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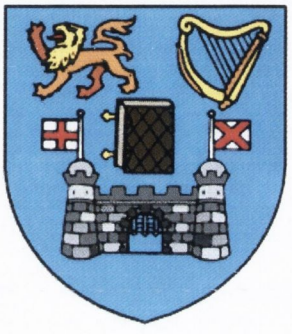
Acylative cleavage of some cyclic ethers and study of a novel potassium complex



by

Gillian Butler

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

June 2003

Trinity College Dublin

Declaration

This thesis has not been submitted for a degree to this or any other University. Except where acknowledgement is given, all work is original and was carried out by the author alone. The author agrees that the Library may lend or copy this thesis upon request.

Gillian Butler.

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Thanks also to my friends outside college. Particuliarly to my fellow PhDers Lisa and Jenny who also knew the pain of writing a thesis and to Aoife, Audrey and Eithne who had to listen to a lot of chemistry talk, sorry.

Finally to my family and Philip thank you for your support and for putting up with someone on the verge of a nervous breakdown for the last few months.

For my grandfather

Summary

Chapter 1 describes ring-opening reactions of cyclic ethers that are described in the literature. The extensive work carried out on tetrahydrofuran is discussed, but it is noted that reactions involving 2,5-dihydrofuran have been significantly less explored. The importance of 7-oxabicyclo[2.2.1]heptanes and their derivatives in natural product synthesis is highlighted, with emphasis on the different methods employed to break the ether bond. The different types of ion-complexing ethers are discussed, as is a reported synthesis of a podate potassium complex, which it is intended to further explore. Chapter 2 discusses the attempted ring-opening reactions of 7-oxabicyclo[2.2.1]heptenes by their reactions with mixed carboxylic-trifluoroacetic anhydrides. The chapter includes a description of modifications to the original system and of repeated attempts at ring-opening. Some other bicyclic ring systems are also discussed.

Chapter 3 describes the Lewis acid-catalysed ring-opening reactions of 2,5-dihydrofuran and acyl chlorides to give 1-acyloxy-4-chlorobut-2-enes where the olefinic geometry of 2,5-dihydrofuran is retained. The preparation of aryl, alkyl and unsaturated esters is reported. The general reactivity of the resulting compounds is investigated, including the reactivity of the chlorine substituent towards a range of nucleophiles. An intramolecular Heck reaction is attempted and a proposed synthesis of a four membered sugar is discussed.

Chapter 4 reports that the reaction of tetrahydrofuran with mixed carboxylic-trifluoroacetic anhydrides in the presence of iodide ion gives 1-acyloxy-4-iodobutanes. The preparation of aryl, alkyl and unsaturated esters is described. The methodology is also applied to a precursor of the drug Mebeverine that leads to a shorter and more efficient synthesis of this pharmaceutical.

Chapter 5 describes the synthesis of a previously proposed potassium complex from a triol derived from geranyl acetate. Another method of complex synthesis is described involving alkali metal silanolates. The attempted synthesis of a borate complex is also discussed.

Abbreviations

Ac	acetyl
br	broad
b.p.	boiling point
$CDCl_3$	deuteriated chloroform
COSY	correlation spectroscopy
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
exch	exchange
g	gram
Hz	Hertz
IR	infrared
LHDMS	lithium hexamethyldisilazide
m	multiplet
mg	milligram
MHz	megahertz
mL	millilitre
mm Hg	millimetres of mercury

m.p.	melting point
NMR	nuclear magnetic resonance
ppm	parts per million
q	quartet
r.t.	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	tri butylsilyl
TFA_2O	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	tri*iso*-propylsilyl
TLC	thin layer chromatography
TMSOTf	trimethylsilyltriflate

Unless otherwise indicated all compounds are racemic.

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Chapter 1

Introduction

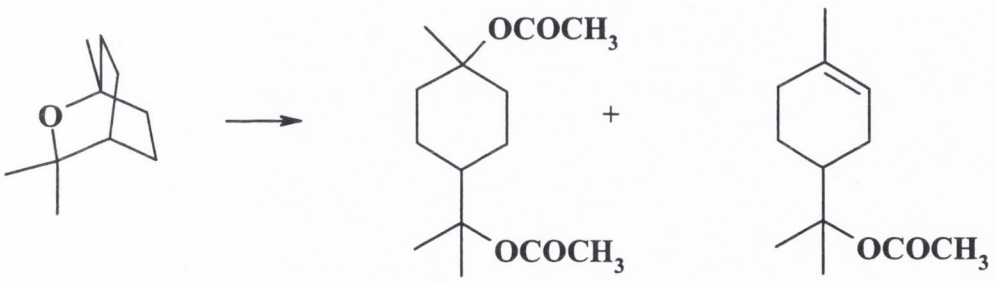
1 Introduction

1.1 Cleavage reactions of ethers

The cleavage and rearrangement of ethers is considered to be a useful reaction, especially in the degradation or transformation of natural products and the synthesis of polyfunctional molecules. The reaction also plays a part in the manufacture of a number of pharmaceuticals, drugs and other fine chemicals.[1] Most of the early work in this area was carried out between 1930 and 1950, and the procedures devised then are still being used today to produce materials where more efficient syntheses are unknown.

The first reported cleavage of a cyclic ether was that of the bicyclic tetrahydropyran derivative 1,8-cineole **1**, a reaction which was carried out by Knoevenagel in 1914.[2] Cleavage was effected using acetic acid containing a trace of sulfuric acid, and the reaction yielded equal amounts of the diacetate **2** and α-terpinyl acetate **3** (**Scheme 1**).

Acid catalysed ring-opening of 1,8-cineole



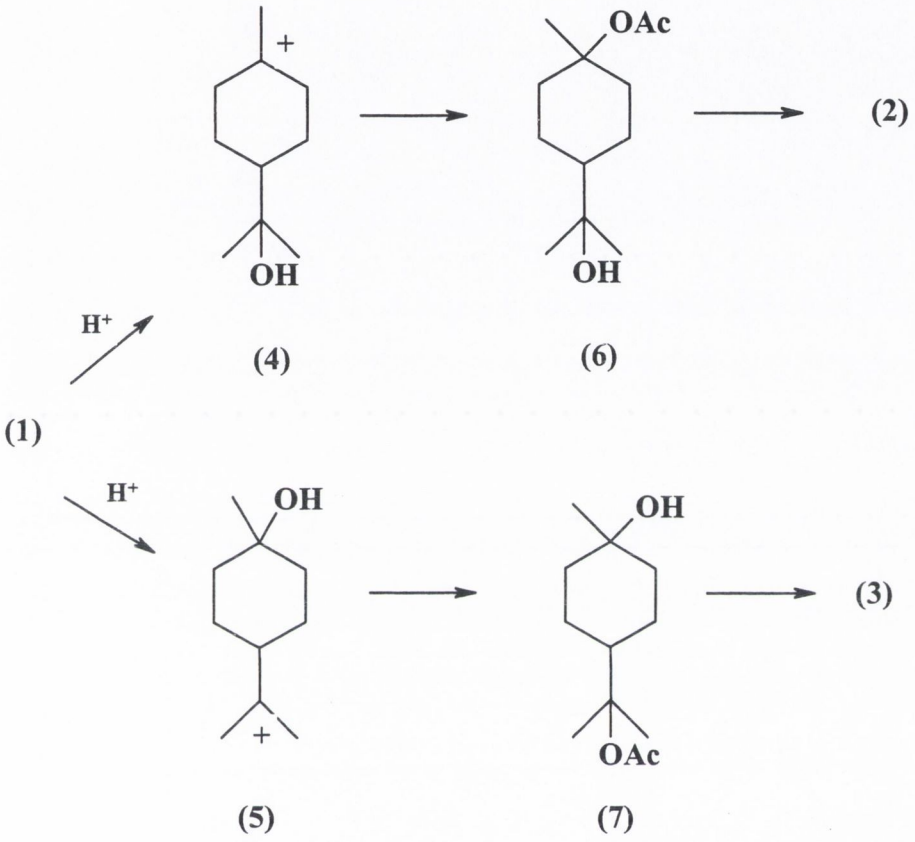
(1) **(2)** **(3)**

Scheme 1

The mechanism of this ring-opening process can be visualised as shown in **Scheme 2**. Firstly, cleavage of the oxygen bridge of 1,8-cineole gives the two possible

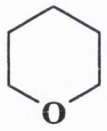
cations **4** and **5** which then are attacked by acetate ion to give the preliminary products **6** and **7**. Further acetylation of these compounds gives the products **2** and **3.**

Mechanism of reaction shown in Scheme 1

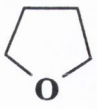


Scheme 2

It has been repeatedly observed[3,4,5,6] that the ring-opening of tetrahydropyran **8** itself requires more extreme conditions. This can be rationalised on the basis that the intermediate would have to be a less stable, primary carbonium ion. Much more work has been done on hydrofuran ring systems, as they are easier to open. More work has been done on tetrahydrofuran **9** and its substituted derivatives than on 2,5-dihydrofuran **10**.



(8)



(9)

(10)

1.1.1 Ring-cleavage reactions of di- and tetrahydrofurans

Starr and Hixon carried out the cleavage of tetrahydrofuran to yield the useful compound 4-chlorobutan-1-ol **11** **(Scheme 3)**.[7] The ether **9** was refluxed during five hours while a slow stream of hydrogen chloride was passed through the reaction vessel. The product was then fractionally distilled to give **11** in 57% yield. Trost *et al.*[8] were still using this inexpensive method for the synthesis of halobutanols nearly 50 years later.

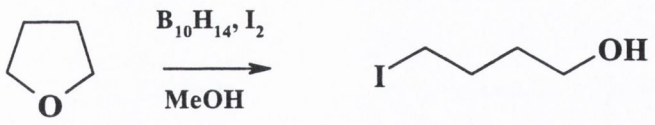
Synthesis of 4-chlorobutan-1-ol from tetrahydrofuran

(9) (11)

Scheme 3

Huang and Liang synthesised the corresponding iodo derivative **12** using decaborane and iodine in methanol **(Scheme 4)**.[9] Decaborane, $B_{10}H_{14}$ is a borane cluster compound, which decomposes in the presence of methanol and iodine to give a borate, hydrogen, and hydrogen iodide which can cleave the ether function of tetrahydrofuran.[10]

Cleavage of tetrahydrofuran using decaborane in methanol

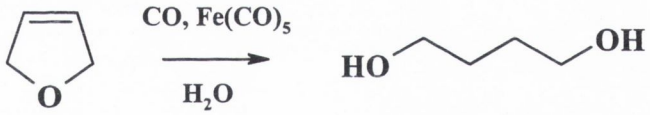


(9) **(12)**

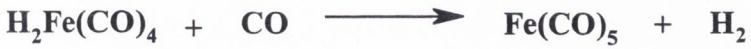
Scheme 4

Reppe and Wetter carried out the synthesis of the diol **13** from 2,5-dihydrofuran **10** using $Fe(CO)_5$ in triethylamine in the presence of carbon monoxide and water **(Scheme 5)**.[11] When iron pentacarbonyl is dissolved in water, it loses one carbonyl group, which is then replaced by hydrogen to give iron hydrocarbonyl. In the presence of carbon monoxide, this gives iron pentacarbonyl and liberates hydrogen which reduces the double bond.

Reaction of 2,5-dihydrofuran with $Fe(CO)_5$, carbon monoxide and water in triethylamine



(10) **(13)**

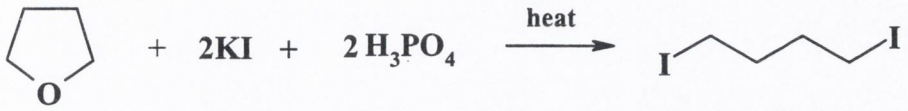


Scheme 5

Acidic cleavage of tetrahydrofuran **9** has also been carried out in the presence of an excess of iodide ions to give 1,4-di-iodobutane **14** in 96% yield.[12] Many acids have

been shown to work well in this reaction but orthophosphoric acid gave the best results **(Scheme 6)**. The di-iodide **14** had been previously made by heating tetrahydrofuran **9** with red phosphorus and finely ground iodine but this yielded the product **14** in only 51% yield.[13]

Acidic cleavage of tetrahydrofuran in the presence of iodide ion

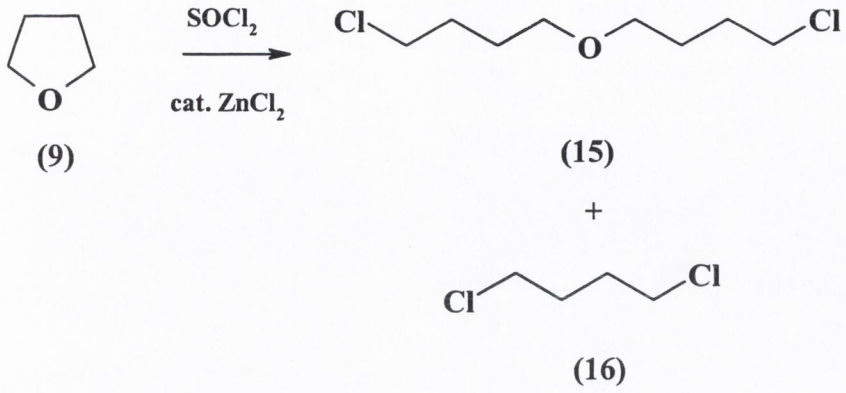


(9) **(14)**

Scheme 6

The cleavage of tetrahydrofuran with phosphorus oxychloride in the presence of sulfuric acid gave 4,4'-dichlorodibutyl ether **15** in 54% yield **(Scheme 7)**.[14] The yield was improved to 64% when thionyl chloride and a Lewis acid (zinc chloride) were used.[15] 1,4-Dichlorobutane **16** was a minor product. However this became the major product when more than one-sixth of an equivalent of the Lewis acid was utilised. These authors[15] concluded that the ether **15** was the immediate product of these ring-opening reactions as it could be transformed into the dihalide **16** by the same mixture of reagents.

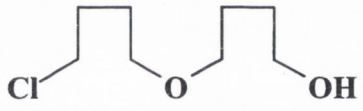
Ring-opening of tetrahydrofuran with phosphorus oxychloride in the presence of sulfuric acid



(9) (15) + (16)

Scheme 7

The products **15** and **16** were also obtained by Delaney *et al.*[16] who used $TiCl_4$ as the Lewis acid. This reaction gave the chloro-alcohol **17** as an additional product.

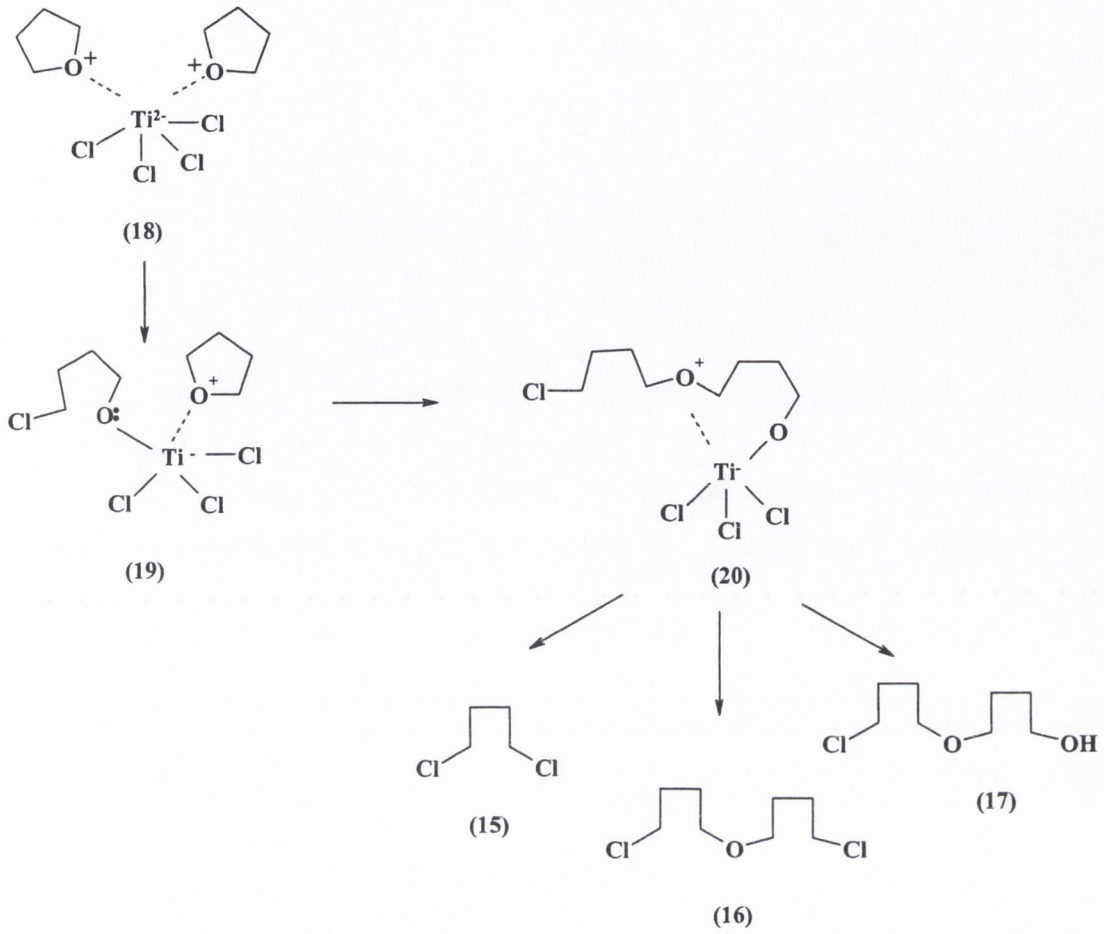


(17)

These authors[16] found that the product was either that of a ring-opening **16** or of a dimerization **15** when the reaction was worked up by direct distillation from the reaction mixture. However, if water was added and an extraction was carried out the product was the chloro-alcohol **17**. The reaction sequence is outlined in **Scheme 8**.

Firstly the titanium tetrachloride becomes coordinately bound to two molecules of tetrahydrofuran to give **18**. Attack by chloride ion causes ring-opening of one of the tetrahydrofuran molecules and this results in its oxygen atom becoming covalently bonded to the titanium to give the structure **19**. This oxygen could then attack the second tetrahydrofuran molecule leading to the intermediate **20**. Whether this intermediate goes on to form **15**, **16** or **17** depends on the work-up and whether the two tetrahydrofuran molecules are in a *cis* or *trans* relationship when coordinated to the titanium atom.

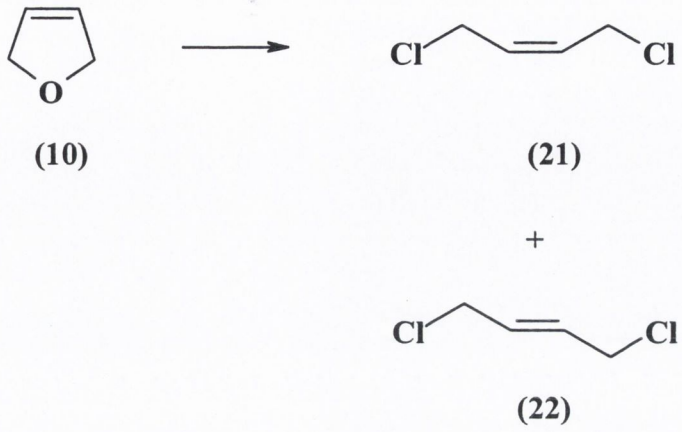
Reaction between tetrahydrofuran and titanium tetrachloride



Scheme 8

Delaney *et al.*[16] also found that 2,5-dihydrofuran **10** reacted with $TiCl_4$ to give a mixture of the (*E*)- and (*Z*)-isomers of 1,4-dichlorobut-2-ene, **21** and **22 (Scheme 9)**. This was an interesting result as the (*Z*)-isomer **18** was the only product expected, because that was what was obtained when 2,5-dihydrofuran was reacted with hydrochloric acid. However, this inversion of geometry of the double bond of 2,5-dihydrofuran in the presence of $TiCl_4$ had been previously reported.[17]

Synthesis of 1,4-dichlorobut-2-ene from 2,5-dihydrofuran and titanium tetrachloride



(10) **(21)** **(22)**

Scheme 9

Delaney *et al.*[16] also found that the ease of ring opening of cyclic ethers using $TiCl_4$ as reagent increased with aliphatic substitution α to the ether linkage and decreased with increasing ring size. The former effect reflects the increased stability of more highly-substituted carbonium ions. The ring size effect is most likely related to strain factors.

1.1.2 Reductive ring-opening with metals

Finely divided alkali metals like sodium, lithium and potassium have been shown to cleave acyclic ethers in the absence of solvent. This methodology has been applied to cyclic ethers. Heating tetrahydrofuran with lithium-biphenyl causes cleavage to give the functionalised lithium alkyl **23 (Scheme 10)**. The reaction of lithium with biphenyl is an equilibrium process, which results in a more soluble and faster reacting source of lithium than that of lithium alone.[18]

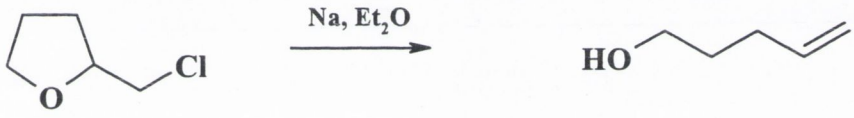
Reaction of tetrahydrofuran with lithium-biphenyl

(9) **(23)**

Scheme 10

Tetrahydrofurfuryl chloride **24** reacts with sodium in ether to give 4-penten-ol **25** in 83% yield **(Scheme 11)**.[19]

Reaction of tetrahydrofurfuryl chloride with sodium

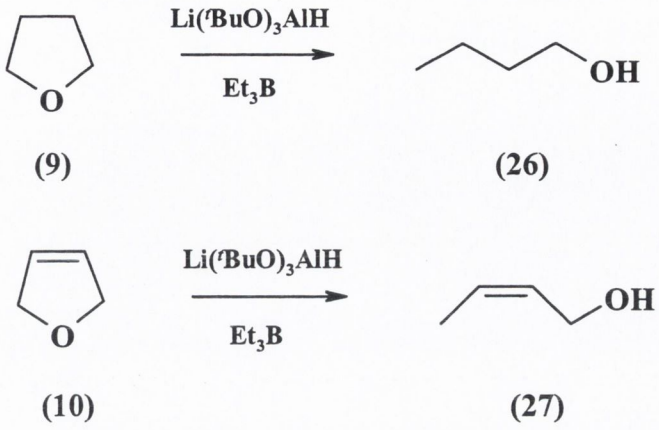


(24) **(25)**

Scheme 11

Solutions of lithium tri-*tert*-butoxyaluminium hydride are stable in both tetrahydrofuran and 2,5-dihydrofuran but in the presence of added triethylborane in tetrahydropyran as solvent they deliver hydride to tetrahydrofuran or 2,5-dihydrofuran to form the alcohols **26** or **27** respectively **(Scheme 12)**.[3] The reaction is attributed to the rapid formation of a lithium triethylborohydride - aluminium *tert*-butoxide complex. The reaction with tetrahydrofuran requires only thirty minutes whereas the reaction time when 2,5-dihydrofuran **10** is the substrate is two hours.

Reactions of both tetrahydrofuran and 2,5-dihydrofuran with tri-*tert*-butoxyaluminium hydride in the presence of triethylborane

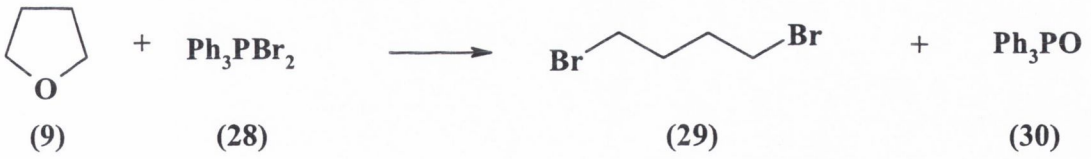


Scheme 12

1.1.3 Organophosphorus reagents

Anderson and Freenor[20] used triphenyldibromophosphorane **28** to cleave a wide variety of ethers. Thus, tetrahydrofuran reacted with this reagent to yield 1,4-dibromobutane **29** together with triphenylphosphine oxide **30 (Scheme 13)**.

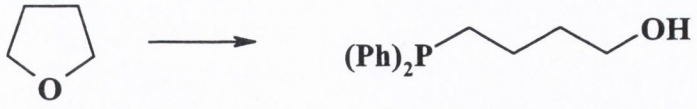
Cleavage of tetrahydrofuran using triphenyldibromophosphorane



Scheme 13

The phosphine **31** was synthesised by Mann *et al.*[21] by refluxing *n*-BuLi and diphenylphosphine (which yields Ph_2PLi *in situ*) with tetrahydrofuran, although the yield (22%) was quite poor **(Scheme 14)**.

Ring-opening reaction of tetrahydrofuran using *n*-BuLi and diphenylphosphine



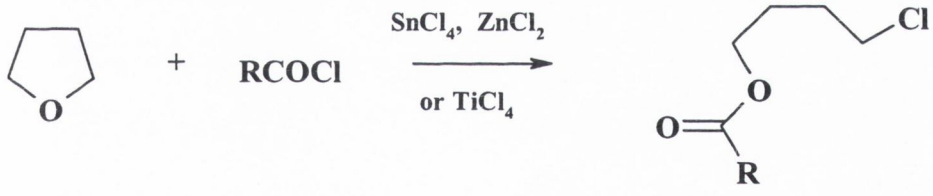
(9) (31)

Scheme 14

1.1.4 Lewis acid-catalysed acylative cleavage of hydrofurans

Underwood *et al.*[22] investigated some cleavage reactions of acyclic ethers, mainly diethyl ether, using a variety of acid chlorides together with zinc chloride as catalyst. These reactions gave alkyl esters as products. Cloke *et al.*[23] then carried out similar experiments on tetrahydrofuran **(Scheme 15)** and some of its substituted derivatives.

Lewis acid-catalysed cleavage of tetrahydrofuran with an acyl chloride



(9) (32) (33)

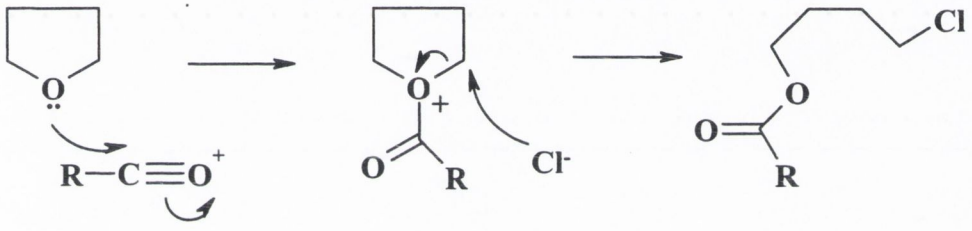
Scheme 15

Here, tetrahydrofuran was reacted with an acyl chloride **32** in the presence of various Lewis acids, particularly zinc chloride. When the amount of Lewis acid specified by Underwood was used, only 10% of the desired product **33** was obtained, although this yield was improved when the quantity of zinc chloride was reduced. This ring-opening reaction has also been carried out using various other Lewis acids such as $SnCl_4$ and $TiCl_4$.[15]

The ring-opening reactions described above probably occur *via* acylium **34** and acyloxonium **35** ion intermediates **(Scheme 16)**. The acylium species is well documented in Friedel-Crafts acylation chemistry and is likely to be formed in the presence of catalytic amounts of Lewis acid **36**.

Mechanism of reaction shown in Scheme 15

(32) **(36)** **(34)**

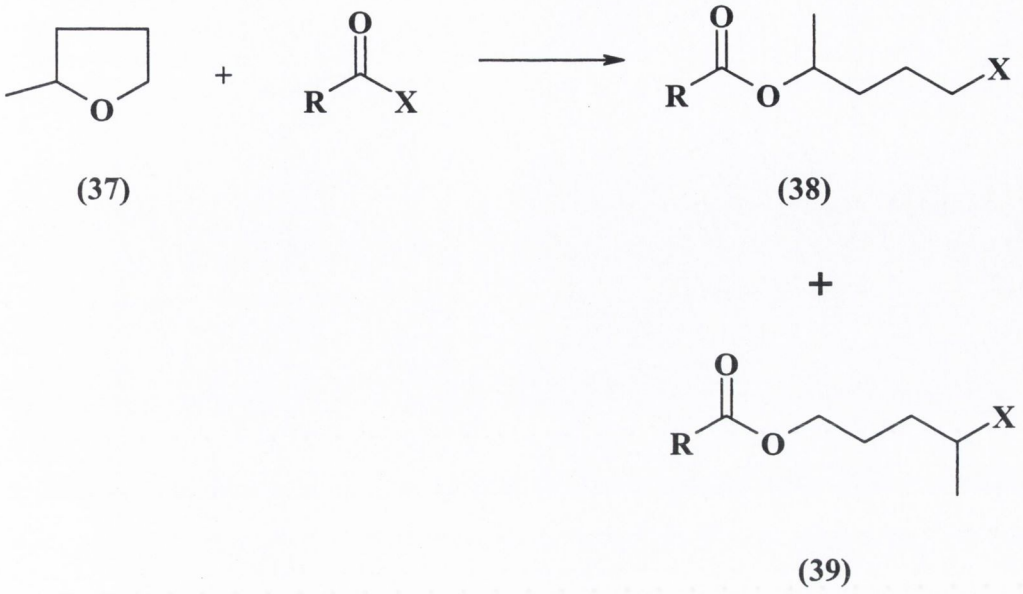


(35) **(33)**

Scheme 16

If the tetrahydrofuran is unsymmetrically substituted, *e.g.* as in 2-methyltetrahydrofuran **37**, acylative cleavage can yield both of the possible products **38** and **39 (Scheme 17)**.

Regioselective ring-opening of unsymmetrical tetrahydrofurans

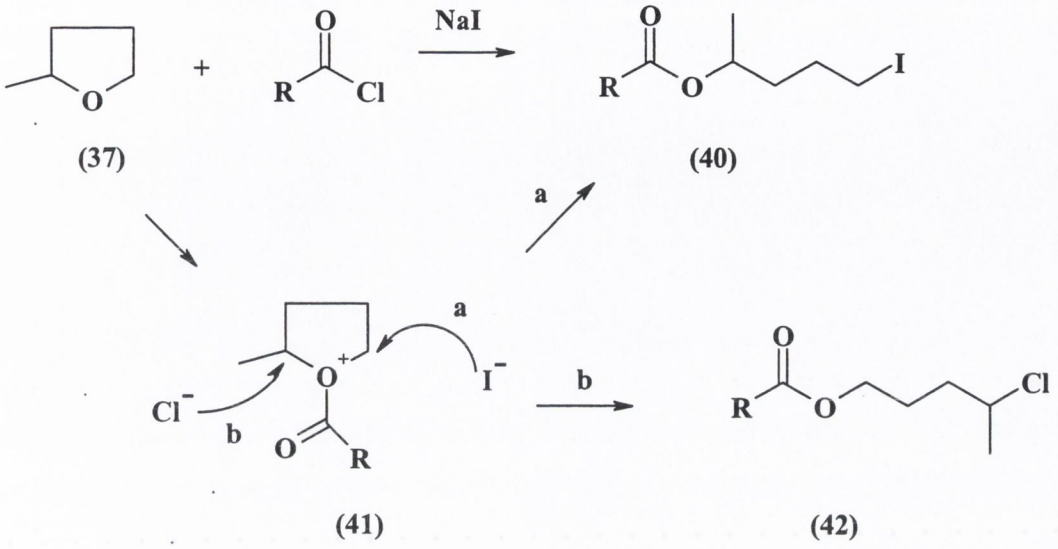


(37) (38) (39)

Scheme 17

Regioselective ring-opening of unsymmetrical tetrahydrofurans has been achieved by careful control of reaction conditions. Amoroux *et al.*[24] found that reaction of 2-methyltetrahydrofuran **37** with an acyl chloride in the presence of sodium iodide gave the primary iodide **40** (pathway a) as the predominant product **(Scheme 18)**. This primary iodide is formed by S_N2 reaction of iodide ion at the less hindered carbon atom α to the tetrahydrofuryl oxygen of the acyloxonium intermediate **41**. When sodium iodide is absent the major product is the secondary chloride **42** (pathway b). These authors suggest that this is due to the fact that chloride is a weaker nucleophile than iodide ion, and so S_N2 attack is disfavoured.

Mechanism of reaction of 2-methyltetrahydrofuran with an acyl chloride in the presence of sodium iodide

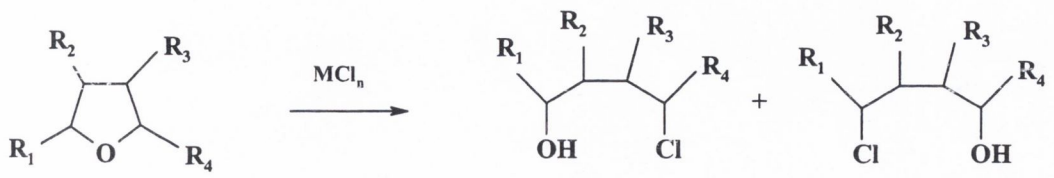


(37) (40) (41) (42)

Scheme 18

The cleavage of cyclic ethers has also been carried out without the presence of a source of acylium species, *i.e.* in the presence of a metal halide alone.[25] Little regioselectivity is achieved in these reactions which poses a problem if unsymmetrically substituted tetrahydrofuran derivatives such as **43** are the substrates as this results in a mixture of the products **44** and **45 (Scheme 19)**.

Cleavage of unsymmetrically substituted tetrahydrofuran without a source of acylium species

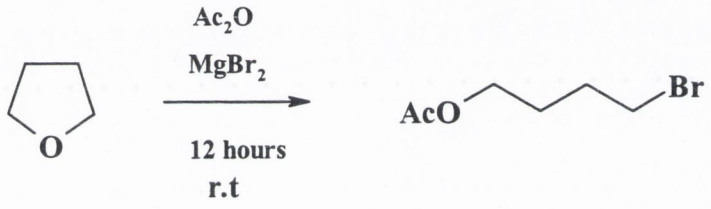


(43) (44) (45)

Scheme 19

Cleavage of the tetrahydrofuran ring has also been carried out using acyl halides without a Lewis acid being present but with the use of high pressures.[26] The main Lewis acids that were used in the work described above are $ZnCl_2$, $SnCl_4$ and $TiCl_4$. Aluminium chloride has also been used but this has been found to cause violent reactions and to give low yields.[27] However, magnesium bromide in the presence of acetic anhydride[4] gives better results **(Scheme 20)**, although various magnesium salts have been reported to be quite ineffective as cleavage catalysts.[28]

Ring-opening of tetrahydrofuran using acetic anhydride in the presence of magnesium bromide



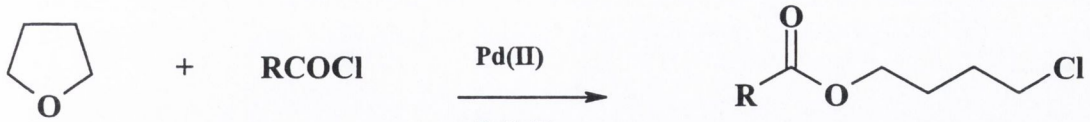
(9) (46)

Scheme 20

1.1.5 Cleavage using tri-organotin halides and Pd(II) complexes

Pri-Bar *et al.*[5] showed that tetrahydrofuran **9** could be cleaved using an acyl halide in the presence of catalytic amounts of a Pd(II) complex and a trialkyltin halide to give compounds of the form **47 (Scheme 21)**.

Cleavage of tetrahydrofuran with an acyl halide in the presence of trialkyltin halide and a palladium(II) complex as catalyst



(9) (47)

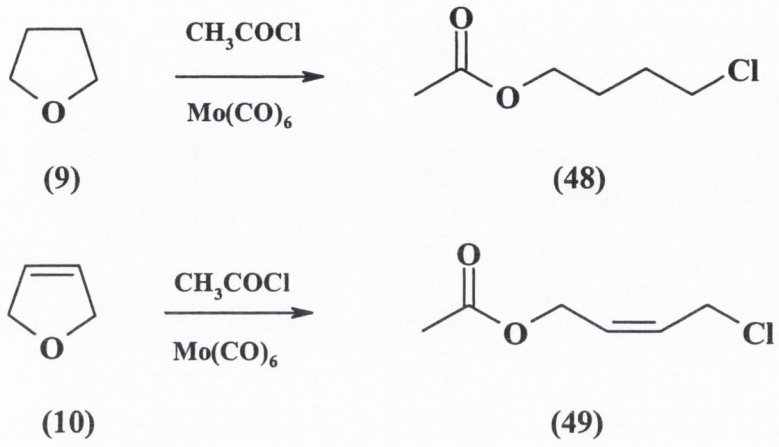
Scheme 21

These reactions were performed at 63 °C using benzylchloro*bis*(triphenyl phosphine)palladium(II) as catalyst, with benzoyl chloride as the acylating agent. The presence of a catalytic amount of a triorganotin halide was found to increase the rate of reaction. This method of ring-cleavage is valuable because certain functional groups, *e.g.* olefins, ketones, benzyl halides and esters that are sensitive to reductive or acidic cleavage methods can be present in the substrate.

1.1.6 Use of Group VI metal carbonyls as catalysts

As a result of the general interest in the cleavage reactions of ethers, coupled with the use of Group VI metal carbonyls as catalysts[29] and stoichiometric reagents[30] in organic synthesis, Alper and Huang carried out cleavage reactions of cyclic ethers with acyl halides using such compounds as catalysts.[31] These cleavage reactions were carried out on 2,5-dihydrofuran **10** and tetrahydrofuran **9** along with some of its substituted derivatives using a variety of acyl chlorides along with the metal carbonyls $Mo(CO)_6$, $W(CO)_6$, and $Cr(CO)_6$ to give chloroesters *e.g.* **48** and **49** **(Scheme 22)**. It was found that yields decreased in the order $Mo(CO)_6 < W(CO)_6 < Cr(CO)_6$.

Cleavage of tetrahydrofuran and 2,5-dihydrofuran using Group VI metal carbonyls as catalysts



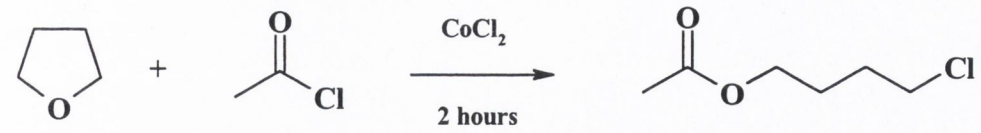
Scheme 22

The formation of the (*Z*)-alkene **49** from 2,5-dihydrofuran is of particular interest because of the retention of stereochemistry of the double bond.

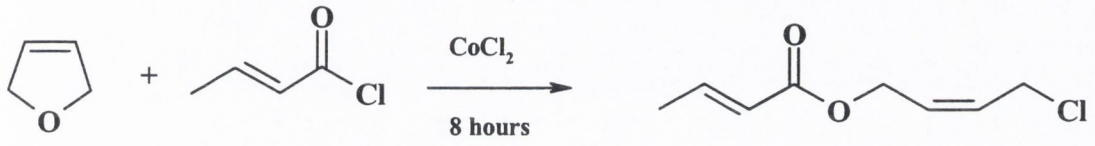
1.1.7 Cobalt(II) chloride-catalysed cleavage of ethers

Iqbal *et al.*[6,32] used $CoCl_2$ to assist the cleavages of tetrahydrofuran **9** and of 2,5-dihydrofuran **10** with acyl halides to give, for example, the chloroesters **50** and **51** **(Scheme 23)**.

Cobalt(II) chloride catalysed cleavage of tetrahydrofuran and 2,5- dihydrofuran



(9) **(50)**



(10) **(51)**

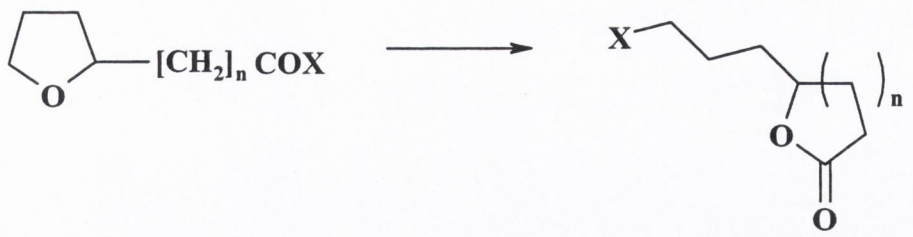
Scheme 23

This is a successful reaction, utilising mild conditions and giving high yields. Once again retention of (*Z*)-geometry is observed in the formation of the ester **51**.

1.1.8 Intramolecular ring-cleavage reactions of tetrahydrofurans

Because of the value of the ring-opening reactions of tetrahydrofuran with acyl halides or anhydrides in the presence of Lewis acids, it was thought[33] that an intramolecular version of the process could be possible. It was considered that using tetrahydrofurylalkanoic acids **52** as substrates would lead to the formation of lactones of the type **53 (Scheme 24)**.

Intramolecular ring-cleavage of tetrahydrofuran



(52) **(53)**

Scheme 24

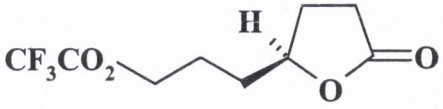
When the (*S*)-acid **54** was mixed with one equivalent of trifluoroacetic anhydride in dry chloroform at 0 °C the mixed anhydride **55** was formed **(Scheme 25)**.

Conversion of a tetrahydrofurylalkanoic acid to its trifluoroacetic mixed anhydride

(54) **(55)**

Scheme 25

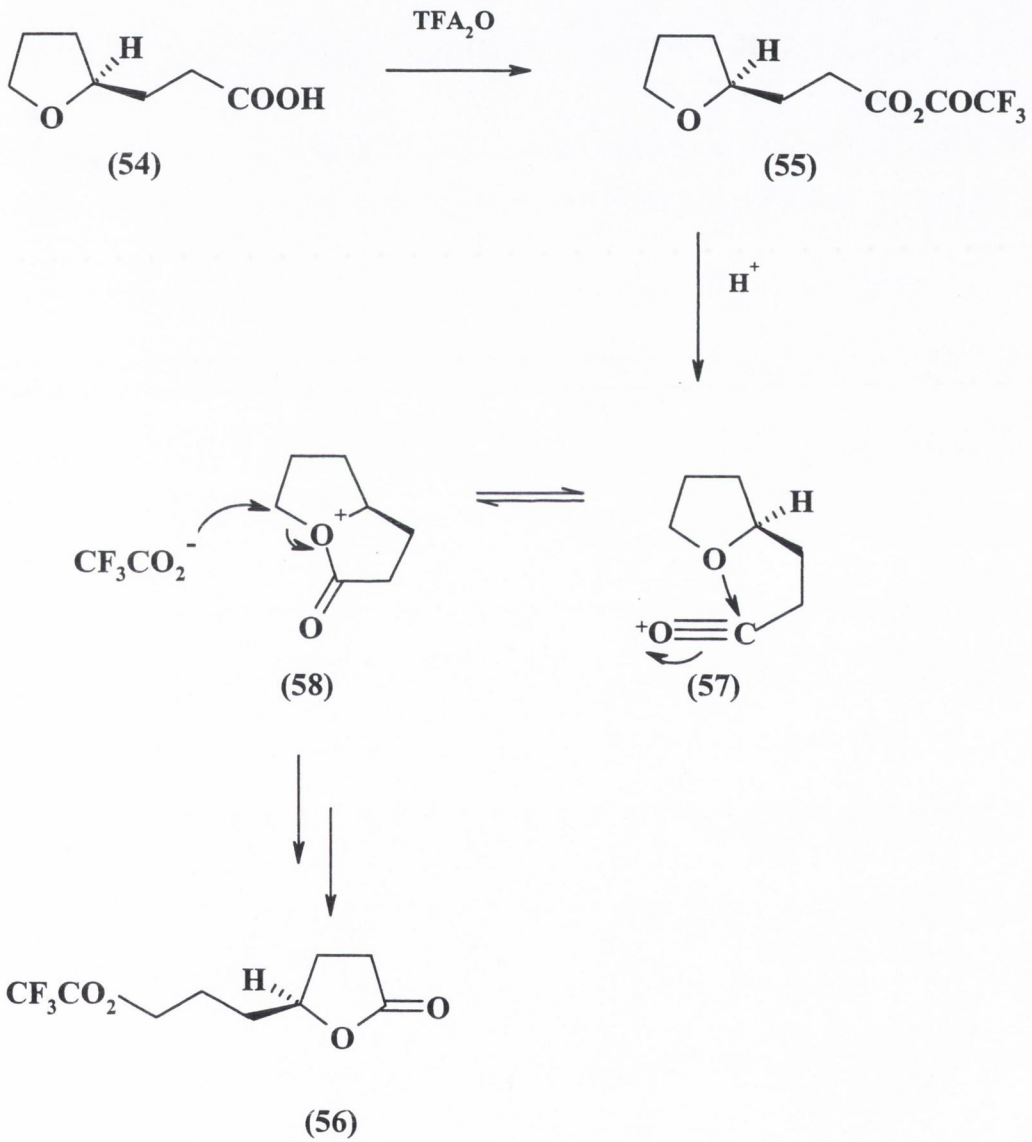
This compound **55** then formed the furanone **56** when heated with a little trifluoroacetic acid.



(56)

The authors[33] found that the overall reaction took place *via* the mechanism shown in **Scheme 26**, *i.e.* the mixed anhydride **55** forms the acylium ion **57** which exists in equilibrium with the acyloxonium ion **58**. The acyloxonium ion **58** undergoes regiospecific ring-cleavage by trifluoroacetate ion, which leads to the formation of the lactone **56**.

Mechanism of reaction shown in Scheme 25



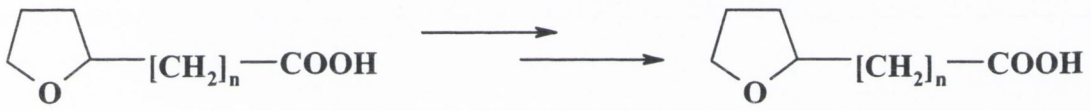
Scheme 26

Many natural products, for example, certain insect pheromones, include the dihydrofuran-2-(*3H*)-one functionality so this result had a very important place in natural product synthesis.

The same investigators[34] then went on to see how this intramolecular reaction would progress with tetrahydrofurans bearing longer side-chains in the hope that this would lead to the formation of macrolides.

In an early example, the chain-extended acid **59** was made **(Scheme 27)** from the acid **60** by the sequence of reactions $RCO_2H \rightarrow RCH_2OH \rightarrow RCH_2OTs \rightarrow RCH_2I \rightarrow RCH_2CH(CO_2Et)_2 \rightarrow$ **59**.

Chain extension of a tetrahydrofurylalkanoic acid

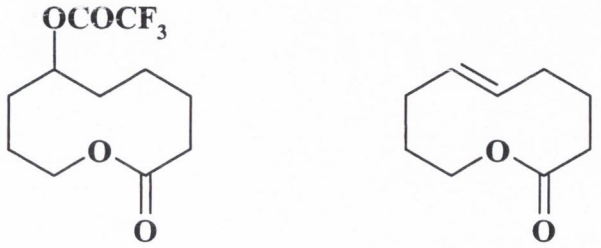


n= 2 **n= 4**

(60) **(59)**

Scheme 27

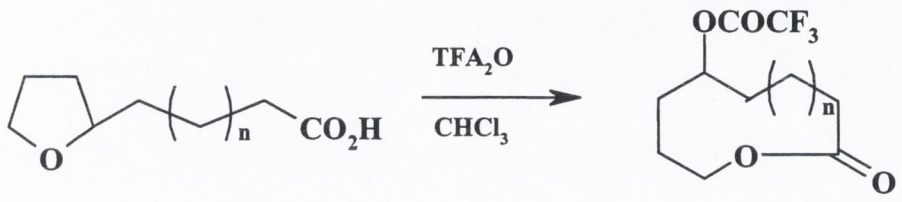
The acid **59** was then reacted as before with one equivalent of trifluoroacetic anhydride in dry chloroform to give the derived mixed anhydride. Heating of this in chloroform solution with some trifluoroacetic acid led to formation of the 10-membered lactones **60** and **61** in a 4:1 ratio.



(60) **(61)**

This methodology was subsequently extended to a series of ω-(tetrahydro-2'-furyl)alkanoic acids of differing chain lengths **62** to give lactones of various sizes **63** **(Scheme 28)** as shown in **Table 1.1**.[35]

Synthesis of lactones from ω- (tetrahydro-2'-furyl)alkanoic acids



(62) **(63)**

Scheme 28

Table 1.1

Yields of lactone(s) 63 obtained from acids 62 (n=1-6)

Acid 62 (n =)	Product 63 ring size	% Yield
1	9	60
2	10	60
3	11	60
4	12	51
5	13	2.5
6	14	4

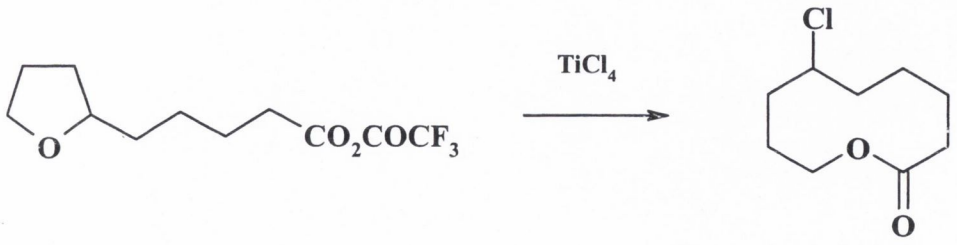
It is clear that the cleavage of tetrahydrofuran compounds bearing side chains has been a valuable tool for the synthesis of lactones. The ether cleavage step in the reaction is very important so it appears worthwhile to look at how other cyclic ethers react under the same conditions.

As described above, many ring-opening reactions have been carried out on hydrofuran systems to yield many different types of compounds. The tetrahydrofuran system has been well-exploited but the same is not true of 2,5-dihydrofuran **10**. In the present work it is planned to open that ring system using acyl chlorides with zinc chloride as catalyst and to investigate the reactivity and uses of the resulting compounds.

1.2 Ring-opening reactions of an ω-(tetrahydro-2'-furyl)alkanoic-trifluoroacetic mixed anhydride in the presence of sodium iodide

Ring-opening reactions have also been carried out using the highly successful mixed anhydride methodology but in the presence of added sodium iodide to give similar lactone products[35] with an iodo group in the place of a trifluoroacetoxy substituent. This work originated with synthesis of the chlorononanolide **64**. This compound was synthesised by treatment of the mixed anhydride **65** in chloroform with an excess of titanium tetrachloride **(Scheme 29)**.

Synthesis of chlorononanolide from a mixed anhydride in the presence of titanium tetrachloride

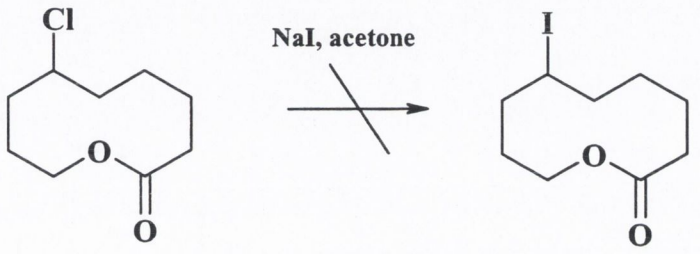


(65) **(64)**

Scheme 29

It was next intended to synthesise the iodo-lactone 6-iodononanolide **66** by Finkelstein[36] reaction of the chlorolactone **64** with sodium iodide in acetone **(Scheme 30)**. However this was unsuccessful, a result that was attributed to the fact that the conformation of the molecule **64** is unable to facilitate a S_N2 reaction mechanism.

Attempted conversion of chlorononanolide to iodononanolide

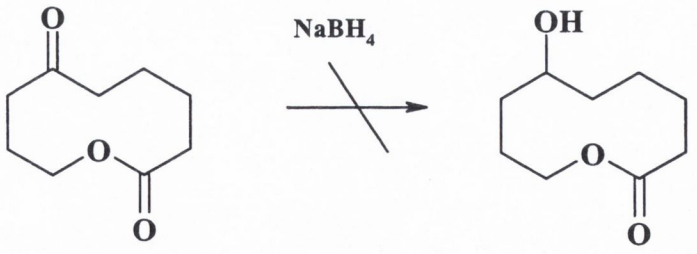


(64) **(66)**

Scheme 30

This explanation may also explain the findings of Borowitz *et al.*[37] who attempted to convert the ketone **67** to the alcohol **68** using sodium borohydride but failed to do so **(Scheme 31)**.

Attempted reduction of ketone 67 to its corresponding alcohol

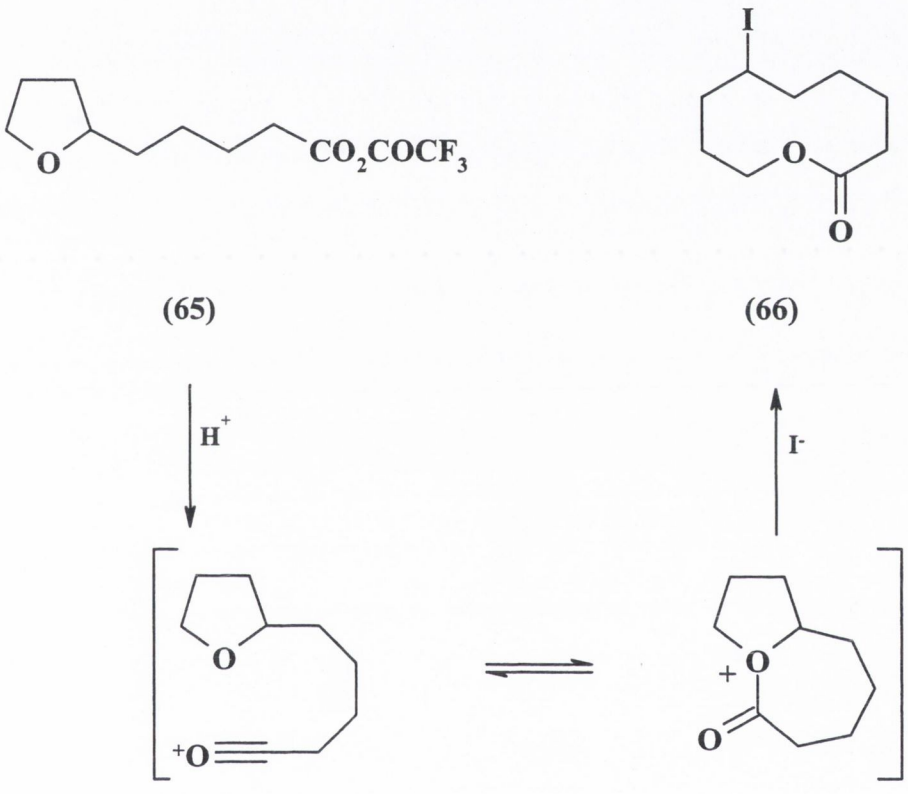


(67) **(68)**

Scheme 31

It was then found[35] that the iodo-lactone **66** could be synthesised directly by reacting the mixed anhydride **65** with sodium iodide in acetone. This reaction was considered to proceed in a similar way to that described in **Scheme 26**, *i.e.* that the mixed anhydride **65** leads to the formation of the acylium ion **69** and/or the acyloxonium ion **70** which are then attacked by the nucleophilic iodide ion.

