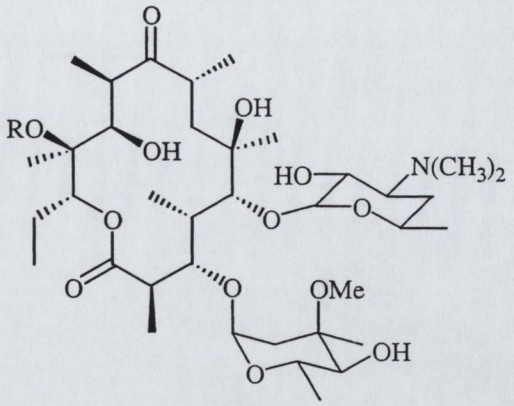
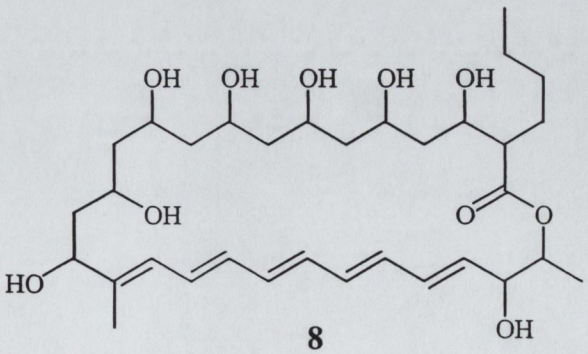


6 R = OH
7 R = H

In the classical sense the term "macrolide", which was coined by Woodward,[6] initially described the class of antibiotics isolated from *Streptomyces* cultures, but it has gradually been used in a broader sense to encompass all macrocyclic lactones, and certain macrocyclic lactams have also been described as macrolides.[9] Structural, stereochemical and conformational studies of this steadily growing family of compounds have been achieved by means of ^{1}H and ^{13}C NMR, mass spectroscopic and, to a limited extent, X-ray crystallographic techniques.

The polyene macrolide antibiotics are a class of compounds that are characterised by strong antifungal activity.[10] They generally have complex structures with large rings accommodating a conjugated polyene with up to seven double bonds and some have sugars attached to the macrocyclic ring. There is also a distinct area in the ring that is hydrophilic due to a concentration of hydroxyl groups. Chainin **8**,[11] a substance containing a twentyeight-membered lactone ring, is a typical example of a polyene macrolide antibiotic.



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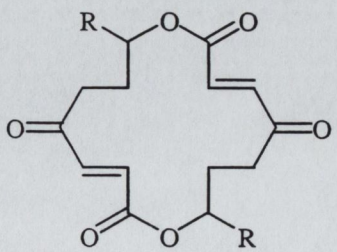
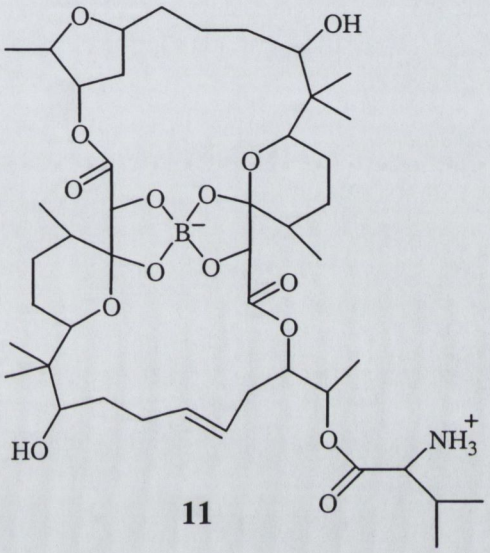


9 R = CH_3
10 R = CH_2COCH_3

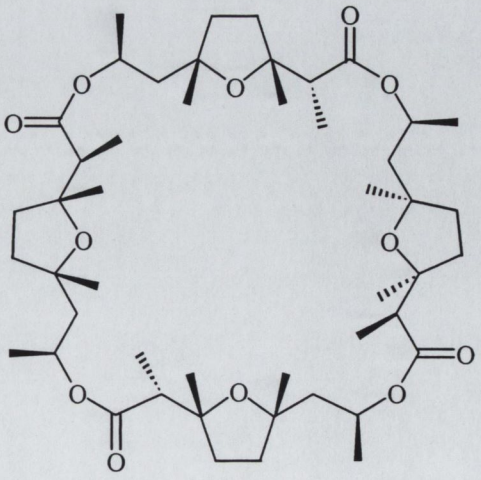
Macrodiolides and macrotetrolides are known to occur in nature and contain two and four ester linkages respectively. Pyrenophorin **9**[12] and vermiculine **10**[13] are diolides both of which have been successfully synthesised.

Boromycin **11**, a twentyeight-membered ring diolide, which was first described in 1967, is one of the rare boron-containing natural products.[14] The boron is bound, as borate, by a very hydrophilic area at the centre of the macrocyclic ring.



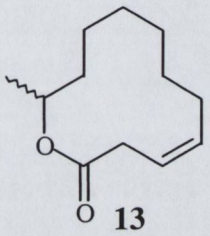
11

Nonactin **12**[15] is an ionophoric macrotetrolide which has been successfully synthesised and has been found to possess antibiotic qualities due to its hydrophilic interior. This hydrophilic interior is capable of binding an alkali metal cation and hence allows it to transport ions in biological systems.



12

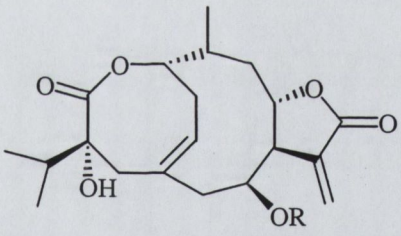
The secretions of the Rusty Grain beetles *Cryptolestes ferrugineus* have been found to contain the twelve-membered ferrulalactone **13** as its (*S*)-enantiomer. The (*R*)-enantiomer has been isolated from *Oryzaephilus mercator.* These beetles are widely distributed pests and primarily infest stored grain, with the male beetles producing aggregation pheromones that have been found to be attractive to both sexes. It is believed that these pheromones serve to promote population growth in suitable habitats.[16]



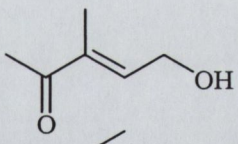
13

Sesquiterpene lactones have been isolated from the aerial parts of *Schkuhria pinnata* which grows mainly in the tropical areas of Central and South America. The structures of the related schkuhripinnatolides A **14**, B **15** and C **16** have been determined and have been found to include eight- and five-membered lactone rings.[17]

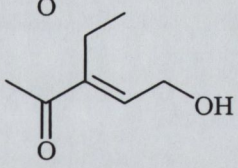
14 R = H



15 R =

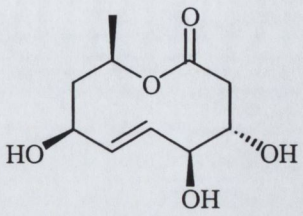


16 R =

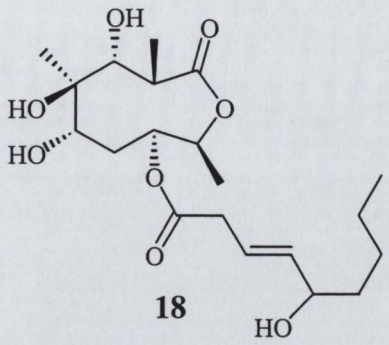


Chemical screening of a number of strains of *fungi imperfecti* resulted in the discovery of a large family of related decarestrictines, many of which are metabolites of *Penicillium simplicissimum* that show cholesterol biosynthesis inhibition. Decarestrictine D, known as tuckolide **17**, is a ten-membered lactone isolated from *Penicillium corylophilum*[18] and independently from the Canadian Tuckahoe fungus *Polyporus tuberaster.*[19] It has been synthesised[20] and has been found to be a potent inhibitor of cholesterol biosynthesis. It has also been used in

poultices and for treating rheumatism, but does not show any significant antibacterial, antiprotozoal or antiviral activity.



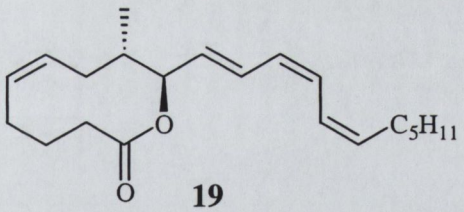
17



18

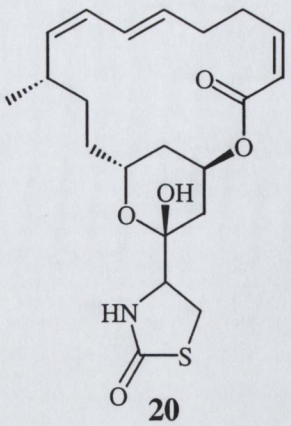
Botcinolide **18**, is a novel, biologically active, nine-membered, highly substituted lactone, isolated from a strain of *Botrytis cinerea* found on cultivated raspberry fruit (*Rubrus ideaus*).[21] It has shown significant phytotoxic properties, inhibiting the growth of wheat and of greenhouse-grown bean, corn and tobacco plants.

Marine organisms have provided a wealth of structurally related complex lactones which have been studied extensively. Ascidiatrienolide A **19**, a ten-membered lactone, has been isolated from the colonial marine ascidian *Didemnum candidum* which can be found off the Florida coast.[22]

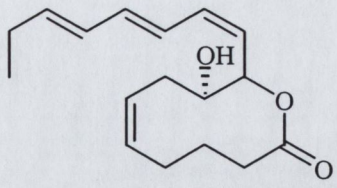


19

The Red Sea sponge *Latrunculia magnifica* excretes the large-ring lactone, (+)-latrunculin A **20** as part of its defence mechanism.[23] This particular ichthyotoxic metabolite was among the first natural products that were found to incorporate the 2-thiazodolinone moiety in their structures.



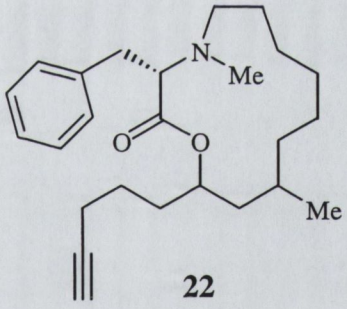
20



21

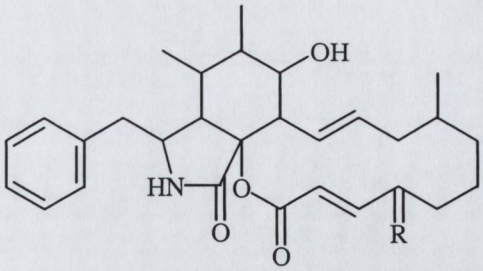
Octalactin A **21**, a lactone which possesses anticancer properties, has been isolated from a marine *Streptomyces* sp.[24] It has shown a significant *in vitro* cytotoxicity towards a type of murine melanoma and also toward human colon tumour cell lines.

Recently, a novel macrolide, spongidepsin **22**, has been isolated from a marine *Spongia* sp. found off the coast of the Vanuata Islands.[25] This thirteen-membered lactone has shown cytotoxic activity against cancer cell lines.



22

Another branch of the macrolide family is represented by the cytochalasins, such as cytochalasin A **23** and cytochalasin B **24**, isolated[26] from cultures of *Helminthosporium dematioideum*. These and other cytochalasins have attracted considerable attention due to their novel biological activities. These include antibiotic, antitumour and cytostatic activities, with some possessing the ability to induce ejection of the cell nucleus.



23 R = O
24 R = H, OH

The diverse physiological properties exhibited by all these medium-ring and macrocyclic lactones indicate that they or their congeners are of interest as potential candidate molecules for the treatment or control of diseases and pests. Their investigation in these respects is often limited by their natural origins which means that only restricted supplies of pure materials are available. Furthermore, very considerable effort may be required to obtain them from these sources and their further chemical transformation into potentially more active compounds is not a viable option. Hence, attention has focused on the search for a general and efficient strategy for the synthesis of medium-ring and macrocyclic lactones.

1.2 Factors determining rate of cyclisation

The term "medium-ring" lactone is usually applied to any alicyclic compound having a ring size in the range eight- to twelve-membered, while thirteen- to eighteen-membered alicyclic compounds are referred to as "large-ring" or "macrocyclic" lactones. In principle, macrocyclic systems can be generated by cleavage of internal bonds in polycyclic systems, or, more generally, by cyclisation of acyclic, long-chain precursors. However, in the latter case the ring closure is disfavoured entropically due to loss of entropy as a result of the formation of the, usually more rigid, cyclic structure. Systematic kinetic studies on the formation of medium-ring lactones have been carried out by Illuminati *et al.*[27] Their work involved the lactonisation of sodium salts of ω-bromocarboxylic acids in DMSO-H_2O (99:1, v/v) solution at 50 °C. Rate studies on the cyclisation of ω-bromocarboxylic acids leading to thirteen- to sixteen-membered lactones have also been carried out by Davies *et al.*[28] These studies proved that five- to seven-membered rings are formed with relative ease whereas eight- to thirteen-membered

rings are formed with difficulty. Cyclisation becomes easy again for fourteen-membered and greater rings. The overall findings are illustrated in **Figure 1.1**[29] and can be explained by ring strain considerations. The rate of cyclisation is determined by the activation energy for the process that is controlled by the ground state energy of the acyclic precursor and the energy of the transition state. The conformation of the transition state will resemble that of the cyclic product and hence will determine the stability of that cyclic product.

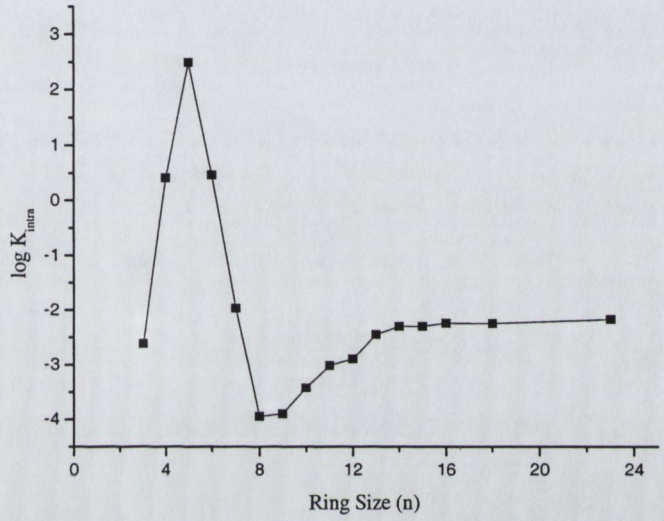


Figure 1.1

The ease of cyclisation will also be affected by the probability with which atoms placed at the chain terminals will come within bonding distance and hence the rate of cyclisation will decrease as the distance between chain terminals increases *i.e.* as the chain length increases. Also, there is a negative change in entropy when a ring-like transition state is approached due to the reduction in rotational freedom of the open chain alicyclic precursor.

Originally, according to the von Baeyer strain theory, it was thought that cyclic compounds were planar and hence it was the Baeyer angle strain that determined the overall strain in both small and large rings. However, this theory was disproved by the mere existence of medium and macrocyclic systems which had previously been thought too unstable to exist. The medium and macrocyclic compounds could indeed exist due to "puckering" of the ring to minimise the angle strain.

There are three determining factors effecting the overall strain of medium-sized rings:

(1) torsional strain in single bonds (Pitzer strain);

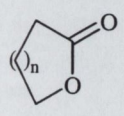
(2) deformation of ring bond angles from their preferred angles (Baeyer strain);

(3) transannular strain (non-bonding interactions) which occurs when atoms on opposite sides of the ring are forced into close proximity.

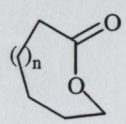
The total degree of strain will be reflected in the energy of activation for the cyclisation.

An additional problem involved in formation of medium and macrocyclic systems is polymerisation due to the entropically-favoured intermolecular rather then intramolecular interactions. This, however, can be controlled experimentally by utilising high dilution conditions, an approach which was first described by Ziegler.[30] However, even under these conditions medium-ring formation was the most difficult to achieve.

Kinetic studies on the hydrolysis of simple lactones ranging in ring size from four- to sixteen-membered were carried out by Huisgen and Ott.[31] It was found that the rate of hydrolysis decreased as the size of the ring increased. These results, and the results of further studies involving the physical properties such as dipole moments and boiling points of the same lactones, suggested that the ester functional group exists in a less stable and more polar *cis* conformation for ring sizes of 7 or less as in lactone **25**. For ring sizes of 10 or greater, lactone **26**, it exists in a more stable and less polar *trans* conformation. The intermediate eight- and nine-membered ring sizes exist in *cis-trans* equilibrium conformations, with the *cis* conformation being more predominant in the eight-membered and the *trans* in the nine-membered ring.



25 n = 0-3



26 n = 4-10

Intramolecular cyclisation reactions can be affected by the presence of a rigid group such as a heteroatom,[32] or *gem*-dimethyl groups[33] within the chain. These rigid groups can substantially decrease entropy loss on cyclisation due mainly to relief of non-bonding interactions and also by restriction of rotation along the chains.

1.3 Synthetic methodologies for the preparation of medium-ring and macrocyclic lactones

The literature reports methodologies for the synthesis of lactones that include a number of general approaches which can be classified according to the type of bond cleaved or formed in the key ring-forming reaction.

1.3.1 Methods involving C-O bond formation

1.3.2 Methods involving intramolecular cyclisation of bifunctional acyclic precursors

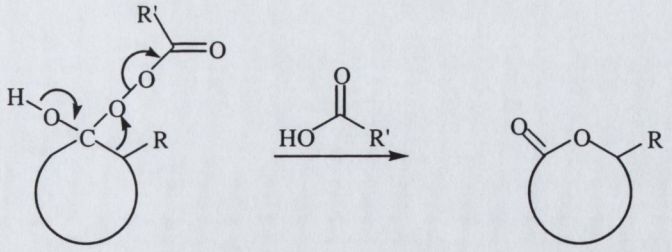
1.3.3 Methods involving C-C bond formation

1.3.4 Methods involving cleavage of fused bonds in bicyclic systems

1.3.5 Miscellaneous strategies

1.3.1 Methods involving C-O bond formation

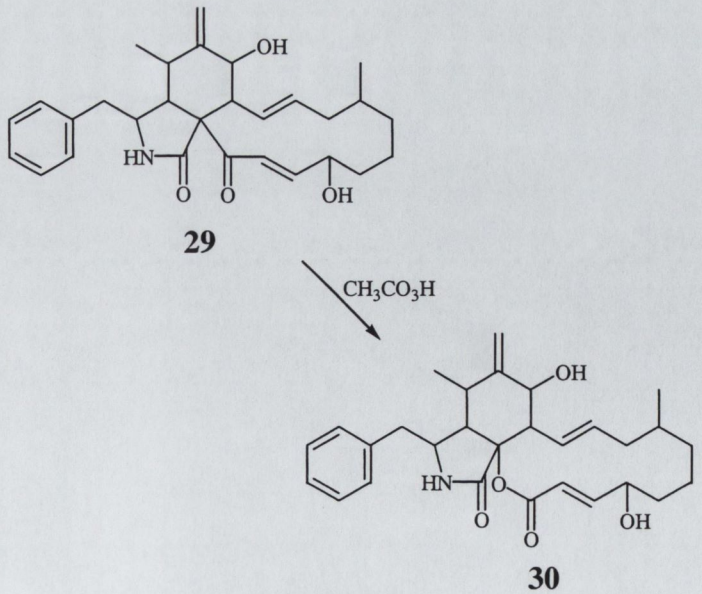
The Baeyer-Villiger reaction,[34] which was reported in 1899, involves conversion of cyclic ketones to the corresponding lactones in the presence of Caro's acid (peroxymonosulfuric acid) or a peroxy-acid *via* the insertion of oxygen into the ring next to the carbonyl group. Reaction between a peroxy-acid ($R'CO_3H$) and a ketone leads to an intermediate **27** which undergoes rearrangement with loss of carboxylic acid to give the product lactone **28**, **Scheme 1.1**.



27 **Scheme 1.1** 28

Ruzicka and Stoll[35] used this classical method for lactone formation as early as 1929 in the preparation of simple macrocyclic lactones. Many cyclic ketones have been oxidised to give the corresponding lactones.[36] However, although this method provides a facile route to simple macrocyclic lactones whenever the requisite ketones are available, the method is not as successful when applied to the formation of more complex naturally occurring lactones. Interference from other functionalities and problems with regiospecificity result in the Baeyer-Villiger reaction, in general, being limited to the formation of simple macrocyclic lactones, although a small number of complex lactones have been synthesised successfully.

Binder and Tamm[37] report the application of this method to the formation of a complex lactone. Phomin **30** was formed, in low yield, *via* treatment of deoxyphomin **29** with peracetic acid and *p*-toluenesulfonic acid, **Scheme 1.2**.

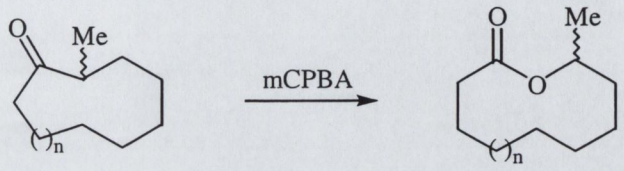


29

30

Scheme 1.2

Baldwin *et al.*[38] synthesised the naturally occurring lactone (±)-phoracantholide I **33** (n = 1) and (±)-dihydrorecifeiolide **34** (n = 3) from the corresponding cyclic ketones **31** and **32** in yields that exceeded 90% by use of the Baeyer-Villiger oxidation, **Scheme 1.3**.



31 n = 1
32 n = 3

33 n = 1
34 n = 3

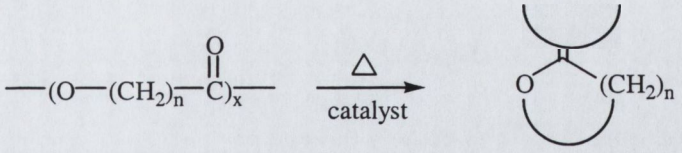
Scheme 1.3

1.3.2 Methods involving intramolecular cyclisation of bifunctional acyclic precursors

Originally, it was thought that preparation of macrocyclic lactones *via* bifunctional acyclic precursors was impossible due to favourable intermolecular reactions and the subsequent formation of linear polyesters.[39] In 1933, Hill and Carothers carried out pioneering research into a new method for the synthesis of macrocyclic esters. At the time, the only generally applicable method known was the oxidation of cyclic ketones with Caro's acid, with lactones being formed in poor yields and the requisite ketones difficult to obtain.

Hill and Carothers proposed an alternative synthesis involving the preparation of large ester rings *via* thermal catalytic depolymerisation of the corresponding linear polyester,[39] thus eliminating the need for the use of high-dilution techniques which was an alternative solution to the polymerisation problem.

Simple eleven- to seventeen-membered lactones **36** were obtained from linear polyesters **35** in good yields using optimised temperatures (270 °C) and a variety of catalysts (*e.g.* $MgCl_2$), **Scheme 1.4**. The eleven- and fourteen-membered lactones were formed with lower yields, and large amounts of the corresponding diolides were also formed.



35 n = 9-15 **36**

Scheme 1.4

However, further research into high-dilution techniques showed that lactonisation of long open-chain bifunctional acyclic precusors was indeed a direct and general method of macrolide formation. Hence, numerous methodologies have been developed and these can be classified according to the precursor employed for the lactonisation step:

(i) Intramolecular cyclisation of ω-halocarboxylic acids

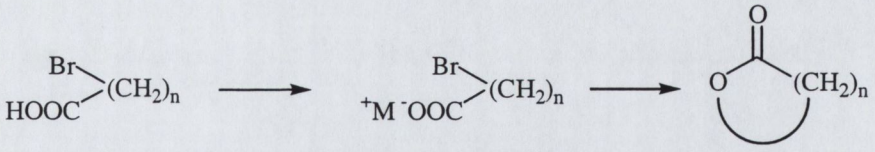
(ii) Intramolecular cyclisation of ω-hydroxycarboxylic acids

(iii) Intramolecular cyclisation *via* oxidation of α,ω-diols

The intramolecular reaction of long open-chain bifunctional acyclic precursors is a popular method for the synthesis of lactones. However, it must be noted that it is entropically disfavoured and, in general, is only successful under highly dilute conditions to facilitate the intramolecular reaction.

(i) Intramolecular cyclisation of ω-halocarboxylic acids

As mentioned previously, Illuminati *et al.*[27] and Davies *et al.*[28] formed medium and macrocyclic lactones by internal nucleophilic displacement of bromide ion by carboxylate ions **38** derived from ω-bromocarboxylic acids **37**, **Scheme 1.5**. Systematic rate and kinetic studies were carried out on these cyclisation reaction, Section 1.2. Similar work was carried out by Hunsdiecker and Erlbach.[40] Ten- to eighteen-membered ring lactones **36** were formed when the potassium carboxylates **38**, generated from the corresponding ω-bromocarboxylic acids **37** and potassium carbonate, were refluxed in 2-butanone under highly dilute conditions, **Scheme 1.5**.



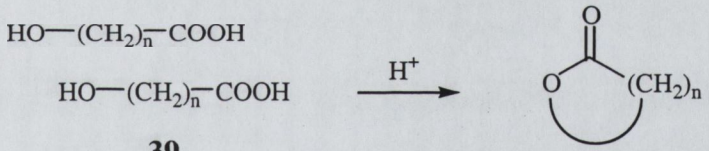
37 **38** M = Na, K n = 8-16 **36**

Scheme 1.5

(ii) Intramolecular cyclisation of ω-hydroxycarboxylic acids

The relative availability of hydroxy-acids has permitted extensive research into this area, and thus, lactonisation *via* the internal esterification of hydroxy acid precursors has become one of the most commonly-used methods to obtain these compounds. Activation of either one or, in some cases, both functional groups of the hydroxy-acid precursor allows cyclisation to occur under mild conditions, permitting the synthesis of structurally complex lactones.

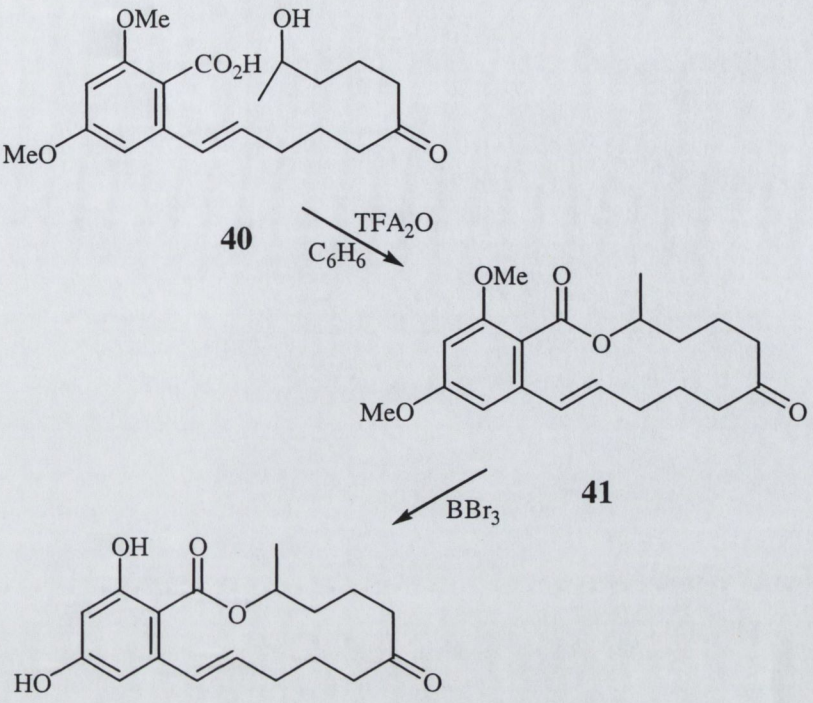
In 1934, Stoll and Rouvé[41] synthesised a large number of simple macrocyclic lactones **36** (up to twentyfour-membered rings) in good yields *via* acid catalysis under highly-dilute conditions. Cyclisation of the requisite acids **39** occurred in refluxing benzene in the presence of benzenesulfonic acid over long periods of time, **Scheme 1.6**.



39 **36** n = up to 22

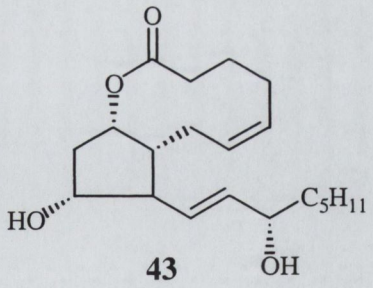
Scheme 1.6

A Merck group,[42] which utilised the mixed trifluoroacetic anhydride method of carboxyl activation, reported a total synthesis of the biologically active macrolide zearalenone **42**, **Scheme 1.7**. The mixed anhydride was prepared from the hydroxy acid **40** by reaction with trifluoroacetic anhydride in benzene and the cyclisation occurred at relatively low temperatures forming the dimethyl ether **41** in poor yield. The dimethyl ether was subsequently treated with BBr_3 to give zearalenone **42**.



42 **Scheme 1.7**

The trifluoroacetic anhydride method of carboxyl activation was also employed in the synthesis of the novel prostaglandins **43** and **44**.[43] Mixed anhydrides were formed from the corresponding hydroxy acids and cyclisation occurred in benzene at low temperature under dilute conditions in relatively good yields.



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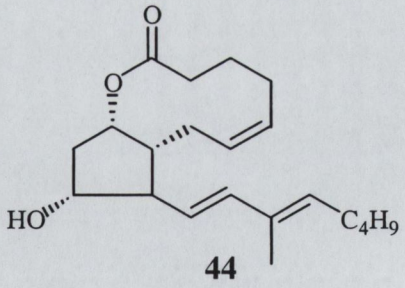
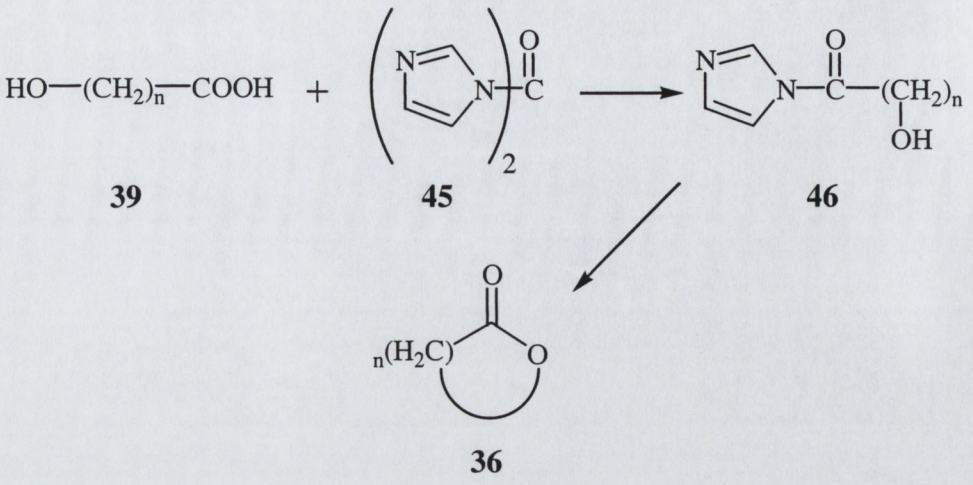


44

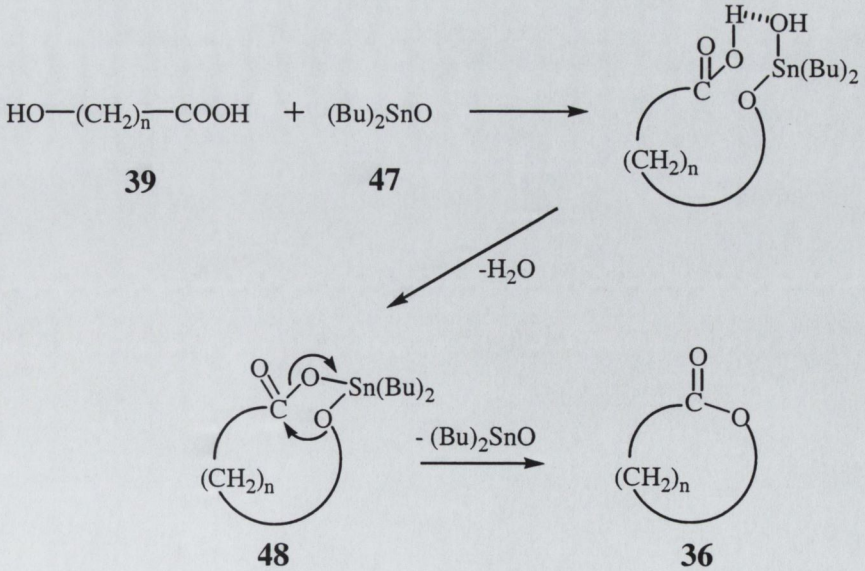
An alternative method of activation of the carboxyl group is conversion to the corresponding *N*-acylimidazolide **46** by treatment of a hydroxy-acid **39** with *N*, *N*'-carbonyldiimidazole **45**. The imidazolide moiety has a very high degree of reactivity in nucleophilic reactions.[44] Base-catalysed internal alcoholysis of the imidazolide results in formation of the desired lactone **36**, **Scheme 1.8**.



39 **45** **46** **36**

Scheme 1.8

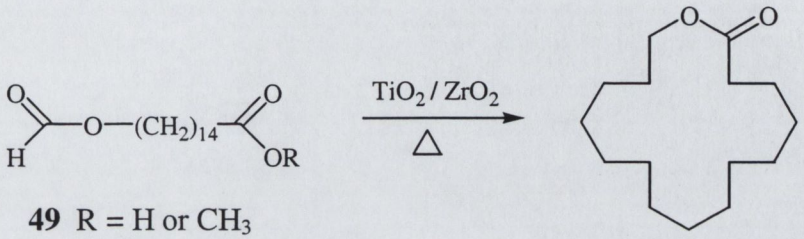
Steliou and Poupart[45] have reported a neutral method for effecting internal macrocyclic esterification of ω-hydroxycarboxylic acids **39** based on a tin "template-driven" process. Various macrolides were successfully synthesised including zearalenone **42** and pyrenophorin **9**. The cyclisation was achieved using catalytic amounts of di-*n*-butyltin oxide **47** which initially reacts with the hydroxyl group of **39** leading to a doubly-activated cyclic alkoxystannylene carboxylate **48**, **Scheme 1.9**. The combined nucleophilicity of the alkoxy group as a consequence of being bonded to tin and the simultaneous activation of the carboxyl group leads to lactonisation with elimination of di-*n*-butyltin oxide.



39 **47** **48** **36**

Scheme 1.9

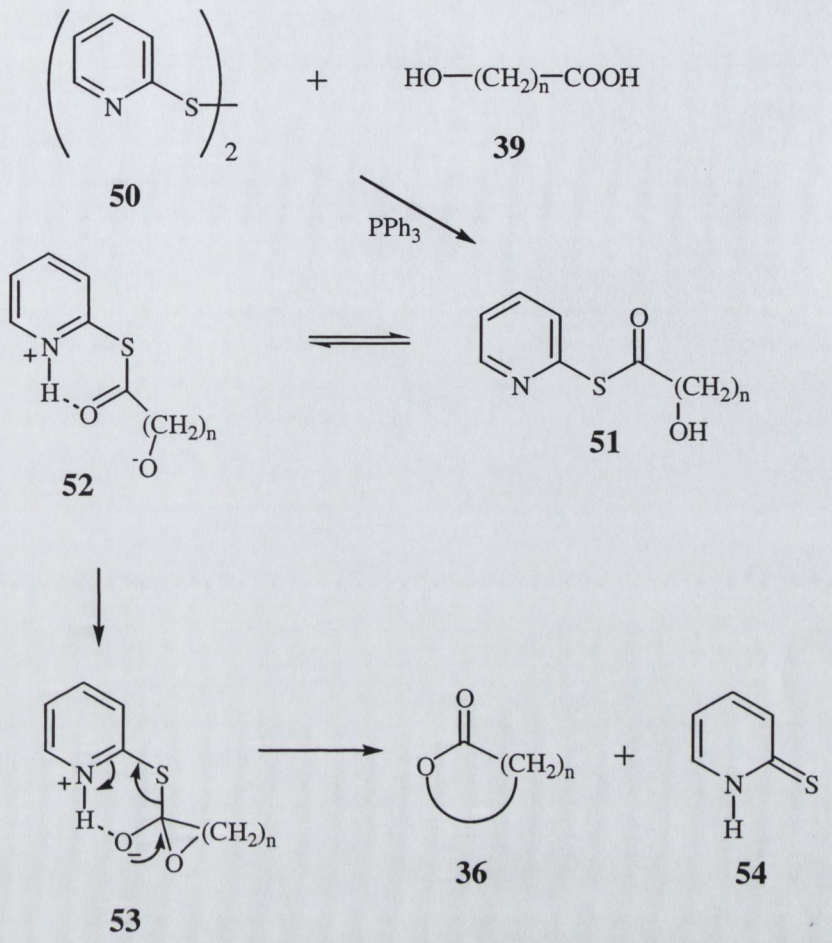
Stolle and Bolle[46] formed pentadecanolide **2** (exaltolide) in approximately 50% yield by heterogeneous gas-phase thermal reaction of the formate ester **49** (R = H), formed from 15-hydroxypentadecanoic acid, over TiO_2 (or ZrO_2) at 290 °C. A similar result was obtained for the reaction of the methyl ester **49** (R = Me), **Scheme 1.10**.



49 R = H or CH_3 **2**

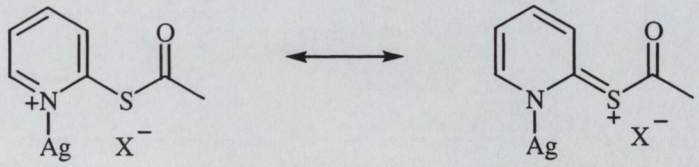
Scheme 1.10

Corey and Nicolaou discovered a highly efficient method for the synthesis of macrocyclic lactones. This involves simultaneous double activation of both the carboxyl and hydroxyl groups of an ω-hydroxy-acid **39** by internal proton transfer from the hydroxyl to the carbonyl oxygen leading to cyclisation of these hydroxy acids *via* 2-pyridinethiol esters.[47] Thus, ω-hydroxyacids **39** are converted to pyridinethiol esters **51** *via* their reaction with dipyridyl disulfide **50** and triphenylphosphine, **Scheme 1.11**.[48] The proton transfer from hydroxyl to carbonyl in **51** is facilitated by the basic nature of the nitrogen atom in the pyridine nucleus present in the thiol ester. The resulting dipolar intermediate **52** then cyclises to form the tetrahedral intermediate **53** which collapses to form the lactone **36** and 2-pyridthione **54**. High-dilution techniques were employed to minimise intermolecular reaction which would lead to the corresponding diolides.



Scheme 1.11

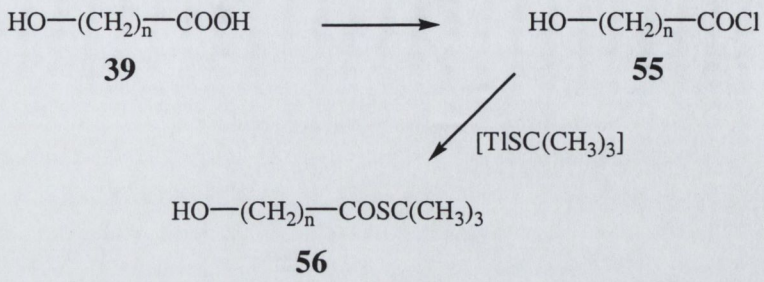
A modification of the Corey-Nicolaou lactonisation method was devised by Gerlach and Thalmann,[49] who used silver ion ($AgClO_4$ or $AgBF_4$)[50], **Scheme 1.12**, to activate 2-pyridinethiolesters by complexation, thus allowing lactones to be formed in a mild and efficient manner at room temperature.



Scheme 1.12

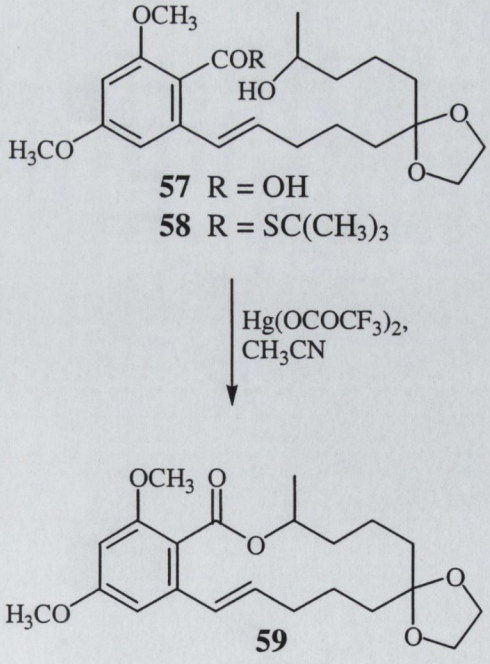
The macrolide antibiotic methymycin was synthesised by Masamune *et al.*,[51] employing S-*tert*-butyl thiolesters of hydroxy acids in the presence of mercuric trifluoroacetate. Lactonisation proceeds rapidly at room temperature in dilute acetonitrile. The required S-*tert*-butyl thiolesters **56** were obtained from the

hydroxy acids **39** by reaction of the corresponding acid chlorides **55** with thallous 2-methylpropane-2-thioate, **Scheme 1.13**.



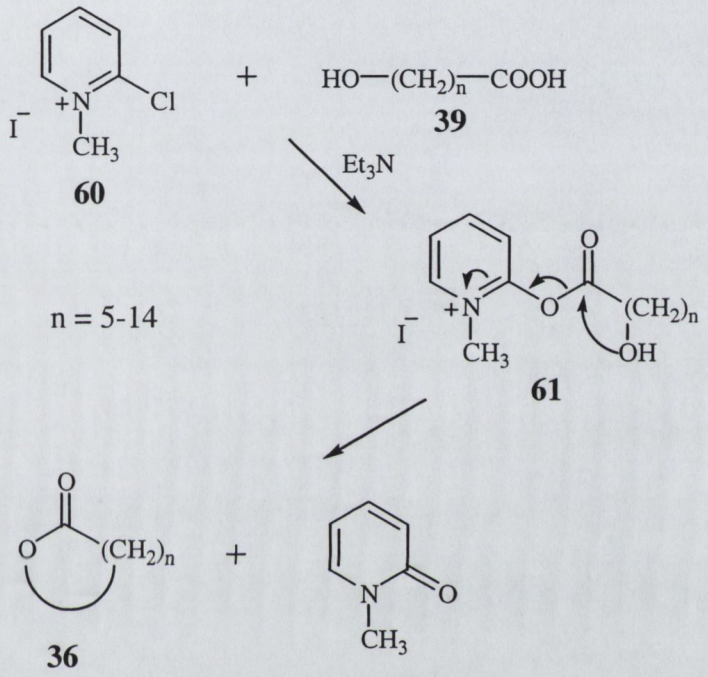
Scheme 1.13

This method has been used in the synthesis of the zearalenone derivative **59**,[52] which was formed in 90% yield when (+)-dimethylzealalenone seco-acid ketal **57** was converted to the corresponding thiolcarboxylate **58**, which was then treated with two equivalents of mercuric trifluoroacetate, **Scheme 1.14**. The mechanism of this reaction has not been clarified, and it may proceed *via* a mercury complex or through the intermediacy of a mixed trifluoroacetic anhydride.



Scheme 1.14

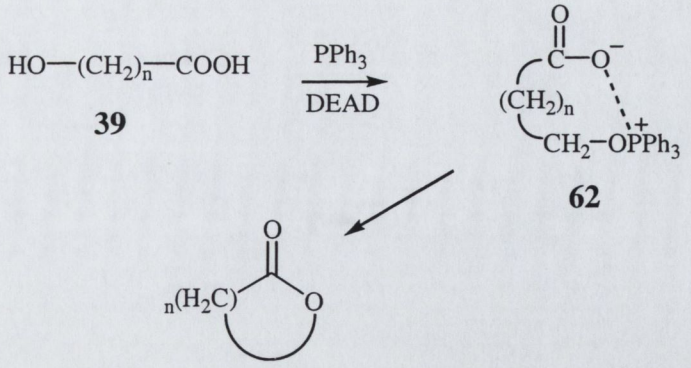
Mukaiyama *et al.*[53] devised a procedure closely related to the double activation method, involving cyclisation of hydroxy acids **39** *via* reaction of the carboxylic function with 1-methyl-2-chloropyridinium iodide **60** in the presence of triethylamine in refluxing dichloromethane or acetonitrile, **Scheme 1.15**. The reaction proceeds *via* **61** which undergoes intramolecular attack by the hydroxyl group.



Scheme 1.15

This procedure was carried out on a series of acids **39**, where n = 5-14, and the corresponding lactones **36** were formed in good yield together with varying amounts of their diolides.

Mitsunobu *et al.*[54] reported a method for the preparation of lactones under mild and neutral conditions. A series of ω-hydroxy acids **39**, where n = 5, 7, or 11, were utilised in the cyclisation studies, **Scheme 1.16**. The acids were treated with diethyl azodicarboxylate (DEAD) and triphenylphosphine at room temperature, giving the corresponding lactones **36** in reasonable yields, together with some diolides. This cyclisation is thought to proceed *via* a dipolar intermediate **62** in which the reacting sites are in close proximity, leading to intramolecular lactonisation. However, in the case of hydroxy acid **39** (n = 7), none of the anticipated nine-membered lactone was formed, but the corresponding diolide was formed in 70% yield.



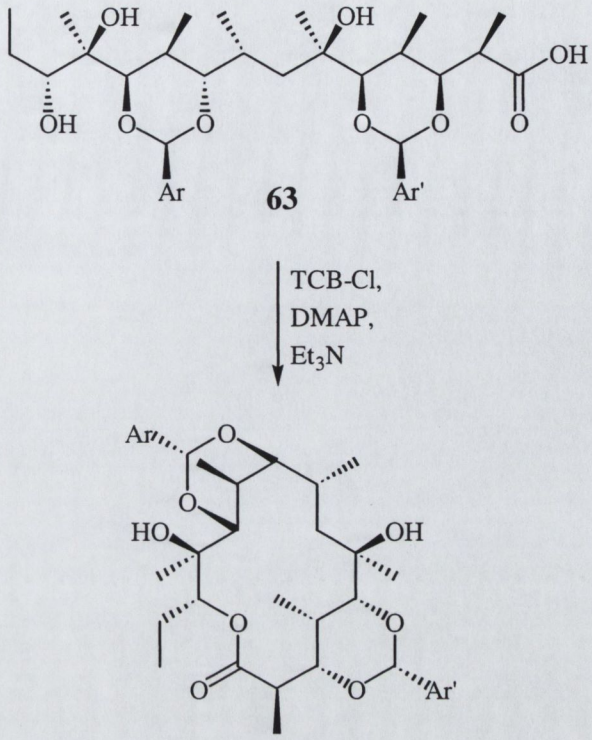
39 **62**

36

Scheme 1.16

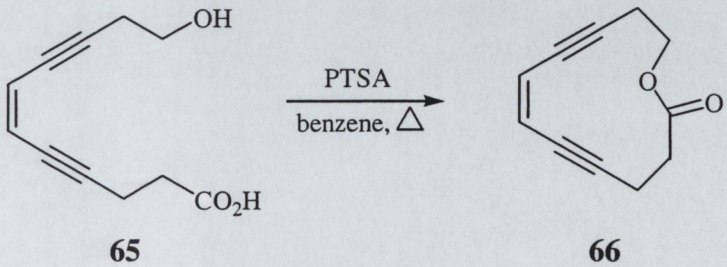
This mild and efficient method for the synthesis of lactones can be applied to the formation of complex lactones whose synthesis had previously proved problematic.[55] The Steglich modification[56] of the Mitsunobu method has been employed in the synthesis of such lactones and involves slow addition of the precursor hydroxy-acid to the preformed Mitsunobu reagent.

Yamaguchi *et al.*[57] and Yonemitsu *et al.*[58] also carried out research into the cyclisation of hydroxy-acids. Treatment of the ω-hydroxy acids with 2,4,6-trichlorobenzoyl (TCB) chloride in the presence of triethylamine and a small amount of 4-dimethylaminopyridine (DMAP) gave the corresponding lactones in almost quantitative yield. A derivative **64** of erythronolide A, a fourteen-membered lactone, was synthesised from the acid **63** in this way, **Scheme 1.17**.



Scheme 1.17

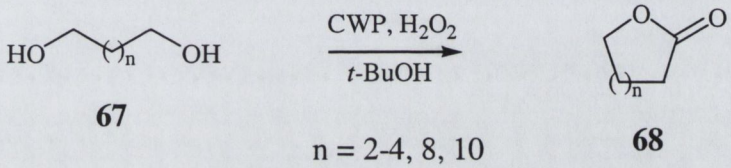
Guillerm and Linstrumelle[59] have reported a facile synthesis of an enediyne twelve-membered lactone by simple acid-catalysed lactonisation of the corresponding enediyne hydroxy-acid precursor with no need for activation of either the hydroxy or carboxylic acid functional groups. The unusual ease of reaction is due to the reacting ends being held relatively close to each other because of geometrical constraints. This is demonstrated by the case of the (*Z*)-enediyne system **65** which undergoes intramolecular reaction to give the twelve-membered lactone **66** in 74% yield, **Scheme 1.18**.



Scheme 1.18

(iii) Intramolecular cyclisation *via* oxidation of α,ω-diols

Ishii and co-workers[60] reported a convenient method for the preparation of lactones involving oxidative dehydrogenation of a wide variety of α,ω-diols with aqueous hydrogen peroxide and the metal catalyst tris(cetylpyridinium)12-tungstophosphate, (CWP), $[\pi\text{-}C_5H_5N^+\text{-}(CH_2)_{15}CH_3]_3(PW_{12}O_{40})^{3-}$. Lactones **68** of various sizes (up to fourteen-membered) were formed in good yield from the corresponding precursor diols **67**, although a decrease in yield was observed as chain length increased, **Scheme 1.19**.

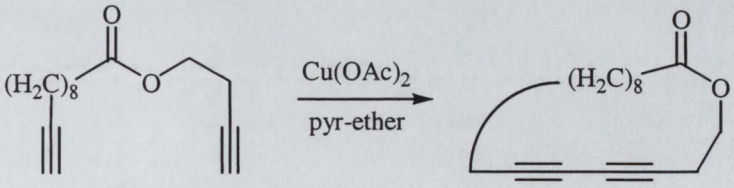


67 n = 2-4, 8, 10 **68**

Scheme 1.19

1.3.3 Methods involving C-C bond formation

Open, long chain structures with ester linkages have been cyclised by C-C bond formation to give macrocyclic lactones by a variety of techniques, one of which is acetylenic coupling. The sixteen-membered lactone exaltolide **2** has been synthesised in this way by Eglinton *et al.*[61] Ring-closure was achieved by a high-dilution intramolecular oxidative coupling[62] involving the terminal ethynyl groups of **69** in the presence of cupric acetate in pyridine-ether, **Scheme 1.20**. Catalytic hydrogenation of the resulting lactone **70** gave pure exaltolide **2**.

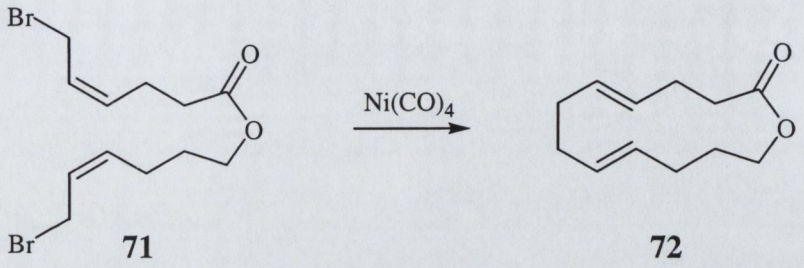


69 **70**

Scheme 1.20

Corey and Kirst[63] devised a novel approach to macrolides involving a nickel carbonyl-catalysed coupling of terminal allylic bromides. The thirteen-membered (*E*,*E*)-dienyl macrolide **72** was formed by slow addition of the dibromoester **71** to

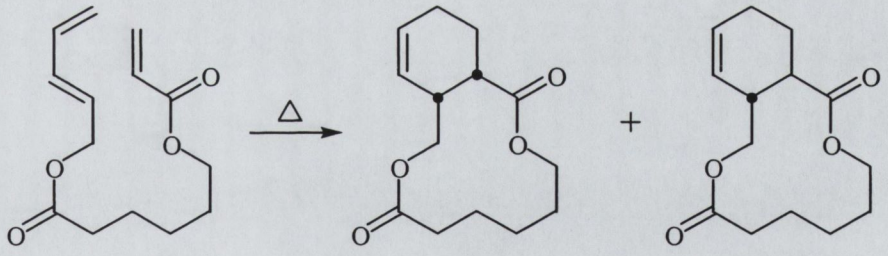
nickel carbonyl in *N*-methylpyrrolidone at 50 °C, **Scheme 1.21**. The corresponding saturated lactone was also formed by catalytic hydrogenation of **72**. This method has been successfully applied to the formation of other complex lactones.[64]



71 **72**

Scheme 1.21

Corey *et al.*[65] also devised a method for the synthesis of macrocyclic lactones *via* the Diels-Alder reaction. Open chain diester **73** which contains both diene and dienophile units separated by 10 atoms was synthesised, and the desired intramolecular reaction was accomplished by its slow addition to refluxing benzonitrile to yield a mixture of bicyclic lactones consisting mainly of **74** and **75** in a 1:1 ratio, **Scheme 1.22**. A noteworthy observation was that the product distribution in this intramolecular Diels-Alder reaction was similar to that found in a related intermolecular reaction, suggesting that during cyclisation the two mutually reactive units in **73** behaved almost as though they were not part of the same molecule.

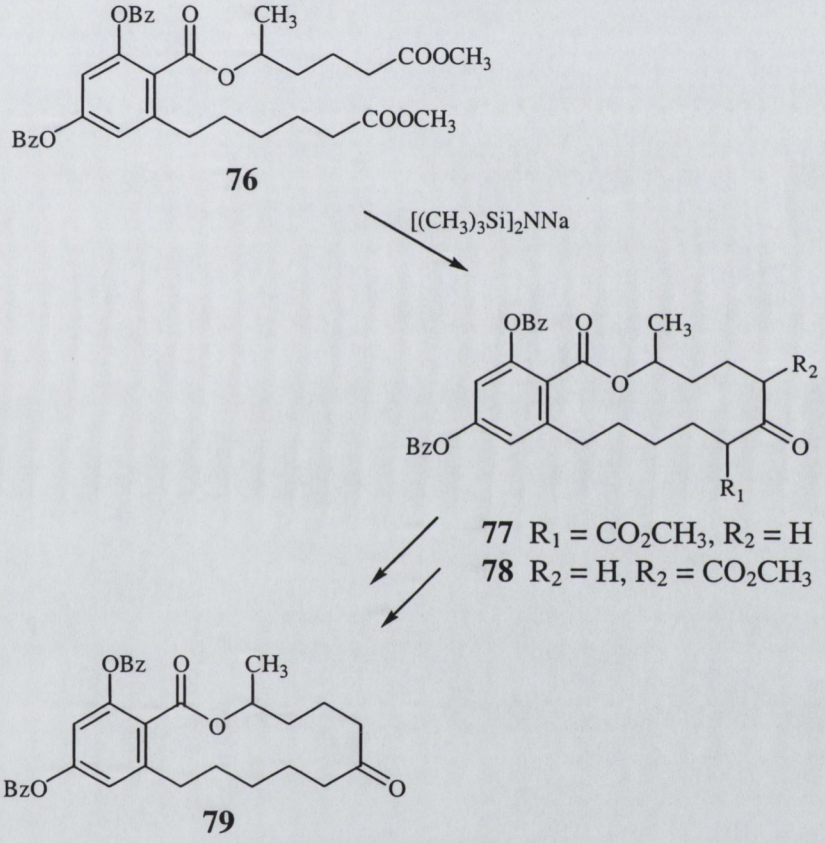


73 **74** **75**

Scheme 1.22

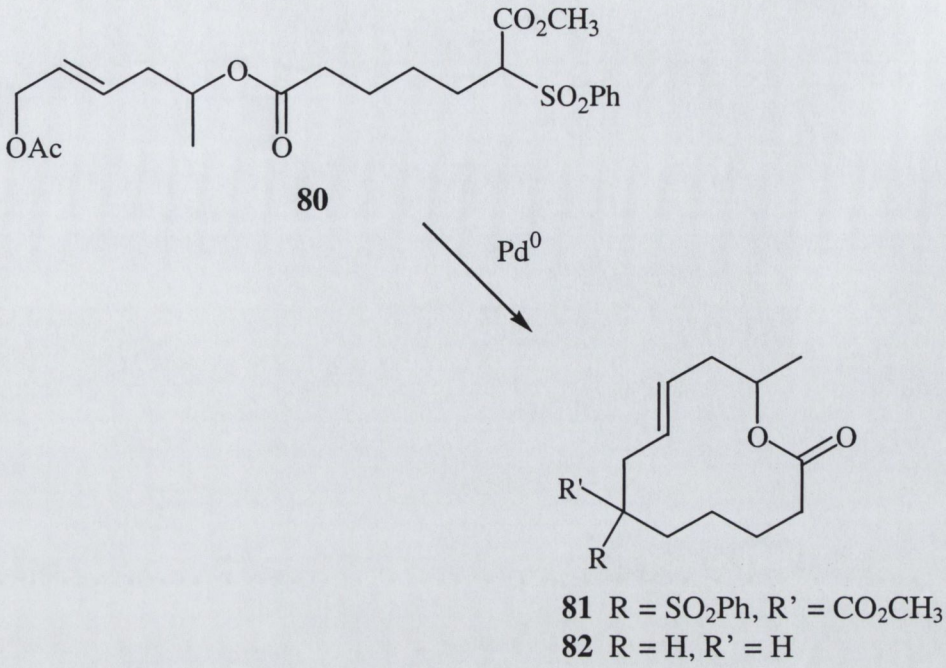
Hurd and Shah,[66] while completing studies towards the total synthesis of zearalanone, discovered an approach involving an adaptation of the Dieckmann condensation reaction. Cyclisation of the α,ω-diester **76**, whose structure contains a third functional group (the lactone function) that was susceptible to basic cleavage, was accomplished by using sodium bis(trimethylsilyl)amide, $[(CH_3)_3Si]_2NNa$ in

refluxing ether under high-dilution conditions, forming the fourteen-membered lactones **77** and **78** in good yield, **Scheme 1.23**. Subsequent saponification to the corresponding β-keto acids followed by decarboxylation gave the dibenzyl ether of (±)-zearalanone **79**. The mild reaction conditions employed, coupled with the preservation of the lactone function under basic conditions at moderate temperatures, suggest that this method may be valuable in the synthesis of other complex macrocycles with base-reactive functions. However, the fact that it can lead to a mixture of products does curtail its effectiveness.



Scheme 1.23

Trost and Verhoeven,[67] carried out studies on macrolide formation *via* palladium(0)-catalysed intramolecular allylic alkylation reactions. For example, the sodium salt derived from the acetate **80** was cyclised in the presence of tetrakis(triphenylphosphine)palladium(0) leading to the formation of the twelve-membered lactone **81** in 78% yield, **Scheme 1.24**. Subsequent decarboxylation followed by reductive desulfonylation, yielded the naturally-occurring lactone recifeiolide **82**. The naturally-occurring macrolides exaltolide **2** and phoracantholide **33** were also synthesised in this manner.

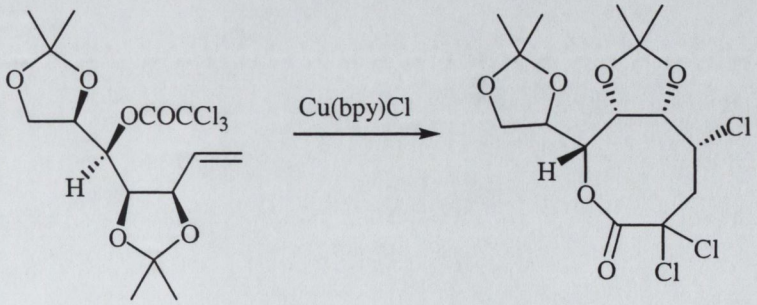


80

81 R = SO_2Ph, R' = CO_2CH_3
82 R = H, R' = H

Scheme 1.24

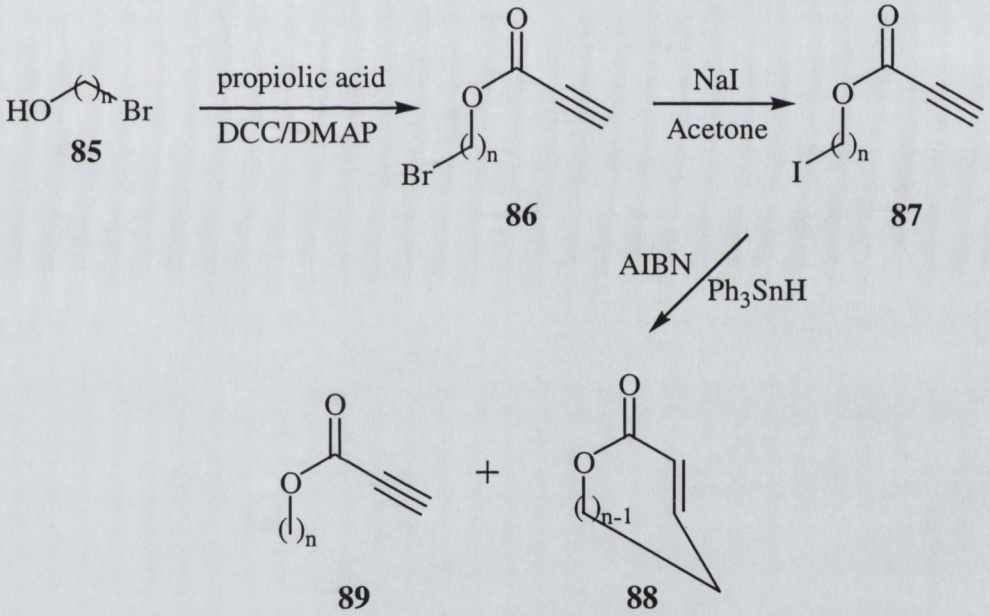
A novel approach to medium-sized lactones has been reported by Pirrung *et al.*,[68] employing a Cu(bpy)Cl catalyst for the cyclisation of trichloroacetates. Alkenyl trichloroacetates were heated in dichloroethane in the presence of the catalyst to effect cyclisation *via* a chlorine-transfer process, leading to eight- and nine-membered lactones in moderate to good yields. Thus, precursor **83**, on treatment with the Cu(byp)Cl catalyst, cyclised to form the eight-membered lactone **84** in 74% yield, **Scheme 1.25**. Interestingly, only a single diastereomer was obtained. This method gave promising results with rigid acyclic precursors. However, attempts to cyclise flexible chains to give ring systems larger then nine-membered met with failure.



83 **84**

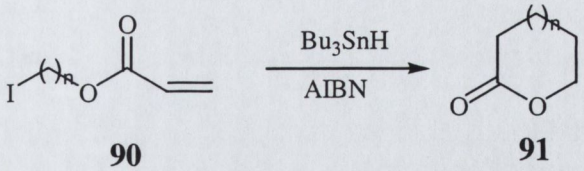
Scheme 1.25

Intramolecular free-radical addition to propiolate esters leads to the formation of (*E*)-α,β-unsaturated macrocyclic lactones.[69] ω-Bromoalkyl-propiolate esters **86** were formed from the respective ω-bromoalcohols **85** and were then converted into the corresponding iodides **87** by reaction with sodium iodide, **Scheme 1.26**. Cyclisation was then achieved in the presence of triphenyltin hydride and azobisisobutyrolnitrile (AIBN) under high-dilution conditions to give the (*E*)-α,β-unsaturated macrocyclic lactones **88** (n = 10-12) in moderate yields (48–60%), along with some of the reduced products **89** (29–37%). The reactions were both regio- and stereospecific, and led to the (*E*)-α,β-unsaturated lactones due to preferential *endo*-attack. This method failed for the synthesis of 6- to 9-membered lactones. Instead, large amounts of the reduced products **89** were formed.



Scheme 1.26

A similar method was devised by Porter *et al.*[70] Cyclisation was achieved by intramolecular free radical addition to acrylate or fumarate esters. Thus, α,ω-halo alcohols were converted to their acrylate esters and the lactones **91** were formed by treatment of the derived iodoalkyl acrylates **90** with tributyltin hydride and a catalytic amount of AIBN. A variety of saturated medium- and large-ring lactones were obtained in moderate yields, **Scheme 1.27**.

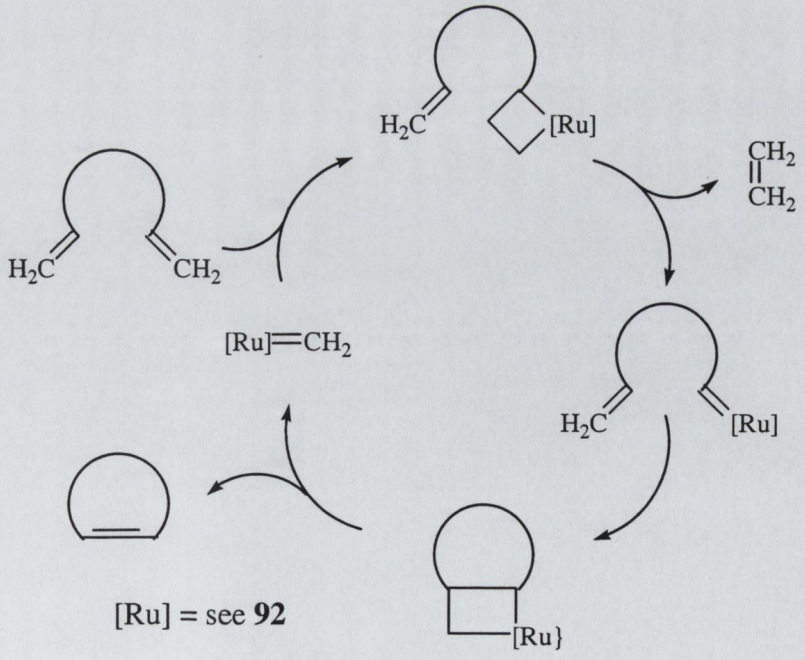


90 **91**

Scheme 1.27

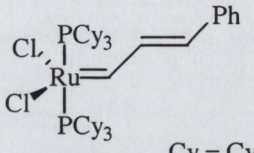
The same conversion of iodoalkyl acrylates to lactones was achieved by Abe *et al.*[71] *via* photostimulation in the presence of metal hydride complexes such as sodium cyanoborohydride, sodium borohydride or potassium borohydride. Lactones varying in ring size from ten- to sixteen-membered were formed in excellent yields (80-93%), together with small amounts of diolides and reduced starting materials.

More recently, olefin metathesis has been recognised as an attractive tool for general organic synthesis. In particular, ring-closing olefin metathesis (RCM), **Scheme 1.28**, has emerged as a straightforward entry into large ring systems and has received a high degree of attention in the last ten years. Carbocyclic and heterocyclic ring systems with sizes varying from five to several dozens of atoms have been synthesised successfully. Furthermore, the smooth reaction conditions of metathetic processes are compatible with almost all functional groups, even in sensitive molecules.[72]



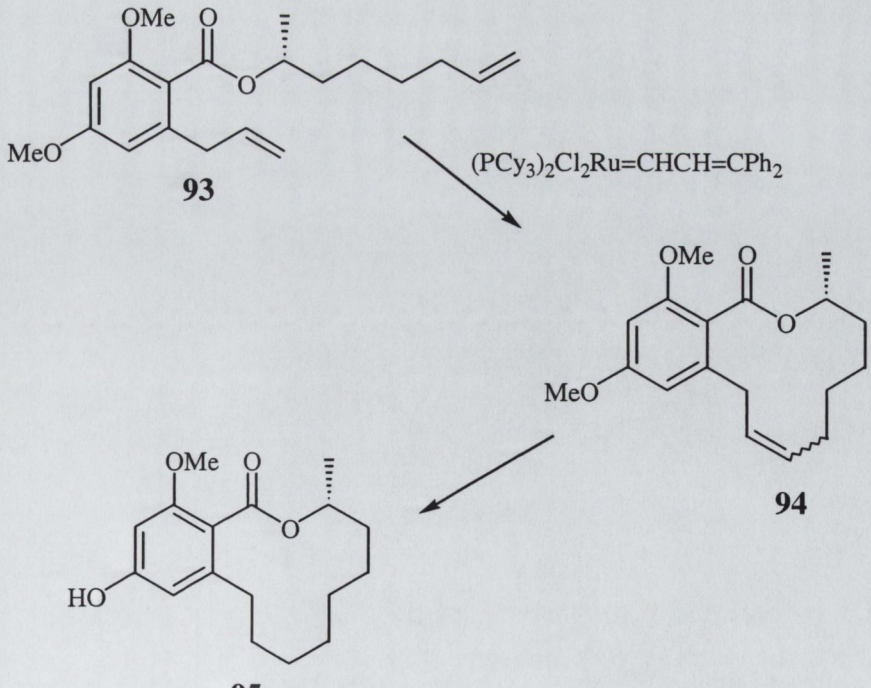
Scheme 1.28

Transition metal complexes are employed as catalysts for this process. Amongst these, the ruthenium carbene $(PCy_3)_2Cl_2Ru{=}CHCH{=}CHPh$ **92**, introduced by Grubbs *et al.*,[73] is particularly noteworthy as it is insensitive toward oxygen and moisture yet highly reactive in metathetic reactions. However, it is somewhat unstable at elevated temperatures.



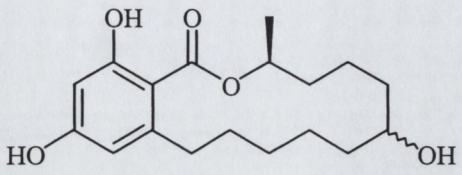
92 Cy = Cyclohexyl

Fürstner, among others, has widely applied RCM in concise, elegant syntheses of naturally-occurring macrocyclic lactones. One such lactone is lasiodiplodin **95**,[74] a twelve-membered lactone isolated from a culture broth of the fungus *Botrysdiplodia theobromae*. The precursor diene **93**, in dichloromethane, was combined slowly with Grubbs catalyst (6 mol %), also in dichloromethane, *via* two dropping funnels, while argon was bubbled through the reaction mixture in order to ensure complete evaporative loss of the ethene formed as the by-product and hence drive the conversion, **Scheme 1.29**. Thus, a mixture of (*E*)- and (*Z*)-isomers of the twelve-membered lactone **94** was formed quantitatively. Hydrogenation and deprotection then produced the desired lactone lasiodiplodin **95**.

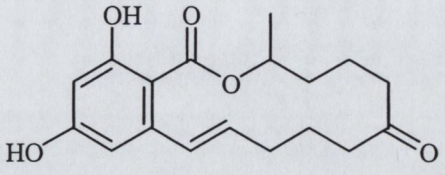


Scheme 1.29

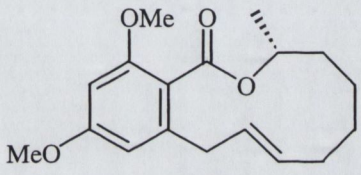
Fürstner has also synthesised zearanol **96**,[75] zearalenone **42**,[76] a truncated analogue **97** of salicylihalamide,[75] and the sophorolipid lactone **98**[77] in a similar fashion.



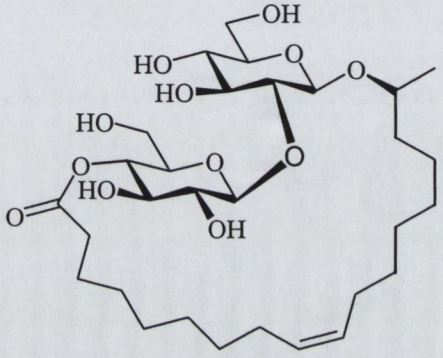
96



42



97



98

Other naturally-occurring lactones synthesised in this way from the corresponding acyclic dienes include halicholactone **99**,[78] coronane **100**,[79] octalactin **101**[80] and brefeldin A **102**[81] to name but a few, **Table 1.1**. Grubbs's catalyst was employed in all syntheses and all lactones were formed in relatively good yield.

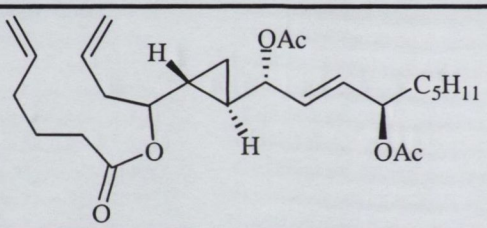
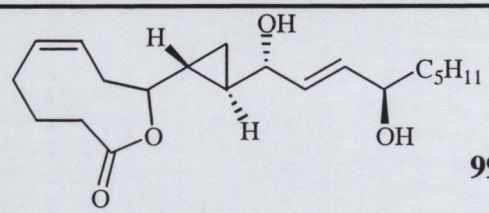
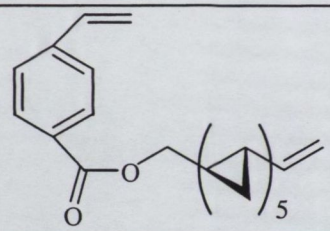
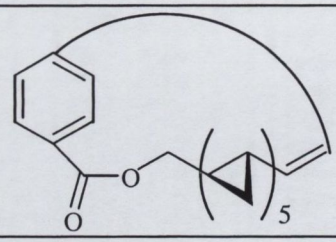
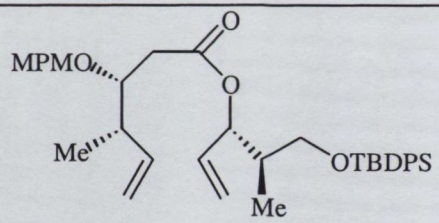
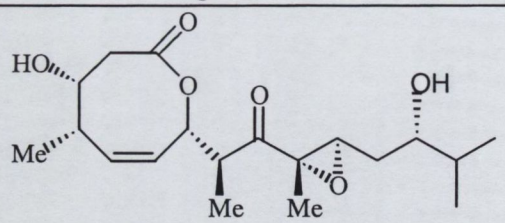
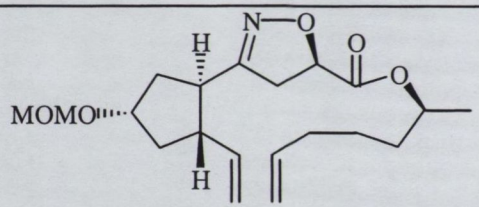
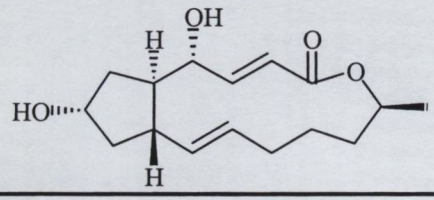
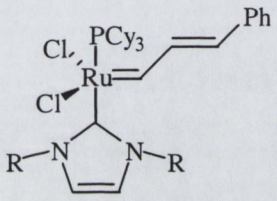
Lactone	% Yield of RCM	Acyclic Diene Precursor	Final Product
Halicholactone **99**[78]	72		 **99**
Coronane **100**[79]	45		 **100**
Octalactin **101**[80]	86		 **101**
Brefeldin **102**[81]	42		 **102**

Table 1.1 **Synthesis of naturally-occurring lactones *via* RCM**

Although Grubbs's catalyst **92** exhibits a remarkably wide scope and excellent compatibility with a range of functional groups, it is very sensitive toward the substitution pattern on the alkene. Tri- and tetrasubstituted alkenes cannot be formed in this way. Hence, a new generation of ruthenium catalysts **103** bearing one bulky imidazol-2-ylidene ligand is under investigation.[82] The presence of the sterically encumbered ligand does not only impart a significantly increased stability of the reactive species in solution but also brings more highly substituted products within reach.



Cy = Cyclohexyl
R = mesityl

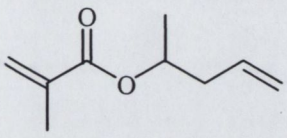
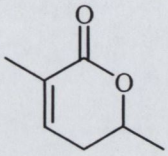
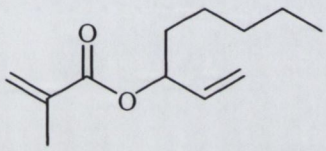
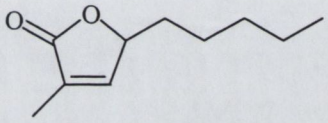
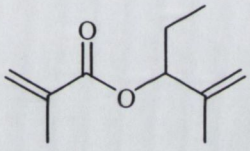
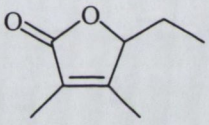
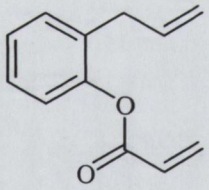
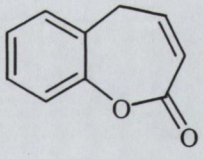
103

This derivative of Grubbs's reagent is in fact less reactive then the parent catalyst at room temperature; however, the reactivity increases dramatically at slightly higher temperatures. Extensive studies have been carried out and results show that the reactivity of **103** in toluene, at 80 °C (5 mol %) is sufficiently high to allow the preparation of di-, tri-, and even tetrasubstituted cycloalkenes in good to excellent yields, **Table 1.2**.[83] All ring sizes including medium and macrocyclic rings can be accessed by this route.

Table 1.2

The synthesis of di-, tri-, and tetrasubstituted cycloalkenes *via* RCM.[83]

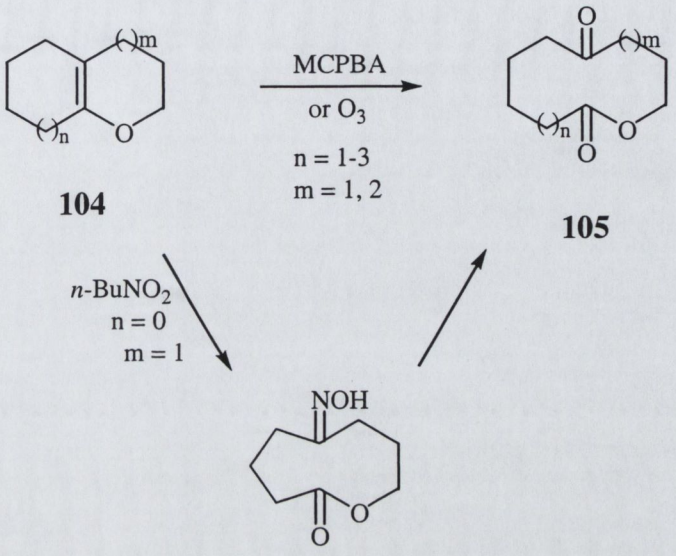
All reactions were carried out with 5 mol % of catalyst **103** in toluene at 80 °C

Acyclic Diene Precursor	Product	time (h)	Yield %	c (mmol/l)
		24	79	20
		2	92	40
		40	63	100
		12	89	4

1.3.4 Methods involving cleavage of bicyclic systems

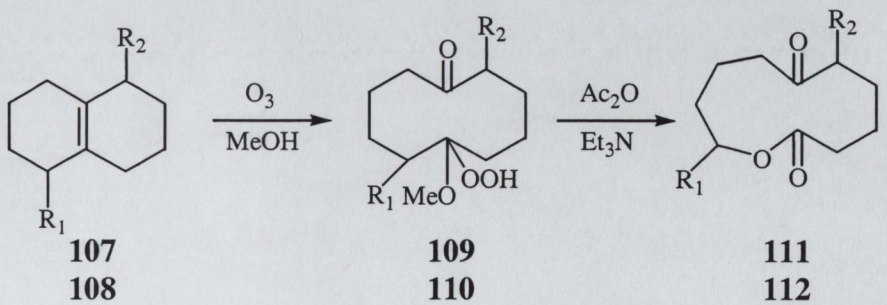
Borowitz *et al.*[84] devised a method for lactone formation from bicyclic enol ethers. Ketolactones with ring sizes varying from ten- to sixteen-membered were synthesised[85] by oxidative cleavage of the corresponding bicyclic ethers **104** using a variety of reagents, **Scheme 1.30**. Treatment with three equivalents of *m*-chloroperoxybenzoic acid (MCPBA) in dry solvent, or, alternatively, by ozonolysis followed by work-up with zinc and acetic acid or chromic acid, produced ketolactones **105**. According to Mahajan,[86] the same cleavage of **104** to **105** (n = 0,

m = 1) was effected by treatment with *n*-butyl nitrite in the presence of aqueous acetic or hydrochloric acid to afford the oximinolactone **106**, which on hydrolysis gave the ketolactone **105** (n = m = 1) in almost quantitative yield.



Scheme 1.30

Schreiber *et al.*[87] described a synthesis of ketolactones by cleavage of bicyclic alkenes **107** and **108** *via* ozonolysis of the fused double bond to form the α-methoxyhydroperoxides **109** and **110**, **Scheme 1.31**. Treatment of these hydroperoxides with acetic anhydride and triethylamine then effected their Criegee rearrangement to yield the eleven-membered lactones **111** and **112**. The regioselective lactone formation observed for the case of unsymmetrically substituted cycloalkene **108** is attributed to the directing ability of the electron-withdrawing acetoxy group.

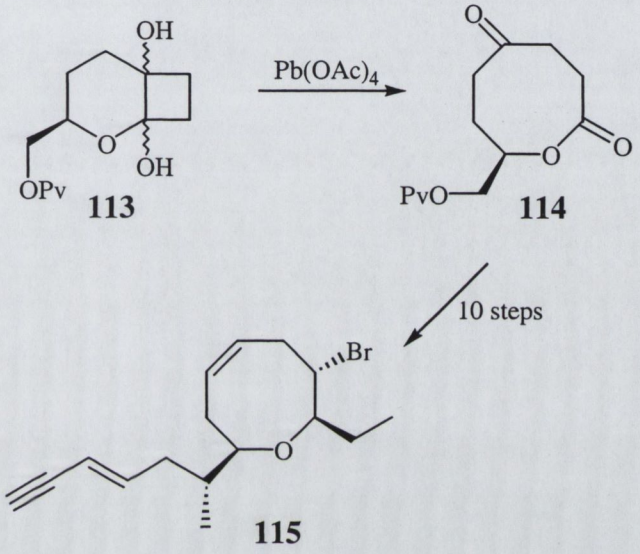


107 **108** **109** **110** **111** **112**

107, **109**, **111** $R_1 = R_2 = H$
108, **110**, **112** R_1 = Me, R_2 = OAc

Scheme 1.31

The red algal metabolite laurencin **115**, is an eight-membered biologically active marine natural product containing a cyclic ether framework. Murai *et al.*[88] have devised a total synthesis for this desirable molecule involving the formation of lactone **114** as a key intermediate. This ketolactone **114** was formed by oxidative cleavage of protected triol **113** with $Pb(OAc)_4$ in toluene, **Scheme 1.32**. The key intermediate was then transformed to the cyclic ether laurencin in a total of 10 steps.



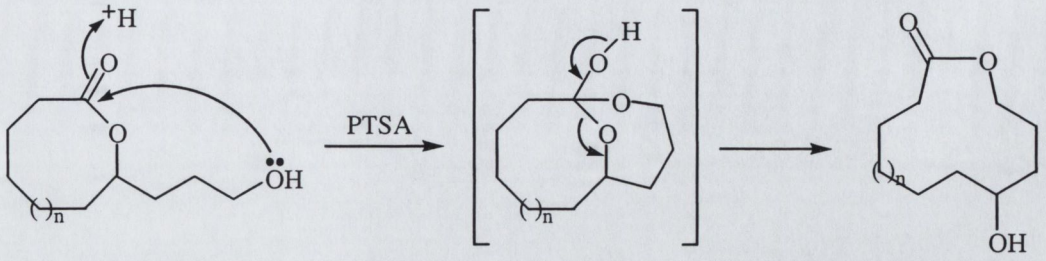
Scheme 1.32

1.3.5 Miscellaneous methods

(i) Ring-enlargement processes

In 1977, Corey *et al.* carried out pioneering research into translactonisation reactions that resulted in the formation of large-ring lactones from medium ring lactones. The intramolecular transesterification reaction can be catalysed by either acid or base and proceeds under thermodynamic control. The driving force for these transformations is the release of ring strain of the thermodynamically unstable medium sized ring. Thus, the nine-membered hydroxy lactone **116** reacts rapidly at room temperature and in the presence of *p*-toluenesulfonic acid (1 mol%) forming the corresponding twelve-membered lactone **117** in 97% yield, **Scheme 1.33**.[89] In comparison, the eight-membered hydroxy lactone **118** undergoes ring expansion (3 mol% *p*-toluenesulfonic acid in methylene chloride, 24 hr, 0 °C), somewhat more

slowly and less efficiently, to form the eleven-membered lactone **119** in 69% yield. Very polar by-products, quite possibly linear polyesters, were also formed.



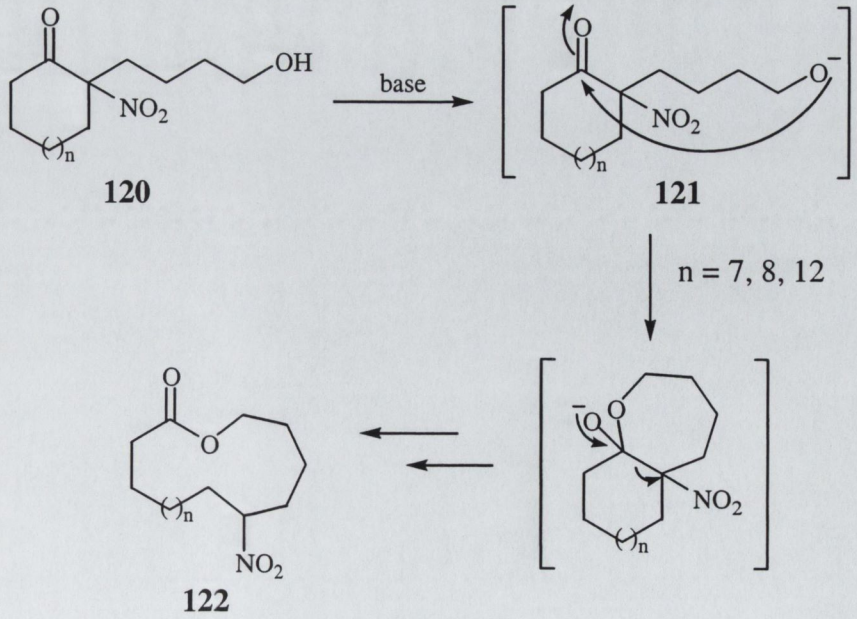
116 n = 2
118 n = 1

117 n = 2
119 n = 1

Scheme 1.33

An additional influencing factor associated with these rearrangement reactions is the length of side chain that can be incorporated into the ring system. The reaction rate decreases with increasing chain length. Thus, an attempt by Corey to incorporate four carbon atoms, *via* an eight-membered intermediate, failed. The aforementioned successful rearrangements involved a relatively more favoured seven-membered intermediate.

Stach and Hesse have utilised the electron-withdrawing ability of the nitro group in a lactonisation process. When the alcohol **120** (n = 7, 8, 12) was treated with base, the lactone **122** was formed *via* the oxyanion intermediate **121**, **Scheme 1.34**.[90] The key ring-enlargement step occurs by charge delocalisation from the oxyanion to the electron-withdrawing nitro group *via* the bicyclic intermediate shown.



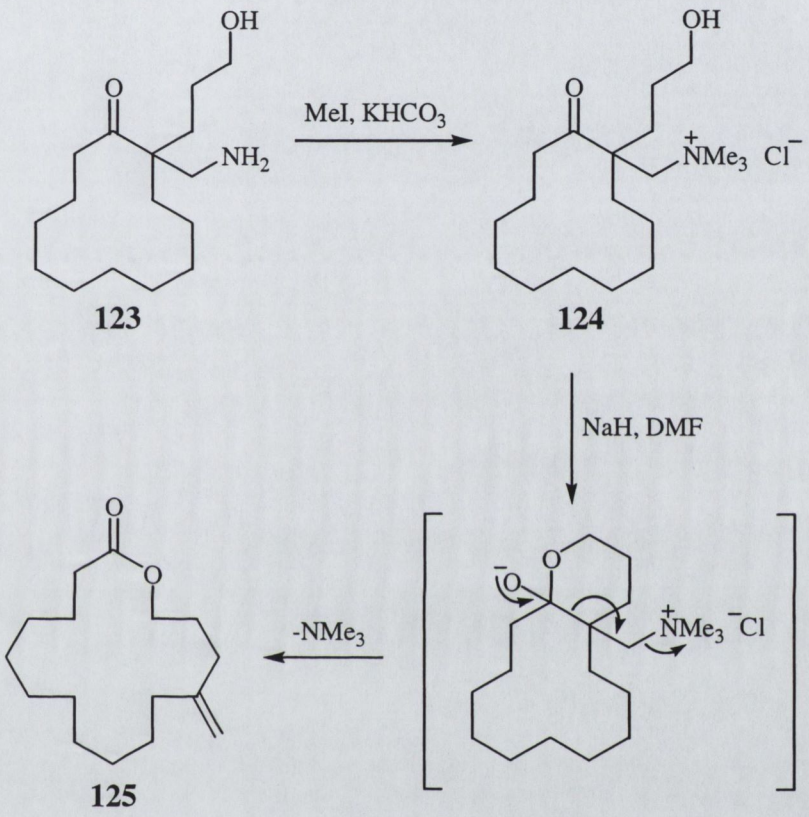
120

121

122

Scheme 1.34

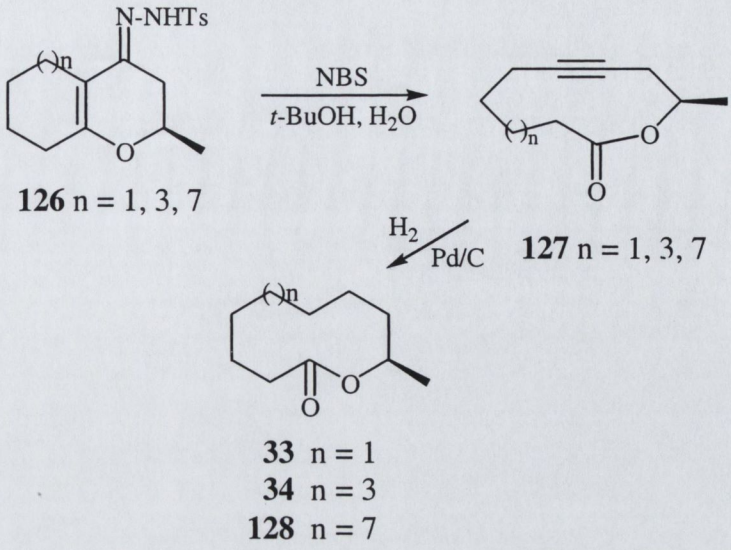
In the case of 2-aminomethyl-2-(3-hydroxypropyl)cyclododecanone **123** a fragmentation reaction occurs following conversion to the corresponding trimethylammonium chloride **124**, resulting in the formation of the fourteen-membered lactone **125**, **Scheme 1.35**.[91]



123 **124** **125**

Scheme 1.35

Mahajan and Resck have developed a synthesis of medium- and large-ring acetylenic lactones by a ring-enlargement process, **Scheme 1.36**.[92] Bicyclic tosylhydrazones **126** were treated with *N*-bromosuccinimide (NBS) in a mixture of water and *t*-butanol to form the acetylenic lactones **127** in excellent yield. Hydrogenation then led to the known compounds phoracantholide **33** (n = 1), dihydrorecifeiolide **34** (n = 3) and 15-hexadecanolide **128** (n = 7).



