METAL/AMMONIA REDUCTION OF FURAN DERIVATIVES AND SYNTHESIS OF CYCLOALKANE-1,3-DIONES

A Thesis

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Doctor of Philosophy

in

The University of Adelaide

by

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CONTENTS

SUMMARY

The introduction presents a survey of the dissolving metal reductions of furan derivatives. The preparation, and synthetic utility, of alkylated cycloalkane-1,3-diones is also discussed.

Chapter I describes the lithium and ammonia reduction of 3-nonyl-2,3-dihydrofuran (55), 3-nonyl-4,5-dihydrofuran (56), 3-nonyl-2,5-dihydrofuran (57) and 3-nonylidenetetrahydrofuran (58). With an added proton source (ethanol) these substrates are reduced to the extent of 18, 12, 26-36 and 67-95 percent respectively under the standard conditions employed. The major product, 3-nonyltetrahydrofuran (59), was accompanied by small quantities of ring cleavage products.

The reduction of 2- and 3-substituted furan derivatives with an oxygen substituent adjacent to the ring (benzylic type leaving group) is also discussed. Without an added proton source, reduction of 3-(1', 1'-ethylenedioxynonyl)furan (76), 1-(furan-3'-yl)nonyl acetate (74) and 3-(1'-methoxynonyl)furan (75) caused fission of the carbon-oxygen bond adjacent to the ring to give only furan products. However, lithium ethanol and ammonia reduction of the acetal (76) afforded 2-ethylundecanol (108) as the major product. The dihydrofurans (55), (56) and (57), the alkenes (58) and the tetrahydrofuran (59) along with other ring reduction and cleavage products were also observed. Under the same conditions, other 3-substituted furans gave similar products.

The lithium and ammonia reduction, with or without an added proton source (ethanol), of 1-(furan-2'-yl)nonyl acetate (146),

2-(1'-methoxynonyl)furan (147), 2-(1',1'-ethylenedioxynonyl)furan (148) and 1-(furan-2'-yl)nonanol(149) provided 2-nonylfuran (145) as the only product. 2-(Pent-1'-enyl)furan (150) gave 2-pentylfuran (161) and the dimer 2-[4'-(furan-2"-yl)-2',3'-dipropylbutyl]furan (162). 1-(Furan-2'-yl)nonan-1-one (160) gave reduced furan and ring cleavage products.

Chapter II describes the synthesis of dihydrofurans (55) and (57) from 4-nonyltetrahydrofuran-3-ol(197a); dihydrofuran (56) and alkenes (58) from dihydro-3 (2H)-furanone (198); the 3-substituted furans from 1-(furan-3'-yl)nonan-1-one (39); and the 2-substituted furans from 1-(furan-2'-yl)nonan-1-one (160) or 1-(furan-2'-yl)nonanol (149). The synthesis of furan reduction products by unambiguous routes is also described.

Chapter III discusses the synthesis of 2,2-dialkylcyclopentane-1,3-diones. The sequence involved alkylation of the anion derived from the cleavage of ethyl 2-(5'-oxotetrahydrofuran-2'-ylidene) propionate (206) with base followed by intramolecular cyclisation.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

R.F.O. WARREN

ACKNOWLEDGEMENTS

I would sincerely like to thank my supervisor, Dr. R.A. Massy-Westropp, for his guidance, encouragement and enthusiasm during the course of this work. I also wish to thank Dr. R.H. Prager for his supervision during 1979.

I am indebted to Mr. C.R. Strauss and to the members of the Organic Chemistry Department who have helped me during my course of study.

I should like to acknowledge the assistance of a University Research Grant.

Finally, I would like to thank my parents for their understanding and support.

Science cannot discover truth, but
is an excellent way to discover error.
The residuum, after error is eliminated,
is called scientific truth.

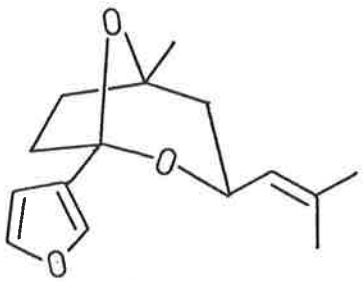
Kenneth Boulding, 1969

INTRODUCTION

0.1 FURAN REDUCTIONS

0.1.1 In 1976 Dimitriadis and Massy-Westropp[1] isolated from the wood of Eremophila rotundifolia, a new β-furanosequiterpene acetal named eremoacetal (1). Their interests in natural product chemistry led to extensive investigations of the stereochemistry of this molecule. Certain aspects of this study required conversion of the acetal (1) to alcohols (eg: the nonanediol (2)) suitable for configurational analysis.

Several observations suggested to these workers that these alcohols could be prepared from (1) by means of a dissolving metal



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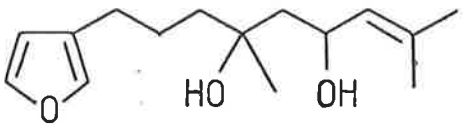

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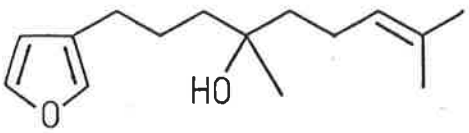

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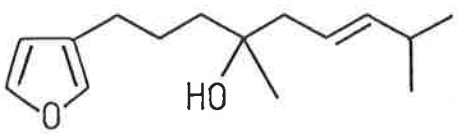

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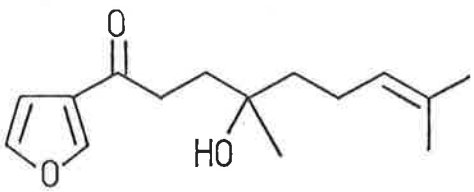

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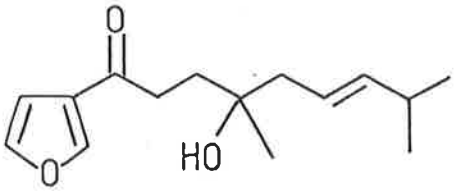

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Figure 0.1

reduction. From an examination of eremoacetal it is evident that this molecule has both benzylic and allylic type ether oxygens. Earlier studies have established that benzylic groups (eg: alcohol,[5,9,13,22-28] ether,[13,28] acetal,[9,13,28] ketone,[9,13,25-28] ester,[13]) undergo reductive fission in the metal-ammonia solutions used for the Birch[2-22] reduction. For example, 1-phenylethanol[23], 2-methyl-2-phenyl-1,3-dioxolane,[28] and acetophenone[28] are smoothly reduced to ethylbenzene in high yield under controlled Birch reduction conditions. Although not as well documented, it is however clear that many allylic hetero atom substituents also undergo efficient hydrogenolysis when treated with dissolving metal solutions.[4,13,29-32,59] Finally, furan and its alkyl derivatives have been shown to be inert to the Birch reduction.[23,33-38]

In the light of these observations, the Birch reduction of eremoacetal could effect hydrogenolysis of the benzylic type ether substituents to afford the diol (2). Cleavage of the allylic alcohol moiety in (2) should be slow, because ready hydrogenolysis of allylic alcohols is achieved only if the intermediate mesomeric anion contains a CH_2 or CHAr group at one or the other end.[4,13,15,31(a)] Alternatively, initial cleavage of the allylic acetal oxygen, and rearrangement of the intermediate hemiacetal, would afford the ketol (5) and/or the ketol (6). Subsequent benzylic type reductive cleavage of the carbonyl oxygen would yield the alcohol (3) and/or the alcohol (4). The final 3-substituted furan alcohols produced should be inert to the Birch reduction conditions employed.

In the event, solutions of lithium, sodium or calcium in liquid ammonia and an added proton source (ethanol), when used to reduce eremoacetal (1), gave complex mixtures of polar products.[1(a)] An examination of the ^{1}HNMR spectrum of the crude products showed no

furan proton resonances and the infrared spectrum showed strong hydroxyl absorptions.[1(a)]

Similarly, reduction with lithium in ammonia without an added proton source for 15 min gave a mixture. The 'HNMR spectrum of the crude reduction products showed no furan proton resonances.[1(a)]

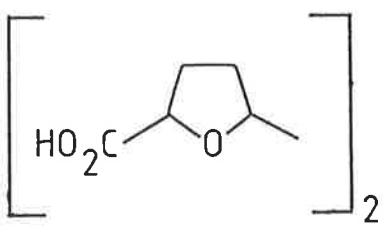
Clearly, these results indicate the observed products and accepted mechanistic pathways for the Birch reduction of benzenoid aromatic compounds can not always be used to predict or rationalise the reduction products derived from the furan analogues.

0.1.2 The Birch reduction of aromatic compounds has been extensively studied and widely applied to synthetic reactions.[4,8,11,13,21] However, only a few papers concern the Birch reduction of furan derivatives, and these are primarily concerned with furan carboxylic acids.[33,39-44]

Several independent studies on the dissolving metal reduction of 2-furoic acid have appeared.[33,39-42,44] Comparison of the results of these investigations is problematical because only superficial experimental details have been reported in some instances. However, it is clear that the product yields in these reactions are extremely sensitive to the nature and concentration of the reactants and to the reaction conditions.

If two equivalents or less of an added proton donor were initially present, the metal in ammonia reduction of 2-furoic acid gave 2,5-dihydro-2-furoic acid, tetrahydro-2-furoic acid, ring opened compounds: 2-oxopentanoic acid, 2-hydroxypentanoic acid, the dimeric species (7) and related polymers.[33,39] A dimeric species, (8), has

also been obtained from the reduction of 5-ethyl-2-furoic acid with sodium and ammonia at -33°C, when the addition of ethanol was delayed for 20 min.[40]



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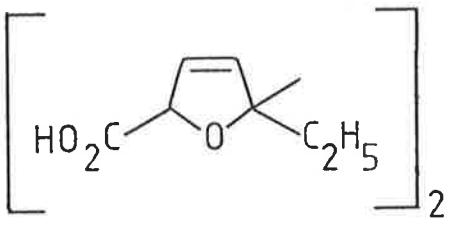


(8)

Ring opening may be due to process (a) (Fig. 0.2), which is known[117] to occur immediately even at low temperatures with (9, R=H); stabilisation of the carbanion in (9, $R=CO_2^-$) might be expected to enable this to survive long enough to undergo protonation or alkylation.

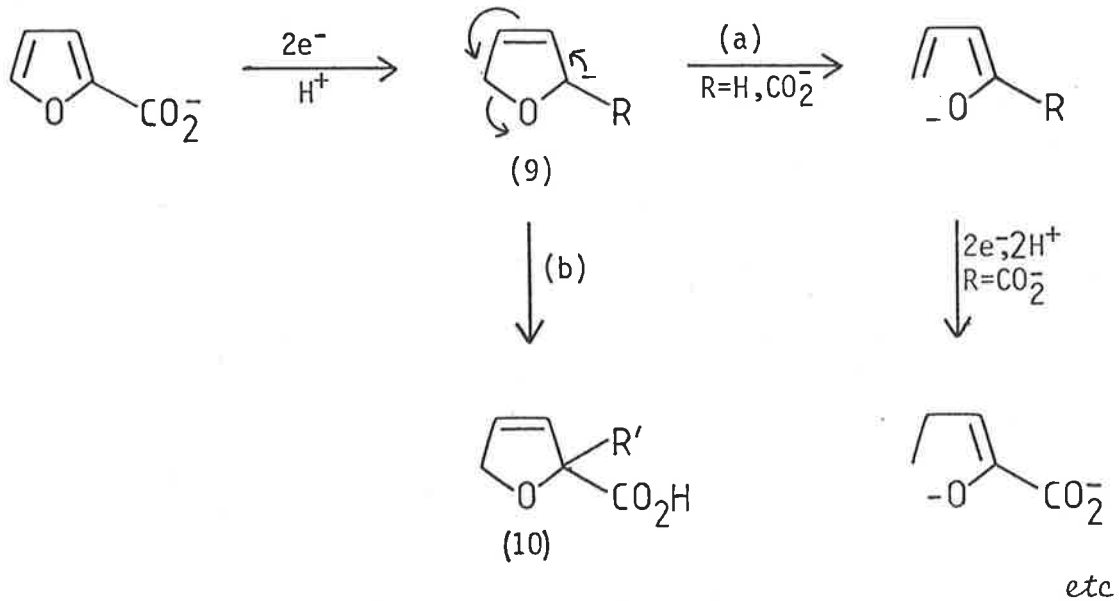


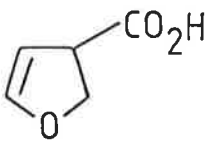
Figure 0.2.

Rapid addition of 2-furoic acid to lithium in ammonia at -78°C(conditions which apparently suppress the ring opening, and under which β-keto enol ethers are reported not to eliminate alkoxide[45]), followed by ammonium chloride within three minutes (process (b), Fig. 0.2) gave an 80% yield of (10,R'=H).

Addition of an alkyl halide instead of ammonium chloride resulted in conversion of the dianion (9,R=CO_2^-) into (10,R'=alkyl) accompanied by 10-20% of (10,R'=H)[42].

The lithium and excess methanol (16 to 30 equivalents) in ammonia reduction, at -33°C, of 2-furoic acid and 5-alkyl-2-furoic acids has been shown to afford good yields (80-90% yield) of the corresponding 2,5-dihydro-2-furoic acid derivative.[40,41]

Treatment of 3-furoic acid with sodium and 2-propanol in liquid ammonia at -33°Cgave 2,3-dihydro-3-furoic acid (11); isolated as the methyl ester in 85% yield.[39]



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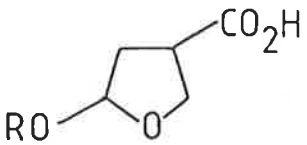

(12a : R=CH_3)
(12b : R=C_2H_5)
(12c : R=H)

When methanol or ethanol were substituted for 2-propanol, the products were the acetals (12a) and (12b); isolated as the methyl esters in 87% or 92% yield respectively.[39] These acetals were formed by acid catalysed alcohol addition to the enol ether moiety of (11)*

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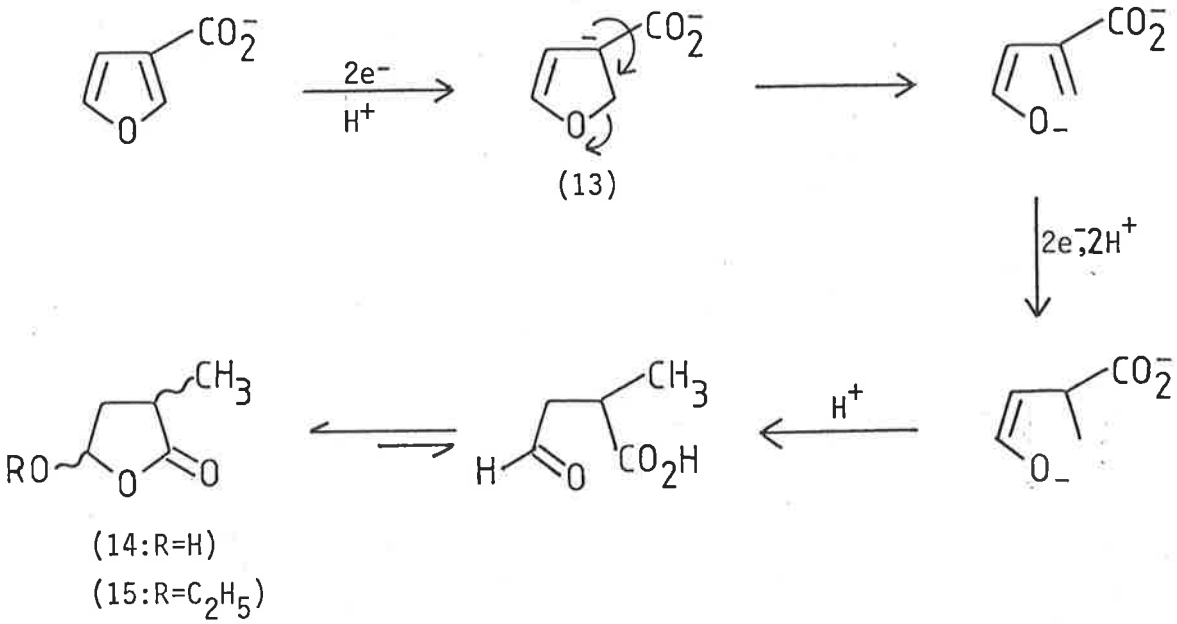
* Acid catalysed addition of alcohols to enol ethers is a well established reaction.[46]

under the work up conditions.[39]

When no added proton source is present, 3-furoic acid consumes four equivalents of lithium** at -33°C giving, on quenching with ammonium chloride, the hydroxylactones (14).[43] The ethoxylactones(15) were also isolated in varying amounts; they result from the work up conditions.[43]

A possible reaction pathway is shown in Scheme 0.1.



Scheme 0.1

As described above, the reduction takes place as for an isolated α,β - unsaturated acid.[39,47] Probably, the difference in the reaction course here reflects the relative rates of protonation of the dianion intermediate (13) by alcohol as opposed to ammonia; the basicity of (13) contrasts with that of the corresponding dianion

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** Reduction with sodium takes exactly the same course as with lithium and gives the same products.

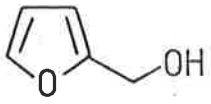
from benzoic acid which is protonated relatively slowly in the presence of methanol.[48] A precedent exists for the β- elimination of the ether group under these conditions.[47] No alkylated products were observed after the reaction had been quenched with methyl iodide.[43]

Addition of 3-furoic acid to a solution of a limited amount of lithium (2.5 equ.) in ammonia at -78°C rapidly consumed the lithium. Immediate quenching with ammonium chloride gave a product which consisted mainly of starting material and the hydroxylactones (14).[43]

The Birch reduction of 2- and 3-furoic acid in the presence of the optically active alcohol, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, gave optically active products, (10,R'=H) and (12c) respectively.[44]

Birch[23] has reported that the reduction of furfuryl alcohol (16) and the pentanol derivative (17a) with sodium and ethanol in liquid ammonia, at -33°C, gave 2-methylfuran and 2-pentylfuran (18) in 20% and 3.5% yield respectively. In both cases, the remaining product was starting material.

Hydrogenolysis is however greatly facilitated by conversion of the hydroxyl group into a derivative which gives a more stable anion.[13,37] Thus, when excess lithium in ammonia at -70°C was used for the reduction of the acetate (17b), the alkylfuran (18) was obtained in 95% yield. Competitive ester reduction, which gave the alcohol (17a) as a by-product, was increased when sodium or potassium was employed in the reaction.[37] This metal effect has been noted previously.[13] The direct removal of acetoxyl groups from 1-(furan-2'-yl)alkyl acetates has been applied to the synthesis of



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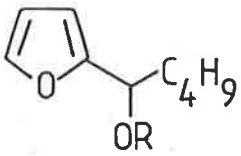
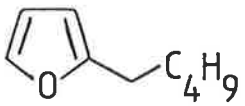


(17a:R=H)
(17b:R=Ac)



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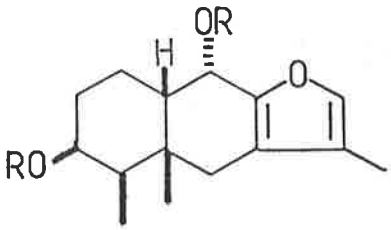
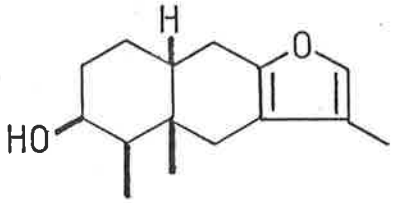


(19a:R=H)
(19b:R=Ac)



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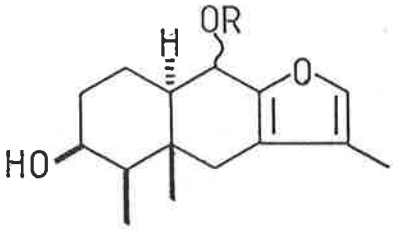
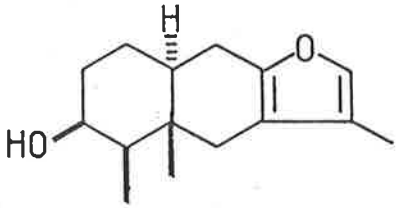


(21a:R=H)
(21b:R=Ac)



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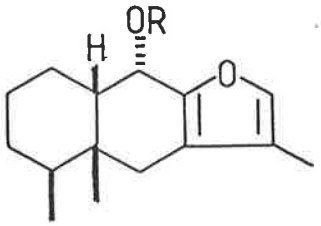
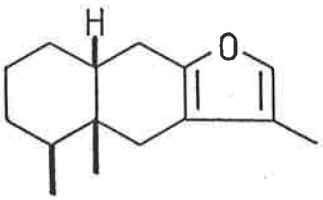


(23a:R=H)
(23b:R=Ac)



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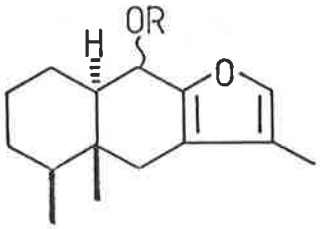
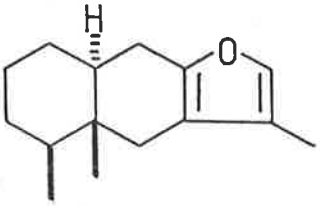


(25a:R=H)
(25b:R=Ac)



(26)

Figure 0.3

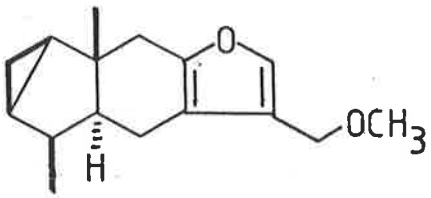
several natural products.[37] The eremophilane derivatives (19a), (21a), (23a) and (25a) were converted to the respective acetates (19b), (21b), (23b) and (25b), and subjected to a reduction by lithium in ammonia at -70°C; the hydrogenolysis products (20), (22), (24) and (26) respectively were obtained in excellent yields (80%-100% yields from the alcohols).[37]

Deacetoxylation of 1-(furan-3'-yl)alkyl acetates by the metal-ammonia reduction procedure has been reported by Takeda *et. al.*[38] Dihydrolinderene acetate (29b) with sodium in ammonia at -70°C afforded the hydrogenolysis product (28) and the alcohol (29a). Similarly, under these conditions linderene acetate (32) gave the hydrogenolysis products (33) and (35), and the alcohol (34).[38]

In contrast with the 1-(furan-2'-yl)alkyl acetates, the 1-(furan-3'-yl)alkyl acetates afforded only a low yield (10% yield) of the hydrogenolytic derivatives; the major products were alcohols given from competitive ester reduction.

The 1'-methoxy-3-substituted furan derivatives, dihydrolinderoxide (27) and linderoxide (30), afforded respectively the hydrogenolysis products (28) and (31) in moderate yields (both *ca* 60% yield) when treated with sodium in ammonia at -70°C.[38]

Interestingly, under these conditions the double bond of the vinyl cyclopropane moiety was extensively reduced (at least 50% reduction) to the saturated analogue, and without fragmentation of the cyclopropyl ring; 2-cyclopropylpent-1-ene was found to be unaffected by sodium in liquid ammonia, but was reduced to 2-cyclopropylpentane by sodium and methanol in liquid ammonia.[49]



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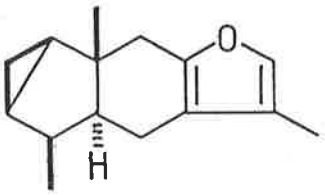

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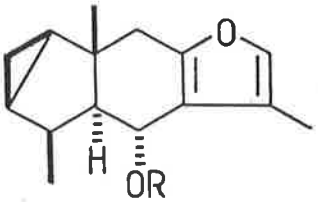
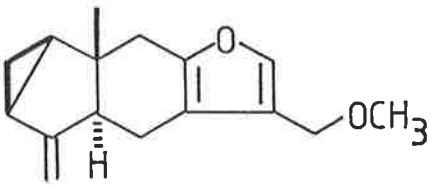


(29a:R=H)
(29b:R=Ac)



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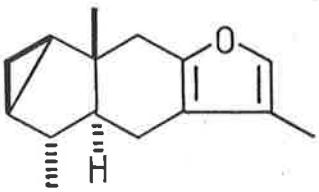

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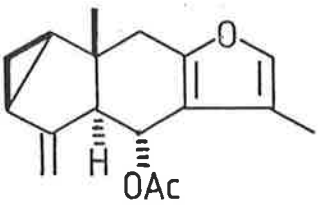

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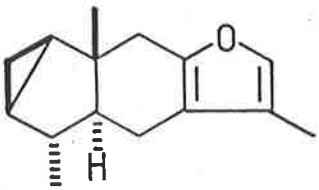

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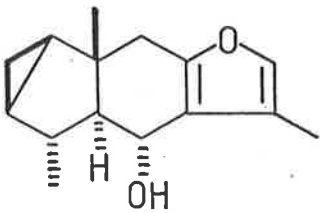

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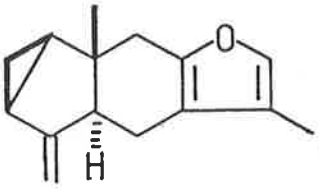
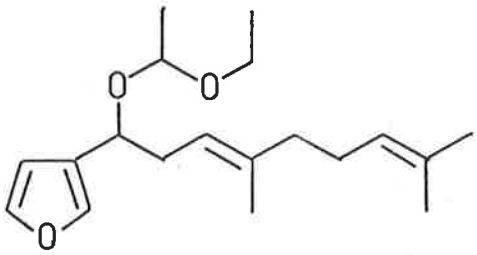


(35)

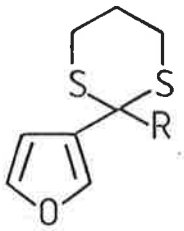
Figure 0.4

The treatment O-ethoxyethyl-9-hydroxydendrolasin (36) with lithium in ammonia caused hydrogenolysis of the benzylic type oxygen functionality to give dendrolasin (38b) as the only product.[35]

The dithianes (37a) and (37b) gave perillene (38a) and dendrolasin (38b) in moderate yield upon reduction with sodium in ammonia.[36] The contribution from benzylic type cleavage, and saturated carbon-sulphur bond cleavage, in the reductive removal of the dithiane function is unclear; but the former process appears to be the faster.[5,9,13,50]



(36)



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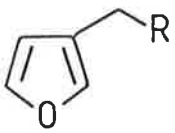
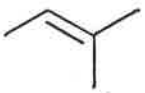
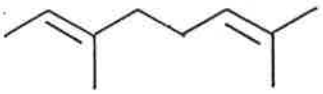


(38)

a:R= 

b:R= 

0.1.3 Apart from the aforementioned examples, we have found no other Birch reductions of furan derivatives reported in the literature.

These reductions show that, in common with many dissolving metal reductions of aromatic compounds, the nature of the products obtained depend upon the exact experimental conditions.

Many factors, of varying influence, can affect the reduction pathway and include: (1) whether the substance is soluble and whether co-solvents are employed; (2) whether the process involves addition of metal (dianion formation) followed by protonation or simultaneous reaction (protonation of the anion radical); (3) whether the ammonia is at the boiling point or lower temperatures, affecting solubility, and the stability of intermediates towards secondary migration processes, elimination reactions, dimerisations, and ease of trapping with a proton donor or alkylating agent; (4) nature of the alcohol (selectivity in protonation) and basicity of the alkoxide anion (rates of bond migration) and whether the alcohol is initially present ["buffering" effects - removal of anionic intermediates, inhibiting secondary processes described in (3)] or added after a period; (5) the period of time the reaction is allowed to proceed (complete reduction/hydrogenolysis of the substrate and further reaction of initial products) and the time involved after all the metal is consumed (dehydrogenation and disproportionation); (6) effects of any substituents on the rate of reduction/hydrogenolysis; (7) reduction potential of the metal in ammonia solution and effect of different metal cations; (8) whether air is rigorously excluded during both reduction and work up; (9) whether the substance is fully in solution or so finely divided that it dissolves rapidly; and (10) whether trace amounts of transition metals, or other group metals, are present. Few

reductions have been investigated with all these points in mind, and the experimental conditions and procedures employed have been diverse.

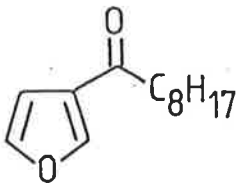
Thus, correlation of the experimental results obtained from the Birch reduction of furan derivatives, for the purpose of rationalisation or prediction of products, and to propose mechanistic generalisations, has presented many difficulties.

The larger proportion of this thesis is aimed at a systematic study of the lithium and ammonia reduction of some 2- and 3- substituted furan derivatives, with the following objectives: (1) characterisation of the reduction products; (2) evaluation of the synthetic utility of furan derivatives in the synthesis of terpenoid compounds; (3) elucidation of mechanistic details relating to the loss of hetero atom (oxygen) substituents adjacent to the furan ring, the reduction of the furan ring, and the reduction of cycloalkenes; (4) to compare and contrast the 2- and 3- substituted furan series from both the mechanistic and synthetic viewpoints.

A variety of benzylic type functional groups were considered appropriate for the survey; these were carbonyl, hydroxyl, acetate, acetal, ether and alkene.

1-(Furan-3'-yl)nonan-1-one (39) and 1-(furan-2'-yl)nonanol (149) were chosen as key intermediates for the preparation of model compounds in the 3-substituted furan and 2-substituted furan series respectively.

A number of methods have been described for the preparation of 3-substituted furan derivatives,[35,36,51-65] but these were considered to be unsuitable for the purpose at hand.



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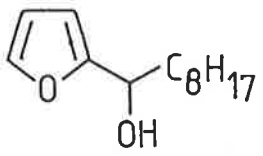


(149)

The most direct and convenient approach to the ketone (39) appeared to be the treatment of commercial 3-furoic acid with octyl lithium.[67]

The alcohol (149) is readily available from condensation of furfural with octyl magnesium bromide.[68]

The desired range of functional groups outlined above would be obtainable from the key compounds by standard functional group transformations.

0.2 CYCLOALKANE-1,3-DIONES

Isolated from the pregnancy urine in 1929, estrone[69] (41) was the first steroid hormone to be obtained in pure form. The medical importance of estrone engendered early interest in its synthesis. More recently, its position as a precursor to commercially important 19-nor-steroids has stimulated development of viable industrial synthesis.[70]

Utilization of a preformed methylated ring D component in the form of 2-methylcyclohexane-1,3-dione (42), or better, 2-methylcyclopentane-1,3-dione (43), has been a key factor in the development of a number of relatively short industrially feasible syntheses of estrone exemplified by the approaches of Smith, Torgov and Velluz.[70a]

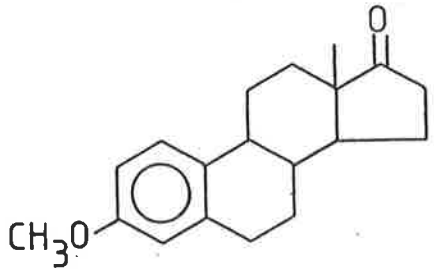
In the Smith synthesis, the carbon system was assembled by condensation of the anion of the 1,3-dicarbonyl compounds, (42) or (43), with the vinyl ketone (44) to afford the steroid precursor (45).

The Torgov approach had its genesis in studies on analogous base catalysed alkylations of (42) or (43)[71] with the allylic bromide (46) with formation of an alternative estrone precursor (47).

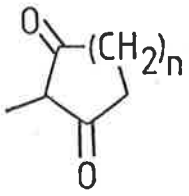
The Velluz synthesis utilized a D→C→B→A scheme analogous to a sequence that had been studied earlier with D-homo intermediates. Michael reaction, under weakly basic conditions, of (43) with methyl 5-oxohept-6-enoate (48) led to the trione acid (49), which as a base unstable 2,2-disubstituted-1,3-diketone was cyclized to the enedione acid (50) under acidic conditions. Further elaboration of this intermediate afforded estrone (41).

Enol lactones can be prepared by using the Wittig reaction between stable phosphorus ylides and cyclic five membered aliphatic anhydrides[72-76].

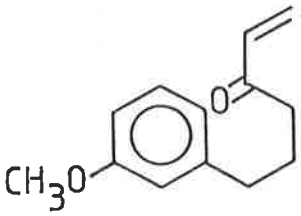
We considered that the enol lactones (51,n=1,n=2) could be utilized to develop a different approach (scheme 0.2) to the synthesis of 2,2-dialkylated cyclohexane-(54,n=2) and cyclopentane-1,3-diones (54,n=1). This method would be experimentally less difficult than



(41)



(42:n=2)
(43:n=1)



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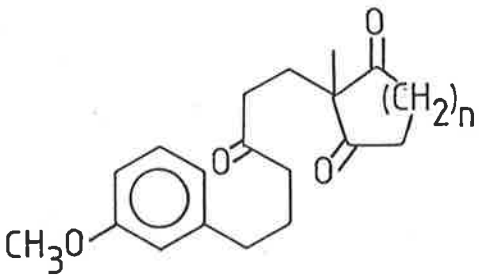
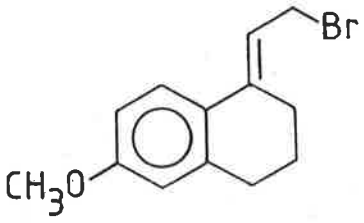
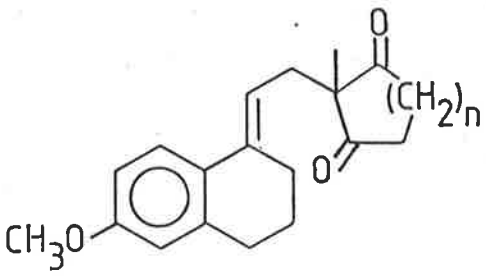


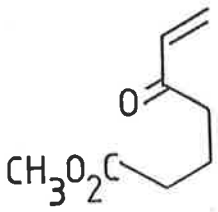
(45a:n=2)
(45b:n=1)



(46)



(47a:n=2)
(47b:n=1)



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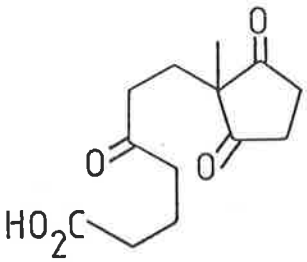
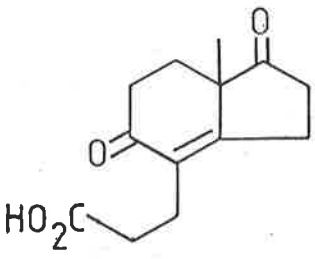
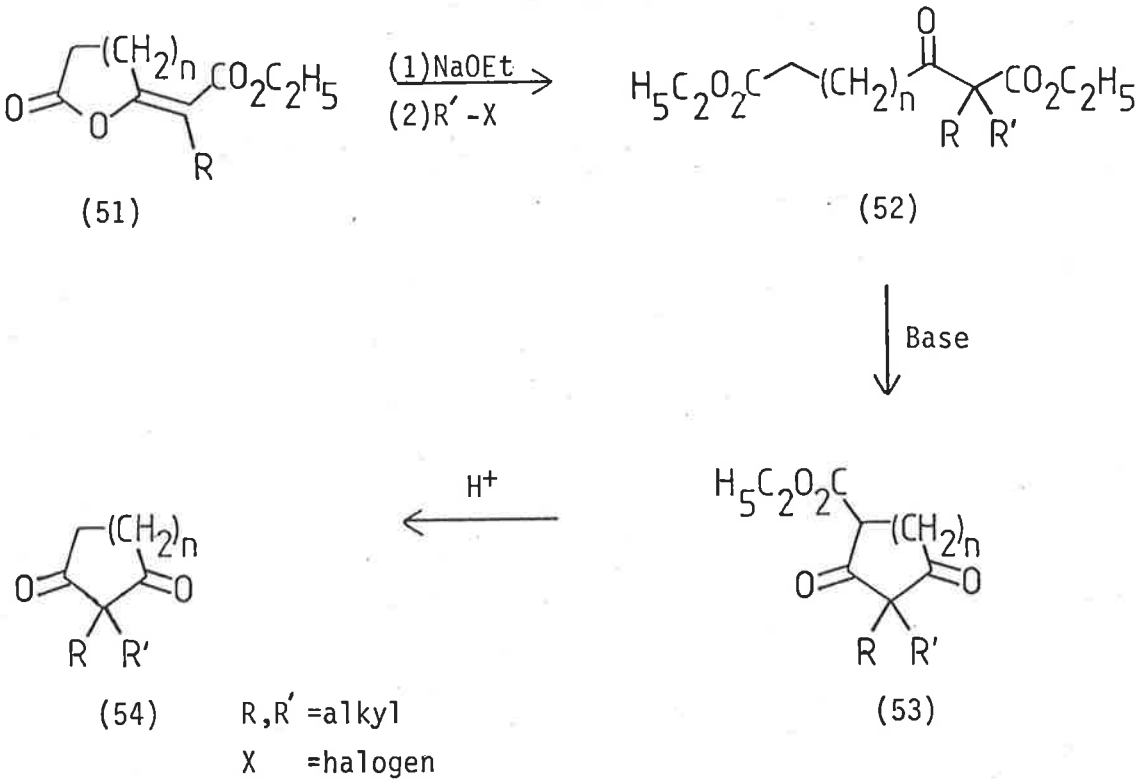


(49)



(50)

Figure 0.5



(51) (52) (53) (54)

Scheme 0.2

alternatives available for 2,2-dialkylatedcycloalkane-1,3-diones synthesis.[77] Introduction of a range of alkyl substituents (R and R') should be possible; unlike other procedures, the second alkyl substituent (R') is introduced during the cycloalkane-1,3-dione synthesis, rather than afterwards.

Base cleavage of the enol lactone (51,n=1,n=2) with sodium ethoxide would be expected to generate the anion of the β-keto ester which could be alkylated to yield the keto diester (52,n=1,n=2).

Dieckman reaction of (52,n=1,n=2) followed by hydrolysis and decarboxylation of the intermediates (53,n=1,n=2) should afford 2,2-dialkylatedcyclohexane-1,3-diones (54,n=2) and 2,2-dialkylated-cyclopentane-1,3-diones(54,n=1).

By using R=CH_3 in (51,n=1), and the bromide (46) as the alkylating agent R'-X in this sequence, a new route to the estrone precursor (47b) would be established.

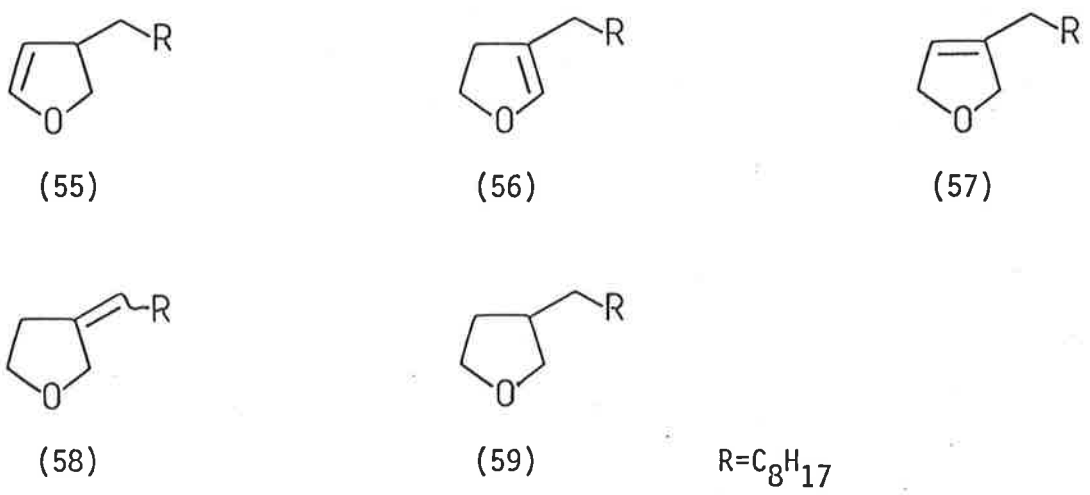
CHAPTER I

THE REDUCTIONS

1.1 ALKENES

In order to explain the origin of the 3-nonyltetrahydrofuran (59) formed during the reduction of the 3-substituted furan substrates, it was necessary to examine the reduction of the alkenes (55), (56), (57) and (58) under the standard conditions employed.

Some of these alkenes were prepared as mixtures. Owing to the difficulties encountered with purification, and because the information sought could be obtained using the substrate mixtures, these mixtures were used directly for the reduction study.



(55) (56) (57)

(58) (59) $R=C_8H_{17}$

Figure 1.1

Thus, the dihydrofurans (55) and (57) were together [2:1 ratio respectively] reduced with lithium and ethanol in ammonia for 1h and were consumed to the extent of 18% and 26% respectively. The products, recovered dihydrofurans (55) and (57), 3-nonyltetrahydrofuran (59), 3-methyldodecanol (92), and two

unidentified products were obtained in a ratio (percent) of 19(55) : 8.6(25) : 2.2(6) : 2.3(7) : 1.2(3.5) : 1(2.9) respectively. From the available data, it appears that the first unidentified product is 2-vinylundecanol, and that the second unidentified product is 3-methylenedodecanol.

When a mixture of the dihydrofurans (56) and (57), and the two isomers of alkene (58) [1(11) : 2.8(31) : 2.4(27) : 2.7(30) ratio (percent) respectively] was reduced with lithium and ammonia for 1h, they were consumed by 12, 36, 65 and 69 percent respectively. The products, recovered dihydrofurans (56) and (57), the two isomers of alkene (58), tetrahydrofuran (59), 2-ethylundecanol (108) and 3-methyldodecanol (92) were present in a ratio (percent) of 3.2(10) : 6.6(20) : 3.0(9.0) : 3.1 (9.3) : 13.9 (42) : 1(3) : 2.5(7) respectively.