Mechanism of the synthesis of iodononanolide from a mixed anhydride



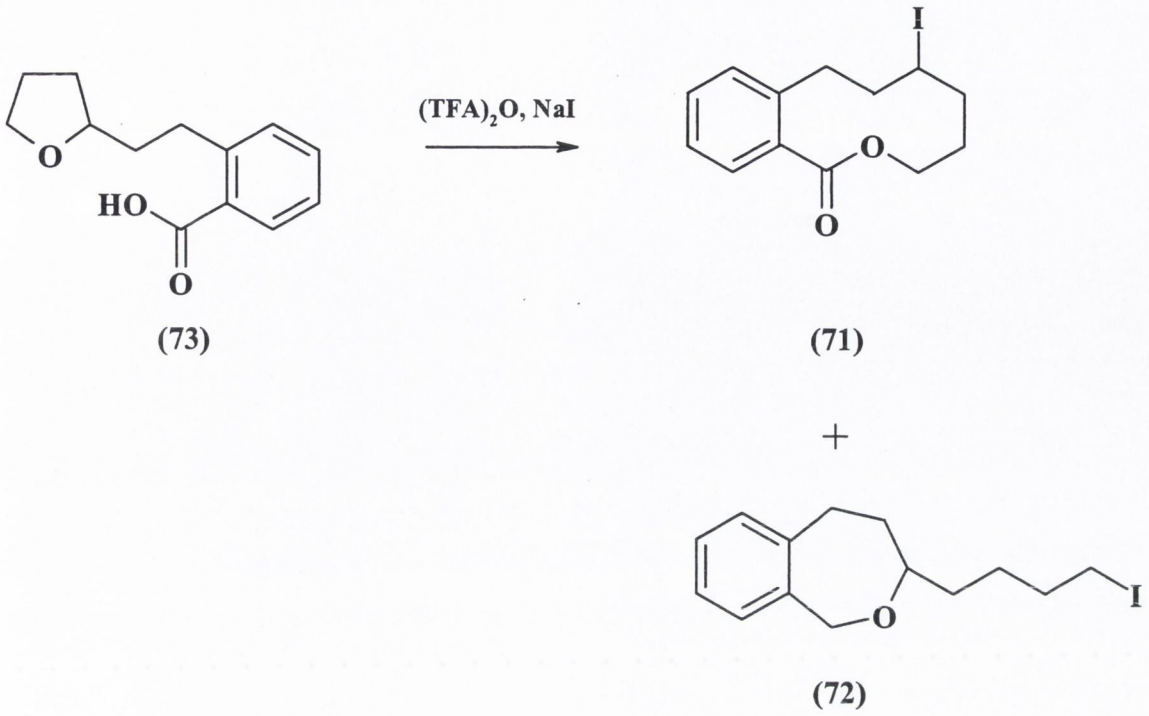
(65) **(66)**

(69) **(70)**

Scheme 32

This general methodology was also applied to the synthesis of benzo-fused lactones of the form **71** and **72** from, *e.g.*, the acid **73**. The iodo substituent of **71** could be easily removed either by reduction[38] or by elimination[35] to give the corresponding saturated or unsaturated lactones.

Synthesis of benzo-fused lactones with iodo substituents



(73) (71) + (72)

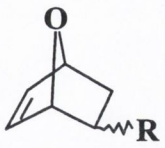
Scheme 33

The reasoning behind the methodology described above is that iodide ion is a much stronger nucleophile than is trifluoroacetate ion. The ring-opening reaction using a mixed anhydride such as **65** in the presence of sodium iodide had only been applied to intramolecular work so the area of intermolecular reactions of this type was still open to investigation.

1.3 Oxabicyclic compounds

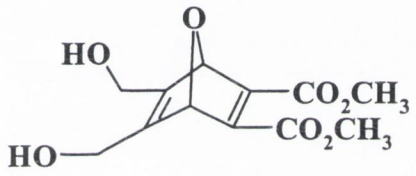
In the synthesis of macrolides two approaches are usually used. Firstly, compounds from the so-called "chiral pool" are used as a source of starting materials. These compounds include terpenoids, amino-acids and especially, carbohydrates. Another approach is to construct highly-substituted precursors that often contain multiple rings, which can then be cleaved to give stereochemically complex molecules. In this respect, six membered rings are the most widely used due to their pronounced conformational preferences and facility to undergo stereoselective reactions.

Accordingly, oxabicyclic compounds of the type **74** have been found to be very useful in the synthesis of natural products.[39]

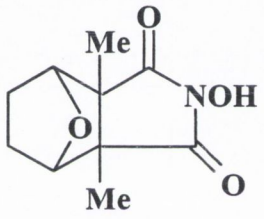


(74)

Some 7-oxabicyclo[2.2.1]heptane derivatives have shown biological promise, possessing anti-tumour[40], *e.g.* 2,3-bis(acetoxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-5,6-dicarboxylate **75**, or anti-inflammatory[41] properties, *e.g.* *N*-hydroxycantharidinimide **76**.



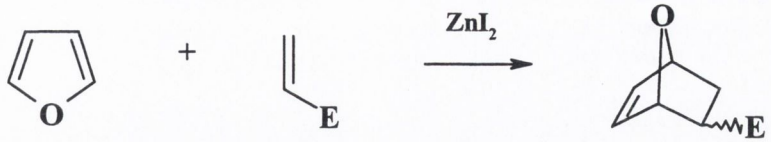
(75)



(76)

These 7-oxabicyclo[2.2.1]heptane compounds are generally formed **(Scheme 34)** by the Diels-Alder reaction of furan **77** with an alkene **78** using a Lewis acid such as zinc iodide as catalyst.[42] A catalyst is required due to the fact that furan is not very reactive as a diene because on cycloaddition its aromaticity is lost. The products **79** from these reactions possess ether, alkene and other electron-withdrawing functionalities, which makes them quite versatile substrates for further transformations.

Formation of 7-oxabicyclo[2.2.1]hept-2-enes from reaction of furan with an alkene in the presence of a Lewis acid

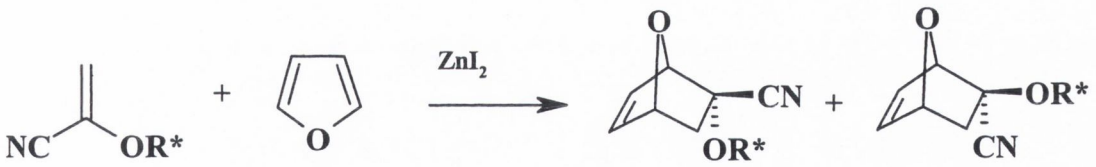


(77) **(78)** **(79)**

Scheme 34

The product in these Diels-Alder reactions can be the *endo* (usually predominant) or *exo* diastereoisomer, or a mixture of both.[43] Changes in temperature, pressure and catalyst have been shown to alter the nature and yield of the product.[44] These compounds have been shown to be capable of being made optically pure quite easily thus enabling them to be used as chiral relay compounds in enantioselective chemistry.[45] For example, as shown in **Scheme 35**, a Diels-Alder reaction was carried out[45] between furan **77** and 1-cyanovinyl (1R')-camphanate **80**.

Reaction of furan with 1-cyanovinyl (1R')-camphanate with zinc iodide as catalyst



(80) **(77)** **(81)** **(82)**

R*= (1*R*)-camphanoyl

(83) **(84)**

The most polar product isomer **81** (by HPLC) could be then recrystallised from hexane-ethyl acetate, whereas isomers **82, 83** and **84** decomposed to give back furan **77** and the alkene **80** which could be recycled to give more of the product **81**.

The nitrile adduct **81** could then be converted to the ketone **85** by saponification **(Scheme 36)**. Compounds of this form are called "naked sugars" as they possess the skeleton of a sugar and can easily be converted into a sugar by modification of the functional groups that are present.

Saponification of nitrile adduct obtained in Scheme 35

(81) **(85)**

Scheme 36

1.3.1 Reactivity of 7-oxabicyclo[2.2.1]hept-2-enes

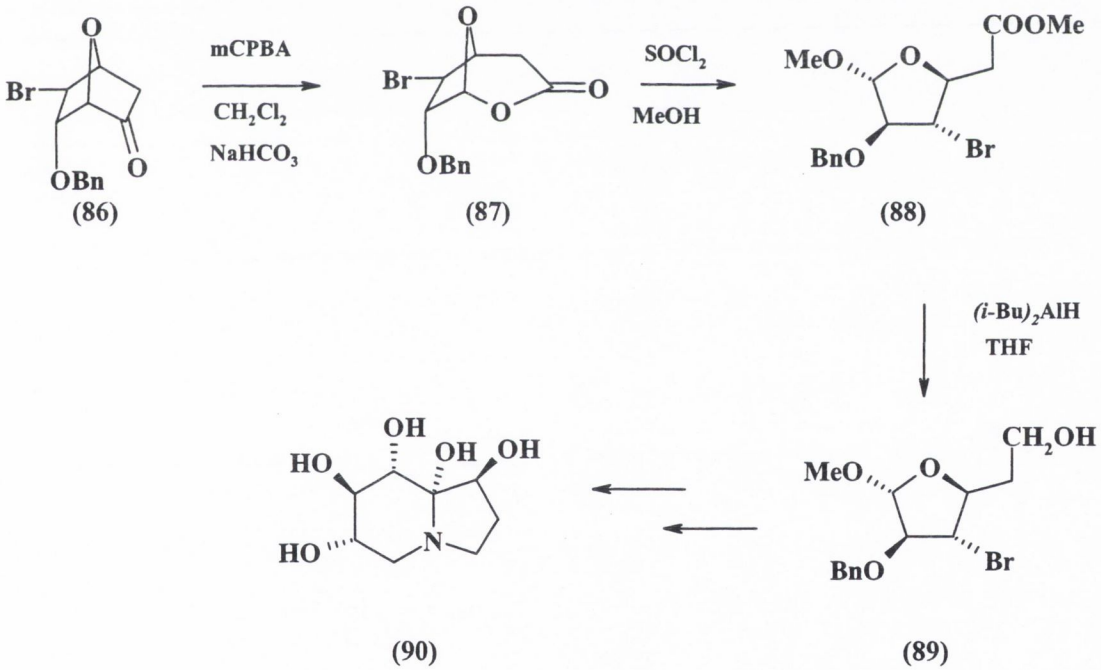
The main reaction which has been carried out on these oxabicyclic compounds **74** is cleavage of one of the bridging oxygen-carbon bonds. An increased interest in ring-cleavage reactions of oxabicyclic compounds commenced in the 1970s and, with improvements that were made to the Diels-Alder cycloaddition reactions of furan, these became attractive processes.

The main pioneers of ring-opening reactions of oxabicyclic Diels-Alder adducts have been the groups of Vogel[45], Lautens[46] and Arjona[47]. This cleavage has been accomplished under acidic, basic or reductive conditions. Additionally, chemistry has been carried out on the alkene function prior to ring-cleavage. In particular, the stereochemistry and regiochemistry of electrophilic additions to the alkene double bond can be controlled by modifying the nature of the substituents at C-2 of

thestarting Diels-Alder adducts. Thus, the cleavage of an ether bond in the 7-oxabicyclo[2.2.1]heptyl system generates a cyclohexyl derivative, which may be highly substituted. Also, due to the facial bias inherent in electrophilic additions to 7-oxabicyclo[2.2.1]hept-2-enes, the stereochemistry of the product cyclohexene can be controlled before ring opening occurs.

If the oxabicyclic substrate contains a carbonyl group α to the oxygen bridge, it can be regiospecifically cleaved by a Baeyer-Villiger oxidation-hydrolysis sequence **(Scheme 37)**.

Baeyer-Villiger oxidation-hydrolysis sequence of a oxabicyclic substrate



Scheme 37

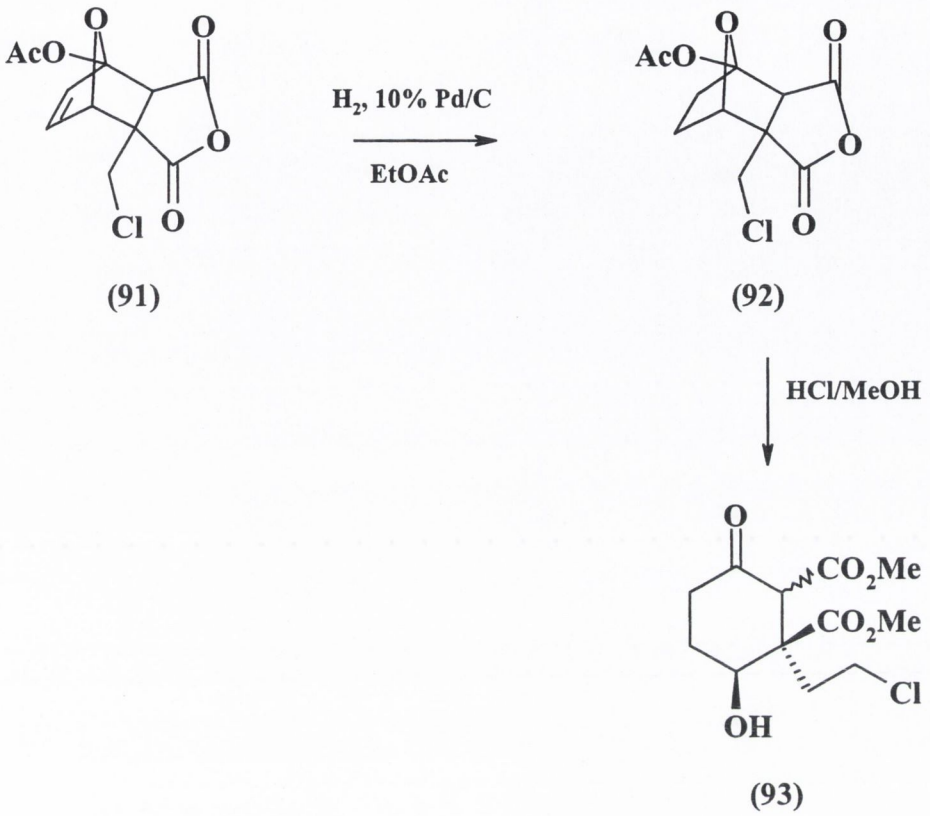
The Baeyer-Villiger product **87** arises *via* migration of the bridgehead carbon atom. The migratory ability of this carbon is enhanced due to through-bond interaction of the bridging oxygen with the carbonyl group. For example, castanospermine **90**,

which is a polyhydroxylated indolizidine isolated from the tree *Castanospermum australe*, and which possesses anti-cancer[48] and anti-AIDS properties[49] due to its ability to inhibit glucosidases, was synthesised by Vogel *et al.*[50] as shown in **Scheme 37**. This highly stereoselective method is very advantageous as it provides an alternative route to that employed previously which used carbohydrates as starting materials.[50] This methodology could also provide a route to give the enantiomer of **90** and other derivatives. Vogel has used this technique extensively. For example, he used similar chemistry in the syntheses of several natural and unnatural sugars, *e.g.* D- and L- allose and D- and L-talose.[51]

Gravel and Brisse[52] used the Diels-Alder adduct **91** obtained by reaction of 2-acetoxyfuran with chloromethylmaleic anhydride to construct 2,3-difunctionalised-4-hydroxycyclohexanones. The saturated compound **92** obtained by hydrogenation of **91** was further processed to form the compound **93** as shown below **(Scheme 38)**.

The placement of an oxygen substituent at the bridgehead (*i.e.* the construction of a bicyclic ketal or masked hemiketal) enabled the bridging ether bond to be cleaved by solvolysis under acidic conditions. The conversion of **92** into **93** was also successful using a methanolic solution of sodium methoxide.

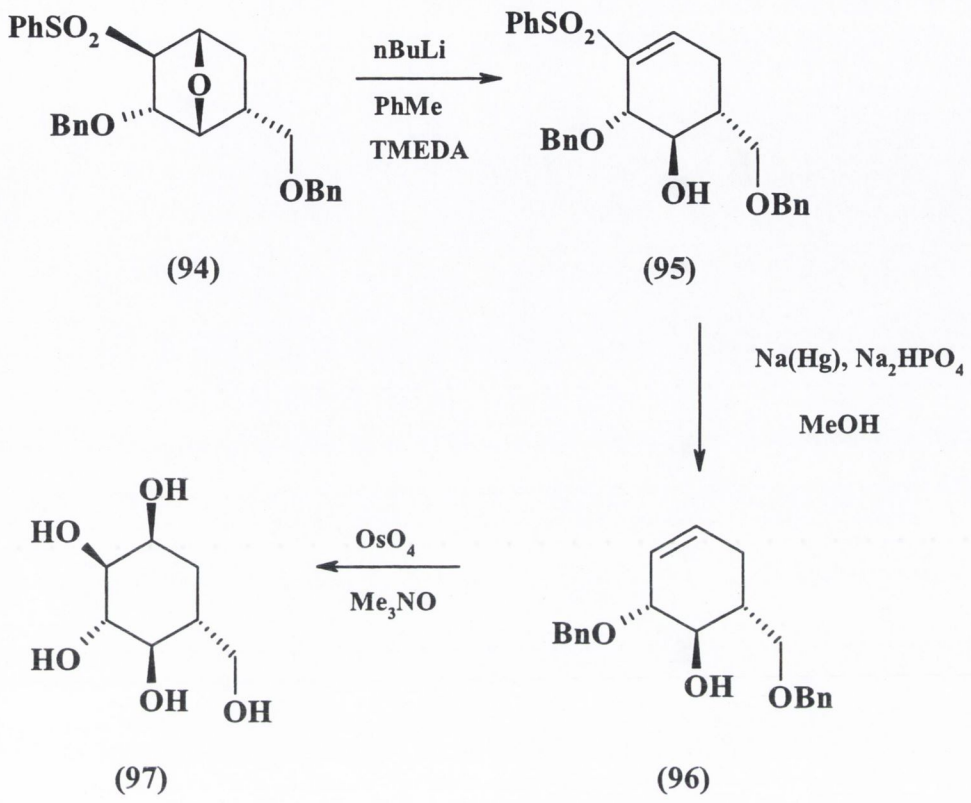
Construction of a 2,3-difunctionalised-4-hydroxycyclohexanone from a Diels-Alder adduct



Scheme 38

Acena *et al.*[47] used the sulfonyl-substituted 7-oxabicyclo[2.2.1]heptane **94** in the synthesis of some pseudo-sugars. On addition of n-BuLi to **94** regioselective ring-opening of the bridging C-O bond ensued yielding **95**. After directing the ring opening reaction the sulfonyl group was easily removed to give the alkene **96** which was then dihydroxylated to give **97 (Scheme 39)**.

Reaction of a sulfonyl-substituted 7-oxabicyclo[2.2.1]heptane to give a pseudo-sugar

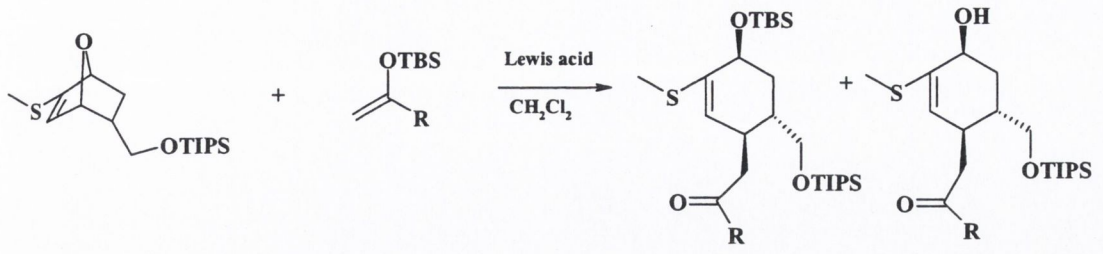


(94) (95) (96) (97)

Scheme 39

Yamamota and Nagasaka[53] also used sulfur components in their work. The authors introduced an activating alkylthio group at the C-3 position of the furan used in the Diels-Alder reaction. The products **98** of the Lewis-acid catalysed reaction between 3-methylthiofuran and various dienophiles bearing silyl enol ether groups reacted with the silyl enol ether **99** under Lewis acid catalysis to give, regioselectively, the substituted compounds **100** and **101 (Scheme 40)**.

Reaction of a Diels-Alder adduct with a silyl enol ether

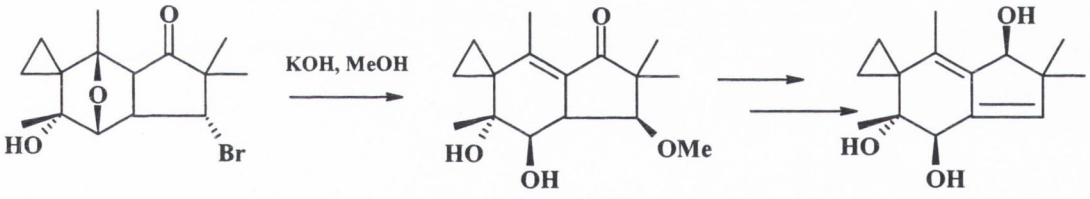


(98) (99) (100) (101)

Scheme 40

A base-induced cleavage of the ether functionality of the compound **102** resulted in the formation of **103**, which was converted into Illudin M **104** *via* a six-step synthesis **(Scheme 41)**.[54] This was a huge improvement on an earlier synthesis which was fifteen steps long and which was not applicable to other illudin analogues.

Synthesis of Illudin M from an oxabicyclic substrate

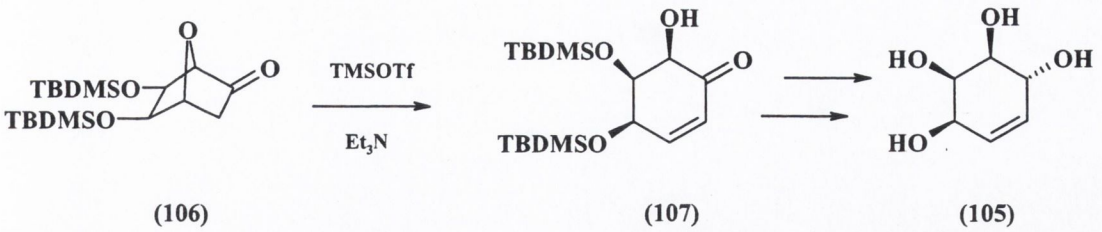


(102) (103) (104)

Scheme 41

The first total synthesis of optically active (–)-conduritol **105** was accomplished by Vogel from the "naked sugar" **106** by using a weak base together with an oxaphilic reagent to effect ring-opening. Thus, the oxygen bridge of **106** was cleaved in the presence of triethylamine and trimethylsilyl triflate to give the enone **107** that was used as an intermediate in the synthesis of **105 (Scheme 42)**.[55]

Synthesis of (–)-conduritol from a "naked sugar"

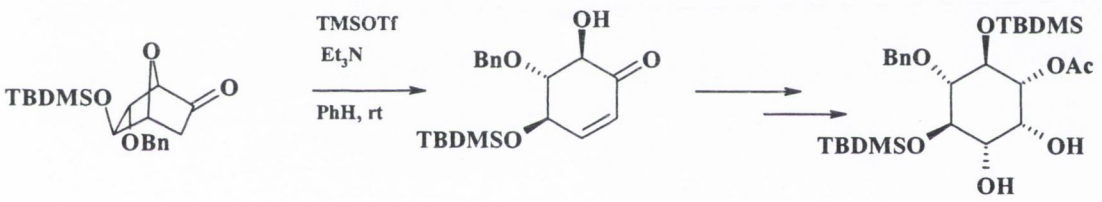


(106) (107) (105)

Scheme 42

The same methodology was used to ring-open the ketone **108**, to yield **109**, further processing of which led to myo-inositol derivatives such as **110 (Scheme 43)**.[56]

Synthesis of myo-inositol derivatives

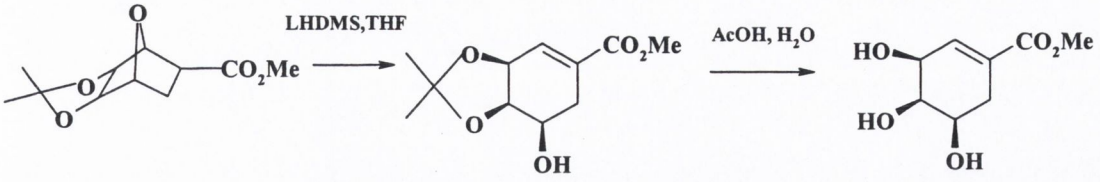


(108) (109) (110)

Scheme 43

The enantiomerically pure oxabicyclo[2.2.1]heptane **111** was treated with lithium hexamethyldisilazide (LHMDS) to give the cyclohexenol **112** which could be deprotected to form methyl (+)-5-epi-shikimate **113 (Scheme 44)**. This compound was then further transformed to give several optically active pseudo sugars.[57]

Reaction of an oxabicyclo[2.2.1]heptane to give methyl (+)-5-epi-shikimate



(111) (112) (113)

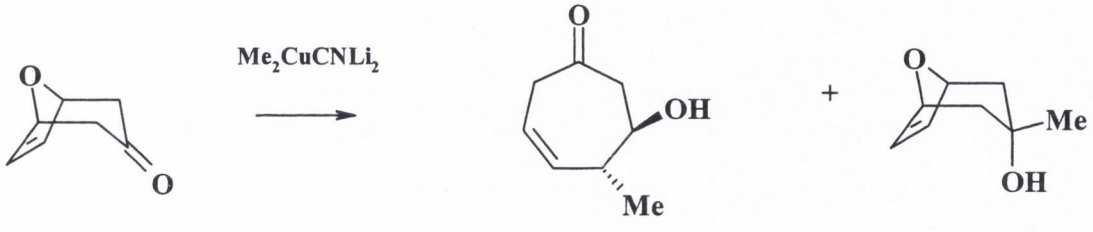
Scheme 44

1.3.2 Ring cleavage of oxabicyclic compounds using organometallic reagents

Lautens and co-workers[46] investigated the use of organocuprate reagents for ring-opening reactions of oxabicyclic compounds.

The first organocuprate reaction to be carried out with an oxabicyclic compound was on the ketone **114**, and the ring-opened product **115** was obtained in only 5 % yield **(Scheme 45)** though this improved slightly when the temperature was increased from 0 °C to room temperature. The major product was the carbonyl addition product **116.** The carbonyl group was deemed essential for the success of this reaction as derivatives not possessing such functionality failed to react.

Ring-opening reaction of a [3.2.1]oxabicyclic compound using an organocuprate reagent

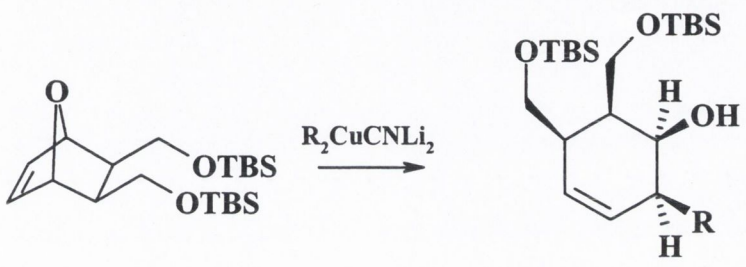


(114) (115) (116)

Scheme 45

Due to the fact that the modified Diels-Alder adduct **117** does not possess a carbonyl group the product **118** in **Scheme 46** was expected to be difficult or impossible to obtain.[58] However, this was not the case, possibly due to the fact that **117** possesses a higher degree of ring strain than **114**.

Ring-opening of a [2.2.1]oxabicyclic compound using an organocuprate reagent

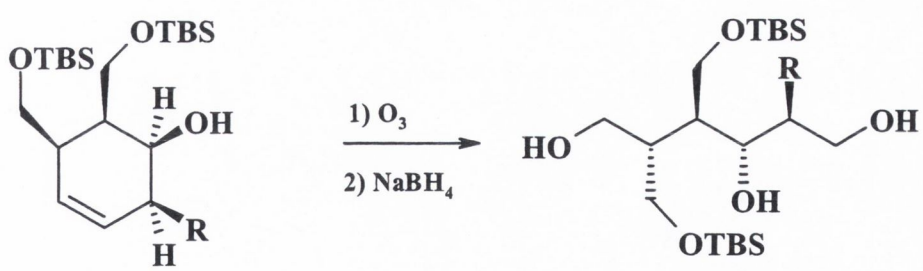


(117) (118)

Scheme 46

Lautens *et al.*[46] then went on to open the monocyclic system of **118** to give the compound **119**, thus generating an acyclic compound with four adjacent stereocentres **(Scheme 47)**.

Conversion of the monocyclic compound obtained in Scheme 46 to an acyclic compound

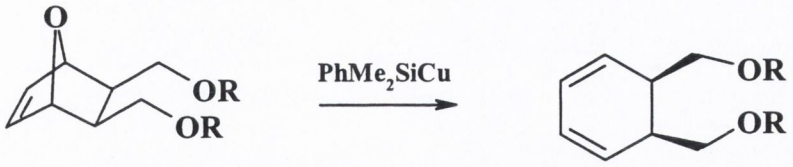


(118) (119)

Scheme 47

Another example of organocopper-mediated ring-opening of the oxabicyclic compound **117** using silylcopper nucleophiles is shown in **Scheme 48**.[59]

Ring-opening of a bicylic compound using a silylcopper nucleophile



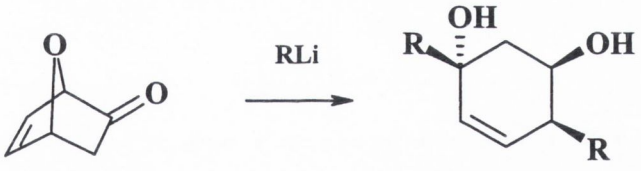
(117) (120)

Scheme 48

In this reaction the compound **117** undergoes tandem ring opening-Peterson elimination yielding the cyclohexadiene **120**. The reaction was also successful when silyllithium nucleophiles were employed.

Another example of a ring-opening by an organolithium reagent is shown in **Scheme 49**. Thus, the ketone **85** formed the substituted six-membered diol **121** when it was reacted with an excess of RLi in pentane.

Ring-opening of a bicylic compound using an organolithium reagent



(85) (121)

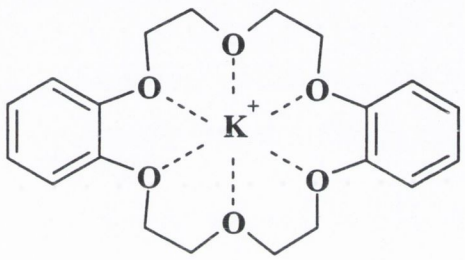
Scheme 49

As described above, ring-opening reactions of oxabicyclic compounds have been very useful in the synthesis of both monocyclic, and acyclic compounds where the maintenance or creation of stereochemistry is very important, due to the possibility of their side-chains affecting the attack of the reactant. In the present work it is planned to react 2-substituted 7-oxabicyclo[2.2.1]hept-2-enes with carboxylic-trifluoroacetic mixed anhydrides, which have been successful in cleaving

tetrahydrofuryl compounds, to synthesise substituted cyclohexanes of definite stereochemistry.

1.4 Macrocyclic complexes

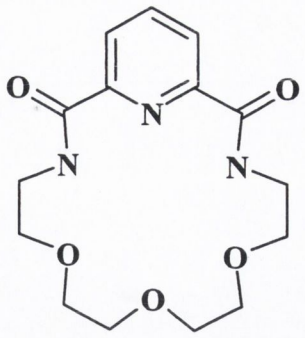
Macrocyclic compounds that incorporate donor atoms into the ring have been attracting intense interest since the chance discovery of crown ethers in 1967 by Pedersen.[60] Thus, dibenzo[18]crown-6 forms a potassium complex **122** as shown.



(122)

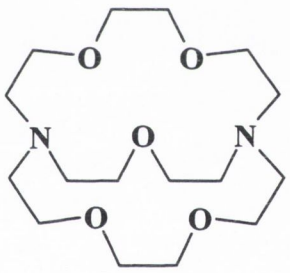
The unusual properties of the crown ethers attracted immediate attention. For example, potassium permanganate is insoluble in benzene but will dissolve if a small amount of uncomplexed crown-6 ether is added. The reason for this is that compounds of this type can act as size-selective ionophores, for metal ions, which can fit snugly into the cavity of the ring.[61] Since Pedersens initial discovery, many related compound classes that have been found to exhibit interesting properties have been synthesised.[62]

For example, coronands such as **123** are cyclic polyethers containing a heteroatom ring.



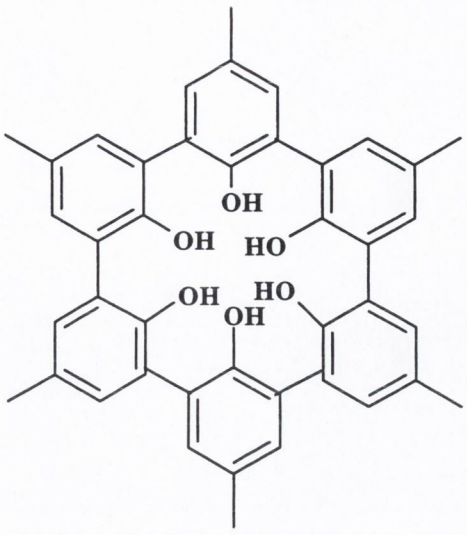
(123)

Cryptands, *e.g.* **124**, are bi- or polycyclic compounds containing any heteroatom, whose ability to bind ions into their cavities is superior to that of monocyclic crown ethers. However, they possess a lower ion size-selectivity and their complexes are less stable due to shielding effects. On the other hand the dissociation rates of these complexes are smaller than those of crown ether complexes.



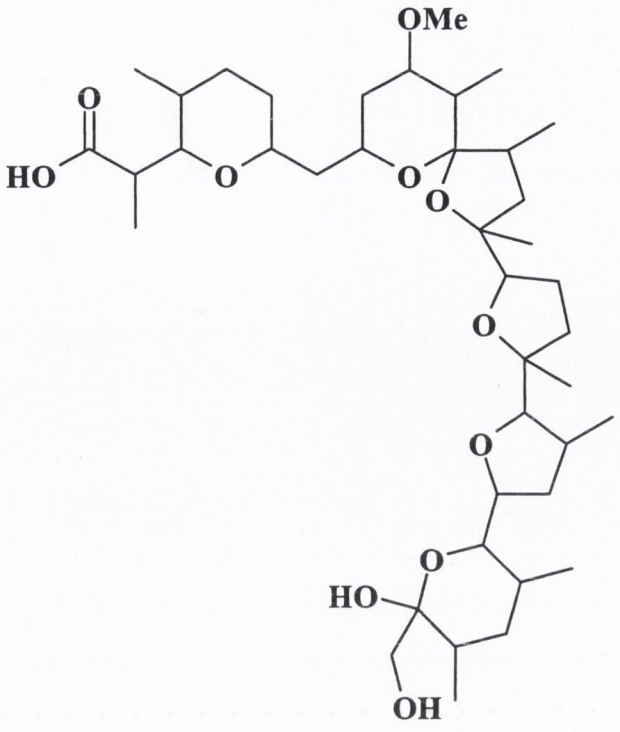
(124)

A spherand, *e.g.* **125**, has a donor centre, which contains substituents that point into the interior of the ring.



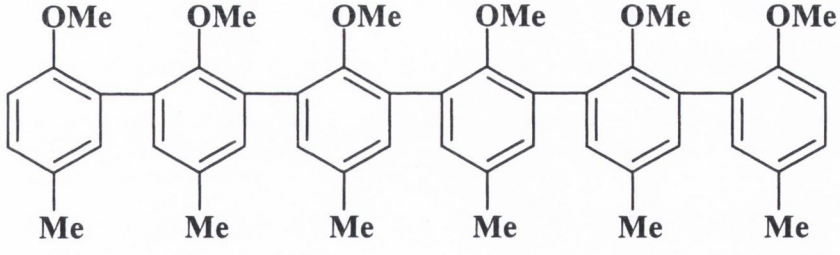
(125)

An open chain analogue of a coronand or a cryptand is called a podand, *e.g.* nigericin **126**, a natural antibiotic that possesses anti-HIV activity.[63] These compounds have pendant binding sites and form complexes with metallic cations.



(126)

The existence and activity of nigericin **126** has prompted chemists to synthesise similar compounds although those that have been made are much less complicated, *e.g.* the podand **127**[64].



(127)

It has been shown that the stability constants of the potassium complexes of acyclic ethers are considerably lower than those of coronands or cryptands **(Table 1.2)**.[65]

Table 1.2

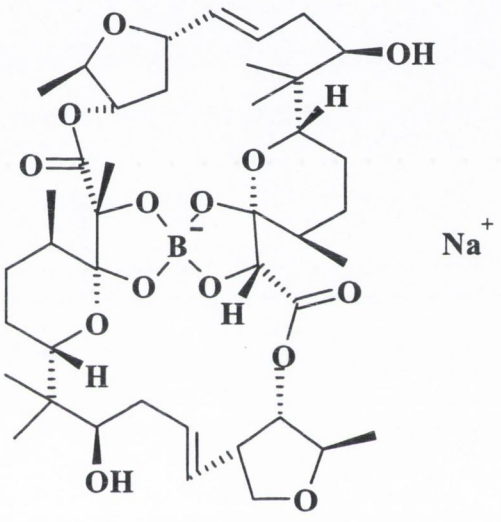
Relative stabilities of ether complexes

Type of ether	Stability constant (kJ mol^{-1})	Type of complex formed
Podand	10^2–10^4	Chelate
Coronand	10^4-10^6	Macrocyclic
Cryptand	10^6–10^{10}	Macrobicyclic

The low stability constants exhibited by complexes formed by podands is due to the fact that most acyclic polyethers do not possess natural intramolecular cavities for binding guests but are capable of building "pseudo cavities" where guest cations can nest. In building these structures a lot of energy is required; firstly to manipulate the compound into a circular type configuration from a linear one and secondly to overcome the lone pair repulsion energy. All this energy is consumed before the cation has bound, and this leads to a very unfavourable entropy of reaction. However acyclic hosts may adopt similar conformations to those of cyclic crown ethers when in the presence of suitable metal cations *e.g.* highly charged lanthanide ions. This extra flexibility can lead to multiple bridging and to helical binding modes, which are unknown for cyclic crown ethers.

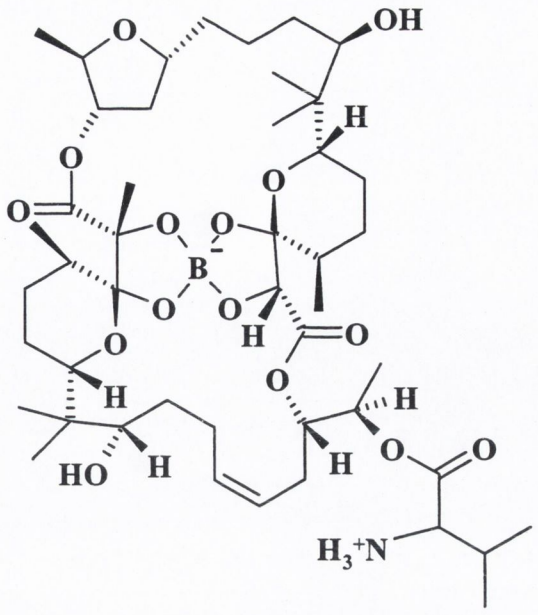
1.4.1 Boron complexes

Boron-based compounds are found extensively in nature *e.g.* as fungal metabolites and as ionophoric macrolide antibiotics. Some of these antibiotics that have been isolated include aplasmomycin[66] **128** and boromycin[67] **129**. The borate core serves as an anionic companion to an alkali-metal cation that is transported in living systems. Aplasmomycin **128**, an example of a natural cryptand, is a metabolite of *Streptomyces griseus*.[68]



(128)

Boromycin is an ionophoric metabolite of *Streptomyces antibioticus* and was the first natural product known to contain boron.[69]



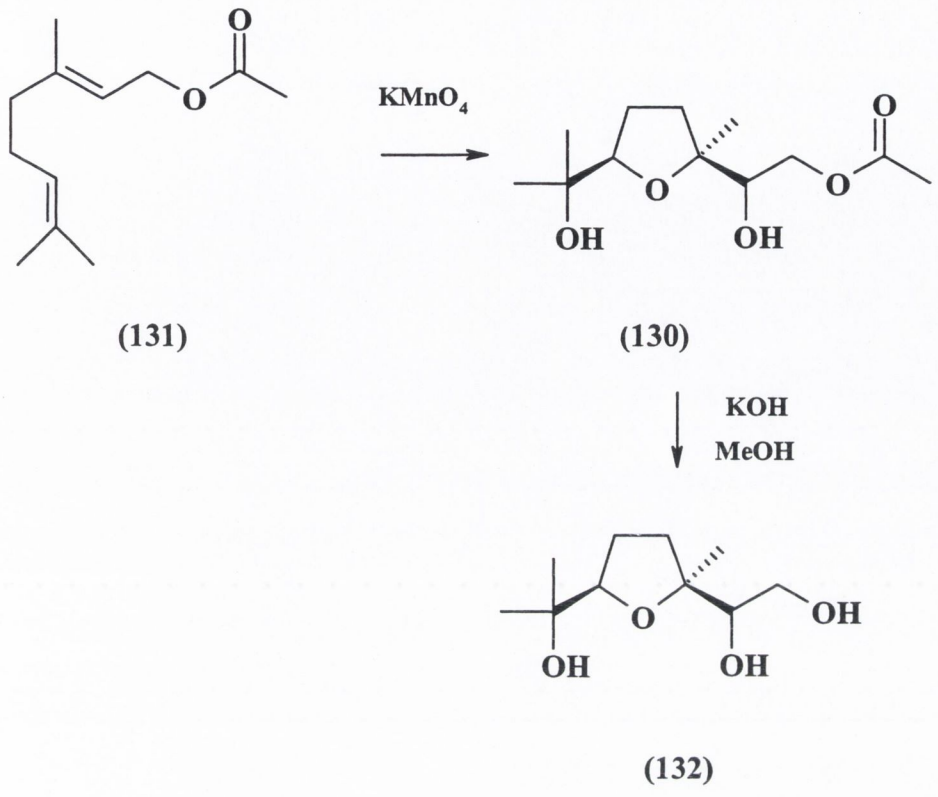
(129)

Boron bears similarities to carbon and, especially, silicon in terms of its reactivity. It mainly forms molecular compounds or those containing complex ions. This is due to the fact that after forming three covalent bonds it is still short two electrons of the structure of an inert gas and so has a strong tendency to behave as an acceptor and form a fourth bond by donor-acceptor behaviour.[70]

1.4.2 A previously synthesised potassium complex

In 1924 Kotz *et al.* [71] synthesised the diol **130** by oxidation of geranyl acetate **131** using potassium permanganate. Forty years later Klein and Rojahn elucidated the structure of the oxidation product.[72] Hydrolysis of **130** afforded the triol **132** **(Scheme 50)**.

Synthesis of a triol derived from geranyl acetate

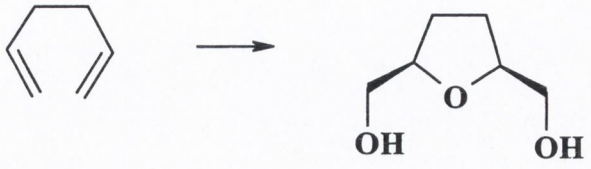


(131) **(130)** **(132)**

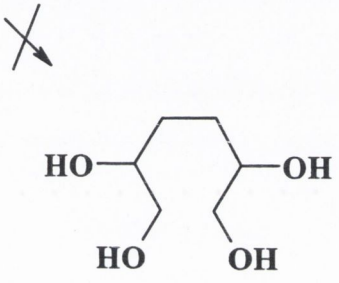
Scheme 50

The reaction involved in this oxidation of geranyl acetate was quite a discovery as it revealed that 1,5-dienes, *e.g.* penta-1,5-diene **133**, are not generally oxidized to tetraols **134** but form 2,5-bis-hydroxymethyltetrahydrofurans **135 (Scheme 51)**. The reaction is stereospecific, yielding the *cis* isomers of the tetrahydrofurans.

Oxidation of 1,5-hexadiene to give 2,5-bis-hydroxymethyltetrahydrofuran



(133) **(135)**

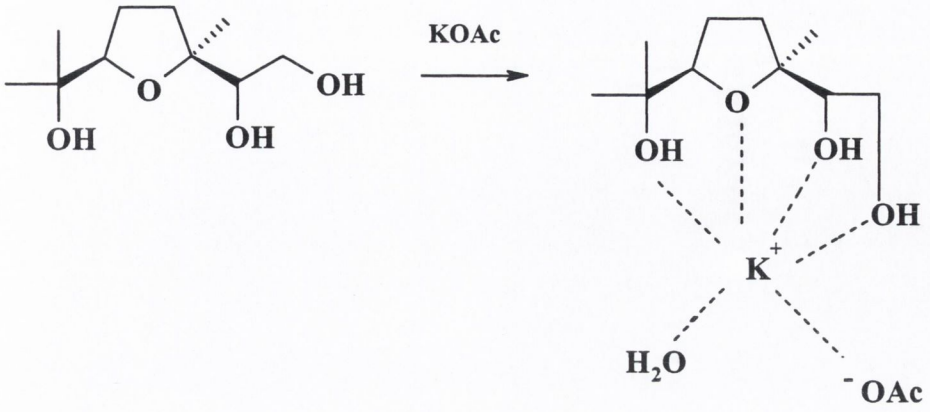


(134)

Scheme 51

Ten years later Hackler[73] claimed that a potassium complex **136** was formed by hydrolysis of the acetate **130** using one equivalent of potassium hydroxide. This potassium complex was soluble in chloroform, and could also be formed from the triol **132** by reaction with potassium acetate **(Scheme 52)**.

Proposed synthesis of a potassium complex from a triol



(132) **(136)**

Scheme 52

The potassium complex **136** was only characterised using 60 MHz proton NMR spectroscopy, and the presence of the water molecule was inferred from the combustion microanalysis results.

The proton NMR data for **136** included three singlets at δ 1·08 ppm , δ 1·13 ppm and δ 1·24 ppm, each representing one of the three methyl groups, as well as a broad singlet at δ 1·92 ppm integrating for seven protons, a multiplet at δ 3·65 ppm integrating for four protons and a singlet at δ 4·91 integrating for five protons, none of which were directly assigned by Hackler. At the present time, with the availability of 400 MHz proton NMR facilities, one would expect a more detailed spectrum, and with the existence of correlation experiments it should be possible to fully confirm the stereochemistry of the tetrahydrofuran moiety.

At the time of Hackler's observations, crown ethers, podands *etc.* were attracting widespread interest. The triol **132** possesses only the minimum of the elements needed to act as a polyoxy ionophore. The four oxygen atoms are each separated by two carbon atoms, but only one of them is an ether oxygen. In the potassium complex **136** claimed by Hackler, a water molecule and an acetate ion act as the fifth

and sixth ligands, which have been shown to be required in order to bind an alkali metal ion. Hackler also attempted to synthesise an analogous sodium complex from the acetate **131** using sodium hydroxide but failed to obtain this.

1.5 Aims and objectives

The first objective of the work described in this thesis was to synthesise a number of Diels-Alder adducts of furan and then subject them to acid-catalysed ring-opening reactions using acylium ions generated from mixed carboxylic-trifluoroacetic anhydrides. The Diels-Alder adducts should each be available in two diastereoisomeric forms. Thus, their ring-opening reactions should yield a variety of products. The overall aim was to make highly substituted six-membered rings with controlled relative stereochemistry.

A related objective was to carry out ring-opening reactions on 2,5-dihydrofuran using acyl halides and a Lewis acid catalyst.

It was also planned to carry out some intermolecular ring-opening reactions of hydrofurans using a mixed anhydride in the presence of sodium iodide.

Finally, it was intended to properly characterize using modern spectroscopic techniques a chloroform-soluble potassium complex analogous to a minimalised polyether complex that had been claimed by Hackler using a tetrahydrofuryl type podand originally derived from geranyl acetate, and to determine if a borate complex could be formed from this.

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Chapter 2

Ring-opening of 2-substituted-7-oxabicyclo[2.2.1]-hept-5-enes with acylium ions derived from carboxylic-trifluoroacetic mixed anhydrides

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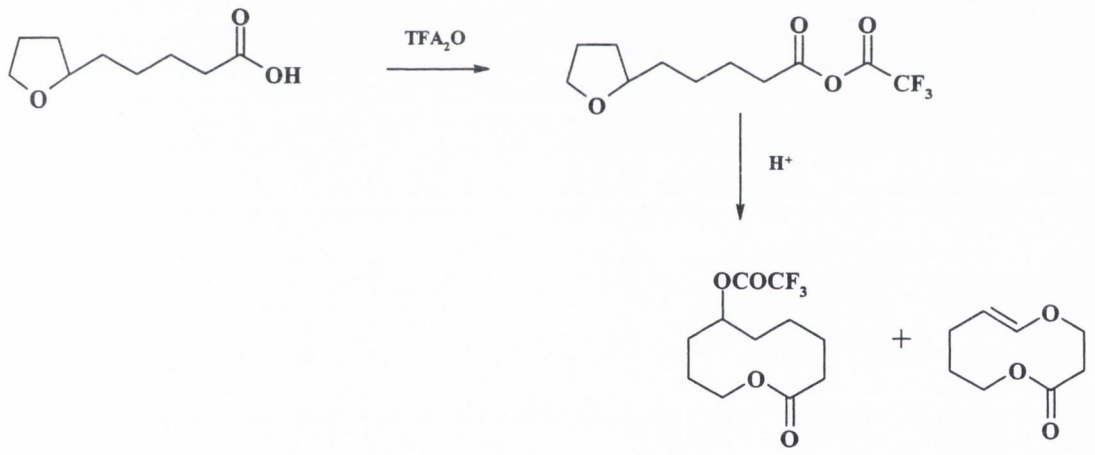
2.1 Introduction

The aim of this work was to attempt to open the 7-oxabicyclo[2.2.1]heptene system using acylium ions generated from carboxylic-trifluoroacetic mixed anhydrides. This approach has been very successful in the synthesis of lactones from tetrahydrofuran substrates **(Scheme 1)**.[1]

Synthesis of lactones from tetrahydrofuran substrates



Scheme 1

The reaction shown above is obviously an intramolecular process. In the present work it is intended to investigate the possibility of the reaction occurring in an intermolecular sense with 7-oxabicyclo[2.2.1]heptenes as substrates.

The mixed anhydrides required for this purpose can be obtained from reactions between trifluoroacetic anhydride **1** and carboxylic acids **2**. These mixed anhydrides

are easy to obtain since the equilibrium for the reaction is strongly in favour of the mixed anhydride **3** and trifluoroacetic acid **4** **(Scheme 2)**.

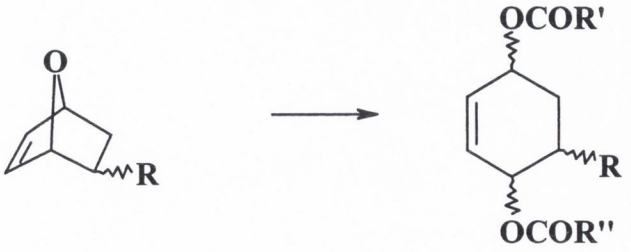
Reaction of a carboxylic acid and trifluoroacetic anhydride to a give a trifluoroacetic mixed anhydride

$$\underset{(1)}{RCOOH} + \underset{(2)}{CF_3CO_2COCF_3} \rightleftharpoons \underset{(3)}{RCO_2COCF_3} + \underset{(4)}{CF_3COOH}$$

Scheme 2

It was anticipated that compounds of the type **5**, derived *via* Diels-Alder reactions between furan and appropriate dienophiles, would react with a mixed anhydride **3**, under conditions that promoted the formation of acylium ions. These electrophiles would then attack the Lewis-basic ether oxygen atom of the bicyclic ether **5** to give an acyloxonium ion, which would react to give highly substituted cyclohexenes of the form **6** **(Scheme 3)**. The stereochemistry of these products **6** might be predicted and controlled in that the stereochemical relationship between the ether bridge and the 2-substituent of the starting material **5** would be both known and fixed.

Proposed ring-opening reaction of a Diels-Alder adduct with a trifluoroacetic mixed anhydride

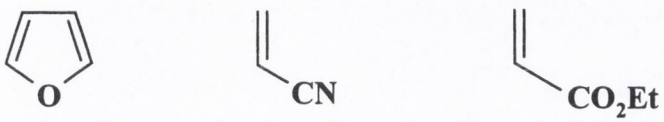


(5) **(6)**

Scheme 3

2.2.1 Synthesis of Diels-Alder adducts

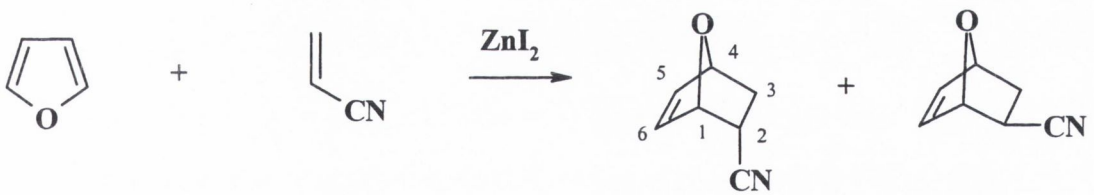
Diels-Alder reactions were initially carried out between furan **7** and the two activated alkenes acrylonitrile **8** and ethyl acrylate **9** using zinc iodide catalyst as described by Brion.[2]



(7) **(8)** **(9)**

In the reaction of furan with acrylonitrile **8** the product obtained (in 90% yield) was a mixture of the *endo*- and *exo*- isomers **10** and **11** of 7-oxabicyclo[2.2.1]hept-5-ene-2 nitrile **(Scheme 4)**. NMR was used to determine the structure and ratio of each isomer. The *exo* and *endo* isomers can be distinguished by their ^{1}H NMR spectra quite easily by measuring the coupling constants for each of the C-1 protons.[3]

Diels-Alder reaction of furan with acrylonitrile



(7) **(8)** **(10)** **(11)**

Scheme 4

For example, in the *endo* compound **10**, a 4Hz doublet at δ 5·13 ppm is assigned to the C-1 proton, its multiplicity is due to coupling with the C-2 *exo* proton. However, in the *exo* compound **11**, a singlet at δ 5·18 ppm is observed and this is due to the fact that the C-2 *endo* proton does not couple to the proton on the bridgehead carbon next to it.

The ratio of *endo*-**10** to *exo*-**11** obtained from this reaction was 1:1·94, thus the *exo*-isomer is more favoured, however usually in the Diels-Alder reaction the *endo*-isomer is favoured.[4] Brion[2] reported an *endo*/*exo* ratio of 1:1 for the same reaction.

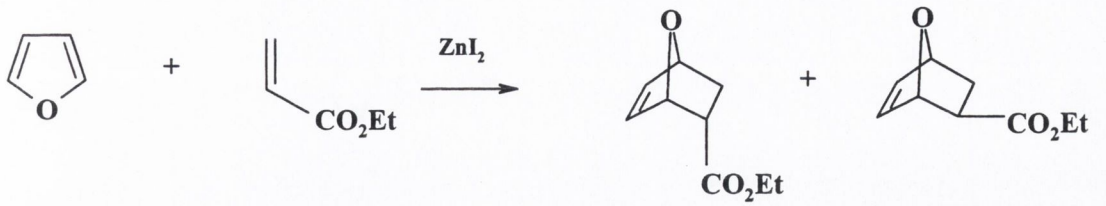
The two isomeric nitriles **10** and **11** were then separated by column chromatography.

The ^{1}H NMR spectrum of the *endo*- isomer **10** displays a double double doublet at δ 1·53 ppm which is assigned to the *endo* proton at C-3. A double double doublet at δ 2·29 ppm corresponds to the *exo* proton on the same carbon. The methine proton at C-2 occurs as a double triplet at δ 2·95 ppm. A doublet at δ 5·13 ppm is due to the bridge-head proton at C-1. The C-4 bridgehead proton appears as a doublet at δ 5·22 ppm. The alkene protons appear as doublets at δ 6·47 ppm and at δ 6·56 ppm, the latter being assigned to the proton at C-6.