126 n = 1, 3, 7

127 n = 1, 3, 7

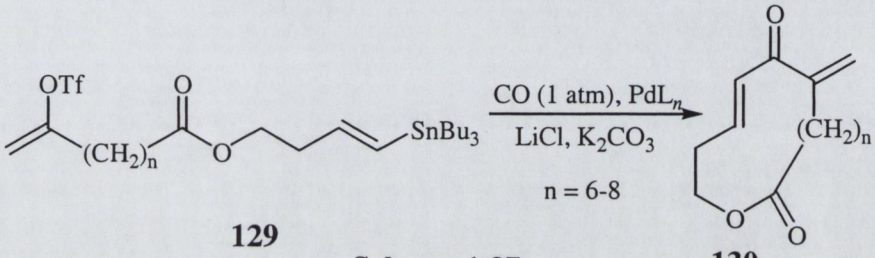
33 n = 1
34 n = 3
128 n = 7

Scheme 1.36

(ii) Cyclisations *via* polymeric supports

Transition metals such as palladium are often employed to catalyse the formation of macrocyclic lactones. However, two disadvantages are associated with these types of intramolecular cyclisations: 1) the formation of dimers, trimers and, more commonly, oligomers; 2) the use of high dilution techniques involving large quantities of solvents and long reaction periods. A method has been devised whereby one end of a potential ring system is anchored to a fixed polymer or resin. Hence, unwanted side reactions are avoided, however, the anchoring sites must be a suitable distance apart, but not so near as to allow the free ends to undergo intermolecular reactions. At first, solid-phase methods incorporated a heteroatom within the linker between the substrate and the polymeric support. Cleavage from the polymer was then achieved by deprotecting the heteroatom, which remained part of the final product. However, cyclative-cleavage strategies have been devised where release from the polymer support is obtained as a consequence of the natural reactivity of the connecting functionality, thus leaving no traces on the target molecules. Also, since detachment from the resin is a step associated with the desired reaction sequence, only substrates that possess the correct functionality and react in the expected way are released into the solution in high purity, leaving all unreacted systems and by-products in the solid-phase.

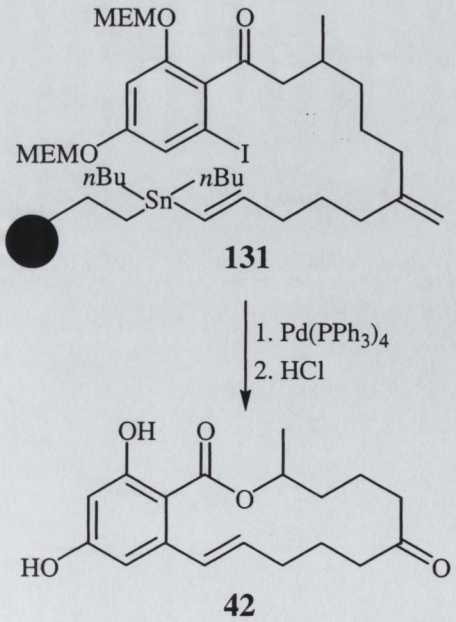
The palladium catalyst Pd(dppf)Cl_2 (dppf = 1,2-bis(diphenylphosphino ferrocene)) has been used in carbonylative couplings and gives reasonable yields (*ca.* 55%). However, when this catalyst is incorporated into *poly*(vinylpyrrolidine) together with palladium(0) (in the form of [Pd(PPh_3)$_4$]), yields are markedly improved. Stille *et al.*[93] have studied the palladium-catalysed carbonylative cross-coupling reaction of organotin reagents with a variety of organic electrophiles. Here, fourteen- to sixteen-membered lactones **130** were formed from the substrate **129** in yields of over 70%, **Scheme 1.37**.



129 **130**

Scheme 1.37

Nicolaou *et al.*[94] have developed a solid-phase synthesis of naturally-occurring lactones *via* a cyclorelease mechanism that employs Stille coupling. Here, the final step involves simultaneous cyclisation and release of the product from the solid support, **Scheme 1.38**. A total synthesis of zearalenone **42** was achieved when the polymer-bound precursor **131** was exposed to [Pd(PPh_3)$_4$] followed by treatment with acid to induce deprotection.



131

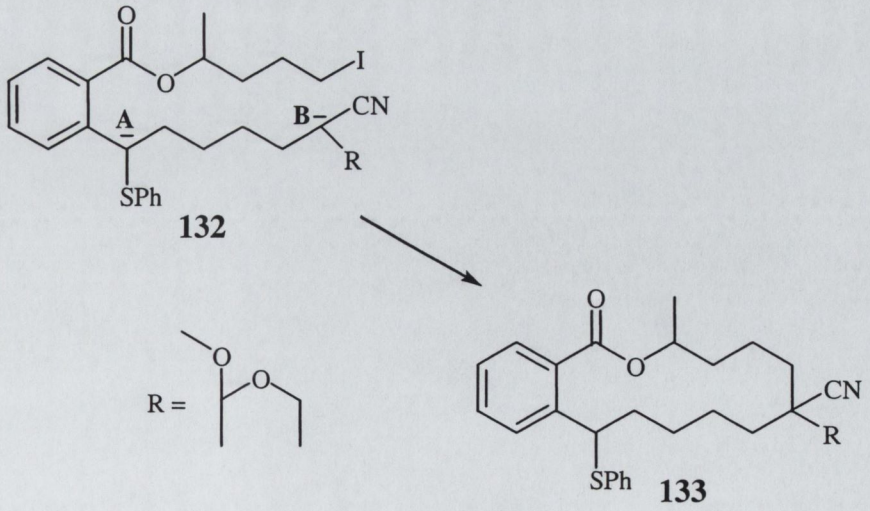
42

Scheme 1.38

A number of reactions have been adapted to fit this valuable carbon-carbon bond forming cyclorelease process, namely, ring-closing metathesis,[95] the Wittig-Horner reaction[96] and Suzuki coupling.[97]

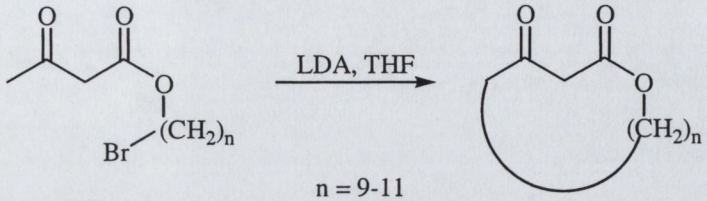
(iii) Intramolecular alkylation of dianions

Takahashi and co-workers devised a synthetic method for macrolides based on intramolecular alkylation of dianions, **Scheme 1.39**.[98] Thus, dianion **132** could be generated from a phenylthiomethyl group and a protected cyanohydrin. The anions differ in reactivity, and since anion *(B)* is more reactive to alkyl halides or tosylates then anion *(A)* it takes part in the cyclisation. The fact that both anions are contained in a single chain restricts the rotational conformations of the chain and hence increases the likelihood of the reacting centres approaching one another. Anion *(A)* protects the neighbouring or conjugated ester group from nucleophilic attack by exerting electronic and steric effects before and after the cyclisation. An additional advantage to this strategy is the presence of two negatively charged carbons in the same molecule which causes larger intermolecular ionic repulsions and hence decreases the likelihood of intermolecular reaction thus eliminating the need for high-dilution conditions. Hence, the dianion **132** cyclised to form lactone **133** in 95% yield, which was then converted to zearalenone **42** in a further three steps.



Scheme 1.39

This methodology has also been used to form fourteen- to sixteen-membered β-ketolactones **135** by formation of the dianions of **134** with excess lithium diisopropylamide (LDA) followed by intramolecular cyclisation, **Scheme 1.40**.[99]

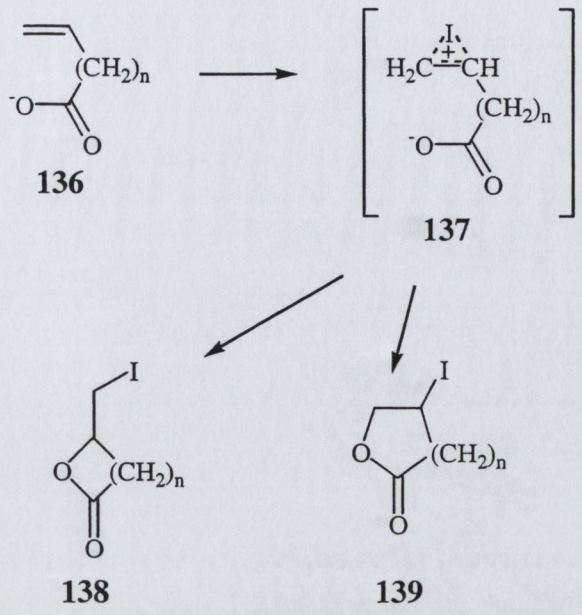


134 **135**

Scheme 1.40

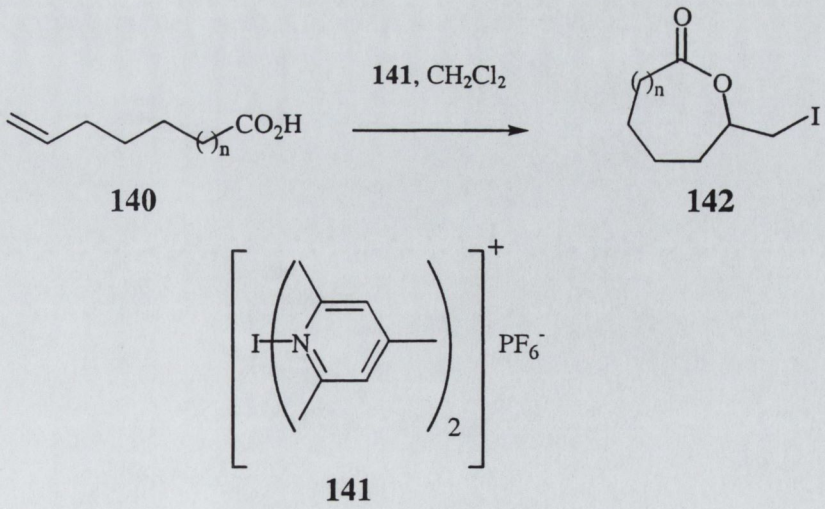
(iv) Iodolactonisation

Lactonisation of unsaturated acids mediated by iodine is a powerful process in synthetic organic chemistry.[100] This methodology involves the treatment of metal carboxylates in either water[101] or organic solvents,[102] or carboxylic acids in organic solvents,[103] with electrophilic iodine sources such as iodine, *N*-iodosuccinimide, cyanogen iodide, or bis(*sym*-collidine)iodine(1) hexafluorophosphate. The accepted mechanistic scheme of van Tamelen and Shamma[104] involves attack by positive halogen on the double bond of an unsaturated acid **136** affording a halonium ion **137**. This then undergoes intramolecular displacement by carboxylate anion to give one of the two possible iodolactone products **138** and **139**, **Scheme 1.41**. Research has shown that, in general, lactone product **138** is obtained; its formation is thought to proceed by an exo mode of closure, thus favouring the formation of products having a smaller ring size.



Scheme 1.41

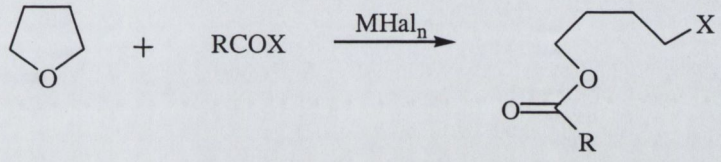
Medium-ring lactones have been synthesised in this manner by Rousseau *et al.*[105] Iodolactonisation of ω-alkenoic acids **140** was achieved using bis(*sym*-collidine)iodine(1) hexafluorophosphate **141** to afford seven- to eleven-membered rings **142** in various yields (76% for seven-membered and 4% for eleven-membered lactones), **Scheme 1.42**. High-dilution conditions are not necessary for this methodology.



Scheme 1.42

1.4 Intramolecular acylative cleavage of tetrahydrofuran derivatives

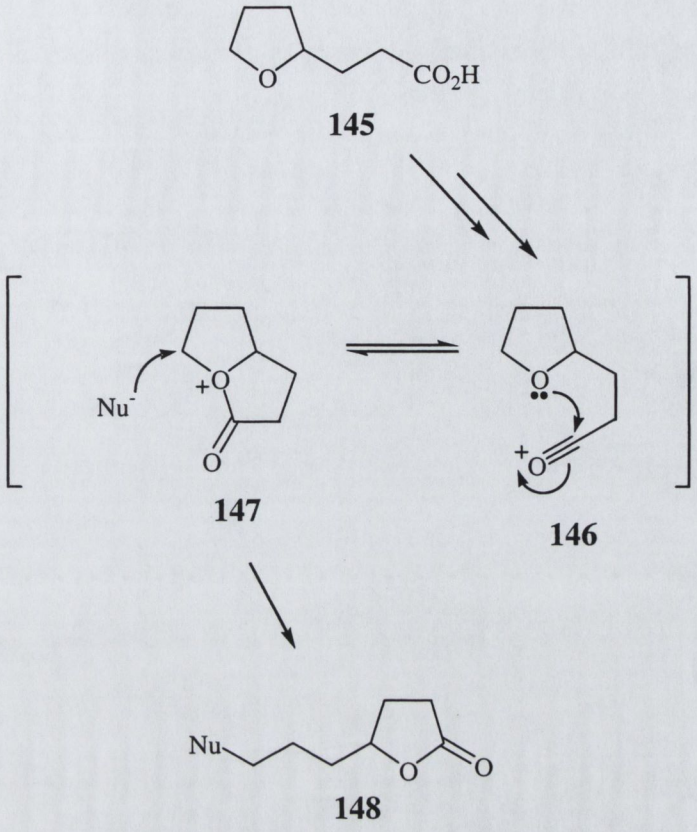
The ring-opening reactions of tetrahydrofurans which occur when they are treated with acyl halides[106] or anhydrides[107] in the presence of Lewis acids provide convenient routes to (4-halobutyl)alkanoates **143** and to diesters of butane-1,4-diol **144**, respectively, **Scheme 1.43**.



143 X = Hal
144 X = OCOR

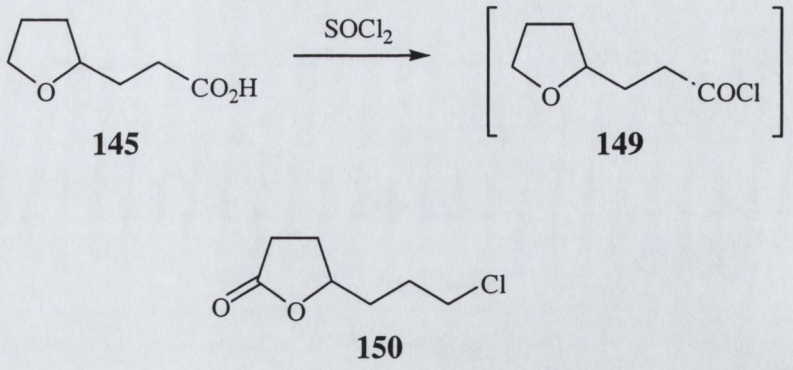
Scheme 1.43

This understanding led to the consideration of a possible intramolecular reaction of tetrahydrofuran derivatives to form lactones. Thus, a novel, facile, intramolecular route for the formation of lactones from ω-(2-tetrahydrofuryl)-alkanoic acids has been reported by Grayson and Roycroft.[108] This research led to the discovery of the ability of the ethereal oxygen atom of the tetrahydrofuryl ring to efficiently trap tethered acylium ions in an intramolecular manner. Thus, an acylium ion such as **146**, derived from 3-(tetrahydro-2'-furyl)propanoic acid **145** reacts to give a bicyclic acyloxonium species **147** which then reacts with nucleophiles which are present in the reaction mixture to yield 5-substituted dihydro-2(3*H*)-furanones **148**, **Scheme 1.44**.



Scheme 1.44

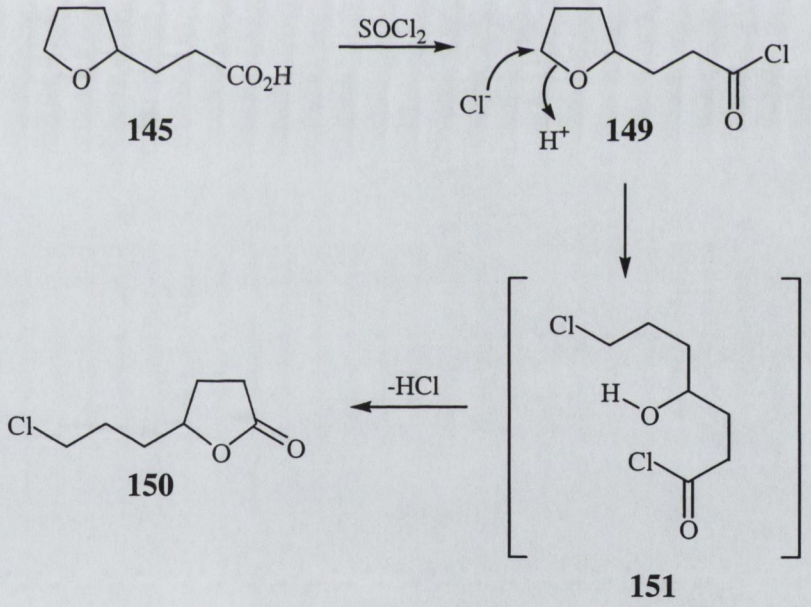
To investigate the scope of this reaction it was necessary to develop an efficient route to the acylium species **146** which was free from side-reactions. An acylium precursor was required which, ideally, would be easily generated, relatively stable and have the ability to form the acylium species under mild conditions. Acyl halides were the first precursors to be investigated. However, reaction of 3-(tetrahydro-2'-furyl)propanoic acid **145** with thionyl chloride did not lead to isolable quantities of the expected acyl chloride **149** but gave instead dihydro-5-(3'-chloropropyl)furan-2(3*H*)-one **150** in 83% yield, **Scheme 1.45**. It was presumed that this conversion occurred due to the presence of the liberated hydrogen chloride which could promote the formation of the corresponding acylium ion from the acyl chloride which could then undergo an intramolecular rearrangement resulting in the formation of the chlorobutanolide **150**.



145 **149** **150**

Scheme 1.45

However, this was not the only possible mechanism. The presence of hydrogen chloride could possibly result in cleavage of the tetrahydrofuran ring of **145** or **149** to afford the intermediate compound **151**, **Scheme 1.46**. This could then cyclise to yield the chlorobutanolide **150**. Consequently this approach to the generation of the desired acylium ion was discarded as it was not possible to clarify which reaction mechanism was employed.



145 **149** **151** **150**

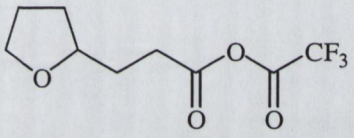
Scheme 1.46

Alternative syntheses of the acyl chloride **149** were also investigated. Reaction[109] of the acid **145** with CCl_4 - PPh_3 resulted in the successful formation of isolable **149**, and even better yields were obtained when the lithium salt of **145** was treated with 0.33 equivalents of PCl_3 in dry chloroform.[110]

However, practical disadvantages were encountered in both of the procedures mentioned above. Furthermore, the acid chloride **149** could not be stored for any length of time as the presence of even minor amounts of hydrogen chloride resulted in its rapid decomposition. Hence it was clear that an alternative precursor to the acylium ion **146** was necessary.

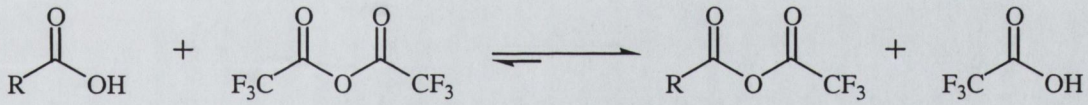
Since Friedel-Crafts acylation reactions may be carried out using carboxylic acids, carboxylic anhydrides and ketenes as alternative reagents to acyl halides, attention was drawn to the possibility of employing an anhydride as an alternative acylium precursor.[111]

Mixed anhydrides can be prepared easily using trifluoroacetic anhydride and a carboxylic acid, thus the trifluoroacetic-carboxylic mixed anhydride **152** was considered as an acylium ion precursor.[112]



152

The equilibrium strongly favours the mixed anhydride and the trifluoroacetic acid, **Scheme 1.47**.

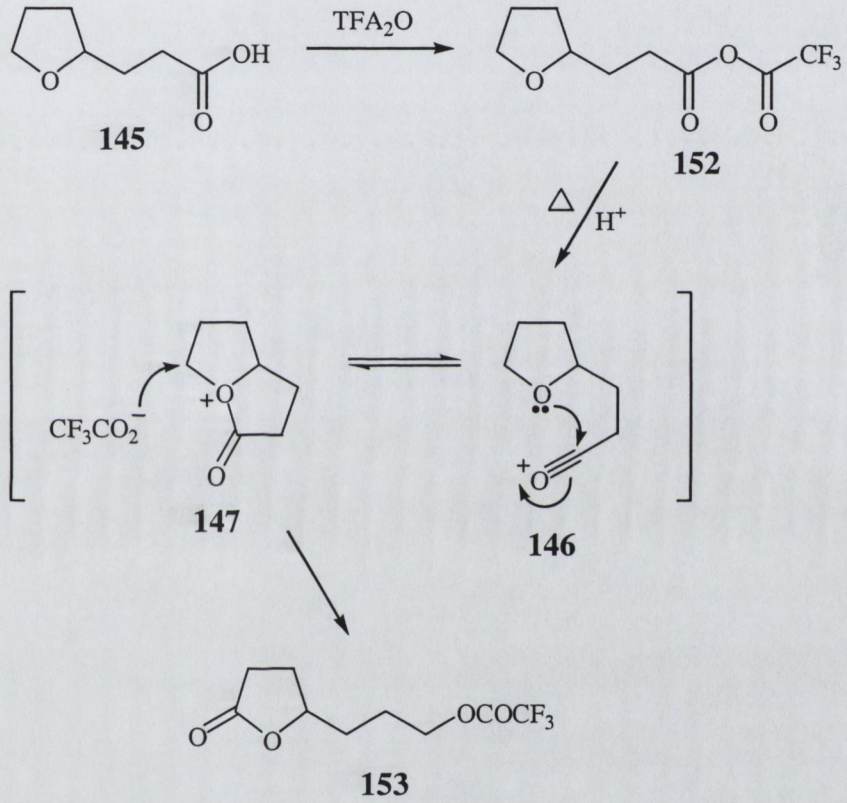


Scheme 1.47

Thus, the mixed anhydride **152** was investigated[108] as an acylium ion precursor, and it was subsequently found that the use of such mixed anhydrides avoided all of the difficulties associated with the labile acyl chlorides. Furthermore, because of the poor nucleophilicity of the trifluoroacetate ion, the use of mixed anhydrides could permit the introduction of a wider variety of functionality into the product butanolides if stronger nucleophiles were present in the reaction mixture.

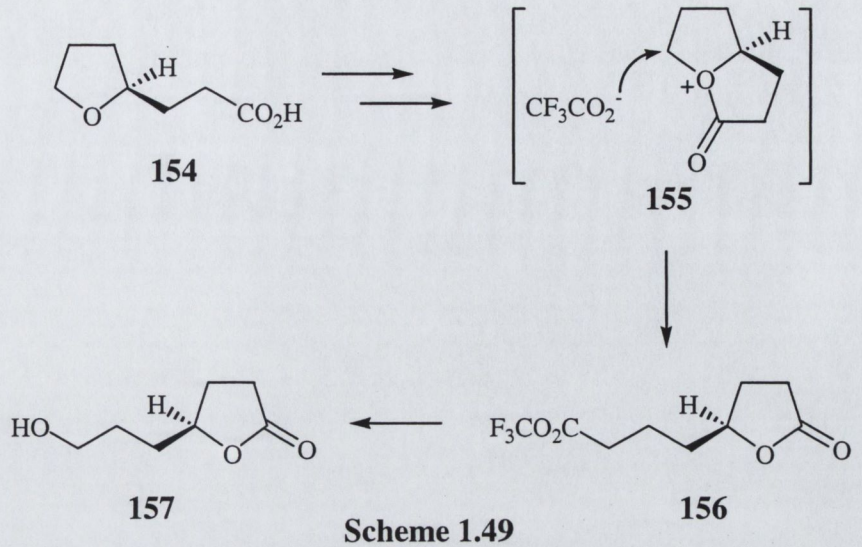
Treatment of 3-(tetrahydro-2'-furyl)propanoic acid **145** with one equivalent of trifluoroacetic anhydride at 0 °C in dry chloroform resulted in the formation of the mixed anhydride **152** in almost quantitative yield, **Scheme 1.48**. Isolation was

achieved simply by evaporation of the solvent and the trifluoroacetic acid by-product. The mixed anhydride was found to be quite stable and survived after prolonged refluxing in dry chloroform. However, if a catalytic amount of trifluoroacetic acid was introduced into the system, or if the trifluoroacetic acid was not removed after formation of the anhydride, then the dihydrofuranone **153** was rapidly formed as the sole product of the reaction in 86% yield.



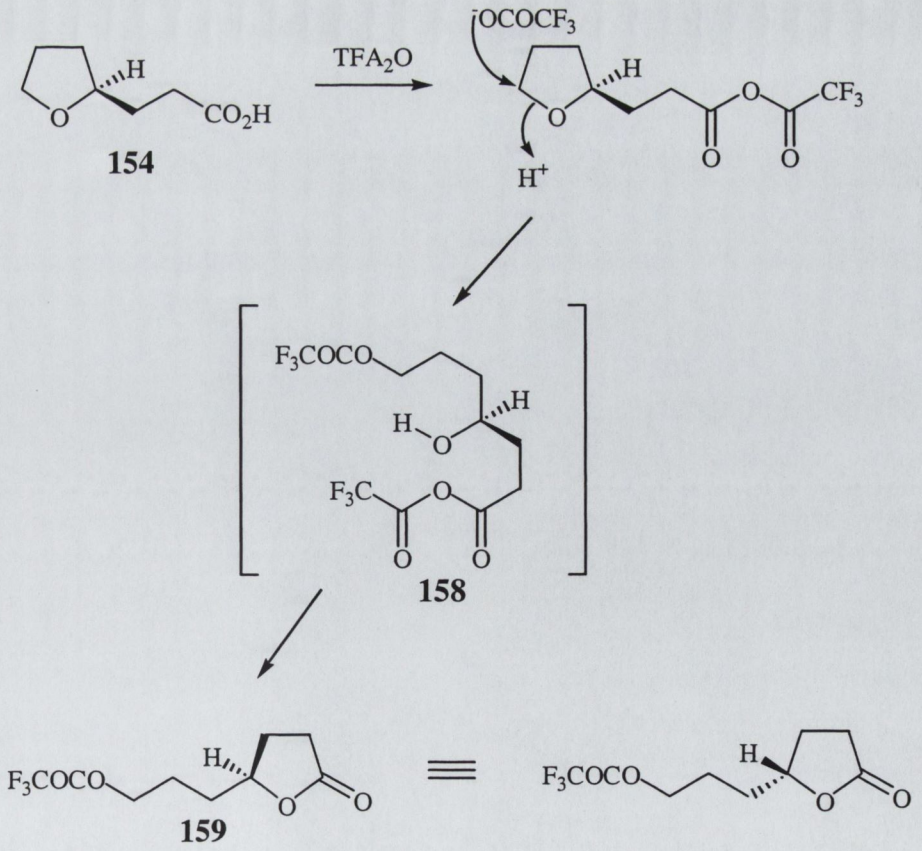
Scheme 1.48

To probe the mechanism of this conversion, an enantiomerically enriched starting acid **154** was employed.[108] Thus, if the reaction proceeded *via* the acylium-acyloxonium reaction mechanism outlined in **Scheme 1.49**, the dihydrofuranone **156** formed should exhibit retention of configuration at the C-2' methine carbon of the starting acid **154**.



Scheme 1.49

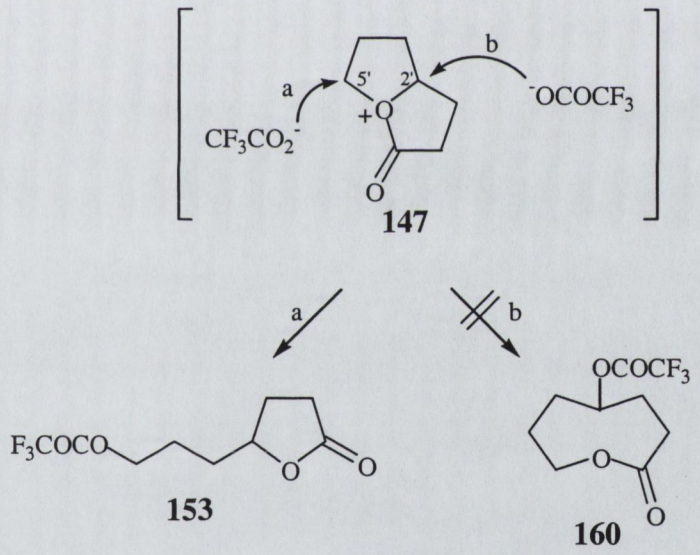
However, if the reaction proceeded *via* a mechanism involving the protonation of the tetrahydrofuryl ether oxygen followed by neighbouring group participation by a carbonyl group located on the side-chain, then the dihydrofuranone **159** formed should exhibit inversion of configuration at the C-2' methine carbon of the starting acid **154**, **Scheme 1.50**.



Scheme 1.50

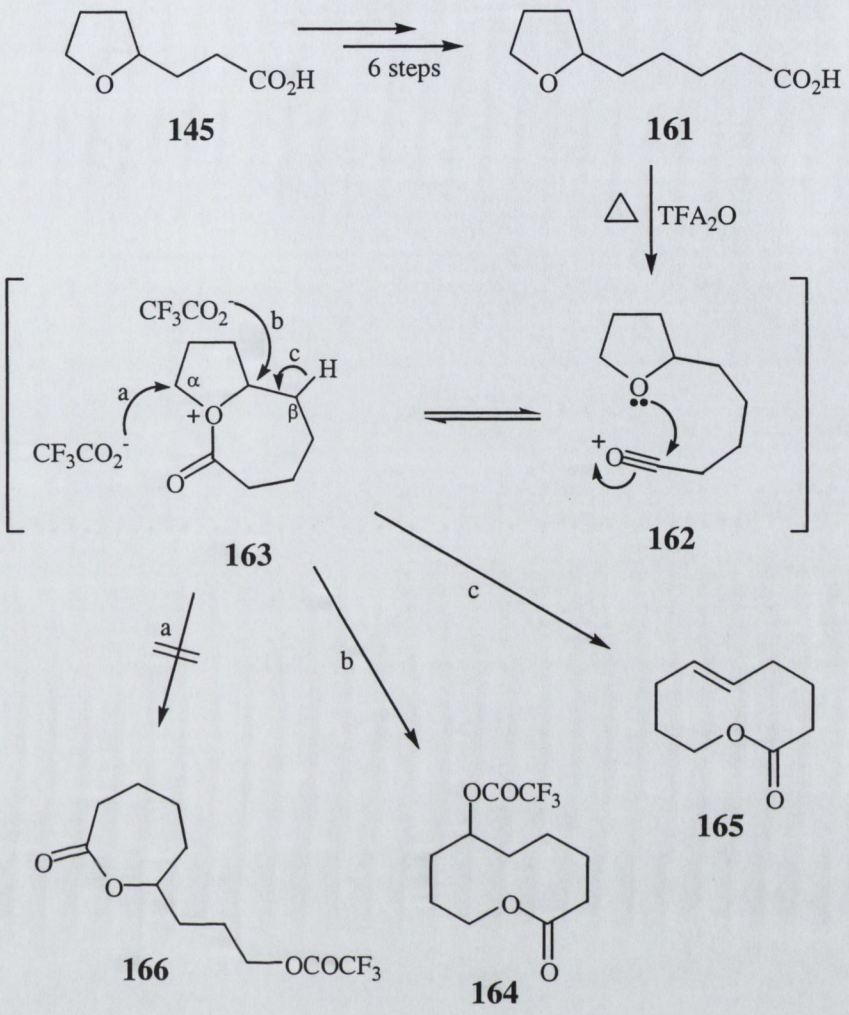
Treatment of (+)-(*S*)-3-(tetrahydro-2-furyl)propanoic acid **154** with trifluoroacetic anhydride gave (-)-(*S*)-**156**. Mild hydrolysis gave the (-)-(*S*)-alcohol **157** whose configuration was known.[113] As the intramolecular lactonisation reaction proceeded with retention of configuration at the C-2' methine carbon, the mechanism involving formation of an acylium ion was adequately accounted for, **Scheme 1.49**.

It was noted that nucleophilic attack of bicyclic intermediates such as **147** occurred exclusively at the exposed C-5' α-carbon (route a) and not at the C-2' bridgehead carbon (route b) which would have resulted in the formation of the seven-membered lactone **160**, **Scheme 1.51**. This is understandable, as the stereoelectronic requirements for this process are incompatible with the rigid butterfly conformation of systems such as **147**.



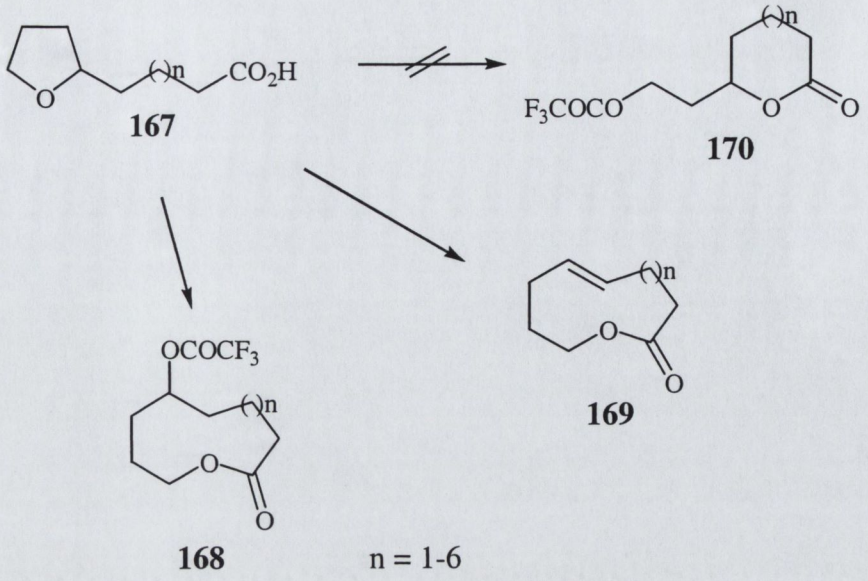
Scheme 1.51

The method was applied to 5-(tetrahydro-2-furyl)pentanoic acid **161** which was obtained from the propanoic acid derivative **145**, **Scheme 1.52**.[114] In this case, the more flexible bicyclic acyloxonium intermediate **163** formed from acylium ion **162** undergoes reaction at its bridgehead carbon to yield a 4:1 mixture (85%) of the ten-membered lactone **164** together with the unsaturated ten-membered lactone **165** formed by competitive regioselective β-elimination of a proton. The alternative heptanolide **166** is not formed.



Scheme 1.52

The same intramolecular acid-catalysed lactonisation rearrangement reaction was applied to the homologous ω-(tetrahydro-2-furyl)alkanoic acids **167** (n = 1-6), **Table 1.3**.[115] For all of the acids **167** (n = 1-6) it was found that attack by trifluoroacetate ion always occurred at the bridgehead carbon leading to the formation of nine- to fourteen-membered lactones **168**, with a small amount of the corresponding unsaturated lactones **169** also being formed in most cases due to β-elimination of a proton, **Scheme 1.53**. Attack at the α-carbon, which would have led to six- to eleven-membered lactones **170**, did not occur. This was presumed to be due to the flexible nature of the bicyclic acyloxonium ions formed as opposed to the rigid ion formed in the case of acid **145** which led to exclusive attack at the α-carbon.



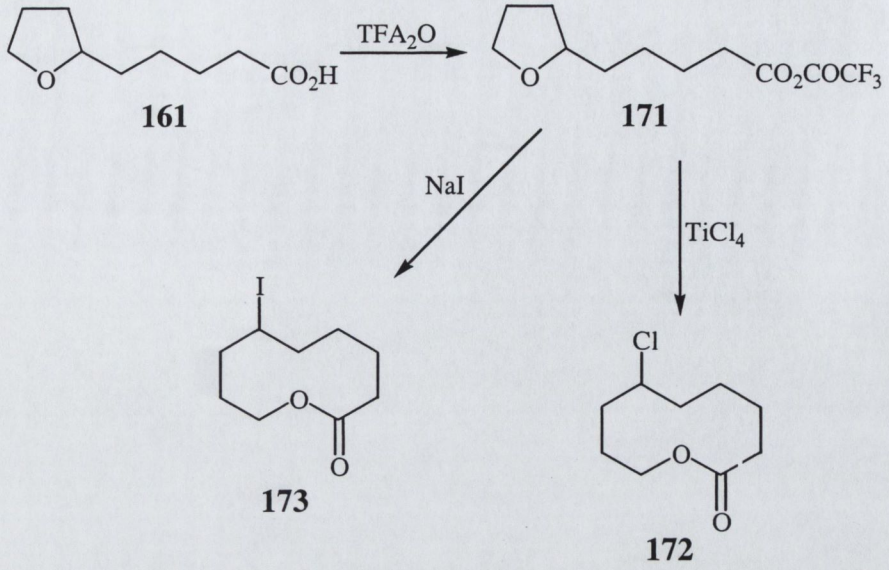
Scheme 1.53

Table 1.3

Yields of lactone(s) from acid 167 (n = 1-6)[114, 115]

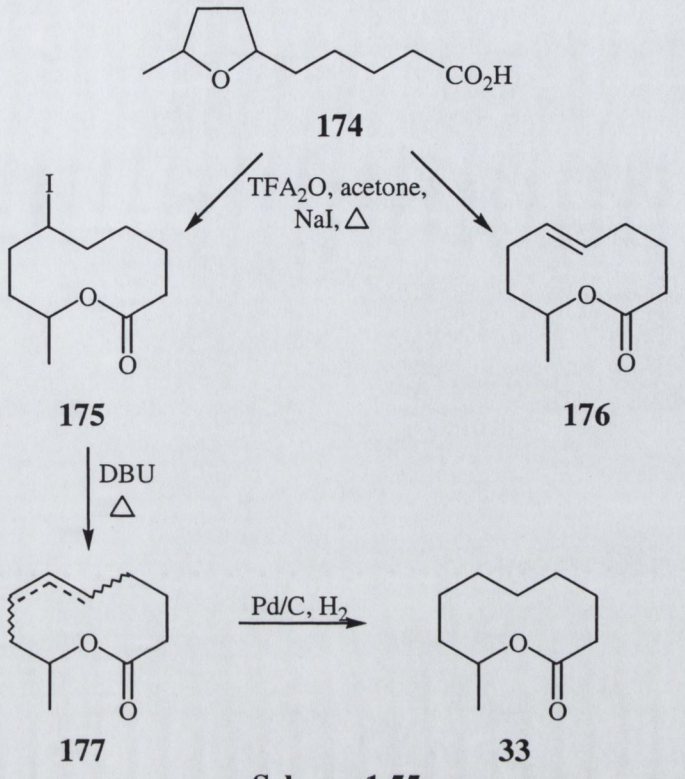
Acid n =	Product ring size	Bridgehead attack product (%)	β-elimination product (%)	% Yield (total)	t (hrs)	Solvent
1	9	60	-	60	1	$CHCl_3$
2	10	48	12	60	1	$CHCl_3$
3	11	26	34	60	72	Toluene
4	12	38	13	51	72	Toluene
5	13	1.5	1	2.5	132	Toluene
6	14	3	1	4	168	Xylenes

An alternative nucleophile to trifluoroacetate can be introduced into the reaction mixture to give the corresponding substituted lactone. Thus, when the mixed anhydride **171**, formed from acid **161**, was treated with titanium(IV) chloride in dry chloroform the chlorolactone **172** was obtained (73%). Also, when the mixed anhydride **171** was formed in acetone in the presence of sodium iodide the corresponding iodolactone **173** was produced (75%), **Scheme 1.54**.[114, 116]



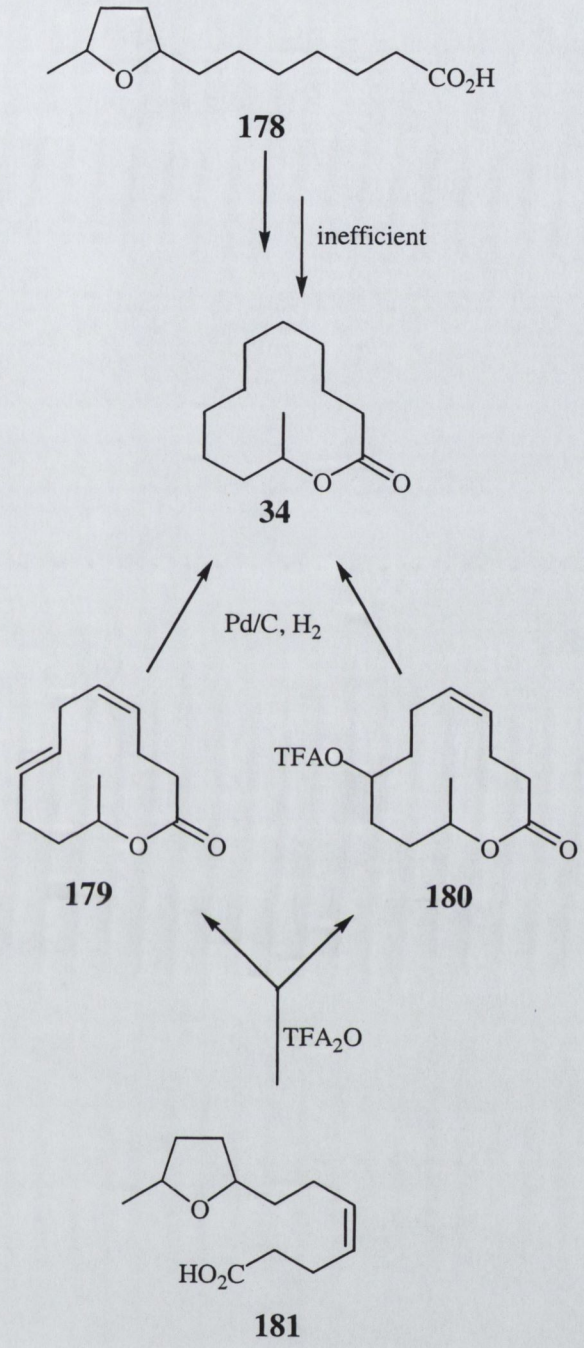
Scheme 1.54

The synthesis of a number of natural products was achieved *via* this route. Thus, (±)-phoracantholide-I **33**, isolated from the metasternal gland of *Phoracantha synonyma* by Moore and Brown,[117] was synthesised, **Scheme 1.55**.[115] The precursor acid **174** was treated with trifluoroacetic anhydride in acetone and then refluxed in the presence of sodium iodide giving the expected mixture of ten-membered lactones **175** and **176**, which were separable by column chromatography. Treatment of the iodolactone **175** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) eliminated hydrogen iodide to give a mixture of unsaturated lactones **177** which, upon hydrogenation, led to the desired product (±)-phoracantholide-I **33**.



Scheme 1.55

The intramolecular acid-catalysed lactonisation rearrangement reaction was also employed to synthesise the fungal metabolite dihydrorecifeiolide **34**.[115] Thus, 7-(5'-methyltetrahydro-2'-furyl)heptanoic acid **178** was subjected to the usual lactonisation conditions. Yields of the expected twelve-membered lactones were very low so an alternative synthesis was carried out involving the formation of an acid precursor that contained a double bond of (*Z*)-configuration which would encourage formation of the mandatory nine-membered ring of the bicyclic acyloxonium intermediate, **Scheme 1.56**. Thus, when the acid **181** was refluxed in toluene in the presence of trifluoroacetic anhydride, a mixture of twelve-membered lactones **179** and **180** was formed that, on catalytic hydrogenation, gave the desired product dihydrorecifeiolide **34**.



Scheme 1.56

1.5 Strategy

The research undertaken in the present study focuses on the synthesis of lactones *via* the intramolecular acid-catalysed lactonisation rearrangement reaction described in Section 1.4 above. Chapter 2 is concerned with intramolecular reactions of 3-(tetrahydro-2'-furyl)propanoic acid which are further probed with regard to the synthesis of functionalised butanolides by the introduction of various nucleophiles into the reaction mixture. These functionalised butanolides might be manipulated to facilitate the synthesis of desirable naturally-occurring lactones. The behaviour in a variety of solvents of the acylium species derived from 3-(tetrahydro-2'-furyl)propanoic acid is also examined.

The primary focus of Chapter 3 centres on the synthesis of ten-membered lactones, which bear hydroxyalkyl side-chains of varying lengths situated adjacent to the lactone ether oxygen atom, with a view to later ring-enlargement *via* an intramolecular translactonisation process. The synthesis of some ring-expanded lactones from these precursors is reported.

Chapter 4 is concerned with the development of a synthetic route towards the precursors required for the synthesis of two naturally-occurring lactones, Cephalosporolide G and Patulolide C.

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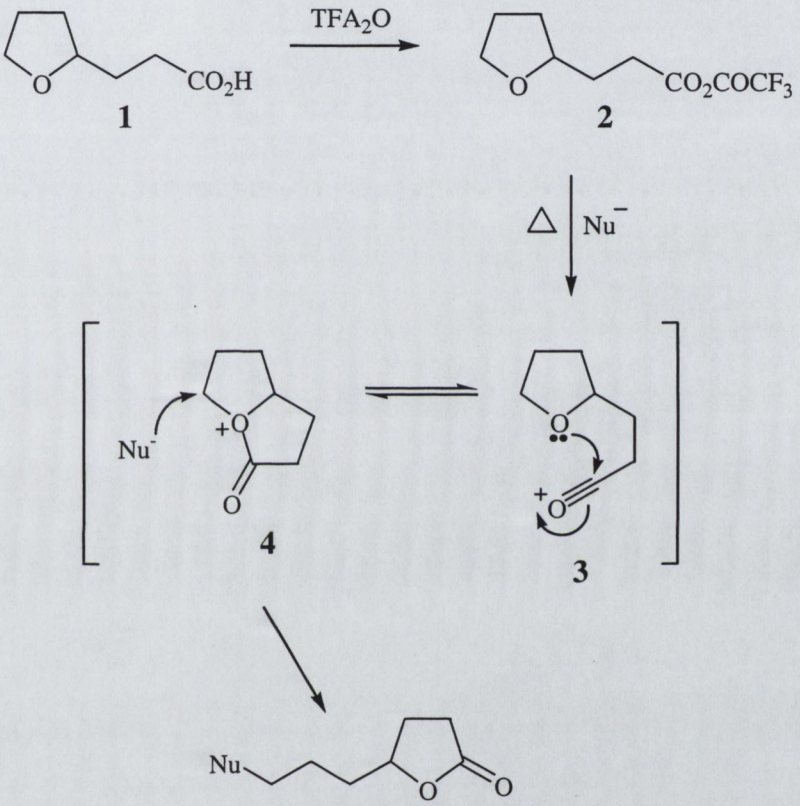
117 B. P. Moore and W. V. Brown, *Aust. J. Chem.*, 1976, **29**, 1365

Chapter 2

Studies on Intramolecular Acylative Ring-Switching Reactions of 3-(Tetrahydro-2'-furyl)propanoic acid

2.1 Strategy

The aim of this body of work is to further probe the intramolecular acylative ring-switching reactions of 3-(tetrahydro-2'-furyl)propanoic acid **1**[1] which were described in Section 1.4, **Scheme 2.1**. Previous work[1] had involved the synthesis of the trifluoroacetoxypropylbutanolide **5** and the chloropropylbutanolide **6** from the acid **1**.



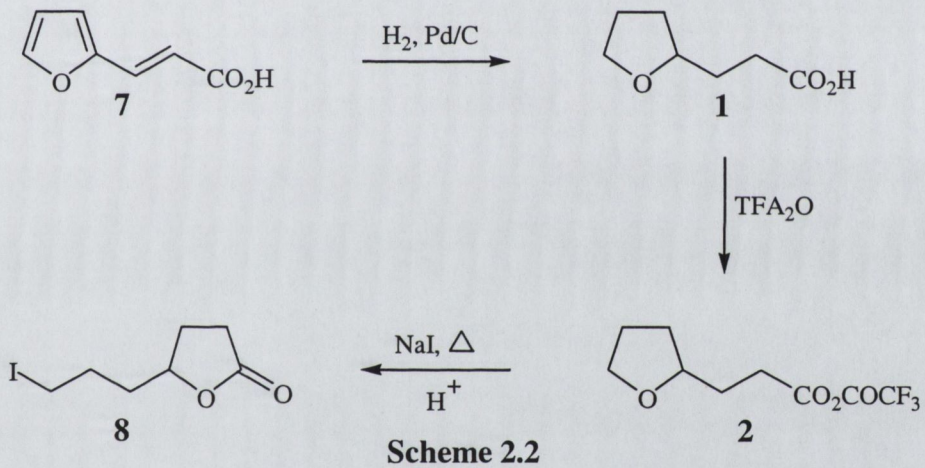
Scheme 2.1

Due to the relatively poor nucleophilicity of trifluoroacetate ion, which is present in the reaction mixture, it was anticipated that formation of functionalised butanolides could be achieved by introducing stronger nucleophiles into the reaction mixture. The functionalised butanolides thus obtained could act as precursors to more complex lactones. The attempted synthesis of one such naturally-occurring lactone from an iodopropyl compound derived from **1** is described.

Additional studies of the fundamental reaction of the acid **1** with trifluoroacetic anhydride were carried out. A solvent study was performed to investigate the relative nucleophilic strength of various solvents in competition with the trifluoroacetate ion.

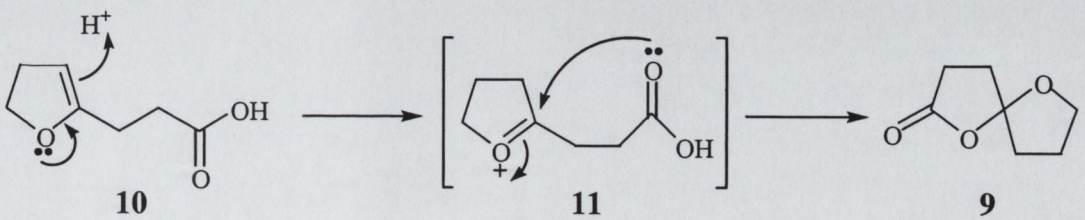
2.2 Synthesis of 5-(3'-iodopropyl)dihydro-3(2*H*)-furanone 8

To investigate the scope of the intramolecular reactions of the acid **1** in the context of the formation of functionalised butanolides, various nucleophiles were considered. It was anticipated that the iodobutanolide **8** could be formed when the mixed anhydride derived from acid **1** was heated in the presence of a small excess of sodium iodide, **Scheme 2.2**.



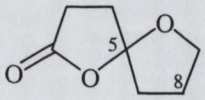
Scheme 2.2

Thus, 3-(tetrahydro-2'-furyl)propanoic acid **1** was obtained by catalytic hydrogenation of (*E*)-3-(2'-furyl)prop-2-enoic acid **7** which had been formed by Knoevenagel reaction between furfuraldehyde and malonic acid. Occasionally, the hydrogenation step resulted in the formation of a side-product (up to 30%) which was identified as 1,6-dioxaspiro[4.4]nonan-2-one **9**, **Scheme 2.3**.



Scheme 2.3

Brimble *et al.*[2] have synthesised (in five steps) this unstable spirolactone as a model for the synthesis of more complex spirolides which are a class of naturally-occurring compounds incorporating the 1,6-dioxaspiro[4.4]nonane unit. Hence, the isolation of spirolactone **9** as a side-product from the hydrogenation of unsaturated acid **7** was significant. This surprising result was possibly due to the presence of traces of acid in the unsaturated carboxylic acid **7** as the formation of this compound involved acidification with hydrochloric acid. Thus, if partial hydrogenation of unsaturated acid **7** resulted in the formation of a dihydrofuran derivative **10**, the intermediate **11** could form which could then lead to formation of the spirolactone **9**, **Scheme 2.3**. When the unsaturated acid **7** was hydrogenated in the presence of PTSA, however, the spirolactone **9** was not isolated.



9

The NMR spectroscopic data obtained for the spirolactone **9** agree with that published by Kitching *et al.*[2b] Distinctive resonances in the ^{1}H NMR spectrum of the volatile spirolactone **9** include a double double doublet at δ_H 2.54 ppm corresponding to one of the protons at C-3 or C-4 of the lactone ring. The protons at C-7 adjacent to the cyclic ether oxygen atom appear as an AB system consisting of two multiplets centred at δ_H 4.01 and 4.10 ppm. In the ^{13}C NMR spectrum of **9**, the C-7 methylene carbon resonates at δ_C 68.6 ppm. The C-5 quaternary carbon is visible at 115.7 ppm whilst a signal at δ_C 175.4 ppm is assigned to the lactone carbonyl carbon. The ^{1}H-^{1}H COSY spectrum of **9** is shown, **Figure 2.1**.

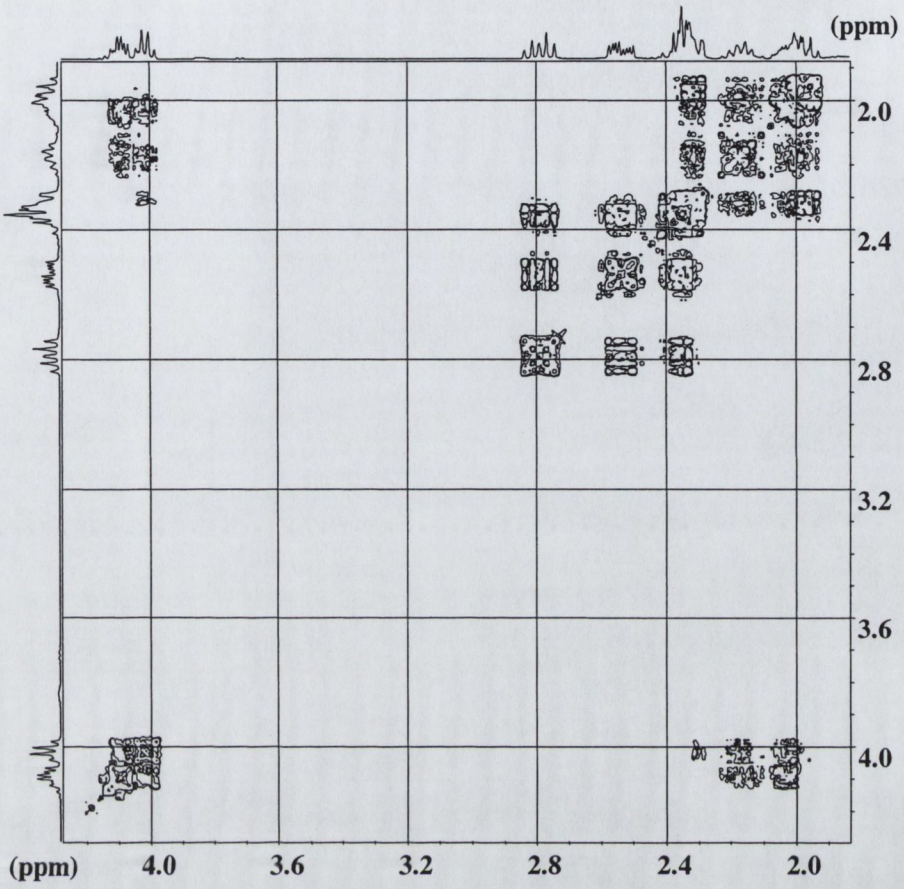


Figure 2.1

^{1}H-^{1}H COSY Spectrum of 1,6-dioxaspiro[4.4]nonan-2-one 9

When the saturated acid **1** was treated with trifluoroacetic anhydride in acetone containing sodium iodide, the sole product obtained after heating was, as anticipated, the iodolactone **8** (70%).

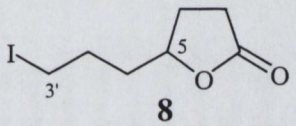
The structure of 5-(3'-iodopropyl)dihydro-3(2*H*)-furanone **8** was readily deduced from its spectroscopic data which agree with those recently published by Wang *et al.*[3] who obtained the iodolactone **8** as a decomposition product of γ-iodoheptanolactone.

The iodide **8** shows an IR absorption at 1774 cm^{-1} attributable to the lactonic carbonyl function. The NMR data obtained for **8** are summarised in **Table 2.1**. Distinctive features of the ^{1}H NMR spectrum of the butanolide **8** include an apparent sextet at δ_H 2.37 ppm which is assigned to one of the non-equivalent

methylene protons of C-4. A multiplet centred at δ_H 3.24 ppm can be assigned to the C-3' methylene protons which are adjacent to the iodide function. The methine proton on C-5 appears as a multiplet centred at δ_H 4.52 ppm. In the ^{13}C NMR spectrum of **8**, the C-3' methylene carbon adjacent to the iodine function appears at δ_C 5.6 ppm. The C-5 methine carbon resonates at δ_C 79.6 ppm while the lactonic carbonyl carbon can be observed at δ_C 176.3 ppm. These assignments were confirmed by ^{13}C-^{1}H and ^{1}H-^{1}H COSY (**Figure 2.2**) experiments.

Table 2.1

NMR Spectroscopic details for 5-(3'-iodopropyl)dihydro-3(2*H*)-furanone 8



8

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
CH_2 5.6	CH_2 3.20-3.27	m	C-3'
CH_2 27.9	CH_a 1.87-1.99 CH_b 2.33-2.41	m ap. sextet, ^{2}J 13.0, ^{3}J = 6.5	C-4
CH_2 28.6	CH_2 2.54-2.58	m	C-3
CH_2 29.2	CH_a 1.87-1.99 CH_b 1.99-2.13	m	C-2'
CH_2 36.4	CH_2 1.78-1.86	m	C-1'
CH 79.6	CH 4.49-4.55	m	C-5
C=O 176.3	-	-	C-2

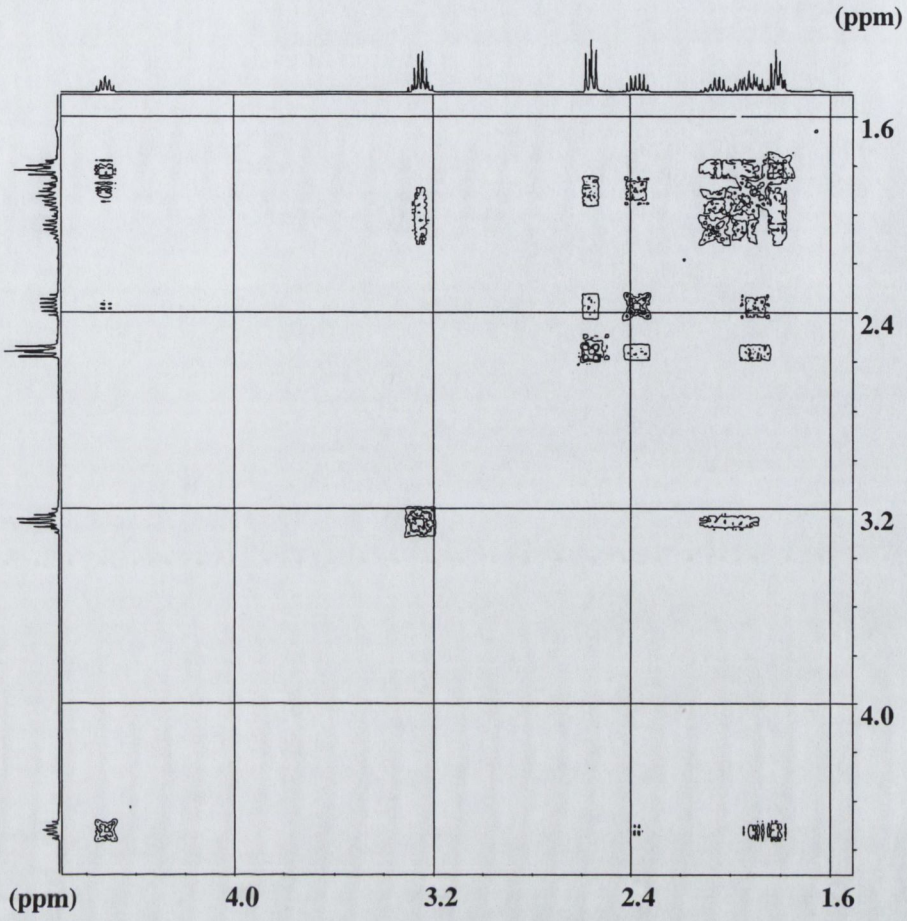
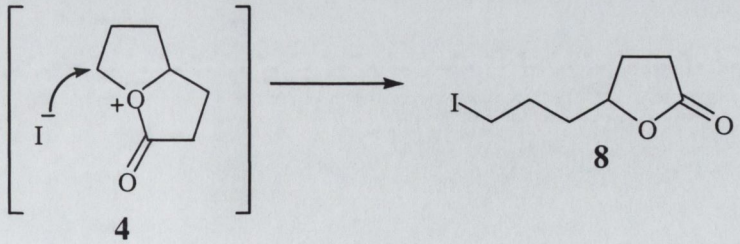


Figure 2.2

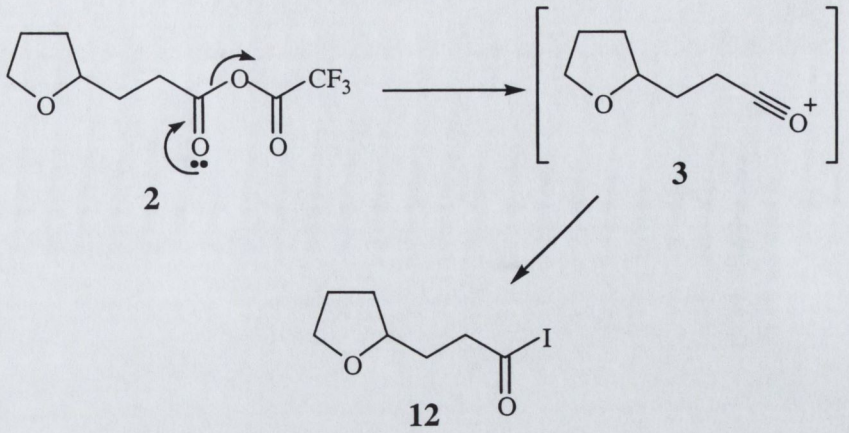
^{1}H-^{1}H COSY Spectrum of 5-(3'-iodopropyl)dihydro-3(2*H*)-furanone 8

The formation of the iodolactone **8** may well occur as a result of nucleophilic attack by iodide ion on the bicyclic acyloxonium system **4** which is formed from the mixed anhydride **2** in the usual way, **Scheme 2.4**.



Scheme 2.4

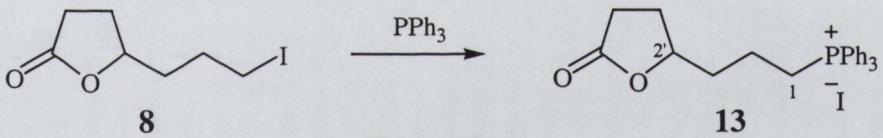
Alternatively, reaction of the mixed anhydride **2** with iodide ion could take place to form the acyl iodide **12**, **Scheme 2.5**. This could then react to give **4** and iodide ion.



Scheme 2.5

2.3 Synthesis of [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenyl-phosphonium iodide 13

The availability of the iodolactone **8** suggested its conversion to phosphonium salt **13**, **Scheme 2.6**. Treatment of **8** with triphenylphosphine in refluxing toluene provided the salt **13** in 72% yield.



Scheme 2.6

The salt **13** shows an IR absorption at 1760 cm^{-1} for the lactone carbonyl group. Distinctive resonances visible in the ^1H NMR spectrum of **13** include two multiplets centred at δ_H 7.82 and 7.73 ppm due to the fifteen aromatic protons of the triphenylphosphonium group. A multiplet centred at δ_H 4.74 ppm is assigned to the C-2' methine proton.

Surprisingly, the C-1 methylene protons adjacent to the triphenylphosphonium group resonate as a well-separated AB system at δ_H 3.67 and 4.12 ppm with a large $\Delta\delta$ value of *ca.* 0.45 ppm. From a ^1H-^1H COSY experiment, it was clear that the nearly-equivalent C-2 methylene protons resonated in the region δ_H 1.76-1.94 ppm. The ^1H-^1H COSY experiment also revealed that,

as expected, the C-3 methylene group adjacent to the asymmetric centre of the butanolide ring also formed an AB system resonating at δ_H 1.85 and 2.46 ppm. However, the observed $\Delta\delta$ value of *ca.* 0.6 ppm was also surprisingly large. To investigate further, CW decoupling experiments were employed. The region δ_H 1.76-1.94 ppm, containing the resonances for the C-2 protons, was irradiated and, as expected, the complexity of both of the C-1 multiplets centred at δ_H 3.67 and 4.00 ppm was reduced and the signals were observed as two baseline-resolved double doublets with coupling constants of J_{gem} 15 Hz and $J_{H,P}$ 13 Hz, **Figure 2.3**.

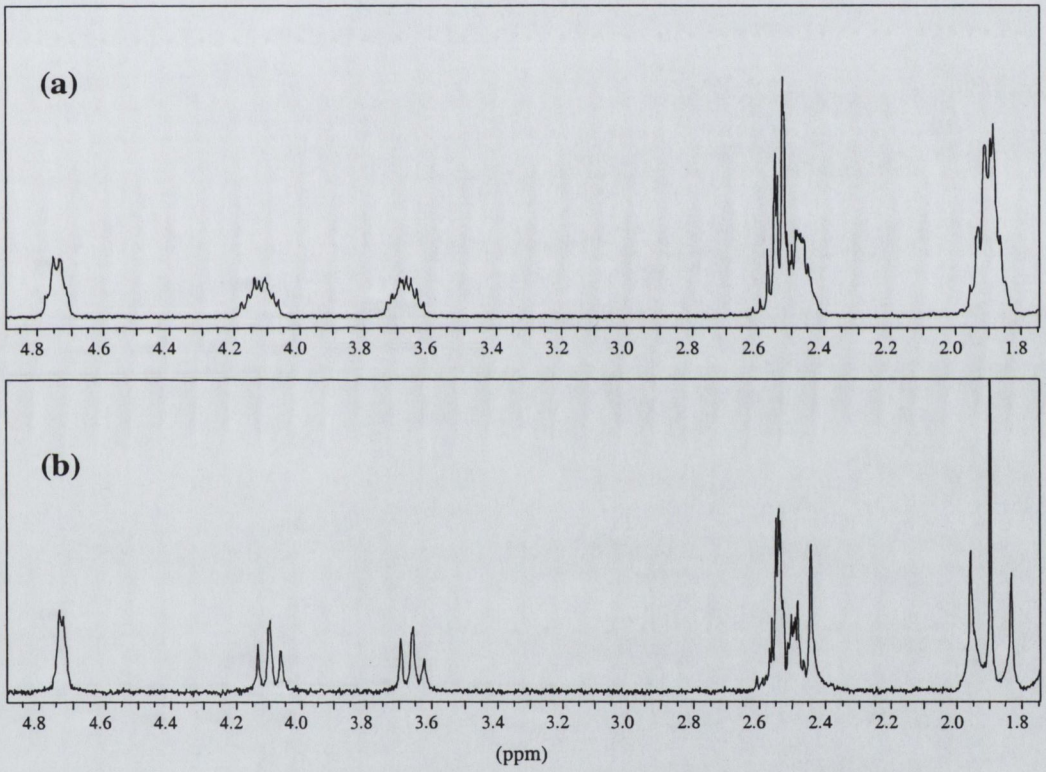
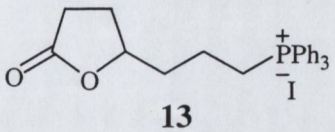


Figure 2.3

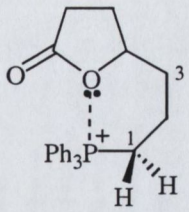
(a) ^{1}H NMR Spectrum of [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide 13

(b) CW decoupling experiment of 13: δ_H 1.76-1.94 ppm irradiated

These unusual findings suggest the presence of a pseudo-ring **14** which is explicable on consideration of the presence of the electropositive phosphorus(VI) which could coordinate electrostatically with the lactone oxygen atom.



13

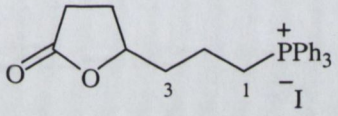


14

The ^{13}C-^{31}P coupling constants that were measured for each of the methylene groups of the side-chain of the phosphonium [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide **13** are in good agreement with typical literature values[4] for alkyl(triphenyl)phosphonium systems, **Table 2.2**.

Table 2.2

^{13}C NMR data obtained for the side-chain carbons of 13



13

^{13}C (ppm)	Assignment	Observed $J_{C,P}$ (Hz)	Lit.[4] $J_{C,P}$ (Hz)
19.4	C-2	3.8	4.3
22.5	C-1	51.5	47.6
35.5	C-3	16.5	15.4

Other signals observed in the ^{13}C NMR spectrum of **13** include a signal at δ_C 80.1 ppm for the C-2' methine carbon and four doublets corresponding to the aromatic carbons of the triphenylphosphine group. The lactonic carbonyl carbon is visible at δ_C 176.8 ppm. All these findings were confirmed by ^{1}H-^{1}H and ^{13}C-^{1}H COSY (**Figure 2.4**) experiments and are summarised in **Table 2.3**. A ^{31}P NMR spectrum of the salt **13** shows a resonance at δ_P 25.5 ppm.

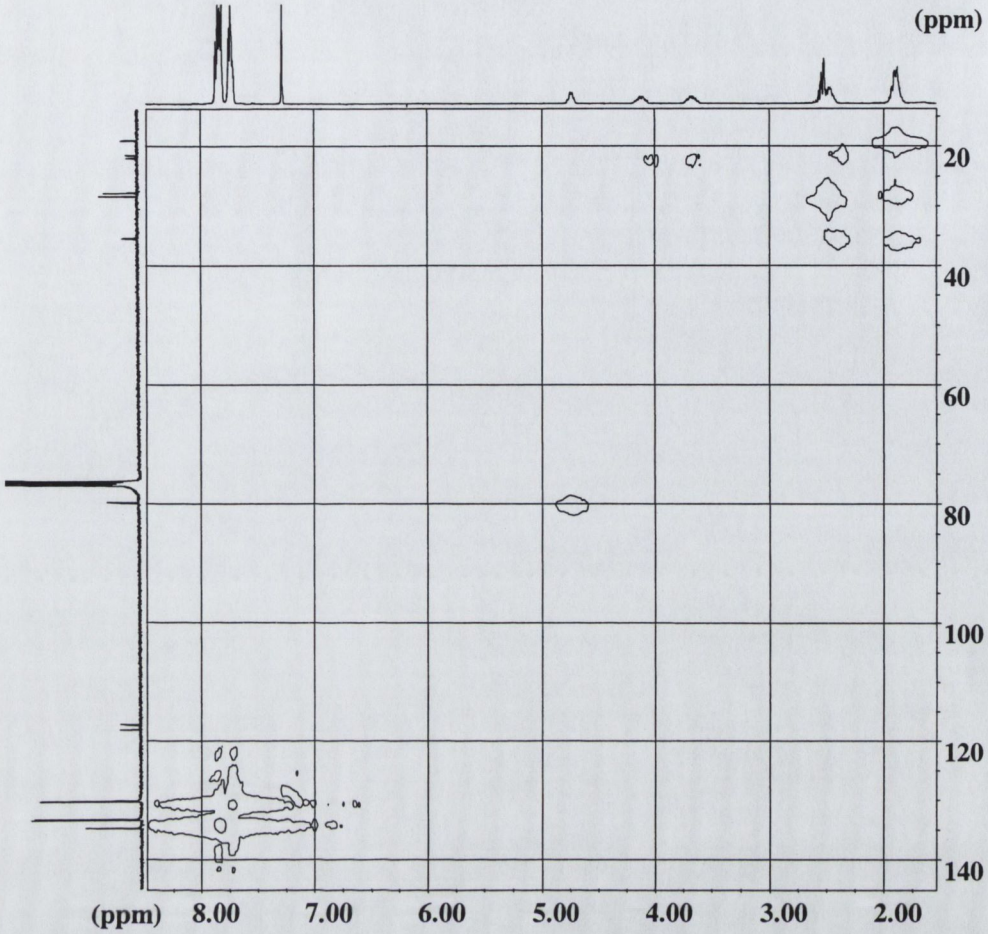
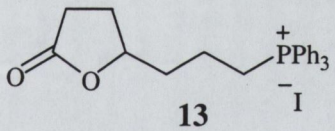


Figure 2.4

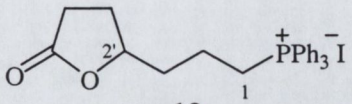
^{13}C-^{1}H COSY spectrum of [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide 13



13

Table 2.3

NMR Spectroscopic data obtained for [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide 13



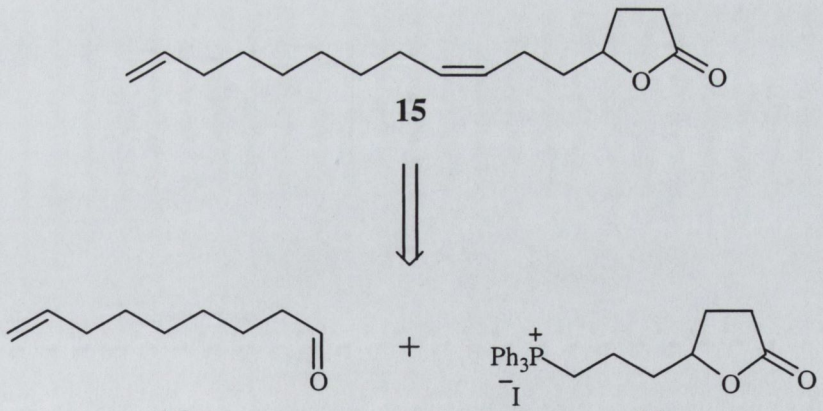
13

^{13}C (ppm)	Multiplicity in ^{13}C Spectrum	^{1}H (ppm)	Multiplicity in ^{1}H Spectrum	Assignment
*C*H$_2$ 19.4	d, $J_{C,P}$ 3.8	C*H*$_2$ 1.76-1.94	m	C-2
*C*H$_2$ 22.5	d, $J_{C,P}$ 51.5	C*H*$_a$ 3.62-3.73 C*H*$_b$ 4.06-4.17	m	C-1
*C*H$_2$ 28.0	s	C*H*$_a$ 1.76-1.94 C*H*$_b$ 2.39-2.54	m	C-3'
*C*H$_2$ 28.7	s	C*H*$_2$ 2.39-2.54	m	C-4'
*C*H$_2$ 35.5	d, $J_{C,P}$ 16.5	C*H*$_a$ 1.76-1.94 C*H*$_b$ 2.39-2.54	m	C-3
*C*H 80.1	s	C*H* 4.69-4.78	m	C-2'
C 117.5	d, $J_{C,P}$ 85.5	-	-	Ar C
*C*H 130.1	d, $J_{C,P}$ 11.6	6xC*H* 7.71-7.75	m	Ar C
*C*H 133.3	d, $J_{C,P}$ 9.7	6xC*H* 7.80-7.84	m	Ar C
*C*H 134.7	d, $J_{C,P}$ 2.9	3xC*H* 7.80-7.84	m	Ar C
C=O 176.8	s	-	-	C-5'

2.4 Attempted synthesis of the sex pheromone 15 of the yellowish elongate chafer, *Heptophylla picea via* Wittig reaction of [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide 13

Due to the availability of [3-(5'-oxotetrahydro-2'-furyl)propyl] triphenylphosphonium iodide **13**, it was anticipated that the ylid derived from this phosphonium salt could potentially lead to the formation of a more complex, naturally-occurring lactone.

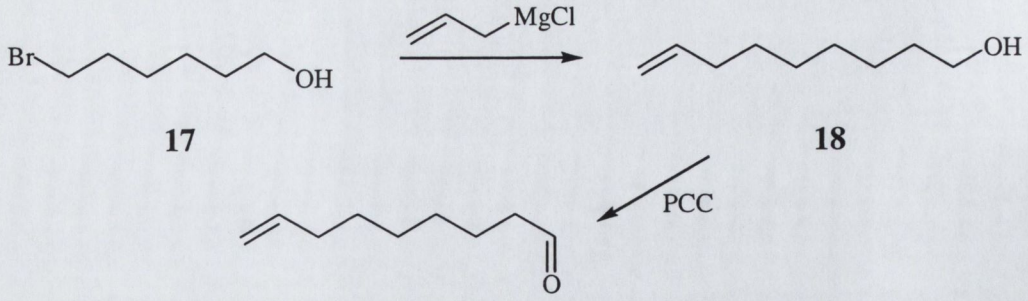
One such lactone is (5*R*,8*Z*)-8,16-hexadecadien-5-olide **15** which was isolated and identified by Leal *et al.*[5] in 1996. This sex pheromone is produced by the female of the yellowish elongate chafer (*Heptophylla picea*) which is an agricultural pest that causes losses in tea and flower production in Japan. The structure of the natural pheromone **15** consists of a dihydro-3(2*H*)-furanone with a twelve-carbon side-chain containing two double bonds, one of which is of (*Z*)-configuration. Retrosynthetic disconnection indicates that this naturally-occurring butanolide might be formed utilising a Wittig reaction involving the ylid derived from **13** and a relatively simple long-chain aldehyde **16**, **Scheme 2.7**.



15 **16** **13**

Scheme 2.7

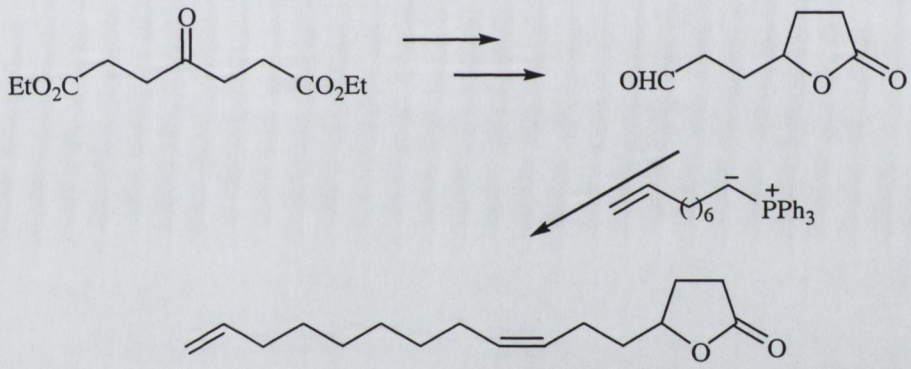
The required aldehyde **16** should be accessible *via* a simple synthesis involving Grignard reaction of oxygen-protected alcohol **17** with allylmagnesium chloride in the presence of dilithium tetrachlorocuprate[6] followed by oxidation of the resulting alcohol **18** with pyridinium chlorochromate (PCC), **Scheme 2.8**.



17 **18** **16**

Scheme 2.8

Nakayama *et al.*[6] have successfully synthesised the racemic pheromone **15** *via* a related route, **Scheme 2.9**, where the aldehyde is part of the lactone moiety and the phosphorus ylid is located on the side-chain precursor.



15

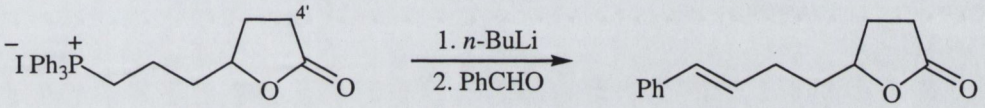
Scheme 2.9

To develop a method for the necessary Wittig reaction of the ylid derived from **13** preliminary tests were performed employing relatively simple aldehydes. Initially, it was proposed to investigate if reaction was possible, then the issue of formation of a double bond of (*Z*)-configuration would be addressed.

As the target aldehyde **16** is enolisable, butanal was chosen as a suitable candidate for the test reaction. Thus, [3-(5'-oxotetrahydro-2'-furyl)propyl] triphenylphosphonium iodide **13** was treated with lithium diisopropylamide (LDA) at –80°C and a solution of butanal in dry tetrahydrofuran was added. TLC studies of the resulting crude product showed the presence of a number of compounds. Column chromatography did not result in the isolation of any identifiable products.

The reaction was repeated employing *n*-BuLi as an alternative to LDA. However, the same complex mixture was obtained.

There are a number of possible explanations for the failure of this reaction. As butanal is susceptible to enolisation due to the presence of its acidic α-protons, the ylid derived from **13** might deprotonate the aldehyde. Accordingly, a reaction was carried out with non-enolisable benzaldehyde, **Scheme 2.10**. Upon work up, a mixture of products was obtained and, after purification *via* column chromatography, a minute quantity (5%) of the expected product **19** was isolated.



13 **19**

Scheme 2.10

A further possible explanation for the failure of the Wittig reaction is that some sort of intramolecular process occurs on formation of the ylid. Brunel and Rousseau[7] carried out studies concerning the Wittig reactions of lactones with methylene and alkylidene triphenylphosphoranes and found that unsaturated alcohols were obtained rather than the expected alkenes which are usually obtained in the case of acyclic esters. To rationalise their results, they proposed a mechanism that involves attack on the lactone carbonyl by the ylid.

To investigate this possibility, the phosphonium salt **13** was treated with *n*-BuLi (1.5 eq.) and then worked up. If an intramolecular process was occurring the salt should not be recovered. In the event, the salt **13** was recovered from the aqueous extract of the reaction mixture.

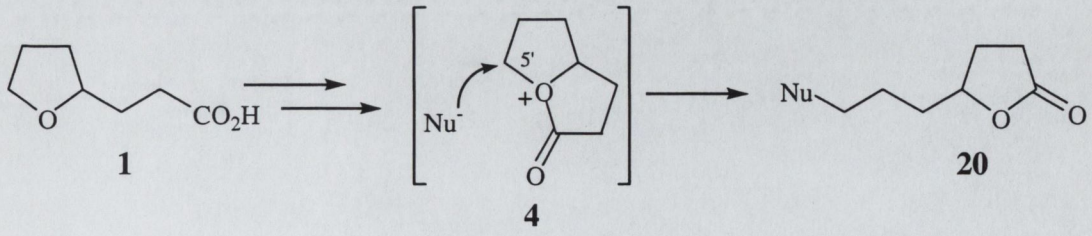
Another possible reason for the unsuccessful Wittig reaction is that the ylid is not being formed at all. Obviously, if the ylid is not formed, no reaction can occur. Hence, the phosphonium salt **13** was treated with *n*-BuLi and deuteriated trifluoroacetic acid CF_3CO_2D was added before work-up. The ^1H NMR spectrum of the recovered salt **13** did not indicate that any deuterium exchange had occurred at C-1.

A further possible explanation for these unsatisfactory results is that the base preferentially deprotonates the C-4' site adjacent to the lactone carbonyl group. Hence, the salt **13** was treated with two equivalents of base (BuLi). However, again no reaction was observed on addition of an aldehyde.

Due to the unsuccessful results obtained for these Wittig reactions, it was reluctantly accepted that the synthesis of pheromone **15** was not possible *via* the proposed route involving the phosphonium salt **13**.

2.5 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in the presence of various nucleophiles

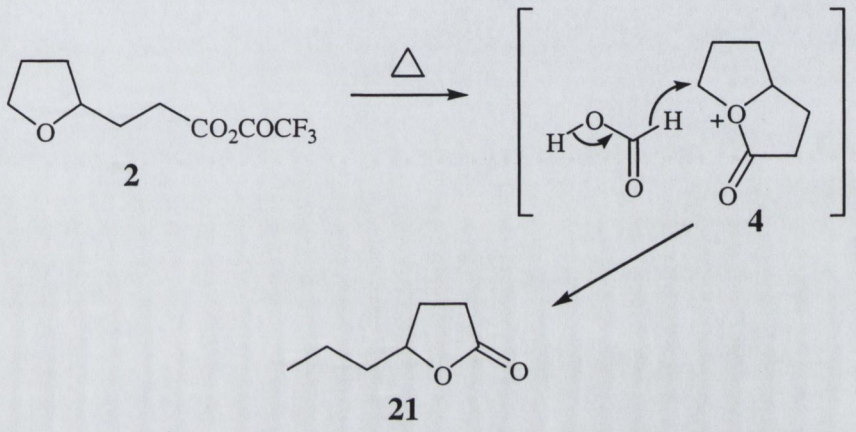
As mentioned previously, by carrying out the intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid **1** in the presence of various nucleophiles, functionalised dihydrofuranones **20** should be accessible. Simultaneously, the relative strengths of such nucleophiles in comparison to trifluoroacetate can be probed as both nucleophiles will be present in the reaction mixture and thus will compete for the reactive C-5' site of the bicyclic acyloxonium intermediate **4**.



Scheme 2.11

2.5.1 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in the presence of formic acid

It was considered that heating the mixed anhydride **2**, formed by treatment of the acid **1** with trifluoroacetic anhydride, in the presence of a small excess of formic acid might result in the formation of the butanolide **21**, **Scheme 2.12**.



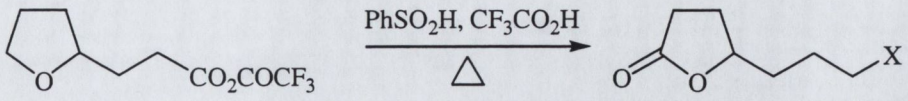
Scheme 2.12

Accordingly, the acid **1** was treated with trifluoroacetic anhydride and then heated in the presence of formic acid. However, following work-up, which involved washing with sodium hydrogen carbonate, there was marginal recovery of a crude neutral product. The aqueous washings were acidified and then extracted with solvent. Spectroscopic analysis of the compound recovered from the aqueous extract led to its identification as the starting acid **1**.

2.5.2 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in the presence of benzenesulfinic acid

Similarly, it was hoped that heating the mixed anhydride **2** in the presence of an excess of benzenesulfinic acid could result in the formation of the butanolide **22**, **Scheme 2.13**. Forming the sulfonyl-substituted butanolide **22** in this "one-pot" fashion would be desirable as sulfones are extensively employed in Julia reactions.[8] Hence, an efficient and facile route to the synthesis of sulfones incorporating a

butanolide ring could enable easy access to a wide range of naturally-occurring butanolides and consequently would be extremely advantageous.



2

22 X = SO_2Ph
5 X = $OCOCF_3$

Scheme 2.13

Thus, the acid **1** was treated with trifluoroacetic anhydride in the presence of benzenesulfinic acid. Spectroscopic analysis of the product obtained showed that the sole product of the reaction was in fact the trifluoroacetoxy butanolide **5** rather than the anticipated sulfonyl-substituted butanolide **22**. This suggests that trifluoroacetate is a stronger nucleophile than benzenesulfinate.

