

NEW METHODS FOR SPIROKETAL SYNTHESIS

a thesis presented by

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ABSTRACT

New methods for carbon-carbon bond formation at the anomeric centre of cyclic ethers have been investigated, and their application to the synthesis of spiroketals. Wittig and Horner-Wittig reactions of tetrahydropyran-2-yl and tetrafuran-2-yl phosphonium salts or phosphine oxides with aldehydes or lactols gave enol ethers, some of which were subsequently cyclised to spiroketals, including the naturally occurring insect pheromone, 1,7-dioxaspiro[5,5]undecane in racemic form.

Sulphone coupling reactions, condensing the anion of 2-benzenesulphonyl tetrahydropyran with aldehydes, bromides, iodides and epoxides gave the desired 2-substituted 5,6 dihydro-4H-pyrans. Again, in certain examples, acid treatment of the enol ether yielded the spiroketal. The insect pheromones 1,7-dioxaspiro[5,5]undecane, 2-methyl-1,6-dioxaspiro[4,5]decane and 4-hydroxy, 1,7-dioxaspiro[5,5]undecane were prepared by this method, the latter two being prepared in optically pure form.

Models for the spiroketal moiety found in the milbemycin and avermectin family of compounds could also be prepared by this route.

The spiroketal unit is a feature of CP-61,405, an antiparasitic agent, similar in structure to Calcimycin. The methodology developed was used to construct this part of the molecule. The required 2-benzenesulphonyl, 6-hydroxy, methyl tetrahydropyran and the corresponding phosphonium salt and phosphine oxide were prepared in racemic form for model studies. The desired chiral material was prepared from tri-O-acetyl-D-glucal in a four step synthesis.

The aromatic portion which would eventually be cyclised to the desired benzoxazole was prepared by two routes. A novel route starting with dihydroquinone (mono-protected by trimethylsilylethoxymethyl) and treatment with benzeneseleninic anhydride and hexamethyldisilazane

gave the selenoimine, which was subsequently reduced to 2-amino-4-O-(2'-trimethylsilylethoxymethyl) dihydroquinone, but this was only partially successful. The conventional approach by nitrating methyl 2,5-dihydroxybenzoate and reduction to methyl 2-amino-3,6-dihydroxybenzoate proved more successful. Finally, model studies of the condensation of methyl 2-amino-3,6-dihydroxybenzoate and benzoic acid with ethyl polyphosphate were investigated.

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ABBREVIATIONS

Bn : Benzyl
bp : Boiling point
nBuLi : n-Butyllithium
Bz : Benzoyl
CHCl₃ : Chloroform
CSA : Camphor sulphonic acid
DIBAL : Diisobutylaluminium hydride
DCM : Dichloromethane
DME : 1,2-Dimethoxyethane
DMF : Dimethylformamide
IR : Infra-red
LDA : Lithium diisopropylamide
mCPBA : Meta-chloroperbenzoic acid
mp : Melting point
Ms : Methanesulphonyl (mesyl)
NaH : Sodium hydride
nmr : Nuclear magnetic resonance
rt : Room temperature
SAMP : (S)-1-amino-2-methoxymethyl pyrrolidine
TBDMS : ^t-Butyldimethylsilyl
TBDPS : ^t-Butyldiphenylsilyl
THF : Tetrahydrofuran
THP : Tetrahydropyran
TMS : Trimethylsilyl
Ts : Toluene-4-sulphonyl (tosyl)

FORMATION OF CARBON - CARBON BONDS AT THE ANOMERIC CENTRE

1.1 Introduction

Efficient and stereocontrolled methods for C-glycosidation are important synthetic objectives not only for C-glycoside and C-nucleoside formation but also for homologation of carbohydrates to serve as chiral templates. These methods may also be applied to cyclic ethers which are important building blocks for many natural product syntheses, especially those with spiroketal moieties.

The following review describes recent progress made in this field and has been divided into the following sections.

1.2 CYANIDE FORMATION

1.3 CONDENSATION WITH CARBANIONS

- a) Wittig
- b) Organometallic
- c) Lithium and sodium generated anions

1.4 CONDENSATION REACTIONS CATALYZED BY LEWIS ACIDS

- a) Enol Ethers, Ketene Acetals and Allyl silanes as Nucleophiles
- b) Friedel-Crafts

1.5 ORGANO-TRANSITION METAL APPROACH

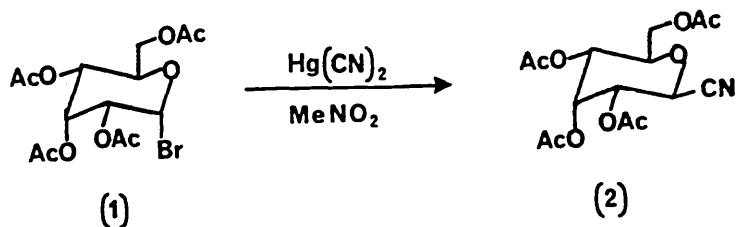
1.6 FORMATION OF ANIONS AT THE ANOMERIC CENTRE

1.7 PHOTOCHEMICAL AND RADICAL REACTIONS

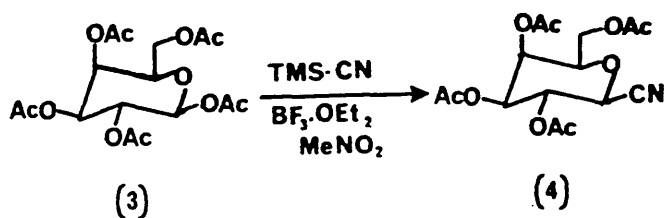
1.8 MISCELLANEOUS

1.2 CYANIDE FORMATION

Glycosyl cyanides are versatile, anomERICALLY functionalised intermediates and useful in the synthesis of many elaborated sugar molecules. Access to these compounds is well known, the first reported synthesis was in 1949 when Helferich and Wedemeyer² prepared the β -D-aldo-pyranosyl cyanide (2) from the reaction of 1-bromo - 2, 3, 4, 6-tetra-O-acetyl- β -D-aldopyranose (1) with mercuric cyanide, albeit in poor yield.



More recently³ the reaction of trimethylsilyl cyanide with 1, 2, 3, 4, 6-penta-O-acetyl- β -D-galactopyranose (3) and boron trifluoride etherate gave (4) as the β -anomer in 82% yield. The addition of the Lewis acid catalysed the reaction and improved the yield.

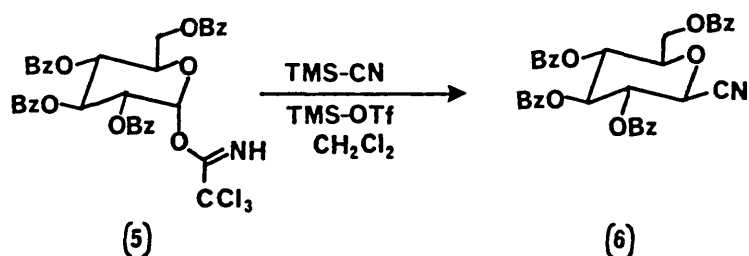


A similar reaction of 1-O-acetyl, 2, 3, 5-tri-O-benzoyl- β -D-ribofuranose with trimethylsilyl cyanide and stannic

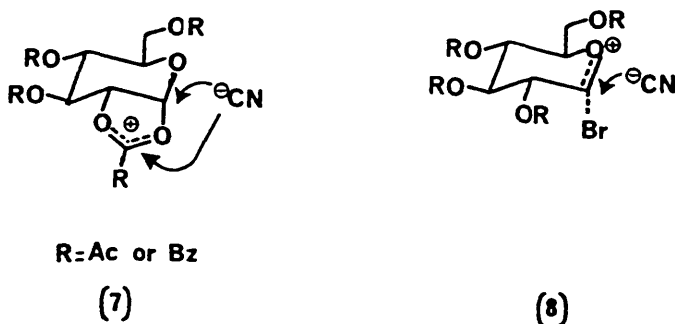
chloride gave the β -anomer in 86% yield.

The ability of the anomeric substituent to act as a leaving group was important in these reactions. Acetoxy and chloride derivatives gave good yields compared to methoxy derivatives which gave poor yields.

Activation of the anomeric substituent by forming the O-(α -D-glucopyranosyl) trichloroacetimidate (5)⁴ and reaction with trimethyl silyl cyanide in the presence of trimethyl silyl triflate gave the β -anomer (6) in 87% yield.



Neighbouring group (anchimeric) participation could be determining the stereoselectivity of those reactions via the formation of the acyloxonium ion (7) but then we might expect two products as the cyanide ion could attack at two carbon atoms. Another mechanism could involve the formation of the oxonium ion (8), where the departing ion shields the α -face, thereby directing the incoming nucleophile to β -attack.

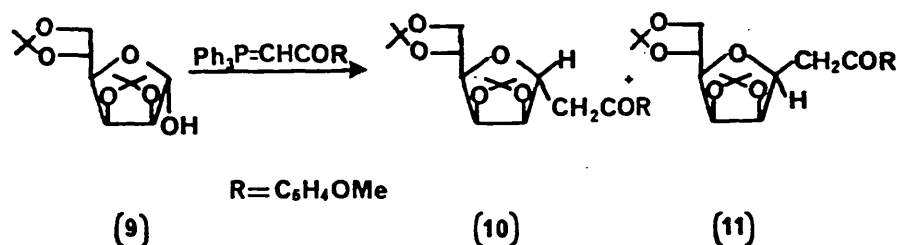


1.3 CONDENSATION WITH CARBANIONS

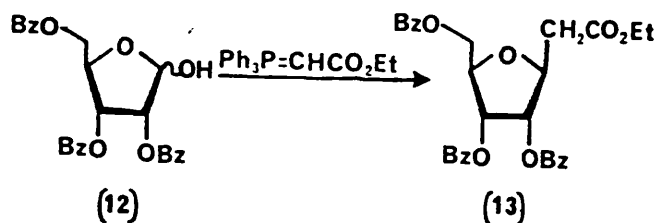
a) WITTIG AND HORNER-WITTIG REACTIONS

The Wittig and Horner-Wittig reactions are useful methods for the formation of carbon-carbon bonds at the anomeric position of cyclic ethers or carbohydrates.

Initial studies by Zhdanov *et al.*⁵ showed 2,3: 5,6-di-O-isopropylidene- α -D-mannofuranose (9) reacted with (p-methoxybenzoyl)-triphenylphosphorane to give two anomers (10) (11) which were separable.



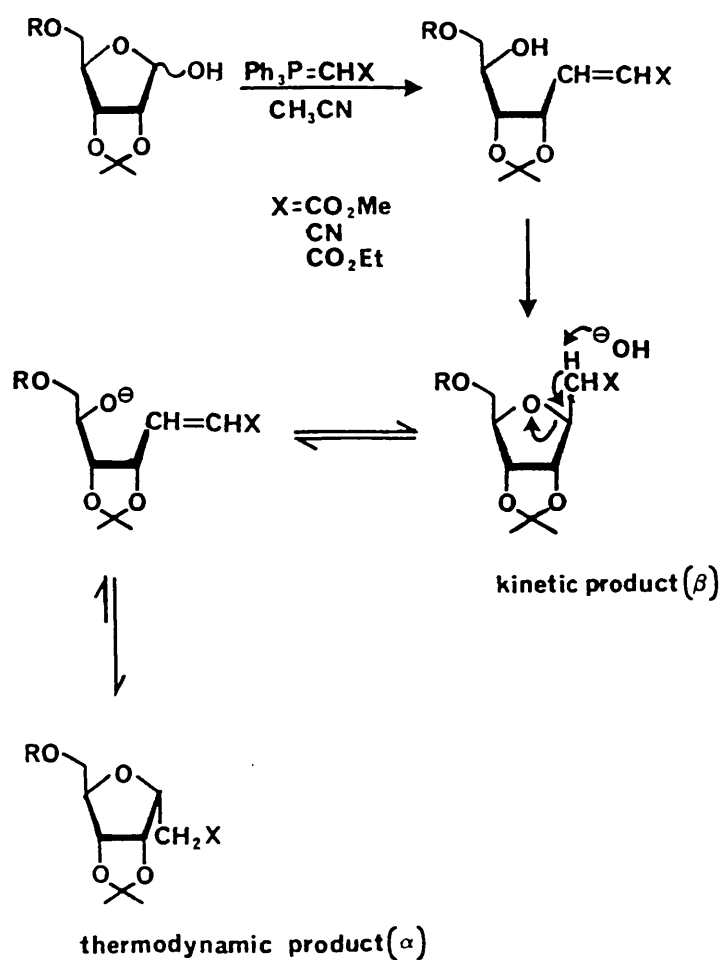
However, Hanessian *et al.*⁶ improved the stereochemical control by changing the protecting groups to benzoyl (12), thereby isolating only the β -anomer (13) in 38% yield.



If this method of carbon-carbon bond formations was to be of any synthetic use, the factors determining the stereo-selectivity (that is α and β anomer ratios) and the application to various protected furanose and pyranose

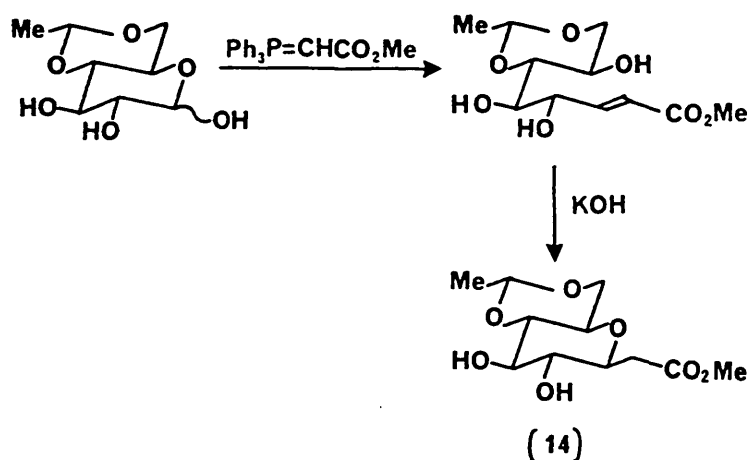
systems needed to be investigated. An extensive study was undertaken by Moffat *et al.*⁷ which showed the scope of the reaction and proposed the following mechanism for the process. (Scheme 1)

Scheme 1



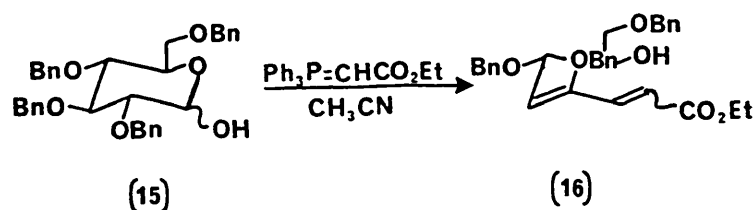
The intermediate unsaturated oxanion under went spontaneous Michael type ring closure. The intermediate was stereo-

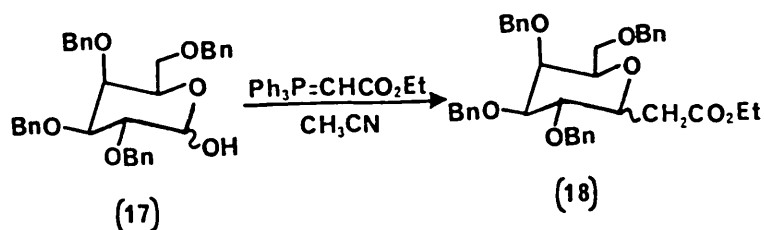
electronically favoured due to an anti-periplanar arrangement of the oxygen lone pair and C-1-O bond. The ring closure gave the β -anomer but the presence of added steric constraint (that is the protecting group) showed the α -anomer was preferred. The ability of deliberately forming the favoured anomer by this equilibrating method via the ring open product was used to form the β -glucopyranoside (14)⁸.



The ring closure was observed by polarimetric methods (the compound obeying Hudson's rule of rotation)⁹.

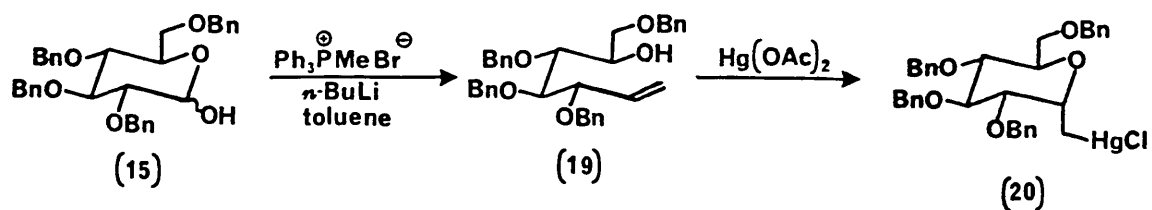
The Moffat C-glycosidation procedure has been examined on the benzylates series of glycosylpyranoses¹⁰. Interestingly, the benzylated glucopyranose (15) gave (16), the eliminated ring open product. The manno, altro and aldo pyranoses all gave the ring opened product with only the galactopyranose (17) giving the cyclised product (18).





The difference in reactivity of these sugars could be attributed to the steric effects of the protected alcohols. The contrasting behaviour of 4,6-O-benzylidene-2,3-di-O-benzyl-D-glucopyranose under the same conditions afforded the C-glycosidation product with no eliminated product confirmed this idea.

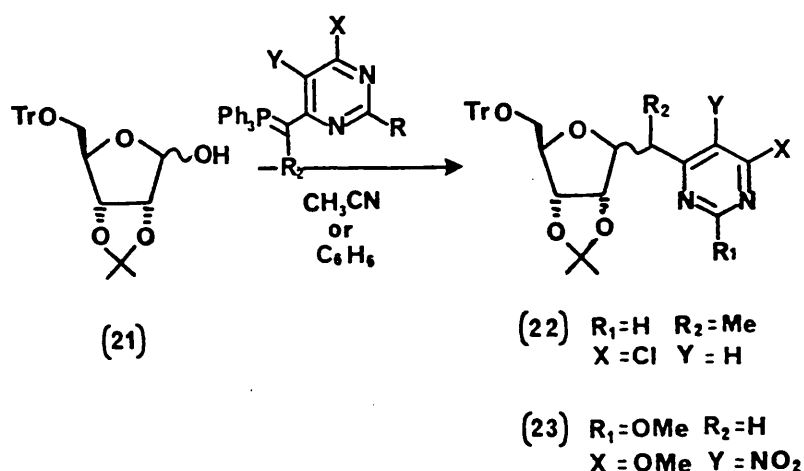
The highly stereoselective route to α -anomers (20), achieved by mercury mediated cyclisation after the initial reaction of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (15) with methylenetriphenylphosphorane via the unsaturated derivative (19), showed that under suitable conditions no eliminated product was formed¹¹.



However, other conditions ($\text{PH}_3\text{P}^{\oplus}\text{MeBr}^{\ominus}$, NaH, dimethylsulphoxide) resulted in quantitative elimination to give the diene. ^{of the}Because ^astrong directing effect of the benzyl groups, they could be expected to co-ordinate with the incoming mercuric species, hence the selectivity observed.

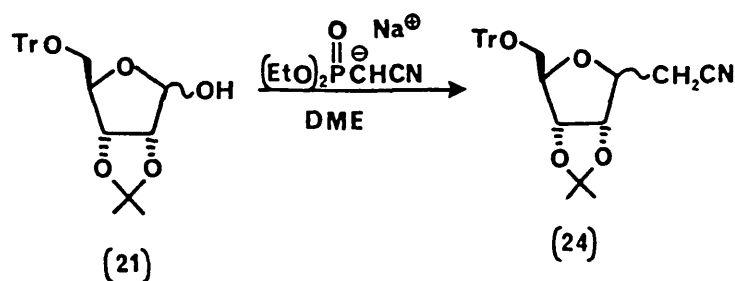
The versatility of this reaction has been extended to many natural product synthesis.