The proton NMR spectrum of the *exo* isomer **11** displays a double doublet at δ 1·76 ppm which is assigned to the *exo* proton at C-3. A multiplet centred at δ 2·19 ppm is assigned to the *endo* proton at C-3. A double doublet at δ 2·44 ppm corresponds to the proton at C-2. The C-1 methine proton appears as a singlet at δ 5·18 ppm. The bridge-head proton at C-4 gives rise to a doublet at δ 5·24 ppm. The most downfield signals are due to the alkene protons, a signal at δ 6·30 ppm being assigned to the proton at C-5 and a doublet resonating at δ 6·42 ppm corresponding to the C-6 proton.

A Diels-Alder reaction between furan and ethyl acrylate **9** gave in 83% yield a mixture of the *endo*- and *exo*- isomers **12** and **13** of ethyl 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate in the ratio 1·17 to 1 **(Scheme 5)**.

Diels-Alder reaction of furan with ethyl acrylate



(7) (9) (12) (13)

Scheme 5

The ^{1}H NMR of the *endo* adduct **12** shows a triplet at δ 1·24 ppm which corresponds to the ester methyl group. A double doublet at δ 1·58 ppm is assigned to the *endo* proton at C-3. The C-3 *exo* proton resonates at δ 2·09 ppm as a double double doublet. The C-2 methine proton appears as a double doublet at δ 3·10 ppm. A multiplet centred at δ 4·09 ppm is due to the methylene protons of the ester group. The bridgehead proton at C-4 appears as a double doublet at δ 5·01 ppm. The C-1 methine proton resonates slightly further downfield as a double doublet at δ 5·16 ppm due to its proximity to the ester group. Similarly the vinylic C-5 proton appears as a double doublet at δ 6·22 ppm which is followed by a double doublet at δ 6·43 ppm that corresponds to the proton at C-6.

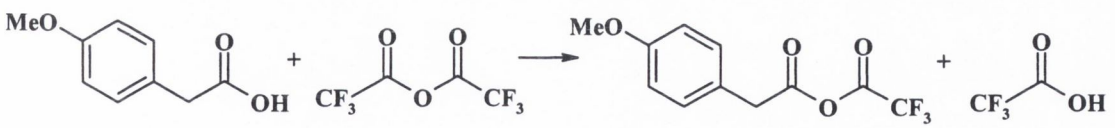
In the ^{1}H NMR spectrum of the *exo* adduct **13**, a triplet at δ 1·30 ppm is assigned to the methyl group. The *endo* proton of the C-3 methylene group appears as a double doublet at δ 1·56 ppm. The corresponding C-3 *exo* proton resonates as a double double doublet at δ 2·18 ppm. The C-2 methine proton appears as a double doublet at δ 2·42 ppm. A quartet at δ 4·20 ppm corresponds to the methylene protons of the ester group. The two bridgehead protons display different multiplicities. The C-4 methine appears as a double doublet at δ 5·07 ppm, whereas the C-1 bridgehead proton resonates as a doublet at δ 5·20 ppm. The olefinic protons at C-5 and at C-6 appear as double doublets at δ 6·38 ppm and at δ 6·40 ppm, respectively.

When the signals for the methylene group in the ester function of each of the isomers **12** and **13** were compared, they were found to be very different. In the ^{1}H NMR spectrum of the *exo* isomer **13** they appear as a simple quartet at δ 4·20 ppm whereas for the *endo* isomer **12** they appear as a multiplet (twelve peaks) centred at δ 4·09 ppm. This is due to the fact that the two protons of the methylene group are diastereotopic due to their proximity to the neighbouring asymmetric centres at C-1 and at C-2 and are subject to splitting by each other. This data was in agreement with that reported in the literature.[5]

2.2.2 Attempted ring-opening of 2-substituted 7-oxabicyclo[2.2.1]heptenes using acylium ions

A general reaction protocol was used to investigate the acylative ring-opening of the synthesised Diels-Alder adducts. These conditions had been satisfactory when analogous intramolecular ring-opening reactions of ω-(2-tetrahydrofuryl)propanoic-trifluoroacetic anhydrides were carried out.[6] Thus, molar equivalents of trifluoroacetic anhydride **2** and of 4-methoxyphenylacetic acid **14** were reacted together at 0 °C in dichloromethane **(Scheme 6)**. This resulted in the formation of the mixed anhydride **15**.

Reaction of 4-methoxyphenylacetic acid and trifluoroacetic anhydride to give a mixed anhydride

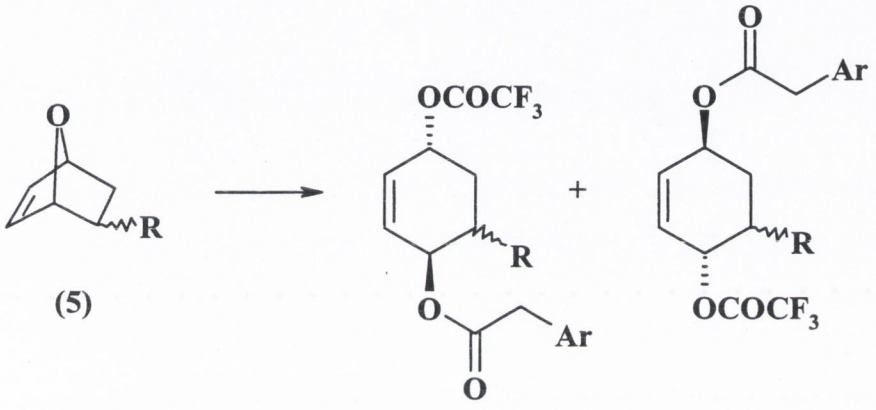


(14) (2) (15) (16)

Scheme 6

A molar equivalent of one of the 7-oxabicyclo[2.2.1]heptenes, **10**, **11**, **12** or **13** was then added and the reaction mixture was refluxed. It was expected that products of the form **17** and **18** would be produced **(Scheme 7)**.

Proposed reaction of a 2-substituted 7-oxabicyclo[2.2.1]heptene with the mixed anhydride of Scheme 6



(5) (17) (18)

R =CN or CO_2Et ,

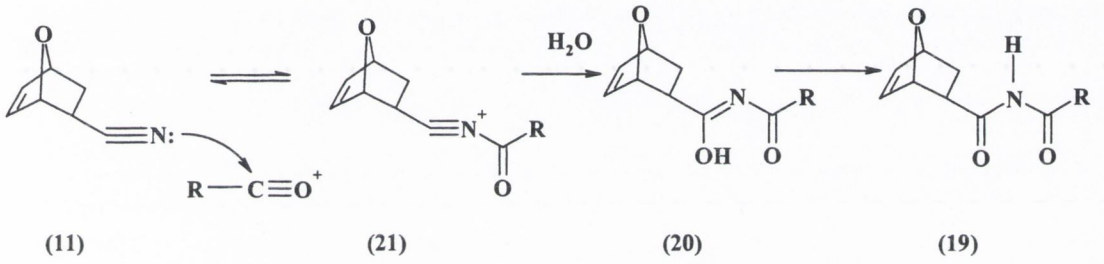
Scheme 7

In all cases there was no reaction. In each instance the starting adduct and the mixed anhydride **15** were the only substances recovered according to the ^1H NMR and infrared spectra of the product. This would suggest that a mixed anhydride is being generated from 4-methoxyphenylacetic acid and trifluoroacetic anhydride but that the derived acylium species is unable to cleave the ether bond of the substrate 7-oxabicylo[2.2.1]hept-2-ene.

Use of the higher-boiling solvent toluene gave the same result. Variation of reaction times from one hour to one day also failed to yield the expected products. Another acid, 3,3-dimethylacrylic acid, was employed in place of 4-methoxyphenylacetic acid **14** but negative results were again obtained. The reaction was also carried out in the absence of a solvent but still no reaction occurred.

A possible reason for the lack of reaction in the case of the nitriles **10** and **11** is that the initial step of a Ritter[7] reaction could have occurred, wherein the lone pair of the nitrogen atom is acylated by the acylium ion **(Scheme 8)**. This reaction usually requires water, which is not present in the reaction mixture, to form the product amide **19** *via* the compound **20**. Consumption of acylium ion to form the Ritter intermediate number **21** could explain why no reaction took place at the ether oxygen atom. However the absence of any amide **19** from the reaction mixture argues against this statement.

Possible Ritter side reaction

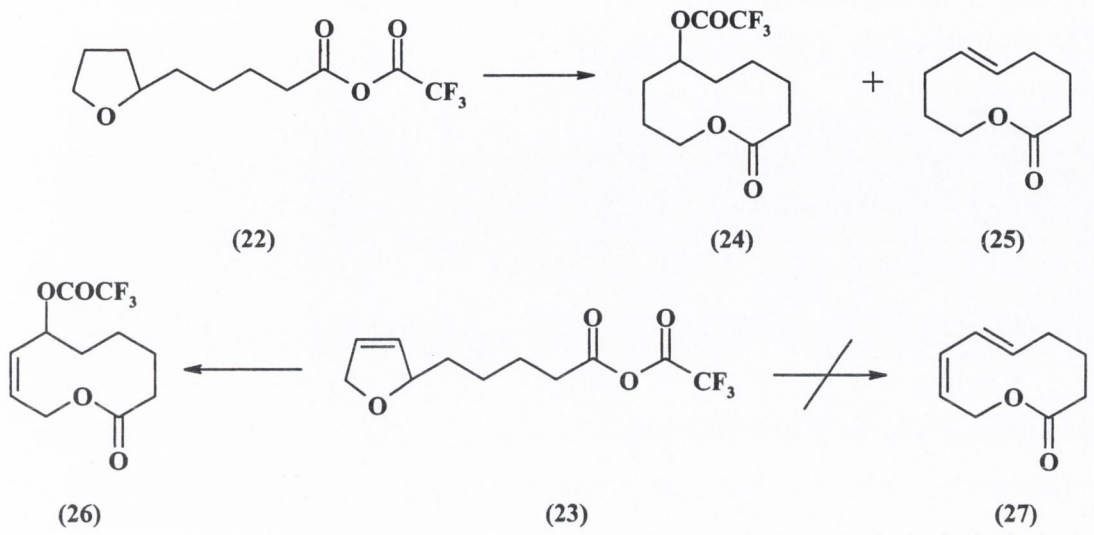


Scheme 8

2.3 Attempted ring-opening of saturated adducts

Intramolecular reactions with acylium ions have been carried out previously with the tetrahydrofuran derivatives **22** and **23**. The saturated compound **22** was found to undergo ring-opening to form the lactones **24** and **25**. This reaction was found to proceed with relative ease on refluxing in chloroform during one hour.[8] However the related unsaturated species **23** required refluxing in toluene with a reaction time of four hours to form the analogous unsaturated lactone **26** however the lactone **27** was not detected. **(Scheme 9)**.[9]

Intramolecular reactions of both saturated and unsaturated tetrahydrofuran derivatives



Scheme 9

It appeared that the reluctance of the oxygen bridge of the Diels-Alder adducts **10-13** to open under acylating conditions might be due to the presence of the double bond. Studies have been carried out comparing the reactivity of saturated and unsaturated cyclic ethers. Bain *et al.*[10] performed photoelectron spectroscopy experiments to study the interaction of non-adjacent groups and found ionisation potential differences between tetrahydrofuran (9·57 eV) and 2,5-dihydrofuran (9·87eV). After taking into account the effect of the double bond, this energy difference implied that a large interaction existed between the non-bonding electrons of the oxygen atom and the π orbitals of the double bond of 2,5-dihydrofuran.

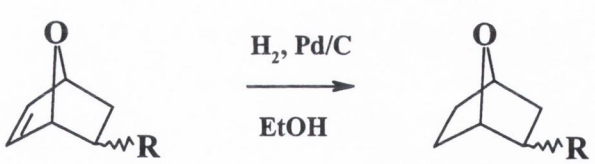
Senda *et al.*[11] performed ^{13}C NMR experiments on 3,4-dihydropyran and 2,5-dihydrofuran to study the interactions between lone pairs of electrons on ether oxygen atoms and the π orbitals of double bonds and found that they were not able to interact because the oxygen atom was in a *syn*-periplanar position with respect to the double bond. Kintzinger[12] and co-workers studied the ^{17}O NMR spectra of some unsaturated ethers in comparison to their saturated analogues and found that in the case of 2,5-dihydrofuran that there was no deshielding of the oxygen atom because

the double bond was too far away. The relative rates of hydroboration of 2,5-dihydrofuran and of cyclopentene using 9-BBN were studied by Brown *et al.*[13] These authors found that the rate of hydroboration for 2,5-dihydrofuran was 4·2 times slower than that of the equivalent reaction carried out on cyclopentene. This result was attributed to the presence of oxygen and its inductive effect pulling electron density from the double bond thus making it less reactive towards hydroboration. However, when Sia_2BH (disiamyl borane) is used as the hydroborating source, the higher reaction rate is observed for the ether.

Although differences of opinion exist amongst the above authors it does seem very possible that the presence of the double bond inhibits the progress of the ring-opening reaction being studied. Thus, the nucleophilicity of the oxygen atom is impaired and although the mixed anhydride **15** is produced under conditions that are known lead to the formation of acylium ions, the ring-opening cannot occur.

Accordingly, it was decided to remove the double bond from the adducts being studied and to then repeat the ring-opening reaction procedure. Thus, the saturated compounds **28** were prepared by hydrogenating each of the unsaturated adducts **10**, **11**, **12** and **13** in ethanol with palladium on carbon as catalyst **(Scheme 10)**.

Hydrogenation of 2-substituted 7-oxabicyclo[2.2.1]heptenes



(5) **(28)**

R = CN or CO_2Et

Scheme 10

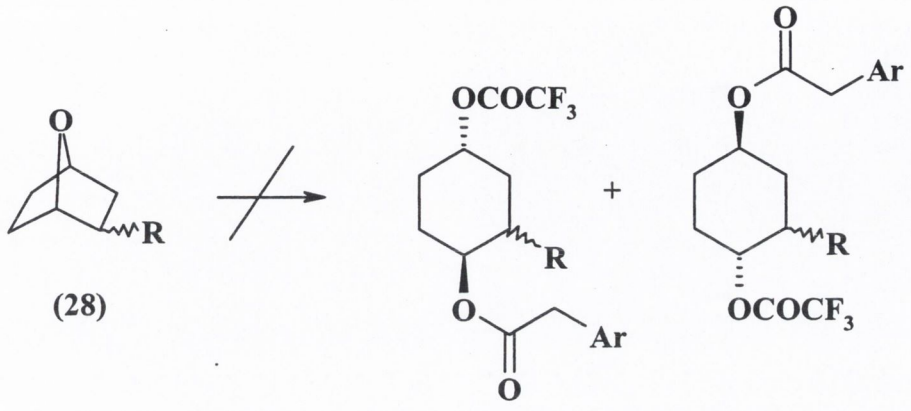
Each of the hydrogenation products exhibited similar spectroscopic data. As expected, alkene stretching absorptions were absent from their infrared spectra and there were no olefinic proton signals in their ^{1}H NMR spectra.

The methyl group of the ester function of **28** (R = *exo*-CO_2Et) appears as a triplet at δ 1·27 ppm. The C-5 methylene group occurs as a multiplet at δ 1·50 ppm. The signals for the C-6 methylene group and for the C-3 *endo* proton overlap and are assigned to a multiplet at δ 1·74 ppm integrating for three protons. A double double doublet is observed at δ 2·13 ppm and is assigned to the C-3 *exo* proton. The C-2 methine proton resonates as a double doublet at δ 2·60 ppm. The methylene protons of the ester function appear as a quartet at δ 4·16 ppm. The bridgehead proton at C-4 resonates as a triplet at δ 4·67 ppm. A doublet at δ 4·83 ppm is assigned to the other bridgehead proton at C-1.

Each of the other hydrogenation products (R = *endo*-CO_2Et, R = *endo*- and *exo* –CN) gave spectra that were consistent with the structures assigned to them (**Experimental 2.8**).

Each of these saturated compounds was then reacted with the mixed anhydride derived from 4-methoxyphenylacetic acid and trifluoroacetic anhydride in the same way as described for the corresponding unsaturated compounds but, once again, there was no evidence for acylative ring-opening **(Scheme 11)**.

Proposed reaction of 2-substituted 7-oxabicyclo[2.2.1]heptanes with the mixed anhydride of Scheme 6

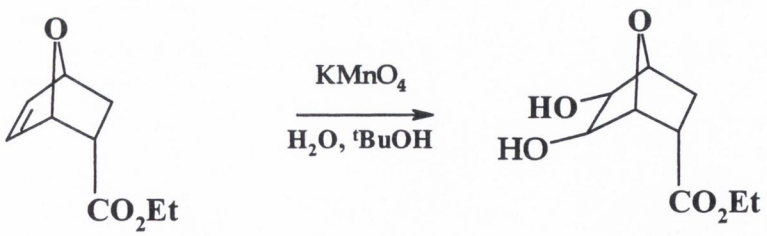


Scheme 11

2.4 Synthesis and reaction of a diol derived from ethyl 7-oxabicyclo[2.2.1]hept-5-ene-2-*endo*- carboxylate

The diol **29** (obtained in 74% yield) was synthesised by potassium permanganate dihydroxylation of the *endo*-ester **11 (Scheme 12)**.

Synthesis of a diol derived from ethyl 7-oxabicyclo[2.2.1] hept-5-ene-2-*endo*-carboxylate



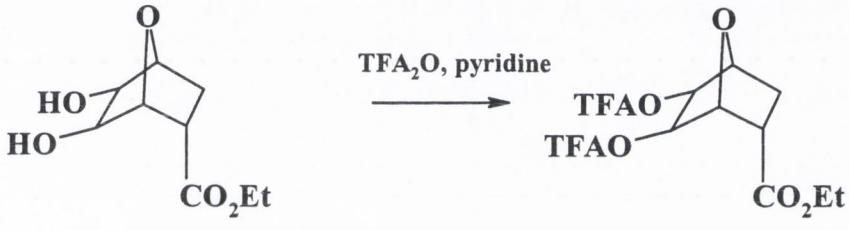
(11) **(29)**

Scheme 12

In the proton NMR spectrum of **29** a multiplet at δ 3·92 ppm corresponds to the protons on C-5 and C-6. A broad peak at δ 3·75 ppm integrating for two protons, which disappears with the addition of D_2O, is indicative of the two hydroxyl groups. In the infrared spectrum of **29** there is a hydroxyl group absorption at 3369 cm^{-1}.

The diol function of **29** was then protected by conversion into its *bis*-trifluoroacetate ester by reaction with trifluoroacetic anhydride in pyridine **(Scheme 13)** which was obtained in 72% yield.

Protection of the diol of Scheme 12



(29) **(30)**

Scheme 13

In the proton NMR spectrum of **30** the two methine protons at C-5 and C-6 appear as a multiplet at δ 4·61 ppm. The downfield shift of *ca.* 0·7 ppm for these protons following esterification of the hydroxyl groups is diagnostic. The infrared spectrum of **30** displays a typical absorption for a trifluoroacetate group at 1787 cm^{-1}.

The trifluoroacetate group was chosen as a suitable protecting group for the diol **29** for two reasons. Firstly it was thought that the group would be compatible with the conditions of the ring-opening reaction that was to be carried out which involved the presence of trifluoroacetic anhydride. Furthermore, whereas neighbouring group participation between a conventional acetate ester **31** and an adjacent carbonium ion would be expected, this interaction would be minimised or suppressed where the more electron-poor trifluoroacetate function **32** is present **(Scheme 14)**.

Neighbouring group participation of an acetate group and a trifluoroacetate group

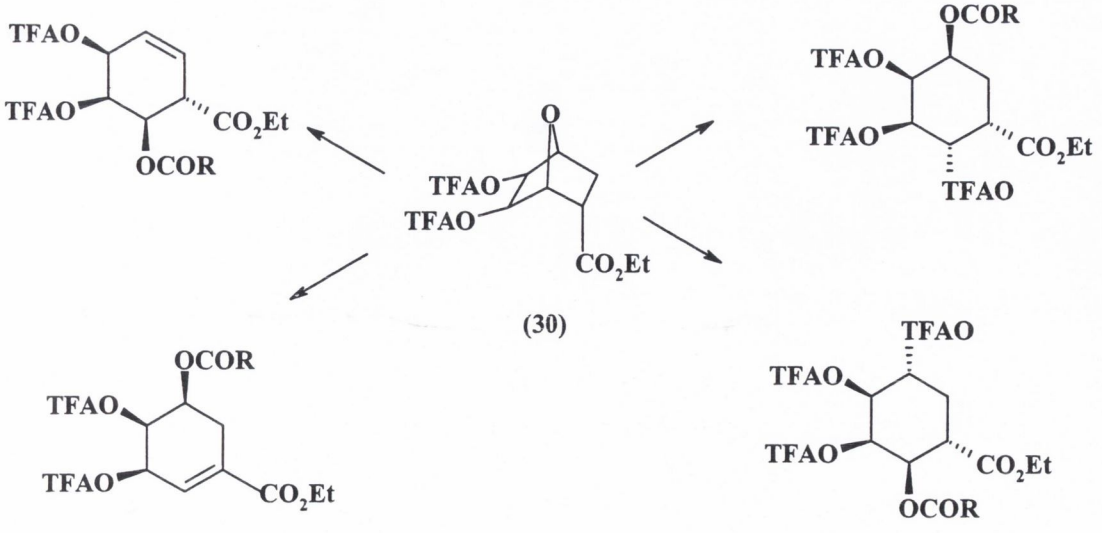
(31)

(32)

Scheme 14

A successful outcome to this reaction would have given a pentasubstituted cyclohexane in just one step. Additionally, alkenes might also be formed which might be further functionalised to give fully substitituted cyclohexanes **(Scheme 15)**.

Possible products of a ring-opening reaction of the protected species of Scheme 13



(30)

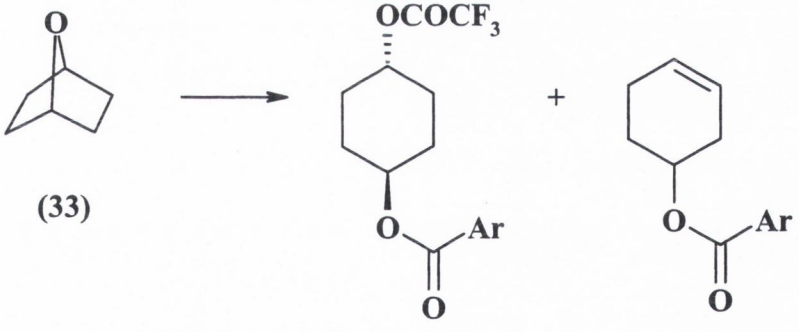
The protected compound **30** was reacted with the mixed anhydride generated from 4-methoxyphenylacetic acid and trifluoroacetic anhydride.

However, the reaction failed, NMR and TLC analysis indicating that the only substances recovered were the mixed anhydride **15** and the oxabicyclic compound **30**.

2.5 Cleavage of 7-oxabicyclo[2.2.1]heptane 33

The next logical step was to perform a ring-opening reaction on 7-oxabicyclo[2.2.1]heptane **33** itself. This was to see if the parent unsubstituted system was susceptible to the acylium ion-mediated ring-cleavage reaction using 4-methoxyphenylacetic-trifluoroacetic mixed anhydride. This strategy was successful, yielding the substituted cyclohexane **34** and the cyclohexene **35** in the ratio 1·2 to 1 **(Scheme 16)**.

Cleavage of 7-oxabicyclo[2.2.1]heptane using a mixed anhydride



(33) **(34)** **(35)**

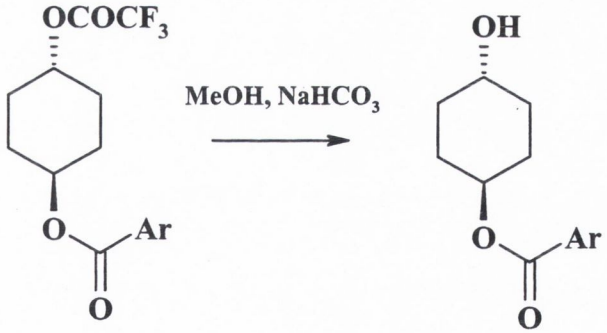
Scheme 16

The proton NMR spectrum of the diester **34** displays a multiplet at δ 4·91 ppm, which is tentatively assigned to the C-1 proton. The C-4 methine proton appears as a multiplet at δ 5·06 ppm. This signal is common to the cyclohexene **35**, as are a singlet at δ 3·56 ppm integrating for two protons arising from the benzylic methylene

group, a singlet at δ 3·81 ppm for the methoxy group and two doublets at δ 6·88 ppm and δ 7·20 ppm for the *para*-disubstituted benzene ring. The alkene functionality of **35** shows up as two multiplets at δ 5·60 ppm and δ 5·70 ppm. The infrared spectrum of **34** shows a signal at 1779 cm^{-1} which is a typical carbonyl absorption for a trifluoroacetoxy group and another at 1735 cm^{-1} which represents the phenylacetic ester.

The trifluoroacetoxy group of **34** could be selectively hydrolysed by stirring the diester with methanolic sodium hydrogen carbonate to give the corresponding alcohol **36 (Scheme 17)** in 87% yield. The proton adjacent to the hydroxyl group resonates at δ 3·66 ppm which is considerably further upfield than the proton next to a trifluoroacetoxy group. Also the disappearance of the infrared absorption at 1779 cm^{-1} and the appearance of a hydroxyl absorption at 3399 cm^{-1} confirmed that hydrolysis of the trifluoroacetate ester function of **34** had taken place. Survival of the other ester function was confirmed by ^1H NMR spectrum of **36**, and by a carbonyl absorption at 1727 cm^{-1} in the infared spectrum.

Hydrolysis of 1-trifluoroacetoxy 4-(4'-methoxyphenylacetoxy)-cyclohexane



(34) **(36)**

Scheme 17

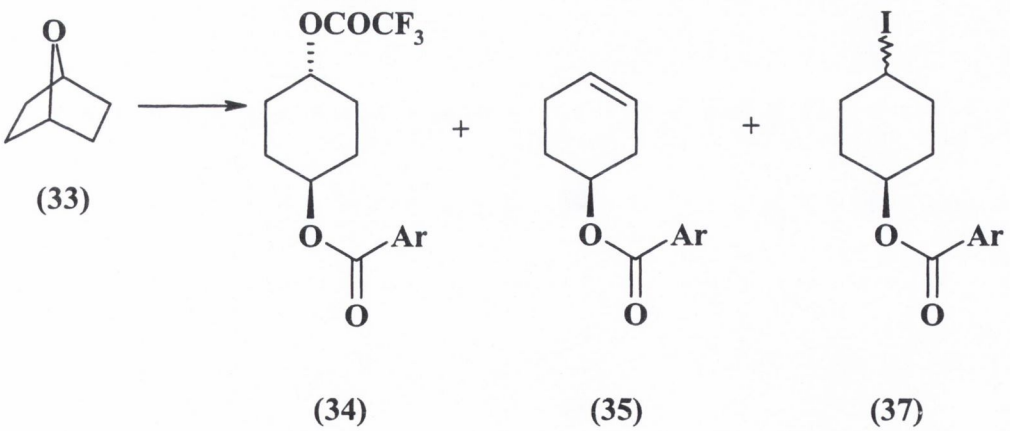
2.5.1 Intermolecular ring-opening reaction of 7-oxabicyclo[2.2.1]heptane 33 in the presence of sodium iodide

Iodolactones have been previously synthesised from tetrahydrofurans by an intramolecular ring-opening reaction *via* the highly successful mixed anhydride methodology in the presence of sodium iodide.[8]

Due to the successful cleavage, described above, of 7-oxabicyclo[2.2.1]heptane **33** to give the products **34** and **35**, it was decided to repeat the experiment in the presence of sodium iodide with the intention of producing the iodide **37** *via* trapping of the acyloxonium ion with iodide as the nucleophile. This was expected due to the fact that iodide ion is a better nucleophile than trifluoroacetate ion.

In the event, when the bicyclic ether **33** was treated with the mixed anhydride **15** in acetone solution in the presence of sodium iodide all of the products **34**, **35**, and **37** were unexpectedly formed **(Scheme 18)**.

Intermolecular ring-opening of 7-oxabicyclo[2.2.1]heptane in the presence of sodium iodide

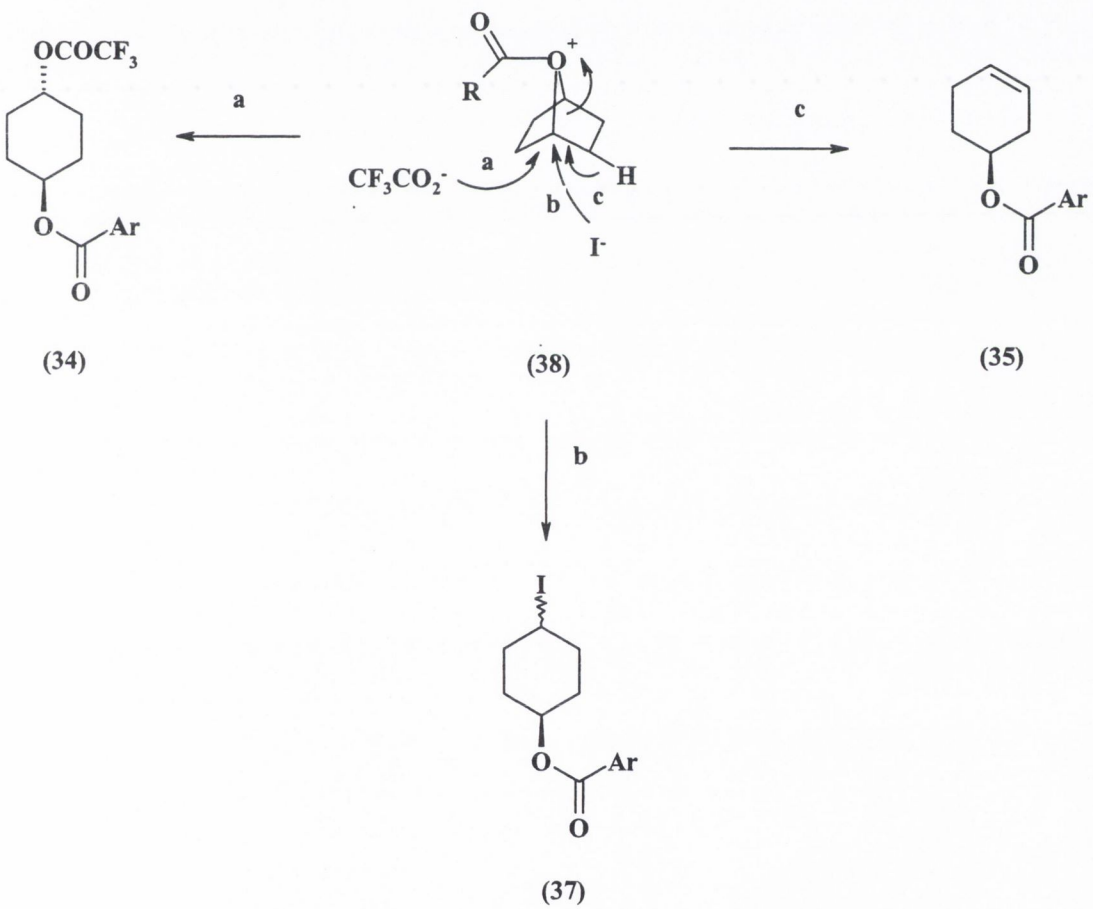


(33) (34) (35) (37)

Scheme 18

This result can be rationalised in the following way. Iodide ion is indeed a much better nucleophile than trifluoroacetate. However the intermediate acyloxonium ion **38** formed in this reaction is a rigid V-shaped species. S_N2 attack at C-1 by a large iodide ion (path b) will be sterically hindered. Accordingly competitive attack by trifluoroacetate ion occurs to give **34** (path a), and β-elimination gives **35** (path c) **(Scheme 19)**.

Possible reactions of the acyloxonium ion generated in previous reaction



(34) (38) (35)

(37)

Scheme 19

Although it had been possible to separate the mixture of the diester **34** and the cyclohexene **35**, this was not the case for the mixture of **34**, **35** and **37**. The iodo compound **37** could not be completely characterised from the NMR spectra of the product mixture but it was clear that another compound had been formed. A characteristic upfield signal at δ 0·55 ppm in the ^{13}C NMR spectrum was indicative of a carbon-iodine bond.

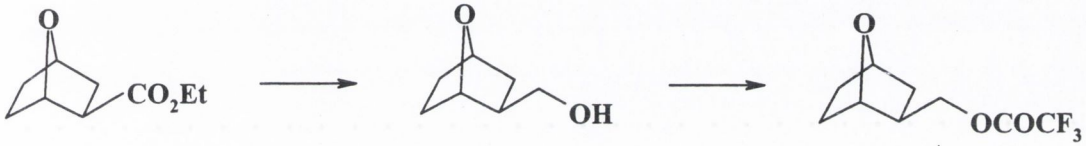
On addition of 1,8-diazobicylo[5.4.0]undec-7-ene (DBU) to the mixture of compounds obtained from the reaction shown in **Scheme 18** above the proton NMR spectrum of the product indicated that the alkene **35** was the only compound present. Thus, the iodo compound **37** reacted with DBU to give an alkene **35** which is a characteristic elimination reaction of an iodide. The trifluoroacetate **34** was presumably lost during the work up.

The work described above shows that the bridging ether functionality in the parent 7-oxabicyclo[2.2.1]heptane **33** can indeed be cleaved by acylium ions derived from mixed carboxylic-trifluoroacetic anhydrides. The reaction fails when cyano or carboethoxy groups are present. The presence of a 5,6-double bond may also affect the reactivity. The nitrile or carboxylic ester groups may possibly hinder the cleavage process due to steric or electronic interactions. Both groups are electron-withdrawing, and this suggests that an acyloxonium ion formed by attack of an acylium ion on such a substrate could be destabilised by their inductive effects.

2.6 Cleavage of 2-*exo*- trifluoroacetoxymethyl-7-oxabicyclo[2.2.1]heptane

In the light of the results outlined above it was decided to convert the carboethoxy group of the oxabicycloheptane **10** into a much less electron-withdrawing group. The alcohol **39**, which is a known compound,[14] was synthesised from the ester **10** by reduction using lithium aluminium hydride and obtained in 68% yield. The alcohol **39** was then protected by converting it into the corresponding trifluoroacetic acid ester **40 (Scheme 20)** (82% yield).

Synthesis of 2-*exo*-triflouroacetoxymethyl-7-oxabicyclo[2.2.1]heptane derived from ethyl 2-*exo*-7-oxabicyclo[2.2.1]hept-5-ene



(10) **(39)** **(40)**

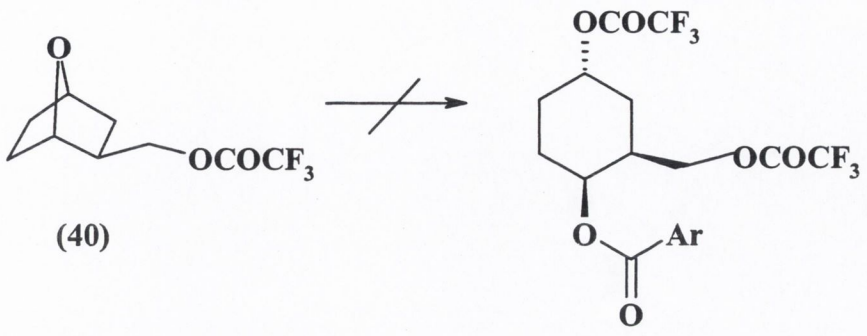
Scheme 20

In the proton NMR spectrum of **39** a broad signal at δ 2·36 ppm which exchanges with D_2O is assigned to the hydroxyl group. A multiplet at δ 3·46 ppm corresponds to the adjacent methylene group. The infrared spectrum of **39** shows the absence of a carbonyl group and the appearance of a hydroxyl absorption at 3399 cm^{-1}.

The proton NMR spectrum of the ester **40** shows a resonance at δ 4·13 ppm which is assigned to the methylene group adjacent to the trifluoroacetoxy function. The infrared spectrum of **40** displays an absorption at 1785 cm^{-1} which is typical for a trifluoroacetoxy carbonyl group.

The trifluoroacetate **40** was then reacted with the mixed anhydride derived from trifluoroacetic anhydride and 4-methoxyphenylacetic acid **(Scheme 21)**.

Proposed reaction of 2-*exo*-triflouroacetoxymethyl-7-oxabicyclo[2.2.1]heptane with a mixed anhydride



(40) (41)

Scheme 21

However the ring-opening reaction failed, and the obtained product consisted of the starting trifluoroacetoxy compound **40** and the mixed anhydride **15**. Therefore the less electron-withdrawing group still present may have exhibited a sufficient inductive effect to destabilise the acyloxonium ion, thus impeding the ring-cleavage reaction which should give the product **41**.

2.7 Reaction of acylium species with other types of oxabicyclic ring systems

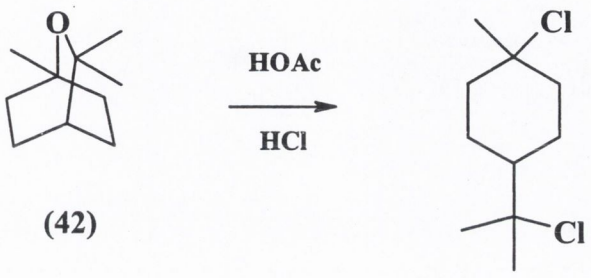
It was then decided to investigate the reactivity of ether functionalities in other types of cyclic compounds towards the acylium ion derived from a carboxylic-trifluoroacetic mixed anhydride.

2.7.1 Cleavage of 1,8-cineole

The terpenoid ether 1,8-cineole **42** was the first compound utilised. This has a structure that is related to the 7-oxabicyclo[2.2.1]heptane studied above except that the oxygen atom is located in a six-membered ring. The bridging ether functionality of cineole **42** has been opened previously. For example, Baeyer[15] carried out an acid catalysed ring-cleavage reaction of 1,8 cineole using hydrochloric acid to give the

product **43 (Scheme 22)**. On reaction with hydrogen bromide, the corresponding bromo-compound was formed.[15]

Acid catalysed ring-opening of 1,8-cineole

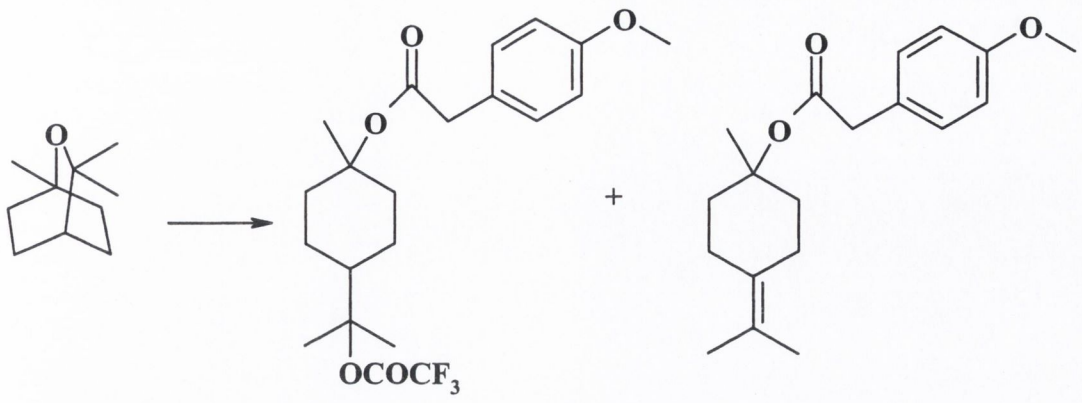


(42) **(43)**

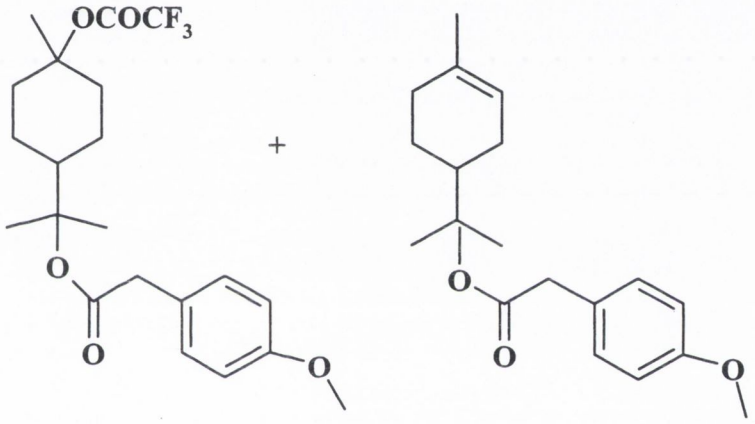
Scheme 22

It was presumed that in a reaction of 1,8-cineole **42** with the mixed ahydride derived from the reaction of 4-methoxyphenylacetic acid with trifluoroacetic anhydride the compounds **44** and **45** would be formed, possibly together with the alkenes **46** and **47** that may arise by β-elimination **(Scheme 23)**.

Proposed ring-opening reaction of 1,8-cineole with a mixed anhydride



(42) (44) (46)



(45) (47)

Scheme 23

As can be seen from **Table 2.1** the ring system of 1,8-cineole **42** proved impossible to cleave under these conditions. This was a surprising result, given that 1,8-cineole **42** has been successfully cleaved under acid-catalysed conditions previously.

Table 2.1

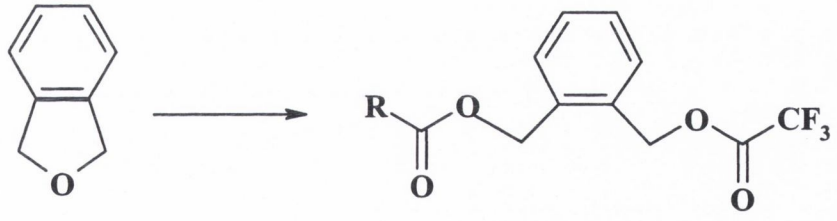
Results of reaction of 1,8-cineole with the mixed anhydride 15

Solvent	Time	Temperature	Result
dichloromethane	3 hours	reflux at 40 ° C	No ring cleavage
dichloromethane	24 hours	reflux at 40 ° C	No ring cleavage
toluene	6 hours-1 month	reflux at 110 ° C	No ring cleavage

2.7.2 Attempted cleavage of phthalan 48

Finally, it was decided to investigate the reactivity of phthalan **48** towards acylium ion-induced ring-opening. If successful, this reaction could yield difunctional benzene derivatives **49 (Scheme 24)**.

Ring-opening reaction of phthalan using acetyl chloride and zinc



(48) **(49)**

Scheme 24

The ether functionality of phthalan **48** was successfully cleaved by Helberger and Sproviero[16] using acetyl chloride and zinc to give 1-chloro-methyl-2-acetoxymethyl-benzene.

A reaction between phthalan and the mixed anhydride derived from 4-methoxyphenylacetic acid and trifluoroacetic anhydride was performed in the usual way, but the proton and carbon NMR spectra of the product showed that the phthalan remained unchanged.

As was the case with cineole **42** it could be concluded that the mixed anhydride method is not suitable for the ring-cleavage of phthalan. As discussed above, in the context of difficulties encountered with the cleavage of 2,5-dihydrofurans in comparison to tetrahydrofurans, it can be assumed that that the presence of a benzene ring impairs the basicity of the ether oxygen atom.

2.8 Conclusions

The results described above permit the following conclusions.

- Acylium ion-mediated cleavage of the oxygen bridge in 2-substituted-7-oxabicyclo[2.2.1]hept-5-enes fails to proceed.

- Removal of potential π-n interactions by hydrogenation of the alkene functionality gives a saturated 2-substituted-7-oxabicyclo[2.2.1]heptane ring system that also fails to undergo ring-opening under these conditions.

- Modification of an electron-withdrawing 2-substituent by reduction does not increase the reactivity of an 7-oxabicyclo[2.2.1]heptane towards acylium ions.

- Reaction of the unsubstituted "parent compound" 7-oxabicyclo[2.2.1] heptane does result in ring-opening giving the anticipated disubstituted cyclohexane as well as a cyclohexene that is formed as a result of β-elimination.

- It follows that the presence of a 2-substituent has a significant effect on the ring-opening process.

- Reactions of the other oxabicyclic compounds 1,8-cineole and phthalan with acylium species were also unsuccessful.

2.9 Experimental

General experimental conditions

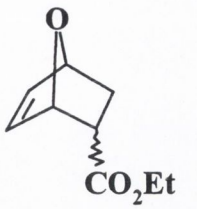
Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} silica gel plates. Visualisation was by means of ultraviolet light at 254nm or by development in potassium permanganate solution. Column chromatography was carried out under gravity using Merck Kieselgel 70-230 mesh silica gel. Evaporation under reduced pressure refers to the use of a Buchi or Bibby rotary evaporator. All solvents were dried using standard techniques. Infrared spectra were recorded as Nujol mulls (N) for solids or as liquid films (L) between sodium chloride plates for oils using a Matteson Genesis FT-IR spectromete and the data was processed using WinFirst software. Nuclear magnetic resonance spectra were recorded using Bruker DPX 400 spectrometer. Chemical shifts were measured in deuteriated chloroform unless otherwise stated. Coupling constants (*J*) are quoted in Hertz. Mass Spectra were obtained using a VG Alto spectrometer (HRMS). Melting points were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus and are uncorrected.

Endo-7-oxabicyclo[2.2.1]hept-5-ene-2-nitrile 10 and _exo_-7-oxabicyclo[2.2.1]hept-5-ene-2-nitrile 11[2]

Furan (0·96 mL, 14 mmol), acrylonitrile, (0·67 mL, 10 mmol) and zinc iodide (0·97 g, 3 mmol) were stirred in a closed system for 48 hours at 40 °C. The reaction mixture was diluted with ethyl acetate, washed with aqueous sodium thiosulfate solution and concentrated to give an oil (1·08 g, 90%) b.p. 59-62 °C (1mm Hg) consisting of two diastereoisomers, which were separated by column chromatography, using hexane-ethyl acetate (7:3) as eluant.

Exo δ_H ($CDCl_3$) 1·76 (1H, dd, *J* 11·5, 8·5, C$\underline{H}_{2\ exo}$ (C-3)), 2·17-2·02 (1H, m, C$\underline{H}_{2\ endo}$ (C-3)), 2·44 (1H, dd, *J* 8·5, 4, C$\underline{H}$ (C-2)), 5·18 (1H, s, C$\underline{H}$, (C-1)), 5·24 (1H, d, *J* 4, C$\underline{H}$, (C-4)), 6·30 (1H, d, *J* 6, C$\underline{H}$, (C-5)) and 6·42 (1H, d, *J* 6, C$\underline{H}$, (C-6)) ppm; δ_C 27·2 (C-2), 31·0 (C-3) 77·6 (C-1), 80·8 (C-4), 133·1 (C-6) and 137·0 (C-5) ppm; *Endo* δ_H ($CDCl_3$) 1·53 (1H, ddd, *J* 13·1, 3·5 and 1·5, C$\underline{H}_{2,\ endo}$ (C-3)), 2·29 (1H, ddd, *J* 13·7, 10 and 3·5 C$\underline{H}_{2,\ exo}$ (C-3)), 2·95 (1H, dt, *J* 9·5 and 4·3, C$\underline{H}$ (C-2)), 5·13 (1H, d, *J* 4·5, C$\underline{H}$ (C-4)), 5·22 (1H, d, *J* 4·5, C$\underline{H}$ (C-1)), 6·47 (1H, d, *J* 6, C$\underline{H}$(C-5)) and 6·56 (1H, d, *J* 6, C$\underline{H}$ (C-6)) ppm; δ_C 25·7 (C-2), 31·0 (C-3), 78·3 (C-1),78·5 (C-4), 121·6 (CN) 132·3 (C-6) and 137·3 (C-5) ppm; ν_{max} 3014, 2962, 2240, 1453, 1319, cm^{-1}.

Ethyl 2-*endo*-7 oxabicyclo[2.2.1]hept-5-ene-2-carboxylate 12 and ethyl 2-*exo*-7 oxabicyclo[2.2.1]hept-5-ene-2-carboxylate 13[14]



Furan (0·96 mL, 14 mmol) ethyl acrylate, (1·1 mL,10 mmol) and zinc iodide (0·97 g, 3 mmol) were stirred in a sealed pressure tube at 40 °C for 24 hours. The mixture was diluted with ethyl acetate and washed with sodium thiosulfate, dried with anhydrous magnesium sulfate and concentrated. The product was obtained as an oil (1·39 g, 83%) b.p. 50-55 °C (1mm Hg) and consisted of a mixture of *endo*- and *exo*-isomers which were separated by column chromatography using hexane-ethyl acetate (10:1) as eluant.

Endo δ_H ($CDCl_3$) δ 1·24 (3H, t, $C\underline{H}_3$, *J* 7), 1·58 (1H, dd, *J* 11·5, 4 $C\underline{H}_{2\ endo}$ (C-3)), 2·09 (1H, ddd, *J* 11, 7, 5, $C\underline{H}_{2exo}$ (C-3)), 3·10 (1H, dd, *J* 8·5, 3·7 C<u>H</u> (C-2)), 4·09 (2H, m, $C\underline{H}_2CH_3$,), 5·01 (1H,dd, *J* 4·5, 1 C<u>H</u>(C-4)), 5·16 (1H, dd, *J* 4·5, 1 C<u>H</u>(C-1)), 6·22 (1H, dd, *J* 6, 1·5, C<u>H</u> (C-5)) and 6·43 (1H, dd, *J* 6, 1·5, C<u>H</u> (C-6)) ppm; δc 13·7 ($\underline{C}H_3$), 28·1 (C-3), 42·5 (C-2), 60·0 ($\underline{C}H_2CH_3$), 78·6 (C-1), 79·7 (C-4),132·1 (C-6), 136·5 (C-5) and 171·6 (C=O) ppm. ν_{max} 3089, 2983, 1735(carbonyl), 1450, 1371, 1321, 1303, 1195, 1130, 1054, 1025, 904, 854, 794 and 701cm^{-1};

Exo δ_H ($CDCl_3$) 1·30 (3H, t, $C\underline{H}_3$, *J* 7), 1·56 (1H, dd, *J* 8·5, 3·7, $C\underline{H}_{2\ endo}$), 2·18 (1H, ddd, *J* 11·5, 4·8, 3·7, $C\underline{H}_{2\ exo}$ (C-3)), 2·42 (1H, dd, *J* 8·5, 3·7, C<u>H</u> (C-2), 4·20 (2H, q, *J* 7, $C\underline{H}_2CH_3$,), 5·07 (1H, dd, *J* 4·8, 1·8, C<u>H</u> (C-4)), 5·20 (1H, d, *J* 1·8 C<u>H</u> (C-1)), 6·38 (1H, dd, *J* 6, 1·2, C<u>H</u> (C-5)) and 6·40 (1H, dd, *J* 6, 1·2, C<u>H</u>(C-6)) ppm; δ_C 14·2 ($\underline{C}H_3$), 28·6 (C-3), 42·5 (C2), 60·4 ($\underline{C}H_2CH_3$), 77·5 (C-4), 80·5 (C-1), 134·3 (C-53), 136·6 (C-6) and 173·2 (C=O) ppm; ν_{max} 3081, 2985, 2906, 1735 (carbonyl), 1450, 1392, 1369, 1342, 1315, 1276, 1214, 1095, 1018, 927, 873,829,808,757 and 721 cm^{-1}

General reaction procedure for acylative ring-opening performed on cyclic ethers

4 methoxy phenyl acetic acid (1 equivalent) was dissolved in toluene (15 mL) and triflouroacetic acid (1 equivalent) was added. The solution was then cooled to 0 °C and a cyclic ether (1 equivalent) was added. The reaction was refluxed for six hours. It then cooled, diluted with water, extracted with diethylether, washed with sodium hydrogencarbonate, dried with magnesium sulfate and the diethylether was removed at reduced pressure.

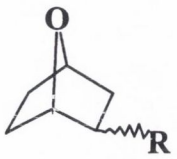
Attempted ring-opening reaction of *Endo*-7-oxabicyclo[2.2.1]hept-5-ene-2-nitrile 10 and *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2-nitrile 11

Each isomer (1·21 g, 0·01 mol) was reacted separately as described above and was returned unchanged (by NMR evidence).

Attempted ring-opening reaction of ethyl 2-*endo*-7 oxabicyclo[2.2.1]hept-5-ene-2-carboxylate 12 and ethyl 2-*exo*-7 oxabicyclo[2.2.1]hept-5-ene-2-carboxylate 13

Each isomer (1·68g, 0·01 mol) was reacted separately as described above and was returned unchanged.

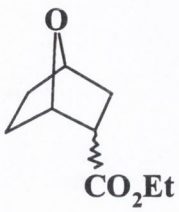
General procedure for the synthesis of 2-substituted 7-oxabicyclo[2.2.1]heptanes 28



The unsaturated compound (1 equivalent) was dissolved in ethanol (10 mL/g). Palladium on carbon catalyst (0·05 equivalent) was then added and the mixture was

left stirring until the hydrogen intake ceased. The catalyst was filtered and the solvent removed at reduced pressure.

Ethyl 7-oxabicyclo[2.2.1]hept-5-ane-2-*exo*-carboxylate and ethyl 7-oxabicyclo[2.2.1]hept-5-an-2-*endo*-carboxylate [14]

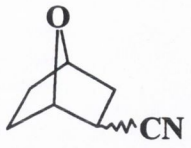


The product was obtained as an oil (0·77 g, 90%) b.p.42-46 °C (1mm Hg) from ethyl 7 oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (0·84 g, 0·005 mol)

Exo δ_H ($CDCl_3$) 1·27 (3H, t, CH_3, *J* 7), 1·50 (2H, m, $C\underline{H}_2$ (C-5)) 1·74 (3H, m, $C\underline{H}_2$ (C-6) and $C\underline{H}_{2\ endo}$), 2·13 (1H, ddd, *J* 12, 10, 5, $C\underline{H}_{2\ exo}$ (C-3)), 2·60 (1H, dd, *J* 9, 5, C<u>H</u> (C-2)) 4·16 (2H, q, *J* 7,$C\underline{H}_2CH_3$,), 4·67 (1H,t, *J* 5, C<u>H</u> (C-4)) and 4·83 (1H,d, *J* 4·5, C<u>H</u> (C-1) ppm; δ_C 13·7 ($\underline{C}H_3$), 28·9 (C-5), 29·1 (C-6), 33·9 (C-3), 47·62 (C-2), 60·3 ($\underline{C}H_2CH_3$), 76·3 (C-4) 78·8 (C-1) and 173·0 (C=O) ppm ; ν_{max} 2989, 2959, 2239, 1816, 1740, 1612, 1513, 1465, 1250, 1179, 1034, 929 and 814 cm^{-1};

Endo δ_H ($CDCl_3$) 1·24 (3H, t, J 7, $C\underline{H}_3$), 1·50 (3H, m, $C\underline{H}_{2\ endo}$ (C-3) and $C\underline{H}_2$ (C-5), 1·87 (2H, d, *J* 7, $C\underline{H}_2$, (C-6)), 2·97 (1H, dd, *J*, 7,1, C<u>H</u> (C-2)), 4·11(2H, q, *J* 7,$C\underline{H}_2CH_3$), 4·56 (1H, t, *J* 5 C<u>H</u>, (C-4)), 4·61 (1H,t, *J* 5, C<u>H</u>, (C-1)) ppm;δ_C 13·7 ($\underline{C}H_3$), 25·8 (C-5), 29·3 (C-6), 32·7 (C-3), 47·5 (C-2), 60·6 ($\underline{C}H_2CH_3$), 77·5 (C-4), 77·7 (C-1) and 172·0 (C=O) ppm; ν_{max} 3463, 2982, 2875, 1731, 1649, 1448, 1370, 1346, 1308, 1274, 1187, 1095, 1063, 1044, 1002, 928, 904, 868, 817 and 702cm^{-1}.