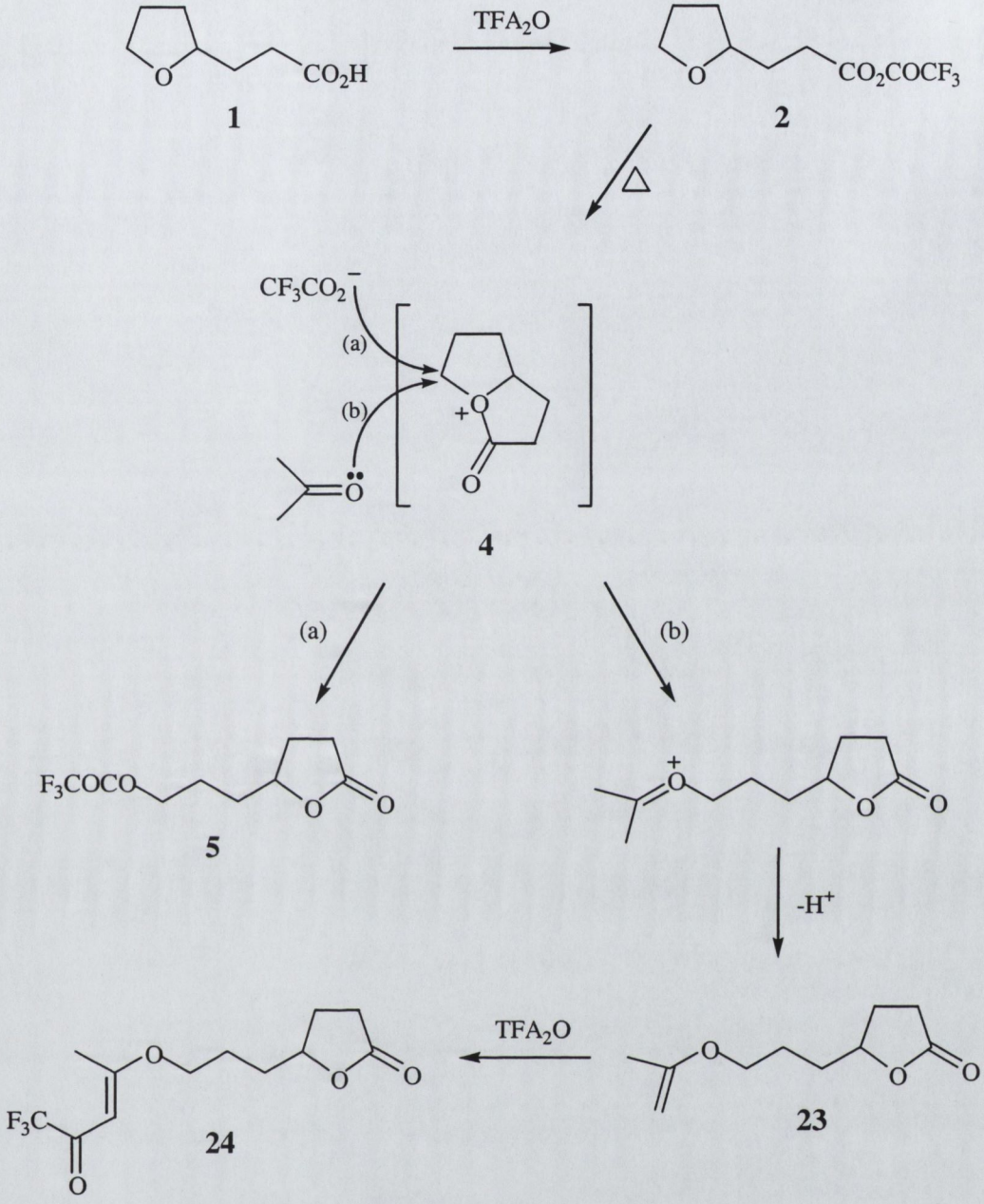
2.6 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in a variety of solvents

Another aspect of the intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid **1** that entices investigation is the nature of the reaction solvent. It was considered that perhaps the reaction solvent itself could act as the nucleophile as opposed to the weakly nucleophilic trifluoroacetate present in the reaction mixture, thus resulting in the formation of a whole range of novel butanolides. Hence, a study was carried out employing various solvents to investigate the likelihood of this occurring.

2.6.1 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in acetone

The acid **1** was dissolved in acetone and treated with trifluoroacetic anhydride at 0 °C. The reaction mixture was then refluxed and worked-up in the usual manner. When the rearrangement reaction of the mixed anhydride derived from the acid **1** is carried out in chloroform the sole product formed is the trifluoroacetoxy butanolide **5**, [route (a)], **Scheme 2.14**. However, on examination of the sole product obtained when the same reaction was performed in acetone it became clear that it bore no resemblance to the butanolide **5** with the exception of the fact that it also possessed a lactone ring.

Formation of the butanolide **23** had originally been anticipated due to the presence of acetone, [route (b)], however, the product obtained did not possess the distinctive characteristics expected for this lactone, **Scheme 2.14**. On careful scrutiny of the spectroscopic data obtained for the compound, which was formed in 64% yield, it was revealed to be (*E*)-5-[3'-(4'',4'',4''-trifluoro-1''-methyl-3''-oxobut-1''-enyloxy)propyl]dihydro-3(2*H*)-furanone **24**.

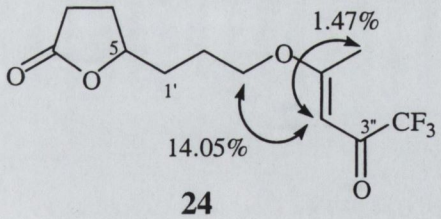


Scheme 2.14

The mechanism proposed for the formation of **24** is outlined in **Scheme 2.14**, [route (b)], and involves the butanolide **23** as an intermediate. However, this electron-rich alkene must undergo aliphatic Friedel-Crafts acylation due to the trifluoroacetic anhydride present in the reaction mixture resulting in the formation of **24**.

(*E*)-5-[3'-(4'',4'',4''-Trifluoro-1''-methyl-3''-oxobut-1''-enyloxy)propyl]-dihydro-3(2*H*)-furanone **24** shows overlapping IR absorptions at 1774 cm^{-1} for the trifluoroacetoxy and lactonic carbonyl groups. Key resonances visible in the ^{1}H

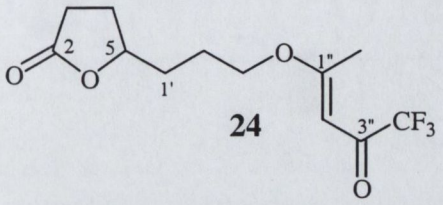
NMR spectrum include a singlet at δ_H 2.43 ppm which is due to the uncoupled methyl protons. A multiplet is observed at δ_H 2.59 ppm and is assigned to the non-equivalent C-3 methylene protons adjacent to the lactone carbonyl group. The C-5 methine proton appears as an apparent quintet centred at δ_H 4.52 ppm, with the C-2'' olefinic proton resonating as a singlet at δ_H 5.68 ppm. Distinctive features of the ^{13}C NMR spectrum of **24** include a signal at δ_C 21.0 ppm due to the terminal methyl carbon. The C-5 methine carbon resonates at δ_C 80.1 ppm whilst the olefinic carbon of C-2'' appears at 91.9 ppm. A quartet centred at δ_C 116 ppm with a coupling constant of 291 Hz is assigned to the 4''-CF_3 group while a second quartet centred at δ_C 178 ppm with a coupling constant of 33 Hz is due to the C-3'' carbonyl adjacent to the trifluoromethyl group. It is difficult to distinguish between the C-1'' quaternary carbon and the C-2 lactone carbonyl carbon, however, with the aid of a HMBC experiment it is clear that the C-2 carbonyl carbon resonates at δ_C 176.4 ppm whilst the C-1'' quaternary carbon appears at 180.2 ppm. All these assignments were confirmed by ^1H-^1H and ^{13}C-^1H COSY experiments, **Figure 2.5**, and the results are summarised in **Table 2.4**. The stereochemistry of **24** was assigned on the basis of a set of n.O.e. experiments that delivered the results indicated on the structural formula below. A ^{19}F NMR spectrum revealed the presence of one CF_3 resonance at δ_F –78.9 ppm.



24

Table 2.4

NMR spectroscopic details of (*E*)-5-[3'-(4'',4'',4''-trifluoro-1''-methyl-3''-oxobut-1''-enyloxy)propyl]dihydro-3(2*H*)-furanone 24



24

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_3$ 21.0	C*H*$_3$ 2.43	s	CH$_3$
*C*H$_2$ 24.5	C*H*$_2$ 1.75-2.05	m	C-2'
*C*H$_2$ 27.8	C*H*$_a$ 1.75-2.05	m	C-4
	C*H*$_b$ 2.31-2.44	m	
*C*H$_2$ 28.5	C*H*$_2$ 2.57-2.61	m	C-3
*C*H$_2$ 31.9	C*H*$_2$ 1.75-2.05	m	C-1'
*C*H$_2$ 68.9	C*H*$_2$ 3.95-4.05	m	C-3'
*C*H 80.1	C*H* 4.52-4.59	apparent quintet, *J* 6.5	C-5
*C*H 91.9	C*H* 5.68	s	C-2''
*C*F$_3$ 116.5	-	q, $J_{F,C}$ 291.5	C-4''
C=O 176.4	-	-	C-2
*C*OCF$_3$ 178.5	-	q, $J_{F,C}$ 33.0	C-3''
C 180.2	-		C-1''

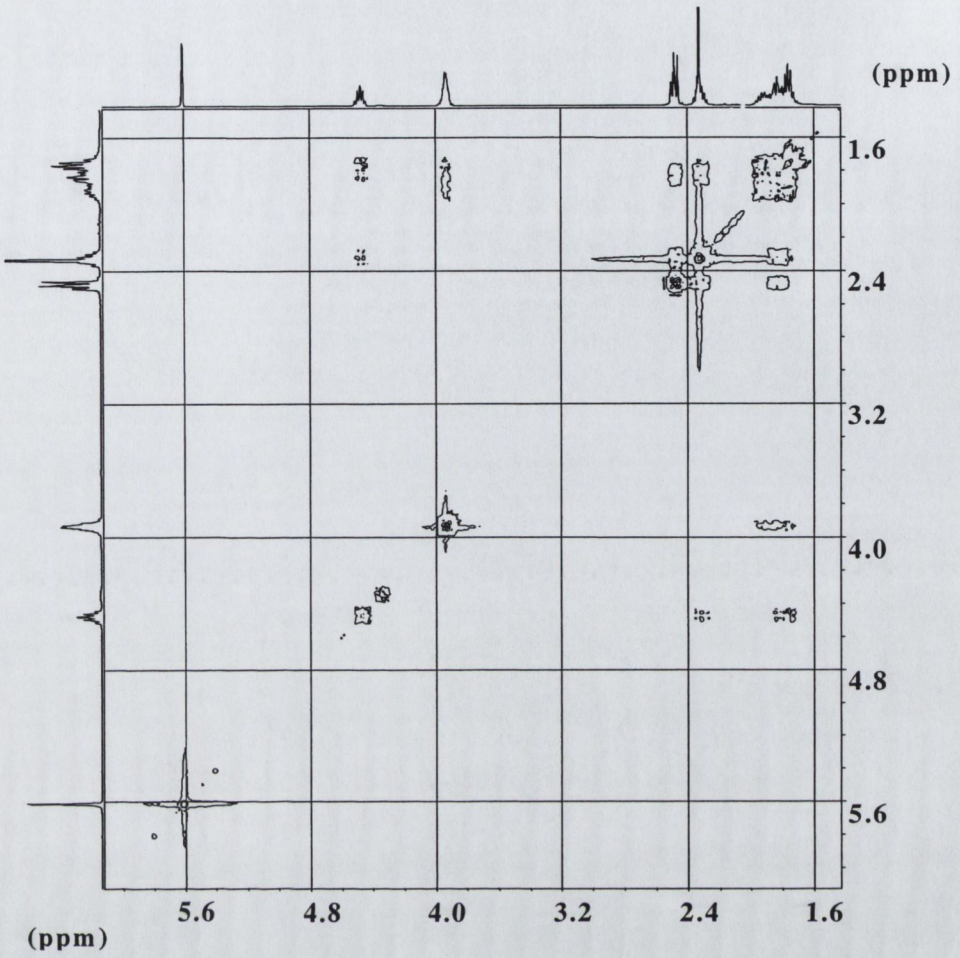


Figure 2.5

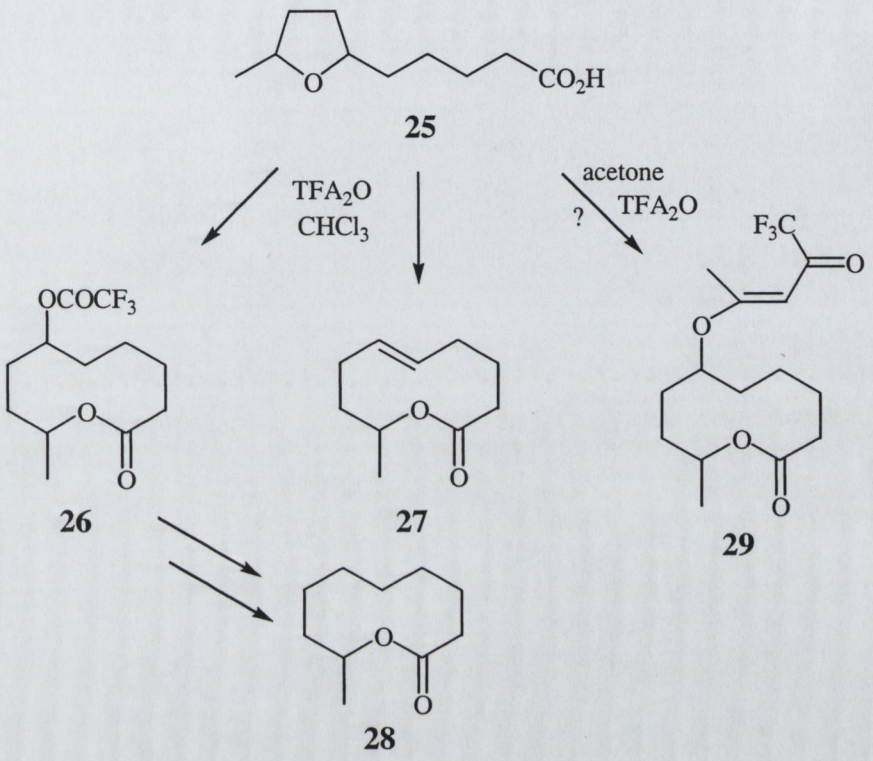
^{1}H-^{1}H COSY Spectrum of (*E*)-5-[3'-(4'',4'',4''-trifluoro-1''-methyl-3''-oxobut-1''-enyloxy)propyl]dihydro-3(2*H*)-furanone 24

2.6.2 Intramolecular acylative ring-switching reaction of 5-(5'-methyltetrahydro-2'-furyl)pentanoic acid 25 in acetone

Due to the interesting result obtained for the intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid **1** in acetone it was proposed to explore the behaviour of a 5-(5'-methyltetrahydro-2'-furyl)pentanoic acid **25** in the same reaction environment.

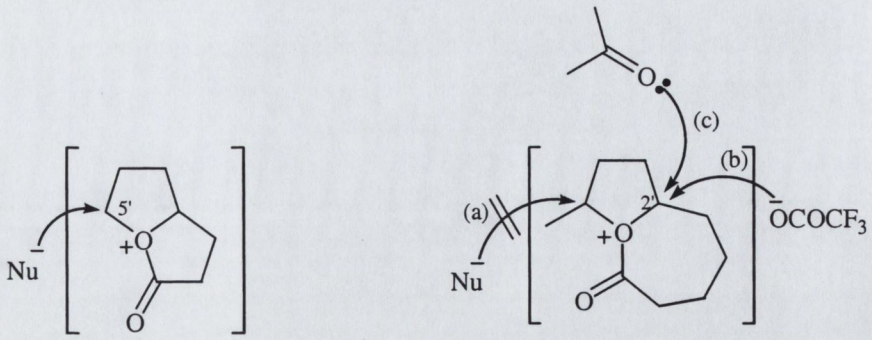
5-(5'-Methyltetrahydro-2'-furyl)pentanoic acid **25** was available due to its isolation as a side product in a reaction described in Section 3.3.1. Previous work by Duffy[9] involved the intramolecular acylative ring-switching reaction of this acid **25** in chloroform. This resulted in the formation of a mixture of the saturated and

unsaturated lactones **26** and **27**, **Scheme 2.15**.[9] The saturated lactone **26** was then converted into the naturally-occurring lactone phoracantholide **28**.



Scheme 2.15

The present work involved the treatment of acid **25** with trifluoroacetic anhydride in refluxing acetone. In the case of the propanoic acid derivative **1** attack occurred at the exposed C-5' α-carbon of the bicyclic acyloxonium system **4** regardless of whether the reaction was carried out in chloroform or acetone, **Scheme 2.16**. However, in the case of the analogous bicyclic acyloxonium system **30**, attack does not take place at the C-5' α-carbon, [route (a)]. When the reaction is carried out in chloroform, the C-2' bridgehead carbon is attacked by a trifluoroacetate ion, [route (b)]. It follows that when the reaction is carried out in acetone, attack by acetone might also occur at the bridgehead carbon, [route (c)], a further aliphatic Friedel-Crafts reaction would then result in the formation of a lactone such as **29**, **Scheme 2.15**.

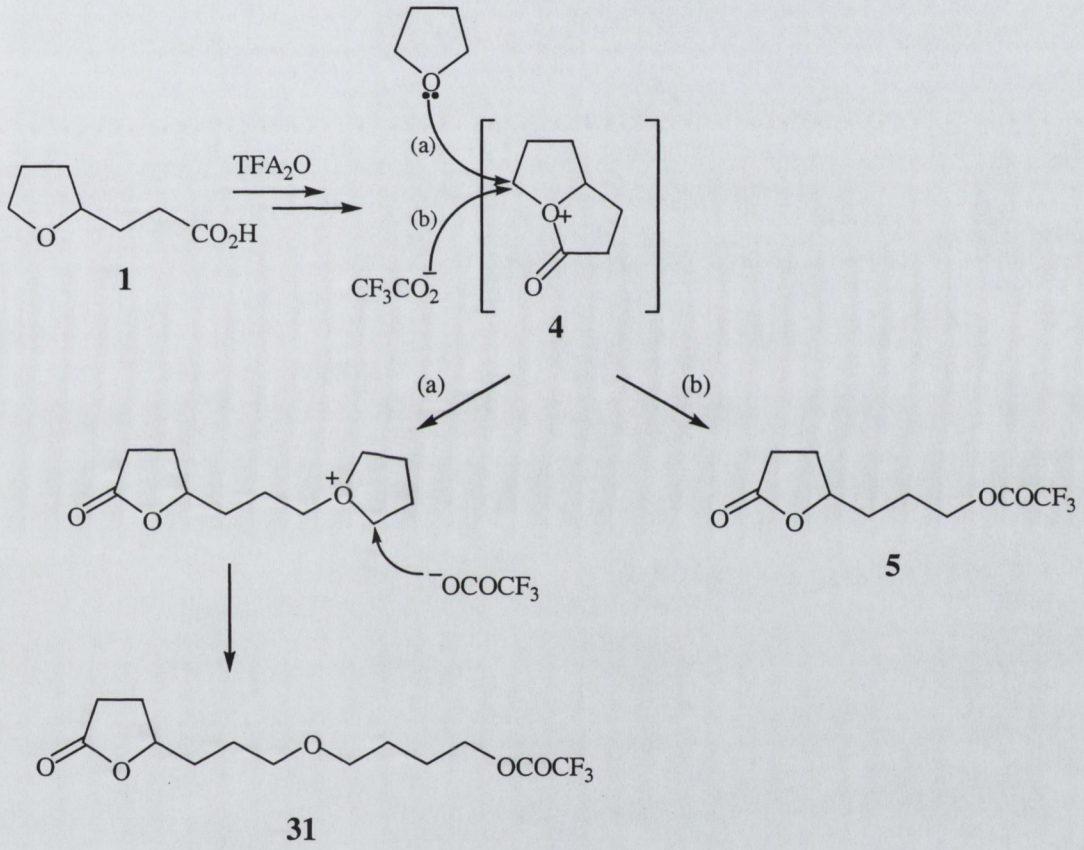


Scheme 2.16

Thus, the pentanoic acid **25** was dissolved in acetone and treated with trifluoroacetic anhydride in the usual way. The crude product was found to consist of two major components that were isolated by column chromatography. The first component to elute was identified as (*E*)-10-methyl-6,7-dihydro-oxecin-2-one **27** (15%), followed by 10-methyl-7-trifluoroacetoxy-oxecan-2-one **26** (30%). The anticipated lactone **29** was not formed. Thus, it is clear that attack by a trifluoroacetate ion occurred at the C-2' brigdehead carbon [route (b)], as was the case when the reaction was carried out in chloroform. It may be concluded that employing acetone rather than chloroform as solvent has no effect on the outcome of the reaction in the case of 5-(5'-methyltetrahydro-2'-furyl)pentanoic acid **25**.

2.6.3 Intramolecular acylative ring-switching reaction of the 3-(tetrahydro-2'-furyl)propanoic acid 1 in tetrahydrofuran

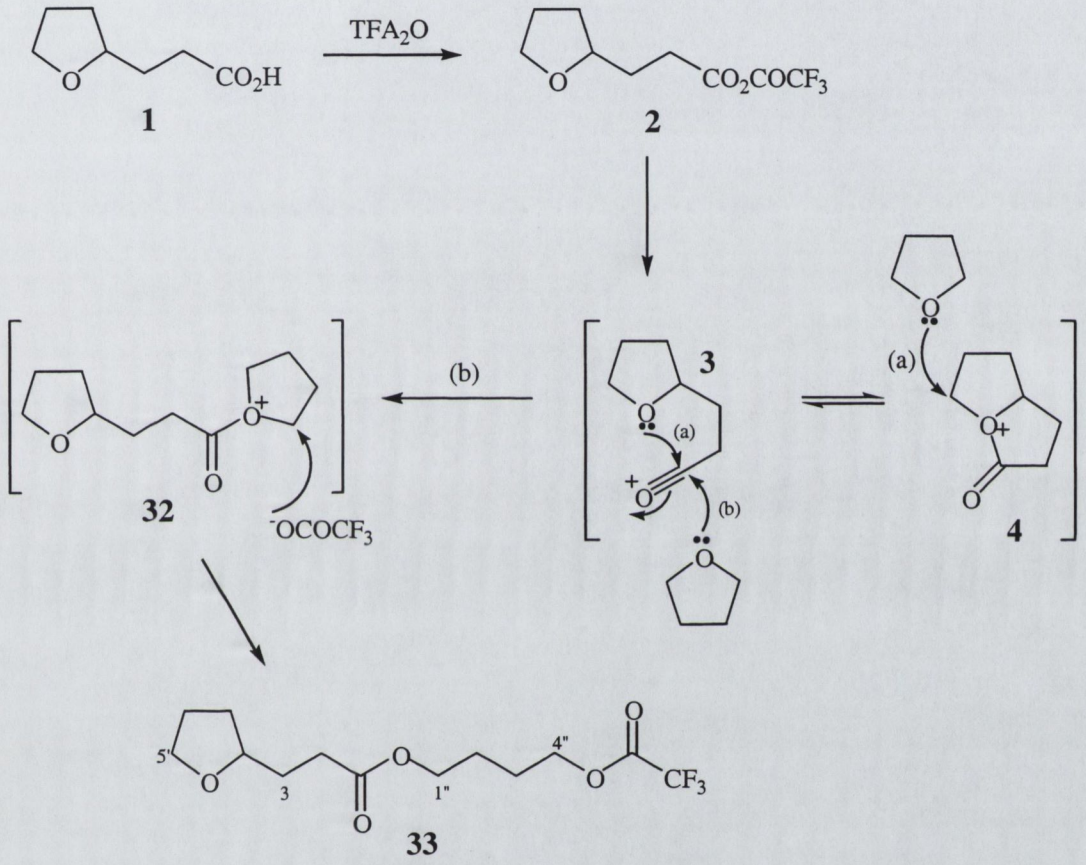
Following the encouraging results of the intramolecular reaction of acid **1** in acetone, the next solvent to be investigated was tetrahydrofuran. It was anticipated that a butanolide such as **31** might be formed due to the presence of the tetrahydrofuran [route (a)] rather than the trifluoroacetoxy butanolide **5** obtained when the reaction is carried out in chloroform [route (b)], **Scheme 2.17**.



Scheme 2.17

Thus, the mixed anhydride derived from the acid **1** was subjected to the usual procedure in refluxing tetrahydrofuran. On examination of the crude product by TLC it was found to consist of three distinctive components. Separation by column chromatography was achieved. The first component to elute was not the anticipated butanolide **31**, on the contrary, it was found not to possess a butanolide ring at all. Upon careful scrutiny of its spectroscopic data, it was identified as 4''-trifluoroacetoxybutyl 3-(tetrahydro-2'-furyl)propanoate **33**. A possible mechanism for the formation of **33** is outlined in **Scheme 2.18**. Here, intermolecular reaction

of solvent tetrahydrofuran with the "linear" acylium species **3** [route (b)] must take precedence over similar attack at the C-5' α-carbon of the bicyclic acylium ion **4** [route (a)]. The intermediate **32** which is formed is then susceptible to attack by trifluoroacetate ion also present in the reaction mixture resulting in the tetrahydrofuran derivative **33**.



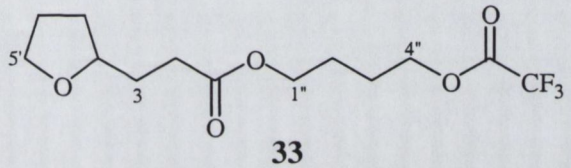
Scheme 2.18

4''-Trifluoroacetoxybutyl 3-(tetrahydro-2'-furyl)propanoate **33** was isolated in 7% yield. This compound shows IR absorptions at 1785 cm^{-1} (trifluoroacetoxy carbonyl) and 1735 cm^{-1} (ester carbonyl). The NMR spectroscopic data obtained for **33** are summarised in **Table 2.5**. Key resonances in its ^1H NMR spectrum include two overlapping double double doublets centred at δ_H 2.40 and 2.47 ppm and possessing a geminal coupling constant of 16.0 Hz which are assigned to the methylene protons of C-2 adjacent to the ester carbonyl. Two triplets with coupling constants of 6.5 Hz are visible at δ_H 4.13 and 4.40 ppm and correspond to to the methylene protons of C-1'' and C-4'' which are adjacent to an ester and a

trifluoroacetoxy function respectively. In the ^{13}C NMR spectrum of **33** the C-2' methine carbon is visible at δ_C 77.7 ppm while the ester carbonyl carbon resonates at δ_C 173.0 ppm. ^{13}C-^{1}H and ^{1}H-^{1}H COSY experiments, **Figure 2.6,** confirmed all these assignments and also aided the assignment of the numerous methylene groups present, **Table 2.5**. A ^{19}F NMR spectrum revealed the presence of one CF_3 resonance at δ_F –75.6 ppm.

Table 2.5

NMR spectroscopic details of 4''-trifluoroacetoxybutyl 3-(tetrahydro-2'-furyl)propanoate 33



33

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
CH_2 24.4	CH_2 1.73-1.94	m	C-2''/3''/4'
CH_2 24.5	CH_2 1.73-1.94	m	C-2''/3''/4'
CH_2 25.2	CH_2 1.73-1.94	m	C-2''/3''/4'
CH_2 30.2	CH_2 1.73-1.94	m	C-3
CH_2 30.6	CH_a 2.40	ddd, ^{2}J 16.0, $^{3}J_1$ 8.0, $^{3}J_2$ 7.0	C-2
	CH_b 2.47	ddd, ^{2}J 16.0, $^{3}J_1$ 8.5, $^{3}J_2$ 7.0	
CH_2 30.7	CH_a 1.49	apparent dq, ^{2}J 11.5, $^{3}J_1 = {}^{3}J_2 = {}^{3}J_3$ 7.5	C-3'
	CH_b 1.96-2.05	m	
CH_2 62.9	CH_2 4.13	t, J 6.5	C-1'' or C-4''
CH_2 67.1	CH_2 4.40	t, J 6.5	C-1'' or C-4''
CH_2 67.2	CH_a 3.69-3.75	m	C-5''
	CH_b 3.83-3.88	m	
CH 77.7	CH 3.83-3.88	m	C-2'
C=O 173.0	-	-	C-1

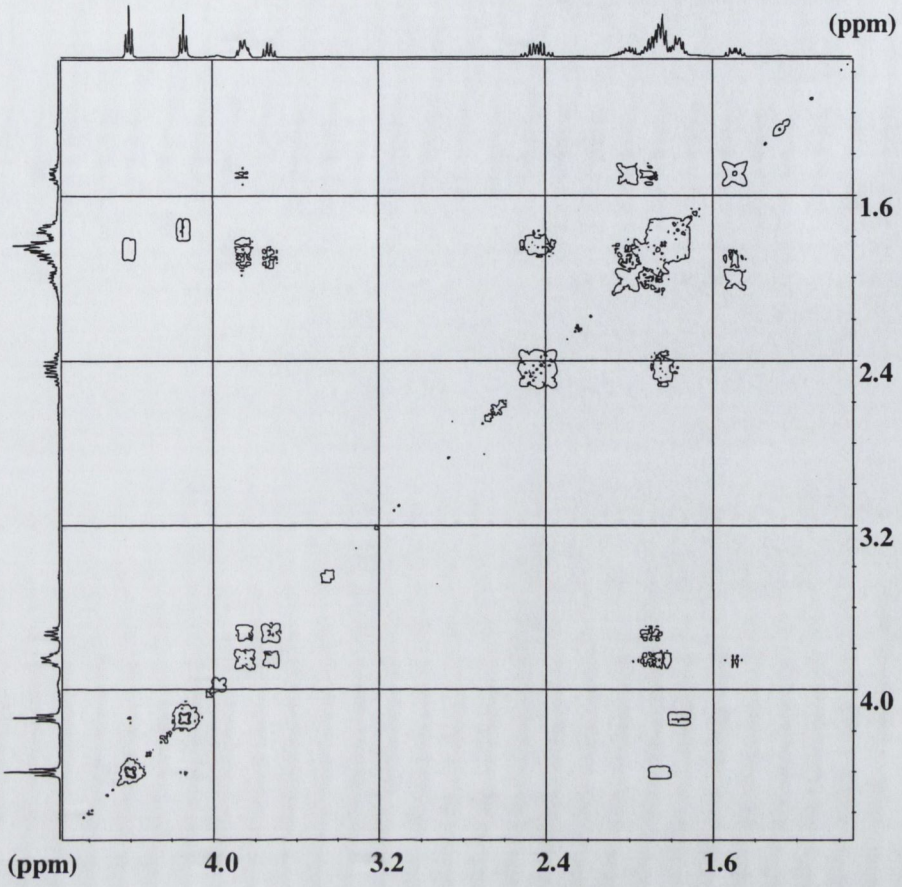
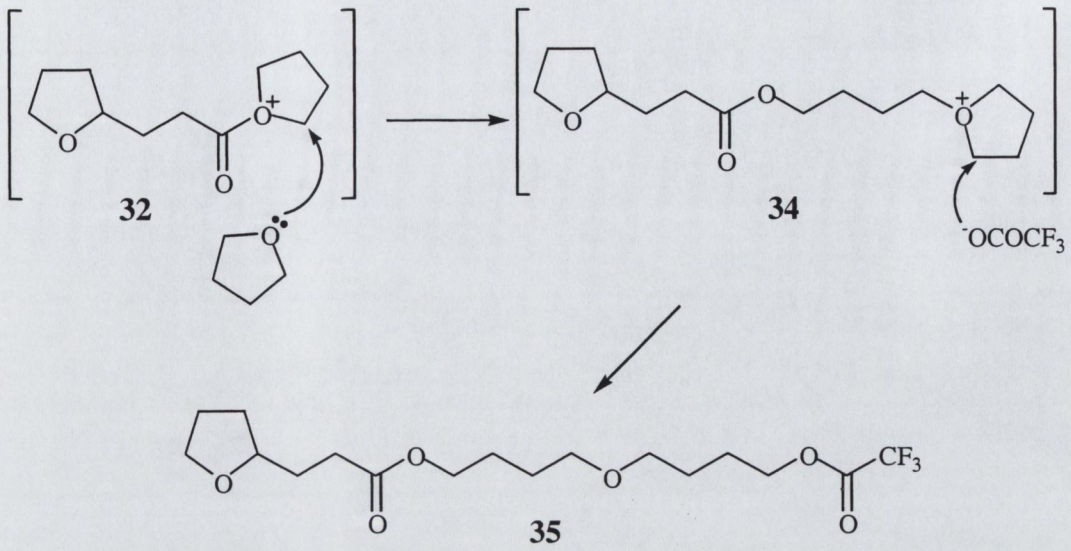


Figure 2.6

^{1}H-^{1}H COSY Spectrum of 4''-trifluoroacetoxybutyl 3-(tetrahydro-2'-furyl)propanoate 33

The second fraction to be eluted by column chromatography of the crude product obtained from the intramolecular reaction of acid **1** in tetrahydrofuran also did not possess a butanolide ring. It was identified as 9''-trifluoroacetoxy-5''-oxanonyl 3-(tetrahydro-2'-furyl)propanoate **35** and is also likely formed *via* intermediate **32**, **Scheme 2.19**. However, in this case, instead of a trifluoroacetate ion attacking **32** as occurred in the formation of **33**, **Scheme 2.18**, a second tetrahydrofuran molecule attacks resulting in the extended intermediate **34**. Subsequent attack by a trifluoroacetate ion then results in the formation of **35**.

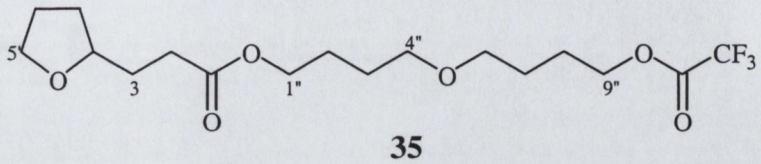


Scheme 2.19

9''-Trifluoroacetoxy-5''-oxanonyl 3-(tetrahydro-2'-furyl)propanoate **35** possessed similar spectroscopic characteristics to **33** and was isolated in 3% yield. This compound shows IR absorptions at 1785 and 1735 cm^{-1} that are attributable to the trifluoroacetoxy and ester carbonyl functions, respectively. The distinctive features of the NMR spectroscopic data obtained for **35** are summarised in **Table 2.6**. Resonances visible in the ^{1}H NMR spectrum include two overlapping apparent double triplets centred at δ_H 2.39 and 2.47 ppm that possess a geminal coupling constant of 15.5 Hz and which are assigned to the C-2 methylene protons adjacent to the ester carbonyl group. The C-2' methine proton of **35** resonates as a multiplet centred at δ_H 3.85 ppm and overlaps with one of the C-5' protons. Two triplets, both with a coupling constant of 6.5 Hz, are observed at δ_H 4.11 and 4.40 ppm and are assigned to the C-1'' and C-9'' methylene groups adjacent to an ester and trifluoroacetoxy function respectively. The ^{13}C NMR spectrum shows signals for six methylene carbons at δ_C 25.2, 25.5, 25.6, 25.7, 26.1 and 30.6 assigned to the C-3, C-4', C-2'', C-3'', C-7'' and C-8'' methylene carbons. However, even with the aid of a ^{13}C-^{1}H COSY experiment, it was not possible to distinguish between these signals. The C-1'' and C-9'' carbons are visible at δ_C 63.7 and 67.7 ppm. The C-2' methine proton resonates at δ_C 77.7 ppm while the ester carbonyl carbon is visible at δ_C 173.1 ppm. A ^{19}F NMR spectrum revealed the presence of one CF_3 resonance at δ_F –75.6 ppm.

Table 2.6

Distinctive features of NMR data obtained for 9''-Trifluoroacetoxy-5''-oxanonyl 3-(tetrahydro-2'-furyl)propanoate 35



35

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
	CH_a 1.49	apparent dq, ^{2}J 12.0,	
CH_2 31.1		$^{3}J_1 = {}^{3}J_2 = {}^{3}J_3$ 8.0	C-3'
	CH_b 1.97-2.07	m	
CH_2 31.1	CH_a 2.39	apparent dt, ^{2}J 15.5, $^{3}J_1 = {}^{3}J_2$ 8.0	C-2
	CH_b 2.47	apparent dt, ^{2}J 15.5, $^{3}J_1 = {}^{3}J_2$ 8.0	
CH_2 63.7	CH_2 4.11	t, J 6.5	C-1''/C-9''
CH_2 67.2	CH_a 3.71-3.76	m	C-5'
	CH_b 3.83-3.88	m	
CH_2 67.6	CH_2 4.40	t, J 6.5	C-1''/C-9''
CH_2 69.4	CH_2 3.42-3.47	m	C-4''/C-6''
CH_2 69.9	CH_2 3.42-3.47	m	C-4''/C-6''
CH 77.7	CH 3.83-3.88	m	C-2'
C=O 173.1	-	-	C-1

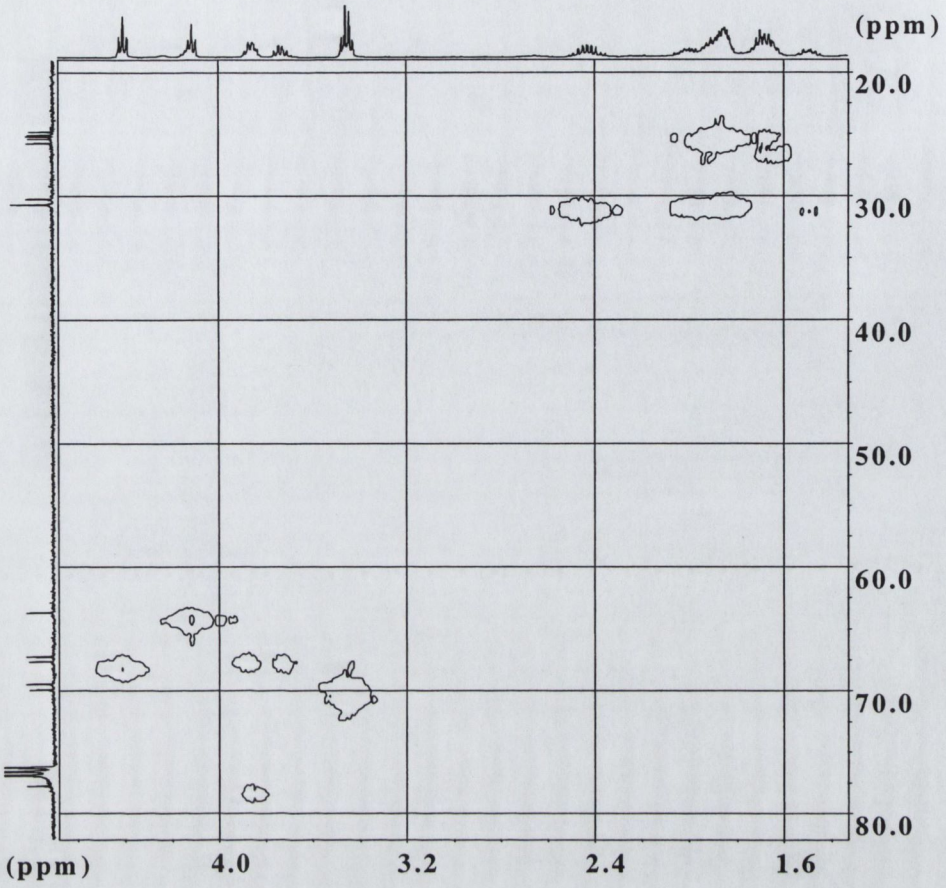
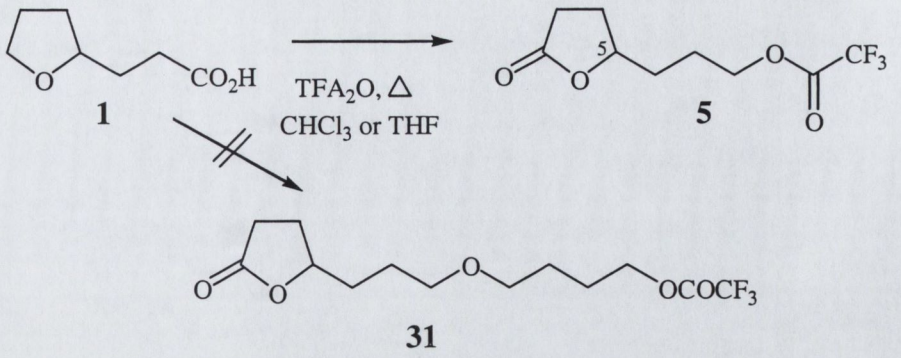


Figure 2.7

^{13}C-^{1}H COSY Spectrum of 9''-trifluoroacetoxy-5''-oxanonyl 3-(tetrahydro-2'-furyl)propanoate 35

The third and final fraction to be eluted from the column of the crude product obtained from the intramolecular reaction of acid **1** in tetrahydrofuran did, unlike the previous two compounds, possess a butanolide ring with a distinctive C-5 methine proton resonating at δ_H 4.5 ppm in the ^{1}H NMR spectrum. It was identified as being the "normal" 5-(3'-trifluoroacetoxypropyl)dihydro-3(2*H*)-furanone **5** (25%) which is also formed when the reaction is carried out in chloroform, **Scheme 2.20**.

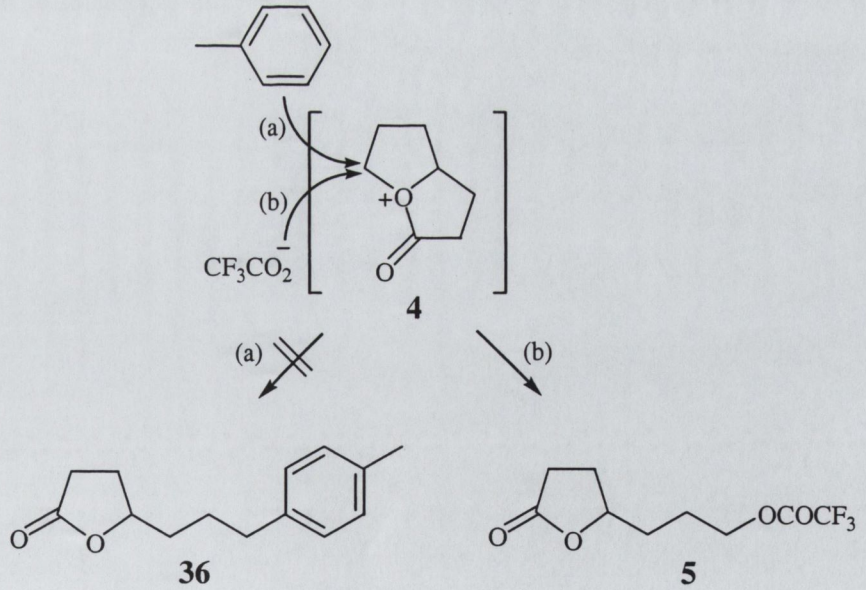


1 5 31

Scheme 2.20

2.6.4 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in toluene

Toluene was the next solvent to be investigated with respect to its ability to act as nucleophile and attack the bicyclic intermediate **4** in the presence of trifluoroacetate ion, [route (a)], **Scheme 2.21**.



36 5

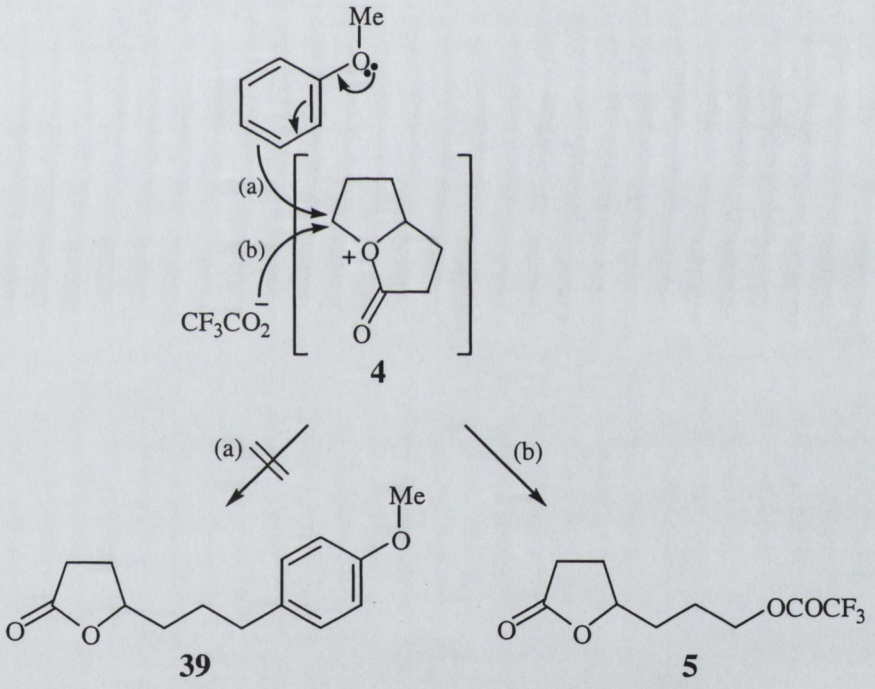
Scheme 2.21

Thus, the acid **1** was dissolved in toluene and treated with trifluoroacetic anhydride in the usual way. However, examination of the spectroscopic data obtained for the sole product that was formed identified it as being the

trifluoroacetoxy butanolide **5**, (70%), [route (b)]. The anticipated butanolide **36** was not formed.

2.6.5 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in anisole

The intramolecular acylative ring-switching reaction of acid **1** was then attempted in refluxing anisole. It was considered that use of this electron-rich, high boiling polar solvent could lead to formation of a butanolide such as **39**, [route (a)], **Scheme 2.22**.

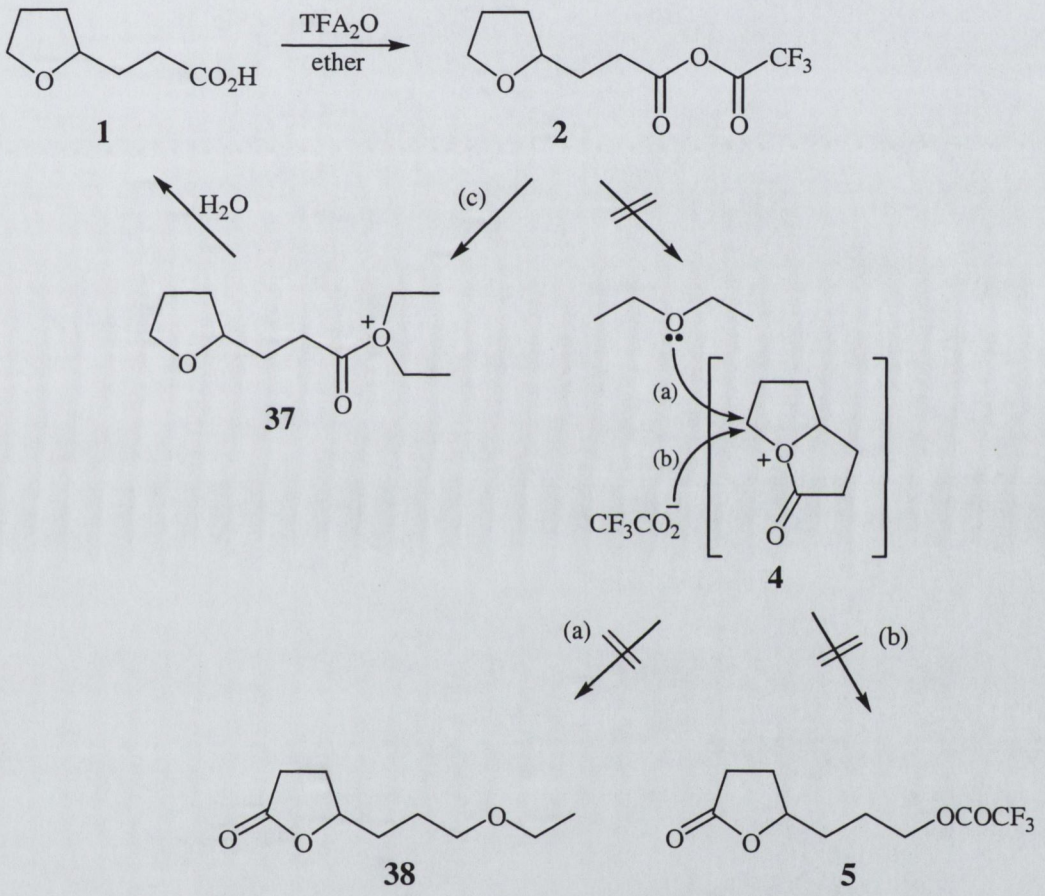


Scheme 2.22

Thus, the acid **1** was dissolved in anisole and treated with trifluoroacetic anhydride in the usual way. However, the sole product obtained was identified as trifluoroacetoxy butanolide **5**, [route (b)], which was formed in 67% yield. The anticipated butanolide **39** was not obtained.

2.6.6 Intramolecular acylative ring-switching reaction of 3-(tetrahydro-2'-furyl)propanoic acid 1 in diethyl ether

The intramolecular acylative ring-switching reaction of acid **1** was then attempted in refluxing diethyl ether to investigate whether a butanolide such as **38** could be formed, [route (a)], **Scheme 2.23**.



Scheme 2.23

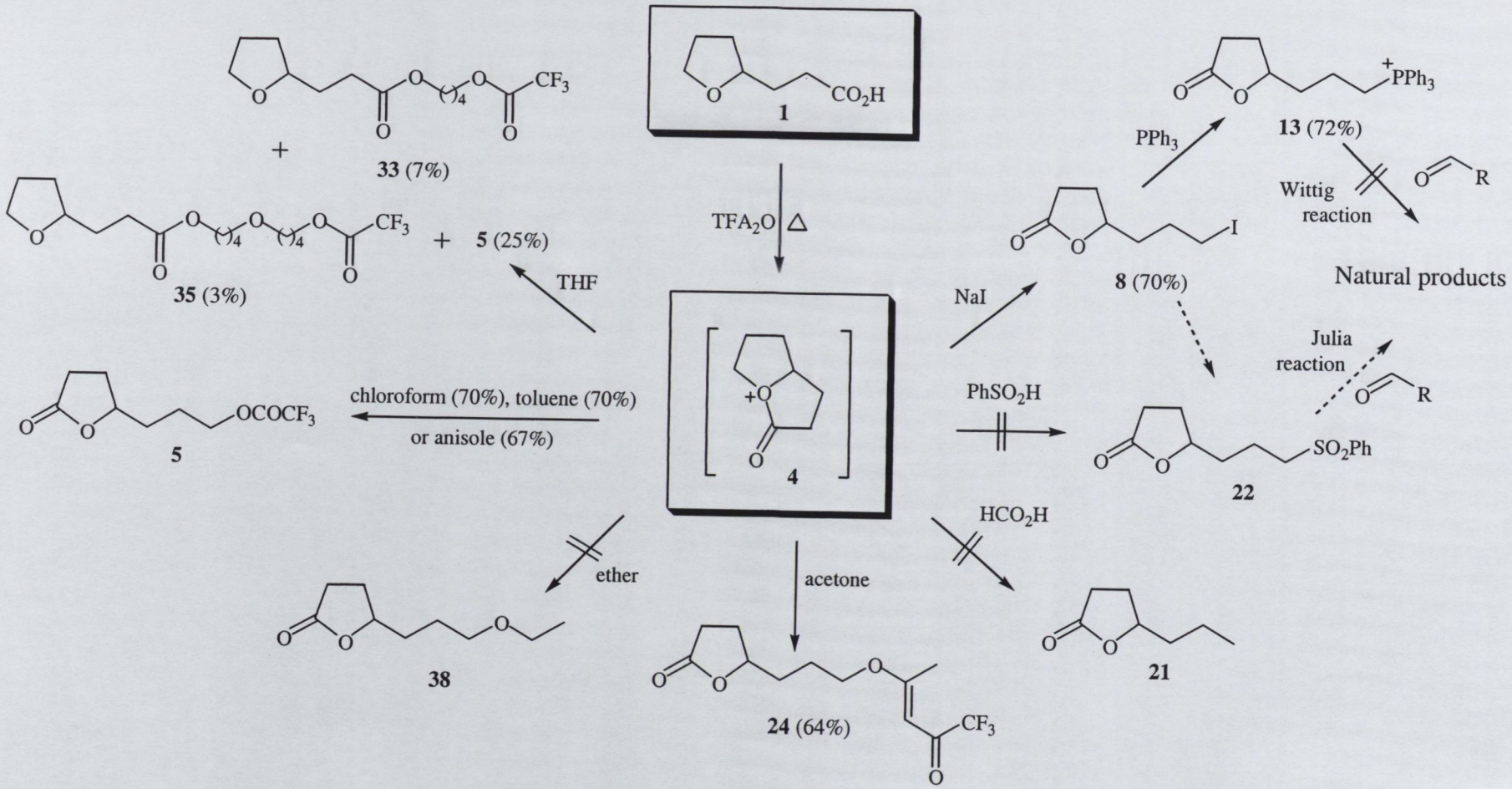
Thus, the acid **1** was dissolved in diethyl ether and treated with trifluoroacetic anhydride in the usual way. However, upon work-up which involved washing with a saturated solution of sodium hydrogen carbonate, there was marginal recovery of a crude neutral product. Consequently, the aqueous washings were analysed and acid **1** was recovered. It may be that reaction pathway (c) is followed resulting in formation of **37** which would be converted into the starting acid **1** upon aqueous work-up.

2.7 Summary and concluding remarks

This Chapter has described research carried out to investigate the scope of the intramolecular lactonisation reaction of 3-(tetrahydro-2'-furyl)propanoic acid **1**. The results that have been obtained are summarised in **Scheme 2.24.**

Iodobutanolide **8** was formed (70%) directly from acid **1** by reaction of the bicyclic acyloxonium ion **4** with sodium iodide. This iodolactone **8** was then efficiently converted (72%) into the corresponding phosphonium salt **13** with a view to its employment in Wittig reactions which could lead to the formation of naturally-occurring butanolides. However, attempts to generate an ylid from this phosphonium salt were unsuccessful. As an alternative, it might be possible to convert the iodolactone **8** into the corresponding sulfone **22** which could then be employed in Julia reactions,[8] **Scheme 2.24**.

An attempt to synthesise the sulfone **22** directly *via* the intramolecular reaction of 3-(tetrahydro-2'-furyl)propanoic acid **1** in the presence of benzenesulfinic acid was unsuccessful. The sole product obtained from this reaction was the trifluoroacetoxy butanolide **5** indicating that trifluoroacetate is a stronger nucleophile than benzenesulfinate. When the reaction was carried out in the presence of formic acid the acid **1** was recovered suggesting that the bicyclic acyloxonium ion **4** did not form due to a competing reaction of formic acid with the mixed anhydride formed from acid **1**.



1
CO_2H
TFA_2O Δ
4
33 (7%)
35 (3%)
5 (25%)
THF
5
$OCOCF_3$
chloroform (70%), toluene (70%)
or anisole (67%)
ether
38
acetone
24 (64%)
CF_3
NaI
8 (70%)
PPh_3
13 (72%)
Wittig reaction
Natural products
Julia reaction
$PhSO_2H$
22
SO_2Ph
HCO_2H
21

Scheme 2.24

A solvent study revealed some interesting conversions and also gave a good indication of the relative nucleophilic strength of the trifluoroacetate ion and the various solvents employed, **Scheme 2.24**, although relative molarities must be taken into account here. When the intramolecular reaction of acid **1** was carried out in acetone, the butanolide **24** was produced, indicating that the bicyclic acyloxonium ion **4** formed from acid **1** must be trapped by acetone rather than trifluoroacetate as was the case when the reaction was carried out in chloroform.

When the reaction was carried out in tetrahydrofuran, this solvent also competed with trifluoroacetate ion to react with the generated acylium and oxonium ions. Thus, although the expected rearrangement to trifluoroacetoxy butanolide **5** did occur, this product was accompanied by small amounts of each of the diesters **33** and **35**, **Scheme 2.24**, indicating that reaction with tetrahydrofuran had also taken place.

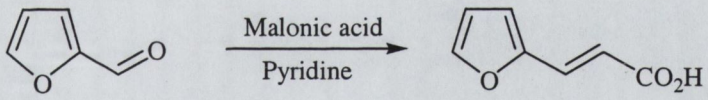
In the cases of toluene and anisole, the "normal" trifluoroacetoxy butanolide **5** was formed indicating that these solvents had no effect on the course of the reaction, **Scheme 2.24**. Diethyl ether however, did have an effect on the outcome of the reaction. Recovery of acid **1** from the aqueous washings suggested that in this case the bicyclic acyloxonium ion **4** did not form due to a competing reaction of ether with the mixed anhydride formed from acid **1**.

In conclusion, the research described in this Chapter indicates that the intramolecular reaction of acid **1** can be manipulated either by the introduction of strong nucleophiles or by the nature of the reaction solvent employed and hence, this methodology creates an efficient route to desirable butanolides.

2.8 Experimental

^{1}H NMR spectra were recorded for solutions in $CDCl_3$ using a Bruker AVANCE DPX-400 MHz spectrometer. Coupling constants (*J*) are recorded in Hz. Assignments were verified by appropriate ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY and ^{13}C-DEPT experiments. IR spectra were recorded for Nujol mulls (N) or for liquid films (L) between sodium chloride plates using a Matteson Genesis spectrometer and were processed using WinFirst software. Mass spectra were obtained using VG Alto Spec (HRMS) and Kratos (FAB) instruments. Melting points (uncorrected) were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} 0.2 mm silica gel plates. Column chromatography was carried out using Merck Keiselgel 60 (70-230 mesh). Organic extracts of reaction products were dried over anhydrous magnesium sulfate. All solvents were dried and distilled before use. Elemental analyses were performed by the Microanalytical Laboratory, University College Dublin.

(*E*)-3-(2'-Furyl)prop-2-enoic acid 7



7

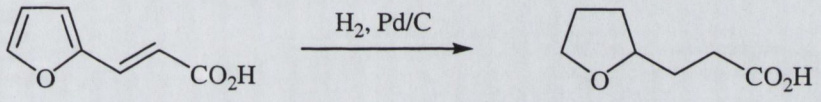
Freshly distilled furfuraldehyde (12 g; 125 mmol), malonic acid (13 g; 125 mmol) and dry pyridine (10 ml) were heated at 100 °C for 2.5 hr. The mixture was then cooled to 0 °C and water (20 ml) and concentrated ammonia (7 ml) were added. The mixture was filtered and the filtrate was acidified to pH 1 with 5.5 M HCl and then cooled to below 5 °C for 1 hr. The crude product was then collected by suction filtration and washed three times with ice-cold water. (*E*)-3-(2'-Furyl)prop-2-enoic acid[10] **7** was obtained as a solid (13.5g; 78%) and recrystallised from aqueous ethanol.

ν_{max} (Neat) 2954 (OH), 2923, 2854, 1695 (C=O), 1627, 1461, 1376, 1228, 1191, 1022 and 754 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 6.34 (1H, J_{trans} 16.0, C-2 C*H*), 6.51 (1H, dd, $^3J_1$ 3.5, $^3J_2$ 2.0, C-4' C*H*), 6.69 (1H, d, *J* 3.5, C-3' C*H*), 7.53 (1H, d, *J* 2.0, C-5' C*H*) and 7.54 (1H, d, J_{trans} 16.0, C-3 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 111.9, 114.4, 115.2, 132.5, 144.8 (5x*C*H), 150.2 (C-2'quat. *C*) and 171.3 (*C*O_2H) ppm

3-(Tetrahydro-2'-furyl)propanoic acid 1



7 **1**

The unsaturated acid **7** (6.56 g; 43 mmol) was dissolved in ethanol (200 ml) and stirred under an atmosphere of hydrogen (1 atm) in the presence of 5% w/w Pd/C (200 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo* to give 3-(tetrahydro-2'-furyl)propanoic acid **1**[11] (6.4 g, 94%) as an oil which had b.p. 110 °C/1 mmHg. Occasionally a neutral side-product was obtained and was separated from the acidic product by washing the mixture with saturated sodium hydrogen carbonate solution followed by extraction into diethyl ether. The clear colourless liquid thus obtained was identified as 1,6-dioxaspiro[4.4]nonan-2-one[2] **9** (up to 20% yield).

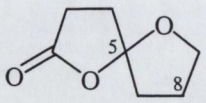
3-(Tetrahydro-2'-furyl)propanoic acid 1

ν_{max} (L) 2966 (OH), 2877, 1779 (C=O), 1710, 1444, 1353, 1261, 1180, 1070 (cyclic ether), 1024, 908 and 788 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.52 (1H, apparent dq, ^2J 12.0, $^3J_1 = {}^3J_2 = {}^3J_3$ 7.5, C-3' CH_a), 1.79-2.08 (4H, m, C-3 CH_2 and C-4' CH_2), 2.00-2.07 (1H, m, C-3' CH_b), 2.43-2.57 (2H, 2 x apparent dt overlapping, dt centred at δ_H 2.47, ^2J 16.5, ^3J 8.0, C-2 CH_a, dt centred at δ_H 2.53, ^2J 16.5, ^3J 8.0, C-2 CH_b), 3.73-3.79 (1H, m, C-5' CH_a), 3.85-3.89 (2H, m, C-2' C*H* and C-5' CH_b) and 10.3 (1H, s, exch. D_2O, CO_2H) ppm

δ_C (100.6MHz; $CDCl_3$) 25.7 (C-4' CH_2), 30.3 (C-3 CH_2), 31.0 (C-2 CH_2), 31.1 (C-3' CH_2), 67.8 (C-5' CH_2), 78.3 (C-2' CH) and 178.2 (CO_2H) ppm

1,6-Dioxaspiro[4.4]nonan-2-one 9



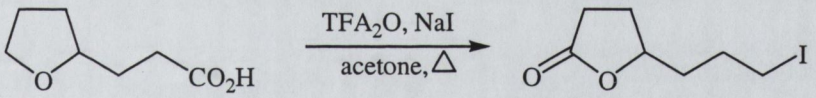
9

ν_{max} (L) 2985, 2960, 2896, 1774 (C=O), 1457, 1353, 1238, 1180, 1085 (cyclic ether), 1024, 970, 908, 877 and 790 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.98 (2H, m, C-8 CH_a and C-9 CH_a), 2.15 (1H, m, C-8 CH_b), 2.35 (3H, m, C-3 or C-4 CH_2 and C-9 CH_b), 2.54 (1H, ddd, ^2J 17.5, $^3J_1$ 8.0, $^3J_2$ 4.5, C-3 or C-4 CH_a), 2.79 (1H, m, C-3 or C-4 CH_b), 4.01 (1H, m, C-7 CH_a) and 4.10 (1H, m, C-7 CH_b) ppm

δ_C (100.6 MHz; $CDCl_3$) 23.1 (C-8 CH_2), 28.7 (C-3 CH_2), 30.8 (C-9 CH_2), 35.6 (C-4 CH_2), 68.6 (C-7 CH_2), 115.7 (C-5 C) and 175.4 (C-2 C=O) ppm

"One-pot" conversion of the acid 4 into 5-(3'-iodopropyl)dihydro-3(2*H*)-furanone 8



1 **8**

The acid **1** (1.5 g; 10 mmol) and dry sodium iodide (4.68 g; 30 mmol) were dissolved in acetone (50 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (2.4 g; 11 mmol) was added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature, the mixture was heated at reflux for 4 hr. The volume of the acetone reaction mixture was then partly reduced by evaporation under reduced pressure. The residue was then diluted with ether and washed sequentially with water, 5% aqueous sodium hydrogen carbonate, 10% sodium thiosulfate and brine, and then dried and evaporated to give 5-(3'-iodopropyl)dihydro-3(2*H*)-furanone **8**[3] (1.85 g, 70%) as a translucent yellow oil.

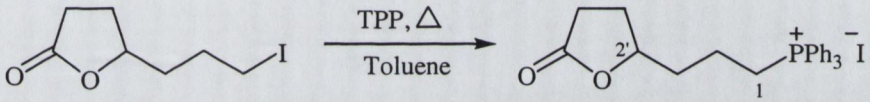
ν_{max} (L) 2935, 1774 (lactone C=O), 1457, 1344, 1218, 1176, 1022 and 914 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.78-1.86 (2H, m, C-1' CH_2), 1.87-1.99 (2H, m, C-2' CH_a and C-4 CH_a), 1.99-2.13 (1H, m, C-2' CH_b), 2.33-2.41 (1H, apparent sextet, ^2J 13.0, $^3J_1 = {}^3J_2 = {}^3J_3$ 6.5, C-4 CH_b), 2.54-2.58 (2H, m, C-3 CH_2), 3.20-3.27 (2H, m, C-3' CH_2) and 4.49-4.55 (1H, m, C-5 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 5.6 (C-3' *C*H_2), 27.9 (C-4 *C*H_2), 28.6 (C-3 *C*H_2), 29.2 (C-2' *C*H_2), 36.4 (C-1' *C*H_2), 79.6 (C-5 *C*H) and 176.3 (lactone *C*=O) ppm.

HRMS (FAB) *m/z* 254.9878: *calculated for* $[C_7H_{11}O_2I + H]^+$ 254.9894

[3-(5'-Oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide 13



8 **13**

The iodolactone **8** (0.92 g; 3.6 mmol) was dissolved in toluene (30 cm^3) and triphenylphosphine (1.05 g; 4 mmol) was added with stirring. The solution was then heated at reflux for 5 hr. Excess triphenylphosphine was then removed from the resultant white solid by decanting the supernatant toluene and then heating the white precipitate with fresh toluene. This process was repeated twice and then the solid thus obtained was dried at reduced pressure to yield the phosphonium salt **13** (1.92 g, 72%). An analytical sample of **13** was obtained by recrystallisation from ethyl acetate (m.p. 148-150 °C).

ν_{max} (N) 2952, 2923, 2853, 1760 (C=O), 1609, 1586, 1483, 1461, 1437, 1405, 1377, 1365, 1315, 1274, 1229, 1187, 1159, 1110, 1044, 1026, 996, 969, 943, 892, 787 and 723 cm^{-1}

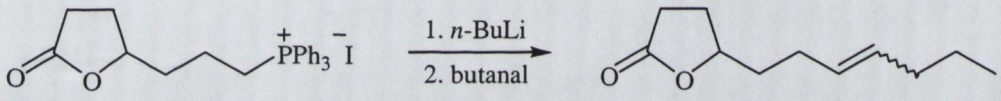
δ_H (400 MHz; $CDCl_3$) 1.76-1.94 (4H, m, C-3 CH_a, C-2 CH_2, C-3' CH_a), 2.39-2.54 (4H, m, C-3 CH_b, C-4' CH_2, C-3' CH_b), 3.62-3.73 (1H, m, C-1 CH_a), 4.06-4.17 (1H, m, C-1 CH_b), 4.69-4.78 (1H, m, C-2' C*H*), 7.71-7.75 and 7.80-7.84 (6H and 9H, 2 x m, Ar H 15xC*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 19.4 (d, $J_{P,C}$ 3.8, C-2 CH_2), 22.5 (d, $J_{P,C}$ 51.5, C-1 CH_2), 28.0 (C-3' CH_2), 28.7 (C-4' CH_2), 35.5 (d, $J_{P,C}$ 16.5, C-3 CH_2), 80.1 (C-2' CH), 117.5 (d, $J_{P,C}$ 85.5,Ar C *C*), 130.1 (d, $J_{P,C}$ 11.6, Ar C *C*H), 133.3 (d, $J_{P,C}$ 9.7, Ar C *C*H), 134.7 (d, $J_{P,C}$ 2.9, Ar C *C*H) and 176.8 (*C*=O) ppm

δ_P (162 MHz; $CDCl_3$) 25.5 (-P^+-$(C_6H_5)_3$) ppm

[*Calculated* for $C_{25}H_{26}IO_2P$: C 58.13, H. 5.04; *found* C 57.94, H 4.97%]

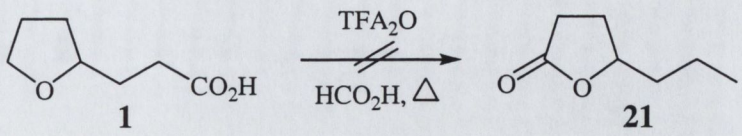
Attempted Wittig reaction with butanal of the ylid derived from [3-(5'-oxotetrahydro-2'-furyl)propyl]triphenylphosphonium iodide 13



13 **40**

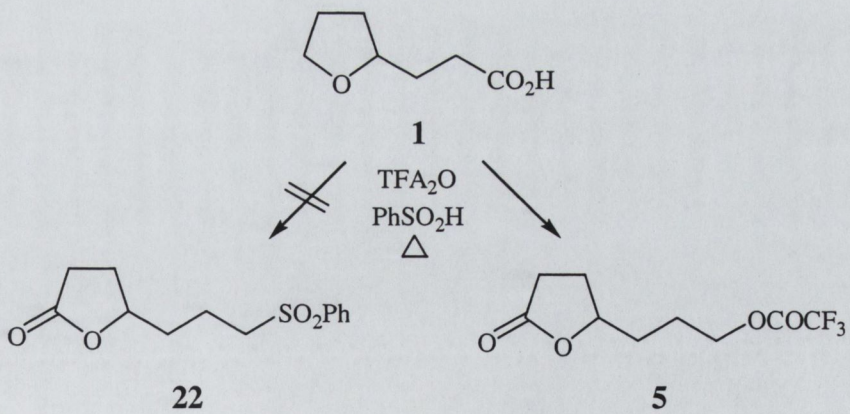
n-BuLi (2.5 M; 0.2 ml; 0.46 mmol) was added to a suspension of the phosphonium salt **13** in dry THF under an atmosphere of nitrogen and at –80 °C. After 0.5 hr at this temperature, butanal (0.033 g; 0.3 mmol) was added and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride solution. Ether and water were then added and the mixture was extracted (x3) with ether. The combined organic extracts were then washed with brine, dried over $MgSO_4$ and evaporated. The complex mixture thus obtained was purified by column chromatography, however, identification of any of the components was not achieved.

Treatment of the mixed anhydride derived from 3-(tetrahydro-2'-furyl)propanoic acid 1 with formic acid



The acid **1** (0.5 g; 3.47 mmol) was dissolved in chloroform (15 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (0.8 g; 3.8 mmol) was added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature formic acid (0.5 g; 10.4 mmol) was added and the mixture was heated at reflux for 2 hr. Ether and water were then added and the ether extract was washed sequentially with 5% sodium hydrogen carbonate and brine, and then dried and evaporated. Recovery of a neutral crude product was minimal and therefore the aqueous washings were examined and found to contain the starting acid **1** (0.25 g; 50% recovery). Butanolide **21** was not formed.

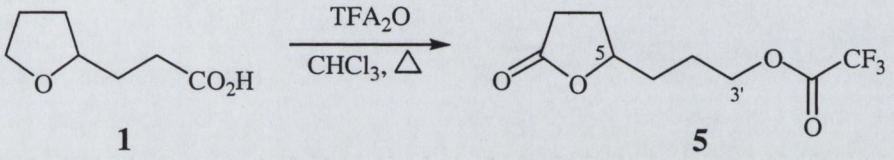
Treatment of the mixed anhydride derived from 3-(tetrahydro-2'-furyl)propanoic acid 1 with benzenesulfinic acid



The acid **1** (0.44 g; 3.05 mmol) was dissolved in chloroform (10 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (0.7 g; 3.35 mmol) was added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature benzenesulfinic acid (1.3 g; 9.14 mmol) was added and the mixture was refluxed for 2 hr. Ether and water were then added and the ether extract was washed sequentially with 5% sodium hydrogen carbonate and

brine, and then dried and evaporated. The crude product obtained was identified as trifluoroacetoxy butanolide **5** (data given below). The sulfonyl butanolide **22** was not formed.

Treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in chloroform



1 **5**

The acid **1** (0.2 g; 1.3 mmol) was dissolved in dry chloroform (9 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (0.32 g; 1.5 mmol) was then added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature, the mixture was heated at reflux for 4 hr. Ether and water were then added and the ether extract was washed sequentially with 5% aqueous sodium hydrogen carbonate and brine, and then dried and evaporated to give 5-(3'-trifluoroacetoxypropyl)dihydro-3(2*H*)-furanone **5** (0.23 g, 70%) as a translucent yellow liquid.

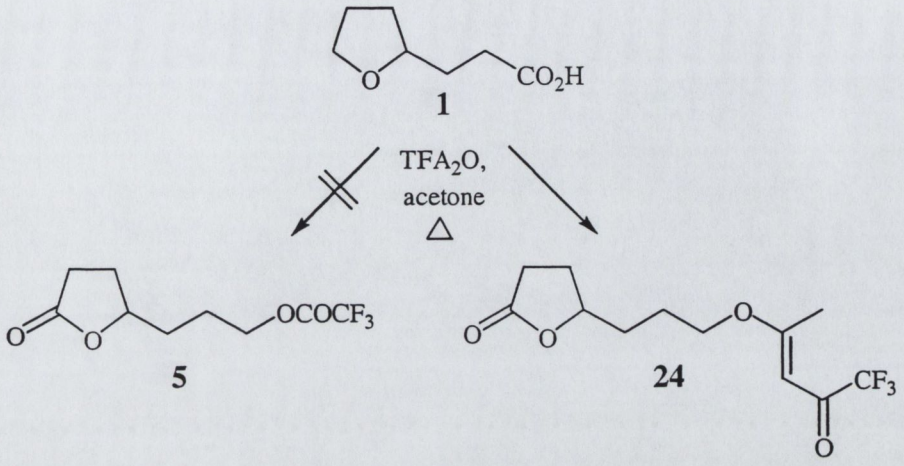
ν_{max} (L) 2954, 1779 (overlapping C=O absorptions), 1463, 1405, 1353, 1220, 1164, 1022, 968, 910, 777 and 730 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.78-2.07 (5H, m, C-4 CH_a, C-1' CH_2 and C-2' CH_2), 2.34-2.43 (1H, m, C-4 CH_b), 2.55-2.59 (2H, 2 x overlapping ddd centred at δ_H 2.56, ^2J 9.0, $^3J_1$ 6.5, $^3J_2$ 1.0, C-3 CH_a and δ_H 2.58, ^2J 9.0, $^3J_1$ 7.0, $^3J_2$ 1.0, C-3 CH_b), 4.37-4.48 (2H, 2 x overlapping apparent dt centred at δ_H 4.41, $^2J = {}^3J_1$ 11.0, $^3J_2$ 6.5, C-3' CH_a, and δ 4.45, $^2J = {}^3J_1$ 11.0, $^3J_2$ 6.0, C-3' CH_b) and 4.49-4.56 (1H, m, C-5 C*H*) ppm

δ_C (100.6MHz; $CDCl_3$) 24.5 (C-2' *C*H_2), 27.9 (C-4 *C*H_2), 28.6 (C-3 *C*H_2), 31.8 (C-1' *C*H_2), 67.3 (C-3' *C*H_2), 79.7 (C-5 *C*H) and 176.1 (lactone *C*=O) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.6 (CF_3) ppm

Treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in acetone



The acid **1** (0.15 g; 1.0 mmol) was dissolved in acetone (9 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (0.48 g; 2.2 mmol) was then added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature, the mixture was refluxed for 4 hr. The volume of the reaction mixture was then partly reduced by evaporation at reduced pressure. The residue was diluted with ether and washed sequentially with water, 5% aqueous sodium hydrogen carbonate and brine, and then dried and evaporated. The crude product was purified by column chromatography using hexane : ethyl acetate 75:25. (*E*)-5-[3'-(4'',4'',4''-Trifluoro-1''-methyl-3''-oxobut-1''-enyloxy)propyl] dihydro-3(2*H*)-furanone **24** (0.29 g, 64%) was obtained as a translucent yellow liquid.

ν_{max} (L) 2954, 2927, 1774 (overlapping C=O absorptions), 1702 (C=C), 1577, 1465, 1421, 1361, 1322, 1259, 1184, 1141, 1103, 1043, 970, 914, 881, 804 and 727 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.75-2.05 (5H, m, C-4 CH_a, C-1' CH_2, C-2' CH_2), 2.35-2.44 (1H, m, C-4 CH_b), 2.43 (3H, s, CH_3), 2.57-2.61 (2H, m, C-3 CH_2), 3.93-4.05 (2H, m, C-3' CH_2), 4.52-4.59 (1H, ap. quintet, *J* 6.5, C-5 C*H*) and 5.68 (1H, s, C-2'' C*H*) ppm

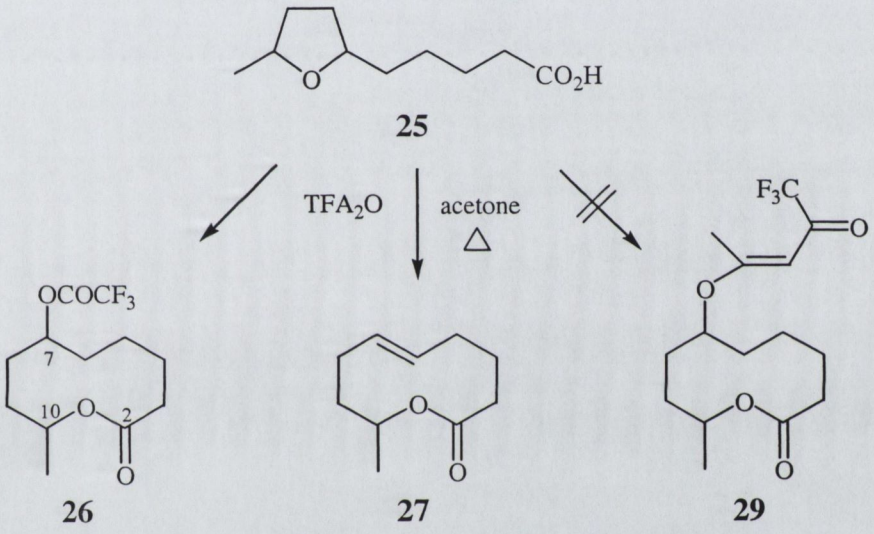
δ_C (100.6 MHz; $CDCl_3$) 21.0 (*C*H_3), 24.5 (C-2' *C*H_2), 27.8 (C-4 *C*H_2), 28.5 (C-3 *C*H_2), 31.9 (C-1' *C*H_2), 68.9 (C-3' *C*H_2), 80.1 (C-5 *C*H), 91.9 (C-2'' *C*H), 116.5 (q,

$J_{F,C}$ 291.5, CF_3), 176.4 (C-2 C=O), 178.5 (q, $J_{F,C}$ 33.0, $COCF_3$) and 180.2 (C-1'' C) ppm

δ_F (376.3 MHz; $CDCl_3$) –78.9 (CF_3) ppm

HRMS (FAB) *m/z* 281.0997: *calculated for* $[C_{12}H_{15}O_4F_3 + H]^+$ 281.1010

Treatment of 5-(tetrahydro-2'-furyl)pentanoic acid 25 with trifluoroacetic anhydride in acetone



The acid **25** (0.2 g; 1.1 mmol) was dissolved in acetone (15 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (0.5 g; 2.4 mmol) was then added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature, the mixture was heated at reflux for 4 hr. The volume of the acetone reaction mixture was then partly reduced by evaporation at reduced pressure. The residue was diluted with ether and washed sequentially with water, 5% aqueous sodium hydrogen carbonate and brine, and then dried and evaporated. Purification of the crude product by column chromatography using 95:5 hexane : ethyl acetone resulted in the isolation of two products. The first component to elute was identified as (*E*)-10-methyl-6,7-dihydro-oxecin-2-one[9] **27** (0.028 g; 15%; clear colourless oil). The next compound to elute was identified as 10-methyl-7-trifluoroacetoxy-oxecan-2-one[9] **26** (0.093 g; 30%; clear colourless oil; 2:1 major:minor isomers). Lactone **29** was not formed.

(*E*)-10-Methyl-6,7-dihydro-oxecin-2-one 27

ν_{max} (L) 2977, 2931, 2850, 1732 (lactone carbonyl), 1442, 1361, 1334, 1252, 1198, 1161, 1125, 1075, 1044, 822 and 731 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.19 (3H, d, *J* 6.5, CH_3), (3xm, 3H, 4H, 3H centred at 1.62, 2.01, 2.28 respectively, C-3, C-4, C-5, C-8 and C-9 5xCH_2), 5.16 (1H, m, C-10 C*H*), 5.26 (1H, m, C-6 or C-7 C*H*) and 5.49 (1H, ddd, ^2J 15.0, $^3J_1$ 11.0, $^3J_2$ 2.5, C-6 or C-7 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 21.6 (*C*H_3), 26.0, 31.6, 33.9, 34.4, 34.9 (C-3, C-4, C-5, C-8 and C-9, 5x*C*H_2), 71.0 (C-10 *C*H), 128.2, 133.2 (C-6 and C-7 *C*H) and 175.6 (C-2 *C*=O)

10-Methyl-7-trifluoroacetoxy-oxecan-2-one 26

ν_{max} (L) 2961, 2875, 1780 (trifluoroacetoxy carbonyl), 1731 (lactone carbonyl), 1636, 1542, 1454, 1392, 1365, 1333, 1260, 1225, 1165, 1122, 1070, 1048, 1011, 971, 868, 821, 798, 778 and 727 cm^{-1}

Major Isomer

δ_H (400 MHz; $CDCl_3$) 1.33 (3H, d, *J* 6.5, CH_3), 1.42-1.90 (8H, m), 1.95-2.16 (2H, m), 2.31-2.45 (2H, m, C-3 CH_2), 4.92-4.99 (1H, m, C-10 C*H*) and 5.02-5.10 (1H, m, C-7 C*H*) ppm

Minor Isomer

δ_H (400 MHz; $CDCl_3$) 1.36 (3H, d, *J* 6.5, CH_3), 1.42-1.90 (8H, m), 1.95-2.16 (2H, m), 2.21 (1H, m, C-3 CH_a), 2.60 (1H, ddd, ^2J 16.0, $^3J_1$ 6.0, $^3J_2$ 2.5, C-3 CH_b), 5.02-5.10 (1H, m, C-10 C*H*) and 5.48-5.52 (1H, m, C-7 C*H*) ppm

Major Isomer

δ_C (100.6 MHz; $CDCl_3$) 20.2 (*C*H_3), 21.5, 22.5, 26.5, 28.2, 28.3 (5x*C*H_2), 34.2 (C-3 *C*H_2), 71.2 (C-10 *C*H) 77.8 (C-7 *C*H), 114.1 (q, *J* 284, CO*C*F_3), 156.6 (q, *J* 41.5, *C*OCF_3) and 173.2 (C-2 *C*=O) ppm

Minor Isomer

δ_C (100.6 MHz; $CDCl_3$) 18.2 (CH_3), 19.7, 24.0, 28.8, 29.1, 29.2 (5xCH_2), 34.1 (C-3 CH_2), 71.0 (C-10 *C*H), 77.1 (C-7 *C*H) and 172.6 (C-2 *C*=O) ppm

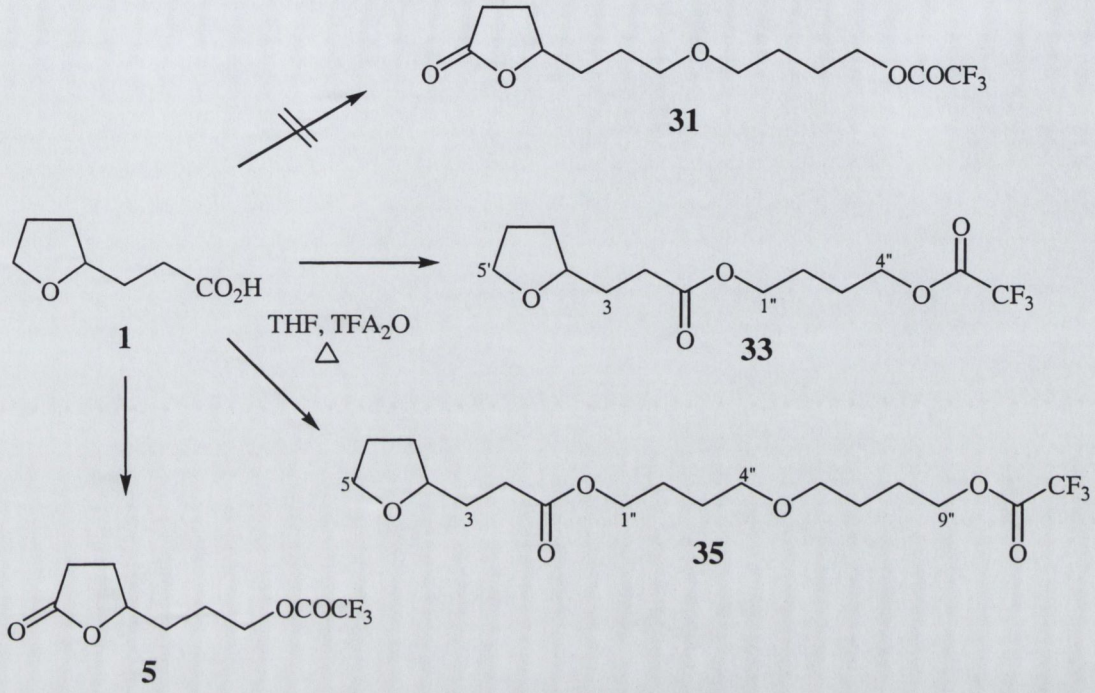
δ_F (376.3 MHz; $CDCl_3$) –75.8 ($COCF_3$) ppm

HRMS *m/z* (CI) 305.0988: *calculated for* $[C_{12}H_{17}O_4F_3 + Na]^+$ 305.0977

General procedure for the treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in a variety of solvents

The acid **1** (0.2 g; 1.3 mmol) was dissolved in the solvent (9 cm^3) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (0.32 g; 1.5 mmol) was then added with stirring at such a rate that the temperature did not rise above 0 °C. After a further 0.5 hr at this temperature, the mixture was refluxed. Ether and water were then added and the ether extract was washed sequentially with 5% aqueous sodium hydrogen carbonate and brine, and then dried and evaporated.

Treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in tetrahydrofuran



Following the general procedure described above, the reaction mixture in THF (containing acid **1** (0.15 g; 1.0 mmol) and 1.1 equivalents of TFA_2O) was heated at reflux for 6 hr and then worked up in the usual way. Purification of the crude product by column chromatography using hexane : ethyl acetate 85:15 resulted in the isolation of three products. The first component to elute was identified as 4''-trifluoroacetoxybutyl 3-(tetrahydro-2'-furyl)propanoate **33** (0.022 g; 7%; clear oil). The second component to elute was identified as 9''-trifluoroacetoxy-5''-oxanonyl 3-(tetrahydro-2'-furyl)propanoate **35** (0.012 g; 3%; clear oil). The third and final compound to be isolated was 5-(3'-trifluoroacetoxypropyl)dihydro-3(2*H*)-furanone **5** (0.062 g; 25%; clear yellow oil). Dihydro-3(2*H*)-furanone **31** was not formed.