The alkene (58) was prepared as a mixture of two isomers which were present in a ratio of 4.8:1. The major isomer was reduced by 94, and the minor isomer by 96 percent, when they were together treated with lithium and ethanol in ammonia for 1h. The two recovered isomers of (58), tetrahydrofuran (59) and 3-methyldodecanol (92) were obtained in a ratio (percent) of 7(6) : 1(0.9) : 88(78) : 16(14) respectively.

Interestingly, only relatively small quantities of ring cleavage products were observed in each case. This result suggests that protonation of a carbanionic centre vicinal to the carbon bearing oxygen occurs faster than ring cleavage. This is In contrast with (9,R=H; Fig 0.2) where a similar ring cleavage is very fast.[117] The saturated alcohols which were derived from an elimination process

(ring cleavage), must be formed via terminal alkene intermediates; this implicit alkene reduction does not appear to be exceptional (*vide infra*), considering the quantities involved, and the conditions used.

Reduction of the disubstituted double bond in (55) and the trisubstituted double bonds in (56), (57) and (58) under the conditions employed is unusual, particularly in the case of (58) where a good yield (78%) of the tetrahydrofuran (59) was produced. Manifold factors can influence the reducibility of an unconjugated double bond, and it seems desirable at this stage to discuss some of the more important and relevant effects.

It is known that isolated double bonds are difficult to reduce with dissolving metals, and that the rate of reduction depends on the degree of alkyl substitution in the order: monosubstituted > disubstituted terminal > disubstituted internal > tetrasubstituted.[9,13,40,78,81] Unless special molecular features are present, only the terminal alkenes are reducible in ammonia,[49,78] but the others can be slowly reduced by the more active electrons in amine solutions.[79,80] The order of reduction rates may be determined by the inductive effects of the attached groups and by their effects on solvation and situation of the metal cation. These influences would retard reduction of the more highly alkylated double bonds by destabilisation of the anion radical intermediate.

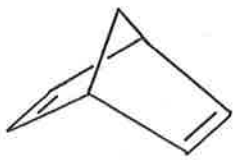
In amine solutions, it has been shown that the reduction rate is increased by ground state strain in the alkene: cis slightly greater than trans; norbornene > cyclohexene; cyclopentenes > cyclohexenes.[78]

Although the highly strained norbornene is reduced very much faster than cyclopentene, only slight reduction of norbornene occurs in ammonia and alcohol solution.[78]

Through-space orbital interactions, operating between the molecular orbitals of two unconjugated π-type systems which are constrained to lie in close proximity (within 2.7Å[89,101]) of each other, have been proposed to explain the efficient Birch reduction of some isolated double bonds.[78,82-88]

For example, the reduction of (60), (62) and (63), to give (61), (64) and (65), proceeds at a rate which is some five orders of magnitude faster than the rate of reduction of norbornene (61).[82] Also, (60), (62), and (63) are reduced at rates comparable with that of lithium benzoate.[82]

The increased reduction rate of (60), (62) and (63) could also be due to ring strain or inductive effects. That ring strain effects enhance the reactivity of norbornadiene (60) has been negated because the cyclobutene (68) was found to be inert to the reduction conditions employed for the reduction of (60).[83] Inductive effects also appear unlikely to cause a significant increase in the reduction rate. If inductive effects are responsible for the observed enhanced reactivity of norbornadiene compared with that of norbornene, then a large rate enhancement should be found for the rate of reduction of (63) compared with that of (62). However, these compounds are reduced at similar rates.[82] Additionally, (66) and (67) are reduced only very slowly[84] and (69) is reduced only slightly faster (11 fold increase) than norbornene under the Birch conditions.[89] Since the methoxy substituent exerts a stronger electron withdrawing effect than a phenyl or double bond (their inductive substituent constants are



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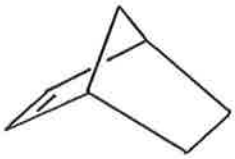

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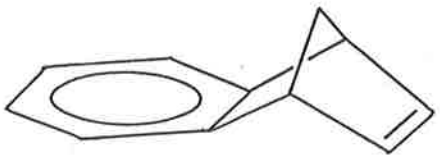

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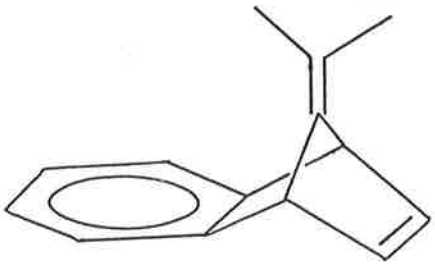

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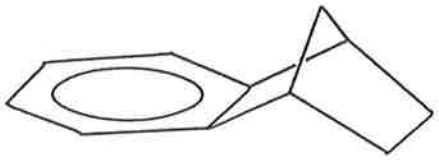

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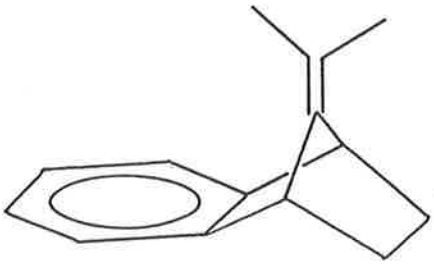

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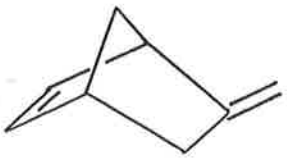

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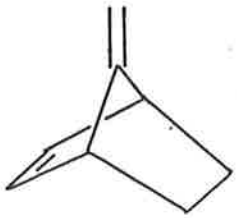

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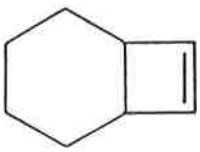

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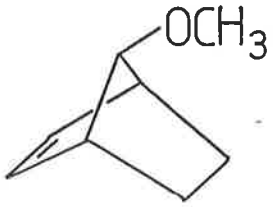

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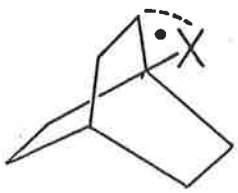

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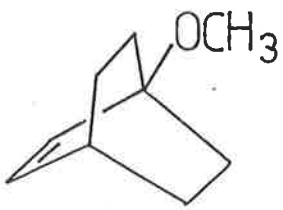

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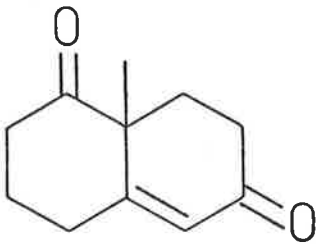

(72)

Figure 1.2

1.81, 0.94 and 0.56 respectively[105]), the rate enhancements for (60), (62) and (63) should be less than 11 if inductive effects alone were operative. The Birch reduction of (60) and (62) is believed to proceed via a classical carbanion intermediate.[86]

Through-bond orbital interactions have also been proposed to explain the enhanced reduction rate of non-conjugated double bonds which are three, four, five and six bonds removed from other π-orbital systems.[89,90] Depending on the separation of the π-systems, and molecular geometry, the orbital interaction through space and orbital interaction through bonds effects can reinforce (separation by an even number of σ-bonds) or oppose (separation by an odd number of σ-bonds) each other.[89,90]

Interestingly, the ultraviolet absorption maxima, which reflect the differences between ground- and excited-state energies, have been used to qualitatively predict the ease with which a bond can accept an electron in its lowest unoccupied molecular orbital.[83]

There are indications that the close proximity of certain functional groups can assist in the reduction of an isolated double bond. For example, reduction of the 2-cyclopropylpent-1-ene double bond[49] has been noted previously. The terminal double bonds in N-allyl- and methallylpiperidine and diethylmethallylamine are efficiently reduced by means of sodium and methanol in ammonia.[91] While an amino substituent decreases the reducibility of the phenyl group towards dissolving metals in amine or ammonia solutions[92,93] it apparently assists in the formation of saturated cyclohexylamine derivatives from 3- and 4-dimethylaminocyclohexene upon treatment with lithium and methylamine;[93,81] but this latter observation has not been confirmed for ammonia solutions.[94]

There is evidence to suggest that an electron donating bridge head substituent can stabilise an intermediate radical of type (70, x=amino, methoxyl).[95] One chemical consequence of this could be that the bridge-ring ether (71), which cannot undergo hydrogenolysis for steric reasons, undergoes reduction of the double bond with rate enhancement compared with norbornene;[95] however, the contribution to this rate increase arising from inductive or other effects is unclear.*

Thus, several examples suggest that donor atoms or groups in appropriate positions may interact nonclassically with an anion radical and assist in the electron addition to an isolated double bond.

The effects of substituents on the rate and orientation of the Birch reduction of benzene derivatives has received considerable attention, and a number of generalisations have been noted.[4,8,13,21] Thus, it is commonly accepted that electron-releasing groups deactivate the ring and direct protonation to unsubstituted 2,5-positions while electron withdrawing groups have the opposite effect, promoting 1,4-reduction at the position bearing the substituent. However, there are some observations that appear to challenge these concepts: 2-Methylnaphthalene[97], 2-naphthol[98], and 3- and 4-methylbiphenyl[96] all undergo reduction at the substituted ring; p-(trimethylsilyl)toluene has been reduced to give the 2,5-dihydro product[99]; and anisole is

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* The alkene (71) is reduced by 15% when treated with lithium-*tert*-butyl alcohol-ammonia[95], and (69) is reduced by 10% after 4h with the same reagent.[89] Unfortunately, the time period involved for the former reduction has not been reported and so no direct comparison can be made.

reported to react 3.28 times faster than benzene.[92] Also, fluorene has been shown to afford a product contrary to theory.[100]

That anisole undergoes reduction faster than benzene is a surprising conclusion if the mesomeric effect of the methoxyl group in stabilising the substrate is of importance (aniline shows a 0.10 attenuation of the reduction rate compared to benzene[92]). A predominant effect is probably the inductive effect of the methoxyl group on formation of the anion radical.

This latter argument may be used to explain the enhancement of the reduction rate of the double bonds in alkenes (55) and (56), compared with the reduction rate of a dialkyl disubstituted internal double bond (*vide supra*). In other words, it appears that the electron withdrawing inductive effect can override the electron donating mesomeric effect in the enol ether moiety of (55) and (56), and assist in addition of an electron to the lowest unoccupied molecular orbital of the π-system to form the anion radical. That alkene (55) was reduced more rapidly than (56) can be attributed to the effect of the additional alkyl substituent at the double bond (*vide supra*) in (56).

As previously indicated, ring strain effects have been shown to exert only a minimal influence upon the reduction rate of a compound subjected to the Birch conditions; therefore, it is likely that they do not account for the enhanced reactivity of the alkenes (55), (56), (57) and (58).

The reduction rate of (58) is significantly faster than the reduction rates of (69) (*ca.* 35 fold increase) and (71), and some

400 times faster than the reduction rate of norbornene (61).* With regard to these results, the enhanced reactivity of (58) is difficult to rationalise in terms of oxygen inductive effects alone. The inspection of models, and of a scaled diagram of (58), reveals that the interatomic distance between the oxygen and nearest alkene carbon (tetrahydrofuran carbon 3) is about 2.4Å. This should be sufficiently close for an orbital interaction through space (OITS) effect to be operative between the oxygen non-bonding orbitals and the alkene π-bond.[89,101] When interacting orbitals are separated by two σ-bonds, it appears that the OITS and orbital interaction through bonds (OITB) effects should reinforce each other, and that these effects would alter the molecular orbital energies of the π-system such that electron addition to the alkene becomes easier.[89,90] Thus, the cumulative effect of the OITS, OITB and oxygen inductive effects might account for the efficient reduction of the alkene (58) when treated with lithium and ethanol in ammonia.

The magnitude of the enhanced reduction rate for the alkene (57) might be explained entirely by the oxygen inductive effect, however, OITS and OITB effects may also assist, but apparently to a lesser degree than for (58). Stabilisation involving non classical anion radical intermediates may also be considered in the reductions of (57) and (58).

The enol ethers (55) and (56) have the interacting π-bond and oxygen non-bonding orbitals separated by one σ-bond. If the same OITS and OITB effects are operative in this situation, they might be expected to oppose each other, and the net result would depend on

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* The rate differences were estimated by comparison of the relevant experimental data.

the relative magnitude of each effect. The combined OITS, OITB and oxygen inductive effects would then determine the reducibility of (55) and (56) such that these compounds are reduced more slowly than (57) and (58).

In support of the above contention concerning orbital interactions, a transannular orbital interaction has been implicated in the lithium and ammonia reduction of some substituted bicyclic enediones;[103] for example the Wieland-Miescher ketone (72).[102,103] Compounds of this type were compared with their respective derivatives (alcohols or acetals) in which the isolated carbonyl function was masked. Although the $\pi \rightarrow \pi^*$ absorption spectrum of the enone chromophores proved to be relatively insensitive to this change, the half-wave reduction potentials were over 0.1V more positive when the carbonyl function was present.[103] This suggests that the neighbouring carbonyl group facilitates addition of an electron to the π-orbital system of the enone.

Further support for this argument based on orbital interactions, comes from the Birch reduction of diene (67). Butler[84] has reported that (67) is reduced very slowly, but no rate data were presented to quantify this measurement. However, it appears that this compound shows a 45-50 fold reduction rate enhancement compared to the reduction rate of norbornene.* Diene (66) may show a similar trend,[84] but insufficient data is available to draw any conclusions for this compound.

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* Alkene (67) was reduced by 47% after 4h with sodium-*tert*-butyl alcohol-ammonia.[84] This represents a rate enhancement of *ca.* 5 fold compared with the alkene (69) (*vide supra*). No yields are reported for alkene (66).[84]

An example has been reported that implicitly involves the reduction of an alkyl substituted non terminal alkene intermediate. Thus, methylenecyclohexene gave methylcyclohexane in 80% yield when reduced with lithium and methanol in ammonia.[78] No explanation has been offered to account for the fully saturated product, and its presence seems to contradict the reactivity patterns observed for alkyl substituted alkenes. Apparently, this product is formed for reasons we do not understand.

In summary then, many factors which are known to influence the reducibility of an isolated double bond towards the Birch conditions have been discussed. Some unusual substituent effects found in the reduction of some benzene derivatives have been noted.

The alkenes (55), (56), (57) and (58) were reduced to the extent of 18, 12, 26-36 and 67-95 percent respectively on treatment with lithium and ethanol in ammonia for a period of 1h; a major product was the tetrahydrofuran (59) which was accompanied by some ring cleavage derived products.

The enhanced reactivity of the alkenes has been explained in terms of OITS, OITB, inductive and mesomeric effects; molecular strain effects have been discounted as a contributing factor. No account has been taken of the metal cation in this discussion.

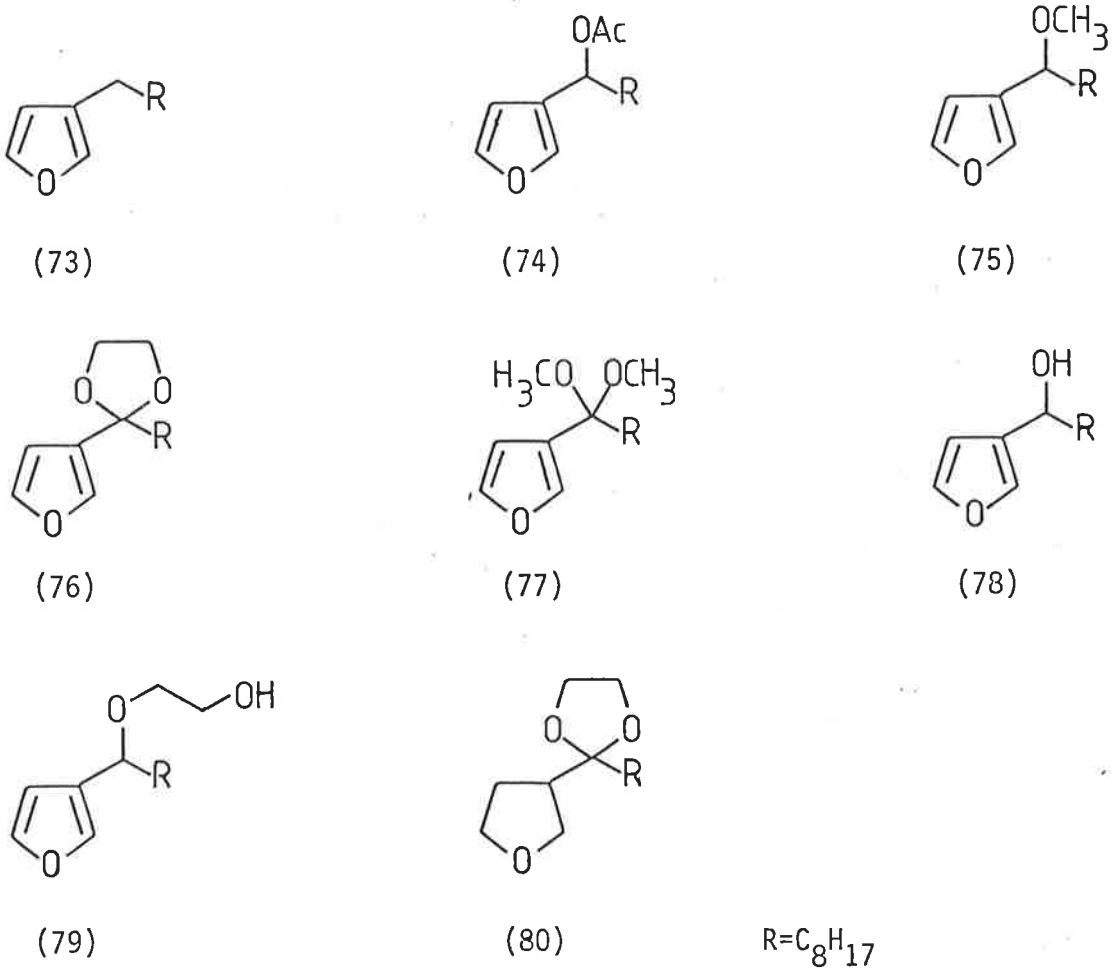
1.2 3-SUBSTITUTED FURANS

Treatment of 3-nonylfuran (73) with lithium and ethanol in ammonia for 1h afforded only recovered starting material. That (73) was inert to the standard reduction conditions employed could be a chemical consequence of the oxygen non-bonding electrons being involved in the aromatic stabilisation; the resultant higher electron density of the furan π-system, compared to that of benzene, inhibiting electron addition such that no reduction can occur.

When the acetate (74) was treated with lithium in ammonia for 15 min, the products were the alkylfuran (73) (75%) and the alcohol (78) (25%). Reduction of the acetate group occurs competitively with hydrogenolysis to afford the alcohol (78).

Reduction of the ether (75) with lithium and ammonia for 15 min gave a mixture of the alkylfuran (73) (12%) and recovered starting material (88%).

The acetal (76), when submitted to a reduction with lithium in ammonia for 15 min, afforded the alkylfuran (73) (23%) and the derived alcohol (79) (58%) accompanied by recovered starting material (19%). Thus, hydrogenolysis of the first acetal oxygen is faster than hydrogenolysis of the methoxyl group in the ether (75), and also faster than hydrogenolysis of the second acetal oxygen (to give (73)), giving rise to an increase in the relative proportion of the alcohol (79) during the course of the reaction. Fission of the second acetal oxygen of (76), and of the methoxyl group in (75) appear to occur at similar rates because the proportion of alkylfuran formed



(73) (74) (75)

(76) (77) (78)

(79) (80)

Figure 1:3

from both reactions is about the same, after allowing for the reaction period difference. This result indicates that the lithium alkoxide has little influence upon the rate of removal of the second acetal oxygen.

Interestingly, the reduction of 2-methyl-2-phenyl-1,3-dioxolane with only 2 equivalents of sodium and methanol in ammonia gave ethylbenzene (39%) together with starting material, but none of the mono fission product alcohol.[28] In other words, if a two-stage mechanism is in fact involved in removal of the acetal oxygens, then the second stage must be easier in this case.

Reduction of the acetal (76) with lithium and ethanol in ammonia for 1h resulted in extensive reduction and cleavage of the furan ring. The fourteen products observed from this reaction were: 3-ethoxy-2-ethylundecanal (109) (1.8%), 3-nonylfuran (73) (14%), the 2,3-dihydrofuran (55) (4.3%), 2-ethylundecanal (107) (7.8%), the 4,5-dihydrofuran (56) (1.2%), the tetrahydrofuran (59) (13%), one isomer of the alkylidenetetrahydrofuran (58) (0.8%), the other isomer of (58) (0.8%), the 2,5-dihydrofuran (57) (6.4%), 2-ethylundecanol(108) (36%), 3-methyldodecanol(92) (2.1%), recovered starting material (3.9%), the alcohol (79) (7%) and the tetrahydrofuran acetal (80) (7.4%).

Except for the aldehyde (109), all the products were identified by a comparison of their mass spectral and gas chromatographic characteristics with those of authentic samples prepared by independent synthetic routes.

The structure of (109) was determined by an interpretation of the mass spectral fragmentation pattern of this compound. No molecular ion was present, but the base peak of the spectrum, observed at m/e 72, could arise from loss of butanal from the molecular ion via a McLafferty rearrangement.* The other daughter ion derived from this rearrangement, having m/e 170, was not observed. However, ions at m/e 155 and m/e 85 could arise by loss of methyl and hexyl radicals respectively from the m/e 170 ion (Fig 1.4), and represent standard ether and allylic cleavages, also respectively.

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* The unusual m/e 72 ion, representing loss of butanal, is found as the base peak in the mass spectrum of the aldehyde (107), and suggests a structural similarity - that both molecules posses a 2-substituted butanal moiety.

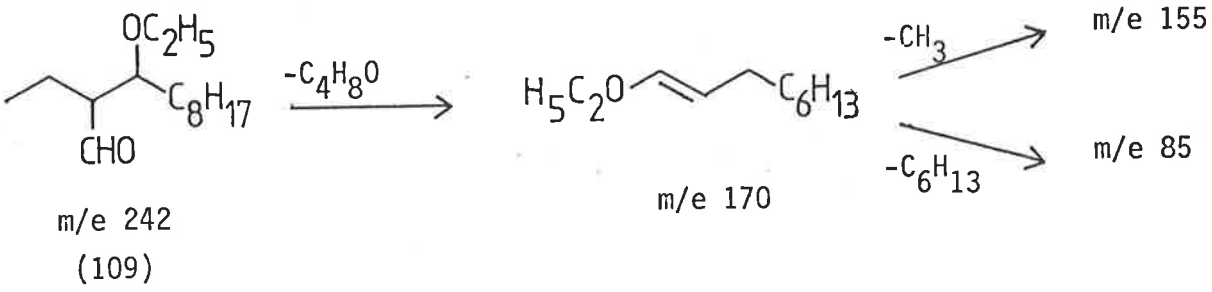


Figure 1.4

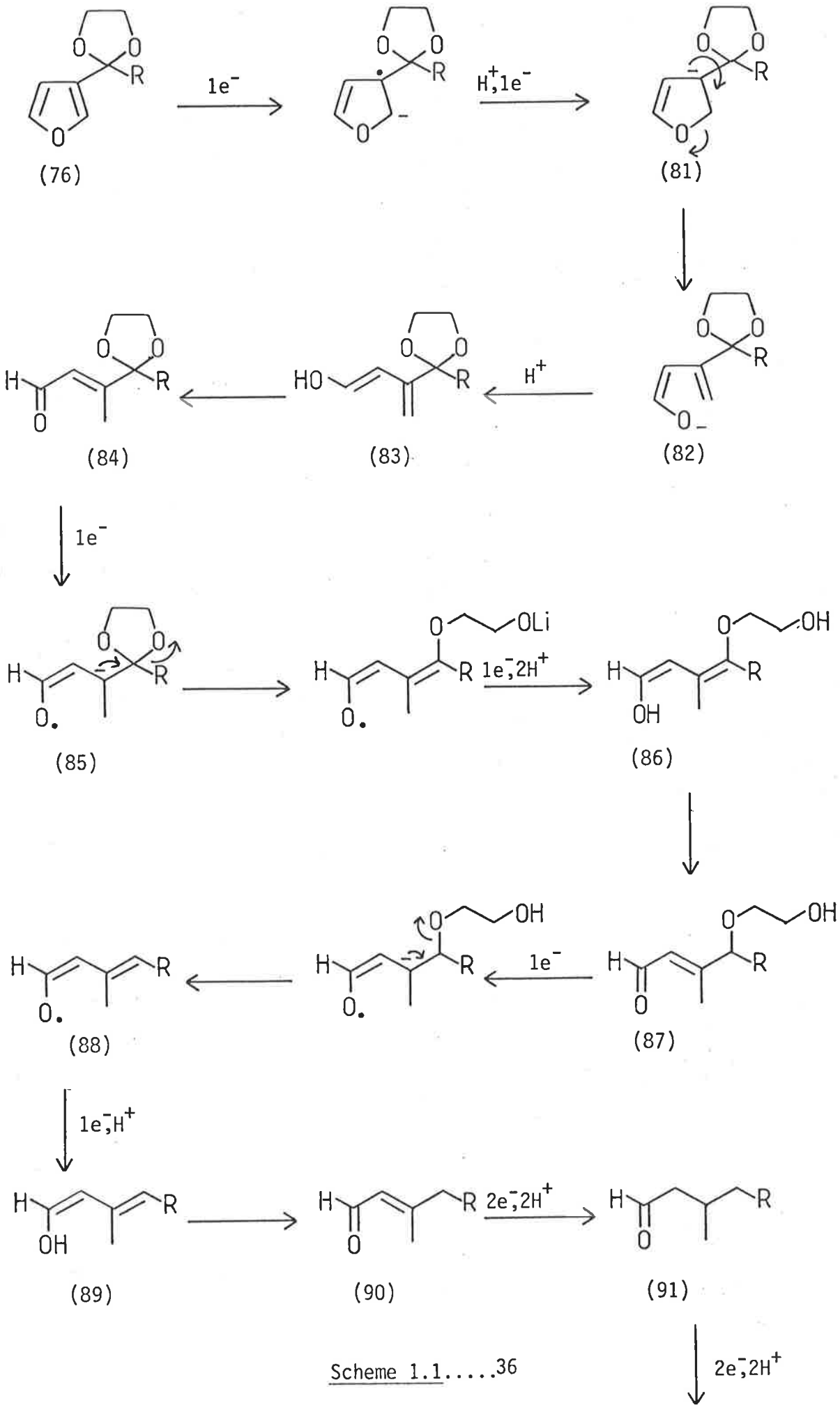
In the reduction of the acetal (76), six reduction pathways can be postulated to rationalize formation of observed products. The first involves stepwise benzylic type fission of the acetal oxygens to give the alkylfuran (73) and the alcohol (79). A second pathway, reduction of the furan ring in the absence of any hydrogenolytic processes, would afford the tetrahydrofuran acetal (80).

A third pathway, denoted path a, is shown in Scheme 1.1. Electron addition to the acetal (76) would produce a radical anion in which it is expected that the greatest electron density would reside on the carbon bearing the electron withdrawing oxygen substituent. Protonation at the furan carbon 2 followed by electron addition would form the anion (81). A ring cleavage process of the type proposed in the reduction mechanism of 3-furoic acid (*vide supra*) would afford the enolate anion (82). Protonation of (82), rearrangement of the enol (83) to the α,β-unsaturated aldehyde (84) and electron addition could afford the anion radical (85). Elimination of one of the acetal oxygens from the γ-carbon,

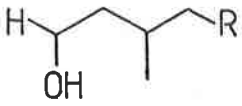
electron addition, protonation, and rearrangement of the enol (86) thus formed, would give the aldehyde (87) (leaving groups at the γ-carbon of an α,β-unsaturated carbonyl system are known to undergo reductive elimination[14]). Another reductive elimination to give (88), electron addition, protonation, and rearrangement of the derived enol (89) would give the α,β-unsaturated aldehyde (90). Further reduction could first yield the aldehyde (91), and then the observed alcohol (92).

A fourth reduction pathway, denoted path b, is shown in Scheme 1.2. If the anion (81) were to suffer elimination of one acetal oxygen, as an alternative to the ring cleavage process of path a, the diene (93) would be formed after protonation at oxygen. Dienes are known to be reduced rapidly under the Birch conditions[13]. Electron addition to (93) would give an anion radical, of which two resonance contributors, namely (94a) and (94b), are shown. Only these resonance forms are shown because the highest electron density is expected to be found at a carbon bearing an oxygen substituent. Protonation at the anionic centre of (94a) followed by electron addition would give (95), which could eliminate the second acetal oxygen to afford (97). The diene (97) would not be isolated, but rapidly reduced under the conditions employed to yield the alkenes (55), (57) and (58). Alternatively, the anion radical (94b) could suffer protonation, followed by an electron addition to give anion (98), and subsequently (99) after a further proton addition step. Hydrogenolysis of the allylic ether (99) could produce the alkenes (57) and (58).

The alkenes (55), (57) and (58) have been shown to yield the tetrahydrofuran (59) when submitted to the reduction conditions employed (*vida supra*).



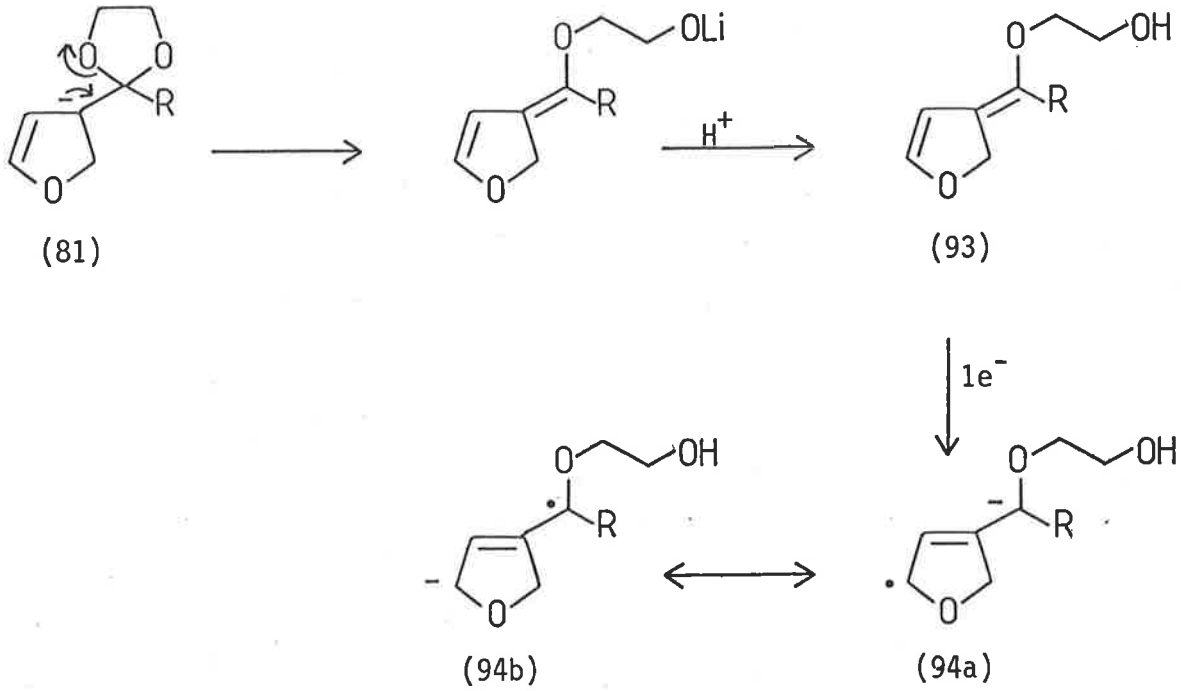
Scheme 1.1.....36



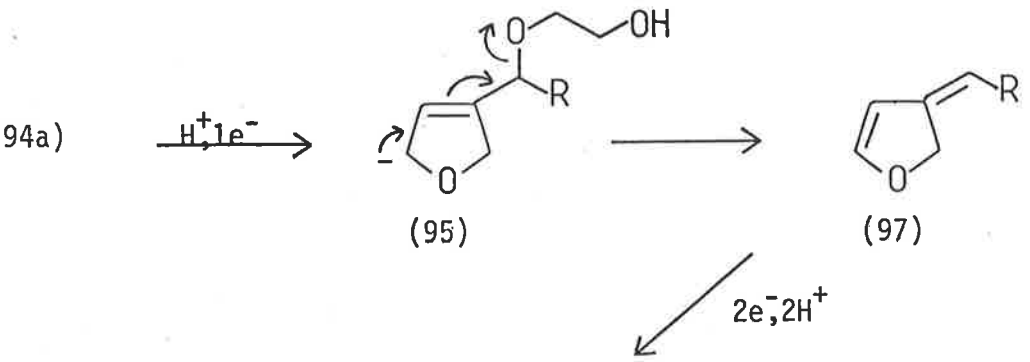
(92)

Path a, $R=C_8H_{17}$

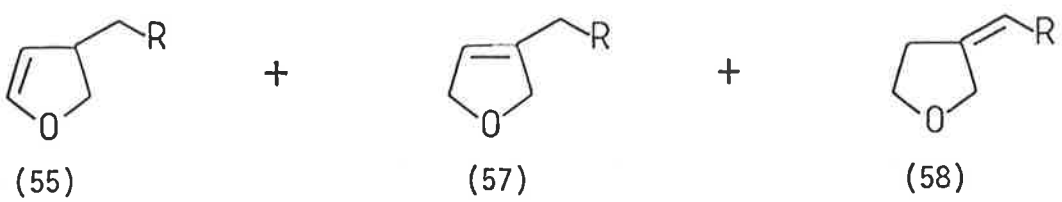
Scheme 1.1



(81) (93) (94b) (94a)

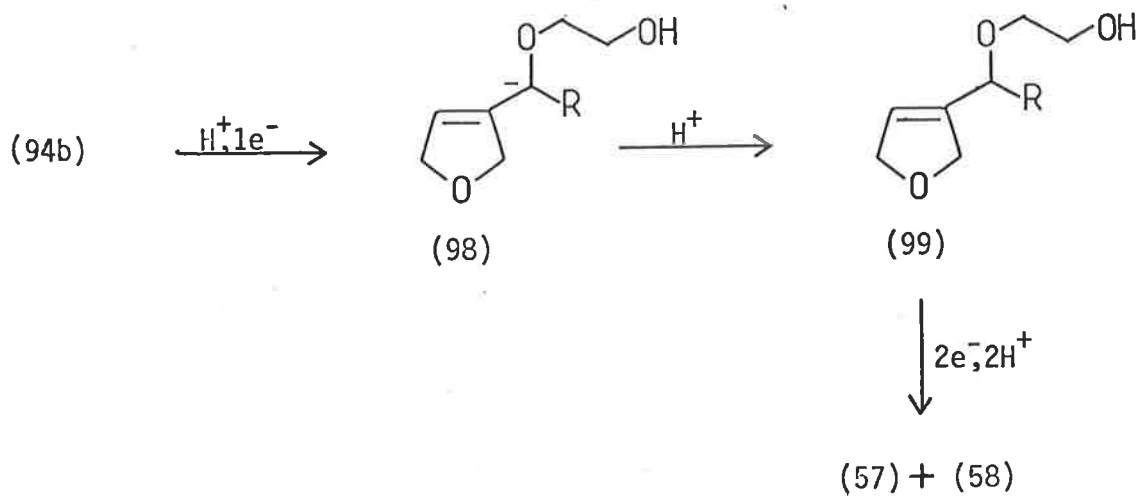


(94a) (95) (97)



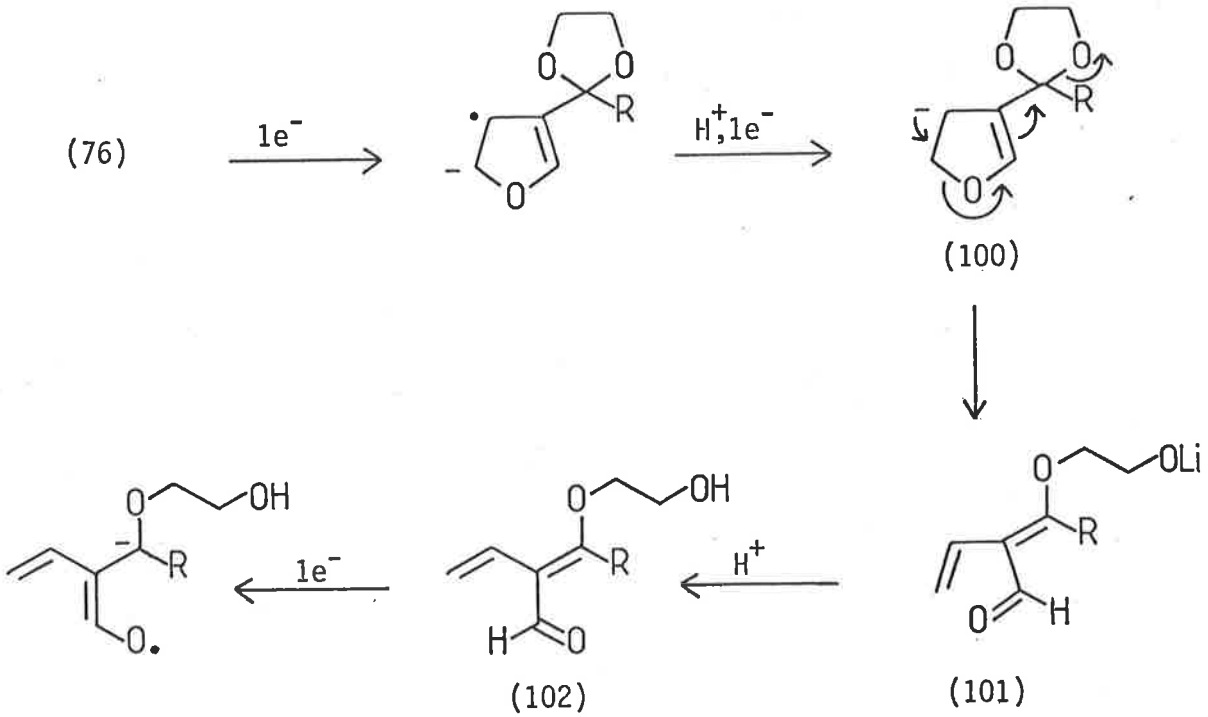
(55) (57) (58)