7-Oxabicyclo-[2.2.1]-hept-5-an-2-*endo*-nitrile and 7-oxabicyclo-[2.2.1]-hept-5-an-2-*exo*-nitrile[17]



An oil (0·54 g, 88%) b.p. 42-46 °C (1mm Hg) was obtained from 7-oxabicyclo-[2.2.1]-hept-5-ene-2-nitrile (0·61 g, 0·005 mol)

Exo δ_H ($CDCl_3$) 1·38 (2H, m, $C\underline{H}_2$ (C-5)), 1·72 (2H, m, $C\underline{H}_2$ (C-6)), 2·14 (2H, m, $C\underline{H}_2$ (C-3)), 2·64 (1H, m, C<u>H</u>, (C-2)), 4·74 (1H, m, C<u>H</u>, (C-4)), 4·78 (1H, m, C<u>H</u> (C-1)) ppm; δ_C 29·7 (C-5), 32·8 (C-2), 39·5 (C-6), 47·5 (C-3),79·1 (C-4) and 120·4 (C-6); ν_{max} 2989, 2959, 2239, 1816, 1740, 1612, 1513, 1465, 1250, 1179, 1034, 929 and 814 cm^{-1} ; *Endo* δ_H ($CDCl_3$) 1·74 (2H, m, $C\underline{H}_2$, (C-5)), 1·96 (2H, m, $C\underline{H}_2$,(C-6)), 2·17 (2H, m, $C\underline{H}_2$ (C-3)), 2·86 (1H, m, C<u>H</u> (C-2)), 4·72 (1H, m, C<u>H</u> (C-4)), 4·79 (1H, m, C<u>H</u> (C-1)); δ_C 25·8 (C-5), 29·3 (C-6), 30·7 (C-2), 35·7 (C-3), 76·7 (C-4) and 120·1 (CN), ppm.

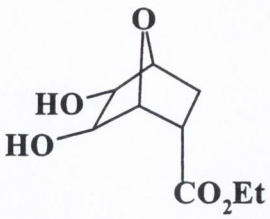
Attempted ring-opening reaction of 7-oxabicyclo-[2.2.1]-hept-5-an-2-*endo*-nitrile and 7-oxabicyclo-[2.2.1]-hept-5-an-2-*exo*-nitrile

A mixture of the two diastereomers (1·23 g, 0·01 mol) was reacted as described above and was returned unchanged.

Attempted ring-opening reaction of ethyl 7 oxabicyclo[2.2.1]hept-5-an-2-carboxylate

A mixture of the two diastereomers (1·70 g, 0·01 mol) was reacted as described above and was returned unchanged.

Ethyl 2 –*exo*,3-*exo*-dihydroxy-7-oxabicyclo-[2.2.1]-heptan-5-*endo*-carboxylate 29

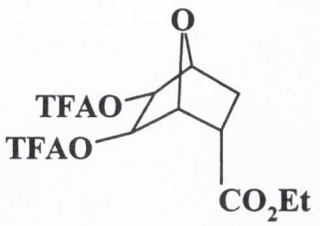


11 (0·5 g, 2·9 mmol) was dissolved in 10 mL of a 7:3 solution of *tert*-butanol and water and cooled to 0 °C. To this was added dropwise potassium permanganate (0·47 g, 2·9 mmol) dissolved in a little water and sodium hydrogencarbonate (0·12 g, 1·45 mmol) also dissolved in a little water. The reaction was then stirred for two and a half hours at 0 °C. The reaction mixture was filtered through Celite to remove manganese dioxide. The filtrate was extracted using ethyl acetate,dried and evaporated.

A solid (0·44 g, 74%) m.p. 76-78 °C, δ_H ($CDCl_3$) 1·28 (3H, t, *J* 7, C$\underline{H}_3$), 1·77 (1H, dd, *J* 9·5,3·5, C$\underline{H}_{2\ endo}$ (C-3)), 1·90 (1H, m, ddd, 13, 7, 1·5 C$\underline{H}_{2\ exo}$(C-3)), 2·95 (1H, m, C$\underline{H}$ (C-2)), 3·75 (2H, br s, OH), 3·92 (2H, m, C$\underline{H}$ (C-5 and C-6), 4·15 (2H, m, C$\underline{H}_2$CH$_3$), 4·38 (1H, d, *J* 5·5, C$\underline{H}$ (C-4)) and 4·49 (1H, d, *J* 5·5, C$\underline{H}$ (C-1)) ppm; δ_C 14·1 (C$\underline{H}_3$), 28·2 (C$\underline{H}_2$), 44·1 (C$\underline{H}$), 61·5 (C$\underline{H}_2$-O), 71·8 (C-5), 74·6 (C-6), 82·7 (C-1) and 83·3 (C-4) ppm; ν_{max} 3369, (br, OH), 2952, 1725,1376, 1346,1317,1261,1191,1072, 1041, 964, 910, 813 and 721cm^{-1}.

HRMS (CI): *Found*: m/z 225·0752; *calculated for* $[C_9H_{14}O_5 + Na]^+$ 225·0739

Ethyl 2 –*exo*,3-*exo*-ditrifluoroacetoxy -7-oxabicyclo-[2.2.1]-heptan-5-*endo*-carboxylate 30



The diol **29** (0·033 g, 0·16 mmol) was dissolved in pyridine (0·5 mL) and cooled to 0 °C. Trifluoroacetic anhydride (0·025 mL, 0·18 mmol) was then added. The reaction mixture was allowed to come to room temperature and then was stirred for 6 hours. The solution was diluted with ether, poured onto ice, stirred and acidified using hydrochloric acid. The ethereal layer was washed with water followed by sodium hydrogen carbonate, dried and evaporated.

An oil (0·05 g, 77%) b.p. 40-43 °C (2mm Hg) δ_H ($CDCl_3$) 1·31 (3H, t, *J* 8 C$\underline{H}_3$), 1·80 (1H, dd, *J* 13, 5, C$\underline{H}_{2\ endo}$), 2·03 (1H, ddd, *J* 12, 6·5, 1·5 , C$\underline{H}_{2\ exo}$), 3·06 (1H, multiplet, C$\underline{H}$ (C-2)), 4·23 (2H, m, C$\underline{H}_2CH_3$), 4·61 (2H, m, C$\underline{H}$ (C-5 and C-6) and 4·65 (1H, d, *J* 6 C$\underline{H}$, (C-4)) and 4·70 (1H, d, *J* 6, C$\underline{H}$ (C-1) δ_C13·6 (C$\underline{H}_3$), 26·3 (C$\underline{H}_2$), 42·2 (C$\underline{H}$), 61·2 (C$\underline{H}_2$-O), 79·9 (C-5), 80·8 (C-6), 81·7 (C-1), 83·8 (C-4), 116·1 (C$\underline{F}_3$) 153·9 (C=OCF_3) and 170·2 (C=O) ppm; δ_F -75·5 (C$\underline{F}_3$) ppm; ν_{max} 3421, 2985, 1787(trifluoroacetate carbonyl), 1729(acetate carbonyl), 1457, 1375, 1348, 1189, 1081, 995, 929, 798 and 732cm^{-1}.

HRMS (CI): *Found*: m/z 225·0752; *calculated for* $[C_9H_{14}O_5 + Na]^+$ 225·0739 = **29**

$[C_{13}H_{12}O_7 - 2 \times COCF_3 + H + Na]$

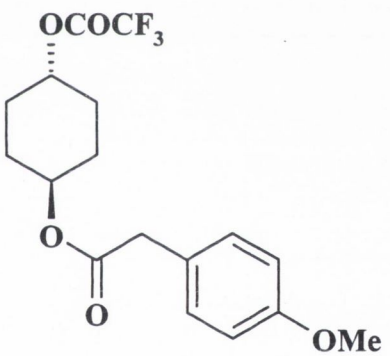
Attempted ring-opening reaction of ethyl 2 –*exo*,3-*exo*-ditrifluoroacetoxy -7-oxabicyclo-[2.2.1]-heptan-5-*endo*-carboxylate 30

The trifluoroacetoxy compound **30** (3·94 g, 0·01 mol) was reacted as described above and was returned unchanged.

Ring-opening reaction of 7-oxabicyclo[2.2.1]heptane 33

7-Oxabicyclo[2.2.1]heptane **33** (1 g, 0·01 mol) gave an oil (1·83 g) which consisted of a mixture of compounds **34** and **35** which were separated by column chromatography using a system of hexane-ethyl acetate (95:5) as eluant.

1-Trifluoroacetoxy,4-(4'-methoxyphenylacetoxy)cyclohexane 34

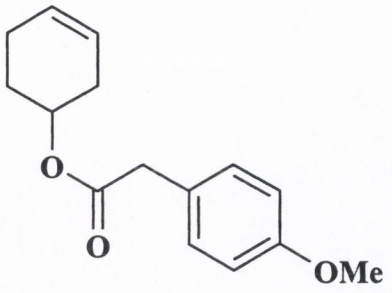


An oil (0·80 g)δ_H ($CDCl_3$) 1·71-1·75 (4H, m, (2 x $C\underline{H}_2$)), 1·84-1·89 (4H, m, (2 x $C\underline{H}_2$)),3·57 (2H, s, $OC\underline{H}_2$), 3·81 (3H, s, $C\underline{H}_3$), 4·91 (1H, m, C<u>H</u> (C-1)),5·06 (1H, m, C<u>H</u> (C-4)), 6·88 (2H, d, *J* 8·5, Ar C<u>H</u> (C-2 & C-6)) and 7·20 (2H, d, *J* 8·5, Ar C<u>H</u> (C-3 & C-5)) ppm; δ_C 26·3 (C-6), 26·6 (C-3), 29·2 (C-5),30·2 (C-2), 40·3 ($\underline{C}H_2$), 54·8 ($\underline{C}H_3$), 69·6 (C-1), 74·5 (C-4), 113·5 (Ar C-3 and C-5) 129·7 (Ar C-2 and C-6), 158·3 ($\underline{C}$-OCF_3) and 170·9 ($\underline{C}$=OCH_2) ppm; δ_F -75·8 ($C\underline{F}_3$) ppm; ν_{max} 2952, 2839, 1779 (trifluoroacetic ester), 1728 (phenyl ester) 1613, 1585, 1513, 1459 cm^{-1}.

HRMS (CI): *Found*: m/z 287·1245; *calculated for* $[C_{15}H_{20}O_4 + Na]^+$ 287·1259 = **36**

$[C_{17}H_{19}O_5F_3 - COCF_3 + H + Na]^+$

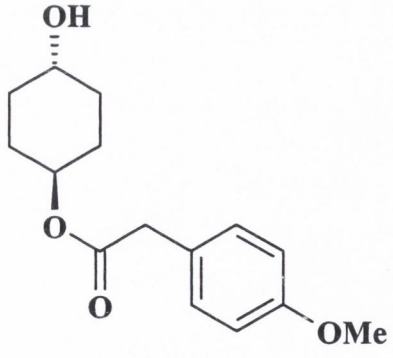
4-(4'-Methoxyphenylacetoxy)cyclohex-1-ene 35



An oil (0·63 g) δ_H ($CDCl_3$) 1·68-1·71 (2H, m, C<u>H</u>$_2$), 1·82-1·88 (2H, m, C<u>H</u>$_2$), 2·10-2·15 (2H, m, C<u>H</u>$_2$), 3·57 (2H, s, C<u>H</u>$_2$), 3·81 (3H, s, C<u>H</u>$_3$), 5·06 (1H, m, C<u>H</u> (C-4)), 5·60 (1H, m, C<u>H</u>, olefinic), 5·70 (1H, m, C<u>H</u> olefinic), 6·88 (2H, d, *J* 8·5, Ar C<u>H</u> (C-2 & C-6)) and 7·20 (2H, d, *J* 8·5, Ar C<u>H</u> (C-3 & C-5) ppm; δ_C 20·9 (<u>C</u>H$_2$), 23·0 (<u>C</u>H$_2$), 29·6 (<u>C</u>H$_2$), 40·7 (<u>C</u>H$_2$), 54·8 (<u>C</u>H$_3$), 69·9 (C-4), 113·6 (Ar C-3 and C-5), 123·5 (C=C), 123·5 (C=C), 130·1 (Ar C-2 and C-6) and 171·1 ppm. ν_{max} 3413, 2941, 1725 (phenyl ester), 1676, 1599, 1512, 1458, 1300, 1247, 1207, 1165, 1067, 1032, 960, 820 and 800cm^{-1}.

HRMS (CI): *Found*: m/z 269·1151; *calculated for* $[C_{15}H_{18}O_3 + Na]^+$ 269·1154

***trans*-4(4'-Methoxyphenylacetoxy)cyclohexanol 36**



The trifluoroacetate **34** (0·208 g, 0·57 mmol) was dissolved in a methanolic solution of sodium hydrogen carbonate (10%) and stirred at room temperature for two hours.

Water was then added and the organic portion was extracted with ether dried with magnesium sulfate and evaporated.

An oil (87%) δ_H ($CDCl_3$) 1·961-1·99 (4H, m, (2 x $C\underline{H}_2$), 2·19-2·22 (4H, m, (2 x $C\underline{H}_2$)),3·54 (2H, s, $OC\underline{H}_2$), 3·81 (3H, s, $C\underline{H}_3$), 3·71-3·75 (1H, m, C<u>H</u> (C-1)),4·75-4·78 (1H, m, C<u>H</u> (C-4)), 6·87 (2H, d, *J* 8·5, Ar C<u>H</u> (C-2 & C-6)) and 7·20 (2H, d, *J* 8·5, Ar C<u>H</u> (C-3 & C-5)) ppm; δ_C 26·6 ($\underline{C}H_2$), 28·3 ($\underline{C}H_2$), 31·9 ($\underline{C}H_2$), 36·6 ($\underline{C}H_2$), 40·3 ($\underline{C}H_2$), 54·8 ($\underline{C}H_3$), 68·4 (C-1), 71·5 (C-4), 113·4 (Ar C-3 and C-5) 129·7 (Ar C-2 and C-6), and 170·9 ($C{=}OCH_2$) ppm; ν_{max} 3399, 2939, 2861, 1727, 1612, 1513, 1457, 1301, 1247, 1164, 1072, 1033, 958, 902, 821, 798 and 725cm^{-1}.

HRMS (CI): *Found*: m/z 287·1245; *calculated for* $[C_{15}H_{20}O_4 + Na]^+$ 287·1259

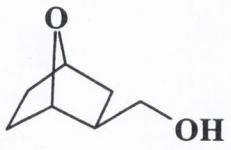
<u>Ring-opening reaction of 7-oxabicyclo[2.2.1] heptane 33 in the presence of sodium iodide</u>

para-Methoxyphenylacetic acid (0·83 g, 5 mmol) and trifluoroacetic anhydride (1·15 g, 0·77 mL, 5·5 mmol) were dissolved in acetone (2 mL). Sodium iodide (2·25 g, 15 mmol) was added and the solution was cooled to 0 °C and 7-oxabicyclo[2.2.1] heptane (0·5 g, 5 mmol) was added in. The resulting solution was then refluxed for 6 hours. The solution was then cooled and worked up by extracting with ether, washing with sodium thiosulfate, drying with magnesium sulfate and concentrating.

<u>Reaction of products obtained from sodium iodide experiment with DBU</u>

The product mixture (54 mg) obtained from the above reaction was reacted with DBU (0·036mL, 0·24 mmol) and heated for one hour at 90 °C. The reaction mixture was diluted with ether and then washed with hydrochloric acid followed by brine, dried with magnesium sulfate and concentrated to give the alkene **35** (0·032 g).

2-*exo*-Hydroxymethyl-7-oxabicyclo[2.2.1]heptane 39[14]

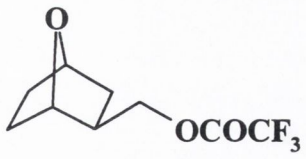


The ester **10** (1·38 g, 8 mmol) was dissolved in THF (50 mL). Under an atmosphere of nitrogen, lithium aluminium hydride (0·37 g, 9·7 mmol) was added and the mixture was refluxed for 11 hours. The reaction mixture was then quenched with aqueous ammonium chloride solution. The product was obtained by extraction with dichloromethane. The organic layer was dried and evaporated under reduced pressure.

An oil (0·70 g, 68%) b.p. 41-45 °C (1mm Hg) δ_H ($CDCl_3$) 1·35 (1H, m, $C\underline{H}_{2\ endo}$ (C-3)) 1·47 (2H, dd, $C\underline{H}_{2\ exo}$, *J* 6·5, 2·5), 1·60 (1H, dd, *J* 12, 3 C<u>H</u> (C-2) 1·70-1·76 (2H, m, $C\underline{H}_2$ (C-6)), 1·93-1·96 (2H, m, $C\underline{H}_2$ (C-5), 2·36 (1H, br. s, O<u>H</u>), 3·46 (2H, m, $C\underline{H}_2OH$), 4·49 (1H, d, *J* 5, C<u>H</u> (C-4)) and 4·57 (1H,t, *J* 4·5,C<u>H</u> (C-1),)ppm; δ_C 28·9 (C-6), 29·5 (C-5), 33·4 (C-3) 44·9 (C-2), 65·1 (<u>C</u>H_2OH), 75·8 (C-4) and 77·8 (C-1) ppm.ν_{max} 3399, 2975, 2872, 1467, 1272, 1203, 1163, 1106, 1047, 988, 929, 863, 808 and 793cm^{-1}.

HRMS (CI): *Found*: m/z 151·0452; *calculated for* $[C_7H_{12}O_2 + Na]^+$ 151·0425

2-*exo*- trifluoroacetoxymethyl-7-oxabicyclo[2.2.1]heptane 40



The alcohol **39** (0·12 g, 0·59 mmol) was dissolved in chloroform (2 mL) and trifluoroacetic anhydride (0·08 mL, 0·62 mmol) was then added. The reaction mixture was refluxed for ninety minutes and cooled. It was washed with sodium hydrogen carbonate, followed by brine, dried and concentrated.

An oil (0·11 g, 82%) δ_H ($CDCl_3$) 1·27-1·33 (1H, m, $C\underline{H}_2$ endo (C-3)), 1·48-1·50 (2H,m, $C\underline{H}_2$ (C-5), 1·66-1·71 (1H, dd, *J* 13, 4, $C\underline{H}_2$ exo (C-3)), 1·74-1·80 (2H, m, $C\underline{H}_2$ (C-6)) 2·20 (1H, ddd, *J* 13, 8·5, 4, C<u>H</u> (C-2)), 4·12-4·14 (2H, m, $C\underline{H}_2$OTFA), 4·43 (1H, d, *J* 5, C<u>H</u> (C-4)) and 4·61 (1H,d, *J* 5, C<u>H</u> (C-1)) ppm; δ_C 29·0 (C-6), 29·8 (C-5), 33·6 (C-3), 41·9 (C-2), 69·5 ($\underline{C}H_2$), 76·1 (C-4) and 77·3 (C-1), 112·6 ($\underline{C}F_3$) and 156·7 (C=O) ppm;δ_F -75·62 ($C\underline{F}_3$) ppm ; ν_{max} 3482, 2983, 2960, 2877, 1785, 1465,1400, 1365, 1342, 1224, 1157, 1054, 991, 933, 867, 809 and 728cm^{-1}.

HRMS (CI): *Found*: m/z 151·0452; *calculated for* $[C_7H_{12}O_2 + Na]^+$ 151·0425 = **39** $[C_9H_{11}O_3F_3 - COCF_3 + H + Na]^+$

Attempted ring-opening reaction of 2-*exo*- trifluoroacetoxymethyl-7-oxabicyclo[2.2.1]heptane 40

The trifluoroacetate compound **40** (2·24 g, 0·01 mol) was reacted as described above and were returned unchanged.

Attempted ring-opening reaction of 1,8-cineole 42

1,8-cineole **42** (1·54 g, 0·01 mol) were reacted under the usual conditions and were returned unchanged.

Attempted ring-opening reaction of phthalan 48

Phthalan (1·20 g, 0·01 mol) was reacted as described above and was returned unchanged.

2.10 References

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Chapter 3

Acylative cleavage of 2,5-dihydrofuran and reactions of the subsequent products

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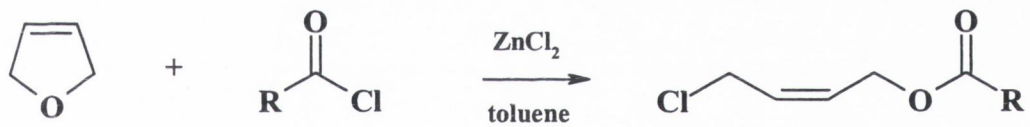
Acylative cleavage of 2,5-dihydrofuran and reactions of the subsequent products

3.1 Lewis acid-catalysed acylative cleavage reactions of 2,5-dihydrofuran

Since most of the reported studies on ring-opening reactions of hydrofurans have concentrated on the tetrahydrofuran system, it seemed appropriate to investigate acylative cleavage of the ether bond of 2,5-dihydrofuran **1** and to carry out some reactions on the resulting products.

In the present work 2,5-dihydrofuran **1** was reacted with various acid chlorides **2** in toluene solution in the presence of the Lewis acid zinc chloride as catalyst to give (Z)-configured 1-acyloxy-4-chlorobut-2-enes of the type **3** **(Scheme 1)**.

Synthesis of 1-acyloxy-4-chlorobut-2-enes from reaction of 2,5-dihydrofuran and an acyl chloride with zinc chloride as catalyst



(1) (2) (3)

Scheme 1

The reaction was successful for different types of acyl chloride *i.e.* aromatic, aryl, alkyl, unsaturated and aliphatic acid chlorides, as indicated below **(Table 3.1)**.

Table 3.1

Zinc chloride catalysed acylative ring-opening reaction of 2,5-dihydrofuran

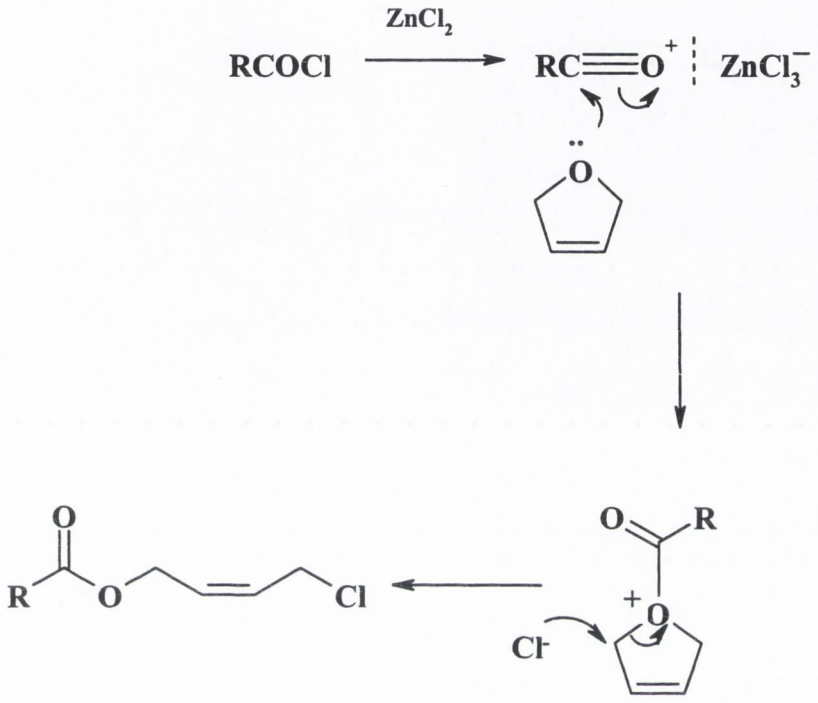
Acyl halide	% Yield of 3
PhCOCl	87
$PhCH_2COCl$	71
$Cl(CH_2)_3COCl$	70
$(CH_3)_2C{=}CHCOCl$	82
BuCOCl	75

Each of the unsaturated chloro-esters **3** displayed in their proton NMR spectra signals in the δ 5-6 ppm region, which are typical of olefinic protons. In some cases the individual multiplicities could not be observed but those resonances which were clearer displayed coupling constants *J* of approximately 11 Hz. This value is borderline *i.e.* it could be at the high end of the recorded range for a *cis*-alkene or at the low end of the range for a *trans*-alkene. Accordingly, further proof of stereochemistry was required. With this in mind n.O.e. experiments were carried out to determine the relationship between the alkene protons and, as anticipated, they were found to be *cis* to each other. For example, in the case of **3** (where R = Bu), on irradiation of the C-4 methylene signal at δ 4·15 ppm, the C-1 methylene signal at δ 4·70 ppm displayed a positive n.O.e of 9%.

Thus, these acylative ring-opening reactions occur with retention of olefin geometry, presumably by the mechanism shown below **(Scheme 2)**. The presence of zinc chloride was found to be essential, as a control experiment showed that in its absence the only product recovered was the carboxylic acid formed by the

hydrolysis of the acid chloride during the work up. Presumably the 2,5-dihydrofuran **1** was lost during the work up due to its low boiling point.

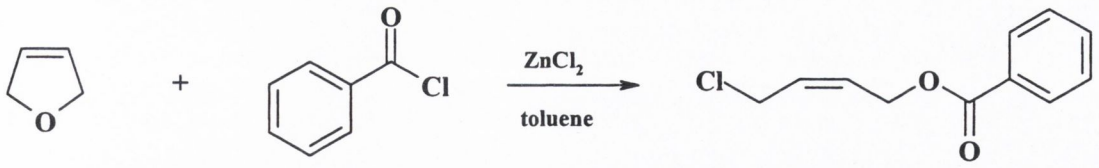
Proposed mechanism of reaction shown in Scheme 1



Scheme 2

The reaction of 2,5-dihydrofuran **1** with benzoyl chloride **4** in the presence of zinc chloride in toluene gave the product **5 (Scheme 3)**. This has been previously synthesised by Iqbal *et al.*[1] by cobalt-catalysed cleavage of 2,5-dihydrofuran **1** with benzoyl chloride. The infrared spectrum of **5** showed a carbonyl absorption for its ester group at 1727 cm^{-1}, a O-C-O bond absorption at 1268 cm^{-1} and an absorption at 710 cm^{-1} which is typical for a monosubstituted benzene ring. The ^1H NMR data for **5** agreed with that reported in the literature.[1] The spectrum displays two methylene group signals, both of which are doublets. The furthest upfield at δ 4·23 ppm is assigned to the chloromethyl group and another at δ 4·95 ppm is assigned to the ester-bearing methylene group at C-1. A 2-H multiplet at δ 5·90 ppm corresponds to the alkene protons. However the individual signals and multiplicities for each of these protons could not be distinguished.

Zinc chloride catalysed reaction of 2,5-dihydrofuran with benzoyl chloride

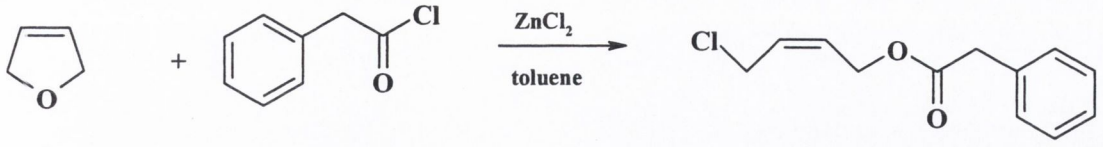


(1) (4) (5)

Scheme 3

The reaction of 2,5-dihydrofuran **1** with phenylacetyl chloride **6** under the same conditions resulted in formation of the expected product **7** **(Scheme 4).** The proton NMR spectrum of **7** displays three methylene group signals. A singlet at δ 3·74 ppm, is assigned to the benzylic methylene group. The remaining two methylene signals are assigned in the same way as in the case of the ester **5**, *i.e.* the signal that is more upfield at δ 4·14 ppm corresponds to the chloromethyl group, and that which is more downfield at δ 4·74 ppm is due to the C-1 methylene group. In contrast with the spectrum of **5** the alkene protons of **7** appeared as two distinct signals which could be individually assigned by a ^{1}H-^{1}H COSY experiment. A double triple triplet at δ 5·74 ppm is assigned to the C-2 olefinic proton and another double triple triplet at δ 5·88 ppm is assigned to the second olefinic proton at C-3. Both of these protons appear as double triple triplets due to coupling with the adjacent two equivalents methylene protons, and with the vicinal olefinic proton. The signal is further split by long-range coupling to the methylene group which lies in the *β*- position relative to each vinyl proton. The infrared spectrum of **7** showed an ester carbonyl group absorption at 1710 cm^{-1}, a O-C-O bond absorption at 1284 cm^{-1} and an aryl absorption at 700 cm^{-1}.

Zinc chloride catalysed reaction of 2,5-dihydrofuran with phenylacetyl chloride



(1) (6) (7)

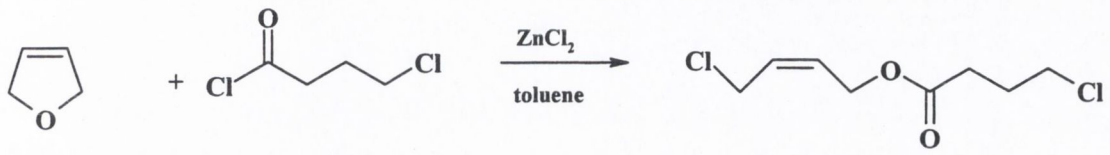
Scheme 4

The reaction of 2,5-dihydrofuran with 4-chlorobutanoyl chloride **8** yielded the product **9 (Scheme 5)**. The proton NMR spectrum of this compound displays five methylene group signals. The signal at highest field is assigned to the C-3' methylene group which appears as a quintet at δ 2·11 ppm. A triplet at δ 2·54 ppm is assigned to the C-2' methylene group. A triplet at δ 3·60 ppm is assigned to the C-4' methylene group. The remaining two methylene group signals resonate as doublets which are assigned in the same way as previously described *i.e.* the signal that is more upfield at δ 4·14 ppm corresponds to the C-4 methylene group and the more downfield signal at δ 4·70 ppm is due to the C-1 methylene group.

The two alkene protons of **9** appear as two distinct signals. A double triple triplet at δ 5·74 ppm is due to the olefinic proton at C-2 and another double triple triplet at δ 5·86 ppm is assigned to the C-3 olefinic proton. The (*Z*)-stereochemistry of the alkene **9** was confirmed from spin-decoupling and n.O.e. NMR experiments. When the resonance at δ 4·14 ppm was irradiated, the complexity of the double triple triplet at δ 5·86 ppm was reduced and the signal was evident as a baseline-resolved double triplet with *J* 11 and 1 Hz. Similarly, when the doublet at δ 4·70 ppm was irradiated, the double triple triplet at δ 5·74 ppm was also reduced and the signal was then apparent as a double triplet with *J* 11 and 1 Hz. Since the *J* value of 11 Hz was quite high for interproton coupling, this could suggest an (*E*)-double bond so n.O.e. experiments were also carried out which substantiated the assignment of (*Z*)-geometry to the double bond. On irradiation of the methylene

signal at δ 4·14 ppm the methylene signal at δ 4·70 ppm displayed a positive n.O.e of 9%. The infrared spectrum of **9** shows absorptions for an ester carbonyl group at 1735 cm^{-1} and for an O-C-O bond at 1240 cm^{-1}.

Zinc chloride catalysed reaction of 2,5-dihydrofuran with 4-chloro-butanoyl chloride

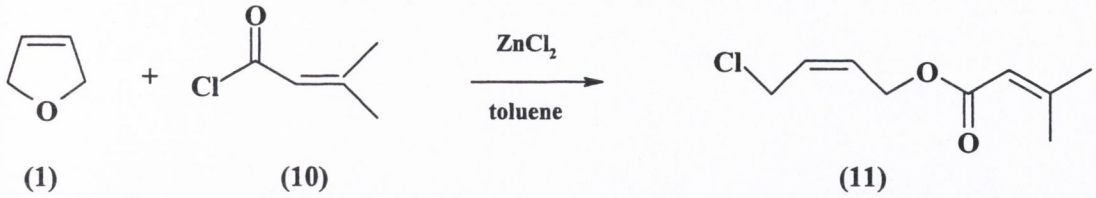


(1) (8) (9)

Scheme 5

The ester **11** was obtained from reaction of 2,5-dihydrofuran **1** with 3,3-dimethylacryloyl chloride **10 (Scheme 6)** under the usual conditions. The proton NMR spectrum of **11** displays two singlets at δ 1·92 ppm and at δ 2·19 ppm, which correspond to the two vinylic methyl groups. The more downfield signal is assigned to the methyl group that is *cis* to the carbonyl group. A doublet at δ 4·17 ppm corresponds to the C-4 methylene group. This is followed by another doublet at δ 4·71 ppm corresponding to the C-1 methylene group. A 1H singlet at δ 5·70 ppm is assigned to the C-2' olefinic proton. The vinyl protons at C-2 and at C-3 appear together as a multiplet at δ 5·81 ppm. The infrared spectrum of **11** shows a carbonyl group absorption at 1720 cm^{-1} an alkene absorption at 1649 cm^{-1} and a O-C-O bond absorption at 1259 cm^{-1}.

Zinc chloride catalysed reaction of 2,5-dihydrofuran with 3,3-dimethylacryloyl chloride

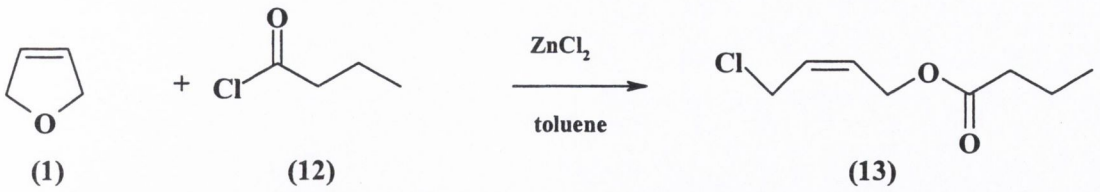


(1) (10) (11)

Scheme 6

The reaction of 2,5-dihydrofuran **1** with butanoyl chloride **12** yielded the product **13 (Scheme 7)**. The proton NMR spectrum of **13** displays a 3H triplet at δ 0·95 ppm which is assigned to the methyl group. There are also four methylene group signals in the spectrum. A sextet at δ 1·67 ppm is assigned to the C-3' methylene group. The C-2 methylene group appears as a triplet at δ 2·32 ppm. Of the two methylene signals that appear further downfield, the C-4 methylene group resonates at δ 4·15 ppm and the C-1 methylene group resonates at δ 4·70 ppm. The vinyl protons of **13** appear as two distinct signals. A double triple triplet at δ 5·75 ppm is due to the olefinic proton at C-2 and another double triple triplet at δ 5·85 ppm is assigned to the olefinic proton at C-3. The (*Z*)-stereochemistry of the double bond was confirmed from spin decoupling and n.O.e. NMR experiments. When the resonance at δ 4·15 ppm was irradiated, the complexity of the double triple triplet at δ 5·85 ppm was reduced and the signal was evident as a baseline-resolved double triplet displaying *J* values of 11 and 1 Hz. Similarly, when the doublet at δ 4·70 ppm was irradiated, the double triple triplet at δ 5·75 ppm was simplified and the signal was then apparent as a doublet with *J* values of 11 and 1 Hz. As a coupling constant of 11 Hz is a borderline value which could be interpreted as indicating that of either an (*E*)- or (Z)-double bond, n.O.e. experiments were carried out which verified the assignment of a double bond with (*Z*)-geometry. On irradiation of the methylene signal at δ 4·15 ppm the methylene signal at δ 4·70 ppm displayed a positive n.O.e. The infrared spectrum of **13** shows a carbonyl group absorption at 1735 cm^{-1} and a O-C-O bond absorption at 1253 cm^{-1}.

Zinc chloride catalysed reaction of 2,5-dihydrofuran with butanoyl chloride



(1) (12) (13)

Scheme 7

The results outlined above reveal that acylative ring-opening reactions of 2,5-dihydrofuran **1** to give a variety of 1-acyloxy-4-chlorobut-2-enes can be carried out successfully and that the *(Z)*-geometry of the double bond of 2,5-dihydrofuran **1** is preserved in the products.

3.2 Nucleophilic substitution reactions of 1-acyloxy-4-chlorobut-2-enes

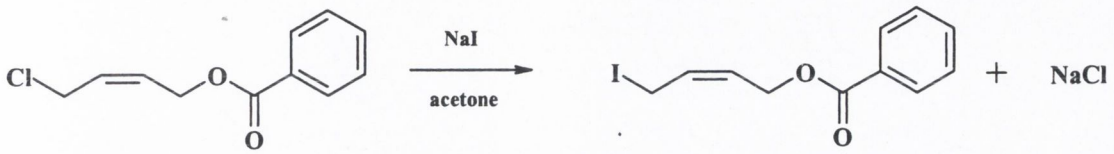
With a variety of (Z)-allylic chlorides in hand it was decided to attempt to displace the chlorine atom with various nucleophiles.

3.2.1 Nucleophilic displacement by iodide ion

The first nucleophile chosen was iodide ion, using sodium iodide as the source. The chloro-ester **5** (the model compound mainly used in this part of the work) was heated under reflux in acetone with 1·1 molar equivalents of sodium iodide during 6 hours but the reaction was found not to go to completion. NMR spectroscopy of the reaction mixture showed some new signals, namely an iodomethyl group at δ 3·91 ppm and two new olefinic signals at δ 5·68 ppm and at δ 6·02 ppm together with signals arising from unreacted starting material. On extension of the reaction time the same result was obtained. Butanone was then substituted as solvent as it has a higher boiling point than acetone and is one of the few other non-protic solvents in which sodium iodide is soluble. The outcome was the same with both solvents *i.e.* with short reaction times it was apparent that a new compound was

formed but not all of the starting material was consumed, and that with extended reaction times decomposition occurred. TLC was not useful as an analytical tool, as the product and starting material had the same Rf values.

Proposed Finkelstein reaction of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene



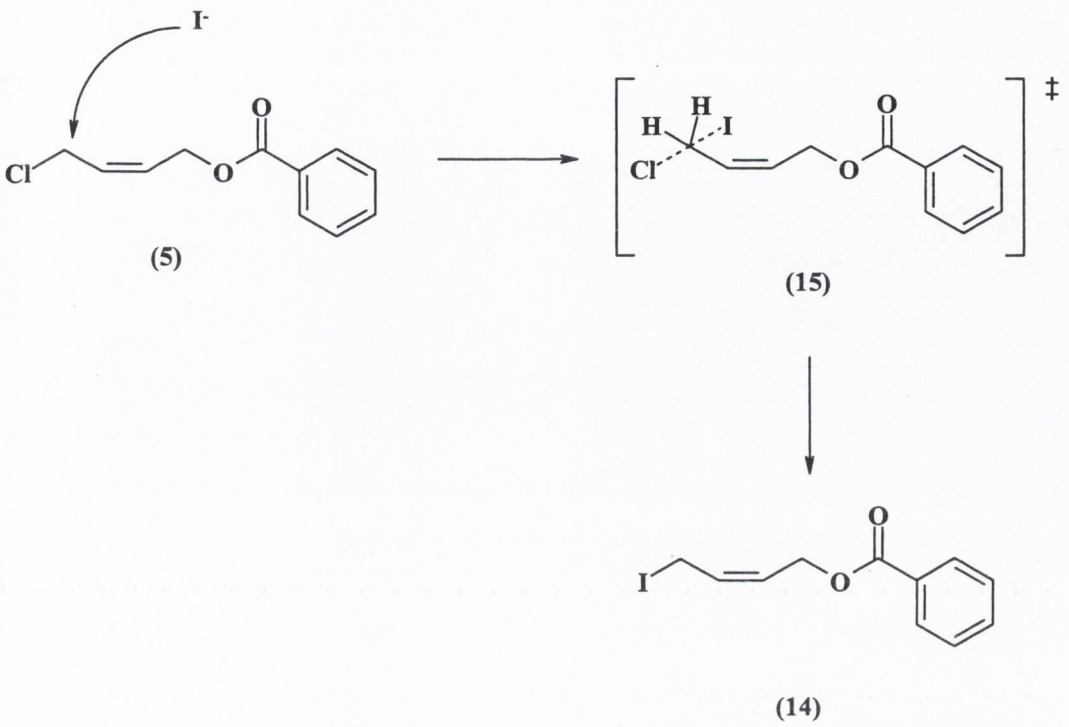
(5) (14)

Scheme 8

The displacement reaction shown in **Scheme 8**, is a Finkelstein[2] reaction which is usually a very straightforward reaction but does not seem to be so in this case. It appears that the chloride **5** does form the expected iodide **14** but that the product is very unstable due to the leaving group ability of iodide ion.

Two mechanisms are possible to cause this outcome. Firstly the reaction could proceed as an S_N2 reaction (**Scheme 9**). The iodide ion approaches the axis of the chlorine-carbon bond of the chloro-ester **5** in a typical S_N2 manner to result in the transition state **15** which then expels chloride ion is to give the iodide **14**.

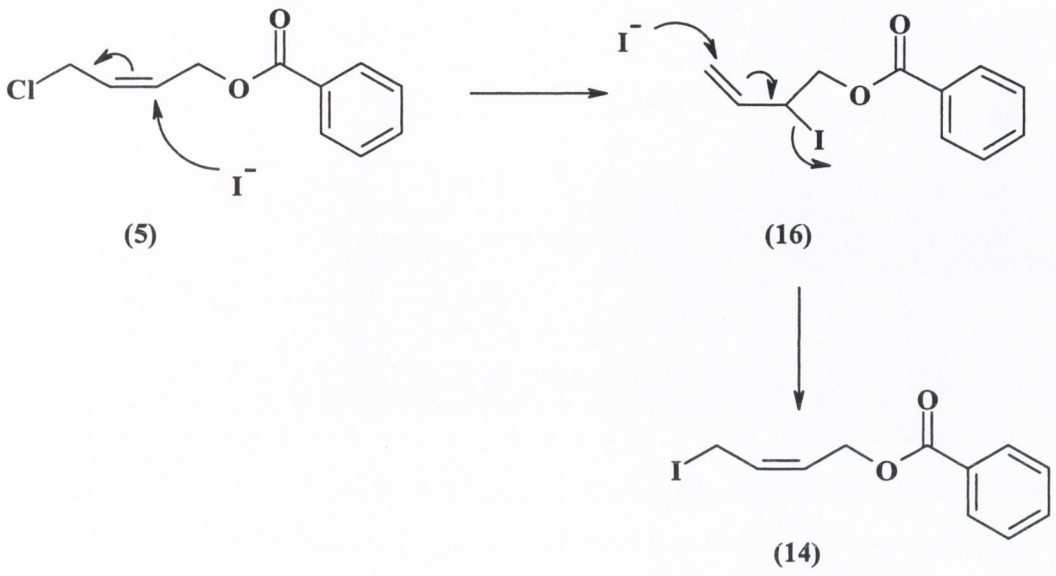
Suggested mechanism for previous reaction



Scheme 9

Alternatively the reaction could occur in an S_N2' manner **(Scheme 10)**. Here the iodide ion attacks the alkene at the least hindered side (as oxygen is a smaller atom than chlorine) resulting in migration of the double bond and expulsion of chloride ion. The newly formed terminal alkene **16** is highly susceptible to further nucleophilic attack by another iodide ion which occurs resulting in another S_N2' expulsion of iodide ion and a return of the double bond to its original position.

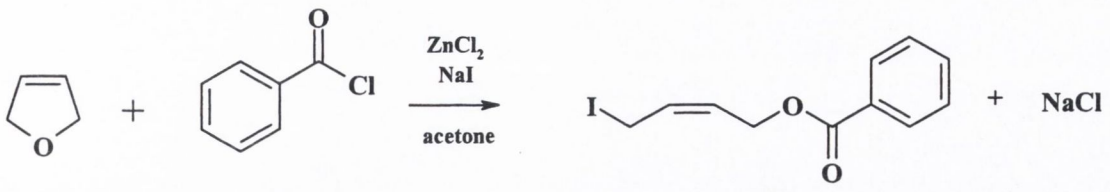
Alternative mechanism for reaction in Scheme 8



Scheme 10

On the basis that the geometry of the chloroester **5** might hinder attack by iodide ion at C-1, the synthesis of the target iodide **14** from 2,5-dihydrofuran **1** was attempted using the same methodology as that employed to synthesise the chloro-esters described above. Thus, the zinc chloride catalysed reaction between 2,5-dihydrofuran and benzoyl chloride was carried out in the presence of sodium iodide in the expectation that the acyl iodide PhCOI would be formed *in situ* from benzoyl chloride and would then react with 2,5-dihydrofuran **1** to give 1-benzoyloxy-4-iodobut-2-ene **14**. Alternatively the acyloxonium ion (shown in **Scheme 2**) derived from 2,5-dihydrofuran and benzoyl chloride might suffer attack by the better nucleophile iodide ion to give **14**.

Direct synthesis of (*Z*)-1-benzoyloxy-4-iodobut-2-ene from 2,5-dihydrofuran



(1) (4) (14)

Scheme 11

This reaction was carried out a number of times with and without zinc chloride being present and using either acetone or butanone as solvents, but the results were not very satisfactory. A complex ^{1}H NMR spectrum was obtained and was attributed as before to decomposition of the anticipated product **14**. Oku *et al.*[3] had performed similar reactions in acetonitrile solution with sodium iodide, an acid chloride and either tetrahydrofuran, its substituted derivatives or tetrahydropyran and the reaction was found to work with various acid chlorides and to give good yields of iodo-esters. No work had been carried out by Oku *et al.*[3] on 2,5-dihydrofuran **1** but, since the method was successful for cleavage of the ether bond of tetrahydropyran which usually requires relatively extreme conditions, it was anticipated that the method would be successful in the case of 2,5-dihydrofuran **1**.

Accordingly the reaction was then performed in acetonitrile using 2,5-dihydrofuran, benzoyl chloride and sodium iodide at room temperature for periods of up to 48 hours and the desired iodide **14** was obtained. The proton NMR spectrum of **14** displays a doublet at δ 3·99 ppm which is assigned to the C-4 methylene group. The C-1 methylene protons resonate as a double doublet at δ 4·92 ppm with coupling constants of 7 and 1·5 Hz. The two olefinic protons appeared as separate signals, *i.e.* as a double triplet at δ 5·68 ppm and as a multiplet centred at δ 6.02 ppm exhibiting $J_{3,4} \sim J_{3,2}$ of approximately 9·5 and 8, together with long-range coupling to the 1-CH_2 group with $J_{3,1} \sim$ 1·5Hz. The differences in multiplicities of each of the methylene groups is also due to the

long range coupling that exists between the protons at C-1 and C-3. Long-range coupling is not evident between the protons of C-2 and C-4.

3.2.2 Nucleophilic displacement reaction on a dichloride

It was then decided to repeat the iodide substitution reaction on the dichloride **9.** It was considered that the reaction of the chloride **5** with iodide ion may have been hindered by the large benzene ring so the chloride **9** was investigated due to its smaller aliphatic side-chain. It was hoped that one of three results would be achieved.

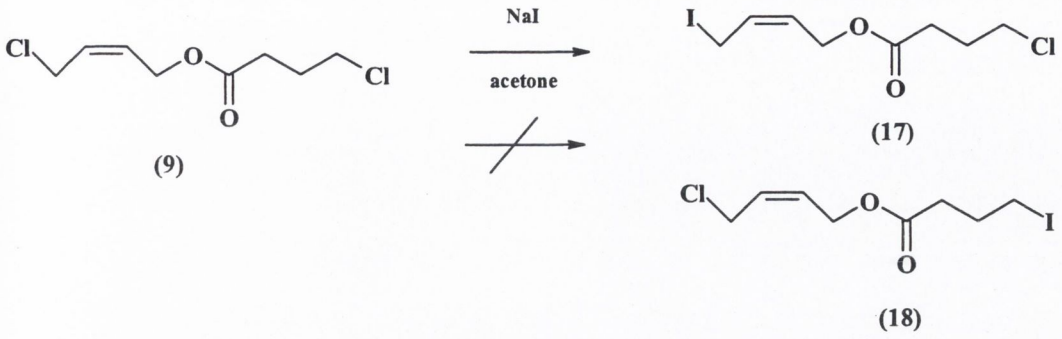
a) A substitution reaction by iodide ion in the saturated aliphatic chain as primary chlorides are quite reactive. This reaction would provide a more reactive chloro-iodo compound which could enable further transformations to be carried out.

b) Alternatively, reaction might proceed at the allylic centre as in the case of the chloro-ester **5**.

c) Substitution by iodide ion might occur at both possible positions.

When a Finkelstein reaction was attempted with the dichloride **9** a surprising result was obtained. The low reactivity of the allylic chlorine in the benzoate **5** had suggested that the 4'-chlorine of **9** might be selectively displaced by iodide ion. In the event, the product obtained when the dichloride **9** was reacted with one equivalent of sodium iodide in acetone was the allylic iodide **17 (Scheme 12)** which was obtained in 80% yield.

Reaction of (*Z*)-1-chloro-4-(4'-chlorobutanoyloxy)but-2-ene with sodium iodide in acetone



(9) (17) (18)

Scheme 12

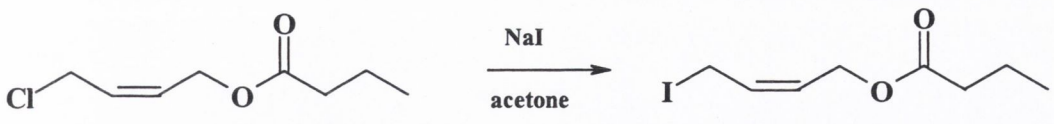
In the starting material **9** the C-4 methylene group resonates at δ 4·14 ppm and the double bond protons appear as two double triple triplets at δ 5·74 ppm and at δ 5·86 ppm. After addition of sodium iodide in acetone and refluxing until a precipitate of sodium chloride was formed (approx. 5 minutes), the reaction mixture was cooled, worked up and promptly analysed by proton NMR. The NMR spectrum of the product displayed a doublet at δ 3·92 ppm which is assigned to the C-4 methylene group of **17**. This slightly more upfield shift is typical of an iodomethyl group. The chemical shift of the olefinic protons also changed to δ 5·55 ppm and δ 5·97 ppm.

The reaction was carried out a few times, using 1 and 2 molar equivalents of sodium iodide, extended reaction times, ambient and reflux temperatures and the reaction results were the same *i.e.* that the saturated iodide **18** was not formed

The (*Z*) stereochemistry of the alkene **17** was retained in the product. CW decoupling experiments provided evidence of the (*Z*) double bond. The carbon NMR spectrum of **17** shows a peak at δ –2·7 ppm which is characteristic of an iodomethyl group, and a shift of the C-3 alkene carbon resonance which changes from δ 126·87 ppm to δ 128·02 ppm.

A Finkelstein reaction was then carried out on the chloro-ester **13**, which is similar to **9** but which only possesses a chloro-substituent at C-4.

Reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene with sodium iodide in acetone



(13) (19)

Scheme 13

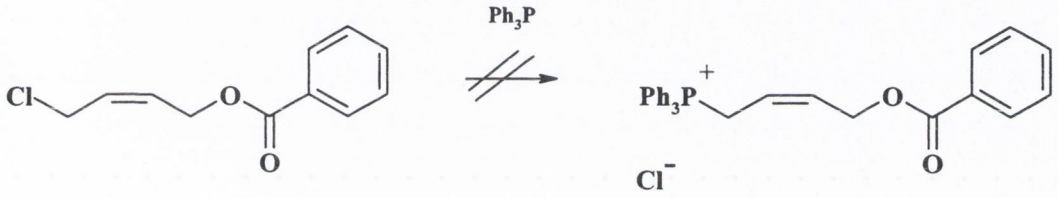
The result paralleled that of the reaction between the dichloride **9** and sodium iodide in that the allylic iodide **19** was formedin 80% yield. In the starting material **13** the C-4 methylene group resonates at δ 4·15 ppm and the double bond protons appear as two double triple triplets at δ 5·75 ppm and at δ 5·85 ppm. Proton NMR analysis of the product **19** showed an upfield change in the position of the C-4 methylene group to δ 3·88 ppm which is typical of a methylene group bearing an iodine atom. The chemical shifts of the olefinic protons also changed to δ 5·79 ppm and δ 6·01 ppm. The stereochemistry was retained in this reaction. This was proved by CW and n.O.e. NMR experiments. When the resonance at δ 3·88 ppm was irradiated, the complexity of the double triple triplet δ 6·01 ppm was reduced and the signal was evident as a baseline resolved double triplet with a coupling constant of 14 Hz and 1 Hz. Since the former *J* value is quite high, this could suggest a (*E*) double bond so an n.O.e. experiment was also carried out which substantiated the claim of a double bond with (*Z*) geometry. When the signal at δ 3·88 ppm was irradiated the signal at δ 4·15 ppm displayed a positive n.O.e. thus confirming the *cis* geometry in the product and the retention of configuration that occurs in the reaction.

3.2.3 Attempted reaction of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene with triphenylphosphine

Triphenylphosphine is well-known to react with organic halides to yield phosphonium salts.[4] With that in mind the chloro compound **5** was stirred with triphenylphosphine in a range of solvents for various periods of time with the

intention of forming the salt **20 (Scheme 14)**. However no indications that any phosphonium salt had been formed *via* S_N2 or S_N2' processes were found. Indeed reaction did not occur at all, as the two starting materials were returned unchanged (from TLC and NMR analysis). This result may be rationalised on the basis of steric factors, since triphenylphosphine is a rather large nucleophile.

Attempted reaction of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene with triphenylphosphine



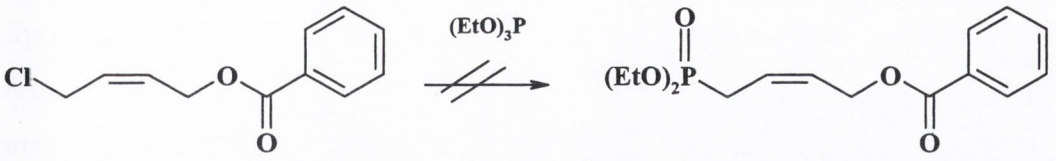
(5) (20)

Scheme 14

3.2.4 Attempted reaction of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene with triethyl phosphite

Due to the reluctance of **5** to react with triphenylphosphine, the reaction was then attempted with the less bulky trivalent phosphorus compound triethylphosphite **(Scheme 15)**. The reaction was carried out in the absence of solvent and the mixture was heated to 220 ° C. NMR spectroscopy of the crude product revealed that the anticipated product **21** had not been formed.

Proposed reaction of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene with triethyl phosphite



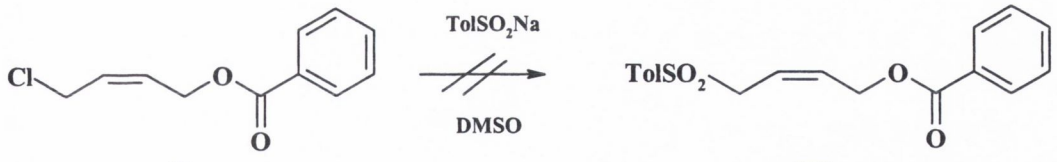
(5) (21)

Scheme 15

3.2.5 Attempted reaction of (*Z*)-1-benzoyloxy-4-chloro-but-2-ene with sulfinate ion

The next nucleophile to be investigated was toluenesulfinate ion. The chloro-ester **5** was reacted with sodium *p*-toluenesulfinate in DMSO at 60 °C during 48 hours **(Scheme 16)**. However the anticipated product **22** was not formed. The same negative result was obtained when a higher temperature was utilised.