4''-Trifluoroacetoxybutyl 3-(tetrahydro-2'-furyl)propanoate 33

ν_{max} (L) 2952, 2871, 1785 (trifluoroacetoxy C=O), 1735 (C=O), 1353, 1220, 1164, 1072, 1025 and 777 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.49 (1H, apparent dq, ^2J 11.5, $^3J_1 = {}^3J_2 = {}^3J_3$ 7.5, C-3' CH_a), 1.73-1.94 (8H, m, C-3, C-4', C-2'' and C-3'' 4 x CH_2), 1.96-2.05 (1H, m, C-3' CH_b), 2.36-2.51 (2H, 2 x ddd overlapping centred at δ_H 2.40, ^2J 16.0, $^3J_1$ 8.0, $^3J_2$

7.0, C-2 CH_a and δ_H 2.47, ddd, ^2J 16.0, $^3J_1$ 8.5, $^3J_2$ 7.0, C-2 CH_b), 3.69-3.75 (1H, m, C-5' CH_a), 3.83-3.88 (2H, m, C-2' C*H* and C-5' CH_b), 4.13 (2H, t, *J* 6.5, C-1'' or C-4'' CH_2) and 4.40 (2H, t, *J* 6.5, C-1'' or C-4'' CH_2) ppm

δ_C (100.6 MHz; $CDCl_3$) 24.4, 24.5, 25.2 (C-2'', C-3'' and C-4' 3x*C*H_2), 30.2, 30.6, 30.7 (C-2, C-3' and C-3 3x*C*H_2), 62.9 (C-1'' or C-4'' *C*H_2), 67.1, 67.2 (C-1'' or C-4'' *C*H_2 and C-5' *C*H_2), 77.7 (C-2' C*H*) and 173.0 (C-1 *C*=O) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.6 (CO*C*F_3) ppm

HRMS *m/z* (FAB) 313.1267: *calculated for* $[C_{13}H_{19}O_5F_3 + H]^+$ 313.12802

9''-Trifluoroacetoxy-5''-oxanonyl 3-(tetrahydro-2'-furyl)propanoate 35

ν_{max} (L) 2952, 2871, 1785 (trifluoroacetoxy carbonyl), 1735, (ester carbonyl), 1457, 1353, 1220, 1164, 1072, 1025, 943, 777 and 730 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.49 (1H, apparent dq, ^2J 12.0, $^3J_1 = {}^3J_2 = {}^3J_3$ 8.0, C-3' CH_a), 1.62-1.75 (6H, m, C-2'' or C-8'', C-3'' and C-7'' 3x*C*H_2), 1.81-1.95 (6H, m, C-2'' or C-8'', C-3 and C-4' 3x*C*H_2), 1.97-2.07 (1H, m, C-3' CH_b), 2.36-2.51 (2H, 2 x apparent dt centred at δ_H 2.39, ^2J 15.5, $^3J_1 = {}^3J_2$ 8.0, C-2 CH_a and δ_H 2.47, ^2J 15.5, $^3J_1 = {}^3J_2$ 8.0, C-2 CH_b), 3.42-3.47 (4H, m, C-4'' CH_2 and C-6'' CH_2), 3.71-3.76 (1H, m, C-5' CH_a), 3.83-3.88 (2H, m, C-2' C*H* and C-5' CH_b), 4.11 (2H, t, *J* 6.5, C-1'' or C-9'' CH_2) and 4.40 (2H, t, *J* 6.5, C-1'' or C-9'' CH_2) ppm

δ_C (100.6 MHz; $CDCl_3$) 25.2, 25.5, 25.6, 25.7, 26.1, 30.6 (C-3, C-4', C-2'', C-3'', C-7'' and C-8'' 6x*C*H_2), 31.1 (C-3' *C*H_2), 31.1 (C-2 *C*H_2), 63.7 (C-1'' or C-9'' *C*H_2), 67.2 (C-5' *C*H_2), 67.6 (C-1'' or C-9'' *C*H_2), 69.4, 69.9 (C-4'' and C-6'' 2x*C*H_2), 77.7 (C-2' *C*H) and 173.1 (C-1 *C*=O) ppm

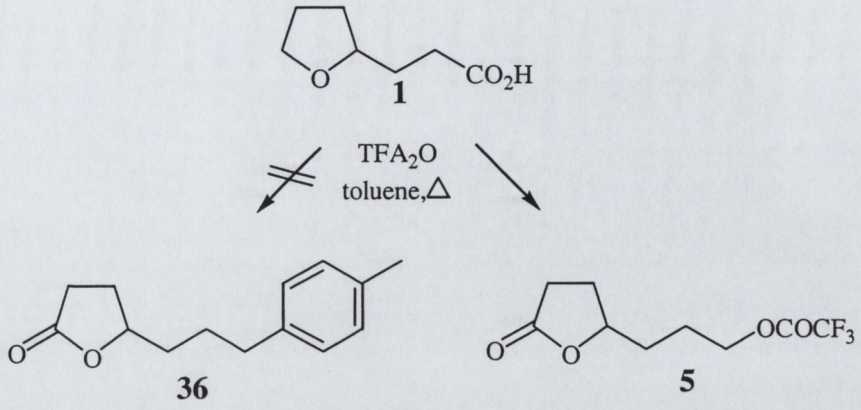
δ_F (376.3 MHz; $CDCl_3$) – 75.6 (CO*C*F_3) ppm

HRMS *m/z* (FAB) 385.1842: *calculated for* $[C_{17}H_{28}O_6F_3 + H]^+$ 385.1852

5-(3'-Trifluoroacetoxypropyl)dihydro-3(2*H*)-furanone 5

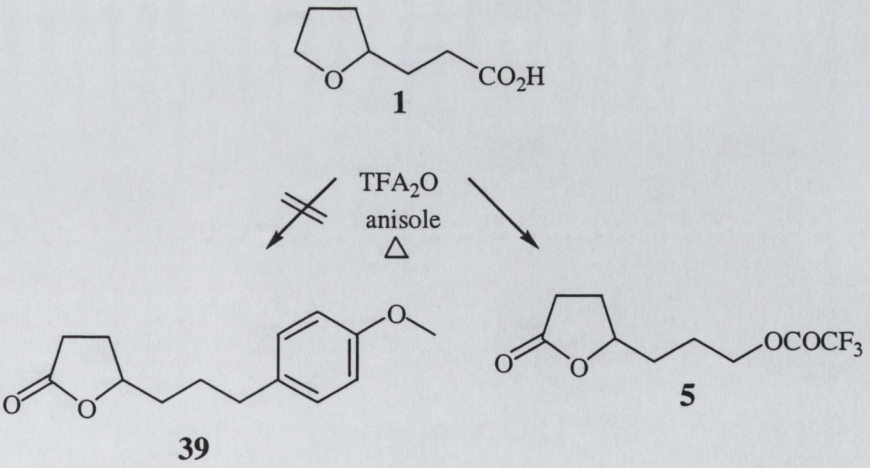
Spectroscopic data for this compound are given above.

Treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in toluene



Following the general procedure described above, the reaction mixture in toluene (containing acid **1** (0.15 g; 1.0 mmol) and 1.1 equivalents of TFA_2O) was heated at reflux for 6 hr and then worked up in the usual way. NMR analysis of the sole product formed identified it as 5-(3'-trifluoroacetoxypropyl)dihydro-3(2*H*)-furanone **5** (0.173 g; 70%), (data given previously). The dihydro-3(2*H*)-furanone **36** was not formed.

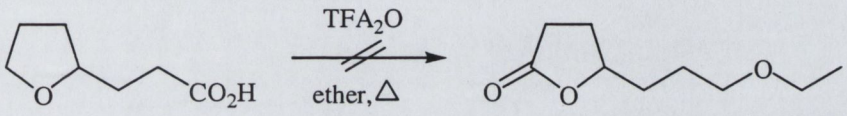
Treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in anisole



Following the general procedure described above, the reaction mixture in anisole (containing acid **1** (0.15 g; 1.0 mmol) and 1.1 equivalents of TFA_2O) was heated at reflux for 6 hr and then worked up in the usual way. NMR analysis of the crude

product identified it as 5-(3'-trifluoroacetoxypropyl)dihydro-3(2*H*)-furanone **5** (0.168 g; 67%), (data given previously). The dihydro-3(2*H*)-furanone **39** was not formed.

Treatment of 3-(tetrahydro-2'-furyl)propanoic acid 1 with trifluoroacetic anhydride in diethyl ether



1 **38**

Following the general procedure described above, the reaction mixture (containing acid **1** (0.15 g; 1.0 mmol) and 1.1 equivalents of TFA_2O in diethyl ether) was heated at reflux for 6 hr and then worked up in the usual way (which involved washing with sodium hydrogen carbonate), however, recovery of a neutral product was marginal. Acidification of the aqueous washings resulted in the recovery of acid **1**.

2. 9 References

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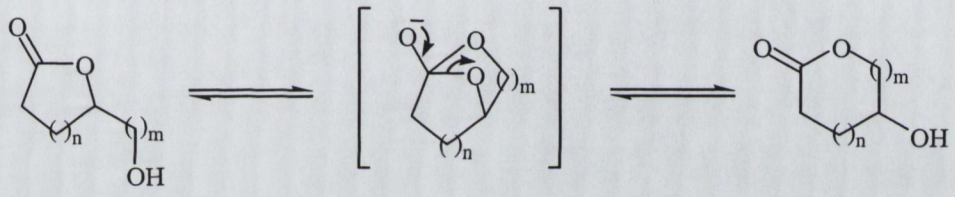
Chapter 3

Ring-enlargement *via* Translactonisation

3.1 Translactonisation reactions

In 1977, Corey *et al.* carried out pioneering research in the area of translactonisation reactions, the general mechanism of which is outlined in **Equation 3.1**.[1] This intramolecular transesterification reaction can be catalysed either by acid or by base and the reversibility of the reaction implies that it proceeds under thermodynamic control, therefore the more stable product will predominate. Thus, for the case where n = 1, the five-membered lactone **1** is relatively more stable then a larger cycle **2** and hence the observed transformation is ring contraction rather then ring expansion.[1] In other cases where medium-ring lactones, n = 4-7, are involved, the driving force for any transformation is the release of ring strain resulting in the formation of a relatively more stable macrocyclic ring.

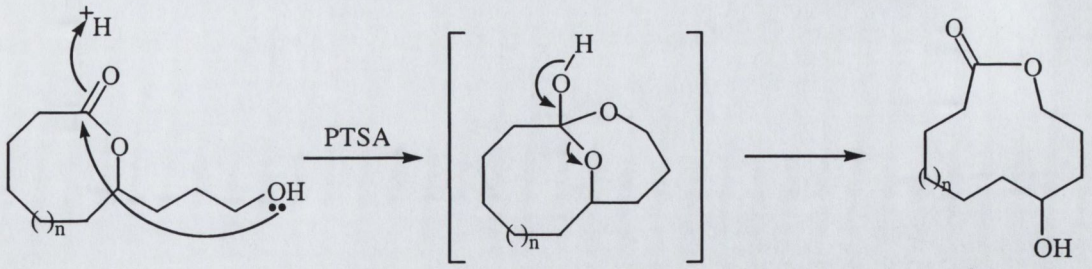


1 n = 1, m = 1- 4 **2** n = 1, m = 1- 4

Equation 3.1

An additional influencing factor associated with these rearrangement reactions is the length of side chain to be incorporated into the ring system. The reaction rate decreases with increasing chain length, m = 1, 2, 3, 4, due to the necessary formation of increasingly large five-, six-, seven-, eight-membered intermediates.

Thus, the less thermodynamically stable nine-membered hydroxy-lactone **3** was found to react rapidly in the presence of *p*-toluenesulfonic acid (1 mol%) at room temperature forming the corresponding, more stable, twelve-membered lactone **4** *via* a seven-membered intermediate in 97% yield after two hours, **Scheme 3.1**.[1] In comparison, the eight-membered hydroxy-lactone **5** undergoes ring expansion (3 mol% *p*-toluenesulfonic acid in methylene chloride, 24 hr, 0 °C) somewhat more slowly, to form the eleven-membered lactone **6** in 69% yield, with the formation of by-products, possibly linear polyesters.[1]

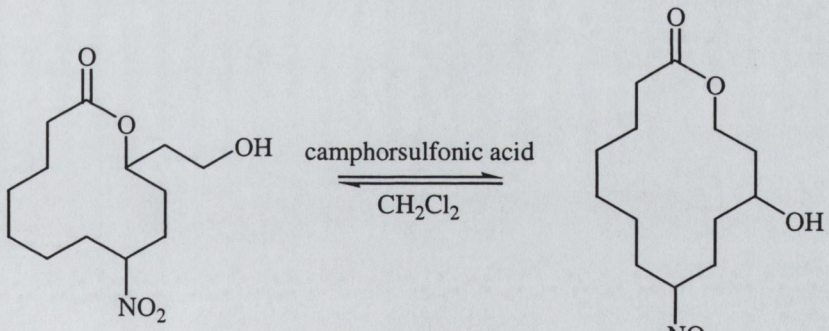


3 n = 2
5 n = 1

4 n = 2
6 n = 1

Scheme 3.1

An attempt by Corey *et al.* to incorporate four carbon atoms into a ring-enlarged lactone *via* an unfavourable eight-membered intermediate failed.[1] It follows that a reaction involving a five- or six-membered intermediate, originating from a hydroxymethyl or 2-hydroxyethyl chain, should proceed smoothly. However, the outcome of the reaction is determined thermodynamically regardless of the length of the hydroxyalkyl chain. This was confirmed by Hesse and co-workers in the case of the twelve-membered lactone **7**.[2] When this lactone **7** was treated with camphorsulfonic acid, a mixture of the starting material and the fourteen-membered lactone **8** was obtained, **Scheme 3.2**. In this expansion by two carbon atoms, a relatively favourable six-membered intermediate is involved, however, the release of ring strain is somewhat insignificant and therefore both compounds remain in a thermodynamic equilibrium in approximately 1:1 ratio.

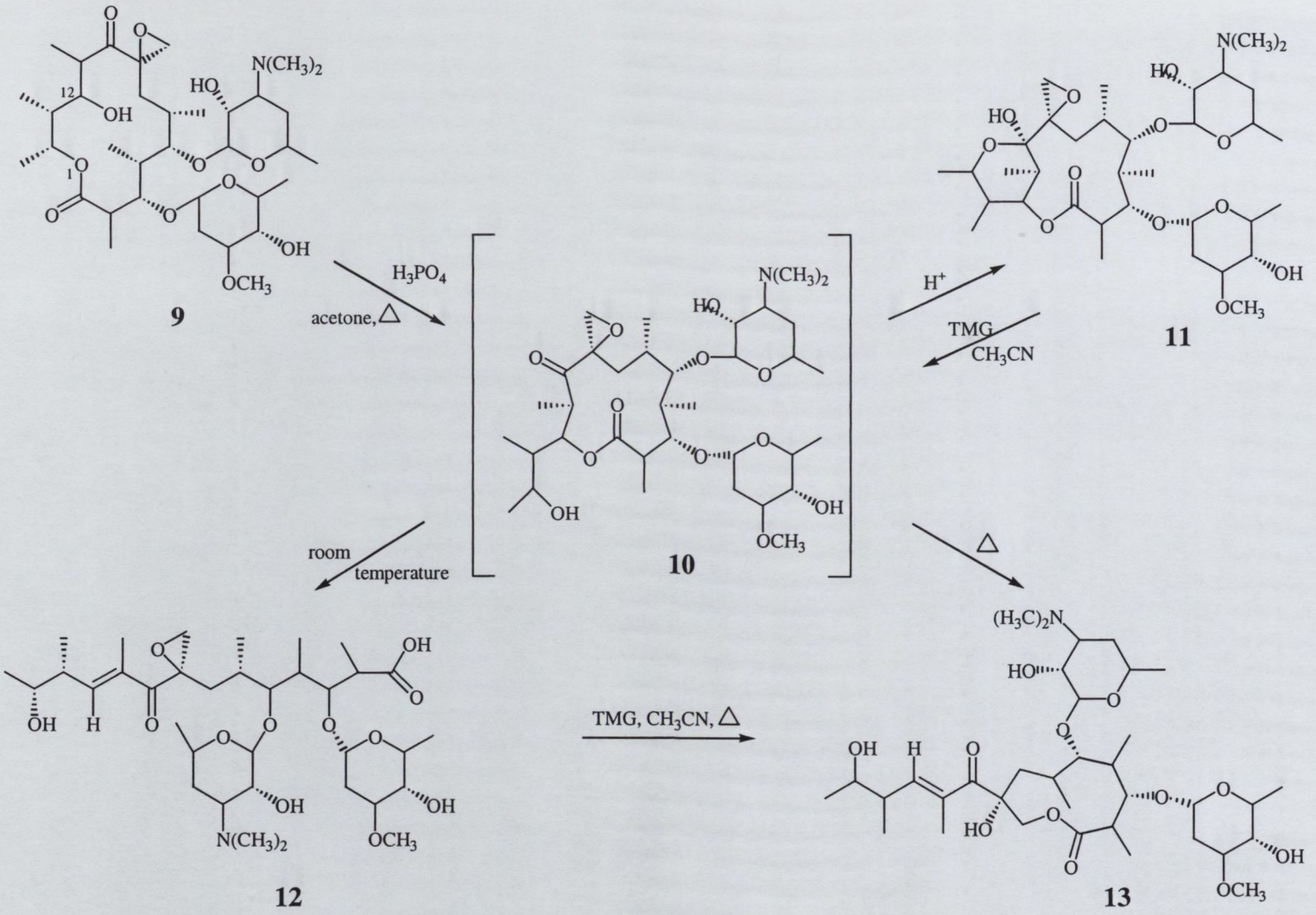


7 **8**

Scheme 3.2

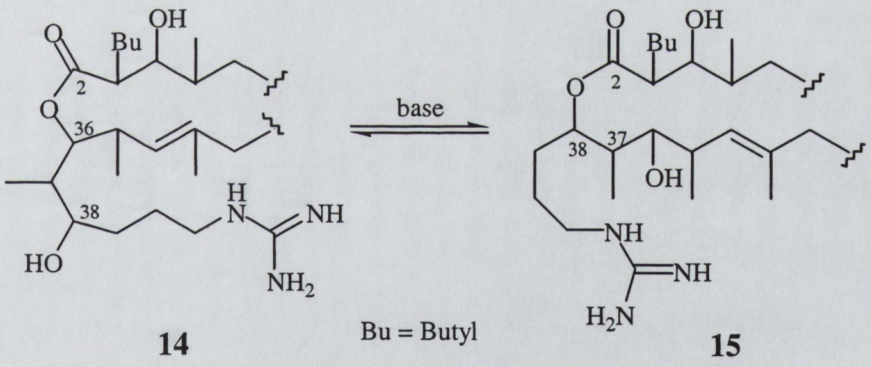
Considerable research has been carried out on translactonisation processes in naturally-occurring lactones. Medium-ring lactones can be obtained *via* the ring-contraction of larger lactones. Nagel *et al.* describe the syntheses of ten- and twelve-membered ring lactones from the fourteen-membered antibiotic lactone

oleandomycin **9**, **Scheme 3.3**.[3] When the phosphate salt of oleandomycin is refluxed in acetone, the twelve-membered lactone **11** is obtained. The mechanism involved in the formation of **11** is postulated to proceed *via* intermediate **10** which involves translactonisation *via* the C-12 alcohol. The translactonisation was found to be irreversible. However, attempts to regenerate oleandomycin from the twelve-membered ring lactone under basic conditions led to a further unexpected rearrangement. Addition of excess tetramethylguanidine (TMG) to a suspension of twelve-membered lactone **11** in refluxing acetonitrile induced the formation of the ten-membered lactone **13**. It was shown that the rearrangement proceeded first with formation of the polar ketone intermediate **10** *via* hemiketal ring opening. On continued refluxing, β-elimination of the lactone resulted in the formation of the acid intermediate **12**. This intermediate subsequently underwent lactonisation through the epoxide functionality resulting in the formation of ten-membered lactone **13**.


9
H_3PO_4
acetone, △
10
H^+
TMG
CH_3CN
11
room temperature
12
TMG, CH_3CN, △
△
13

Scheme 3.3

Translactonisation processes have proved valuable in the search for techniques to enhance the isolation of desired compounds. For example, primycin **14**, a non-polyene macrolide antibiotic complex with a thirtyfive-membered lactone ring containing a side chain with a terminal guanidine moiety, has been found to consist of a mixture of several structurally related compounds.[4] Primycin sulfate is the active ingredient of EBRIMYCIN® antiseptic gel, however, separation and purification is difficult due to poor solubility of the sulfate end product of the fermentation process used to obtain this desirable lactone. It was discovered that, on treatment with nucleophiles, primycin is transformed in a reversible reaction into water- and alcohol-soluble compounds containing a thirtyseven-membered lactone ring, **Scheme 3.4**. These so-called pseudo-primycins **15**, are formed by intramolecular transesterification between the C-38 hydroxyl group and the lactone function and, due to the reversible nature of the reaction, offer a solution to the solubility problem encountered with the isolation of the desired primycin sulfate. Additionally, pseudo-primycins represent a new generation of thirtyseven-membered macrolides that possess a pronounced tendency toward gel formation, an extremely useful tool in drug formulation.[5]

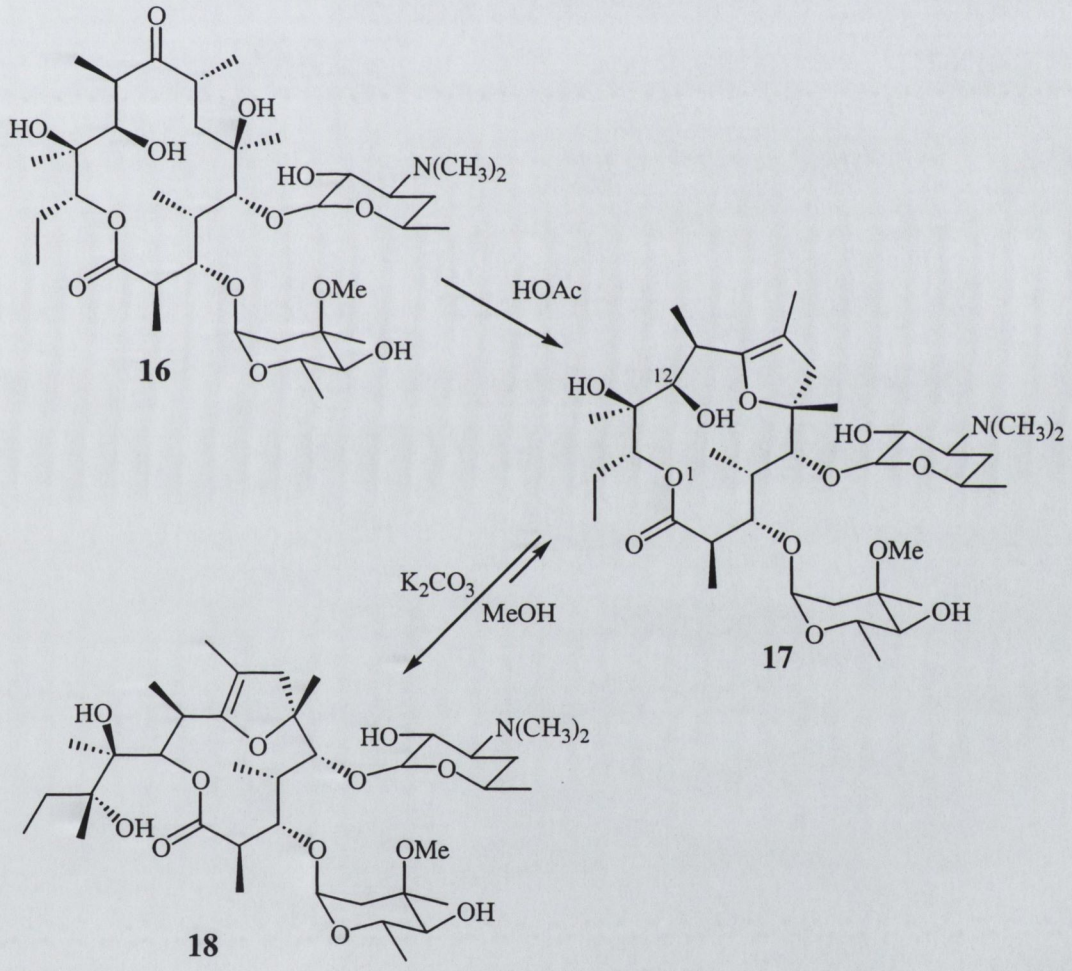


14 Bu = Butyl **15**

Scheme 3.4

The fourteen-membered naturally-occurring erythromycin lactones have been the subject of steady investigation for more than 50 years, thus, it is not surprising that substantial research has been carried out on the translactonisation processes that they undergo. Kirst *et al.*[6] realised the significance of the fourteen-membered lactone as a precursor to potentially useful antibiotics and reported the synthesis of several ring-contracted analogues. It has been established that erythromycin **16** undergoes acid-catalysed conversion to its 8,9-anhydro-6,9-

hemiketal derivative **17**, **Scheme 3.5**.[7] Intramolecular transesterification between the lactone group and the C-12 hydroxyl group of **17** was achieved under a wide variety of acidic, basic or thermal (refluxing toluene) conditions to yield the twelve-membered enol ether derivative **18**. The formation of the dihydrofuran ring overcomes the factors disfavouring twelve-membered rings and hence ring-contraction resulting in a relatively less stable product is achieved. Similar work was carried out by Kibwage *et al.*[8] Translactonisation processes have also been demonstrated for various derivatives of erythromycin.[9]



Scheme 3.5

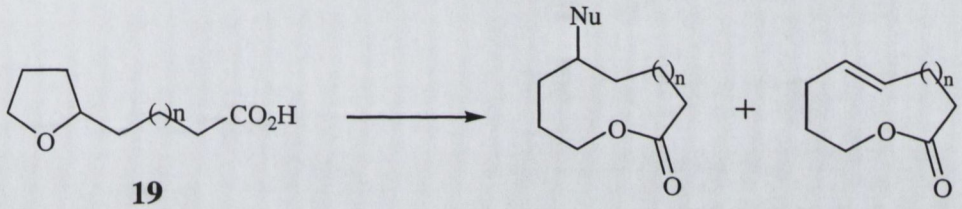
Translactonisation processes, regardless of the nature of the lactone concerned, represent a novel approach to the synthesis of potentially useful lactones. Their relevance as a method for the synthesis of macrocyclic lactones has been tentatively explored and results show considerable promise.

3.2 Strategy

The ability of the lactonisation method developed in this laboratory involving the intramolecular acid-catalysed rearrangement reaction of ω-(tetrahydro-2-furyl)alkanoic acid derivatives, as described in Section 1.4, has been investigated for the synthesis of macrocyclic lactones.[10] Results indicated that although the method was efficient for the synthesis of medium ring lactones (nine- to twelve-membered), it was far from ideal in the case of larger rings, **Table 3.1**.

Table 3.1

Yields of lactone(s) obtained from acids **19** (n = 1-6)



19

20 Bridgehead attack product

21 β-Elimination product

19 n =	Product ring size	Bridgehead attack product 20 (%)	β-elimination product 21 (%)	% Yield (total)	t (hrs)	Solvent
1	9	60	-	60	1	$CHCl_3$
2	10	48	12	60	1	$CHCl_3$
3	11	26	34	60	72	Toluene
4	12	38	13	51	72	Toluene
5	13	1.5	1	2.5	132	Toluene
6	14	3	1	4	168	Xylenes

Due to the obvious value of macrocyclic lactones in both the scientific and medicinal communities, the development of an efficient general method for their synthesis would be of exceptional interest. As the lactonisation method involving the intramolecular acid-catalysed rearrangement reaction of tetrahydrofuran derivatives is efficient in the case of the synthesis of medium-ring lactones, it was

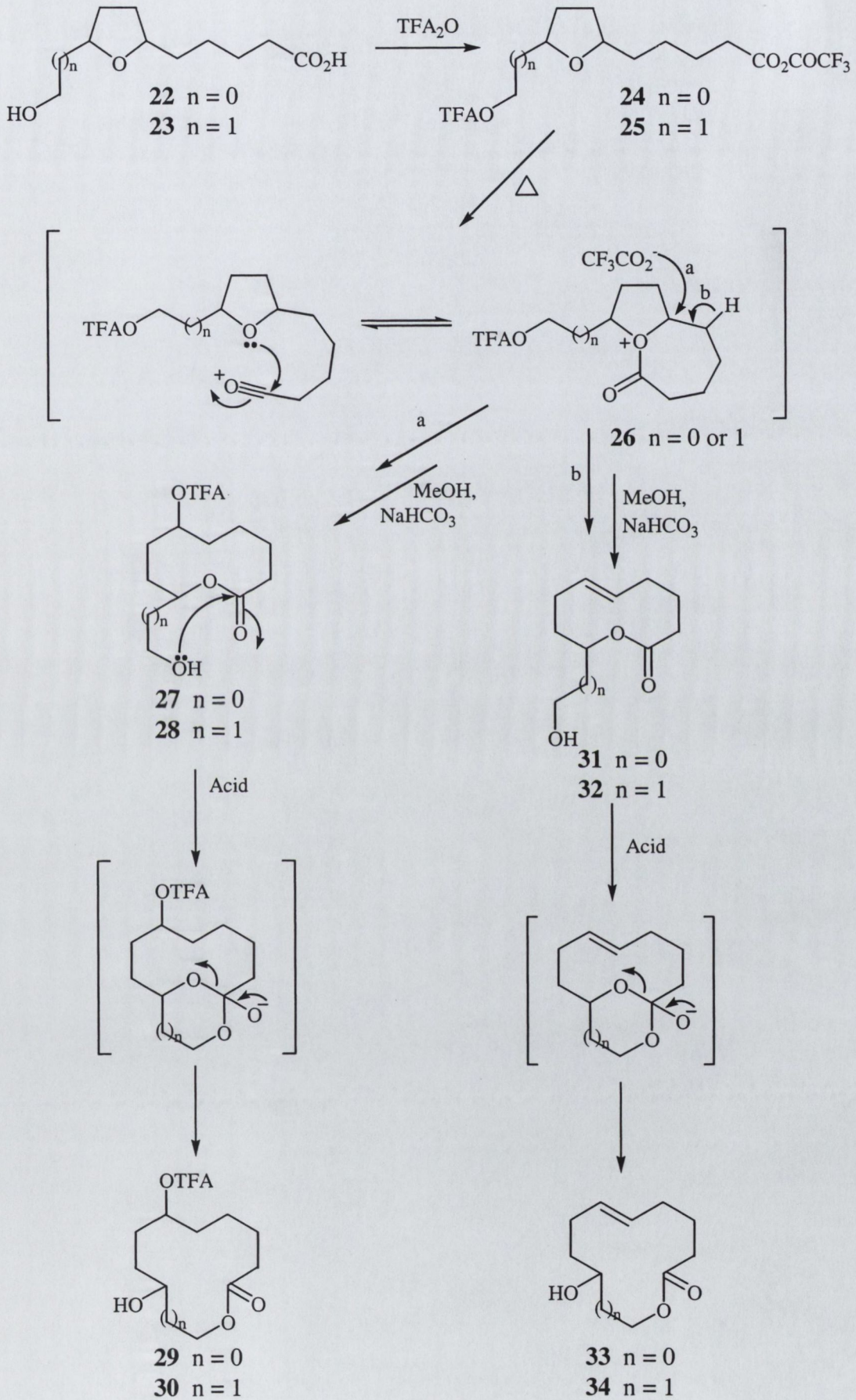
proposed to employ this method to synthesise medium-ring lactones that had the ability to undergo a translactonisation process resulting in ring enlargement and thus accomplish the formation of macrocyclic lactones. The aim of the present study was to synthesise, in good yield, medium-ring lactones bearing hydroxyalkyl chains of varying lengths adjacent to the lactone ether oxygen which were ideal candidates for such a tranlactonisation process, **Scheme 3.6**.

The synthesis of two such lactones, **27** and **28**, was proposed. It was anticipated that the eleven- and twelve-membered lactones **29** and **30** should be accessible *via* these ten-membered hydroxyalkyl lactones which should be obtained efficiently from the corresponding tetrahydrofuryl alkanoic acids **22** and **23** *via* the bicyclic intermediates **26**, (route a), **Scheme 3.6**.

When the tetrahydrofuryl alkanoic acids **22** and **23** undergo intramolecular rearrangement in the presence of trifluoroacetic anhydride, the unsaturated lactones **31** and **32** should also be formed as minor products as a result of β-elimination of a proton from the bicyclic intermediates **26**, (route b). Hence, it should also be possible to investigate the ability of these unsaturated lactones to undergo translactonisation processes resulting in the formation of eleven- and twelve-membered unsaturated lactones **33** and **34**, respectively, **Scheme 3.6**.

The synthesis of macrocyclic lactones *via* ring-enlargement reactions involving ≥ two-carbon ring enlargement by various methods is fairly well documented,[11] however, surprisingly, one-carbon ring enlargement is relatively infrequent.[12] Hence, the rearrangement of the ten-membered lactone **27** to the eleven-membered lactone **29** is of particular interest.

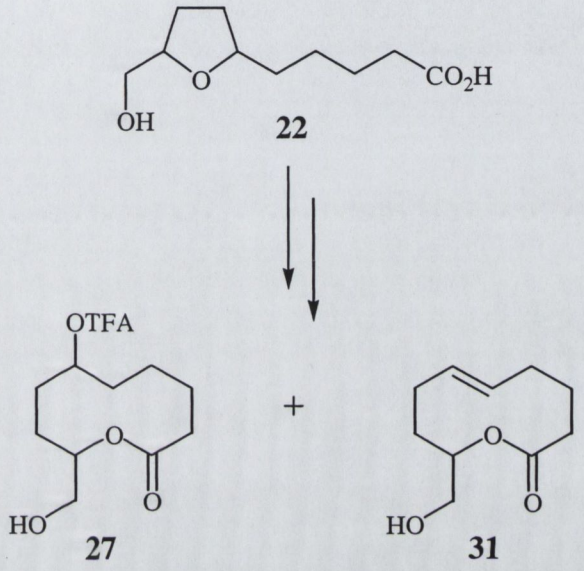
This Chapter describes the synthesis of the ten-membered hydroxymethyl lactones **27** and **31** and the synthesis of the ten-membered hydroxyethyl lactones **28** and **32**, **Scheme 3.6**. As these lactones possess diverse characteristics as regards the rigidity of the ring or the nature of the hydroxyalkyl chain, a comparative study of their abilities to undergo translactonisation processes could be conducted. Subsequently, the translactonisation of lactones **27** and **28** is described, together with the attempted translactonisation of the unsaturated lactones **31** and **32**.


TFA2O
22 n = 0
23 n = 1
24 n = 0
25 n = 1
26 n = 0 or 1
MeOH, NaHCO3
MeOH, NaHCO3
Acid
Acid
27 n = 0
28 n = 1
29 n = 0
30 n = 1
31 n = 0
32 n = 1
33 n = 0
34 n = 1

Scheme 3.6

3.3 Synthesis of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27 and of (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31

To obtain the hydroxymethyl lactones **27** and **31** it was first necessary to synthesise the required precursor acid **22, Scheme 3.7**.

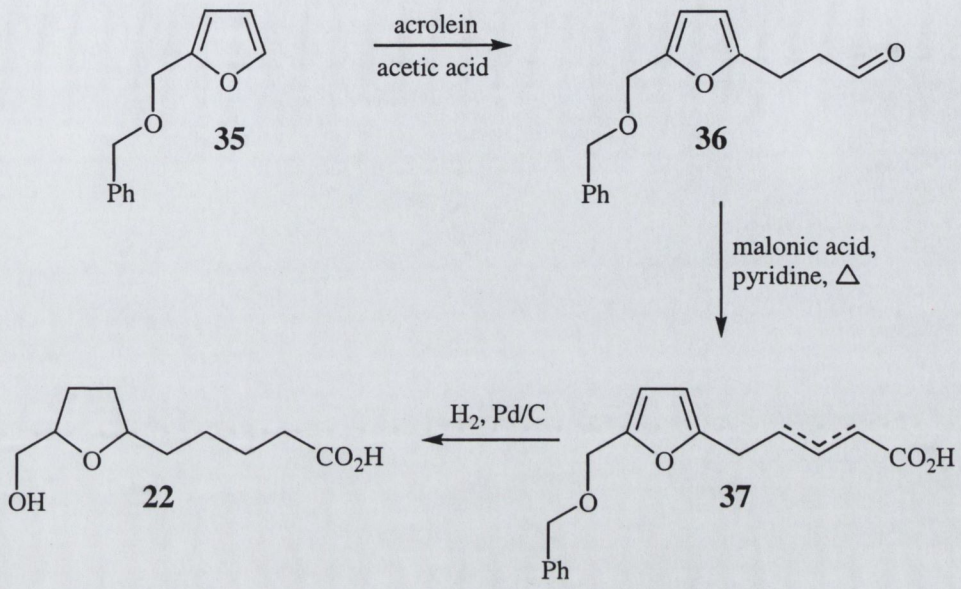


Scheme 3.7

3.3.1 Synthesis of 5-(2'-[5'-hydroxymethyl]tetrahydrofuryl)pentanoic acid 22

A synthetic strategy for the necessary precursor acid **22** for the synthesis of ten-membered lactones **27** and **31** is outlined in **Scheme 3.8**. 2-(1'-Benzyloxymethyl)furan **35** was formed (95%) from furfuryl alcohol by reaction of its sodium alkoxide with benzyl chloride.[13] Michael addition of the benzyl ether **35** to acrolein[14] in the presence of acetic acid led to formation of 3-(2'-[5'-{1''-benzyloxymethyl]furyl)propanal **36** in poor yield (crude yield 40% by weight). The aldehyde **36** was obtained as an extremely viscous orange liquid. ^{1}H NMR data showed that this crude product consisted of 55% starting material **35** and 45% product; there were no side products present. In the ^{1}H NMR spectrum of **36** some broadened peaks were observed at δ_H 1.75 and 2.00 ppm that suggested the presence of polymer, possibly arising from the acrolein which is very prone to polymerisation. Altering the reaction conditions (times, temperatures and substrate ratios) or utilising freshly distilled acrolein affected no improvement to the yield.

Isolation of the product by column chromatography proved inefficient (14%) due to decomposition of the crude aldehyde on the column.



Scheme 3.8

As the yield of aldehyde **36** was poor, alternative protecting groups for furfuryl alcohol were investigated. Furfuryl acetate was formed using acetic anhydride, however its Michael addition to acrolein failed. The synthesis of furfuryl trifluoroacetate was attempted, but without success. Alternatives to acetic acid as catalyst for the Michael addition reaction were also investigated. However, procedures involving titanium tetrachloride[15] or sulfur dioxide[16] as catalysts were unsuccessful.

Attention returned to the benzyl protecting group which, although far from ideal, was found to be the most successful. Thus, the product **36** was not purified by column chromatography as this was responsible for substantial loss. Instead, Knoevenagel reaction between crude aldehyde **36** and malonic acid in pyridine containing piperidine gave crude acid **37** in 75% yield based on the amount of aldehyde **36** present (NMR) in the crude starting material. The acid **37** was separated from unreacted benzyl ether **35** which was present in the crude aldehyde **36** used as starting material for the Knoevenagel reaction by partitioning the product between ether and aqueous base. As for the case of aldehyde **36**, the acid **37** was formed as a thick, extremely viscous orange liquid and further purification *via* chromatography proved inefficient with substantial loss of product. ^{1}H NMR

data for the acid **37** revealed that the product consisted of a mixture of α,β- and β,γ-isomers [(*E*)-α,β 39%; (*Z*)-β,γ 61%]. The spectroscopic data for all of the intermediates involved in the synthesis of acid **37** showed characteristics in agreement with their structures.

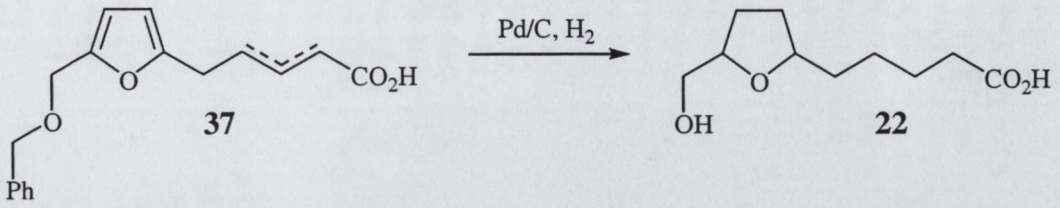
It was anticipated that hydrogenation of the acid **37** would lead to formation of the desired precursor acid **22**. Thus, it was expected that saturation of the olefinic bond and the furan ring, together with hydrogenolysis of the protecting benzyl group could be performed in a one-pot process. However, this proved more problematic than originally anticipated.

Furans, in general, undergo both saturation and hydrogenolysis in the presence of hydrogen and a catalyst, with a tendency toward hydrogenolysis at higher temperatures. The catalyst, in some cases, has a marked influence on the course of reduction. Palladium, ruthenium and rhodium tend to favour hydrogenation. A variety of solvents such as ethyl acetate, ethanol and methanol have been reported to yield successful results.[17] Some furan compounds, in particular alcohols and aldehydes, require pressure and a Raney Nickel catalyst, e.g. furfuraldehyde yields tetrahydrofurfuryl alcohol *via* hydrogenation with Raney nickel catalyst at 5 atm. hydrogen.[18] Palladium on activated charcoal (Pd/C) is widely used and has also yielded successful results in the hydrogenation of furan compounds.

To establish a procedure for the hydrogenation of acid **37**, preliminary trials were performed on the crude acid, however, the results were extremely unsatisfactory, **Table 3.2**.

Table 3.2

Results of trial hydrogenations on unsaturated crude acid **37**

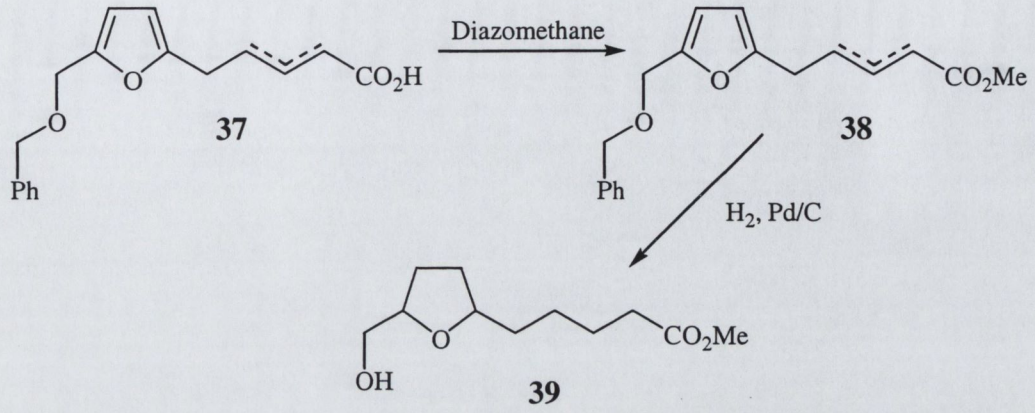


Entry	Solvent	Catalyst	Yield of desired satd. product 22	Pressure (atm.)
1	EtOAc	Pd/C	0	1
2	EtOH	Pd/C	0	1
3	MeOH	Pd/C	Traces	1
4	aq. $NaCO_3$	Pd/C	0	1
5	MeOH	$[(Ph_3P)_3RhCl]$	0	1
6	EtOAc	Pd/C	23%	2

Various solvents were investigated using 5% palladium on activated charcoal as catalyst at room temperature at pressures of 1 or 2 atmospheres of hydrogen. Saturation was achieved but in most cases the complex mixtures obtained showed no evidence of the presence of the desired product. The crude acid **37** was converted into the corresponding sodium salt and hydrogenation was attempted in aqueous conditions however there was no improvement in results (entry 4). Hydrogenation using Wilkinson's catalyst was also attempted, however no saturation was observed (entry 5). The most promising results were obtained using ethyl acetate as solvent at 2 atmospheres pressure (entry 6) where the complex mixture obtained was purified and a small amount of the desired saturated product **22** was isolated, however, the yield (23%) was far from ideal.

The most likely explanation for the failure of the hydrogenation process seemed to be the low degree of purity of the unsaturated acid **37**, and hence, purification of this was imperative. Consequently, the acid was converted into its methyl ester **38** by reaction with diazomethane,[19] **Scheme 3.9**. The ester **38** was

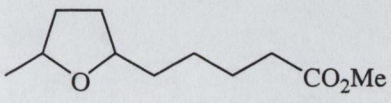
purified by column chromatography (hexane : ethyl acetate 80:20; 17% recovery) and shown (NMR) to consist of a mixture of α, β (81%) and β, γ (19%) isomers.



Scheme 3.9

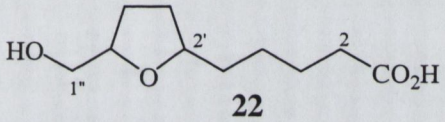
Facile hydrogenation of the pure ester **38** was anticipated. However, as before, only traces of the desired product were obtained when the same trials (refer to **Table 3.2**) were carried out. Contamination of the hydrogen gas source (zinc and sulfuric acid) was considered. However, using an alternative hydrogen source (cylinder) showed no improvement in results. Contamination of the catalyst stock was then seriously considered as a possible cause of the problem. Previously this possibility had been disregarded as co-workers had obtained successful results with the same catalyst stock, however, these results were obtained for a relatively simple reduction and did not involve saturation of a furan ring.

Consequently, newly purchased Pd/C was employed and, gratifyingly, successful results were obtained. Upon hydrogenation of pure methyl ester **38** in ethanol solution, the methyl ester **39** was obtained in a diastereomeric ratio of 5:1 as judged by inspection of relevant integral ratios in the ^{1}H NMR spectrum, the *cis*-isomer presumably being dominant. Unfortunately, the yield (40%) was still not ideal due to the formation of the hydrogenolysis product methyl 5-(5'-methyltetrahydro-2'-furyl)pentanoate **40** (35%) however it was acceptable in comparison to previous yields obtained.



40

Base-catalysed hydrolysis of the ester function of **39** then resulted in the formation of 5-(2'-[5'-hydroxymethyl]tetrahydrofuryl)pentanoic acid **22** as an oil showing IR absorptions at 3465 cm^{-1} (OH) and 1710 cm^{-1} (C=O). The ^1H NMR spectrum of the saturated acid **22** shows a triplet at δ_H 2.38, *J* 7.5, due to the C-2 methylene protons adjacent to the carboxylic acid function. Two sets of signals are observed in the δ_H 3.87-4.17 ppm region and are assigned to the C-2' and C-5' methine protons of the major and minor diastereomers. The integrated values of these signals are in the ratio 5:1 as was the case for the ester **39**. The non-equivalent C-1'' methylene protons of the major isomer appear as a set of double doublets at δ_H 3.50 and 3.72 ppm with a geminal coupling constant of 11.5 Hz. A similar splitting pattern is observed for the corresponding protons of the minor *trans*-isomer.



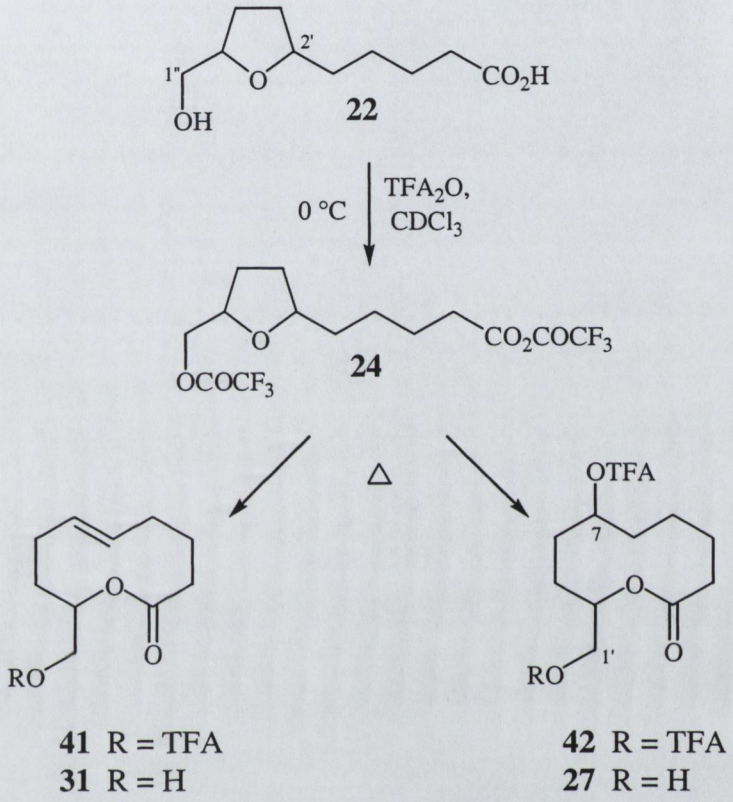
22

3.3.2 Intramolecular rearrangement of the mixed anhydride derived from 5-(2'-[5'-hydroxymethyl]tetrahydrofuryl)pentanoic acid 22

Treatment of the carboxylic acid **22** with trifluoroacetic anhydride in deuteriated chloroform at 0 °C resulted in formation of the mixed anhydride **24** which was detected by NMR analysis. On comparison of the ^1H NMR spectrum of the anhydride **24** with that of the starting acid **22**, it is apparent that the characteristic triplet due to the C-2 methylene protons observed at δ_H 2.38 ppm in the spectrum of the acid **22** had shifted to δ_H 2.64 ppm in the spectrum of the anhydride. The signals due to the non-equivalent C-1'' methylene protons observed at δ_H 3.50 and 3.72 ppm in the spectrum of the acid **22** were also shifted and were observed at δ_H 4.34 and 4.46 ppm in the spectrum of the mixed anhydride. This shift indicates that the alcohol group of the acid **22** was protected as a trifluoroacetate ester.

When the anhydride **24** was refluxed for 15 hr in deuteriated chloroform, TLC indicated the presence of two major non-polar products. ^1H NMR spectroscopy indicated that both of the anticipated lactones **41** and **42** were present

in the reaction mixture in an approximate ratio of 20:80. The first compound to be eluted by column chromatography of the reaction mixture was the saturated trifluoroacetoxy lactone **42**, obtained in very low yield (8%). Surprisingly, there was no evidence for the elution of the unsaturated trifluoroacetoxy lactone **41**.



Scheme 3.10

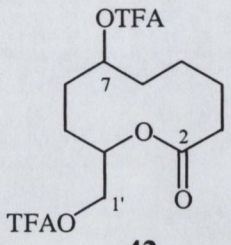
10-Trifluoroacetoxymethyl-7-trifluoroacetoxyoxecan-2-one **42** shows IR absorptions at 1784 cm^{-1} (trifluoroacetoxy C=O) and 1735 cm^{-1} (lactone C=O). Relevant integral values obtained from the ^1H NMR spectrum show a diastereomeric ratio of 6:1 due to the presence of isomers in the acid precursor **22**. The NMR spectroscopic data obtained for lactone **42** are summarised in **Table 3.3**. The assignment of the carbon and proton resonances was aided by ^{13}C-^1H COSY and ^1H-^1H COSY experiments. In the ^1H NMR spectrum of the diastereoisomeric mixture, the non-equivalent C-3 methylene protons adjacent to the lactone carbonyl function in the major diastereoisomer are evident as an AB system observed as two apparent double triplets centred at δ_H 2.38 ppm, ^2J 13.5, $^3J_1 = {}^3J_2$ 8.0 Hz, and δ_H 2.49 ppm, ^2J 13.5, $^3J_1 = {}^3J_2$ 5.0 Hz. In the case of the minor diastereoisomer, the corresponding signals are visible at δ_H 2.27 and 2.63 ppm with similar splitting patterns observed. The non-equivalent C-1' protons adjacent to the

trifluoroacetoxy group appear as two overlapping double doublets centred at δ_H 4.48 and 4.53 ppm for the major isomer and also overlap with the corresponding signals due to the minor isomer. The two methine protons of C-7 and C-10 of the major isomer overlap fully resulting in a multiplet at δ_H 5.05-5.13, however, they do not overlap in the case of the minor isomer where they appear at δ_H 5.20 and 5.39 ppm.

In the ^{13}C NMR spectrum of **42**, the minor diastereoisomer is not visible clearly. The C-1' methylene carbon of the major diastereoisomer appears at δ_C 68.0 ppm and the two methine carbons, C-7 and C-10, are visible at δ_C 71.4 and 77.4 ppm with the lactonic carbonyl carbon evident at δ_C 172.8 ppm. A ^{13}C-^{1}H COSY experiment shows the C-4 methylene carbon resonance at δ_C 23.8 ppm and a signal at δ_C 33.6 ppm is assigned to the C-3 methylene carbon. The ^{19}F NMR spectrum of **42** shows the presence of two CF_3 resonances at δ_F –75.5 and –75.9 ppm.

Table 3.3

NMR Spectroscopic details for 10-trifluoroacetoxymethyl-7-trifluoroacetoxyoxecan-2-one 42 (Major diastereoisomer)

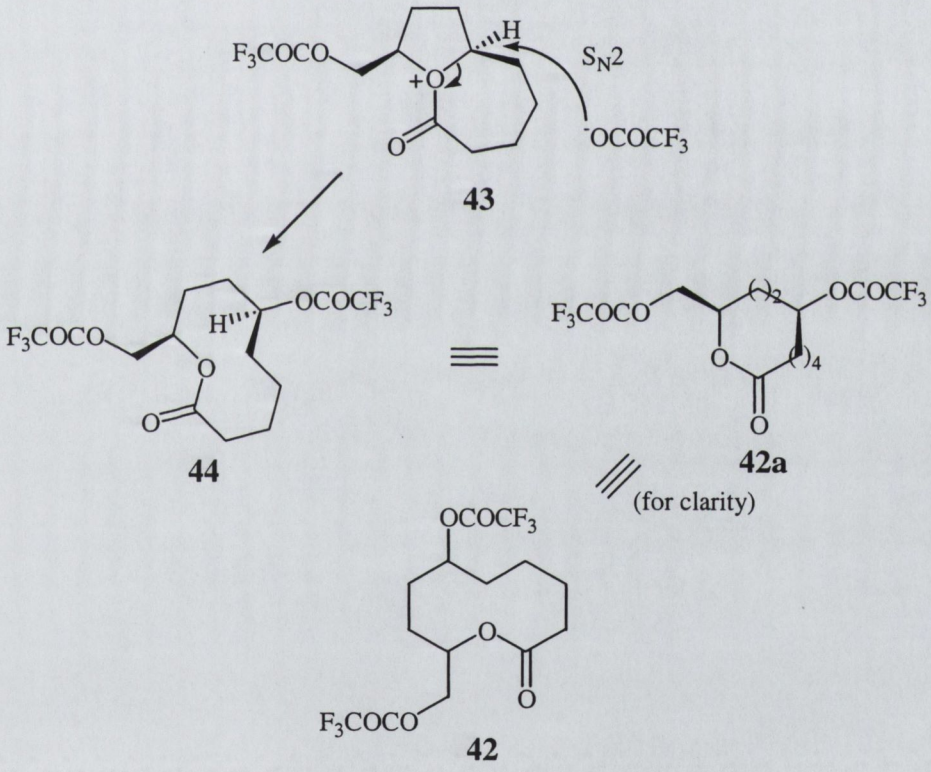


42

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 22.1	C*H*$_a$ 1.41-1.49 C*H*$_b$ 1.57-1.74		C-5/6/8/9
*C*H$_2$ 22.6	C*H*$_a$ 1.41-1.49 C*H*$_b$ 1.76-1.94		C-5/6/8/9
*C*H$_2$ 23.8	C*H*$_2$1.96-2.14	m	C-4
*C*H$_2$ 27.0	C*H*$_a$ 1.76-1.94 C*H*$_b$ 1.96-2.14		C-5/6/8/9
*C*H$_2$ 28.5	C*H*$_a$ 1.57-1.74 C*H*$_b$ 1.96-2.14		C-5/6/8/9
*C*H$_2$ 33.6	C*H*$_a$ 2.35-2.42 C*H*$_b$ 2.46-2.52	apparent dt, ^{2}J 13.5, $^{3}J_1 = {}^{3}J_2$ 8.0 apparent dt, ^{2}J 13.5, $^{3}J_1 = {}^{3}J_2$ 5.0	C-3
*C*H$_2$ 68.0	C*H*$_a$ 4.46-4.51 C*H*$_b$ 4.49-4.57	dd, ^{2}J 11.5, ^{3}J 6.0 dd, ^{2}J 11.5, ^{3}J 4.5	C-1'
*C*H 71.4	C*H* 5.05-5.13	m	C-7/C-10
*C*H 77.4	C*H* 5.05-5.13	m	C-7/C-10
C=O 172.8	-	-	C-2

The major isomer of the precursor acid **22** was presumed to be *cis*-isomer as it was formed *via* hydrogenation. Thus this major isomer should form the bicyclic intermediate **43**, **Scheme 3.11**. Generally, in the case of the formation of ten-membered trifluoroacetoxy lactones from 5-(tetrahydro-2-furyl)pentanoic acid

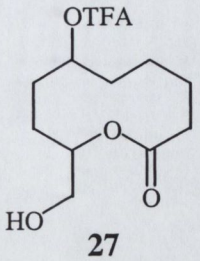
derivatives, the mechanism of attack by the trifluoroacetoxy nucleophile at the bridgehead carbon of the bicyclic acyloxonium intermediate has been found to proceed *via* a S_N2 pathway.[25] Therefore, in the case of the bicyclic intermediate **43** the bridgehead carbon will experience inversion of configuration resulting in the formation of lactone **44**. However, the relationship between the trifluoroacetoxy group on C-7 of the ten-membered lactone and the hydroxymethyl group of C-10 cannot be straightforwardly defined due to the flexible nature of the ten-membered ring. Hence, the most truthful representation of the ten-membered lactone formed is illustration **42a**. For clarity, the ten-membered lactone will be represented omitting stereochemistry as in lactone **42**, although this will be discussed when relevant.



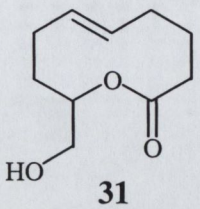
Scheme 3.11

Due to the unexpectedly small yield of the saturated trifluoroacetoxy lactone **42** (8%), and the perplexing disappearance of the unsaturated lactone **41**, the column washings were examined closely and found to contain two compounds. NMR and IR spectroscopic analysis of the mixture showed the presence of hydroxyl and alkene functions suggesting that hydrolysis could have occurred

during chromatography, possibly resulting in the formation of the corresponding hydrolysed lactones **27** and **31**.

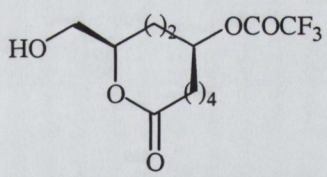


27

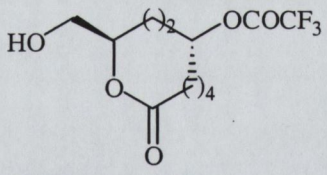


31

Following vigilant chromatography (hexane : ethyl acetate 95:5), 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one **27** was isolated as an oil (18%). Thus, partial (and selective) hydrolysis of **42** occurred during chromatography on silica gel. This may reflect the differing steric environments about the primary and secondary trifluoroacetoxy groups of **42**. The hydroxy-trifluoroacetoxy lactone **27** shows IR absorptions at 3434 cm^{-1} (OH), 1779 cm^{-1} (trifluoroacetoxy C=O), and 1729 cm^{-1} (lactone C=O). Relevant integral values obtained from the ^1H NMR spectrum show a diastereomeric ratio of 6:1, as was the case for the trifluoroacetoxy lactone **42**. The major and minor diastereoisomers of **27** can be represented by illustrations **27a** and **27b**, respectively, although the mixture will be referred to as "lactone **27**" for clarity.



27a Major diastereoisomer



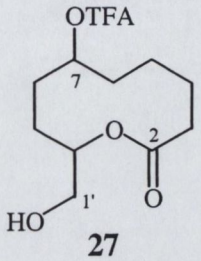
27b Minor diastereoisomer

The NMR spectroscopic data obtained for **27** are summarised in **Table 3.4**. In the ^1H NMR spectrum, **Figure 3.1**, the non-equivalent C-3 methylene protons adjacent to the lactone carbonyl function appear as an AB system consisting of two double double doublets centred at δ_H 2.36 and 2.53 ppm for the major isomer **27a**. Similar signals are observed for the minor isomer **27b**. The C-1' methylene protons adjacent to the hydroxyl group in the case of the major diastereoisomer appear as two overlapping double doublets centred at δ_H 3.76 and 3.81 ppm which also overlap slightly with the corresponding signals of the minor diastereoisomer.

The C-7 and C-10 methine protons are observed as multiplets centred at δ_H 5.45 and 4.97 ppm respectively for the major diastereoisomer and δ_H 4.97 and 5.44 ppm respectively for the minor diastereoisomer. In the ^{13}C NMR spectrum, the distinguishing signals of the C-3 and C-1' methylene carbons appear at δ_C 34.6 and 64.8 ppm respectively. The methine carbons of C-7 and C-10 resonate at δ_C 77.4 and 78.4 ppm respectively with the lactonic carbonyl signal visible at δ_C 174.0 ppm. With the aid of ^{13}C-^{1}H COSY, **Figure 3.2**, and ^{1}H-^{1}H COSY experiments the carbon and proton resonances of the methylene components of the lactone ring were tentatively assigned. The ^{19}F NMR spectrum showed the presence of one CF_3 resonance at δ_F –75.8 ppm.

Table 3.4

NMR Spectroscopic details for 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27a (major diastereoisomer)



27

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 22.3	C*H*$_a$ 1.75-1.87 C*H*$_b$ 1.87-2.04		C-5/6
*C*H$_2$ 22.7	C*H*$_a$ 1.47-1.58 C*H*$_b$ 1.75-1.87		C-5/6
*C*H$_2$ 23.7	C*H*$_a$ 1.75-1.87 C*H*$_b$ 2.05-2.15	m	C-4
*C*H$_2$ 28.1	C*H*$_a$ 1.45-1.70 C*H*$_b$ 2.05-2.15		C-8/9
*C*H$_2$ 28.2	C*H*$_2$ 1.87-2.04		C-8/9
*C*H$_2$ 34.6	C*H*$_a$ 2.33-2.40 C*H*$_b$ 2.50-2.56	ddd, ^{2}J 14.0, $^{3}J_1$ 11.0, $^{3}J_2$ 4.0 ddd, ^{2}J 14.0, $^{3}J_1$ 6.0, $^{3}J_2$ 4.0	C-3
*C*H$_2$ 64.8	C*H*$_a$ 3.74-3.78 C*H*$_b$ 3.79-3.83	dd, ^{2}J 12.5, ^{3}J 6.0 dd, ^{2}J 12.5, ^{3}J 4.0	C-1'
*C*H 77.4	C*H* 5.19-5.25	m	C-7
*C*H 78.4	C*H* 4.76-4.81	m	C-10
C=O 174.0	-	-	C-2

The NMR spectra of the saturated lactone **27** compare well with those of the related derivative **45**, **Table 3.5**.[10]

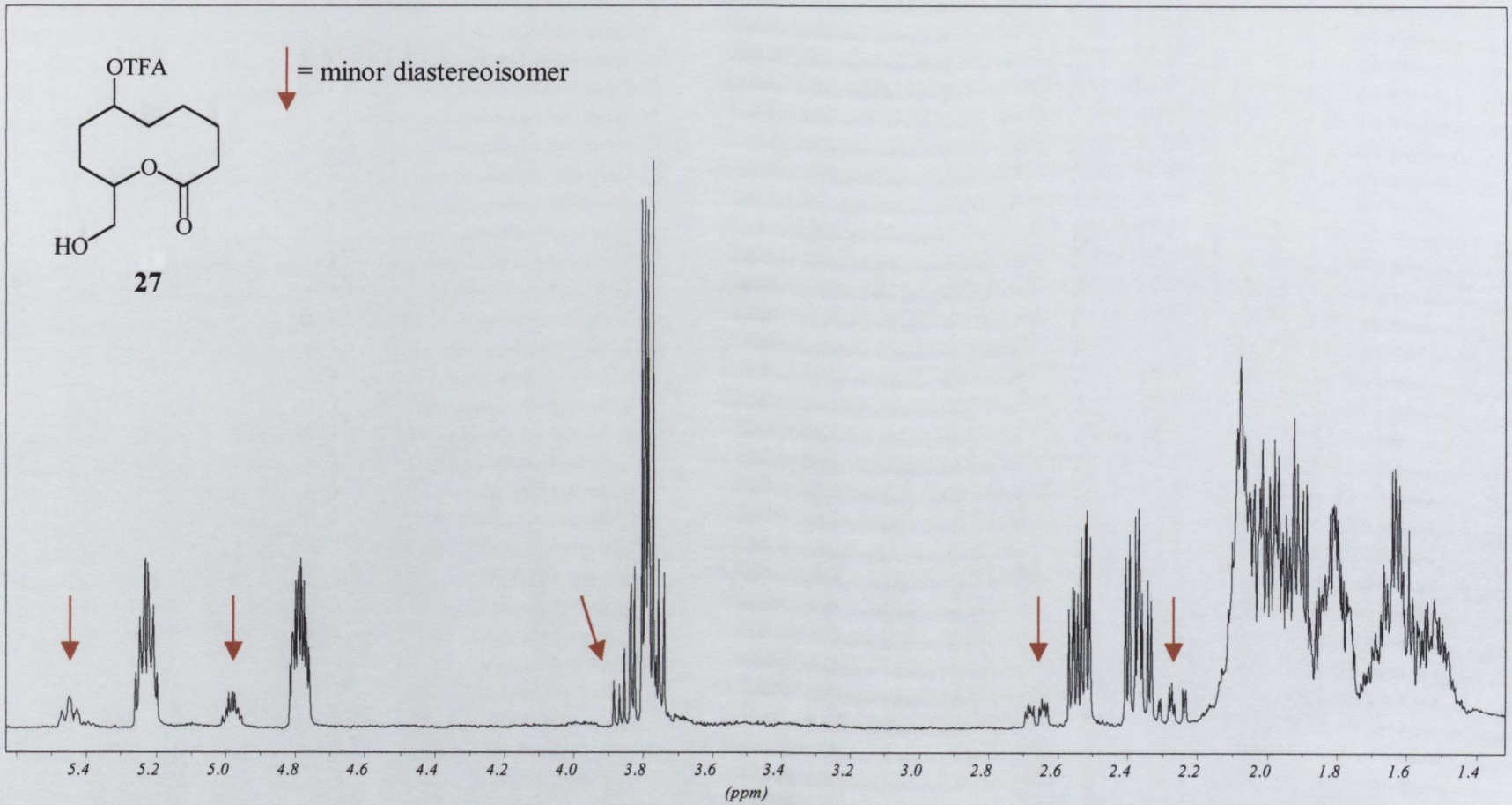


Figure 3.1

^{1}H NMR spectrum of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27

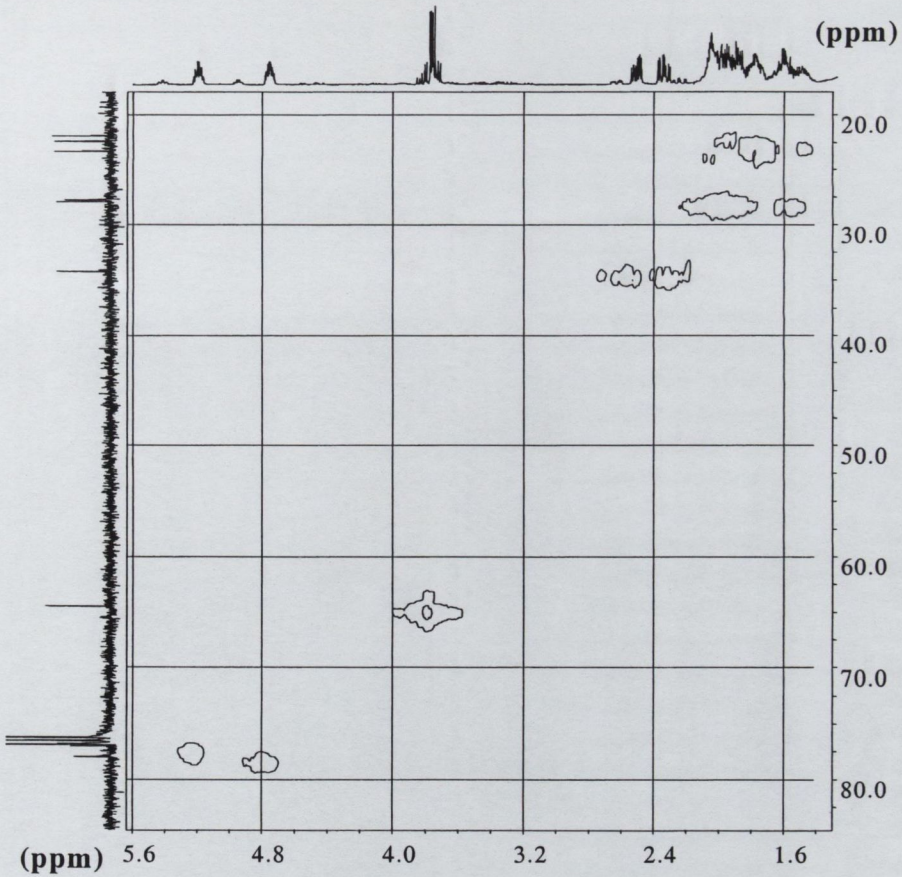


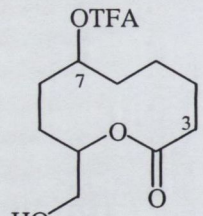
Figure 3.2

^{13}C-^{1}H COSY spectrum of 27

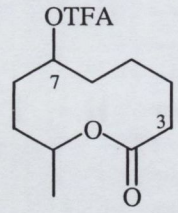
Table 3.5

Comparison of ^{1}H NMR spectra of lactones 27 and 45

(distinctive features)



27



45

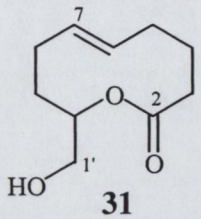
Lactone 27				Lactone 45[10]		
^{13}C (ppm)	^{1}H (ppm)	*Mult.	Assignment	^{13}C (ppm)	^{1}H (ppm)	*Mult.
34.6	2.36	ddd	C-3 CH_a	34.2	2.47	m
34.6	2.53	ddd	C-3 CH_b	34.2	2.47	m
77.4	5.22	m	C-7 CH	77.8	5.05	m
78.4	4.79	m	C-10 CH	71.2	4.95	m
174.0	-	-	C-2 C=O	173.1	-	-

*Mult. = multiplicity in ^{1}H NMR spectrum

The next compound to elute from the chromatography column was (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one **31**. The ^{1}H NMR spectrum of the mixture prior to chromatography showed a 10% content of this unsaturated lactone. However, separation was extremely difficult resulting in an isolated yield of only 2.5%. This oily compound shows IR absorptions at 3417 cm^{-1} (OH) and 1729 cm^{-1} (lactone C=O). Key resonances in the ^{1}H NMR spectrum include a set of two double doublets centred at δ_H 3.60 and 3.65 ppm that are assigned to the C-1' methylene protons adjacent to the hydroxyl group. A double double double doublet is observed at δ_H 5.13 ppm arising from the methine proton of C-10 which is coupled to the methylene groups of C-1' and C-9. The olefinic protons of C-6 and C-7 appear as two double double doublets centred at δ_H 5.27 and 5.51 ppm respectively. A geminal coupling constant of 15 Hz is observed. ^{13}C-^{1}H COSY and ^{1}H-^{1}H COSY experiments assisted the rough assignment of the proton and carbon resonances to their respective positions in the lactone ring, **Table 3.6**. In the ^{13}C NMR spectrum, the olefinic carbons, C-6 and C-7, appear at δ_C 128.0 and 132.7 ppm respectively.

Table 3.6

NMR Spectroscopic details for (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31



31

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
CH_2 25.7	CH_2 1.91-2.16		C-3/4
CH_2 28.3	CH_a 1.60-1.67 CH_b 1.73-1.83		C-9
CH_2 30.8	CH_2 1.91-2.16	m	C-3/4
CH_2 33.4	CH_a 1.91-2.16 CH_b 2.27-2.42		C5
CH_2 34.4	CH_a 1.91-2.16 CH_b 2.27-2.42		C-8
CH_2 65.2	CH_a 3.60 CH_b 3.65	dd, ^{2}J 11.5, ^{3}J 6.0 dd, ^{2}J 11.5, ^{3}J 4.0	C-1'
CH 74.9	CH 5.13	dddd, $^{3}J_1$ 11.5, $^{3}J_2$ 6.0, $^{3}J_3$ 4.0, $^{3}J_4$ 1.5	C-10
CH 128.0	CH 5.27	ddd, $^{3}J_{trans}$ 15.0, $^{3}J_1$ 10.5, $^{3}J_2$ 4.0	C-6
CH 132.7	CH 5.51	ddd, $^{3}J_{trans}$ 15.5, $^{3}J_1$ 11.0, $^{3}J_2$ 3.5	C-7
C=O 177.7	-	-	C-2

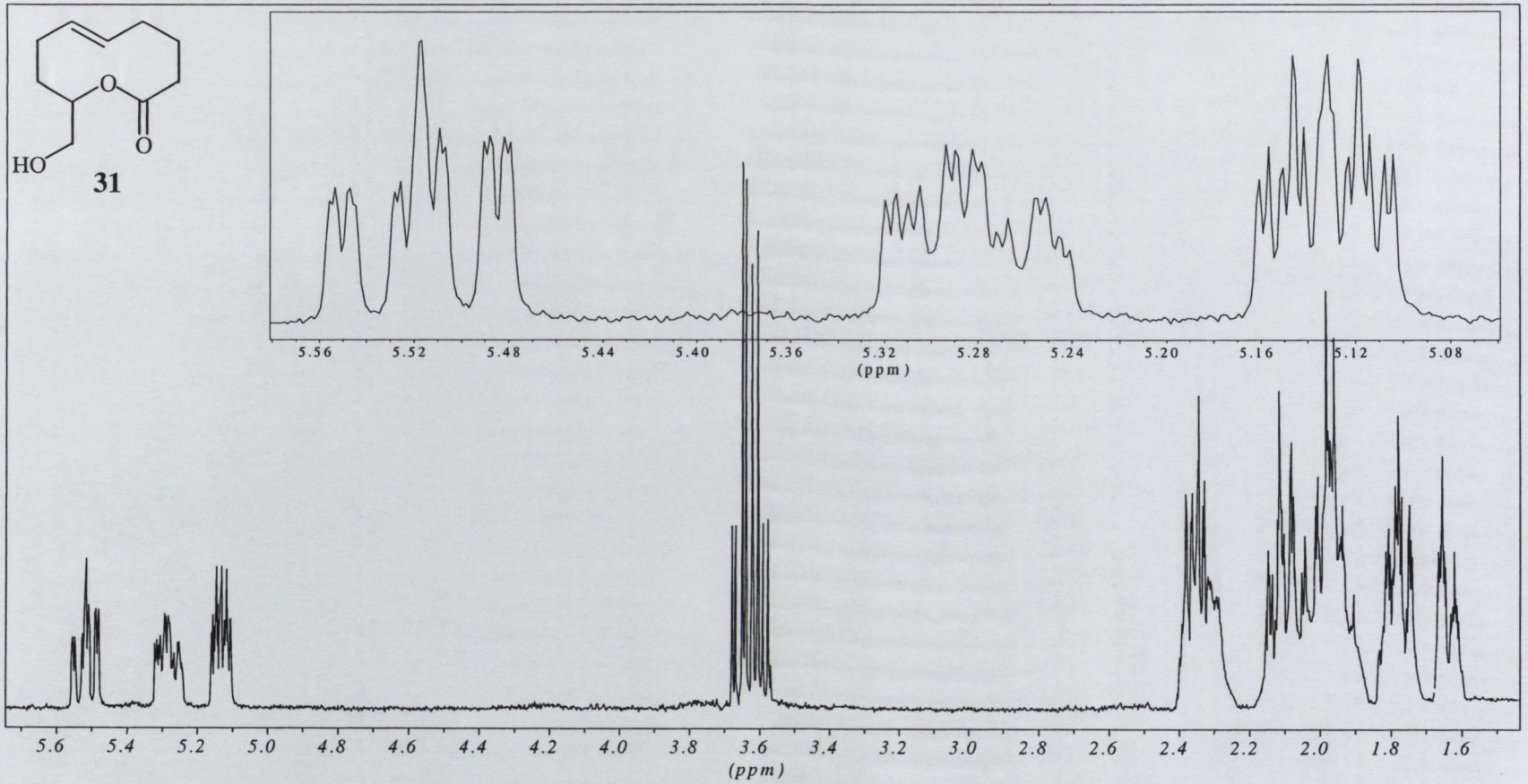


Figure 3.3

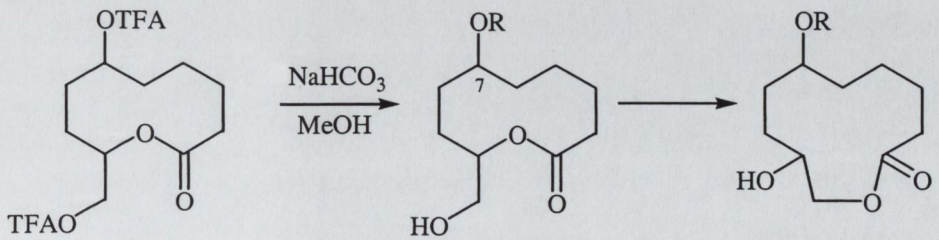
^{1}H NMR spectrum of (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31

In summary, rearrangement of the mixed anhydride derived from the acid **22** resulted in a product mixture from which lactones **42**, **27** and **31** could be isolated and characterised.

3.3.3 Hydrolysis of 10-trifluoroacetoxymethyl-7-trifluoroacetoxyoxecan-2-one 42

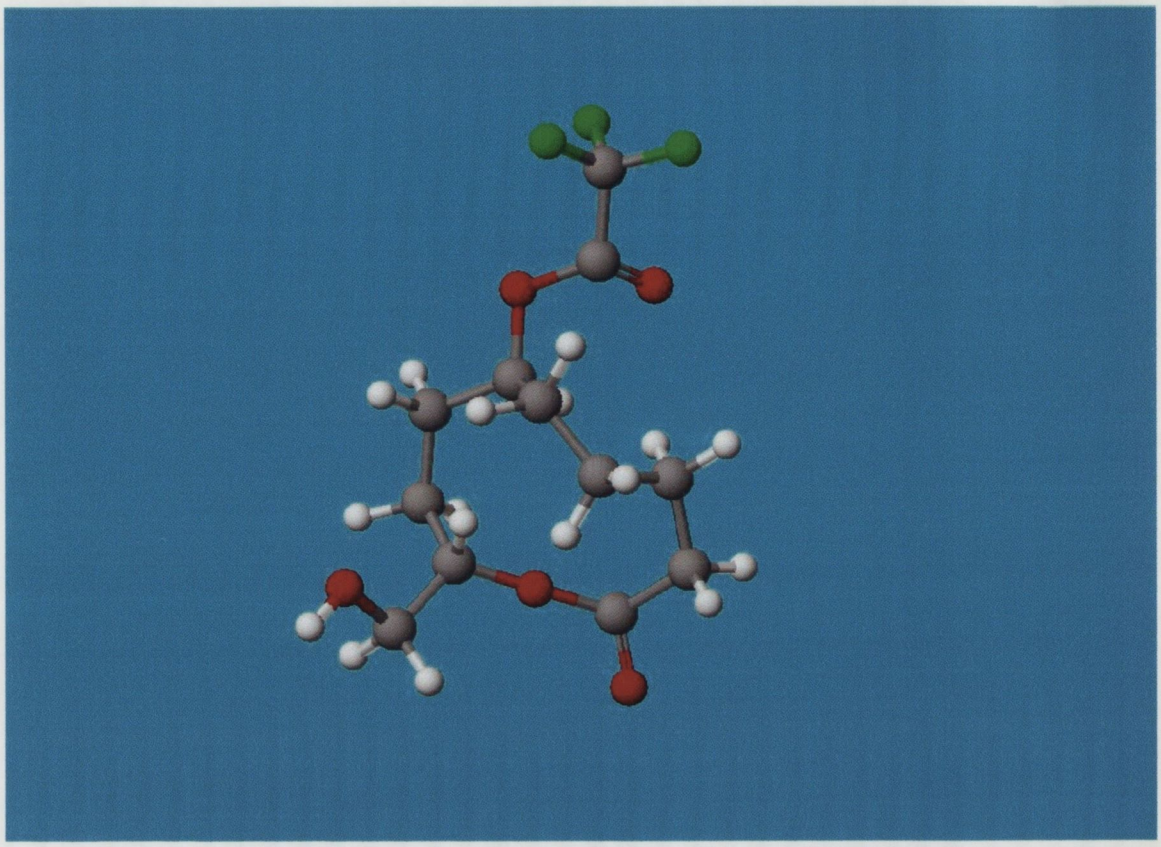
The next reaction to be investigated was the hydrolysis of the trifluoroacetoxy groups of the lactone **42**. One of these trifluoroacetates had, as described above, undergone hydrolysis during column chromatography to give the mono-trifluoroacetoxy lactone **27**.

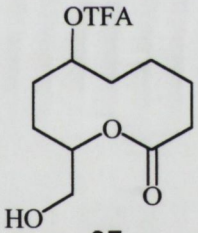
Treatment of the bis-trifluoroacetoxy lactone **42** with methanolic sodium hydrogen carbonate did not yield the expected diol **46**, **Scheme 3.12**. Instead, the product was identified as being the semi-hydrolysed lactone **27**. The trifluoroacetoxy group at C-7 remained intact. The NMR and IR spectroscopic data of the product of this hydrolysis reaction were identical in every respect to that of the semi-hydrolysed lactone **27** isolated by column chromatography of the crude product obtained from the intramolecular lactonisation reaction of the acid **22**, Section 3.3.2. It was considered that perhaps the C-7 site was hindered and thus nucleophilic attack was hampered by steric constraints. To investigate this hypothesis, an energy-minimised molecular model was obtained for lactone **27**, **Figure 3.4**. However, according to this model, the C-7 site is relatively exposed suggesting that hydrolysis should occur. This issue was investigated further in the case of the hydroxyethyl analogue **28** and is discussed in Section 3.4.3.



42 **27** R=TFA **46** R=H **29** R=TFA

Scheme 3.12





27

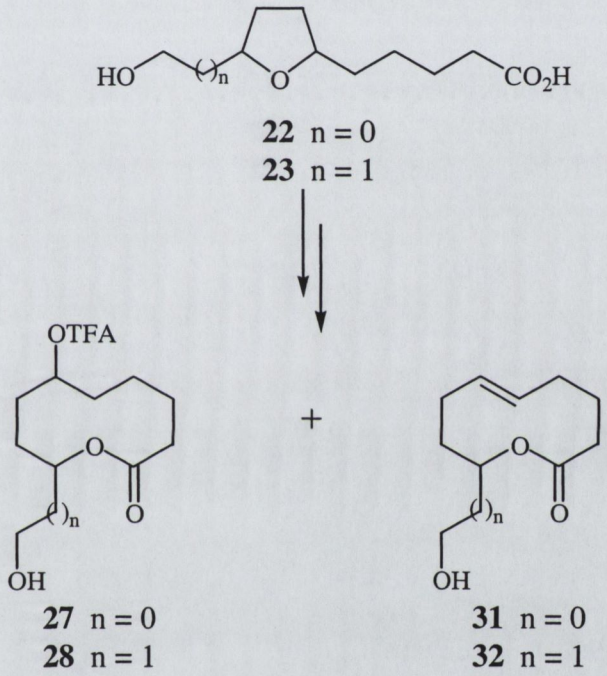
Figure 3.4

Energy-minimised molecular model (MM3)[20] of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27

Fortunately, semi-hydrolysed lactone **27** was a perfectly adequate candidate molecule for the proposed investigation into the possibility of a translactonisation process to obtain an eleven-membered lactone **29**, **Scheme 3.12**. Consequently, no further efforts to obtain diol **46** were undertaken.

3.4 Synthesis of 10-hydroxyethyl-7-trifluoroacetoxyoxecan-2-one 28 and (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32

Having successfully synthesised the hydroxymethyl lactones **27** and **31** from precursor acid **22**, Section 3.3.2, the synthesis of the analogous hydroxyethyl lactones **28** and **32** was undertaken, **Scheme 3.13**. A comparative study could then be conducted on the ability of these varied lactones to undergo tranlactonisation.

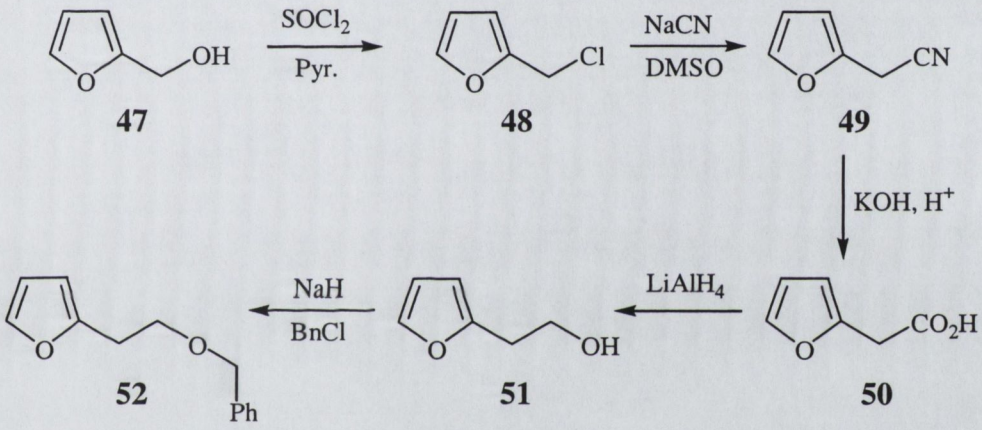


Scheme 3.13

3.4.1 Synthesis of 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoic acid 23

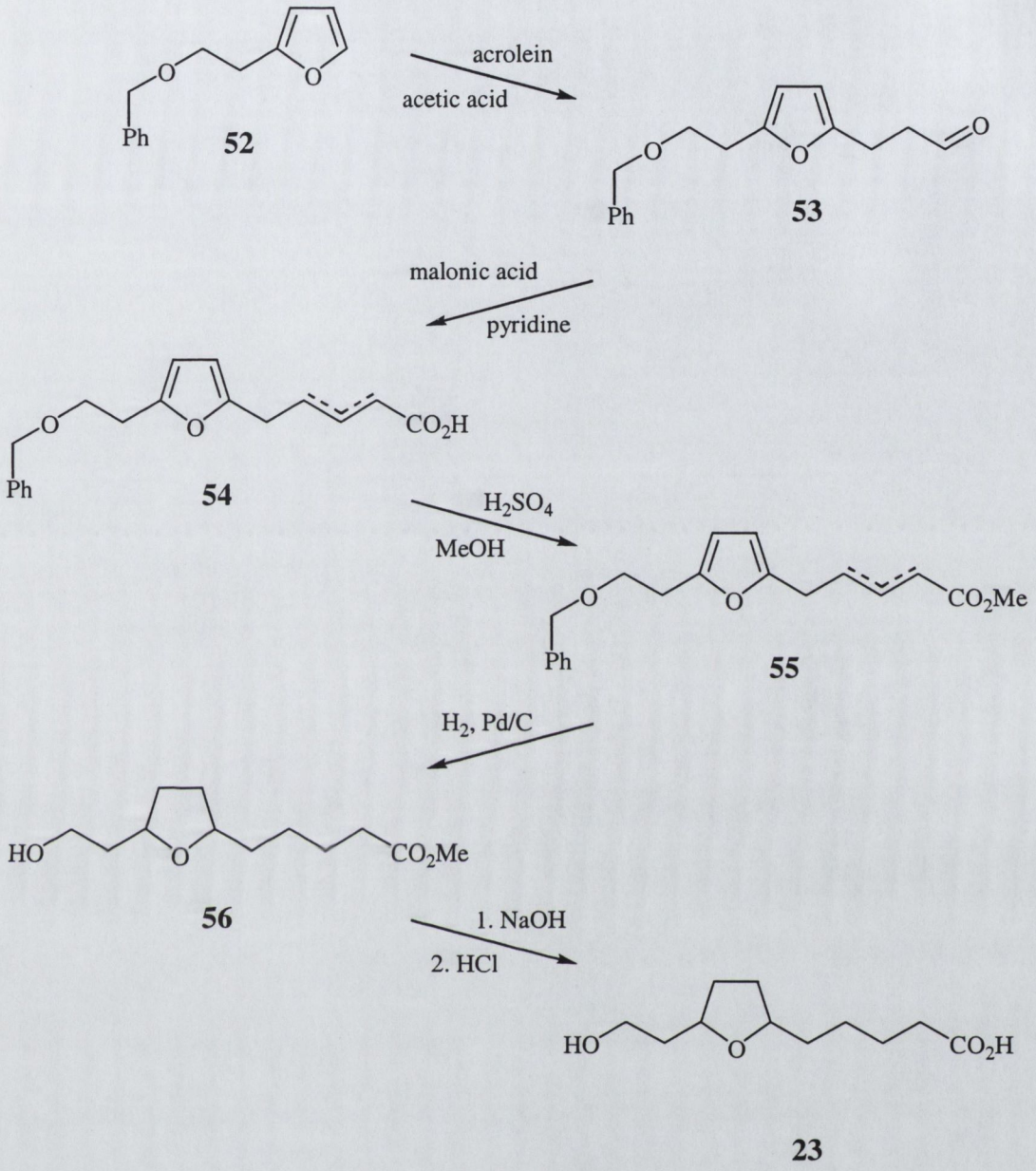
To synthesise the necessary precursor acid **23** a synthetic strategy similar to that utilised for the lower homologue **22** was employed. Firstly, it was necessary to obtain 2-furylethanol **51**, **Scheme 3.14**. Standard preparative methods were employed to create the hydroxyethyl side-chain.[21] Furfuryl alcohol **47** was converted into furfuryl chloride **48** using thionyl chloride (crude yield 57%). Literature reports concerning the synthesis of this compound describe numerous occasions when it has proven to be highly unstable; hence, the necessary precautions were undertaken. It is advised that the chloro compound should always

be stored in solution, as neat samples have been found to decompose even at –20 °C, to give hydrogen chloride, which then catalyses polymerisation of the furan ring with explosive violence.[22] The chloro compound **48** was therefore used immediately to form 2-furylacetonitrile **49** (64%) by reaction with sodium cyanide. The nitrile was then hydrolysed using potassium hydroxide to yield 2-furylacetic acid **50**[21] (81%) which was then converted into 2-furylethanol **51**[23] (72%) by reduction using lithium aluminium hydride. All the intermediates involved in the synthesis of alcohol **51** displayed spectroscopic features in agreement with their structures.



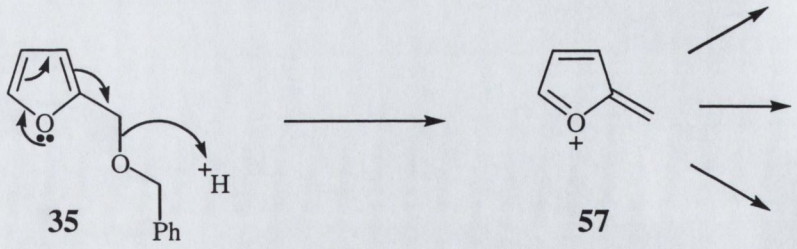
Scheme 3.14

The alcohol **51** was then protected by reaction with benzyl chloride to provide 2-(2'-benzyloxyethyl)furan **52**[24] (92%) which was necessary for the proposed synthesis of the precursor **23**, **Scheme 3.15**.



Scheme 3.15

Conjugate addition of the benzyl ether **52** to acrolein[14] to form 3-(2'-[5'-{2''-benzyloxyethyl}]furyl) propanal **53** was satisfactory, unlike the case of the addition of hydroxymethyl benzyl ether **35**. A reasonable explanation for this is that the benzyl ether **35** can potentially undergo acid-catalysed reaction to give the cation **57** which may then suffer unwanted chemistry, **Scheme 3.16**. This is not an option for the homologous benzyl ether **52**.



Scheme 3.16

The ^{1}H NMR spectrum of crude **53** showed the presence of a side-product (20%) however there was good conversion to the desired aldehyde, with only traces of unreacted starting material **52** present. Following column chromatography the side product was isolated and identified as benzyl acetate (20%). Hence, it was concluded that the competing reaction involved cleavage of the benzyl group, possibly involving carbonium ion formation, and trapping by acetate.