The reaction of 2, 3-O-isopropylidene-5-O-trityl-β-D-ribofuranose (21) with the pyrimidinyl methylene phosphoranes gave a concise synthesis of homo-C-nucleosides (22)¹² (23)¹³ respectively.

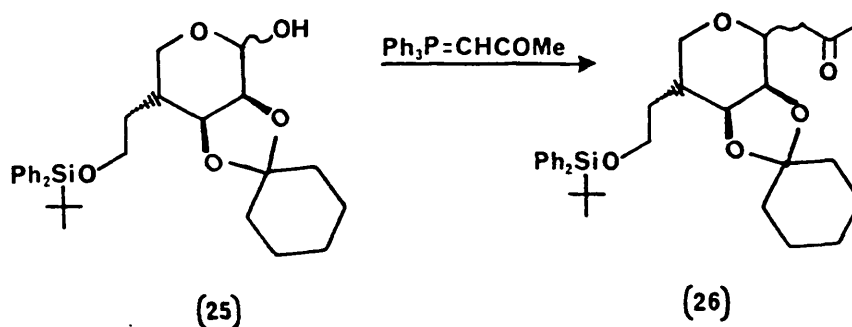


In the first example, the β-anomer was the major product over a series of R_1 and R_2 substituents, contrasting with the second example where the α-anomer was the slightly predominant product.

The Wittig-Horner modification using sodium diethyl cyanomethyl phosphonate was successfully applied to the synthesis of Oxazinomyan¹⁴, the key intermediate being the ribosyl-acetonitrile (24) formed in excellent yield (97%).



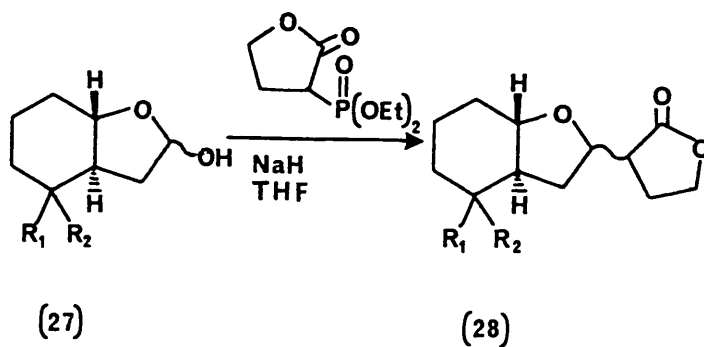
The above examples have shown the application of the Wittig and Horner-Wittig reaction under relatively mild conditions (RT, reflux), however in the synthesis of Pseudomonic Acid C^{15} , the Wittig reaction had to be performed in a sealed tube at 170°C for 10h. The functionalised lactol (25) was treated with acetylmethylenetriphenylphosphorane under the conditions described to give the desired pyran (26) as a mixture of α -anomer (kinetic product) and β -anomer (thermodynamic product) (ratio 2.5:1).



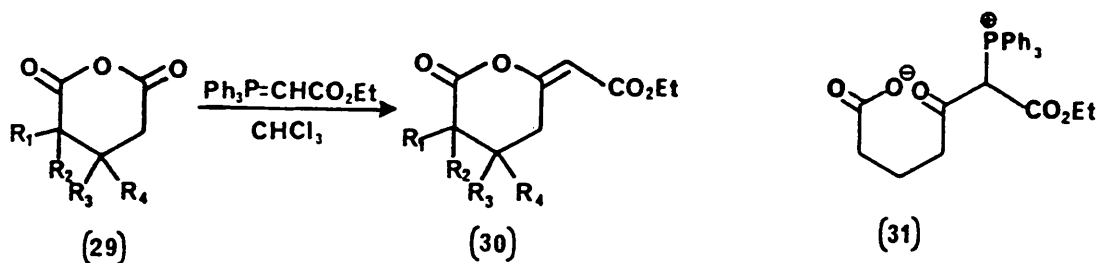
An improvement to this route using other methodology has since been reported and will be discussed later.

In the synthesis of dl-Ancistrofuran¹⁶, the reaction of the lactol (27) with the phosphonate anion (Wadsworth-Emmons reaction) gave the desired ring closed product (28)

whereas reaction with the phosphorane gave the ring open product. This suggests the medium was sufficiently basic to ensure ring closure in the former example.



The Wittig reaction has also been applied to simple cyclic α -O-ethers. Glutaric anhydride (29) reacted with (ethoxycarbonylmethylene) triphenylphosphorane to yield the enol δ -lactone (30)¹⁷.

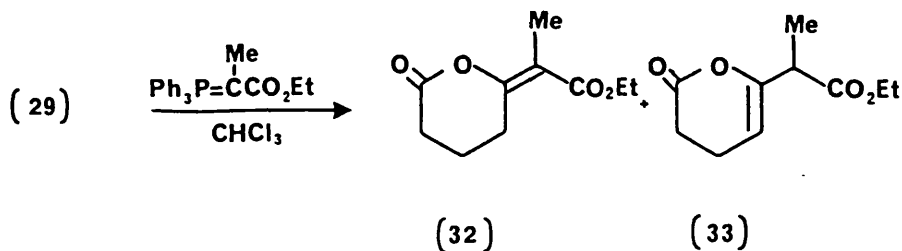


The reaction proceeded via the intermediate phosphonium salt (31) which was isolated before ring closure.

When $R_1=R_2=R_3=R_4=H$, the E-enol δ -lactone was observed after 168h, however, alkyl substitution, that is $R^1=R^2=Me$ or $R^3=R^4=Me$ gave good yields after 24h.

A slight modification of the Wittig reagent¹⁸ gave the E-and endo-enol δ -lactone (32) (33) when reacted with glutaric

anhydride.

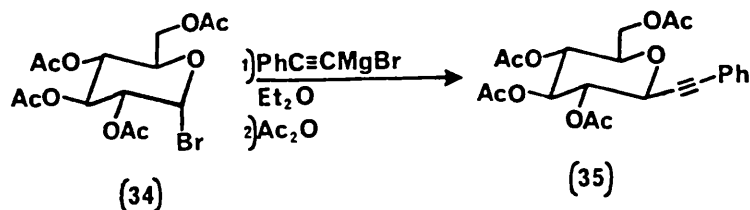


Again, substitution on the glutaric anhydride improved the yield of product and gave the E-isomer only.

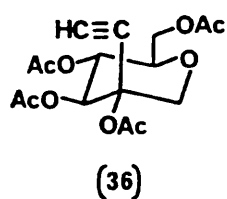
In neither of these examples was the formation of two new carbon-carbon bonds attempted, either by using excess phosphorane or treating the enol- δ -lactone with a second equivalent. This would be of interest to see whether the tetrahydropyran ring would remain closed or favour the open chain product.

b) ORGANOMETALLIC REACTIONS

The reactions of per-O-acetylglycosyl halides with organo-magnesium reagents (that is the Grignard reaction) was extensively investigated by Bonner¹⁹. However, a large excess of reagent was required and the reactions often remained incomplete. Other attempts to react 2, 3, 4, 6-tetra-O-acetyl- α -D-glucopyranosyl bromide (34) with phenylethynyl magnesium bromide proved moderately successful²⁰, although the product had to be re-acetylated (35).

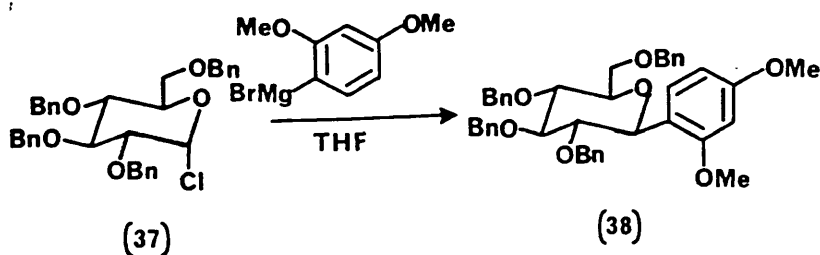


However, Ogura²¹ et al. failed to isolate the desired compound from this reaction when performed in tetrahydrofuran, and observed 5-anhydro-2, 3, 4, 6-tetra-o-acetyl-2-C-ethynyl-D-glucitol (36).



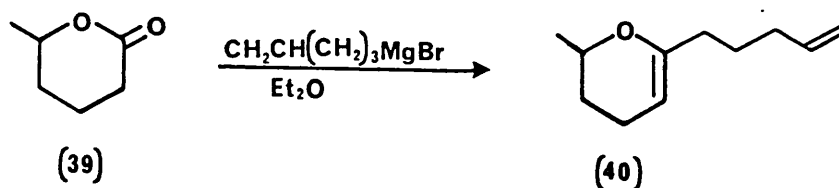
Obviously this choice of protecting groups could be hindering the reaction and in fact when these were changed to benzyl, which were not prone to react under Grignard conditions, the yield of the reactions were greatly improved.

Reaction of 2, 3, 4, 6-tetra-O-benzyl- α -D-glucopyranosyl chloride (37) with the Grignard reagent gave good yields of the C-glycoside product (38) and was used as the first step in the synthesis of C-glycosyl flavonoids²².

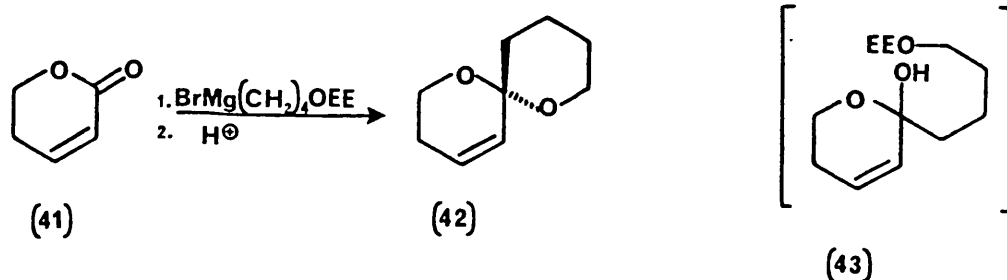


However, recently Hanessian et al.²³ used acetyl or benzyl protecting groups and successfully achieved the reaction of the anomeric bromide with allyl magnesium bromide in the synthesis of 'Quantamycin'.

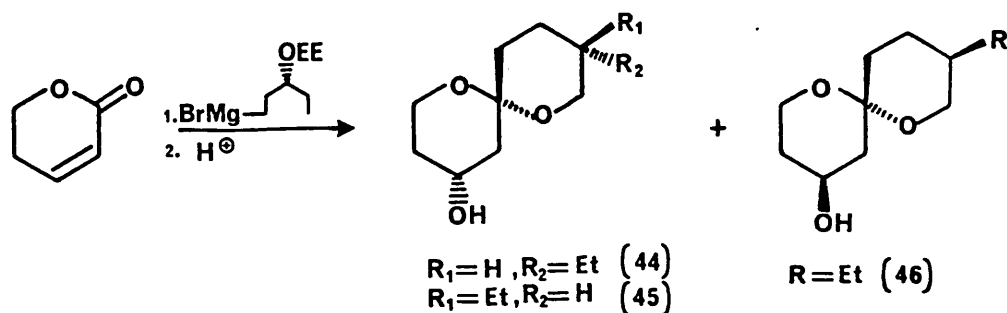
The reaction of lactones and Grignard reagents proved promising in model studies towards the synthesis of the macrolide Zearalenone²⁴. The methyl-valerolactone (39) was treated with pent-4, -enyl magnesium bromide under mild conditions to yield the 1,2 adduct (that is the ring opened form) which was cyclised by distillation or acid treatment to the enol ether (40).



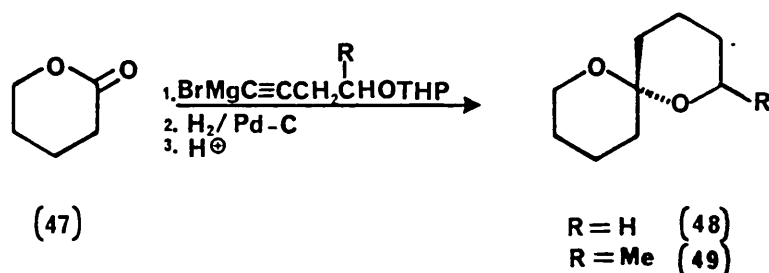
Model studies by Smith et al.²⁵ towards the enantioselective synthesis of Talaromycin A and B, showed the lactone (41) reacted with the Grignard reagent derived from 4-bromo-1-butanol ethoxy ether, to give the Spiroketal (42) after acid work-up. Surprisingly, the double bond does not rearrange under these conditions, although one would expect the intermediate hemiketal (43) to be rather unstable.



In a similar sequence the chiral Grignard reagent and lactone (41) gave 3 spiroketal products after acid work-up (44) (45) (46).



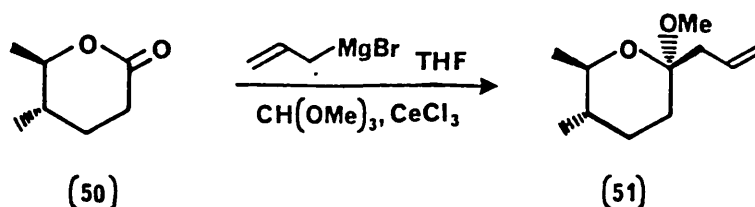
In a study of the stereoelectronic effects and conformational analysis of spiroketals, Deslongchamps *et al.*²⁶ prepared the spiroketals (48) and (49) by addition of the acetylenic Grignard reagent to valerolactone (47), followed by catalytic hydrogenation, protective group hydrolysis and acid catalyzed cyclisation.



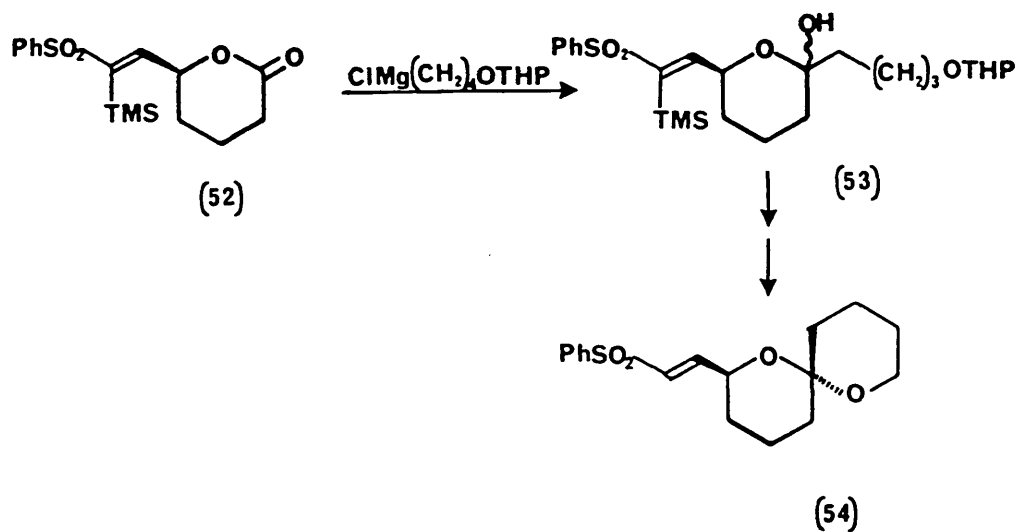
The same sequence was used by Baker *et al.*²⁷ in the synthesis of the minor component of the olive fly pheromone.

Studies by Smith *et al.*²⁸ towards the synthesis of Milbemycin β_3 reacted allyl magnesium bromide with the chiral functionalised lactone (50) prepared from citronellol. The hemi-ketal (51) was further modified by extension of the side chain to give the desired spiroketal of Milbemycin

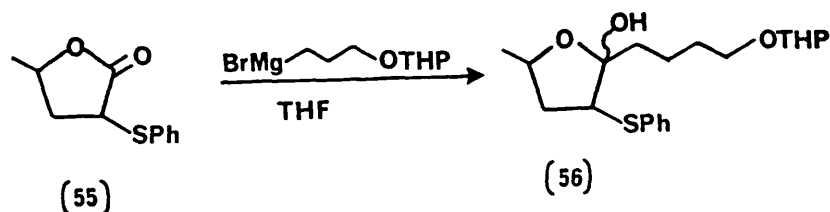
83.



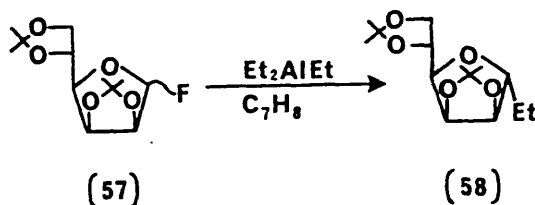
The ability to design functionalised chiral lactones as well as chiral Grignard reagents enables other natural products with chiral centres to be concisely formed. Reaction of the lactone (53) with the Grignard reagent and subsequent treatment of the hemiketal (53) gave the spiroketal (54) a precursor to Okadaic acid²⁹. The vinylsulphone moiety was less reactive towards the Grignard reagent than the lactone carbonyl.



Iwata *et al.*³⁰ reacted the Grignard reagent with 5-methyl-3-phenylthiotetrahydro-furan-2-one (55) to yield the hemiketal (56) forming the first step in a novel route to the spiroketal skeleton.



Organoaluminium reagents have converted glycosyl fluorides into C-glycosides, by a mild and efficient route.³¹ The requisite organoaluminium reagents are easily prepared via hydroalumination of terminal acetylenes or via organoaluminium chloride metaXthesis with organolithium species. When 2,3: 5,6 di-O-isopropylidene-D-ribofuranose fluoride (57) was treated the triethylaluminium species at 0°C, the C-glycoside (58) was obtained in good yield (79%).



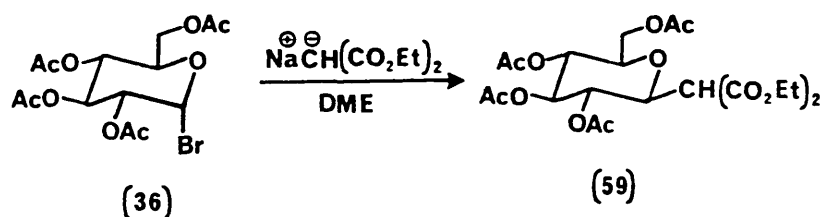
The reaction maybe assumed to proceed via the intermediate oxonium ion, as indicated by both α and β fluorides yielding the α -anomer as the major product. The reaction utilises the strong affinity of aluminium for fluorine.

c) CARBANIONS GENERATED BY SODIUM OR LITHIUM

The condensation of a carbanionic reagent with the appropriate

carbohydrate derivative or cyclic ether provides a direct method to carbon-carbon bond formation at the anomeric position and has been used extensively in natural product synthesis.

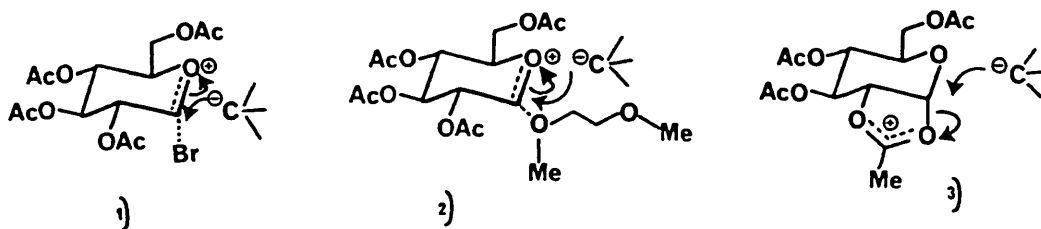
Hanessian et al.³² performed a systematic study of the reaction of O-acylglycosyl halides with carbanions generated from the treatment of diethylmalonate with sodium hydride. Choice of solvent was important in these reactions. Reaction of 2,3,4,6-tetra-O-acetyl- α -D-glycopyranosyl bromide (36) with diethylsodiomalonate in dimethoxyethane gave exclusively the β -anomer (59) in 20% yield. Surprisingly the yield was increased to 80% when dibenzylsodiomalonate was used; this is probably a reflection of the difference in solubility between the two reagents.