Scheme 1.2.....37

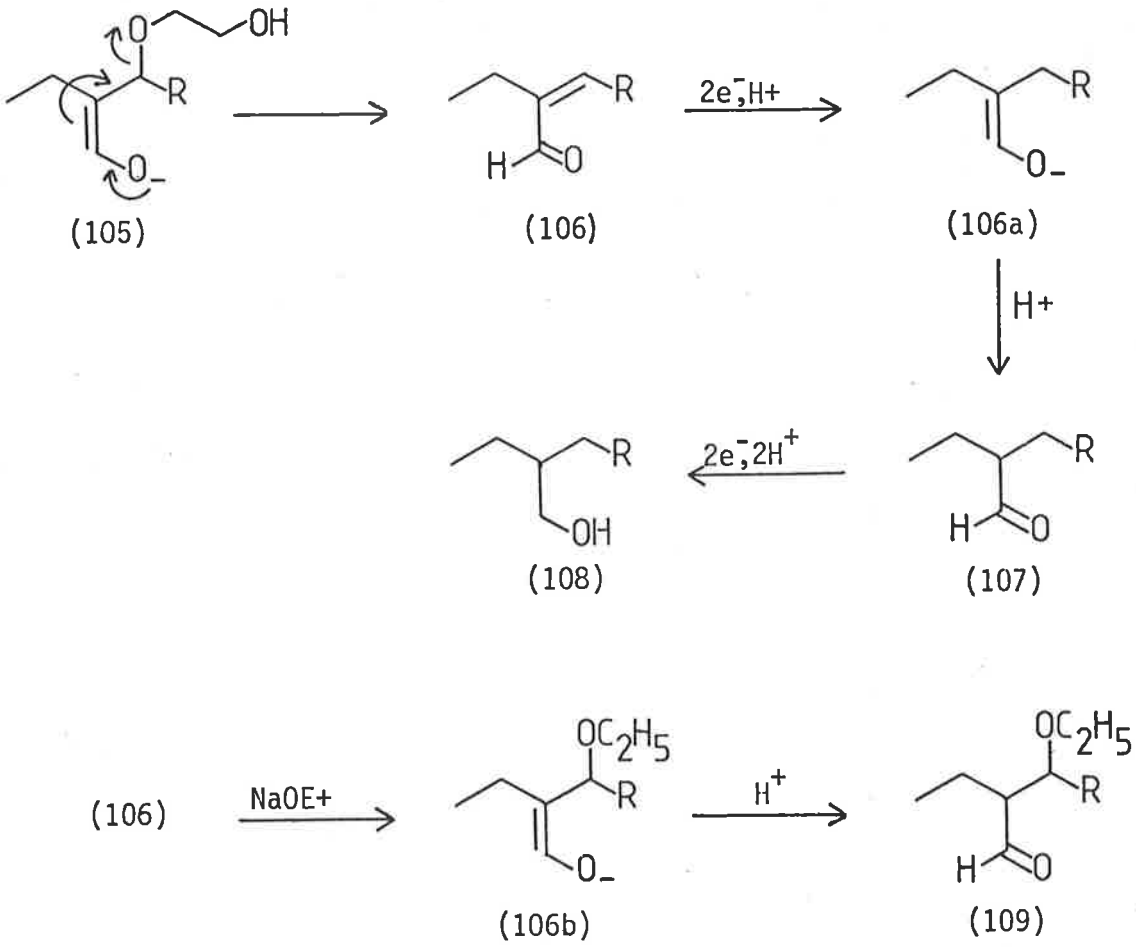


Path b., $R=C_8H_{17}$

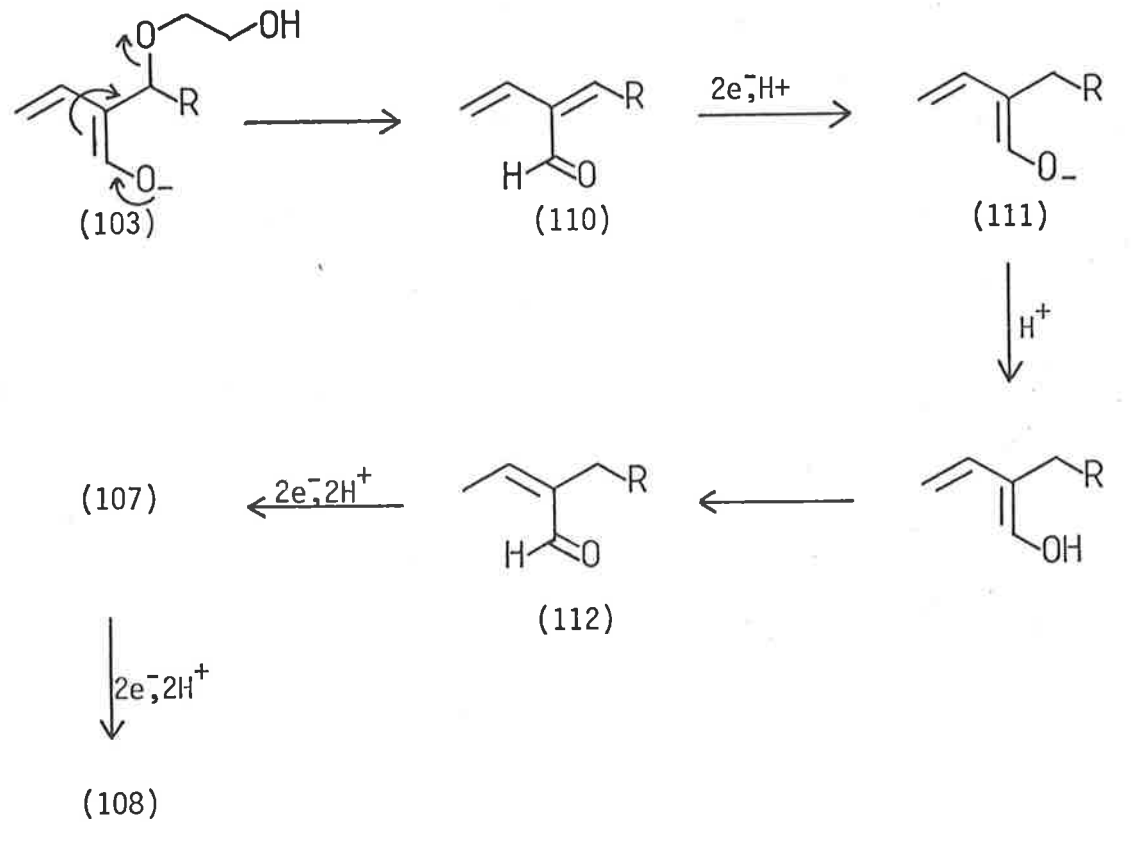
Scheme 1.2



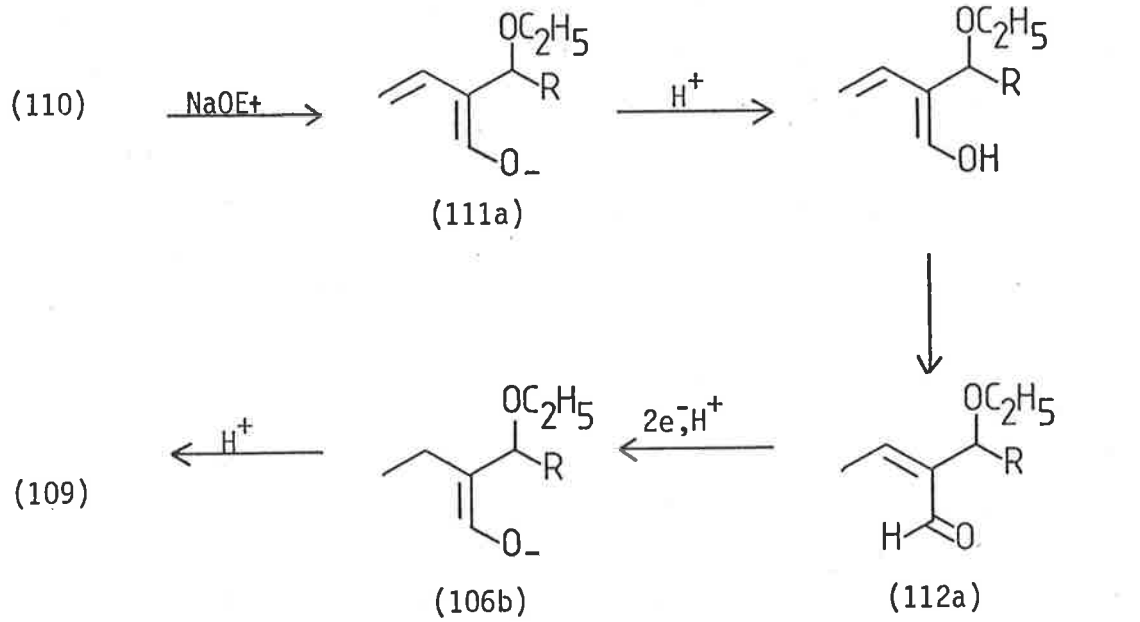
Scheme 1.3.....38



Path C1, $R=C_8H_{17}$

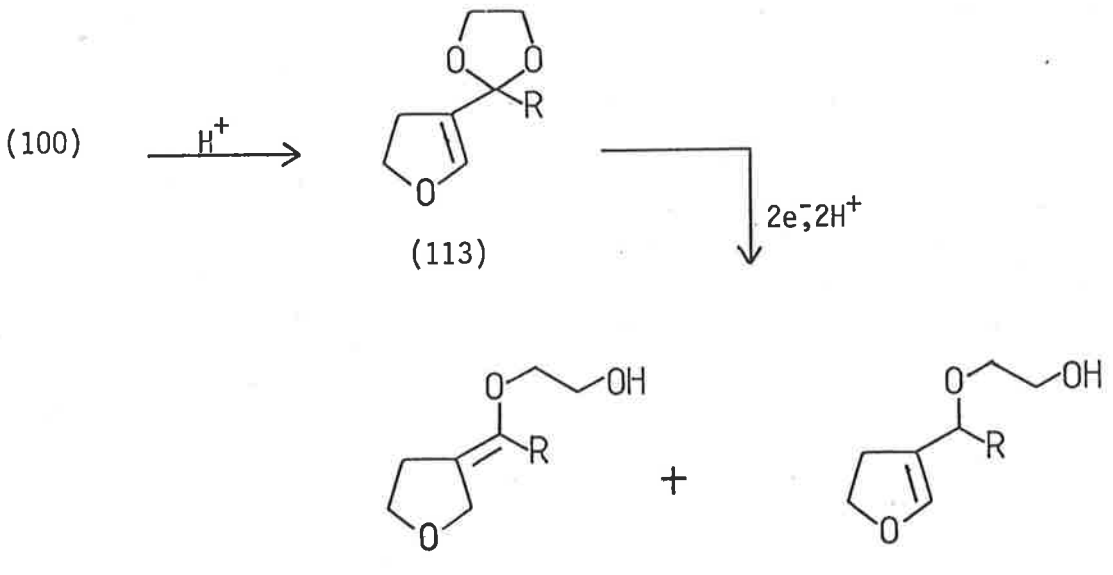


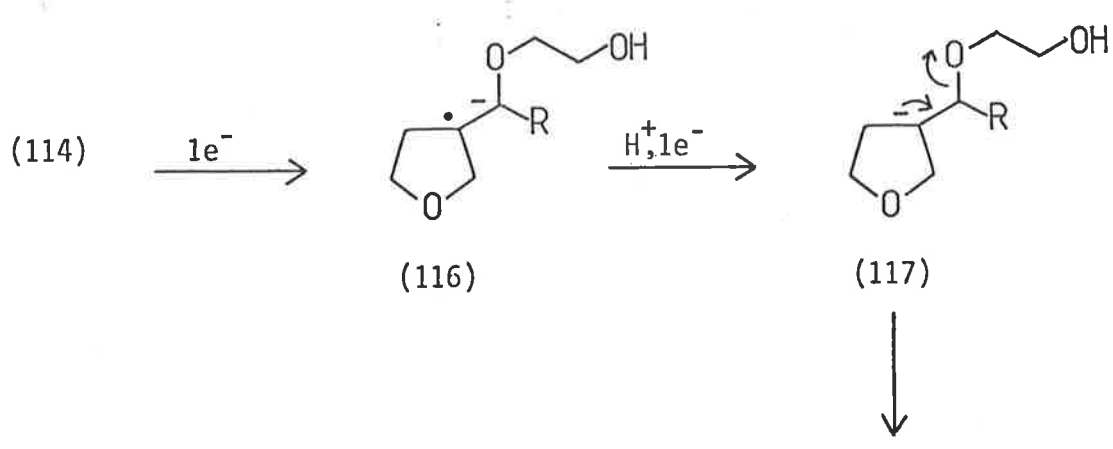
Scheme 1.3..... 39



Path C2, $R=C_8H_{17}$

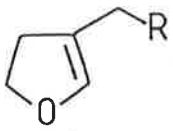
Scheme 1.3





Scheme 1.4.....40

(58)

(115) $\xrightarrow{2e^-,2H^+}$  + (58)

(56)

Path d, R=C_8H_{17} Scheme 1.4

A fifth reduction pathway, denoted path C1, is depicted in Scheme 1.3. Formation of a radical anion by an electron addition to the acetal (76), followed by protonation at the furan carbon 5 (instead of initial protonation at the furan carbon 2 described in a and b), and a further electron addition would yield the anion (100). The familiar ring cleavage process could take place with concomitant or stepwise elimination of one of the acetal oxygens to yield (101), and (102) after protonation of the lithium alkoxide. Reduction of the α,β-unsaturated aldehyde (102), by accepted pathways[14], could give the enolate anion intermediate (103), which, after protonation and rearrangement to (104) could suffer a further reduction to the enolate anion (105). Elimination of the second acetal oxygen from (105) would afford the aldehyde (106). Another reduction step would yield the observed aldehyde (107), which could be converted to the major product (36% yield) of the reaction, the alcohol (108). Conjugate addition[21] of sodium ethoxide to the α,β-unsaturated aldehyde (106) intermediate would produce the observed aldehyde (109).

Alternatively (path C2, scheme 1.3), the enolate anion (103) could suffer elimination of the second acetal oxygen to afford the dienal (110). Reduction to the anion (111), protonation at oxygen

and rearrangement could yield the α,β-unsaturated aldehyde (112). Further reduction could afford the observed products, (107) and (108). Conjugate addition[21] of sodium ethoxide to (110) would form the enolate anion (111a) which, after protonation and rearrangement to the aldehyde (112a) could be reduced to the observed aldehyde (109). There is no evidence to decide if either or both of the alternative routes from (103) to (108) and (109) (paths C1 and C2, Scheme 1.3) are operative in this reaction.

That the aldehydes (107) and (109) can be identified amongst the products seems surprising, and suggests that protonation of their respective inert[28] lithium enolate anions, (106a) and (106b), is relatively slow, or that (107) and (109) are not reduced as fast as it would be anticipated, or that both of these processes are slow. The former possibility seems more likely because it is known that some enol salts are stable enough in ammonia to protect the carbonyl group even when the reduction demands the presence of an alcohol.[28]

The sixth reduction pathway, denoted path d, is shown in Scheme 1.4. If the anion (100) were to undergo protonation instead of the ring cleavage process, then the dihydrofuran (113) would be formed. Hydrogenolytic cleavage of one acetal oxygen might form (114) or (115). Electron addition to (114) could produce the radical anion (116), in which the highest electron density is expected to be found on the carbon bearing oxygen. Sequential protonation and electron addition to (116) could give the anion (117). Implicitly, an anion generated at a tetrahydrofuran carbon 3 has been found to cause elimination (ring cleavage) of the oxygen at carbon 2 relatively slowly (see Section 1.1). Accordingly, preferential

elimination of the second acetal oxygen would give the alkene (58). Hydrogenolysis of the second acetal oxygen in the allylic ether (115) could yield the alkenes (56) and (58).

Since the alkenes (113), (114) and (115) are not observed in the reduction products, and because (56) is only formed in a very low proportion (1% yield), it would seem that path d represents only a minor reduction pathway. However, no information is available concerning the reaction rates and products formed upon reduction of compounds such as (114) and (115), which possess both an enol ether and an allylic ether oxygen function. Path a also seems to be a minor reduction pathway because only a 2% yield of the alcohol (92) is obtained, and none of the proposed intermediates have been observed.

Thus, many of the products occur as intermediates, or end products of the proposed reduction pathways b (Scheme 1.2) and c (Scheme 1.3). An examination of the product proportions, and their proposed reduction pathway genesis, indicates that about 28% of the products are derived from initial protonation at the acetal furan carbon 2, and that about 45% of the products are derived from initial protonation at the acetal furan carbon 5. A further 20% of the products arise from a benzylic type cleavage process, and the remaining products from saturation of the furan ring and recovery of the acetal (76).

Many individual steps of the multistep reduction pathways must occur very rapidly because many of the proposed intermediates are not observed amongst the reaction products. Some of these steps may be reversible.

Reduction of the acetal (76) with lithium and ethanol in ammonia for 12 min gave results which were similar to those obtained for the 1h reduction. Ten products were observed from this reduction: 3-ethoxy-2-ethylundecanal (109) (3.2%), 3-nonylfuran (73) (4.5%), 2-ethylundecanal (107) (13%), the tetrahydrofuran (59) (2.9%), one isomer of the alkylidenetetrahydrofuran (58) (4%), the other isomer of (58) (2.1%), the 2,5-dihydrofuran (57) (8.7%), 2-ethylundecanol (108) (3.9%), recovered starting material (40%) and the tetrahydrofuran acetal (80) (6.1%).

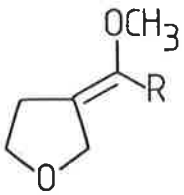
The relatively high proportion of the alkenes (57) and (58) suggests that these are intermediates in the formation of the tetrahydrofuran (59), and the high proportion of the aldehyde (107) suggests that it is an intermediate in formation of the alcohol (108). These observations again suggest that the proposed reduction pathways b and c are the major reduction pathways.

The reduction of the dimethoxyacetal (77) shows similarities, but also differences, when compared to the reduction of the ethylenedioxy acetal (76). When (77) was treated with lithium and ethanol in ammonia for 30 min, the observed products were: the tetrahydrofuran (59) (1.2%), one geometric isomer of the alkylidenetetrahydrofuran (58) (1.1%), the other isomer of (58) (0.9%), the 2,5-dihydrofuran (57) (1.7%), recovered starting material (77%), an unidentified component (2.7%), another unidentified component (10%), and another unidentified component (5.3%).

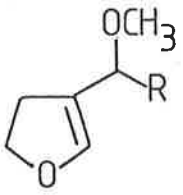
The highest mass ion in the mass spectrum of the first unidentified component was observed at m/e 222 (11% relative abundance). This ion mass does not correspond to the molecular formula of any

expected products, and the component is therefore considered to be an impurity.

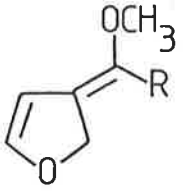
Evidence from the mass spectra of the last two unidentified components suggests that they are geometric isomers of the alkene (118). The base peak, a major feature and highest mass ion in the



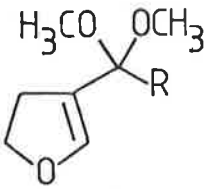
(118)



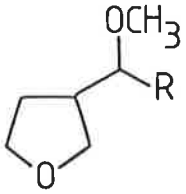
(119)



(120)



(121)



(122)

$R=C_8H_{17}$

Figure 1.4

mass spectrum of both components, was observed at m/e 113.

The mass spectra of the alkenes (55) and (57) showed their base peaks at m/e 69, which apparently arise from loss of C_9H_{19} from the molecular ion. On the other hand, the base peak in the mass spectra of the alkenes (56) and (58) was observed at m/e 83, and apparently arises from loss of C_8H_{17} from the molecular ion. If it is assumed that these fragmentations observed for the dihydrofurans (55), (56) and (57), and for the alkylidenetetrahydrofuran (58) are a characteristic of these structural units, then the m/e

113 ion found for the unidentified components could be explained by the loss of C_8H_{17} from the molecular ion of (118) or (119). Since the mass spectra were almost identical, the isomers of (118) appear to be the most likely.

The dihydrofuran (57), the alkene (58), and the tetrahydrofuran (59) could be derived from (77) by mechanisms directly analogous to those outlined in Schemes 1.2 and 1.4, in which these products are derived from (76).

Diene (120) (analogous to diene (93), Scheme 1.2, and derived similarly) could be reduced, with retention of the exocyclic double bond and methoxyl group, to give the alkenes (118). Alkene (121) (analogous to the alkene (113), Scheme 1.4, and derived similarly) could undergo hydrogenolysis to afford (118) or (119) (analogous to (114) and (115) respectively, Scheme 1.4).

The reduction of (120) and (121) to (118) and (119) would suggest that hydrogenolysis of the methoxyl group of the acetal (77) is less efficient than hydrogenolysis of the 2-alkoxyethanol group in (93), (114) and (115). That a lithium cation could coordinate more strongly to a 2-alkoxyethanol moiety, by chelation to the two oxygens, than to a methoxyl substituent might explain such an observation. That is, the lithium cation might act as a more effective Lewis acid catalyst with the 2-alkoxyethanol group.

A high proportion of the alkenes (118), and an absence of the saturated derivative (122) amongst the reduction products of (77), would suggest that (118) is reduced considerably more slowly than the alkenes (58); the reasons why these reduction rates would be different are unclear.

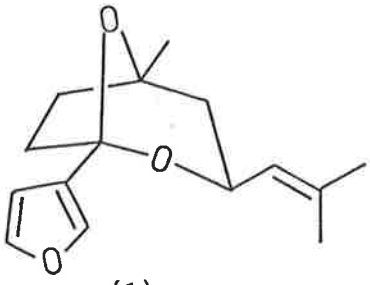
Interestingly, none of the hydrogenolysis products, (73) or (75), were observed in the reaction products. Further speculation, however, seems unwarranted until all the products have been fully characterised.

That the acetal (76) was nearly all consumed after a 1h reduction (3% starting material), but that 70% of the acetal (77) remained after 30 min, was surprising. However, when a mixture of the acetals (76) and (77) (1:1.8 ratio respectively) was treated with lithium and ethanol in ammonia for 30 min, they were consumed by 97% and 79% respectively.

All the acetals studied in our laboratories to date, eremoacetal (1),[1(a),1(b)] dihydroeremoacetal (123),[1(b)] (76) and (77) are all efficiently reduced under the metal-alcohol-ammonia conditions employed. The products contain only small amounts of furan compounds, but much ring reduction and cleavage products.

In contrast, reduction of the acetals (76), (123)[1(b)], (124)[1(b),106], (125)[1(b)] and (126)[106] with lithium and ammonia (no ethanol) gave only hydrogenolytic products in which no reduction of the furan ring had occurred. Also, the rate at which the benzylic type oxygen substituent is cleaved from the molecule is substrate dependent.

As previously detailed, the acetal (76) afforded the alkylfuran (73) (23%), the mono fission product (79) (58%) and starting material (19%) after a 15 min reduction period. Under the same conditions for 15 min, dihydroeremoacetal (123) returned more than 99% of the starting material, but after 7h, 30% of the starting material was recovered in addition to the oxepanes (127) (20%) and



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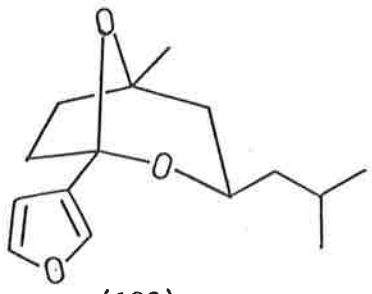

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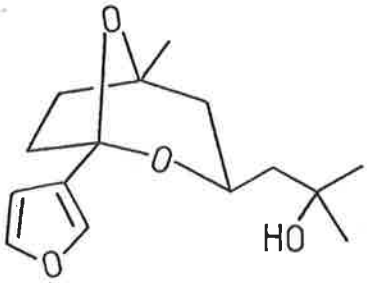

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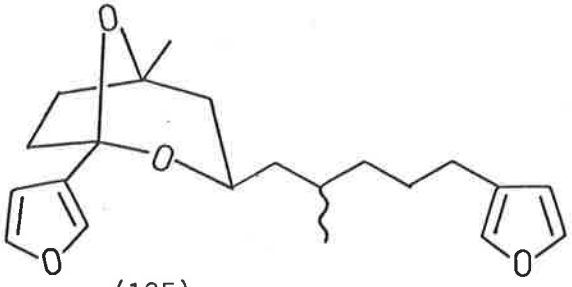

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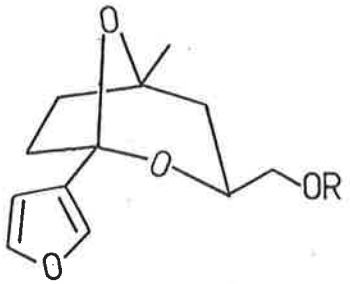
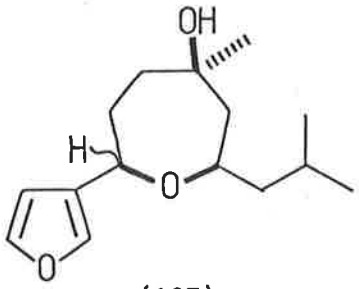


(126a:R=H)

(126b:R=CH_2OCH_3)



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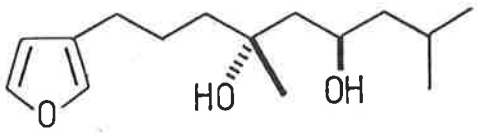

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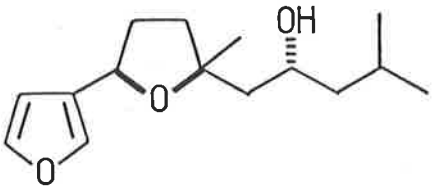

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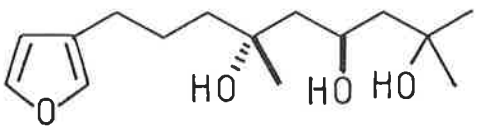

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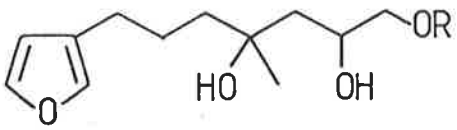
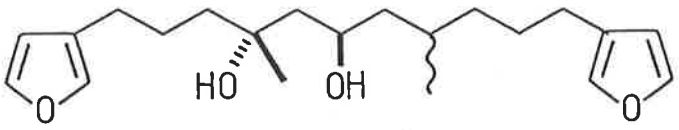


(131a:R=H)

(131b:R=CH_2OCH_3)

Figure 1.5..... 48



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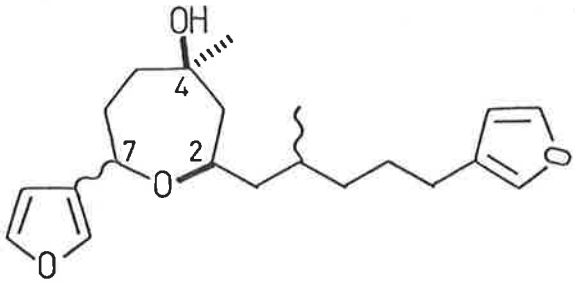


(133)

Figure 1.5

the diol (128) (40%).[1(b)] None of the tetrahydrofuran isomers (129) were detected in the reduction products.[1(b)] The hydroxyacetal (124) was treated with lithium and ammonia for 4h to give the triol (130) (60%) and starting material (20%);[1(b)] the acetal (125) gave the diols (132) (22%), a mixture of the separable C7 epimers of the oxepane (133) (35%) and starting material (30%) after a 9h reduction period.[1(b)] The acetal (126a) gave (131a) (50%) and starting material (50%), and its derivative (126b) gave (131b) (90%) and starting material (10%) after reduction with lithium and ammonia for 5.5h.

The reasons for the differences in the hydrogenolysis rates between the bicyclic acetals (123), (124), (125) and (126) and the acetals (76) (monocyclic) and (77) (acyclic) are not clear. The rates may reflect differences in the strain energy of these compounds,

or differences in orbital overlap of the developing anion (or raidcal) at the furan carbon 3 with the breaking carbon oxygen bond. An examination of Dreiding models did not provide any insight into orbital overlap and explain the results obtained.

Dimitriadis and Massy-Westropp[1(b)] have also reported that the oxepanes (127) are reduced much more slowly than the tetrahydrofuran (129). When a mixture (1:1) of (127) and (129) was reduced with lithium in ammonia for 1h, product analysis showed that only a trace of the tetrahydrofuran (129) remained, but that 90% of the oxepanes (127) were recovered in addition to the diol (128) (50%). It is difficult to rationalize the differences in the reduction rates of the various cyclic ethers and the acyclic methyl ether (75) (12% conversion to (73) after 15 min).

Possibly, the reduction rates of the ethers (127) and (129), and of the acetals (124) and (126), are affected by the situation of the hydroxyl substituent present in these molecules. Examples exist in the literature to show that the rate[95] and stereochemical course[108] of a reduction can be influenced by a neighbouring hydroxyl group. Further work is proceeding in this area.

Reduction of the ether (75) with lithium and ethanol in ammonia for 30 min resulted, as observed for the acetal (76), in extensive reduction and cleavage of the furan ring. The product mixture could be separated into eleven components: 3-ethoxy-2-ethylundecanal (109) (2%), 3-nonylfuran (73) (6%), the 2,3-dihydrofuran (55) (4%), 2-ethylundecanal (107) (18%), the tetrahydrofuran (59) (9%), one isomer of the alkylidenetetrahydrofuran (58) (6%), the other isomer of (58) (2%), the 2,5-dihydrofuran (57) (13%), recovered starting material (26%), 2-ethylundecanol (108) (12%), and 3-methyldodecanol (92) (2%).

Five reduction pathways, which are similar to those proposed for reduction of the acetal (76), can account for the products formed.

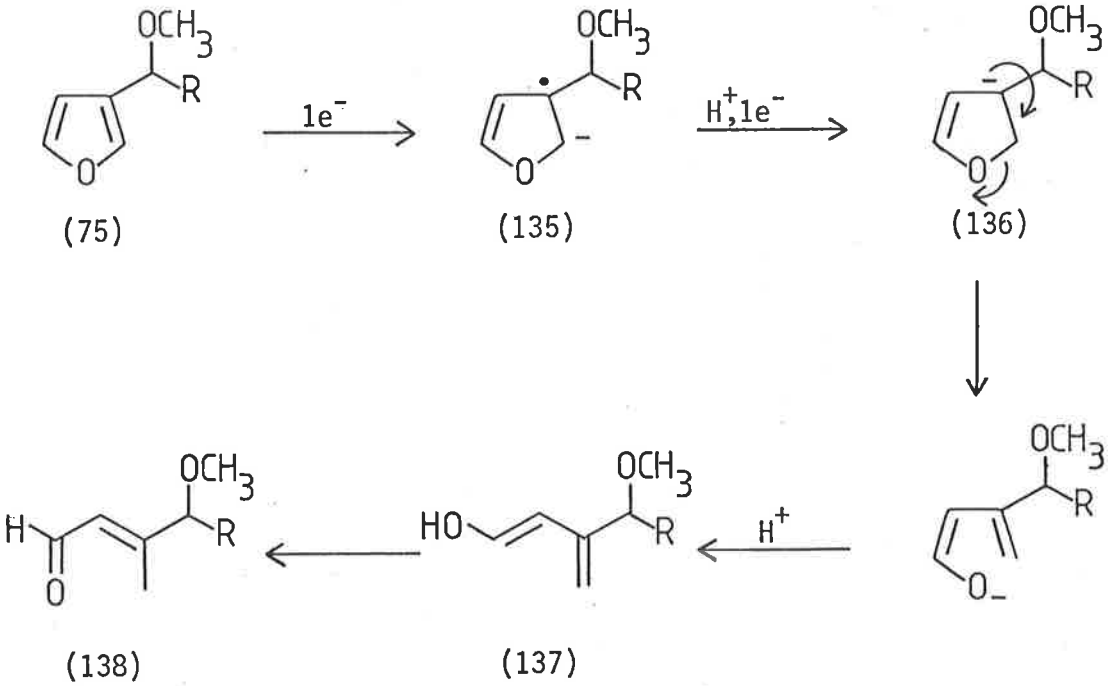
The alkylfuran (73) could be formed by hydrogenolysis of the benzylic type leaving group from the ether (75).

Path e (Scheme 1.5) involves addition of an electron to the ether (75) to give the anion radical (135) which leads to the anion (136) after protonation and electron addition. Ring cleavage of (136) followed by protonation and rearrangement of the enol (137) thus formed would yield the aldehyde (138). Alcohol (92) could be derived from the γ-alkoxy-α,β-unsaturated aldehyde (138) in the same way that (92) is considered to be derived from (87) in path a, Scheme 1.1.

Path f, Scheme 1.6, shows that the anion (136) could alternatively suffer elimination of the methoxyl group to give the diene (97), which has been proposed as an intermediate in the formation of the alkenes (55), (57) and (58) in reduction path b, Scheme 1.2.

Path g, Scheme 1.7, requires an electron addition to the ether (75) to give the radical anion (139). Sequential proton and electron addition to (139) could give the anion (140), which could undergo ring cleavage with simultaneous or stepwise elimination of the methoxyl function to afford the dienal (110). The aldehydes (107) and (109), and the alcohol (108) could be derived from (110) by the route proposed in path C2, Scheme 1.3.

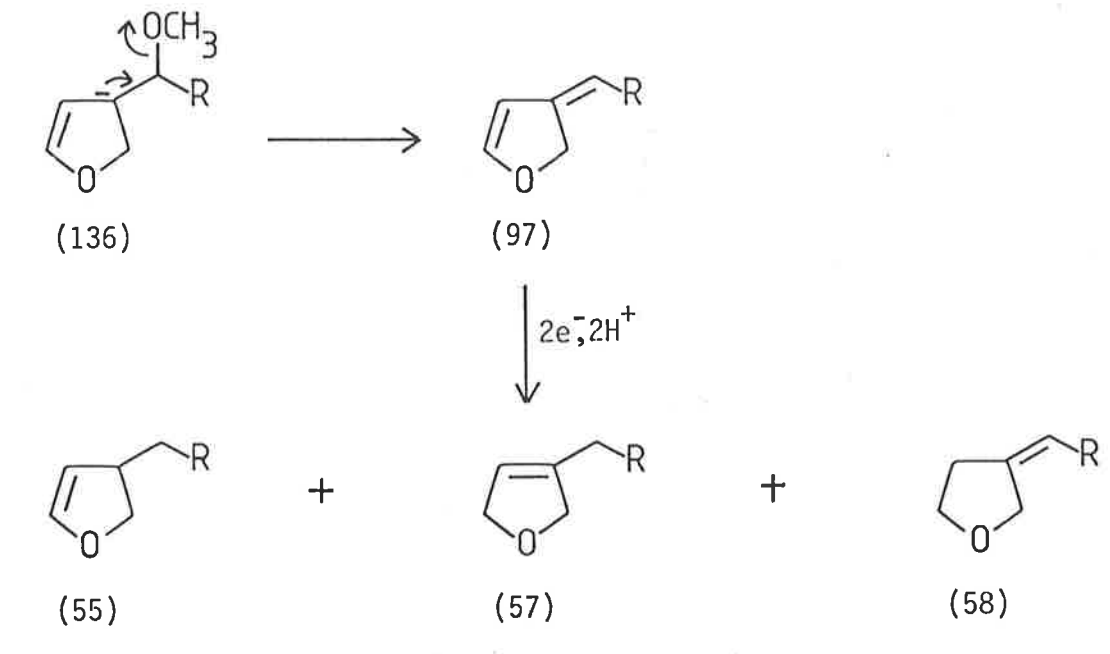
Alternatively, according to path h, Scheme 1.8, the anion (140) could undergo protonation to yield the alkene (119). This alkene, which is analogous to (115) (path d, Scheme 1.4) could suffer



(75) (135) (136) (137) (138) (92)

Path e, $R=C_8H_{17}$

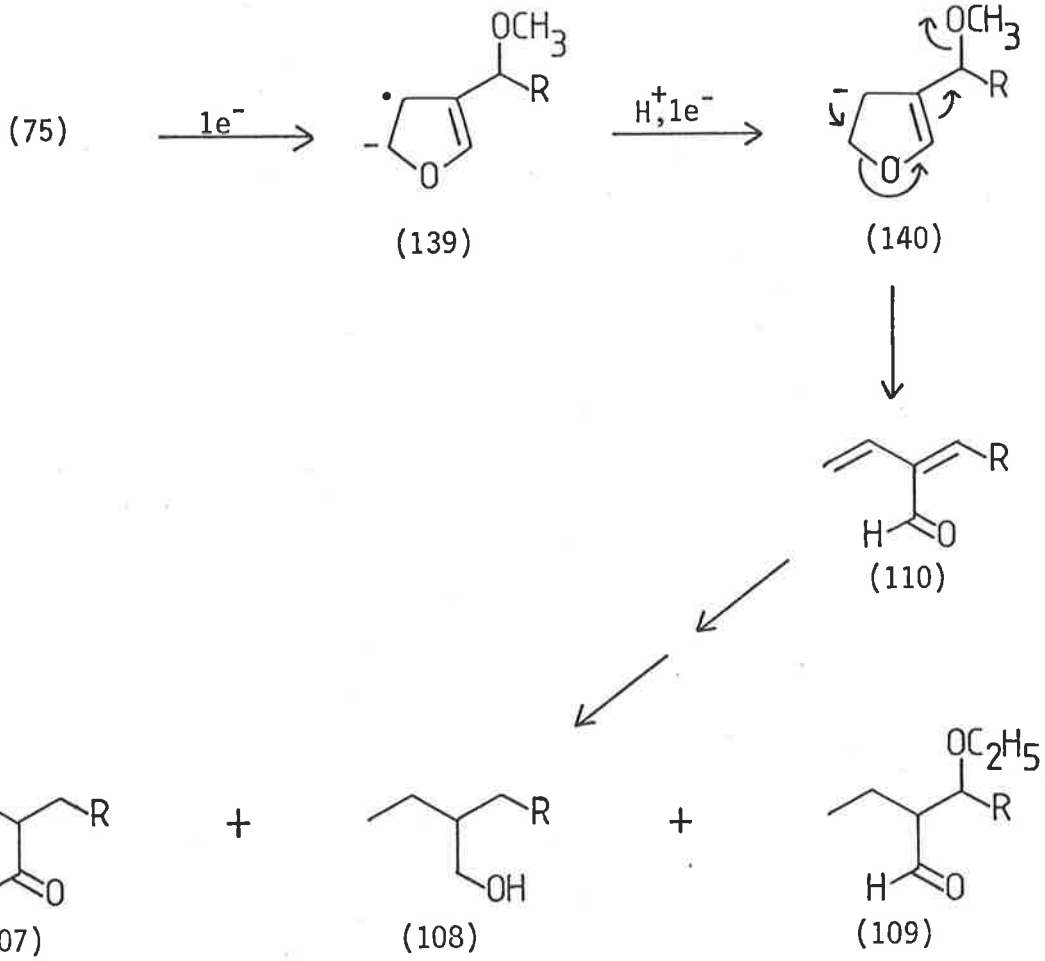
Scheme 1.5



(136) (97) (55) (57) (58)

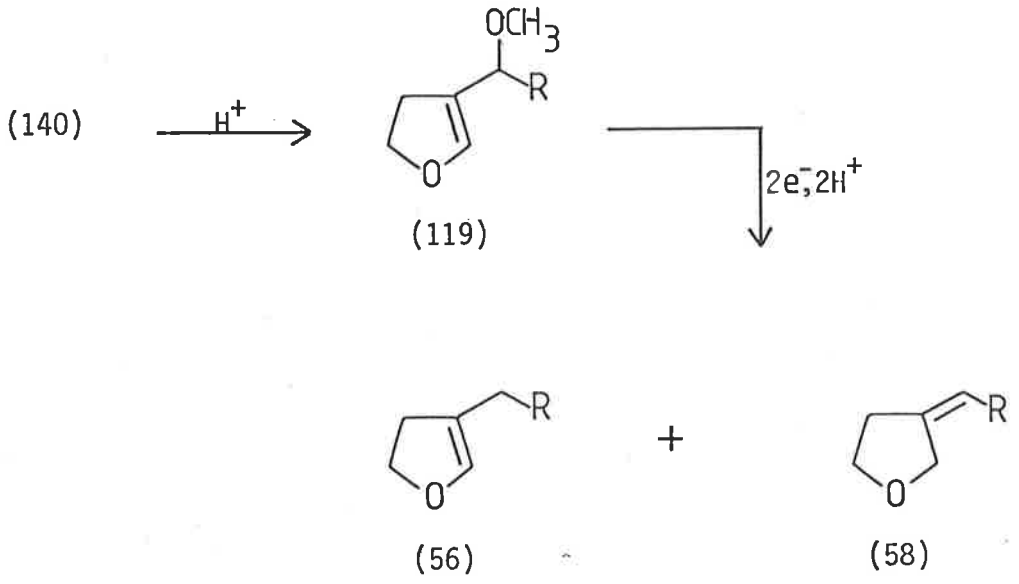
Path f, $R=C_8H_{17}$

Scheme 1.6



Path g, $R=C_8H_{17}$

Scheme 1.7



Path h, $R=C_8H_{17}$

Scheme 1.8

hydrogenolysis of the methoxyl group with formation of the alkenes (56) and (58). That (56) was not observed requires that (58) is the only product from this hydrogenolysis, or that path h is not followed by the reduction process. If it is assumed that path h is of only minor importance (the alkene (56) undergoes reduction relatively slowly), then about 36% of the products are derived from initial protonation at the furan carbon 2, and about 32% of the products are derived from initial protonation at the furan carbon 5. Benzylic type fission can account for a further 6% of the product; the 26% remaining product was recovered starting material.

The acetate (74) was reduced with lithium and ethanol in ammonia for 15 min. Unfortunately, the SCOT column equipped gas chromatograph was not available for our use when this reaction was performed, and unlike the other reductions, has not been repeated since the SCOT column facility became available.

Analysis of the acetate (74) reduction products using a gas chromatograph equipped with a conventional packed column resolved the mixture into five components which, in order of increasing retention time, were obtained in a ratio of 52:2:1:5:6. Retention time comparison with authentic samples, and an examination of the infrared and proton NMR spectra of the crude product, indicated that the first and major product was 3-nonylfuran (73), and that the final and penultimate major product eluted was the alcohol (78). Further retention time comparison with authentic samples indicated that the second peak eluted could be a mixture of the 2,3-dihydrofuran (55) and 2-ethylundecanal (107); that the third peak could be a mixture of 3-nonyltetrahydrofuran (59), 2-ethylundecanol (108) and 3-methyldodecanol (92); and that the fourth peak could be a mixture

of the 2-5-dihydrofuran (57) and 3-nonylidenetetrahydrofurans (58).

The results obtained from reductions of the acetals (76) and (77), and the ether (75), suggest that the second peak eluted was the aldehyde (107); that the third peak was mainly the alcohol (108); and that the fourth peak was a mixture of the alkenes (57) and (58).

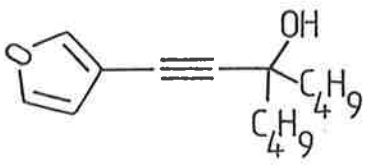
The reduction pathways for the acetate (74) are envisaged as being identical to those proposed for the reduction of the ether (75).

The benzylic cleavage process can account for 79% of the acetate reduction product; and a further 9% from competitive ester reduction to afford the alcohol (78). Ring cleavage, cycloalkene and tetrahydrofuran products combined form the remaining 12%.

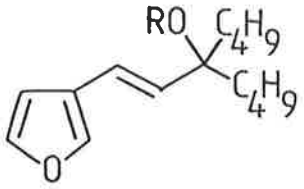
While the alcohol (78) has not been subjected to the standard reduction conditions employed in this study, it seems likely that it would undergo hydrogenolysis of the hydroxyl function only very slowly (*vide infra*). It is difficult to draw any conclusions for the alcohol (78) concerning other reduction pathways, but the above results suggest that they might be relatively slow.

The acetylene (142) has been shown to afford the trans alkene (143,R=H) after treatment with lithium and ammonia (no ethanol) for 4h.[107] Interestingly, when the alcohol (143,R=H) was subjected to the same conditions for 1h, hydrogenolysis of the hydroxyl substituent occurred to give the trisubstituted alkene (144) in which the double bond is not conjugated to the furan ring.