As was the case for the hydroxymethyl analogue, column chromatography of **53** proved inefficient with substantial loss of product observed. The yield of **53** was approximately 85% according to the ^{1}H NMR spectrum of the crude product. However, only 13% of this was isolated *via* column chromatography. The loss of product was thought to be due to decomposition of the aldehyde during the chromatography, and once again, it was decided to refrain from isolating the product and to continue with the Knoevenagel step using the crude aldehyde **53**. This reaction was successful, and an approximately 1:1 mixture of (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}] furyl)pent-2-enoic and (*Z*)-5-(2'-[5'-{2''-benzyloxyethyl}] furyl)pent-3-enoic acid **54** was formed in a yield of 60% based on the amount of aldehyde present in the crude starting material.

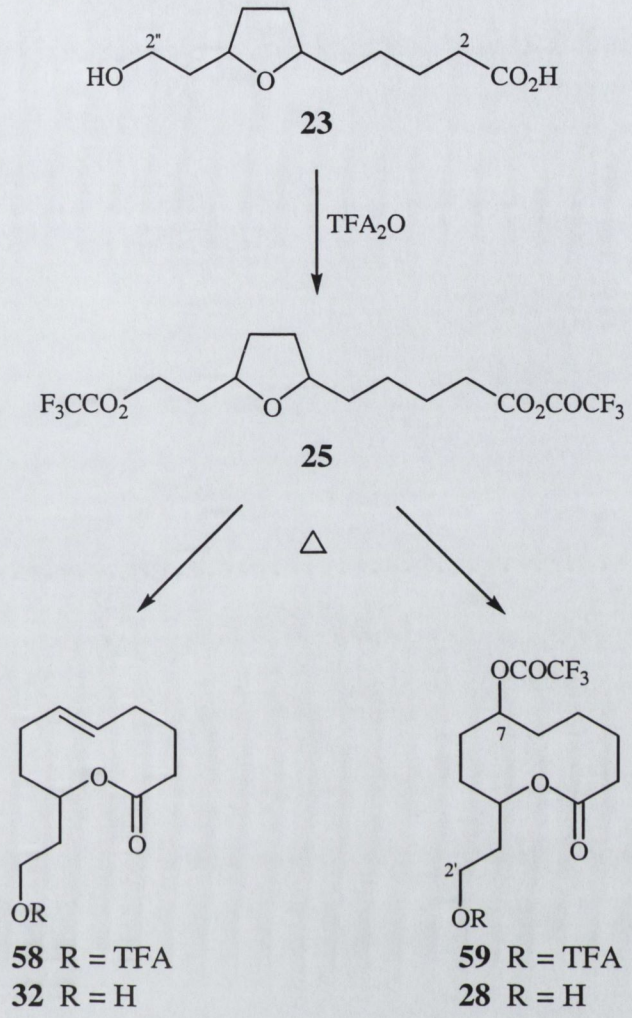
The crude acids **54** were converted into their methyl esters **55** using sulfuric acid and methanol and then purified *via* column chromatography. Hydrogenation of **55** in ethanol over Pd/C provided the derived saturated hydroxyl ester **56** in 14:1 diastereomeric ratio, the *cis*-isomer presumably being dominant. Simple base-catalysed hydrolysis using sodium hydroxide led to the desired 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoic acid **23**. This shows IR absorptions at 3431 cm^{-1} (OH) and 1710 cm^{-1} (C=O). The ^{1}H NMR spectrum of **23** shows a triplet at δ_H 2.37 ppm, *J* 7.5, due to the C-2 methylene protons adjacent to the acid function. Twin sets of signals are observed in the δ_H 3.80-4.48 ppm region and are

assigned to the C-2' and C-5' methine protons overlapping with the C-2'' methylene protons of the major and minor diastereoisomers.

3.4.2 Intramolecular rearrangement of the mixed anhydride derived from 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoic acid 23

Treatment of the carboxylic acid **23** with trifluoroacetic anhydride in deuteriated chloroform at 0 °C resulted in formation of the corresponding trifluoroacetylated mixed anhydride **25**, **Scheme 3.17**, which was detected by NMR spectroscopy. On comparison of the ^{1}H NMR spectrum of the anhydride **25** with that of the acid precursor **23** it was apparent that the characteristic triplet due to the C-2 methylene protons observed at δ_H 2.36 ppm in the spectrum of the acid **23** shifted to δ_H 2.65 ppm in the spectrum of the anhydride. The signals due to the C-2'' methylene protons observed at δ_H 3.84 ppm in the spectrum of the acid **23** were also shifted and were observed at δ_H 4.48 ppm in the spectrum of the mixed anhydride. This confirms that the alcohol group of the acid **23** was protected as a trifluoroacetate ester.

The reaction mixture was then refluxed (in $CDCl_3$) and monitored by NMR spectroscopy. Following 5 hr reflux, TLC studies detected the presence of two major non-polar products. ^{1}H NMR spectroscopy indicated that both of the anticipated lactones **58** and **59** were present in the reaction mixture in an approximate ratio of 20:80, **Scheme 3.17**. As in the case of the reaction of the hydroxymethyl analogue **22**, the less polar product, which was thought to be the unsaturated lactone **58**, was not isolated upon purification of the reaction mixture *via* column chromatography.



Scheme 3.17

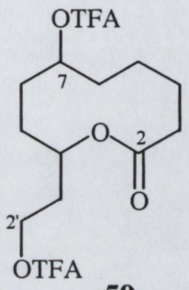
The first compound to be eluted was identified as 10-(2'-trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one **59** (13%). This shows IR absorptions at 1783 cm^{-1} (trifluoroacetoxy C=O) and 1735 cm^{-1} (lactone C=O). Relevant integral values obtained from the ^1H NMR spectrum show a diastereomeric ratio of 12.5:1 arising from the presence of isomers in the precursor acid **23**.

Key resonances observed in the ^1H NMR spectrum of **59** (major diastereoisomer) include an AB system consisting of two apparent double triplets, centred at δ_H 2.35 and 2.46 ppm, which are assigned to the non-equivalent methylene protons of C-3, **Figure 3.5**. A geminal coupling constant of 13.5 Hz is observed. Similar signals are observed for the minor diastereoisomer. For the major diastereoisomer a multiplet at δ_H 4.37-4.47 ppm is assigned to the two

methylene protons of C-2' adjacent to the trifluoroacetoxy group. The C-10 and C-7 methine protons of the major diastereoisomer are apparent as two multiplets centred at δ_H 4.95 and 5.08 ppm respectively and δ_H 5.08 and 5.47 ppm respectively for the minor diastereoisomer. The region between δ_H 1.40 and 2.30 ppm is complex due to the presence of six sets of largely non-equivalent methylene protons. Rough assignment of the resonances arising from these was aided by ^{13}C-^{1}H COSY and ^{1}H-^{1}H COSY experiments and is summarised in **Table 3.7**. Key resonances present in the ^{13}C NMR spectrum of **59** include a signal at δ_C 64.5 ppm assigned to the C-2' methylene carbon adjacent to the trifluoroacetoxy group. The signals arising from the C-7 and C-10 methine carbons appear at δ_C 77.6 and 72.0 ppm respectively, with the lactone carbonyl carbon resonating at δ_C 173.2 ppm. The ^{19}F NMR spectrum revealed the presence of two CF_3 resonances at δ_F –75.8 and –75.5 ppm.

Table 3.7

NMR Spectroscopic details for 10-(2'-trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one 59 (Major diastereoisomer)



59

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
CH_2 21.9	CH_a 1.40-1.51 CH_b 1.74-1.81		C-5
CH_2 22.7	CH_2 1.74-1.94		C-4
CH_2 27.0	CH_2 1.83-2.11		C-6/8/9
CH_2 27.2	CH_2 1.72-1.82	m	C-6/8/9
CH_2 28.4	CH_a 1.56-1.74 CH_b 2.05-2.18		C-6/8/9
CH_2 33.2	CH_a 1.93-2.06 CH_b 2.19-2.30		C-1'
CH_2 34.3	CH_a 2.35 CH_b 2.46	apparent dt, ^{2}J 13.5, $^{3}J_1 = {}^{3}J_2$ 8.0 apparent dt, ^{2}J 13.5, $^{3}J_1 = {}^{3}J_2$ 5.0	C-3
CH_2 64.5	CH_2 4.37-4.47	m	C-2'
CH 72.0	CH 4.93-4.99	m	C-10
CH 77.6	CH 5.05-5.11	m	C-7
C=O 173.2	-	-	C-2

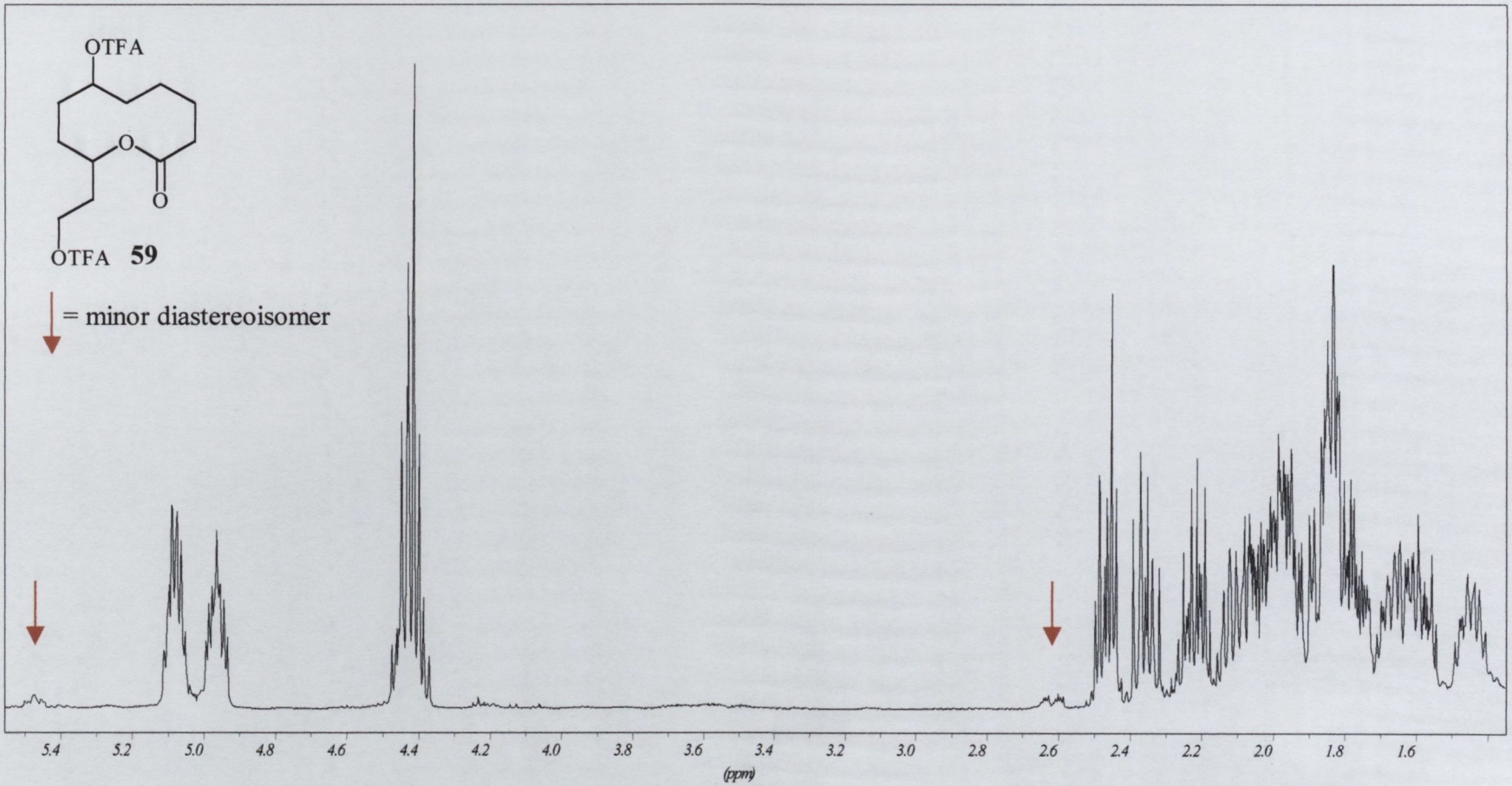
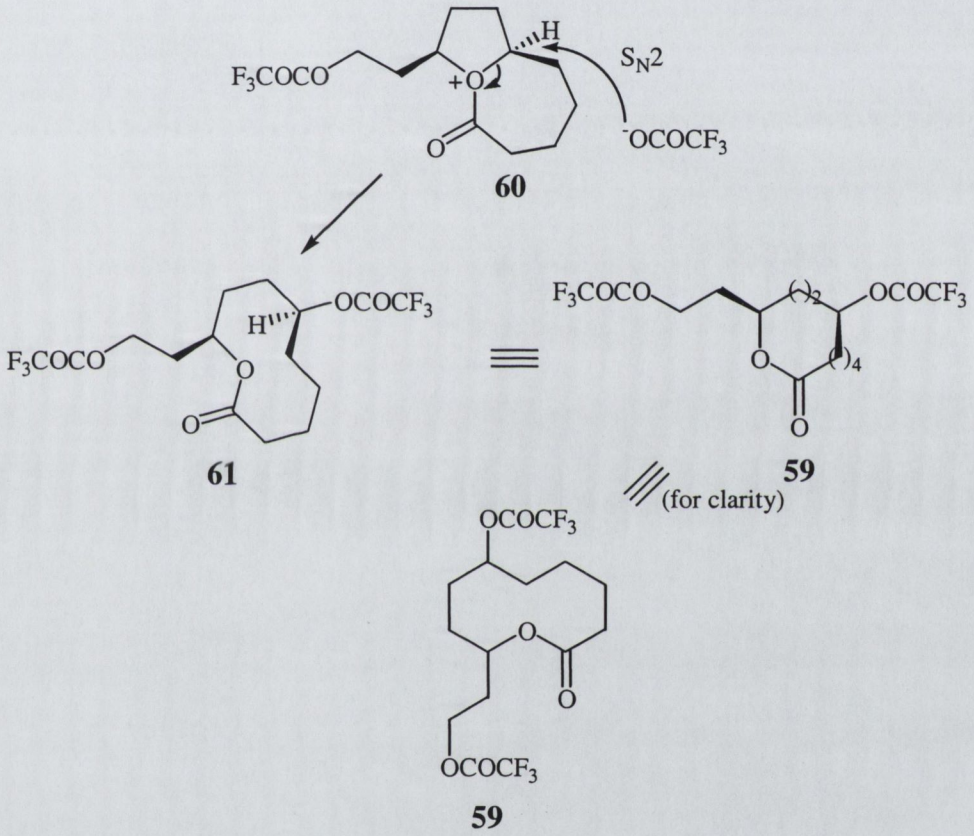


Figure 3.5

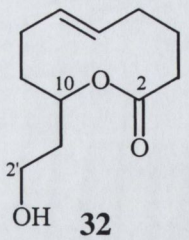
^{1}H NMR Spectrum of 10-(2'-trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one 59

As in the case of the analogous hydroxymethyl lactone **42**, the major isomer of the precursor acid **23** designed to provide lactone **59** was presumed to be the *cis*-isomer as it was formed *via* hydrogenation. Thus, this major isomer should form the bicyclic intermediate **60**, **Scheme 3.18**. Hence, the major diastereoisomer of lactone mixture **59** can be represented by illustration **59a**. For clarity, this ten-membered lactone will be represented omitting stereochemistry as in lactone **59**, although this will be discussed when relevant.



Scheme 3.18

The next compound to elute from column chromatography of the crude product obtained from the intramolecular lactonisation reaction of acid **23** was identified as (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one **32** (10%), with hydrolysis presumably occurring during chromatography as was the case for the analogous hydroxymethyl lactones **27** and **31**. The lactone **32** shows IR absorptions at 3446 cm^{-1} (OH) and 1725 cm^{-1} (lactone C=O). Assignments for all of the proton and carbon resonances were aided by ^{13}C-^{1}H COSY, ^{1}H-^{1}H COSY and HMBC experiments and are summarised in **Table 3.8**.



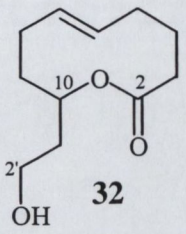
32

Key resonances in the ^{1}H NMR spectrum of **32**, **Figure 3.6**, include a set of overlapping double double doublets centred at δ_H 3.55 and 3.61 ppm which are assigned to the methylene protons of C-2' adjacent to the hydroxyl function. A double double double doublet appears at δ_H 5.10 ppm arising from the methine proton of C-10 split by the non-equivalent vicinal methylene protons of C-9 and C-1'. The olefinic protons of C-6 and C-7 are observed as two double double doublets at δ_H 5.28 and 5.56 ppm respectively. These signals show evidence of some long range coupling, possibly to the C-4 protons in the case of the signal assigned to the C-6 olefinic proton and to the C-9 protons in the case of the signal due to the C-7 olefinic proton. A vicinal *trans* coupling constant of 15.0 Hz is observed which is consistent for a double bond of (*E*)-geometry. CW decoupling experiments provided further evidence for the (*E*)-double bond. When the resonance at δ_H 2.36 ppm was irradiated, the complexity of the double double doublet at δ_H 5.56 ppm was reduced and the signal was evident as a baseline resolved double doublet with *J* 15.0 and 12.0 Hz. Furthermore, when the resonance at δ_H 2.30 ppm was irradiated, the complexity of the double double doublet at δ_H 5.28 ppm was reduced and the signal was evident as a baseline resolved double doublet also with *J* 15.0 and 11.0 Hz. This substantiates the presence of a double bond with (*E*)-geometry. The multiplet at δ_H 2.29-2.38 ppm in the ^{1}H NMR spectrum of **32** was found to contain the signals for 3 non-equivalent protons with the aid of the ^{13}C-^{1}H COSY NMR experiment. These protons belong to the C-3, C-5 and C-8 methylene carbon atoms.

Significant signals in the ^{13}C NMR spectrum of **32** include that of the C-2' methylene carbon adjacent to the hydroxyl group which appears at δ_C 57.5 ppm. The olefinic carbons C-6 and C-7 appear at δ_C 127.3 and 133.4 ppm respectively and were distinguished with the aid of the two-dimensional spectra. The C-2 lactonic carbonyl carbon is visible at δ_C 177.5 ppm.

Table 3.8

NMR spectroscopic details for (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32



32

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 25.6	C*H*$_a$ 1.70-1.84 C*H*$_b$ 1.88-2.01		C-4
*C*H$_2$ 31.7	C*H*$_a$ 2.01-2.15 C*H*$_b$ 2.29-2.38		C-8
*C*H$_2$ 32.4	C*H*$_a$ 1.59-1.67 C*H*$_b$ 1.70-1.84		C-9
*C*H$_2$ 33.4	C*H*$_a$ 1.88-2.01 C*H*$_b$ 2.29-2.38	m	C-5
*C*H$_2$ 34.4	C*H*$_a$ 2.01-2.15 C*H*$_b$ 2.29-2.38		C-3
*C*H$_2$ 37.7	C*H*$_a$ 1.59-1.67 C*H*$_b$ 1.70-1.84		C-1'
*C*H$_2$ 57.5	C*H*$_a$ 3.52-3.58 C*H*$_b$ 3.58-3.63	ddd, ^{2}J 11.5, $^{3}J_1$ 10.0, $^{3}J_2$ 3.5 ddd, ^{2}J 11.5, $^{3}J_1$ 5.5, $^{3}J_2$ 3.5	C-2'
*C*H 72.6	C*H* 5.10	dddd, $^{3}J_1 = {}^{3}J_2$ 10.5, $^{3}J_3$ 3.0, $^{3}J_4$ 1.5	C-10
*C*H 127.3	C*H* 5.28	ddd, $^{3}J_{trans}$ 15.0, $^{3}J_1$ 11.0, $^{3}J_2$ 4.0	C-6
*C*H 133.4	C*H* 5.56	ddd, $^{3}J_{trans}$ 15.0, $^{3}J_1$ 12.0, $^{3}J_2$ 3.0	C-7
C=O 177.5	-	-	C-2

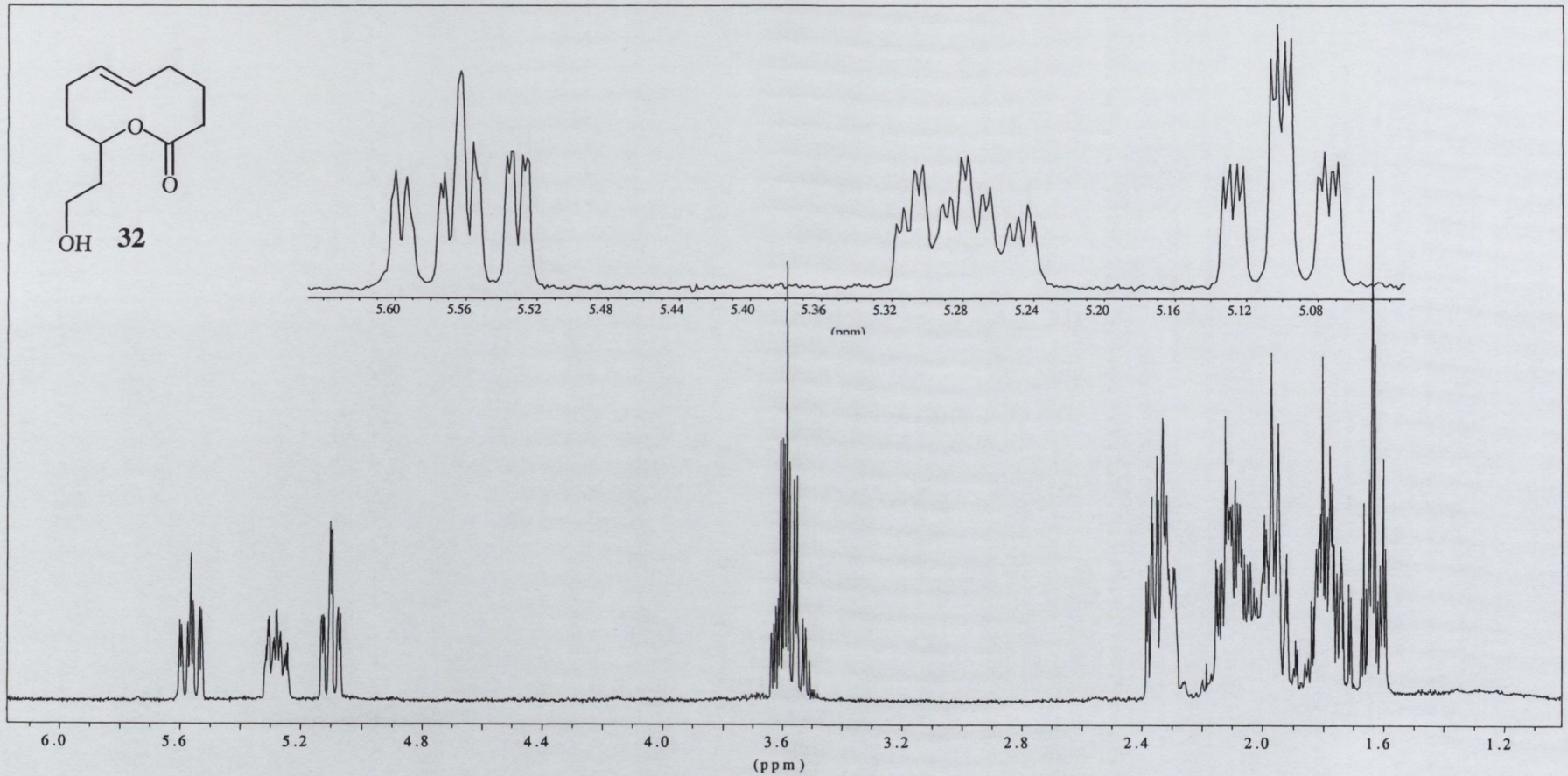


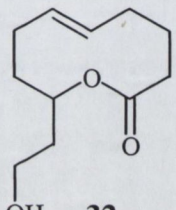
Figure 3.6

^{1}H NMR spectrum of (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32

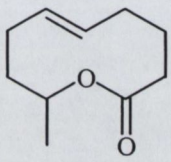
The spectra of the unsaturated lactone **32** compare well with those of the previously synthesised unsaturated lactone **45**.[10] Their ^{1}H NMR spectra are compared in **Table 3.9**. Interestingly, the ^{13}C-^{1}H COSY spectrum of lactone **45** also showed that a multiplet at δ_H 2.31 ppm contained resonances for three non-equivalent protons as in the case of lactone **32**.

Table 3.9

Comparison of ^{1}H NMR spectra of unsaturated lactones 32 and 45



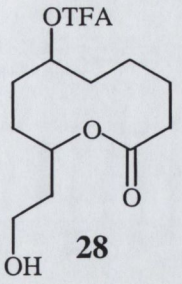
32



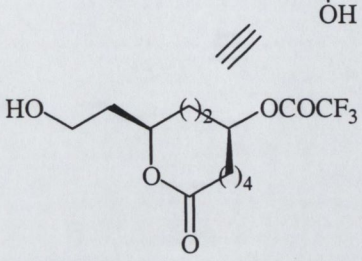
45

Unsaturated lactone 32				**Unsaturated lactone 45**		
^{13}C (ppm)	**^{1}H (ppm)**	**Multiplicity**	**Assignment**	**^{13}C (ppm)**	**^{1}H (ppm)**	**Multiplicity**
72.6	5.10	dddd	C-10 CH	71.0	5.15	m
127.3	5.28	ddd	C-6 CH	128.2	5.22	m
133.4	5.56	ddd	C-7 CH	133.2	5.49	ddd

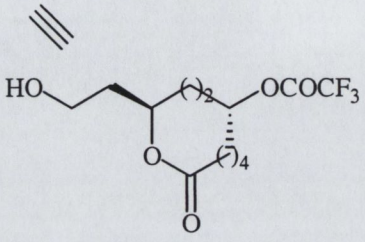
The final compound to elute from column chromatography of the crude product obtained from the intramolecular reaction of acid **23** was identified as 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one **28**, presumably formed during the chromatography process. The major and minor diastereoisomers of lactone **28** can be represented by illustrations **28a** and **28b** respectively, however the mixture will be referred to as "lactone **28**" for clarity.



28



28a major diastereoisomer

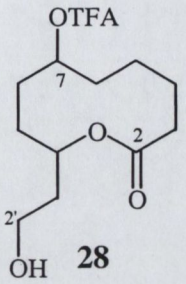


28b minor diastereoisomer

Lactone **28** shows IR absorptions at 3446 cm^{-1} (OH), 1779 cm^{-1} (trifluoroacetoxy C=O) and 1718 cm^{-1} (lactone C=O). The diastereomeric ratio obtained from relevant integral values in the ^{1}H NMR spectrum of **28**, **Figure 3.7**, is 5:1. Distinctive resonances observed include an AB system consisting of a set of two overlapping apparent double triplets centred at δ_H 2.42 and 2.48 ppm assigned to the non-equivalent protons of C-3 adjacent to the lactone carbonyl of the major diastereoisomer **28a**. An additional AB system consisting of two double double doublets is observed at δ_H 2.26 and 2.63 ppm due to the non-equivalent protons of C-3 of the minor diastereoisomer **28b**. The methylene protons of C-2' adjacent to the hydroxyl function appear as a set of overlapping double double doublets centred at δ_H 3.60 and 3.69 ppm for the major diastereoisomer, however, the system is somewhat obscured due to further overlapping of the corresponding set of double double doublets arising from the minor diastereoisomer. The signals due to the C-7 and C-10 methine protons overlap fully and are visible as a multiplet at δ_H 4.99-5.09 ppm. Due to the complete overlap of these key resonances, it was difficult to distinguish between the C-7 and C-10 carbons in the ^{13}C-^{1}H COSY spectrum of **28**, **Figure 3.8**. However two-dimensional experiments did facilitate assignment of the seven methylene groups appearing in the δ_H 1.37-2.51 ppm region, **Table 3.10**. A ^{19}F NMR spectrum showed the presence of one CF_3 resonance visible at δ_F –75.8 ppm.

Table 3.10

NMR Spectroscopic details for 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28a (major diastereoisomer)



28

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 22.4	C*H*$_a$ 1.37-1.46 C*H*$_b$ 1.58-1.76		C-5
*C*H$_2$ 22.8	C*H*$_2$ 1.76-1.93		C-4
*C*H$_2$ 28.0	C*H*$_2$ 1.76-2.14	m	C-8/9
*C*H$_2$ 28.1	C*H*$_2$ 1.76-2.14		C-8/9
*C*H$_2$ 28.6	C*H*$_a$ 1.58-1.76 C*H*$_b$ 2.16-2.29		C-6
*C*H$_2$ 34.3	C*H*$_a$ 2.42 C*H*$_b$ 2.48	apparent dt, ^{2}J 13.0, $^{3}J_1 = {}^{3}J_2$ 7.5 apparent dt, ^{2}J 13.0, $^{3}J_1 = {}^{3}J_2$ 5.5	C-3
*C*H$_2$ 37.9	C*H*$_2$ 1.76-1.93	m	C-1'
*C*H$_2$ 58.2	C*H*$_a$ 3.60 C*H*$_b$ 3.65-3.73	ddd, ^{2}J 12.0, $^{3}J_1$ 9.0, $^{3}J_2$ 4.5 m	C-2'
*C*H 73.0	C*H* 4.99-5.09	m	C-7/10
*C*H 77.8	C*H* 4.99-5.09	m	C-7/10
C=O 174.6	-	-	C-2

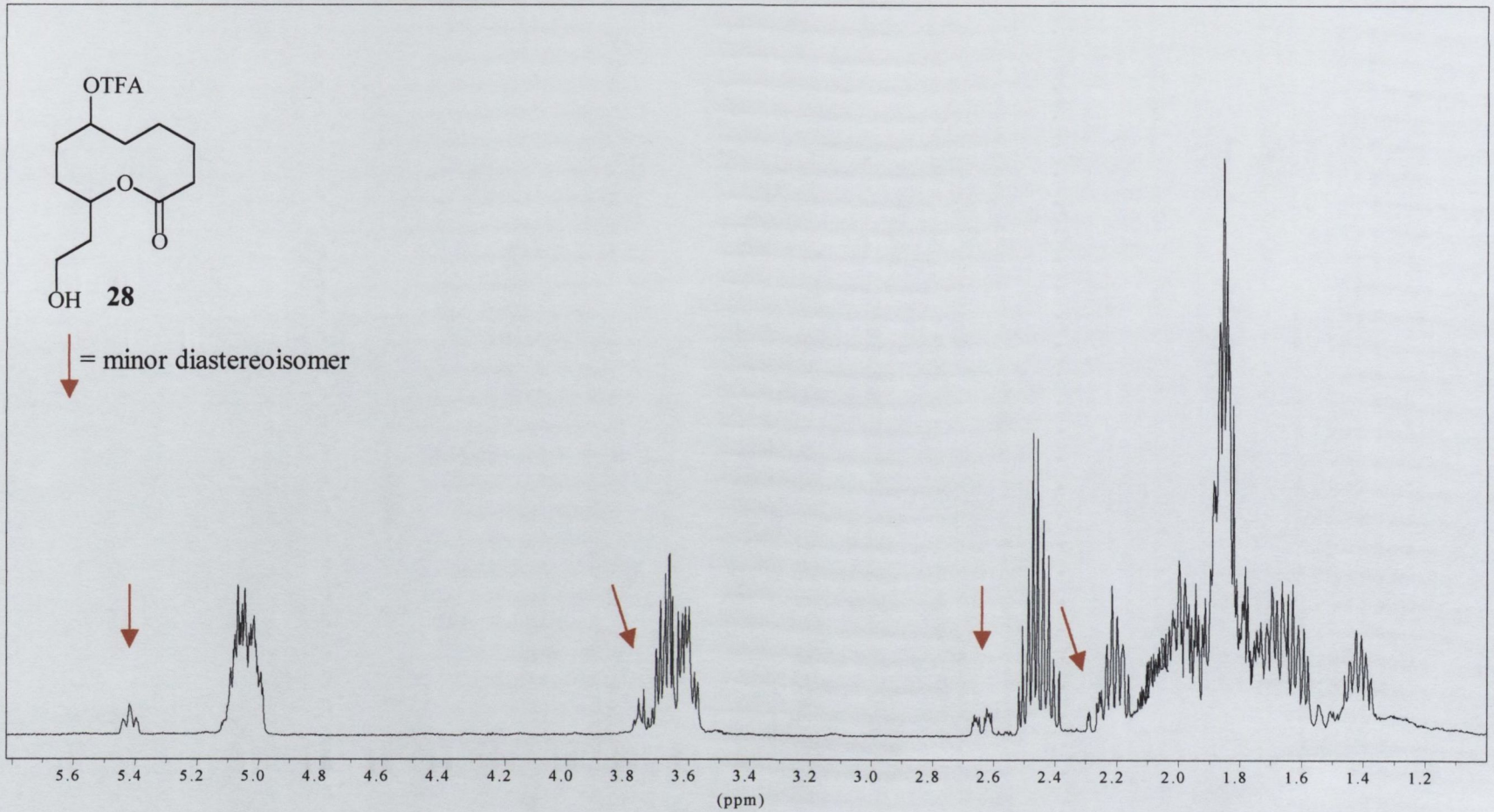


Figure 3.7

^{1}H NMR spectrum of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28

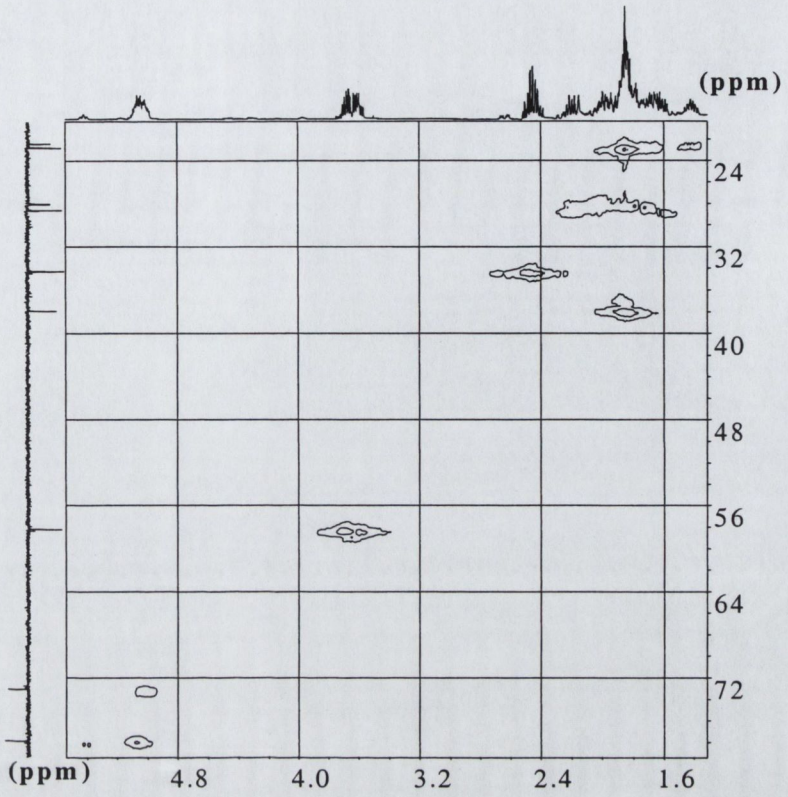
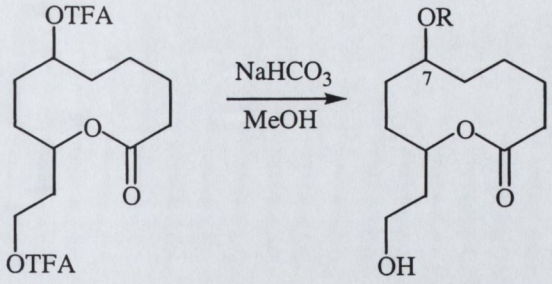


Figure 3.8

^{13}C-^{1}H COSY spectrum of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28

3.4.3 Hydrolysis of 10-(2'-trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one 59

The next reaction to be investigated was the hydrolysis of the trifluoroacetoxy groups of the lactone **59**. One of these trifluoroacetate functions had, as described above, undergone hydrolysis during column chromatography to give the mono-trifluoroacetate **28**. When the trifluoroacetoxy lactone **59** was treated with methanolic sodium hydrogen carbonate, **Scheme 3.19**, the expected diol **62** was not obtained, as had been the case with the hydroxymethyl analogue **42**. The resulting compound was identified as the semi-hydrolysed derivative, in this case lactone **28**. The trifluoroacetoxy group at C-7 once again remained intact. The NMR and IR spectroscopic data for the product of this hydrolysis reaction were identical in almost every respect to that of the semi-hydrolysed lactone isolated from the column of the crude product of the intramolecular lactonisation reaction of the acid **23** (a minor difference was observed in the diastereomeric ratio).

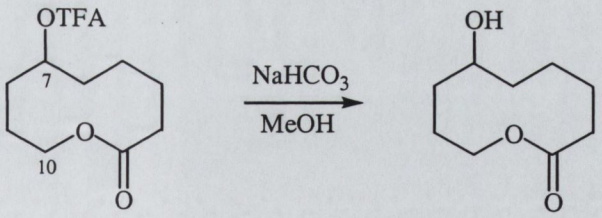


59 **28** R=TFA
62 R=H

Scheme 3.19

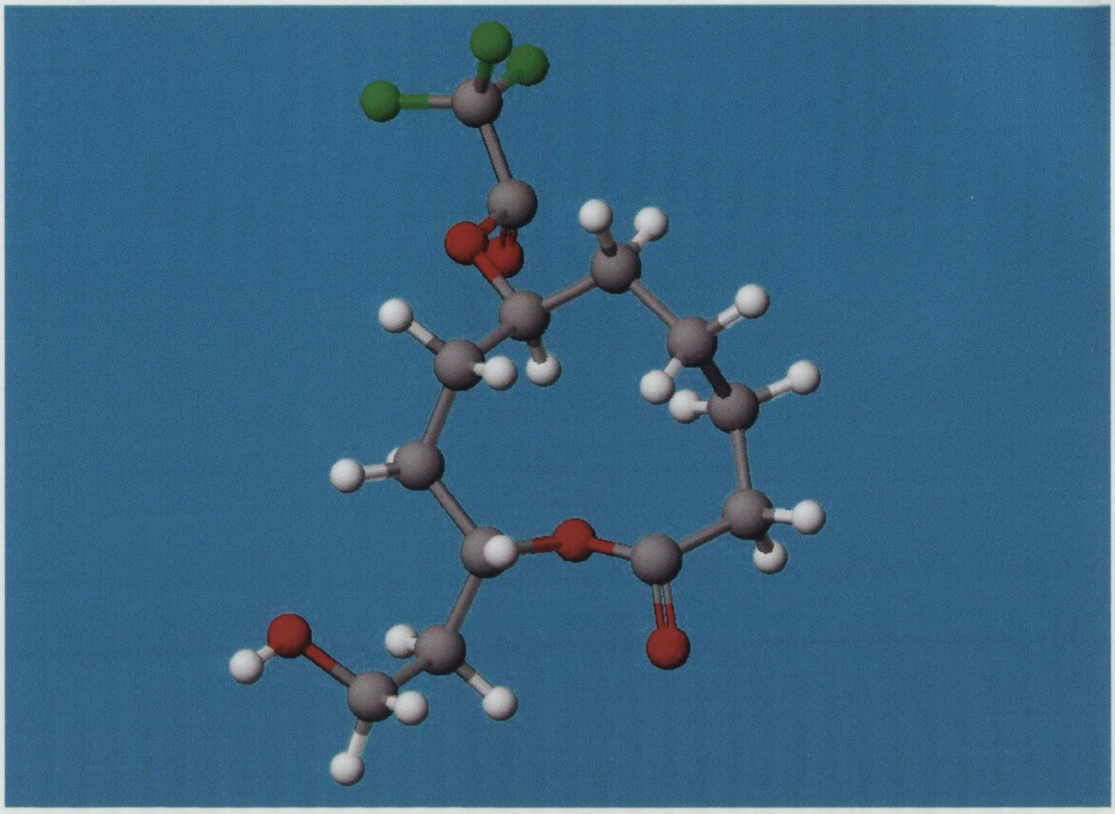
Once more, it was considered that perhaps the trifluoroacetoxy carbonyl at C-7 is hindered in some way and thus nucleophilic attack is hampered by steric constraints. Consequently, an energy-minimised molecular model was obtained to probe the situation, **Figure 3.9**. However, according to this model, it seems the C-7 trifluoroacetoxy function is relatively exposed and therefore should undergo hydrolysis.

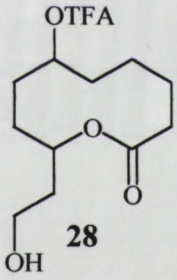
Previous work had involved the hydrolysis of the ten-membered lactone **63** which had yielded the hydroxylactone **64**, **Scheme 3.20**.[25] In this case the trifluoroacetoxy lactone **63**, which had a vacant C-10 site, was exposed to methanolic sodium hydrogen carbonate for 1 hr, although it was presumed that the hydrolysis had occurred in a shorter time. It was considered that the fact that the ten-membered lactone **28** had a relatively large substituent on C-10 might have some effect on the hydrolysis of the C-7 trifluoroacetate function of this lactone.



63 **64**

Scheme 3.20



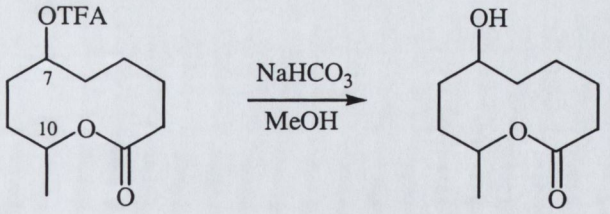


28

Figure 3.9

Energy-minimised molecular model (MM3)[20] of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28

To investigate this hypothesis, the ten-membered trifluoroacetoxy lactone **65** which had been obtained previously, Section 2.6.2, and which possessed a methyl substituent on C-10, was exposed to the same conditions and the reaction was monitored by TLC. It was found that hydrolysis of the C-7 trifluoroacetoxy function did occur but somewhat slowly with hydroxy-lactone **66** formed following two hours of exposure to methanolic sodium hydrogen carbonate, **Scheme 3.21**.

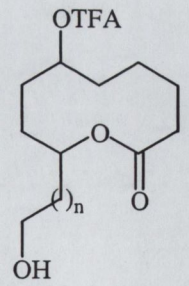


65 **66**

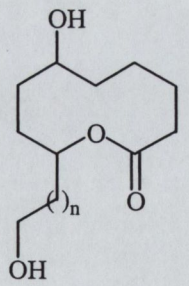
Scheme 3.21

Hydroxy-lactone **66** shows IR absorptions at 3384 cm^{-1} (OH) and 1718 cm^{-1} (C=O). Principal resonances in the ^1H NMR spectrum of this lactone include a doublet at δ_H 1.23 ppm which is assigned to the methyl group protons. The methine protons at C-7 and C-10 resonate at δ_H 4.35 and 3.84 ppm respectively. The ^{13}C NMR spectrum shows a signal at δ_C 22.6 for the methyl group. The methine protons of C-7 and C-10 are visible at δ_C 67.1 and 79.7 ppm while the lactonic carbonyl carbon resonates at δ_C 175.4 ppm.

Thus, it was clear that hydrolysis of trifluoroacetoxy lactone **28** and indeed that of the hydroxymethyl analogue **27** should be possible with prolonged exposure to methanolic sodium hydrogen carbonate. However, since both of these semi-hydrolysed lactones **27** and **28** possessed the hydroxyalkyl chains necessary for the proposed investigation into the area of translactonisation processes, no further attempts to obtain diols **46** and **62** were carried out.



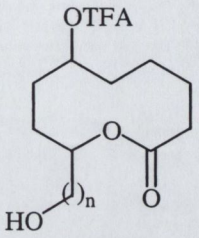
27 n = 0
28 n = 1



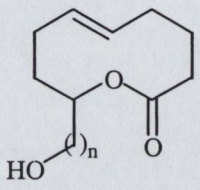
46 n = 0
62 n = 1

3.5 Translactonisation Reactions

This section describes translactonisation experiments that were carried out using the lactones **27**, **28** and **31**, **32** which were synthesised as described above.



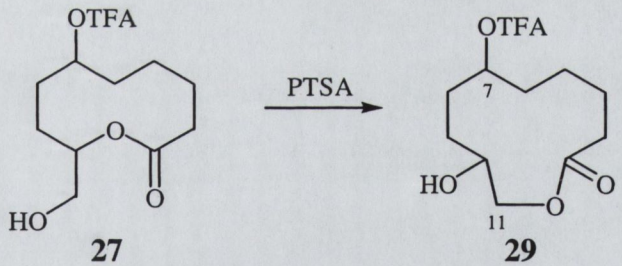
27 n = 1
28 n = 2



31 n = 1
32 n = 2

3.5.1 Translactonisation of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27

Using a procedure similar to that devised by Corey,[1] the hydroxymethyl lactone **27** was dissolved in deuteriated dichloromethane; 5 mol% PTSA was then added and the reaction was monitored by NMR spectroscopy, **Scheme 3.22**.

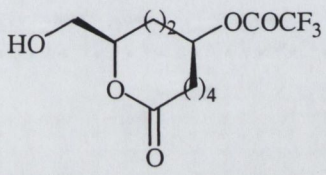


27 **29**

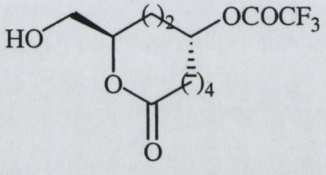
Scheme 3.22

Gratifyingly, new peaks corresponding to those expected for the desired eleven-membered lactone **29** were observed, **Figure 3.10**. Distinctive features of these new sets of signals included a well-separated AB system consisting of two double doublets visible at δ_H 4.10 and 4.46 ppm. These signals were thought to be due to the methylene protons of C-11 of **29** which experience geminal and vicinal coupling. Other new signals that were observed included two multiplets centred at δ_H 4.17 and 5.40 ppm corresponding to the methine protons of C-10 and C-7 respectively.

Interestingly, the minor diastereoisomer **27b** of ten-membered lactone **27** was unaffected by the presence of the acid and the relevant signals remained unchanged in the ^{1}H NMR spectrum of the reaction mixture, **Scheme 3.23**. The lack of reactivity of this minor diastereoisomer must be due to its lactone ring puckering in such a way that the hydroxymethyl side-chain cannot come into close proximity to the lactone carbonyl group and therefore no reaction occurs. The major diastereoisomer **27a** does not experience this problem and therefore it can be concluded that the conformation of the lactone ring must play a central role in the translactonisation process.



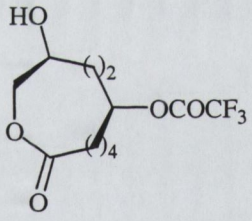
27a major diastereoisomer



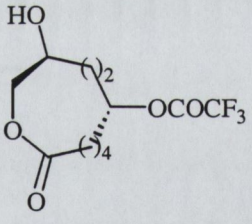
27b minor diastereoisomer

PTSA

PTSA



29a major diastereoisomer



29b minor diastereoisomer

Scheme 3.23

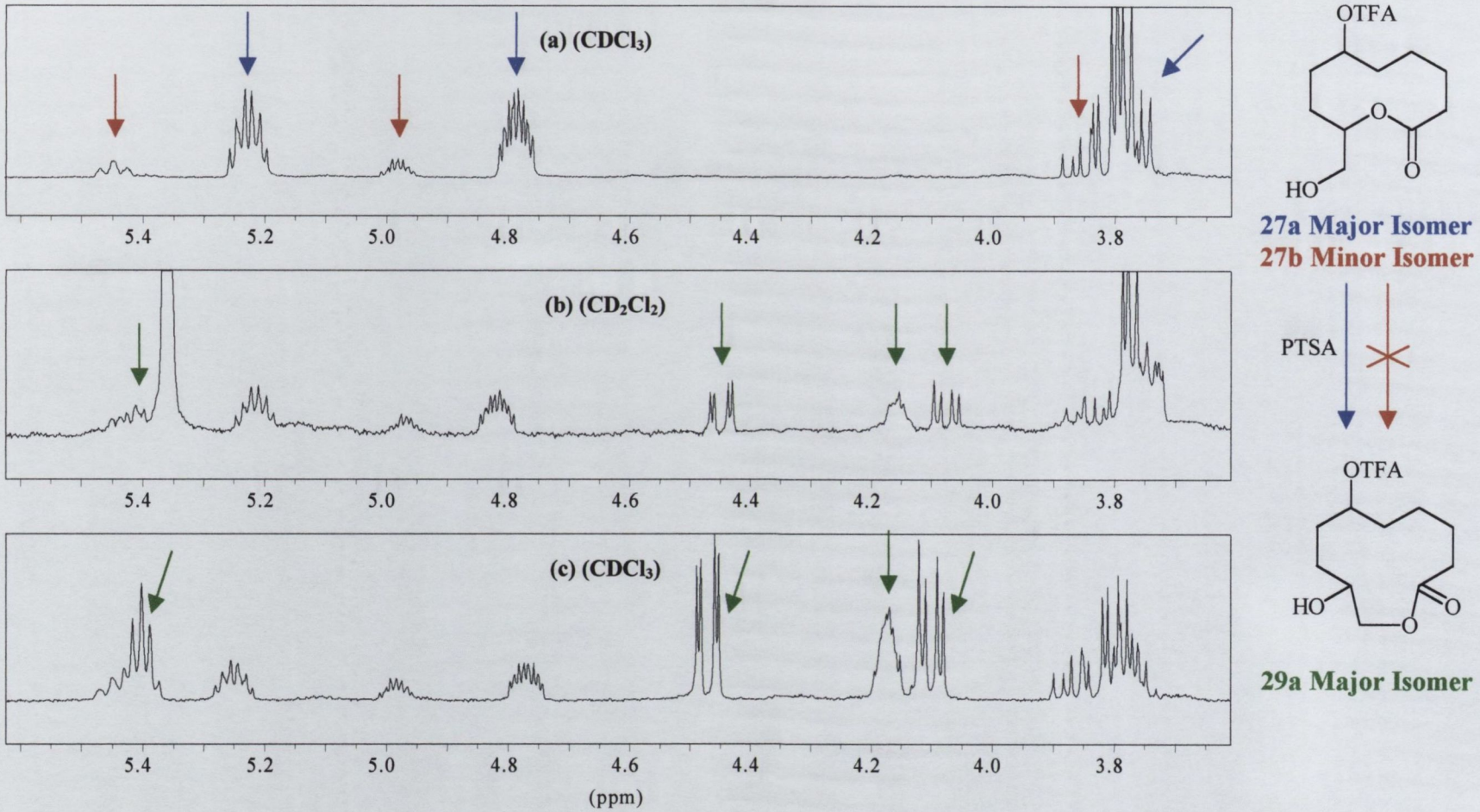


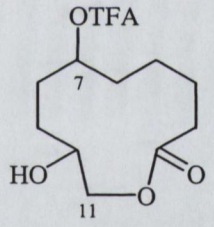
Figure 3.10 **(a)** - Lactones **27** before exposure to PTSA **(b)** - reaction mixture 2 hr after addition of PTSA, major isomer **27a** 35% converted to **29a**

(c) - Isolated product mixture consisting of minor isomer **27b** (23%), major isomer **27a** (27%) and corresponding major isomer product **29a** (50%).

NMR spectroscopy showed that this reaction had reached equilibrium after 72 hr at room temperature. The ^{1}H NMR spectrum of the reaction mixture at this time showed 64% conversion of the major diastereoisomer **27a** to the eleven-membered lactone **29a** with no reaction observed in the case of the minor diastereoisomer **27b**. Separation of the ten- and eleven-membered lactones, **27** and **29**, by column chromatography was unsuccessful due to the fact that the two lactones had exactly the same R_f values in all solvent systems that were examined. The isolated product mixture consisted of the minor isomer **27b** (23%), the major isomer **27a** (27%) and the corresponding ring-expanded major isomer product **29a** (50%).

Table 3.11

Distinguishing NMR spectroscopic details for 10-hydroxy-7-trifluoroacetoxy-oxacycloundecan-2-one 29a



29

^{13}C (ppm)	^{1}H (ppm)	Multiplicity	Assignment
CH_2 33.5	CH_a 2.39	ddd ^{2}J 14.0, $^{3}J_1$ 7.5, $3J_2$ 6.0	C-3
	CH_b 2.54-2.61	m	
CH_2 66.3	CH_a 4.10	dd, ^{2}J 12.0, ^{3}J 4.5	C-11
	CH_b 4.46	dd, ^{2}J 12.0, ^{3}J 3.0	
CH 67.8	CH_2 4.15-4.19	m	C-10
CH 77.9	CH_2 5.37-5.43	m	C-7
C=O 172.7	-	-	C-2

The IR spectrum of the oily mixture of the ten- and eleven-membered lactones **27** and **29** shows absorptions at 3440 cm^{-1} (OH), 1779 cm^{-1} (trifluoroacetoxy C=O) and 1735 cm^{-1} (lactone C=O). The details of the NMR spectra of the eleven-membered lactone 10-hydroxy-7-trifluoroacetoxy-oxacycloundecan-2-one **29a** were obtained by subtraction of the relevant peaks that were due to the ten-membered lactones **27** from the spectra of the mixture. Hence, the distinguishing features were identified and are summarised in **Table 3.11**. Assignment was aided by ^{1}H-^{1}H COSY and ^{13}C-^{1}H COSY experiments, **Figure 3.11**. Assignment of the complicated upfield area was difficult due to the presence of the ten-membered lactones **27**. The ^{19}F NMR spectrum of the mixture showed one CF_3 resonance at δ_F –75.7 ppm.

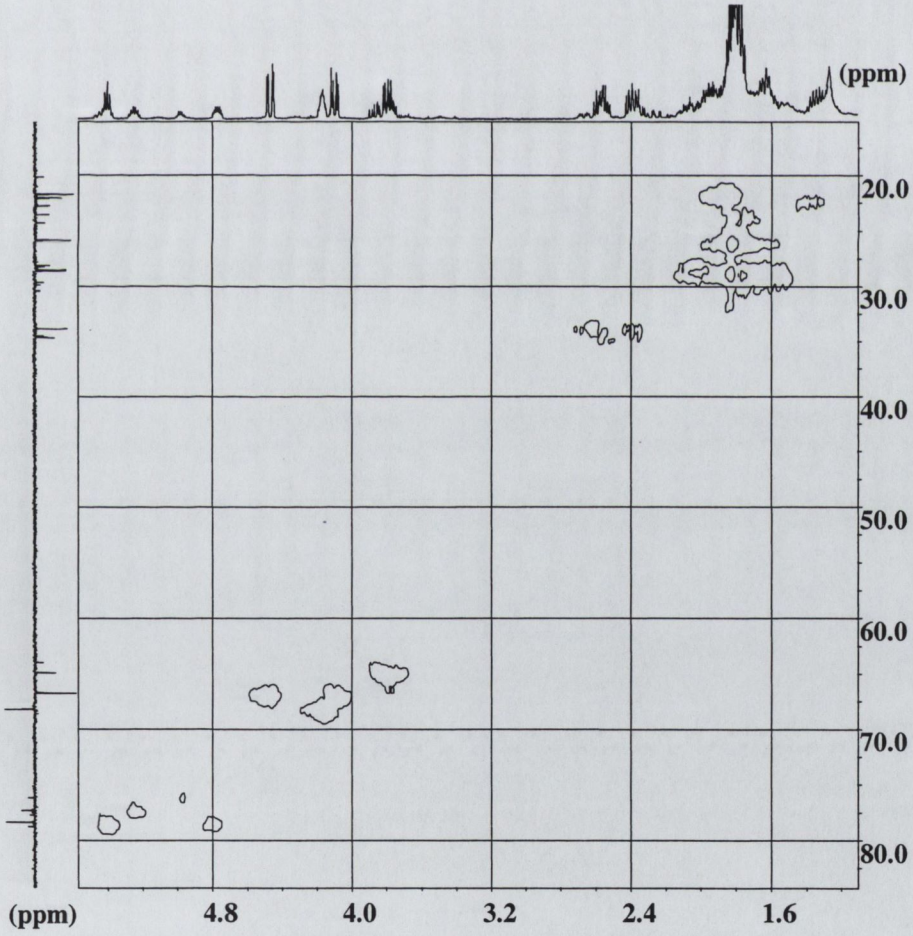


Figure 3.11

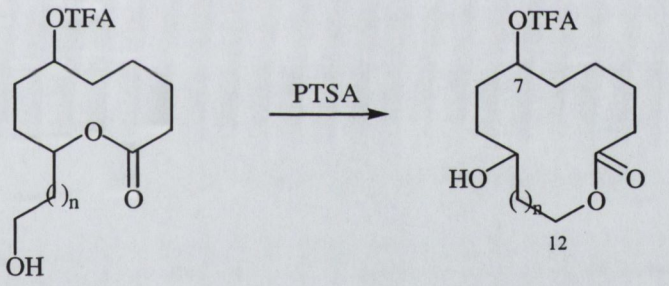
^{13}C-^{1}H COSY Spectrum of a mixture of 10-hydroxy-7-trifluoroacetoxy-oxacycloundecan-2-one 29 and 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27

It was noted that the major diastereoisomer **27a** underwent translactonisation even in the absence of PTSA. When a sample of **27** was left standing in chloroform at room temperature for four days, an 18% conversion into the eleven-membered lactone **29a** was observed. This presumably occurred due to the presence of trace amount of hydrochloric acid in the chloroform.

Following this promising result, the translactonisation reaction of the analogous hydroxyethyl lactone **28** was attempted.

3.5.2 Translactonisation of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28

10-(2'-Hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one **28**, **Scheme 3.24**, was subjected to the usual acidic conditions (5 mol% PTSA in CD_2Cl_2 at room temperature) and the reaction was monitored by NMR spectroscopy.



28 n = 1
27 n = 0

30 n = 1
29 n = 0

Scheme 3.24

As in the case of the reaction of the hydroxymethyl analogue, Section 3.5.1, new peaks corresponding to those expected for the anticipated twelve-membered lactone **30** were observed in the ^1H NMR spectrum of the reaction mixture, **Figure 3.12**. Distinctive features of these new sets of signals included a well-separated AB system consisting of two double double doublets centred at δ_H 4.31 and 4.47 ppm. These signals were thought to be due to the non-equivalent methylene protons of C-12 which experience geminal and vicinal coupling. Other new signals that were observed included two multiplets centred at δ_H 3.97 and 5.18 ppm corresponding to the methine protons of C-10 and C-7 respectively.

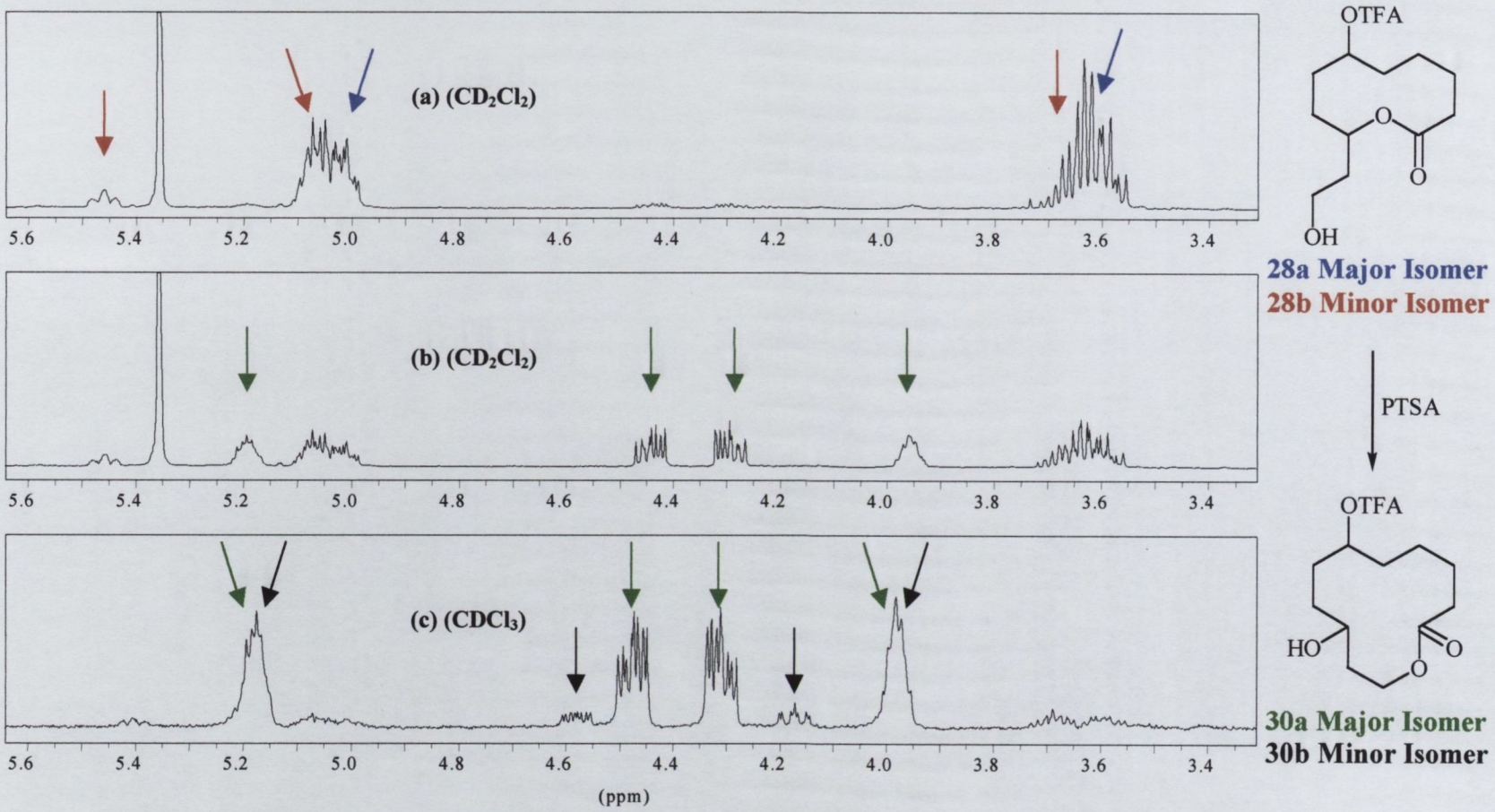
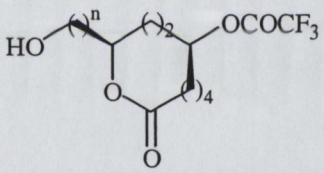
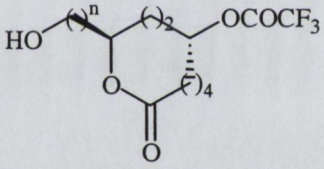


Figure 3.12 **(a)** – Lactones **28** before exposure to PTSA **(b)** - Reaction mixture 3 hr after addition of PTSA, major isomer **28a** 57% converted to **69** **(c)** –Product mixture ($CDCl_3$) isolated after 66 hr, major isomer **28a** 92% converted to **30a**, minor isomer **28b** 63% converted to **30**

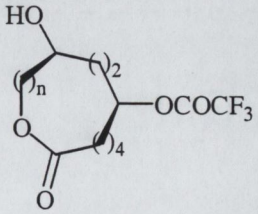
The crude product was found to consist of a mixture of ten-membered lactones **28** and twelve-membered lactones **30**. For the major isomer **28a** there was 92% conversion to the corresponding twelve-membered lactone **30a** after 22 hr at room temperature, **Scheme 3.25**. Interestingly, in this case, the minor isomer **28b** did undergo tranlactonisation with 63% conversion to the corresponding twelve-membered lactone **30b**, however, the reaction was slower then that of the major isomer with conversion occurring over 66 hr at room temperature. In the analogous reaction of the hydroxymethyl lactone **27** the minor isomer **27b** was unaffected by exposure to PTSA. It would seem that the conformation of the ring of the minor diastereoisomer in both the hydroxymethyl and hydroxyethyl ten-membered lactones must be such that translactonisation cannot occur readily. However, in the case of the hydroxyethyl lactone **28b**, the fact that the hydroxyalkyl chain is longer than in the hydroxymethyl lactone **27b** enables reaction to occur, although somewhat more slowly then in the case of the major isomer **28a**. These results are presented in graphical form below, **Figure 3.13**.



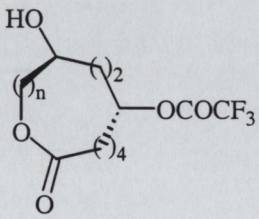
27a n = 1 major diastereoisomer
28a n = 2 major diastereoisomer



27b n = 1 minor diastereoisomer
28b n = 2 minor diastereoisomer



29a n = 1, major diastereoisomer
30a n = 2, major diastereoisomer



29b n = 1, minor diastereoisomer
30b n = 2, minor diastereoisomer

Scheme 3.25

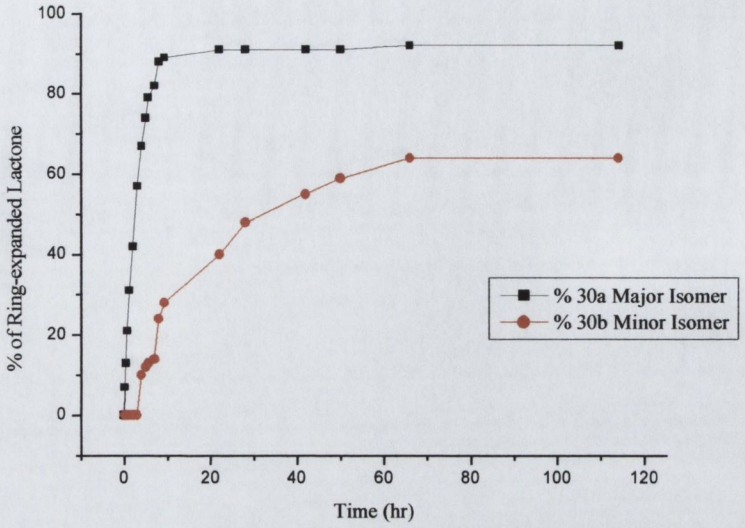
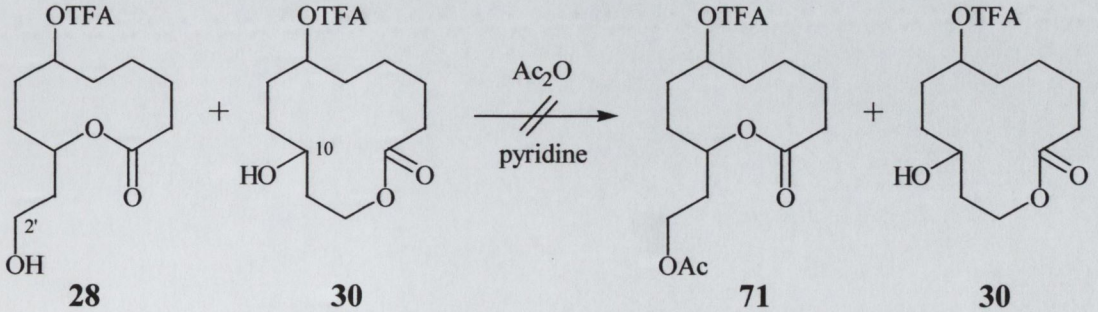


Figure 3.13

Plot of % of ring-expanded products 30a and 30b *vs* reaction time

Purification of the crude product mixture by column chromatography was attempted. However, as for the case of the analogous hydroxymethyl lactones **27** and **29**, separation of the ten- and twelve-membered lactones **28** and **30** failed. In an attempt to separate these lactones, the mixture was exposed to acetic anhydride and pyridine in the hope that the exposed C-2' hydroxyl function of the ten-membered lactone **28** would be converted into the corresponding acetate while the somewhat hindered C-10 hydroxyl group of the twelve-membered lactone **30** would remain unaffected, **Scheme 3.26**. If successful, this would facilitate separation of the two lactones *via* column chromatography. Unfortunately, none of the lactones were acetylated under these conditions.



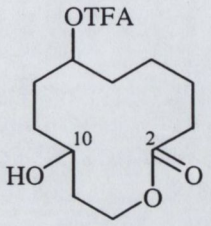
Scheme 3.26

The mixture of lactones **28** and **30** shows IR absorptions at 3424 cm^{-1} (OH), 1779 cm^{-1} (trifluoroacetoxy C=O) and 1732 cm^{-1} (lactone C=O). The NMR spectroscopic details for compounds **30** were obtained by subtraction of the relevant peaks due to the ten-membered lactones **28** and are summarised in **Table 3.12**. Key resonances in the ^1H NMR spectrum of **30** include a multiplet at δ_H 2.42-2.46 ppm which resembles two double double doublets overlapping almost completely. This signal is assigned to the C-3 methylene protons adjacent to the lactone carbonyl function of both the major and minor diastereoisomers. A multiplet δ_H 3.96-3.99 ppm is assigned to the C-10 methine protons of the major and minor isomers. The non-equivalent methylene protons on C-12 appear as an AB system consisting of two double double doublets centred at δ_H 4.31 and 4.47 ppm for the major isomer **30a** and at δ_H 4.17 and 4.57 ppm for the minor isomer **30b**, with a geminal coupling constant of 11.5 Hz observed in both cases. A multiplet at δ_H 5.16-5.20 ppm is assigned to the C-7 methine proton adjacent to the trifluoroacetoxy function in both the major and minor isomers. ^1H-^1H COSY and ^{13}C-^1H COSY experiments confirmed these assignments. The upfield area of the ^1H NMR spectrum was complex due to the numerous methylene protons present, however, a distinctive multiplet at δ_H 1.92-1.97 ppm was assigned to the C-11 protons since coupling to the signals of the C-10 protons was observed in the ^1H-^1H COSY.

The ^{13}C NMR spectrum of **30** shows features in agreement with the proposed structure, **Table 3.12**. A quartet with a coupling constant of 284 Hz is observed at δ_C 114 ppm and is assigned to the CF_3 group of the trifluoroacetoxy function. Similarly, a quartet with a coupling constant of 41.5 Hz is observed at δ_C 156 ppm which is typical for a carbonyl group of a trifluoroacetoxy function. The lactonic carbonyl carbon appears at 172.5 ppm. The ^{19}F NMR spectrum shows the presence of one CF_3 resonating at δ_F –75.8 ppm.

Table 3.12

NMR Spectroscopic details for 10-hydroxy-7-trifluoroacetoxy-oxacyclododecan-2-one 30a (major isomer)

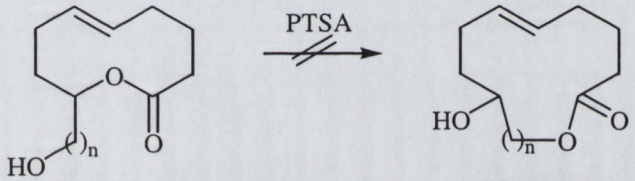


30

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 19.8	C*H*$_2$ 1.37-1.55		
*C*H$_2$ 22.9	C*H*$_2$ 1.64-1.90		
*C*H$_2$ 24.5	C*H*$_2$ 1.64-1.90		C-4/5/6/8/9
*C*H$_2$ 27.0	C*H*$_2$ 1.64-1.90	m	
*C*H$_2$ 29.3	C*H*$_2$ 1.64-1.90		
*C*H$_2$ 32.0	C*H*$_2$ 2.42-2.46		C-3
*C*H$_2$ 32.9	C*H*$_2$ 1.92-1.97		C-11
*C*H$_2$ 59.8	C*H*$_a$ 4.31 C*H*$_b$ 4.47	ddd, ^{2}J 11.5, $^{3}J_1$ 7.0, $^{3}J_2$3.5 ddd, ^{2}J 11.5, $^{3}J_1$ 6.5, $^{3}J_2$ 3.0	C-12
*C*H 69.4	C*H* 3.96-3.99	m	C-10
*C*H 77.9	C*H* 5.16-5.20	m	C-7
CO*C*F$_3$ 114.0	-	q, $J_{F,C}$ 284.0	CO*C*F$_3$
*C*OCF$_3$ 156.0	-	q, $J_{F,C}$ 41.5	*C*OCF$_3$
C=O 172.5	-	-	C-2

3.5.3 Attempted translactonisation reactions of unsaturated lactones (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31 and (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32

When (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one **31** was subjected to the usual acidic conditions (PTSA 5 mol% in CD_2Cl_2 at room temperature) a rearrangement resulting in the formation of an eleven-membered lactone **33** was anticipated, **Scheme 3.27**. However, surprisingly, no change was observed even after prolonged exposure to the acid. When the homologous (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one **32** was subjected to the same acidic conditions, again no reaction was observed.

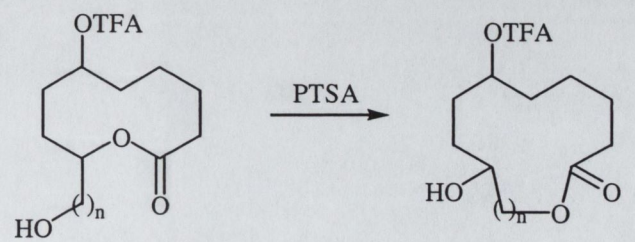


31 n = 1
32 n = 2

33 n = 1
34 n = 2

Scheme 3.27

In both cases, there must be some conformational restriction, presumably originating from the presence of the double bond, that effects the positions of the hydroxyalkyl chains to such an extent that they cannot come into close proximity with the lactone carbonyl group and therefore reaction is not possible. Due to the fact that saturated trifluoroacetoxy lactones **27** and **28** underwent relatively facile translactonisation, **Scheme 3.28**, whereas the unsaturated lactones **31** and **32** were unaffected by the presence of acid, **Scheme 3.27**, it was apparent that the hybridisation of positions C-6 and C-7 had some pivotal role in determining the conformation of the ring.

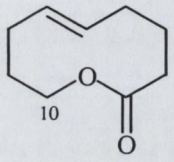


27 n = 1
28 n = 2

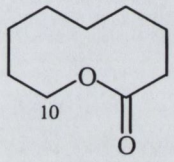
29 n = 1
30 n = 2

Scheme 3.28

A similar observation was noted by Roycroft[25] with regard to the ten-membered lactone **72**. In the ^{1}H NMR of this lactone, the methylene protons on C-10 appear as an AB system displaying a very large separation with resonances centred at δ_H 3.60 and 5.00 ppm. In the saturated analogue **73**,[26] these protons both resonate at δ_H 4.25 ppm. The unusual findings for the case of unsaturated lactone **72** were thought to arise from the conformation adopted by the lactone due to the presence of the olefinic function.



72

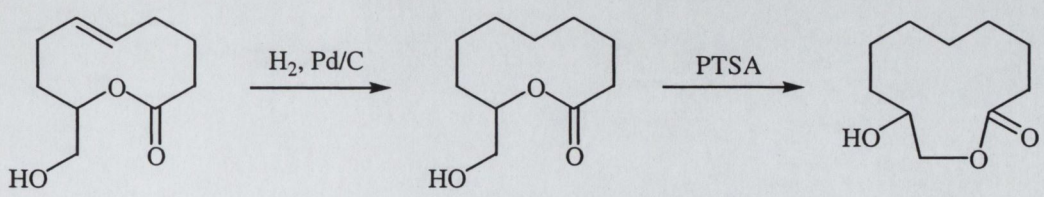


73

Simple catalytic hydrogenation of the unsaturated lactones **31** and **32** would lead to the formation of the corresponding saturated lactones which do not bear a substituent on C-7. Hence, the ability of these lactones to undergo a ring-expansion reaction was investigated.

3.5.4 Hydrogenation of (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31

Unsaturated lactone **31** was hydrogenated in the presence of palladium on activated charcoal, **Scheme 3.29** to give 10-hydroxymethyl-oxecan-2-one **74** (85%). This saturated lactone, which did not possess a substituent on C-7, had the potential to undergo rearrangement in the presence of acid to form the eleven-membered saturated lactone **75**.



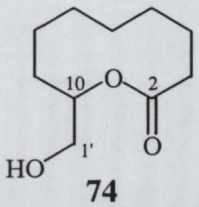
31 **74** **75**

Scheme 3.29

10-Hydroxymethyl-oxecan-2-one **74** shows IR absorptions at 3421 cm^{-1} (OH) and 1718 cm^{-1} (lactone carbonyl). The NMR spectroscopic data of **74** show features characteristic of all the other ten-membered lactones obtained. Key features in the ^1H NMR spectrum, **Figure 3.14**, include two double double doublets centred at δ_H 2.28 and 2.54 ppm that are assigned to the methylene protons at C-3. The methine proton on C-10, split by the non-equivalent protons of C-9 and C-1', appears as a double double double doublet centred at δ_H 4.94. ^1H-^1H COSY and ^{13}C-^1H COSY experiments assisted the assignment of the various proton and carbon resonances and are summarised in **Table 3.13**.

Table 3.13

NMR Spectroscopic details for 10-hydroxymethyl-oxecan-2-one 74



74

^{13}C (ppm)	^1H (ppm)	Multiplicity (^1H NMR)	Assignment
CH_2 20.4	CH_2 1.42-1.80	↑	↑
CH_2 23.5	CH_2 1.42-1.80		
CH_2 24.0	CH_2 1.42-1.80	m	C-5/6/7/8
CH_2 24.1	CH_2 1.42-1.80	↓	↓
CH_2 26.4	CH_a 1.42-1.80	m	C-4
	CH_b 1.98-2.10	m	
CH_2 27.1	CH_a 1.42-1.80	m	C-9
	CH_b 1.87	dddd, ^2J 10.5, $^3J_1$ 7.5, $^3J_2$ 4.0, $^3J_3$ 2.5	
CH_2 34.6	CH_a 2.28	ddd, ^2J 15.5, $^3J_1$ 11.0, $^3J_2$ 3.0	C-3
	CH_b 2.54	ddd, ^2J 15.5, $^3J_1$ 7.0, $^3J_2$ 3.5	
CH_2 64.6	CH_a 3.72	dd, ^2J 11.5, ^3J 4.0	C-1'
	CH_b 3.77	dd, ^2J 11.5, ^3J 6.5	
CH 77.6	CH 4.94	dddd, $^3J_1$ 9.5, $^3J_2$ 6.5, $^3J_3$ 4.0, $^3J_4$ 2.5	C-10
C=O 174.6	-	-	C-2

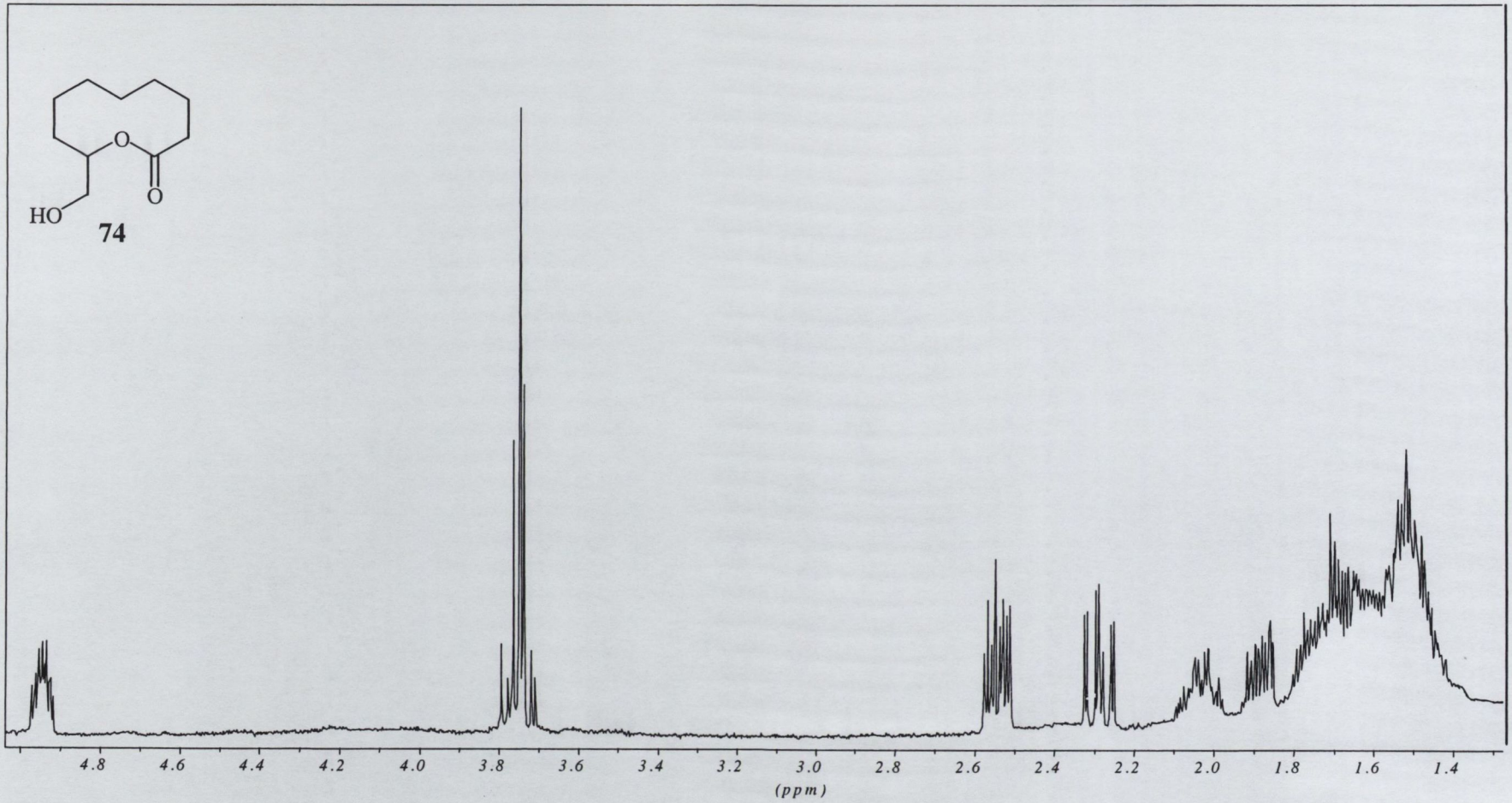
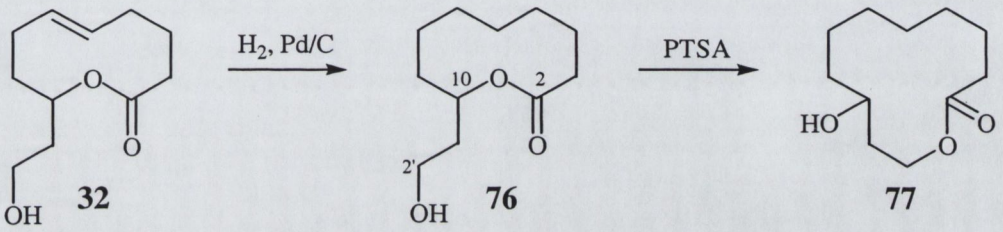


Figure 3.14

^{1}H NMR Spectrum of 10-hydroxymethyl-oxecan-2-one 74

3.5.5 Hydrogenation of (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32

Lactone **32** was also reduced by hydrogenation in the presence of palladium on activated charcoal, **Scheme 3.30**, and 10-(2'-hydroxyethyl)-oxecan-2-one **76** was obtained. This could possibly undergo rearrangement in the presence of acid, resulting in formation of twelve-membered saturated lactone **77**.



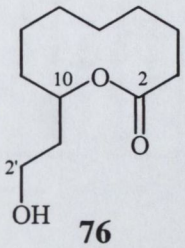
Scheme 3.30

10-(2'-Hydroxyethyl)-oxecan-2-one **76** was obtained as an oil and shows IR absorptions at 3408 cm^{-1} (OH) and 1725 cm^{-1} (C=O). Key resonances observed in the ^1H NMR spectrum,

Figure 3.15, include an AB system consisting of a set of two double double doublets centred at δ_H 2.25 and 2.54 ppm which are assigned to the non-equivalent methylene protons of C-3. A geminal coupling constant of 15.0 Hz is observed. The protons of C-2' adjacent to the hydroxyl function are observed as two double double doublets centred at δ_H 3.55 and 3.65 ppm with a geminal coupling constant of 11.5 Hz. The methine proton of C-10 appears as a double double double doublet at δ_H 5.03 due to vicinal coupling to the methylene protons of C-9 and C-1'. The region between δ_H 1.26 and 2.09 ppm is complex due to the presence of seven sets of largely non-equivalent methylene protons. Significant signals in the ^{13}C NMR spectrum of **76** include that of the C-2' methylene carbon which appears at δ_C 57.9 ppm. A signal due to the C-10 methine carbon appears at δ_C 73.6 ppm while the lactonic carbonyl carbon is visible at δ_C 175.6 ppm. ^{13}C-^1H COSY and ^1H-^1H COSY experiments substantiated all these assignments that are summarised in **Table 3.14**.

Table 3.14

NMR Spectroscopic details for 10-(2'-hydroxyethyl)-oxecan-2-one 76



76

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 20.3	C*H*$_a$ 1.54-1.68 C*H*$_b$ 1.99-2.09		C-4
*C*H$_2$ 24.1	C*H*$_2$ 1.41-1.68		
*C*H$_2$ 24.2	C*H*$_2$ 1.72-1.91		
*C*H$_2$ 24.5	C*H*$_a$ 1.26-1.32 C*H*$_b$ 1.41-1.68	m	C-5/6/7/8/9/1'
*C*H$_2$ 26.5	C*H*$_2$ 1.41-1.68		
*C*H$_2$ 32.1	C*H*$_a$ 1.41-1.68 C*H*$_b$ 1.72-1.91		
*C*H$_2$ 34.6	C*H*$_a$ 2.25 C*H*$_b$ 2.54	ddd, ^{2}J 15.0, $^{3}J_1$ 12.0, $^{3}J_2$ 3.0 ddd, ^{2}J 15.0, $^{3}J_1$ 6.5, $^{3}J_2$ 3.0	C-3
*C*H$_2$ 37.4	C*H*$_2$ 1.72-1.91	m	C-5/6/7/8/9/1'
*C*H$_2$ 57.9	C*H*$_a$ 3.55 C*H*$_b$ 3.65	ddd, ^{2}J 11.5, $^{3}J_1$ 10.0, $^{3}J_2$ 4.0 ddd, ^{2}J 11.5, $^{3}J_1$ 5.5, $^{3}J_2$ 4.0	C-2'
*C*H 73.6	C*H* 5.03	dddd $^{3}J_1$ 11.0, $^{3}J_2$ 9.0, $^{3}J_3$ 3.5, $^{3}J_4$ 2.5	C-10
C=O 175.6	-	-	C-2

It was noted that the ^{1}H NMR spectrum of the lactone **76**, **Figure 3.15**, displayed some peaks that corresponded to those expected for the structure of the ring-enlarged twelve-membered lactone **77**. Thus, facile translactonisation for **76** was anticipated.

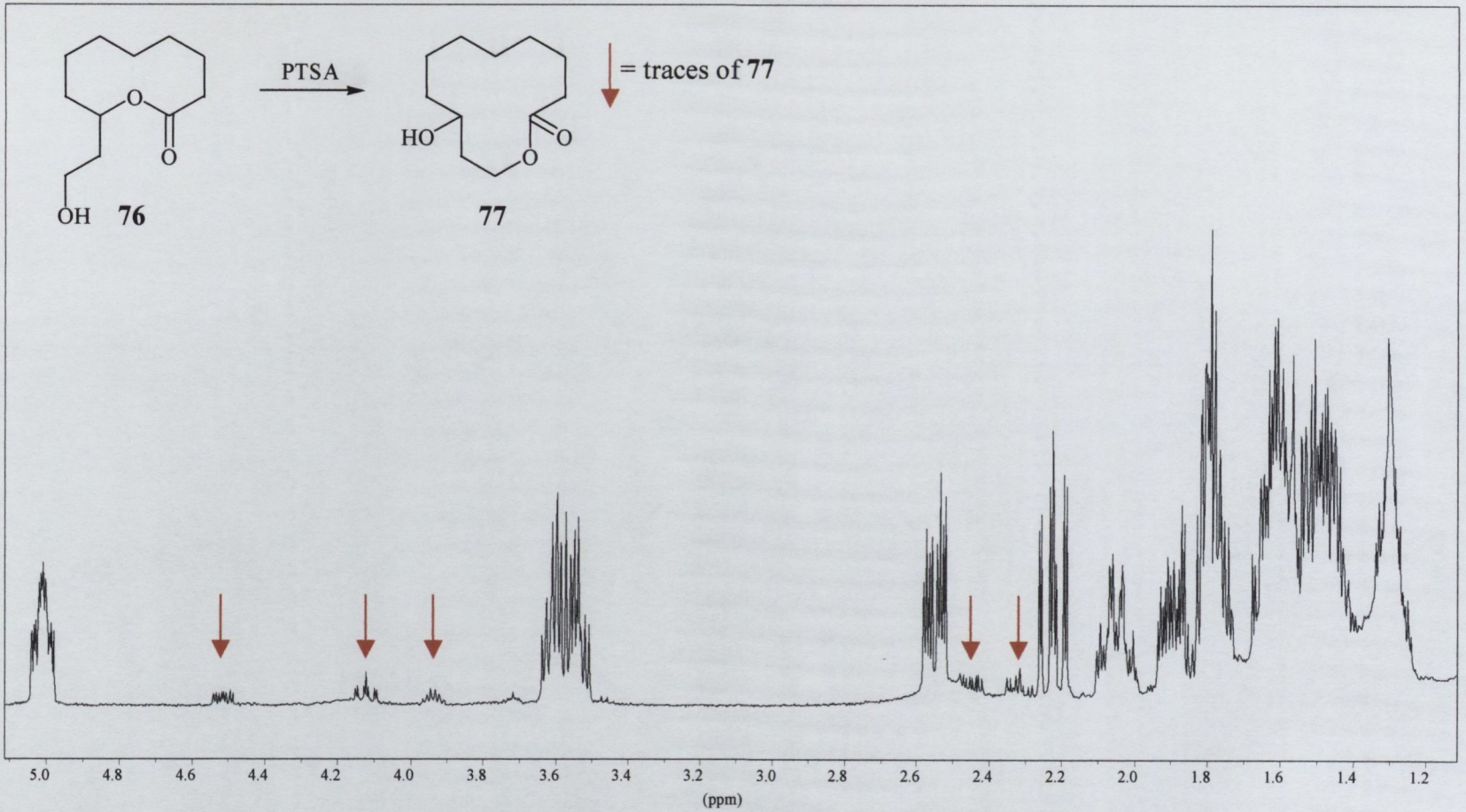
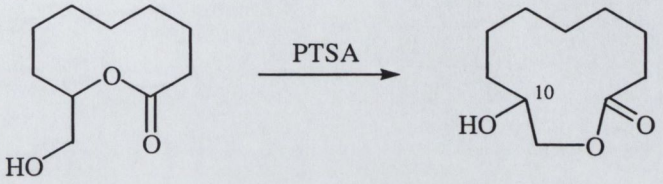


Figure 3.15

^{1}H NMR Spectrum of 10-(2'-hydroxyethyl)-oxecan-2-one 76

3.5.6 Translactonisation reaction of 10-hydroxymethyl-oxecan-2-one 74

10-Hydroxymethyl-oxecan-2-one **74** was subjected to the usual acidic conditions (PTSA 5 mol% in CD_2Cl_2 at room temperature) and the reaction was monitored by NMR spectroscopy, **Scheme 3.31**.