The proposed mechanism of the formation of the β -C-glycosyl compound was explained by the following:-

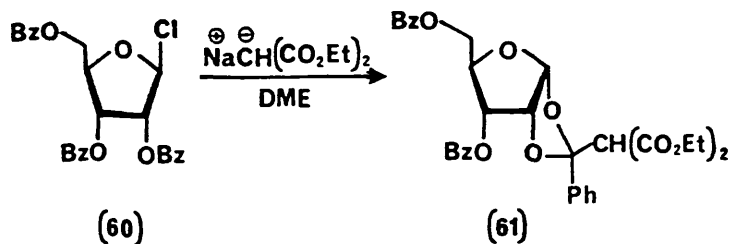
- 1) An S_N2 type reaction at the anomeric carbon of the halide or an ion pair intermediate in which the halide has α -orientation.
- 2) Formation of an oxonium ion with stabilization from the solvent, followed by β -attack by the carbanion.

- 3) Anchimeric participation leading to the formation of a 1,2 acetoxonium ion from the initial oxonium ion and subsequent attack of the carbanion at the anomeric carbon.
- 4) Irreversible epimerisation of any α -anomer formed.



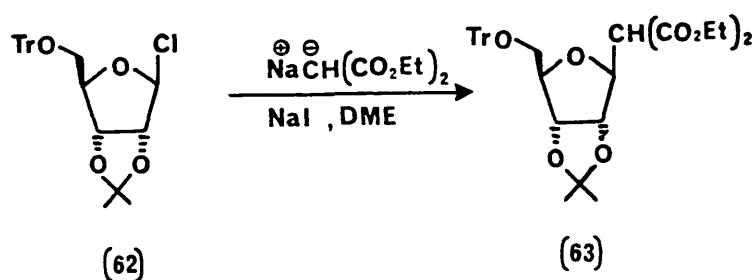
1) and 3) were the more likely factors influencing the stereochemical outcome of the reaction. Dimethoxyethane could be envisaged to form a bidentate complex with the cation, generating a harder nucleophile which attacked the anomeric carbon giving exclusively the β -anomer.

The same reasoning cannot be applied so easily to the ribofuranosyl derivatives³³. Treatment of 2, 3, 5-tri-O-benzoyl β -D-ribofuranosyl chloride (60) with diethylsodiummalonate in dimethoxyethane gave the acetal (61) resulting from attack of the benzoyl to form the benzoxonium ion and attack of the carbanion at this centre.

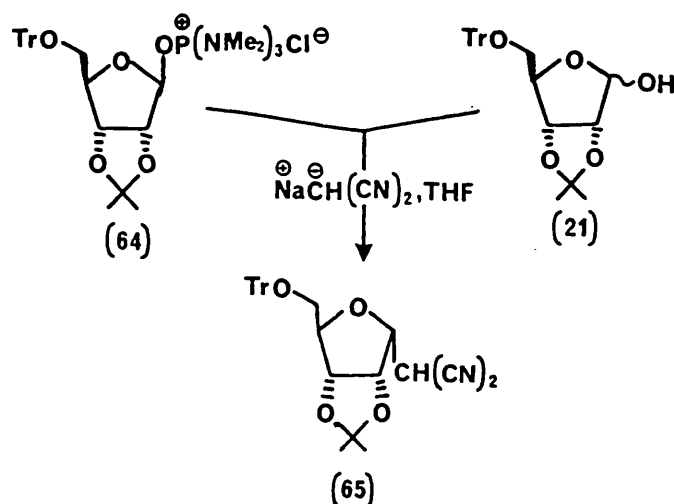


The formation of the desired C-glycosyl compound was achieved by changing the protecting group to benzyl, that is a non-participating group. Treatment of the chloride under the same conditions gave a mixture of the α - and β -anomers in approximately a 1:1 ratio.

Further studies by Ohrui³⁴, bearing in mind that there should be no anchimeric participation from the 2-substituent and the predominant isomer (by subsequent equilibration conditions) should be the β -anomer, showed the condensation of 2,3-O-isopropylidene-5-O-trityl- β -D-ribose chloride (62) with sodium diethylmalonate gave the β -anomer (63) after 24h. The acidic proton at C-2 facilitated the 'anomeric equilibration' via the acyclic intermediate under basic conditions to the thermodynamic isomer (β -anomer).



Activation of the anomeric hydroxyl by formation of alkoxytris (dimethylamino) phosphonium salt (64) and condensation with sodiomalonitrile gave the C-glycoside (65) in 41% yield and only the α -anomer observed³⁵. However, further studies showed C-glycofuranosyl malonates could be prepared by direct condensation of the free anomeric hydroxy sugar (21) and sodiomalonnate at room temperature gave the α -anomer (65) in 84% yield.

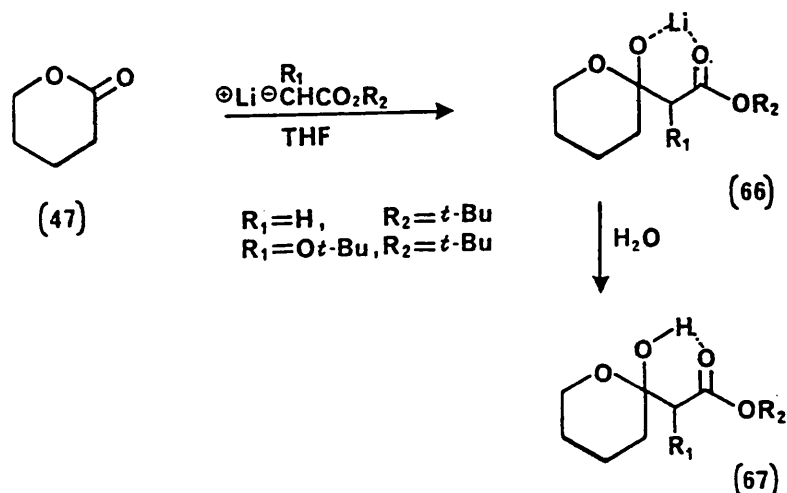


The mechanism of the reaction was assumed to proceed via the formation of the acyclic unsaturated intermediate and ring closure by Michael addition on the activated alkene. Therefore, the thermodynamically more stable anomer would predominate. The exclusive formation of the α -anomer (65) was because the malonyl and isopropylidene moieties assume a cis-relationship. This was confirmed by exclusive β -anomer formation when 2,3:5,6-di-O-isopropylidene-D-mannose was subjected to the same conditions.

In comparison with the C-glycofuranosyl chloride or bromide, the hydroxy analogue (21) condensed with diethylsodiomalonnate rather sluggishly, requiring two days in refluxing tetrahydropyran, to obtain a modest 30% yield, and therefore not a better method.

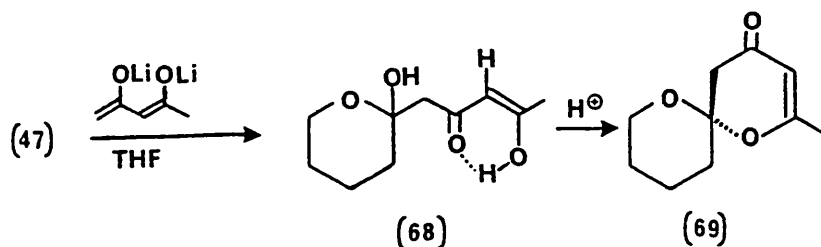
There are few precedents for the condensation of cyclic-haloethers with diethylsodiomalonnate, possibly due to the instability of the anomeric chloride or bromide.

However, diethyl-DL-tetrahydropyran-2-yl malonate was prepared from the reaction of 2-chloro or 2-bromo tetrahydropyran with diethylsodiomaltonate in 78% yield³⁷. The reaction of lactones with enolate and acetylide anions has been more thoroughly explored. The condensation of δ -valerolactone (47) with the lithium enolate anion, generated in situ at -78°C , gave the hemiketal (67) in excellent yield³⁸. No ring opened ketol was observed, and this can be rationalised by the stabilization of the hemiketal via lithium chelation (66) and hydrogen bonding (67) after hydrolysis.



The synthetic application of this reaction was realised in the synthesis of 1,3,6-trioxaspiro[4,5]decane, utilising an elaborated lithium enolate where R was a protected hydroxyl.

Model studies towards the synthesis of Milbemycin β_3 ³⁹, showed the addition of pentane, 2,4-dione dianions to δ -valerolactone (47) gave a concise route to the spiroketal moiety (69) via the hemiketal (68).



In numerous studies (Table 1) directed towards the synthesis of milbemycin and avermectin family of compounds, the condensation of the lithioacetylenide derivative (71) (prepared in situ by treating the acetylene derivative with n-butyllithium) and chiral lactones (70) generated the hemiketal (72), a precursor to the spiroketal moiety.

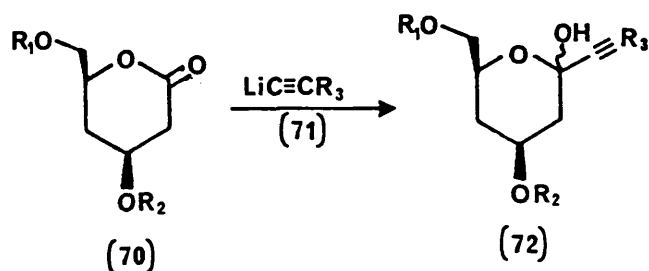
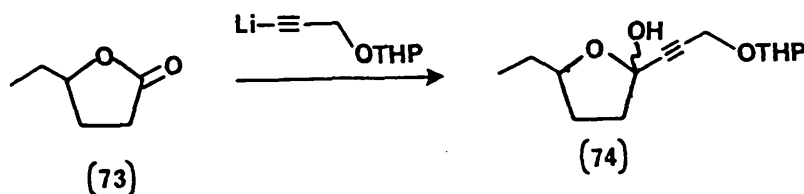


Table 1

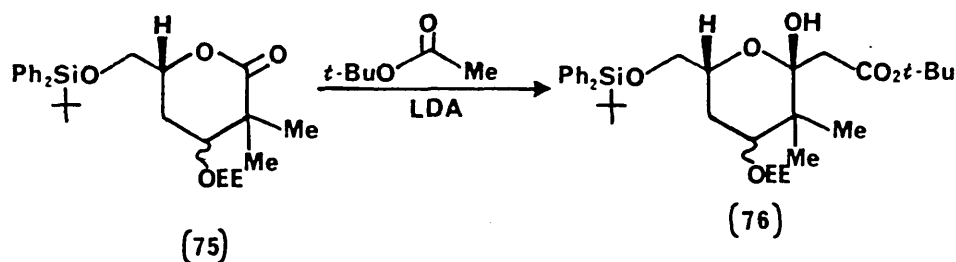
R_1	R_2	R_3	Yield (%)	SPIROKETAL	Ref
CH_2PH	$SiPh_2^tBu$		90	Milbemycin $\beta_1\beta_3$	40
CH_2PH	CH_2Ph		80	Milbemycin $\alpha_7\alpha_8$	41
CH_2PH	CH_2Ph		54	Avermectin B_{1b} B_{2b}	42
$SiPh_2^tBu$	CH_2Ph		38	Avermectin B_{1a}	43
$SiPh_2^tBu$	CH_2Ph		82	Avermectin B_{1a}	44

It is interesting to note, that initial studies by Deslong-champs *et al.*⁴⁵ suggested only ring open product was formed when δ -valerolactone (66) condensed with acetylenide anions, although the intermediate was not characterised but cyclised to the spiroketal by acid treatment.

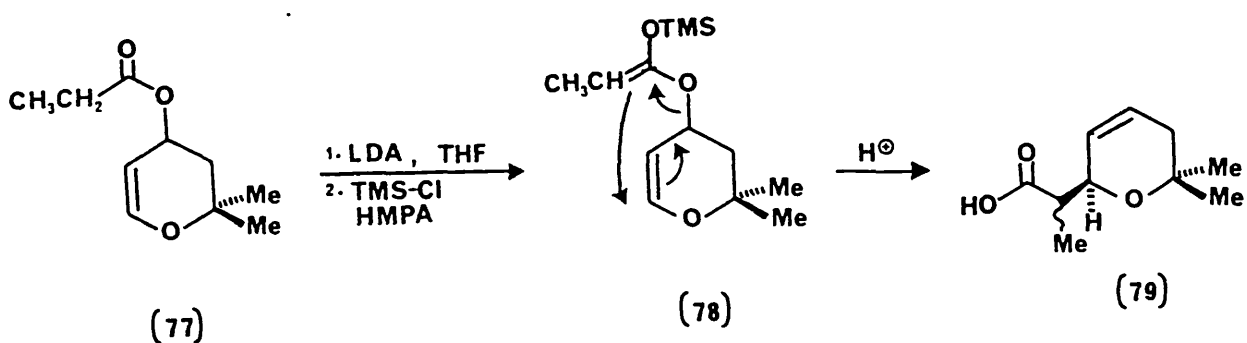
Condensation of γ -caprolactone (73) with lithiopropargyl alcohol tetrahydropyranyl ether provided a facile synthesis of 2-ethyl, 1,6-dioxaspiro [4.4] nonane⁴⁶, via the hemiketal (74).



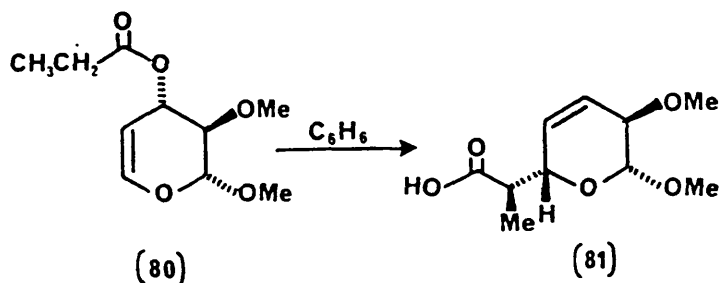
The synthesis of (+) benzoylpedamide⁴⁷ involved the condensation of the functionalised lactone (75) and the lithioacetyl ester, generated in situ to yield the hemiketal (76) with complete stereocontrol at the anomeric centre.



A novel enolate- Claisen rearrangement by in situ generation of the lithium enolate provided a concise route to carbon-carbon bond formation at the anomeric centre ⁴⁸. The enol ether (77) under treatment with lithium diisopropylamide and formation of the silyl ester, gave (79) via the intermediate (78) in 79% yield.

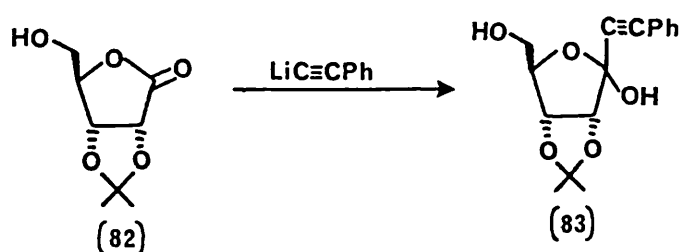


There was complete stereoselectivity in the carbon-carbon bond formation at the anomeric centre but the diastereoisomeric ratio of substituents on the side chain was influenced by solvent effects. Non-bonded interactions between the substituents on the heterocyclic ring and the silyl ketene acetal does not always allow exclusive access to the preferred chair-like transition state and a mixture of products resulted.



This rearrangement also occurred under thermolysis, where the preferred boat-like transition state with the substituents adopting a trans relationship, resulted in complete stereocontrol of the methyl group ⁴⁹.

C-glycoylation via various lithiated species has been applied in sugar chemistry. Acetylenic lactols (83) were easily synthesised from the corresponding lactone (82) and lithio-ethynylide ⁵⁰.

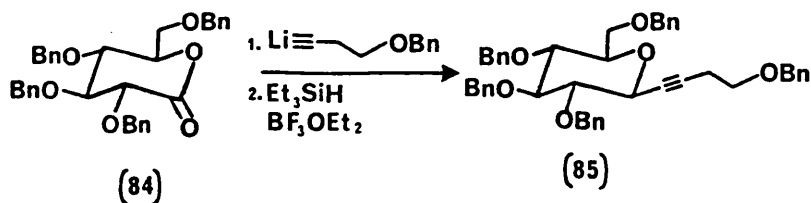


This complements the corresponding Grignard reaction which gave only ring open product.

In the preparation of chiral models of the furenone moiety, the first step in the synthetic sequence was the introduction of a methyl substituent at the anomeric position which was achieved by treating 2,3 :5,6- di-O- isopropylidene- D-mannofuranone with methyl lithium ⁵¹. The methyl adopted the β -confirmation due to the influence of the anomeric effect which dictated the hydroxyl was axial.

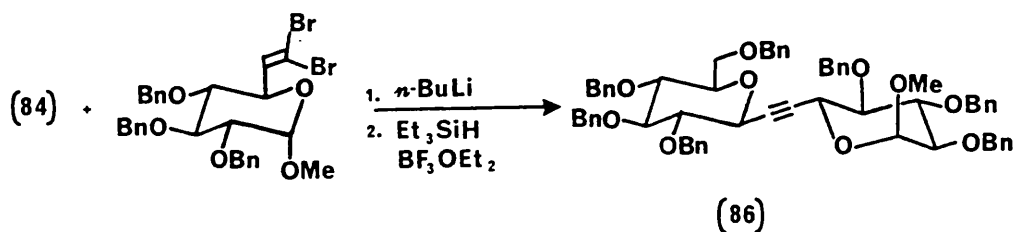
Sinaÿ et al. found a stereoselective route to β -D-C-glucopyranosides by condensing the lithio-acetylenide

with 2,3,4,6 tetra-O-benzyl-D-glucopyranone (84), followed by reduction of the hemiketal to yield (85).



The stereochemical control was achieved by the axially orientated addition of the hydride ion to the oxonium ion.

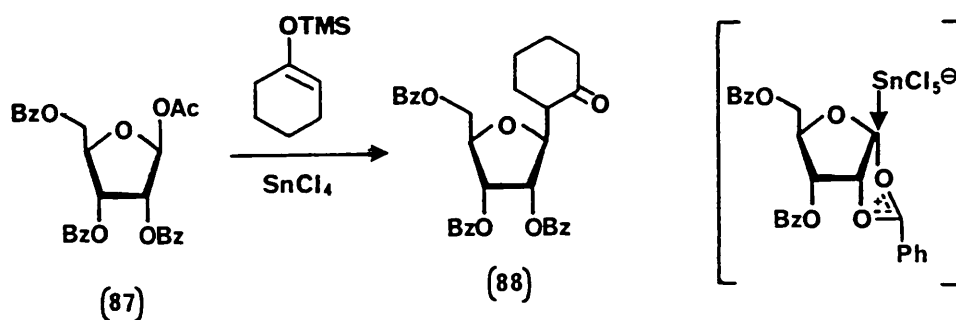
The lithio-alkynyl species can also be generated in situ from dibromoethane, and this lead to the first synthesis of a β -C-disaccharide (86)⁵³ from the glucopyranone (84) in 67% yield.



1.4 CONDENSATION REACTIONS CATALYSED BY LEWIS ACIDS

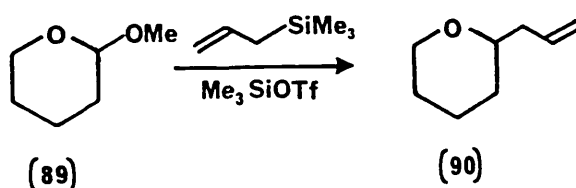
a) ENOL ETHERS, KETENE ACETALS AND ALLYL SILANES AS NUCLEOPHILES

Enol ethers and ketene acetals are sufficiently reactive species in the presence of a Lewis acid to react at the anomeric carbon of carbohydrates, thereby forming a carbon-carbon bond at the anomeric position. Early work by Hanessian *et al.*⁵⁴ showed treatment of 2,3,5 -tri-O-benzoyl- β -D-ribofuranosyl acetate (87) with the trimethylsilyl enol ether derived from cyclohexanone in the presence of a stoichiometric amount of stannic (IV) chloride gave 2-(2,3,5 -tri-O-benzoyl- β -D-ribofuranosyl) cyclohexanone (88) via the formation of the intermediate acyloxonium ion which necessitated the approach of the silyl ether from the α -face.