Attempted reaction of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene with *p*-toluenesulfinate ion



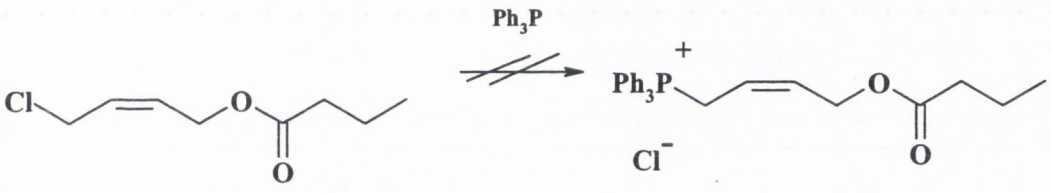
(5) (22)

Scheme 16

3.2.6 Attempted reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene 13 with triphenylphosphine

Since the nucleophilic displacement reaction with iodide ion was more successful for (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene **13** than for *(Z)*-1-benzoyloxy-4-chloro-but-2-ene **5** it was anticipated that the other nucleophilic reactions attempted on **5** may perform better also. The reaction of **13** with triphenylphosphine performed under the same conditions gave unfortunately the same outcome as the reaction with **5 (Scheme 17)**.

Proposed reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene with triphenylphosphine



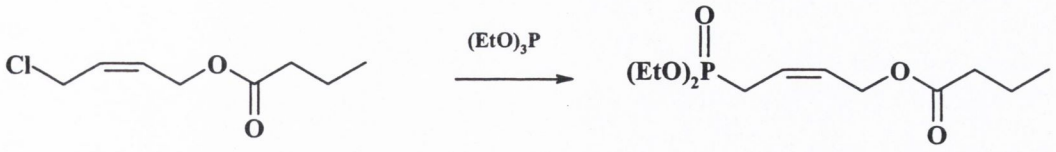
(13)

Scheme 17

3.2.7 Arbuzov reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene 13

As in the case of **5**, the less bulky phosphorus nucleophilic source triethylphosphite was then reacted with **19**. However, this time the reaction was successful giving the phosphonate **23 (Scheme 18)** in 32% yield.

Arbuzov reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene

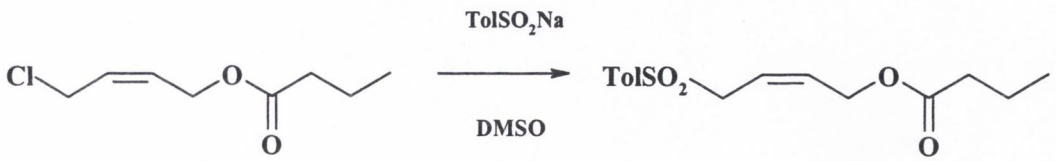


(13) (23)

Scheme 18

The compound **25** was identified by spectroscopic data. A triplet at δ 0·96 ppm is assigned to the ester methyl group. The two methyl groups of the phosphonate group apprear as a 6H triplet at δ 1·33 ppm. The C-3' methylene group appears as a sextet at δ 1·66 ppm. A triplet at δ 2·30 ppm is attributed to the C-2' methylene group. The C-4 methylene group appear as a double doublet at δ 2·71 ppm with coupling constants of 22 and 8. The former *J* value is very large and is due to phosphorus coupling. A 4-H multiplet centred at δ 4·13 ppm is assigned to the phosphonate methylene groups. The C-1 methylene group appears as a doublet at δ 4·66 ppm. The olefinic protons appear as a multiplet centred at δ 5·75 ppm. the infrared spectrum of **25** contains absorptions at 1052 cm^{-1} and at 1027 cm^{-1} which are typical of carboxylic and phosphonate ester C-O stretching vibrations.

3.2.8 Reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene 13 with sulfinate ion



(13) (24)

Scheme 19

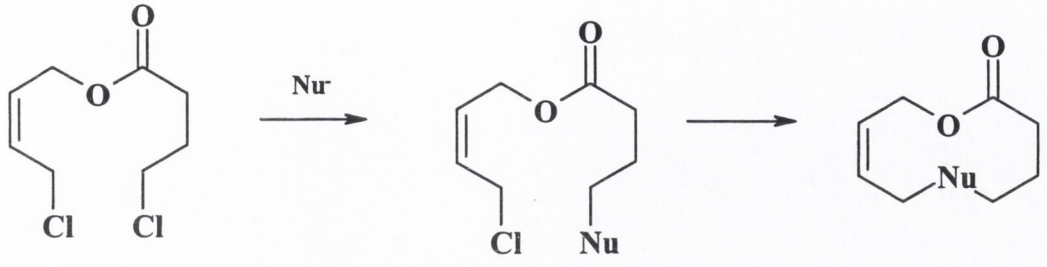
The chloroester **13** was reacted with sulfinate ion in the same manner as for the benzoate **5** was and gave the anticipated product **24 (Scheme 19)** in 39% yield.

The proton NMR spectrum of **24** displayed a triplet δ 0·92 ppm which was assigned to the ester methyl group. The C-3' methylene group resonated as a sextet at δ 1·66 ppm. The methyl substituent of the sulfonyl group appears as a singlet at δ 2·46 ppm. The C-4 methylene group appears as a doublet at δ 3·94 ppm and another doublet at δ 4·35 ppm is assigned to the C-1 methylene group. The alkene protons appear as double triplets at δ 5·88 ppm and at δ 6·65 ppm, the more downfield being assigned to the C-2 proton. Two doublets are evident at δ 7·36 ppm and δ 7·77 ppm and are assigned to the aryl protons. The infrared spectrum of **26** displays absorptions at 1317 cm^{-1} and 1141 cm^{-1} which are typical of a sulfonyl group, and at 847 cm^{-1} which corresponds to the benzene ring.

3.2.9 Attempted cyclisation of (Z)-1-chloro-4-(4-chlorobutanoyloxy)but-2-ene using a bidentate ligand

It was considered that it might be possible to carry out a cyclisation reaction on the dichloride **9** by displacing one of its chlorine atoms with a bidentate nucleophile to give a compound of the form **25**. This might then participate in a second intramolecular displacement reaction to give a ten–membered lactone **26** **(Scheme 20)**.

Proposed cyclisation reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene using a bidentate ligand

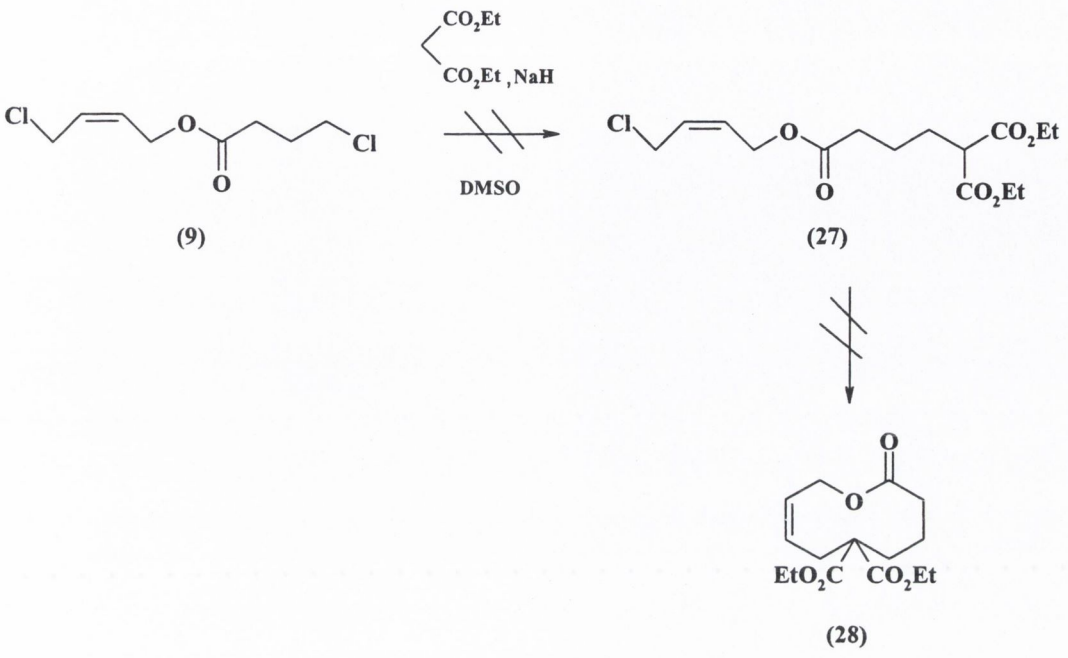


(9) **(25)** **(26)**

Scheme 20

The nucleophile chosen was a stabilised carbanion. Diethyl malonate was reacted with sodium hydride to generate the derived carbanion which was then reacted with the dichloride **9** in DMSO **(Scheme 20)**. Spectroscopic analysis of the product showed that a complex mixture had been formed. None of the components of this mixture appeared to be the required products **27** or **28**.

Proposed cyclisation reaction of (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene using a stabilized carbanion



(9) (27) (28)

Scheme 21

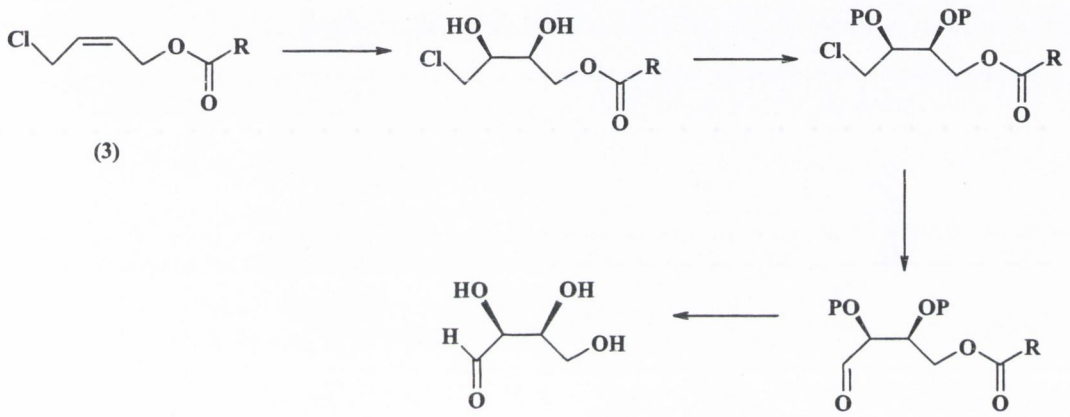
3.2.10 Conclusions

It appears that the allylic chloride function in the series of 1-acyloxy-4-chlorobut-2-enes that have been studied is quite reactive but that steric factors play an important role. When comparing the reactivity of the two chloroesters **5** and **13** nucleophilic displacement reactions involving triphenylphosphine both failed, thus demonstrating the inability of a large nucleophile to approach the chlorine-carbon bond along the correct axis for displacement. Nucleophilic displacement reactions with triethylphosphite and with toluenesulfinate ion were successful in the case of the butanoyloxy compound **13** but not for the benzoate **5**, so here the problem lies with the large benzene ring encroaching on an already limited space adjacent to the carbon-chlorine bond. Substitution products were successfully obtained from the benzoate **5** when iodide ion was used as nucleophile, but two sequential S_N2' processes may have been involved in this case.

3.3.1 Dihydroxylation of the double bond of the chloro-ester 5

Having carried out a study on the reactivity of a number of nucleophiles towards 1-benzoyloxy-4-chlorobut-2-ene **5**, and finding distinct lack of reactivity, it was decided to turn attention to the (*Z*)-configured double bond and exploit its reactivity with a view to the synthesis of C-4 sugars as set out in **Scheme 22**.

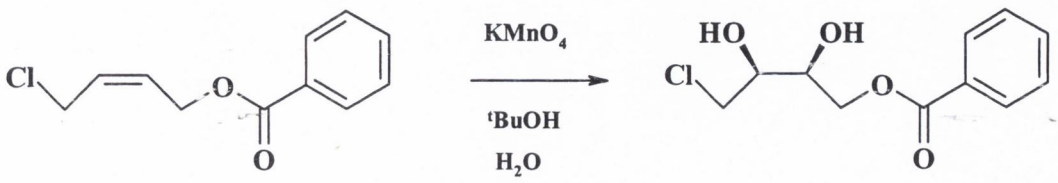
Proposed reaction sequence to synthesise a C-4 sugar from a 1-acyloxy-4-chlorobut-2-ene



Scheme 22

The chloro-ester **5** was converted into the *cis*-diol **29** by reaction with potassium permanganate in basic aqueous solution at 0 °C **(Scheme 23)** and was obtained in 65% yield.

Dihydroxylation of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene



(5) **(29)**

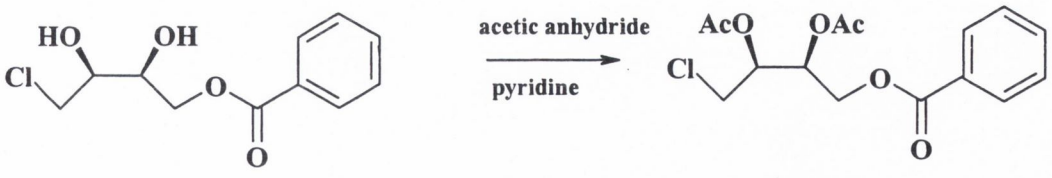
Scheme 23

The diol **29** was identified by infrared spectroscopy from the appearance of a hydroxyl absorption at 3413 cm^{-1}. In the ^1H NMR spectrum of **29** the C-1 methylene group appears as an AB system of double doublets. Each of these exhibits a geminal coupling constant of 12 Hz. One double doublet, at δ 4·59 ppm, displays a vicinal coupling constant of 5·5 Hz and the other, resonating at δ 4·68 ppm, shows J_{vic} 3 Hz. The C-2 methine proton appears at δ 4·05 ppm as a double double doublet since it couples to the each of the C-1 methylene protons and also to the adjacent C-3 methine with J_{vic} 7·5 Hz. The resonances due to the other methylene and methine proton of **29** are not as easy to distinguish. They appear as two signals at δ 3·85 ppm and δ 3·92 ppm. It appears that the more upfield signal could be one half of another AB system arising from the C-4 methylene group as it is a double doublet with a vicinal coupling constant of 7 Hz and a geminal coupling constant of 12 Hz. The other half of the AB system overlaps with the signal for the C-3 methine proton.

3.3.2 Protection of the diol 29 by esterification using acetic anhydride

It was then decided to protect the diol functionality of **29** for the subsequent reaction procedures. The diol **29** was reacted with acetic anhydride in pyridine to give the diacetate **30 (Scheme 24)** in 88% yield.

Protection of the diol generated in Scheme 23



(29) **(30)**

Scheme 24

In the ^{1}H NMR spectrum of the diacetate **30** two 3H singlets at δ 2·11 ppm and at δ 2·15 ppm are assigned to the two acetoxy groups. An AB system of two double doublets is assigned to the C-4 methylene group. The first double doublet resonates at δ 3·71 ppm and displays a vicinal coupling constant of 5·5 Hz. The other double doublet appears at δ 3·82 ppm and has a vicinal coupling constant of 3·5 Hz. Each signal also displays a geminal coupling constant of 12 Hz.

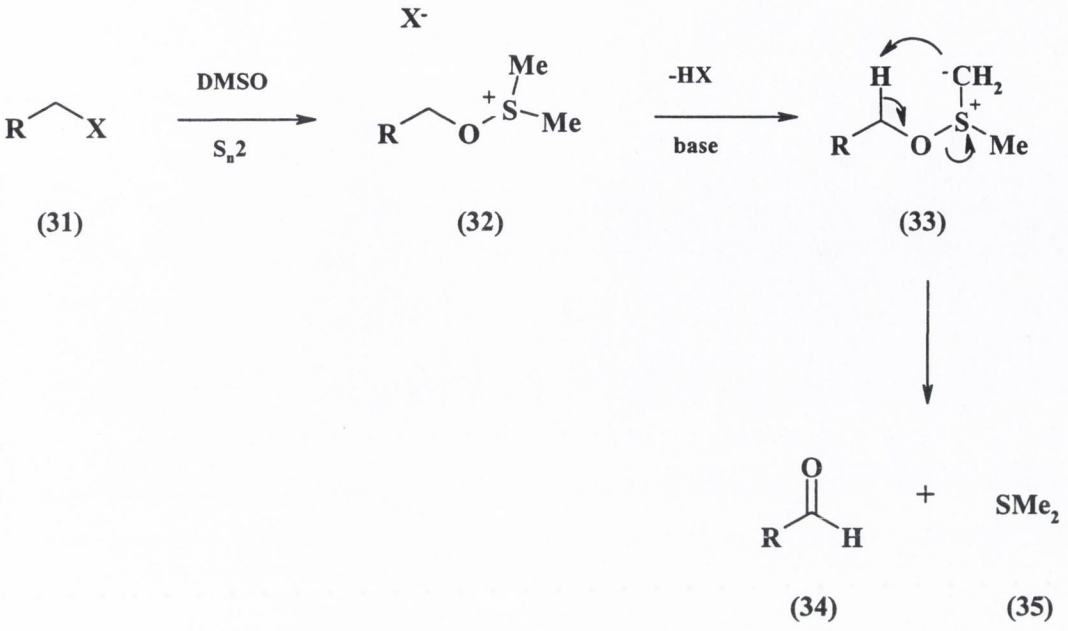
Another AB system of two double doublets is assigned to the C-1 methylene group. A double doublet centred at δ 4·42 ppm with a vicinal coupling constant of 5 Hz is observed. The other double doublet appears at δ 4·68 ppm and displays a coupling constant of 7·5 Hz. The geminal coupling constant is 12·5 Hz. The C-2 and C-3 methine protons appear as double double doublets centred at δ 5·41 ppm and δ 5·47 ppm. The more downfield signal is assigned to the C-2 methine proton on the basis of spin-decoupling experiments. On irradiation of the resonance at δ 3·71 ppm the complexity of the double double doublet at δ 5·47 ppm was reduced and the signal was evident as a baseline-resolved double doublet.

3.3.3 Attempted Kornblum reaction of the diacetate 30

With the first two steps of the proposed sugar synthesis completed the next requirement was conversion of the chloromethyl group of **30** into an aldehyde function.

The Kornblum reaction[5] is a useful reaction which transforms a halomethyl group into an aldehyde. The oxidising agent is dimethylsulfoxide which also functions as solvent. The nucleophilic oxygen atom of DMSO attacks the alkyl halide **31** by an S_N2 mechanism and expels bromide ion. The resulting positively charged species **32** then loses a proton due to attack by bromide ion to give the ylid **33**, which then abstracts a proton from the α-methylene group to give the aldehyde **34** and dimethylsulfide **35 (Scheme 25)**.

General sequence of a Kornblum reaction

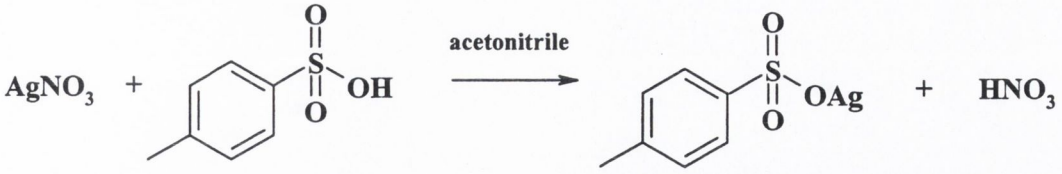


Scheme 25

Since chloride ion is not a very good leaving group it was decided to convert it into a better one. Kornblum *et al.*[6] have previously reported an efficient synthesis of aldehydes from halides *via* tosylates for those halides which cannot be converted to aldehydes directly. This involves the synthesis of the tosylate derivative and then treatment of the crude tosylate with a sodium bicarbonate - dimethylsulfoxide mixture. This methodology was proven to be successful in the case of chloro-compounds.

Silver tosylate **36** was synthesised by the reaction of silver nitrate **37** with *para*-toluenesulfonic acid **38** in acetonitrile **(Scheme 26)**.[7]

Synthesis of silver tosylate from silver nitrate and *p*-toluenesulfonic acid

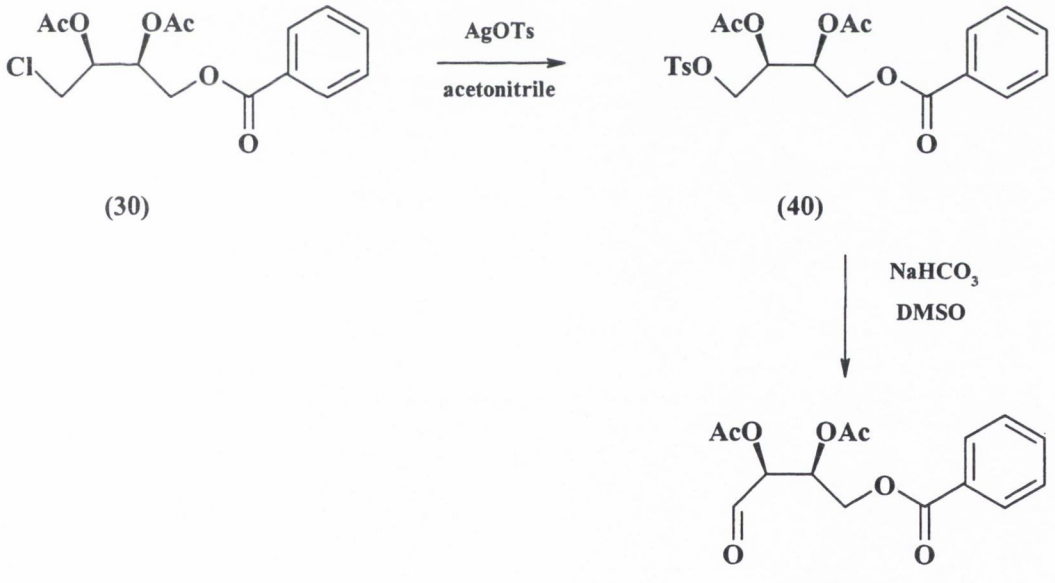


(37) (38) (36)

Scheme 26

The diacetate **30** was stirred with silver tosylate **36** in acetonitrile (protected from light) at room temperature as the authors[5] had outlined **(Scheme 27)**.

Proposed reaction of the diacetate from Scheme 24 with silver tosylate



(30) (40) (39)

Scheme 27

The reaction was worked up and the resulting oil was added to a solution of sodium bicarbonate in dimethylsulfoxide at 150 ° C.

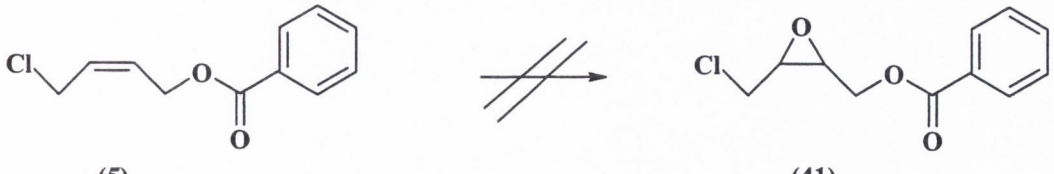
However, the expected aldehyde **39** was not formed. The proton NMR spectrum of the crude product was that of the starting material **30**. The conditions of the initial tosylate forming reaction were altered by extending the reaction time and increasing the reaction temperature, however the anticipated tosylate **40** was not formed. It seems likely that steric hindrance by neighbouring acetoxy or other groups prevents reaction at C-4 of **30**.

3.4 Attempted synthesis of an epoxide from the alkene 5

The *cis*-diol **29** had been obtained from the chloro-ester **5** as described above. It was thought that the corresponding *trans*-diol might be accessible *via* an epoxide derived from **5**. Epoxides are generally synthesised by the reaction of an alkene with a peroxyacid. They can be cleaved by acid-catalysed reaction with water to give *trans*- diols. The synthesis of an epoxide from **5** was attempted using urea – hydrogen peroxide, trifluoroacetic anhydride and disodium hydrogen phosphate. This methodology was developed by Heaney[8] and co-workers as a safer alternative to the use of *meta*-chloroperbenzoic acid has been used successfully for a variety of different alkenes. It is particularly effective for the epoxidation of less reactive mono- and disubstituted alkenes.

However, the anticipated product **41** was not formed, in fact the starting material **5** was returned unchanged after reaction with this oxidising agent **(Scheme 28)**.

Proposed epoxidation of (*Z*)-1-benzoyloxy-4-chlorobut-2-ene



(5) (41)

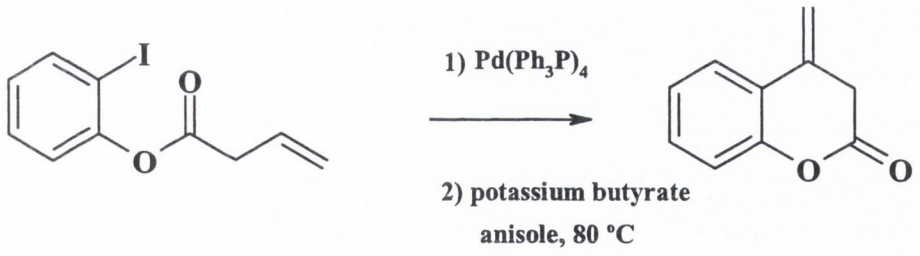
Scheme 28

3.5 Synthesis of (*Z*)-1-(2'-bromobenzoyloxy)-4-chlorobut-2-ene, and attempted intramolecular Heck reactions

The Heck reaction[9] has been well-documented as a valuable tool in organic synthesis. It relies on the formation of a reactive Pd(0) complex which is formed *in situ* by reaction of a Pd(II) species with *e.g.* triphenylphosphine. This newly formed catalyst of the form $[Pd(0)L_2]$ then reacts with an organic halide *via* oxidative addition to give a highly reactive Pd(II) species which then interacts with an alkene function within the molecule or with that of another compound. Reductive elimination yields a product containing a new carbon-carbon bond together with Pd(0) which enters a new catalytic cycle.

Intramolecular Heck reactions have been highly successful in many syntheses where they have enabled cyclisations to occur. For example, the *ortho*-iodobenzoate **42** was converted into the lactone **43** by a Heck reaction as shown below **(Scheme 30)**.[10]

Synthesis of a lactone from an iodobenzoate



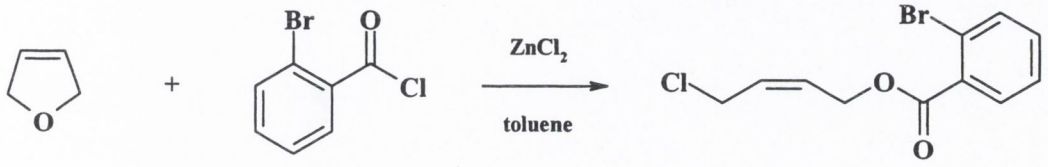
(42) **(43)**

Scheme 29

In the present work it was decided to synthesise a 1-acyloxy-4-chlorobut-2-ene embodying a reactive aryl halide as it was considered that an intramolecular Heck reaction might then be possible.

The bromo compound **44** was synthesised under the conditions described in Section **3.1** using 2,5-dihydrofuran **1** and 2-bromobenzoyl chloride **45 (Scheme 30)** and obtained in 66% yield.

Synthesis of (*Z*)-1-(2'-bromobenzoyloxy-4-chlorobut-2-ene from 2,5-dihydrofuran



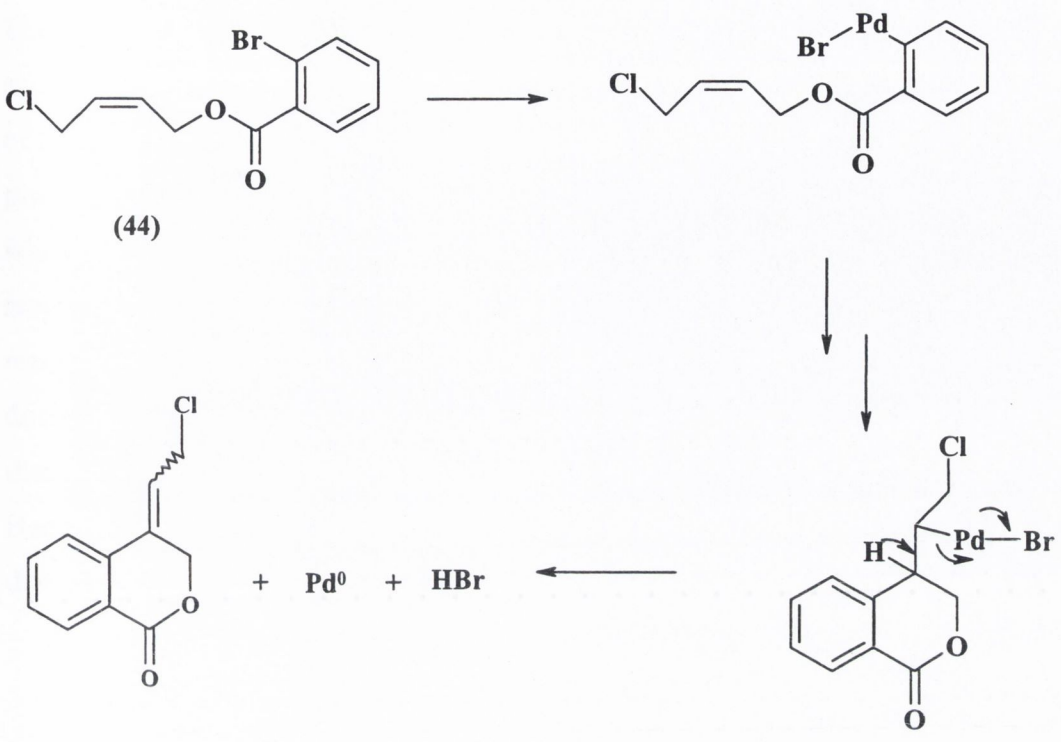
(1) (45) (44)

Scheme 30

The ^{1}H NMR spectrum of **44** displayed a 2H doublet at δ 4·22 ppm that is assigned to the C-4 methylene group. Another 2H doublet at δ 4·96 ppm corresponds to the C-1 methylene group. The alkene protons at C-2 and C-3 appear as a multiplet centred at δ 5·92 ppm. The infrared spectrum of **44** shows absorptions for an ester carbonyl group at 1729 cm^{-1}, a CO-O stretch band at 1249 cm^{-1} and a benzene ring at 744 cm^{-1}.

Since chlorides are not usually used in Heck reactions, and since the general unreactivity of the allylic chloride function of compound **5** which is analogous to **44** has been demonstrated in Section **3.2** above, it was assumed that the bromo-substituent on the benzene ring would take part in any Heck reaction and that the allylic chloride would remain unchanged in the product. Thus, reaction was expected to occur as shown in **Scheme 31**.

Proposed Heck reaction of (*Z*)-1-(2'-bromobenzoyloxy-4-chlorobut-2-ene



Scheme 31

Two sets of conditions for the Heck reaction were employed.

Firstly, the reaction was carried out in DMF solution in the presence of palladium acetate, triphenylphosphine, tetra-(n-butyl)ammonium chloride as phase transfer agent and potassium acetate as base. The starting material **44** was recovered unchanged.

Secondly, a literature method[11] that involves *bis*(triphenylphosphine)palladium dichloride as catalyst, copper(I) iodide and triphenylphosphine in triethylamine containing some pyridine was employed. This resulted in the formation of an approximately 1:1 mixture of starting material **44** and a "product". It was thought that this product was formed by the starting material **44** reacting with the solvent, triethylamine, and this was confirmed by a control experiment. The "product" was not further investigated.

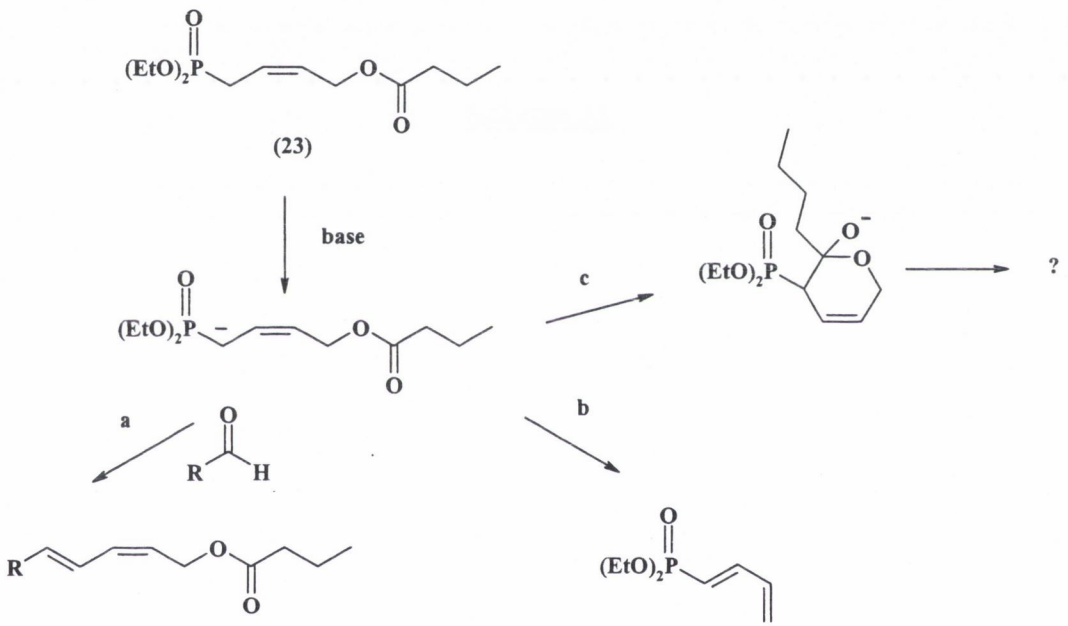
3.6 Summary

The Lewis acid-catalysed acylative cleavage reaction of 2,5-dihydrofuran was successful with a variety of acid chlorides. Nucleophilic displacement reactions of the allylic chloride function from the derived (*Z*)-1-acyloxy-4-chlorobut-2-enes proved to be sensitive to steric factors. When a large nucleophile was reacted, or when the chloroester itself contained a large esterifying R group, the desired S_N2 reaction was unsuccessful. Some less bulky nucleophiles could be successfully reacted with substrates containing an alkyl ester function. Functionalisation of the double bond of these (*Z*)-1-acyloxy-4-chlorobut-2-enes was successful, suggesting that they could behave as precursors to four-carbon sugars. An intramolecular Heck reaction involving a bromobenzoyl ester was attempted but failed, possibly due to competing reactions with solvent.

3.7 Future work

The successful nucleophilic substitution reactions carried out with the chloro-ester **13** gave products which are potentially very useful in synthesis. For example, the phosphonate **23** might be reacted with base to give an anion that could lead to a variety of products (**Scheme 32**). On addition to an aldehyde, a Horner-Emmons[12] reaction could occur as shown in path a. Elimination or cyclisation products arising from either of paths b or c could also be produced.

Possible reaction pathway of the phosphinate 25 on reaction with base



Scheme 32

The sulfonate **24** could participate in a Julia[13] reaction as shown below (**Scheme 33**). The Julia reaction always yields an (*E*) alkene so the resulting product in the scheme below would be an (*E*,*Z*)-diene.

3.8 Experimental

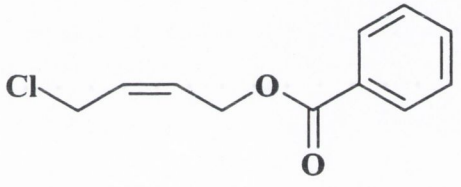
General experimental conditions

Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} silica gel plates. Visualisation was by means of ultraviolet light at 254nm or by development in potassium permanganate solution. Column chromatography was carried out under gravity using Merck Kieselgel 70-230 mesh silica gel. Evaporation under reduced pressure refers to the use of a Buchi or Bibby rotary evaporator. All solvents were dried using standard techniques. Infrared spectra were recorded as Nujol mulls (N) for solids or as liquid films (L) between sodium chloride plates for oils using a Matteson Genesis FT-IR spectrometer and the data was processed using WinFirst software. Nuclear magnetic resonance spectra were recorded using Bruker DPX 400 spectrometer. Chemical shifts were measured in deuteriated chloroform unless otherwise stated. Coupling constants (*J*) are quoted in Hertz. Mass Spectra were obtained using a VG Alto spectrometer (HRMS) and Kratos (FAB) instruments. Melting points were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus and are uncorrected.

General procedure for the synthesis of (*Z*)-1-acyloxy-4-chlorobut-2-enes

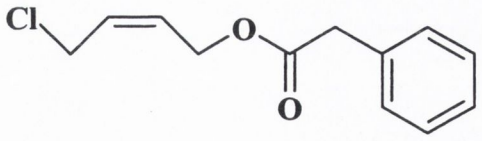
2,5-Dihydrofuran (1·5 equivalent) and an acid chloride (1 equivalent) were dissolved in toluene (10 mL/g). To this solution, freshly fused zinc chloride (0·07 equivalents) was added and the reaction was stirred at room temperature for six hours. Water was then added and the resulting mixture was extracted with diethyl ether, dried with magnesium sulfate and concentrated.

(*Z*)-1-Benzoyloxy-4-chlorobut-2-ene 5[1]



(Z)-1-Benzoyloxy-4-chloro-but-2-ene **5** was obtained from 2,5-dihydrofuran **1** (2g) and benzoyl chloride (3·1g) as a solid (4·01g, 87 %) (m.p. 33-35 °C ;*lit.*[1] m.p.. 33·5-34 °C), δ_H ($CDCl_3$) 4·23 (2H, d, *J* 8 C<u>H</u>$_2$Cl,), 4·95 (2H, d, *J* 6, C<u>H</u>$_2$O), 5·86-5·90 (2H, m, olefinic protons), 7·46 (2H, t, *J* 7·5, 3- and 5- Ar H), 7·59 (1H, t, *J* 7·5 4- Ar H) and 8·08 (2H, d, *J* 7·5, 2- and 6- Ar H) ppm; δc 38·3 (C-1), 59·4 (C-4), 127·5 (C-3), 127·9 (C-4'), 129·2 (C-3' and C-5') 129·6 (C-2' and C-6'), 132·6 (C-2*)* and 167·2 (C=O) ppm; ν_{max} (N) 2914, 2856, 2724, 1727, 1602, 1459, 1376, 1314, 1268, 1175, 1109, 1069, 1026, 964 and 710 cm^{-1}.

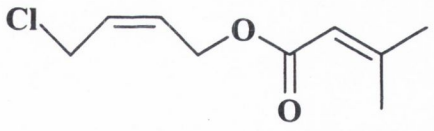
(*Z*)-1-Chloro-4-phenylacetoxybut-2-ene 7



(Z)-1-Chloro-4-phenylacetoxy-but-2-ene **7** was obtained from 2,5-dihydrofuran **1** (0·89 g) and phenylacetyl chloride (1·19 g) as a liquid (1·35 g, 71 %) (b.p. 110-114 °C (2mm Hg), δ_H ($CDCl_3$) 3·68 (2H, s, C-2'C$\underline{H}_2$Ph) 4·12 (2H, d, *J* 7·5, C-4, C$\underline{H}_2$Cl), 4·72 (2H, d, *J* 7, C-1, C$\underline{H}_2$O), 5·74 (1H, dtt, *J* 11, 6·5,1,C$\underline{H}$ C-2), 5·86 (1H, dtt, *J* 11, 6·5,1 C$\underline{H}$ C-3) and 7·35 (5H, m, Ar H) ppm; δ_C 38·6 (C-2'), 41·2 (C-4), 59·7 (C-1), 127·1 (C-3), 127·7, (C-4'), 128·6 (C-3' and C-5'), 129·2 (C-2' and C-6'), 129·9 (C-2), 133·7 (C-1') and 171·2 (C=O) ppm; ν_{max}(N) 3023, 2946, 2865, 1710, 1602, 1513, 1456, 1411, 1284, 1234, 1160, 1074, 1031, 941, 809, 742 and 700 cm^{-1}.

HRMS (FAB): *Found*: *m/z* 225·0696; *calculated* for $[C_{12}H_{13}O_2Cl + H]^+$ 225·0682

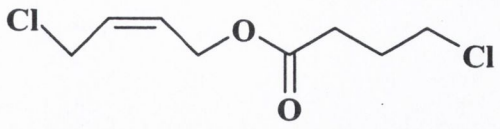
(*Z*)-1-Chloro-4-(3',3'-dimethylbutenoyloxy)but-2-ene 9



(*Z*)-1-Chloro-4-(3',3'-dimethylbutenoyloxy)-but-2-ene **9** was obtained from 2,5-dihydrofuran **1** (0·89 g) and 3,3-dimethylacryloyl chloride (0·94 g) as an oil (0·97 g, 65%)(b.p.100-104 °C (2mm Hg)), δ_H ($CDCl_3$) 1·92 (3H, s, C$\underline{H}_3$,), 2·19 (3H, s, C$\underline{H}_3$,), 4·17 (2H, d, *J* 8, C$\underline{H}_2$Cl), 4·71 (2H, d, *J* 7·5, C$\underline{H}_2$O) 5·74 (1H, s, C$\underline{H}$ C-2') and 5·81 (2H, m, C$\underline{H}$, C-2 & C-3) ppm; δ_C 20·2 (C$\underline{H}_3$), 38·3 (C-4), 62·2 (C-1), 127·2 (C-2'), 128·9 (C-3') 129·4 (C-2), 130·3 (C-3)and 165·7 (C=O) ppm; ν_{max} (L) 2923, 2855, 1720, 1649, 1446, 1378, 1359, 1259, 1226, 1145, 1077, 1010, 851 and 759 cm^{-1}.

HRMS (FAB): *Found*: *m/z* 189·0668; *calculated* for $[C_8H_{15}O_2I + H]^+$ 189·0682

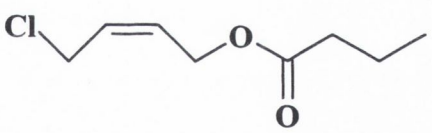
(*Z*)-1-Chloro-4-(4'-chlorobutanoyloxy)but-2-ene 11



(*Z*)-1-Chloro-4-(4'-chlorobutanoyloxy)-but-2-ene **11** was obtained from 2,5-dihydrofuran **1** (0·89 g) and 4-chlorobutanoyl chloride (1·12 g) as an oil (1·68 g, 70 %) (b.p. 86-90 °C (2 mm Hg)), δ_H ($CDCl_3$) 2·11 (2H,quintet, *J* 6·5, $C\underline{H}_2$ C-3'), 2·54 (2H, t, *J* 7, $C\underline{H}_2$ C-2'), 3·60 (2H, t, *J* 6·5, $C\underline{H}_2$ C-4'), 4·14 (2H, d, *J* 7, $C\underline{H}_2$ C-4), 4·70 (2H,d, *J* 7, $C\underline{H}_2$ C-1), 5·75 (1H, dt, *J* 10·5, 7 C<u>H</u>,C-2) and 5·85 (1H, dtt, *J* 11, 8, 1·5, C<u>H</u> C-3) ppm; δ_C 27·2 (C-3'), 38·2 (C-2'), 43·5 (C-4'), 59·0 (C-1), 63·2 (C-4), 126·9 (C-3), 131·6 (C-2) and 171·8 (C=O) ppm; ν_{max} (L) 2966, 2670, 1735, 1444, 1417,1380, 1303, 1240, 1145, 979, 950, 881, 784, 759 and 653 cm^{-1}.

HRMS (FAB): *Found*: *m/z* 211·0302; *calculated* for $[C_8H_{12}O_2Cl_2 + H]^+$ 211·0293

(*Z*)-1-Chloro-4-(butanoyloxy)but-2-ene 13



(*Z*)-1-Chloro-4-(butanoyloxy)-but-2-ene **13** was obtained from 2,5-dihydrofuran **1** (0·89 g) and butanoyl chloride **12** (0·85 g) as a oil (1·05 g ,75 %) (b.p. 76- 80 °C (2 mm Hg)), δ_H ($CDCl_3$) 0·96 (3H, t, *J* 8·5, $C\underline{H}_3$), 1·67 (2H, sextet, *J* 7·5, $C\underline{H}_2$, C-3'), 2·31 (2H, t, *J* 7·5, $C\underline{H}_2$, C-2'), 4·15 (2H,d, *J* 7·5, $C\underline{H}_2$, C-4), 4·69 (2H, d, J 6·5, $C\underline{H}_2$, C-1) 5·75 (1H, dt, *J* 11, 7·5) C<u>H</u> C-2) and 5·86(1H, dt, *J* 11, 6·5 C<u>H</u>, C-3) ppm; δ_C δ 13·2 ($\underline{C}H_3$), 17·9 (C-3'), 35·6 (C-2'), 38·3 (C-4), 58·7 (C-1), 127·6 (C-2), 129·3 (C-3) and 171·4 (C=O) ppm; ν_{max} (L) 3448, 2966, 2937, 2877,1735, 1457, 1419, 1380, 1303, 1253, 1176, 1095, 1045, 977 and 754 cm^{-1}.

HRMS (FAB): *Found*: *m/z* 177·0669; *calculated* for $[C_8H_{13}O_2Cl + H]^+$ 271·0682

Control Experiment

2,5-Dihydrofuran (2·1 mL, 0·027 mol) and benzoyl chloride, (2·5mL; 0·019mol) were dissolved in toluene and the solution was stirred at room temperature for six hours. Water was then added and the resultant reaction mixture was extracted with diethyl ether, dried with magnesium sulfate and concentrated to give benzoic acid. δ_H ($CDCl_3$) 7·51 (2H, t, *J* 7, 3- and 5- Ar H), 7·65 (1H, t, *J* 7 4- Ar H) and 8·16 (2H, d, *J* 7·5, 2- and 6- Ar H) ppm.

Synthesis[3] of *(Z)*-1-benzoyloxy-4-iodobut-2-ene 14 from 2,5-dihydrofuran

2,5-Dihydrofuran (1·5 mL) and sodium iodide (3·6 g) were each dissolved separately in acetonitrile (10 mL) and the solutions were then combined and cooled to 0° C. Benzoyl chloride (2·7 mL) was then added and the solution was allowed to come to room temperature and stirred for 24 hours. The reaction mixture was then filtered, diluted with water and extracted with ether. The extract was washed with aqueous sodium thiosulfate solution dried and evaporated.

The product **14** was obtained as an oil (4·2 g, 70%) δ_H ($CDCl_3$) 3·99 (2H, d, *J* 8·5, C$\underline{H}_2$ C-4), 4·92 (2H, dd, *J* 7, 1·5 C$\underline{H}_2$ C-1), 5·68 (1H, dt, *J* 10·5, 6·5 C$\underline{H}$, C-2), 6·02 (1H, m, *J* 9·5, 8, 1·5, C$\underline{H}$ C-3), 7·38 (2H, d, *J* 7, Ar H_3 and H_5), 7·60 (1H, t, *J* 7, Ar H_4) and 7·87 (2H, d, *J* 7·5, Ar H_2 and H_6) ppm; δ_C –2·4 (C-4), 58·9 (C-1), 127·9 (C-3), 128·4 (Ar), 129·2 (Ar), 130·0 (Ar) 134·0 (C-2) and 165·3 (C=O).

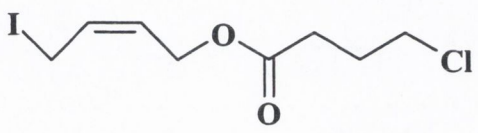
A full characterisation was not carried out due to the instability of the compound

General reaction procedure for Finkelstein reaction

Sodium iodide (1·1 equivalent) was dissolved in dry acetone (10 mL/g) and the solution was cooled to 0 °C and a 1-acyloxy-4-chlorobut-2-ene (1 equivalent) was

then added. The resulting solution was then heated under reflux until a precipitate of sodium chloride appeared. It was then cooled and the precipitate of sodium chloride was removed by filtration. The filtrate was then diluted with ether, washed with water and aqueous sodium thiosulfate solution, dried over anhydrous magnesium sulfate and concentrated.

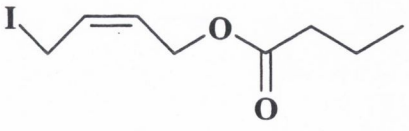
(*Z*)-1-Iodo-4-(4'-chlorobutanoyloxy)but-2-ene 17



(*Z*)-1-Iodo-4-(4'-chlorobutanoyloxy)but-2-ene **17** (3.06 g, 80%) was obtained from (*Z*)-1-chloro-4-(4'-chlorobutanoyloxy)but-2-ene (2·67 g, 0·0127 mol) and sodium iodide (2·1 g, 0·014 mol)δ_H ($CDCl_3$) 2·10 (2H,quintet, *J* 6·5, $C\underline{H}_2$ C-3'), 2·52 (2H, t, *J* 7, $C\underline{H}_2$ C-2'), 3·60 (2H, t, *J* 6·5, $C\underline{H}_2$ C-4'), 3·92 (2H, d, *J* 9, $C\underline{H}_2$ C-4), 4·68 (2H,d, *J* 7, $C\underline{H}_2$ C-1), 5·56 (1H, dt, *J* 11, 6·5, C<u>H</u>,C-2) and 6·02 (1H, dt, *J* 15, 8,(C<u>H</u>) (C-3)) ppm; δ_C –2·7 ($\underline{C}H_2I$) 27·1 (C-3'), 30·7 (C-2'), 43·5 (C-4'), 63·2 (C-1), 127·3 (C-3), 132·0 (C-2) and 171·8 (C=O) ppm.

A full characterisation was not carried out due to the instability of the compound

(*Z*)-1-Iodo-4-(butanoyloxy)but-2-ene 19



(*Z*)-1-Iodo-4-(butanoyloxy)but-2-ene **19** (2 82 g , 80%) was obtained from (*Z*)-1-chloro-4-(butanoyloxy)but-2-ene (2·23 g, 0·0127 mol) and sodium iodide (2·1 g, 0·014 mol) δ_H ($CDCl_3$) 0·96 (3H, t, *J* 7·5, $C\underline{H}_3$),1·67 (2H, sextet, *J* 7·5, $C\underline{H}_2$, C-3'), 2·32 (2H, t, *J* 7, $C\underline{H}_2$, C-2'), 3·88 (2H,d, *J* 8, $C\underline{H}_2$, C-4), 4·57 (2H, d, J 6, $C\underline{H}_2$, C-1), 5·52-5·58 (1H, dt, *J* 10·5, 6·5,C<u>H</u> C-2) and 6·00(1H, dt, *J* 11, 6·5, C<u>H</u>, C-3)

ppm ; δ_C –2·2 (CH_2I) 27·5 (C-3'), 30·8 ($\underline{C}H_3$), 31·0 (C-2'), 58·9 (C-1), 126·5 (C-2), 131·4 (C-3) and 170·4 (C=O) ppm.

A full characterisation was not carried out due to the instability of the compound

Attempted displacement of chloride ion from the chloro-esters 5 and 13 with triphenylphosphine

The chloro-compound **5** (1·18 g, 0·005 mol) and triphenylphosphine (1·44 g, 0·0055 mol) were combined in toluene (10 mL) and the solution was heated under reflux for six hours. The reaction mixture was then cooled, extracted with ether dried over magnesium sulfate and concentrated to give the chloro-ester **5** unchanged.

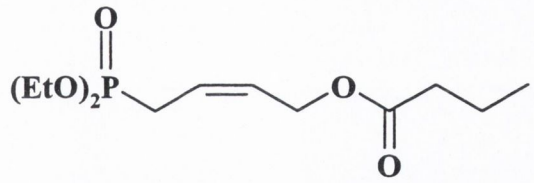
The reaction was also carried out in diethyl ether at room temperature for 6 hours and also in refluxing benzene for 18 hours with the same outcome.

The same result was obtained on reaction of **13** under the same conditions

Attempted displacement of chloride ion from the chloro-ester 5 with triethylphosphite

The chloro-compound **5** (1 g, 0·005 mol) and triethylphosphite (0·86 mL, 0·005 mol) were combined under an atmosphere of nitrogen and the mixture was heated to 220 °C for two hours. The solution was then cooled, extracted with diethyl ether, dried and concentrated to give the chloro-ester **5** unchanged.

(2*Z*)-1-butanoyloxy-4-phosphonobut-2-ene 23



23 was obtained as an oil (0·25 g, 32%) (b.p. 76- 80 °C (760 mm Hg)) from **13** (0·5 g, 0·003 mol) δ_H ($CDCl_3$) 0·96 (3H, t, *J* 7·5, C<u>H</u>$_3$), 1·33 (6H, t, *J* 7, 2x C<u>H</u>$_3$ $(EtO)_2$), 1·66 (2H, sextet, *J* 7·5, C<u>H</u>$_2$ (C-3')), 2·30 (2H, t, C<u>H</u>$_2$ (C-2'), 2·71 (2H, dd, *J* 22, 8, C<u>H</u>$_2$ (C-4)), 4·13 (4H, m, 2x C<u>H</u>$_2$ $(EtO)_2$), 4·66 (2H, d, *J* 6 C<u>H</u>$_2$, (C-1)), 5·72-5·78 (2H, m, olefinic protons)ppm; δ_C 13·1 (<u>C</u>H$_3$ (C-4')), 15·9 (<u>C</u>H$_3$(OEt)), 15·9 (<u>C</u>H$_3$(OEt)), 17·9 (C-3'), 35·5 (C-2'), 38·2 (C-4), 58·7 (C-1), 127·6 (C-2), 129·3 (C-3) and 171·4 (C=O) ppm; δ_P 27·8 ppm; ν_{max} (L) 2967, 2935, 2877, 1735, 1459, 1446, 1419, 1390, 1369, 1253, 1178, 1052, 1027 and 966 cm^{-1}.

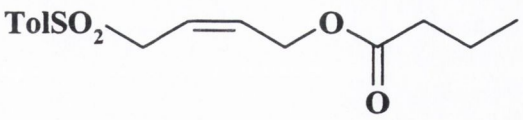
HRMS (CI): *Found*: *m/z* 301·1181; *calculated* for $[C_{12}H_{23}O_5P + Na]^+$ 301·1198

Attempted displacement of chloride ion from the chloro-ester 5 with toluenesulfinate ion

The chloro-compound **5** (1 g, 4·7 mmol) and sodium toluenesulfinate (0·9 g, 5 mmol) were combined in DMSO (20 mL) and the solution was heated for 48 hours at 60 °C. The reaction mixture was then cooled, diluted with water, extracted with ether, dried and concentrated to give the chloro-ester **5** unchanged.

The reaction was also carried out at 80 °C and at 120 °C for 7 hours and gave the same result.