Apparently, (142) is reduced to the lithium alkoxide (143,R=Li), which is inert to the reaction conditions because the negative charge prevents addition of another electron, but which is liberated as the alcohol (143,R=H) upon work up.



(142)



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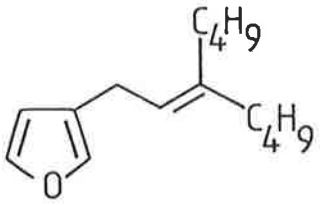
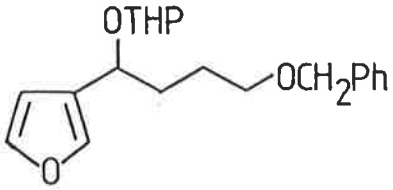


(144)



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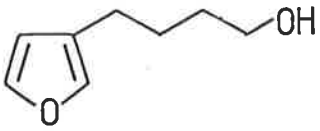


(191)

Figure 1.6

The tetrahydropyranyl ether (190) afforded a good yield (76% yield) of the hydrogenolytic product (191) upon treatment with lithium and ammonia for 20 min[1(b)] (Figure 1.6). This result again[35] reflects the good leaving group behaviour of the acetal function (see Section 0.1.2).

1.3 2-SUBSTITUTED FURANS

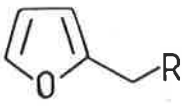
Although not directly studied, the available evidence suggests that 2-nonylfuran (145) is inert to the standard reduction conditions employed in this work (*vide infra*).

Reduction of the acetate (146) or the ether (147) with lithium in ammonia for 10-15 min caused hydrogenolysis of the benzylic type substituent to afford the alkylfuran (145) as the exclusive product. The course of the reaction was unaffected by the presence or absence of an added proton source (ethanol).

Treatment of the acetal (148) with lithium and ammonia (no ethanol) for 15 min gave the alkylfuran (145) in quantitative yield. When the acetal (148) was reduced with lithium and ethanol in ammonia two products were obtained in a ratio of 17:1. The major product was shown to be the alkylfuran (145). The highest mass ion in the mass spectrum of the minor component was observed at m/e 196, and suggests that this compound is a 2-nonyldihydrofuran.

2-Nonylfuran (145) and recovered starting material were obtained from reduction of the alcohol (149) with lithium in ammonia. More hydrogenolysis product was obtained when an added proton source (ethanol) was present during the reaction, and when the reaction period was increased (Table 1.1).

The alkene (150) gave a mixture of 2-pentylfuran (161) (47%) and the dimer (162) (45%) upon reduction with lithium in ammonia for 8 min. Addition of a proton source (ethanol) decreased the dimer formation to 15%.



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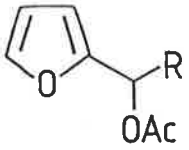

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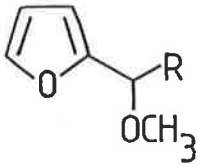

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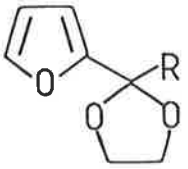

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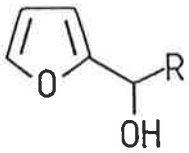

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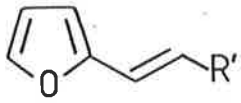

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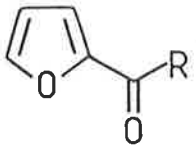

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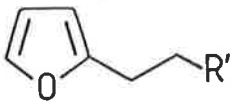

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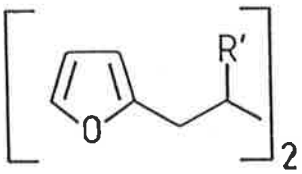

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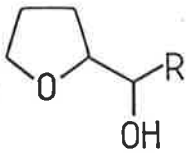


(163)

$R=C_8H_{17}$

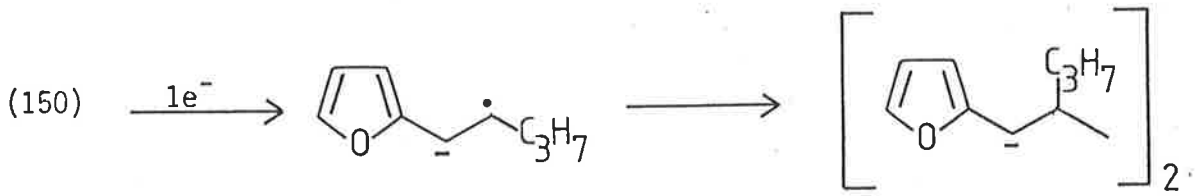
$R'=C_3H_7$

Figure 1.7

Table 1.1

Time (min)	Proton Source	Yield (%) (145)	(149)
10	none	8	92
10	ethanol	18	79
60	ethanol	36	62

Analogous products have been observed from the reduction of styrene and its derivatives with dissolving metals.[4,21,109] The highest unpaired electron density in styrene anion radicals is found at the β-carbon atom.[21,110] Probably, the anion radical (164) resultant from addition of an electron to the alkene (150) can undergo dimerisation, to give the dianion (165) (Scheme 1.9), at a rate which is similar to the rate of its protonation (an anion radical is far less basic than a similar monoanion[13,111]). Proton addition to (164) and further reduction would yield the alkylfuran (161), and protonation of the dianion (165) would afford (162).



(164) (165)

Scheme 1.9

The presence and nature of an added proton source was found to have a marked affect on the products obtained from reduction of the ketone (160).

With lithium and ammonia (no added proton donor) for 35 min, (160) afforded the enone (171) (25%), the alcohol (149) (12%) and recovered starting material (62%). However, reduction of (160) with lithium and *tert*-butyl alcohol (1 molar equivalent) in ammonia for 45 min gave the enone (171) (56%), the alcohol (149) (2%), an unidentified component (12%), the ketone (177) (11%) and recovered starting material (19%). The unidentified compound is believed to

be the enone (174). The mass spectrum of this product showed an ion at m/e 210 which is ascribable to the molecular ion of this compound. Ions observed at m/e 69 (base peak) and m/e 141 can be explained by a fragmentation of the dihydrofuran carbon 2 to carbonyl carbon bond. That the base peak of the spectrum was derived from loss of $C_8H_{17}CO$ from the molecular ion, and that no ion derived from loss of C_8H_{17} was observed ($M^{+\cdot}-C_8H_{17}$ was found for (171)), suggests that the dihydrofuran double bond is not situated at the dihydrofuran carbon 2. Since the major reduction product, (171), is a substituted 2,3-dihydrofuran, it appears that the unidentified component should be a 2,5-dihydrofuran derivative. Further, the 'H NMR spectrum showed two overlapping multiplet resonances at δ5.6-6.1 that are ascribable to dihydrofuran C3-H and C4-H alkene resonances.

Reduction of the ketone (160) with lithium and ethanol (12 molar excess) in ammonia for 35 min afforded 2-nonylfuran (145) (0.9%), an unidentified product (4%), the enone (171) (8%), the alcohol (149) (7%), the tetrahydrofurylketone (177) (30%), and tridecane-1,5-diol (182) (50%). Mass spectral evidence suggests that the unidentified product is a dihydrofuran. The base peak at m/e 69 could arise from loss of C_9H_{19} from the molecular ion which was observed at m/e 196.

Possible mechanisms for the formation of these products are outlined in Scheme 1.10. The anion radical formed by addition of an electron to the ketone (160) is represented by the resonance contributors (166), (167) and (168).* Sequential proton and electron addition to

---

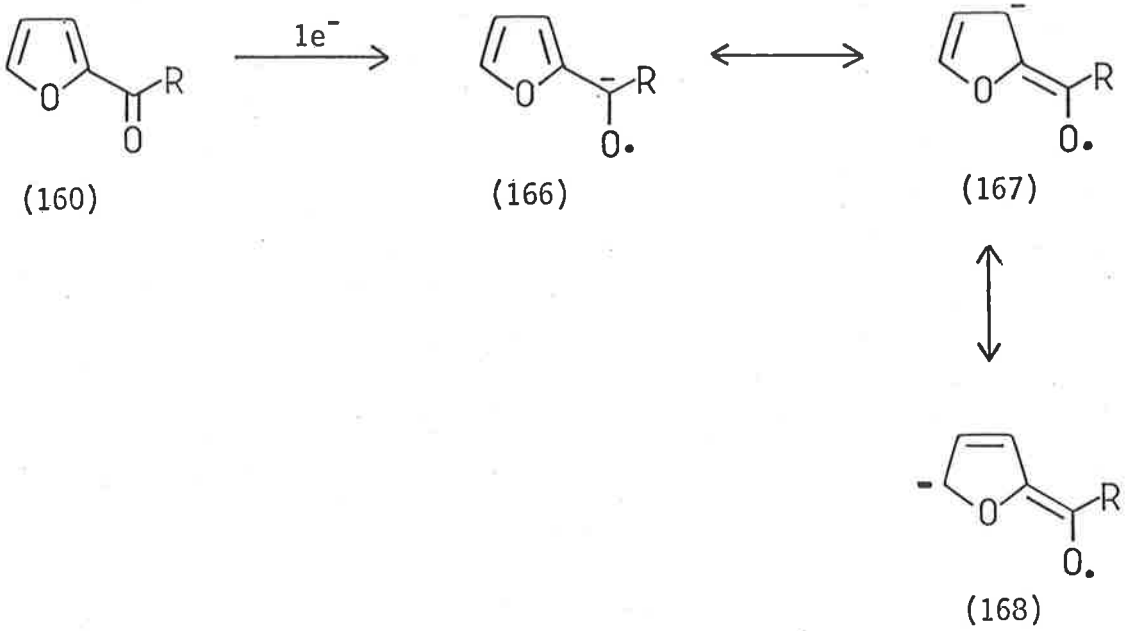
* The radical anion molecular orbital electron distribution has not been determined. Therefore, the atom bearing the greatest negative charge is unknown.

(166) would form the alkoxide anion (169) and addition of another proton would give the observed alcohol (149). Initial protonation at the furan carbon 3 and electron addition would give, from (167), the enolate anion (170). Another proton addition followed by rearrangement should give the observed enone (171).

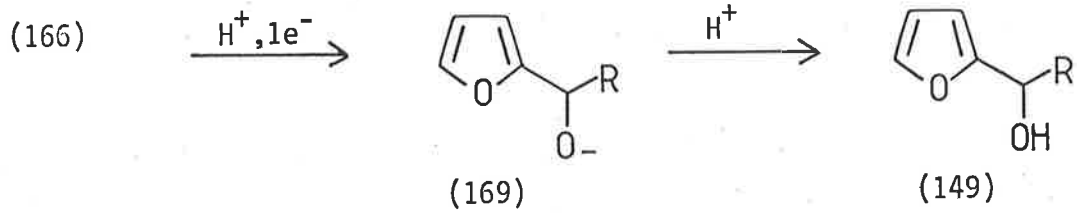
Alternatively, initial protonation at the furan carbon 5 in (168) and electron addition should afford the enolate anion (172). Proton addition to (172) would give the enol (173) which could tautomerise to the unconjugated enone (174), or the conjugated enone (175). The observed ketone (177) could be formed by reduction of the α,β-unsaturated ketone (175). Reduction of (177)[111] to the anion (179) and elimination of the adjacent oxygen would afford (180) (the reduction of an α-substituted ketone to its anion (e.g: 179) may be followed by loss of the α-substituent if the latter is a reasonably good leaving group[21]). Proton addition to (180), rearrangement of the product to (181), and further reduction would form the observed diol (182). The reduction of (177) with lithium and ethanol in ammonia for 35 min has been shown to give the diol (182) in high yield (*vide infra*, Section 2.2.2).

Reduction of (171) to the anion (183) followed by elimination of the vicinal oxygen substituent would give (184). Proton addition to (184) and tautomerisation of the subsequent enol would give (185). Reduction of both the carbonyl groups of (185) would yield the diol (182).

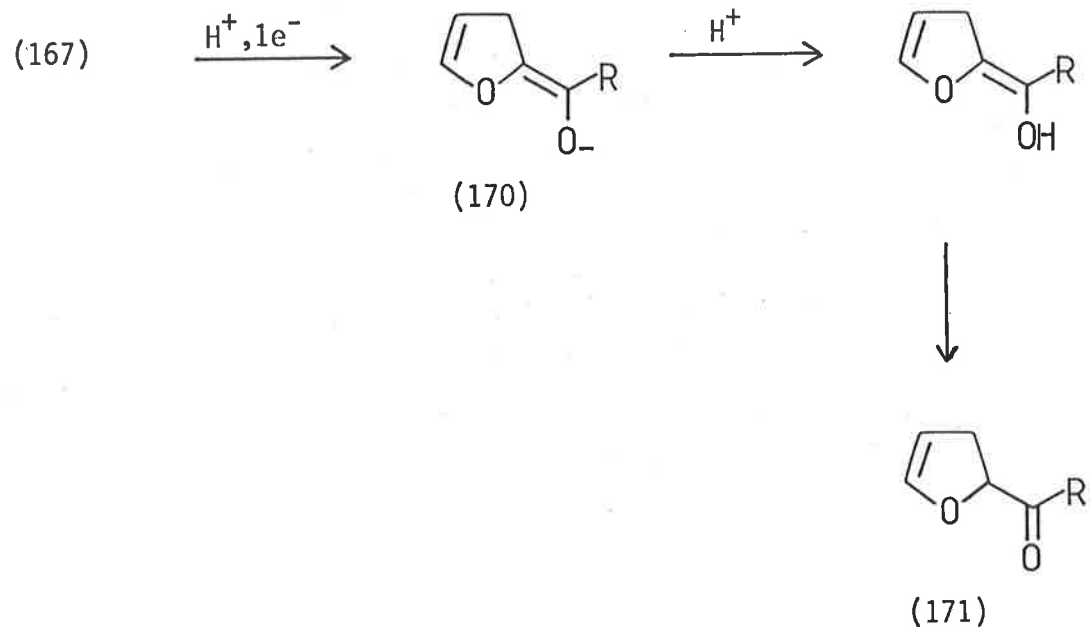
The anion (186), from reduction of (174), could suffer elimination of the oxygen substituent to afford (187). Protonation of (187) and rearrangement of the derived enol (188) to the enone (189) and further reduction could also produce the diol (182).



(160) (166) (167) (168)

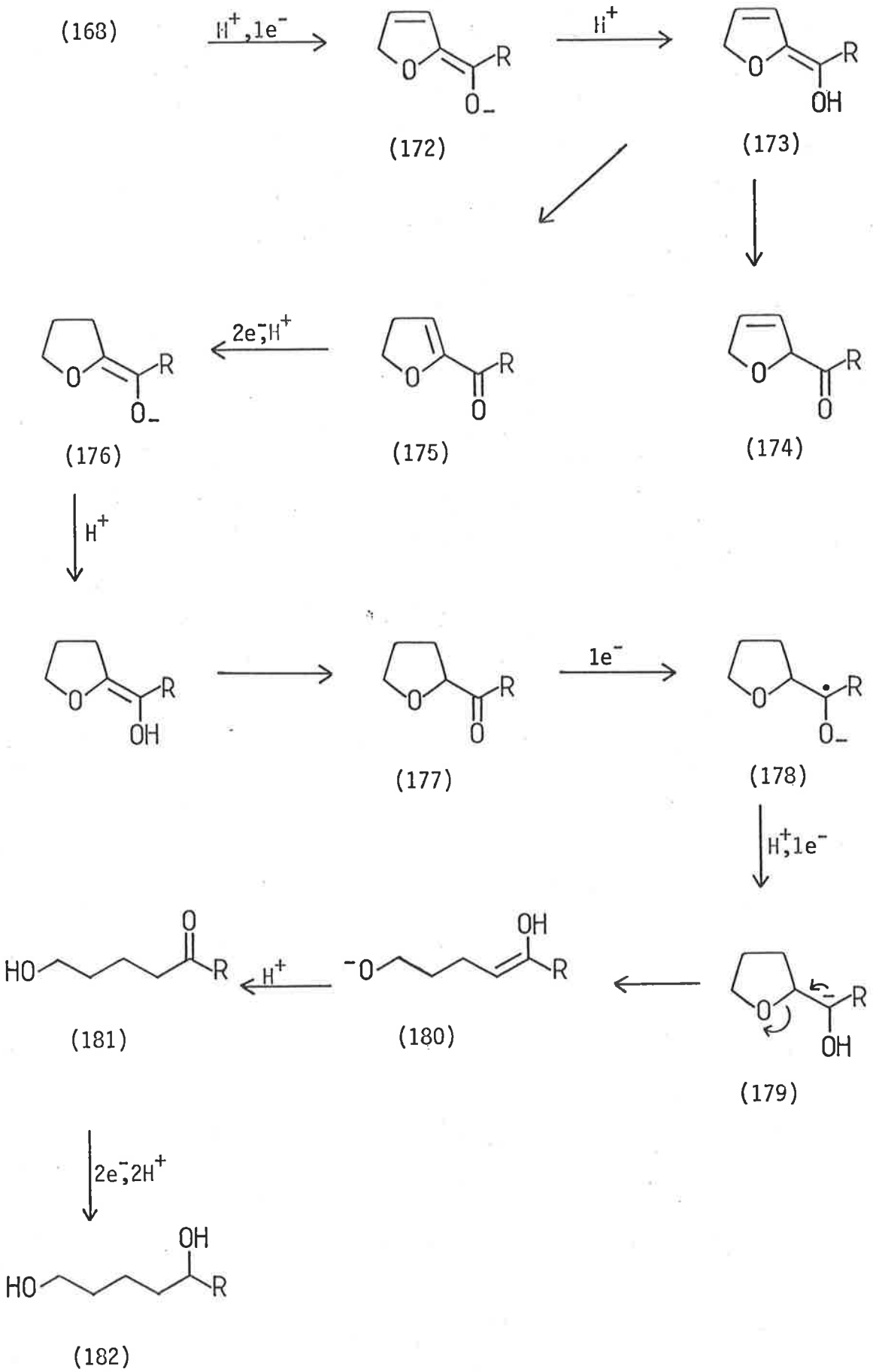


(166) (169) (149)

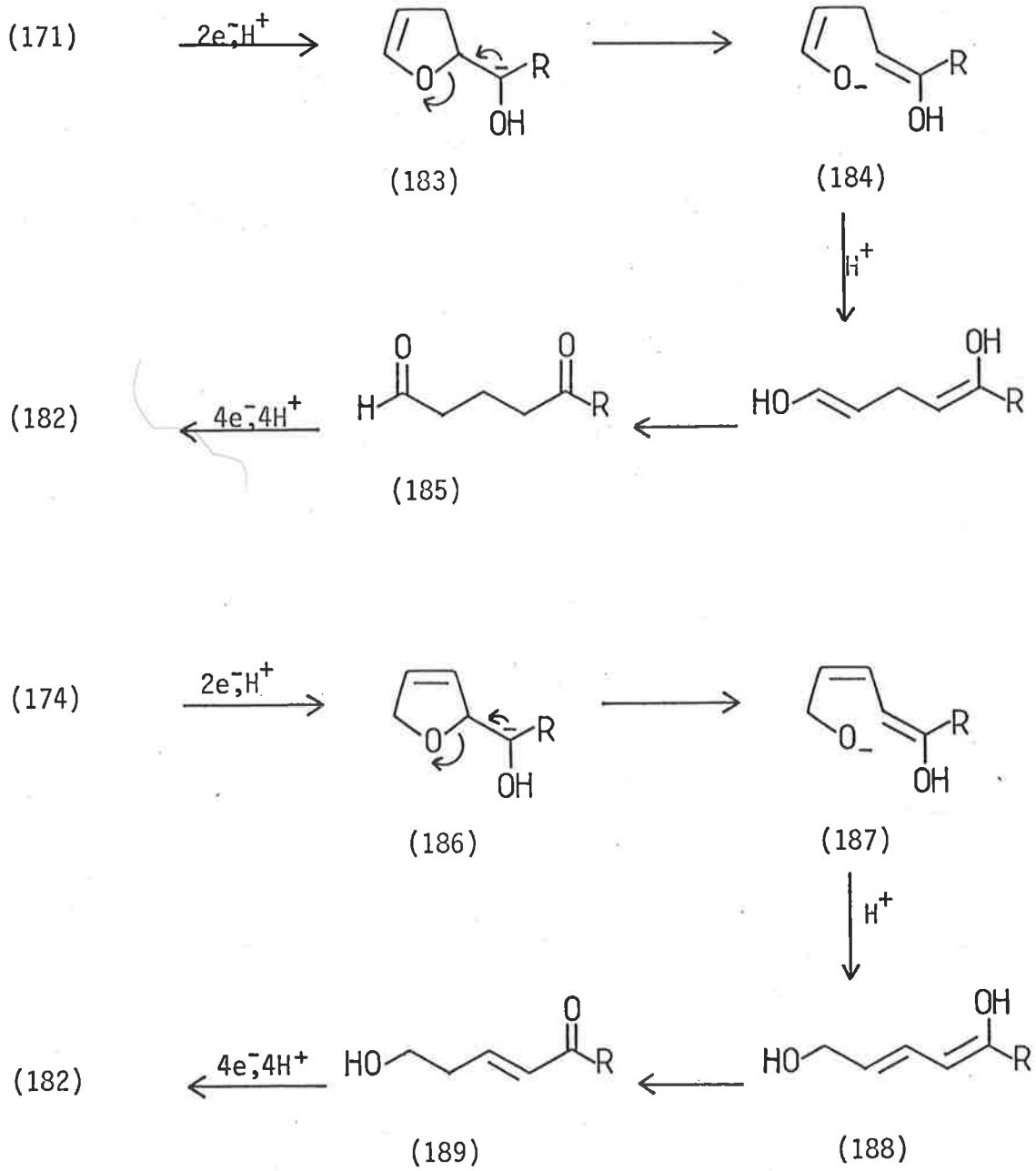


(167) (170) (171)

Scheme 1.10.... 62



Scheme 1.10..... 63



$R=C_8H_{17}$

Scheme 1.10

Thus, when less than one equivalent of an added alcohol is available, the ketone (160) can act as a proton donor and be converted to its enolate anion which is inert to the reduction conditions. Protonation upon work up would reconstitute the starting material.

With no added alcohol, or one equivalent of *tert*-butyl alcohol, the major site of initial protonation at the radical anion from (160) is apparently at carbon 3 with subsequent formation of (171) as the major product of the reduction. This ketone is probably present as its enolate anion (170) until work up.[28]

With excess ethanol (12 molar equivalents) the furan carbon 5 appears to be the major site of initial protonation with resultant formation of (177), and its derivative (182), as the major products. The high proportion of the readily reducible ketone (177) observed in the product mixture suggests that its enolate anion precursor, (176), is only slowly protonated under the reduction conditions employed.[28]

The low yield of (171), obtained when excess ethanol is employed, serves to exclude carbon 3 of the radical anion derived from (160) as a major site of initial protonation, provided that the enolate anions (170) and (172) suffer protonation at similar rates. If the rate of formation of (182) from (170) is significantly faster than the rate of formation of (182) from (172), the intermediates from (170) to (182) may not be observable. This situation would mask the occurrence of initial protonation of carbon 3 of the radical anion derived from (160); because (182) is a common product formed from (170) and (172). Protonation of the inert enolate anions (170) and (172) is, however, expected to occur at similar rates. The ketone (171) should be rapidly reduced under the conditions employed.

That none of the tetrahydrofuryl carbinol (163) was observed in the reduction products indicates that reduction of the carbonyl group of (177) to give the corresponding alcohol (163) is insignificant.

The reasons for the differences found in the reduction products and their proportions when using *tert*-butyl alcohol or ethanol as an added proton source are unclear. The acidity and concentration of the added alcohol might be important.

It is not expected that (177) would be formed by reduction of the dihydrofuran double bond in (171) or any of its precursors.

1.4 CONTRAST AND COMPARISON: 2- AND 3-SUBSTITUTED FURANS

In general, electron addition to an unsaturated molecule is reversible, and the electron can often be removed in various ways.[4,13] The overall reduction rate can be affected by the rate of electron addition, or by the equilibrium position which determines the concentration of anion radical. The equilibrium position is related to the substrate structure in predictable ways. The greater the extent of the unsaturation, the higher the electron affinity of the system, and the greater the ground state strain, the more the equilibrium will tend towards electron addition. Conversely, the greater the ground state stabilisation, as in aromatic molecules, the further the equilibrium will be towards dissociation. Since the reduction rate is dependent, as one factor at least, on the equilibrium concentration of anion radical, it can be qualitatively related to these factors.

John and Ra dom[113] have conducted an ab initio molecular orbital study on furan and a number of 2- and 3-monosubstituted furans. From their results, the furyl group prefers to act, relative to phenyl, as a π-electron donor and a σ-electron acceptor. Inductive σ-electron withdrawal is more pronounced at the 2 position. At the same time, the π-electron distributions show enhanced π-electron density at the 2 position compared with the 3 position both overall and in the highest occupied molecular orbital. As a consequence, and in the absence of other interactions, furan is stabilised by substituents which are π-electron acceptors and σ-electron donors and destabilised by substituents which are π-electron donors and σ-electron acceptors. These effects are greater at the 2 than at the 3 position.

Thus, the aromatic system of an alkylfuran possessing a σ-electron withdrawing benzylic type substituent would be destabilised compared with the parent alkylfuran. One chemical manifestation of this substituent effect would be an increase in the equilibrium concentration of the radical anion; apparently sufficient for these derivatives to be reducible, even though the alkylfurans are inert to the Birch reduction conditions.

A carbon-carbon double bond or carbonyl group would cause σ-electron withdrawing destabilisation, π-electron accepting stabilisation, and extension of the unsaturation when conjugated to a furan ring; the nett effect increases the substrate electron affinity and allows the reduction to proceed.

Co-ordination of a solvated lithium cation to a benzylic type oxygen substituent might hold this ion in sufficiently close proximity to the furan ring such that the positive charge can assist electron addition to the aromatic system; but no evidence is available to support such a contention.

Hydrogenolysis of many benzylic type substituents proceeds rapidly and efficiently in the 2-substituted furan series. For 3-substituted furans, this process is much slower and when an added proton source is present, proton addition to the furan ring can compete effectively with hydrogenolysis; concomitant ester reduction is observed with (74), but not with (146).

These observed hydrogenolysis rate differences between the 2- and 3-substituted furans may reflect a localisation of negative charge at the 2 position, compared with the 3 position, in the anion

radical (*cf.* ground state): sufficient to cause rapid elimination of a benzylic type substituent at a 2-substituted furan, but much slower elimination of a similar group in a 3-substituted furan.

During reduction, the preferential initial addition of a proton from ethanol to carbons 2 and 5 of a 3-substituted furan also suggests a higher negative charge density at these carbons, compared with the 3 and 4 position, of an anion radical formed from furan substrates.

The radical anion formed on addition of an electron to a substituted furan system is insufficiently basic to suffer a protonation by ammonia. In the absence of a proton source more acidic than ammonia, only hydrogenolytic products in which the furan ring is intact are formed.

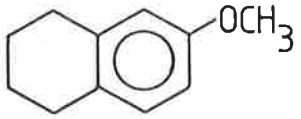
It appears that in many cases, the rate at which a benzylic type substituent undergoes hydrogenolysis is qualitatively related to the stability of the leaving group. Fission of substituents in the 2-substituted furans are mostly too fast for any conclusions to be drawn in this regard, but in the 3-substituted furan series, the rate of substituent removal is found to be in the order acetate > tetrahydropyranyl ether > methyl ether > hydroxyl. However, some acetal and cyclic ether substrates do not conform with this pattern, and for reasons which are totally obscure and completely mysterious. Slow cleavage of the hydroxyl group in both 2- and 3-substituted furans may also reflect rapid formation of a stable metal alkoxide salt.

Lower reaction temperatures apparently decrease the rate of hydrogenolysis. For example, the linderene derivatives, acetates (29b) and (32), and methyl ethers (27) and (30) (Section 0.1.2) with sodium and ammonia at -60°C gave less hydrogenolysis product than did the

acetate (74) and ether (75) (Section 1.2) with lithium and ammonia at -33°C, after allowing for reaction time differences; but these product proportion changes may in part reflect the greater ability of lithium, compared with sodium, to promote hydrogenolytic processes.

Tzeng and Weber[114] have presented evidence to show that the radical anion formed by electron transfer from sodium metal to an allylic or benzylic methyl ether undergoes heterolysis of the carbon oxygen bond to yield a radical-methoxide anion pair, rather than radical fragmentation of the carbon oxygen bond to form a carbanion-methoxide radical pair. These results give corroborative evidence for the analogous type of carbanion mediated elimination of oxygen substituents from radical anion intermediates proposed in several furan reduction pathways.

There are indications that monobenzenoid systems can undergo expulsion of a hydride ion to some extent, with regeneration of the aromatic system. The result is catalytic hydrogen gas evolution. For example, (192) is reducible in good yield to the 1,4-dihydro derivative with only a small excess of lithium and ethanol in ammonia, but (193) requires about 80 equivalents of metal with ethanol to produce a 40%-50% yield of the 3,8a-dihydro derivative, although the metal rapidly disappears and hydrogen gas is evolved.[13] The intermediate anion (194) may be unstable, expelling a hydride ion to regenerate (193) and leading to inefficient reduction.



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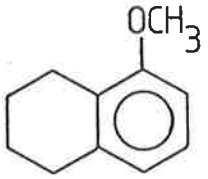
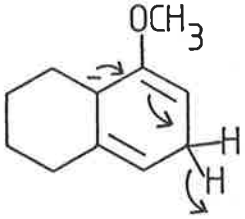


(193)



(194)

The different reduction rates observed between the various furan substrates might in some cases be partially due to differences in the rate of regeneration of starting material by hydride elimination; but no evidence is available to suggest the extent, or indeed the occurrence, of this process.

From a synthetic viewpoint, the acetate group appears to be the most suitable, after considering its ease of formation and reduction product yield, for the removal of a benzylic type oxygen substituent from a 2-substituted furan derivative by means of a metal-ammonia reduction; a methyl ether or ethylenedioxy group can also be successfully employed. A proton source (ethanol) can be added to effect reduction of other functionality.

Removal of a benzylic type oxygen substituent from a 3-substituted furan derivative would be best achieved by means of the lithium and ammonia (no added proton source) reduction of a tetrahydropyranyl ether. The acetate, methyl ether and ethylenedioxy acetal groups may also be employed, but use of the acetate group is disadvantaged by competitive ester reduction. The addition of an alcohol proton source (e.g.: ethanol) clearly results in extensive reduction of the furan ring in the 3-substituted furan series.

With or without an added proton source, the metal-ammonia reduction of a 2-substituted furan ring conjugated with a carbon-carbon double bond or carbonyl group is complicated by the formation of dimers and ring reduction and cleavage products respectively.

1.5 MISCELLANEOUS REDUCTIONS

Hydrogenation of 3-nonylfuran (73) over platinum catalyst afforded 3-nonyltetrahydrofuran (59) (41%), 2-ethylundecanol (108) (41%) and 3-methyldodecanol (92) (18%). Furfural and its derivatives have been shown also to give ring opening products upon hydrogenation over platinum catalyst.[115]

Treatment of the dimethoxy acetal (77) with lithium aluminium hydride for 30 min at 20°C afforded an 80% yield of the methyl ether (75). Aluminium chloride catalysis is usually required to effect nucleophilic hydride displacement of an acetal oxygen to afford an ether.[21,116] The reasons why (77) should undergo this transformation with such ease are unclear. Our observations indicate that the ethylenedioxy acetal (76) exhibits normal behaviour and is only slowly, if at all, reactive toward lithium aluminium hydride. However, these results have not been further explored.

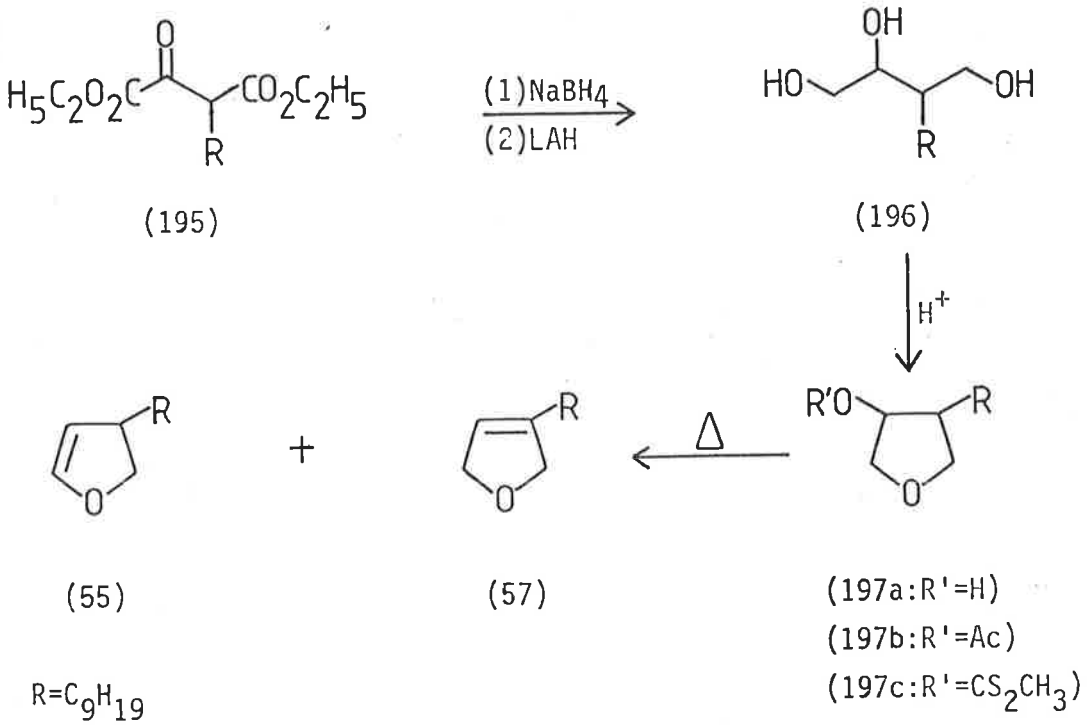
CHAPTER II

SYNTHESIS OF REDUCTION SUBSTRATES AND SYNTHESIS OF REDUCTION PRODUCTS.

2.1 SYNTHESIS OF REDUCTION SUBSTRATES

2.1.1 ALKENES

Direct synthetic methods of general applicability for dihydrofurans have received limited attention. From the examples in the literature, the procedure of Gianturco *et.al.*[119-121] appeared to be the method of choice for preparation of requisite 2,3- and 2,5-dihydrofurans, (55) and (57). Unfortunately, numerous attempts to develop this sequence for our purpose were fraught with difficulties[122] and the procedure was abandoned in favour of the alternative sequence illustrated in Scheme 2.1.



Scheme 2.1

The keto diester (195) was prepared by sodium ethoxide mediated reaction of ethyl undecanoate with diethyl oxalate.[123] Reduction of (195) to the triol (196) by means of lithium aluminium hydride was not viable. Non-uniform loss of oxygen during the reduction proved to be a serious complication that has been encountered previously with β-keto esters.[124,125] However, sequential reduction[126] with sodium borohydride and lithium aluminium hydride afforded the triol (196) in 78% overall yield from (195).

The product obtained from sodium borohydride reduction of (195) was isolated but not completely characterised. The IR spectrum showed strong absorptions at 3420 cm^{-1} and 1745 cm^{-1} ascribable to hydroxyl and ester functions respectively; but the ^1H NMR spectrum showed no resonances attributable to an ester ethoxyl group. A white solid could be crystallised from the crude product. The mass spectrum of this compound and the remaining oil could not be rationalised in terms of any expected products. Doubly charged ions were a feature of both spectra and suggest the inclusion of boron in the molecule.

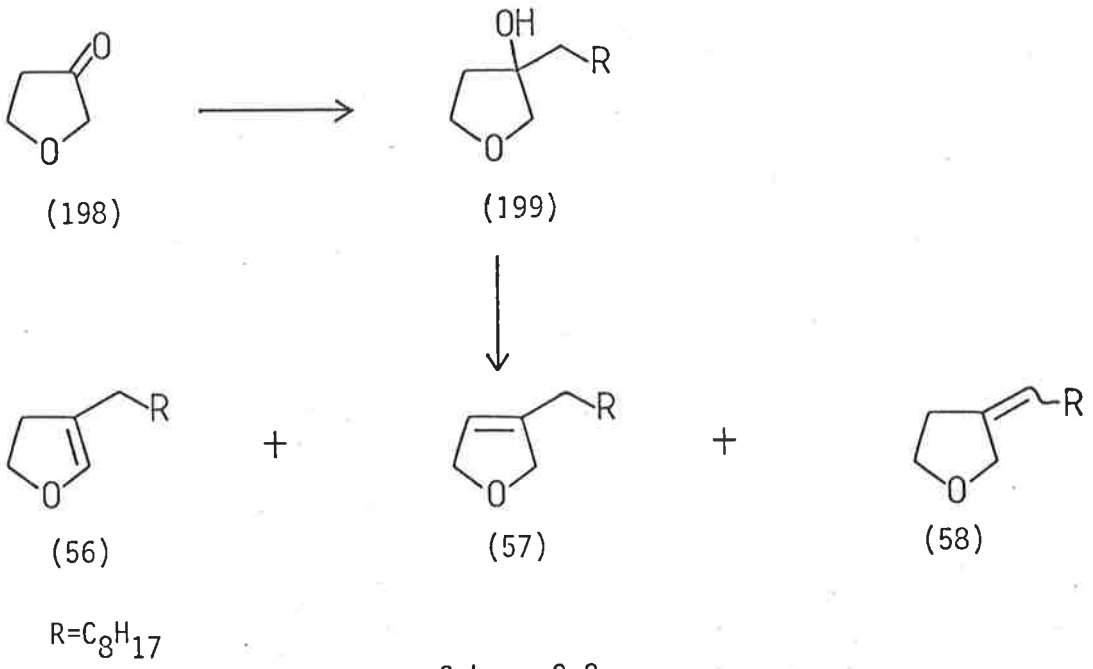
β-Keto esters are known to undergo over-reduction to diols,[21,127] and 1,2- and 1,3-diones are known to form stable (sometimes crystalline) complexes[21,128] with sodium borohydride. Apparently, after initial attack at the ketone function of (195), intramolecular delivery of hydride ion takes place at one or other of the ester groups to form an alkoxide anion; lactonisation follows with boron remaining complexed to the molecule.

Acid catalysed cyclodehydration[130,131] of the 1,2,4-triol (196) gave, in moderate yield (54%), the alcohol (197a) as a mixture of its diastereoisomers. The ^1H NMR spectrum of the derived acetate (197b)

indicated a 1:1.6 isomer ratio as demonstrated by the appearance of two sets of multiplets at 5.0 and 5.4δ for the methine hydrogen at carbon 3. Explorative work concerning conversion of the hydroxyl function to a superior leaving group (tosylate or chloride) followed by base (potassium *tert*-butoxide) promoted elimination to produce the alkenes (55) and (57) was unsuccessful at the second stage. Apparently, the introduction of a double bond into a tetrahydrofuran ring is a slow process; possibly owing to incorrect orbital geometry in the transition state or the introduction of bond angle strain into the ring system. The procedure was not further investigated.

Application of pyrolytic techniques was more successful. Although pyrolysis of the acetate (197b) gave ring cleavage products and the alkylfuran (73), the xanthate ester (197c) smoothly and cleanly provided the alkenes (55) and (57) in good yield (81%), and in a 2.2:1 ratio respectively. Some features of the ^{1}H NMR spectrum of (55) seem worthy of comment. The dihydrofuran carbon 2 methylene protons exhibit an AB system (J_{AB}=9.1Hz) whose resonances are centred at δ3.9 and δ4.3. The AB quartet is further split by the carbon 3 methine proton (J_{AX}=6.6Hz, J_{BX}=8.9Hz) to form an eight line pattern. The alkene product mixture was used directly in the dissolving metal reduction studies.

A mixture of the 4,5-dihydrofuran (56), the 2,5-dihydrofuran (57), and the exocyclic alkenes (58) were prepared as outlined in Scheme 2.2. Tetrahydrofuran-3-ol[129,130,131] was prepared according to a modified procedure of Olsen[129] and oxidised to dihydro-3(2H)-furanone[131] (198) by means of Jones'[132] reagent. Reaction of (198) with nonyl magnesium bromide at low temperature[133] afforded the alcohol (199) (48%).



Scheme 2.2

Treatment with thionyl chloride in pyridine gave (56), (57) and the isomers of (58) in a 1:2:2.2:2.5 ratio respectively. Elimination products away from the ring oxygen are more favourable. This mixture of alkene products was also used directly in the dissolving metal reduction studies.

3-Nonylidenetetrahydrofuran (58) was obtained in low yield (33%) after treatment of the ketone (198) with triphenylnonylidenephosphorane. The two isomers of (58) were observed in a 9:1 ratio. An examination of the 'H and ^{13}C NMR spectra did not provide an indication of the stereochemistry of the major isomer. The reasons for the selective formation of one isomer are unclear. Further investigations on this topic are currently in progress.

2.1.2 3-SUBSTITUTED FURANS

The commercial availability of 3-furoic acid has greatly simplified the preparation of 3-substituted furan derivatives and has been used as a starting material in this work. Initially, 3-furoic acid was prepared from furan-3,4-dicarboxylic acid (Aldrich) according to the procedure of Deady and Shanks.[134] Subsequently commercial (Aldrich) 3-furoic acid was used.

Reaction of octyl lithium prepared from sodium doped lithium* and 1-bromooctane with 3-furoic acid afforded the ketone (39), mp 42-45°C, in moderate yield. (52%).