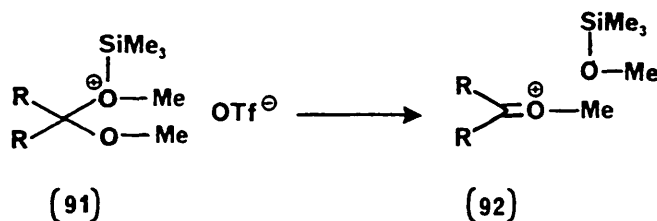


Another approach,¹ using stoichiometric quantities of stannic chloride enabled (87) to condense with terminal alkenes to give a C-D-ribofuranosyl derivative which could be further modified. More important, this suggested other "soft" nucleophiles could be used, for example allyl silanes.

Obviously, the reaction would be more attractive if a Lewis acid could be used in catalytic rather than stoichiometric amounts. Noyori *et al.*⁵⁵ had investigated reactants with various Lewis acids (titanium tetrachloride, boron trifluoride etherate, aluminium trichloride) which required stoichiometric amounts to be efficient. However, they found in the presence of a catalytic amount (10mol%) of trimethylsilyl trifluoromethane sulphonate, allyl trimethylsilane reacted with the acetal (89) to yield homoallyl ethers (90).



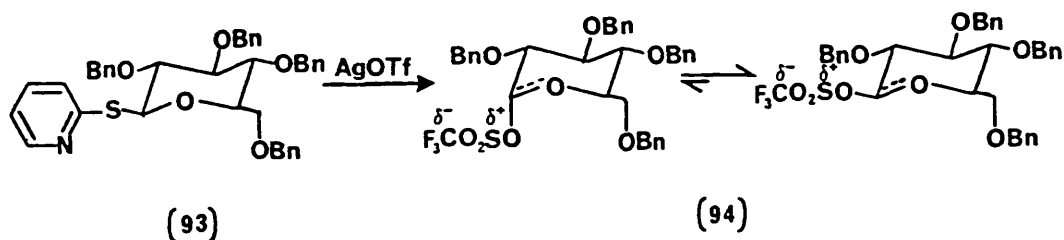
The trimethylsilyl moiety has an affinity for the oxygen atom, forming the intermediate oxonium ion (92) via the carboxonium ion/methyl trimethylsilyl ether contact pair (91) which reacted with the allyl silane. The catalytic cycle was attained under mild conditions at low temperatures.

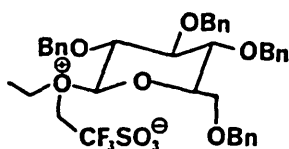


The anomeric centres of substituted β -D-ribofuranosyl acetates could be expected to react under similar conditions with allyl trimethyl silane in the presence of trimethylsilyl triflate ⁵⁶. Surprisingly, the reaction required an excess of the Lewis acid, but the β -anomer was the major isomer formed ($\beta/\alpha = 10:1$) suggesting the intermediate acyloxonium ion was formed.

C-allylation of glycopyranosides by Sakurai et al. ⁵⁷ showed trimethylsilyl triflate and iodotrimethylsilane in catalytic quantities were sufficient to promote the reaction of allylsilanes with 1-methoxy-2,3,4,6-tetra-O-benzyl- α -D-glucopyranose and the reaction was stereoselective with preference for the α -isomer.

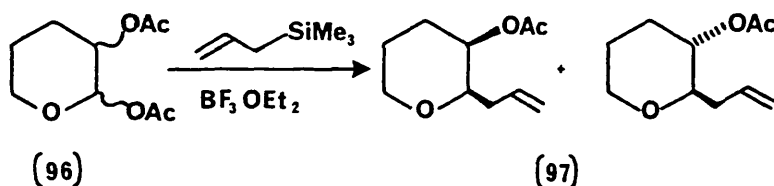
Further work by Stewart and Williams ⁵⁸ investigating the C-glycosidation of pyridyl thioglycosides (93), suggested the stereoselectivity in these reactions was determined by the solvent participation. In a non-polar, non-participating solvent, a solvent separated triflate ion pair (94) was formed where the β -triflate was the predominant species (Reverse anomeric effect) leading to an α -isomer as the major product, on coupling. In more polar solvents, for example ether, α -selectivity was observed exclusively, involving the solvent-stabilised β -oxonium ion (95).



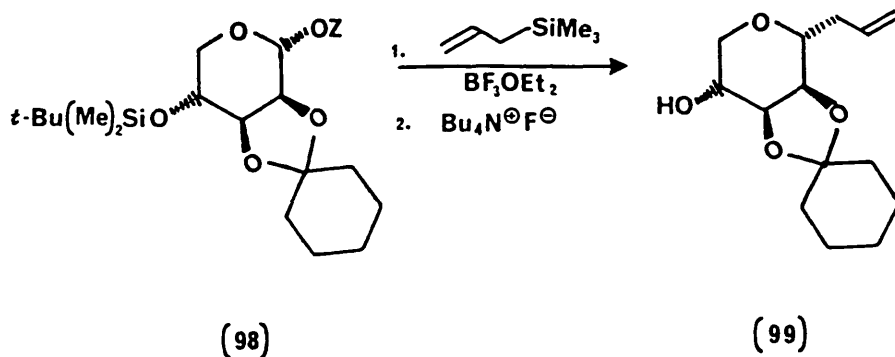


(95)

Boron trifluoride etherate has been widely used as a Lewis acid in this type of work, although stoichiometric quantities were required. Kozikowski *et al.*⁵⁹ initial studies on methods for pyranoannulation treated diacetates (96) with allyl trimethyl silane in the presence of borontrifluoride etherate to give a 2.4:1 cis:trans mixture of products (97).

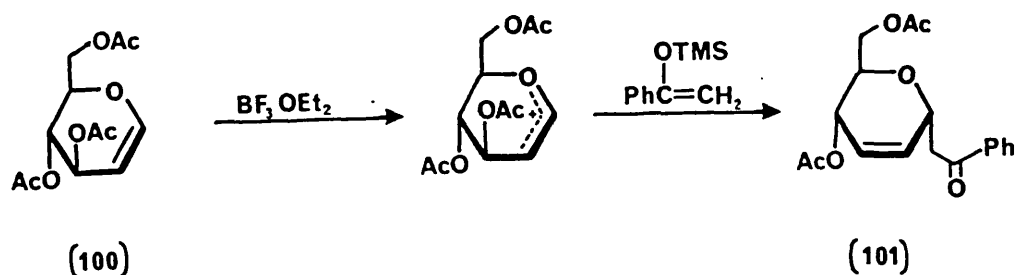


In the preparation of other natural compounds,⁶⁰ the nature of the leaving group improved the stereoselectivity, as did the choice of solvent. Starting with the protected lyxose (98) where Z= para-nitrobenzaldehyde, only the α -isomer (99) was observed, suggesting total formation of the oxonium ion which reacted under stereoelectronic and steric control in an axial addition. With L-lyxose tetrabenzoate derivative, more β -isomer was observed, but here there was neighbouring group participation influencing the stereoelectronic outcome as was shown previously.



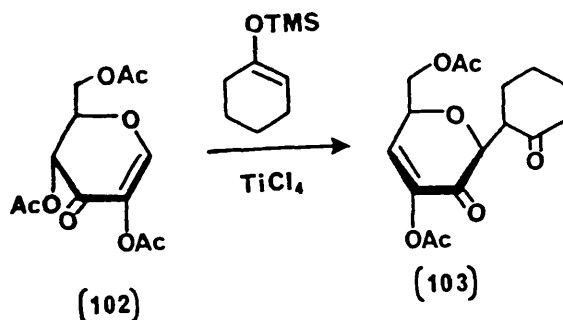
With the protected lyxose (98) where $OZ = \text{acetate}$ and allyl trimethyl silane in nitromethane, the stereoselectivity was $\alpha/\beta = 19:1$, whereas in acetonitrile it improved to be $\alpha/\beta = 80:1$. Solvent participation was possibly a controlling factor in the reaction. Sandhoff and Giannis⁶¹ also reported improved stereoselectivity of α -anomer formation in the preparation of C-allyl-glycopyranosides in acetonitrile. Kishi *et al.*⁶² found the reaction of 1-para-nitrobenzoyl-2,3,4,6-tetra-O-benzyl- α -D-glucopyranose under the same conditions gave a 10:1 mixture of isomers, the α -anomer being the predominant isomer.

Fraser-Reid and Dawe⁶³ found the reaction of acetylated glycals (100) with silyl enol ethers in the presence of boron trifluoride etherate, resulted in the α -anomer (101) as the major product. The axial attack resulted in anti S_N2' displacement of the acetate at C-3.



Acetylated glycals (100) also reacted with β -dicarbonyls in the presence of boron trifluoride etherate to give the α -anomer as the predominant product ⁶⁴. Here, only a catalytic quantity (50mol%) of the Lewis acid was required.

Titanium tetrachloride has also been used to catalyse the addition of allyl trimethyl silane to glycal acetates (100) giving the α -anomer as the major isomer ⁶⁵. However, the addition of silyl enol ether to 2,4,6-tri-O-acetyl-1-deoxy-D-erythro-hex-1-eno-pyran-3-uloses (102) catalysed by titanium tetrachloride, followed by elimination of the 4-acetoxy substituent gave the β -anomer (103) as the major product ⁶⁶. The reverse stereocontrol was due to the formation of a Ti-complex with the carbonyl and enol ether oxygen atoms, directing the nucleophile from the α -face and subsequent dipole-dipole interactions offered by the chair conformation.



Kozikowski and Sorgi⁶⁷ reacted glycosyl acetates with allyl trimethyl silane in the presence of zinc bromide at 110°C. The choice of protecting groups would enable anchimeric assistance, but this was not observed.

L-lyxose tetrabenzoate derivative reacted with no stereoselectivity and the protected lyxose (98) where OZ=acetate gave considerably inferior results compared with the boron trifluoride etherate/acetonitrile method discussed previously.

2,3,4,6-tetra-O-benzyl-D-glucopyranosyl fluoride reacted with nucleophilic reagents in the presence of a catalytic amount (20mol%) of Lewis acid to give C-glycosides⁶⁸. Activated nucleophiles, for example trimethylaluminium, required no catalyst. Although the yields were good, the stereoselectivity was not as good as found in other examples (α/β =20:1).

Watanabe et al.⁶⁹ found the optimum time (5min) and quantity of catalyst (5mol%) for the reaction of 2,3,5-tri-O-benzyl-ribofuranosyl fluoride with silyl enol ethers catalysed by boron trifluoride etherate gave the α -anomer as the major isomer (α/β =50:1).

b) FRIEDEL-CRAFTS REACTION

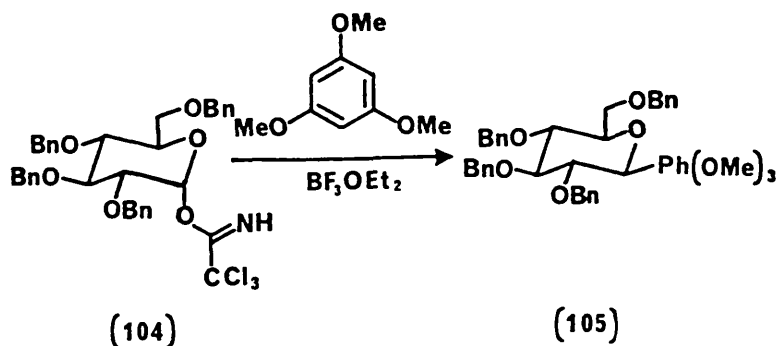
The Friedel-Crafts reaction of a carbon nucleophile in the presence of aluminium chloride has successfully been employed in carbon-carbon bond formation at the anomeric centre. Hurd and Bonner⁷⁰ prepared 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl benzene by treatment of the α -chloride with benzene in the presence of aluminium chloride.

Sorm et al.⁷¹ reported the first synthesis of Shondomycin, which was prepared by reacting 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl bromide with 1,3,5-trimethoxybenzene in the presence of zinc oxide which was further modified to the α -keto acid ester, the key intermediate in the synthesis.

Under similar conditions,⁷² C-glycosyl flavonoids were prepared by treating 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide with 1,3,5-trimethoxybenzene to yield the β -anomer as the major isomer. The unimolecular process was via the stabilised oxonium ion, the halide ion shielding the face from which it departed.

Schmidt and Hoffmann⁷³ used the modified O- α -D-glucopyranosyl imidate (104) which was a more reactive species, with 1,3,5-trimethoxybenzene in the presence of boron trifluoride etherate at room temperature and isolated exclusively the β -anomer (105). By activating the anomeric carbon, the reaction was greatly enhanced giving better yields and stereoselectivity. The analogous

series with the ribofuranosyl imidate gave equally good results.

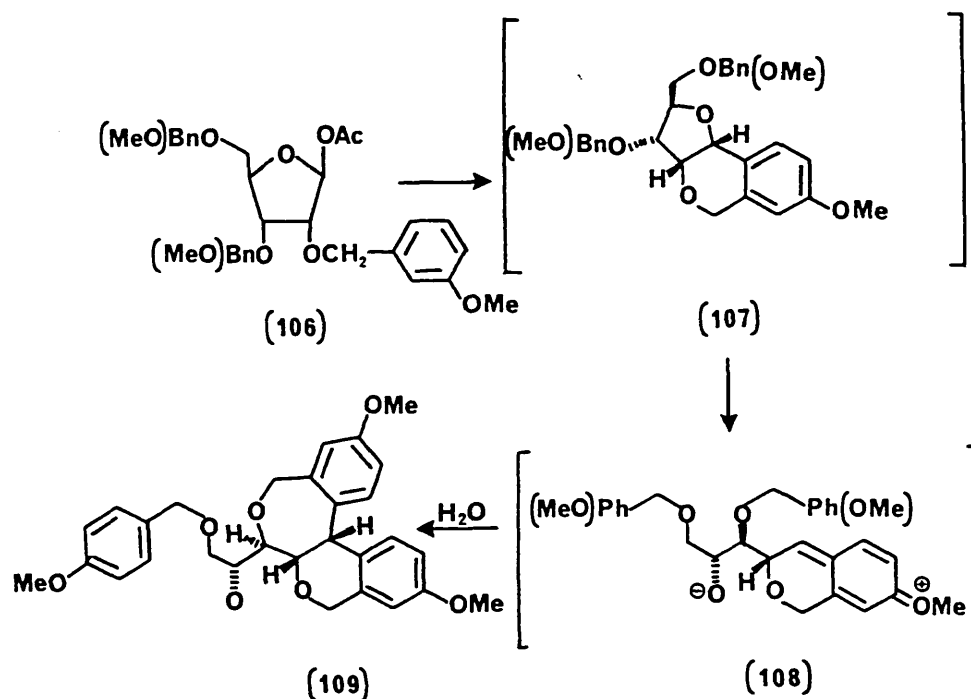


2,3,4,6-Tetra-O-benzyl-1- β -(2'-mercaptopyridinyl) glucopyranose reacted with a variety of electron-rich aromatics in the presence of silver triflate⁵⁸. The coupling suggested an intermediate oxonium ion or common ion pairs were the reactive electrophilic species. With 1,3,5-trimethoxybenzene, the oxonium ion was intercepted from the least hindered face before equilibrium of the triflates was established, to give the β -anomer, but with 1,3-dimethoxybenzene, the β -triflate ion pair was formed, hence the α -anomer was isolated.

An interesting intramolecular Friedel-Crafts reaction with perbenzylated glycofuranosyl acetates in the presence of tin (IV) chloride with no external nucleophile, created a carbon-carbon bond between the anomeric centre and the phenyl ring ⁷⁴. This demonstrated the high reactivity of the 2-O-benzylsubstituent of perbenzylated carbohydrate derivatives under Lewis acid conditions. The by-product of the reaction of

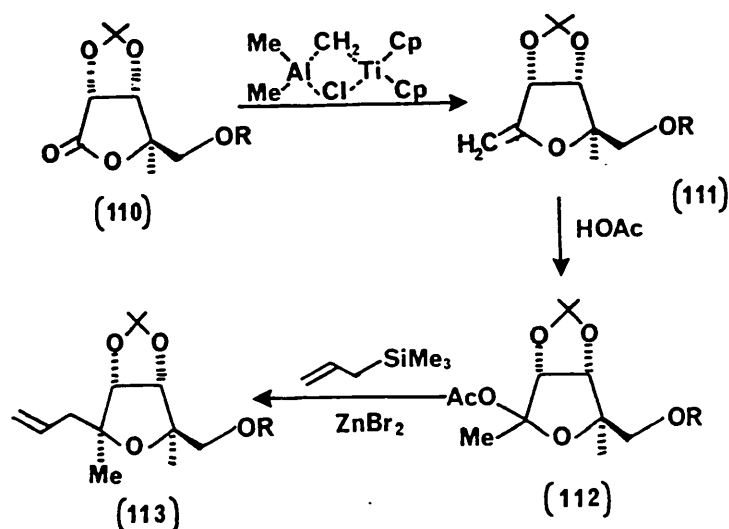
tri-O-benzyl-D-ribofuranosyl bromide with mercuric cyanide also had this structure, although it had previously been incorrectly assigned.

The reaction of D-ribofuranose derivatives with 'activated' benzyl groups, for example methylbenzyl or methoxybenzyl were also investigated ⁷⁵. Treatment of 2,3,5-tri-O-meta-methoxybenzyl- β -D-ribofuranosyl acetate (106) with tin (IV) chloride gave the intermediate (107), but because of its high reactivity, the Lewis acid promoted cleavage of the C-1-O-4 bond to an oxocarbenium ion type intermediate (108). Intramolecular alkylation by the nearest meta-methoxybenzyl substituent lead to the polyheterocyclic compound (109). The second intramolecular C-arylation occurred stereospecifically with retention of configuration at C-2. These reactions constituted a double C-glycosidation.



1.5 ORGANO-TRANSITION METAL APPROACH

Dialkylation reactions making two carbon-carbon bonds at the anomeric centre are required in the synthesis of some natural products, for example citreoviridin. Wilcox *et al.*⁷⁶ strategy converted the aldolactone (110) to the exocyclic enol ether (111) using the titanium carbene complex (Tebbe reagent). The second alkylation relied on the generation of the electrophile, which was best achieved by a two-step process via the acetate (112) and subsequent treatment with allyl trimethyl silane in the presence of zinc bromide to afford the bis- alkylated product (113). (R'=^t-BDMS)

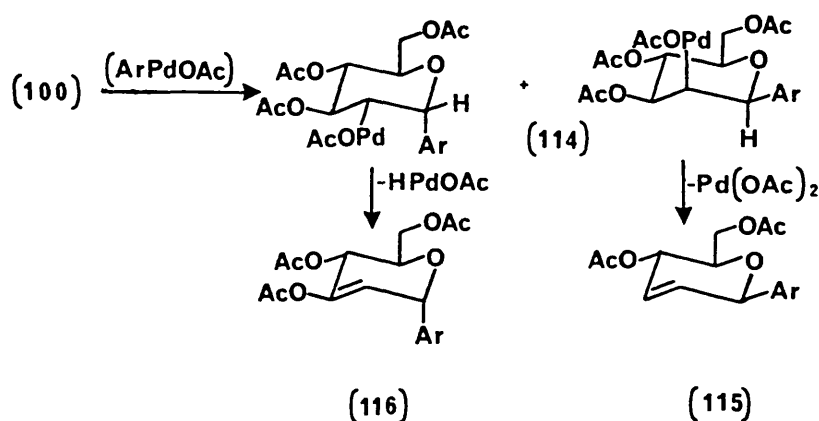


Interestingly, the anomERICALLY methylated substrate (112) yielded only one isomer under these conditions whereas Kozikowski⁶⁷ reported a mixture of isomers when 1-O-acetyl-2,3-O-isopropylidene-5-O-^t-butyldi-phenyl silyl-D-ribose was subjected to the same reaction. One must therefore conclude the reaction's

stereo outcome is determined by the relative steric bulk of the isopropylidene and C-5 protecting group.