(2*Z*)-1-butanoyloxy-4-(4'-toluenesulfinyl)but-2-ene 24



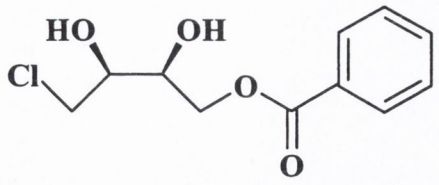
24 was obtained as a solid (EtOAc: Hexane) (0·32 g, 39%) from **13** (0·5 g, 0·003 mol) δ_H ($CDCl_3$) 0·92 (3H, t, *J* 8·5, C<u>H</u>$_3$), 1·61 (2H, sextet, *J* 7·5, C<u>H</u>$_2$, C-3'), 2·46 (3H, s, C<u>H</u>$_3$ (Tol)), 3·94 (2H, d, *J* 8, C<u>H</u>$_2$, C-4) , 4·35 (2H,d, *J* 7, C<u>H</u>$_2$, C-1), 5·65 (1H, dt, *J* 11,7·5,*J* C<u>H</u> C-3) and 5·87(1H, dt, *J* 11, 7 C<u>H</u>, C-2), 7·36 (2H, d, *J* 8, Ar H_x) and 7·77 (2H, d, *J* 6, Ar H_x) ppm; δ_C 13·1 (<u>C</u>H_3), 17·8 (C-3'), 21·2 (<u>C</u>H_3(Tol)), 35·4 (C-2'), 54·8 (C-4), 58·6 (C-1), 119·5 (C-2), 127·9 (Ar), 129·4 (Ar), 132·4 (Ar), 134·9 (C-3), 144·5 and 172·3 (C=O) ppm; ν_{max} (L) 3037, 2966, 2935, 2875, 1733, 1596, 1457, 1415, 1380, 1317, 1251, 1174, 1141 (S=O), 1087, 1045, 981, 817, 715 and 688 cm^{-1}.

HRMS (CI): *Found*: *m/z* 319·0976; *calculated* for $[C_{15}H_{20}O_4S + Na]^+$ 319·0908

Attempted cyclisation reaction of 13 using diethyl malonate

Diethyl malonate (0·25g, 1·5 mmol) was dissolved in DMSO (8 mL) under an atmosphere of nitrogen. Sodium hydride (0·072 g, 3 mmol) was then added and hydrogen gas was evolved. The dichloride **13** (0·29 g, 1·4 mmol) was then added and the solution was heated under reflux for six hours. The reaction was then quenched using ethanol. Water was added to dilute the solution which was then extracted with diethyl ether, dried with magnesium sulfate and concentrated to give unreacted **13**.

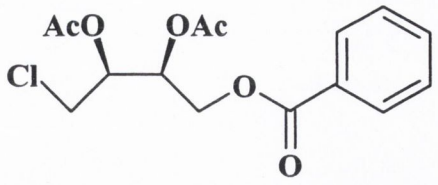
1-Benzoyloxy-4-chloro-2,3-dihydroxybutane 29



(Z)-1-Benzoyloxy-4-chlorobut-2-ene **5** (4·2 g, 0·02 mol) was dissolved in water (18 mL) and *tert*-butanol (42 mL). Potassium permanganate (3·16 g, 0·02 mol) and sodium hydrogen carbonate (0·84 g, 0·01 mol) were each dissolved in the minimum amount of water. These solutions were both added to the solution containing the ester **5** and the mixture was stirred for one hour at 0 °C. It was then filtered through Celite to remove manganese dioxide. The filtrate was diluted with water (50 mL) and extracted with diethyl ether (3x 15 mL), and the extract was dried with magnesium sulfate and concentrated to give a solid (3·17 g, 65%) (m.p. 36-38 °C), δ_H ($CDCl_3$) 3·85 (1H, dd, *J* 12, 7, CH_2 C-4), 3·34 (2H, br.s, exch. D_2O, OH) 3·92 (2H, m, CH_2, C-4), 3·92 (1H, m, C<u>H</u> C-3) ,4·05 (1H, ddd, *J* 7·5, 5·5, 3, C<u>H</u> C-2) 4·59 (1H, dd, *J* 12, 5·5, C<u>H</u>$_2$ C-1), 4·68 (1H, dd, *J* 12,3 C<u>H</u>$_2$ C-1), 7·45 (2H, d, *J* 8·5 , Ar H_2 and H_5), 7·48 (1H, t, *J* 8, Ar H_3) and 7·60 (2H, d, *J* 6, Ar H_1 and H_4) ppm; δ_C 46·9 (C-4), 65·8 (C-1), 70·7 (C-3), 71·3 (C-2), 127·9 (C-4'), 129·7 (C-3' and C-5'), 132·9 (C-2' and C-6'), and 166·9 (<u>C</u>=O) ppm; ν_{max} (N) 2919, 2726, 2670, 1697, 1458, 1376, 1288, 1155, 1025, 936 and 722 cm^{-1}.

HRMS (CI): *Found*: *m/z* 267·0395; *calculated* for $[C_{11}H_{13}O_4Cl + Na]^+$ 267·0400

1-Benzoyloxy-4-chloro-2,3-diacetoxybutane 30



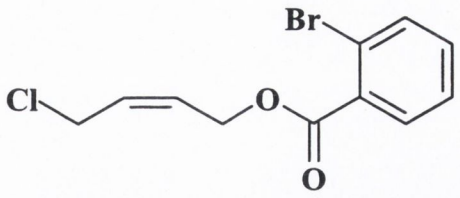
The diol **29** (0·96 g, 4 mmol) was dissolved in dry pyridine (3 mL). Acetic anhydride (1·1 mL, 0·01 mol) was then added and the solution was stirred at room temperature overnight. The mixture was then poured on to ice (20 g) and excess sodium hydrogen carbonate. It was then extracted with diethyl ether (3x 1mL). The organic layer was washed with hydrochloric acid followed by water, dried with magnesium sulfate and concentrated to give an oil (0·94 g, 88%), δ_H ($CDCl_3$) 2·11 (3H, s, C<u>H</u>$_3$), 2·15 (3H, s, C<u>H</u>$_3$), 3·71 (1H, dd, *J* 12, 5·5, C<u>H</u>$_2$ C-4), 3·82 (1H, dd, *J* 12, 3·5 C<u>H</u>$_2$ C-4), 4·42 (1H, dd, *J* 12·5, 5 C<u>H</u>$_2$ C-1), 4·68 (1H, dd, *J* 12·5, 7·5, C<u>H</u>$_2$ C-1), 5·41 (1H, ddd, *J* 5·5, 3·5, 2, C<u>H</u> C-3), and 5·47 (1H, ddd, *J* 7, 3·5, 2, C<u>H</u> C-2) ppm; δ_C 20·0 (<u>C</u>H$_3$), 20·2 (<u>C</u>H$_3$), 42·5 (C-1), 61·2 (C-4), 128·0 (C-4') 129·2 (C-3' and C-5'), 132·9 (C-2' and C-6'), 165·6 (CH_3C=O) and 169·1 (PhC=O) ppm; ν_{max} (L) 3066, 2966, 1752,1724, 1602, 1450, 1436,1373, 1315, 1272, 1220, 1178, 1112, 1070, 1027, 956, 914, 732, 713, 686 and 647cm^{-1}.

HRMS (CI): *Found*: *m/z* 351·0628; *calculated* for $[C_{15}H_{17}O_6Cl + Na]^+$ 351·0611

Attempted epoxidation of the chloro-ester 5

Trifluoroacetic anhydride (3 mL, 20 mmol) was added dropwise to a stirred mixture of urea-hydrogen peroxide complex (7·6 g, 80 mmol), disodium hydrogen phosphate (9·9 g, 70 mmol) and the chloro-ester **5** (1·68 g, 8 mmol) in dichloromethane (50 mL). The mixture was then heated under reflux for 5 days. A saturated aqueous solution of sodium hydrogen carbonate was added to neutralise the acids present and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated to yield the chloro-ester **5** unchanged.

(*Z*)-1-(2'-Bromobenzoyloxy)-4-chlorobut-2-ene 44



(*Z*)-1-(2'-Bromobenzoyloxy)-4-chlorobut-2-ene **44** was obtained from 2,5-dihydrofuran **1** (0·89 g) and 2-bromobenzoyl chloride **45** (1·74 g) as a solid (1·52 g, 66 %), m.p. 42-45 °C, δ_H ($CDCl_3$) 4·22 (2H, d, *J* 7·5,C$\underline{H}_2$Cl), 4·96 (2H, d, *J* 5·5, C$\underline{H}_2$O,), 5·90-5·94 (2H, m, C$\underline{H}$ (C-2)& (C-3)), 7·36 (2H, m, 4- and 5- Ar H), 7·68 (1H,d, *J* 7·5, 6- Ar H) and 7·81 (1H,d, *J* 7·5, 3- Ar H) ppm; δ_C 38·58 (C$\underline{H}_2$), 60·25 (C$\underline{H}_2$), 127·11 (C-Br), 127·41 (C-3), 130·37 (C-4' and C-5'), 131·28 (C-2), 132 ·64 (C-6'), 134·33 (C-3') and 165·40 (C=O) ppm; ν_{max} (N) 2960, 1729 (carbonyl group), 1589, 1469, 1432, 1355, 1290, 1249 (C-O) 1133, 1029, 960 and 744 (benzene ring) cm^{-1}.

HRMS (FAB): *Found*: *m/z* 289·5669; *calculated* for $[C_{11}H_{10}O_2ClBr + H]^+$ 289·5682

Attempted intramolecular Heck reaction of (*Z*)-1-(2'-Bromobenzoyloxy)-4-chlorobut-2-ene 44

(a) Palladium(II) acetate (5·6 mg, 0·025 mmol) was placed in a flask under an atmosphere of nitrogen and dissolved in DMF (15 mL). Triphenylphosphine (0·013 g, 0·005 mmol) along with the ester **44** (0·29 g, 3 mmol), tetrabutylammonium chloride (0·277 g, 1 mmol), and potassium acetate (0·86 g, 9 mmol) were then added. The mixture was heated under reflux for 8 hours. It was then cooled, diluted with ether, washed with water and brine, dried with magnesium sulfate and the ethereal extract was then evaporated to give the chloro-ester **44** unchanged.

(b) The chloro-ester **44** (0·5 g, 1·7 mmol) was dissolved in pyridine (15 mL) and triethylamine (4 mL). To this solution was added triphenyl phosphine (5 mg, 0·019 mmol), followed by copper (I) iodide (1·3 mg, 0·007 mmol). Finally *bis*(triphenylphosphine)palladium dichloride (1·4 mg, 0·002 mmol) was then added and the reaction mixture was heated under reflux during 4 hours. It was then cooled and filtered. The filtered solid was washed with ether and triethylamine until the washings were colourless. The filtrate was washed with water, then with hydrochloric acid solution and again with water, dried over magnesium sulfate and concentrated to give a 1:1 mixture of **46** and a new substance that was not characterised.

Control reaction of (*Z*)-1-(2'-bromobenzoyloxy)-4-chlorobut-2-ene 44 with triethylamine

The chloro-ester **44** (0·5 g, 1·7 mmol) was dissolved in pyridine (15 mL) and triethylamine (4 mL) and the solution was heated under reflux during 4 hours. The reaction mixture was cooled, and extracted with ether and the extract was washed sequentially with water, hydrochloric acid and again with water, dried over magnesium sulfate and concentrated to give the same outcome as in the previous experiment.

3.8 References

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Chapter 4

Reactions of mixed carboxylic-trifluoroacetic anhydrides with tetrahydrofuran in the presence of iodide ion

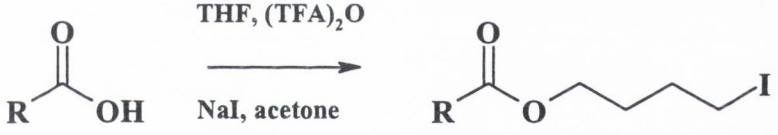
Chapter 4

Reactions of mixed carboxylic-trifluoroacetic anhydrides with tetrahydrofuran in the presence of iodide ion

4.1 Introduction

Due to the moderate success of the ring-opening reaction of 7-oxabicyclo[2.2.1]heptane using a carboxylic-trifluoroacetic mixed anhydride in the presence of sodium iodide that is described in Chapter 2, it was planned to investigate the reaction of tetrahydrofuran **1** under similar circumstances with the intention of synthesising 1-acyloxy-4-iodobutanes **2 (Scheme 1)**.

Reaction of a carboxylic acid to give a 1-acyloxy-4-iodobutane

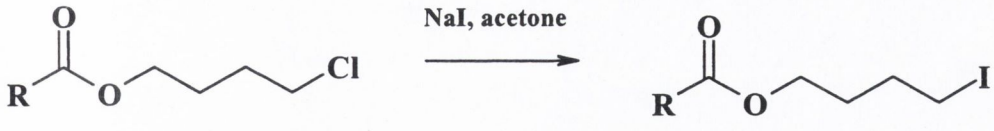


(1) (2)

Scheme 1

Previous syntheses of such compounds include, *e.g.*, Finkelstein[1] reactions of the corresponding chloro-compounds **3 (Scheme 2)** and ring-opening of tetrahydrofuran using the reagent combination of an acyl chloride and sodium iodide.[2]

Coversion of a 1-acyloxy-4-chlorobutane to a 1-acyloxy-4-iodobutane



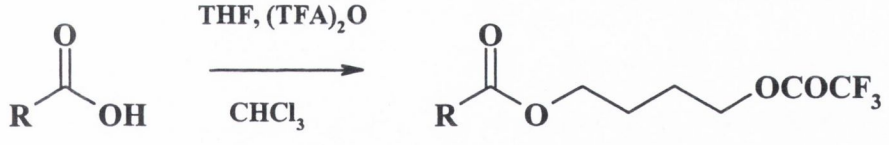
(3) (2)

Scheme 2

If the reaction outlined in **Scheme 1** was successful it would provide a more efficient route than that of Oku *et al.*[2] to compounds of the form **2**, saving on time, manipulation and reactants, because the initial preparation of an acyl chloride would not be required.

Previously work carried out[3] in this laboratory involved the synthesis of 1,4-monoesters of butanediol of the type **4 (Scheme 3)**.

Synthesis of 1,4- butanediol monoesters

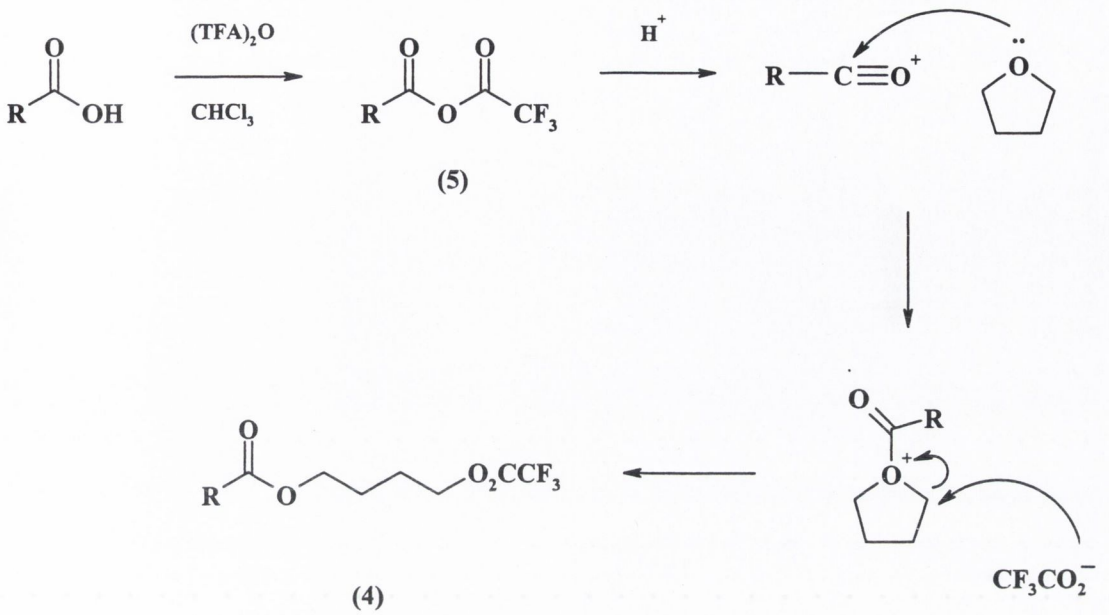


(1) (4)

Scheme 3

This occurs due to the formation of a mixed anhydride **5** from a carboxylic acid and trifluoroacetic anhydride that then gives an acylium ion which attacks the ether functionality of tetrahydrofuran **(Scheme 4)**.

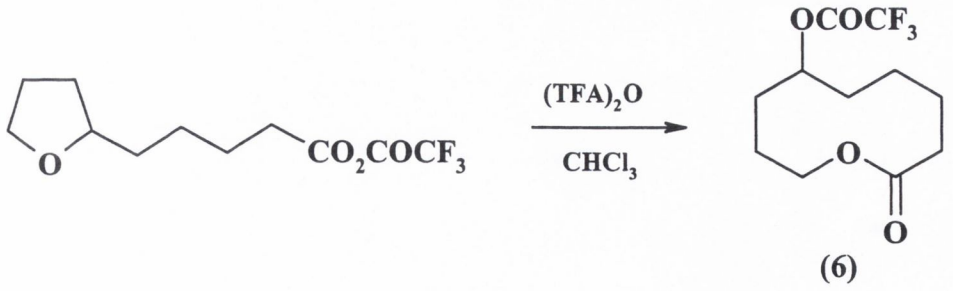
Mechanism of reaction shown in Scheme 3



Scheme 4

The intramolecular version of such a reaction also proved to be successful,[4] and has provided a new method for the synthesis of lactones, *e.g.*, of the ten-membered compound **6** (**Scheme 5**).

Synthesis of a trifluoroacetoxy-lactone from substituted tetrahydrofuran

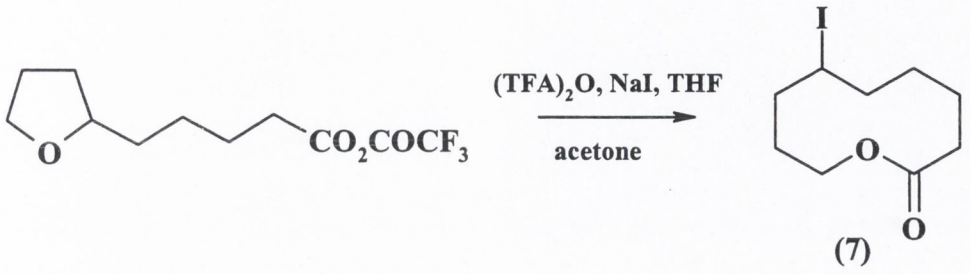


Scheme 5

An analogous intramolecular reaction was performed[4] using sodium iodide as an additional reactant and it was found that, since iodide ion is a better nucleophile than

trifluoroacetate ion, the reaction yielded the corresponding iodide **7** as product **(Scheme 6)**.

Synthesis of an iodo-lactone from substituted tetrahydrofuran

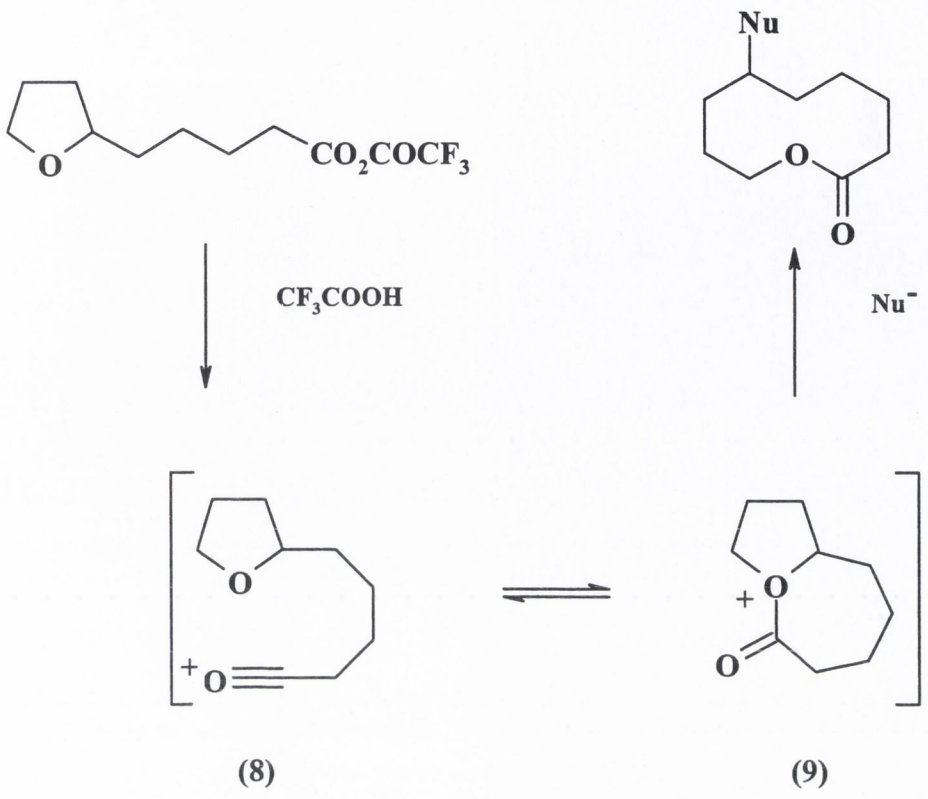


(7)

Scheme 6

It was thought that these reactions proceeded in the usual way, *i.e.* that a mixed anhydride was produced which led to the production of an acylium ion **8**. This ion then formed the acyloxonium ion **9** that was attacked by either trifluoroacetate ion or by iodide ion **(Scheme 7)**.

Mechanism of reaction shown in Scheme 6



(8) (9)

Scheme 7

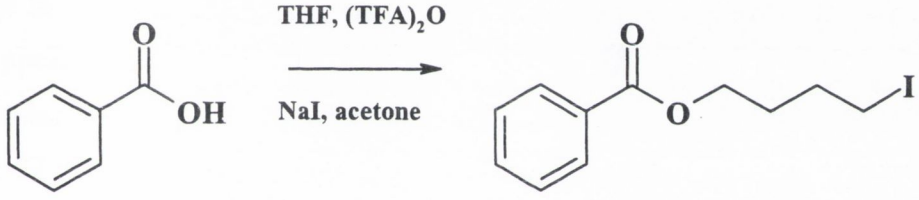
4.1.1 Synthesis of some 1-acyloxy-4-iodobutanes

The present work involved carrying out intermolecular ring cleavage reactions of tetrahydrofuran using mixed carboxylic - trifluoroacetic anhydrides in the presence of iodide ion. A variety of different acids were employed as described below.

The first of these reactions to be attempted was carried out using benzoic acid **10**. The acid was dissolved in acetone with two equivalents of tetrahydrofuran and three equivalents of sodium iodide. This solution was cooled to 0 °C and 1·5 equivalents of trifluoroacetic anhydride were then added. After allowing time for a mixed anhydride to form, the mixture was heated under reflux. The usual work-up gave the iodo-ester **11** in 54% yield.

The iodide **11**, which has been previously synthesised,[5] by Green *et al.* by ring cleavage of tetrahydrofuran with benzoyl chloride, aluminium chloride and 1-ethyl-3-methyl imidazolium iodide, was obtained in the present work as shown in **Scheme 8**. The infrared spectrum of **11** shows absorptions including a carbonyl group at 1721 cm^{-1}, a CO-O stretching band at 1275 cm^{-1} and an aryl ring absorption at 710 cm^{-1}. The proton NMR spectrum of the iodide **11** shows four methylene signals. There are two multiplets centred at δ 1·89 ppm and at δ 2·01 ppm. From CW decoupling and ^{13}C-^{1}H COSY experiments it was deduced that the signal at δ 1·89 ppm is due to the C-3 methylene group and that the signal at δ 2·01 ppm occurs due to the C-2 methylene group. A triplet at δ 3·28 ppm is assigned to the C-4 methylene group. Another triplet at δ 4·37 ppm corresponds to the C-1 methylene group.

Synthesis of 4–iodobutyl benzoate

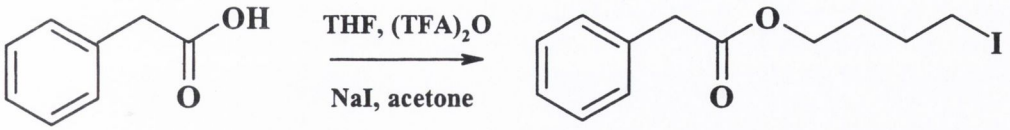


(10) **(11)**

Scheme 8

Similar reactions were carried out using various other carboxylic acids. Phenylacetic acid **12** yielded the iodo-compound **13 (Scheme 9)**. The infrared spectrum of the iodide **13** was very like that of 4-iodobutyl benzoate **11** due to their structural similarities. A carbonyl absorption is evident at 1735 cm^{-1}, a CO-O stretching band at 1259 cm^{-1} and an aryl ring absorption at 696 cm^{-1}. The proton NMR spectrum of **13** also shows signals similar to those of the ^{1}H NMR spectrum of the iodide **11**. The two methylene groups at C-3 and C-2 appear as multiplets centred at δ 1·76 ppm and at δ 1·84ppm. The iodomethyl group appears as a triplet at δ 3·17 ppm. The benzylic methylene group appears as a singlet at δ 3·64 ppm and the C-1 methylene group resonates at δ 4·13 ppm. The benzene ring protons appear as a multiplet at δ 7·31 ppm integrating for five protons.

Synthesis of 4-iodobutyl phenylacetate

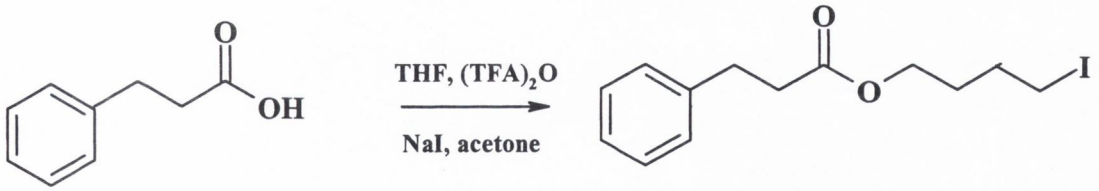


(12) **(13)**

Scheme 9

Phenylpropanoic acid **14** gave the expected iodide **15** as product **(Scheme 10)**. The infrared spectrum of the iodide **15** shows absorptions for an ester carbonyl group at 1735 cm^{-1}, a CO-O stretching at 1259 cm^{-1} and an aryl ring absorption at 700 cm^{-1}. Six sets of methylene signals are evident in the proton NMR spectrum, the first two as in the previous two cases represent the C-3 and C-2 methylene groups which appear at δ 1·72 ppm and at δ 1·84 ppm, respectively. The benzylic methylene protons resonate at as a triplet at δ 2·66 ppm. The C-2 methylene group appears at δ 2·97 ppm. The methylene groups at C-4' and C-1' appear at δ 3·19 ppm and δ 4·10 ppm. The benzene ring protons appear as two multiplets the first at δ 7·23 ppm integrating for three protons and at δ 7·31 ppm integrating for two protons.

Synthesis of 4-iodobutyl 3-phenylpropanoate

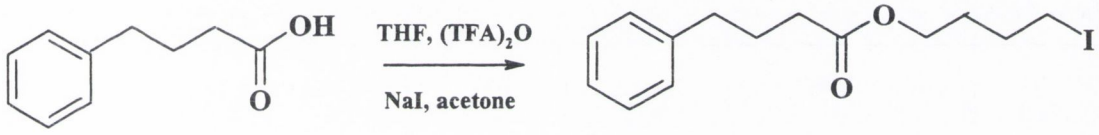


(14) **(15)**

Scheme 10

Phenylbutanoic acid **16** reacted under the conditions described above to give the iodoester **17** **(Scheme 11)** which displays similar spectroscopic data as the 1-acyloxy-4-iodobutanes just discussed. The infrared spectrum includes a carbonyl absorption at 1735 cm^{-1}, a CO-O stretching at 1226 cm^{-1} and an aryl ring absorption at 700 cm^{-1}. The proton NMR spectrum of **17** displays two multiplets centred at δ 1·77 ppm and at δ 1·89 ppm which correspond to the methylene groups on C-3' and C-2'. A quintet at δ 1·92 ppm is assigned to the CH_2 at C-2. A triplet at δ 2·35 ppm is assigned to the benzylic methylene group. Another triplet at δ 2·67 ppm corresponds to the methylene group on C-1. The two methylene groups on C-1' and C-4' resonate as multiplets centred at δ 3·23 ppm and δ 4·11 ppm. The aryl protons appear as two multiplets, one at appearing at δ 7·20 ppm and the other at δ 7·30 ppm.

Synthesis of 4-iodobutyl 4-phenylbutanoate

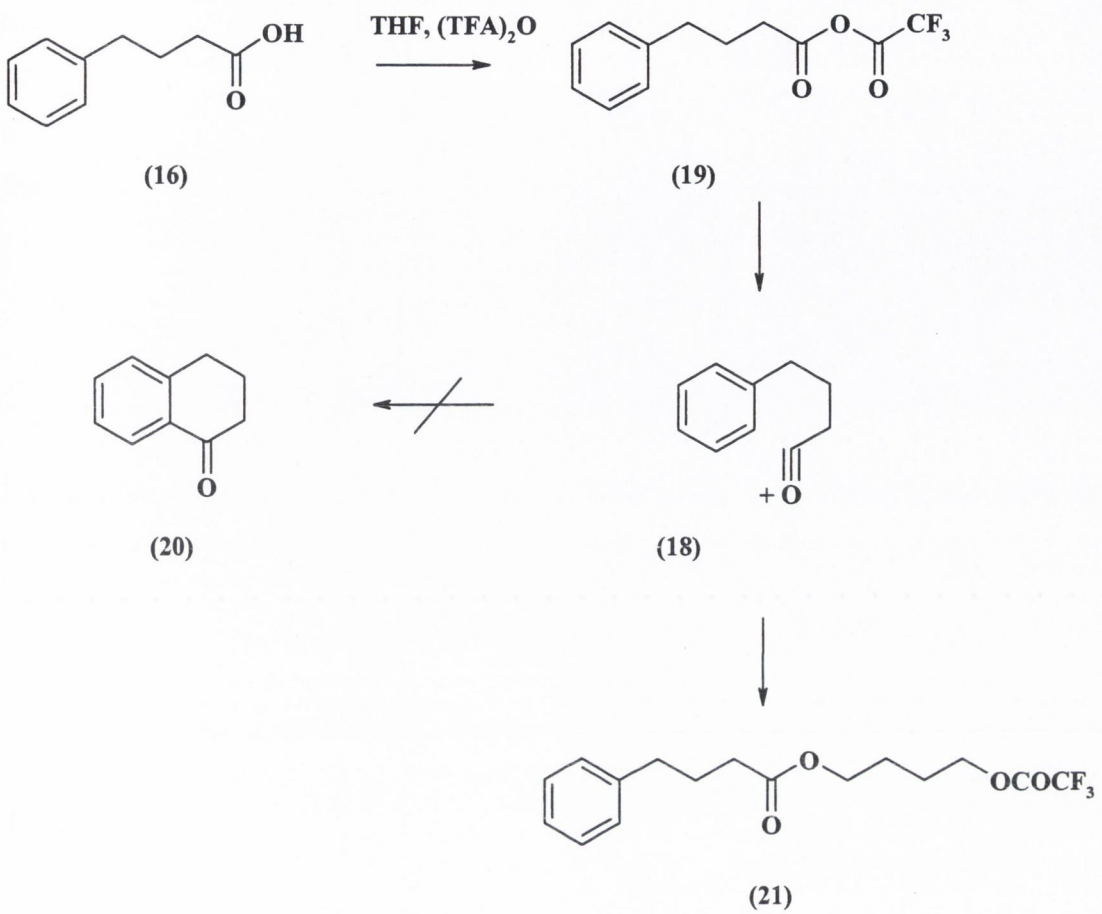


(16) **(17)**

Scheme 11

An interesting observation in the synthesis of the iodide **17** was that there was no side reaction to form a cyclic ketone. It was considered that the acylium ion **18** formed from the mixed anhydride **19** could cyclise to give α-tetralone **20** but this was found not to be the case. Such a side reaction was also not observed by O'Neill[3] in the synthesis of monoesters of butane-1,4-diol when the acid employed was 4-phenylbutanoic acid. The anticipated product **21** was formed but none of the competing intramolecular Friedel-Crafts cyclisation product **20** was detected **(Scheme 12)**. This surprising result is attributed to the powerful donor properties of the tetrahydrofuryl oxygen atom.

Possible side reaction of synthesis in Scheme 11



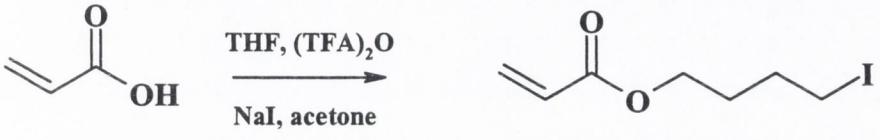
Scheme 12

After establishing the reactivity of tetrahydrofuran towards acylium ions derived from the aryl-substituted acids described above, the next class of acids to be investigated were the unsaturated acids acrylic acid **22** and 3,3-dimethylacrylic acid **23**.

A reaction involving acrylic acid **22** gave the iodoester **24** as product **(Scheme 13)**. The infrared spectrum of the iodide **24** displays absorptions for an ester carbonyl group at 1727 cm^{-1}, an alkene at 1637 cm^{-1} and a CO-O stretch at 1222 cm^{-1}. A multiplet centred at δ 1·80 ppm is assigned to the C-3' methylene group. The methylene group at C-2' resonates as a multiplet centred at δ 1·91 ppm. A triplet at δ 3·22 ppm is assigned to the C-1' methylene group. The C-4' methylene group appears as a triplet at δ 4·15 ppm. Three individual signals are evident in the alkene

region of the spectrum. Firstly, a 8 Hz doublet at δ 5·85 ppm is assigned to the proton at C-2 which is *cis* in relation to the proton at C-1. A double doublet is assigned to the C-1 proton. The signal displays coupling constants of 16 and 8 Hz which are typical *J* values for *cis* and *trans* coupling. The other C-2 proton appears as a doublet at δ 6·42 ppm and displays a coupling constant of 16 Hz which is typical for a *trans J* value.

Synthesis of 4-iodobutyl acrylate



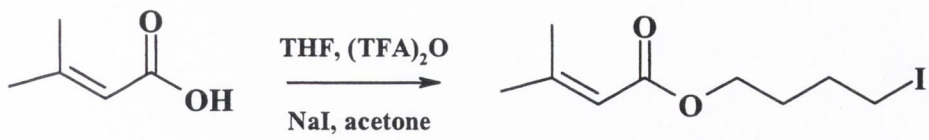
(22) **(24)**

Scheme 13

Reaction of tetrahydrofuran with 3,3-dimethylacrylic acid **23** under the previously described conditions gave the iodoester **25 (Scheme 14)**.

The infared spectrum of the iodide **25** displays an ester carbonyl absorptions at 1717 cm^{-1}, a band at 1654 cm^{-1} confirming the presence of a double bond and a CO-O absorption at 1270 cm^{-1}. The proton NMR of **25** spectrum shows, as is common with all these iodides, two multiplets representing the C-3' and C-2' methylene groups that are centred at δ 1·77 ppm and at δ 1·94 ppm, respectively. A singlet at δ 1·91 ppm is assigned to the methyl group which is *trans* to the carbonyl group. A singlet at δ 2·17 ppm is assigned to the other methyl group. The methylene group at C-4' appears as a triplet at δ 3·23 ppm and the methylene group at C-1' resonates as a triplet at δ 4·12 ppm. The final signal is a singlet at δ 5·69 ppm and is assigned to the olefinic proton.

Synthesis of 4-iodobutyl 3'-methylbut-2'-enoate

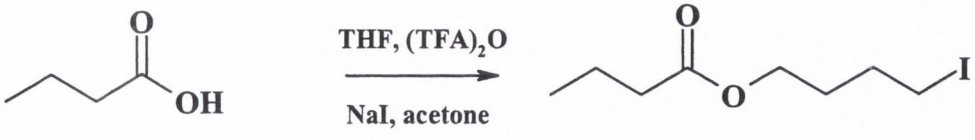


(23) **(25)**

Scheme 14

The next family of acids to be investigated were the aliphatic acids butyric acid **26** and *iso*-butyric acid **27**. Butyric acid reacted under the usual conditions to give the anticipated product **28 (Scheme 15)**. The infrared spectrum of the iodide **28** shows a carbonyl group absorption at 1735 cm^{-1} and a O-C-O bond absorption at 1226 cm^{-1}. The proton NMR spectrum of **28** shows a triplet integrating for three protons at δ 0·96 ppm which is assigned to the terminal methyl group. A sextet at δ 1·65 ppm is assigned to the methylene group at C-2. A multiplet centred at δ 1·77 ppm is assigned to the C-3' methylene group. The C-2' methylene group resonates as a multiplet centred at δ 1·92 ppm. The C-1 methylene group appears as a triplet at δ 2·30 ppm. A multiplet at δ 3·22 ppm corresponds to the iodomethyl group. The C-1' methylene group appears as a multiplet at δ 4·09 ppm.

Synthesis of 4-iodobutyl butanoate

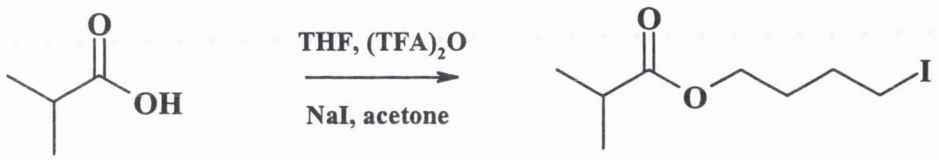


(26) **(28)**

Scheme 15

The iodide **29** was synthesised by reaction of tetrahydrofuran with the acid **27** in the usual manner **(Scheme 16)**. The infrared spectrum of the iodide product **29** shows an absorption at 1733 cm^{-1} representative of the carbonyl group and one at 1226 cm^{-1} indicative of an O-C-O bond. The proton NMR spectrum displays a doublet at δ 1·18 ppm integrating for six protons and is assigned to the two equivalent methyl groups. A multiplet at δ 1·77 ppm corresponds to the C-3' methylene group and a multiplet at δ 1·92 ppm is assigned to the C-2' methylene group. The methine group appears as a septet at δ 2·56 ppm. The C-4' methylene group appears as a triplet at δ 3·23 ppm and the C-1' methylene protons resonate at δ 4·11 ppm.

Synthesis of 4-iodobutyl 2'-methylpropanoate



(27) **(29)**

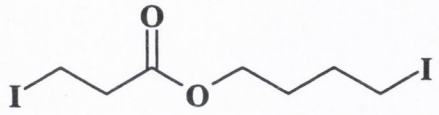
Scheme 16

During the course of the reactions described above the formation of a precipitate was observed. This was isolated by filtration, and by infrared analysis it was inferred that the solid was sodium trifluoroacetate, formed by reaction of the liberated trifluoroacetic acid with sodium ions.

4.1.2 Summary

The yields of the 1-acyloxy-4-iodobutanes that were obtained in this work were quite good overall **(Table 4.1)**, except for the case of the acrylate **24** which was formed in only 21% yield. This is assumed to be due to the reactivity of the activated double bond of **22** towards iodide ion. The proton NMR spectrum of the crude product obtained from the reaction in **Scheme 13** shows more signals than are expected,

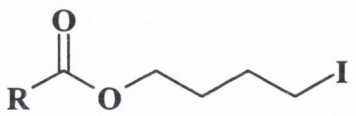
including a triplet at δ 2·71 ppm which is typical for a methylene group adjacent to a carbonyl group. The ^{13}C NMR spectrum of the crude product displays two signals which are very upfield at δ 5·76 ppm and δ 5·70 ppm which are characteristic of iodomethyl groups so it is thought that the expected iodide **24** was formed but then reacted further to form the di-iodide **30**. This compound is expected to be very unstable and so would decompose quite readily thus causing the low yield obtained.



(30)

Table 4.1

Yields[1] of 1-acyloxy-4-iodobutanes obtained from tetrahydrofuran, a mixed anhydride and sodium iodide

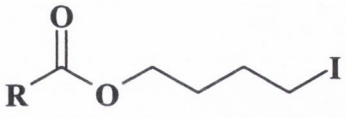
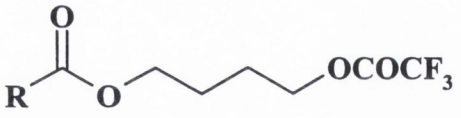
Compound no.	R	% yield of 
11	Ph	54
13	$PhCH_2$	67
15	$PhCH_2CH_2$	61
17	$PhCH_2CH_2CH_2$	75
24	$CH_2=CH$	21
25	$(CH_3)_2C=CH$	67
28	$CH_3(CH_2)_2$	75
29	$(CH_3)_2CH$	90

[1]based on reacting carboxylic acid

The trifluoroacetoxy analogues **31** of some of the above iodides have been previously synthesised[3] and some common patterns can be observed when their yields and those of the iodides synthesised in the present work are compared as shown in **Table 4.2**. These trends can be interpreted in terms of the ease of formation of carboxylic-trifluoroacetic mixed anhydrides from the various acids and the percentages of these mixed anhydrides that are present at equilibrium. Benzoic acid gave the lowest yield of all the aryl compounds examined suggesting that steric factors are important. In the synthesis of the trifluoroacetoxy compounds **31** the yields of the products derived from acrylic acid **22** and from dimethyl acrylic acid **23** (**Table 4.2**; entries 5 and 6) the yields were 90% and 91% respectively. However, in the case of the related iodo compounds **24** and **25** the yields differed considerably. The acrylate **24** was only formed in 21% yield whereas the dimethyl acrylate **25** was produced in 67% yield. This difference can be attributed to the possible nucleophilic additin of iodide ion to the double bond of **24** as discussed earlier (page 149).

Table 4.2

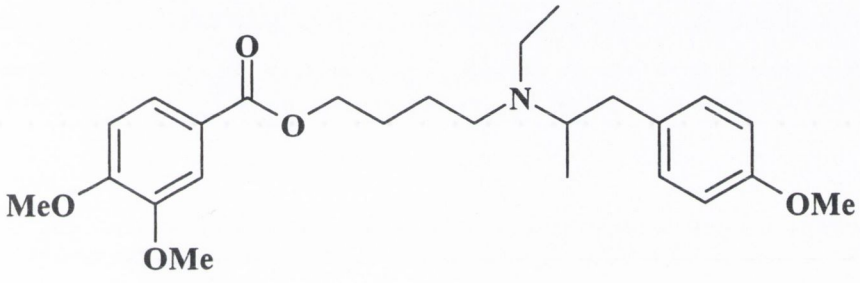
Comparison of yields of iodo compounds 2 with those of trifluoroacetoxy compounds 31

Entry	R	% yield of 2 	% yield[3] of 31 
1	**Ph**	54	56
2	**$PhCH_2$**	67	74
3	**$PhCH_2CH_2$**	61	70
4	**$PhCH_2CH_2CH_2$**	75	69
5	**CH_2=CH**	21	90
6	**$(CH_3)_2$C=CH**	67	91

4.1.3 An alternative synthesis of a Mebeverine precursor

The successful synthesis of a range of 1-acyloxy-4-iodobutanes as described above suggested a novel route to an intermediate required for the synthesis of Mebeverine **32**.

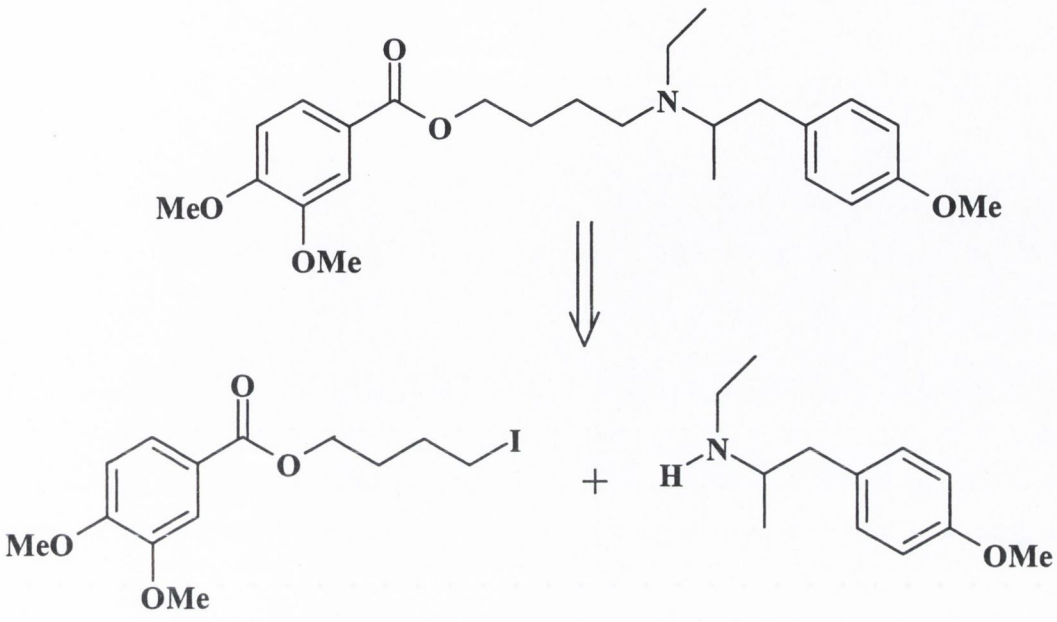
Mebeverine **32** is the active ingredient of the drug Colofac™ which is a musculotropic spasmolytic agent that is used to treat illnesses of the gastro-intestinal tract.



(32)

The existing synthesis of **32**[6] involves a route which relies for its final step on formation of the bond between the nitrogen atom and the terminal carbon chain of the benzoate ester **33** by reaction of this iodide with the amine **34 (Scheme 17)**.

Reaction of the iodide 33 and the amine 34 to give Mebeverine 32



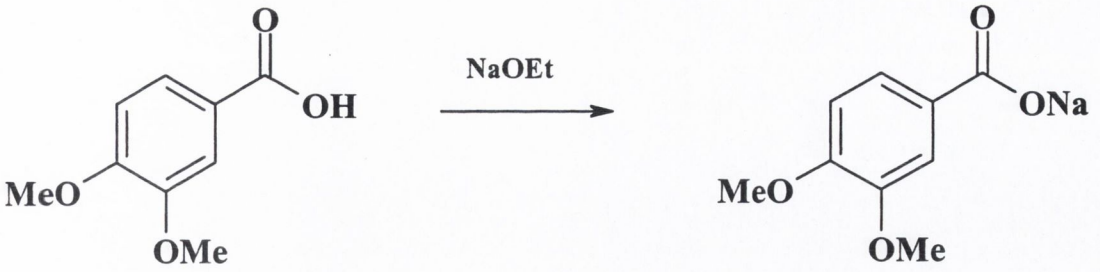
(33) **(34)**

Scheme 17

It appeared that the iodide **33** could potentially be synthesised quite easily using the methodology described earlier in this chapter. This would be very beneficial since the literature route[6] to **32** requires three steps as discussed below.

Firstly, veratric acid **35** was converted[6] into its sodium salt **36** by stirring with sodium ethoxide **(Scheme 18)**.

Conversion of veratric acid to its sodium salt

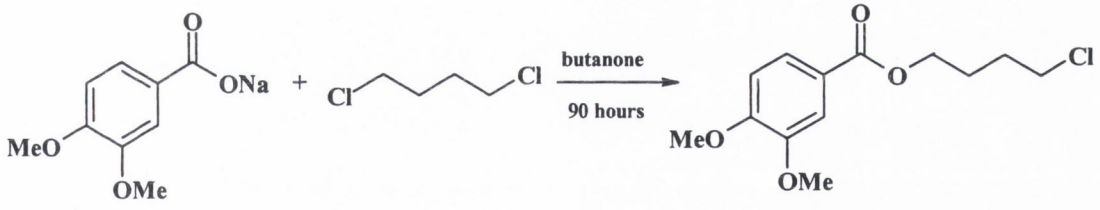


(35) **(36)**

Scheme 18

This sodium salt **36** was then heated under reflux in butanone with excess 1,4-dichlorobutane **37** during ninety hours to give the chloroester **38** in 62% yield **(Scheme 19)**.

Reaction of the sodium salt 36 with 1,4-dichlorobutane to give the chloride 38

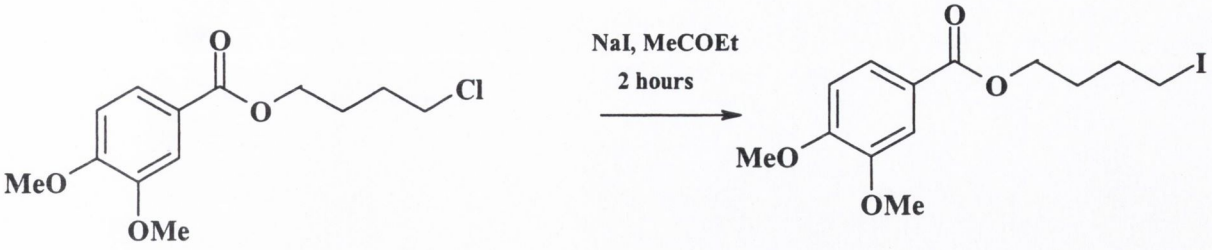


(36) **(37)** **(38)**

Scheme 19

The iodide **33** was then obtained by Finkelstein[1] reaction of the chloride **38** with sodium iodide in butanone **(Scheme 20)**. This substitution was essential due to the fact that chloride is a leaving group that is not reactive enough to undergo displacement by the secondary amine **38** in the final step that leads to the target molecule **33**.

Conversion of the chloride 38 to its corresponding iodide 33



(38) **(33)**

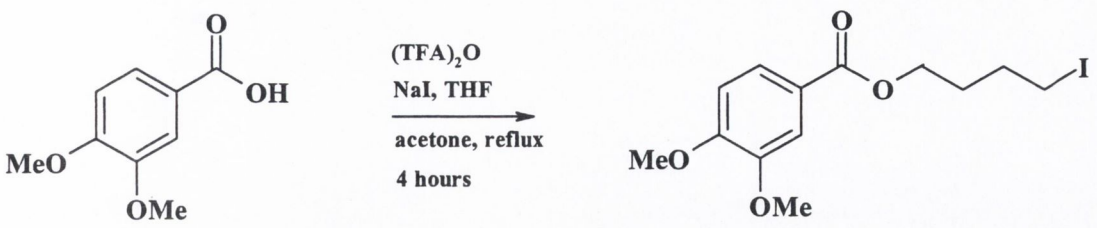
Scheme 20

This reaction pathway is relatively long and the overall yield of the iodide **33** from 3,4-dimethoxybenzoic acid **35** is just over 50%.

5.1.4 One-step synthesis of the iodide 33

In the present work the iodide **33** was synthesised using the mixed anhydride formed from veratric acid **35** and trifluoroacetic anhydride. Veratric acid was dissolved with tetrahydrofuran (2 eq.) and sodium iodide (3 eq.) in acetone at 0 °C. Trifluoroacetic anhydride (1·5 eq.) was then added and the mixture was heated under reflux to give the target iodide **33** directly in 89% crude yield **(Scheme 21)**.

One-step synthesis of the iodide 33 from veratric acid

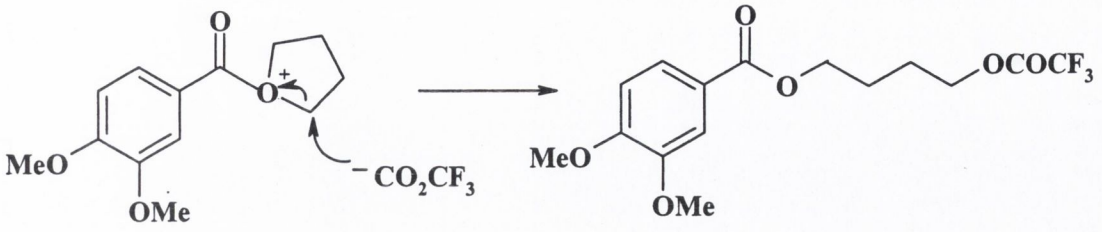


(35) **(33)**

Scheme 21

This crude material was then purified by column chromatography. The desired iodide **33** was obtained as a pure substance in 71 % yield from veratric acid **35** in one step. The infrared spectrum of 4'-iodobutyl 3,4-dimethoxybenzoate **33** showed an absorption for the carbonyl group at 1710 cm^{-1} the CO-O bond at 1292 cm^{-1} and the benzene ring at 727 cm^{-1}. The proton NMR spectrum of **33** shows the C-3 methylene group as a multiplet resonating at δ 1·91 ppm. The C-2 methylene group appears as another multiplet at δ 1·99 ppm. A triplet at δ 3·28 ppm is assigned to the iodo-methyl group. A singlet at δ 3·95 ppm that integrates for six protons is assigned to the two methoxy groups on the benzene ring. The C-1-methylene group appears as a triplet at δ 4·95 ppm. The three benzene ring protons appear as an AMX system. Firstly, the C-5'-proton appears as a 8 Hz doublet at δ 6·90 ppm. The C-2' proton resonates as a 2 Hz doublet at δ 7·56 ppm. The proton on C-6' appears as a double doublet with coupling constants of 8 and 2 Hz at δ 7·69 ppm. Also isolated was the trifluoroacetoxy derivative **39** (16 %). The formation of **39** is obviously due to competitive attack by trifluoroacetate ion on the acyloxonium ion **40** generated as a reaction intermediate **(Scheme 22)**.

Mechanism of by-product formation in Scheme 21



(40) **(39)**

Scheme 22

The compound **39** was identified by its spectroscopic data. The infrared spectrum displayed an absorption at 1782 which is typical for a trifluoroacetate group. The methylene group at C-2 appears as a multiplet centred at δ 1·74 ppm. The C-3 methylene group resonates as another multiplet at δ 1·86 ppm. The two methoxyl groups appear as a singlet at δ 3·95 ppm integrating for six protons. A triplet at δ 4·02 ppm is assigned to the C-4 methylene group. The aryl protons appear as three signals similar to the iodo compound **33**. Firstly, the C-5'-proton appears as an 8 Hz doublet at δ 6·89 ppm. The C-2' proton resonates as a 2 Hz doublet at δ 7·55 ppm. The proton on C-6' appears as a double doublet at δ 7·69 ppm with coupling constants of 8 and 2 Hz.

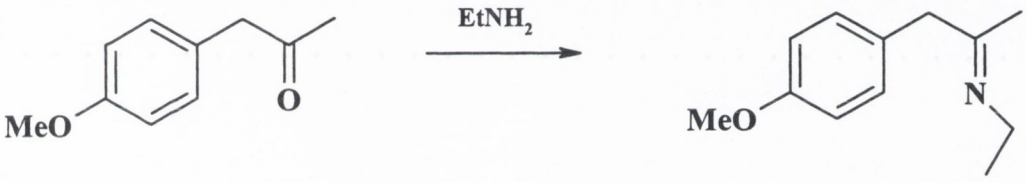
Since the iodide **33** is a drug precursor, an improvement in its synthesis is very valuable. The methodology described above represents a far superior way of obtaining the iodide **33** as it saves on time, taking 4 hours to execute in comparison to approximately 4 days required for the original synthesis. Also, fewer ancillary reagents are employed and less manipulation of compounds is required which is extremely important from an industrial point of view since the reaction procedure has to be applicable to a large-scale reaction environment. Additionally, a superior

overall yield was obtained. All these factors would potentially reduce production costs.

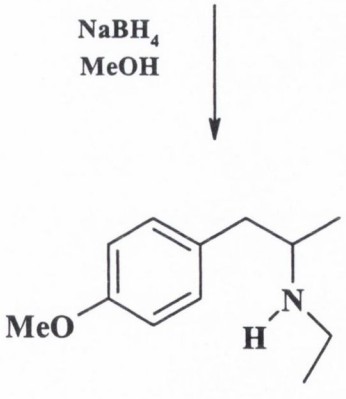
4.1.4 Synthesis of ethyl[2-(4-methoxyphenyl)-1-methylethyl]amine[9] 34

The amine **34** required for the reaction with the iodide **33** to give Mebeverine **32** was obtained by the reduction of the imine **41**, which was produced by the reaction of 4-methoxyphenylacetone **42** with ethylamine **(Scheme 23)**.