When a mixture of (39), ethylene glycol, *p*-toluenesulphonic acid and benzene was heated under reflux in a system equipped with a Dean and Stark apparatus, only starting materials were recovered along with some polymeric material. Apparently, the quantity of water in the solvent returning to the reaction vessel was sufficiently large such that the reaction equilibrium was moved entirely towards starting materials. With dichloroethane as solvent, and a modified Dean and Stark apparatus where the solvent was sieve dried before returning to the reaction vessel, the ethylenedioxy acetal (76) was obtained in good yield (76%).

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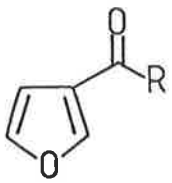
* Low yields of alkyl lithium reagent were obtained when high purity lithium was employed. The use of sodium doped lithium (1% sodium) prepared in these laboratories, or commercial impure lithium (0.02% sodium, Aldrich) greatly enhanced the yield.[135,136]



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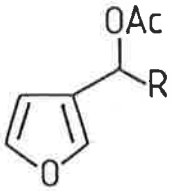

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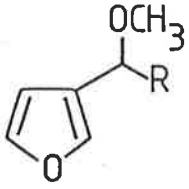

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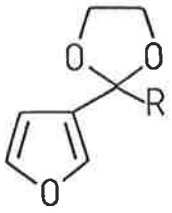
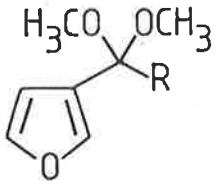


(76)

$R=C_8H_{17}$



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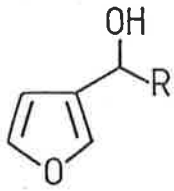


(78)

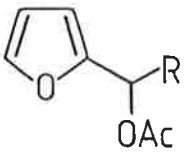
Figure 2.1

The dimethoxy acetal (77) was provided in good yield (87%) when a mixture of the ketone (39), trimethyl orthoformate and methanol was heated under reflux[137] for 20h. Without methanol present, the reaction was very slow and only very low yields of (77) resulted in addition to polymeric and starting materials.

Sodium borohydride reduction of (39) gave the alcohol (78) (93%). The ether (75) and acetate (74) were prepared from (78) by standard procedures.

2.1.3 2-SUBSTITUTED FURANS

Treatment of 2-furfural with octyl magnesium bromide provided the alcohol[138] (149) in good yield (65%). The acetate (146) and the ether (147) were derived from (149) by standard functional group transformations.



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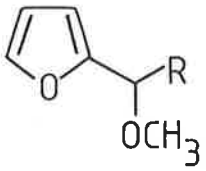

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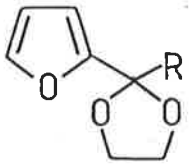

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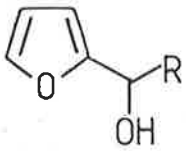
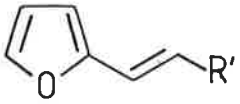


(149)



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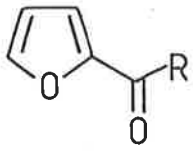


(160)

$R=C_8H_{17}$ $R'=C_3H_7$

Figure 2.2

Oxidation of the alcohol (149) with pyridinium chlorochromate[139] or Collins reagent[140] proved to be deceptively difficult. The ketone (160) was obtained in low yields (47%) and was accompanied by black tarry residues. Apparently, simultaneous oxidation of the furan ring takes place when a hydroxyl function is situated in close proximity to the heterocycle. To avoid this problem we treated 2-furoic acid with octyl lithium which afforded (160) in superior yields. (55%)

Preparation of the ethylenedioxy acetal (148) was effected when a mixture of the ketone (160), ethylene glycol, *p*-toluenesulphonic acid and chloroform was heated under reflux for 10h in a system equipped with a Dean and Stark apparatus. Formation of (148) was very slow unless the solvent was dried before returning to the reaction flask.

The heated heterogeneous mixture of butyltriphenylphosphonium bromide, 2-furfural, dioxane and water[141] afforded the alkene (150) in low yield (10%). Extensive polymerisation of the product occurred with this procedure.

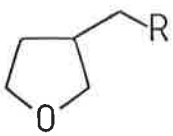
2.2 SYNTHESIS OF REDUCTION PRODUCTS

2.2.1 ALKENES AND 3-SUBSTITUTED FURANS

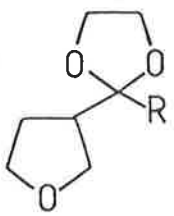
The alkenes (55), (56), (57) and (58) all occur as reduction products of 3-substituted furan substrates. Their synthesis has been described previously.

Several compounds are found to be products of reduction of both the alkene and 3-substituted furan substrates and their synthesis, along with other 3-furan products, is described in this section.

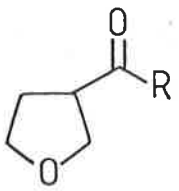
Rhodium and ruthenium catalysts have found effective use when a minimum of hydrogenolysis is required during reduction of an aromatic ring or alkene double bond.[21] Thus, hydrogenation of the alkene (58), the ethylenedioxyacetal (76) and the ketone (39) with rhodium on alumina catalysis afforded good yields of the tetrahydrofuran derivatives (59), (80) and (200) respectively. Selective saturation of the furan ring in the presence of the ketone



(59)



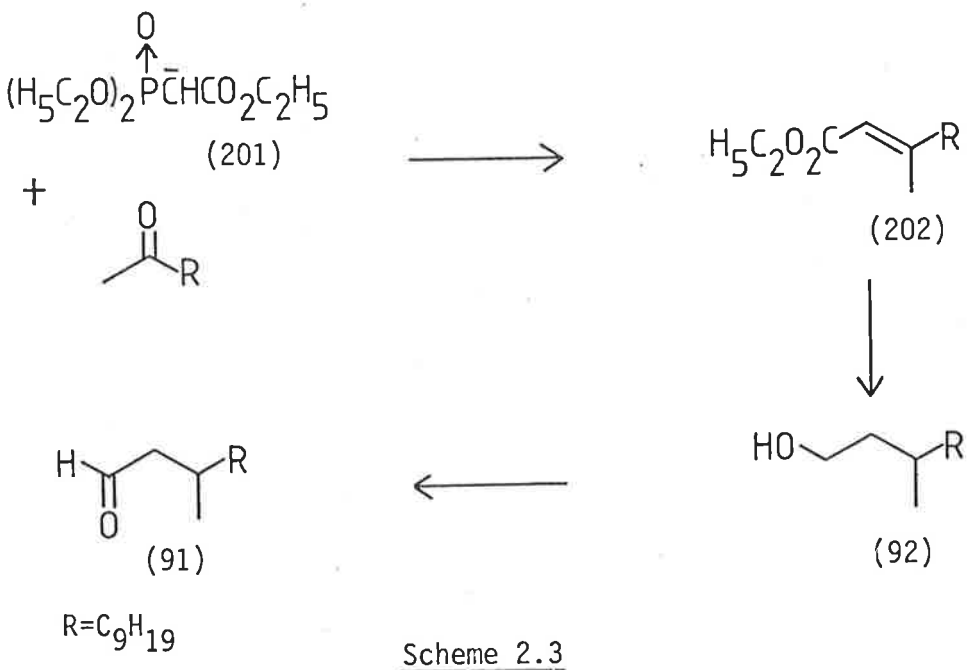
(80)



(200)

function was easily achieved on reduction of (39). The ketone (200) could not be found amongst any furan dissolving metal reduction products.

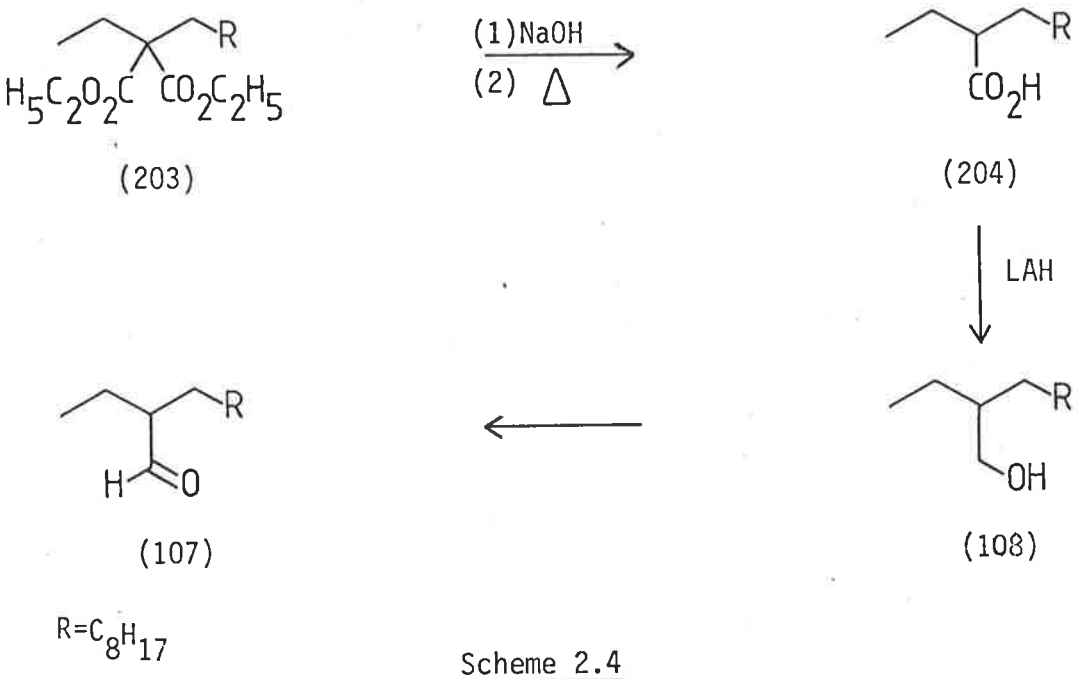
The alcohol (92) was prepared as illustrated in Scheme 2.3 The reaction of phosphonate carbanions containing electron-withdrawing groups with aldehydes or ketones constitutes a useful alkene synthesis which has advantages over the "Wittig" reaction.[142] Reaction of undecan-2-one with carboethoxymethylphosphonate anion (201) returned the alkene (202) (62%). Lithium-ethanol-ammonia reduction



Scheme 2.3

of (202) gave the alcohol (92) (90%). Subsequent oxidation with oxalyl chloride activated dimethyl sulphoxide[143,144] provided the aldehyde (91) in good yield (*ca.* 90%).

Scheme 2.4 outlines synthesis of the alcohol (108) and aldehyde (107). Sodium ethoxide mediated reaction of diethyl 2-ethylpropanedioate with 1-bromononane[145] furnished the diester (203) (52%). Base hydrolysis followed by thermally (180-190°C) activated decarboxylation[145] of the derived diacid produced the monoacid (204).



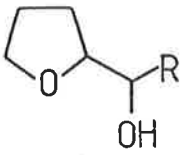
Scheme 2.4

Treatment of (204) with lithium aluminium hydride afforded the alcohol (108) in 52% overall yield from (203). Oxalyl chloride activated dimethyl sulphoxide oxidation of (108) gave the aldehyde (107) in good yield. (*ca.*95%).

2.2.2 2-SUBSTITUTED FURANS

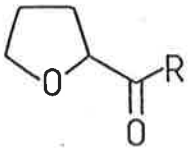
Many of the 2-substituted furans produced 2-nonylfuran (145) as the exclusive product. Therefore, and independent synthesis was required for only a few products.

Hydrogenation of the alcohol (149) with rhodium on alumina catalyst furnished the tetrahydrofuran alcohol (163) (89%). Treatment



(163)

$R=C_8H_{17}$



(177)

of (163) with Jones' reagent afforded the ketone (177) (64%). Lithium-ethanol-ammonia reduction of (177) afforded a good yield (73%) of tridecane-1,5-diol (182).

CHAPTER III

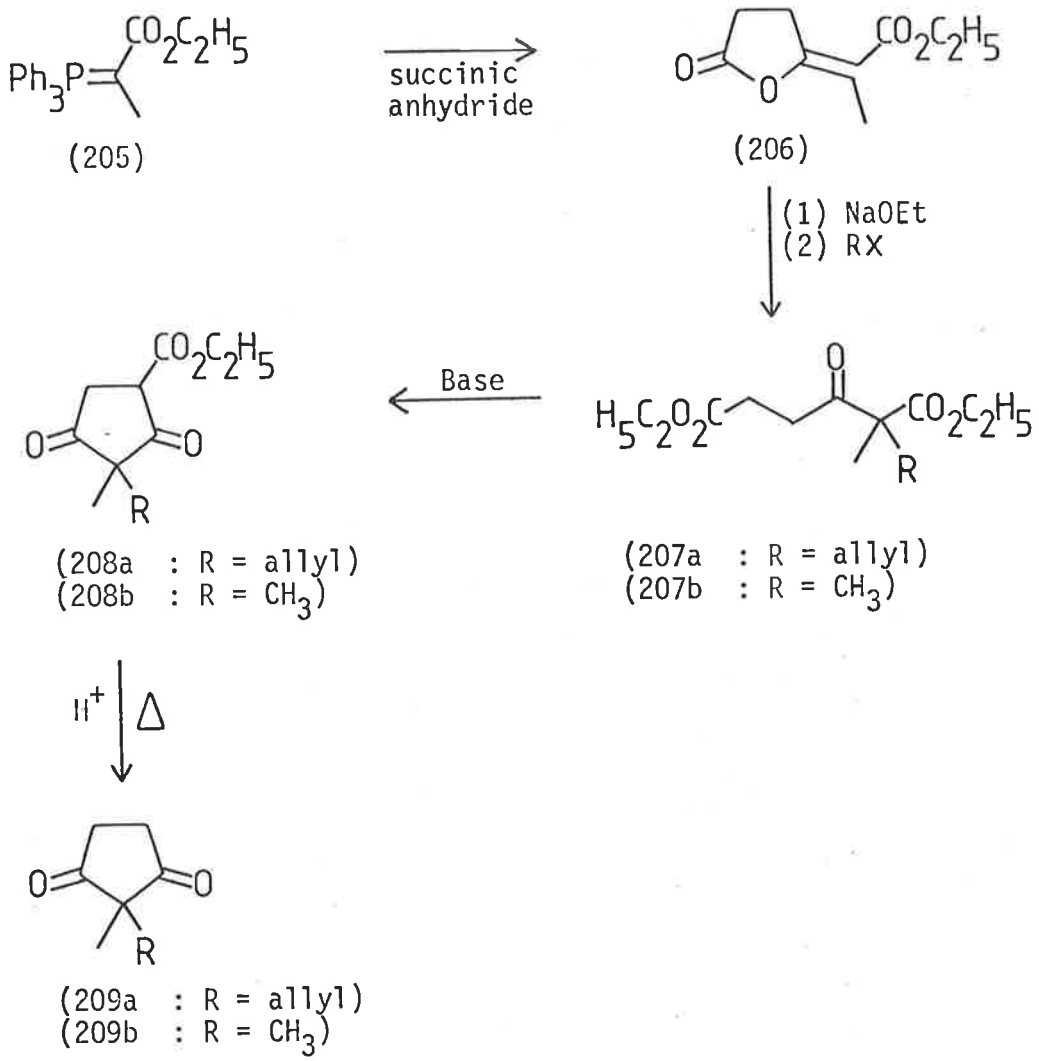
CYCLOALKANE-1,3-DIONES

3.1 Cycloalkane-1,3-diones

Our synthesis of 2,2-dialkylcyclopentane-1,3-diones was accomplished by the reaction sequence outlined in scheme 3.1. (*cf.* scheme 0.2, n=1, R=CH_3). Reaction of equimolar proportions of succinic anhydride and the stabilised phosphorane (205)[167] gave the enol lactone (206) (60%). Short contact times with chromatographic adsorbents (silicagel) were required during purification to prevent product decomposition. Compound (206) can be assigned the (E) configuration from comparison of its ^{1}H NMR data with those of related lactonic esters.[151]

Base (sodium ethoxide) cleavage of (206) followed by alkylation of the intermediate β-keto ester anion with allyl bromide or methyl iodide provided the keto diesters (207a) (91%) and (207b) (82%) respectively. The yields were diminished when crude enol lactone was employed. Thus, synthesis of (206) in benzene, substitution of the solvent with ethanol and treatment with sodium ethoxide followed by the alkyl halide, RX, gave (207a) and (207b) in 16% and 45% yield respectively.

Sodium ethoxide in ethanol, and potassium *tert*-butoxide in benzene[152,153] or *tert*-butyl alcohol,[154] did not efficiently promote Dieckman[21] reaction of (207a). However, utilisation of sodium methylsulphinylmethide[155] (dismyl anion) in dimethyl sulphoxide (DMSO) provided the dioxo esters (208a) (30%) and (208b)[168] (43%) from the diesters (207a) and (207b) respectively. With potassium *tert*-butoxide in DMSO, (207b) afforded (208b) in 60% yield. The ^{1}H NMR spectra of both (208a) and (208b) exhibited a singlet resonance at δ3.1 (2H) due to the ring C5 methylene protons and broad singlet resonances at δ9.4 (1H) and δ8.8 (1H) respectively due to enol proton resonances.



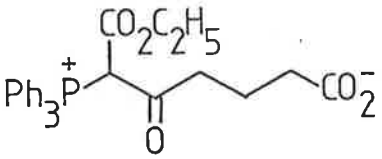
Scheme 3.1

The IR spectra showed no hydroxyl absorptions but strong carbonyl absorptions. Evidently, (208a) and (208b) exist almost entirely in their enol forms in chloroform solution, but as their keto forms in the neat liquid.

Efficient hydrolysis and decarboxylation of the β-keto esters was effected by means of hot aqueous acid to give the 2,2-dialkylcyclopentane-1,3-diones (209a)[70(a)] and (209b).[71(a),168] We have therefore

demonstrated a viable new route to these compounds from cheap and readily available starting materials. Previous syntheses have relied upon the alkylation of commercial 2-methylcyclopentane-1,3-dione[70(a),71(a)] and have suffered from extensive oxygen alkylation. Our procedure has the capacity for the ready incorporation of different alkyl substituents and also circumvents the problem of alkylation at oxygen.

Our attempts to prepare enol lactones from the phosphorane (205) and glutaric anhydride, under conditions suitable for preparation of (206), were unsuccessful and seem to parallel those of previous reports which indicate that the product from reaction of carboethoxymethylene-phosphorane (210) and glutaric anhydride is the zwitterion (211).[158]



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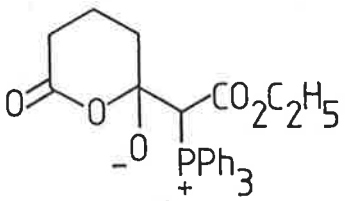


(212)

More recently, Abell and Massy-Westropp[159] have shown that glutaric anhydride and (210) provide enol lactones over extended reaction periods (1 week) and that substituted glutaric anhydrides give good yields of enol lactones. The reasons for these latter reactivity differences are unclear. Possibly, the Thorpe-Ingold effect[160] arising from glutaric anhydride substituents renders more favourable a cyclic intermediate of the type (212) which leads to enol lactones.

The preparation of 2,2-dialkyclcyclohexane-1,3-diones from enol lactones derived from glutaric anhydrides has not been explored. Work in this area will be continued.

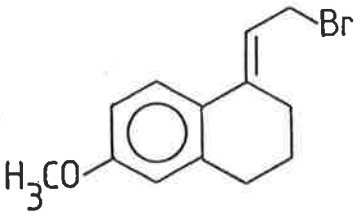
3.2 Towards estrone

The successful synthesis of 2,2-dialkylcyclopentane-1,3-diones prompted us to investigate a new synthetic approach towards the estrone precursor (47b)[70(a),157,161,162] Although the allyl bromide (46) has been successfully employed as an alkylating agent with 2-methylcyclopentane-1,3-dione,[70(a)] its instability and low reactivity[157] inspired the use of the stable, more reactive isothiouronium acetate (214)[71(a),162] as the alkylating agent, RX, in scheme 3.1.

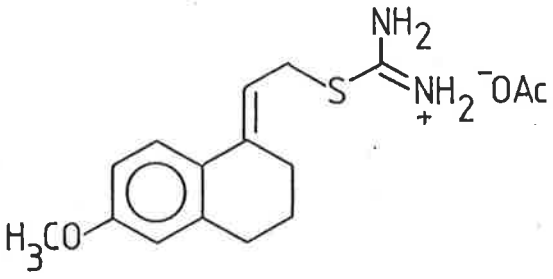
The acetate (214), mp 128-130°C (lit.[162] 125-127°C) was prepared in 76% yield from the alcohol (213)[71(a),169,170] and thiourea in acetic acid. The product was found to include 1.1 molar equivalents of acetic acid of crystallisation even after extensive drying under vacuum.

Treatment of the enol lactone (206) with sodium ethoxide followed by (214) furnished the diester (215) (93%). Reduced yields were obtained if insufficient base was employed to remove the acetic acid introduced along with (214). This indicates that the alkylation step is not acid catalysed.[71(a)]

Difficulty was experienced in the purification of (215), and with its conversion to (216). Chromatography on silica returned only the diester (217). Reaction with dimsyl anion or potassium *tert*-butoxide in DMSO gave low yields of unidentified products. The IR spectra showed no carbonyl absorption and the ^{1}H NMR spectra indicated that extensive alteration of the aromatic system had occurred. The product appeared to be a soluble polymer.



(46)



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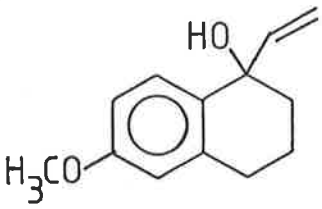

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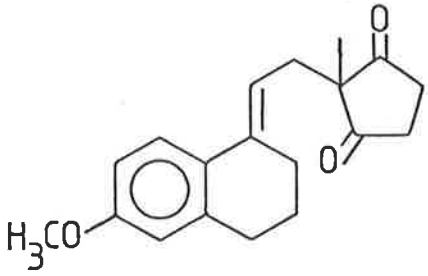
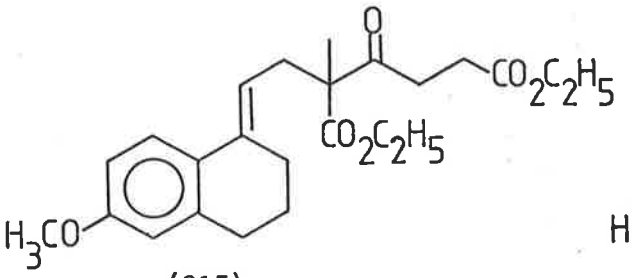


(47b)



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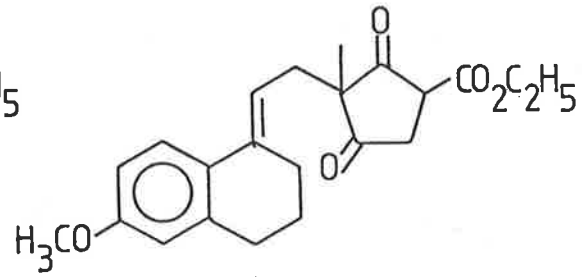

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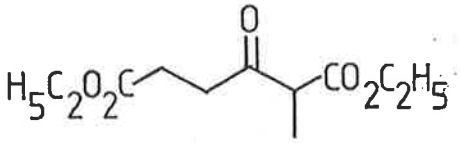

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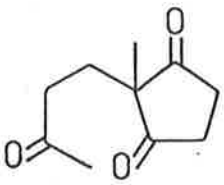

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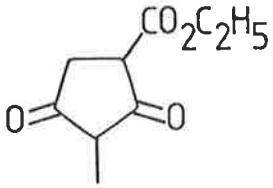

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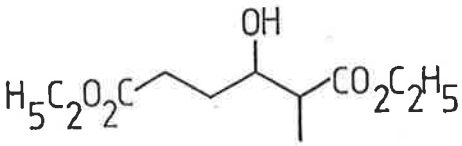

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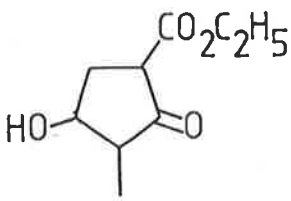

(221)

Figure 3.1

The trione (218) has been shown to readily undergo a reverse Michael reaction under basic conditions.[71(c)] Possibly, acid (silica) or base mediated expulsion of the diester (217) or dione (219) from (215) or (216) proceeds with assistance of the p-methoxyl substituent to produce uncertain products.

Ester enolate anions have been generated at low temperature (-78°C) by means of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and subsequently alkylated.[163,164] Certain "β-leaving groups" have survived these conditions.[164] Treatment of the ester (215) with LDA in THF at -72°C followed by quenching with ammonium chloride solution provided none of the requisite dioxo ester (216). The product has not been completely characterised. The IR spectrum showed a strong carbonyl absorption at 1740cm^{-1} and no hydroxyl absorption. The ^{1}H NMR spectrum showed aromatic resonances at δ7.7 and δ6.6, a vinyl proton at δ5.9, methyl ether protons at δ3.7 and a quaternary methyl resonance at δ1.2. No resonances ascribable to an ethyl ester were observed. Spectrum integration revealed that the aliphatic resonances had decreased intensity with respect to the aromatic resonances in the product compared with the starting diester (215). No structure which can account for the spectral data has been postulated.

The instability of (215) might be obviated by reduction[127] of the ketone function to a hydroxyl group. Heterolytic fragmentation of the allylic carbon bond would then yield enolate anions of (220) or (221), which are much poorer leaving groups than the anions of β-dicarbonyl compounds (217) and (219). A successful Dieckman reaction might then be achieved. However, the reduction product, being a β-hydroxy ester might require further protection. The use of thiolesters, which are known to undergo Dieckman reaction under condition which are milder than their oxygen analogues,[165,166] could also prove to be advantageous. Work in this area will be continued.

CHAPTER IV

EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared spectra were recorded on either a Unicam SP200, Jasco IRA-1 or Perkin-Elmer 397 infrared spectrophotometer. The $1603cm^{-1}$ band of polystyrene was used as a reference. The characteristics of the infrared bands have been expressed in the text as follows: s, strong; m, medium; w, weak; b, broad; sh, shoulder.

^1H nuclear magnetic resonance (NMR) spectra were recorded on either a Varian T60 spectrometer operating at 60 MHz, a Jeol HNM-PMX60 spectrometer operating at 60 MHz, or a Bruker WP80 DS Fourier Transform spectrometer operating at 80 MHz. ^{13}CNMR spectra were recorded on a Bruker WP80 DS Fourier Transform spectrometer operating at 20.1 MHz. Chemical shifts are in ppm downfield from the internal standard, tetramethylsilane; multiplicities are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; c, complex; sh, sharp; D_2O exch implies that the signal exchanges on the addition of D_2O to the sample.

Mass spectra were recorded on either a Hitachi Perkin-Elmer RMU-7D double focussing mass spectrometer or an AEI MS-30 mass spectrometer. The operating voltage was 70 eV unless otherwise indicated. The mass spectra of gas-liquid chromatograph elutants were recorded on an AEI MS-30 mass spectrometer coupled to a Pye-Unicam 104 gas chromatograph or a Finnigan model 4021 GC/MS data system. Fragments are quoted with their relative abundance in parenthesis.

Analytical gas-liquid chromatography (GLC) was carried out on a Perkin-Elmer 990 or Pye-Unicam 104 gas chromatograph. Preparative GLC was carried out on a Pye-Unicam 104 gas chromatograph. Helium carrier gas was used for GC/MS determinations. Nitrogen carrier gas was used for other GLC work unless alternatively specified. All gas chromatographs were equipped with flame ionisation detectors. The Perkin-Elmer 990 gas chromatograph was fitted with a Perkin-Elmer 194B printing integrator. The following columns were used:-

A. GSCOT carbowax 20M, 60m x 0.5mm, glass.

B. 10% OV17 on chromosorb W (60/80), 1.4m x 4mm, glass.

C. 3% OV17 on chromosorb W (80/100), 4m x 4mm, glass.

D. 10% OV17 on chromosorb W (80/100), 2m x 8mm, glass.

E. 3% OV17 on silanised chromosorb Q (100/120), 2.2m x 3.5mm, glass.

F. GSCOT SP1000, 65m x 0.5mm, glass.

The carrier gas rate was 50ml min^{-1} for columns B-D, 35ml min^{-1} for column E, and 3.0ml min^{-1} for capillary columns A and F.

All preparative thin layer chromatography (TLC) plates were prepared from 50% kieselgel G and 50% HF254 applied to glass plates as a suspension in water.

Petrol ether refers to the hydrocarbon fraction bp 60-70°C. Solvent liquid ammonia was redistilled from sodium amide before use. All solvents were purified by standard procedures.

Reagents for Reductions

Dry ether and tetrahydrofuran were prepared by distillation from sodium and benzophenone. Ethanol was dried with magnesium in the usual manner. Lithium (BDH) was used.

Ammonia was distilled from the cylinder and sodium and anhydrous ferric nitrate were added to it. After the formation of sodium amide was complete the mixture was stirred for 30 min before distillation of the ammonia. All reactions in ammonia were protected with soda lime guard tubes and stirred magnetically with a glass encased magnet.

Volatility of Substrates and Products

3-Nonylfuran and 3-nonyltetrahydrofuran were checked for volatility during the evaporation of the ammonia. Ammonia (40 ml) was condensed into a flask containing 3-nonylfuran (83 mg) and the ammonia allowed to evaporate under the conditions used for the reductions. 3-Nonylfuran was recovered in 97% yield. A similar result was obtained with 3-nonyltetrahydrofuran.

In another experiment a mixture of 3-nonylfuran, 3-nonyl-2,3-dihydrofuran (55), 3-nonyl-2,5-dihydrofuran (57) and octadecane in tetrahydrofuran was added to sodium amide (prepared from sodium 540 mg) in liquid ammonia (50 ml). After 1 h, ammonium chloride was added, the ammonia allowed to evaporate, water added and the mixture extracted three times with ether. G.l.c. analysis of the product gave a ratio of components which was within experimental error of that found for the original tetrahydrofuran solution. It was concluded from the results above that the products from the metal/ammonia reductions would probably all be essentially non-volatile in ammonia.

51.8, 54.3, 62.6, 63.7, 72.1 min respectively. Retention time comparison and peak enhancement showed that the products were, in order of elution, (1) butyl nonyl ether; (2) 3-nonyl-2,3-dihydrofuran (55); (3) 3-nonyltetrahydrofuran (59); (4) 3-nonyl-2,5-dihydrofuran (57); (5) octadecane; (6) an unidentified component, possibly 2-vinylundecanol; (7) an unidentified component, possibly 3-methylenedodecanol; (8) 3-methyldodecanol (92). Therefore, dihydrofurans (55) and (57) have reduced by 18% and 26% respectively.

Mass spectral data were recorded for components (6) and (7) using a Finnigan gas liquid chromatograph/mass spectrometer data system, model 4021 [column F, 130°C (isothermal 1 min)-180°C at 1°/min]. Component (6) had mass spectrum 197 (5), 168 (2), 140 (2), 125 (1), 123 (3), 111 (4), 110 (2), 109 (6) 97 (17), 95 (9), 85 (15), 84 (8), 83 (24), 82 (10), 81 (12), 75 (27), 70 (21), 69 (100), 68 (12), 67 (10), 57 (40), 56 (31), 55 (43), 47 (10), 43 (47), 41 (59). Component (7) had mass spectrum 198 (0.3), 197 (8), 168 (2), 140 (1), 125 (1), 123 (3), 112 (2), 111 (4), 110 (2), 109 (9), 99 (2), 98 (4), 97 (16), 96 (4), 95 (12), 85 (17), 84 (7), 83 (23), 82 (11), 81 (15), 75 (22), 71 (8), 70 (19), 69 (100), 67 (12), 57 (39), 56 (27), 55 (42), 47 (10), 43 (46), 42 (9), 41 (59).

3-Nonyl-4,5-dihydrofuran (56), 3-nonylidenetetrahydrofuran (58) and 3-nonyl-2,5-dihydrofuran (57):

A solution of the mixture of dihydrofurans (56) and (57), and alkene (58) (198mg, 1.01 mmol), butyl nonyl ether (32mg, 0.160 mmol) and octadecane (37mg, 0.146 mmol) in dry ether (5ml) was submitted to GLC analysis (column A, 70°C (isothermal 8 min)-140°C at 1°/min; He carrier gas). Six components were observed in a ratio of 1:0.487:1.15: 1.33:1.37:0.996 with retention times 20.4, 45.0, 49.7, 50.5, 52.0 and

54.5 min respectively. The components were identified by retention time comparison and peak enhancement to be, in order of elution, (1) butyl nonyl ether; (2) 3-nonyl-4,5-dihydrofuran (56); (3) one isomer of 3-nonylidenetetrahydrofuran (58); (4) the other isomer of alkene (58); (5) 3-nonyl-2,5-dihydrofuran (57); (6) octadecane. Dry ethanol (2.37g, 3ml, 51 mmol) was added to the above substrate solution and the mixture reduced with lithium (350mg, 50 mmol) and liquid ammonia (50ml). GLC analysis (column A, above conditions) revealed nine components in a ratio of 1:0.426:1.84:0.397:0.415:0.875:1.06:0.132:0.333 with retention times 20.4, 45.0, 46.0, 49.7, 50.5, 52.0, 54.9, 72.1 and 74.7 min respectively. Retention time comparison and peak enhancement showed that the products were, in order of elution, (1) butyl nonyl ether; (2) 3-nonyl-4,5-dihydrofuran (56); (3) 3-nonyltetrahydrofuran (59); (4) one isomer of 3-nonylidenetetrahydrofuran (58); (5) the other isomer of alkene (58); (6) 3-nonyl-2,5-dihydrofuran (57); (7) octadecane; (8) 2-ethylundecanol (108); (9) 3-methyldodecanol (92). Thus, 3-nonyl-4,5-dihydrofuran (56) and 3-nonyl-2,5-dihydrofuran (57) have been reduced by 12% and 36% respectively. Both the (E) and (Z) isomers of 3-nonylidenetetrahydrofuran (58) have been reduced by approximately 66%.

3-Nonylidenetetrahydrofuran (58):

A solution of alkene (58) (89mg, 0.454 mmol) and octadecane (83mg, 3.27 mmol) in dry tetrahydrofuran (5ml) was analysed by GLC (column A, 70°C (isothermal 8 min)-145°C at 1°/min; He carrier gas). Three components were observed in a ratio of 1.36:0.282:1 with retention times 50.7, 51.4 and 55.3 min respectively. The components were identified by retention time comparison and peak enhancement. The first two components eluted were assigned, non specifically, to the (E) and

(Z)isomers of alkene (58). The third component was octadecane. Dry ethanol (1.58g, 2ml, 34.3 mmol) was added to the above substrate solution and the mixture reduced with lithium (179mg, 25.6 mmol) and ammonia (50ml) for 1h. GLC analysis (column A, above conditions) of the product showed five components in a ratio of 1.03:0.0826: 0.0117:1:0.185 with retention times 46.4, 50.3, 51.0, 55.3 and 75.5 min respectively. Retention time comparison and peak enhancement showed the products were, in order of elution, (1) 3-nonyltetrahydrofuran (59); (2) one isomer of 3-nonylidenetetrahydrofuran (58); (3) the other isomer of alkene (58); (4) octadecane; (5) 3-methyldodecanol (92). The two isomers of alkene (58) had reduced by 94% and 96% respectively.

Part 1.2

General Reduction Procedure

A solution of the substrate and ethanol (when required) in dry ether (10ml) or dry tetrahydrofuran (10ml) was added to a stirred solution of lithium in ammonia (50ml). Stirring was continued for the specified time and isoprene (where specified, solid ammonium chloride was used instead of isoprene) added to remove the excess metal. The ammonia was allowed to evaporate and wet ether (20ml) followed by water (20ml) was introduced. The layers were separated after shaking and the aqueous phase extracted with ether (2x20ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed by distillation through a 20cmx2.5cm vigreux column. Where specified, the product was not isolated and the combined ether extracts were submitted directly for GLC analysis.

3-Nonylfuran (73):

A solution of the alkylfuran (108mg, 0.557 mmol) in ether (5ml) was treated with lithium (256mg, 36.6 mmol), ethanol (1.97g, 2ml, 42.9 mmol) and ammonia for 1 h. GLC analysis (column A, 70°C (isothermal 8 min)-160°C at 1°/min) of the crude product ether extract revealed one component with retention time 32.3 min. The product was identified, by GLC retention time (column A, above conditions) comparison and peak enhancement with an authentic sample, and found to be starting material.

3-(1',1'-Ethylenedioxynonyl)furan (76):

(a) Without ethanol

Reduction of the acetal (76) (271mg, 1.08 mmol) solution in tetrahydrofuran with lithium (76mg, 10.9 mmol) and ammonia for 15 min (ammonium chloride) afforded 233mg of a clear liquid. A portion of the product (198mg) was resolved into three components by preparative TLC (ether-petrol ether; 2:8). In order of increasing Rf, the products were, (1) 2-[1'-(furan-3"yl) nonyloxy]ethanol (79); 114mg (49%); bp 98°C (0.01mm); IR (film) 3440, 1510, 1470, 1155, 1105, 1158, 1112, 880, 790, 720cm^{-1}; ^{1}H NMR (CCl_4)δ 0.9(3H,distorted t, terminal-CH_3), 1.1-1.9 (14H, merged m and s, -$(CH_2)_7$-), 2.1 (1H, brs, D_2O exch, -O<u>H</u>), 3.2-3.7 (4H, m, -$\underline{CH_2}\underline{CH_2}$OH), 4.2 (1H, t, J=7Hz, C1'-H), 6.3 (1H, m, furan C4"-H), 7.3 (2H, m, furan C2"-H and furan C5"-H); mass spectrum 254 (3,$M^{+\cdot}$), 193 (9, $M^{+\cdot}$-$C_2H_5O_2$), 141 (100, $M^{+\cdot}$-C_8H_{17}), 97 (94), 81 (36), 69 (16), 55 (15), 45 (36), 43 (17), 41 (35), 39 (12).

Anal calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found : C, 71.10; H, 10.42.

(2) A clear liquid (34mg, 15%) which was identical (IR, ^{1}H NMR) to starting material;

(3) 3-nonylfuran (73): 44mg (25%); bp 62°C (0.15mm); IR (film) 1503, 1470 1160, 1062, 1025, 878, 778, 715cm^{-1}; ^{1}H NMR (CCl_4)δ 0.9 (3H, distorted t, terminal -CH_3), 1.3 (14H, s, -$(CH_2)_7$-), 2.4 (2H, t, J=7Hz, alkane C1'-H_2), 6.1 (1H, m, furan C4-H), 7.1 (1H, m, furan C2-H), 7.2 (1H, m, furan C5-H); mass spectrum 194 (4, $M^{+\cdot}$), 146 (6), 95 (23), 82 (100), 81 (32), 67 (11), 57 (10), 55 (17), 53 (15), 43 (25), 41 (39), 39 (18).

Anal calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.43; H, 11.59.

GLC analysis (column E, 180°C) resolved the crude product into three components in a ratio of 1.2:1:3 with retention times 1.7, 5.6 and 8.3 min respectively.

The products were identified by GLC retention time comparison (column E, 180°C) with authentic samples and were found to be, in order of increasing retention time, 3-nonylfuran (73); starting material; and 2-[1'-(furan-3"yl)nonyloxy]ethanol (79).