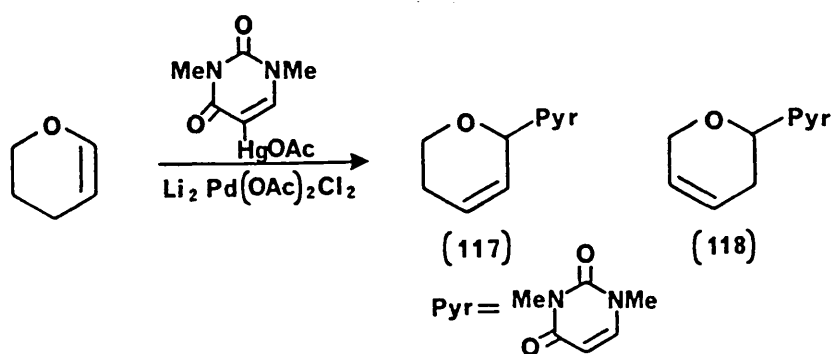
Organometallic catalysts were also applied to reactions previously initiated by Lewis acids. Acetylated glycals (100) reacted with β -dicarbonyls in the presence of bis (benzonitrile) dichloro-palladium (0.26mol%) to yield the C-glucopyranoside with reasonable stereoselectivity at the anomeric centre⁶⁴.

The arylation of acetylated glycal (100) requiring a stoichiometric quantity of the palladium salt achieved the desired carbon-carbon bond formation⁷⁷. The mechanism involved syn-addition of the aryl-palladium to the glycal double bond (114) followed by syn-elimination to give the β -anomer (115). However, the by product (116) resulted from the elimination of HPdOAc, but this was diminished to negligible amounts by short reaction times (1-2h) and high temperatures (120°C).



The regiospecific addition of carbanions to dihydrofuran and acetoxydihhydropyran has been assisted by palladium (II) species ⁷⁸. The formation of the palladium (II) π -complex, followed by treatment with the anion gave only substitution at the 2 and not the 3 carbon. The mechanism of the β -elimination of "PdH" and a series of re-addition-elimination reactions terminated when the double bond was endocyclic and in conjugation with the ring oxygen.

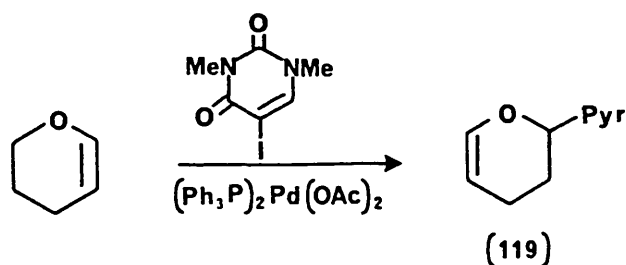
Another example where this re-addition-elimination moved the double bond was observed in the palladium catalysed synthesis of 1,3-dimethyl-5-(dihydropyran-2'-yl)-2,4-pyrimidine diones (117) (118) ⁷⁹. 3,4-Dihydro-2H-pyran, when treated with the mercuric species in the presence of the organopalladium species, regio-specifically formed a carbon-carbon bond between the C-5 of the pyrimidine and C-2 of the enol ether but subsequent isomerisation led to the two products.



When 3,4,6-tri-O-acetyl-D-glucal was subjected to the same conditions, the reaction process was more complex

yielding only 20% of the desired product (that is carbon-carbon bond formation at C-2) but 73% ring cleaved product resulting from anti-elimination followed by alkoxide expulsion, ring cleavage and alkene formation.

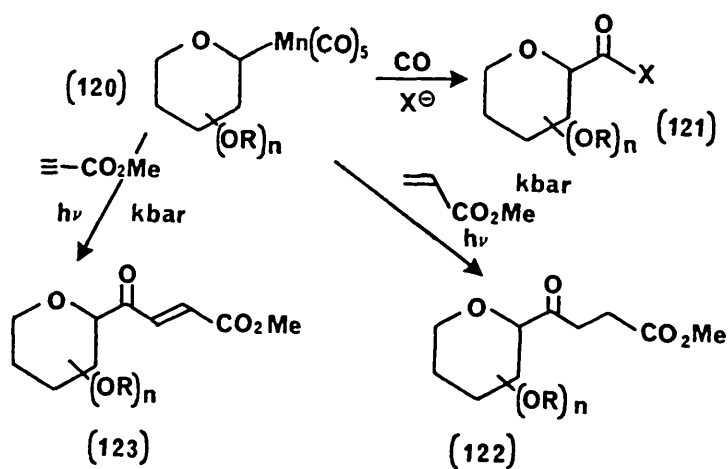
Treatment of 3,4-dihydro-2H-pyran with the iodide species in the presence of organopalladium species at 100°C led to the most thermodynamically stable enol ether (119) ⁸⁰. Interestingly, the fourth isomer where the double bond was in conjugation with the pyrimidine ring was never observed.



Similarly, the reaction with the aryl-iodide under the same conditions gave only the one product where the double bond had migrated to be in conjugation with the oxygen ⁸¹.

Recently an organo-transition-metal-based approach involving the stereoselective preparation of glycosyl manganese pentacarbonyl complexes (120) has been reported ⁸². Subsequent carbonylation of this species gave the C-glycoside with retention of configuration at the anomeric centre (121). The glycosyl manganese

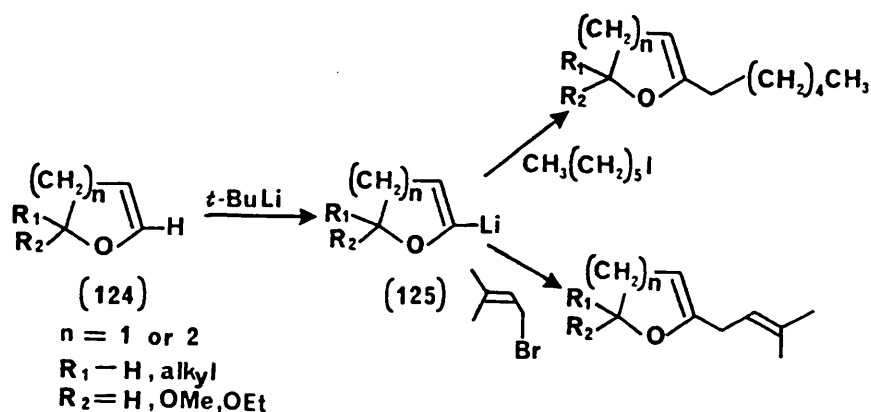
complex also readily underwent insertion reactions with methyl acrylate and methyl propiolate followed by photodemetalation of the manganacyl to produce the C-glycoside (122) and (123) respectively. Both pyranosyl and furanosyl systems gave good yields, with the β -anomer predominating, but the extremely high pressure limited the process and application.



1.6 GENERATION OF ANIONS AT THE ANOMERIC CENTRE

Most of the syntheses of C-glycosides developed rely on the electrophilic character at the anomeric centre of the carbohydrate or cyclic- α -substituted ether. However, with suitable α -substituents it is possible to reverse the character at the anomeric centre, generating a carbohydrate or cyclic vinyl ether carbanion which can react with a variety of electrophiles.

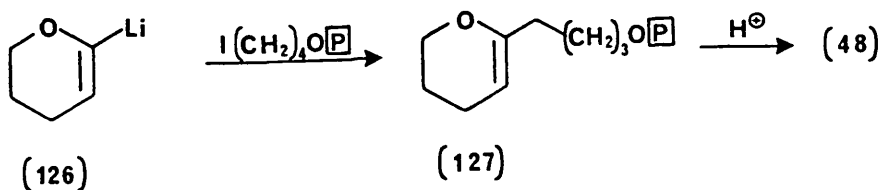
Schlosser *et al.*⁸³ showed 3-chloro, 4,5 dihydrofuran could be substituted at the 2-position by metalation with *n*-butyllithium, followed by condensation with an electrophile to form a new carbon-carbon bond at the anomeric position. Boeckman and Bruza⁸⁴ extended the application of this reaction to dihydropyran and dihydrofuran cyclic ethers (124). *t*-Butyllithium was required to lithiate at the C-2, the hydrogen was notably less acidic than in the former example (vinyl chloride), hence a stronger base was needed. The lithiated species (125) was quenched with a variety of electrophiles.



Further work showed the carbanion reacted as a typical hard, unstabilised organometallic anion would be expected to, reacting cleanly with alkyl halides, aldehydes and ketones, but not with reactive acylating agents, for example acid chlorides or anhydrides.

Nicolaou *et al.*⁸⁵ have applied this methodology in the stereospecific synthesis of 1,1-dialkylglycosides. The tris (silyl) glycal was alkylated using the Boeckman procedure, followed by reintroduction of the acetate groups. The dialkylated species was achieved using the trimethyl-aluminium/titanium tetrachloride method⁷⁶. This route was particularly novel in that the bis-alkylated product was obtained by sequential electrophilic and nucleophilic reactions.

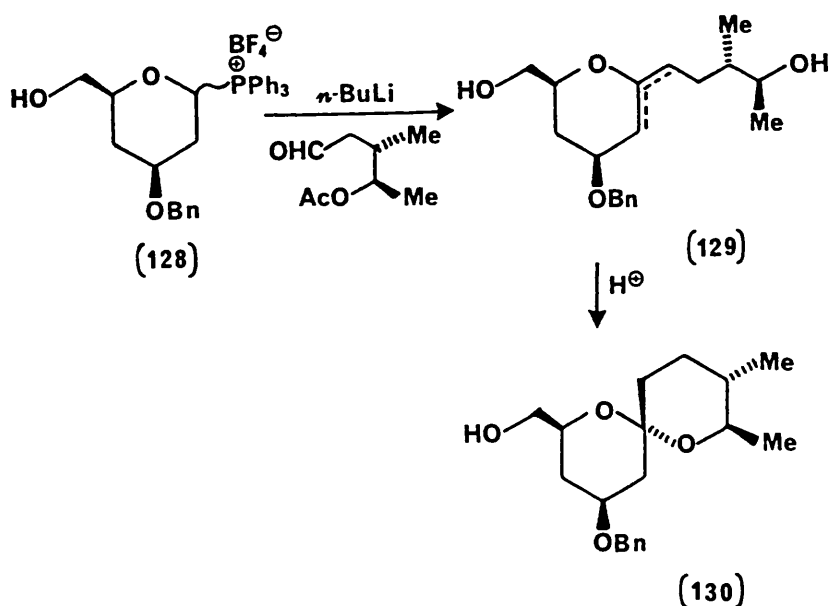
Amouroux⁸⁶ extended the application of this method to the synthesis of spiroketals. By condensing an electrophile containing a suitably protected alcohol with the anion (126) generated from 3,4-dihydro-2H-pyran, the intermediate enol ether (127) was cyclised in acid to give the spiroketal (48).



Our own work⁸⁷ showed the Wittig and Horner-Wittig coupling of 2-triphenylphosphonium tetrafluoroborate or 2-diphenylphosphinoxy cyclic ethers with aldehydes or lactols gave

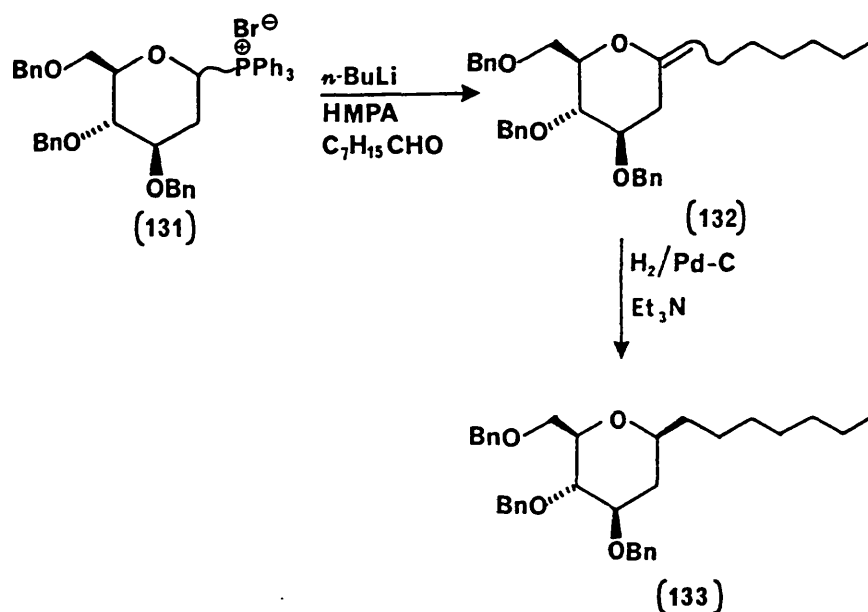
enol ethers, some of which could subsequently be cyclised to spiroketals after acid treatment. A route to enantiomerically pure 1,7-dioxaspiro [5,5] undecanes, an important building block for the milbemycin and avermectin synthesis can be constructed by this method ⁸⁸.

The Wittig reaction of the substituted cyclic ether (128) with the appropriate aldehyde, followed by acid cyclisation of the intermediate enol ether (129) gave the spiroketal (130), the stereochemistry at the spiro centre controlled by the anomeric effect.

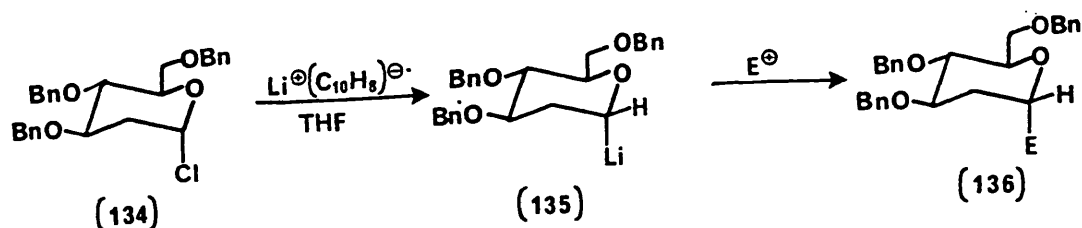


Falck et al. ⁸⁹ prepared 2-triphenylphosphonium bromide cyclic ethers which were used in Wittig coupling reactions with various aldehydes. The synthesis of a C-glycoside was achieved by Wittig coupling of the phosphonium bromide (131) with octanal to yield the enol ether (132). Catalytic reduction of (132) in the presence of base gave the β -C-octyl-D-glycopyranoside exclusively (133), whereas

reduction in the absence of base gave a mixture of α - and β -anomers, presumably due to the exo-endo isomerisation of the enol ether.

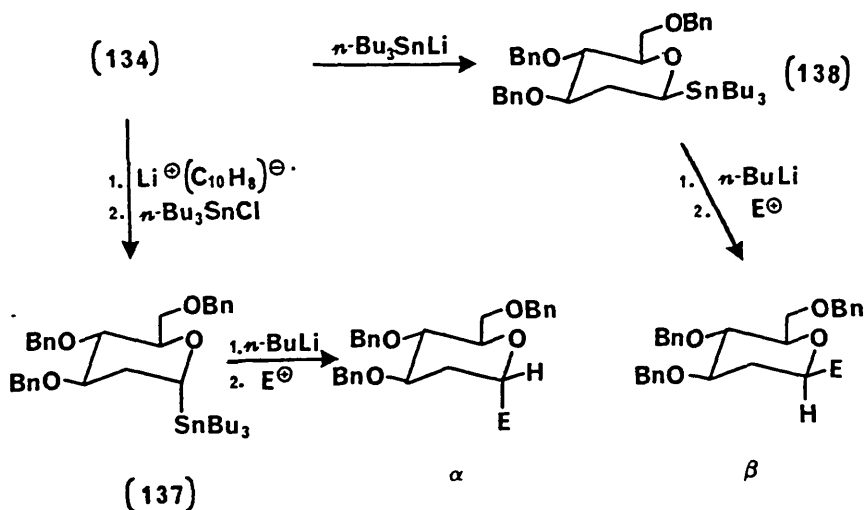


Sinaÿ et al.⁹⁰ generated the reactive 3,4,6-tri-O-benzyl-2-deoxy- α -D-arabinohexopyranosyl lithium species (135) by the reductive lithiation of the corresponding chloride (134). Treatment of (135) with a variety of electrophiles suggested the coupling occurred at -78°C and the electrophiles was introduced in the axial position (136).

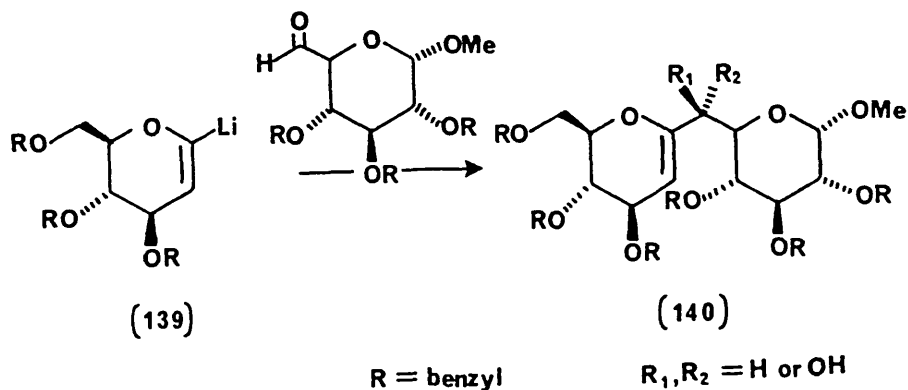


Further work⁹¹ showed it was possible to stereospecifically generate the α and β -glycosyl lithium derivatives from tri-n-butyl stannyl glucopyranosides (137) (138), which

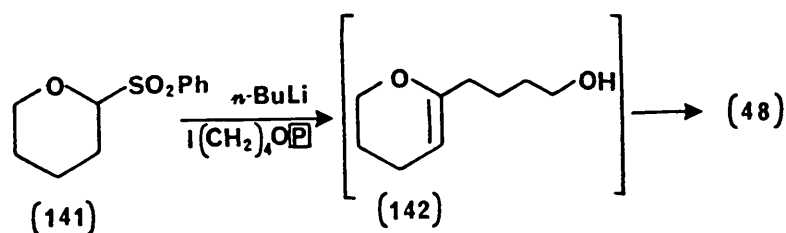
accepted the electrophile with retention of configuration at the anomeric centre. The kinetically generated axial glycosyl-lithium species from (137) was configurationally stable under these conditions and did not invert to the more stable equatorial anomer, therefore α - and β -anomers were formed exclusively from the respective lithium reagents.



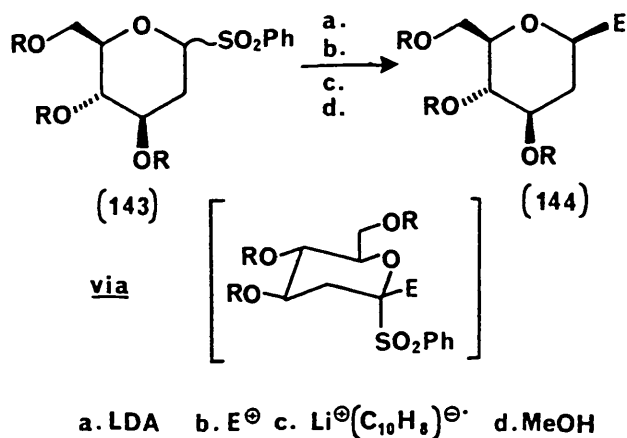
Hanessian et al.⁹² have shown the alkylation of 3,4,6-tri-O-benzyl-1-lithio-D-glucal (139) generated from the corresponding 1-tributylstannyl derivative gave a concise route to C-glycosides. Of particular interest, was the extension of the reaction to electrophiles derived from carbohydrates; providing a simple concise route to C-saccharides (140).