Synthesis of the amine 34



(42) **(41)**



(34)

Scheme 23

The condensation reaction to yield **41** was carried out at room temperature using 2·5 equivalents of ethylamine per mole of the ketone **42**. This imine **41** was reduced, without isolation, using sodium borohydride in methanol.

The infrared spectrum of the amine **34** displays an amino group absorption at 3500 cm^{-1}. The ^1H NMR spectrum of **34** displays a 6 Hz doublet at δ 1·07 ppm which is assigned to the secondary methyl group. The primary methyl group adjacent to the methylene group resonates as a triplet at δ 1·10 ppm. A broad singlet at δ1·70 ppm that is exchangeable with D_2O, is assigned to the NH group. Two 2H multiplets appear in very close proximity at δ 2·59 ppm and at δ 2·73 ppm. By means of a ^1H-^1H COSY experiment their assignments were determined. The multiplet at δ 2·59 ppm is assigned to the benzylic methylene group and that at δ 2·73 ppm is assigned to the methylene group adjacent to the nitrogen. The methine proton appears as a sextet centred at δ 2·90 ppm with a coupling constant of 7 Hz. The methoxy group on the benzene ring resonates as a singlet at δ 3·81 ppm. The aryl protons then appeared as two signals. The two protons on C-3 and C-5 appear as a 8 Hz doublet at δ 6·85 ppm and the C-2 and C-6 protons appear as another 8 Hz doublet at δ 7·12 ppm.

The amount of ethylamine used in the synthesis of the amine **34** was found to be quite important as the reaction of a ketone with an amine gives water as a side-product and the reactant ethylamine was used as an aqueous solution. It follows that the reaction will only proceed to equilibrium under these circumstances.

The reductive amination of the ketone **42** using ethylamine followed by sodium borohydride was carried out under a number of conditions shown in **Table 4.2**. In each of these reactions, the product after borohydride reduction was partitioned into base and neutral fractions. The latter consisted of recovered ketone **42**. Thus, reduction of the imine **41** by sodium borohydride is much faster than reduction of the ketone **42**. Surprisingly, the best overall results were obtained (**Table 4.2**), not with anhydrous ethylamine, but with 70% aqueous ethylamine (Entry 2). Here, the yield of amine **34** based on reacted starting material was 88%.

Table 4.3

Reductive amination of the ketone 42 using various concentrations of ethylamine

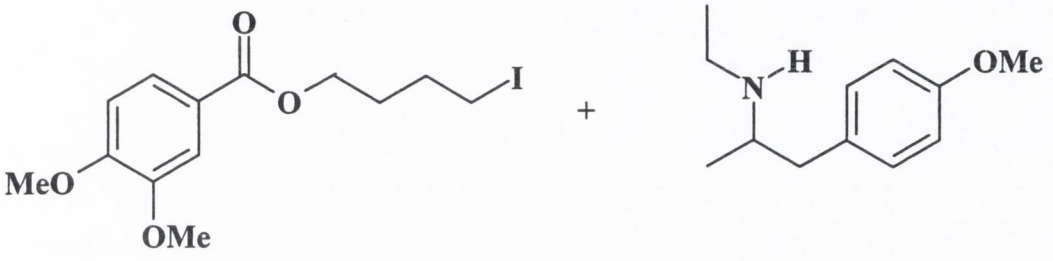
Entry	Equivalents of ethylamine	Temperature	% yield of 34	recovered 42 (%)
1	2·5	r.t.	33%	30%
2	2·5 and 0 °C	0 °C	88%	40%
3	2·5 with removal of excess ethylamine before reduction	0 °C	42%	45%
4	5	r.t.	51%	26%
5	anhydrous ethylamine	r.t.	58%	15%

4.1.5 Synthesis of Mebeverine 32

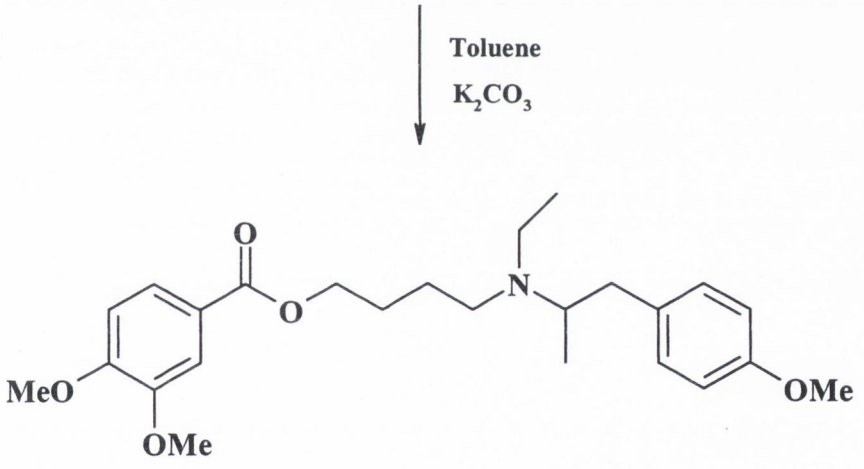
The synthesis of Mebeverine **32** was then carried out. The iodo compound **33** was treated with the amine **34** in refluxing toluene to give **32 (Scheme 24)**. The hydrogen iodide formed as a side product of the reaction was scavenged by solid potassium carbonate that was added to the mixture. The authors of the published synthesis[6] had effected this transformation by refluxing the amine **34** with the iodo-ester **33** in butanone as solvent for 20 hours. Butanone has a boiling point of 80 °C

so a study was undertaken to determine if use of another, higher boiling solvent would decrease the reaction time and also to see if the reaction would proceed better in the absence of any solvent.

Synthesis of Mebeverine



(33) **(34)**

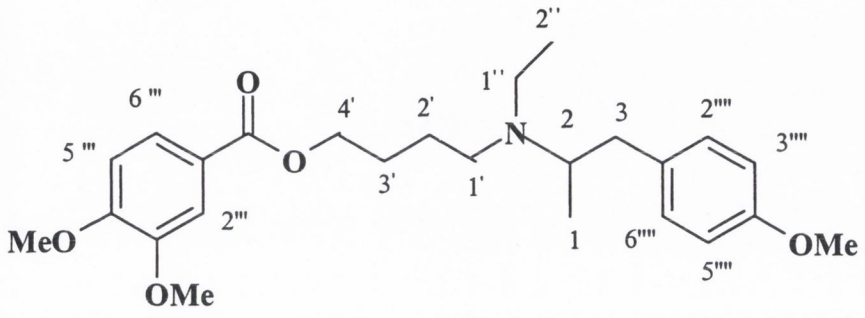


(32)

Scheme 24

Accordingly the alkylation reaction was carried out both in refluxing toluene and in the absence of any solvent. In both cases, the mixture was heated to the same temperature *i.e.* 110 °C for the same length of time. When toluene was used the crude yield was 96% whereas without toluene present it was 53%. It was concluded

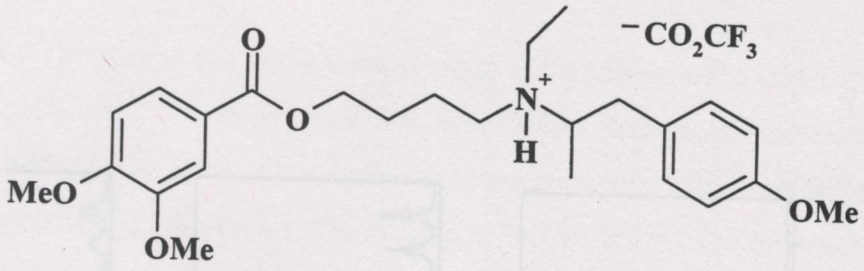
that the reaction could proceed in the absence of any solvent but that it gave a low yield. The reaction that was performed in toluene gave an almost quantitative yield of crude product **32**, which surpassed the yield previously reported (54%). The crude product was then purified by column chromatography to give pure material as an oil.



(32)

The proton NMR spectrum of **32**, which is shown in **Figure 4.1**, displays the C-1 methyl group as the most upfield signal which appears as a broad singlet at δ 0·96 ppm. Another broad singlet at δ 1·09 ppm is assigned to the protons of the other methyl group. The methoxyl groups appear as singlets integrating for three and six protons at δ 3·79 and δ 3·95 ppm respectively. The C-4' methylene group resonates as a triplet at δ 4·30 ppm. The aromatic region of the spectrum consists of five signals. Two 8 Hz doublets at δ 6·83 and at δ 7·13 ppm, each integrating for two protons, are assigned to the disubstituted benzene ring, the protons in close proximity to the methoxyl group being the more upfield. The protons on the trisubstituted benzene ring appear further downfield. The *meta*-proton resonates as an 8 Hz doublet at δ 6·89 ppm. The *ortho* -proton adjacent to the methoxyl group appears as a singlet at δ 7·55 ppm. The other *ortho*-proton appears as an 8Hz doublet at δ 7·70 ppm.

The methyl and most of the methylene proton signals are not very clear in the NMR spectrum of Mebeverine free base **32** because of quadropolar broadening due to the nitrogen atom. In an attempt to try and sharpen these resonances, trifluoroacetic acid was progressively added to the sample to form the quaternary ammonium salt **43** and another spectrum was run.



(43)

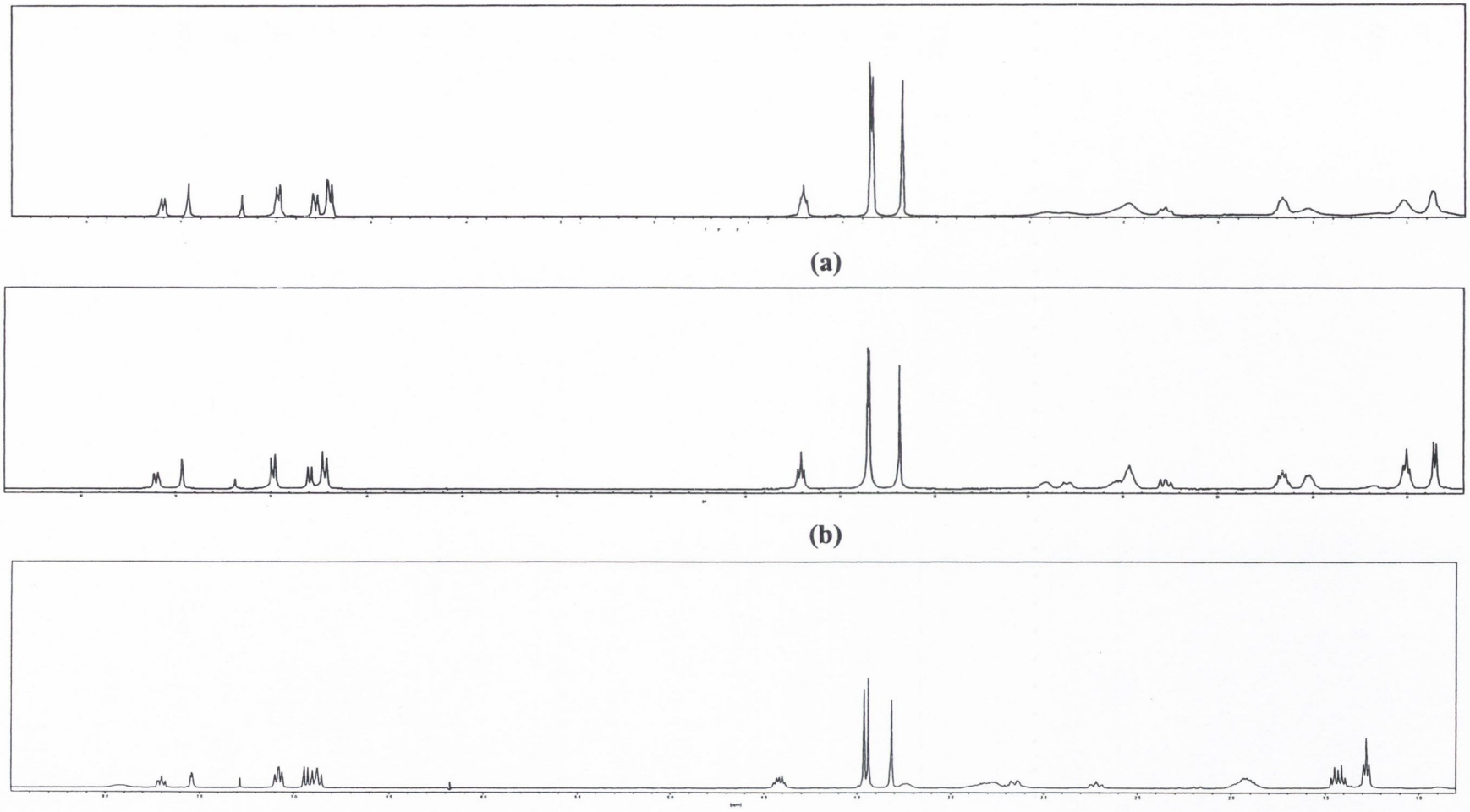
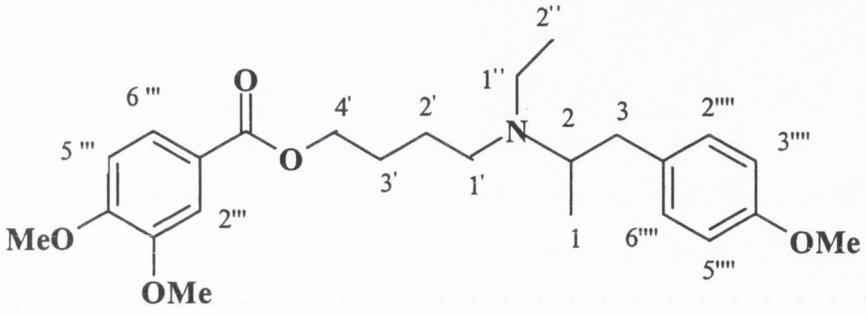


Figure 4.1 (a) Mebeverine free base; (b) Mebeverine after addition of some trifluoroacetic acid;(c) fully protonated Mebeverine showing both diastereomeric ammonium forms

Figure 4.1 (b) shows the same sample after the addition of a small quantity of trifluoroacetic acid. It was assumed that, since a less than molar equivalent of acid had been added, only some of the amine had been converted into its ammonium form so the spectrum in **Figure 4.1 (b)** represents a mixture of the amine **32** and its ammonium salt **43**.

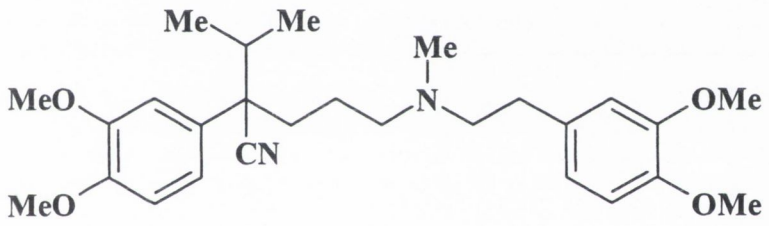


The spectrum in **Figure 4.1 (b)** is much clearer than that of the free base (**Figure 4.1 (a)**. The signal at δ 0·96 ppm has shifted slightly upfield to δ 0·94 ppm and now resonates as a clear 6 Hz doublet. The broad singlet formerly at δ 1·09 ppm now appears as a clean triplet. A multipet integrating for two protons at δ 1·61 ppm is assigned to the C-2' methylene group. A resolved quintet at δ 1·75 ppm is assigned to the C-3' methylene group due to its coupling with the downfield C-4' methylene group which is evident from a ^{1}H-^{1}H COSY spectrum. A 1H double doublet is observed at δ 2·36 ppm which displays coupling constants of 12·5 Hz and 3·5 Hz. A 12·5 Hz doublet is observed at δ 2·88 ppm integrating for one proton. Due to the common *J* value and the fact that both of the signals exhibit coupling with the methine proton (from the ^{1}H-^{1}H COSY experiment) it was deduced that the signals were due to the benzylic methylene protons and that they resonate as an AB system of double doublets but that the second signal at δ 2·88 ppm is not well resolved and is apparent as a doublet. A multiplet at δ 2·61 ppm integrating for four protons is observed and is identifiable as the C-1'' methylene group due to its coupling with the adjacent methyl group observed in the ^{1}H-^{1}H COSY experiment. The signal also seems to represent the C-1' methylene group. A 1H multiplet at δ 3·73 ppm

corresponds to the methine group. The multiplicity cannot be determined but coupling is observed between it and the methyl group at C-1.

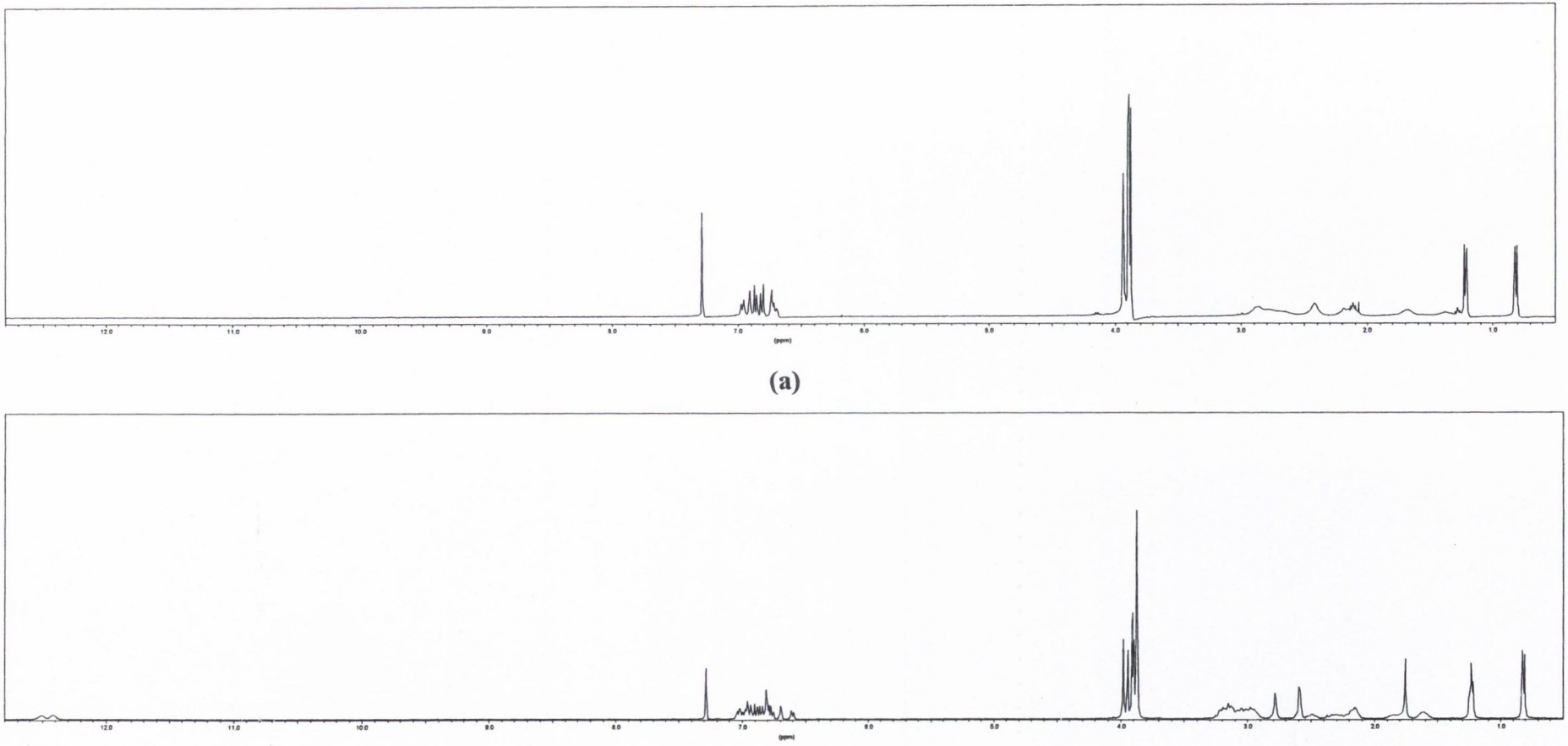
The effect of adding further acid is shown in **Figure 4.1 (c)**. It is a spectrum of the ammonium salt **43** but it displays some interesting properties. It is obvious that some of the signals have merged. This suggests that there are two compounds present.

A similar observation has been previously made by Grayson *et al.*[7] when NMR experiments were carried out on the drug Verapamil **44** which displayed similar findings. The structures of Mebeverine **32** and Verapamil **44** are very similar, both comprising two methoxy-substituted benzene rings connected by an aliphatic chain that contains a tri-substituted nitrogen atom.



(44)

The effect of adding acid to the free base of Verpamil **44** is shown in **Figure 4.2**.



(a)

(b)

Figure 4.2 (a) Verapamil free base; (b) fully protonated Verapamil showing both diastereomeric ammonium form

Figure 4.2 (a) shows the proton NMR spectrum of Verapamil free base. Much of the aliphatic region of the spectrum is difficult to interpret due to the broadening of many of the signals as is the case in the spectrum of Mebeverine [**Figure 4.1 (a)**]. The *iso*propyl methyl groups are apparent as two 3H doublets at δ 0·81 ppm and at δ 1·21 ppm. The four methoxyl groups appear as 3H singlets resonating at δ 3·87 ppm, δ 3·88 ppm, δ 3·89 ppm and δ 3·93 ppm. The aryl protons resonate as a complex system of multiplets centred at δ 6·83 ppm. Ignoring *meta*-coupling, this system should contain a maximum of ten lines, all of which are easily seen.

Figure 4.2 (b) shows the ^{1}H NMR spectrum of Verapamil hydrochloride **45**.

The *iso*propyl methyl groups now appear as a 3H doublet at δ 0·81 ppm and as an apparent 3H triplet at δ 1·23 ppm. The latter arises from two overlapping doublets.

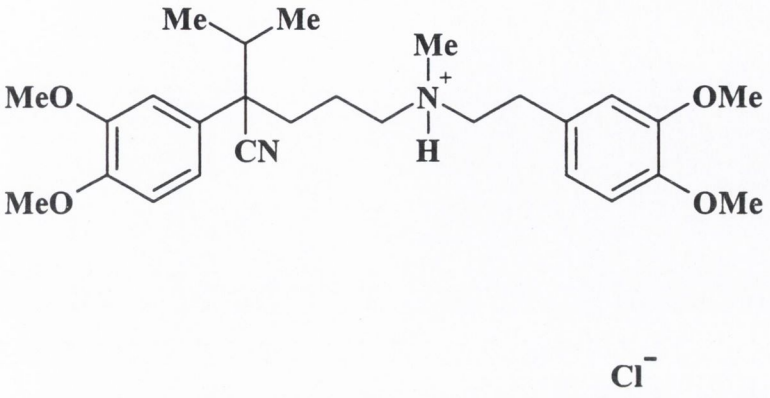
From a H-H COSY experiment the methylene proton resonances of Verapamil hydrochloride can be identified. Thus, a 6H multiplet at δ 3·94 ppm is assigned to the two methylene groups adjacent to the nitrogen and to the diastereotopic protons of the benzylic methylene group. The methylene group adjacent to the cyano group appears as two broad signals at δ 1·60 ppm and at δ δ 1·85 ppm. The methylene group next to this also appears as two signals at δ 2·15 ppm and at δ 2·25 ppm.

The methyl group which is bonded to the protonated nitrogen atom appears as two doublets at δ 2·58 ppm and at δ 2·77 ppm, both of which possess a coupling constant of 4 Hz.

The four methoxyl groups each appear as five 3H singlets at δ 3·87 ppm and at δ 3·89 ppm, at δ 3·90 ppm and at δ 3·94 ppm and at δ 3·97 ppm, indicating that some doubling of signals has occurred.

The aromatic region of the spectrum is again complicated and difficult to interpret, but it is obvious that there has been a doubling of most of the signals (a total of 17

lines can now be observed), thus confirming the presence of the two diastereomers of the ammonium salt **45**.



(45)

Protonation of the nitrogen atom of Mebeverine **32** creates a second chiral centre and so two diastereomers exist when the compound is in the ammonium form.

In the ^{1}H NMR spectrum of Mebeverine free base shown in **Figure 4.1 (a)** a broad singlet at δ 0·96 ppm is assigned to the C-2 methyl group whereas for protonated Mebeverine [**Figure 4.1 (c)**] the same group appears as an apparent triplet at δ 1·27 ppm. This is actually a pair of overlapping doublets. Another broad singlet at δ 1·12 ppm in the spectrum of the free base [**Figure 4.1 (a)**] is assigned to the C-1'' methyl group but the signal for this methyl group appears as a pair of overlapping triplets at δ 1·42 ppm in the protonated form [**Figure 4.1 (c)**]. Two broad singlets at δ 1·62 ppm and δ 1·76 ppm [**Figure 4.1 (a)**], each integrating for 2H, show up as a complicated multiplet at δ 1·90 ppm in **Figure 4.1 (c)**. The C-4' methylene group of Mebeverine free base appears as a 2H triplet at δ 4·30 ppm [**Figure 4.1 (a)**], but in the ammonium form [**Figure 4.1 (c)**] two separate triplets, one for each diastereoisomer, resonate at δ 4·40 ppm and at δ 4·42 ppm.

The aryl protons of Mebeverine free base **32** [**Figure 4.1 (a)**] appear as five signals. The protons of the disubstituted ring resonate as an AB system of doublets centred at

δ 6·83 ppm and at δ 7·09 ppm. The protons of the trisubstituted ring appear as a doublet (*J* 8 Hz) at δ 6·89 ppm, a doublet at δ 7·56 ppm (*J* 1.5 Hz) and as a double doublet at δ 7·70 ppm (*J* 8.0 and 1.5 Hz).

For protonated Mebeverine [**(Figure 4.1 (c)**] the picture is quite different. Thus, in the trisubstituted benzene ring the C-2'''proton appears as a closely spaced *pair* of overlapping doublets at δ 7·53 ppm. The C-6''' proton appears as a *pair* of overlapping double double at δ 7·69 ppm but the C-5''' proton appears as a simple doublet at δ 6·93 ppm. For the disubstituted benzene ring, each of the C-2''''/C-6'''' and C-3''''/C-5'''' protons resonate as *pairs* of doublets at δ 6·89 ppm and at δ 7·07 ppm.

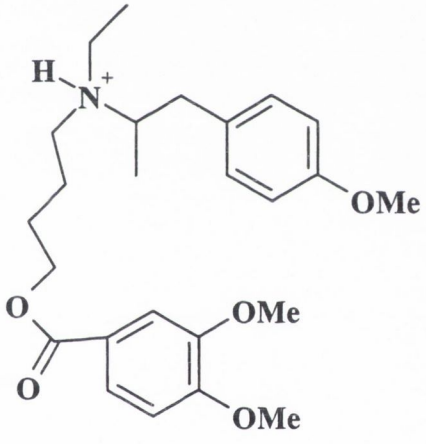
All of these assignments were secured by means of H-H COSY experiments.

Table 4.4

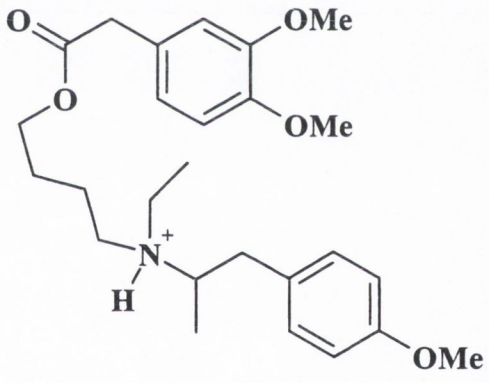
Comparison of chemical shifts of the Mebeverine free base 32 and the ammonium salt 43

	Free base	**Ammonium salt**
C-1	0·96, 3H, br s	1·27, 3H, apparent triplet (2 overlapping doublets)
C-2''	1·12, 3H, br s	1·42, 3H, 2 overlapping triplets
C-2'	1·62, 2H, br s	1·90, 4H, m
C-3'	1·76, 2H, br s	
C-3, C-1' and C-1''	2·38, 1H, t (H-3_a), 2·57, 3H, br s (2H-1'$_a$ and H-3_b), 2·90, 1H, br s (H-1'$_b$ and H-1''$_a$) 3·01, 1H, br s (H-1''$_b$)	2·71, 1H, m, (H-3_a) 3·16, 2H, m, (2H-1'$_a$ and H-3_b) 3·31, 3H, m, (H-1'$_b$ H-1''$_a$) and H-1''$_b$)
C-2	no signal observed	3·72, 1H, m
C-4'	4·30, 2H, t	4·41, 2H, 2 overlapping triplets
C-3''''& C-5''''	6·83, 2H, d, *J* 8	6·89, 2H, 2 overlapping doublets
C-5'''	6·89, 1H, d, *J* 8	6·93, 1H, d, *J* 8
C-2'''' and C-6''''	7·09, 2H, d, *J* 8	7·07, 2H, 2 overlapping doublets
C-2'''	7·56, 1H, d, *J* 1·5	7·53, 1H, 2 overlapping doublets
C-6'''	7·70 ,dd, *J* 8·5	7·69, 2 overlapping dd

The fact that the aromatic region of the ^{1}H NMR spectrum of Mebeverine **32** changes so much on protonation of the nitrogen atom gives information about the conformation of Mebeverine in its ammonium form. It would be reasonable to assume that the proton signals of the disubstituted benzene ring of protonated Mebeverine would be affected by the asymmetric nature of the nitrogen atom because of their close proximity. However one would not expect the same to be true of the protons on the trisubstituted benzene ring since there are six atoms between this ring and the ammonium nitrogen. This suggests that salts of Mebeverine are not linear but may possess structures more similar to **46** where the two benzene rings are close to each other and therefore are in much the same spatial relationship with respect to the asymmetric nitrogen atom and the adjacent asymmetric carbon atom.



(46)



(47)

The lack of doubling of the signal assigned to the C-5''' proton in the ammonium form of Mebeverine is noteworthy, and can be attributed either to accidental equivalence or to its positioning so that it does not "see" the asymmetric centres. Alternatively, the molecule may adopt some other conformation, *e.g.* **47**, where through space an ammonium-electron rich aryl interaction is possible and a similar rationale can be applied.

4.1.6 Conclusion

The acylium ion-mediated cleavage of tetrahydrofuran in the presence of sodium iodide was successful and gave 1-acyloxy-4-iodobutanes as products in good yields. This methodology was then used in the synthesis of a precursor of the drug Mebeverine and gave higher yields than previously reported of both the precursor and the target molecule.

4.2 Experimental

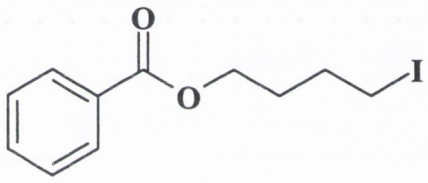
General experimental conditions

Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} silica gel plates. Visualisation was by means of ultraviolet light at 254 nm or by development in potassium permanganate solution. Column chromatography was carried out under gravity using Merck Kieselgel 70-230 mesh silica gel. Evaporation under reduced pressure refers to the use of a Buchi or Bibby rotary evaporator. All solvents were dried using standard techniques. Infrared spectra were recorded as Nujol mulls (N) for solids or as liquid films (L) between sodium chloride plates for oils using a Matteson Genesis FT-IR spectrometer and the data was processed using WinFirst software. Nuclear magnetic resonance spectra were recorded using Bruker DPX 400 spectrometer. Chemical shifts were measured in deuteriated chloroform unless otherwise stated. Coupling constants (*J*) are quoted in Hertz. Mass Spectra were obtained using a VG Alto (HRMS) and Kratos (FAB) instruments. Melting points were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus and are uncorrected.

4.2.1 General procedure for the synthesis of 1-acyloxy-4-iodobutanes

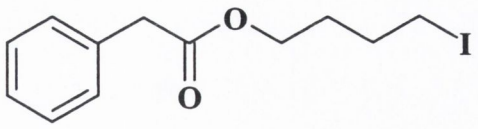
A carboxylic acid (1 equivalent), tetrahydrofuran (2 equivalents) and dry sodium iodide (3 equivalents) were dissolved in dry acetone (10 mL/g acid) and the stirred solution was cooled to 0 °C. Trifluoroacetic anhydride (1·5 equivalents) was added at such a rate that the temperature did not rise above 0 °C. After a further 30 minutes at this temperature the mixture was heated under reflux during 4 hours. The acetone was then removed by evaporation at reduced pressure and the residue was diluted with ether, washed sequentially with water, aqueous sodium hydrogen carbonate, sodium thiosulfate and brine, and then dried and evaporated to give the product.

4–Iodobutyl benzoate 11[5]



Obtained from benzoic acid (0·5 g, 0·004 mol) as an oil (0·66 g, 54 %),δ_H ($CDCl_3$) 1·89-1·96 (2H, m, $OCH_2C\underline{H_2}$), 1·98-2·04 (2H, m, $C\underline{H_2}CH_2I$), 3·28 (2H, t, *J* 6·75, $C\underline{H_2}I$,), 4·37 (2H, t, *J* 6·5 $C\underline{H_2}O$), 7·45-7·50 (2H, m, Ar), 7·57-7·59 (1H, m, Ar) and 8·04 (2H, dd, *J* 8, 1·5, Ar) ppm; δ_C 6·02 ($\underline{C}H_2I$), 29·69 ($\underline{C}H_2CH_2I$), 30·09 (OCH_2-$\underline{C}H_2$), 63·71 ($O\underline{C}H_2$), 125·83 (Ar), 128·38 (Ar), 129·51 (Ar), 129·90(Ar), 132·96 (Ar), 133·27(Ar) and 166·16 (C=O) ppm; ν_{max} 3063, 2957, 1721 (C=O),1601, 1451, 1385, 1314,1275 (CO-O), 1221, 1175, 1111, 1069, 1025, 878 and 710 (Ar) cm^{-1}.

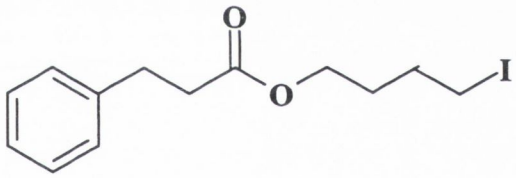
4-Iodobutyl phenylacetate 13



Obtained from phenylacetic acid (5 g, 0·036 mol) as an oil (7·65 g, 67 %), b.p.. 98-100 °C (1mm Hg), δ_H ($CDCl_3$) 1·74-1·78 (2H, m, $OCH_2C\underline{H_2}$), 1·81-1·88 (2H, m, $C\underline{H_2}CH_2I$), 3·17 (2H, t, *J* 7, $C\underline{H_2}I$), 3·64 (2H, s, $PhC\underline{H_2}$), 4·13 (2H, t, *J* 6·5, $C\underline{H_2}O$) and 7·31 (5H, m, Ar) ppm; δ_C 5·50 ($\underline{C}H_2I$), 29·01 ($\underline{C}H_2CH_2I$), 29·48 ($OCH_2\underline{C}H_2$), 40·98 ($Ph\underline{C}H_2$), 63·21 ($O\underline{C}H_2$), 126·69 (Ar), 128·16 (Ar), 128·78 (Ar), 133·52(Ar), and 171·13(C=O)ppm; ν_{max} 3106,3062, 3029, 2954, 2850, 1735 (C=O), 1496, 1456, 1386, 1342, 1259 (C-O), 1159, 1076, 1008 and 696 (Ar) cm^{-1}.

HRMS (FAB): *Found*: *m/z* 319·0179; *calculated* for $[C_{12}H_{15}O_2I + H]^+$ 319·0195

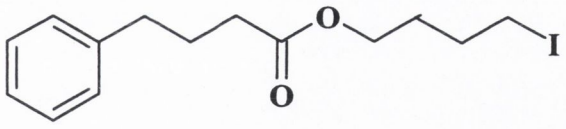
4-Iodobutyl 3-phenylpropanoate 15



Obtained from 3-phenylpropanoic acid (5 g, 0·033 mol) as an oil (6·66 g, 61 %) b.p. 110-114 °C (1mm Hg), δ_H ($CDCl_3$) 1·69-1·76 (2H, m, $OCH_2C\underline{H_2}$), 1·81-1·88 (2H, m, $C\underline{H_2}CH_2I$), 2·66 (2H, t, *J* 7·5, $PhC\underline{H_2}$), 2·97 (2H, t, *J* 7·5,$C{=}OC\underline{H_2}$) 3·19 (2H, t, *J* 6·5, $C\underline{H_2}I$), 4·10 (2H, t, *J* 6, CH_2O) 7·23 (3H, m, Ar) and 7·31 (2H,m, Ar) ppm; δ_C 5·57 ($\underline{C}H_2I$), 29·07 ($\underline{C}H_2CH_2I$), 29·45 ($\underline{C}H_2CH_2O$), 30·52($Ph\underline{C}H_2$), 35·40 ($C{=}O\underline{C}H_2$) 62·79 ($\underline{C}H_2O$), 125·86(Ar), 127·84 (Ar), 128·07 (Ar), 139·96 (quaternary carbon) and 172·45 (C=O) ppm; ν_{max} 3027, 2956, 2935, 2867, 1735 (C=O), 1496, 1454, 1292 (C-O), 1259, 1226, 1164, 1078, 1029, 750 (Ar) and 700 (Ar) cm^{-1}.

HRMS (FAB): *Found*: *m/z* 333·0331; *calculated* for $[C_{13}H_{17}O_2I + H]^+$ 333·0352

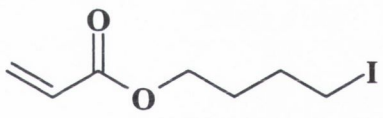
4-Iodobutyl 4-phenylbutanoate 17



Obtained from 4-phenylbutanoic acid (5 g, 0·03 mol) as an oil (7·81 g, 75 %) b.p. 118-120 °C (1mm Hg), δ_H ($CDCl_3$) 1·73-1·80 (2H, m, $OCH_2C\underline{H}_2$), 1·88-1·90 (2H, m, $C\underline{H}_2CH_2I$), 1·91-1·93 (2H, quintet, *J* 3, $PhCH_2C\underline{H}_2$), 2·35 (2H, t, *J* 7·6, $PhC\underline{H}_2$), 2·67 (2H, t, *J* 7·6, $C\underline{H}_2C{=}O$), 3·23 (2H, t, *J* 6·7, $C\underline{H}_2I$,), 4·11 (2H, t, *J* 6·4, $C\underline{H}_2O$), 7·20 (3H, m, Ar) and 7·30 (2H, m, Ar) ppm; δ_C 5·50 ($\underline{C}H_2I$), 26·04($\underline{C}H_2CH_2Ph$), 29·13($\underline{C}H_2CH_2I$), 29·55 ($\underline{C}H_2CH_2O$), 33·15 ($Ph\underline{C}H_2$) 34·68 ($\underline{C}H_2C{=}O$), 62·72 ($\underline{C}H_2O$) 125·56(Ar), 127·74 (Ar), 128·05 (Ar), 140·87 (quaternary carbon) and 173·12 (C=O) ppm; ν_{max} 3083, 3062, 3025, 2954, 2865, 1735 (C=O), 1602, 1496, 1454, 1388, 1349, 1226, 1170, 1081, 1029, 746 and 700 (Ar) cm^{-1}.

HRMS (FAB): *Found*: *m/z* 347·0496; *calculated* for $[C_{14}H_{19}I + H]^+$ 347·0508

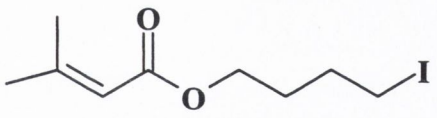
4-Iodobutyl acrylate 24



Obtained from acrylic acid (5 g, 0·069 mol) as an oil (4·01 g, 21%), b.p.102-104 ° C (2mm Hg), δ_H ($CDCl_3$) 1·80 (2H, m, $C\underline{H}_2$ (C-3)), 1·91 (2H, m, $C\underline{H}_2$, (C-2)), 3·22 (2H, t *J* 6, $C\underline{H}_2$ (C-1)), 4·15 (2H, m, $C\underline{H}_2$ (C-4)), 5·85 (1H, d, *J* 8, $C\underline{H}$, (C-1')), 6·11 (1H, dd, *J* 8, 16, $C\underline{H}$ (C-2')) and 6·42 (1H, d, *J* 16, $C\underline{H}$ (C-2')) ppm; δ_C 5·90 ($\underline{C}H_2I$), 29·48 (C-2), 29·83 (C-3), 63·28 (C-1), 127·64 (C-2') 130·62 (C-1') and 166·18($\underline{C}{=}O$) ppm; ν_{max} 2960, 1727, 1637, 1407, 1361, 1295, 1222, 1176, 1060, 985, 809 and 730 cm^{-1}.

HRMS (FAB): *Found*: *m/z* 254·9894; *calculated* for $[C_7H_{11}O_2I + H]^+$ 254·9882

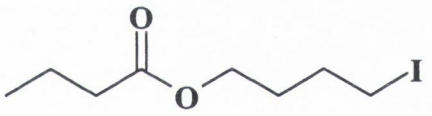
4-Iodobutyl 3'-methylbut-2'-enoate 25



Obtained from 3-methylbut-2-enoic acid (5 g, 0·05 mol) as an oil (0·944 g, 67 %) δ_H ($CDCl_3$) 1·74-1·81 (2H, m, $OCH_2C\underline{H_2}$), 1·89-1·95 (2H, m, $C\underline{H_2}CH_2I$), 2·17 (3H, s, $C\underline{H_3}$), 3·23 (2H, t, *J* 6·5, $C\underline{H_2}I$), 4·12 (2H, t, *J* 6, $C\underline{H_2}O$) and 5·67-5·69 (1H, m, olefinic proton) ppm; δ_C 5·68 ($\underline{C}H_2I$), 19·78 ($\underline{C}H_3$), 26·99 ($\underline{C}H_3$) 29·23 ($\underline{C}H_2CH_2I$), 29·66 ($OCH_2\underline{C}H_2$), 61·81 ($O\underline{C}H_2$), 115·36 (olefinic carbon) and 166·18($\underline{C}$=O)ppm; ν_{max} 2952, 2915, 2848, 1717 (C=O), 1654, 1445, 1376, 1347, 1270, 1228, 1148, 1078, 1009, 851 and 728cm^{-1}.

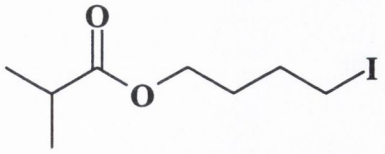
HRMS (CI): *Found*: *m/z* 283·0188; *calculated* for $[C_9H_{15}O_2I + Na]^+$ 283·0195

4-Iodobutyl butanoate28[8]



Obtained from butanoic acid (2·41 g;0·027 mol) as an oil (5·46 g, 75 %), δ_H ($CDCl_3$) 0·96 (3,H, t, *J* 7·5, $C\underline{H_3}$), 1·65 (2H, sextet, *J* 7·5, $C\underline{H_2}CH_3$), 1·73-1·80 (2H, m, $OCH_2C\underline{H_2}$), 1·88-1·96 (2H, m, $C\underline{H_2}CH_2I$), 2·30 (2H, t, *J* 7·25, C=O$C\underline{H_2}$), 3·22 (2H, t, *J* 6·75, $C\underline{H_2}I$) and 4·09 (2H, t, *J* 6, $C\underline{H_2}O$) ppm; δ_C 5·5 ($\underline{C}H_2I$), 13·23 ($\underline{C}H_3$), 17·99 ($\underline{C}H_2CH_3$), 29·12 ($\underline{C}H_2CH_2O$), 29·55 ($\underline{C}H_2CH_2I$), 35·73 (C=O$\underline{C}H_2$), 62·58 ($\underline{C}H_2O$) and 173·36 (C=O) ppm; ν_{max} 2960, 2927, 2873, 1735 (C=O), 1458, 1226, 1176 and 1091 cm^{-1}.

4-Iodobutyl 2'-methylpropanoate 29



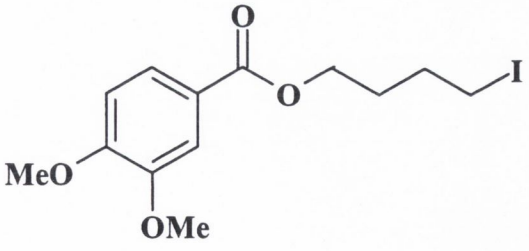
Obtained from 2-methylpropanoic acid (5 g, 0·5 mol) as an oil (1·39 g, 90 %), δ_H ($CDCl_3$) 1·18 (6H, d, *J* 8, 2 x C<u>H</u>$_3$), 1·75-1·79 (2H, m, OCH$_2$C<u>H</u>$_2$), 1·90-1·94 (2H, m, C<u>H</u>$_2$CH$_2$I, m), 2·56 (1H, septet, *J* 7, C<u>H</u>), 3·23 (2H, t, *J* 6·5, C<u>H</u>$_2$I) and 4·11 (2H, t, *J* 6·5, C<u>H</u>$_2$O) ppm; δ_C 5·54 (<u>C</u>H$_2$I), 18·55 (<u>C</u>H$_3$), 29·12(<u>C</u>H$_2$CH$_2$I), 29·55(<u>C</u>H$_2$CH$_2$O), 33·55(<u>C</u>H), 62·58 (<u>C</u>H$_2$O) and 176·70 (C=O) ppm; ν_{max} 2971, 1733, 1469, 1226,1193,1157 and 1078 cm^{-1}.

HRMS (FAB): *Found*: *m/z* 271·0179; *calculated* for $[C_8H_{15}O_2I + H]^+$ 271·0195

Reaction of 3,4-dimethoxybenzoic acid 35

3,4-Dimethoxybenzoic acid (1 g, 0·005 mol) was reacted with tetrahydrofuran as described above and gave a mixture of **29** and **35** (1·79, 89 %). The two compounds were separated by column chromatography using a system of hexane : ethyl acetate (7:3) as eluant.

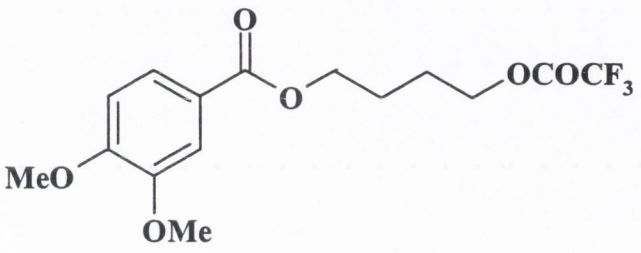
4-Iodobutyl 3,4-dimethoxybenzoate 33[6]



Obtained as an oil (1·43, 71 %), δ_H ($CDCl_3$) 1·88-1·94 (2H, m, OCH$_2$C<u>H</u>$_2$), 1·96-2·02 (2H, m, C<u>H</u>$_2$CH$_2$I), 3·28 (2H, t, *J* 7, C<u>H</u>$_2$I), 3·95 (6H, s, OC<u>H</u>$_3$), 4·35 (2H, t, *J* 6·5,OC<u>H</u>$_2$,), 6·90 (1H, d, *J* 8·5, Ar H$_5$), 7·56 (1H, d, *J* 2 Ar H$_2$) and 7·69 (1H, dd *J* 8·5, 2 Ar H$_6$) ppm; δ_C 5·40(<u>C</u>H$_2$I), 29·24 (<u>C</u>H$_2$CH$_2$I), 29·73 (OCH$_2$<u>C</u>H$_2$), 55·58

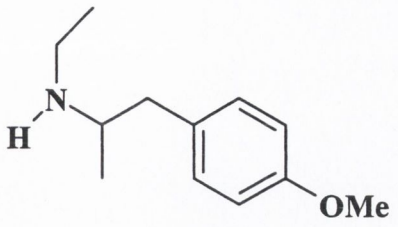
(O<u>C</u>H$_3$), 63·16 (O<u>C</u>H$_2$), 109·89 (Ar), 111·67 (Ar), 123·09 (Ar), 148·27 (C-O), 152·65 (C-O) and 165·84 (C=O) ppm; ν_{max} 3002, 2958, 2937, 2838, 1710 (C=O), 1602, 1513, 1463, 1417, 1348, 1292 (C-O), 1222, 1176, 1133, 1108, 1025, 939, 877, 821, 763 and 727 cm^{-1}.

4-Trifluoroacetoxybutyl 3,4-dimethoxybenzoate 39



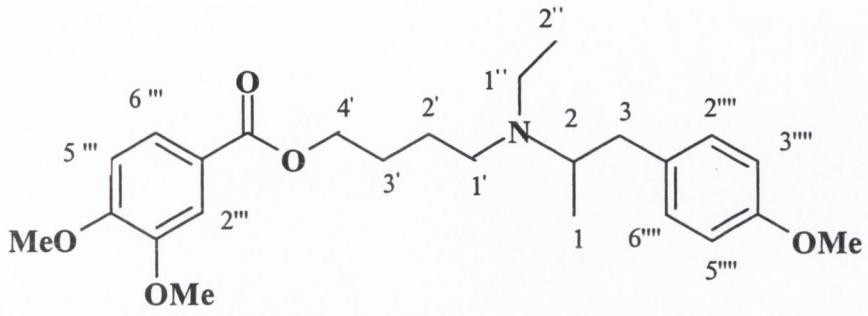
An oil (0·30 g, 16%) δ_H (CDCl$_3$) 1·72-1·77 (2H, m, OCH$_2$C<u>H</u>$_2$), 1·84-1·89 (2H, m, C<u>H</u>$_2$CH$_2$I), 3·95 (6H, s, OC<u>H</u>$_3$), 4·02 (2H, t, *J* 6·5, C<u>H</u>$_2$OTFA), 4·35 (2H, t, *J* 6·5,OC<u>H</u>$_2$,), 6·89 (1H, d, *J* 8·, Ar H$_5$), 7·55 (1H, d *J* 2, Ar H$_2$) and 7·69 (1H, dd *J* 8, 2 Ar H$_6$) ppm; δ_C 29·17 (OCH$_2$<u>C</u>H$_2$) 29·73 (<u>C</u>H$_2$CH$_2$OTFA), 56·23 (O<u>C</u>H$_3$), 62·36 (O<u>C</u>H$_2$), 64·59 (<u>C</u>H$_2$OTFA) 109·89 (Ar), 111·67 (Ar), 113· 11 (<u>C</u>F$_3$),123·09 (Ar), 148·27 (Ar C-O), 152·65 (Ar C-O) 156·74 (<u>C</u>-OCF$_3$)and 166·00 (C=O)ppm; δ_F –77·12 (C<u>F</u>$_3$) ppm ν_{max} 2960, 1782, 1707,1600, 1514, 1464, 1418, 1346, 1267 (C-O), 1223, 1177, 1110, 1024, 875, 821, and 765 cm^{-1}.

Ethyl-[-2-(4-methoxyphenyl)-1-methylethyl]amine 34[9]



4-Methoxyphenylacetone **42** (10 g, 0·061 mol) was added to a 70% solution of ethylamine in water (12·09 mL, 0·152 mol) and stirred at room temperature for twelve hours to give the imine **41**. This mixture was then diluted with methanol, and sodium borohydride (0·58 g, 0·152 mol.) was added and the solution was then stirred for ten minutes. The reaction mixture was then diluted with water and evaporated under reduced pressure to remove the methanol. The aqueous solution was then acidified with hydrochloric acid to approximately pH 1. This solution was then extracted using diethyl ether. The organic layer was then evaporated to give the unreacted ketone **42** (4 g , 40%). The aqueous layer was then basified with sodium hydroxide solution to pH 8 and then extracted with ether and the combined extract was dried and concentrated to give the product **34** as an oil (6·18 g, 53 %), δ_H ($CDCl_3$) 1·07 (3H, d, *J* 6, $C\underline{H}_3CH$), 1·10 (3H, t, *J* 7, $C\underline{H}_3CH_2$),1·70 (1H, br. s, N<u>H</u>, D_2O exchange), 2·55-2·64 (2H, m, $C\underline{H}_2Ar$), 2·69-2·77 (2H, m, $C\underline{H}_2NH$), 2·90 (1H, sextet, *J* 7 C<u>H</u>N), 3·81 (3H, s, $OC\underline{H}_3$), 6·85 (2H, d, *J* 8,Ar) and 7·12 (2H, d, *J* 8, Ar) ppm; δ_C 14·86 ($CH_2\underline{C}H3$), 19·59 ($\underline{C}H_3CH$), 30·48 (<u>C</u>H), 41·03 ($\underline{C}H_2CH_3$), 42·15 ($\underline{C}H_2N$), 54·67(<u>C</u>H), 54·76 ($O\underline{C}H_3$), 113·31(Ar), 130·96(Ar), and 165·61(C=O) ppm; ν_{max} 3500, 2963, 2926, 2834, 1612, 1512, 1467, 1300, 1247, 1177,1036 and 808 cm^{-1}.

N-Ethyl-N-[4-(3,4-dimethoxybenzoyloxy)-butyl]-3-(4-methoxyphenyl)-prop-2-ylamine 32



The iodide **33** (0·5 g, 0·00137 mol) was combined with the amine **34** (0·26 g, 0·00137 mol) and dry potassium carbonate (0·2 g, 0·0014 mol) in toluene (5 mL) and the solution was then heated under reflux for 8 hours. The solution was then cooled, diluted with ethyl acetate, washed with water, dried and concentrated to give **32** as an oil (0·56 g, 96 %), which was then purified by column chromatography using a system of hexane-ethyl acetate (6:4) as eluant.

δ_H ($CDCl_3$) 0·94 (3H, d, *J* 6, $C\underline{H}_3CH_2$), 1·09 (3H, t, *J* 6·9, $C\underline{H}_3CH$), 3·79 (3H, s, $OC\underline{H}_3$), 3·95 (6H, s, 2 x $OC\underline{H}_3$), 4·30 (2H, t, *J* 6, $C\underline{H}_2O$,), 6·82 (2H, d, *J* 8·5, Ar in disub ring,), 6·89 (1H, d, *J* 8·5, Ar H,), 7·09 (2H, d, *J* 8, Ar 2H in disub ring), 7·56 (1H, d, *J* 1·5, Ar) and 7·70 (1H, dd, *J* 8·5, 2 Ar H) ppm; δ_C 10·10 (C-1), 12·72 (C-2''), 21·64 (C-2'), 25·77 (C-3'), 36·62 (C-3), 46·68 (C-1''), 50·48 (C-1'), 55·63 (C-2), 55·95 (OCH_3), 64·08 (C-4'), 110·49 (Ar), 112·05 (Ar), 114·67 (Ar), 124·34 (Ar), 130·11 (Ar), 148·12 (quaternary Ar), 152·43 (quaternary Ar and 166·01 (C=O) ppm; ν_{max} 2955, 2924, 2852, 1709, 1600, 1513, 1462, 1417, 1346, 1267, 1177, 1107, 1027, 803 and 765cm

4.3 References

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Chapter 5

Investigation of a simple potassium complex

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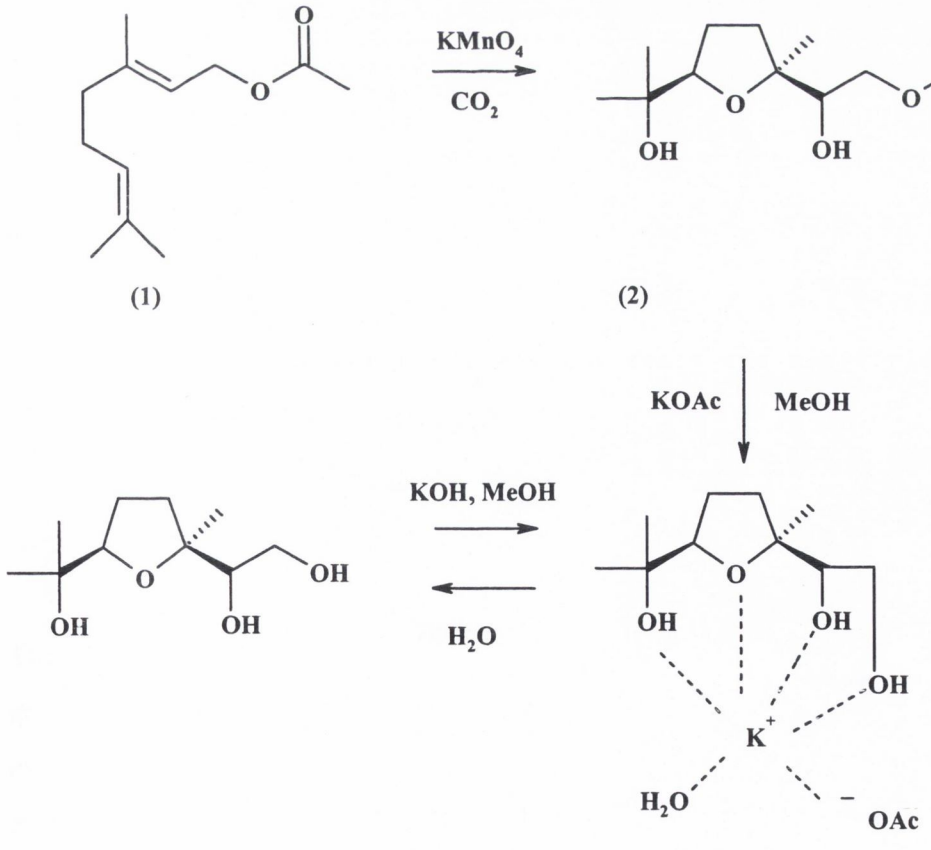
Investigation of a simple potassium complex

5.1 Introduction

The aim of this work was to repeat an experiment described by Hackler[1] in which geranyl acetate **1** was oxidised using potassium permanganate to give the monoacetate **2** which was then hydrolysed using potassium hydroxide to yield an initial product for which the structure **3** was claimed. Hydrolysis of this potassium complex then yielded the triol **4**. Alternatively, the triol **4** could be converted into the potassium complex **3** by treatment with potassium acetate **(Scheme 1)**.