(b) With ethanol (for 1h)

Reduction of the acetal (76) (218mg, 0.875 mmol) solution in ether with lithium (138mg, 19.7 mmol), ethanol (2.37g, 3ml, 51.4 mmol) and ammonia for 1h gave 161mg of a clear mobile liquid. GLC analysis [column A, 70°C (isothermal 8min)-160°C (isothermal 12min) at 1°/min] resolved the mixture into thirteen components in a ratio (percent) of 2.4 (1.8) : 17 (14) : 5.6 (4.3) : 10 (7.8) : 1.6 (1.2) : 17 (13) : 1.1 (0.84) : 1 (0.76) : 8.3 (6.4) : 48 (36) : 2.7 (2.1) : 5.1 (3.9) : 9.7 (7.4) with retention times 38.1, 38.9, 39.5, 41.5, 45.2, 46.0, 49.9, 50.7, 52.2, 71.8, 75.0, 88.1 and 105.9 min respectively. Excluding the last component, the mass spectrum of each product was recorded using a Finnigan gas liquid chromatograph/mass spectrometer data system, model 4021 [column F, 60°C (isothermal 10min)-180°C at 1°/min]. The first eluted product has not been fully characterised, but the mass spectrum 155 (19, M^+ - C_4H_8O-CH_3), 85 (28, $M^{+\cdot}$ - C_4H_8O-C_6H_{13}), 73 (23), 72 (91, $M^{+\cdot}$ - $C_{11}H_{22}O$), 71 (29), 57 (100), 55 (16), 43 (82), 41 (36) is consistent with the product being 3-ethoxy-2-ethylundecanal (109). Excluding the first and last eluted products, the components of the mixture were identified by GLC retention time (column A, above conditions) comparison, peak enhancement and mass

spectra comparison with authentic samples. These products were, in order of increasing retention time, and starting from the second eluted product inclusive: 3-nonylfuran (73); 3-nonyl-2,3-dihydrofuran (55); 2-ethylundecanal (107); 3-nonyl-4,5-dihydrofuran (56); 3-nonyltetrahydrofuran (59); one isomer of 3-nonylidenetetrahydrofuran (58); the other isomer of (58); 2-ethylundecanol (108); 3-methyl-dodecanol (92); and starting material. GLC retention time (column A, above conditions) comparison (but not mass spectral comparison) and peak enhancement with an authentic sample showed the last product eluted to be 2-octyl-2-(tetrahydrofuran-3'-yl)-1,3-dioxolane (80). Further GLC analysis (column C, 180°C) resolved the crude product into seven components with retention times 3.8, 4.5, 6.0, 6.6 (shoulder on previous peak), 16.5, 25.3, and 36.2 min respectively. GLC retention time (column C, 180°C) comparison and peak enhancement with authentic samples showed these to be, in order of increasing retention time, (1) 3-nonylfuran (73); (2) 2-ethylundecanal (107); (3) a mixture of 3-nonyltetrahydrofuran (59), 2-ethylundecanol (108), and 3-methyl-dodecanol (92); (4) a mixture of 3-nonyl-2,5-dihydrofuran (57), and the (E) and (Z) isomers of 3-nonylidenetetrahydrofuran (58); (5) starting acetal; (6) 2-[1'-(furan-3"-yl)nonyloxy]ethanol (79); (7) 2-octyl-2-(tetrahydrofuran-3'-yl)-1,3-dioxolane (80). The mass spectrum of each component was recorded using a Pye 104 gas chromatograph connected to an AEI-GEC MS3074 mass spectrometer (column C, 180°). The first, second, fifth, sixth and seventh products eluted had identical mass spectra to authentic samples of 3-nonylfuran (73); 2-ethylundecanal (107), starting acetal, 2-[1'-(furan-3"-yl)nonyloxy]ethanol (79), and 2-octyl-2-(tetrahydrofuran-3'-yl)-1,3-dioxolane (80) respectively. The first, second and seventh product eluted could be purified by preparative GLC (column C, 180°C) and were identical (IR, 'HNMR) to 3-nonylfuran (73),

2-ethylundecanal (107) and 2-[1'-(furan-3"-yl) nonyloxy]ethanol (79) respectively. This latter component and 2-octyl-2-(tetrahydrofuran-3'-yl)ethanol (80) were evident in approximately equal proportions.

(c) With ethanol (for 12 min)

The acetal (76) (106mg, 0.121 mmol) solution in ether was treated with lithium (134mg, 19 mmol), ethanol (1.58g, 2ml, 34.3mmol) and ammonia for 12 min. GLC analysis [column A, 70°C(isothermal 8 min)-160°C(isothermal 12min) at 1°/min] of the crude product ether extract resolved the mixture into eleven components in a ratio (percent) of 1.5 (3.2) : 5.6 (12) : 2.2 (4.5) : 6.2 (13) : 1.4 (2.9) : 2.0 (4.1) : 1 (2.1) : 4.2 (8.7) : 1.8 (3.9) : 19 (40) : 2.9 (6.1) with retention times 37.8, 38.6, 39.1, 41.2, 45.5, 49.5, 50.3, 51.8, 72.0, 86.9 and 105.3 min respectively. GLC retention time (column A, above conditions) comparison revealed that the products were, in order of increasing retention time, 2-ethyl-3-ethoxyundecanal (109); 3-nonylfuran (73); 3-nonyl-2,3-dihydrofuran (55); 2-ethylundecanal (107); 3-nonyltetrahydrofuran (59); one isomer of 3-nonylidenetetrahydrofuran (58); the other isomer of (58); 3-nonyl-2,5-dihydrofuran (57); 2-ethylundecanol (108); starting material; and 2-octyl-2-(tetrahydrofuran-3'-yl)-1,3-dioxolane (80). Further GLC analysis (column C, 180°C) of the product ethereal extracts resolved the mixture into seven components with retention times 4.0, 4.7, 6.2, 6.7, 16.5, 26.5, and 35.6 min. GLC retention time (column C, above conditions) comparison and peak enhancement with authentic samples revealed that the products were, in order of increasing retention time, (1) 3-nonylfuran (73); (2) 2-ethylundecanal (107); (3) a mixture of 3-nonyltetrahydrofuran (59) and 2-ethylundecanol (108); (4) a mixture of (E) and (Z) isomers of 3-nonylidenetetrahydrofuran (58) and 3-nonyl-2,5-dihydrofuran (57); (5) starting acetal; (6) 2-[1'-

(furan-3''-yl) nonyloxy]ethanol (79); (7) 2-octyl-2-(tetrahydrofuran-3'-yl)-1,3-dioxolane (80). The last two components were present in approximately equal proportions.

3-(1',1'-Dimethoxynonyl)furan (77):

The acetal (77) (144mg, 0.567 mmol) in ether was reduced with lithium (77mg, 11 mmol), ethanol (789mg, 1ml, 17 mmol) and ammonia for 30 min. GLC analysis [column A, 70°C (isothermal 8min)-160°C (isothermal 12min) at 1°/min] of the crude product ether extract resolved the mixture into eight components in a ratio (percent) of 1.3 (1.2) : 1.1 (1.1) : 1.0 (0.9) : 1.8 (1.7) : 83 (77) : 2.9 (2.7) : 11 (10) : 5.7 (5.3) with retention times 46.8, 50.7, 51.5, 53.0, 67.3, 73.3, 76.8 and 78 min respectively. GLC retention time (column A, above conditions) comparison with authentic samples revealed that the first four components were, in increasing order of retention time, 2-nonyltetrahydrofuran (59); one isomer of 3-nonylidenetetrahydrofuran (58); the other isomer of alkene (58); and 3-nonyl-2,5-dihydrofuran (57). The mass spectrum of each of the last four components was recorded using a Finnigan gas liquid chromatograph/mass spectrometer data system, model 4021 [column F, 100°C (isothermal 5min)-180°C at 1°/min]. The fifth component eluted was identical [GLC retention time (column A, above conditions) and mass spectrum] to starting acetal. The last three products eluted have not been fully characterised, and in order of increasing retention time had mass spectra: (a) 222 (11), 138 (7), 137 (100), 111 (2), 95 (12), 94 (7), 81 (8), 79 (7), 77 (9), 73 (2), 57 (3), 55 (8), 45 (6), 43 (6), 41 (10), 39 (13); (b) 114 (6), 113 (100), 109 (13), 97 (9), 96 (5), 85 (15), 83 (7), 81 (11), 79 (7), 72 (12), 71 (8), 67 (11), 55 (21), 53 (10), 45 (6), 43 (25), 42 (7), 41 (40), 39 (11); (c) 113 (100), 109 (14), 96 (3), 95 (14), 85 (17), 81 (13), 79 (14), 73 (9), 72 (11), 67 (13), 57 (8), 45 (10), 43 (33), 42 (10),

41 (53), 40 (10).

The highest mass ion in the mass spectrum of component (a), at m/e 222, does not correspond to the molecular formula of any expected products, and the component is considered to be an impurity. The mass spectra of (b) and (c) suggests that they are the geometric isomers of 3-(1'-methoxynonylidene)tetrahydrofuran (118) (see section 1.2.)

Competitive reduction of 3-(1',1'-ethylenedioxynonyl)furan (76) and 3-(1',1'-dimethoxynonyl)furan (77):

An ether solution of ethylenedioxy acetal (76) (50mg, 0.198 mmol), dimethoxy acetal (77) (54mg, 0.212 mmol), octadecane (32mg) and butyl nonyl ether (36mg) was submitted to GLC analysis (column A, 70°C (isothermal 8min)-140°C at 1°/min). Four components were observed in a ratio of 1 : 1.05 : 0.827 : 1.49 with retention times 20.0, 54.5, 65.3 and 87.4 min respectively. The components were identified by GLC retention time (column A, above conditions) comparison and peak enhancement to be, in order of increasing retention time, butyl nonyl ether; octadecane; dimethoxy acetal (77); and ethylenedioxy acetal (76). Dry ethanol (1.58g, 2ml, 34 mmol) was added to the above ethereal substrate solution and the mixture reduced with lithium (105mg, 15 mmol) and ammonia for 30 min. GLC analysis (column A, above conditions) of the crude product ether extract revealed that the GLC internal standards and acetal substrates had retention times 20.3, 54.5, 65.4 and 87.4 min and were present in a ratio of 1 : 0.992 : 0.160 : 0.040 respectively. GLC retention time (column A, above conditions) comparison identified these components, in order of increasing retention time, to be butyl nonyl ether; octadecane; dimethoxy acetal (77); and ethylenedioxy acetal (76).

Therefore, relative to the GLC internal standards, the dimethoxy acetal (77) and ethylenedioxy acetal (76) were reduced by 79% and 97% respectively.

1-(Furan-3'-yl)-5-methyl-3-(2"-methylpropyl)-2,8-dioxabicylo[3.2.1]-octane (123)(Dihydroeremoacetal):

Reduction of the acetal (123) (407mg, 1.63 mmol) solution in tetrahydrofuran with lithium (110mg, 15.7 mmol) and ammonia for 15 min (ammonium chloride) gave 338mg of a clear liquid. GLC analysis (column E, 182°C) of the product showed one component with retention time 3.7min. The product was identical [IR, 'HNMR, GLC retention time (column E, 182°C)] to starting material.

3-(1'-Methoxynonyl)furan (75):

(a) Without ethanol

Reduction of the ether (75) (113mg, 0.505 mmol) solution in tetrahydrofuran with lithium (56mg, 6.3 mmol) and ammonia for 15 min (ammonium chloride) gave 105mg of a clear liquid. A portion (95mg) of the crude product could be separated into two components by preparative TLC (ether-petrol ether; 1:9). The higher Rf product was a clear liquid (46mg, 47% yield) which was identical (IR 'H NMR) to 3-nonylfuran (73). The lower Rf product was a clear liquid (55mg, 48% yield) which was identical (IR, 'H NMR) to starting material. GLC analysis (column D, 220°C) of the crude product resolved the mixture into two components in a ratio of 1:7 with retention times 6.4 and 10.5 min respectively. GLC retention time (column D, 220°C) comparison with authentic samples showed that the minor product was 3-nonylfuran (73) and that the major product was starting material.

(b) With ethanol

Reduction of the ether (75) (115mg, 0.513 mmol) solution in ether with lithium (90mg, 12.8 mmol), ethanol (1.58g, 2ml, 34.4 mmol) and ammonia for 30 min gave 92mg of a clear liquid. GLC analysis [column A, 70°C (isothermal 8min)-160° (isothermal 6min) at 1°/min] resolved the mixture into eleven components in a ratio (percent) of 1 (2) : 3.6 (6) : 2.2 (4) : 10.2 (18) :5.1 (9) : 3.4 (6) : 1.2 (2) : 7.3 (13) : 15.2 (26) : 7.1 (12) : 1 (2) with retention times 38.8, 39.6, 40.2, 42.2, 46.7, 50.6, 51.4, 52.9, 58.9, 73.3 and 75.9 min respectively. GLC retention time (column A, above conditions) comparison with authentic samples identified the products to be, in order of increasing retention time, 3-ethoxy-2-ethylundecanal (109); 3-nonylfuran (73); 3-nonyl-2,3-dihydrofuran (55); 2-ethylundecanal (107); 3-nonyltetrahydrofuran (59); one isomer of 3-nonylidenetetrahydrofuran (58); the other isomer of (58); 3-nonyl-2,5-dihydrofuran (57); starting material; 2-ethylundecanol (108); and 3-methyldodecanol (92).

1-(Furan-3'-yl)nonyl acetate (74):

(a) Without ethanol

Reduction of the acetate (74) (291mg, 1.15 mmol) solution in tetrahydrofuran with lithium (78mg, 11.1 mmol) and ammonia for 15 min (ammonium chloride) afforded 220mg of a clear liquid. A portion (195mg) of the product was separated into two components by preparative TLC (ether-petrol ether; 2:8). The higher Rf product was a clear liquid (93mg, 47% yield) which was identical (IR, ^{1}H NMR) to 3-nonylfuran (73). The lower Rf product was a clear liquid (50mg, 23% yield) which was identical (IR, ^{1}H NMR) to 1-(furan-3'-yl)nonanol (78). GLC analysis (column D, 220°C) resolved the crude product into two components in

a ratio of 3:1 with retention times 6.6 and 16.1 min respectively. GLC retention time (column D, 220°C) comparison with authentic samples revealed that the major component was 3-nonylfuran (73) and that the minor component was 1-(furan-3'-yl)nonanol (78).

(b) With ethanol

Reduction of the acetate (74) (157 mg, 0.623 mmol) solution in tetrahydrofuran with lithium (100mg, 14.3 mmol), ethanol (789mg, 1ml, 17.1 mmol) and ammonia for 15 min (ammonium chloride) gave 116mg of a clear liquid. The ^{1}H NMR spectrum of the crude product was dominated by resonances ascribable to 3-nonylfuran (73). The infrared spectrum showed a weak hydroxyl absorption at 3380cm^{-1} and a strong characteristic furan ring absorption at 880cm^{-1}. GLC analysis (column D, 219°C) of the crude product resolved the mixture into five components in a ratio of 52 : 2 : 1 : 5 : 16 with retention times of 6.9, 8.0, 10.3 and 16 min respectively. GLC retention time (column D, 219°C) comparison with authentic samples revealed that the first and last components eluted were 3-nonylfuran (73) and 1-(furan-3'-yl)nonanol (78); that the second peak could be a mixture of 3-nonyl-2,3-dihydrofuran (55) and 2-ethylundecanal (107); that the third peak could be a mixture of 3-nonyltetrahydrofuran (59), 2-ethylundecanol (108) and 3-methyldodecanol (92); and that the fourth peak could be a mixture of 3-nonyl-2,5-dihydrofuran (57) and 3-nonylidenetetrahydrofuran (58).

Part 1.3

General Reduction Procedure

Lithium was dissolved in liquid ammonia (50ml). Ethanol (when required) was added with stirring. A solution of the substrate in dry tetrahydrofuran (10ml) was added and stirring continued for the specified time. Unless otherwise indicated, solid ammonium chloride was added to remove the excess of metal. The ammonia was allowed to evaporate, and wet ether (20ml) followed by water (20ml) introduced. The layers were separated after shaking and the aqueous phase extracted with ether (2x20ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed by distillation through a 20cmx2.5cm vigreux column to afford the product.

1-(Furan-2'-yl)nonyl acetate (146):

(a) Without ethanol

Reduction of the acetate (146) (1.00g, 3.97 mmol) solution in tetrahydrofuran with lithium (177mg, 25.2 mmol) and ammonia for 10 min afforded a clear mobile liquid which was homogeneous by analytical GLC (column B, 145°C) and proved to be 2-nonylfuran (145): 700mg (70%); bp 40°C (0.01mm); IR (film) 1600, 1516, 1470, 1140, 1076, 1000, 921, 880, 790, 717cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.1 (14H, s, $-(CH_2)_7-$), 2.5 (2H, t, J=7Hz, C1'-H_2), 5.8 (1H, apparent d, furan C3-H), 6.1 (1H, apparent t, furan C4-H), 7.1 (1H, m, furan C5-H); mass spectrum 194 (1, $M^{+\cdot}$), 137 (3), 123 (4), 110 (3), 109 (4), 95 (36), 82 (34), 81 (100, $M^{+\cdot}-C_8H_{17}$), 67 (12), 53 (24), 43 (38), 41 (44). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found : C, 80.12; H, 11.41.

(b) With ethanol

Reduction of the acetate (146) (186mg, 0.738 mmol) solution in tetrahydrofuran with lithium (80mg, 11.4 mmol), ethanol (789mg, 1ml, 17.1 mmol) and ammonia for 10 min afforded 128mg (89% yield) of a clear mobile liquid which was homogeneous by analytical GLC (column B, 145°C) and identical [IR,'H NMR, GLC retention time (column B, 145°C)] to 2-nonylfuran (145).

2-(1'-Methoxynonyl)furan (147):

(a) Without ethanol

Reduction of the ether (147) (176 mg, 0.786 mmol) with lithium (60mg, 8.6 mmol) and ammonia for 10 min afforded 112 mg (73% yield) of a pale yellow liquid which was homogeneous by analytical GLC (column B, 145°C) and was identical [IR,'H NMR, GLC retention time (column B, 145°C)] to 2-nonylfuran (145).

(b) With ethanol

Reduction of the ether (147) (123mg, 0.549 mmol) solution in tetrahydrofuran with lithium (116mg, 16.6 mmol), ethanol (1.58g, 2ml, 34.3 mmol) and ammonia for 15 min gave 83mg (78% yield) of a clear mobile liquid which was homogeneous by analytical GLC (column B, 145°C) and was identical [IR,'H NMR, GLC retention time (column B, 145°C)] to 2-nonylfuran (145).

2-(1',1'-Ethylenedioxynonyl)furan (148):

(a) Without ethanol

Reduction of the acetal (148) (231 mg, 0.916 mmol) solution in tetrahydrofuran with lithium (93mg, 13.3 mmol) and ammonia for 15 min afforded 174mg (98% yield) of a pale yellow mobile liquid which was homogeneous by analytical GLC (column D, 217°C) and was identical [IR,'H NMR, GLC retention time (column D, 217°C)] to 2-nonylfuran (145).

(b) With ethanol

Reduction of the acetal (148) (119mg, 0.473 mmol) solution in tetrahydrofuran with lithium (103mg, 14.7 mmol), ethanol (1.5g, 2ml, 34.3 mmol) and ammonia for 15 min gave 74mg of a clear mobile liquid. GLC analysis (column B, 182°C) showed two components in a ratio of 17(95%) : 1(5%) with retention times 1.5 and 1.9 min respectively. Mass spectra were determined using a gas-liquid chromatograph connected to a mass spectrometer (column B, 182°C). The major component was identical [mass spectrum, GLC retention time (column B, 182°C)] to 2-nonylfuran (145). The minor component had mass spectrum 196 (12), 157 (35), 111 (15), 98 (46), 97 (56), 83 (18), 73 (100), 69 (67), 55 (100), 43 (22). The 'HNMR($CDCl_3$) spectrum of the crude product showed a low intensity complex multiplet resonance at 3.2-4.2δ in addition to resonances ascribable to the alkylfuran. The minor product has not been fully characterized, but the spectral data suggests that it is a dihydrofuran derivative.

1-(Furan-2'-yl)nonanol (149):

(a) Without ethanol

Reduction of the alcohol (149) (780mg, 3.71 mmol) with lithium (80mg, 11.4 mmol) and ammonia for 8 min gave 778mg of a pale yellow liquid. GLC (column D, 218°C) analysis of the product showed two components in a ratio of 1(6%) : 16(94%) with retention times 5.6 and 12.4min respectively. GLC (above conditions) retention time comparison, and peak enhancement with authentic samples, showed that the minor component was 2-nonylfuran (145) and that the major component was starting material.

(b) With ethanol

Reduction of alcohol (149) (178mg, 0.848 mmol) with lithium (84mg, 12mmol) and ammonia for 8 min afforded 165 mg of a pale yellow liquid. GLC (column D, 218°C) analysis showed two components in a ratio of 1(20%) : 4.1(80%) with retention times 5.6 and 12.4min respectively. Comparison of GLC (above conditions) retention times with authentic samples showed that the minor component was 2-nonylfuran (149) and that the major component was starting material.

2-(Pent-1'-enyl)furan (150):

(a) Without ethanol

The alkene (150) (458mg, 3.87 mmol) was treated with lithium (80mg, 10.1 mmol) and ammonia for 8 min to give 254mg of a pale yellow liquid. A 197mg portion of the product was resolved into two components by preparative TLC (petrol ether). The higher Rf product proved to be 2-pentylfuran[118] (161): 93mg (47%); IR (film) 1590, 1510, 1415, 1373, 1092, 1002, 915, 878, 786, 716cm^{-1}; ^{1}H NMR ($CDCl_3$)δ 0.8-1.7 (9H, c, $-C_4H_9$),

2.7 (2H, t, J=7Hz, C1'-H_2), 6.1 (1H, apparent d, furan C3-H) 6.3 (1H, apparent t, furan C4-H), 7.7 (1H, m, furan C5-H); mass spectrum 138 (26, $M^{+\cdot}$), 103 (5), 95 (9), 82 (34, $M^{+\cdot}-C_4H_8$), 68 (5), 67 (6), 53 (19), 43 (8), 41 (9), 39 (8).

The lower Rf component proved to be the dimer 2-[4'-(furan-2"-yl)-2',3'-dipropylbutyl)furan (162): 88mg (45%); IR (film) 1590, 1510, 1465, 1373, 1140, 1010, 915, 878, 785, 715cm^{-1}; 'H NMR ($CDCl_3$) δ 0.9-2.1 (16H, c, two -$CH(CH_2)_2CH_3$), 2.6 (4 H, d, J=7Hz, C1'-H_2 and C4'-H_2), 6.0 (2H, m, furan C3-H and furan C3"-H), 6.3 (2H, m, furan C4-H and furan C4"-H), 7.3 (2H, m, furan C5-H and furan C5"-H); mass spectrum 274 (24, $M^{+\cdot}$), 183 (7, $M^{+\cdot}-C_9H_{13}O$), 137 (14), 81 (100, $M^{+\cdot}-C_{13}H_{21}O$), 69 (14), 55 (18), 53 (21), 43 (12), 41 (11); Found: $M^{+\cdot}$274.193977. Calcd for $C_{18}H_{26}O_2$: 274.1932678.

(b) With ethanol

The alkene (150) (460mg, 3.38 mmol) was treated with lithium (110mg, 11.4 mmol), ethanol (789mg, 1ml, 17.1 mmol) and ammonia for 8 min to afford 337mg of a pale yellow liquid. A 217mg portion of the product was resolved into two components by preparative TLC (petrol ether). The higher Rf band gave 95mg (44% yield) of a clear mobile liquid which was identical (IR, 'H NMR) to 2-pentylfuran[118] (161). The lower Rf band afforded 66mg (15% yield) of a clear mobile liquid which was identical (IR, 'H NMR) to the dimer (162).

1-(Furan-2'-yl) nonan-1-one (160):

(a) Without ethanol

Reduction of the ketone (160) (297mg, 1.43 mmol) solution in tetrahydrofuran with lithium (100mg, 14.3 mmol) and liquid ammonia

for 35 min afforded 177mg of a pale yellow liquid. GLC (column D, 221°C) showed the presence of three components in a ratio of 2:1:5 with retention times 12.6, 13.5 and 17.2 min respectively. The first two eluted components were collected together by preparative GLC (above conditions) and subsequently separated by preparative TLC (ether-petrol ether; 2:8). The lower Rf band afforded a clear liquid (7mg) which was identical ['H NMR, GLC retention time (above condition)] to 1-(furan-2'-yl)nonanol (149). The higher Rf band gave a clear liquid (11mg) which was identical [IR, 'H NMR, GLC retention time (above conditions)] to 1-(2',3'-dihydrofuran-2'-yl)-nonan-1-one (171).

The major component of the reduction product mixture was isolated by preparative GLC (above conditions) and was identical ['H NMR, GLC retention time (above conditions)] to starting material.

(b) With ethanol

Reduction of the ketone (160) (297mg, 1.43 mmol) solution in tetrahydrofuran with lithium (120mg, 17.1 mmol), ethanol (789mg, 1ml, 17.1 mmol) and ammonia for 35 min (isoprene) gave 284 mg of a pale yellow liquid. GLC analysis (column C, 180°C) resolved the product into six components in a ratio of 1 : 4.2 : 8.1 : 7.4 : 32 : 53 with retention times 3.0, 4.0, 6.4, 7.0, 8.6 and 16.7 min respectively. The mass spectrum of each component was determined using a gas-liquid chromatograph (column C, 180°C) connected to a mass spectrometer. Except for the first two eluted components, the products could be purified by preparative GLC (column D, 221°C).

In order of elution, the reduction products were: (1) A compound which was identical [mass spectrum, GLC retention time (column C, 180°C)]

to 2-nonylfuran (145); (2) A 2-nonyldihydrofuran with mass spectrum 196 (0.5), 182 (1), 143 (10), 141 (15), 97 (16), 87 (17), 83 (50), 69 (100), 57 (42), 55 (73), 43 (58), 41 (40); (3) A clear liquid which was identical [IR, 'H NMR, mass spectrum, GLC retention time (column C, 180°C)] to 1-(2',3'-dihydrofuran-2'-yl)nonan-1-one (171); (4) A clear liquid which was identical [IR, 'H NMR, mass spectrum, GLC retention time (column C, 180°C)] to 1-(furan-2'-yl)nonanol (149); (5) A clear liquid which was identical [IR, 'H NMR, mass spectrum, GLC retention time (column C, 180°C)] to 1-(tetrahydrofuran-2'-yl)-nonan-1-one (177); (6) A white crystalline solid which was identical [mp, IR, 'H NMR, GLC retention time (column C, 180°C)] to tridecane-1,5-diol (182).

(c) With *tert*-butyl alcohol:

Reduction of a solution of the ketone (160) (712mg, 3.42 mmol) and *tert*-butyl alcohol (244mg, 3.39 mmol) in tetrahydrofuran with lithium (180mg, 25.7 mmol) and ammonia for 45 min(isoprene) afforded 678 mg of a pale yellow liquid. GLC analysis (column C, 175°C) resolved the product into five components in a ratio of 22 : 1 : 4.6 : 4.2 : 7.7 with retention times 7.8, 8.6, 9.3, 10.6 and 11.3 min respectively. The mass spectrum of each component was determined using a gas-liquid chromatograph (column C, 175°C) connected to a mass spectrometer. The second, fourth and fifth component eluted from the chromatograph were identified by comparison of mass spectra, GLC retention times (above conditions) and peak enhancement with authentic samples. The first, and major product was isolated from a portion (143mg) of the product by preparative TLC (ether-petrol ether; 8:92) and proved to be 1-(2',3'-dihydrofuran-2'-yl)nonan-1-one (171): 22mg (decomposes on silica); IR (film) 1725, 1625, 1460, 1400, 1375,

1270, 1130, 1050, 930, 695cm^{-1}; ^{1}H NMR (CCl_4) 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (12H, s, $-(CH_2)_6-$), 2.5 (2H, t, J=7Hz, $-CH_2\underline{CH_2}CO-$), 2.8 (2H, m, dihydrofuran C3'-H_2), 4.5 (1H, apparent d, dihydrofuran C2'-H), 4.8 (1H, m, dihydrofuran C4'-H), 6.1 (1H, m, dihydrofuran C5'-H), mass spectrum 210 (5, $M^{+\cdot}$), 141 (4), 112 (12, $M^{+\cdot}-C_7H_{14}$), 97 (90, $M^{+\cdot}-C_8H_{17}$), 69 (100, $M^{+\cdot}-C_9H_{19}O$), 68 (100), 57 (64), 43 (50), 41 (75); Found: $M^{+\cdot}$ 210.162076. Calcd for $C_{13}H_{22}O_2$: 210.1619694.

The other products, in order of increasing retention time, were (1) 1-(furan-2'-yl)nonanol (149); (2) an unidentified component, possibly 1-(2',5'-dihydrofuran-2'-yl)nonan-1-one (174): mass spectrum 210 (0.7, $M^{+\cdot}$), 141 (29, $M^+ - C_4H_5O$) 123 (5), 110 (18), 97 (15, $M^+ - C_8H_{17}$), 81 (10), 71 (47), 69 (100, $M^{+\cdot}-C_9H_{17}O$), 57 (62), 55 (20), 43 (58), 41 (63). A small sample (<1mg) of this product, contaminated with aliphatic impurities, could be isolated by preparative GLC (column C, 175°C): ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.8 - 2.0 (strong absorption, three merged m, methylene envelope), 2.5 (low intensity absorption, m, $-\underline{CH_2}CO$), 4.7 - 5.2 (low intensity absorption, m, dihydrofuran C5'-H_2), 5.6 - 6.1 (low intensity absorption, two merged m, dihydrofuran C3'-H_2, dihydrofuran C4'-H_2 and dihydrofuran C2'-H); (3) 1-(tetrahydrofuran-2'-yl)nonan-1-one (177); (4) starting material.

Part 1.5:

Hydrogenation of 3-nonylfuran (73):

Platinum oxide (20mg) was added to a solution of the alkylfuran (73) (171mg, 0.881 mmol) in ethanol (15ml) and the mixture shaken under a hydrogen atmosphere at 55 psi and 20°C for 20h. The solution was filtered through celite and the solvent distilled to afford 111mg of a tan mobile liquid. GLC analysis (column A, 70°C (isothermal 8 min)-160°C at 1°/min) resolved the product into three components in a ratio of 2.2 : 2.2 : 1 with retention times 45.9, 72.5 and 75.0 min respectively. GLC retention time (column A, above conditions) comparison and peak enhancement identified the products to be, in order of elution, 3-nonyltetrahydrofuran (59), 2-ethylundecanol (108) and 3-methyldodecanol (92).

Lithium aluminium hydride reduction of 3-(1',1'-dimethoxynonyl)furan (77):

A mixture of dimethoxy acetal (77) (397mg, 1.56 mmol) and lithium aluminium hydride (200mg, 5.26 mmol) in dry ether (15ml) was stirred at ambient temperature for 30 min. Sodium sulphate (0.5ml, saturated) was cautiously added during 20min, the solution filtered to remove the white granular precipitate, and the solvent distilled to afford a pale yellow liquid. The product was purified by chromatography on alumina (10g, gradient elution from neat petrol ether to 10% ether in petrol ether) to give 260mg (80% yield) of a clear mobile liquid which was identical (IR, ^{1}H NMR) to 3-(1'-methoxynonyl)furan (75).

Work Described in Chapter II

Part 2.1

Section 2.1.1

Ethyl undec-10-enoate[146]:

The procedure was adapted from the method of Natalson and Gottfried[147] for the preparation of ethyl bromoacetate. A mixture of commercial undec-10-enoic acid (124g, 0.675 mol), ethanol (307g, 390ml, 6.69mol), benzene (610ml) and sulphuric acid (1ml, SG 1.84) was heated under reflux for 3h in a system equipped with a Dean and Stark apparatus. The side arm of this apparatus was drained every 15 min and 140ml of distillate was collected in 12ml portions. Further ethanol (40ml) was added and heating under reflux continued for 40 min. About 500ml of the solvent was removed by distillation, the mixture cooled, washed with ammonia (1x500ml, 10%), dried ($MgSO_4$), and the remaining solvent removed at reduced pressure to afford a pale yellow mobile liquid: 139g (97%); IR (film) 1730, 1635, 1460, 1360, 1160, 1020, 900cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (12H, c, $-(CH_2)_6-$ and $-OCH_2\underline{CH_3}$), 2.1 (4H, m, C2-H_2 and C9-H_2), 4.1 (2H, q, J=7Hz, $-O\underline{CH_2}CH_3$), 5.0 (1H, apparent d, $-CH=C\underline{H_2}$), 5.5-6.1 (1H, m, $-C\underline{H}=CH_2$).

Ethyl undecanoate[148]:

A solution of ethyl undec-10-enoate (139g, 0.656mol) in ethanol (250ml) was reduced with hydrogen at 50psi pressure in the presence of platinum oxide (0.6g) catalyst until hydrogen uptake ceased. After filtration through celite the solvent was removed at reduced pressure and the residue distilled to give the ester: 111g (79%), bp 79°C (0.1mm) [lit.[148] bp 115.5°C (5mm)]; IR (film) 1735, 1480, 1365, 1160, 1100, 1025cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9-1.8 (22H, c, $-(CH_2)_8CH_3$ and ester $-OCH_2\underline{CH_3}$), 2.2 (2H, distorted t, C2-H_2), 4.0 (2H, q, J=7Hz, ester $-O\underline{CH_2}CH_3$).

Ethyl 3-nonyl-2-oxobutanedioate (195):

The procedure was adapted from the method of Schinz and Minder[123] for the preparation of ethyl 3-pentyl-2-oxobutanedioate.

A mixture of alcohol free sodium ethoxide (7.56g. 0.146mol) and diethyl oxalate (20.7g, 19.3ml, 0.142mol) in dry ether (150ml) was stirred at ambient temperature for 1.5h and ethyl undecylate (30.0g, 34.7ml, 0.140mol) introduced. After heating under reflux for 28h the solution was poured into cooled (ice bath) and stirred sulphuric acid (150ml, 10%). The organic layer was separated and the aqueous layer extracted with ether (2x50ml). The combined organic phases were washed with sodium bicarbonate (1x50ml, 10%), sodium chloride (1x50ml, saturated) and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave the crude keto diester (195) as a pale yellow mobile liquid: 42.9g (97%); bp 98°C (0.01mm); IR (film) 1720, 1650(w), 1470, 1370, 1290, 1240, 1190, 1100, 1030, 880, 815, 785, 710cm^{-1}; ^{1}H NMR δ 0.9-1.6 (25H, c, $-(CH_2)_8CH_3$ and two ester $-OCH_2\underline{CH_3}$), 3.9-4.5 (5H, two q and one t merged, two ester $-O\underline{CH_2}CH_3$ and $-CO\underline{CH}CO_2Et$); mass spectrum 315 (1), 314 (2, $M^{+\cdot}$), 286 (1), 268 (2), 242 (26), 241 (100, $M^{+\cdot} - CO_2Et$), 214 (9), 195 (18), 167 (20), 160 (13), 149 (39), 143 (6), 129 (7), 125 (7), 115 (15), 101 (49, $M^{+\cdot} - C_{10}H_{19}CO_2Et$), 88 (80), 83 (49), 73 (39), 69 (55), 43 (85), 41 (55).

Lithium aluminium hydride reduction of ethyl 3-nonyl-2-oxobutanedioate (195)

A solution of lithium aluminium hydride (402mg, 10.6mmol) and the ester (195) (1.76g, 5.60mmol) in dry ether (20ml) was heated under reflux for 1h. After cooling, sodium sulphate (1ml, saturated) was added cautiously during 5min with stirring. The mixture was stirred for

a further 2h and sulphuric acid (12ml, 2M) added to dissolve the salts. The solution was saturated with sodium sulphate, the organic layer was separated and the aqueous phase extracted with ether (3x20ml). The combined organic extracts were dried and the solvent removed *in vacuo* to afford a pale yellow liquid: 1.28g; IR (film) 3350, 1430, 1130cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal -CH_3), 1.2 (21H, s, methylene envelope), 3.3 (2H brc, -CH_2OH or -CHOH), 5.1 (2H, brs, D_2O exch, -OH).

The ^{1}H NMR spectrum suggested that the loss of one oxygen substituent had occurred and the compound was not further characterised.

3-Hydroxymethyldodecane-1,2-diol (196):

Sodium borohydride (4.82g, 126mmol) was added in one portion to a stirred and cooled (ice bath) solution of the keto diester (195) (20g, 63.6mmol) in ethanol (120ml). After the initial vigorous reaction had subsided (10min), the cooling bath was removed and the solution stirred at ambient temperature for 2.5h. The solution was concentrated to 75ml, poured slowly into ice-cold sulphuric acid (200ml, 5N), stirred 0.5h and extracted with dichloromethane - tetrahydrofuran (9:1) (5x50ml). The combined organic extracts were washed with sodium chloride (1x50ml, saturated), dried (Na_2SO_4) and the solvent evaporated to afford a pale yellow liquid: 15.6g; IR (film) 3420, 1780(w), 1745(s), 1470, 1170, 1025cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (distorted t, terminal-CH_3), 1.3 (s, methylene envelope), 1.9-2.6 (brc), 2.9 (s), 3.5-4.3 (brc). These resonances had relative areas 3:22:3:1:5 respectively.

A 5.8g portion of the crude product was crystallised from chloroform-petroleum ether (4:1) to give a white solid: 1.7g;

IR (nujol) 3450, 1740, 1470, 1025, 975cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (distorted t, terminal -CH_3), 1.3 (s, methylene envelope), 2.0-2.8 (ć), 4.3 (apparent d), 4.6 (ć), these resonances had relative areas 3:17:2:2:1 respectively; ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.5 (t), 23.2 (t) 27.5, 29.2, 29.4, 31.7, 45.4 (d), 69.1 (d), 74.4 (t), 178.3 (s, C=O); mass spectrum 249 (5), 248 (8), 198 (41), 197 (36), 173 (23), 172 (15), 115 (85), 102 (100), 85 (70), 57 (18), 56 (12), 55 (27), 44 (32), 43 (30), 41 (40). Double charge ions were observed at m/e 138.5, 98.5, 86.5, 85.5 - all with a relative abundance of less than 1%.

Evaporation of the solvent from the crystallisation mother liquor gave a clear viscous liquid which solidified slowly: IR (film) 3420, 1780(w), 1740 (s), 1460, 1160, 1120cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (s), 1.3 (s), 2.0-2.5 (brc), 3.5-4.4 (brc), these resonances had relative areas 3:14:1:3; ^{13}C NMR ($CDCl_3$) δ 13.8, 22.4, 26.7, 28.3, 29.1, 29.3, 31.6, 34.2, the resonances observed above 40δ had a very low intensity; mass spectrum 214 (11), 185 (3), 169 (23), 157 (12), 143 (8), 129 (5), 115 (15), 101 (66), 88 (100), 73 (24), 69 (26), 61 (37), 60 (35), 57 (29), 55 (44), 43 (55), 41 (54).

A solution of the crude reduction product (15.6g), in dry ether (50ml) was added to a stirred solution of lithium aluminium hydride (4.35g, 114mmol) in dry ether (100ml) during 10 min. A vigorous exothermic reaction ensued during the addition. The mixture was heated under reflux for 1h, cooled, and sodium sulphate (10ml, saturated) added dropwise with vigorous stirring. The white precipitate was filtered off and the solvent evaporated to give a clear viscous liquid: 2.58g. The precipitate salts were dissolved in sulphuric acid (250ml, 10N) and the solution extracted with dichloromethane - tetrahydrofuran (9:1) (6x150ml). The combined organic extracts were dried (Na_2SO_4)

and the solvent evaporated to give a pale yellow viscous liquid: 8.8g. The combined crude products afforded the triol (196): 11.5g [78% from (195)]; IR (film) 3350, 1470, 1200(w), 1130, 875(w)cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (17H, s, C3-H and $-(CH_2)_8-$), 3.9 (5H, brs, -CHOH and $-CH_2OH$), 5.2 (3H, brs, -OH, D_2O exch).

4-Nonyltetrahydrofuran-3-ol (197a):

A mixture of the crude triol (196) (11.5g, 49.6mmol) and *p*-toluenesulphonic acid (0.5g) in benzene (50ml) was heated under reflux for 4.5h in a system equipped with a Dean and Stark apparatus. After cooling, the solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel (100g; gradient elution from 1% ethyl acetate in petrol ether to 15% ethyl acetate in petrol ether) to afford (197a) as a mobile amber liquid: 5.71g (54%); bp 110-115°C (0.07mm); IR (film) 3420, 1465, 1100, 1050, 900cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (16H, s, $-(CH_2)_8-$), 1.9 (1H, brs, C4-H), 2.4 (1H, brs, -OH), 3.3-4.4 (5H, brc, C2-H_2, C3-H, C5-H_2); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.7, 28.6, 29.4, 29.7, 30.0, 32.0, 45.1 and 48.7 (pair of d, C4 of each diastereoisomer), 71.6, 72.6, 72.9, 74.7, 76.3, 77.5 (the last six resonances are ascribable to C2, C3 and C5 of the two diastereoisomers); mass spectrum 183 (36), 165 (23), 154 (15), 126 (18), 109 (34), 83 (50), 69 (69), 57 (100), 55 (74), 43 (80), 41 (84). Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 73.05; H, 11.90.

4-Nonyltetrahydrofuran-3-yl acetate (197b):

A solution of the alcohol (197a) (509mg, 2.38mmol) and acetic anhydride (681mg, 0.630ml, 6.68mmol) in dry pyridine (1ml) was allowed to stand at 5°C for 23h. Water (0.4ml) was added followed by ether

(30ml) after 20min. The mixture was washed with water (1x10ml), hydrochloric acid (2x10ml, 10%), ammonia (1x10ml, 10%), sodium chloride (1x10ml, saturated) and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded a pale yellow mobile liquid: 533mg (87%); IR (film) 1745, 1475, 1370, 1235, 1090, 1020cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (16H, s, $-(CH_2)_8-$), 2.1 (4H, s, with shoulder on upfield side, $-COCH_3$ and C4-H), 3.4-4.4 (4H, c, C2-H_2 and C5-H_2), 5.0 and 5.4 (1H, pair of m, C3-H for diastereomeric acetates; 1:1.6 respectively).

4-Nonyltetrahydrofuran-3-yl xanthate (197c):

Sodium hydride (162mg, 6.7mmol; 50% suspension in oil) was washed with pentane (2x5ml) under a nitrogen atmosphere. Dry ether (20ml) was introduced followed by a solution of the alcohol (197a) (616mg, 2.8mmol) in dry ether (1ml) and the mixture was stirred for 2h at room temperature. Carbon disulphide (504mg, 0.400ml. 6.64mmol) and methyl iodide (912mg, 0.400ml, 6.4mmol) were added and stirring continued for 15h. Water (15ml) was added, the layers separated and the aqueous phase extracted with ether (2x20ml). The combined ether extracts were dried (K_2CO_3) and the solvent distilled to afford a pale yellow liquid: 836mg (98%); IR (film) 1465, 1210(s), 1055(s)cm^{-1}; ^{1}H NMR (CDCl) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (16H, s, $-(CH_2)_8-$), 2.5 (3H, s, $-OCS_2CH_3$), 3.3-4.2 (4H, c, C2-H_2 and C5-H_2), 5.5 and 5.9 (1H, pair of m, C3-H of each diastereomer; 1:1.6 respectively).