74 **75**

Scheme 3.31

As expected, new signals corresponding to those expected for the anticipated eleven-membered lactone **75** were observed, **Figure 3.16**. Distinctive features of these new sets of signals included a well-separated AB system consisting of two double doublets visible at δ_H 4.11 and 4.20 ppm. These signals were thought to be due to the methylene protons at C-11 of **75**. A multiplet centred at δ_H 4.02 ppm was also observed and corresponds to the C-10 methine proton.

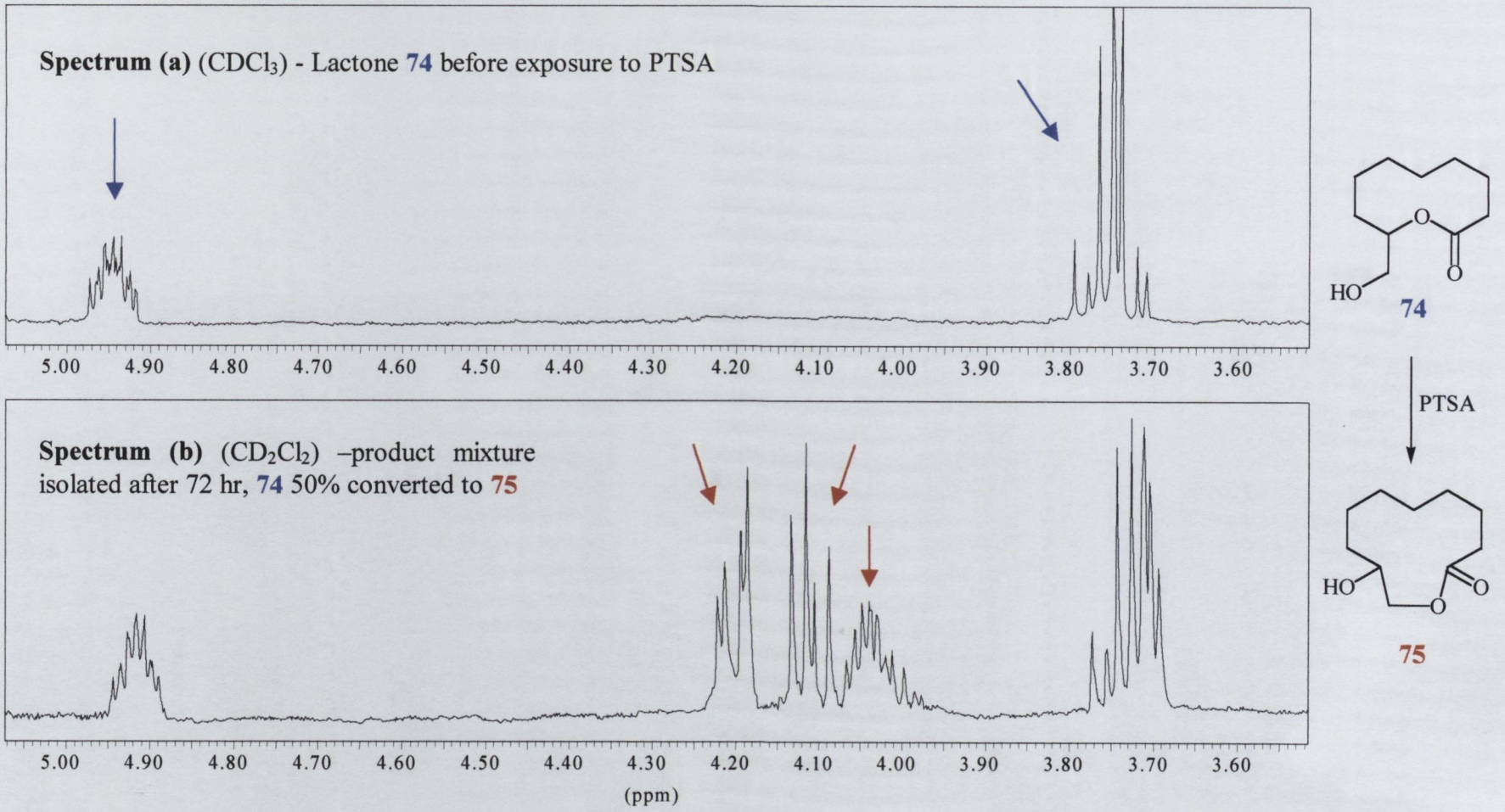
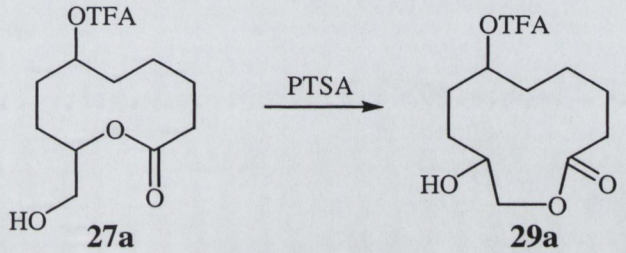

Spectrum (a) (CDCl3) - Lactone 74 before exposure to PTSA
5.00 4.90 4.80 4.70 4.60 4.50 4.40 4.30 4.20 4.10 4.00 3.90 3.80 3.70 3.60
Spectrum (b) (CD2Cl2) –product mixture isolated after 72 hr, 74 50% converted to 75
5.00 4.90 4.80 4.70 4.60 4.50 4.40 4.30 4.20 4.10 4.00 3.90 3.80 3.70 3.60
(ppm)
HO
O
O
74
PTSA
HO
O
O
75

Figure 3.16

NMR spectroscopy showed that this reaction had reached equilibrium after 72 hr at room temperature. The ^{1}H NMR spectrum of the reaction mixture at this time showed 50% conversion to the eleven-membered lactone **75**. This result is comparable to that obtained for the analogous trifluoroacetoxy lactone **27a** (major diastereoisomer) which also underwent ring-enlargement to form eleven-membered **29a** in 72 hr with 64% conversion, **Scheme 3.32**.



27a **29a**

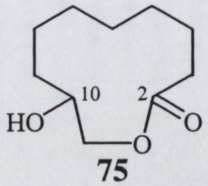
Scheme 3.32

Purification of the crude product obtained from the reaction of lactone **74** by column chromatography was attempted. However, as in the case of the lactone mixture containing ring-expanded lactone **29**, separation of the ten- and eleven-membered lactones, **74** and **75** failed.

The isolated product mixture consisting of **74** and **75** shows IR absorptions at 3421 cm^{-1} (OH) and 1733 cm^{-1} (C=O). The NMR spectroscopic details for the eleven-membered lactone **75** were obtained by subtraction of the relevant peaks due to the ten-membered lactone **74** from the spectra of the mixture. Hence, the distinguishing features were identified and are summarised in **Table 3.15**. These assignments were aided by ^{1}H-^{1}H and ^{13}C-^{1}H COSY experiments, however, assignment of the complicated upfield area was difficult due to the presence of the ten-membered lactone **74**.

Table 3.15

Distinguishing NMR spectroscopic details for 10-hydroxy -oxacycloundecan-2-one

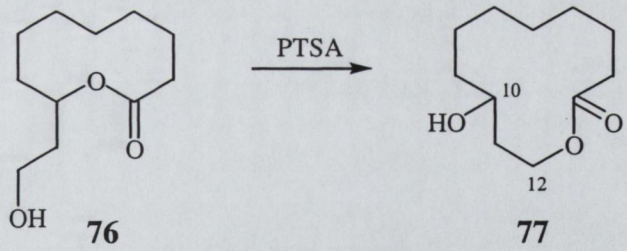


75

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
*C*H$_2$ 34.6	C*H*$_2$ 2.34-2.45	m	C-3
*C*H$_2$ 66.6	C*H*$_a$ 4.20	dd, ^{2}J 11.0, ^{3}J 3.0	C-11
	C*H*$_b$ 4.11	dd, ^{2}J 11.0, ^{3}J 7.0	
*C*H 67.9	C*H* 3.99-4.06	m	C-10
C=O 174.3	-	-	C-2

3.5.7 Tranlactonisation of 10-(2'-hydroxyethyl)-oxecan-2-one 76

10-(2'-Hydroxyethyl)-oxecan-2-one **76** was subjected to the usual acidic conditions (PTSA 5 mol% in CD_2Cl_2 at room temperature), **Scheme 3.33**, and the reaction was monitored by NMR spectroscopy.



76 **77**

Scheme 3.33

The ^{1}H NMR spectrum of the ten-membered lactone **76** before exposure to acid had displayed signals that suggested the presence of traces of the ring-enlarged lactone **77**. Therefore, it was not surprising that on the addition of PTSA, these signals showed an increase in size relative to those corresponding to ten-membered **76**, **Figure 3.17**. Distinctive features of these signals included a well-separated AB system consisting of two double double doublets centred at δ_H 4.12 and 4.51 ppm. These new signals were thought to be due to the C-12 methylene protons of **77**. A multiplet centred at δ_H 3.94 ppm corresponds to the C-10 methine proton.

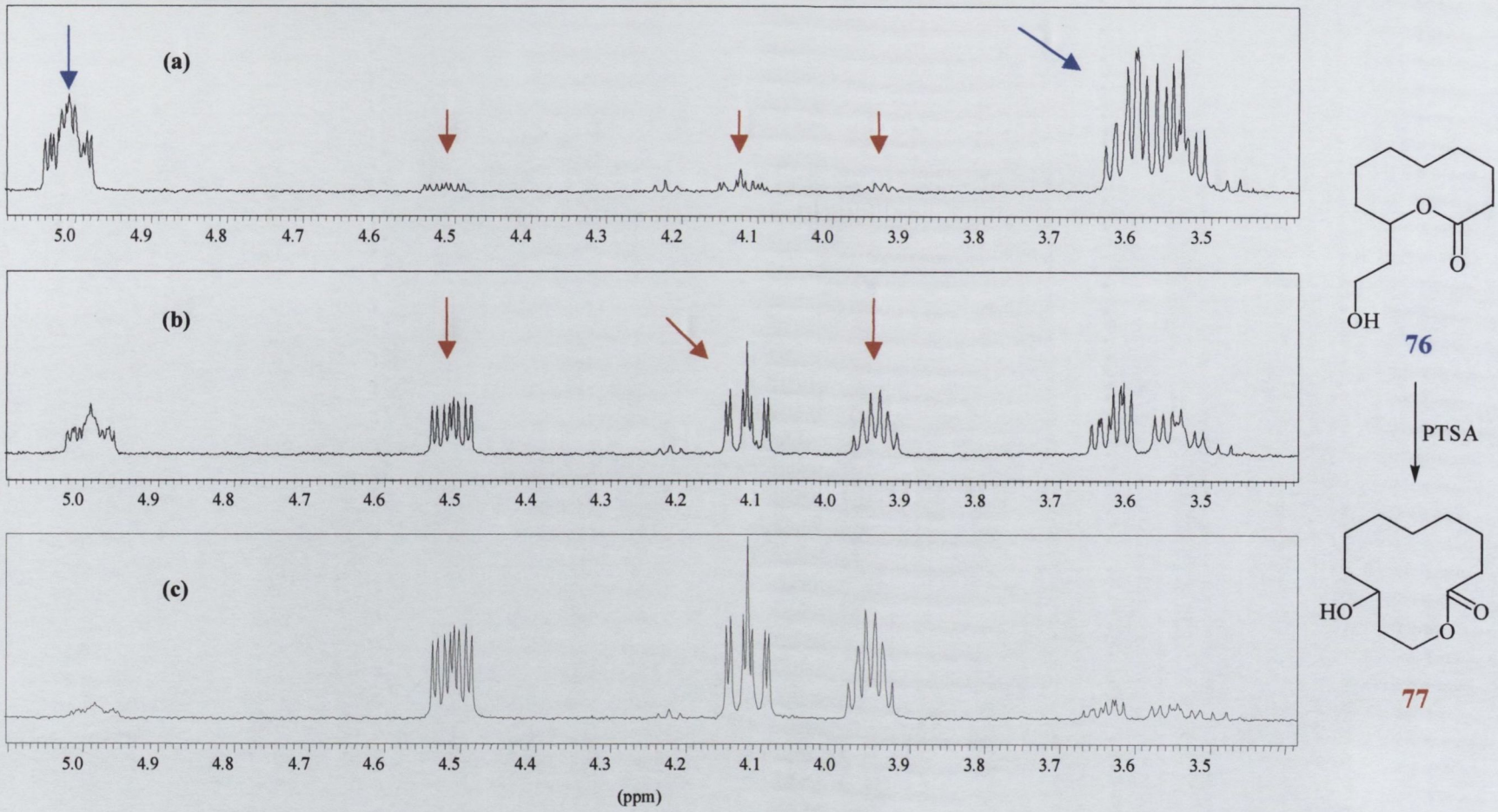
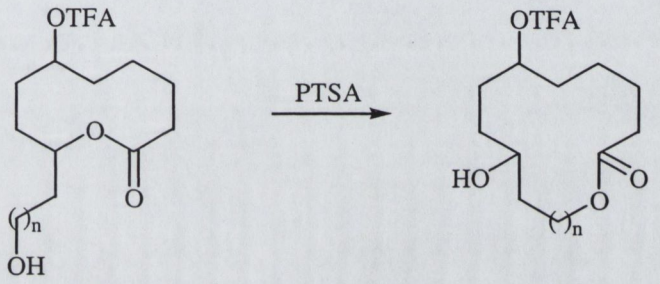


Figure 3.17 **(a)** - Lactone **76** before exposure to PTSA **(b)** – Reaction mixture 5 hr after addition of PTSA, **76** 48% converted to **77**

(c) – Isolated product mixture (after 24 hr) consisting of 14% **76** and 86% **77**

NMR spectroscopy showed that this reaction had reached equilibrium after 24 hr of exposure to PTSA. The ^{1}H NMR of the reaction mixture at this time showed 86% conversion to the twelve-membered lactone **77**. Again, this result is comparable to that obtained for the trifluoroacetoxy lactone **28a** which underwent translactonisation in 22 hr to form the ring-expanded lactone **30a** with 92% conversion, **Scheme 3.34**.



28a **30a**

Scheme 3.34

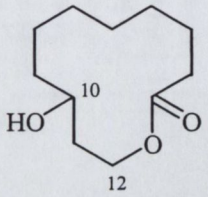
As with every other mixture of lactones obtained during this series of translactonisation reactions, all attempts to separate the ten-membered lactone **76** from the ring-expanded lactone **77** failed.

The oily mixture containing lactones **76** and **77** shows IR absorptions at 3384 cm^{-1} (OH) and 1735 cm^{-1} (C=O). The NMR spectroscopic details of the twelve-membered lactone 10-hydroxy-oxacyclododecan-2-one **77** were obtained by subtraction of the relevant peaks that were due to the ten-membered lactone **76** from the spectra of the mixture. Hence, the distinguishing features were identified and are summarised in **Table 3.16**. Assignment of the complicated upfield area was difficult due to the presence of the ten-membered lactone **76**.

Table 3.16

Distinguishing NMR spectroscopic details for

10-hydroxy-oxacyclododecan-2-one 77



77

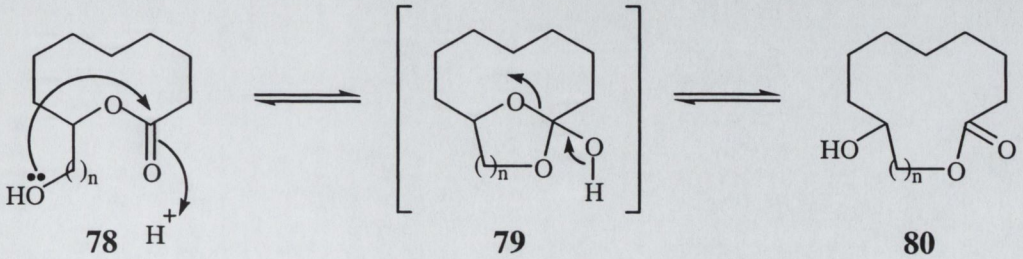
^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
CH_2 34.0	CH_a 2.31	ddd, ^{2}J 14.0, $^{3}J_1$ 10.5, $^{3}J_2$ 4.0	C-3
	CH_b 2.45	ddd, ^{2}J 14.0, $^{3}J_1$ 7.0, $^{3}J_2$ 4.0	
CH_2 60.2	CH_a 4.12	ddd, ^{2}J 11.0, $^{3}J_1$ 7.0, $^{3}J_2$ 2.5	C-12
	CH_b 4.51	ddd, ^{2}J 11.0, $^{3}J_1$ 6.5, $^{3}J_2$ 2.5	
CH 67.9	CH 3.91-3.97	m	C-10
C=O 174.2	-	-	C-2

3.6 Summary and conclusions

This Chapter has described the synthesis of a variety of ten-membered lactones *via* the intramolecular acylative cleavage reaction of tetrahydrofuran derivatives. These lactones all possessed hydroxyalkyl chains situated adjacent to the lactone ether oxygen and hence had the intrinsic ability to undergo a translactonisation process. This set of lactones varied with regard to the rigidity of the ring and also in the length of the hydroxyalkyl chain to be incorporated into the ring, hence, a comparative study was conducted on their ability to form ring-enlarged lactones.

The results obtained for all of the translactonisation reactions that were carried out are summarised in **Table 3.17**. The maximum conversion observed was for the hydroxyethyl lactones **28** and **76** which underwent translactonisation resulting in the formation of the twelve-membered lactones **30** (92%) and **77** (86%) (entries 3 and 8). The hydroxymethyl lactones **27** and **74** also rearranged under acidic conditions, albeit to a lesser extent, to form the ring-expanded products **29** (64%) and **75** (50%) (entries 1 and 7). Interestingly, exposure to PTSA had no effect on the unsaturated lactones **31** and **32** (entries 5 and 6).

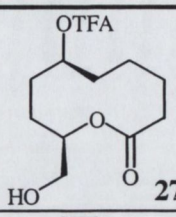
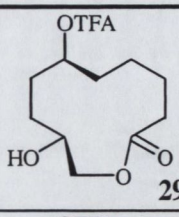
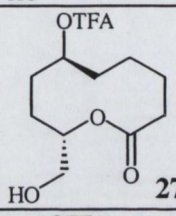
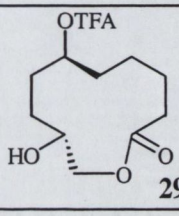
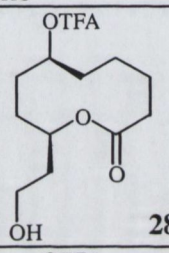
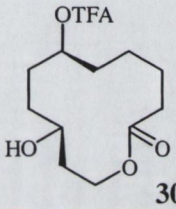
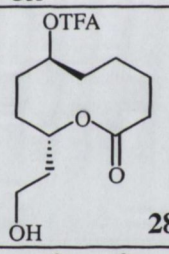
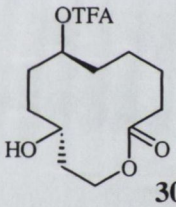
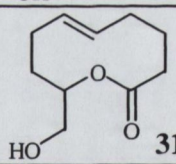
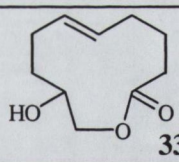
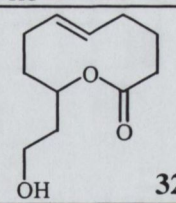
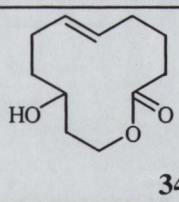
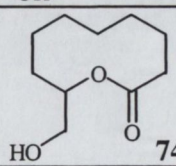
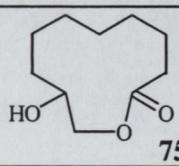
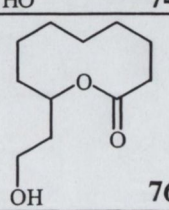
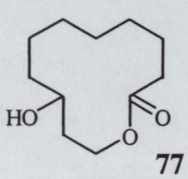
Generally, in the case of medium-ring lactones **78** the driving force for a translactonisation process is the release of ring strain resulting in the formation of a relatively more stable macrocyclic ring **80**, **Scheme 3.35**. Since the ring-expansion reaction is reversible, this macrocyclic ring is in equilibrium with the starting material. However, an additional influencing factor associated with such a transformation is the length of the side-chain to be incorporated into the ring system. The reaction rate decreases with increasing chain length due to the consequential increase in the size of the new ring within the cyclic reaction intermediate **79**.



78 **79** **80**

Scheme 3.35

Table 3.17 Summary of results obtained from translactonisation reactions

Entry	Starter	Expected Product	T (hr)	*Ratio	Conversion
1	 **27a**	 **29a**	72	1:1.8	64%
2	 **27b**	 **29b**	-	no reaction	-
3	 **28a**	 **30a**	22	1:11	92%
4	 **28b**	 **30b**	66	1:1.7	63%
5	 **31**	 **33**	-	no reaction	-
6	 **32**	 **34**	-	no reaction	-
7	 **74**	 **75**	72	1:1	50%
8	 **76**	 **77**	24	1:6.25	86%

***Ratio** = Starting material : ring-enlarged product

On examination of the results obtained for the translactonisation reactions that were carried out, **Table 3.17**, some trends are observed. For the saturated lactones **27a**, **28a**, **74** and **76**, (entries 1, 3, 7 and 8 respectively), **Table 3.17**, the practical result demonstrated by this work is that, although ring-expansion is successful in all cases, the conversions of hydroxymethyl lactones **27a** to **29a** (entry 1) and **74** to **75** (entry 7) reach relatively unfavourable equilibrium positions, with conversion to the ring-enlarged lactones ranging from 50% to 64%. This is unfortunate since the lactone pairs **27a** and **29a**, and **74** and **75**, are not amenable to separation by column chromatography.

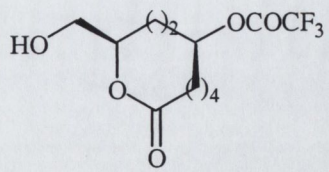
Conversely, the conversion of hydroxyethyl lactone **28a** to **30a**, (entry 3), **Table 3.17**, is practically complete (92% at equilibrium) and this degree of purity is probably adequate for further transformations to be carried out. A similar result was obtained for hydroxyethyl lactone **76** to **77**, (entry 8), with 86% conversion to the ring-enlarged lactone at equilibrium.

A trend is also observed in relation to the time elapsed before equilibrium is reached. For the hydroxymethyl lactones **27a** and **74** (entries 1 and 7), **Table 3.17**, conversion to the corresponding eleven-membered lactones **29a** and **75** is complete after 72 hr exposure to acid. The analogous conversions of hydroxyethyl lactones **28a** and **76** (entries 3 and 8) are complete after just 24 hr exposure to acid.

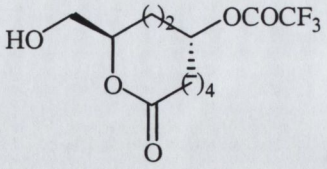
Hence, it can be concluded that, in general, a conversion involving the translactonisation of a saturated hydroxyethyl ten-membered lactone to the corresponding twelve-membered lactone is more efficient than the analogous reaction involving the conversion of a ten-membered hydroxymethyl lactone to the corresponding eleven-membered lactone. This efficiency is two-fold involving the percentage conversion to the twelve-membered ring-expanded lactone and also the reaction time required for attainment of equilibrium.

For trifluoroacetoxy lactones **27** and **28** (entries 1-4), each of which consisted of a mixture of diastereoisomers, differences in reactivity were observed within each isomeric pair. In the case of the diastereoisomers of the hydroxymethyl lactone **27** (entries 1 and 2), which can be represented by illustrations **27a** and **27b**,

respectively, the minor diastereoisomer was unaffected by exposure to acid (entry 2), **Table 3.17**.

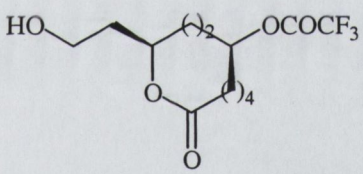


27a major diastereoisomer

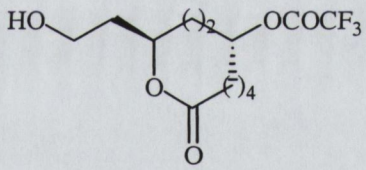


27b minor diastereoisomer

However, in the case of the diastereoisomers of the hydroxyethyl analogue **28** (entries 3 and 4), which can be represented by illustrations **28a** and **28b**, the minor diastereoisomer **28b** did undergo tranlactonisation with 63% conversion to the corresponding twelve-membered lactone **30b** (entry 4), **Table 3.17**. However, its translactonisation reaction was slower than that of the major diastereoisomer **28a** with attainment of equilibrium requiring 66 hr at room temperature. These effects likely reflect minor conformational differences between the members of the pairs **27a/b** and **28a/b**.



28a major diastereoisomer



28b minor diastereoisomer

The inherent lack of reactivity for the unsaturated lactones **31** and **32** (entries 5 and 6), **Table 3.17**, also implies that the conformation of the ten-membered ring plays a pivotal role in controlling whether a translactonisation process can occur or not. These unsaturated lactones must possess some conformational restriction, presumably originating from the presence of the double bond, that affects the positions of the hydroxyalkyl chains to such an extent that they cannot come in close proximity to the lactone carbonyl and therefore reaction is not possible.

Figure 3.18 compiles all of the results that were obtained for the translactonisation reactions of the saturated lactones studied during the course of this work.

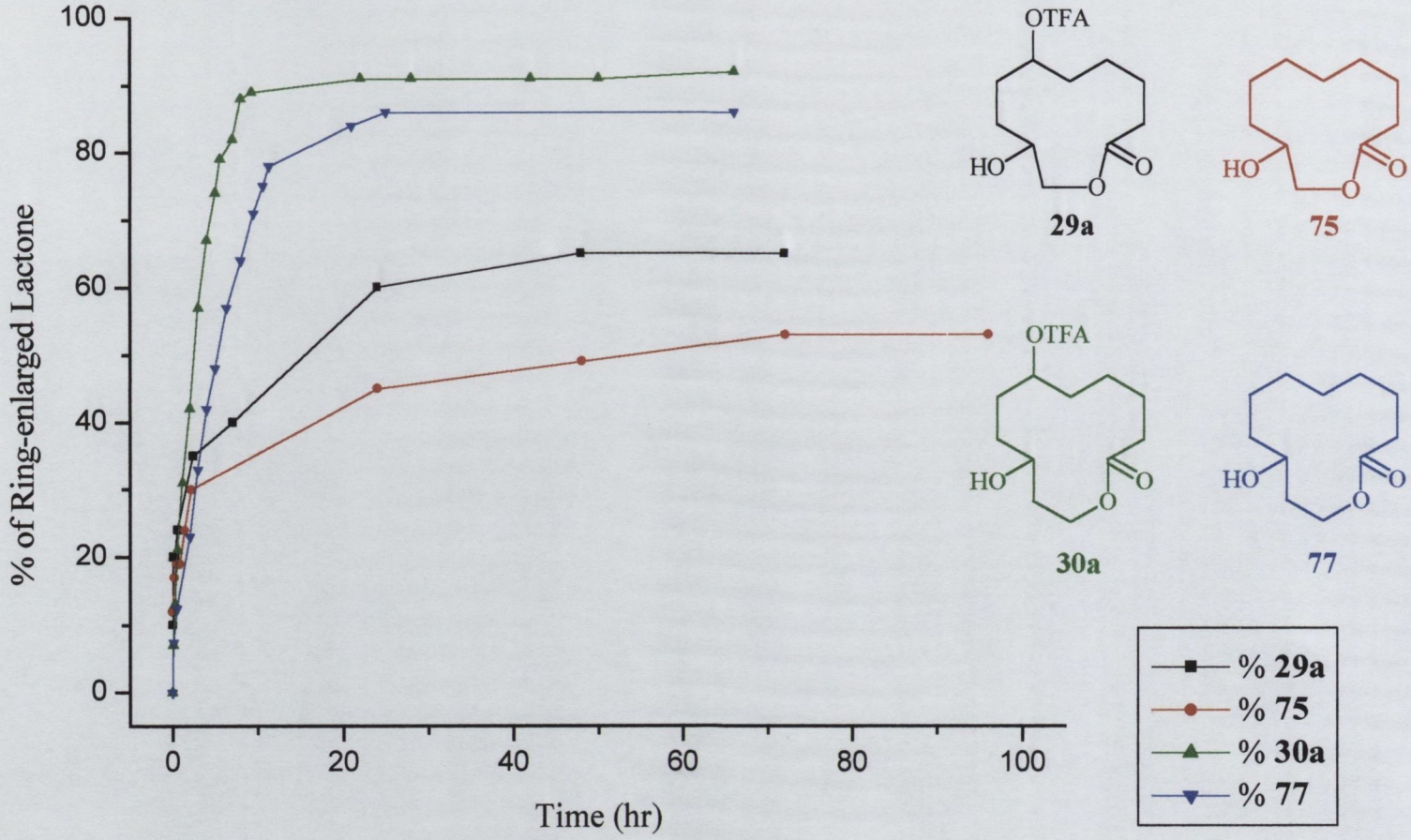


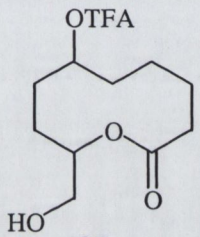
Figure 3.18 Plot of % of ring-expanded products formed *vs* reaction time

In conclusion, the lactonisation methodology involving the acylative cleavage reaction of (tetrahydro-2-furyl)alkanoic acid derivatives was successfully manipulated for the synthesis of an assortment of desired ten-membered lactones. The availability of these lactones facilitated a comprehensive study into their ability to undergo ring-enlargement *via* a translactonisation process. The results thus obtained demonstrated that this route to eleven- and twelve-membered lactones is successful and furthermore efficient, especially in the case of the formation of twelve-membered lactones. Although the formation of macrocyclic lactones *via* tranlactonisation processes has been previously documented, Section 3.1, the availability of the requisite precursor lactones has limited the study and the development of the scope of this creative route. Thus, the research described within this Chapter creates a benchmark for further research into this fascinating area.

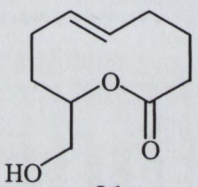
3.7 Experimental

General experimental conditions as for Chapter 2.

3.7.1 Synthesis of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27 and (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31

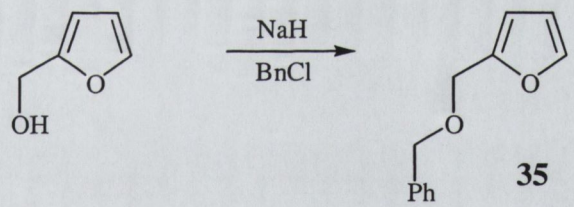


27



31

2-(1'-Benzyloxymethyl)furan 35



35

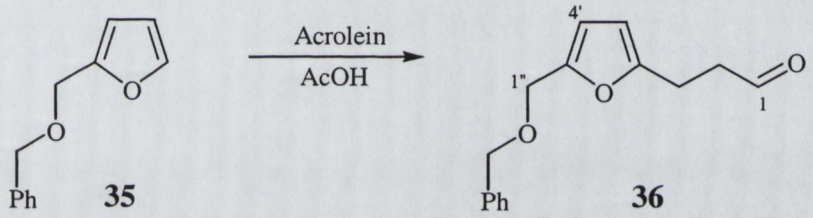
Freshly distilled furfuryl alcohol (6.18 g; 63 mmol) in DMSO (25 ml) was added dropwise to a stirred solution of sodium hydride (1.5 g; 63 mmol) in DMSO (75 ml). After 1.5 hr, when evolution of H_2 gas had ceased, the mixture was cooled in an ice-bath and benzyl chloride (7.91 g; 63 mmol) was added dropwise. The mixture was then left to warm to room temperature over 1 hr and then heated to 60 °C for 0.5 hr. Ethanol was added to destroy any unreacted sodium hydride. The reaction was quenched with H_2O (250 ml) and extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude benzyl ether **35** as a brown liquid. The crude product was then dissolved in ether and passed through silica and sintered glass. 2-(1'-Benzyloxymethyl)furan[13] **35** (11.96 g; 95%) was obtained as a clear oil.

ν_{max} (L) 2922, 2855, 1603, 1498 (C-H furan), 1453, 1356, 1223, 1149, 1070 (ether), 1015 and 918 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 4.51 (2H, s, C-1' CH_2), 4.58 (2H, s, OCH_2Ph), 6.35 (1H, d, *J* 3.0, C-3 C*H*), 6.37 (1H, dd, *J* 3.5 and 2, C-4 C*H*), 7.36 (5H, m, Ph 5xC*H*) and 7.45 (1H, d, *J* 3.0, C-5 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 63.4 (C-1' *C*H_2), 71.4 (O*C*H_2Ph), 108.9, 109.8 (C-3 *C*H and C-4 *C*H), 127.2-127.9 (Ph 5x*C*H), 137.5 (Ph *C*), 142.3 (C-5 *C*H) and 151.4 (C-2 *C*) ppm

3-(2'[5'-{1''-Benzyloxymethyl}]furyl)propanal 36



Acetic acid (1.5 ml) was added rapidly to a stirred solution of benzyl ether **35** (1.88 g; 10 mmol), acrolein (1.11 g; 20 mmol) and hydroquinone (0.04 g) and the mixture was left at room temperature for 3 days under an atmosphere of nitrogen. The mixture was then diluted with H_2O, extracted with ether, washed sequentially with aqueous saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude 3-(2'[5'-{1''-benzyloxymethyl}]furyl)propanal **36** (1.02 g; crude yield 40%) as a very viscous orange liquid. The crude product was used directly as purification by column chromatography was inefficient. (Yield of aldehyde according to ^1H NMR data: 45%).

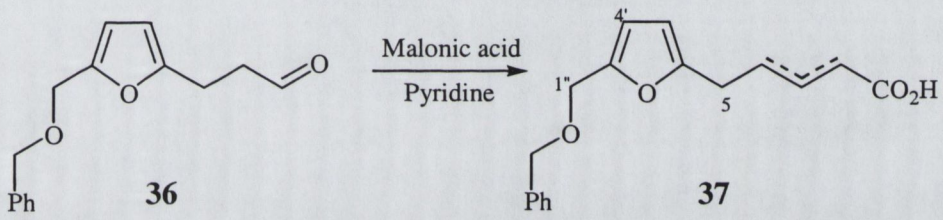
ν_{max} (L) 3063, 3030, 2915, 2854, 2728, 1724 (CHO), 1560, 1498 (C-H furan), 1453, 1357, 1216, 1069 (ether), 1025, 940 and 740 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.82 (2H, t, *J* 7.5, C-2 CH_2), 3.00 (2H, t, *J* 7.5, C-3 CH_2), 4.45 (2H, s, C-1'' CH_2), 4.56 (2H, s, OCH_2Ph), 6.00 (1H, d, *J* 3.0, C-3' C*H*), 6.24 (1H, d, *J* 3.0, C-4' C*H*), 7.31 (5H, m, C*H* Ph) and 9.83 (1H, s, C*H*O) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.8 (C-3 CH_2), 41.7 (C-2 CH_2), 63.8 (C-1'' CH_2), 71.8 (OCH_2Ph), 106.2 (C-3' CH), 110.2 (C-4' CH), 127.6-128.3 (Ph 5xCH), 137.9 (Ph C), 150.5 (C-5' C), 154.2 (C-2' C) and 200.8 (CHO) ppm

HRMS (CI) *m/z* 267.1017: *calculated for* $[C_{15}H_{16}O_3 + Na]^+$ 267.0997

(*E*)-5-(2'-[5'-{2''-Benzyloxymethyl}]furyl)pent-2-enoic and (*Z*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-3-enoic acid 37



36 37

Crude aldehyde **36** (13 mmol – amount of aldehyde in crude according to ^1H NMR), malonic acid (2.07 g; 20 mmol), pyridine (15 ml), piperidine (1 drop) were heated at 90-100 °C for 2 hr after which time CO_2 evolution had ceased. The mixture was then poured onto ice (30 g) and ether, then acidified with concentrated HCl (pH 1) and washed with brine. Preliminary purification was accomplished by extraction of the acidic product with $NaHCO_3$ solution followed by acidification and extraction with ether (x3). The organic extract was then washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude (*E*)-5-(2'-[5'-{1''-benzyloxymethyl}]furyl)pent-2-enoic and (*Z*)-5-(2'-[5'-{1''-benzyloxymethyl}]furyl)pent-3-enoic acid **37** (2.1 g; crude yield 53% by weight, 75%-based on amount of aldehyde **36** present in the crude starting material by ^1H NMR) [(*E*)-α,β 39%, (*Z*)-β,γ 61%) as a brown viscous liquid. Purification by column chromatography failed.

ν_{max} (L) 2924 (OH), 2858, 1707 (C=O), 1655, 1559, 1496 (C-H furan), 1453, 1418, 1357, 1283, 1213, 1069 (ether), 1023 and 793 cm^{-1}

(*E*)-5-(2'-[5'-{2''-Benzyloxymethyl}]furyl)pent-2-enoic acid (α,β) 37:

δ_H (400 MHz; $CDCl_3$) 2.62 (2H, ap. q, *J* 7.0, C-4 CH_2), 2.84 (2H, t, *J* 7.5, C-5 CH_2), 4.47 (2H, s, C-1'' CH_2), 4.57 (2H, s, OCH_2Ph), 5.89 (1H, br. d, *J* 15.5, C-2 *CH*), 6.00 (1H, d, *J* 3.0, C-3' *CH*), 6.25 (1H, d, *J* 3.0, C-4' *CH*), 7.11 (1H, dt, *J* 15.5 and 7.0, C-3 *CH*) and 7.36 (5H, m, C_6H_5) ppm

(*Z*)-5-(2'-[5'-{2''-Benzyloxymethyl}]furyl)pent-3-enoic acid: (β,γ) 37:

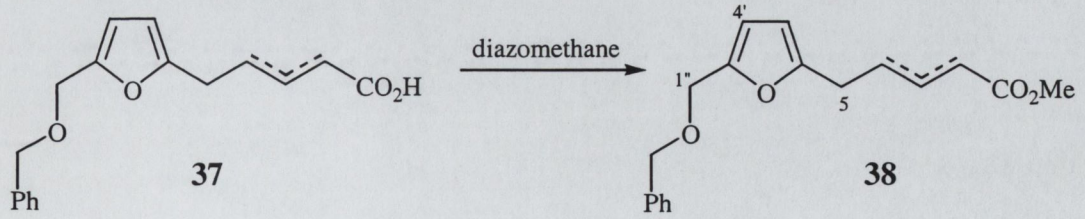
δ_H (400 MHz; $CDCl_3$) 3.15 (2H, d, *J* 5.5, C-2 CH_2), 3.42 (2H, d, *J* 6.0, C-5 CH_2), 4.47 (2H, s, C-1'' CH_2), 4.57 (2H, s, OCH_2Ph), 5.72 (2H, m, C-3 *CH* and C-4 *CH*), 6.00 (1H, d, *J* 3.0, C-3' *CH*), 6.25 (1H, d, *J* 3.0, C-4' *CH*) and 7.36 (5H, m, C_6H_5) ppm

(α,β)- and (β,γ)-isomer mixture:

δ_C (100.6 MHz; $CDCl_3$) 26.1, 30.1 (C-4 CH_2 and C-5 CH_2, α, β), 30.9, 37.1 (C-2 CH_2 and C-5 CH_2, β, γ), 63.9, 71.7 (C-1'' CH_2 and OCH_2Ph), 105.8, 109.9 (C-3' *CH* and C-4' *CH*), 120.9 (C-2 *CH*, α, β), 123.2, 129.6 (C-3 *CH* and C-4 *CH*, β, γ), 126.5-128.1 (Ph 5x*CH*), 137.5 (Ph *C*), 149.8 (C-3 *CH*, α, β), 153.7, 154.2 (C-2' *C* and C-5' *C*) and 170.9, 177.1 (2xCO_2H) ppm

HRMS (CI) *m/z* 309.1116: *calculated for* $[C_{17}H_{18}O_4 + Na]^+$ 309.1103

Methyl (*E*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-2-enoate and methyl (*Z*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-3-enoate 38



Following the procedure devised by Arndt *et al*,[19] a distilled ethereal solution (200 ml) of diazomethane (obtained from *N*-Methyl-*N*-nitrosourea[19] (5 g) and 50% potassium hydroxide solution (100 ml)) was added with care to the acid **37** (5.05 g, 17.6 mmol), which was dissolved in ether (100 ml) and cooled in an ice-bath. On

addition of the yellow diazomethane solution, the yellow colour was dispelled, indicating diazomethane consumption. When the reaction was complete the yellow colour remained indicating the diazomethane was in excess. This excess diazomethane was neutralised by the addition of glacial acetic acid until the yellow colour was no longer evident. The ethereal solution was then washed sequentially with aqueous sodium hydrogen carbonate and brine and then dried over magnesium sulfate and the solvent removed *in vacuo*. Crude methyl (*E*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-2-enoate and methyl (*Z*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-3-enoate **38** were obtained as a brown viscous liquid (1.5 g, 29%). Purification was then achieved by column chromatography with hexane : ethyl acetate 80:20. Pure methyl (*E*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-2-enoate and methyl (*Z*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-3-enoate **38** were obtained as a clear oil (0.9 g, 17%), [(*E*)-α, β 19%, (*Z*)-β, γ 21%).

ν_{max} (L) 2949, 2921, 2854, 1723 (C=O), 1656, 1560, 1496 (C-H furan), 1436, 1353, 1321, 1273, 1202 (ester C-O), 1175, 1152, 1070 (ether), 1025, 972, 851 and 792 cm^{-1}

Methyl (*E*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-2-enoate (α,β) 38:

δ_H (400 MHz; $CDCl_3$) 2.62 (2H, ap. q, *J* 7.0, C-4 CH_2), 2.82 (2H, t, *J* 7.5, C-5 CH_2), 3.73 (3H, s, CO_2CH_3), 4.45 (2H, s, C-1'' CH_2), 4.56 (2H, s, OCH_2Ph), 5.88 (1H, br. d, *J* 15.5, C-2 C*H*), 5.99 (1H, d, *J* 3.0, C-3' C*H*), 6.23 (1H, d, *J* 3.0, C-4' C*H*), 7.01 (1H, dt, *J* 15.5 and 7.0, C-3 C*H*) and 7.36 (5H, m, C_6H_5) ppm

Methyl (*Z*)-5-(2'-[5'-{2''-benzyloxymethyl}]furyl)pent-3-enoate (β,γ) 38:

δ_H (400 MHz; $CDCl_3$) 3.11 (2H, d, *J* 4.5, C-2 CH_2), 3.41 (2H, d, *J* 3.5, C-5 CH_2), 3.70 (3H, s, CO_2CH_3), 4.46 (2H, s, C-1'' CH_2), 4.56 (2H, s, OCH_2Ph), 5.71 (2H, m, C-3 C*H* and C-4 C*H*), 5.99 (1H, d, *J* 3.0, C-3' C*H*), 6.23 (1H, d, *J* 3.0, C-4' C*H*) and 7.36 (5H, m, C_6H_5) ppm

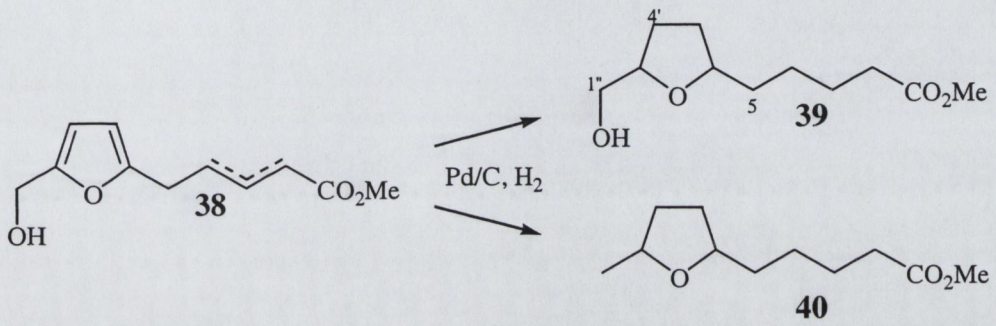
(α,β)- and (β,γ)-isomer mixture:

δ_C (100.6 MHz; $CDCl_3$) 26.2, 29.9 (C-4 CH_2 and C-5 CH_2, α, β), 30.9, 37.2 (C-2 CH_2 and C-5 CH_2, β, γ), 51.6, 51.3 (2xCO_2CH_3), 63.9, 71.7 (C-1'' CH_2 and OCH_2Ph), 106.2 and 110.2 (C-3' C*H* and C-4' C*H*), 121.6 (C-2 C*H*, α, β), 124.2,

129.4 (C-3 *C*H and C-4 *C*H, β, γ), 127.5-128.3 (Ph 5x*C*H), 137.5 (Ph *C*), 147.6 (C-3 *C*H, α, β), 154.3, 166.3 (C-2' *C* and C-5' *C*) and 171.6 (*C*O_2Me) ppm

HRMS (CI) *m/z* 323.1245: *calculated for* $[C_{18}H_{20}O_4 + Na]^+$ 323.1259

Methyl 5-(2'-[5'-hydroxymethyl]tetrahydrofuryl)pentanoate 39



The ester mixture **38** (1.13 g; 3.8 mmol) was dissolved in ethanol (80 ml) and was stirred under an atmosphere of hydrogen (1 atm) in the presence of 5% w/w Pd/C (100 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo*. The crude product was found to consist of two major components. Purification by column chromatography with hexane : ethyl acetate 60:40 gave the desired product methyl 5-(2'-[5'-hydroxymethyl]-tetrahydrofuryl)pentanoate **39** as a clear oil (0.33 g; 40%; major : minor isomers 5:1). Methyl 5-(5'-methyltetrahydro-2'-furyl)pentanoate **40** was also isolated as a clear oil (0.27 g; 35%; major : minor isomers 2.5:1).

Methyl 5-(2'-[5'-hydroxymethyl]tetrahydrofuryl)pentanoate 39:

ν_{max} (L) 3432 (OH), 2940, 2865, 1735 (C=O) , 1457, 1440, 1367, 1240, 1203 (C-O), 1172, 1089 (cyclic ether), 1043 and 883 cm^{-1}

Major isomer:

δ_H (400 MHz; $CDCl_3$) 1.34-1.76 (8H, m, C-3 CH_2, C-4 CH_2, C-5 CH_2, C-3' CH_a and C-4' CH_a), 1.87-2.07 (2H, m, C-3' CH_b and C-4' CH_b), 2.33 (2H, t, *J* 7.5, C-2 CH_2), 3.46-3.51 (1H, m, C-1'' CH_a), 3.67-3.71 (4H, m, C-1'' CH_b and CO_2CH_3), 3.84-3.90 (1H, m, C-2' C*H*) and 3.97-4.03 (1H, m, C-5' C*H*) ppm

Minor isomer:

δ_H (400 MHz; $CDCl_3$) 1.34-1.76 (8H, m, C-3 CH_2, C-4 CH_2, C-5 CH_2, C-3' CH_a and C-4' CH_a), 1.87-2.07 (2H, m, C-3' CH_b and C-4' CH_b), 2.33 (2H, t, *J* 7.5, C-2 CH_2), 3.46-3.51 (1H, m, C-1'' CH_a), 3.63 (1H, dd, ^2J 11.5, ^3J 3.5, C-1'' CH_b), 3.67 (3H, s, CO_2CH_3), 3.92-3.96 (1H, m, C-2' C*H*) and 4.07-4.14 (1H, m, C-5' C*H*) ppm

Major isomer only: (minor isomer not visible clearly)

δ_C (100.6MHz; $CDCl_3$) 24.8 (C-4 CH_2), 25.7 (C-3 CH_2), 26.9 (C-4' CH_2), 31.4 (C-3' CH_2), 33.8 (C-2 CH_2), 35.4 (C-5 CH_2), 51.4 (CO_2CH_3), 65.2 (C-1'' CH_2), 79.2 (C-5' CH), 79.8 (C-2' CH) and 173.6 (CO_2CH_3) ppm

HRMS (CI) *m/z* 239.1241: *calculated for* $[C_{11}H_{20}O_4 + Na]^+$ 239.1259

Methyl 5-(5'-methyltetrahydro-2'-furyl)pentanoate 40:

ν_{max} (L) 2952, 2865, 1741 (C=O), 1457, 1436, 1375, 1236, 1201 (C-O), 1170, 1093 (cyclic ether), 1014 and 732 cm^{-1}

Major isomer:

δ_H (400 MHz; $CDCl_3$) 1.25 (3H, d, *J* 6.0, CH_3), 1.37-1.69 (8H, m, C-3' CH_a, C-4' CH_a, C-3 CH_2, C-4 CH_2 and C-5 CH_2), 1.95-2.06 (2H, m, C-3' CH_b and C-4' CH_b), 2.33 (2H, t, *J* 7.5, C-2 CH_2), 3.68 (3H, s, OCH_3), 3.76-3.82 (1H, m, C-2' C*H*) and 3.93-3.99 (1H, m, C-5' C*H*) ppm

Minor isomer:

δ_H (400 MHz; $CDCl_3$) 1.22 (3H, d, *J* 6.0, CH_3), 1.37-1.69 (8H, m, C-3' CH_a, C-4' CH_a, C-3 CH_2, C-4 CH_2 and C-5 CH_2), 1.95-2.06 (2H, m, C-3' CH_b and C-4' CH_b), 2.33 (2H, t, *J* 7.5, C-2 CH_2), 3.68 (3H, s, OCH_3) 3.93-3.99 (1H, m, C-2' C*H*) and 4.07-4.15 (1H, m, C-5' C*H*) ppm

Major Isomer:

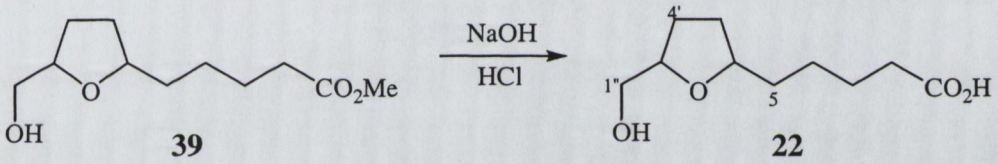
δ_C (100.6 MHz; $CDCl_3$) 21.2 (CH_3), 24.9 (C-4 CH_2), 25.7 (C-3 CH_2), 31.2, 32.7 (C-3' CH_2 and C-4' CH_2), 33.9 (C-2 CH_2), 35.7 (C-5 CH_2), 51.4 (OCH_3), 75.1, 79.2 (C-2' CH and C-5' CH) and 173.7 (C-1 CO_2CH_3) ppm

Minor Isomer:

δ_C (100.6 MHz; $CDCl_3$) 21.3 (CH_3), 24.5 (C-4 CH_2), 25.7 (C-3 CH_2), 32.3, 33.8 (C-3' CH_2 and C-4' CH_2), 33.9 (C-2 CH_2), 35.7 (C-5 CH_2), 51.4 (OCH_3), 74.4, 78.4 (C-2' CH and C-5' CH) and 173.7 (C-1 CO_2CH_3) ppm

HRMS (CI) *m/z* 223.1311: *calculated for* $[C_{11}H_{20}O_3 + Na]^+$223.1310

5-(2'-[5'-Hydroxymethyl]tetrahydrofuryl)pentanoic acid 22



The saturated ester **39** (0.67 g; 3.0 mmol) was dissolved in methanol (18 ml) and 40% NaOH (1.85 ml; 4.5 mmol) was added. The mixture was heated at reflux for 2 hr. The methanol was then removed *in vacuo* and the residue was acidified (pH 1) with 5.5 M HCl. Brine (3 ml) and ethyl acetate (10 ml) were then added and the aqueous layer was extracted (x5) with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to yield 5-(2'-[5'-{1''-hydroxymethyl}]tetrahydrofuryl)pentanoic acid **22** as a clear oil (0.5 g; 80%; major : minor isomers 5:1).

ν_{max} (L) 3465 (OH), 2935, 2865, 1710 (C=O), 1457, 1411, 1278, 1240, 1076 (cyclic ether), 1033 and 970 cm^{-1}

Major isomer:

δ_H (400 MHz; $CDCl_3$) 1.37-1.77 (8H, m, C-3 CH_2, C-4 CH_2, C-5 CH_2, C-3' CH_a and C-4' CH_a), 1.88-2.04 (2H, m, C-3' CH_b and C-4' CH_b), 2.38 (2H, t, *J* 7.5, C-2 CH_2), 3.50 (1H, dd, ^2J 11.5, ^3J 5.5, C-1''CH_a), 3.72 (1H, dd, ^2J 11.5, ^3J 3.0, C-1'' CH_b) and 3.87-3.94 (1H, m, C-2' CH), 4.01-4.06 (1H, m, C-5' CH) ppm

Minor isomer:

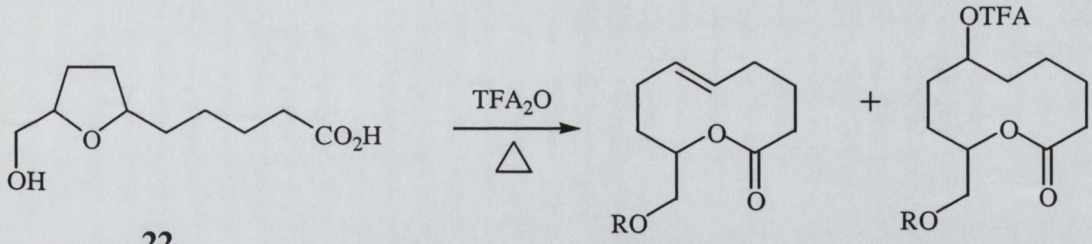
δ_H (400 MHz; $CDCl_3$) 1.37-1.77 (8H, m, C-3 CH_2, C-4 CH_2, C-5 CH_2, C-3' CH_a and C-4' CH_a), 1.88-2.04 (2H, m, C-3' CH_b and C-4' CH_b), 2.38 (2H, t, *J* 7.5, C-2 CH_2), 3.51 (1H, dd, ^2J 11.5, ^3J 6.5, C-1'' CH_a), 3.66 (1H, dd, ^2J 11.5, ^3J 3.0, C-1'' CH_b), 3.96-3.99 (1H, m, C-2'C*H*), and 4.13-4.15 (1H, m, C-5' C*H* (minor isomer)) ppm

Major isomer only: (minor isomer not visible clearly)

δ_C (100.6 MHz; $CDCl_3$) 24.7 (C-4 CH_2), 25.6 (C-3 CH_2), 26.9 (C-4' CH_2), 31.3 (C-3' CH_2), 33.6 (C-2 CH_2), 35.3 (C-5 CH_2), 65.2 (C-1'' CH_2), 79.3 (C-5' C*H*), 79.8 (C-2' C*H*) and 174.8 (CO_2H) ppm

HRMS (CI) *m/z* 209.1382: *calculated for* $[C_{10}H_{18}O_4 + Li]^+$ 209.1365

Intramolecular reaction of 5-(2'-[5'-Hydroxymethyl]tetrahydrofuryl) pentanoic acid 22



22

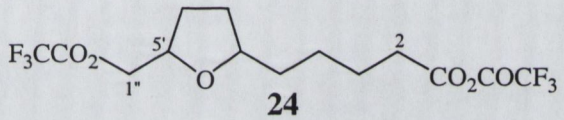
41 R = TFA
31 R = H

42 R = TFA
27 R = H

The hydroxy-acid **22** (0.44 g; 2.19 mmol), dissolved in deuteriated chloroform (11ml), was cooled in an ice bath. Trifluoroacetic anhydride (2.3 g; 10.9 mmol) was then added. After 0.5 hr at this temperature NMR analysis indicated that the mixed anhydride derived from acid **22** had been formed. The mixture was refluxed and monitored at intervals by NMR spectroscopy. After 15 hr reflux the solvent and the excess trifluoroacetic anhydride were removed *in vacuo*. TLC and NMR studies at this point indicated the presence of two major products, possibly the unsaturated **41** and the saturated **42** trifluoroacetoxy lactones. However, upon

purification by column chromatography, hexane : ethyl acetate 95:5, the unsaturated trifluoroacetoxy lactone **41** was not isolated. 10-Trifluoroacetoxymethyl-7-trifluoroacetoxyoxecan-2-one **42** (70 mg; 8%; major : minor isomers 6:1; clear oil) was isolated. Further chromatography of the column washings resulted in the isolation of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one **27** (120 mg; 18%; major : minor isomers 6:1; clear oil). Last to elute was (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one **31** (10 mg; 2.5% isolated yield (10% yield by ^{1}H NMR prior to chromatography); translucent yellow oil) which was extremely difficult to separate from the semi-hydrolysed lactone **27**.

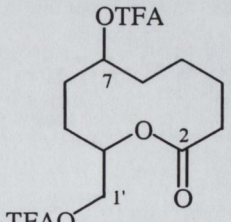
Mixed anhydride 24 derived from 5-(2'-[5'-hydroxymethyl]tetrahydrofuryl) pentanoic acid 22 (major isomer)



24

δ_H (400 MHz; $CDCl_3$) 1.47 (3H, m), 1.73 (4H, m), 1.90 (1H, m), 2.15 (2H, m), 2.64 (2H, t, *J* 6.5, C-2 C*H*$_2$), 4.21 (1H, m, C-2' or C-5' C*H*), 4.34 (1H, m, C-1'' C*H*$_a$) and 4.46 (2H, m, C-2' or C-5' C*H* and C-1'' C*H*$_b$) ppm

10-Trifluoroacetoxymethyl-7-trifluoroacetoxyoxecan-2-one 42



42

ν_{max} (L) 2952, 2925, 1784 (trifluoroacetoxy C=O), 1735 (lactone C=O), 1458, 1364, 1223, 1161, 1077 and 978 cm^{-1}

Major isomer 42a

δ_H (400 MHz; $CDCl_3$) 1.42-2.03 (10H, m, 5xCH_2), 2.35-2.42 (1H, apparent dt, ^2J 13.5, $^3J_1 = {}^3J_2$ 8.0, C-3 CH_a), 2.46-2.52 (1H, apparent dt, ^2J 13.5, $^3J_1 = {}^3J_2$ 5.0, C-3 CH_b), 4.46-4.57 (2H, 2xdd overlapping, centred at 4.49 ppm, ^2J 11.5, ^3J 6.0, C-1' CH_a, and 4.51 ppm, ^2J 11.5, ^3J 4.5, C-1' CH_b) and 5.05-5.13 (2H, m, C-7 C*H* and C-10 C*H*) ppm

Minor isomer 42b

δ_H (400 MHz; $CDCl_3$) 1.42-2.03 (10H, m, 5xCH_2), 2.27 (1H, ddd, ^2J 15.5, $^3J_1$ 12.5, $^3J_2$ 3.0, C-3 CH_a), 2.63 (1H, ddd, ^2J 16.0, $^3J_1$ 6.0, $^3J_2$ 3.0, C-3 CH_b), 4.46-4.57 (2H, m, C-1' CH_2), 5.19-5.22 (1H, m, C-7 C*H* or C-10 C*H*) and 5.37-5.41 (1H, m, C-7 C*H* or C-10 C*H*) ppm

Major isomer 42a

δ_C (100.6 MHz; $CDCl_3$) (major isomer) 22.1, 22.6 (2xCH_2), 23.8 (C-4 CH_2), 27.0, 28.5 (2xCH_2), 33.6 (C-3 CH_2), 68.0 (C-1' CH_2), 71.4, 77.4 (C-7 *C*H or C-10 *C*H) and 172.8 (CO_2R) ppm

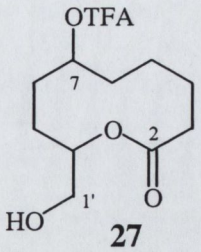
Minor isomer 42b

δ_C (100.6 MHz; $CDCl_3$) (minor isomer) 19.8, 23.2, 23.7, 25.7, 29.1 (5xCH_2), 33.7 (C-3 CH_2), 67.3 (C-1' CH_2), 70.8, 76.9 (C-7 *C*H or C-10 *C*H) and 172.8 (CO_2R) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.5, -75.9 (2x$COCF_3$) ppm

HRMS (CI) *m/z* 321.0935: *calculated for* $[C_{12}H_{17}F_3O_5 + Na]^+$ 321.0926 { = **42** $C_{14}H_{16}F_6O_6 - COCF_3 + H + Na$}

10-Hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27



27

ν_{max} (L) 3434 (OH), 2954, 2929, 1779 (trifluoroacetoxy C=O), 1729 (lactone C=O), 1457, 1365, 1259, 1222, 1164, 1064, 1037, 777 and 727 cm^{-1}

Major isomer 27a

δ_H (400 MHz; $CDCl_3$) 1.49-2.12 (10H, m, 5xCH_2), 2.33-2.40 (1H, ddd, ^2J 14.0, $^3J_1$ 11.0, $^3J_2$ 4.0, C-3 CH_a), 2.50-2.56 (1H, ddd, ^2J 14.0, $^3J_1$ 6.0, $^3J_2$ 4.0, C-3 CH_b), 3.74-3.86 (2H, 2xdd overlapping, dd centred at 3.76 ppm, ^2J 12.5, ^3J 6.0, C-1' CH_a, dd centred at 3.81 ppm, ^2J 12.5, ^3J 4.0, C-1' CH_b), 4.76-4.81 (1H, m, C-10 C*H*) and 5.19-5.25 (1H, m, C-7 C*H*) ppm

Minor isomer 27b

δ_H (400 MHz; $CDCl_3$) 1.49-2.12 (10H, m, 5xCH_2), 2.23-2.31 (1H, ddd, ^2J 16.0, $^3J_1$ 12.5, $^3J_2$ 3.0, C-3 CH_a), 2.63-2.65 (1H, ddd, ^2J 16.0, $^3J_1$ 6.0, $^3J_2$ 3.0, C-3 CH_b), 3.74-3.78 (1H, m, C-1' CH_a), 3.85 (1H, dd, ^2J 11.5, ^3J 6.5, C-1' CH_b) 4.95-5.00 (1H, m, C-10 C*H*), and 5.42-5.47 (1H, m, C-7 C*H*) ppm

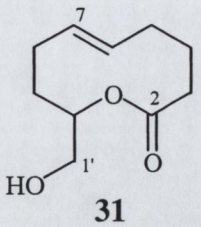
Major isomer 27a only (minor isomer not visible clearly)

δ_C (100.6 MHz; $CDCl_3$) 22.3, 22.7 (C-5 and C-6 2xCH_2), 23.7 (C-4 CH_2) 28.1, 28.2 (C-8 and C-9 2xCH_2), 34.6 (C-3 CH_2), 64.8 (C-1' CH_2), 77.4 (C-7 CH), 78.4 (C-10 CH) and 174.0 (CO_2R) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.8 ($COCF_3$) ppm

HRMS (CI) *m/z* 225.1085: *calculated for* $[C_{10}H_{18}O_4 + Na]^+$ 225.1103 { = **27** $C_{12}H_{17}F_3O_5 - COCF_3 + H + Na$}

(6*E*)-10-Hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31



31

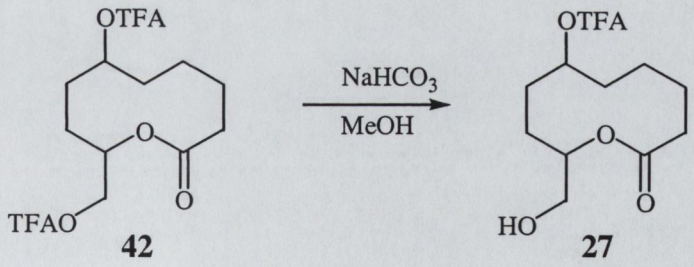
ν_{max} (L) 3417 (OH), 2924, 2852, 1729 (lactone C=O), 1440, 1364, 1256, 1209, 1178, 1152, 1060 and 984 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.60-1.67 (1H, m, C-9 CH_a), 1.73-1.83 (1H, m, C-9 CH_b), 1.91-2.16 (6H, m, C-3 CH_2, C-4 CH_2, C-5 CH_a and C-8 CH_a), 2.27-2.42 (2H, m, C-5 CH_b and C-8 CH_b), 3.60 (1H, dd, ^2J 11.5, ^3J 6.0, C-1' CH_a), 3.65 (1H, dd, ^2J 11.5, ^3J 4.0, C-1' CH_b), 5.13 (1H, dddd, $^3J_1$ 11.5, $^3J_2$ 6.0, $^3J_3$ 4.0, $^3J_4$ 1.5, C-10 C*H*), 5.27 (1H, ddd, $^3J_{trans}$ 15.0, $^3J_1$ 10.5, $^3J_2$ 4.0, C-6 C*H*) and 5.51 (1H, ddd, $^3J_{trans}$ 15.5, $^3J_1$ 11.0, $^3J_2$ 3.5, C-7 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 25.7 (C-3/C-4 *C*H), 28.3 (C-9 *C*H_2), 30.8 (C-3/C-4 *C*H), 33.4 (C-5 *C*H_2), 34.4 (C-8 *C*H_2), 65.2 (C-1' *C*H_2), 74.9 (C-10 *C*H), 128.0 (C-6 *C*H), 132.7 (C-7 *C*H) and 177.7 (C-2 C=O) ppm

HRMS (CI) *m/z* 207.0985: *calculated for* $[C_{10}H_{16}O_3 + Na]^+$ 207.0997

Hydrolysis of 10-trifluoroacetoxymethyl-7-trifluoroacetoxyoxecan-2-one 42



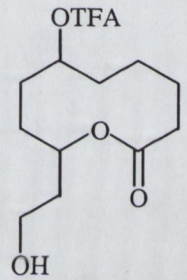
42 **27**

Saturated $NaHCO_3$ solution (0.1 ml) was added to the trifluoroacetoxy lactone **42** (70 mg; 0.18 mmol) in methanol (1 ml) and the mixture was left to stand for 0.5 hr. Water (1 ml) and ethyl acetate (1 ml) were then added and the aqueous layer was extracted (x4 ethyl acetate). The combined organic extracts were then dried over

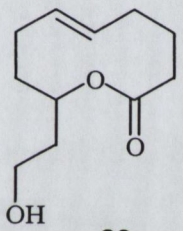
$MgSO_4$ and the solvent removed *in vacuo*. The crude product (33 mg) was then purified by column chromatography, gradient elution hexane : ethyl acetate 90:10 to 70:30. 10-Hydroxymethyl-7-trifluoroacetoxyoxecan-2-one **27** was isolated as a clear oil (23 mg; 43%; major : minor isomers 6:1).

The NMR and IR spectra of **27** were identical to the semi-hydrolysed saturated lactone isolated from the column of the crude product obtained from the intramolecular reaction of acid **22** with trifluoroacetic anhydride.

3.7.2 Synthesis of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28 and (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32

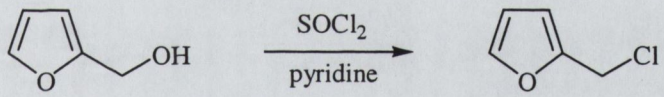


28



32

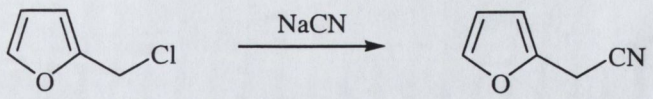
Furfuryl Chloride 48



47 **48**

Thionyl chloride (14.19 g; 120 mmol) in dry ether (30 ml) was added dropwise with stirring to tetrahydrofurfuryl alcohol **47** (9.81 g; 100 mmol) in dry pyridine (9.8 ml) and dry ether (50 ml) at –15 °C. The mixture was allowed to warm to 3 °C over 1 hr and was then quenched with ice water (60 ml). The organic layer was quickly washed sequentially with cooled HCl solution (0.5 M; 80 ml), cooled KOH solution (0.5 M; 80 ml) and cooled brine, dried over $MgSO_4$ and the solvent removed *in vacuo* (temperature kept below 25 °C at all times) to yield crude furfuryl chloride[21] **48** (6.63 g; 57%) as an orange liquid. Due to the unstable nature of the product no analysis was possible, the crude product was used immediately for the preparation of 2-furylacetonitrile **49**.

2-Furylacetonitrile 49



48 **49**

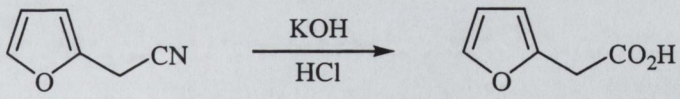
2-Furfuryl chloride **48** (6.63 g; 57 mmol) in DMSO (7 ml) was added dropwise with stirring to a suspension of sodium cyanide (3.35 g; 68 mmol) in DMSO (11 ml) at a temperature not exceeding 40-45 °C. The mixture was stirred for 12 hr at room temperature. Toluene (150 ml) and brine (100 ml) were then added. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude 2-furylacetonitrile **49** (3.94 g) as a brown liquid. The crude product was passed through an alumina column and eluted with toluene to yield 2-furylacetonitrile[21] **49** (3.41 g, 64%) as a clear oil, b.p. 86-88 °C at 20 mm/Hg, (lit.[21] b.p. 64-65 °C at 9 mm/Hg).

ν_{max} (L) 3153, 3126, 2967, 2928, 2256 (CN), 1718, 1600, 1505 (C-H furan), 1408, 1311, 1257, 1216, 1145, 1071, 950 and 883 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 3.78 (2H, s, C*H*$_2$), 6.34 (1H, d, *J* 3.0, C-3 C*H*). 6.38 (1H, dd, *J* 3.0, 2.0, C-4 C*H*) and 7.41 (1H, d, *J* 1.5, C-5 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 17.0 (*C*H$_2$), 108.0 (C-3 *C*H), 110.4 (C-4 *C*H), 114.9 (*C*N), 142.2 (C-5 *C*H) and 153.1 (C-2 *C*) ppm

2-Furylacetic Acid 50



49 **50**

2-Furylacetonitrile **49** (8.79 g; 82 mmol) was heated at reflux in the presence of KOH (20%; 100 ml) for 6 hr, after which time no more NH_3 gas was evolved. The mixture was extracted with ether to remove any unreacted nitrile **49**. The aqueous layer was then acidified (pH 1) with concentrated HCl and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$ and the solvent

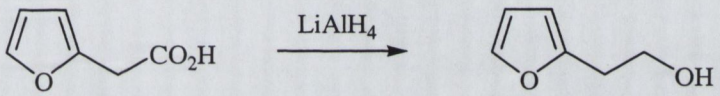
removed *in vacuo* to yield furylacetic acid **50** (8.37 g, 81%) as a cream solid, m.p. 67-67.5 °C, (lit.[21] m.p. 68-69 °C).

ν_{max} (Neat) 2925 (OH), 1705 (C=O), 1459 (C-H furan), 1425, 1393, 1377, 1279, 1250, 1232, 1202, 1168, 1012, 953, 890 and 782 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 3.76 (2H, s, CH_2), 6.27 (1H, d, *J* 3.0, C-3 C*H*), 6.36 (1H, dd, *J* 3.0, 1.5, C-4 C*H*) and 7.39 (1H, d, *J* 1.5, C-5 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 33.1 (CH_2), 107.9 (C-3 *C*H), 110.1 (C-4 *C*H), 141.8 (C-5 *C*H), 146.4 (C-2 *C*) and 173.6 (CO_2H) ppm

2-Furylethanol 51



50 **51**

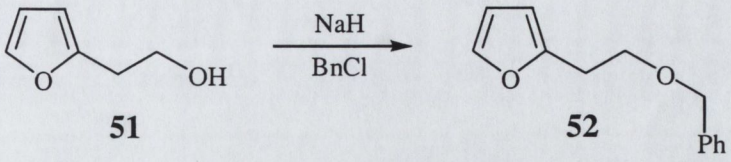
2-Furylacetic acid **50** (11 g; 87 mmol) in dry ether (60 ml) was added to a stirred solution of lithium aluminium hydride (4.3 g; 114 mmol) in dry ether (90 ml) under an atmosphere of nitrogen at 0 °C. The mixture was heated at reflux for 1 hr, quenched with saturated aqueous NH_4Cl solution and then acidified with concentrated HCl. The ether layer was decanted and the aqueous layer was extracted with ether. The combined organic extracts were washed sequentially with aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield 2-furylethanol[23] **51** (7.08 g, 72%) as a clear oil.

ν_{max} (L) 3348 (OH), 2995, 2926, 2887, 1598, 1507 (C-H furan), 1423, 1338, 1239, 1146, 1048, 924 and 732 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.93 (2H, t, *J* 6.5, CH_2CH_2OH), 3.86 (2H, t, *J* 6.5, CH_2CH_2OH), 6.09 (1H, d, *J* 3.0, C-3 C*H*), 6.29 (1H, dd, *J* 3.0, 2.0, C-4 C*H*) and 7.32 (1H, d, *J* 1.5, C-5 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 31.5 (CH_2CH_2OH), 61.1 (CH_2CH_2OH), 106.0 (C-3 *C*H), 109.8 (C-4 *C*H), 141.1 (C-5 *C*H) and 152.2 (C-2 *C*) ppm

2-(2'-Benzyloxyethyl)furan 52



51 **52**

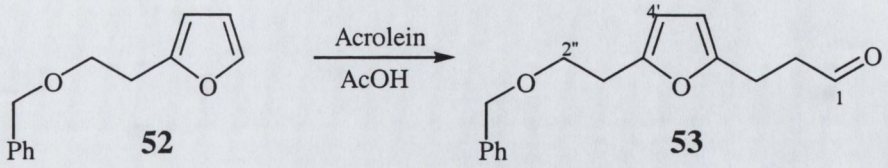
The alcohol **51** (7.06 g; 63 mmol) in DMSO (25 ml) was added dropwise to a stirred solution of sodium hydride (1.5 g; 63 mmol) in DMSO (75 ml). After 1.5 hr, when evolution of H_2 gas had ceased, the mixture was cooled in an ice-bath and benzyl chloride (7.91 g; 63 mmol) was added dropwise. The mixture was then left to warm to room temperature over 1 hr and then heated to 60 °C for 0.5 hr. Ethanol was added to destroy any unreacted sodium hydride. The reaction was quenched with H_2O (250 ml) and extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude benzyl ether as a brown liquid. The crude product was dissolved in ether and passed through silica and sintered glass. 2-(2'-Benzyloxyethyl)furan[24] **52** (11.58 g; 92%) was obtained as a clear colourless liquid.

ν_{max} (L) 2922, 2860, 1610, 1523, 1470 (C-H furan), 1362, 1190, 1112 (ether), 1025 and 720 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.98 (2H, t, *J* 7.0, C-1' CH_2), 3.75 (2H, t, *J* 7.0, C-2' CH_2), 4.59 (2H, s, OCH_2Ph), 6.10 (1H, d, *J* 3.0, C-3 *CH*), 6.31 (1H, t, *J* 2.5, C-4 *CH*) and 7.29-7.39 (6H, m, C-5 *CH* and C_6H_5) ppm

δ_C (100.6 MHz; $CDCl_3$) 28.4 (C-1' CH_2), 67.8 (C-2' CH_2), 72.5 (OCH_2Ph), 105.5 (C-3 *CH*), 109.7 (C-4 *CH*), 127.1-127.3 (Ph 5x*CH*) and 137.8 (Ph *C*) ppm

3-(2'[5'-{2''-Benzyloxyethyl}]furyl)propanal 53



Acetic acid (1.5 ml) was added rapidly to a stirred solution of the benzyl ether **52** (2.02 g; 10 mmol), acrolein (1.11 g; 20 mmol) and hydroquinone (0.04 g) and the mixture was left at room temperature for 24 hr. The mixture was then diluted with H_2O, extracted with ether, washed sequentially with aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude 3-(2'[5'-{2''-benzyloxyethyl}]furyl)propanal **53** (2.48 g; crude yield 97%) as a very viscous orange liquid. The crude product was used directly as purification by column chromatography proved inefficient. (Yield of aldehyde according to ^1H NMR data: 3-(2'[5'-{2''-benzyloxyethyl}] furyl)propanal **53**: 85%).

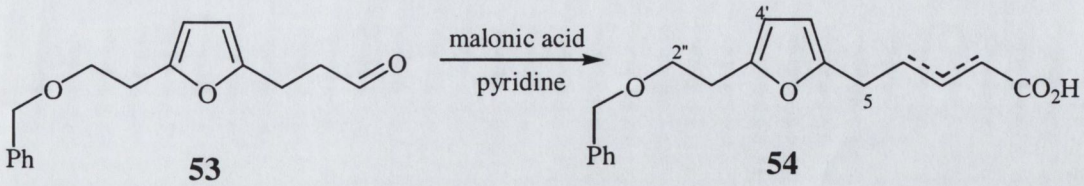
ν_{max} (L) 3030, 2918, 2858, 2725, 1725 (CHO), 1566, 1453, 1362, 1178, 1102 (ether), 1011 and 785 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.79 (2H, t, *J* 7.5, C-1'' CH_2), 2.90-2.97 (4H, m, C-2 CH_2 and C-3 CH_2), 3.72 (2H, t, *J* 7.0, C-2'' CH_2), 4.55 (2H, s, OCH_2Ph), 5.92 (1H, d, *J* 2.5, C-3' CH), 5.97 (1H, d, *J* 2.5, C-4' CH), 7.34 (5H, m, C_6H_5) and 9.82 (1H, s, CHO) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.8 (C-3 CH_2), 28.8 (C-1'' CH_2), 41.9 (C-2 CH_2), 68.3 (C-2'' CH_2), 72.8 (OCH_2Ph), 106.1, 106.4 (C-3' CH and C-4' CH), 127.5-128.3 (Ph 5xCH), 137.8 (Ph C), 151.3, 151.8 (C-2' C and C-5' C) and 201.1 (CHO) ppm

HRMS (CI) *m/z* 281.1138: *calculated for* $[C_{16}H_{18}O_3 + Na]^+$281.1154

(*E*)-5-(2'-[5'-{2''-Benzyloxyethyl}]furyl)pent-2-enoic acid and (*Z*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-3-enoic acid 54



53 **54**

Crude aldehyde **53** (13 mmol – amount of aldehyde in crude according to ^{1}H NMR), malonic acid (2.07 g; 20 mmol), pyridine (15 ml), piperidine (1 drop) were heated at 90-100 °C for 2 hr after which time CO_2 evolution had ceased. The mixture was then poured onto ice (30 g) and ether, then acidified with concentrated HCl (pH 1) and washed with brine. Preliminary purification was accomplished by extraction of the acidic product with aqueous $NaHCO_3$ solution followed by acidification and extraction with ether (x3). The organic extract was then washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoic and (*Z*)-5-(2'-[5'-{2''-benzyl-oxyethyl}]furyl)pent-3-enoic acid **54** (2.4 g; crude yield 60%), [(*E*)-α,β 48%, (*Z*)-β,γ 52%] as a brown viscous liquid. Purification by column chromatography failed so the crude product was employed directly in the next step.

ν_{max} (L) 3030, 2922 (OH), 2861, 1703 (C=O), 1652, 1565, 1495 (C-H furan), 1453, 1420, 1363, 1283, 1206, 1100 (ether), 1026, 971 and 785 cm^{-1}

Methyl (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoic acid: (α,β)

δ_H (400 MHz; $CDCl_3$) 2.58 (2H, ap. q, *J* 7.0, C-4 C*H*$_2$), 2.78 (2H, t, *J* 7.5, C-5 C*H*$_2$), 2.93 (2H, t, *J* 6.5, C-1'' C*H*$_2$), 3.73 (2H, t, *J* 7.0, C-2'' C*H*$_2$), 4.56 (2H, s, OC*H*$_2$Ph), 5.87 (1H, br. d, *J* 16.0, C-2 C*H*), 5.93 (1H, d, *J* 3.0, C-3' C*H*), 5.97 (1H. d, *J* 3.5, C-4' C*H*), 7.11 (1H, dt, *J* 15.5, 6.5, C-3 C*H*) and 7.35 (5H, m, C$_6$*H*$_5$) ppm

Methyl (*Z*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-3-enoic acid: (β,γ)

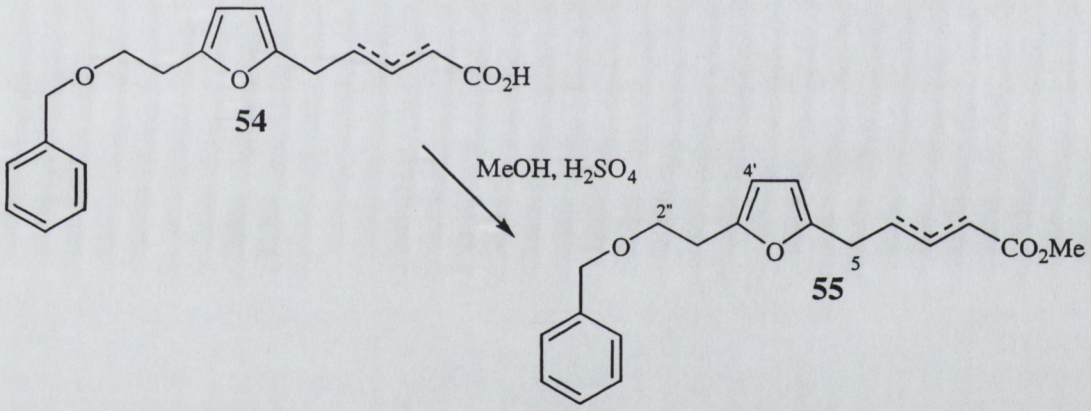
δ_H (400 MHz; $CDCl_3$) 2.93 (2H, t, *J* 6.5, C-1'' C*H*$_2$), 3.14 (2H, d, *J* 6.0, C-2 C*H*$_2$), 3.37 (2H, d, *J* 5.5, C-5 C*H*$_2$), 3.73 (2H, t, *J* 7.0, C-2'' C*H*$_2$), 4.56 (2H, s, OC*H*$_2$Ph), 5.71 (2H, m, C-3 C*H* and C-4 C*H*), 5.93 (1H, d, *J* 3.0, C-3' C*H*), 5.97 (1H, d, *J* 3.5, C-4' C*H*) and 7.35 (5H, m, C$_6$*H*$_5$) ppm

(α,β)- and (β,γ)-isomer mixture:

δ_C (100.6 MHz; $CDCl_3$) 26.0, 28.5, 30.3, 30.9, 31.3, 37.5 (C-4 CH_2, C-5 CH_2 and C-1'' CH_2, α, β; C-2 CH_2, C-5 CH_2 and C-1'' CH_2, β, γ), 68.3, 72.8 (C-2'' CH_2 and OCH_2Ph), 105.6, 105.7 (C-3' CH and C-4' CH), 120.9 (C-2 CH, α, β), 122.9, 130.3 (C-3 CH and C-4 CH, β, γ), 126.5-128.1 (Ph 5xCH), 137.8 (Ph C), 150.5 (C-3 CH, α, β), 152.2 (C-2' C and C-5' C) and 171.1, 177.2 ($2xCO_2H$) ppm

HRMS (CI) *m/z* 323.1263: *calculated for* $[C_{18}H_{20}O_4 + Na]^+$ 323.1259

Methyl (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoate and methyl (*Z*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-3-enoate 55



Crude 5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoic acid mixture **54** (3.31 g; 11 mmol), methanol (120 ml) and H_2SO_4 (1.7 ml) were stirred at room temperature for 24 hr. The mixture was then poured onto ice (180 g), extracted with ether, washed sequentially with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield crude methyl ester **55** (2.1g; 61%) as a brown viscous liquid. Purification by column chromatography on silica gel with hexane : ethyl acetate 90:10 yielded methyl (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoate and methyl (*Z*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-3-enoate **55** (0.76 g; 22%) as a clear fragrant oil [(*E*)-α,β 85%, (*Z*)-β,γ 15%].

ν_{max} (L) 3464, 3029, 2928, 2861, 1725 (C=O), 1658, 1565, 1436, 1362, 1271, 1200 (C-O), 1100 (ether), 1027 and 738 cm^{-1}

Methyl (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoate: (α,β)

δ_H (400 MHz; $CDCl_3$) 2.55 (2H, apparent q, *J* 7.0, C-4 CH_2), 2.77 (2H, t, *J* 7.5, C-5 CH_2), 2.93 (2H, t, *J* 6.5, C-1'' CH_2), 3.70-3.74 (2H, m, C-2'' CH_2), 3.73 (3H, s, CO_2CH_3), 4.56 (2H, s, OCH_2Ph), 5.88 (1H, br. d, *J* 15.5, C-2 *CH*) 5.93 (1H, d, *J* 2.5, C-3' *CH*), 5.98 (1H, d, *J* 3.0, C-4' *CH*), 7.01 (1H, dt, *J* 15.5, 7.0, C-3 *CH*) and 7.35 (5H, m, C_6H_5) ppm

Methyl (*Z*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-3-enoate: (β,γ)

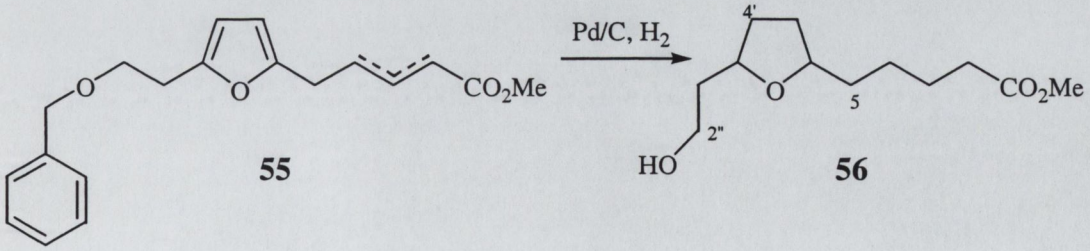
δ_H (400 MHz; $CDCl_3$) 2.93 (2H, t, *J* 6.5, C-1'' CH_2), 3.10 (2H, d, *J* 5.0, C-2 CH_2), 3.36 (2H, d, *J* 4.0, C-5 CH_2), 3.70-3.74 (2H, m, C-2'' CH_2), 3.73 (3H, s, CO_2CH_3), 4.56 (2H, s, OCH_2Ph), 5.69 (2H, m, C-3 *CH* and C-4 *CH*), 5.93 (1H, d, *J* 2.5, C-3' *CH*), 5.98 (1H, d, *J* 3.0, C-4' *CH*) and 7.35 (5H, m, C_6H_5) ppm

Methyl (*E*)-5-(2'-[5'-{2''-benzyloxyethyl}]furyl)pent-2-enoate: only (α,β) isomer visible

δ_C (100.6 MHz; $CDCl_3$) 26.2, 28.5, 30.2 (C-4, C-5 and C-1'' 3xCH_2), 50.9 (OCH_3), 64.9 (C-2'' CH_2), 65.4 ($OCH_2C_6H_5$), 105.6, 106.0 (C-3' and C-4' 2x*CH*'), 121.1 (C-2 *CH*), 126.5, 127.0, 127.2, 127.8, 128.1 (Ph 5x*CH*), 137.2 (Ph *C*), 147.4 (C-3 *CH*), 155.2, 155.3 (C-2' and C-5' *C*) and 165.9 (CO_2CH_3) ppm

HRMS (CI) *m/z* 321.1696: *calculated for* $[C_{19}H_{22}O_4 + Li]^+$ 321.1678

Methyl 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoate 56



55 **56**

The unsaturated esters **55** (0.86 g; 2.7 mmol) were dissolved in ethanol (60 ml) and stirred under an atmosphere of hydrogen (1 atm) in the presence of 5% w/w Pd/C (100 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo*. The crude product was then purified by column

chromatography with hexane : ethyl acetate 60:40 to give the desired methyl 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoate **56** as a clear oil (0.38 g; 60%; major : minor isomers 14:1).