The generation of an anion from 2-benzenesulphonyl tetrahydropyran (141) has provided an alternative and more flexible approach than the Wittig and Horner-Wittig methodology⁹³. Deprotonation with *n*-butyllithium and reaction with a variety of electrophiles (benzyl and alkyl halides, aldehydes, ketones and certain epoxides) gave a concise route to enol ethers (142) since the benzenesulphinic acid was eliminated during the reaction process. In fact, with acid sensitive protecting groups, spiroketals were produced by a one-pot synthesis.



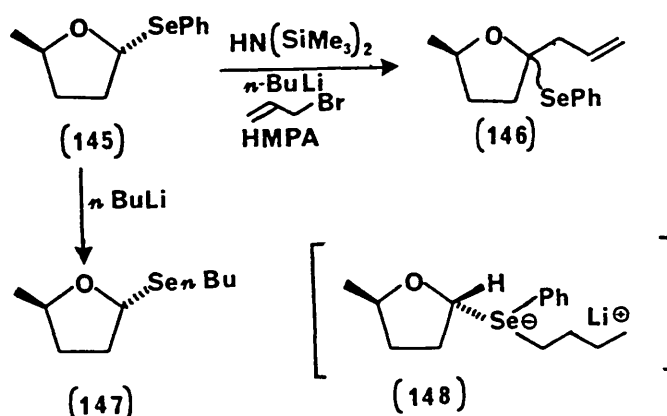
The preparation of D-glucopyranosyl phenylsulphones (143) proved equally facile and generation of the anion, followed by electrophile quenching and reductive lithiation provided a novel stereoselective synthesis of β -C-glycosides (144)⁹⁴.



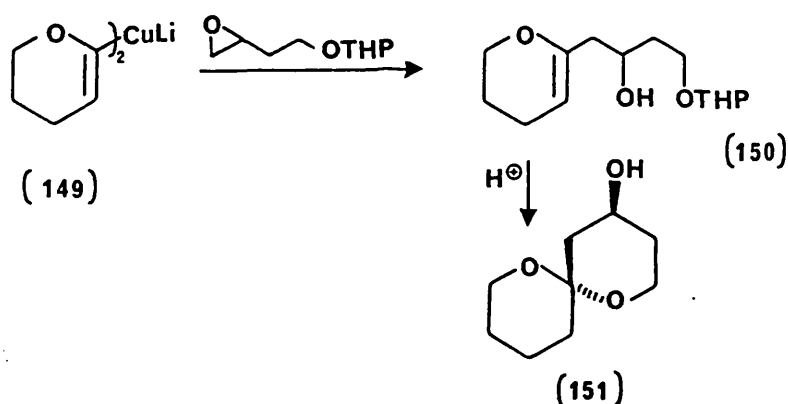
Interestingly, the same reaction, when the anion was quenched with activated carboxylic acid derivatives (for example dimethyl carbonate) yielded the α -anomer. The formation of the α -anomer was postulated by a mechanism involving the generation of the lithium enolate at C-2 after elimination of the benzylsulphone which was in equilibrium with the corresponding ketone, allowing the lithiated species to epimerise to the β -anomer, hence on protonation the α -anomer was observed.

Similar unusual results were observed when the anion of (141) was quenched with methyl chloroformate promoting no elimination of the benzenesulphonic acid as usually observed, and the new carbon-carbon bond formed was axial.

Liotta *et al.*⁹⁵ found the deprotonation of α -phenylselenenyl ethers (145) and quenching was not oversuccessful and required activated conditions (146). Alkyl lithium failed completely, only alkyl exchange (147) via an "ate" complex (148) was observed.

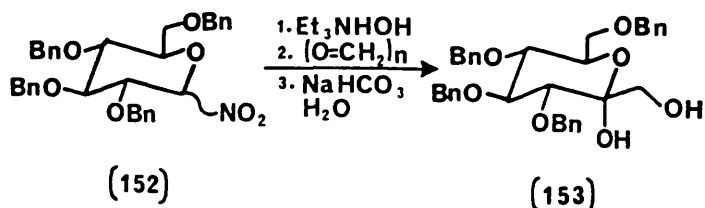


In Kocienski's⁹⁶ synthesis of 1,7-dioxaspiro [5,5] undecanes the lithiated dihydropyran species was converted to the organo-cuprate (150) which was sufficiently nucleophilic to attack the oxirane ring of tetrahydropyranyl ether of 3,4-epoxybutan-1-ol to form a new carbon-carbon bond (151). The enol ether was cyclised by acid treatment to the spiroketal (152). A similar sequence with the requisite epoxide was used in the synthesis of Talaromycin B⁹⁷.

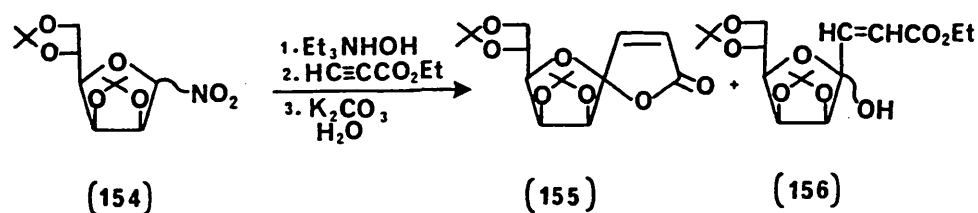


The use of 1-deoxy-1-nitro sugars, where the nitro group can act as an anion stabilizing substituent, for the generation of a reactive anomeric anion under mild conditions, has been applied in several syntheses. The addition to aldehydes and Michael acceptors and solvolytic replacement of the nitro group by a hydroxy group gave ketoses in good yields⁹⁸.

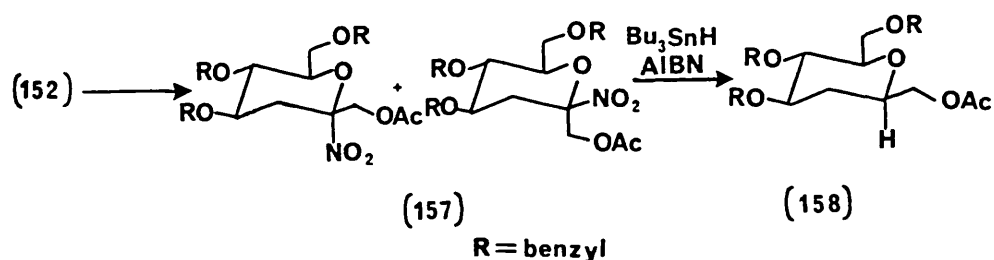
When 2,3,4,6-tetra-O-benzyl-1-deoxy-1-nitroglucopyranose (152) was treated with triethylammounium hydroxide followed by formaldehyde, then solvolysis, the chain elongated ulose derivative (153) was formed.



Similarly, Michael addition of 2,3; 5,6-di-O-isopropylidene-1-deoxy-1-nitroribofuranose (154) to ethyl propiolate under solvolytic conditions gave the unsaturated spirolactone (155) and the hemiacetal (156).



Further work⁹⁹ showed stereoselective reductive denitration of tertiary esters (157) with tri-n-butyl stannyl chloride gave the β -anomer exclusively (158). As a control, 4 t-butyl-1-nitrocyclohexane was subjected to the same reductive denitration, yielding a mixture of acetates, thereby confirming the oxygen influenced the stereoelectronic outcome of the reaction.

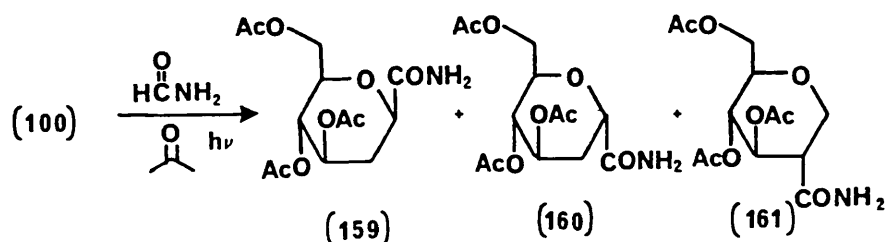


The preparation of ulose-1-phosphonic esters followed the same route from (154) and α, β -ethylenephosphonic acid esters via a Michael addition¹⁰⁰.

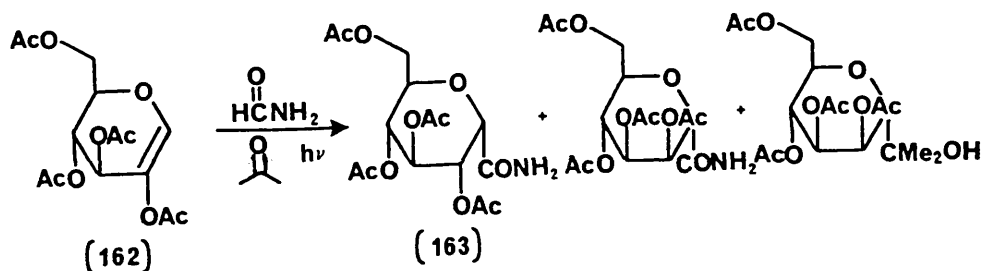
1.7 PHOTOCHEMICAL AND RADICAL REACTIONS

The disadvantage of photochemical or radical initiated methods for the formation of carbon-carbon bonds is there is often no stereoselectivity in the addition. However, if the anomers are easily separable, this need not present an unsurmountable problem!

The acetone sensitized photochemical addition of formamide, that is photoamidation, to unsaturated carbohydrates (100) gave a mixture of products (159), (160), (161) in good yield (75%)¹⁰¹.

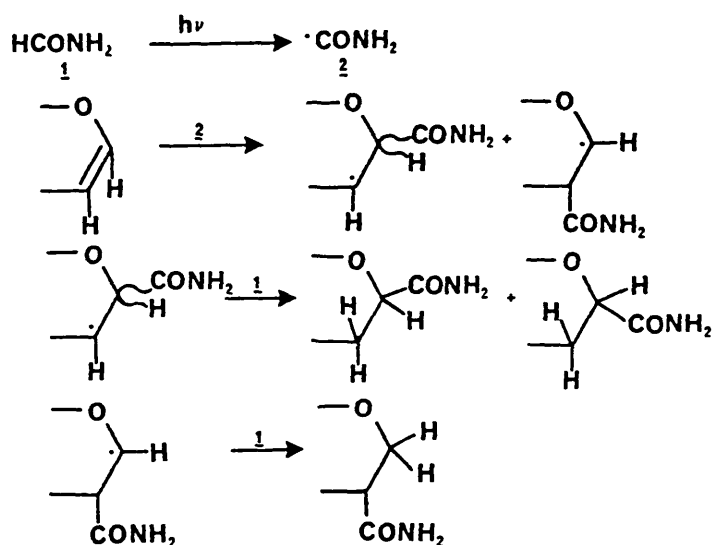


The addition during hydrocarbamylation has been shown to be anti-Markovnikov¹⁰² (the tertiary radical is more stable), by subjecting (162) to a similar set of conditions, (163) being the major product (55%).

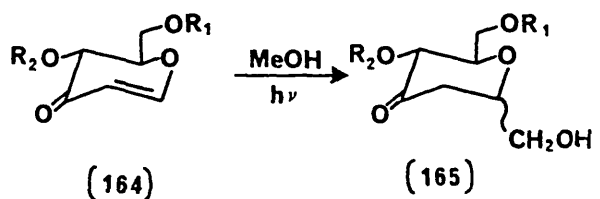


The free radical mechanism for the photoamidation of unsaturated carbohydrates was proposed (Scheme 2).

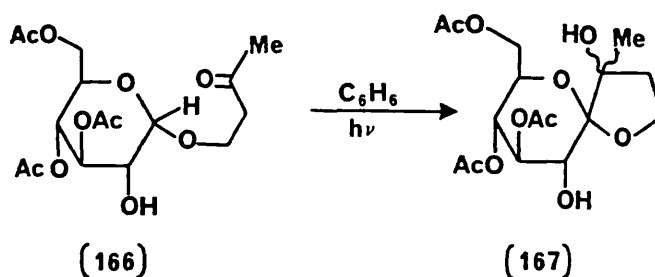
Scheme2



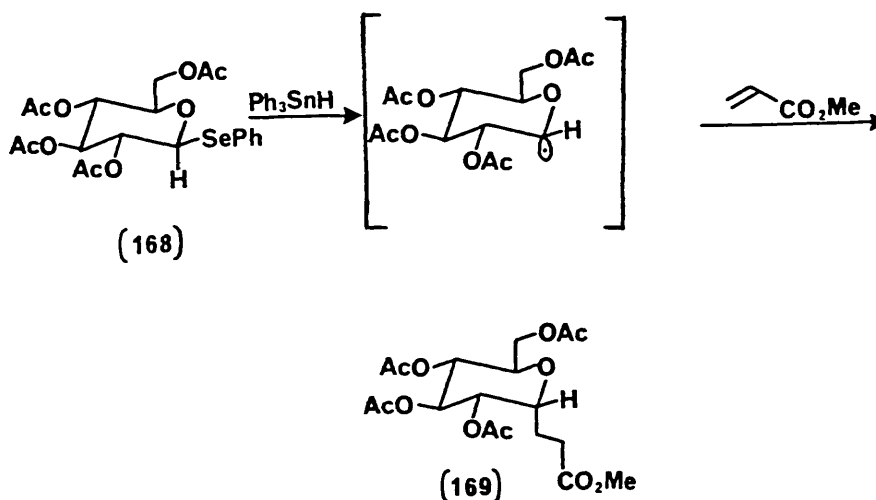
The photochemically induced addition of methanol could be stereospecifically controlled to a certain degree by the choice of protecting groups which were conformationally mobile (164) ¹⁰³. When $\text{R}_1 = \text{Ph}_3\text{C}$ or PhCO and $\text{R}_2 = \text{Ac}$, the axial anomer was favoured (7:3) as the upper face was more shielded (165).



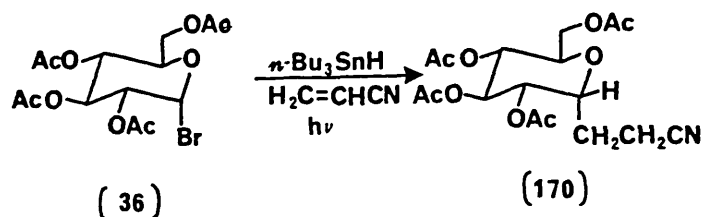
A novel route to spiroketals (167) was achieved by the photocyclisation of 3-oxobutylglycopyranoside (166) in benzene ¹⁰⁴. This proceeded by a Norrish type II mechanism. The α -anomer would not cyclise whereas the β -anomer readily did, suggesting the radical was formed by abstraction of the axial anomeric hydrogen atom, hence retention of configuration in the final product.



Generation of a glucosyl radical by addition of triphenyl tin hydride to the selenophenyl glucopyranoside (168) gave exclusive axial radical formation, which subsequently gave the α -anomer as the sole product (169) ¹⁰⁵.

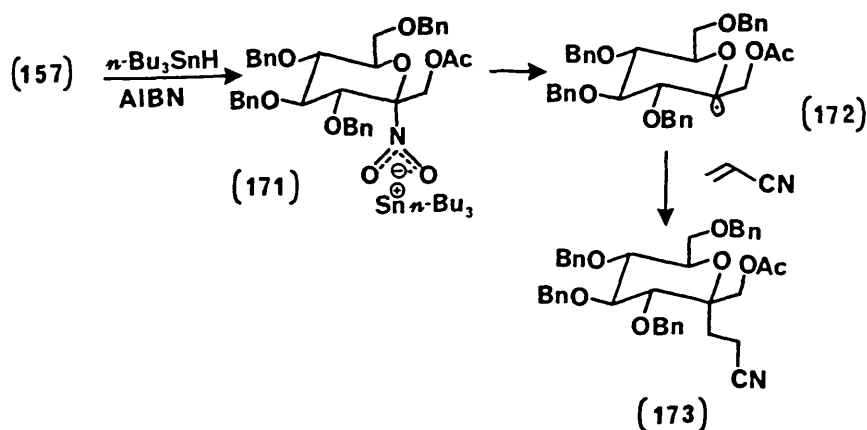


The reaction of the anomeric bromide (36) with acrylonitrile, initiated by tri-*n*-butyl tin hydride and light gave the α -anomer (170) exclusively ¹⁰⁶.

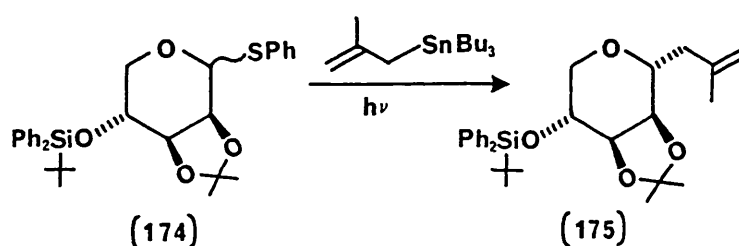


This confirmed the α -radical must be formed, indicating either the anomeric effect exists in radical carbon-carbon formation or the α -radical formed is trapped by acrylonitrile before it has chance to invert.

Nitro compounds (157) were also used as precursors for radical carbon-carbon bond formation ¹⁰⁷. After formation, the radical ion pair (171) was assumed to decompose rapidly to give the radical species (172) which was trapped by acrylonitrile (173). The addition was stereoselective, although the authors were not conclusive about whether the α - or β -anomer had formed. However, given the same criteria as the above examples, it would suggest the α -anomer was formed.



Thiophenyl glycosides (174) were also converted to C-glycosides by reaction with allyl or methylallyl tri-n-butyl stannane. The thiophenyl moiety was an excellent substrate for radical allylation, initiated photochemically it gave predominantly the α -anomer (175) ¹⁰⁸.

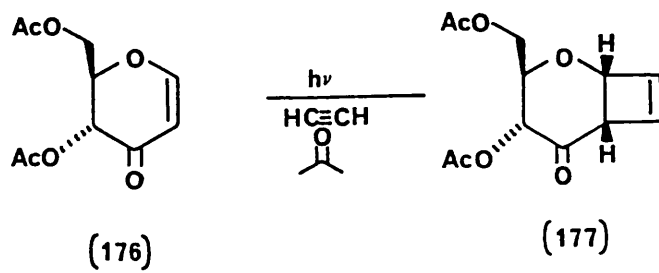


The initiation yielded the carbon-centred radical, followed by the addition of allylstannane and β -scission of the trialkyl stannyl radical.

The reaction of 2,3:5,6-di-O-acetyl- α -D-ribose chloride with allyl tri-n-butylstannane also gave good yields of α -alkylated product, without cleavage of the acetal groups cf Grignard reaction¹⁰⁹.

However, if tri-n-butylstannyl triflate was used as a catalyst, the mechanism involved a two electron process and the favoured product was the β -anomer.

In an approach towards the synthesis of optically active trichothecenes,¹¹⁰ the unsaturated ketone (176) underwent photochemical cycloaddition with acetylene to give the cis fused product (177).



1.8 MISCELLANEOUS

Finally, the synthesis of the major sex pheromone of the Olive fly was achieved by the base catalysed dimerisation of lactones¹¹¹. δ -Valerolactone dimerised to give the intermediate enol ether which rearranged under acid conditions to give the spiroketal (48). However, this was not a generally applicable method.