Pyrolysis of 4-nonyltetrahydrofuran-3-yl acetate (197b):

The acetate (197b) (235mg, 0.918mmol) was heated to 100°C at 15mm of Hg pressure and distilled through a 35cm x 3cm quartz glass column packed with quartz glass helices and heated at 545°C to afford 111mg of a pale yellow liquid. GLC analysis (column B, 145°C) resolved the product into four components in a ratio of 5.9 : 1.1 : 4.2 : 1 with retention times of 4.6, 5.6, 8.2, 9.4 min respectively. The first eluted component had a retention time identical to that of 3-nonylfuran (73). The ^{1}H NMR ($CDCl_3$) of the crude product showed resonances at 0.9 and 1.3δ ascribable to a $-(CH_2)_8CH_3$ moiety. Low intensity multiplet resonances were observed at 2.5 and 5.5δ. Resonances ascribable to 3-nonylfuran (73) were observed at 6.2δ (furan C4-H), 7.1 and 7.3δ (furan C2-H and furan C5-H). No evidence was obtained for the formation of the requisite dihydrofurans and the procedure was not further investigated.

3-Nonyl-2,3-dihydrofuran (55) and 3-nonyl-2,5-dihydrofuran (57):

The xanthate (197c) (860mg, 2.83 mmol) was heated to 220°C at 15mm of Hg pressure and slowly distilled through a 35cm x 3cm quartz glass column packed with quartz glass helices and heated at 320°C to afford 450mg (81%) of a pale yellow liquid. GLC analysis (column A, 70°C (isothermal 8 min)-140°C at 1°/min) revealed the presence of two components in a ratio of 2.2 : 1 with retention times 39.1 and 51.7 min respectively. The products were purified by preparative GLC (column B, 145°C).

The major component proved to be 3-nonyl-2,3-dihydrofuran (55): IR ($CDCl_3$) 1620(w), 1480(m), 1380(m), 1135, 1090cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (16H, s, $-(CH_2)_8-$), 2.9 (1H, brm,

C3-H), 3.9 and 4.3 (2H, ABX, J_{AX}=6.6Hz, J_{BX}=8.9Hz, J_{AB}=9.1Hz, C2-H_2) 4.9 (1H, apparent t, C4-H), 6.3 (1H, apparent t, C5-H); mass spectrum 196 (5, $M^{+\cdot}$), 83 (5, $M^{+\cdot}$-C_8H_{17}), 69 (100, $M^{+\cdot}$-C_9H_{19}), 55 (6), 41 (15); Found: $M^{+\cdot}$ 196.18310. Calcd for $C_{13}H_{26}O$: $M^{+\cdot}$ 196.1827045.

The minor component was 3-nonyl-2,5-dihydrofuran (57): IR ($CDCl_3$) 1450(w), 1430(w), 1370(w), 1090, 1050cm^{-1}; ^{1}H NMR ($CDCl_3$)δ 0.9 (3H, distorted t, terminal -CH_3), 1.3 (14H, s, -$(CH_3)_7$-), 2.0 (2H, m, C=C-CH_2-), 4.5 (4H, brs, C2-H_2 and C5-H_2), 5.4 (1H, brs, -CH=C-); mass spectrum 196 (4, $M^{+\cdot}$), 195 (3), 111 (7), 97 (31), 83 ($M^{+\cdot}$-C_8H_{17}), 69 (100 , $M^{+\cdot}$-C_9H_{19}), 55 (42), 43 (34), 41 (42); Found: $M^{+\cdot}$ 196.18202. Calcd for $C_{13}H_{26}O$: $M^{+\cdot}$ 196.1827045.

Tetrahydrofuran-3-ol:

The procedure was a modified version of that described by Olsen[129]. A mixture of paraformaldehyde (196g, 6.52mol), acetic acid (650ml) and sulphuric acid (12ml, SG 1.84) was heated at 100-110°C for 0.5h until the paraformaldehyde had dissolved. A solution of allyl acetate (465g, 4.65mol) in acetic acid (270ml) was added during 2h, with stirring, while the temperature was maintained at 100-110°C. Stirring was continued for 80h at 100-110°C, the solution cooled, acetic anhydride (518g, 48ml, 5.08mol) added during 2h and stirring continued for 15h. The solvent was removed by distillation and the residue distilled under reduced pressure. The fraction with bp 60°C (23mm) - 100°C (7mm) afforded 114g of a clear liquid. ^{1}H NMR indicated that this fraction was a mixture of tetrahydrofuran-3-yl acetate and acetic acid in a 1:6.2 molar ratio respectively. The fraction with bp 87-95°C (0.02mm) afforded 2,4-diacetoxybutyl acetate as a clear mobile liquid: 299g (28%); lit.[129] bp 144-7°C (9mm); IR (film) 1740, 1440, 1375, 1230, 1040cm^{-1}; ^{1}H NMR (CCl_4) δ 1.6-2.1 (11H, merged m

and shs, $-CH_2-$ and three $-COC\underline{H}_3$), 3.5-4.2 (5H, brc, $-C\underline{H}OCOCH_3$ and two $-C\underline{H}_2OCOCH_3$).

The acetic acid was distilled from the tetrahydrofuran-3-yl acetate and methanol (150ml) and hydrochloric acid (10ml, 12M) added and the solution allowed to stand at ambient temperature for 2 days. Addition of sodium acetate (10g) and removal of the methanol by distillation afforded a brown viscous liquid which was taken up in acetone (50ml) and filtered to remove the white solid precipitate. The solvent was removed by distillation and the residue distilled to afford tetrahydrofuran-3-ol[129,130,131]: 25.1g, (7%); bp 89°C (18mm) [lit.[131] bp 82-88°C (24mm)]; IR (film) 3410, 1440(m), 1330(m), 1225(m), 1115, 1165, 1000, 900cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.0 (2H , m, C4-H_2), 3.4 (1H, s, D_2O exch, $-O\underline{H}$), 3.8 (4H, m, C2-H_2 and C5-H_2), 4.4 (1H, m, C3-H).

Dihydro-3(2H)-furanone (198):

Jones'[132] reagent was added dropwise, with stirring, to a solution of tetrahydrofuran-3-ol (5.41g, 61.4mmol) in acetone (75ml) until an orange colour persisted. The supernatant liquid was decanted, dried (K_2CO_3) and concentrated to 10ml by distillation. Benzene (50ml) was added, the solution concentrated to 8ml by distillation, filtered through a short column of silica gel to remove any chromium salts, and the solvent distilled to afford 4.05g of a pale yellow liquid. ^{1}H NMR indicated that the product was a mixture of benzene and dihydro-3-(2H)-furanone[131](198) in a 1:2 molar ratio respectively. The ketone was used directly in subsequent reactions without further purification and was characterised by the ^{1}H NMR (CCl_4/Benzene) δ 2.3 (2H, t, J=8Hz, C4-H_2), 3.6 (2H,s,C2-H_2), 4.1 (2H, t, J=7Hz, C5-H_2).

3-Nonyltetrahydrofuran-3-ol (199):

The Grignard reagent prepared from magnesium (873mg, 36.3mmol) suspension in dry ether (30ml) and nonyl bromide (4.99g, 4.56ml, 24.1mmol) solution in dry ether (10ml) under a nitrogen atmosphere was cooled to -70°C and a solution of dihydro-3(2H)-furanone (198) (1.40g, 16.3mmol) in benzene (0.3ml) was added, with stirring, during 5 min. After 15 min the cooling bath was removed, the mixture allowed to warm to room temperature, poured into ammonium chloride (50ml, saturated) and extracted with ether (3x30ml). The combined ether extracts were dried (K_2CO_3), the solvent distilled and the residue purified by chromatography on silica gel (50g: gradient elution from neat petrol ether to 20% ether in petrol ether) to afford a pale yellow liquid: 1.68g (48%); bp 89°C (0.01mm); IR (film) 3420, 1480, 1280(w), 1155, 1060, 940, 920cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (16H, s, $-(CH_2)_8-$), 2.3 (1H, brm, C4-H), 3.1 (1H, brs, D_2O exch, -OH), 3.2-4.0 (4H, c, C2-H_2 and C5-H_2); mass spectrum 214 (17, $M^{+\cdot}$), 171 (12), 145 (69), 115 (100), 102, (72), 87 (59, $M^{+\cdot}-C_9H_{19}$), 85 (53), 83 (59), 72 (85), 57 (40), 55 (32), 43 (47), 41 (59).

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23.
Found: C, 73.19; H, 12.29.

3-Nonyl-4,5-dihydrofuran(56),3-nonylidenetetrahydrofuran(58) and 3-nonyl-2,5-dihydrofuran (57):

To a stirred and cooled (ice bath) solution of 3-nonyltetrahydrofuran-3-ol (199) (507mg, 2.37mmol) and pyridine (579mg, 0.590ml, 7.33mmol) in dry ether (20ml) was added thionyl chloride (410mg, 0.250ml, 3.44mmol) during 5 min. Stirring at ice bath temperature was continued

for 2h, water (20ml) added, the layers separated and the aqueous phase extracted with ether (2x15ml). The combined organic extracts were dried (K_2CO_3) and the solvent distilled to afford 443mg of a pale yellow liquid. GLC analysis (column A, 70°C (isothermal 8min)--170°C at 1°/min) revealed the presence of four components in a ratio of 1: 2 : 2.24 : 2.48 with retention times 45.1, 49.9, 50.8, and 52.2min respectively.

The first component could be purified by preparative GLC (column B, 150°C) and proved to be 3-nonyl-4,5-dihydrofuran (56): IR ($CDCl_3$) 1600(w), 1460, 1380, 1100cm^{-1}; ^1H NMR ($CDCl_3$, 80MHz) δ 0.78 (3H, distorted t, terminal $-CH_3$), 1.22 (14H, s, $-(CH_2)_7-$), 1.94 (2H, brs, C=C-CH_2) 2.44 (2H, distorted t, C4-H_2), 4.27 (2H, t, J=9Hz, C5-H_2), 6.04 (1H, brs, C2-H); mass spectrum 196 (5, $M^{+\cdot}$), 99 (12), 95 (12), 93 (10), 83 (100, $M^{+\cdot}-C_8H_{17}$), 70 (34), 55 (31), 43 (28), 41 (38); Found: $M^{+\cdot}$ 196.18293. Calcd for $C_{13}H_{26}O$: $M^{+\cdot}$ 196.1827045.

The second and third eluted components were identical (GLC retention time), to the (E) and (Z) isomer mixture of 3-nonylidene-tetrahydrofuran (58). The fourth component was identical (GLC retention time) to 3-nonyl-2,5-dihydrofuran (57).

Nonyltriphenylphosphonium bromide:

A solution of nonyl bromide (6.39g, 30.8mmol) and triphenyl phosphine (8.10g, 30.9mmol) in benzene (40ml) was purged with nitrogen and heated at 120°C for 25h in a sealed vessel. The phosphonium salt separated as a clear viscous liquid which could not be caused to crystallise, and was used without further purification.

3-Nonylidenetetrahydrofuran (58):

Under a nitrogen atmosphere, a butyl lithium (12ml, 18mmol, 1.5M) solution in hexane was added to a stirred and cooled (ice-bath) solution of nonyltriphenylphosphonium bromide (8.23g, 18.0mmol) in dry tetrahydrofuran (70ml). After stirring for a further 20 min the mixture was cooled to -70°C and a solution of dihydro-3(2H)-furanone (198) (1.41g, 16.4mmol) in benzene (0.6ml) introduced during 5min. The solution was stirred for 1h at -70°C, allowed to warm to room temperature during 2h, poured into water (100ml) and extracted with ether (3x30ml). The combined ether extracts were dried (K_2CO_3), the solvent distilled and the residue purified by column chromatography on alumina (50g: gradient elution from neat petrol ether to 10% ether in petrol ether) to afford a clear mobile liquid: 954mg, (33%), bp 45°C (0.01mm); IR (film) 1475, 1460, 1435, 1075, 1055, 990(w), 960(w), 920cm^{-1}; ^{1}H NMR [$(CD_5)_2CO$, 80MHz] δ 0.84 (3H, distorted t, terminal -CH_3), 1.25 (12H, s, -$(CH_2)_6$-), 1.93 (2H, brm, C=C-$\underline{CH}_2$), 2.41 (2H, m, C4-H_2), 3.71 (2H, t, J=7.5Hz, C5-H_2), 4.12 (2H, brs, C2-H_2), 5.12 (1H, brm, C=$\underline{CH}$-); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.8, 27.1, 29.4, 29.6, 29.9, 32.1, 32.9, 68.4 and 68.7 (pair of t, C2 and C5) 71.3 (low intensity t, C2 and C5 of minor isomer), 119.7 (low intensity d, C=$\underline{CH}$ of minor isomer), 120.6 (d, C=$\underline{CH}$), 138.7 (s, C3); mass spectrum 196 (14, $M^{+\cdot}$), 97 (40), 83 (100, $M^{+\cdot}$-C_8H_{17}), 69 (14, $M^{+\cdot}$-C_9H_{19}), 67 (12), 55 (24), 41 (23). Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.50; H, 12.57.

GLC analysis (column A; 70°C (isothermal 8 min)-140°C at 1°/min; He carrier gas) revealed the presence of two components in a ratio of 4.0 : 1 with retention times 49.4 and 50.1 min respectively. The two peaks were assigned non specifically to the (E) and (Z) isomers of the alkene (58).

Section 2.1.2

3-Furoic acid:

Initially, 3-Furoic acid, mp 123-124°C (lit.,[134] 122-123°C), was prepared in 67% yield from commercial (Aldrich) furan-3,4-dicarboxylic acid (mp 212-214°C) according to the procedure described by Deady and Shanks.[134] Later, commercial 3-furoic acid available from Aldrich was used.

Lithium-Sodium alloy:[135,136]

A suspension of Lithium (10g) in silicon oil was heated until molten, and 0.5mm sodium wire (100mg) was added in 10mg to 20mg portions. The alloy was maintained in a molten state for 3h to ensure homogeneity. After cooling the oxide coating was removed, and the alloy stored under parafin oil.

1-Bromooctane:

1-Bromooctane, bp 80°C (8mm) [lit.[149] 91-93°C (22mm)], was prepared from octanol (78.4g, 95.8ml, 0.602mol), hydrobromic acid (268g, 180ml, 38%, 1.56mol) in 81% yield according to the procedure described by Kamm and Marvel.[149]

Octyl Lithium:

The procedure was adapted from the method used by Gilman[150] for the preparation of butyl lithium.

A 250ml three necked flask was provided with a dropping funnel, nitrogen inlet and low temperature thermometer. The apparatus was flame dried at reduced pressure and refilled with nitrogen. Lithium-

sodium alloy[135,136] (2.65g, 378mmol, 1% sodium) was pressed into a thin foil which was cut into small pieces that fell directly into the flask through an emergent stream of nitrogen. Anhydrous ether (55ml) was introduced to the reaction vessel, and 1-bromooctane (33.3g, 30ml, 173mmol) and anhydrous ether (20ml) to the dropping funnel. The lithium suspension in ether was stirred vigorously and 30 drops of the bromide solution added to initiate the reaction. The mixture was then cooled to -10°C in a dry ice/acetone bath held between -30 and -40°C and the remainder of the bromide solution added during 70min. Vigorous stirring was continued and the temperature maintained between -10 and -15°C during the addition. After the addition was completed, the mixture was stirred for 1.5h while the temperature was allowed to rise to 0-10°C.

An aliquot of the solution (1ml) was withdrawn and hydrolysed in distilled water (30mls). The hydrolysate was titrated with 0.1M hydrochloric acid using phenolphthalein as an indicator. The average yield was 77%.

1-(Furan-3'-yl)nonan-1-one (39):

To a stirred and cooled (ice bath) solution of 3-furoic acid (9.10g, 81.2mmol) in dry ether (110mls) under a nitrogen atmosphere was added a solution of octyl lithium in dry ether (155ml, 206mmol, 1.33M) during 0.5h.[67] A voluminous white precipitate (the lithium carboxylate salt) separated and redissolved as the addition was continued. The resulting opaque green solution was stirred for a further 3h at ice bath temperature, allowed to warm to room temperature during 0.5h, and slowly poured onto stirred, cold, ammonium chloride (200ml, saturated). The layers were separated after shaking, the aqueous phase extracted

with ether (3x50ml), the combined organic extracts dried (Na_2SO_4), and the solvent distilled to afford a dark brown mobile liquid (24g) which was submitted to chromatography on alumina (200g, gradient elution from neat petrol ether to 30% ether in petrol ether) to afford a white crystalline solid: 8.76g (52%), mp 42-45°C (petrol ether); bp 53°C (0.02mm); IR (Nujol) 1680, 1560, 1510, 1460, 1370, 1145, 870 730cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (12H, s, $-(CH_2)_6-$), 2.6 (2H, t, J=7Hz, $-CH_2\underline{CH_2}CO-$), 6.8 (1H, m, furan C4'-H), 7.4 (1H, m, furan C5'-H), 8.0 (1H, m, furan C2'-H); mass spectrum 209 (0.7), 208 (0.7, $M^{+\cdot}$), 165 (3), 152 (1), 151 (3), 137 (4), 123 (10), 110 (100, $M^{+\cdot} - C_7H_{14}$), 95, (83, $M^{+\cdot} - C_8H_{17}$), 81 (3), 69 (3), 68 (4), 67 (4), 57 (5), 56 (3), 55 (9), 54 (4), 53 (2), 43 (9), 41 (12), 39 (13); Found: $M^{+\cdot}$208.146215. Calcd for $C_{13}H_{20}O_2$: 208.1463202.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found C, 75.05; H, 9.98.

3-(1',1'-Ethylenedioxynonyl)furan (76):

Under a nitrogen atmosphere, a mixture of the ketone (39) (1.99g, 9.57 mmol), ethylene glycol (5.94g, 5.40ml, 95.8mmol) and *p*-toluenesulphonic acid (80mg) in 1,2-dichloroethane (40ml) was heated under reflux for 6h in a system equipped with a modified Dean and Stark apparatus in which the solvent passed through a short column of 4Å sieves before returning to the reaction flask. After cooling, triethylamine (0.5ml) was added, the mixture poured into ammonia (25ml, 10%), the layers separated after shaking, and the aqueous phase extracted with dichloromethane (2x20ml). The combined organic phases were dried (K_2CO_3), the solvent distilled, and the residue purified by chromatography on alumina (50g, gradient elution from neat petrol ether to 15% ether in petrol ether) to afford a pale yellow mobile liquid:

1.65g (70%); bp 108°C (0.2mm); IR (film) 1500, 1470, 1160, 1105, 1045, 938, 867, 790, 720, 680cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.1-2.0 (14H, overlapping m and s, $-(CH_2)_7-$), 3.9 (4H, shm, $-OCH_2CH_2O-$), 6.2 (1H, m, furan C4-H), 7.2 (2H, c, furan C2-H and furan C5-H); mass spectrum 252 (3, $M^{+\cdot}$), 185 (5, $M^{+\cdot} - C_4H_3O$), 139 (93, $M^{+\cdot} - C_8H_{17}$), 95 (100).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59.

Found: C, 71.80; H, 9.59.

3-(1',1'-Dimethoxynonyl)furan (77):

A mixture of the ketone (39) (308mg, 1.48 mmol), trimethyl orthoformate (339mg, 0.350ml, 3.20 mmol), methanol (474mg, 0.599ml, 14.8 mmol), and *p*-toluenesulphonic acid (15mg) was heated under reflux for 20h.[137] Triethylamine (0.4ml) was added followed by ammonia (8ml, 10%). The layers were separated, the aqueous phase extracted with dichloromethane (3x8ml), the combined organic extracts dried (K_2CO_3) and the solvent distilled. The residue was submitted to chromatography on alumina (10g, gradient elution from neat petrol ether to 5% ether in petrol ether) to afford a clear mobile liquid: 326mg (87%); bp 70°C (0.01mm); IR (film) 1600, 1500, 1375, 1310, 1200, 1150, 1130, 1060, 880, 800, 725, 700cm^{-1}; ^{1}H NMR δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.0-1.9 (14H, overlapping m and s, $-(CH_2)_7-$), 3.0 (6H, s, $-OCH_3$), 6.1 (1H, m, furan C4-H) 7.2 (2H, c, furan C2-H and furan C5-H); mass spectrum 223 (30, $M^{+\cdot} - OCH_3$), 141 (100, $M^{+\cdot} - C_8H_{17}$), 137 (7), 111 (7), 95 (27), 81 (4), 59 (4), 57 (5), 55 (6), 43 (8), 41 (6).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30.

Found: C, 71.18; H, 10.64.

1-(Furan-2'-yl)nonanol (78):

Sodium borohydride (154mg, 4.05mmol) was added to a solution of the ketone (39) (537mg, 2.53 mmol) in ethanol (20ml). After stirring for a further 20h the mixture was poured into water (40ml), allowed to stand for 30 min, saturated with sodium chloride, and extracted with dichloromethane (3x40ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to 10ml by distillation. The remaining solvent was removed at reduced pressure to afford 503mg (93%) of the crude alcohol (78) as a clear mobile liquid. A portion of the product was purified by sequential preparative TLC (ether-petrol ether, 3:7) and distillation to afford a clear liquid: bp 60°C (0.02mm); IR (film) 3370, 1505, 1465, 1375(w), 1155, 1100(w), 1060, 1020, 875, 790, 715cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (14H, s, $-(CH_2)_7-$), 4.6 (1H, t, J=7Hz, -CHOH), 6.3 (1H, m, furan C4-H), 7.2 (2H, c, furan C2-H and furan C5-H); mass spectrum 210 (27, $M^{+\cdot}$), 193 (7, $M^{+\cdot}$-OH), 166 (4), 140 (5), 121 (3), 111 (5), 98 (26), 97 (100, $M^{+\cdot}-C_8H_{17}$), 90 (8), 81 (7), 69 (15), 57 (4), 55 (7), 43 (6), 41 (19), 39 (8); Found: $M^{+\cdot}$ 210.162375. Calcd for $C_{13}H_{22}O_2$: 210.1619694. Anal. Calcd $C_{13}H_{22}O_2$: C, 74.24; H, 10.52. Found:C, 74.19; H, 10.69.

3-(1'-Methoxynonyl)furan (75):

A 50% dispersion of sodium hydride (44mg, 18.5 mmol) in oil was washed with pentane (2x5ml) under a nitrogen atmosphere. Dry N,N-dimethylformamide (10ml) was introduced, and a solution of the alcohol (78) (790mg, 3.76mmol) in dry N,N-dimethylformamide (1.5ml) was added with stirring during 8 min. The mixture was further stirred at ambient temperature for 45 min, at 60°C for 2.5h, cooled, methyl iodide (1.04g, 0.5mls, 7.4mmol) added, and stirred for a further 15h at room temperature. Water (20ml) and ether (20ml) were added,

the layers separated, and the aqueous layer extracted with ether (3x20ml). The combined organic phases were dried (K_2CO_3) and the solvent distilled to give 756mg (90%) of the methyl ether (75) as a tan mobile liquid. A portion was purified by preparative TLC (ether-petrol ether, 1:9) to afford a pale yellow mobile liquid: bp 60°C (0.01mm); IR (film) 1500, 1460, 1150, 1090, 1020, 890, 785, 715cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (14H, s, $-(CH_2)_7-$), 3.1 (3H, s, $-OCH_3$), 3.9 (1H, t, J=8Hz, $-CHOCH_3$), 6.2 (1H, m, furan C4-H), 7.2 (2H, m, furan C2-H and furan C5-H); mass spectrum 224 (38, $M^{+\cdot}$), 191 (6, $M^{+\cdot}-OCH_3$), 141 (32), 121 (9), 111 (100, $M^{+\cdot}-C_8H_{17}$), 95 (47), 94 (42), 83 (50), 71 (27), 69 (18), 67 (15), 55 (42), 43 (50), 41 (42).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78.

Found: C, 75.13; H, 10.90.

1-(Furan-3'-yl)nonyl acetate (74):

A mixture of the alcohol (78) (902mg, 4.26mmol), acetic anhydride (920mg, 0.90ml, 9.0mmol) and pyridine (3ml) was allowed to stand at 5°C for 16h. Water (0.3ml) was added, followed by ether (30ml) after 15min, and the mixture washed with water (1x10ml) and ammonia (1x10ml, 10%). The ether layer was dried (K_2CO_3) and the solvent distilled to afford 977mg (84%) of the crude acetate (74) as a tan mobile liquid. A portion of the product was purified by sequential preparative TLC (ether-petrol ether, 1:4) and distillation to give a clear liquid: bp 63°C (0.02mm); IR (film) 1740, 1500, 1465, 1365, 1230, 1155, 1118, 935, 875, 790, 760, 718cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (14H, s, $-(CH_2)_7-$), 2.0 (3H, s, $-COCH_3$), 5.7 (1H, t, J=7Hz, $-CHOCOCH_3$), 6.2 (1H, m, furan C4'-H), 7.3 (2H, c, furan

C2'-H and furan C5'-H); mass spectrum 253 (3), 252 (12, $M^{+\cdot}$), 211 (14), 210 (98, $M^{+\cdot}$-C_2H_2O), 192 (10, $M^{+\cdot}$-CH_3CO_2H), 181 (10), 161 (5), 139 (10), 135 (12), 125 (8), 121 (10), 107 (20), 98 (26), 97 (87, $M^{+\cdot}$-C_2H_2O-C_8H_{17}), 90 (15), 79 (25), 69 (10), 67 (10), 55 (30), 41 (100), 39 (30), 37 (15); Found: $M^{+\cdot}$ 252.173162. Calcd for $C_{15}H_{24}O_3$: 252.1725327.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59.

Found: C, 71.56; H, 9.85.

Section 2.1.3

1-(Furan-2'-yl)nonanol[138] (149):

To a stirred solution of the Grignard reagent prepared from 1-bromooctane (9.98g, 8.99ml, 51.6 mmol) and magnesium (1.36g, 57.7 mmol) in dry ether (50ml) under a nitrogen atmosphere, was added a solution of furfural (4.93g, 5.37ml, 51.4 mmol) in dry ether (10ml) during 20 min. The mixture was stirred an additional 15h and decomposed with cold ammonium chloride (50ml, saturated). The layers were separated and the aqueuos layer extracted with ether (3x30ml). The combined organic phases were washed with hydrochloric acid (1x20ml, 10%), ammonia (1x15ml , 10%), dried (K_2CO_3) and the solvent removed at reduced pressure. The residue was distilled to afford the alcohol (149) as a clear liquid: 7.26g (65%); bp 99°C (0.16mm) [lit.[138] 137-138°C(3mm)]; IR (film) 3380, 1470, 1150, 1070, 1010, 878, 855, 733cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal -CH_3), 1.3 (14H, s, -$(CH_2)_7$-), 2.1 (1H, brs, D_2O exch, -O<u>H</u>), 4.7 (1H, t, J=6Hz, -C<u>H</u>OH), 6.3 (2H, c, furan C3'-H and furan C4'-H), 7.4 (1H, m, furan C5'-H); mass spectrum 210 (5, $M^{+\cdot}$), 193 (4, $M^{+\cdot}$-OH), 110 (4), 107 (2), 98 (6), 97 (100, $M^{+\cdot}$-C_8H_{17}), 41 (7).

1-(Furan 2-'yl)nonyl acetate (146):

A mixture of the alcohol (149) (715mg, 3.4mmol), acetic anhydride (649mg, 0.6ml, 6.36 mmol) and dry pyridine (1.5ml) was allowed to stand for 2.5 days at 5°C. Ether (20ml) was added and the mixture washed with water (1x10ml), hydrochloric acid (3x5ml, 10%) and sodium bicarbonate (2x10ml, 10%). The organic phase was dried (K_2CO_3) and the solvent removed at reduced pressure to give 790mg (92%) of the crude acetate as a mobile tan liquid. A portion was purified sequentially by preparative TLC (ether-petrol ether, 1:4), and distillation to afford a clear liquid: bp 115°C (0.5mm); IR (film) 1740, 1500, 1410, 1365, 1230, 1145, 1000, 950, 875, 800, 730cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (14H, s, $-(CH_2)_7-$), 2.0 (3H, s, $-CHOCOC\underline{H}_3$), 5.8 (1H, t, J=7Hz, $-C\underline{H}OCOCH_3$), 6.3 (2H, c, furan C3'-H and furan C4'-H), 7.4 (1H, m, furan C5'-H); mass spectrum 252 (9,$M^{+\cdot}$),210 (50, $M^{+\cdot}-C_2H_2O$), 183 (7), 139 (19), 135 (7), 121 (5), 107 (25), 97 (100, $M^{+\cdot}-C_2H_2O-C_8H_{17}$), 94 (84), 81 (34), 55 (14), 43 (86), 41 (30).
Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.04; H, 9.66.

2-(1'-Methoxynonyl)furan (147):

A 50% sodium hydride (495mg, 12.4 mmol) dispersion in oil was washed with pentane (2x5ml) under a nitrogen atmosphere. Dry N,N-dimethylformamide (10ml) was introduced, the mixture stirred, and a solution of the alcohol (149) (971mg, 4.61 mmol) in dry N,N-dimethylformamide (5ml) added. After the addition, the mixture was stirred for 1h at room temperature, for 3h at 70-90°C, cooled, and methyl iodide (3.27g, 1.5ml, 22.0 mmol) added. Stirring was

continued for 60h at room temperature. Water (20ml) and ether (20ml) were added, the layers separated and the aqueous phase extracted with ether (1x20ml). The combined ether extracts were filtered through celite, washed with hydrochloric acid (1x10ml, 10%) and ammonia (1x10ml, 10%), dried (K_2CO_3) and the solvent distilled to afford 850mg (82%) of crude methyl ether as a dark brown mobile liquid. A portion of the product was purified sequentially by preparative TLC (ether-petrol ether, 5:95) and distillation to give a clear liquid: bp 108°C (0.9mm); IR (film) 1500, 1460, 1333, 1223, 1170, 1145, 1128, 1090, 1000, 876, 800, 728cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.2-2.1 (14H, merged s and m, $-(CH_2)_7-$), 3.2 (3H, s, $-O\underline{CH}_3$), 4.1 (1H, t, J=7Hz, $-\underline{CH}OCH_3$), 6.2 (2H, c, furan C3-H and furan C4-H), 7.3 (1H, m, furan C5-H); mass spectrum 224 (14, $M^{+\cdot}$), 193 (4, $M^{+\cdot}-OCH_3$), 157 (12), 111 (100, $M^{+\cdot}-C_8H_{17}$), 94 (8), 83 (14), 81 (12), 69 (31), 57 (18), 55 (20), 45 (12), 43 (18), 41 (17).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78.

Found: C, 75.16; H, 10.51.

1-(Furan-2'-yl)nonan-1-one (160):

A. Pyridinium chlorochromate[139] (12.8g, 5.95 mmol) and sodium acetate (882mg, 1.06 mmol) were suspended in dry dichloromethane (50ml) and a solution of the alcohol (149) (4.85g, 2.31 mmol) in dry dichloromethane (5ml) was added in one portion to the magnetically stirred solution. After 15h, ether (100ml) was added and the supernatant liquid decanted from the black gum. The insoluble gum was triturated under ether (50ml) whereupon it became a black granular solid. The ether was decanted from the solid. The combined organic phases were

washed with hydrochloric acid (1x10ml, 10%) whereupon a black precipitate separated and was removed by filtration through a celite pad. The solution was further washed with hydrochloric acid (1x15ml, 10%), followed by water (1x10ml) and ammonia (1x10ml, 10%). After drying (K_2CO_3) the solvent was distilled to give 1.62g (34%) of crude ketone as a dark brown mobile liquid. 'H NMR indicated that the crude product was greater than 75% ketone. A portion of the product was purified sequentially by preparative TLC (ether-petrol ether, 1:3) and distillation to give a clear liquid: bp 103°C (0.4mm); IR (film) 1680, 1570, 1468, 1395, 1155, 1080, 1005, 878, 755cm^{-1}; 'H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.1-2.0 (12H, merged m and s, $-(CH_2)_6-$), 2.8 (2H, t, J=7Hz, $-CH_2\underline{CH_2}CO-$), 6.6 (1H, m, furan C4'-H), 7.1 (1H, m, furan C3'-H), 7.6 (1H, m, furan C5'-H); mass spectrum 209 (0.5), 208 (0.7, $M^{+\cdot}$), 151 (1), 110 (100, $M^{+\cdot}-C_7H_{14}$), 95 (48, $M^{+\cdot}-C_8H_{17}$), 81 (6), 68 (4), 57 (4), 55 (7), 43 (10), 41 (18), 39 (18).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68.

Found: C, 74.89; H, 9.81.

B. Chromium trioxide (15.5g, 15.2 mmol) was added to a stirred solution of dry pyridine (12.6g, 8.5ml, 160 mmol) in dry dichloromethane (300ml).[140] After the addition, the mixture was stirred for 20 min and a solution of the alcohol (149) (3.19g, 15.2 mmol) in dry dichloromethane (10ml) was added in one portion. After stirring for an additional 1h at room temperature, the supernatant liquid was decanted from the tarry black residue and the solvent removed at reduced pressure to afford 1.51g (47%) of a pale yellow liquid which was identical (IR, 'H NMR) with 1-(furan-2'-yl)nonan-1-one (160).

C. A solution of the alkyl lithium reagent prepared (by the method described in the experimental part of section 2.2) from 1-bromooctane (13.7g, 12.3ml, 71.0 mmol) and lithium-sodium alloy (1.06g, 151 mmol, 1% sodium) in dry ether (70ml) was added dropwise during 35 min to a stirred and cooled (ice bath) solution of 2-furoic acid (3.13g, 27.9 mmol) in dry ether (40ml).[67] A voluminous white precipitate (the lithium carboxylate salt) separated and redissolved as the addition was continued. The resultant opaque tan solution was stirred for a further 3.5h at ambient temperature, and slowly poured onto stirred, cold ammonium chloride (200ml, saturated). The layers were separated and the aqueous phase extracted with ether (2x40ml). The combined organic extracts were dried (K_2CO_3) and the solvent distilled. The product was purified by chromatography on silica (150g, gradient elution from neat petrol ether to 10% ether in petrol ether) to afford 3.18g, (54%) of a pale yellow mobile liquid which was identical (IR, ^{1}H NMR) with the ketone (160).

2-(1',1'-Ethylenedioxynonyl)furan (148):

A mixture of the ketone (160) (1.00g, 3.97 mmol), ethylene glycol (6ml) and *p*-toluenesulphonic acid (30mg) in chloroform (25ml) was heated under reflux in a system equipped with a modified Dean and Stark apparatus. Phosphorous pentoxide was placed in the side arm of the water separator such that the solvent filtered through the dehydrating agent before returning to the reaction vessel. After 10h under reflux, the mixture was cooled and triethylamine (0.3ml), followed by ammonia (15ml , 10%) and ether (25ml) were added. The layers were separated and the aqueous phase extracted with ether (2x20ml). The combined organic extracts were dried (K_2CO_3) and the solvent distilled to give 1.11g (92%) of crude acetal. A portion (490mg) of the product

was purified by preparative TLC (15% ether in petrol ether) to afford a pale yellow mobile liquid (477mg): bp 86°C (0.02mm); IR (film) 1505, 1470, 1378, 1180, 1145, 1075, 1040, 1004, 968, 945, 880, 808, 730cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, m, terminal -CH_3), 1.1-2.1 (14H, merged m and s, -$(CH_2)_7$-), 4.0 (4H, s, -OCH_2CH_2O-), 6.3 (2H, c, furan C3-H and furan C4-H), 7.4 (1H, m, furan C5-H); mass spectrum 252 (0.1, $M^{+\cdot}$), 139 (100, $M^{+\cdot}$-C_8H_{17}), 115 (15).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59.

Found: C, 71.61; H, 9.47.

2-(Pent-1'-enyl)furan (150):

The alkene (150) was prepared by a modified version of the procedure of Delas and Bigot.[141]

A mixture of butyltriphenylphosphonium bromide[141] (7.98g, 20 mmol), powdered sodium hydroxide (3.05g), furfural (1.96g, 20.4 mmol), 1,4-dioxane (20ml) and water (0.5ml) was mechanically stirred at 50-120°C for 3h, and at 70°C for a further 10h. After cooling, ether (20ml) was added and the mixture filtered through celite. The solvent was removed by distillation and the residue submitted to chromatography on silica (50g, petrol ether). The alkene (150) was obtained as a pale yellow liquid: 280mg (10%); IR (film) 1490, 1460, 1390, 1375, 1170, 1120, 1115, 1085(w), 1010(s), 980, 960, 920, 880, 800, 720cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9-1.9 (5H, apparent merged d and pentet, -CH_2CH_3), 2.4 (2H, c, C3'-H_2), 5.5 (1H, d of t, $J_{H1'-H2'}$= 12Hz, $J_{H2'-H3'}$= 7Hz, C2'-H), 6.2 (3H, c, furan C3-H and furan C4-H and alkene C1'-H), 7.2 (1H, m, furan C5-H); mass spectrum 136 (64, $M^{+\cdot}$), 107 (94, $M^{+\cdot}$-C_2H_5), 94 (51), 79 (78), 77 (56), 65 (16), 55 (43), 43 (44), 41 (70), 39 (100).

Part 2.2

Section 2.2.1

3-Nonyltetrahydrofuran (59):

A solution of 3-nonylidenetetrahydrofuran (58) (315mg, 1.61mmol) in ethanol (8ml) was reduced with hydrogen at atmospheric pressure in the presence of 5% rhodium on alumina until hydrogen uptake ceased. The mixture was filtered through a celite pad and the solvent distilled to afford 307mg of a clear mobile liquid. The product was taken up in acetone (10ml) and Jones'[132] reagent (0.3ml) added when the orange colour persisted. The mixture was filtered through a short column of silica, the solvent distilled, and the residue purified by chromatography on alumina (50g, gradient elution from neat petrol ether to 5% ether in petrol ether) to afford (59) as a clear mobile liquid: 209mg (66%); bp 40°C (0.02mm); IR (film) 1465, 1375, 1050, 910cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, distorted t, terminal -CH_3), 1.3 (16H, s, -$(CH_2)_8$-), 2.0 (3H, brc tetrahydrofuran C3-H and tetrahydrofuran C4-H_2), 2.9-4.0 (4H, brc, tetrahydrofuran C2-H_2 and tetrahydrofuran C5-H_2); ^{13}C NMR δ 73.5 (<u>C</u>O), 67.9 (<u>C</u>O), 39.5, 33.4, 32.5, 31.9, 29.7, 29.6, 29.3, 28.6, 22.6, 13.9; mass spectrum 199(12,$M^{+\cdot}$+1), 198 (1), 153 (2), 152 (15), 151 (35) 137 (5), 126 (11), 125 (4), 124 (7), 123 (8), 111 (19), 110 (24), 109 (47), 98 (16), 97 (45), 96 (39), 95 (100), 85 (15), 84 (35), 83 (65), 71 (25), 70 (60), 69 (95), 64 (60), 63 (65), 57 (65), 56 (88), 55 (100), 54 (35), 53 (18), 45 (12), 43 (100), 42 (53), 41 (100), 39 (35); Found: ($M^{+\cdot}$+1) 199.20570. Calcd for $C_{13}H_{27}O$: 199.2061783. Anal. Calcd for $C_{13}H_{26}O$: C, 78.72, H, 13.21. Found: C, 78.94; H, 13.33.

2-Octyl-2-(tetrahydrofuran-3'-yl)-1,3-dioxolane (80):

Rhodium on alumina (88mg, 5%) was added to a solution of the acetal (76) (115mg, 0.456 mmol) in ethanol (15ml), and the mixture shaken under a hydrogen atmosphere at 50 psi for 20h. The solution was filtered through a celite pad, the solvent distilled, and the product purified by chromatography on alumina (10g, gradient elution from neat petrol ether to 15% ether in petrol ether) to afford a clear mobile liquid: 115mg, (98%), bp 98°C (0.005mm); IR (film) 1470, 1200, 1150 1070, 950, 920cm^{-1}; ^{1}HNMR (CCl_4) δ 0.9 (3H, distorted triplet, terminal $-CH_3$), 1.3 (14H, s, $-(CH_2)_7-$), 1.8 (2H, m, tetrahydrofuran C4'-H_2), 2.5 (1H, m, tetrahydrofuran C3'-H), 3.2-3.9 (4H, m, tetrahydrofuran C2'-H_2 and tetrahydrofuran C5'-H_2), 3.9 (4H, s, dioxolane C4-H_2 and dioxolane C5-H_2); mass spectrum 185 (92, $M^{+\cdot}-C_4H_7O$), 143 (100, $M^{+\cdot}-C_8H_{17}$), 113 (11), 99 (17), 69 (23), 57 (29), 55 (25), 43 (38), 41 (55). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H,11.01. Found: C, 70.46; H, 11.17.

1-(Tetrahydrofuran-3'-yl)nonan-1-one (200):

Rhodium on alumina (31mg, 5%) was added to a solution of the ketone (39) (314mg, 1.51 mmol) in ethanol (15ml) and the mixture shaken under a hydrogen atmosphere at 60 psi for 15h. The solution was filtered through celite, the solvent distilled, and the product purified by chromatography on silica gel (15g, gradient elution from neat petrol ether to 25% ether in petrol ether) to afford a clear mobile liquid: 224mg (70%); bp 91°C (0.01mm); IR (film) 1720, 1470, 1380, 1170, 1070, 920cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal $-CH_3$), 1.3 (12H, s, $-(CH_2)_6-$), 1.9-2.6 (4H, m, $COCH_2-$ and tetrahydrofuran C4'-H_2), 3.1 (1H, m, tetrahydrofuran C3'-H), 3.8 (4H, m, tetrahydrofuran C2'-H_2 and tetrahydrofuran C5'-H_2); mass spectrum 213 (4), 212 (6, $M^{+\cdot}$),

169 (30), 141 (35, $M^{+\cdot}-C_4H_7O$), 99 (100, $M^{+\cdot}-C_8H_{17}$), 86 (18), 84 (16), 81 (16), 71 (82), 57 (59), 43 (71), 41 (42).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.91; H, 11.46.