ν_{max} (L) 3440 (OH), 2940, 2865, 1737 (C=O), 1459, 1437, 1373, 1318, 1237, 1198 (C-O), 1172, 1058 (cyclic ether), 1019 and 882 cm^{-1}

Major isomer:

δ_H (400 MHz; $CDCl_3$) 1.32-1.88 (10H, m, C-3' C*H*$_a$, C-4' C*H*$_a$, C-3 C*H*$_2$, C-4 C*H*$_2$, C-5 C*H*$_2$ and C-1'' C*H*$_2$), 1.93-2.09 (2H, m, C-3' C*H*$_b$ and C-4' C*H*$_b$), 2.33 (2H, t, *J* 7.5 and C-2 C*H*$_2$), 2.38 (1H, br. s, C-2'' CO*H*), 3.68 (3H, s, CO_2CH_3), 3.78-3.88 (3H, m, C-2'' C*H*$_2$ and C-2' C*H*) and 3.97-4.08 (1H, m, C-5' C*H*) ppm

Minor isomer:

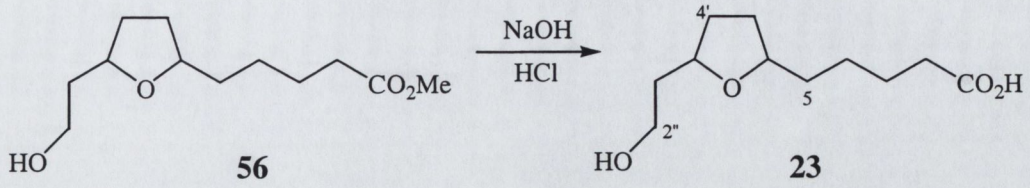
δ_H (400 MHz; $CDCl_3$) 1.32-1.88 (10H, m, C-3' C*H*$_a$, C-4' C*H*$_a$, C-3 C*H*$_2$, C-4 C*H*$_2$, C-5 C*H*$_2$ and C-1'' C*H*$_2$), 1.93-2.09 (2H, m, C-3' C*H*$_b$ and C-4' C*H*$_b$), 2.33 (2H, t, *J* 7.5 and C-2 C*H*$_2$), 2.38 (1H, br. s, C-2'' CO*H*), 3.68 (3H, s, CO_2CH_3), 4.12-4.20 (3H, m, C-2'' C*H*$_2$ and C-2' C*H*) and 4.41-4.48 (1H, m, C-5' C*H*) ppm

Major isomer: (minor isomer not visible clearly)

δ_C (100.6MHz; $CDCl_3$) 24.8 (C-4 *C*H_2), 25.8 (C-3 *C*H_2), 30.8, 31.2 (C-3' and C-4' *C*H_2), 33.9 (C-2 *C*H_2), 35.4 (C-5 *C*H_2), 37.5 (C-1'' *C*H_2), 51.5 (CO_2CH_3), 61.7 (C-2'' *C*H_2), 79.5, 79.7 (C-2' and C-5' *C*H) and 173.7 (CO_2Me) ppm

HRMS (CI) *m/z* 253.1399: *calculated for* $[C_{12}H_{22}O_4 + Na]^+$253.1416

5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoic acid 23



The saturated ester **56** (0.2 g; 0.9 mmol) was dissolved in methanol (5 ml) and 40% NaOH (0.5 ml; 1.35 mmol) was added. The mixture was heated at reflux for 2 hr. The methanol was then removed *in vacuo* and the residue was acidified (pH 1) with 5.5 M HCl. Brine (1 ml) and ethyl acetate (5 ml) were then added and the aqueous layer was extracted (x5) with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to yield 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl)pentanoic acid **23** as a clear oil (0.17 g; 91%; major : minor isomers 14:1)

ν_{max} (L) 3431 (OH), 2932, 2866, 1710 (C=O), 1462, 1413, 1377, 1237, 1200, 1056 (cyclic ether), 933, 880, 802 and 735 cm^{-1}

Major isomer:

δ_H (400 MHz; $CDCl_3$) 1.32-1.89 (10H, m, C-3' C*H*$_a$, C-4' C*H*$_a$, C-3 C*H*$_2$, C-4 C*H*$_2$, C-5 C*H*$_2$ and C-1'' C*H*$_2$), 1.92-2.10 (2H, m, C-3' C*H*$_b$ and C-4' C*H*$_b$), 2.37 (2H, t, *J* 7.5 and C-2 C*H*$_2$), 3.80-3.87 (3H, m, C-2'' C*H*$_2$ and C-2' C*H*) and 3.95-4.10 (1H, m, C-5' C*H*) ppm

Minor isomer:

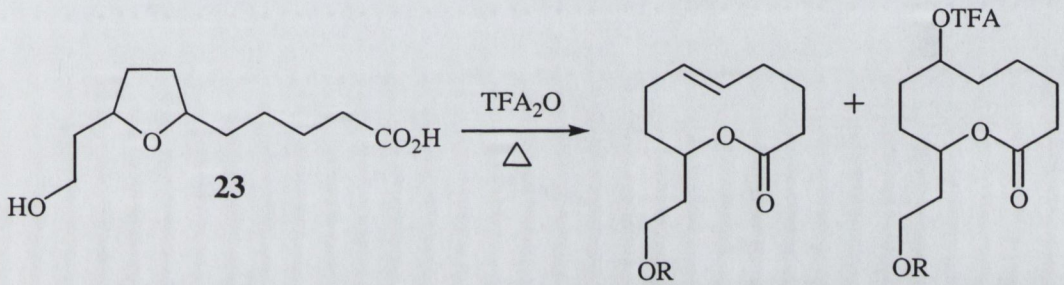
δ_H (400 MHz; $CDCl_3$) 1.32-1.89 (10H, m, C-3' C*H*$_a$, C-4' C*H*$_a$, C-3 C*H*$_2$, C-4 C*H*$_2$, C-5 C*H*$_2$ and C-1'' C*H*$_2$), 1.92-2.10 (2H, m, C-3' C*H*$_b$ and C-4' C*H*$_b$), 2.37 (2H, t, *J* 7.5 and C-2 C*H*$_2$), 4.13-4.20 (3H, m, C-2'' C*H*$_2$ and C-2' C*H*) and 4.40-4.48 (1H, m, C-5' C*H*) ppm

Major isomer: (minor isomer not visible clearly)

δ_C (100.6MHz; $CDCl_3$) 24.6 (C-4 CH_2), 25.6 (C-3 CH_2), 30.7, 31.2 (C-3' and C-4' CH_2), 33.8 (C-2 CH_2), 35.6 (C-5 CH_2), 37.5 (C-1'' CH_2), 61.5 (C-2'' CH_2), 79.3, 79.7 (C-2' and C-5' CH) and 177.8 (CO_2H) ppm

HRMS (CI) *m/z* 239.1255: *calculated for* $[C_{11}H_{20}O_4 + Na]^+$239.1259

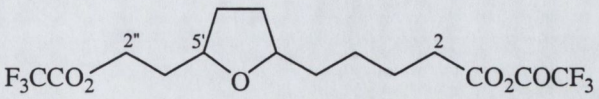
Intramolecular reaction of 5-(2'-[5'-{2''-hydroxyethyl}]tetrahydrofuryl) pentanoic acid 23



58 R = TFA **59** R = TFA
32 R = H **28** R = H

The hydroxy-acid **23** (175 mg; 0.8 mmol) was dissolved in deuteriated chloroform (5 ml) and the solution was cooled in an ice bath. Trifluoroacetic anhydride (0.5 g; 2.5 mmol) was then added. After 0.5 hr at this temperature NMR analysis indicated that the mixed anhydride derived from acid **23** had been formed. The mixture was then refluxed and monitored by NMR. After 5 hr reflux the solvent and the excess trifluoroacetic anhydride were removed *in vacuo*. TLC and NMR studies at this point indicated the presence of two major products, possibly the unsaturated and saturated trifluoroacetoxy lactones **58** and **59**. However, upon purification by column chromatography, hexane : ethyl acetate 95:5, the unsaturated trifluoroacetoxy lactone **58** was not isolated. The first component to elute was 10-(2'-trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one **59** (43 mg; 13%; major : minor isomers 12.5:1; clear oil). (6*E*)-10-(2'-Hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one **32** was next to elute (15 mg; 10%; translucent yellow oil) followed closely by 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one **28** (120 mg; 48%; major : minor isomers 5:1; clear oil).

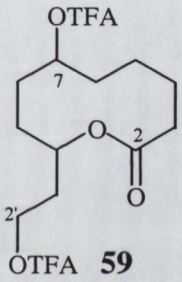
Mixed anhydride 25 derived from 5-(2'-[5'-{2''-hydroxyethyl}] tetrahydrofuryl)pentanoic acid 23 (major isomer)



25

δ_H (400 MHz; $CDCl_3$) 1.51 (3H, m), 1.72 (5H, m), 2.01 (2H, m), 2.16 (2H, m), 2.65 (2H, t, *J* 7.0, C-2 C*H*$_2$), 4.15 (1H, m, C-2' or C-5' C*H*), 4.26 (1H, m, C-2' or C-5' C*H*) and 4.48 (2H, m, C-2'' C*H*$_2$) ppm

10-(2'-Trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one 59



59

ν_{max} (L) 2935, 2873, 1783 (trifluoroacetoxy C=O), 1735 (lactone C=O), 1457, 1335, 1333, 1222, 1164, 1078, 975 and 777 cm^{-1}

Major isomer 59a

δ_H (400 MHz; $CDCl_3$) 1.40-2.26 (12H, m, 6xC*H*$_2$), 2.35 (1H, apparent dt, ^2J 13.5, $^3J_1 = {}^3J_2$ 8.0, C-3 C*H*$_a$), 2.46 (1H, apparent dt, ^2J 13.5, $^3J_1 = {}^3J_2$ 5.0, C-3 C*H*$_b$), 4.37-4.47 (2H, m, C-2' C*H*$_2$), 4.93-4.99 (1H, m, C-10 C*H*) and 5.05-5.11 (1H, m, C-7 C*H*) ppm

Minor isomer 59b

δ_H (400 MHz; $CDCl_3$) 1.40-2.26 (13H, m, 6xC*H*$_2$ and C-3 C*H*$_a$), 2.58-2.65 (1H, ddd, ^2J 16.0, $^3J_1$ 5.5, $^3J_2$ 3.0, C-3 C*H*$_b$), 4.37-4.47 (2H, m, C-2' C*H*$_2$), 5.05-5.11 (1H, m, C-10 C*H*) and 5.44-5.50 (1H, m, C-7 C*H*) ppm

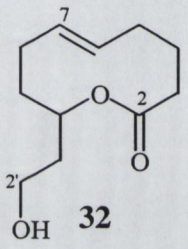
Major isomer 59a (Minor isomer was not visible clearly)

δ_C (100.6 MHz; $CDCl_3$) 21.9 (C-5 CH_2), 22.7 (C-4 CH_2), 27.0, 27.2, 28.4 (3xCH_2 C-6, C-8 and C-9), 33.2 (C-1' CH_2), 34.3 (C-3 CH_2), 64.5 (C-2' CH_2), 72.0 (C-10 CH), 77.6 (C-7 CH) and 173.2 (lactone C=O) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.8 and –75.5 (2x$COCF_3$) ppm

HRMS (CI) *m/z* 239.1265: *calculated for* $[C_{11}H_{20}O_4 + Na]^+$ 239.1259 { = **59** $C_{15}H_{18}F_6O_6 - 2(COCF_3) + 2(H) + Na$}

(6*E*)-10-(2'-Hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32



32

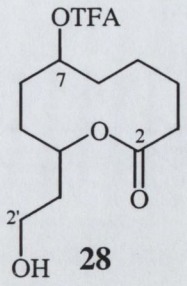
ν_{max} (L) 3446 (OH), 2921, 2852, 1725 (lactone C=O), 1438, 1363, 1342, 1209, 1176, 110, 1058 and 979 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.59-1.67 (2H, m, C-1' CH_a and C-9 CH_a), 1.70-1.84 (3H, m, C-1' CH_b, C-4 CH_a and C-9 CH_b), 1.88-2.15 (4H, m, C-3 CH_a, C-4 CH_b, C-5 CH_a, and C-8 CH_a), 2.29-2.38 (3H, m, C-3 CH_b, C-5 CH_b and C-8 CH_b), 3.53 (1H, ddd, ^2J 11.5, $^3J_1$ 10.0, $^3J_2$ 3.5, C-2' CH_a), 3.60 (1H, ddd, ^2J 11.5, $^3J_1$ 5.5, $^3J_2$ 3.5, C-2' CH_b), 5.10 (1H, dddd, $^3J_1 = {}^3J_2$ 10.5, $^3J_3$ 3.0, $^3J_4$ 1.5, C-10 C*H*), 5.28 (1H, ddd, $^3J_{trans}$ 15.0, $^3J_1$ 11.0, $^3J_2$ 4.0, C-6 C*H*) and 5.56 (1H, ddd, $^3J_{trans}$ 15.0, $^3J_1$ 12.0, $^3J_2$ 3.0, C-7 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 25.6 (C-4 CH_2), 31.7 (C-8 CH_2), 32.4 (C-9 CH_2), 33.4 (C-5 CH_2), 34.4 (C-3 CH_2), 37.7 (C-1' CH_2), 57.5 (C-2' CH_2), 72.6 (C-10 CH), 127.3 (C-6 CH), 133.4 (C-7 CH) and 177.5 (C-2 C=O) ppm

HRMS (CI) *m/z* 221.1136: *calculated for* $[C_{11}H_{18}O_3 + Na]^+$ 221.1154

10-(2'-Hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28



28

ν_{max} (L) 3446 (OH), 2933, 2877, 1779 (trifluoroacetoxy C=O), 1718 (lactone C=O), 1457, 1367, 1222, 1164, 1051, 975 and 777 cm^{-1}

Major isomer 28a

δ_H (400 MHz; $CDCl_3$) 1.37-1.46 (1H, m), 1.57-2.23 (11H, m), 2.42 (1H, apparent dt, ^2J 13.0, $^3J_1 = {}^3J_2$ 7.5, C-3 CH_a), 2.48 (1H, apparent dt, ^2J 13.0, $^3J_1 = {}^3J_2$ 5.5, C-3 CH_b), 3.60 (1H, ddd, ^2J 12.0, $^3J_1$ 9.0, $^3J_2$ 4.5, C-2' CH_a), 3.65-3.73 (1H, m, C-2' CH_b) and 4.99-5.09 (2H, m, C-7 C*H* and C-10 C*H*) ppm

Minor isomer 28b

δ_H (400 MHz; $CDCl_3$) 1.37-1.46 (1H, m), 1.57-2.23 (11H, m), 2.26 (1H, ddd, ^2J 15.5, $^3J_1$ 12.0, $^3J_2$ 3.0, C-3 CH_a), 2.63 (1H, ddd, ^2J 16.0, $^3J_1$ 5.5, $^3J_2$ 3.0, C-3 CH_b), 3.56-3.76 (2H, m, C-2' CH_2), 4.99-5.09 (1H, m, C-10 C*H*) and 5.39-5.43 (1H, m, C-7 C*H*) ppm

Major isomer 28a

δ_C (100.6 MHz; $CDCl_3$) 22.4, 22.8, 28.0, 28.1, 28.6 (5x*C*H_2), 34.3 (C-3 *C*H_2), 37.9 (*C*H_2), 58.2 (C-2' *C*H_2), 73.0, 77.8 (C-7 and C-10 *C*H) and 174.6 (*C*O_2R) ppm

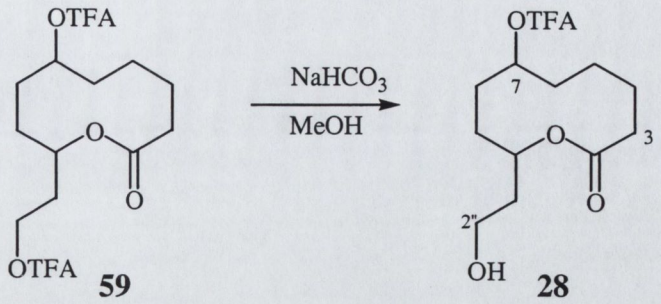
Minor isomer 28b

δ_C (100.6 MHz; $CDCl_3$) 20.2, 24.3, 29.5, 29.7, 30.1 (5x*C*H_2), 34.4 (C-3 *C*H_2), 36.6 (*C*H_2), 58.3 (C-2' *C*H_2), 72.7, 78.0 (C-7 and C-10 *C*H) and 174.6 (*C*O_2R) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.8 (COC*F*$_3$) ppm

HRMS (CI) *m/z* 239.1269: *calculated for* $[C_{11}H_{20}O_4 + Na]^+$ 239.1259 { = **28** $C_{13}H_{19}F_3O_5 - COCF_3 + H + Na$)

Hydrolysis of 10-(2'-trifluoroacetoxyethyl)-7-trifluoroacetoxyoxecan-2-one 59

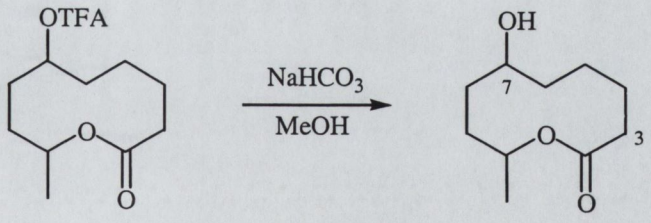


59 **28**

Saturated $NaHCO_3$ solution (0.1 ml) was added to the trifluoroacetoxy lactone **59** (73 mg; 0.18 mmol) in methanol (1 ml) and the mixture was left to stand for 0.5 hr. Water (1 ml) and ethyl acetate (1 ml) were then added and the aqueous layer was extracted (x4 ethyl acetate). The combined organic extracts were then dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product (30 mg) was then purified by column chromatography, hexane : ethyl acetate 90:10 to 70:30. 10-(2'-Hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one **28** was isolated as a clear oil (23 mg; 43%; major : minor isomers 7:1).

The NMR and IR spectra of **28** were identical to the semi-hydrolysed saturated lactone isolated from the column of the crude product obtained from the intramolecular reaction of acid **23** with trifluoroacetic anhydride.

Hydrolysis of 10-methyl-7-trifluoroacetoxy-oxecan-2-one 65



65 **66**

Saturated $NaHCO_3$ solution (0.3 ml) was added to the trifluoroacetoxy lactone **65** (4.7 mg; 0.017 mmol) in methanol (1 ml). The reaction was then monitored by TLC. After 2 hr at room temperature, water (1 ml) and ethyl acetate (1 ml) were then added and the aqueous layer was extracted (x4). The combined organic extracts were then dried over $MgSO_4$ and the solvent removed *in vacuo*. The

product thus obtained was identified as 10-methyl-7-hydroxy-oxecan-2-one **66** (2 mg; 66%) as a clear oil.

ν_{max} 3384 (OH), 2929, 2856, 1718 (C=O), 1560, 1457, 1375, 1261, 1176, 1016 and 798 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.23 (3H, d, *J* 6.3, C*H*$_3$), 1.61 (5H, m), 1.89 (5H, m), 2.65 (2H, m, C-3 C*H*$_2$), 3.84 (1H, m, C-10 C*H*) and 4.35 (1H, m, C-7 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 22.6 (*C*H$_3$), 23.2, 27.8, 31.8, 34.0, 34.1 (5x*C*H$_2$), 34.5 (C-3 *C*H$_2$), 67.1 (C-10 *C*H), 79.7 (C-7 *C*H) and 175.4 (C-2 *C*=O) ppm

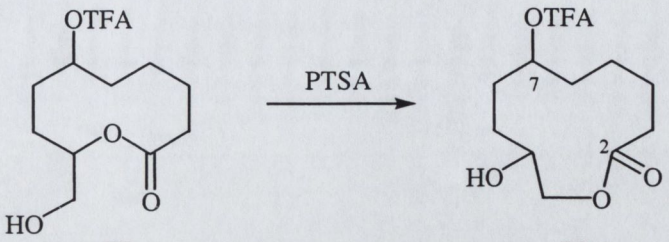
HRMS *m/z* (CI) 187.1326: *calculated for* $[C_{10}H_{18}O_3 + H]^+$ 187.1334

3.7.3 Translactonisation reactions

General procedure for a translactonisation reaction

The saturated/unsaturated lactone (0.05 mmol) was dissolved in deuteriated dichloromethane (0.75 ml). *p*-Toluenesulfonic acid in deuteriated dichloromethane was added (1 mg/ml; 0.5 ml; 5 mol%) and the reaction was monitored by ^1H NMR spectroscopy at a probe temperature of 30 °C. When the reaction was complete, the mixture was diluted with ether (3 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (2 ml). The aqueous wash was extracted (x4) with ether and the combined ether layers were dried over $MgSO_4$ and the solvent removed *in vacuo*.

Translactonisation of 10-hydroxymethyl-7-trifluoroacetoxyoxecan-2-one 27 to form 10-hydroxy-7-trifluoroacetoxy-oxacycloundecan-2-one 29



27 **29**

Reaction time: 72 hr

Isolated yield of starting material/product mixture: 80%

The starting material and the product were inseparable.

Starting material : product ratio in isolated mixture:

1:2 (67% conversion) for the major isomer **29a**.

The minor isomer **29b** did not rearrange.

Appearance of product mixture: clear oil.

Spectroscopic data for 10-hydroxy-7-trifluoroacetoxy-oxacycloundecan-2-one **29a**:

ν_{max} (L) 3440 (OH), 2960, 2927, 2871, 1779 (trifluoroacetoxy C=O), 1735 (lactone C=O), 1457, 1367, 1259, 1222, 1164, 1043, 800 and 777 cm^{-1}

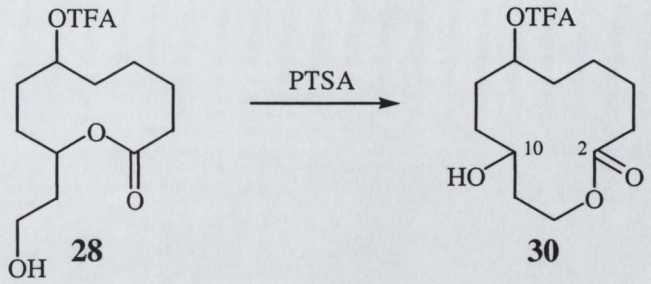
δ_H (400 MHz; $CDCl_3$) 1.26-1.40 (1H, m), 1.50-2.14 (9H, m), 2.39 (1H, ddd, ^2J 14.0, $^3J_1$ 7.5, $^3J_2$ 6.0, C-3 CH_a), 2.54-2.61 (1H, m, C-3 CH_b), 4.10 (1H, dd, ^2J 12.0, ^3J 4.5, C-11 CH_a), 4.15-4.19 (1H, m, C-10 C*H*), 4.46 (1H, dd, ^2J 12.0, ^3J 3.0, C-11 CH_b) and 5.37-5.43 (1H, m, C-7 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 21.4, 21.7, 25.6, 28.2, 28.4 (C-4, 5, 6, 8, 9, 5xCH_2), 33.5 (C-3 CH_2), 66.3 (C-11 CH_2), 67.8 (C-10 *C*H), 77.9 (C-7 *C*H) and 172.7 (C-2 *C*=O) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.7 ($COCF_3$) ppm

HRMS (CI) *m/z* 321.0910: *calculated for* $[C_{12}H_{17}O_5F_3 + Na]^+$ 321.0926

Translactonisation of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28 to form 10-hydroxy-7-trifluoroacetoxy-oxacyclododecan-2-one 30



Reaction time: 22 hr

Isolated yield of starting material/product mixture: 80%

The starting material and product were inseparable

Starting material : product ratio of isolated mixture:

1:11 (92% conversion) for the major isomer **30a**

1:1.7 (63% conversion) for the minor isomer **30b**

Appearance of twelve-membered product: clear oil.

Spectroscopic details for diastereomeric mixture 10-hydroxy-7-trifluoroacetoxy-oxacyclododecan-2-one **30a** and **30b**:

ν_{max} (L) 3424 (OH), 2956, 2875, 1779 (trifluoroacetoxy C=O), 1732 (lactone C=O), 1454, 1392, 1349, 1219, 1164, 1053, 978 and 776 cm^{-1}

Major isomer 30a

δ_H (400 MHz; $CDCl_3$) 1.37-1.55 (2H, m), 1.64-1.90 (8H, m), 1.92-1.97 (2H, m), 2.42-2.46 (2H, m, C-3 CH_2), 3.96-3.99 (1H, m, C-10 C*H*), 4.31 (1H, ddd, ^2J 11.5, $^3J_1$, 7.0, $^3J_2$ 3.5, C-12 CH_a), 4.47 (1H, ddd, ^2J 11.5, $^3J_1$ 6.5, $^3J_2$ 3.0, C-12 CH_b) and 5.16-5.20 (1H, m, C-7 C*H*) ppm

Minor isomer 30b

δ_H (400 MHz; $CDCl_3$) 1.37-1.55 (2H, m), 1.64-1.90 (8H, m), 1.92-1.97 (2H, m), 2.42-2.46 (2H, m, C-3 CH_2), 3.96-3.99 (1H, m, C-10 C*H*), 4.17 (1H, ddd, ^2J 11.5, $^3J_1$ 9.0, $^3J_2$ 2.5, C-12 CH_a), 4.57 (1H, ddd, ^2J 11.5, $^3J_1$6.5, $^3J_2$ 3.0, C-12 CH_b) and 5.16-5.20 (1H, m, C-7 C*H*) ppm

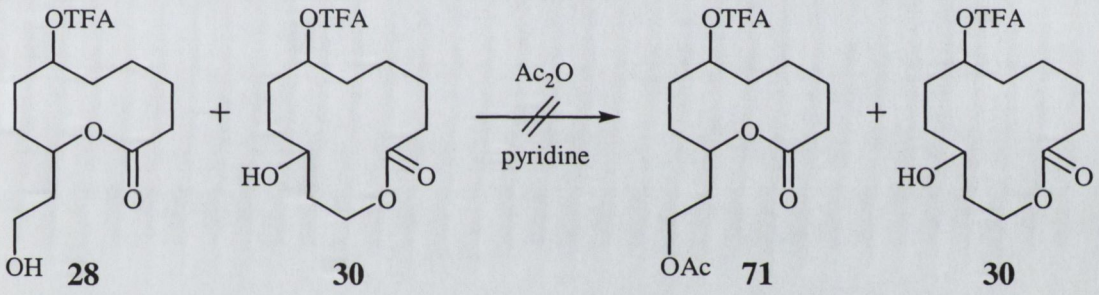
Major Isomer 30a (Minor isomer not visible clearly)

δ_C (100.6 MHz; $CDCl_3$) 19.8, 22.9, 24.5, 27.0, 29.3 (C-4, 5, 6, 8, 9, 5xCH_2), 32.0 (C-3 CH_2), 32.9 (C-11 CH_2), 59.8 (C-12 CH_2), 69.4 (C-10 CH), 77.9 (C-7 CH), 114 (q, $J_{F,C}$ 284.0, $COCF_3$), 156 (q, $J_{F,C}$ 41.5, $COCF_3$), 172.5 (C-2 C=O) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.8 ($COCF_3$) ppm

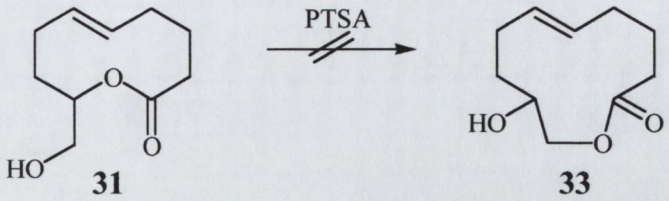
HRMS (CI) *m/z* 239.1278: *calculated for* $[C_{11}H_{20}O_4 + Na]^+$ 239.1259 { = **30** $C_{13}H_{19}F_3O_5 - COCF_3 + H + Na$}

Attempted conversion of 10-(2'-hydroxyethyl)-7-trifluoroacetoxyoxecan-2-one 28 to the corresponding acetate 71



The mixture of lactones **28** and **30** (0.013 g; 0.04 mmol) was dissolved in dry pyridine (0.1 ml) cooled to 0 °C. Acetic anhydride (5 µl) was then added and the mixture was left at 0 °C for 0.5 hr. The mixture was then poured on to ice and extracted (x3) with ether. The combined ether extracts were acidified with 5.5 M HCl to pH 1 and then washed with water, dried over $MgSO_4$ and evaporated. The product mixture thus obtained was found to consist of the two starting lactones **28** and **30**. The acetate **71** was not detected.

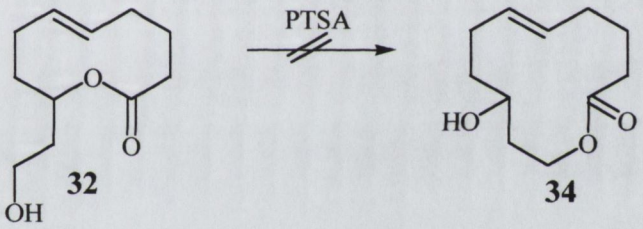
Attempted Translactonisation of (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31



31 **33**

Exposure to PTSA had no effect on (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one **31**.

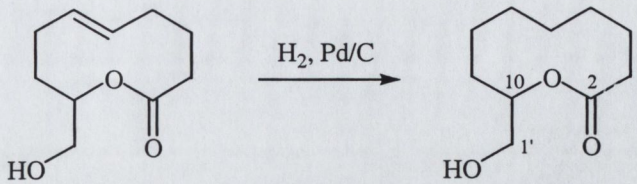
Attempted Translactonisation of (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32



32 **34**

Exposure to PTSA had no effect on (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one **32**.

Hydrogenation of (6*E*)-10-hydroxymethyl-3,4,5,8,9,10-hexahydro-oxecin-2-one 31 to form 10-hydroxymethyl-oxecan-2-one 74



31 **74**

The unsaturated lactone **31** (7 mg; 0.038 mmol) was dissolved in ethyl acetate (4 ml) and was stirred under an atmosphere of hydrogen (1 atm) in the presence of 5% w/w Pd/C (1 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo*. 10-Hydroxymethyl-oxecan-2-one **74** (6 mg; 85%) was obtained as a clear oil.

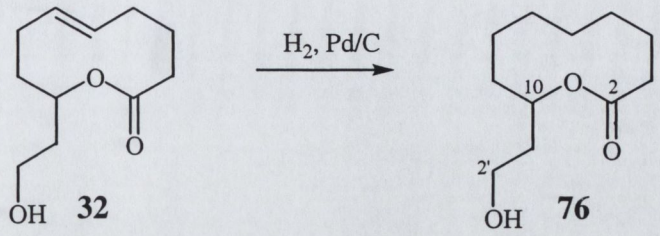
ν_{max} (L) 3421 (OH), 2960, 2927, 2858, 1718 (lactone C=O), 1457, 1259, 1072, 1020, and 800 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.42-1.80 (1H, 10H, 2xm, C-5, C-6, C-7, C-8 CH_2, C-4 CH_a and C-9 CH_a), 1.85-1.92 (1H, dddd, ^2J 10.5, $^3J_1$ 7.5, $^3J_2$ 4.0, $^3J_3$ 2.5, C-9 CH_b), 1.98-2.10 (1H, m, C-4 CH_b), 2.28 (1H, ddd, ^2J 15.5, $^3J_1$ 11.0, $^3J_2$ 3.0, C-3 CH_a), 2.54 (1H, ddd, ^2J 15.5, $^3J_1$ 7.0, $^3J_2$ 3.5, C-3 CH_b), 3.72 (1H, dd, ^2J 11.5, ^3J 4.0, C-1' CH_a), 3.77 (1H, dd, ^2J 11.5, ^3J 6.5, C-1' CH_b) and 4.94 (1H, dddd, $^3J_1$ 9.5, $^3J_2$ 6.5, $^3J_3$ 4.0, $^3J_4$ 2.5, C-10 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.4, 23.5, 24.0, 24.1 (C-5,6,7,8 4x*C*H_2), 26.4 (C-4 *C*H_2), 27.1 (C-9 *C*H_2), 34.6 (C-3 *C*H_2), 64.6 (C-1' CH_2), 77.6 (C-10 *C*H) and 174.6 (C-2 *C*=O) ppm

HRMS (CI) *m/z* 209.1147: *calculated for* $[C_{10}H_{18}O_3 + Na]^+$ 209.1154

Hydrogenation of (6*E*)-10-(2'-hydroxyethyl)-3,4,5,8,9,10-hexahydro-oxecin-2-one 32 to form 10-(2'-hydroxyethyl)-oxecan-2-one 76



The unsaturated lactone **32** (11 g; 0.056 mmol) was dissolved in ethyl acetate (4 ml) and was stirred under an atmosphere of hydrogen (1 atm) in the presence of 5% w/w Pd/C (1 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo*. The crude product was then purified by column chromatography with hexane : ethyl acetate 80:20 to give 10-(2'-hydroxyethyl)-oxecan-2-one **76** (6.6 mg, 60%) as a clear oil.

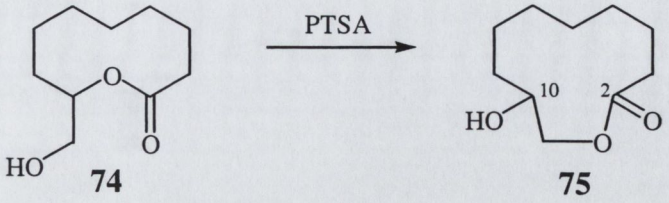
ν_{max} (L) 3408 (OH), 2959, 2926, 2868, 1725 (C=O), 1466, 1260, 1072, 1050, 1021 and 799 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.26-1.32 (1H. m), 1.41-1.68 (7H, m), 1.72-1.91 (5H, m), 1.99-2.09 (1H, m), 2.25 (1H, ddd, ^2J 15.0, $^3J_1$ 12.0, $^3J_2$ 3.0, C-3 CH_a), 2.54 (1H, ddd, ^2J 15.0, $^3J_1$ 6.5, $^3J_2$ 3.0, C-3 CH_b), 3.55 (1H, ddd, ^2J 11.5, $^3J_1$ 10.0, $^3J_2$ 4.0, C-2' CH_a), 3.65 (1H, ddd, ^2J 11.5, $^3J_1$ 5.5, $^3J_2$ 4.0, C-2' CH_b) and 5.03 (1H, dddd, $^3J_1$ 11.0, $^3J_2$ 9.0, $^3J_3$ 3.5, $^3J_4$ 2.5, C-10 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.3 (C-4 CH_2), 24.1, 24.2, 24.5, 26.5, 32.1 (5xCH_2), 34.6 (C-3 CH_2), 37.4 (CH_2), 57.9 (C-2' CH_2), 73.6 (C-10 *C*H) and 175.6 (C-2 *C*=O) ppm

HRMS (CI) *m/z* 223.1310: *calculated for* $[C_{11}H_{20}O_3 + Na]^+$ 223.1310

Translactonisation of 10-hydroxymethyl-oxecan-2-one 74 to form 10-hydroxy-oxacycloundecan-2-one 75



74 **75**

Reaction time: 72 hr

Isolated yield of starting material/product mixture: 77%

The starting material and product were inseparable.

Starting material : product ratio of isolated mixture: 1:1 (50% conversion)

Appearance of product mixture: clear oil.

Spectroscopic details for 10-hydroxy-oxacycloundecan-2-one **75**:

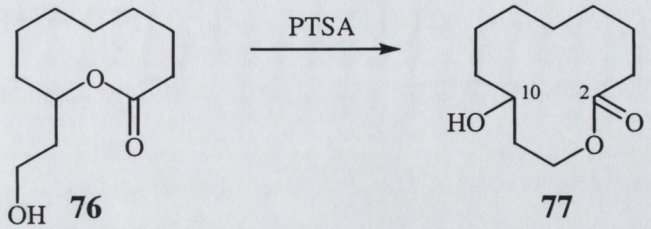
ν_{max} (L) 3421 (OH), 2960, 2927, 2854, 1733 (C=O), 1465, 1413, 1375, 1259, 1089, 1020 and 798 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.32-1.82 (12H, m, 6xCH_2), 2.34-2.45 (2H, m, C-3 CH_2), 3.99-4.06 (1H, m, C-10 C*H*), 4.11 (1H, dd, ^2J 11.0, ^3J 7.0, C-11 CH_a) and 4.20 (1H, dd, ^2J 11.0, ^3J 3.0, C-11 CH_b) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.9, 21.8, 23.9, 24.5, 29.2, 32.7 (6xCH_2), 34.6 (C-3 CH_2), 66.6 (C-11 CH_2), 67.9 (C-10 C*H*) and 174.3 (C-2 *C*=O) ppm

HRMS *m/z* (CI) 209.1163: *calculated for* $[C_{10}H_{18}O_3 + Na]^+$ 209.1154

Translactonisation of 10-(2'-hydroxyethyl)-oxecan-2-one 76 to form 10-hydroxy-oxacyclododecan-2-one 77



76 **77**

Reaction time: 24 hr

Isolated yield of starting material/product mixture: 70%

The starting material and product were inseparable.

Starting material : product ratio of isolated mixture: 1:6.25 (86% conversion)

Appearance of starting material/product mixture: clear oil.

Spectroscopic details for 10-hydroxy-oxacyclododecan-2-one **77**

ν_{max} (L) 3384 (OH), 2925, 2852, 1735 (C=O), 1708, 1457, 1261, 1145, 1070, 1020, 869 and 800 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.23-1.82 (14H, m), 2.31 (1H, ddd, ^2J 14.0, $^3J_1$ 10.5, $^3J_2$ 4.0, C-3 CH_a), 2.45 (1H, ddd, ^2J 14.0, $^3J_1$ 7.0, $^3J_2$ 4.0, C-3 CH_b), 3.91 (1H, m, C-10 C*H*), 4.12 (1H, ddd, ^2J 11.0, $^3J_1$ 7.0, $^3J_2$ 2.5, C-12 CH_a) and 4.51 (1H, ddd, ^2J 11.0, $^3J_1$ 6.5, $^3J_2$ 2.5, C-12 CH_b) ppm

δ_C (100.6 MHz; $CDCl_3$) 23.0, 23.6, 23.9, 24.1, 29.2, 33.4, 33.8, 34.0 (8xCH_2), 60.2 (C-12 CH_2), 68.4 (C-10 *C*H) and 174.2 (C-2 *C*=O) ppm

HRMS (CI) *m/z* 223.1330: *calculated for* $[C_{11}H_{20}O_3 + Na]^+$ 223.1310

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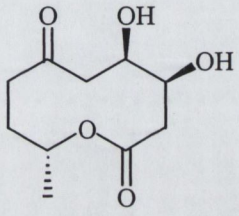
Chapter 4

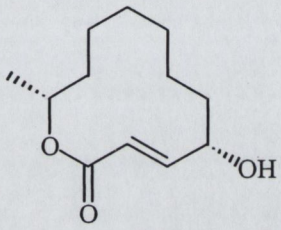
Towards Syntheses of Cephalosporolide G and Patulolide C

4.1 Introduction

The success of the intramolecular acylative ring-switching reactions of ω-(tetrahydro-2'-furyl)alkanoic acid derivatives in the synthesis of medium-ring lactones generates the opportunity for further manipulation of these primary products. This can result in the synthesis of more complex lactones which exhibit desirable biological activities. Cephalosporolide G **1**[1] and Patulolide C **2**[2] exemplify two target molecules in this category.



1 Cephalosporolide G

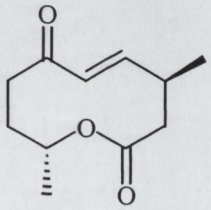


2 Patulolide C

This chapter describes the attempted syntheses of the ω-(tetrahydro-2'-furyl)alkenoic acid precursors which are necessary to investigate the possibility of synthesising these naturally occurring lactones *via* the intramolecular acylative ring-switching route.

4.2 Towards the synthesis of (Z)-5-(5'-methyl-tetrahydro-2'-furyl) pent-3-enoic acid (6), a precursor for Cephalosporolide G (1)

The fungus, *Cephalosporium aphidicola*, produces a number of ten-membered lactones known as the Cephalosporolides B-G, (Cephalosporolides B **3**, C **4** and G **1** are shown). Some of these lactones have been found to inhibit various stages of steroid biosynthesis.[1]



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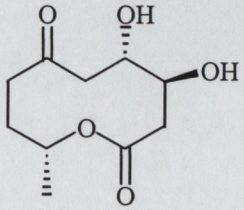

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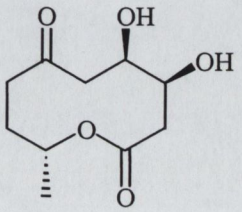
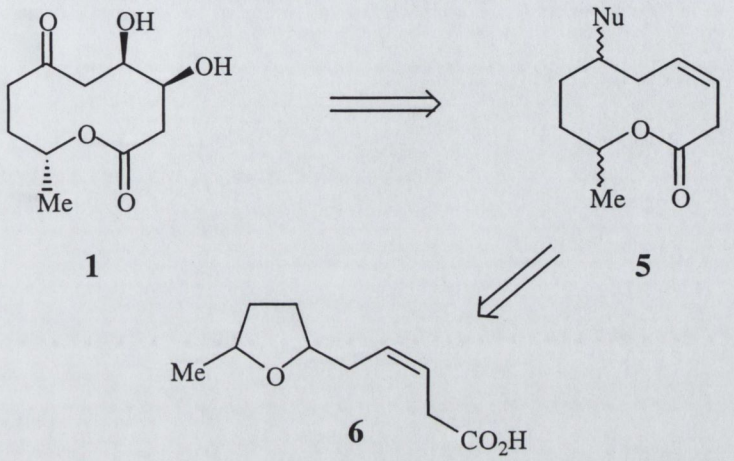


1

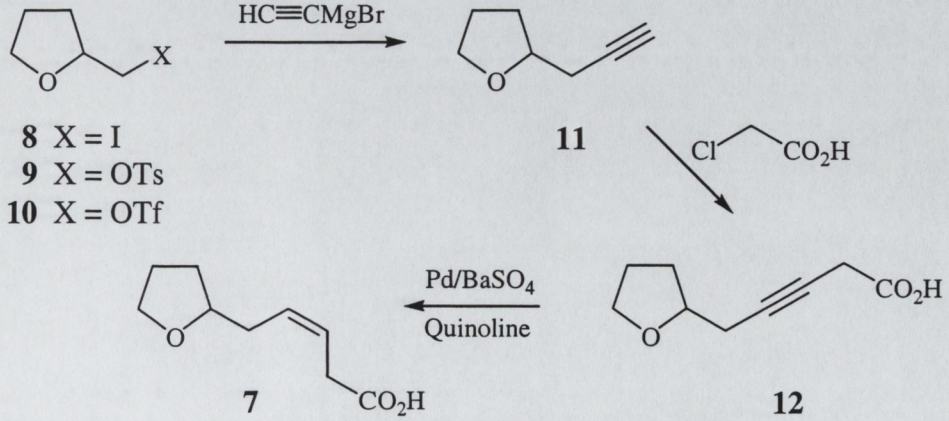
Employing the lactonisation method involving the acylative ring-expansion of ω-(tetrahydro-2'-furyl)alkanoic acids, Cephalosporolide G **1**, which was first isolated in 1995,[1] should be accessible *via* a precursor such as (Z)-5-(5'-methyl-tetrahydro-2'-furyl)pent-3-enoic acid **6**, **Scheme 4.1**.



Scheme 4.1

4.2.1 Attempted synthesis of (Z)-5-(tetrahydro-2'-furyl)pent-3-enoic acid 7 *via* an alkynoic acid derivative

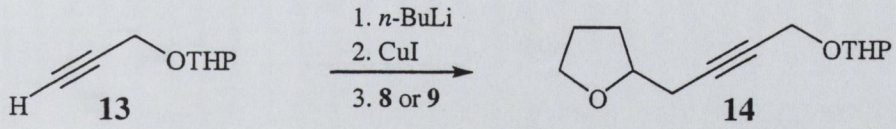
In investigating an approach to the (Z)-acid **6**, it was proposed to first develop a route to the somewhat simpler analogue **7**. A distinctive feature of both **6** and **7** is the (Z)-configured double bond in the alkenoic acid chain. (Z)-Alkenes can be accessed *via* selective hydrogenation of alkynes in the presence of Pd/barium sulfate poisoned with quinoline.[3] Thus, a model synthetic route involving the formation of ω-(tetrahydro-2'-furyl)alkynoic acid **12** was investigated, **Scheme 4.2**.



Scheme 4.2

Tetrahydrofurfuryl iodide **8** was successfully obtained by reaction of tetrahydrofurfuryl alcohol with triphenylphosphite methiodide.[4] The synthesis of 2-prop-2'-ynyl-tetrahydrofuran **11** was then attempted *via* a Grignard reaction of **8** with ethynylmagnesium bromide. The NMR spectra of the crude product mixture obtained showed no resemblance to that expected for the required alkyne product. Thus, tetrahydrofurfuryl tosylate **9** was formed in order to investigate the viability of the tosyloxy group as an alternative leaving group to iodide. Tosylate **9**[5] was obtained by treating tetrahydrofurfuryl alcohol with *p*-toluenesulfonyl chloride in pyridine. Reaction of the tosylate **9** with ethynylmagnesium bromide was carried out in the presence of copper(1) iodide and the NMR spectra of the crude product indicated that the desired alkyne **11** was indeed present. However, separation by distillation resulted in decomposition. The reaction was repeated with a view to separation *via* column chromatography however, decomposition occurred during work-up and thus this synthetic route to precursor **7** was abandoned. The reaction of ethynylmagnesium bromide with tetrahydrofurfuryl triflate **10**, formed by reaction of tetrahydrofurfuryl alcohol with triflic anhydride,[6] was also investigated, however, the ^{1}H NMR spectrum of the crude product obtained showed no evidence for the presence of the desired product **11**.

An alternative route employing an organocuprate prepared *in situ* from the protected propargyl alcohol **13**, was next attempted, **Scheme 4.3**.

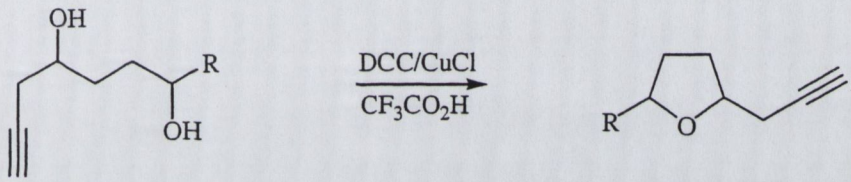


Scheme 4.3

The hydroxyl group of propargyl alcohol was protected with 2,3-dihydropyran to form a base-stable acetal. This tetrahydropyranyloxy ether function is widely employed as a protecting group in chemical syntheses due to the low cost of 2,3-dihydropyran and its ease of installation which can be achieved in the presence of catalytic quantities of pyridinium *p*-toluenesulfonate[7] or phosphorus oxychloride. Tetrahydro-2-(2-propynyloxy)pyran **13**[8] was formed using pyridinium *p*-toluenesulfonate as catalyst and was purified by distillation (70%).

The synthesis of the protected acetylenic alcohol **14** by reaction of the Gilman reagent derived from protected propargyl alcohol **13** with iodide **8** was unsuccessful with only starting materials recovered. However, a very small amount of product was formed when the tosylate **9** was used as electrophile yet this synthetic pathway was abandoned due to the unsatisfactory yield.

Due to these unsuccessful results it was obvious that an alternative approach was necessary. Thus, it was proposed to firstly introduce the alkyne function to a molecule which possessed the intrinsic ability to react intramolecularly to form a tetrahydrofuran ring. Initially, the most logical candidate molecule for this approach appeared to be a 1,4 diol, **15** or **16**, as these would allow facile tetrahydrofuran ring formation, **Scheme 4.4**.[9]

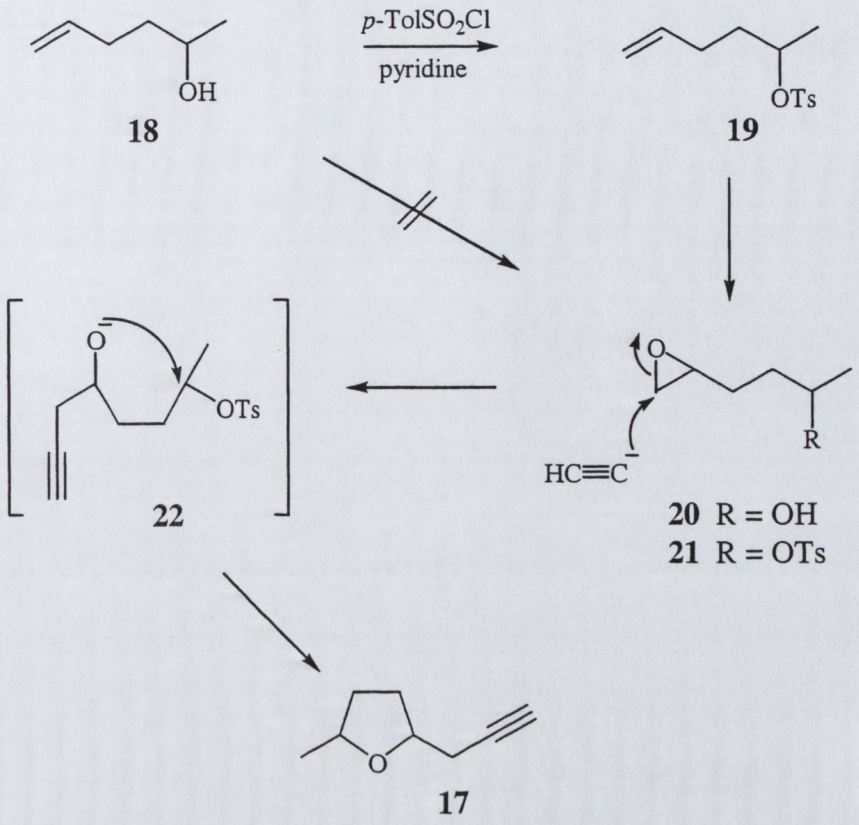


15 R = H
16 R = Me

11 R = H
17 R = Me

Scheme 4.4

However, it also appeared that a novel, tandem-reaction approach to tetrahydrofurans that by-passed the need to synthesise intermediate 1,4-diols might be possible, **Scheme 4.5**.



Scheme 4.5

Here, Grignard reaction of the epoxy-tosylate **21** with ethynylmagnesium bromide should result in formation of tetrahydrofuran **17**.

Thus, 5-hexen-2-one was converted into the corresponding alcohol **18**[10] by treatment with sodium borohydride (90%). Initially, conversion of the alkene function of **18** to a terminal epoxide **20** was attempted *via* conventional methods. The Payne epoxidation reaction[11] employing hydrogen peroxide and acetonitrile in the presence of potassium carbonate or alternatively in the presence of sodium hydroxide was attempted, however, no reaction was observed in either case.

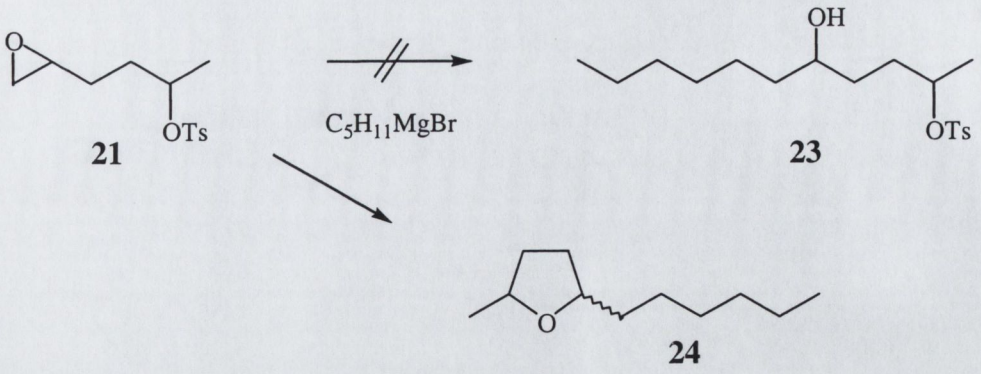
Epoxidation of **18** was then attempted using magnesium monoperoxyphthalate (MMPP), a reagent which exhibits high stability at ambient temperatures and has been employed in the oxidation of a wide range of substrates under mild conditions.[12] MMPP was developed as an alternative to *m*CPBA (*m*-chloroperoxybenzoic acid), a peracid that is an efficient oxidation reagent which is seldom used in large scale synthesis due to safety and cost considerations - *m*CPBA in its pure form is both shock sensitive and potentially explosive in the condensed

phase. Unfortunately, reaction of 5-hexen-2-ol **18** with MMPP was also unsuccessful.

At this point, it was considered sensible to convert the alcohol function to a good leaving group. Consequently, 5-hexen-2-ol **18** was treated with *p*-toluenesulfonyl chloride in pyridine to give the tosylate **19**[13] (84%), **Scheme 4.5**.

An additional safe alternative to *m*CPBA had been developed[14] employing urea - hydrogen peroxide (UHP) which, although it has a relatively high hydrogen peroxide content, is relatively stable. In the case of isolated or terminal alkenes a typical reaction is carried out in the presence of trifluoroacetic anhydride. Interaction of UHP with the anhydride results in the formation of peroxytrifluoroacetic acid which then reacts with the double bond. In the present work, 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** was formed from 2-tosyloxyhex-5-ene **19** (92%) using this reagent, **Scheme 4.5**.

1,2-Epoxy-5-*p*-toluenesulfonyloxyhexane **21** was then treated with ethynylmagnesium bromide. It was anticipated that addition would occur resulting in the formation of intermediate **22** which could potentially cyclise to give the di-substituted tetrahydrofuran **17**, **Scheme 4.5**. However, on examination of the crude product by NMR spectroscopy, it was clear that it consisted of a complex mixture that did not contain the desired compound. Identification of any of the components present in the crude mixture was not achieved. To investigate the situation further, 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** was treated with pentylmagnesium bromide, a relatively simple Grignard reagent. As in the case of the analogous reaction using ethynylmagnesium bromide, a complex product mixture was obtained. However, in this instance, separation by column chromatography resulted in the isolation of a yellow oil which, on examination by NMR spectroscopy was identified as the tetrahydrofuran derivative **24** (13%) as a 50:50 mixture of *cis*- and *trans*-diastereoisomers, **Scheme 4.6**.



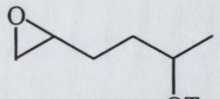
Scheme 4.6

2-Hexyl-5-methyltetrahydrofuran **24**[15] shows an IR absorption at 1137 cm^{-1} (tetrahydrofuran ether). Distinctive signals in the ^1H NMR spectrum of the mixture **24** include two triplets at δ_H 0.88 and 0.90 ppm, both with *J* 6.5 Hz, for each of the terminal methyl groups of the hexyl side-chains of both diastereoisomers. The methyl groups of the tetrahydrofuran rings resonate as two doublets at δ_H 1.23 and 1.25 ppm, *J* 6.0 Hz. The C-2 and C-5 methine protons of the two diastereoisomers overlap slightly and are observed as multiplets centred at δ_H 3.79 (1H), 3.95 (2H) and 4.10 (1H) ppm. In the ^{13}C NMR spectrum of **24**, two signals overlap at δ_C 14.1 ppm and are assigned to the two terminal methyl groups of the hexyl side-chains present in the mixture. The methyl groups of the tetrahydrofuran rings are visible at δ_C 21.3 and 21.4 ppm while the C-2 and C-5 methine carbons of each diastereoisomer are evident at δ_C 74.3, 75.0, 78.8 and 79.6 ppm.

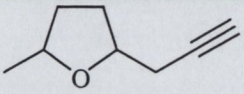
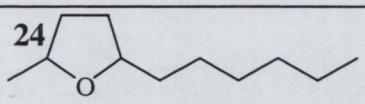
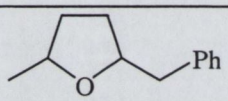
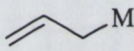
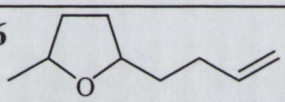
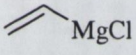
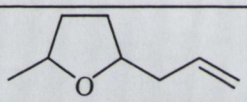
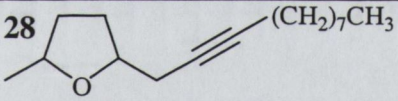
This direct formation of 2-hexyl-5-methyltetrahydrofuran **24** from the epoxy-tosylate **21** suggested that perhaps other tetrahydrofuran derivatives could be prepared using this concise method. Hence, the products obtained on reaction of various Grignard reagents with 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** were examined and the results are summarised in **Table 4.1**.

Table 4.1

Reaction of Epoxide 21 with various reagents



21

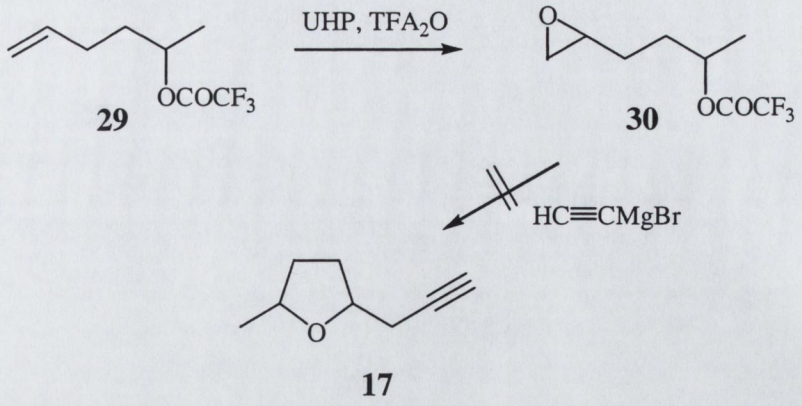
Entry	Reagent	Anticipated Product	Yield (%)
1	HC≡CMgBr	**17** 	0
2	$C_5H_{11}MgBr$	**24** 	13
3	PhMgBr	**25** 	24
4		**26** 	0
5		**27** 	0
6*	$HC{\equiv}C(CH_2)_7CH_3$	**28** 	13

Entries 1-5: Grignard reactions were carried out at 0 °C under an atmosphere of nitrogen.

Entry 6*: 1-Decyne was treated with *n*-BuLi and boron trifluoride-THF complex in dry THF at –78 °C prior to addition of a solution of **21**

The tetrahydrofuran derivatives **25** and **28** showed spectroscopic characteristics in agreement with their structures, and all consisted of a 50:50 mixture of *cis*- and *trans*-diastereoisomers.

The trifluoroacetate protecting group was also investigated as a possible alternative to the tosylate group. Hence, 2-trifluoroacetoxyhex-5-ene **29**[16] (62%) was obtained by treatment of 5-hexen-2-ol with trifluoroacetic anhydride in pyridine. It was then converted into the corresponding epoxide **30** *via* treatment with UHP and trifluoroacetic anhydride (79%).[14] However, on addition of ethynylmagnesium bromide to a solution of this epoxide in THF the desired tetrahydrofuran derivative **17** was not formed, **Scheme 4.7**.



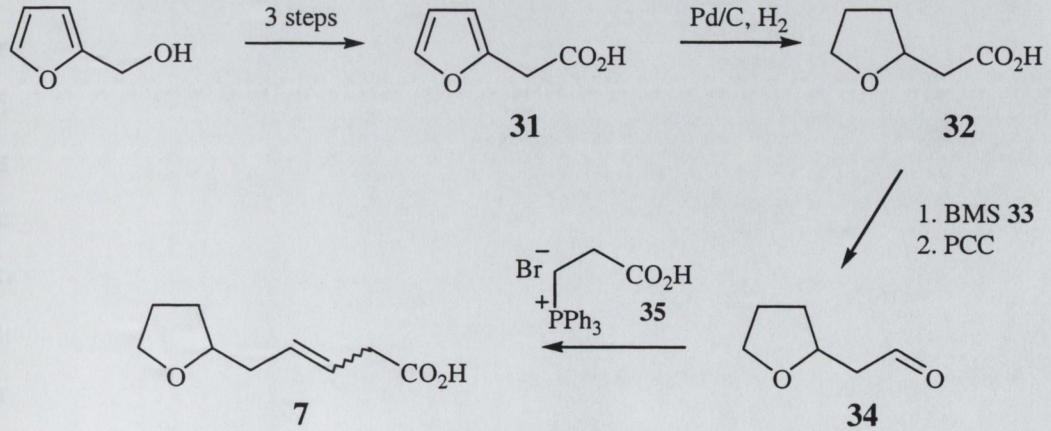
Scheme 4.7

It is clear from the results described above that although some tetrahydrofuran derivatives were obtained when the epoxy-tosylate **21** was treated with various Grignard reagents (entries 2, 3 and 6, **Table 4.1**) the poor yields and the limited scope of this method do not warrant further investigation.

The synthesis of 5-(tetrahydro-2'-furyl)pent-3-enoic acid **7** *via* the alkynoic acid **12** was proving problematic, and hence a new approach was considered.

4.2.2 Synthesis of (*Z*)-5-(tetrahydro-2'-furyl)pent-3-enoic acid 7 *via* a Wittig reaction

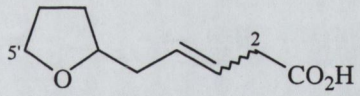
An alternative approach to (*Z*)-5-(tetrahydro-2'-furyl)pent-3-enoic acid **7**, which involves formation of the (*Z*)-double bond *via* a Wittig reaction was considered, **Scheme 4.8**.



Scheme 4.8

2-Furylacetic acid **31** was formed by conventional methods from furfuryl alcohol *via* conversion to the corresponding chloride, then to the nitrile followed by its hydrolysis to the carboxylic acid **31**.[17] Hydrogenation of **31** in the presence of palladium on activated charcoal then led to the corresponding saturated acid **32**.[18] Treatment of **32** with borane-methyl sulfide complex (BMS) resulted in the formation of 2-tetrahydrofurylethanol **33**[19] which was easily converted to the aldehyde **34**[20] using PCC. All of these intermediates showed spectroscopic characteristics in agreement with their structures.

It was anticipated that a Wittig reaction employing (2'-carboxyethyl) triphenylphosphonium bromide **35** would lead to the desired precursor **7**, although it was not known whether the predominant product would be the (*E*)- or (*Z*)-isomer. The requisite phosphonium salt **35** was obtained by treatment of 3-bromopropionic acid with triphenylphosphine in refluxing benzene.[21] Aldehyde **34** was then reacted at –5 °C with the ylide formed from phosphonium salt **35** and 3.9 eq. of *n*-butyllithium in THF : DMSO (4:1) as suggested by Baker *et al.*[22] The previously published conditions[23] for such a reaction employing sodium hydride as base in THF : DMSO (1:1) at 0 °C proved unsatisfactory. 5-(Tetrahydro-2'-furyl)pent-3-enoic acid **7** was obtained in 30% yield. The (*E*):(*Z*) isomeric ratio was found to be in the region of 6:1, which was unfortunate as the (*Z*)-isomer was the desired precursor for Cephalosporolide G **1**.



7

The mixture of carboxylic acids **7** show IR absorptions at 3451 cm^{-1} (OH) and 1724 cm^{-1} (C=O). Distinctive features apparent in the ^1H NMR spectrum of the (*E*/*Z*) mixture include two multiplets centred at δ_H 2.26 and 2.37 ppm which are assigned to the two methylene protons of C-5 which are adjacent to the asymmetric centre of C-2'. The methylene protons of C-2, adjacent to the C-3 olefinic proton and the carboxylic acid function, appear as a triplet at δ_H 3.16 ppm for the (*E*)-isomer and a multiplet centred at δ_H 3.24 ppm for the (*Z*)-isomer. The two olefinic protons of C-3 and C-4 overlap as a multiplet centred at δ_H 5.69 for the (*E*)-isomer and at δ_H 5.62 ppm for the (*Z*)-isomer. Key features of the ^{13}C NMR spectrum include two signals at δ_C 122.7 and 129.5 ppm for the two olefinic carbons. A

signal at δ_C 175.5 ppm is assigned to the carboxylic acid carbonyl. All these assignments were confirmed by ^1H-^1H and ^{13}C-^1H COSY experiments, **Figure 4.1**, and the details obtained for the (*E*)-isomer are summarised in **Table 4.2**.

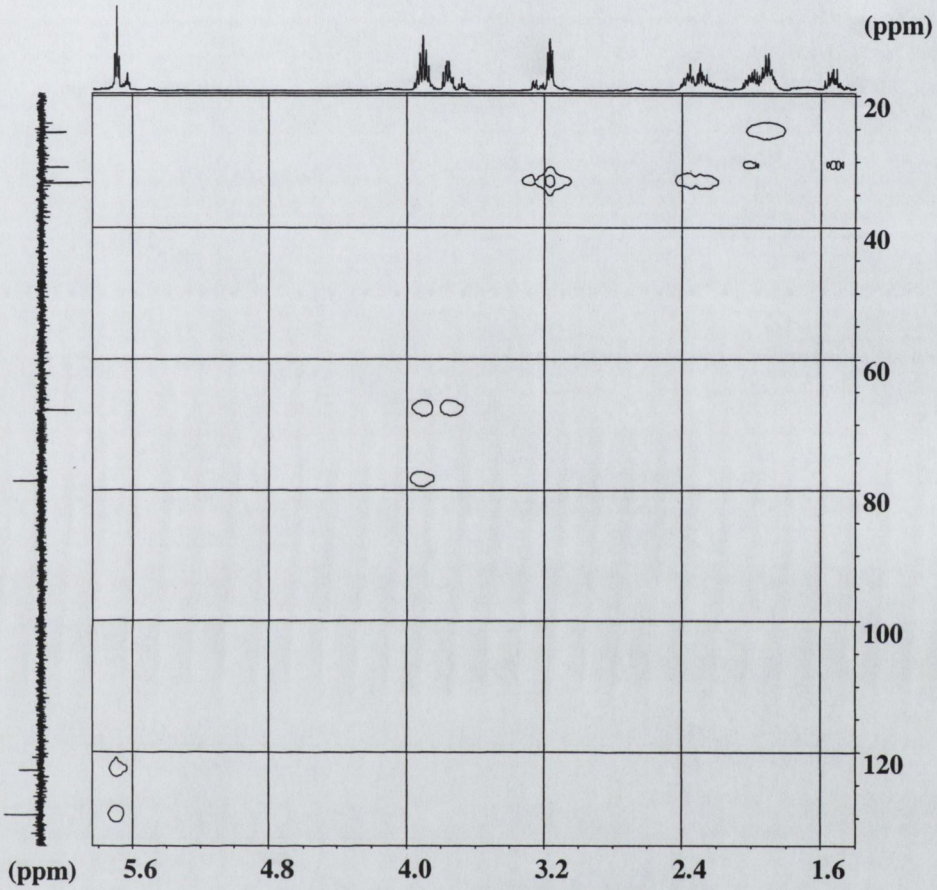
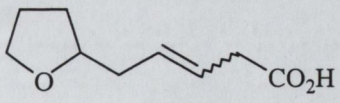


Figure 4.1

^{13}C-^1H COSY Spectrum of

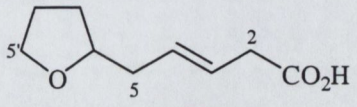
(*E*)- and (*Z*)-5-(tetrahydro-2'-furyl)pent-3-enoic acid 7



7

Table 4.2

NMR Spectroscopic details of (*E*)-5-(tetrahydro-2'-furyl)pent-3-enoic acid 7



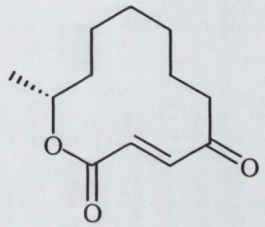
7

^{13}C (ppm)	^{1}H (ppm)	Multiplicity (^{1}H NMR)	Assignment
CH_2 25.5	CH_2 1.86-1.96	m	C-4'
CH_2 30.8	CH_a 1.52	dq, ^{2}J 12.0, ^{3}J 8.0	C-3'
	CH_b 1.96-2.04	m	
CH_2 33.2	CH_a 2.23-2.29	m	C-5
	CH_b 2.35-2.40	m	
CH_2 33.3	CH_2 3.16	t, J 5.5	C-2
CH_2 67.8	CH_a 3.73-3.78	m	C-5'
	CH_b 3.87-3.95	m	
CH 78.5	CH 3.87-3.95	m	C-2'
CH 122.7	CH 5.69	m	C-3/C-4
CH 129.5	CH 5.69	m	C-3/C-4
C=O 175.5	CO_2H 9.13	br. s	C-1

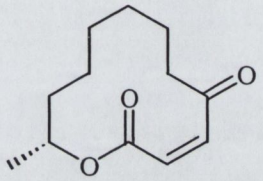
Due to the low yield (30%) of the final Wittig reaction of **Scheme 4.8**, and also due to the fact that the product **7** was largely the (*E*)-isomer rather then the desired (*Z*)-isomer, this synthetic pathway toward the synthesis of naturally occurring lactone, Cephalosporolide G **1**, was not pursued any further.

4.3 Synthesis of (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid, a precursor for Patulolide C (2)

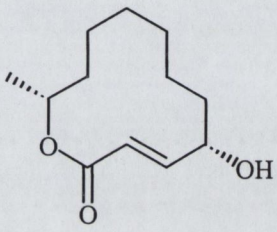
In 1985, Sekiguchi *et al.* isolated three new antimicrobial macrolides from the culture broth of *Penicillium urticae* mutant S11R59 and named them Patulolide A **36**, B **37** and C **2**.[24] These compounds were found to possess both antifungal and antibacterial activities.



Patulolide A **36**



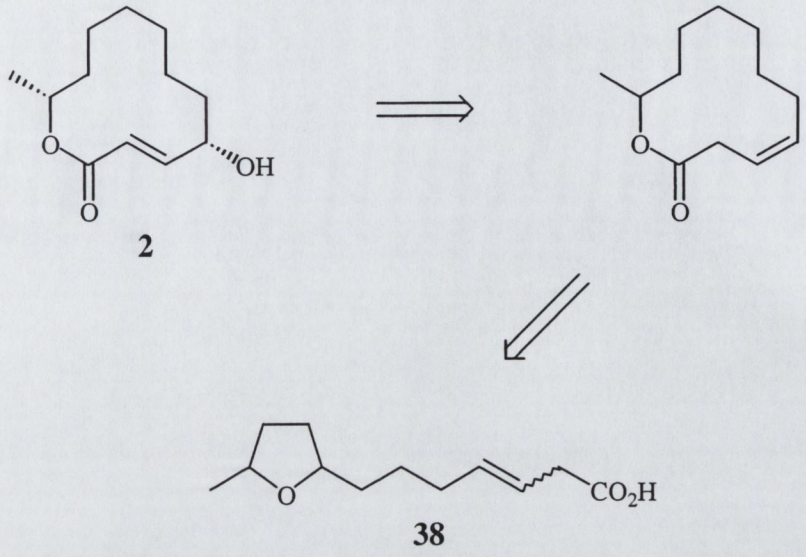
Patulolide B **37**



Patulolide C **2**

Since their discovery, the Patulolides have been the subject of a number of synthetic studies. In 1987 Yang *et al.*[25] successfully synthesised Patulolides A **36** and C **2** *via* a modified Yamaguchi lactonisation method[26] which involved treatment of a hydroxy acid with 2,4,6-trichlorobenzoyl chloride and triethylamine followed by 4-dimethylaminopyridine (DMAP) in refluxing xylene. The original Yamaguchi method[27] was employed in the syntheses of Patulolides A **36**, B **37** and C **2** in separate studies carried out by Mori *et al.*[28] and Thijs *et al.*[29] Patulolide C has also been obtained *via* the Mitsunobu lactonisation method[30] which involves treatment of a ω-hydroxy acid with triphenylphosphine and diethyl azodicarboxylate (DEAD).[31]

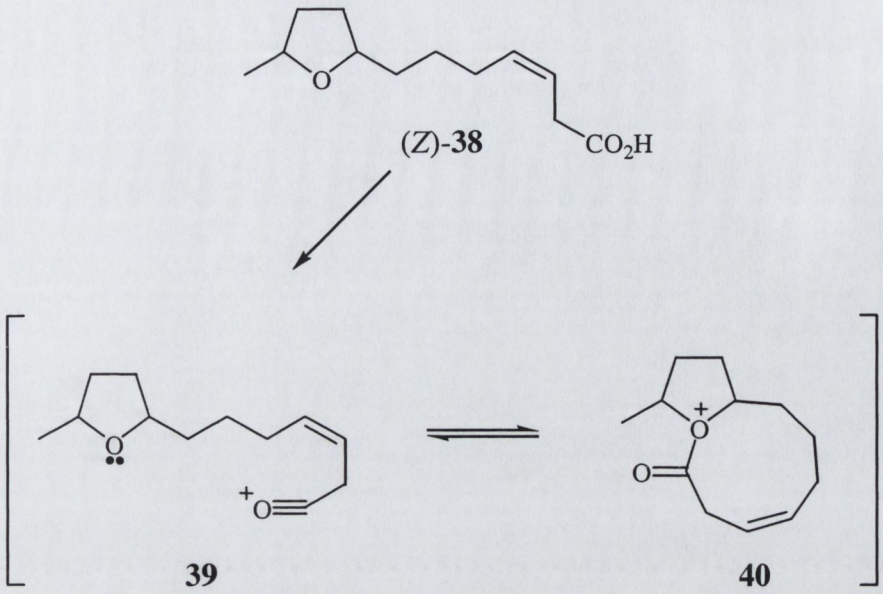
Employing the lactonisation method involving the acylative ring-expansion of ω-(tetrahydro-2'-furyl)alkanoic acids, Patulolide C **2** should be accessible *via* a precursor such as (*E*)- or (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid **38**, **Scheme 4.9**.



2 **38**

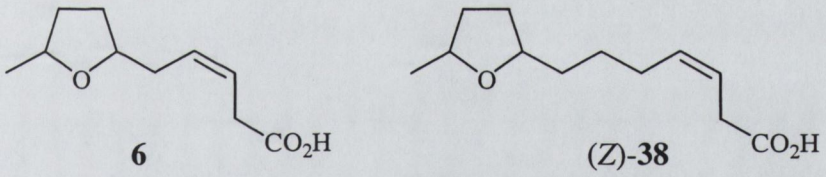
Scheme 4.9

Previous work involving the synthesis of macrocyclic lactones *via* the acylative ring-expansion of ω-(tetrahydro-2'-furyl)alkanoic acids indicated that the synthesis of twelve-membered lactones in this way was relatively inefficient, possibly due to the somewhat large distance between the tetrahydrofuryl ether oxygen and the acylium ion.[32] Thus, it was anticipated that if the double bond of precursor **38** was of (*E*)-configuration, the yield of the desired lactone would be unacceptably low as the reacting functions would be less likely to come into close proximity to each other. It follows that if the double bond is of (*Z*)-configuration as in (*Z*)-**38, Scheme 4.10**, the acylium extremity in **39** would be more likely to come within reacting distance to the tetrahydrofuryl ether oxygen thus encouraging formation of the mandatory nine-membered ring of the bicyclic acyloxonium intermediate **40** resulting in an improved yield. Consequently, the desired precursor is that possessing a double bond of (*Z*)-configuration.

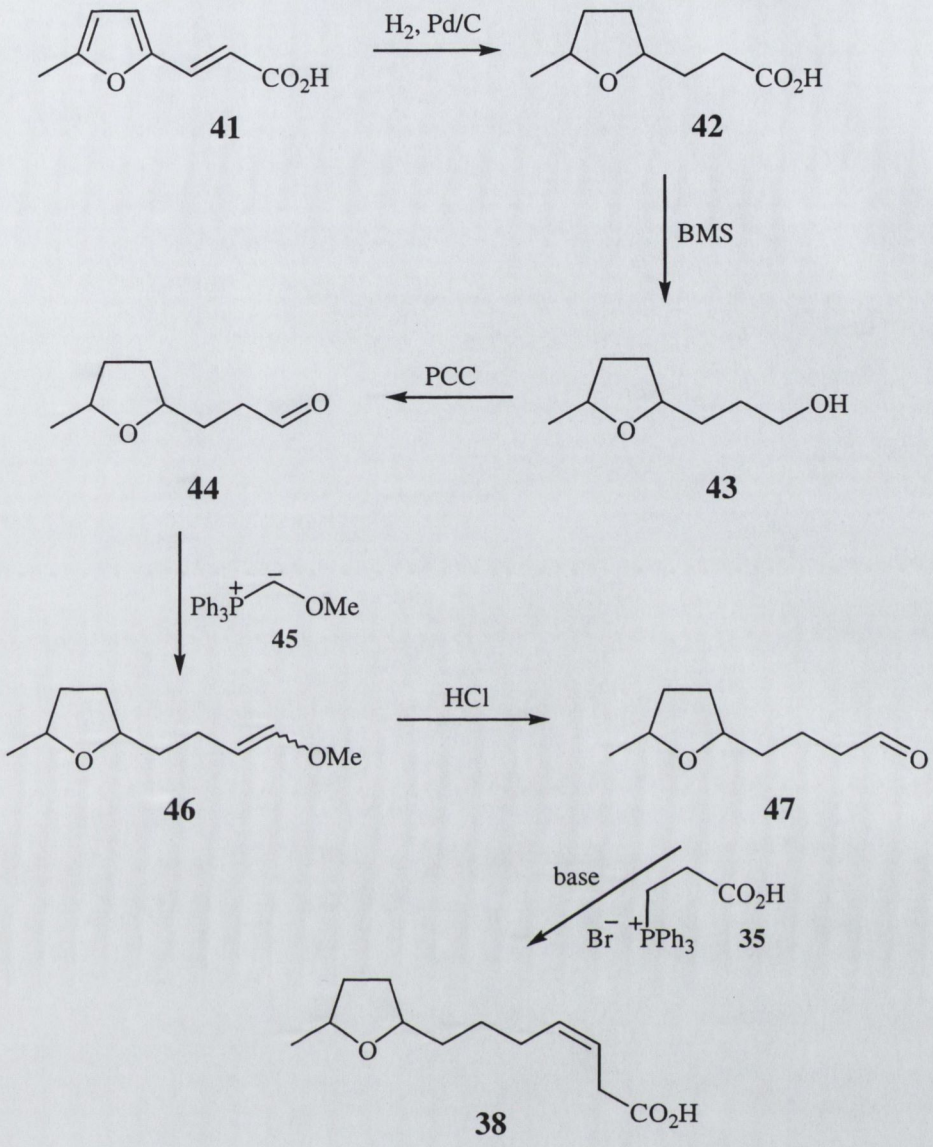


Scheme 4.10

The synthetic challenge to obtain this (Z)-precursor **38** can be compared to that encountered in the synthesis of the previously described precursor **6** necessary for the synthesis of Cephalosporolide G **1**.



The most sensible approach toward a (Z)-double bond involves synthesis of an alkyne that can then be selectively reduced to the desired (Z)-alkene. However, on consideration of the numerous problems encountered in the attempted synthesis of the model alkynoic acid **12** for the synthesis of the precursor **6** to Cephalosporolide G **1**, Section 4.2.1, it seemed unwise to approach a synthesis of the acid **38** in this way. Therefore an approach involving a Wittig reaction was considered with the anticipation that a (Z)-double bond could be selectively obtained by manipulation of the reaction conditions, **Scheme 4.11**.



Scheme 4.11

Thus, (*E*)-3-(5'-methyl-2'-furyl)prop-2-enoic acid **41**[33] was obtained by Knoevenagel reaction of 5-methylfurfural with malonic acid (81%). Hydrogenation in the presence of palladium on activated charcoal then resulted in the formation of the corresponding saturated acid **42**[34] (95%) with a *cis*/*trans* ratio of 5:1. Treatment of **42** with borane-methyl sulfide complex (BMS) yielded alcohol **43**[35] (93%) which was in turn converted into aldehyde **44**[36] using PCC (70%).

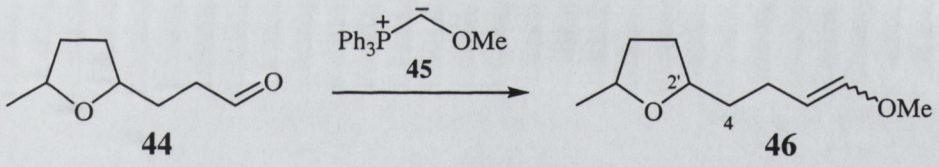
It was anticipated that homologation of the aldehyde **44** could be achieved *via* a Wittig reaction with commercially available (methoxymethyl)triphenyl-phosphonium chloride **45** followed by hydrolysis of the enol ether **46** thus obtained.

There are numerous literature reports documenting reactions with **45**, however, the results were obtained using widely contrasting reaction conditions. Bases employed include potassium *t*-butoxide,[37] *n*-butyllithium,[38] *t*-butyllithium[39] and lithium diisopropylamide.[40] Reaction temperatures range from –78 °C to room temperature, and reaction times for formation of the ylide range from fifteen minutes to two hours. In general tetrahydrofuran was used as reaction solvent. The success of the reaction varied with yields ranging from 30% to 96%.

Consequently, in the present work, a range of reaction conditions was investigated and the results obtained are summarised in **Table 4.3**.

Table 4.3

Results obtained for Wittig reaction of 3-(5'-methyltetrahydro-2'-furyl)propanal 44 to obtain (*E*)/(*Z*) 4-(5'-methyltetrahydro-2'-furyl)butenyl methyl ether 46



44 **46**

		Equivalence						
Entry	**Base**	**44**	**45**	**Base**	**Solvent**	**T(°C)[a]**	**t(min)[b]**	**% Yield[c]**
1	*t*-BuLi	1	1.5	1.2	THF	r.t.	15	10
2	*t*-BuOK	1	2.5	6	THF	r.t.	-	-
3	*n*-BuLi	1	2.5	3	THF	0	30	38
4	*t*-BuLi	1	1.2	1	THF	–90	30	16
5	*n*-BuLi	1	1.4	1.2	THF	–80	30	13
6	*t*-BuLi	1.1	1	1	Ether	0	45	15

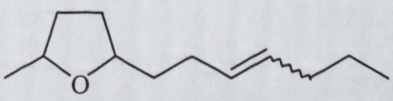
a – Temperature on addition of base

b – Time after addition of base, before addition of aldehyde **44**

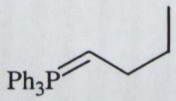
c – Isolated yield of desired product **46**

The desired enol ether **46** was obtained when either *n*-butyllithium or *t*-butyllithium was employed as base (entries 1, 3-6). When potassium *t*-butoxide was added to the phosphonium salt at room temperature (entry 2), the reaction mixture did not display the characteristic red/wine colour suggesting that ylide formation had not occurred.

When *n*-butyllithium was added to the phosphonium salt **45** at –80 °C (entry 5), and the ylide was then allowed to react with the aldehyde **44**, the crude reaction product was found to contain significant quantities of a side product which was identified as 5-methyl-2-hept-3'-enyl-tetrahydrofuran **48**. The requisite phosphorane **49** responsible for this competing reaction was perhaps generated through displacement of the methoxymethide anion from **45** by *n*-butyllithium.[41] A similar result was obtained by Trost *et al.*[41] in the homologation of (*Z*)-2-acetoxy-1-formyl-3-cyclohexene.



48



49

When *t*-butyllithium was employed as base, this competing reaction did not occur. However, the yield of the desired enol ether **46** was not good (16%, entry 4). The highest yield (38%) was obtained using *n*-butyllithium at 0 °C (entry 3) in a relatively small-scale reaction (1.4 mmol of aldehyde **44**) despite the presence of the competing reaction that leads to **49**. When these reaction conditions were employed on a larger scale (9 mmol of aldehyde **44**) the isolated yield dropped to 10%. However, the ^{1}H NMR of the crude product suggested a higher conversion to the desired enol ether **46** which indicated that perhaps the low yields of isolated product were due to complications incurred during purification. The method of purification was by column chromatography using hexane : ethyl acetate : dichloromethane. It was considered that perhaps hydrolysis had occurred on the column due to the slightly acidic nature of the silica and thus the aldehyde **47** could have been formed. However, on close examination of all the column washings, the aldehyde **47** was not located. To confirm this, a sample of the crude material was chromatographed in the presence of 5% triethylamine to combat the possible

effects of the acidic silica, however, the yield of the desired enol ether **46** showed no improvement.

A mixture of (*E*)- and (*Z*)-4-(5'-methyltetrahydro-2'-furyl)butenyl methyl ethers **46** was obtained as an oil. This mixture shows IR absorptions at 1213 cm^{-1} (ether) and 1656 cm^{-1} (C=C). Relevant integral values in the ^{1}H NMR show a major : minor isomeric ratio of 4:1 with an (*E*):(*Z*) isomeric ratio of 1:1.7. Distinctive features of the ^{1}H NMR spectrum include those corresponding to the olefinic protons of C-1 and C-2. For the (*E*)-isomer, the C-2 olefinic proton resonates at δ_H 4.76 ppm and appears as a double triplet, J_{trans} 12.5, ^{3}J 7.5 Hz, while the C-1 olefinic proton is observed at δ_H 6.32 ppm as a doublet, J 13.0 Hz. For the (*Z*)-isomer, the C-2 olefinic proton appears as a multiplet centred at δ_H 4.37 ppm while the C-1 olefinic proton is visible at δ_H 5.87 as a doublet, J 6.0 Hz. The ^{13}C NMR spectrum shows the presence of four olefinic carbons in total resonating at δ_C 102.8 and 147.2 ppm for the (*E*)-isomer and δ_C 106.5 and 146.2 ppm for the (*Z*)-isomer. All of these assignments were confirmed ^{1}H-^{1}H and ^{13}C-^{1}H COSY experiments, **Figure 4.2**.

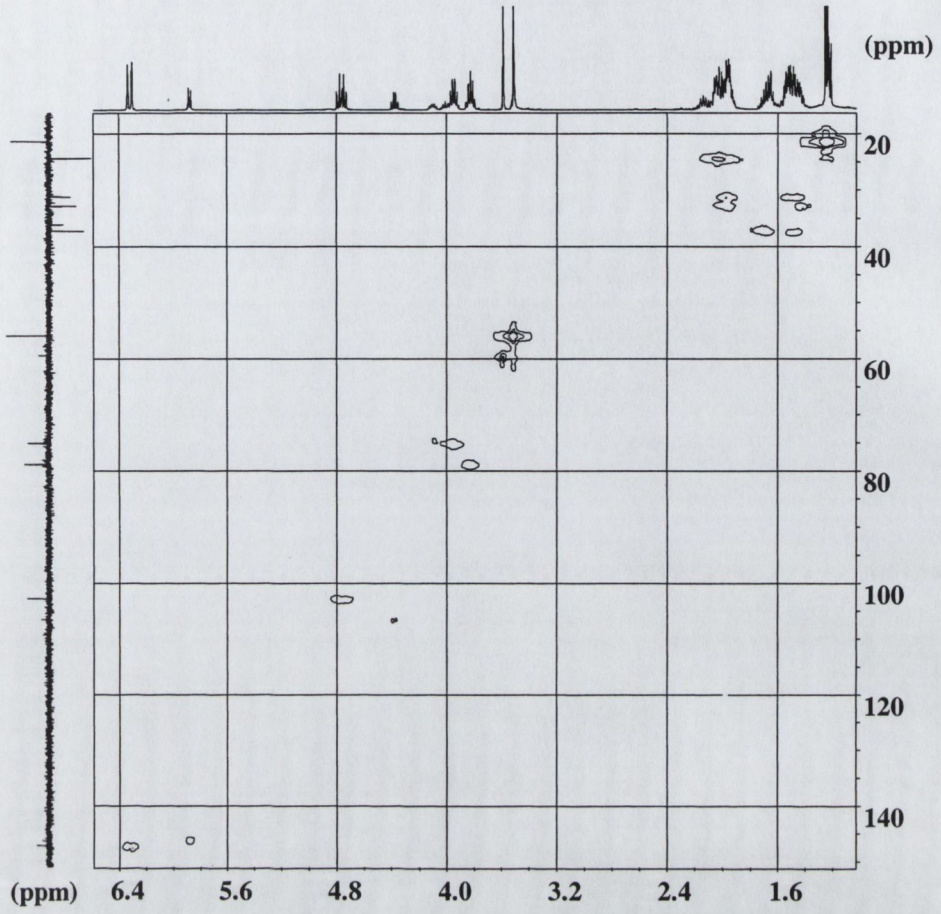
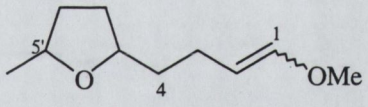


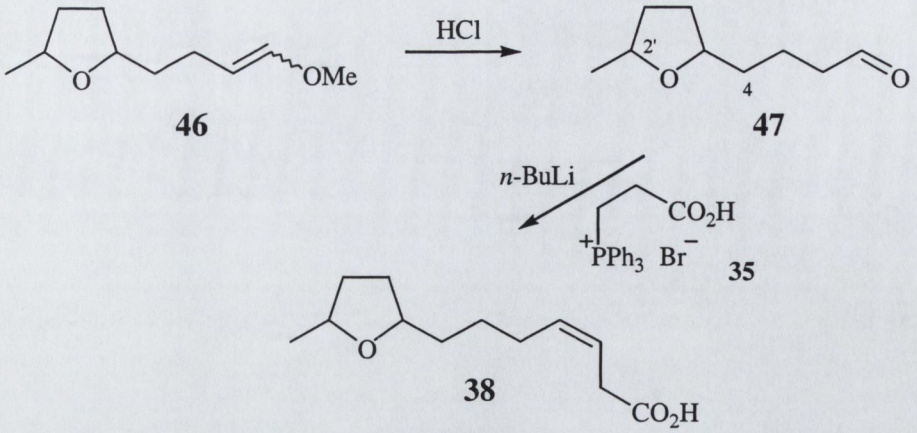
Figure 4.2

^{13}C-^{1}H COSY Spectrum of (*E*) and (*Z*) 4-(5'-methyltetrahydro-2'-furyl)butenyl methyl ether 46



46

It was noted that on repeating this Wittig reaction a number of times using identical reaction conditions, results obtained did not show any consistency. This situation was far from ideal. However, it was proposed to continue with the present synthetic pathway, **Scheme 4.12**, and to return to this problematic step if the final target molecule, acid **38**, was successfully obtained.