Synthesis of a potassium complex from geranyl acetate as proposed by Hackler



(1) (2) (3) (4)

Scheme 1

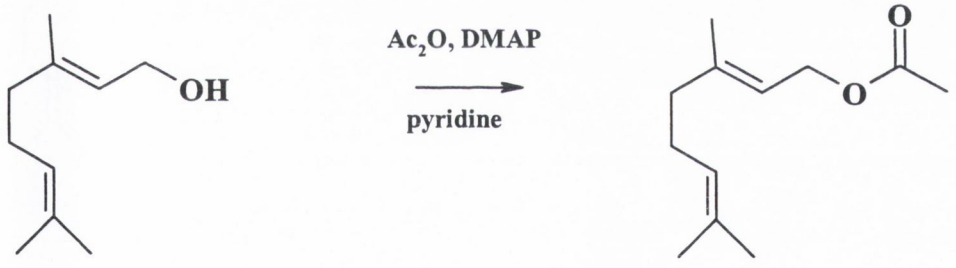
In the present work it was intended to properly characterise Hackler's claimed potassium complex **3** and indeed the starting triol **4**, using an array of spectroscopic methods and paying particular attention to stereochemistry. Also, it was intended to attempt the synthesis of a boron complex of the triol **4** using methodology similar to that employed in the synthesis of Aplasmomycin (*cf.* Section 1.4.1) to try and further exploit the potential of the triol **4** as a podate ligand.

5.2 Synthesis of the "potassium complex" 3

5.2.1 Synthesis of geranyl acetate 1

Geraniol **5** and acetic anhydride were stirred in pyridine at room temperature with DMAP as catalyst to give geranyl acetate **1 (Scheme 2)** in 92% yield.

Synthesis of geranyl acetate



(5) **(1)**

Scheme 2

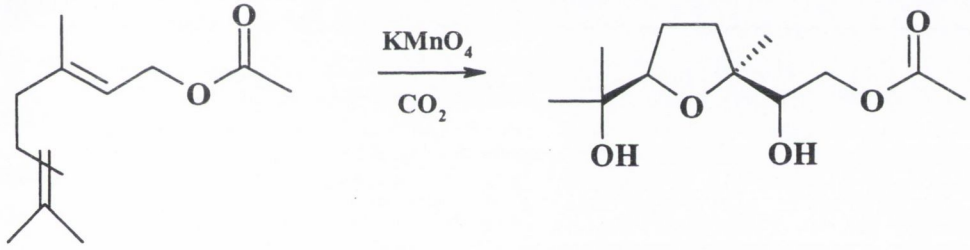
The IR spectrum of geranyl acetate **1** displays absorptions for an ester carbonyl group at 1743 cm^{-1} and for an alkene at 1673 cm^{-1}. The proton NMR spectrum ofg eranyl acetate **1** displays three singlets at δ 1·61 ppm, 1·69 ppm and δ 1·71 ppm, which are assigned to the vinylic methyl groups. A 3-H singlet at δ 2·06 ppm corresponds to the acetoxy group resonance. This overlaps with the signal due to the one of the allylic methylene groups. The other allylic methylene group appears

slightly more downfield as a triplet at δ 2·11 ppm. A doublet at δ 4·59 ppm is assigned to the methylene group adjacent to the acetoxy group. The two alkene protons appear as triplets at δ 5·08 ppm and at δ 5·33 ppm.

5.2.2 Conversion of geranyl acetate 3 into 1-[5'-(1''-hydroxy-1''-methylethyl) -2'-methyltetrahydro-2'-furyl]-2-acetoxy-1-hydroxyethane 2

The diol **2** was synthesised by the oxidation of geranyl acetate **1** with potassium permanganate in the presence of carbon dioxide using a method first employed by Kotz[2] **(Scheme 3)**.

Synthesis of 1-[5'-(1''-hydroxy-1''-methylethyl)-2'-methyltetrahydro-2'-furyl]-2-acetoxy-1-hydroxyethane 2



(1) **(2)**

Scheme 3

The yield of the diol **2** was consistently very low (approximately 10%) when the experimental procedure reported by Kotz[2] was followed. The reaction involves using 1·5 molar equivalents of oxidant per equivalent of alkene, and the yield of crude diol was approximately 10%, with 30 % of the starting alkene being recovered. Due to these issues the reaction had to be carried out on a very large scale. In an effort to improve these shortcomings the work-up was altered slightly to determine if this would improve the yield. After a first extraction using hexane (to remove unreacted geranyl acetate), the aqueous layer was saturated with sodium chloride and then extracted again with dichloromethane. This approach was very successful and

increased the overall yield three-fold. Thus, the low yield previously obtained is attributable to some of the product diol remaining in the aqueous layer.

IR and NMR spectroscopy of **2** confirmed the identity of the product. IR absorptions include a hydroxyl group absorption at 3321 cm^{-1}, a carbonyl absorption typical of an ester group at 1733 cm^{-1}, a CO-O group at 1250 cm^{-1} and an absorption at 1079 cm^{-1} indicative of a cyclic ether bond.

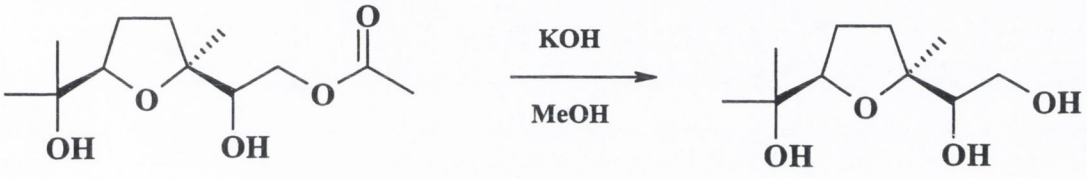
In the ^{1}H NMR spectrum of the diol **2**, four 3H singlets were evident, and these are assigned to the methyl groups. These were individually identified by means of a ^{13}C-^{1}H COSY experiment. Thus, the singlets at δ 1·14 ppm and at δ 1·23 ppm are assigned to the diastereotopic methyl groups adjacent to the tertiary alcohol function. The C-2' methyl group resonates at δ 1·29 ppm. From the ^{13}C-^{1}H COSY NMR spectrum of **2** it is evident that the C-3' methylene group appears as two distinct signals, the first being a 1-H double triplet at δ 1·71 ppm with coupling constants of 12 and 8 Hz. The second proton of the C-3' methylene group resonates as a multiplet at δ 2·20 ppm. The C-4' methylene group appears as a multiplet at δ 1·98 ppm. A singlet at δ 2·12 ppm is due to the methyl group of the acetate moiety. The ^{13}C-^{1}H COSY spectrum of **2** also indicates that a double doublet at δ 3·71 ppm is due to the C-1 methine proton and the ^{1}H-^{1}H COSY spectrum shows coupling with the methylene protons adjacent to the acetoxy group. The C-5' methine proton appears as an apparent triplet at δ 3·88 ppm due to its coupling with the two protons at C-4'. The diastereotopic protons of the C-2 methylene group appear in the form of an AB system, as a double doublet at δ 4·13 ppm with coupling constants of 11 and 8 Hz and as another double doublet at δ 4·32 ppm with coupling constants of 11 and 3 Hz.

The stereochemistry of the tetrahydrofuran ring was confirmed by an n.O.e experiment. On irradiation of the signal at δ 1·29 ppm due to the C-2' methyl group, the signal due to the C-5' methane proton at δ 3·88 ppm displayed a positive n.O.e. of 9% thus confirming the relative stereochemistry of the terahydrofuran ring as shown above.

5.2.3 Synthesis of 1-[5'-(1''-hydroxy-1''-methylethyl)-2'-methyltetrahydro-2' furyl]ethane-1,2-diol 4

The ester function of **2** was then hydrolysed using potassium hydroxide in methanol to form the triol **4 (Scheme 4)** in 51% yield.

Synthesis of 1-[5'-(1''-hydroxy-1''-methylethyl)-2'-methyltetrahydro-2' furyl]ethane-1,2-diol 4



(2) (4)

Scheme 4

In the infrared spectrum of the triol **4** there were no carbonyl or CO-O signals thus confirming that hydrolysis of the ester group had occurred. An intense hydroxyl group band at 3371 cm^{-1} and a cyclic ether absorption at 1079 cm^{-1} were also observed. The proton NMR spectrum of the triol **4** displays signals very similar to that of the diol **2**, except for the methylene protons at C-2, which again appear as an AB system of double doublets but are much further upfield. One proton appears at δ 3·71 ppm with coupling constants of 11 and 3 Hz. The other C-2' methylene proton appears at δ 3·81 ppm with coupling constants of 11 and 6 Hz.

5.2.4 Synthesis of the "potassium complex" 3

Following the procedure described by Hackler[1], the triol **4** was dissolved in aqueous methanol and treated with one equivalent of anhydrous potassium acetate. Evaporation of solvent left a viscous, oily material that failed to solidify. This was taken up in the minimum amount of methanol, and ether was added dropwise until faint turbidity was evident. The solution was then cooled at –20 °C until crystals had formed. These, which were few, were removed and identified (IR) as being

potassium acetate. Further ether was then added until turbidity was again achieved and the solution was chilled again at –20 °C. A second small crop of crystals was obtained after 12 hours and these were again identified as being potassium acetate. A third iteration of this procedure gave another, very small crop of potassium acetate crystals. At this stage it appeared that no further potassium acetate could be recovered from the solution. Accordingly, a substantial amount of ether was added until turbidity was again achieved, and the solution was chilled at –20 °C during 48 hr. After this time, a large crop of long, thin needle-like crystals had formed. These were recovered by decanting the solvent and then washing them with ether. Evaporation of the mother liquor gave unreacted triol **4**.

The crystals that were obtained were dried *in vacuo* (0.1 mm/Hg) at room temperature when they were obtained as a slightly sticky mass. However, after standing in air for a short time they became "dry". This behaviour may suggest the uptake of water from the air, or the replacement of methanol of crystallisation (or ligation) by water. On measuring its melting point, the recrystallised solid softened and became transparent at 58 °C, but did not exhibit true melting behaviour. Hackler[1] quotes m.p. 55-57 °C for his material.

The IR spectrum of this product exhibited absorption bands that largely mirrored those present in the spectra of the triol **4** and that of potassium acetate. However, additional absorption bands were also present, at 3422 and 1638 cm^{-1}. Additionally, the carboxylate absorption shown in the infrared spectrum of potassium acetate had shifted from 1575 cm^{-1} to 1560 cm^{-1}

In the ^1H NMR spectrum of the product (**Figure 5.1 (b)**) obtained in $CDCl_3$ solution, three methyl singlets appear as in the spectrum of the triol, however they are slightly more upfield. The C-3' tetrahydrofuryl methylene protons appear as two mulitplets at δ 1·62 ppm and at δ 2·07 ppm. A 2H multiplet centred at δ 1·91 ppm is assigned to the two C-4' protons. This multiplet is overlapped by a sharp singlet at δ 1·93 ppm, and the entire integrates for ~ 3·5H. The sharp singlet could be identified by a C-H COSY experiment. Its chemical shift is consistent with it being an acetate methly group. Its net integration of ~ 1·5H implies that there is 0·5 acetate group or

ion per triol moeity. The C-1 and C-2 protons display slight upfield shifts. A double doublet at δ 3·55 ppm is assigned to the C-1 methine proton. The C-2 methylene protons appear separately as two double doublets at δ 3·64 ppm, and at δ 3·69 ppm. A triplet at δ 3·84 ppm is assigned to the C-5 methine proton.

Significantly, as pointed out above integration revealed that the complex could not possess the structure **5** claimed by Hackler[1]. Thus, it was obvious from integration of the methyl resonances that the ratio of "triol" to "acetate" was 2 : 1, rather than 1 : 1 as claimed by Hackler.

In the ^{13}C NMR spectrum of the complex, when compared with that of the triol **4** there were minor variations in resonance positions for each of the carbon atoms. A noteworthy feature of this spectrum was that the intensities of the signals for the two carbon atoms of the acetate moiety were relatively weak. This suggests that the position of the acetate ion within the complex is such that spin-lattice relaxation is severely inhibited.

Addition of one equivalent of anhydrous TBAF to a $CDCl_3$ solution of the complex, which was expected to replace acetate ion by fluoride ion as a ligand to potassium, caused the C-3' and C-4' methylene resonances to appear as four separate 1H multiplets at approximately δ 1·56 ppm, δ 1·88 ppm, δ 2·05 ppm and δ 2·35 ppm (**Figure 5.1 (c)**). The signal for the methyl group of the acetate ion appeared as a baseline-resolved singlet at δ 1·95 ppm. Integration of this signal now suggested a value of 2·5 H *vs* values of ~3H for each of the methyl resonances. However, addition of D_2O (**Figure 5.1 (d)**) caused the integration of this acetate resonance to reduce again to approximately 1·5 H relative to a methyl signal, exactly as seen in the ^1H NMR spectrum of the original complex.

Thus, it can be concluded that the acetate signal overlapped a signal due to water, which appears close to its position in $CDCl_3$ at the temperature of the probe. These data again suggest that the "triol" to "acetate" ratio for the complex is 2:1, and not 1:1 as claimed by Hackler.[1]

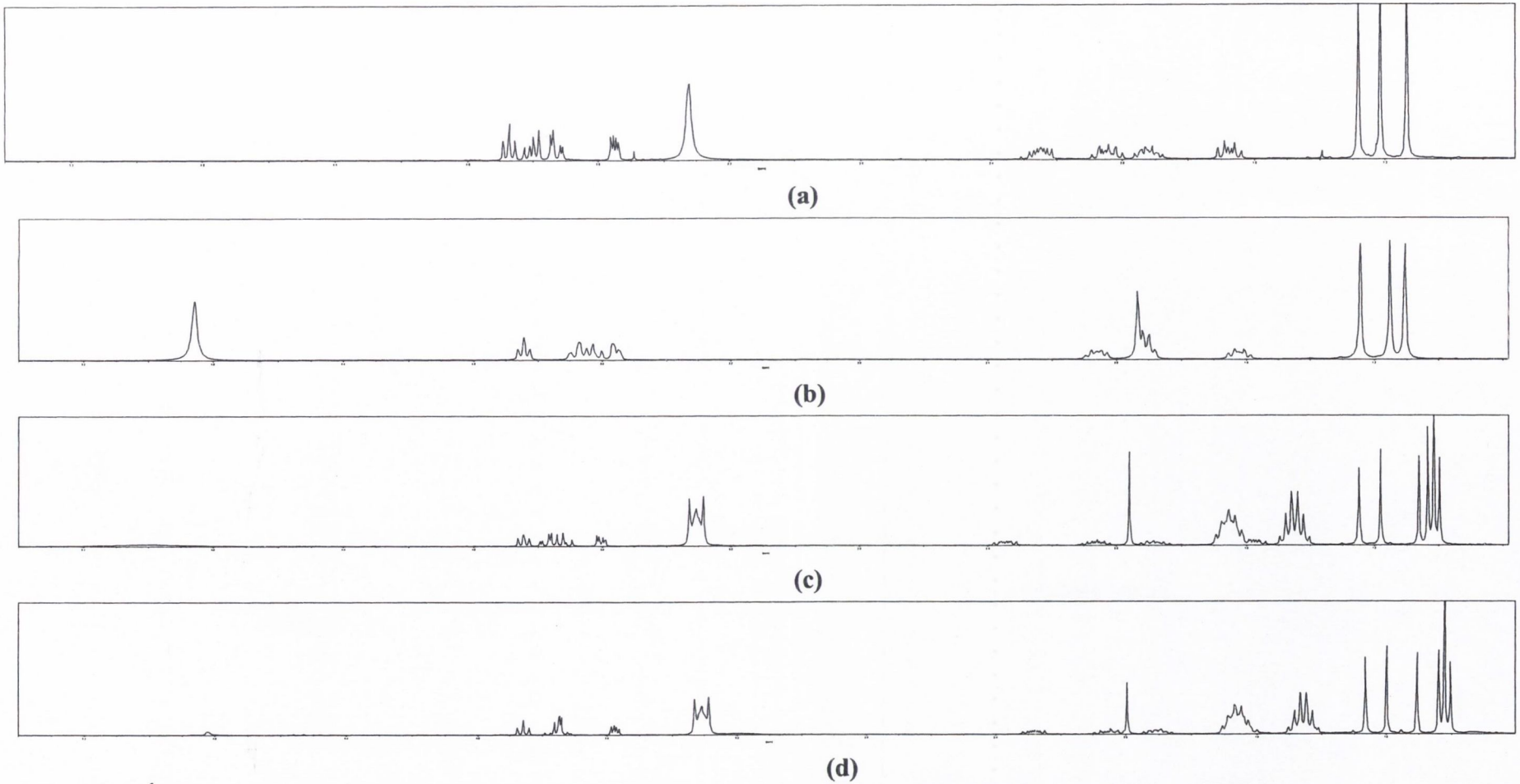


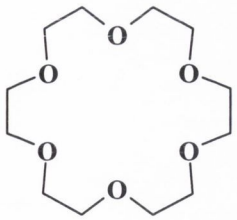
Figure 5.1 ^{1}HNMR spectra of **(a)** triol **4** **(b)** potassium complex **(c)** after addition of TBAF **(d)** after addition of D_2O

A mass spectrum of the potassium complex was run and the observed mass was that of the triol plus a potassium ion. This experiment was carried out in the following way: firstly a mass spectrum of the triol was obtained and this showed a mass $M^+ = [C_{10}H_{20}O_4+Na]^+$. A mass spectrum of the potassium complex was then obtained and this gave $M^+ = [C_{10}H_{20}O_4+K]^+$. The species $[C_{10}H_{20}O_4+Na]^+$ was also observed but at a much reduced intensity. Hydrolysis of the dimeric complex under the conditions (electrospray) of the experiment is not unexpected.

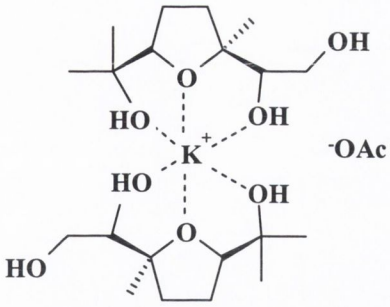
The same potassium complex could be produced from the triol **4** and potassium acetate in the following way. A mixture of the triol **4** and potassium acetate was placed in a small mortar. The two dry solids were ground together using a pestle. After a very short time, the entire mixture liquefied and then rapidly became solid again. Some acetic acid was liberated. When the solid product was examined by IR and NMR spectroscopies it proved to be identical with the material prepared *via* solution chemistry using Hackler's method.

All of the results described above can be accommodated in the structural proposal **5** shown below. Here, two molecules of the triol **4** (arbitrarily chosen to possess the same absolute configurations) coordinate to a potassium ion to give the C_2-symmetric complex **5**. The acetate counterion is expected to be positioned above or below the general plane formed by coordination of the potassium ion and coordinated oxygen atoms. A molecule of water may occupy the diametrically opposite position.

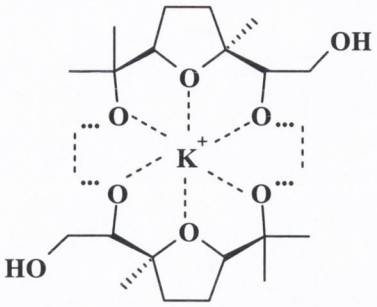
The bimolecular "podand" complex **5** possesses a superficial relationship with the well-known [18]-crown-6 **6** which preferentially complexes potassium ions. Thus, if imaginary ethane bridges, shown by dotted lines in **7**, are introduced in order to "complete" an 18-membered macrocycle, this relationship becomes obvious.



(5)



(6)



(7)

Table 5.1

Comparison between chemical shifts of the triol 4 and the obtained potassium complex 5

	^{1}H [*Triol*]	^{1}H [*K complex*]	^{13}C [*Triol*]	^{13}C [*K complex*]
C-1''	1·15, 3H, s 1·22, 3H, s	1·11, 3H, s 1·16, 3H, s	23·54 25·50	22·46 24·79
C-2'	1·29, 3H, s	1·24, 3H, s	26·47	26·44
C-3'	1·68, 1H, m 2·24, 1H, m	1·62, 1H, m 2·07, 1H, m	27·76	27·72
C-4'	1·92, 1H, m 2·02, 1H, m	1·90, 2H, m	35·72	35·38
C-1	3·55, 1H, dd, *J* 6, 3	3·55, 1H, dd, *J* 7·5, 3	76·56	77·07
C-2	3·71,1H, dd, *J* 11, 3 3·81, 1H, dd, *J* 11, 3	3·64, 1H, dd, *J* 11·5, 7·5 3·69, 1H, dd, *J* 11·5, 3	63·66	63·22
C-5	3·88,1H, t, *J* 7·5	3·84,1H, t, *J* 7	85·74	84·99

5.2.5 Comparison of experimental data with reported data for 5

The spectroscopic data for the potassium complex **5** that was obtained in the present work differs considerably from that reported[1] by Hackler. The main reason for this is likely due to the less accurate spectroscopic apparatus available at the time of Hackler's synthesis. The total number of protons derived by integration differs from that reported by Hackler. The potassium complex formed in the present work was found to contain an acetate group as had been reported by Hackler. This was confirmed by the presence of a carboxylate absorption at 1560 cm^{-1} in the IR spectrum. In the ^{1}H NMR spectrum of the "potassium complex" a signal attributable to an acetate methyl group appears at δ 1·95 ppm, where it overlaps methylene resonances of the tetrahydrofuran ring, but this does integrate for the value expected on the basis of Hacklers[1] structure. In the ^{13}C NMR spectrum of the potassium complex there are weak signals for acetate methyl and carbonyl groups. These data, together with the solubility of the product in chloroform, suggested that a "potassium complex" was indeed present, but the ^{1}H NMR spectrum provided information that did not fully agree with Hackler's structural proposal.

Table 5.2

Comparison of ^{1}H NMR chemical shifts for Hackler's complex and for the complex obtained in the present work

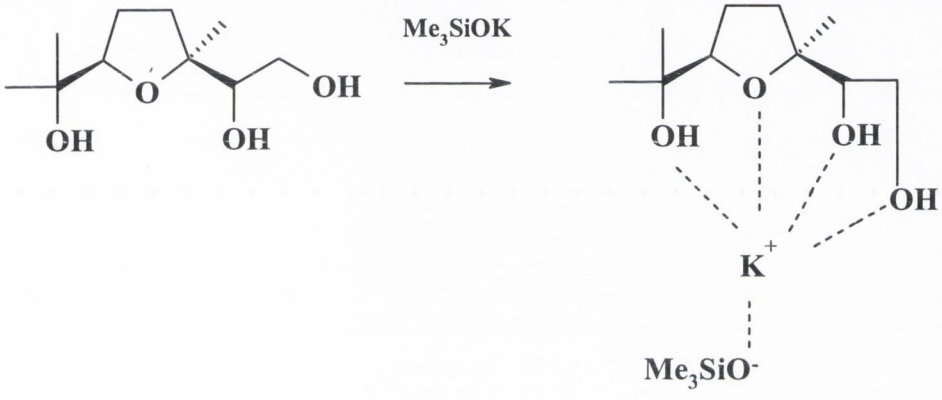
Hackler[1] δ ppm	Observed δ ppm
1·08, 3H, s	1·11, 3H, s
1·13, 3H, s	1·16, 3H, s
1·24, 3H,s	1·24, 3H, s
1·92, 7H, br s	1·62, 1H, m, 1·90, 2H, m, 2·07, 1H, m
3·65, 4H, m	3·55, 1H, dd, 3·64, 1H, dd, 3·69, 1H, dd, 3·84, 1H, t
4·91, 5H, s	4·85, 4H, s
Total = 25 H	Total = 21 H

5.2.6 Alternative synthesis of a potassium complex from the triol 4

Since the potassium complex **5** is soluble in chloroform it was decided to investigate a method of direct synthesis of a 1:1 complex in chloroform using a potassium source that would also be chloroform-soluble. The reagent chosen was potassium trimethylsilanolate, Me_3SiOK. The triol **4** was dissolved in deuteriated chloroform and a molar equivalent of the silanolate reagent dissolved in the same solvent was

added portion-wise in two approximately equal amounts. A ^{1}H NMR spectrum was run after each addition. It was hoped that the complex **7** shown below would be formed. However the triol appeared to undergo no change. This is possibly due to the fact that potassium needs six binding sites to form a complex and there are only five available in the structure **7 (Scheme 5)**.

Attempted synthesis of a potassium complex by reaction of the triol 4 with potassium trimethylsilanolate



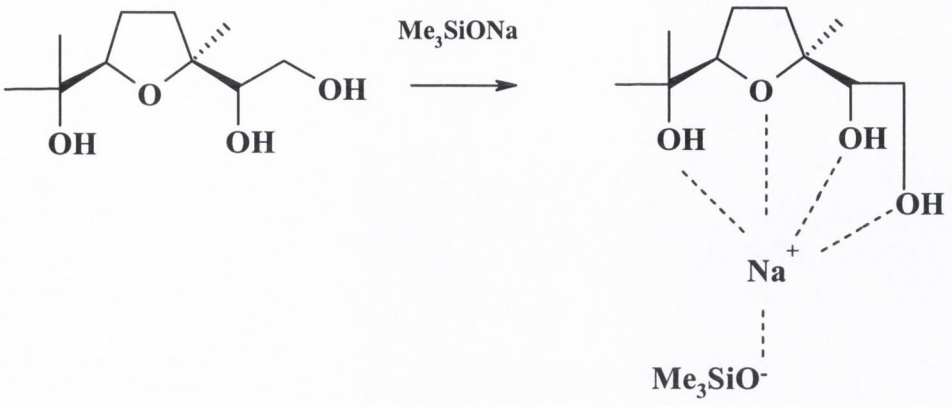
(4) (7)

Scheme 5

5.2.7 Attempted preparation of a sodium complex

Since sodium can form a complex by using either five or six binding sites[3] it was decided to repeat the above reaction using sodium trimethylsilanolate, Me_3SiONa. Hackler[1] had attempted to make a sodium complex analogous to his potassium species **3** by reacting the triol **4** with sodium acetate but failed to obtain a product.[1] Since, in the present experiment, there was no water present, it was considered that any sodium complex formed would possess the structure **8** as shown below **(Scheme 6)**.

Synthesis of a sodium complex by reaction with sodium trimethylsilanolate



(4) **(8)**

Scheme 6

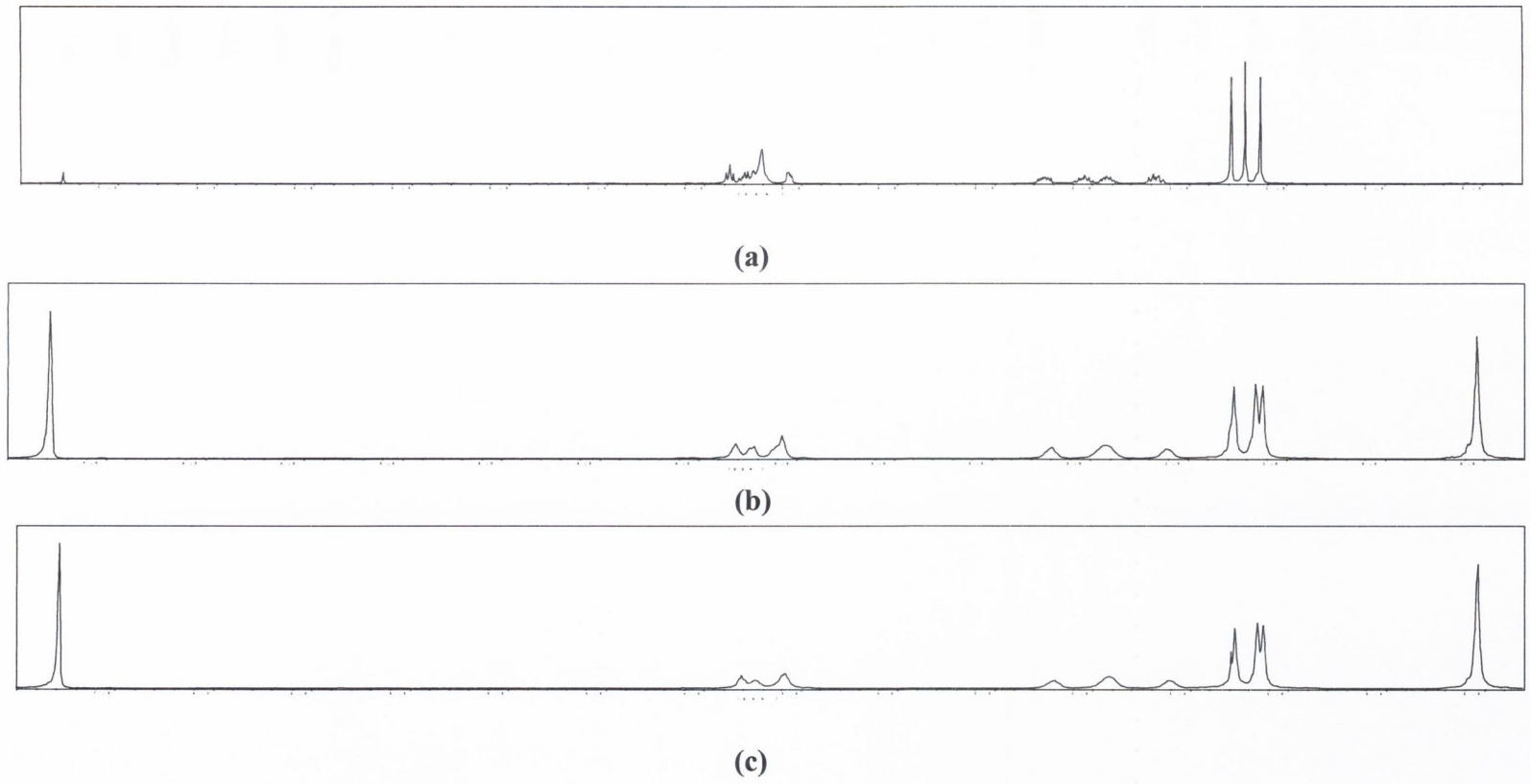


Figure 5.1 (a) the triol 4 (b) after addition of half a molar equivalent of sodium trimethylsilanolate (c) after addition of a molar equivalent of sodium trimethylsilanolate

As can be seen in **Figure 5.1**, the ^{1}H NMR spectrum changes considerably when sodium trimethylsilanolate is gradually added to a chloroform solution of the triol **4**. As with the other experiments described above, the upfield regions of the spectra do not exhibit drastic changes. Thus, only slight changes occur to the resonance positions of the methyl groups.

The signals arising from the C-3' protons of the triol **4**, where they appear as multiplets centred at δ 1·68 and δ 2·24 ppm, change in the "sodium complex" to multiplets resonating at δ 1·63 and δ 2·17 ppm. The two signals assigned to the C-4' methylene protons appear as two distinct resonances at δ 1·92 ppm and at δ 2·02 ppm in the spectrum of the triol **4**. However, in the derived "sodium complex" the same protons are found to resonate as a multiplet centred at δ 1·89 ppm.

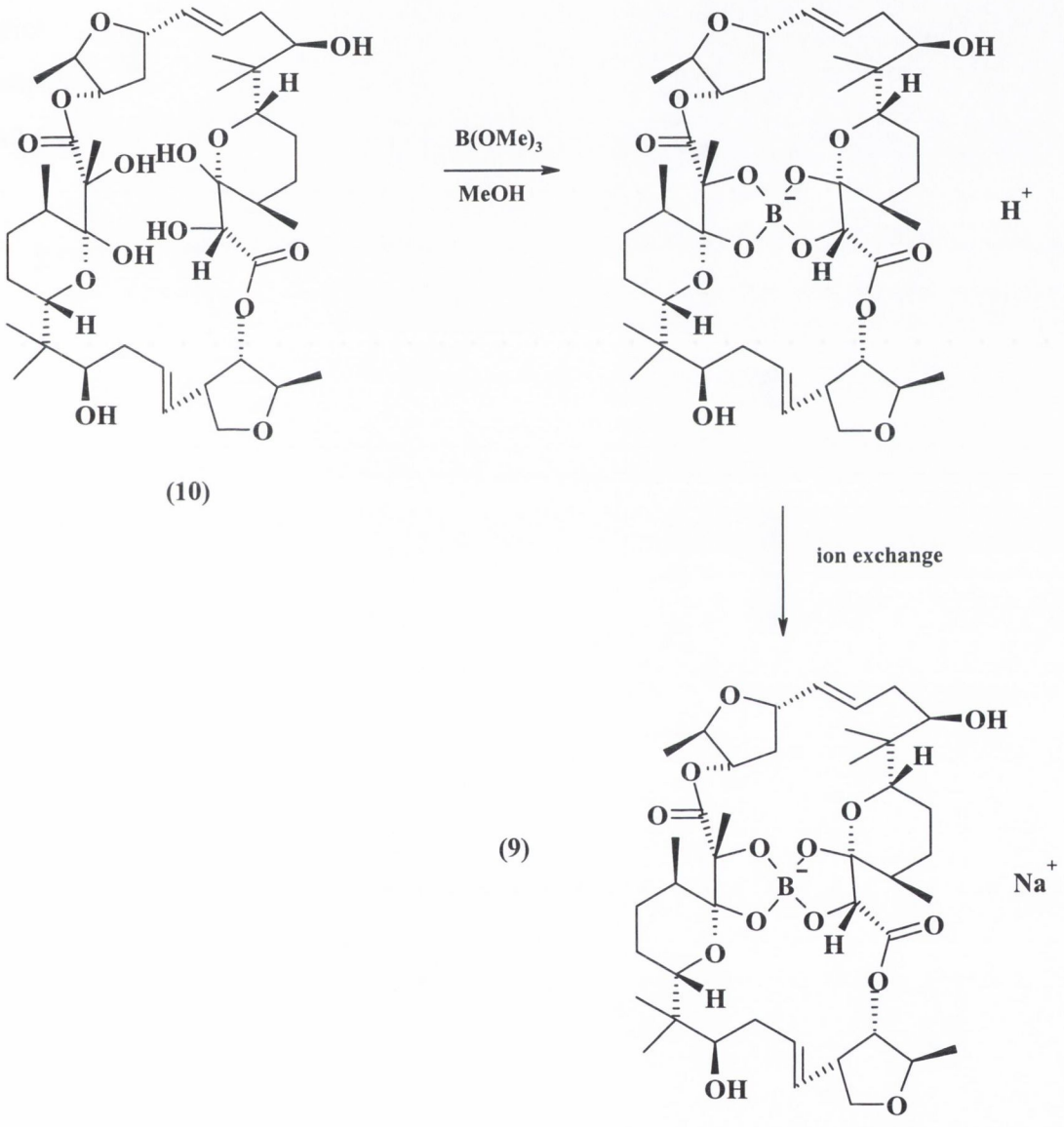
The downfield protons display the most obvious changes in the spectrum of the "sodium complex". In the proton NMR spectrum of the triol **4** four 1H signals are observed at δ 3·55 ppm, δ 3·71, δ 3·81 ppm and δ 3·88 ppm and are assisgned to the protons on C-1, C-2 and C-5 respectively. However in the proton NMR spectrum of the sodium complex three signals are evident. Firstly a 2H signal is seen at δ 3·57 ppm and is assigned to the C-1 proton and one proton of the C-2 methylene. A signal at δ 3·73 ppm is observed and assigned to the other C-2 proton. a triplet at δ 3·79 ppm corresponds to the C-5 methine proton. These changes are similar to those observed when comparing the spectrum of the triol **4** with that of the potassium complex **5** so it would appear that a sodium complex had been formed.

5.3 Attempted synthesis of a borate complex from the triol 4

It was next decided to try to synthesise a borate complex from the triol **4**. Many boron complexes exist in nature. For example, Aplasmomycin[4] **9** ($X = Na^{+}$) is a metabolite of *Streptomyces griseus* and together with the closely related Boromycin[5] belong to a unique group of ionophoric antibiotics. In a synthesis of Aplasmomycin, trimethyl borate was reacted in methanol with the alcohol **10**. The counterion of the initial complex **9** ($X = H^{+}$) that was formed was then exchanged for sodium by

passing the compound through a column of silica which acts as a source of sodium ion **(Scheme 7)**.

Synthesis of Aplasmomycin



(10)

(9)

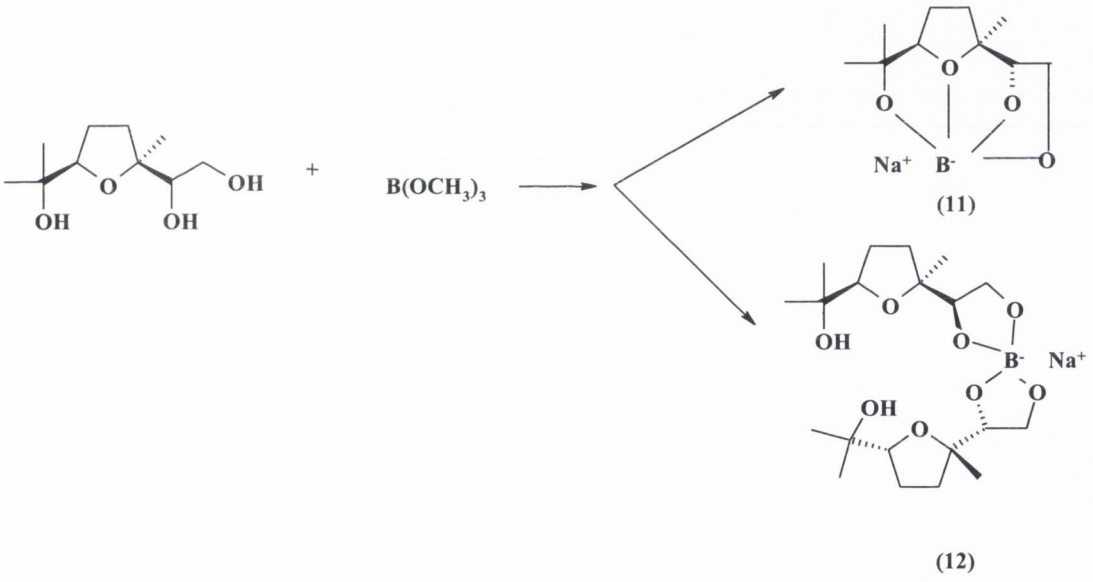
Scheme 7

Since there were indications that the triol **4** might act as a podand in the synthesis of both sodium and potassium complexes it was planned to investigate its conversion into a borate complex. A previous experiment carried out[6] in this laboratory had

suggested that this was a strong possibility. Following a protocol used in a synthesis of Asplasomycin **9**, the source of boron employed in the present work was trimethyl borate. It was considered that two possible structures could be obtained on reaction of this reagent with the triol **4**.

Firstly, the boron atom could complex with the four binding sites available on the triol to give the complex **11**. Secondly two molecules of the triol could become attached to boron *via* the 1,2-diol function of **4** to form, for example, the compound **12 (Scheme 8)**.

Proposed reaction of triol 4 with trimethyl borate to give borate complexes



(12)

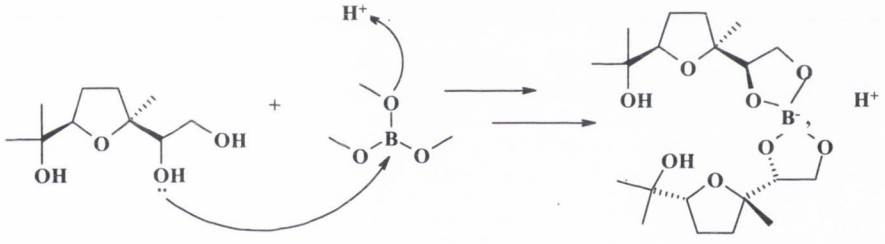
Scheme 8

Thus, the triol **4** was treated with ten equivalents of trimethyl borate in methanol at reflux temperature during five hours. The resulting solution was then concentrated *in vacuo* and passed through a silica gel column using ethyl acetate as eluant but the triol **4** was returned unchanged. It was thought that the silica used might not have possessed a high enough sodium content to permit cation exchange. In order to ensure that this was not the case, the silica was stirred with aqueous sodium chloride

and then recovered by filtration. The silica was then oven-dried and the reaction product passed through the column. The ^{1}H NMR spectrum of the residue remaining after evaporation of solvent revealed only unchanged triol **4**. This suggests that the complexation reaction itself did not work, and not that the exchange procedure failed.

It was then considered that the reaction between the triol **4** and trimethyl borate might require the presence of an acid in order to facilitate the first step, which is the cleavage of one of the methoxyl groups attached to boron. Once this occurs it results in a positively charged boron, which is more susceptible to attack by the oxygen lone pair of an alcohol group of the attacking triol **(Scheme 9)**.

Acid catalysed reaction of trimethyl borate with the triol 4



Scheme 9

Hence, the reaction between the triol **4** and trimethyl borate described above was repeated in the presence of a catalytic amount of *p*-toluenesulfonic acid but without any change to the outcome.

It was then considered that the problem might lie with the molar ratio of trimethyl borate employed. The reaction procedure followed was based upon that for the synthesis of Aplasmomycin **9**, but it was considered that the polyols **4** and **10** are quite different in nature. Thus, for the Asplasomycin precursor **10**, formation of a single O-B bond greatly increases the rate of formation of the remaining three O-B bonds since all of these are formed *intramolecularly*. On the other hand, formation of

a bimolecular complex from the triol **4** requires two separate, sequential *intermolecular* reactions. Accordingly, it was decided to repeat the reaction using two equivalents of triol **4** and one equivalent of trimethyl borate. In the event, no evidence for formation of a borate complex was obtained. Similarly, when boric acid was utilised instead of trimethyl borate the triol **4** was again recovered unchanged.

5.4 Conclusions

A potassium complex derived from the triol **4** and potassium acetate appeared to form using the methodology described by Hackler[1]. However, from the data obtained in the present work it is clear that the structure proposed by Hackler is not correct. It is now apparent that the complex most probably is a dimeric structure which includes an acetate ion and possibly a water molecule. Definite confirmation of this structure will require X-Ray analysis of suitable crystals at some future time.

5.5 Experimental

General experimental conditions

Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} silica gel plates. Visualisation was by means of ultraviolet light at 254nm or by development in potassium permanganate solution. Column chromatography was carried out under gravity using Merck Kieselgel 70-230 mesh silica gel. Evaporation under reduced pressure refers to the use of a Buchi or Bibby rotary evaporator. All solvents were dried using standard techniques. Infrared spectra were recorded as Nujol mulls (N) for solids or as liquid films (L) between sodium chloride plates for oils using a Matteson Genesis FT-IR spectrometer and the data was processed using WinFirst software. Nuclear magnetic resonance spectra were recorded using Bruker DPX 400 spectrometer. Chemical shifts were measured in deuteriated chloroform unless otherwise stated. Coupling constants (*J*) are quoted in Hertz. Mass Spectra were obtained using a VG Alto spectrometer (HRMS). Melting points were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus and are uncorrected.

(*E,E*)-1-Acetoxy-3,7-dimethylocta-2,6-diene 1[7]

Geraniol **5** (46·2 g, 0·3 mol.) was dissolved in pyridine (60 mL) and 4-dimethylaminopyridine (15 mg, 1 x 10^{-4} mol.) was then added. The mixture was cooled to 0 C and acetic anhydride (33 g, 0·3mol.) was then added. The solution was stirred at room temperature overnight and then poured on to crushed ice (900 g). After the ice had melted, the product was extracted with ether. The organic layer was washed sequentially with water, hydrochloric acid and sodium hydrogen carbonate solution. The organic phase was dried with magnesium sulfate, ether was removed at reduced pressure and the product was obtained as an oil (54 g, 92 %), δ_H ($CDCl_3$) 1·61 (3H, s, $C\underline{H}_3$), 1·69 (3H, s, $C\underline{H}_3$), 1·71 (3H, s, $C\underline{H}_3$), 2·06 (3H, s, $O_2CC\underline{H}_3$), 2·07 (2H, m, $C\underline{H}_2$), 2·11 (2H, t, $C\underline{H}_2$), 4·59 (2H, d, $C\underline{H}_2$ (C-8)), 5·08 (1H, t, C<u>H</u> olefinic) and 5·33 (1H, t, C<u>H</u> olefinic)) ppm; δ_H δ 16·38 ($\underline{C}H_3$) 17·60 ($\underline{C}H_3$), 20·94 ($\underline{C}H_3$), 25·58 ($C{=}O\underline{C}H_3$), 26·28 ($\underline{C}H_2$), 39·49 ($\underline{C}H_2$), 61·33 (C-8), 118·30 (olefinic <u>C</u>H), 123·72 (olefinic <u>C</u>H), 131·74 (quaternary), 142·13 (quaternary) and 170·99 (C=O) ppm; ν_{max} 2972, 2930, 2861, 1743 (C=O), 1673(C=C), 1444, 1378, 1366, 1233 (O-C-O), 1023 and 954 cm^{-1}.

1-[5'-(1''-Hydroxy-1''-methylethyl)-2'-methyltetrahydro-2'-furyl]-ethane-1-hydroxy-2-monoacetate 2

Potassium permanganate (37·83 g, 0·24mol.) was dissolved in acetone (1000 mL) and water (120 mL). These two solutions were added to a solution of geranyl acetate (31·53 g, 0·16 mol.) in acetone (100 mL) and water (25 mL) that was being cooled in ice. The solution was then left stirring for forty minutes in the presence of carbon dioxide. The mixture was then filtered through Celite to remove manganese dioxide. The acetone was removed under reduced pressure and the resulting solution was extracted using hexane. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent geranyl acetate (3.8 g 0·019 mol) was recovered. The aqueous layer was then saturated with sodium chloride, extracted with dichloromethane (3 x 500 mL) and dried over anhydrous

magnesium sulfate. After filtration of the magnesium sulfate and evaporation of the dichloromethane, the product was obtained as white crystals (17·71 g ,30 %),

δ_H ($CDCl_3$) 1·14 (3H, s, $C\underline{H}_3$), 1·23 (3H, s, $C\underline{H}_3$) 1·29 (3H, s, $C\underline{H}_3$), 1·71 (1H, dt, *J* 12, 8, $C\underline{H}_2$ (C-3')), 1·98 (2H, m, $C\underline{H}_2$), 2·12 (3H, s, C=O$C\underline{H}_3$) 2·20 (1H, m, $C\underline{H}_2$), 3·71 (1H, dd, *J* 8, 2, $C\underline{H}$ (C-1)), 3·88 (1H, t, *J* 7·5, $C\underline{H}$ (C-5'), 4·13 (1H, dd, *J* 11, 8, $C\underline{H}_2$ (C-2)) and 4·32 (1H, dd, *J* 11·5, 3, $C\underline{H}_2$ (C-2) ppm; δ_C 20·96 (C=O$\underline{C}H_3$), 22·85 ($\underline{C}H_3$), 25·24 ($\underline{C}H_3$), 26·57 (C-3'), 27·65 ($\underline{C}H_3$), 35·53 (C-4'), 66·02 (C-2), 75·37 ($\underline{C}$-1) and 85·61 (C-5') ppm; ν_{max} 3397, 3321, 1733, 1452, 1381, 1344, 1320, 1251, 1215, 1179, 1137, 1079, 1036, 994, 978, 946, 914, 888, 868, 840, 783, 760, and 722 cm^{-1}.

1-[5'-(1''-Hydroxy-1''-methylethyl)-2'-methyltetrahydro-2'-furyl]-ethane-1,2-diol 4

The diol **2** (1g, 0·004 mol.) was dissolved in ethanol (10 mL) and water (2 mL) and sodium hydroxide (0·4 g, 0·01 mol.) was then added and the solution was then stirred overnight at room temperature. The ethanol was then evaporated at reduced pressure and 10 mL saturated sodium chloride solution was then added to the resulting oil. A solid (15 mg) then precipitated out and was filtered off. The filtrate was then acidified to pH 2 using concentrated hydrochloric acid. This solution was then extracted with dichloromethane, dried and evaporated to give a white solid (400mg, 51 %) δ_H ($CDCl_3$) 1·15 (3H, s, $C\underline{H}_3$), 1·22 (3H, s, $C\underline{H}_3$) 1·29 (3H, s, $C\underline{H}_3$), 1·68 (1H, m, $C\underline{H}_2$ (C-3'), 1·92 (1H, m, $C\underline{H}_2$ (C-4')), 2 02 (1H, m, $C\underline{H}_2$ (C-4')), 2·24 (1H, m, $C\underline{H}_2$ (C-3') 3·55 (1H, dd, *J* 6, 3· $C\underline{H}$ (C-1)), 3·71 (1H, dd, *J* 11, 3, $C\underline{H}_2$ (C-2)), 3·81 (1H, dd, *J* 11, 6, $C\underline{H}_2$ (C-2)) and 3·88 (1H, t, *J* 7·5 $C\underline{H}$ (C-5')) ppm; δ_C 23·54 ($\underline{C}H_3$), 25·50 ($\underline{C}H_3$), 26·47(C-3'), 27·76 ($\underline{C}H_3$), 35·72 (C-4'), 63·66 (C-2), 76·56 (C-1) and 85·74 (C-5') ppm; ν_{max} 3271, 1459, 1377, 1343, 1183, 1161, 1129, 1079, 1055, 1025, 950 and 911 cm^{-1}.

Potassium complex

Potassium acetate (0·19 g, 2 x 10^{-3} mol) was dissolved in the minimum amount of water and added to the triol **4** (0·4 g, 2 x 10^{-3} mol) in methanol (4 mL). This solution was stirred for twenty minutes and solvents were removed under vacuum. The resulting oil was dissolved in a little methanol, ether was added and, after cooling overnight at –20 °C, the crystals that formed were collected by filtration and dried.

A solid (61 %) δ_H ($CDCl_3$) 1·11(3H, s, C$\underline{H}_3$ (C-1'')), 1·16 (3H, s C$\underline{H}_3$ (C-1'')), 1·24 (3H, s, C$\underline{H}_3$ (C-2')), 1·62 (1H, m, C$\underline{H}_2$ (C-3')), 1·90 (2H, m, C$\underline{H}_2$ (C-4')), 2·07 (1H, m, C$\underline{H}_2$, (C-3')), 3·55 (1H, dd, *J* 3, 7·5, C$\underline{H}$ (C-1)), 3·64 (1H, dd, *J* 7·5,11·5, C$\underline{H}_2$ (C-2)), 3·69 (1H, dd, *J* 3, 11·5, C$\underline{H}_2$ (C-2)) and 3·84 (1H,t, *J* 7, C$\underline{H}$ (C-5')) ppm; δ_C 22·46 (C$\underline{H}_3$), 24·79 (C$\underline{H}_3$), 26·44(C-3'), 27·72 (C$\underline{H}_3$) 35·38 (C-4'), 63·22 (C-2), 77·07 (C-1), and 84·99 (C-5); $\nu_{max:}$ 3289, 1560, 1463, 1378, 1342, 1182, 1130, 1078, 1056, 1025, 950 and 871 cm^{-1}.

HRMS (CI): *Found*: m/z 243·1190; *calculated for* $[C_{10}H_{20}O_4 + K]^+$ 243·0998

Attempted formation of complexes *via* reaction with alkali metal silanolates

The triol **1** (10 mg, 0·049 mmol) was dissolved in 0·5 mL chloroform and placed in a NMR tube. Sodium trimethylsilanoate (5·4 mg, 0·049 mmol) was then dissolved in 0·5 mL chloroform. Half of this solution was then added to the NMR tube and a spectrum was run. The other half was added promptly and another spectrum was run.

δ_H ($CDCl_3$) 1·14 (3H, s, C$\underline{H}_3$), 1·26 (3H, s, C$\underline{H}_3$) 1·29 (3H, s, C$\underline{H}_3$), 1·59 (1H, m, C$\underline{H}_2$ (C-3'), 1·90 (2H, m, C$\underline{H}_2$ (C-4')), 2·17 (1H, m, C$\underline{H}_2$ (C-3') 3·57 (2H, m, C$\underline{H}$ (C-1) and C$\underline{H}_{2a}$ (C-2)), 3·73 (1H, m, C$\underline{H}_{2b}$ (C-2)), and 3·79 (1H, t, *J* 7·5 C$\underline{H}$ (C-5')) ppm; δ_C 22·80 (C$\underline{H}_3$), 24·84 (C$\underline{H}_3$), 25·83(C-4), 27·42 (C$\underline{H}_3$) 35·13 (C-3), 62·47 (C-2), 71·08 (C-1), 84·49 (quaternary carbon) and 85·07 (C-5) ppm.

The same experiment was carried out using triol **1** (10 mg, 0·049 mmol) and potassium trimethylsilanoate (4·6 mg, 0·049 mmol) and there was no change in the ^{1}HNMR spectrum

Attempted synthesis of a borate complex from the triol 4

The triol **4** (300 mg, 1.4 x 10^{-3} mol) and trimethyl borate (1·45 g, 1.4 x 10^{-2} mol) were dissolved in methanol (15 mL) and refluxed for 5 hours. Methanol was then removed under vacuum. The resulting product was then passed through a column of silica with ethyl acetate as eluent. On evaporation of the solvent the triol **1** was returned unchanged.

Reaction of the triol 4 with boric acid

The triol **4** (0·4 g, 2 mmol)was dissolved in water (1 mL). Boric acid (0·061 g, 1mmol) was also dissolved in (1 mL) and the two solutions were combined and stirred at room temperature for five minutes. Sodium hydrogen carbonate (0·084 g 1 mmol) was then added to remove any unreacted boric acid. The water was then removed at reduced pressure to give the triol **4** unchanged.

Repeating the reaction using one equivalent of triol and using methanol as solvent gave the same result.

5.1.10 References

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