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NEW METHODS FOR SPIROKETAL SYNTHESIS.

The formation of carbon-carbon bonds at the 2-position of cyclic ethers is of particular interest in natural product synthesis.

The first section of this thesis involves the use of Wittig and Horner-Wittig methodology for the preparation of enol ethers and how this can be extended for the preparation of spiroketals.

The second section investigates a range of sulphone coupling reactions in the preparation of enol ethers and the synthesis of spiroketals. This section includes model studies towards the spiroketal moiety of milbemycin β_1 .

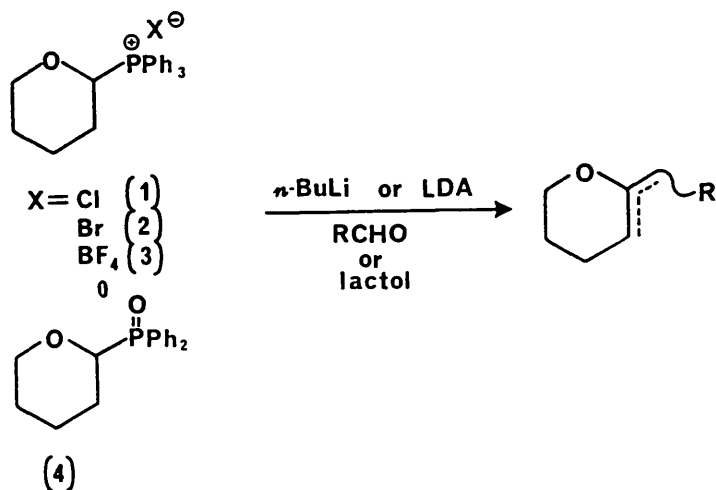
The final section extends the methodology developed towards the synthesis of the spiroketal containing natural product CP,61-405.

WITTIG AND HORNER-WITTIG COUPLING REACTIONS.

2.1 Introduction.

Possible Wittig and Horner-Wittig coupling reactions of tetrahydropyran 2-triphenylphosphonium salts (1-3) or 2-diphenylphosphine oxides (4) with aldehydes or lactols could provide a concise route to the corresponding enol ethers (Scheme 1). This series could also be extended to include the corresponding tetrahydrofuran salts (7) and (8).

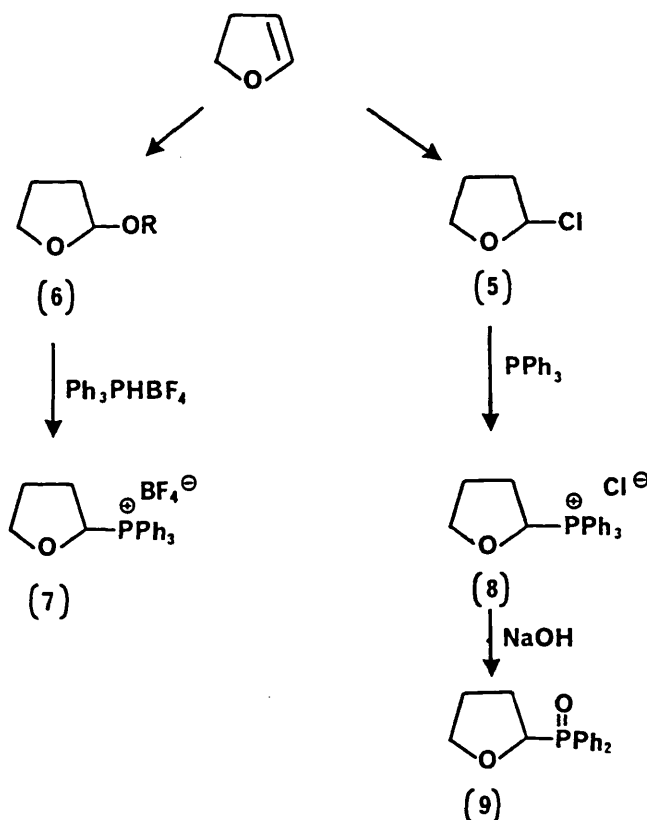
Scheme 1



Although some work had been done in this field¹, the extent of application of this methodology had not been fully investigated. Previous work described the preparation of phosphonium salts (7) and (8) from the corresponding anomeric acetal (6) and chloride (5) respectively (Scheme 2)². Hydrolysis of the salt (8) to the phosphine oxide (9) was also studied, but no Wittig or Horner- Wittig couplings had been investig-

ated. Preparation of the phosphine oxide (11) by treating 2,5 - dimethoxy tetrahydrofuran (10) with chlorodiphenylphosphine had been reported³, but again no reactions had been studied, (see page 82).

Scheme 2

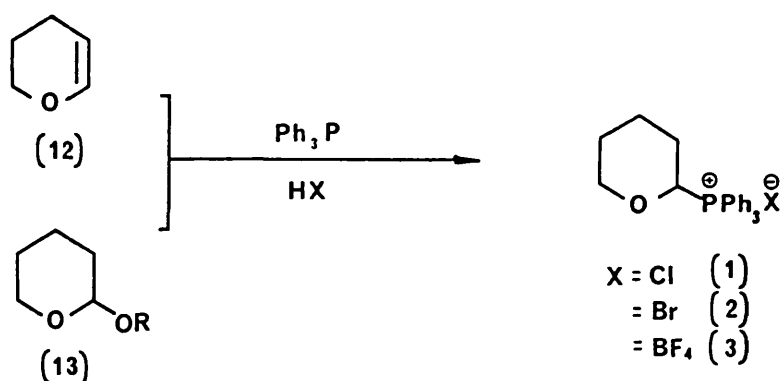


2.2 Preparation of the Phosponium Salts.

Reaction of triphenylphosphine with the requisite anomeric chloride gave poor results due to the instability of the starting material. However, this was overcome by forming the chloride in situ, achieved by bubbling dry hydrogen chloride gas through a solution of 3,4 - dihydro-2H-pyran (12) in benzene. The addition of triphenylphosphine and stirring for 5h at room temperature gave the phosphonium chloride (1)

in good yield (90%). However, it was difficult to purify the salt and it seemed particularly unstable to heat. Previous communications had reported similar difficulties and the preparation of other salts was investigated ².

It was shown that if hydrogen bromide was used in the above reaction, the resulting phosphonium bromide (2) was formed in good yield,¹ and was easily purified. Reaction of the anomeric acetal (13) with triphenylphosphonium tetrafluoroborate gave the corresponding phosphonium tetrafluoroborate salt (3) which was also easily purified by recrystallisation from dichloromethane - diethyl ether mixtures, to give the pure compound. This salt appeared more stable than the corresponding chloride.

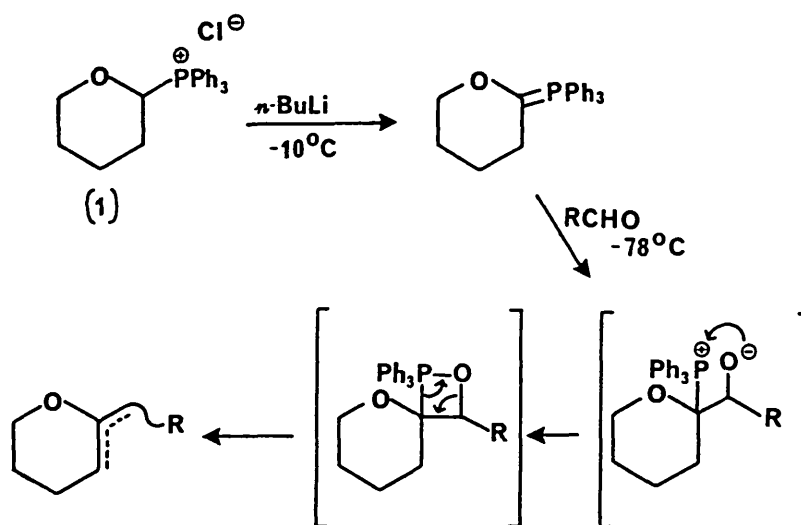


2.3 Wittig coupling Reactions

The phosphonium chloride (1) was deprotonated with n-butyllithium in tetrahydrofuran at -10°C , to generate the deep red phosphorane. However, coupling reactions with aldehydes or lactols afforded low yields of the products (benzaldehyde yield 24%). Elimination of

the triphenylphosphine oxide was spontaneous as the reaction warmed to room temperature via the betaine intermediate, to give a mixture of three alkene isomers, the endo isomer arising due to isomerisation on work-up (Scheme 3).

Scheme 3

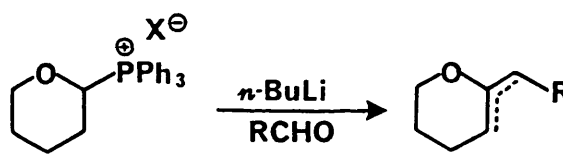
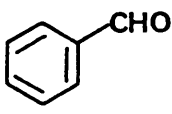
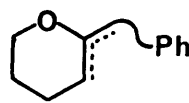
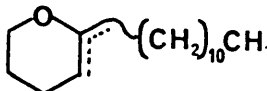
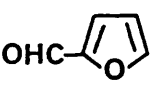
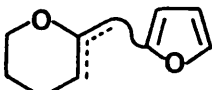
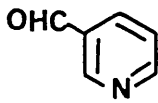
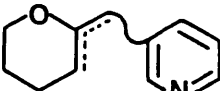


It was possible that under the reaction conditions, the salt decomposed and further evidence in the literature suggested that phosphoranes with a α -oxygen substituent are thermally unstable and do not react particularly well in the Wittig reaction ⁴.

Deprotonation of the tetrafluoroborate salt (3) with n -butyllithium in tetrahydrofuran at -78°C , generated the deep red phosphorane as previously described. Coupling reactions with aldehydes or lactols gave better yields of products than the corresponding chloride salt, (Table 1), however the range of electrophiles studied was limited, the phosphorane failing to re-

act cleanly with cinnamylaldehyde or phenyl acetaldehyde, giving a mixture of products.

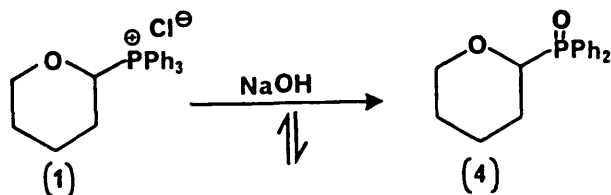
Table 1

				
RCHO	Yield (%)		X=Cl	X=BF ₄
	(14)		24	75
CH ₃ (CH ₂) ₁₀ CHO	(15)		5	40
	(16)		12	60
	(17)		-	41

2.4 Preparation of Phosphine oxides

An alternative modification to the Wittig coupling reaction is the Horner-Wittig coupling reaction using the corresponding phosphine oxide which has been made popular in recent years following extensive studies by Warren et al.⁵ The triphenylphosphonium salt (1) was converted to the phosphine oxide (4) by hydrolysis (Scheme 4) in 83% yield.

Scheme 4



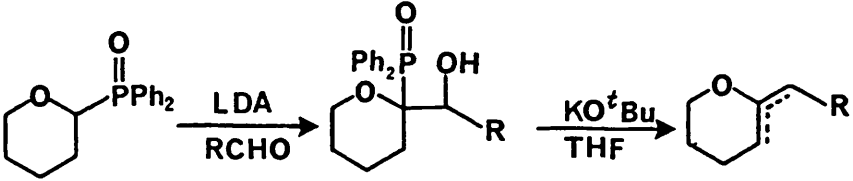
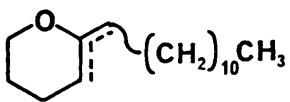
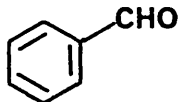
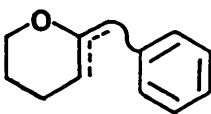
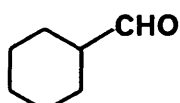
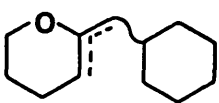
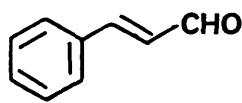
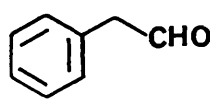
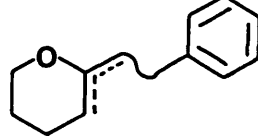
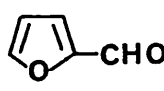
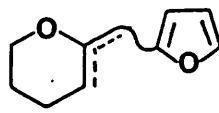
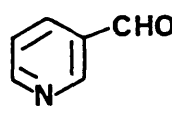
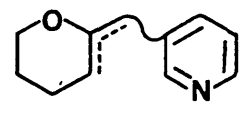
2.5 Horner-Wittig coupling Reactions

Deprotonation of (4) was achieved with lithium diisopropylamide at -78°C in tetrahydrofuran, generating a deep red anion which was quenched by an aldehyde or lactol. The intermediate hydroxy-phosphine oxide adduct was isolated and treated with either potassium *t*-butoxide in tetrahydrofuran at room temperature,⁶ or sodium hydride in dimethylformamide at 50°C .⁵ This encouraged the elimination of diphenylphosphinic acid, to yield a mixture of the three alkene isomers in good yield, (benzaldehyde yield 76%).

Although the Horner-Wittig route involved an additional step, overall yields and the wider range of aldehydes tolerated (Table 2), made this the preferred reaction for carbon-carbon bond formation at the anomeric position in this series of reactions.

Some of the substrates formed had potential ionophoric properties, allowing chelation between the two heteroatoms and should be further investigated.

Table 2

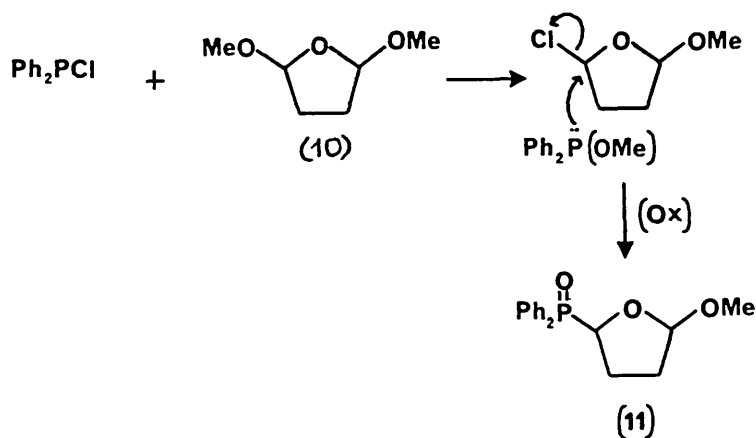
	
RCHO	Yield(%)
$\text{CH}_3(\text{CH}_2)_{10}\text{CHO}$	(15)  71
	(14)  76
	(18)  68
	(19)  78
	(20)  68
	(16)  41
	(17)  64

2.6 Preparation and Reaction of the tetrahydrofuran derivatives

The corresponding Wittig and Horner-Wittig coupling reactions of the tetrahydrofuran derivatives were also investigated. Again, the phosphonium chloride (8) was generated by bubbling hydrogen chloride gas through a benzene solution of dihydrofuran and triphenylphosphine, but could not be satisfactorily purified. However, hydrolysis gave the phosphine oxide (9) in good yield. The corresponding tetrafluoroborate salt (7) was prepared by treating the acetal with triphenylphosphonium tetrafluoroborate.

Also of interest in this series was the ability to form functionalised phosphine oxides and phosphonium salts. The phosphine oxide (11) was prepared following the normal Arbusov method³. Chlorodiphenylphosphine was added to 2,5-dimethoxy tetrahydrofuran (10) at 0°C in dichloromethane to yield the phosphine oxide (11) (Scheme 5). Continuous trituration with petrol of the oil recovered gave a crystalline product.

Scheme 5



The corresponding diethoxyphosphine (21) was prepared from diethylchlorophosphite and 2,5-dimethoxy tetrahydrofuran, since it would be easier to purify as we except the product to be an oil. This was indeed the case, although the yield was considerably lower (48% cf 67%) and the sticky oil more difficult to handle. 2,5-Dimethoxy tetrahydrofuran (10) also reacted with one equivalent of triphenylphosphonium tetrafluoroborate, to give the phosphonium salt (22) in 68% yield.

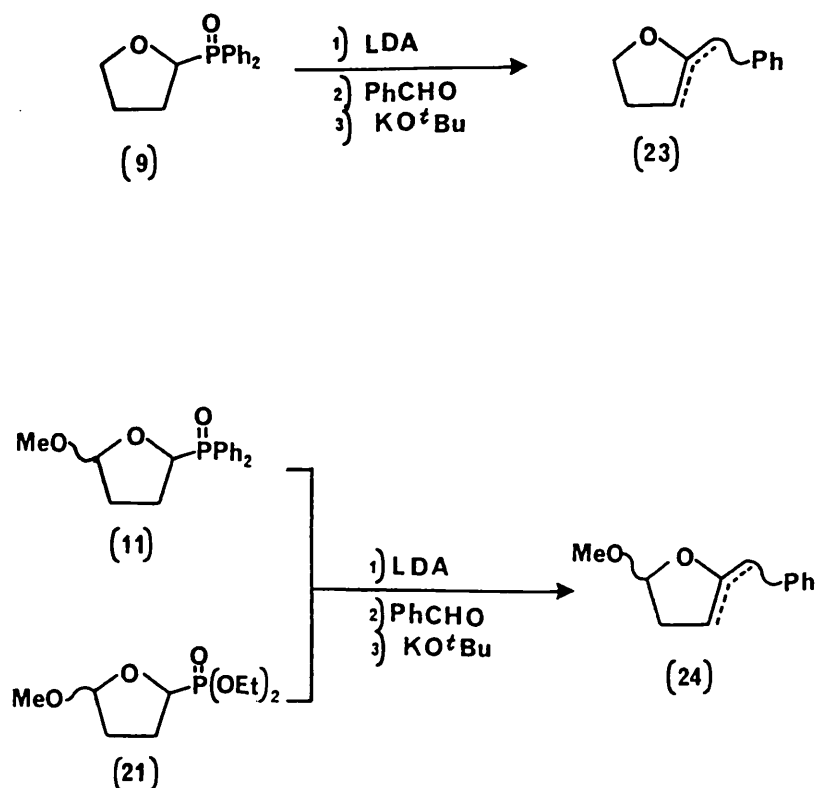
Attempts to form bis-phosphonium salts or phosphine oxides by treating 2,5-dimethoxy tetrahydrofuran with excess phosphorylating reagent were not successful, a mixture of ring cleaved products were the only ones to be isolated. The tetrahydropyran salts prepared by generating 2,6-dimethoxy tetrahydropyran in situ were equally unsuccessful.

As previously, the tetrafluoroborate salts were deprotonated with n-butyllithium in tetrahydrofuran at -78°C and coupled with aldehydes and lactols. However, isolation of the enol ethers derived from the condensation with benzaldehyde suggested a mixture of ring open products and the desired enol ethers. These products also appeared considerably more hygroscopic than their tetrahydropyran counterparts, and the hemi-ketals were also isolated.

The phosphine oxides were deprotonated with lithium diisopropylamide in tetrahydrofuran at -78°C and

reacted with benzaldehyde to give the desired enol ethers after treating the intermediate hydroxy-phosphine oxide with potassium *t*-butoxide as previously described (Scheme 6).