Scheme 4.12

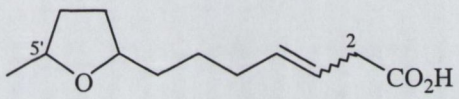
Thus, the enol ether **46** was hydrolysed to the aldehyde **47** by treatment with 1M HCl (90%). 4-(5'-Methyltetrahydro-2'-furyl)butanal **47** shows an IR absorption at 1725 cm^{-1} for the carbonyl group. For the major isomer, distinctive features visible in the ^1H NMR spectrum of aldehyde **47** include a doublet at δ_H 1.25 ppm, *J* 6.5 Hz which corresponds to the methyl group. The C-2 methylene protons adjacent to the aldehyde function resonate as a triplet at δ_H 2.49 ppm, *J* 7.5 Hz. The C-2' methine proton appears as an apparent quintet, *J* 6.5 Hz, at δ_H 3.82 ppm, while the C-5' methine proton is observed as a multiplet centred at δ_H 3.96 ppm. The aldehydic proton resonates at δ_H 9.79 ppm. In the ^{13}C NMR spectrum, the methyl group is visible at δ_C 21.3 ppm. The C-2' and C-5' methine carbons appear at δ_C 78.8 and 75.2 ppm respectively while the aldehydic carbonyl carbon resonates at δ_C 202.4 ppm. All of these assignments were confirmed by ^1H-^1H and ^{13}C-^1H COSY experiments.

The final step in the synthetic pathway towards the synthesis of precursor **38** involved Wittig reaction of aldehyde **47** with the ylide derived from (2'-carboxyethyl)triphenylphosphonium bromide **35** which had also been employed in the synthesis of the precursor **7** in the study toward the synthesis of Cephalosporolide G **1** discussed above. Thus, a similar procedure was employed using *n*-butyllithium as base at –10 °C. A 1:1 mixture of (*E*)- and (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid **38** was obtained although the yield was not ideal (44%). The mixture shows IR absorptions at 3446 cm^{-1} (OH) and 1716 cm^{-1} (C=O). The ^1H NMR spectrum of the mixture shows two doublets at δ_H 3.07 and 3.14 ppm that are assigned to the C-2 methylene protons of the (*E*)- and

(*Z*)-isomers. The C-3 and C-4 olefinic protons of both isomers resonate as a multiplet centred at δ_H 5.58 ppm. In the ^{13}C NMR spectrum, the C-5' and C-2' tetrahydrofuryl methine carbons are visible at δ_C 75.3 and 79.3 ppm respectively. The C-3 and C-4 olefinic carbons of both the (*E*)- and (*Z*)-isomers are apparent at δ_C 120.4, 121.2, 133.4 and 134.8 ppm while the carboxylic acid carbonyl carbon resonates at δ_C 175.4 ppm. ^1H-^1H and ^{13}C-^1H COSY (**Figure 4.3**) experiments aided rough assignment of the numerous methylene groups, **Table 4.4**

Table 4.4

NMR Spectroscopic details for (*E*)- and (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid 38 (Major isomer)



38

^{13}C (ppm)	^1H (ppm)	Multiplicity (^1H NMR)	Assignment
*C*H$_3$ 21.3	C*H*$_3$ 1.24	d, *J* 6.0	Me
*C*H$_2$ 25.5	C*H*$_2$ 1.54	m	C-6
*C*H$_2$ 27.4	C*H*$_2$ 2.08	m	C-5 (*E*)/(Z)
*C*H$_2$ 31.1	C*H*$_2$ 1.54	m	C-3' or C-4'
*C*H$_2$ 32.4	C*H*$_2$ 1.97	m	C3' or C-4'
*C*H$_2$ 32.6	C*H*$_2$ 2.08	m	C-5 (*E*)/(Z)
*C*H$_2$ 32.7	C*H*$_2$ 3.14	d, *J* 6.0	C-2 (*E*)/(Z)
*C*H$_2$ 35.5	C*H*$_2$ 1.54	m	C-7
*C*H$_2$ 37.3	C*H*$_2$ 3.07	d, *J* 6.0	C-2 (*E*)/(Z)
*C*H 75.3	C*H* 3.97	m	C-5'
*C*H 79.3	C*H* 3.82	m	C-2'
*C*H 120.4	C*H* 5.58	m	C-4 (*E*)/(Z)
*C*H 121.2	C*H* 5.58	m	C-4 (*E*)/(Z)
*C*H 133.4	C*H* 5.58	m	C-3 (*E*)/(Z)
*C*H 134.8	C*H* 5.58	m	C-3 (*E*)/(Z)
*C*O$_2$H 175.4	-	-	C-1

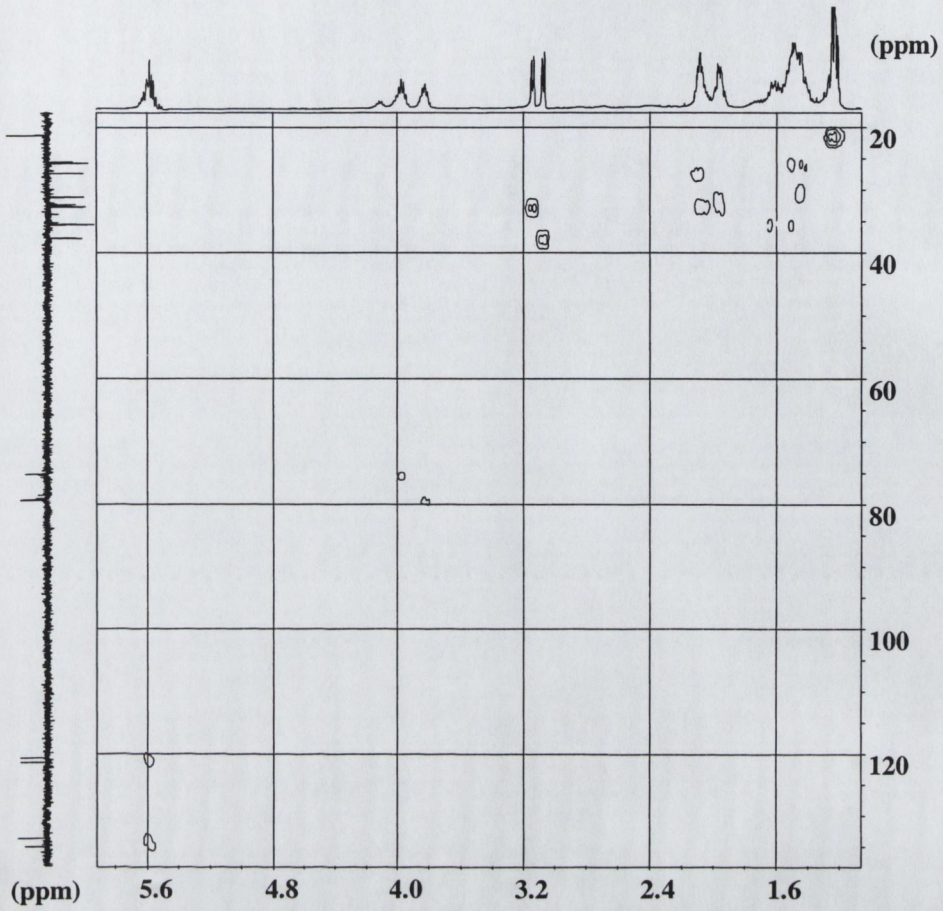
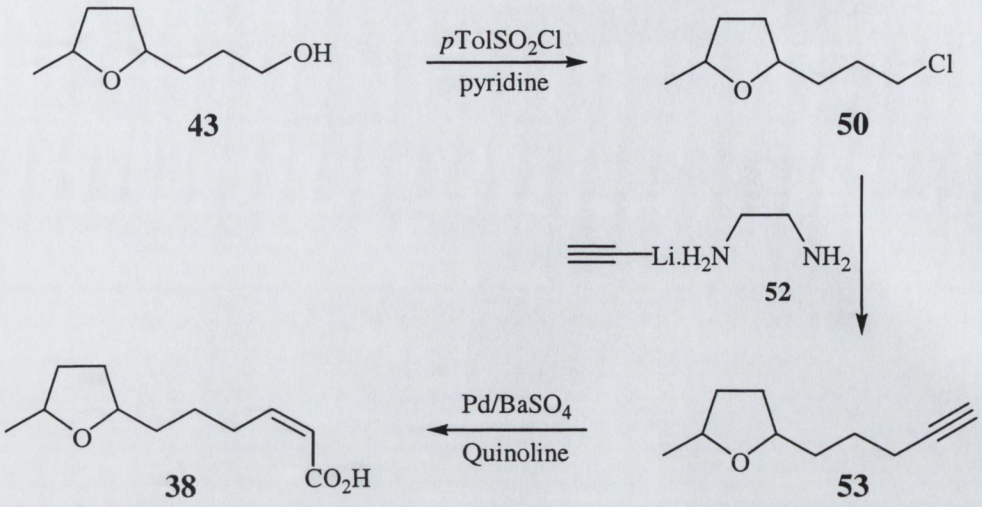


Figure 4.3

^{13}C-^{1}H COSY Spectrum of (*E*)- and (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid 38

This synthetic approach to (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid **38**, although successful, was not ideal. The synthesis was long and the yields of the two Wittig reactions were unacceptable. This coupled with the fact that the desired (*Z*)-acid product **38** was formed as a 1:1 mixture of the (*E*)- and (*Z*)-isomers suggested the need for an improved synthesis of the acid **38**.

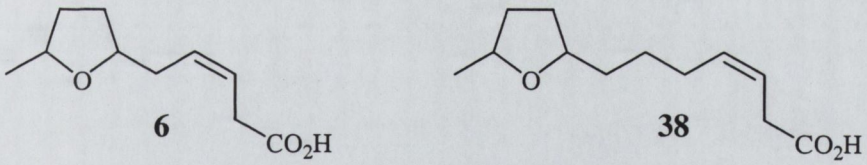
As mentioned previously, the (*Z*)-acid **38** could, in principle, be obtained *via* selective reduction of an alkyne bond. Lithium acetylide stabilised as its ethylenediamine complex **52** has been employed as a reagent for the ethynylation of alkyl halides.[42] Thus, 3-(5'-methyltetrahydro-2'furyl)chloropropane **50**, obtained by reaction of alcohol **43** with *p*-toluenesulfonyl chloride in pyridine, was treated with this reagent however no reaction was observed, **Scheme 4.13**.



Scheme 4.13

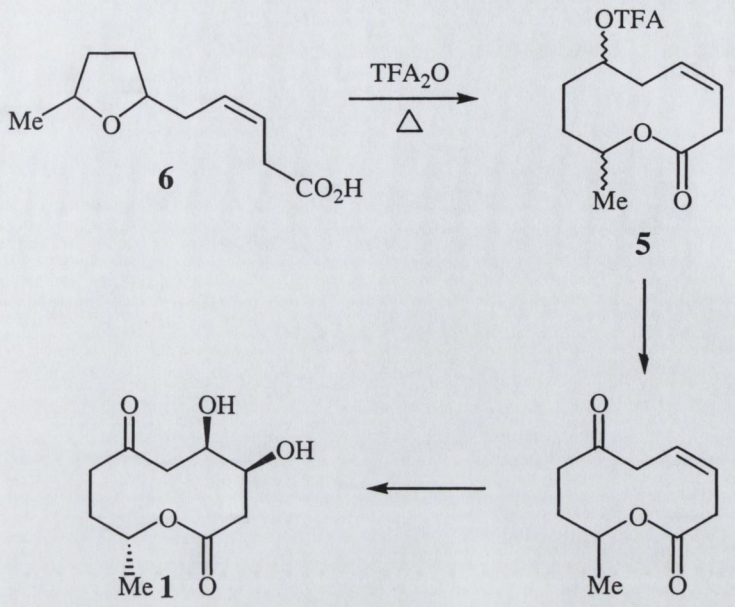
4.4 Concluding remarks

This Chapter has described research into the development of syntheses of (Z)-ω-(tetrahydro-2-furyl)alkenoic acids **6** and **38** as synthons for the formation of two naturally-occurring lactones, Cephalosporolide G and Patulolide C respectively. Although both acid **38** and an analogue of acid **6** were obtained by Wittig procedures, the synthetic paths were long and inefficient with isomeric mixtures obtained in both cases.



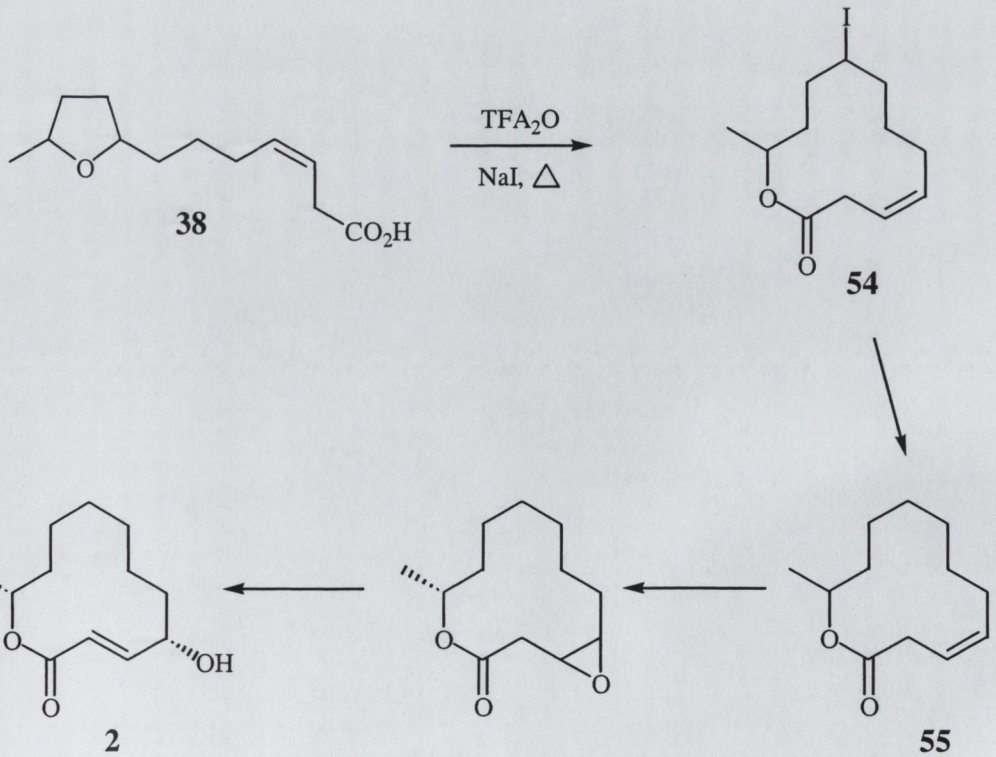
Further research into the development of efficient syntheses of these acids is necessary before the intramolecular reaction of the corresponding mixed anhydrides can be investigated.

When (Z)-5-(5'-methyl-tetrahydro-2'-furyl)pent-3-enoic acid **6** is obtained, the mixed anhydride derived from this acid can be expected to undergo the intramolecular lactonisation reaction in the presence of trifluoroacetic acid. The trifluoroacetoxy unsaturated lactone **5** thus obtained can then be converted to the naturally-occurring lactone Cephalosporolide G **1**, **Scheme 4.14**.



Scheme 4.14

Similarly, when (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid **38** is obtained, intramolecular reaction of the derived mixed anhydride in the presence of sodium iodide would lead to iodolactone **54**, **Scheme 4.15**. This could then be converted into Patulolide C *via* intermediate lactone **55** which is also a naturally-occurring lactone, ferrulalactone II **55**.[43]



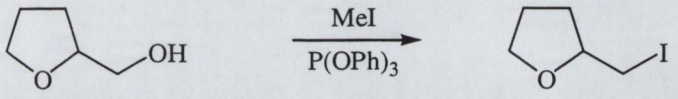
Scheme 4.15

4.5 Experimental

General experimental conditions as for Chapter 2.

4.5.1 Towards Cephalosporolide G (1)

Tetrahydrofurfuryl Iodide 8



8

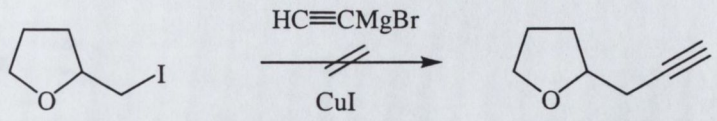
Triphenyl phosphite (117.8 g; 380 mmol) and methyl iodide (81.7 g; 575 mmol) were heated under gentle reflux for 7 hr after which time the internal temperature had reached 120 °C and the mixture was dark and viscous.[4a] The mixture was then allowed to cool to room temperature. Furfuryl alcohol (38.8 g; 380 mmol) was added slowly to the oily triphenylphosphite methiodide and an exothermic reaction occurred. The mixture was shaken until homogeneous and allowed to stand overnight at room temperature. The mixture was then distilled to yield pure tetrahydrofurfuryl iodide **8** (36.23 g; 45%), b.p. 113-115 °C at 12 mm/Hg, (lit.[44] b.p. 30-32 °C at 0.2 mm/Hg).

ν_{max} (L) 2970, 2867, 1734, 1458, 1442, 1412, 1348, 1299, 1279, 1238, 1210, 1179, 1100, 1055 (cyclic ether), 1010, 922 and 869 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.61-1.69 (1H, m, C-3 or C-4 CH_a), 1.90-2.05 (2H, m, C-3 or C-4 CH_2), 2.10-2.21 (1H, m, C-3 or C-4 CH_b), 3.21 (1H, dd, ^2J 10.0, ^3J 7.0, CH_aI), 3.27 (1H, dd, ^2J 10.0, ^3J 5.0, CH_bI), 3.83-3.87 (1H, m, C-2 CH) and 3.94-4.02 (2H, m, C-5 CH_2) ppm

δ_C (100.6 MHz; $CDCl_3$) 10.2 (CH_2I), 26.1 (C-4 CH_2), 31.9 (C-3 CH_2), 68.9 (C-5 CH_2) and 82.4 (C-2 CH) ppm

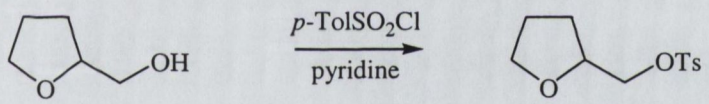
Attempted synthesis of 2-prop-2'-ynyl-tetrahydrofuran 11



8 **11**

Ethynylmagnesium bromide (0.5 M in THF; 18.8 ml; 9.4 mmol) was added dropwise to a stirred solution of tetrahydrofurfuryl iodide **8** (2 g; 9.4 mmol) in dry THF (30 ml) at 0 °C under an atmosphere of nitrogen. Cuprous iodide (0.09 g; 0.5 mmol) was then added and the mixture was heated under reflux for 7 hr. The viscous mixture was then poured on to ice and extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The complex ^1H NMR spectrum of the crude product thus obtained indicated that the desired product **11** had not been formed.

Tetrahydrofurfuryl Tosylate 9



9

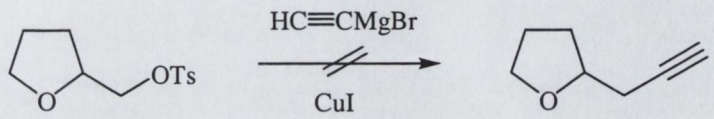
p-Toluenesulfonyl chloride (40.0 g; 209 mmol) was added to a stirred solution of tetrahydrofurfuryl alcohol (24.3 ml; 251 mmol) and dry pyridine (100 ml) at 0 °C. The reaction mixture was stirred at this temperature for 0.5 hr then left overnight at room temperature. The mixture was then poured on to ice (400 g) and extracted with ethyl acetate, washed sequentially with dilute HCl and brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Tetrahydrofurfuryl tosylate **9** was obtained as a white solid (39.75 g; 74%), m.p. 36-38 °C, (lit.[5] m.p. 37-38 °C).

ν_{max} (Neat) 2925, 2852, 1598, 1459, 1375 (SO_2), 1309, 1292, 1177 (SO_2), 1096 (cyclic ether), 1023, 967 and 824 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.68 (1H, m, C-3 C*H*$_a$), 1.88 (2H, m, C-4 C*H*$_2$), 1.98 (1H, m, C-3 C*H*$_b$), 2.46 (3H, s, Ar C*H*$_3$), 3.78 (2H, m, C-5 C*H*$_2$), 3.97-4.05 (2H, 2xdd overlapping, centred at δ_H 3.98, ^2J 9.9, ^3J 5.8, and δ_H 4.03, ^2J 9.9, ^3J 4.0, C*H*$_2$OTs), 4.09 (1H, m, C-2 C*H*), 7.36 (2H, d, *J* 8.0, 2'- and 6'-H 2xC*H*) and 7.81 (2H, d, *J* 8.0, 3'- and 5'-H 2xC*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 21.1 (Ar CH_3), 25.1 (C-4 CH_2), 27.3 (C-3 CH_2), 68.1 (C-5 CH_2), 71.1 (OTsCH_2), 75.4 (C-2 CH), 127.4-127.8 (Ar C 4xCH), 134.5 (Ar C C) and 144.3 (Ar C C) ppm

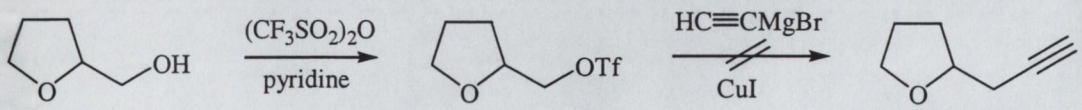
Attempted synthesis of 2-prop-2'-ynyl-tetrahydrofuran 11



9 **11**

Ethynylmagnesium bromide (0.5 M in THF; 42.97 ml; 21.4 mmol) was added dropwise to a stirred solution of tetrahydrofurfuryl tosylate **9** (5.50 g; 21.4 mmol) in dry THF (80 ml) at 0 °C under an atmosphere of nitrogen. Cuprous iodide (0.20 g; 1 mmol) was then added and the mixture was heated under reflux for 8 hr. The viscous mixture was then poured on to ice and extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product (1.20 g) was obtained as a yellow oil. The complex ^1H NMR spectrum of the crude product showed presence of starting material **9** and a small amount of the desired product **11**. Separation by distillation failed due to decomposition of the crude product on heating. Repeated attempts failed with decomposition occurring during work-up. No further analysis was possible

Formation of tetrahydrofurfuryl triflate 10 and subsequent attempted reaction with ethynylmagnesium bromide[6]

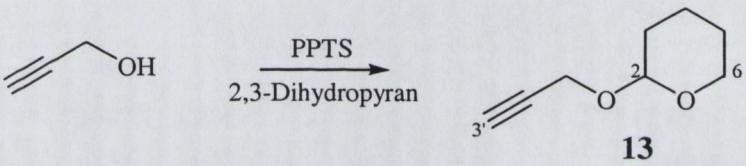


10 **11**

Tetrahydrofurfuryl alcohol (0.4 g; 3.9 mmol) was dissolved in dry pyridine (1 ml) and dry dichloromethane (10 ml) and the solution was cooled to –15 °C under an atmosphere of nitrogen. A solution of triflic anhydride (1.66 g; 5.87 mmol) and dry dichloromethane (5 ml) was then added dropwise. After stirring at this temperature for 20 min, the mixture was diluted with dichloromethane, washed sequentially

with dilute HCl and brine, dried with $MgSO_4$ and evaporated (temperature of water bath did not exceed 25 °C). The translucent orange oil thus obtained was then dissolved in dry ether (7 ml) and added dropwise to a precooled (O °C) mixture of ethynylmagnesium bromide (0.5 M in THF; 11.68 ml; 5.87 mmol) in dry ether (11 ml) containing copper(1) bromide (0.13 g; 0.9 mmol). The mixture was then stirred at 0 °C for 2 hr. Saturated aqueous ammonium chloride was then added and the mixture was diluted with ether, washed sequentially with water and brine, dried with $MgSO_4$ and evaporated. The ^1H NMR spectrum of the crude product thus obtained indicated that the desired product **11** had not been formed.

Tetrahydro-2-(2'-propynyloxy)pyran 13



13

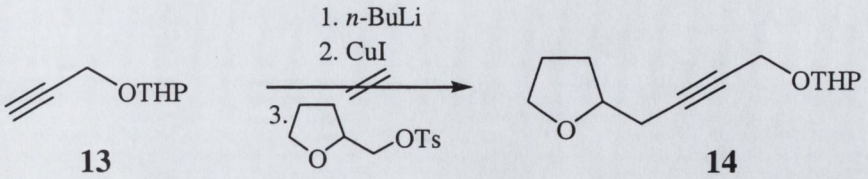
Propargyl alcohol (1.26 g; 4.5 mmol) was dissolved in dry dichloromethane (40 ml). PPTS[7] (1.13 g; 4.5 mmol) and 2,3-dihydropyran (3.78 g; 45 mmol) were added and the mixture was left at room temperature for 34 hr. The mixture was then extracted with diethyl ether, the organic layer washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Distillation afforded pure tetrahydro-2-(2-propynyloxy)pyran **13** (2.51g, 79%) as a clear oil, b.p. 80-83 °C at 2 mm/Hg, (lit.[8] b.p. 83 °C at 2 mm/Hg).

ν_{max} (L) 3277 (alkyne C-H), 2948, 2869, 1598, 1494, 1451, 1358, 1291, 1262, 1172, 1118, 1095 (THP ether), 1020, 971 and 902 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.55 (6H, m, THP C-3, C-4 and C-5 CH_2), 2.34 (1H, t, *J* 3.0, C≡C*CH*), 3.77 (2H, m, THP C-6 CH_2), 4.15 (1H, dd, ^2J 15.5, ^3J 2.5, C-1' CH_a), 4.22 (1H, dd, ^2J 16.0, ^3J 2.5, C-1' CH_b) and 4.75 (1H, t, *J* 3.5, THP C-2 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.9 (THP C-4 CH_2), 27.2, 32.1 (THP C-3 and C-5 CH_2), 55.9 (C-1' CH_2), 63.9 (THP C-6 CH_2), 75.8 (C-3' CH), 81.7 (C-2' *C*) and 98.8 (THP C-2 CH) ppm

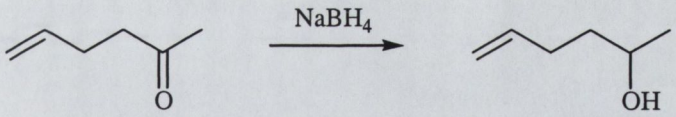
Attempted synthesis of 1-(tetrahydro-2'-furyl)-4-(tetrahydro-2''-pyranyloxy) but-2-yne 14



13 **14**

n-Butyllithium (2.32 M in hexane, 2.46 ml; 5.7 mmol) was added to a stirred solution of tetrahydro-2-(2-propynyloxy)pyran **13** (0.74 g; 5.2 mmol) in dry THF (7 ml) at –50 °C under a blanket of nitrogen. After 10 min, a mixture of cuprous iodide (507 mg; 2.6 mmol) in dimethyl sulfide (3 ml) and dry THF (6 ml) was added *via* syringe. The mixture containing a yellow precipitate was allowed to stir for 10 min and was then added *via* syringe to a stirred solution of tetrahydrofurfuryl tosylate **9** (1.31 g; 5.1 mmol) in dry THF (3 ml) at –15 °C. The mixture was stirred overnight and was then quenched with water, extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The ^1H NMR spectrum of the crude product showed the presence of starting material **13** and traces of the desired product. However, separation by column chromatography failed and no further analysis was possible.

5-Hexen-2-ol 18



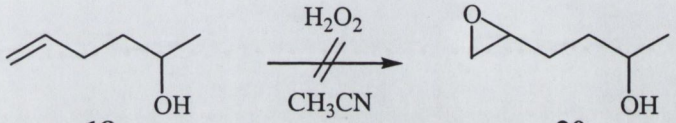
18

5-Hexen-2-one (2 g; 20 mmol) was dissolved in methanol (8 ml) and water (2 ml) and cooled in a cold-water bath. $NaBH_4$ (0.26 g; 6.8 mmol) was then added slowly with stirring and the mixture was left for 2 hr at room temperature. The reaction was then quenched with acetic acid. Water and dichloromethane were then added and the organic extract was washed sequentially with saturated aqueous sodium hydrogen carbonate solution and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. 5-Hexen-2-ol[10] **18** was obtained as a clear oil (1.83 g; 90%).

δ_H (400 MHz; $CDCl_3$) 1.22 (3H, d, *J* 6.0, C-1 CH_3), 1.56 (2H, m, C-3 CH_2), 2.17 (2H, m, C-4 CH_2), 3.85 (1H, m, C-2 *CH*), 4.97-5.01 (1H, m, C-6 CH_a), 5.04-5.09 (1H, m, C-6 CH_b) and 5.86 (1H, ddt, J_{trans} 17.0, $^3J_1$ 10.5, $^3J_2$ 7.0, C-5 *CH*) ppm

δ_C (100.6 MHz; $CDCl_3$) 23.5 (C-1 CH_3), 30.1 (C-4 CH_2), 38.3 (C-3 CH_2), 67.7 (C-2 *CH*), 114.7 (C-6 CH_2) and 138.5 (C-5 *CH*) ppm

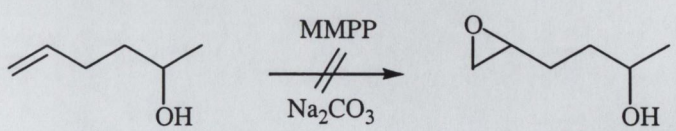
Attempted synthesis of 1,2-epoxyhexan-2-ol 20 *via* a Payne epoxidation reaction[11]



18 **20**

5-Hexen-2-ol **18** (1.5 g; 15 mmol) was dissolved in methanol (12 ml) and acetonitrile (1.18 ml; 22.7 mmol). Potassium carbonate was then added until the mixture was pH 10. The mixture was then heated to 60 °C and hydrogen peroxide (30% soln; 1.3 ml) was added dropwise. The pH of the mixture was then readjusted to pH 10 and heated at this temperature for a further 2 hr. The volume was then partly reduced by evaporation of the methanol. Water was added and the mixture was extracted (x3) with ether. The combined organic extracts were then washed with brine, dried with $MgSO_4$ and evaporated. The product obtained was identified as the starter 5-hexen-2-ol **18**. A similar result was obtained when 1M sodium hydroxide solution was employed to regulate the pH of the mixture.

Attempted synthesis of 1,2-epoxyhexan-2-ol 20 using MMPP[12]

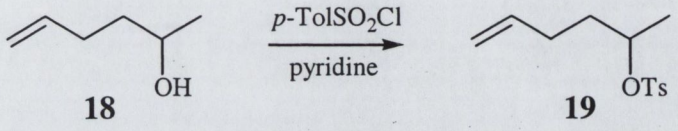


18 **20**

5-Hexen-2-ol **18** (0.8 g; 8.2 mmol) was dissolved in methanol (9 ml) and saturated aqueous sodium carbonate solution (3 ml) was added (mixture was pH 8). The solution was cooled to 0 °C and monoperoxyphthalate (MMPP) (4.0 g; 8.2 mmol) was added with stirring. The mixture was allowed to warm to room temperature

over 1 hr and then left stirring at this temperature overnight. Brine and ether were then added and 1 M sodium hydroxide was added until the aqueous layer was pH 12. The organic extract was then washed with brine, dried over $MgSO_4$ and evaporated. The product obtained was identified as the starter 5-hexen-2-ol **18**.

2-Tosyloxyhex-5-ene 19



18 **19**

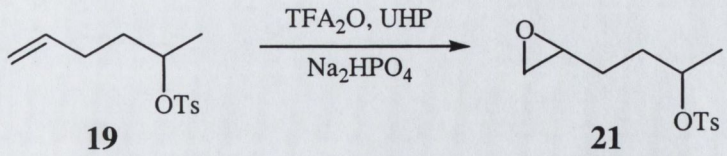
5-Hexen-2-ol **18** (7.95 g; 80 mmol) was dissolved in dry pyridine (40 ml) and the solution was cooled in an ice bath. *p*-Toluenesulfonylchloride (18.34 g; 96 mmol) was then added with stirring and the mixture was left for 0.5 hr at this temperature. After a further 3 hr at room temperature the mixture was poured on to ice and extracted three times with ethyl acetate. The organic extracts were then washed sequentially with dilute HCl (2M) and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. 2-Tosyloxyhex-5-ene[13] **19** was obtained as a translucent orange oil (17.21 g; 84%).

ν_{max} (L) 3077, 2980, 2934, 1641, 1598 (C=C), 1448, 1360 (SO_2), 1176 (SO_2), 1097, 1040, 1019, 997, 914, 816 and 743 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.28 (3H, d, *J* 6.3, C-1 CH_3), 1.61 (1H, m, C-3 CH_a), 1.75 (1H, m, C-3 CH_b), 2.03 (2H, m, C-4 CH_2), 2.46 (3H, s, OTs CH_3), 4.67 (1H, m, C-2 C*H*), 4.93-4.97 (2H, m, C-6 CH_2), 5.66-5.73 (1H, m, C-5 C*H*), 7.35 (2H, d, *J* 8.5 Ar H 2xC*H*) and 7.81 (2H, d, *J* 8.5, Ar H 2xC*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.3 (C-1 *C*H_3), 21.1 (OTs *C*H_3), 28.5 (C-4 *C*H_2), 35.2 (C-3 *C*H_2), 79.4 (C-2 C*H*), 114.8 (C-6 *C*H_2), 127.2 (Ar C *C*H), 129.2 (Ar C *C*H), 134.2 (Ar C *C*), 136.6 (C-5 *C*H) and 143.9 (Ar C *C*) ppm

1,2-Epoxy-5-*p*-toluenesulfonyloxyhexane 21



19 **21**

2-Tosyloxyhex-5-ene **19** (5.0 g; 20 mmol) was dissolved in dichloromethane (100 ml). Urea - hydrogen peroxide (18.49 g; 200 mmol) and disodium hydrogen phosphate (24.42 g; 170 mmol) were then added and a reflux condenser was fitted. Trifluoroacetic anhydride (10.3 g; 50 mmol) was then added dropwise to the suspension with stirring. The mixture was left stirring at room temperature overnight. Saturated aqueous sodium hydrogen carbonate was then added slowly until all acids had been neutralised and any visible reaction had subsided. The aqueous layer was then extracted with dichloromethane and the combined organic layers were washed sequentially with saturated aqueous sodium hydrogen carbonate solution and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. 1,2-Epoxy-5-*p*-toluenesulfonyloxyhexane **21** was obtained as an oil (4.88 g; 92%).

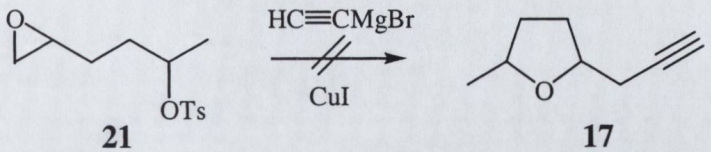
ν_{max} (L) 2977, 2934, 2872, 1784, 1598, 1494, 1449, 1358 (SO_2), 1238 (epoxide), 1176 (SO_2), 1096, 1018, 909 and 816 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.28 (3H, apparent t, *J* 6.0, C-6 CH_3), 1.59-1.79 (4H, m, C-3 and C-4 CH_2), 2.44 (1H, m, C-1 CH_a), 2.46 (3H, s, OTs CH_3), 2.73 (1H, m, C-1 CH_b), 2.86 (1H, m, C*H*), 4.73 (1H, C-5 C*H*), 7.36 (2H, d, *J* 7.5, Ar H 2xC*H*) and 7.81 (2H, d, *J* 7.5, Ar H 2xC*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 20.6 (C-6 *C*H_3), 20.8 (OTs *C*H_3), 28.0, 32.6 (C-3 and C-4 *C*H_2), 46.8 (C-1 *C*H_2), 51.5 (C-2 C*H*), 79.4 (C-5 *C*H), 127.6, 127.9, 129.7, 129.8 (Ar C 4x*C*H) and 134.0, 144.0 (Ar C *C*) ppm

HRMS *m/z* (CI) 271.1015: *calculated for* $[C_{13}H_{18}O_4S + H]^+$ 271.1004

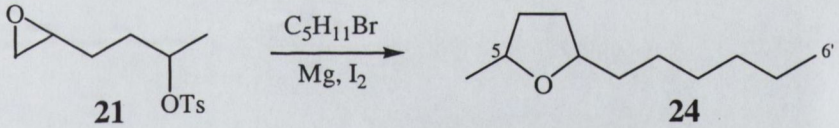
Attempted synthesis of 5-methyl-2-prop-2'-ynyltetrahydrofuran 17



21 **17**

Under an atmosphere of nitrogen, 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** (0.6 g; 2.2 mmol) was dissolved in dry tetrahydrofuran (15 ml). Cuprous iodide (5 mol%) was added and the solution was cooled in an ice-bath. Ethynylmagnesium bromide (0.5 M in THF, 4.4 ml; 2.2 mmol) was then added by syringe and after 15 min at this temperature the mixture was allowed to warm to room temperature and was then heated at reflux for 3 hr. The mixture was then poured on to ice and extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and evaporated. The NMR spectroscopic data of the crude product indicated that the required product **17** had not been formed.

2-Hexyl-5-methyltetrahydrofuran 24



21 **24**

Under an atmosphere of nitrogen, bromopentane (0.67 g; 4.4 mmol) was added dropwise at room temperature to a mixture containing magnesium turnings (0.12 g; 4.9 mmol) and a crystal of iodine in dry tetrahydrofuran (35 ml). Addition was controlled at such a rate so as a gentle reflux was observed. When the reaction had subsided the mixture was heated at reflux for a further 10 min. The Grignard reagent thus formed was then added dropwise to an ice-cooled solution of 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** (1.2 g; 4.4 mmol) in dry THF (30 ml) containing cuprous iodide (5 mol%). The mixture was then allowed to warm to room temperature and left stirring overnight. Saturated ammonium chloride was then added and the mixture was poured on to ice and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was then chromatographed using

hexane : ethyl acetate 90:10 and 2-hexyl-5-methyltetrahydrofuran[15] **24** (0.1 g; 13%; 50:50 mix of diastereoisomers) was isolated as a translucent yellow oil.

ν_{max} (L) 2954, 2927, 2856, 1137 (cyclic ether), 1022 and 800 cm^{-1}

Diastereoisomer (a)

δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t, *J* 6.5, hexyl C*H*$_3$), 1.23 (3H, d, *J* 6.0, *C*H$_3$), 1.29-1.72 (10H, m, hexyl 5xC*H*$_2$), 1.96 (2H, m, C-3 or C-4 C*H*$_2$), 2.04 (2H, m, C-3 or C-4 C*H*$_2$), 3.79 (1H, m, C-2 or C-5 C*H*) and 3.95 (1H, m, C-2 or C-5 C*H*) ppm

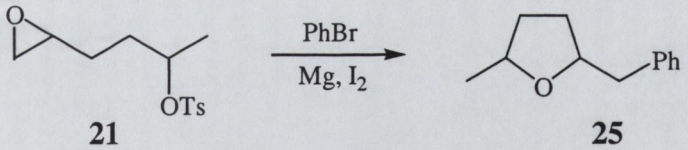
Diastereoisomer (b)

δ_H (400 MHz; $CDCl_3$) 0.90 (3H, t, *J* 6.5, hexyl C*H*$_3$), 1.25 (3H, d, *J* 6.0, *C*H$_3$), 1.29-1.72 (10H, m, hexyl 5xC*H*$_2$), 1.96 (2H, m, C-3 or C-4 C*H*$_2$), 2.04 (2H, m, C-3 or C-4 C*H*$_2$), 3.95 (1H, m, C-2 or C-5 C*H*) and 4.10 (1H, m, C-5 or C-5 C*H*) ppm

Diastereoisomeric mixture of (a) and (b)

δ_C (100.6 MHz; $CDCl_3$) 14.1, 14.1 (hexyl 2x*C*H$_3$), 21.3, 21.4 (2x*C*H$_3$), 22.6, 26.1, 26.2, 29.4, 31.2, 31.8, 32.3, 32.7, 33.9, 36.2 (*C*H$_2$), 74.3, 75.0 (C-2 or C-5 2x*C*H) and 78.8, 79.6 (C-2 or C-5 2x*C*H) ppm

2-Benzyl-5-methyltetrahydrofuran 25



21 **25**

Under an atmosphere of nitrogen, bromobenzene (0.98 g; 6.2 mmol) was added dropwise at room temperature to a mixture containing magnesium turnings (0.16 g; 6.8 mmol) and a crystal of iodine in dry diethyl ether (15 ml). Addition was controlled at such a rate so as a gentle reflux was observed. When the reaction had subsided the mixture was heated at reflux for a further 10 min. The Grignard reagent thus formed was then added dropwise to an ice-cooled solution of 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** (1.7 g; 6.2 mmol) in dry ether (40 ml) containing cuprous iodide (5 mol%). The mixture was then allowed to warm to

room temperature and left stirring overnight. Saturated ammonium chloride was then added and the mixture was poured on to ice and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was then chromatographed using hexane : ethyl acetate 75:25 and 2-benzyl-5-methyltetrahydrofuran **25** (0.26 g; 24%; 50:50 mix of diastereoisomers) was isolated as a pale yellow oil.

ν_{max} (L) 3027, 2967, 2928, 2867, 1603 (Ar C=C), 1496, 1452, 1373, 1276, 1161, 1084 (cyclic ether), 1030, 910 and 747 cm^{-1}

Diastereoisomer (a)

δ_H (400 MHz; $CDCl_3$) 1.24 (3H, d, *J* 6.5, C*H*$_3$), 1.44 (1H, m, C-3 or C-4 C*H*$_a$), 1.60 (1H, m, C-3 or C-4 C*H*$_b$), 1.95 (2H, m, C-3 or C-4 C*H*$_2$), 2.72 (1H, m, C*H*$_a$Ph), 2.97 (1H, m, C*H*$_b$Ph), 4.00 (1H, m, C-2 or C-5 C*H*), 4.09 (1H, m, C-2 or C-5 C*H*) and 7.24 (5H, m, Ar H 5xC*H*) ppm

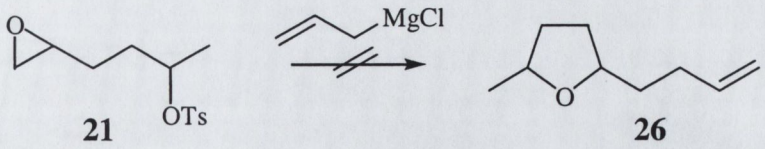
Diastereoisomer (b)

δ_H (400 MHz; $CDCl_3$) 1.26 (3H, d, *J* 6.0, C*H*$_3$), 1.44 (1H, m, C-3 or C-4 C*H*$_a$), 1.60 (1H, m, C-3 or C-4 C*H*$_b$), 1.95 (2H, m, C-3 or C-4 C*H*$_2$), 2.72 (1H, m, C*H*$_a$Ph), 2.97 (1H, m, C*H*$_b$Ph), 4.16 (1H, m, C-2 or C-5 C*H*), 4.25 (1H, m, C-2 or C-5 C*H*) and 7.24 (5H, m, Ar H 5xC*H*) ppm

Diastereoisomeric mixture of (a) and (b)

δ_C (100.6 MHz; $CDCl_3$) 21.4, 21.4 (2xC*H*$_3$), 30.7, 31.6, 32.6, 33.7 (2xC-3 *C*H$_2$ and 2xC-4 *C*H$_2$), 42.2, 42.4 (2x*C*H$_2$Ph), 74.8, 75.4, 79.3, 80.0 (2xC-2 *C*H and 2xC-5 *C*H), 125.6, 125.6, 127.7, 127.8, 128.1, 128.8 (Ar C *C*H) and 138.4, 138.4 (Ar C *C*) ppm

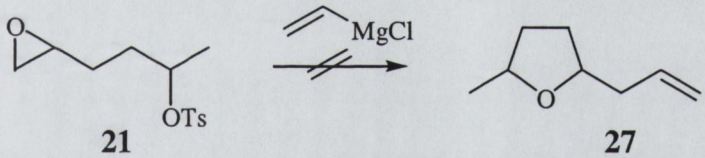
Attempted synthesis of 2-but-3'-enyl-5-methyltetrahydrofuran 26



21 **26**

Under an atmosphere of nitrogen, allylmagnesium chloride (2 M, 1.85 ml; 3.7 mmol) was added dropwise to an ice-cold solution of 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane 21 (1.0 g; 3.7 mmol) in dry THF (20 ml) containing cuprous iodide (5 mol%). The mixture was then allowed to warm to room temperature and left stirring overnight. Saturated ammonium chloride was then added and the mixture was poured on to ice and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was chromatographed using hexane : ethyl acetate 95:5 however the desired product 2-but-3'-enyl-5-methyltetrahydrofuran **26** was not isolated. Traces of 2-tosyloxyhex-5-ene (0.04 g) were isolated.

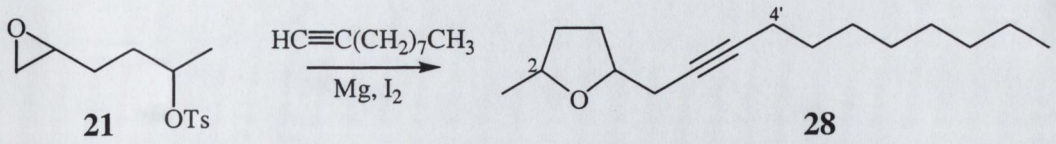
Attempted synthesis of 2-prop-2'-enyl-5-methyltetrahydrofuran 27



21 **27**

Under an atmosphere of nitrogen, vinylmagnesium chloride (1.6 M, 2.31 ml; 3.7 mmol) was added dropwise to an ice-cold solution of 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** (1.0 g; 3.7 mmol) in dry THF (20 ml) containing cuprous iodide (5 mol%). The mixture was then allowed to warm to room temperature and left stirring overnight. Saturated ammonium chloride was then added and the mixture was poured on to ice and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was chromatographed using hexane : ethyl acetate 95:5 however the desired product 2-prop-2'-enyl-5-methyltetrahydrofuran **27** was not isolated.

2-Methyl-5-undec-2'-ynyltetrahydrofuran 28



21 **28**

Under an atmosphere of nitrogen, *n*-butyl lithium (2.5 M, 1.88 ml; 4.7 mmol) was added dropwise to a stirred solution of 1-decyne (0.5 g; 3.6 mmol) in dry THF at –78 °C. After 0.5 hr at this temperature, boron trifluoride-THF complex (0.658 g; 4.7 mmol) was added. After 20 min a solution of 1,2-epoxy-5-*p*-toluenesulfonyloxyhexane **21** (1.173 g; 4.3 mmol) in dry THF was added and the mixture was left stirring at –78 °C for 2 hr. Saturated ammonium chloride solution was then added and the mixture was extracted three times with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was chromatographed using hexane : ethyl acetate 80:20 as eluant. 2-Methyl-5-undec-2-ynyltetrahydrofuran **28** was isolated (0.11 g; 13%; 50:50 mix of diastereoisomers) as a clear oil.

ν_{max} (L) 2958, 2927, 2856, 1459, 1377, 1340, 1187, 1138, 1086 (cyclic ether), 1021, 917, 887 and 807 cm^{-1}

Diastereoisomer (a)

δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t, *J* 7.0, decynyl C*H*$_3$), 1.23 (3H, d, *J* 5.8, C*H*$_3$), 1.27-1.37 (10H, m, decynyl C*H*$_2$), 1.49 (2H, m, C-5' C*H*$_2$), 1.78 (1H, m), 2.03 (3H, m), 2.15 (2H, m, C-4' C*H*$_2$), 2.30-2.49 (2H, m, C-1' C*H*$_2$), 3.98 (1H, m, C-2 or C-5 C*H*) and 4.16 (1H, m, C-2 or C-5 C*H*) ppm

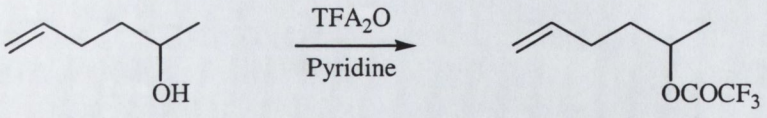
Diastereoisomer (b): as for isomer (a) except:

δ_H (400 MHz; $CDCl_3$) 0.90 (3H, t, *J* 6.5, decynyl C*H*$_3$) and 1.24 (3H, d, *J* 5.8, C*H*$_3$) ppm

Diastereoisomeric mixture of (a) and (b)

δ_C (100.6 MHz; $CDCl_3$) 14.1, 14.1 (2xdecynyl *C*H$_3$), 18.8 (*C*H$_2$), 21.2, 21.3 (2x*C*H$_3$), 22.6, 25.9, 26.1, 28.8, 29.0, 29.1, 29.2, 30.6, 31.5, 31.8, 32.7, 33.8 (*C*H$_2$), 75.4, 75.9, 77.2, 77.8 (2xC-2 *C*H and 2xC-5 *C*H) and 81.6, 81.7 (2xalkyne *C*) ppm

2-Trifluoroacetoxyhex-5-ene 29



18 **29**

Trifluoroacetic anhydride (4.66 g; 22 mmol) was added to an ice-cold solution of 5-hexen-2-ol **18** (2 g; 20 mmol) and dry pyridine (8 ml). The mixture was allowed to warm to room temperature over 2 hr. It was then poured on to ice and extracted twice with diethyl ether. The combined organic extracts were then washed sequentially with dilute HCl, saturated aqueous sodium hydrogen carbonate solution and brine, and then dried over $MgSO_4$ and the solvent removed *in vacuo*. 2-Trifluoroacetoxyhex-5-ene[16] **29** (2.45 g; 62%) was obtained as a clear oil.

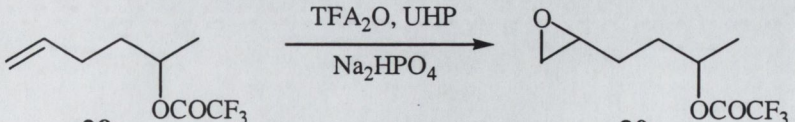
ν_{max} (L) 2986, 2941, 1783 (trifluoroacetoxy carbonyl), 1643 (C=C), 1451, 1383, 1339, 1221, 1166, 996, 917 and 777 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.38 (3H, d, *J* 6.0, C-1 CH_3), 1.73 (1H, m, C-3 CH_a), 1.86 (1H, m, C-3 CH_b), 2.14 (2H, m, C-4 CH_2), 5.01-5.16 (3H, m, C-2 *CH* and C-6 CH_2) and 5.8 (1H, m, C-5 *CH*) ppm

δ_C (100.6 MHz; $CDCl_3$) 19.4 (C-1 CH_3), 29.2 (C-4 CH_2), 34.4 (C-3 CH_2), 75.7 (C-2 *C*H), 115.6 (olefinic C-6 CH_2) and 136.7 (olefinic C-5 CH_2) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.9 ($COCF_3$) ppm

1,2-Epoxy-5-trifluoroacetoxyhexane 30



29 **30**

2-Trifluoroacetoxyhex-5-ene **29** (1.5 g; 7.6 mmol) was dissolved in dichloromethane (60 ml). Urea - hydrogen peroxide (7.19 g; 76 mmol) and disodium hydrogen phosphate (9.5 g; 67 mmol) were then added and a reflux condenser was fitted. Trifluoroacetic anhydride (4.01 g; 19 mmol) was then added dropwise with stirring to the suspension. The mixture was left stirring at room

temperature overnight. Saturated aqueous sodium hydrogen carbonate was then added slowly until all acids had been neutralised and any visible reaction had subsided. The aqueous layer was then extracted with dichloromethane and the combined organic layers were washed sequentially with saturated aqueous sodium hydrogen carbonate solution and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. 1,2-Epoxy-5-trifluoroacetoxyhexane **30** was obtained (1.28 g; 79%) as a clear oil.

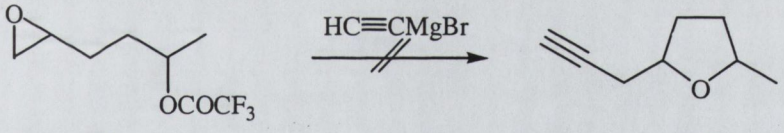
ν_{max} (L) 3055, 2989, 2940, 2874, 1783 (trifluoroacetoxy carbonyl), 1452, 1384, 1339, 1220 (epoxide), 1166, 1094, 1057, 967, 923, 909, 854, 777 and 729 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.39 (3H, d, *J* 6.5, C-6 CH_3), 1.53 (1H, m, C-3 or C-4 CH_a), 1.68-1.94 (3H, m, C-3 and/or C-4 CH_2 and CH_b), 2.50 (1H, m, C-1 CH_a), 2.78 (1H, m, C-1 CH_b), 2.94 (1H, m, C-2 C*H*) and 5.17 (1H, m, C-5 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 19.3 (C-6 *C*H_3), 27.8 (C-3 *C*H_2), 31.5 (C-4 *C*H_2), 46.7 (olefinic C-1 *C*H_2), 51.2 (C-2 *C*H) and 75.9 (C-5 *C*H) ppm

δ_F (376.3 MHz; $CDCl_3$) –75.9 (COCF_3) ppm

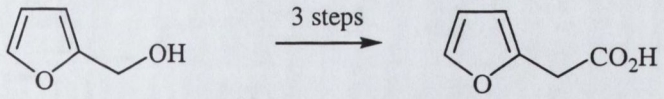
Attempted synthesis of 2-prop-2'-ynyltetrahydrofuran 17



30 **17**

1,2-Epoxy-5-trifluoroacetoxyhexane **30** (1.0 g; 4.7 mmol) was dissolved in dry tetrahydrofuran (15 ml). Cuprous iodide (5 mol%) was added and the solution was cooled in an ice-bath. Ethynylmagnesium bromide (0.5 M in THF, 9.4 ml; 4.7 mmol) was then added by syringe and after 15 min at this temperature the mixture was allowed to warm to room temperature and then was then heated at reflux for 3 hr. The mixture was then poured on to ice and extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and evaporated. The NMR spectroscopic data of the crude product indicated that the required product **17** had not been formed.

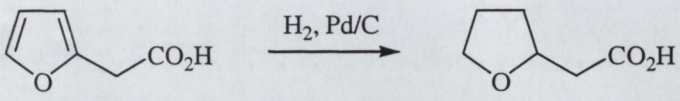
2-Furylacetic acid 31



31

See Chapter 3, Section 3.7.2, for a three-step synthesis[17] of 2-furylacetic acid **31**.

2-Tetrahydro-2-furylacetic acid 32



31 **32**

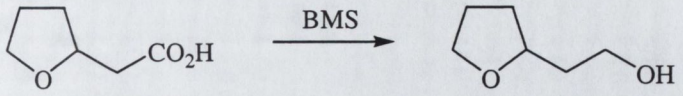
2-Furylacetic acid **31** (4 g; 32 mmol) was dissolved in ethyl acetate (150 ml) and was stirred under one atmosphere of hydrogen in the presence of 5% w/w Pd/C (150 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo*. 2-Tetrahydro-2-furylacetic acid[18] **32** (3.6 g; 85%) was obtained as a clear oil.

ν_{max} (L) 2973, 2879 (OH), 1710 (C=O), 1411, 1284, 1199, 1064 (cyclic ether), 923, 879 and 829 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.60 (1H, dddd, ^2J 12.5, $^3J_1 = {}^3J_2 = {}^3J_3$ 8.0, C-3 CH_a), 1.95 (2H, m, C-4 CH_2), 2.12 (1H, m, C-3 CH_b), 2.56 (1H, dd, ^2J 15.5, ^3J 5.5, C$H_a$$CO_2H$), 2.63 (1H, dd, ^2J 15.5, ^3J 7.5 C$H_b$$CO_2H$), 3.80 (1H, m, C-5 C$H_a$), 3.92 (1H, m, C-5 C$H_b$) and 4.26 (1H, m, C-2 C*H*) ppm

δ_C (100.6 MHz; $CDCl_3$) 25.5 (C-4 *C*H_2), 31.1 (C-3 *C*H_2), 40.2 (*C*H_2CO_2H), 68.0 (C-5 *C*H_2), 74.9 (C-2 *C*H) and 175.5 (*C*=O) ppm

2-Tetrahydro-2-furylethanol 33



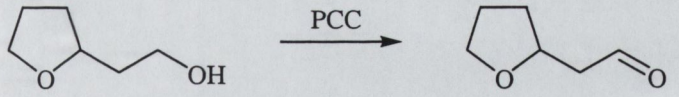
32 **33**

BMS (0.64 g; 8.45 mmol) was added dropwise to an ice-cold stirred solution of 2-tetrahydro-2-furylacetic acid **32** (1 g; 7.68 mmol) in dry THF (8 ml) under an atmosphere of nitrogen. The mixture was allowed to warm to room temperature overnight. Methanol (10 ml) was then added to destroy any unreacted BMS and the solvents were evaporated. The crude product thus obtained was then filtered through a plug of silica. 2-Tetrahydro-2-furylethanol[19] **33** (0.65 g; 73%) was obtained as a clear oil.

δ_H (400 MHz; $CDCl_3$) 1.55 (1H, dddd, ^2J 12.0, $^3J_1 = {}^3J_2 = {}^3J_3$ 7.5, C-3 CH_a), 1.77 (2H, m, CH_2CH_2OH), 1.91 (2H, m, C-4 CH_2), 2.03 (1H, m, C-3 CH_b), 2.96 (1H, br. s, O*H*), 3.77 (3H, m, C-5 CH_a and CH_2CH_2OH), 3.91 (1H, m, C-5 CH_b) and 4.03 (1H, m, C-2 C*H*) ppm

δ_C (100.6MHz; $CDCl_3$) 25.4 (C-4 CH_2), 31.6 (C-3 CH_2), 37.1 (CH_2CH_2OH), 61.6 (CH_2CH_2OH), 67.9 (C-5 CH_2) and 79.3 (C-2 CH) ppm

2-Tetrahydro-2-furylethanal 34



33 **34**

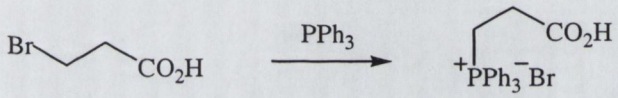
2-Tetrahydro-2-furylethanol **33** (0.65 g; 5.60 mmol) in dichloromethane (10 ml) was added dropwise with stirring to a suspension of PCC (1.45 g; 6.7 mmol) in dichloromethane (15 ml) and the mixture was left stirring for 4 hr. The supernatant liquid was then poured off and the residue washed three times with dichloromethane. The combined organic fractions were then evaporated and the crude product was filtered twice through a plug of silica. 2-Tetrahydro-2-furylethanal[20] **34** (0.45 g; 70%) was obtained as a clear oil.

ν_{max} (L) 3421, 2960, 2875, 1727 (C=O), 1687, 1459, 1380, 1278, 1189, 1164, 1066 (cyclic ether), 1020 and 919 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 1.58 (1H, dddd, ^2J 12.5, $^3J_1 = {}^3J_2 = {}^3J_3$ 8.0, C-3 CH_a), 1.94 (2H, m, C-4 CH_2), 2.12 (1H, m, C-3 CH_b), 2.63 (2H, m, CH_2CHO), 3.76 (1H, m, C-5 CH_a), 3.90 (1H, m, C-5 CH_b), 4.31 (1H, m, C-2 C*H*) and 9.82 (1H, t, *J* 2.5, C*H*O) ppm

δ_C (100.6 MHz; $CDCl_3$) 25.0 (C-4 *C*H_2), 31.0 (C-3 *C*H_2), 48.9 (*C*H_2CHO), 67.5 (C-5 *C*H_2), 73.4 (C-2 *C*H) and 200.5 (*C*HO) ppm

(2'-Carboxyethyl)triphenylphosphonium bromide 35[21]

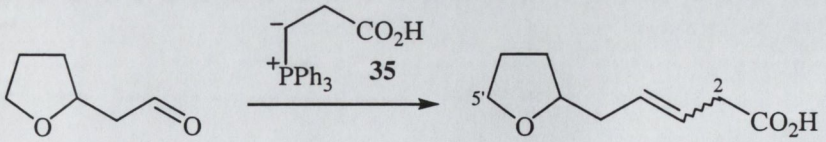


35

3-Bromopropanoic acid (15.3 g; 100 mmol) was dissolved in dry toluene (50 ml) and triphenylphosphine (28.8 g; 110 mmol) was added with stirring. The mixture was heated at reflux for 24 hr. The supernatant liquid was then decanted off and the residue was triturated with cold acetone. The white precipitate was filtered off and recrystallised from chloroform and acetone to give (2'-carboxyethyl)-triphenylphosphonium bromide **35** (26.9 g; 65%) as a white crystalline solid, m.p. 195-197 °C, (lit.[21] m.p. 196-197 °C).

δ_H (400 MHz; $CDCl_3$) 3.13 (2H, m), 3.75 (2H, m) and 7.75 (15H, m) ppm

(*E*)- and (*Z*)-5-(tetrahydro-2'-furyl)pent-3-enoic acid 7



34 **7**

n-BuLi (2.5 M, 1.37 ml; 3.42 mmol) was added dropwise to a stirred solution of (2'-carboxyethyl)triphenylphosphonium bromide **35** (0.545 g; 1.3 mmol) in dry THF (12 ml) and DMSO (3 ml) at –10 °C and under an atmosphere of nitrogen. After 25 min at this temperature, 2-tetrahydro-2-furylethanal **34** (0.1 g; 0.88 mmol)

was added to the red reaction mixture. After a further 0.5 hr at this temperature the mixture was allowed to warm to room temperature overnight. The reaction was then quenched with saturated ammonium chloride solution. Water was added and the mixture was extracted twice with diethyl ether. The aqueous layer was then acidified to pH 1 with 5.5 M aqueous HCl and then extracted three times with ether. The ether extracts were then washed with brine and dried over $MgSO_4$ and evaporated. The crude product (0.07 g) was then dissolved in ether (5 ml) and washed with saturated aqueous sodium hydrogen carbonate. The aqueous layer was then acidified to pH 1 with 5.5 M aqueous HCl solution and extracted with ether. The ether extract was dried over $MgSO_4$ and evaporated. (*E*)- and (*Z*)-5-(tetrahydro-2'-furyl)pent-3-enoic acid **7** was obtained as a clear oil (0.045 g; 30% yield; (*E*):(*Z*) 6:1).

ν_{max} (L) 3451 (OH), 2952, 2877, 1724 (C=O), 1624 (C=C), 1438, 1411, 1184, 1051 (cyclic ether), 989, 923, 875, 804 and 723 cm^{-1}

(*E*)-Isomer

δ_H (400 MHz; $CDCl_3$) 1.52 (1H, dq, ^2J 12.0, ^3J 8.0, C-3' CH_a), 1.86-1.96 (2H, m, C-4' CH_2), 1.96-2.04 (1H, m, C-3' CH_b), 2.23-2.29 (1H, m, C-5 CH_a), 2.35-2.40 (1H, m, C-5 CH_b), 3.16 (2H, t, *J* 5.5, C-2 CH_2), 3.73-3.78 (1H, m, C-5' CH_a), 3.87-3.95 (1H, m, C-2' C*H* and C-5' CH_b), 5.69 (2H, m, C-3 C*H* and C-4 C*H*) and 9.13 (1H, br. s, CO_2H) ppm

(*Z*)-Isomer

As for (*E*)-isomer except: δ_H (400 MHz; $CDCl_3$) 3.24 (2H, m, C-2 CH_2), 3.68 (1H, m, C-5' CH_a), 3.87-3.95 (2H, m, C-2' C*H* and C-5' CH_b) and 5.62 (2H, m, C-3 C*H* and C-4 C*H*) ppm

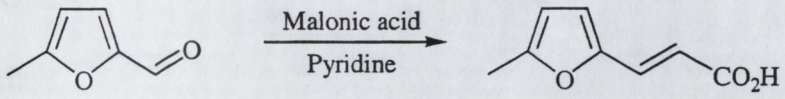
(*E*)-Isomer only [(*Z*) not visible clearly]

δ_C (100.6 MHz; $CDCl_3$) 25.5 (C-4' *C*H_2), 30.8 (C-3' *C*H_2), 33.2, 33.3 (C-5 *C*H_2 and C-2 *C*H_2), 67.8 (C-5' *C*H_2), 78.5 (C-2' *C*H), 122.7, 129.5 (C-3 *C*H and C-4 *C*H) and 175.5 (C-1 *C*O_2H) ppm

HRMS *m/z* (CI) 171.1028: *calculated for* $[C_9H_{14}O_3 + H]^+$ 171.1021

4.5.2 Towards Patulolide C (2)

(*E*)-3-(5'-Methyl-2'-furyl)prop-2-enoic acid 41



41

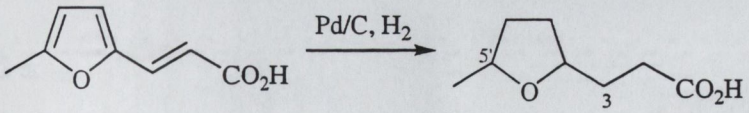
Freshly distilled 5-methyl furfural (12 g; 109 mmol), malonic acid (11.34 g; 109 mmol, dry pyridine (10 ml) and piperidine (0.2 ml) were heated to 100 °C for 2.5 hr. The mixture was then cooled to 0 °C and water (20 ml) and concentrated ammonia (7 ml) were added. The mixture was then acidified with 50:50 HCl and left for 1 hr at 0 °C. The resultant precipitate was then filtered off and suspended three times in ice-cold water and dried on an oil pump. (*E*)-3-(5'-Methyl-2'-furyl)prop-2-enoic acid[33] **41** was obtained as a pale yellow solid (13.36 g; 81%), m.p. 150-152 °C, (lit. m.p. 152-153 °C).

ν_{max} (L) 2923 (OH), 2854, 1687 (C=O), 1627, 1577, 1529, 1461 (furan), 1376, 1311, 1261, 1205, 1024, 937, 850, 794 and 721 cm^{-1}

δ_H (400 MHz; $CDCl_3$) 2.38 (3H, s, CH_3), 6.12 (1H, d, *J* 3.0, C-4' C*H*), 6.24 (1H, d, J_{trans} 15.5, C-2 C*H*), 6.58 (1H, d, *J* 3.0 C-3' C*H*) and 7.46 (1H, d, J_{trans} 15.5, C-3 C*H*) ppm

δ_C (100.6MHz; $CDCl_3$) 13.8 (CH_3), 108.9 (C-4' *C*H), 112.8 (C-3' *C*H), 117.4 (C-2 *C*H), 132.9 (C-3 *C*H), 148.8 (C-2' *C*), 155.7 (C-5' *C*) and 171.6 (CO_2H) ppm

3-(5'-Methyltetrahydro-2'-furyl)propanoic acid 42



41 **42**

The acid **41** (13.36 g; 88 mmol) was dissolved in ethanol (400 ml) and was stirred under an atmosphere of hydrogen (1 atm) in the presence of 5% w/w Pd/C (700 mg) until hydrogen uptake had ceased. The mixture was then filtered and the solvent removed *in vacuo*. 3-(5'-Methyltetrahydro-2'-furyl)propanoic acid[34] **42** was obtained (13.15 g; 95%; major : minor diastereoisomers 5:1) as a clear oil.

ν_{max} (L) 2969 (OH), 2931, 2873, 1710 (C=O), 1446, 1415, 1376, 1346, 1261, 1187, 1085 (cyclic ether), 1012, 952, 889 and 844 cm^{-1}

Major diastereoisomer

δ_H (400 MHz; $CDCl_3$) 1.25 (3H, d, *J* 6.0, CH_3), 1.52 (2H, m, C-3 CH_2), 1.81-1.94 (2H, m, C-3' CH_2 or C-4' CH_2), 1.98-2.03 (2H, m, C-3' CH_2 or C-4' CH_2), 2.51 (2H, m, C-2 CH_2), 3.95 (1H, m, C-2' C*H*), 4.01 (1H, m, C-5' C*H*) and 10.65 (1H, br. s, CO_2H) ppm

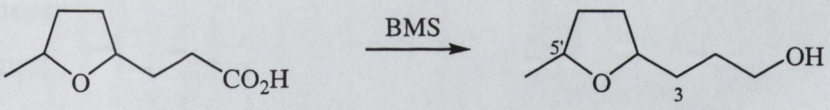
Minor diastereoisomer

δ_H (400 MHz; $CDCl_3$) 1.23 (3H, d, *J* 6.0, CH_3), 1.52 (2H, m, C-3 CH_2), 1.81-1.94 (2H, m, C-3' CH_2 or C-4' CH_2), 1.98-2.03 (2H, m, C-3' CH_2 or C-4' CH_2), 2.51 (2H, m, C-2 CH_2), 4.13 (2H m, C-2' and C-5' C*H*) and 10.65 (1H, br. s, CO_2H) ppm

Major and minor diastereoisomeric mixture

δ_C (100.6MHz; $CDCl_3$) 20.6, 20.7 (2xCH_3), 30.2, 30.3, 30.4, 30.5, 31.4, 32.3 (CH_2), 74.7 (C-5' *C*H (minor isomer)), 75.6 (C-5' *C*H (major isomer)), 77.6 (C-2' *C*H (minor isomer)), 78.1 (C-2' *C*H (major isomer)) and 178.0 (CO_2H) ppm

3-(5'-Methyltetrahydro-2'-furyl)propanol 43



42 **43**

The saturated acid **42** (13.15 g; 83 mmol) was dissolved in dry THF (65 ml) under an atmosphere of nitrogen and cooled to 0 °C. BMS (7.58 g; 98 mmol) was then added dropwise *via* syringe. The mixture was allowed come to room temperature over 1 hr and was then heated at reflux for 1 hr. Methanol (40 ml) was added (dropwise at first) to destroy any unreacted BMS and the solvent was removed *in vacuo*. The product was then filtered through a plug of silica to give 3-(5'-methyltetrahydro-2'-furyl)propanol[35] **43** (11.1 g; 93%; major : minor diastereoisomers 5:1) as a clear oil.

ν_{max} (L) 3394 (OH), 2966, 2869, 1729, 1446, 1376, 1263, 1174, 1087 (cyclic ether), 1006 and 890 cm^{-1}

Major diastereoisomer

δ_H (400 MHz; $CDCl_3$) 1.26 (3H, d, *J* 6.0, CH_3), 1.46-1.75 (6H, m, C-2, C-3 CH_2 and C-3' or C-4' CH_2), 1.99 (2H, m, C-3' or C-4' CH_2), 3.68 (2H, m, C-1 CH_2), 3.85 (1H, m, C-2' C*H*) and 4.01 (1H, C-5' C*H*) ppm

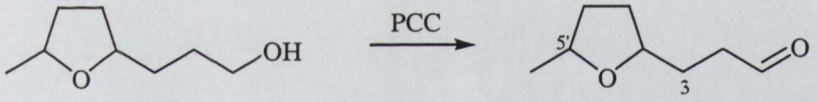
Minor diastereoisomer: as for major diastereoisomer except:

δ_H (400 MHz; $CDCl_3$) 1.23 (3H, d, *J* 6.0, CH_3) and 4.15 (2H, m, C-2' and C-5' C*H*) ppm

Major diastereoisomer only

δ_C (100.6 MHz; $CDCl_3$) 21.2 (CH_3), 29.7, 31.3, 32.7, 33.2 (4xCH_2), 62.8 (C-1 CH_2OH), 75.5 (C-5' C*H*) and 79.4 (C-2' C*H*) ppm

3-(5'-Methyltetrahydro-2'-furyl)propanal 44



43 **44**

The alcohol **43** (1.62 g; 11 mmol), in dichloromethane (8 ml), was added to a stirred suspension of pyridinium chlorochromate (PCC) (2.9 g; 13.5 mmol) in dichloromethane (20 ml). The mixture was stirred at room temperature for 3 hr (monitored by tlc). The supernatant liquid was then decanted off and the residue extracted (x 4) with dichloromethane. The combined organic extracts were then filtered through a plug of silica (x2). The solvent was removed *in vacuo* to give 3-(5'-methyltetrahydro-2'-furyl)propanal[36] **44** (1.12 g; 70%; major : minor diastereoisomers 4:1) as a clear oil.

ν_{max} (L) 2967, 2929, 2869, 1725 (C=O), 1448, 1375, 1245, 1091 (cyclic ether), 1004, 910 and 808 cm^{-1}

Major diastereoisomer

δ_H (400 MHz; $CDCl_3$) 1.23 (3H, d, *J* 6.0, CH_3), 1.52 (2H, m, C-3 CH_2), 1.91 (4H, m, C-3' and C-4' CH_2), 2.55 (2H, m, C-2 CH_2), 3.86 (1H, m, C-2' *CH*), 3.94 (1H, m, C-5' *CH*) and 9.80 (1H, s, *CH*O) ppm

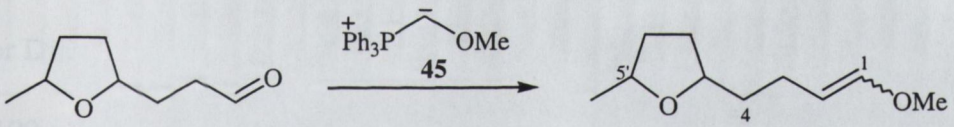
Minor diastereoisomer

δ_H (400 MHz; $CDCl_3$) 1.21 (3H, d, *J* 6.0, CH_3), 1.52 (2H, m, C-3 CH_2), 1.91 (4H, m, C-3' and C-4' CH_2), 2.55 (2H, m, C-2 CH_2), 4.05 (2H, m, C-2' and C-5' *CH*) and 9.80 (1H, s, *CH*O) ppm

Major diastereoisomer only

δ_C (100.6MHz; $CDCl_3$) 21.2 (CH_3), 28.4 (C-3 CH_2), 31.0 (C-3' CH_2), 32.8 (C-4' CH_2), 40.5 (C-2 CH_2), 75.4 (C-5' *C*H), 78.1 (C-2' *C*H) and 202.2 (*C*HO) ppm

(*E*)- and (*Z*)-4-(5'-methyltetrahydro-2'-furyl)butenyl methyl ether 46



44 **46**

n-BuLi (2.5 M, 1.7 ml; 4.25 mmol) was added to (methoxymethyl)-triphenylphosphonium chloride **45** (1.2 g; 3.5 mmol) in dry THF (20 ml) under an atmosphere of nitrogen at 0 °C. After 0.5 hr at this temperature, a solution of 3-(5'-methyltetrahydro-2'-furyl)propanal **44** (0.2 g; 1.41 mmol) in dry THF (5 ml) was added to the red reaction mixture which then allowed to warm slowly to room temperature and left overnight. The reaction was quenched with saturated ammonium chloride solution and ether and water were then added. The aqueous layer was extracted three times with ether and the combined ether extracts were washed with brine, dried over $MgSO_4$ and evaporated. The resultant crude product was then purified by column chromatography using hexane : ethyl acetate : dichloromethane 90:5:5 as eluant. Subsequently, a mixture of (*E*)- (36%) and (*Z*)- (64%) isomers of 4-(5'-methyltetrahydro-2'-furyl)butenyl methyl ether **46** was isolated as a clear oil (0.09 g; 38%; major : minor isomers 4:1). A side-product was also isolated and identified as a mixture of (*E*)- and (*Z*)-diastereoisomers (50:50) of

2-methyl-5-hept-3'-enyl-tetrahydrofuran **48** (0.03 g; 11%; major : minor diastereoisomers 4:1).

(*E*)- and (*Z*)-4-(5'-methyltetrahydro-2'-furyl)butenyl methyl ether 46

ν_{max} (L) 2966, 2929, 2856, 1739, 1656 (C=C), 1454, 1373, 1241, 1213 (ether), 1108, 1047 (cyclic ether), 919, 796 and 734 cm^{-1}

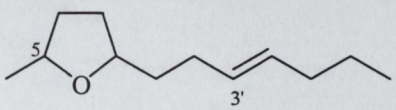
δ_H (400 MHz; $CDCl_3$) 1.22 (3H, d, *J* 6.5, C*H*$_3$ (minor isomer)), 1.25 (3H, d, *J* 6.0, C*H*$_3$ (major isomer)), 1.42-1.57 (3H, m, C-3' C*H*$_a$, C-4' C*H*$_a$ and C-4 C*H*$_a$ (major and minor isomers)), 1.63-1.75 (1H, m, C-4 C*H*$_b$ (major and minor isomer)), 1.93-2.16 (4H, m, C-3' C*H*$_b$, C-4' C*H*$_b$ (major and minor isomers) and C-3 C*H*$_2$), 3.51 (3H, s, OC*H*$_3$ ((*E*)-isomer)), 3.58 (3H, s, OC*H*$_3$ ((*Z*)-isomer)), 3.79-3.85 (1H, ap. quintet, *J* 6.5, C-2' C*H*$_2$ (major isomer)), 3.91-3.97 (1H, m, C-5' C*H*$_2$ (major isomer)), 3.99-4.04 (1H, m, C-2' C*H*$_2$ (minor isomer)), 4.07-4.12 (1H, m, C-5' C*H*$_2$ (minor isomer)), 4.37 (1H, m, C-2 C*H* ((*Z*)-isomer)), 4.76 (1H, dt, J_{trans} 12.5, ^3J 7.5, C-2 C*H* ((*E*)-isomer)), 5.87 (1H, d, *J* 6.0, C-1 C*H* ((*Z*)-isomer)) and 6.32 (1H, d, *J* 13.0, C-1 C*H* ((*E*)-isomer)) ppm

Major Diastereoisomer only

δ_C (100.6MHz; $CDCl_3$) 20.6 (*C*H$_3$), 24.5 (C-3 *C*H$_2$), 31.2, 32.8 (C-3' and C-4' 2x*C*H$_2$), 36.2 (C-4 *C*H$_2$ ((*Z*)-isomer)), 37.3 (C-4 *C*H$_2$ ((*E*)-isomer)), 55.9 (O*C*H$_3$ ((*E*)-isomer)), 57.9 (O*C*H$_3$ ((*Z*)-isomer)), 75.1 (C-5' *C*H), 78.0 (C-2' *C*H), 102.8 (C-2 *C*H ((*E*)-isomer)), 106.5 (C-2 *C*H ((*Z*)-isomer)), 146.2 (C-1 *C*H ((*Z*)-isomer)) and 147.2 (C-1 *C*H ((*E*)-isomer)) ppm

HRMS *m/z* (CI) 171.1375: *calculated for* $[C_{10}H_{18}O_2 + H]^+$ 171.1385

(*E*)- and (*Z*)-5-methyl-2-hept-3'-enyl-tetrahydrofuran 48

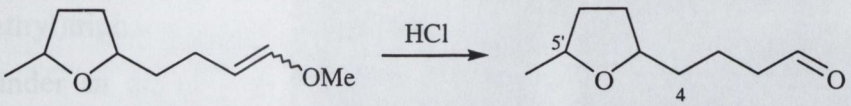


48

δ_H (400 MHz; $CDCl_3$) 0.90 (3H, m, C-7' C*H*$_3$ ((*E*)- and (*Z*)-isomers)), 1.22 (3H, d, *J* 6.0, C*H*$_3$ (minor isomer)), 1.27 (3H, d, *J* 6.0, C*H*$_3$ (major isomer)), 1.36-2.17 (12H, 4xm centred at 1.38, 3H, 1.51, 3H, 1.71, 1H and 2.04, 5H, 6xC*H*$_2$), 3.82 (1H,

m, C-2 C*H* (major isomer)), 3.96 (2H, m, C-5 C*H* (major isomer) and C-2 C*H* (minor isomer)), 4.12 (1H, m, C-5 C*H* (minor isomer)), 5.37-5.45 (4H, 2xm, C-3' C*H* and C-4' C*H* ((*E*)- and (*Z*)-isomers) ppm

4-(5'-Methyltetrahydro-2'-furyl)butanal 47



46 **47**

1M HCl (1.5 ml; 1.5 mmol) was added to the methyl ether **46** (0.26 g; 1.5 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature overnight. Dichloromethane (8 ml) and water (6 ml) were added and the organic layer was washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and the solvent removed *in vacuo*. 4-(5'-Methyltetrahydro-2'-furyl)butanal **47** was obtained (0.21 g; 90%; major : minor diastereoisomers 4:1) as a clear oil.

ν_{max} (L) 2967, 2931, 2870, 1725 (C=O), 1458, 1376 and 1090 (cyclic ether) cm^{-1}

Major Diastereoisomer

δ_H (400 MHz; $CDCl_3$) 1.25 (3H, d, *J* 6.5, CH_3), 1.57 (4H, m, C-4 CH_2 and C-3' CH_2), 1.74 (2H, m, C-3 CH_2), 1.98 (2H, m, C-4' CH_2), 2.49 (2H, t, *J* 7.5, C-2 CH_2), 3.82 (1H, ap. quintet, *J* 6.5, C-2' C*H*), 3.96 (1H, m, C-5' C*H*), and 9.79 (1H, s, C*H*O) ppm

Minor diastereoisomer: as for major diastereoisomer except:

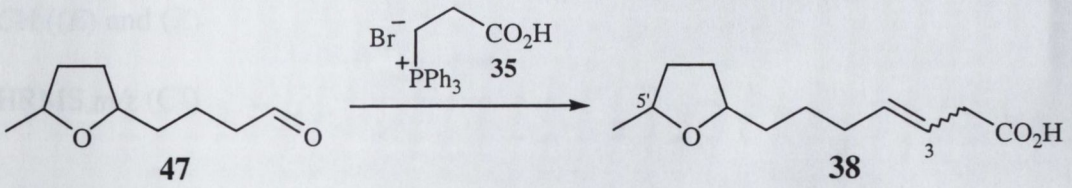
δ_H (400 MHz; $CDCl_3$) 1.22 (3H, d, *J* 6.0, CH_3), 2.06 (2H, m, C-4' CH_2), 2.42 (2H, t, *J* 7.5, C-2 CH_2), 3.96 (1H, m, C-2' C*H*) and 4.11 (1H, m, C-5' C*H*) ppm

Major Diastereoisomer only

δ_C (100.6MHz; $CDCl_3$) 18.8 (C-3 *C*H_2), 21.3 (*C*H_3), 31.2 (C-3' *C*H_2), 32.7 (C-4' *C*H_2), 35.4 (C-4 *C*H_2), 43.7 (C-2 *C*H_2), 75.2 (C-5' *C*H), 78.8 (C-2' *C*H) and 202.4 (*C*HO) ppm

HRMS *m/z* (CI) 157.1225: *calculated for* $[C_9H_{16}O_2 + H]^+$ 157.1229

(*E*)- and (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid 38



47 38

n-BuLi (2.5 M, 0.384 ml; 0.96 mmol) was added with stirring to a mixture of (2'-carboxyethyl)triphenylphosphonium bromide **35** (200 mg; 0.48 mmol) in dry THF (4 ml) under an atmosphere of nitrogen and at –10 °C. After 25 min at this temperature, a solution of 4-(5'-methyltetrahydro-2'-furyl)butanal **47** (50 mg; 0.32 mmol) in dry THF (1.5 ml) was added to the dark red reaction mixture which was then allowed warm slowly to room temperature and left overnight. The dark brown reaction mixture was then quenched with saturated ammonium chloride solution and water was added. The mixture was then extracted twice with diethyl ether. The aqueous layer was acidified to pH 1 with a 5.5 M solution of HCl and extracted three times with ether. The organic extracts were then washed with brine, dried over $MgSO_4$ and evaporated. A 1:1 mixture of (*E*)- and (Z)-7-(5'-methyltetrahydro-2'-furyl)hept-3-enoic acid **38** (0.03 g; 44%; major : minor diastereoisomers 4:1) was obtained as a pale yellow oil.

ν_{max} (L) 3446 (OH), 2966, 2933, 2871, 1716 (C=O), 1457, 1438, 1378, 1253, 1164, 1083 (cyclic ether), 971, 894, 806 and 723 cm^{-1}

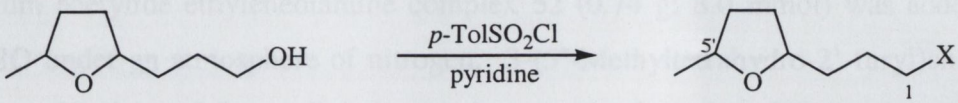
δ_H (400 MHz; $CDCl_3$) 1.22 (3H, d, *J* 6.5, C*H*$_3$ (minor isomer)), 1.24 (3H, d, *J* 6.0, C*H*$_3$ (major isomer)), 1.54 (6H, m, C-3' or C-4' C*H*$_2$, C-6 C*H*$_2$ and C-7 C*H*$_2$), 1.97 (2H, m, C-3' or C-4' C*H*$_2$), 2.08 (4H, m, C-5 C*H*$_2$ ((*E*)- and (Z)-isomers)), 3.07 (2H, d, *J* 6.0, C-2 C*H*$_2$ ((*E*)/(Z)-isomer)), 3.14 (2H, d, *J* 6.0, C-2 C*H*$_2$ ((*E*)/(Z)-isomer)), 3.82 (1H, m, C-2' C*H* (major isomer)), 3.97 (1H, m, C-5' C*H* (major isomer) and C-2' C*H* (minor isomer)), 4.1 (1H, m, C-5' C*H* (minor isomer)), 5.58 (4H, m, ((*E*) and (Z)-isomers) C-3 C*H* and C-4 C*H*) and 8.83 (1H, br. s, CO_2H) ppm

δ_C (100.6MHz; $CDCl_3$) (major diastereoisomer only) 21.3 (*C*H$_3$), 25.5, 27.4, 31.1, 32.4, 32.6, 35.5 (C-3' *C*H$_2$, C-4' *C*H$_2$, C-7 *C*H$_2$, C-6 *C*H$_2$ and 2 x C-5 *C*H$_2$ ((*E*) and (Z)-isomers), 32.7, 37.3, (2 x C-2 *C*H$_2$ ((*E*) and (Z)-isomers)), 75.3 (C-5' *C*H), 79.3

(C-2' *C*H), 120.4, 121.2 (2 x C-4 *C*H ((*E*) and (*Z*)-isomers)), 133.4, 134.8 (2 x C-3 *C*H ((*E*) and (*Z*)-isomers)) and 175.4 (*C*O_2H) ppm

HRMS *m/z* (CI) 235.1290: *calculated for* $[C_{12}H_{20}O_3 + Na]^+$ 235.1310

Synthesis of 3-(5'-methyltetrahydro-2'-furyl)chloropropane 50



43

50 X = Cl
51 X = OTs

p-Toluenesulfonylchloride (3.65 g; 19 mmol) was added to a well stirred solution of 3-(5'-methyltetrahydro-2'-furyl)propanol **43** (2.3 g; 16 mmol) in pyridine (20 ml) at 0 °C. Following 0.5 hr at this temperature the mixture was stirred at room temperature for 3 hr and then poured onto ice and water and extracted with ethyl acetate. The organic extract was then washed sequentially with dilute HCl and brine, dried over $MgSO_4$ and evaporated. The crude product (1.3 g) thus obtained was identified as a mixture of 3-(5'-methyltetrahydro-2'-furyl)chloropropane **50** and tosyloxy-3-(5'-methyltetrahydro-2'-furyl)propane **51** in a ratio of 3:1. (**50** and **51** were not separated.)

ν_{max} (L) 2966, 2929, 2869, 1735, 1685, 1457, 1375, 1361 (SO_2), 1189, 1176 (SO_2), 1089, 1033 (cyclic ether), 1008, 968, 908, 815 and 728 cm^{-1}

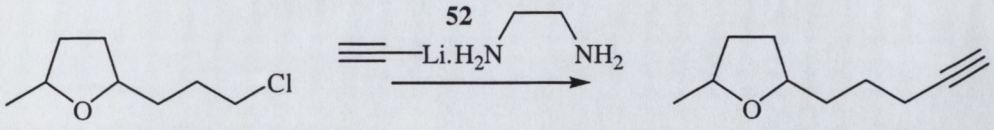
3-(5'-Methyltetrahydro-2'-furyl)chloropropane **50**

δ_H (400 MHz; $CDCl_3$) 1.25 (3H, d, *J* 6.0, Me), 1.56 (4H, m, C-2 and C-3 2xCH_2), 1.96 (4H, m, C-3' and C-4' CH_2), 3.59 (2H, m, C-1 CH_2), 3.84 (1H, m, C-2' or C-5' C*H*) and 4.11 (1H, m, C-2' or C-5' C*H*) ppm

Tosyloxy-3-(5'-methyltetrahydro-2'-furyl)propane **51**

δ_H (400 MHz; $CDCl_3$) 1.22 (3H, d, *J* 6.0, Me), 1.56 (4H, m, C-2 and C-3 2xCH_2), 1.96 (4H, m, C-3' and C-4' CH_2), 3.75 (2H, m, C-1 CH_2), 3.95 (1H, m, C-2' or C-5' C*H*), 4.11 (1H, m, C-2' or C-5' C*H*), 7.34 (2H, d, *J* 8.0, Ar *H*) and 7.81 (2H, d, *J* 8.0, Ar *H*) ppm

Attempted reaction of 3-(5'-methyltetrahydro-2'-furyl)chloropropane 50 with lithium acetylide ethylenediamine complex 52



50 **53**

Lithium acetylide ethylenediamine complex **52** (0.74 g; 8.0 mmol) was added to DMSO under an atmosphere of nitrogen. 3-(5'-Methyltetrahydro-2'-furyl)chloropropane **50** (1.3 g; 8.0 mmol) (mixture also contained tosylate **51**) was then added rapidly with stirring while the temperature of the mixture was controlled by external cooling so as it did not rise above 25 °C.[42] After 40 min at this temperature the mixture was heated to 60 °C for 3 hr. Excess lithium acetylide complex **52** was then destroyed by addition of 5.5 M HCl. The mixture was poured onto water and extracted (x3) with ether. The combined ether extracts were then washed with brine, dried over $MgSO_4$ and evaporated. NMR analysis of the product obtained showed it to be the starting compound **50**.

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