Ethyl 3-methyldodec-2-enoate (202):

Under a nitrogen atmosphere, a 50% dispersion of sodium hydride (1.29g, 26.9 mmol) in oil was washed with pentane (2x5ml), and dry ether introduced. To the stirred slurry was added triethylphosphonoacetate[142] (6.00g, 26.8mmol). Stirring was continued for 1h at room temperature and undecan-2-one (4.42g, 26mmol) added. After the addition, the mixture was stirred for 1h at room temperature, water (90ml) added, the layers separated and the aqueous phase extracted with ether (2x30ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed at reduced pressure to afford 5.38g of a clear mobile liquid. Chromatography on silica gel (80g, gradient elution from neat petrol ether to 10% ethyl acetate in petrol ether) did not separate the ester (202) and starting ketone. A solution of the product mixture (5.36g) in ethanol (20ml) was treated with sodium borohydride (197mg, 5.18mmol). After stirring the mixture at room temperature for 1hr, water (5ml) was added and the solution concentrated to 10ml at reduced pressure. Water (40ml) was added and the mixture extracted with dichloromethane (3x30ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed at reduced pressure. The residue was purified by chromatography on silica gel (150g, gradient elution from neat petrol ether to 10% ethyl acetate in petrol ether) to afford the ester (202) as a clear mobile liquid: 3.69g, (62%); bp 63°C (0.01mm); IR (film) 1720, 1642, 1460, 1270, 1220, 1070, 1015, 1040, 860, 720cm^{-1}; ^{1}H NMR (CCl_4) 0.9-1.6 (20H, c, $-C_8H_{17}$ and $-COOCH_2\underline{CH_3}$), 1.9-2.3 (5H, c, $\underline{CH_2}$-C=C and C=C-$\underline{CH_3}$), 4.1 (2H, q, J=7Hz, $-COO\underline{CH_2}CH_3$), 5.6 (1H, brs,

C=CH); mass spectrum 241 (6), 240 (11, $M^{+\cdot}$), 195 (37, $M^{+\cdot}-C_2H_5O$), 152 (22), 141 ($M^{+\cdot}-C_7H_{15}$), 128 (100), 113 (31),100 (32), 95 (21), 87 (22), 69 (29), 56 (39), 55 (48), 43 (34), 41 (63).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.64; H, 11.61.

3-Methyldodecanol (92):

Lithium (741mg, 106 mmol) was added to a stirred solution of the ester (202) (1.44g, 6.00mmol) in dry ethanol (9.47g, 12ml, 206mmol), dry ether (10ml) and liquid ammonia (80ml). After the addition, the mixture was stirred for 1.5h and isoprene (250mg) added to remove the excess of metal. The ammonia was allowed to evaporate and ether (20ml), followed by water (20ml), added. The layers were separated after shaking and the aqueous phase extracted with dichloromethane-tetrahydrofuran (9:1) (2x30ml). After drying (Na_2SO_4) the combined organic extracts, the solvent was distilled to afford a pale yellow mobile liquid whichwas homogeneous by analytical GLC (column B, 180°C) : 1.08g (90%); bp 65°C (0.01mm); IR (film) 3300, 1460, 1375, 1055cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8-1.6 (25H, c, $-CH_2CH(CH_3)-CH_2(CH_2)_7CH_3$), 3.1 (1H, brs, D_2O exch, -OH), 3.6 (2H, t, J=8Hz, $-CH_2OH$); mass spectrum 182 (2, $M^{+\cdot}-H_2O$), 154 (12), 141 (2), 126 (6), 125 (6), 111 (14), 97 (36), 83 (44), 71 (32), 70 (85), 69 (46), 57 (65), 56 (90), 55 (80), 43 (100), 41 (42).

Anal. Calcd for $C_{13}H_{28}O$: C, 77.93; H, 14.09. Found: C, 78.13; H, 14.26.

3-Methyldodecanal (91):

A stirred solution of oxalyl chloride (296mg, 0.200ml, 2.33 mmol) in dichloromethane (10ml) was cooled to -55°C and dimethyl sulphoxide (330mg, 0.300ml, 4.23 mmol) solution in dichloromethane (2ml) was added

in 5 min. Stirring was continued at -55°C for 2 min and the alcohol (335mg, 1.67 mmol) solution in dichloromethane (2ml) was added in 5 min. The reaction mixture was stirred for 15 min and triethylamine (872mg, 1.20ml, 8.63 mmol) was added in 5 min with stirring at -55°C[143,144] The cooling bath was removed and the mixture allowed to warm to room temperature. Water (20ml) was added, the layers separated and the aqueous phase extracted with dichloromethane (1x20ml). The combined organic layers were dried and the solvent removed at reduced pressure to afford 320mg (96%) of the crude aldehyde as a pale yellow liquid. 'H NMR indicated the product was greater than 90% aldehyde. A portion was purified by distillation to afford a clear liquid: bp 70°C (0.01mm); IR (film) 2730, 1730, 1470, 1375, 1020cm^{-1}; 'H NMR (CCl_4) δ 0.8-1.6 (23H, c, $-CH(CH_3)CH_2(CH_2)_7CH_3$), 2.1 (2H, brm, $CHC\underline{H}_2CHO$), 9.5 (1H, m, $-C\underline{H}O$); mass spectrum 154 ($M^{+\cdot}-C_2H_4O$), 123 (18), 111 (15), 97 (28), 83 (35), 71 (69), 70 (35), 69 (57), 57 (79), 56 (35), 55 (87), 43 (100), 41 (100); mass spectrum (20eV) 199 (4, $M^{+\cdot}+1$), 198 (0.2), 197 (0.8), 185 (2), 171 (11), 157 (5), 155 (4), 154 (19), 143 (5), 129 (2), 126 (4), 125 (5), 115 (4), 113 (4), 112 (4), 111 (5), 110 (2), 101 (5), 100 (2), 99 (7), 98 (5), 97 (9), 96 (3), 88 (6), 87 (100), 85 (19), 84 (7), 83 (9), 82 (4), 83 (3), 73 (4), 71 (22), 70 (7), 69 (11), 68 (3), 61 (8), 60 (24), 57 (31), 56 (6), 50 (6), 43 (14); Found: ($M^{+\cdot}+1$) 199.20665. Calcd for $C_{13}H_{27}O$: 199.2061783.

Diethyl 2-ethyl-2-nonylpropanedioate (203):

Sodium (1.46g, 63.5 mmol) was dissolved in dry ethanol (70ml), commercial (Fluka) diethyl 2-ethylpropanedioate (12.3g, 12.0ml, 65.6 mmol) was added and the solution heated under reflux for 5h.[145] A white precipitate formed during the reflux. The mixture was cooled and the solvent removed at reduced pressure. To the residue, was added

ammonium chloride (40ml, saturated) and the product extracted with dichloromethane-tetrahydrofuran (9:1) (2x50ml). The combined organic phases were dried (Na_2SO_4) and the solvent removed at reduced pressure. The residue was first purified by chromatography on silica gel (200g, gradient elution from neat petrol ether to 10% ethyl acetate in petrol ether) to give 17.0g of a clear mobile liquid. ^{1}H NMR indicated the product was a mixture of starting diester and (203). Distillation afforded pure diester (203) as a clear liquid: 10.3g (52%), bp 115°C (0.05mm); IR (film) 1730, 1460, 1380, 1360, 1300, 1230, 1030, 860cm^{-1}; ^{1}H NMR (CCl_4) δ 0.8-2.0 (30H, c, $-C_9H_{19}$,$-C_2H_5$,$-OCH_2\underline{CH_3}$), 4.1 (4H, q, J=7Hz, $-COOCH_2CH_3$); mass spectrum 314 (0.3, M^+·), 286 (3), 269 (5), 241 (14), 188 (100), 173 (69), 142 (45), 129 (25), 101 (24), 99 (15), 97 (12), 83 (19), 69 (32), 56 (15), 55 (61), 43 (35), 41 (42).
Anal. Calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 69.07; H, 11.16.

2-Ethylundecanol (108):

A mixture of the ester (203) (3.12g, 9.94 mmol) and potassium hydroxide (2.01g, 30.5 mmol, 85%) in ethanol-water (9.5:0.5) (50ml) was stirred and heated under reflux for 8h. After cooling, the mixture was concentrated to 10ml at reduced pressure, diluted with water (40ml), acidified with 3N hydrochloric acid (20ml) and extracted with dichloromethane-tetrahydrofuran (9:1) (3x20ml). The combined organic phases were dried (Na_2SO_4) and the solvent removed at reduced pressure to afford 3.05g of crude 2-ethyl-2-nonylpropanedioic acid as a viscous clear liquid. ^{1}H NMR indicated that the product was a mixture of the diacid and tetrahydrofuran in an 8:2 molar ratio.

The diacid was heated at 180-190°C for 40 min when the initial effervescence had ceased. This procedure afforded 2.38g of crude 2-ethylundecanoic acid (204) as a mobile pale yellow liquid.

The acid (204) was dissolved in dry ether (60ml) and lithium aluminium hydride (730mg, 19.2 mmol) added in two equal portions during 10 min with vigorous stirring. The solution was heated under reflux for 1.5h, cooled, and saturated sodium sulphate (0.8ml) cautiously added during 20 min. After filtration through celite, the solution was dried (Na_2SO_4) and the solvent distilled. The product was purified by chromatography on silica gel (30g, gradient elution from neat petrol ether to 10% ethyl acetate in petrol ether) to afford 2-ethylundecanol (108) as a clear mobile liquid: 1.03g [52% from the diester (203)]; bp 125-129°C (0.65mm); IR (film) 3350, 1460, 1380, 1035cm^{-1}; ^{1}H NMR (CCl_4) δ 0.8-1.6 (25H, c, C_2H_5-CH-C_9H_{19}), 2.5 (1H, s, D_2O exch, -OH), 3.4 (2H, brs, -CH_2OH); mass spectrum 182 (2, $M^{+\cdot}$-H_2O), 169 (1), 168 (2), 154 (2), 153 (1), 140 (1), 139 (1), 125 (2), 111 (8), 97 (18), 85 (26), 83 (25), 71 (53), 57 (100), 51 (51), 43 (95), 41 (57).

Anal. Calcd for $C_{13}H_{28}O$: C, 77.93; H, 14.09. Found: C, 77.74; H, 13.98.

2-Ethylundecanal (107):

A stirred solution of oxalyl chloride (294mg, 0.200ml, 2.31 mmol) in dichloromethane (14ml) was cooled to -60°C, and dimethyl sulphoxide (374mg, 0.340ml, 4.79 mmol) solution in dichloromethane (2ml) was added in 5 min. Stirring was continued at -60°C for 2 min and the alcohol (108) (400mg, 2 mmol) solution in dichloromethane (2ml) was added in 5 min. The reaction mixture was stirred for 15 min and

triethylamine (1.02g, 1.40ml, 13.0 mmol) was added in 5 min with stirring at -55°C.[143,144] The cooling bath was removed and the mixture allowed to warm to room temperature. Water (20ml) was added, the layers separated and the aqueous phase extracted with dichloromethane (1x15ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed at reduced pressure to afford 388mg (97%) of the crude aldehyde as a pale yellow liquid. A portion was purified by distillation to give a clear liquid: bp 70°C (0.01mm); IR (film) 2720, 1739, 1460, 1380, 770, 725cm^{-1}; ^{1}H NMR (CCl_4) δ 0.8-1.6 (25H, c, C_2H_5-CH-C_9H_{19}), 2.1 (1H, brm, C<u>H</u>CHO), 9.3 (1H, d, J=3Hz, -C<u>H</u>O); mass spectrum 199 (7, $M^{+\cdot}$+1), 198 (2, $M^{+\cdot}$), 169 (1), 157 (2), 151 (2), 142 (6), 126 (10), 109 (9), 95 (19), 85 (38), 72 (100, $M^{+\cdot}$-C_4H_8O), 57 (45), 55 (45), 43 (60), 41 (50); Found: $M^{+\cdot}$ 198.197075. Calcd for $C_{13}H_{26}O$: 198.1983537. Found: ($M^{+\cdot}$+1): 199.20570 Calcd for $C_{13}H_{27}O$: 199.2061783.

<u>Section 2.2.2</u>

<u>1-(Tetrahydrofuran-2'-yl)nonanol (163)</u>:

Rhodium on alumina (150mg, 5%) was added to a solution of 1-(furan-2'-yl)nonanol (149) (613mg, 2.92 mmol) in ethanol (50ml) and the mixture shaken under a hydrogen atmosphere at 50 psi pressure. Hydrogen absorption ceased after 2h. The mixture was filtered through celite and the solvent distilled to afford a clear mobile liquid which was homogeneous by analytical GLC (column B, 175°C): 549mg (89%); bp 78°C (0.01mm); IR (film) 3450, 1475, 1380, 1070, 925cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal -CH_3), 1.1 (14H, s, -$(CH_2)_7$-), 1.8 (4H, m, tetrahydrofuran C3'-H_2 and tetrahydrofuran C4'-H_2), 2.3

(1H, s, D_2O exch, -O<u>H</u>), 3.7 (4H, brc, -C<u>H</u>OH, tetrahydrofuran C2'-H and tetrahydrofuran C5'-H_2); mass spectrum 214 (0.5, $M^{+\cdot}$), 142 (5), 124 (2), 101 (8), 97 (15), 83 (15), 71 (100), 55 (30), 43 (78), 41 (45).
Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 72.70; H, 12.13.

<u>1-(Tetrahydrofuran-2'-yl)nonan-1-one (177)</u>:

To a solution of 1-(tetrahydrofuran-2'-yl)nonanol (163) (106mg, 0.495 mmol) in acetone (5ml) was added Jones'[132] reagent, dropwise, with stirring until the orange colour persisted. The supernatant liquid was decanted and the residual salts washed with ether (2x5ml). The combined organic phases were filtered through a short column of sorbsil, dried (Na_2SO_4) and the solvent distilled. The product was purified by chromatography on alumina (5g, gradient elution from neat petrol ether to 5% ether in petrol ether) to afford a clear mobile liquid: 68mg (64%); bp 82°C (0.05mm); IR (film) 1720, 1470, 1405, 1380, 1075, 940cm^{-1}; ^{1}H NMR (CCl_4) δ 0.9 (3H, distorted t, terminal -CH_3), 1.1 (12H, s, -$(CH_2)_6$-), 1.9 (4H, m, tetrahydrofuran C3'-H_2 and tetrahydrofuran C4'-H_2), 2.4 (2H, distorted t, -COC<u>H</u>$_2$-), 3.6-4.2 (3H, c, tetrahydrofuran C2'-H and tetrahydrofuran C5'-H_2); mass spectrum 213 (4, $M^{+\cdot}$+1), 212 (6, $M^{+\cdot}$), 159 (2), 141 (7), 110 (13), 95 (8), 87 (28), 83 (18), 71 (100), 60 (16), 57 (23), 55 (21), 43 (21), 41 (29).
Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.66; H, 10.99.

<u>Tridecane-1,5-diol (182)</u>:

To a stirred solution of lithium (270mg, 38.6 mmol) in liquid ammonia (50ml, redistilled from $NaNH_2$) was added ethanol (1ml),

followed by a solution of the ketone (177) (280mg, 1.32 mmol) in dry tetrahydrofuran (10ml). After the addition, the solution was stirred for 35 min and solid ammonium chloride added to remove the excess of metal. The ammonia was allowed to evaporate, and water saturated ether (20ml) followed by water (15ml) added. The layers were separated, and the aqueous layer extracted with ether (3x20ml). The combined organic phases were dried ($MgSO_4$), concentrated to 5ml, and allowed to stand at -15°C whereupon 208mg (73%) of tridecane-1,5-diol (182) crystallised from the solution as white prisms: mp 51-52°C (petrol ether); IR (Nujol) 3350, 3300, 3220, 1520, 1470, 1380, 1130, 1005, 1070, 1055, 1031, 905, 900, 849, 712; ^{1}H NMR (CCl_4) δ0.8-1.6 (23H, c, methylene envelope), 2.9 (2H, brs, D_2O exch, -OH), 3.4 (3H, brm, -CH_2OH and -CHOH); mass spectrum 173 (1), 143 (20), 103 (82). 85 (100), 69 (47), 57 (40), 55 (37), 43 (35), 41 (40).

Anal. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.47; H, 12.84.

Work Described in Chapter III

Part 3.1

1-Ethoxycarbonylethylidenetriphenylphosphorane (205):[167]

Ethyl 2-bromopropionate(15.1g, 83 mmol) was added to a solution of triphenylphosphine (22g, 83 mmol) in benzene and the mixture stirred and heated at 70°C for 15h. After cooling, the benzene was decanted and the remaining solvent removed at reduced pressure. The crude phosphonium salt was dissolved in water (200ml; less than 70°C, decomposes), filtered and extracted with ether (3x50ml) to remove any benzene. The aqueous solution was treated with 10% sodium hydroxide whereupon a yellow oil precipitated which crystallised after trituration. Sodium hydroxide addition was continued until pH10 had been reached and no more precipitate formed. The precipitate was filtered, washed with water (3x50ml) and dried *in vacuo* to give the ylide as a yellow crystalline solid: 25g (97%); mp 145-150°C (ethyl acetate) [lit.[167] mp 159-160°C]; ^{1}H NMR ($CDCl_3$) δ 0.7 (3H, t, J=7Hz, ester $-OCH_2\underline{CH_3}$), 1.6 (3H, d, J_{C-P}=13Hz, $Ar_3P=C-\underline{CH_3}$), 4.0 (2H, q, J=7Hz, ester $-O\underline{CH_2}CH_3$), 7.3 (15H, m, aromatic).

Ethyl 2-(5'-oxotetrahydrofuran-2-'ylidene)propionate (206):

A mixture of the phosphorane (205) (9.01g, 27.3 mmol) and succinic anhydride (2.73g, 27.3 mmol) in benzene (50ml) was stirred at ambient temperature for 20h. The solvent was removed at reduced pressure and the residue extracted with ether (3x20ml). Removal of the solvent at reduced pressure from the combined extracts afforded a tan mobile liquid. The crude product was preabsorbed on kieselguhr and purified by chromatography on silica gel (55g, ether-petrol ether, 6:4) to give the enol lactone as a white crystalline solid: 3.22g (64%);

mp 37-44°C (ether-petrol ether); IR (Nujol) 1810, 1700, 1658, 1450, 1371, 1330, 1310, 1263, 1210, 1120, 1000, 945, 890, 810, 770cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, t, J=7Hz, ester -$OCH_2\underline{CH_3}$), 1.9 (3H, t, J=1Hz, C=C-$\underline{CH_3}$), 2.7 (2H, m, enol lactone C4'-H_2), 3.3 (2H, m, enol lactone C3'-H_2), 4.2 (2H, t, J=7Hz, ester -OCH_2CH_3).

Diethyl 2-allyl-2-methyl-3-oxohexanedioate (207a):

A. To a stirred solution of enol lactone (206) (1.55g, 8.43 mmol) in dry ethanol (15ml) was added a solution of sodium ethoxide (579mg, 8.54 mmol) in dry ethanol (2.8ml) under a nitrogen atmosphere. After the addition, the mixture was stirred for 45 min at room temperature and allyl bromide (1.26g, 0.90ml, 10.4 mmol) added. After the addition, the mixture was stirred for 20h at room temperature and poured onto ammonium chloride (30ml, saturated), and extracted with dichloromethane (3x20ml). The combined organic phases were washed with water (2x20ml), dried (Na_2SO_4) and the solvent removed at reduced pressure to afford a tan mobile liquid: 2.07g (91%); bp 140°C (0.35mm); IR (film) 1735, 1715, 1640, 1450, 1375, 1205, 1165, 1010, 920, 855cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1-1.5 (9H, merged s and two t, aliphatic -CH_3 and ester -$OCH_2\underline{CH_3}$), 2.5-3.0 (6H, c, -$CO\underline{CH_2}\underline{CH_2}CO_2C_2H_5$ and -$\underline{CH_2}C$=C), 4.0-4.4 (4H, two q, δ4.1, J=7Hz and δ4.2, J=7Hz, ester -OCH_2CH_3), 5.0 and 5.2 (1H, apparent t at 5.0, 1H, m at 5.2, -C=$\underline{CH_2}$), 5.4-6.0 (1H, brm, -$\underline{CH}$=C); mass spectrum 171 (2, $M^{+\cdot}$+1), 225 (17, $M^{+\cdot}$-OC_2H_5), 197 (20), 179 (10), 151 (14), 141 (9, $M^{+\cdot}$-$C_6H_9O_3$), 129 (85, $M^{+\cdot}$-$C_8H_{13}O_2$), 123 (9), 114 (14), 109 (7), 101 (100, $M^{+\cdot}$-$C_9H_{13}O_3$), 95, (14), 73 (27), 61 (31), 55 (50), 43 (18), 41 (40), 39 (17).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.24: H, 8.20.

B. A mixture of the phosphorane (205) (1.79g, 5.43 mmol) and succinic anhydride (0.547g, 5.47 mmol) in benzene (10ml) was heated under reflux for 2h while under a nitrogen atmosphere. The mixture was cooled and the solvent removed at reduced pressure. The residue was placed under a nitrogen atmosphere. Dry ethanol (10ml) was introduced followed by a solution of sodium ethoxide (296mg, 5.49 mmol) in dry ethanol (1.8ml) with stirring. After the addition, stirring was continued for 1h at ambient temperature and allyl bromide (671mg, 0.490ml, 5.62 mmol) added. The mixture was stirred for a further 20h at ambient temperature, poured onto ammonium chloride (20ml, saturated) and extracted with ether (3x20ml). The combined organic extracts were washed with water (1x20ml), dried (Na_2SO_4) and the solvent removed at reduced pressure. The product was purified by chromatography on silica gel (22g, ether-petrol ether, 1:1) to give 242mg (16%) of a clear mobile liquid which was identical (IR, ^{1}H NMR) to the diester (207a).

Diethyl 2,2-dimethyl-3-oxohexanedioate (207b):

A. The diester (207b), a clear mobile liquid, was prepared in 82% yield from a solution of the enol lactone (206) (200mg, 11 mmol) in dry ethanol (5ml), a solution of sodium ethoxide (70mg, 13 mmol) in dry ethanol (6ml) and methyl iodide (160mg, 0.070ml, 11.2 mmol) according to the procedure described in part A of the preparation of the diester (207a). The following physical properties were recorded for (207b): bp 85°C (0.01mm); IR (film) 1735, 1709, 1455, 1370, 1250, 1190, 1150, 1130, 1068, 1000, 845cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1-1.5 (12H, merged s and t, aliphatic $-CH_3$ and ester $-OCH_2\underline{CH_3}$), 2.4-2.9 (4H, c, $-COC\underline{H_2}C\underline{H_2}CO_2C_2H_5$), 4.0-4.4 (4H, two q, δ4.1, J=7Hz, δ4.2, J=7Hz, ester $-OC\underline{H_2}CH_3$); mass

spectrum 245 (0.5, $M^{+\cdot}+1$), 199 (22, $M^{+\cdot}-OCH_2H_5$), 171 (29, $M^{+\cdot}-C_3H_5O_2$), 129 (95, $M^{+\cdot}-C_6H_{11}O_2$), 95 (25), 116 (17), 101 (100, $M^{+\cdot}-C_7H_{11}O_3$), 97 (7), 88 (28), 73 (35), 70 (26), 59 (12), 55 (46), 45 (10), 43 (15), 42 (21), 41 (27), 39 (10).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.19; H, 8.41.

B. The enol lactone (206) was prepared from succinic anhydride (5.42g, 54.2 mmol) and the phosphorane (205) (18g, 54.3 mmol) in benzene (50ml) and subsequently converted, without purification, to the diester (207b) in 66% yield using sodium ethoxide (2.96g, 54.8 mmol) and methyl iodide (7.75g, 3.4ml, 54.6 mmol) according to the procedure described in part B for the preparation of diester (207a). The product was a clear mobile liquid which was identical (IR, ^{1}H NMR) to the diester (207b) prepared in part A above.

Ethyl 3-allyl-3-methyl-2,4-dioxocyclopentanecarboxylate (208a):

A. Sodium ethoxide in ethanol

A solution of the diester (207a) (50mg, 0.185 mmol) and sodium ethoxide (31mg, 1.9 mmol) in dry ethanol (3ml) was stirred for 18h at room temperature and under a nitrogen atmosphere. Only starting material could be detected by analytical TLC (ether-petrol ether, 3:2) after this time. Therefore, the solution was heated under reflux for 5h. The pale yellow solution became dark red, and a brown precipitate formed during the reflux. The mixture was cooled, poured onto ammonium chloride (5ml, saturated) and extracted with ether (2x10ml). The combined ethereal extracts were dried ($MgSO_4$) and the solvent removed to afford 18mg of a pale yellow liquid. The ^{1}H NMR was inconsistent with any anticipated products. The procedure was abandoned.

B. Potassium *tert*-butoxide in benzene.[152,153]

Freshly prepared alcohol free potassium *tert*-butoxide (2.46g, 22 mmol) was suspended in dry benzene (15ml) under a nitrogen atmosphere. A solution of the diester (207a) (151mg, 0.560 mmol) in dry benzene (1.5ml) was introduced and the mixture heated and stirred under reflux for 4h. After cooling, the mixture was poured onto ammonium chloride (10ml, saturated), the layers separated, and the aqueous phase extracted with dichloromethane (2x10ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed at reduced pressure to give 30mg of an intractable yellow liquid. The procedure was abandoned.

C. Potassium *tert*-butoxide in *tert*-butyl alcohol.[154]

Potassium (60mg, 1.54 mmol) was dissolved in dry *tert*-butyl alcohol (5ml) and the diester (207a) (154mg, 0.570 mmol) added.

After the addition, the mixture was stirred for 16h at ambient temperature, poured onto ice (5g) and hydrochloric acid (5ml, 10%), and extracted with ether (3x10ml). The combined extracts were dried ($MgSO_4$) and the solvent distilled to give 80mg of a dark brown liquid. The 'H NMR indicated that only a low yield (*ca.* 10%) of the dione (208a) had been obtained. The procedure was abandoned.

D. Sodium methylsulphinylmethide in dimethyl sulphoxide[155]

A 50% dispersion of sodium hydride (201mg, 8.39 mmol) in oil was washed with pentane (2x3ml) under a nitrogen atmosphere. Dry dimethyl sulphoxide (5ml) was introduced and the mixture stirred and heated at 70-80°C for 45 min. After cooling (ice bath), a solution of the diester (207a) (1.00g, 3.71 mmol) in dry dimethyl sulphoxide (1ml)

was added, and stirring continued for 4h at ambient temperature. The dark green solution was poured onto ice (10g) and hydrochloric acid (20ml, 10%) and extracted with dichloromethane (3x20ml). The combined organic extracts were evaporated to dryness. The ^{1}H NMR revealed that the residue was contaminated with dimethyl sulphoxide. The product was taken up in ether (20ml) and washed with water (2x5ml). The solvent was removed at reduced pressure and the residue distilled to afford the dioxo ester (208a) as a clear mobile liquid: 248mg (30%); bp 78°C (0.01mm); IR (film) 1745, 1740, 1720, 1660, 1622, 1450, 1440, 1325, 1290, 1238, 1025, 925, 788cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1-1.5 (6H, merged s and t, aliphatic $-CH_3$ and ester $-OCH_2\underline{CH_3}$), 2.3 (2H, d, J=7Hz, $-\underline{CH_2}-CH=C$), 3.1 (2H, s, C5-H_2), 4.3 (2H, q, J=7Hz, ester $-O\underline{CH_2}CH_3$), 4.9 and 5.1 (1H, m at 4.9, 1H, m at 5.1, $-C=\underline{CH_2}$), 5.2-6.0 (1H, brm, $-\underline{CH}=CH_2$), 9.5 (1H, brs, enol $-\underline{OH}$); mass spectrum 224 (70, $M^{+\cdot}$), 196 (21), 183 (18), 179 (25), 178 (35), 155 (32), 151 (57), 150 (92), 141 (30), 137 (55), 127 (38), 122 (30), 109 (15), 107 (14), 100 (21), 99 (31), 97 (20), 96 (100), 95 (43), 83 (66).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.01; H, 7.41.

Ethyl 3,3-dimethyl-2,4-dioxocyclopentanecarboxylate (298b)[168]

A. Sodium methylsulphinylmethide[155] in dimethyl sulphoxide:

A 50% dispersion of sodium hydride (226mg, 4.73 mmol) in oil was washed with pentane (1x2ml) under a nitrogen atmosphere. Dry dimethyl sulphoxide (4ml) was introduced and the mixture stirred and heated at 70-80°C for 45 min. After cooling (ice bath), a solution of diester (207b) (497mg, 2.03 mmol) in dry dimethyl sulphoxide (1ml) was added, and stirring continued for 4h at ambient temperature. The dark green solution was poured onto ice (10g) and hydrochloric acid (10ml, 10%) and extracted with dichloromethane (3x15ml). The combined

organic extracts were washed with water (5x10ml) until optically clear, dried (Na_2SO_4) and the solvent removed at reduced pressure to afford the crude dioxo ester (208b) as a red liquid: 174mg (43%); IR (film) 1760, 1730, 1660, 1625, 1465, 1419, 1380, 1315, 1280, 1240, 1181, 1014, 757cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-1.5 (9H, merged t and s, ester $-OCH_2\underline{CH_3}$ and aliphatic $-CH_3$), 3.1 (2H, brs, C5-H_2) 4.2 (2H, q, J=7Hz, ester - $OCH_2\underline{CH_3}$), 8.8 (1H, very brs, enol -O<u>H</u>); mass spectrum 198 (80, $M^{+\cdot}$), 170 (35), 153 (28), 152 (55), 124 (30), 123 (25), 70 (100), 55 (30), 43 (60), 42 (45), 41 (72), 39 (31).

B. Potassium *tert*-butoxide in dimethyl sulphoxide:

To a stirred solution of potassium *tert*-butoxide (281mg, 2.53 mmol) in dry dimethyl sulphoxide (2ml) under a nitrogen atmosphere was added a solution of the diester (207b) (214mg, 0.876 mmol) in dry dimethyl sulphoxide (0.5ml). A mild exothermic reaction ensued concomitant with the solution changing colour from pale to dark green. Stirring was continued for 7h at ambient temperature. The solution was poured onto ice (10g) and hydrochloric acid (5ml, 10%) and extracted with dichloromethane (3x15ml). The combined organic extracts were washed with water (5x5ml), dried (Na_2SO_4) and the solvent removed at reduced pressure to give 120mg of a red mobile liquid. The ^1H NMR spectrum revealed that the product was greater than 90% dione (208b). Therefore the yield of (208b) was *ca.* 65%.

2-Allyl-2-methylcyclopentane-1,3-dione (209a):[71(a),168]

A mixture of the β-keto ester (208a) (167mg, 0.746 mmol), water (3ml) and hydrochloric acid (2ml, 12 M) was stirred and heated at 60-70°C for 3h. The product was extracted with dichloromethane (3x10ml),

the combined organic extracts dried ($MgSO_4$), and the solvent removed at reduced pressure to give 110mg of a red mobile liquid. The 'H NMR showed that the crude product was at least 95% the dione (209a). The product was purified by distillation: bp 80°C (7mm) [lit.[71(a)] bp 60-62°(0.03mm)]; IR (film) 1765(w), 1725(s), 1640, 1450, 1420, 1370, 1320, 1200, 1020, 1030, 995, 925cm^{-1}; 'H NMR ($CDCl_3$) 1.1 (3H, s, aliphatic $-CH_3$), 2.2 (2H, d, J=7Hz, $-\underline{CH}_2-CH=C$), 2.7 (4H, s, C3-H_2 and C4-H_2), 4.9 and 5.1 (1H, m, at 4.9, 1H, m at 5.1, $-C=\underline{CH}_2$), 5.2-6.0 (1H, brm, $-CH_2-\underline{CH}=CH_2$); mass spectrum 152 (100, $M^{+\cdot}$), 137 (54), 109 (59), 97 (50), 69 (92), 67 (63), 57 (39), 55 (37), 41 (82).

2,2-Dimethylcyclopentane-1,3-dione (209b):[71(a),168]

A mixture of the β-keto ester (208b) (179mg, 0.904 mmol), water (3ml) and hydrochloric acid (2ml, 12M) was stirred and heated at 70-75°C for 3h. The product was extracted with dichloromethane (3x15ml), the combined organic extracts dried (Na_2SO_4) and the solvent removed at reduced pressure to give 115mg of a red mobile liquid. 'H NMR showed that the dione (209b) was the only product. The crude product was purified by sublimation to give the dione (209b) as a white crystalline solid: sublimed 85-90°C (0.01mm); mp 45-47°C (lit.[71(a)] mp 45-47°C); IR (Nujol) 1770(w), 1730(s), 1460, 1418, 1380, 1280, 1098, 1070, 1042, 988, 795, 755cm^{-1}; 'H NMR ($CDCl_3$) δ 1.1 (6H, s, two $-CH_3$), 2.8 (4H, s, C4-H_2 and C5-H_2); mass spectrum 126 (100, $M^{+\cdot}$), 111 (31), 85 (19), 70 (71), 56 (17), 55 (17), 43 (28), 42 (48), 41 (48), 39 (22).

Part 3.2

6-Methoxy-1-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol (213):[71(a),169,170]

A solution of the Grignard reagent prepared from vinyl bromide (17.9g, 12ml, 166 mmol) and magnesium (3.27g, 136 mmol) in dry tetrahydrofuran (40ml)[171] was cooled to -10°C and a solution of commercial (Fluka) 6-methoxy-1-tetralone (8.33g, 47.3 mmol) in dry tetrahydrofuran (20ml) was added with stirring during 20 min. The reaction mixture temperature was maintained between -5°C and -10°C during the addition and for 2h after. Subsequent to stirring for an additional 10h at ambient temperature, the mixture was poured onto ice (50g) and ammonium chloride (50ml, saturated). The layers were separated and the aqueous phase extracted with ether (3x50ml). The combined organic extracts were washed with sodium chloride (1x40ml, saturated), dried (K_2CO_3) and the solvent removed at reduced pressure to give (213) as a tan viscous liquid: 9.44g (98%); IR 3430(s), 1600, 1582, 1573, 1500, 1465, 1318, 1263, 1242, 1233, 1145, 1120, 1030, 990, 978, 920, 885, 873, 850, 830, 815cm^{-1}; ^{1}H NMR (CCl_4) δ 1.7 (4H, brs, C2-H_2 and C3-H_2), 2.2 (1H, s, D_2O exch, -O<u>H</u>), 2.7 (2H, m, C4-H_2), 3.6 (3H, s, $-OCH_3$), 4.9-5.3 (2H, c, -CH=C<u>H</u>$_2$), 5.9 (1H, dd, J_1=17Hz, J_2=10Hz, -C<u>H</u>=CH_2), 6.4-6.6 (2H, merged s and dd, C5-H and C7-H), 7.2 (1H, d, J=8Hz, C8-H).

2-(6'-Methoxy-1',2',3',4'-tetrahydro-1'-naphthylidene)ethyl-isothiouronium acetate (214):[71(a),162]

The isothiouronium acetate [mp 128-130°C (lit.[162] 125-127°C)] was prepared in 76% yield from (213) (1.01g, 4.95 mmol) and thiourea (400mg, 5.32 mmol) in acetic acid (4ml) according to the procedure of Kuo, Taub and Wendler.[162] The crystalline product was dried at

reduced pressure (0.4mm, 25°C,4h). A solution of the isothiouronium acetate (200mg) in ethanol (5ml) was titrated with standard sodium hydroxide (0.1M) using phenolphthaleine as indicator. This procedure revealed the presence of a 1.1 molar equivalent excess of acetic acid of crystallisation.

Diethyl 2-[2'-(6''-methoxy-1,''2,''3,''4,''-tetrahydro-1''-naphthylidene)ethyl]-2-methy-3-oxohexanedioate (215)

A solution of sodium ethoxide (387mg, 5.70 mmol) in dry ethanol (6ml) was added to a solution of enol lactone (206) (383mg, 2.08 mmol) in dry ethanol (3ml) under a nitrogen atmosphere. After the addition, the mixture was stirred for 15 min and a solution of the isothiouronium acetate (214) (926mg; 768mg, 2.38 mmol of (214) and 158mg, 2.63 mmol of acetic acid) in dry ethanol (6ml) and dry dimethyl sulphoxide (11.5ml) introduced. The solution was stirred for another 9h at ambient temperature, poured onto ammonium chloride (30ml, saturated) and extracted with ether (3x30ml). The combined organic phases were dried (Na_2SO_4) and the solvent removed at reduced pressure to afford 775mg (93%) of a brown mobile liquid which solidified slowly: IR (film) 1740, 1720, 1600, 1570, 1490, 1445, 1370, 1360(w), 1343(w), 1315(w), 1300(w), 1265, 1250, 1223, 1200, 1180, 1115, 1085(w), 1030(m), 855, 830, 810cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2 (9H, c, aliphatic-CH_3 and two ester -$OCH_2\underline{C}H_3$), 1.9 (2H, c, C3''-H_2), 2.6 (10H, c, C4-H_2, C5-H_2, C1'-H_2, C2''-H_2 and C4''-H_2), 3.7 (3H, s,-OCH_3), 3.9-4.2 (4H, two q, J_1=7Hz, J_2= 7Hz, two ester -$O\underline{C}H_2CH_3$), 5.8 (1H, m, -$\underline{C}H$=C), 6.6 (2H, merged dd and s, C5''-H and C7''-H), 7.4 (1H, d, J=8Hz, C8''-H); mass spectrum 261 (16), 186 (40), 157 (31), 148 (14), 139 (24), 129 (100), 115 (14), 111 (14), 101 (100), 76 (22), 73 (23), 56 (21), 55 (42), 43 (19).

Attempted synthesis of ethyl 3-[2'-(6''-methoxy-1'',2'',3'',4''-tetrahydro-1''-naphthylidene)ethyl]-3-methyl-2,4-dioxocyclopentanecarboxylate (216):

A. Sodium methylsulphinylmethide was prepared from a 50% dispersion of sodium hydride (103mg, 4.30 mmol) in oil and dimethyl sulphoxide (4ml) by the usual method.[155] To the cooled (ice bath), stirred mixture was added a solution of the diester (215) (166mg, 0.415 mmol) in dry dimethyl sulphoxide and stirring continued for 4.5h. The mixture was poured onto ice (10g) and ammonium chloride (10ml, saturated) and extracted with ether (3x15ml). The combined ethereal extracts were dried (Na_2SO_4) and the solvent removed at reduced pressure to give 80mg of a tan liquid. The IR spectrum of the product showed a moderate hydroxyl absorption at 3420cm^{-1} but no carbonyl absorption. The 'H NMR spectrum showed strong singlet resonances at δ1.3 and δ3.7, and complex patterns at δ0.9, 1.8, 5.9, 6.6 and 7.4. No resonances ascribable to an ester ethyl group were observed. The procedure was not further investigated.

B. To a stirred, cooled (ice bath) solution of potassium *tert*-butoxide (205mg, 1.83 mmol) in dry dimethyl sulphoxide (2.5ml) under a nitrogen atmosphere was added a solution of the diester (215) (93mg, 0.232 mmol) in dry dimethyl sulphoxide (0.5ml). After the addition, the mixture was stirred for 30 min at ambient temperature, poured onto ice (5g) and ammonium chloride (10ml, saturated), acidified to pH3 with 10% hydrochloric acid, and extracted with ether (3x15ml). The combined ether extracts were washed with water (1x5ml), dried (Na_2SO_4) and the solvent removed at reduced pressure to give 51mg of a dark brown viscous liquid. The IR spectrum of the product showed a strong hydroxyl absorption at 3420cm^{-1} but no carbonyl absorption.

The 'H NMR indicated that extensive alteration of the aromatic system had occurred and was consistent with formation of a soluble polymer.

C. Lithium diisopropylamide was prepared by treatment of a solution of diisopropylamine (79mg, 0.110ml, 0.781 mmol) in tetrahydrofuran (5ml) with a solution of butyl lithium in hexane (0.470ml, 1.7M, 0.799 mmol) at 4°C for 15 min.[163,164] The stirred solution under a nitrogen atmosphere was cooled to -72°C and the diester (215) (101mg, 0.252 mmol) added as a solution in tetrahydrofuran (1ml). The solution was stirred at -72°C for 2h, ammonium chloride (2ml, saturated) added and the mixture allowed to warm to room temperature. Water (3ml) was added and the product extracted with ether (3x10ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed at reduced pressure to give 113mg of a viscous red liquid. The IR spectrum showed a strong carbonyl absorption at 1740cm^{-1} and no hydroxyl absorption. The 'H NMR spectrum showed aromatic resonances at δ7.7 and δ6.6, a vinyl proton resonance at δ5.9, a methyl ether at δ3.7 and a quaternary methyl at δ1.2. No ethyl ester resonances were apparent. Comparison of the 'H NMR spectra for the starting material and product revealed that the integration for the region δ1.7-3.1 had decreased relative to the aromatic region in the product.

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Pure logical thinking cannot yield us any knowledge of the empirical world.

A. Einstein