Scheme 6



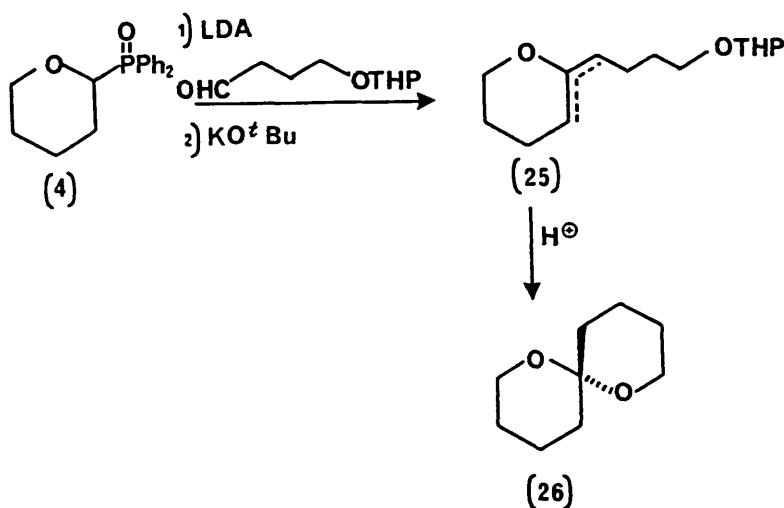
2.7 Application to Spiroketal Synthesis

The objective behind this study was that many of the enol ethers prepared by this methodology are precursors for spiroketals formed under anomeric control⁷ in the presence of acidic conditions.

Reaction of the phosphine oxide anion of (4) with 4-((tetrahydro-2H-pyran-2-yl)oxy)butanal followed by treatment with potassium *t*-butoxide and distillation

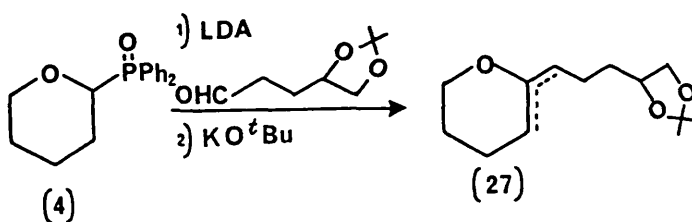
gave (25). Deprotection and cyclisation using a catalytic amount of camphor sulphonic acid (pyridinium tosylate was also efficient) in methanol gave the naturally occurring spiroketal (26), a sex pheromone component from the Olive fly, Dacus oleae⁸ (Scheme 7).

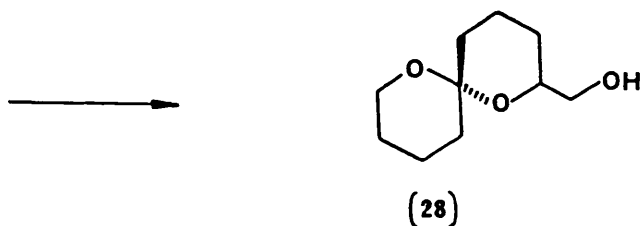
Scheme 7



Similarly, reaction with 4,5-isopropylidene, 4,5 dihydroxy pentanal (26)⁹ gave after elimination, the enol ether (27) which was cyclised exclusively to the trans spiroketal (28) (Scheme 8). The additional functionality at the 2-position could be elaborated and was useful for model studies of milbemycin β_1 .

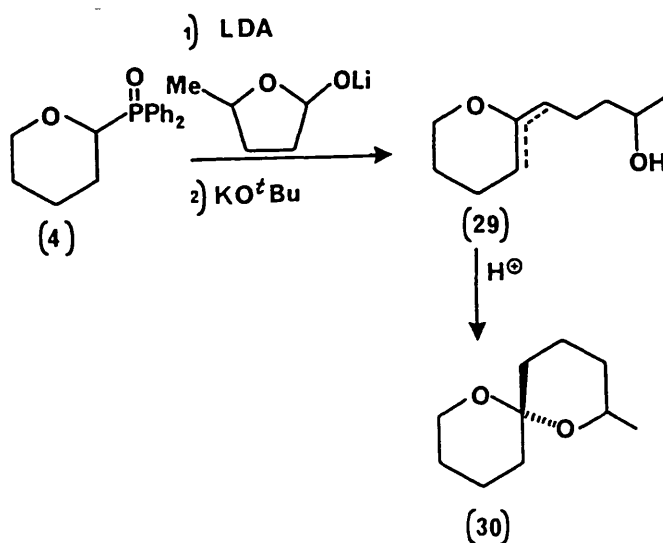
Scheme 8





The reaction of the phosphine oxide anion and lactol gave the best results when a solution of the lactol anion was used, rather than adding an excess of base to effect deprotonation. Reaction of the lactol anion gave after elimination, the enol ethers (29) which upon acid cyclisation, gave the spiroketal (30) (Scheme 9).

Scheme 9



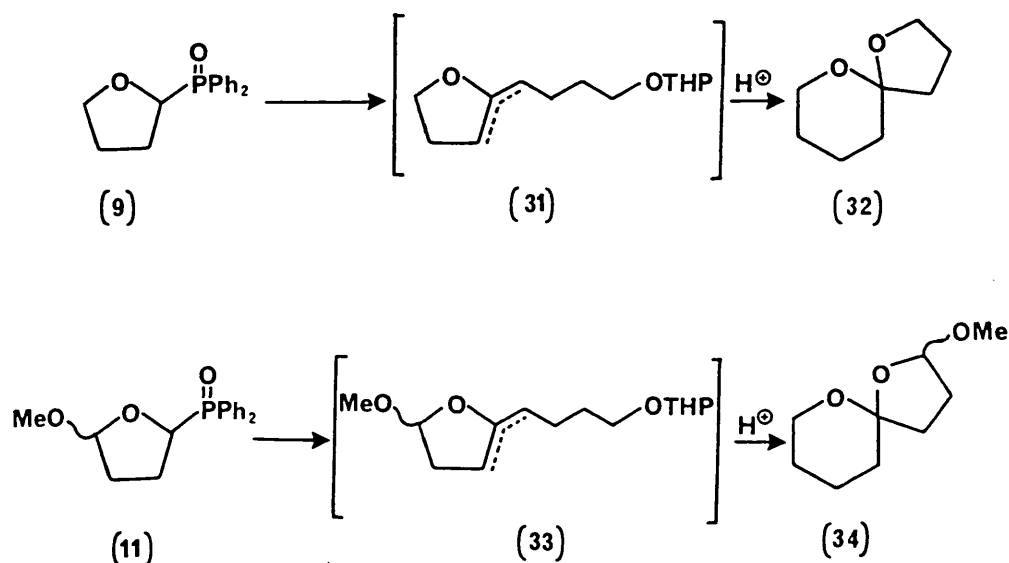
The actual coupling reaction was notably slower than previously, requiring warming to 0°C to effect the complete reaction. This was also observed when the phosphonium tetrafluoroborate salt (3) was used.

Many naturally occurring spiroketals have a 5,6 ring structure, for example the common wasp pheromone Paravespula vulgaris.¹⁰ Therefore the reaction of the tetrahydrofuran derivatives with the aldehydes and lactols described above afforded the synthesis of this class of spiroketals.

Reaction of the phosphine oxide anion of (9) with 4-((tetrahydro-2H-pyran-2-yl) oxy) butanal gave after elimination the enol ethers (31) which were directly converted to the spiroketal (32) (Scheme 10). The corresponding tetrafluoroborate salt (7) anion underwent the same reaction to give a mixture of ring open and closed products (31), all of which cyclised to the spiroketal (32).

The 5-methoxy phosphine oxide anion of (11) and (21) were also condensed with the aldehyde to yield the enol ethers (33) after elimination, which were immediately cyclised to the spiroketals (34) (Scheme 10).

Scheme 10



The last example is of particular interest as further elaboration to the phosphonium salt could lead to the formation of tricyclic spiroketal structures, and to date only one synthesis of these compounds has been reported ¹¹.

SULPHONE COUPLING REACTIONS

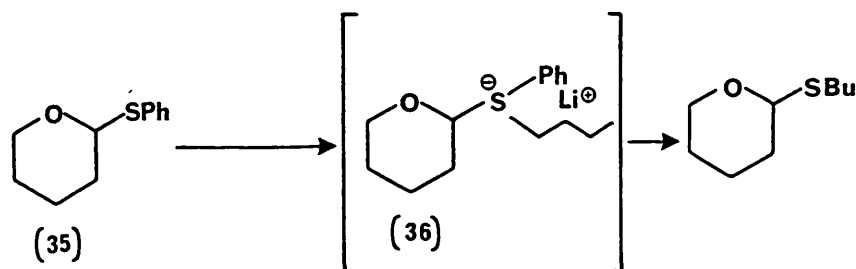
3.1 Introduction

The ability to generate an anion α to a sulphide and acetal functionality and alkylate has recently been reported in the literature¹² and it seemed this method could be applied to cyclic ethers, thereby forming a carbon - carbon bond at the anomeric centre. While this study was undertaken in our laboratories, Sinaÿ et al.¹³ independently reported the lithiation and alkylation of a D- glucal species derived from the corresponding phenyl thioglycoside. Carbohydrates substituted at the anomeric position by a sulphone group were also known, prepared by oxidation of the requisite sulphide^{14,15}, however attempts to deprotonate these compounds had not been reported.

3.2 Preparation of the Sulphones

In the initial studies, 2- benzenesulphenyl tetrahydro-pyran (35) was prepared by treating 3,4-dihydro-2H-pyran with thiophenol and stirring at room temperature for 12h. Exhaustive attempts to deprotonate at the anomeric position were unsuccessful, the major product resulting from alkyl exchange via the "ate" complex (36) (Scheme 11)¹⁶.

Scheme 11



The sulphide was oxidised to the sulphoxide (37), anticipating that the more acidic anomeric centre would readily deprotonate. Methods of oxidation included sodium periodate, meta-chloroperbenzoic acid and oxone, all requiring buffered conditions (sodium acetate) to prevent the acid catalysed elimination of benzenesulphenate. However, attempts to deprotonate were again unsuccessful, so the sulphide was oxidised to the sulphone (38) using an excess of oxone under buffered conditions to prevent the elimination of benzenesulphinate. Fortunately, the sulphone was readily deprotonated.

The sulphone (38) was a crystalline solid, ^1H nmr showed only one isomer with the benzenesulphonyl group occupying the equatorial position. However, purification by silica chromatography lead to the decomposition of the material, presumably due to the acid catalysed elimination.

Preparation of sulphones directly from alkyl halides using sodium benzenesulphinate as a sulphur nucleophile¹⁷ is known, so this method was applied to 3,4 -dihydro-2H-pyran. Reaction of the corresponding acid,¹⁸ benzenesulphinic acid, generated by treating the commercially available sodium salt with 7% sulphuric acid and 3,4 -dihydro-2H-pyran in dichloromethane gave the crystalline sulphone in 82% yield. The acidity of the medium obviously catalyses the initial oxonium ion formation and the benzenesulphinate species attacks the intermediate to give the sulphone.

Preparation of the sulphone from 2-methoxy tetrahydropyran using this method was rather sluggish, but the addition of calcium chloride speeded up the reaction, presumably due to quenching the liberated methanol. It appeared some product from the attack of the benzenesulphinic acid on the oxygen was also generated.

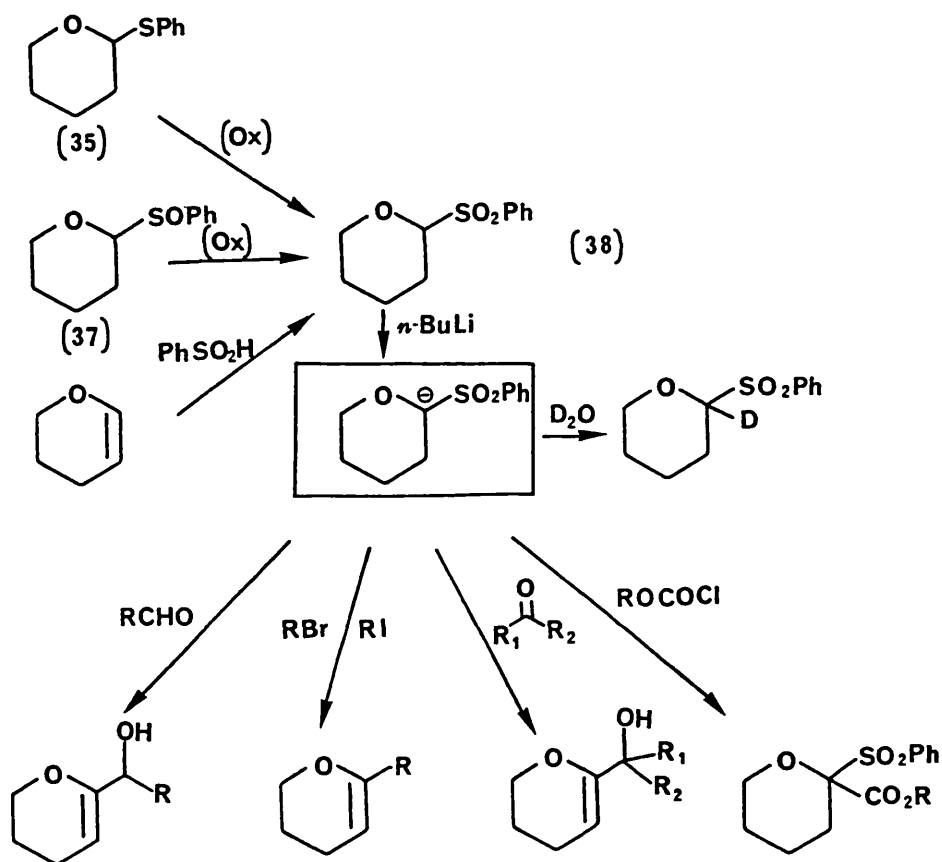
The corresponding 2-benzenesulphonyl tetrahydrofuran (39) was prepared by treating dihydrofuran with benzenesulphinic acid to yield a white crystalline solid in 84% yield. However, deprotonation using a variety of bases was not successful, starting material being recovered.

The possibility of preparing an anomerically functionalised sulphone was also investigated. 6-methoxy, dihydro-2H-pyran was treated with benzenesulphinic acid to yield 2-benzenesulphonyl, 6-methoxy tetrahydropyran (40) in 74% yield. Although deprotonation and electrophilic quenching appeared to be successful the loss of the methoxy resonance observed by ^1H nmr and the isolation of many products by thin-layer chromatography limited any application of this sulphone in synthesis.

3.3 Reactions of 2-benzenesulphonyl tetrahydro-2H-pyran(38) with electrophiles

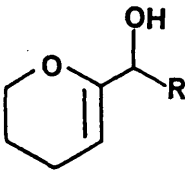
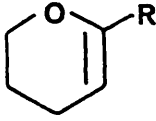
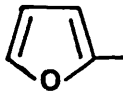
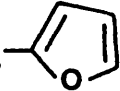
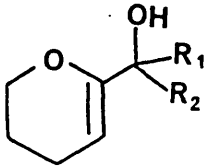
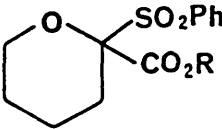
The sulphone was deprotonated with n-butyllithium at -78°C in tetrahydrofuran. This generated a pale yellow anion solution which could be quenched with a variety of electrophiles. (Scheme 12) (Table 3)

Scheme 12

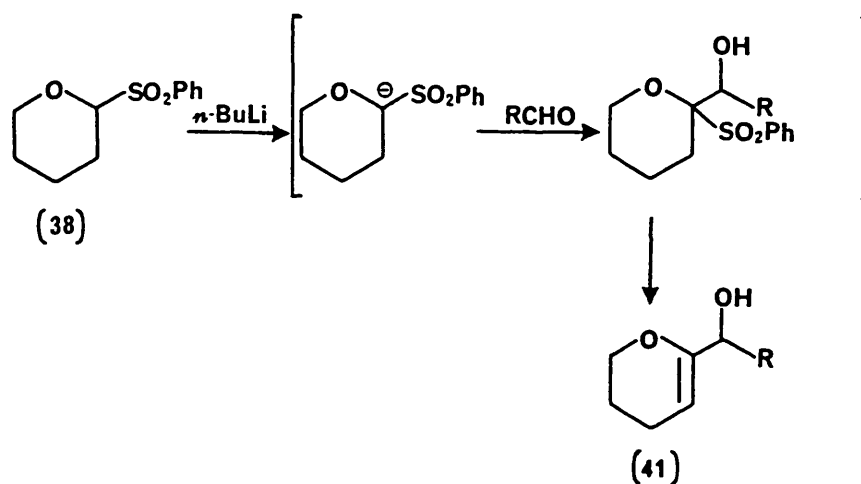


Deuterium oxide gave complete incorporation at the 2-position. The reaction of the anion with alkyl and aryl aldehydes at -78°C proceeded cleanly to yield a single product which was identified as the cyclic endo enol ether. Spontaneous elimination of benzenesulphinate occurred between -78°C and warming the reaction to room temperature. This suggested once the 2-position was substituted, elimination was facile, presumably due to the inherent ability of the benzenesulphinate as a good leaving group and increased steric compression in the intermediate alkylated product. (Scheme 13)

Table 3

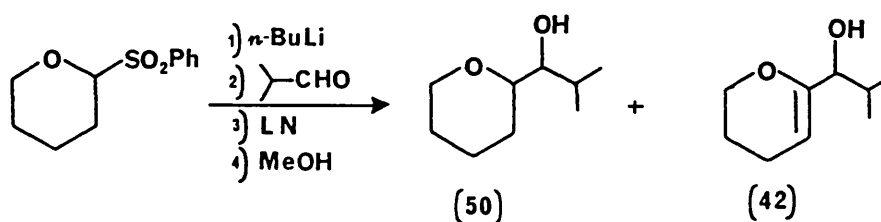
	
<u>R</u> CH(CH₃)₂ (42) (CH₂)₅CH₃ (43) (CH₂)₃CH₃ (44) (CH₂)₂(CH)₂(CH₂)₄CH₃ (45)  (46) (CH)₂CH₃ (47) Ph (48) Ph(NO₂) (49)	<u>R</u> CH₂(CH)CH₂ (51) (CH₂)₄- (52) CH₂Ph (53) Ph (54) (CH₂)₄CH₃ (55)
	
<u>R</u>₁ <u>R</u>₂ CH₃ CH(CH₃)₂ (56) c-C₅H₈ (57) Ph CH₃ (58)	<u>R</u> CH₃ (59) CH₂CH₃ (60) CH₂Ph (61)

Scheme 13



Further studies suggested elimination occurred at -78°C , since the addition of lithium naphthalenide to initiate the reductive desulfonylation of the intermediate adduct, after quenching with isobutyraldehyde gave a mixture of ether (50) and enol ether (42) products (Scheme 14). Sodium naphthalenide has since been shown to be a superior reagent for this process,¹⁹ isolating a greater proportion of the desired product (2:1).

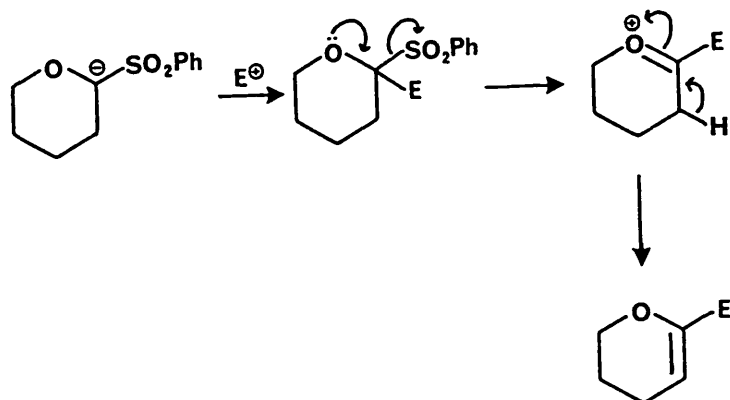
Scheme 14



The possibility of the elimination occurring by an intramolecular proton transfer was not feasible as the reaction of the sulphone anion with alkyl and aryl

halides also underwent the same elimination process. This was further confirmed by treating the sulphone with potassium *t*-butoxide as the external alkoxy anion which yielded only starting material. It seems more probable that the strain at the anomeric position after substitution can be relieved by formation of the oxonium ion intermediate with the elimination of benzenesulphonate (Scheme 15).

Scheme 15

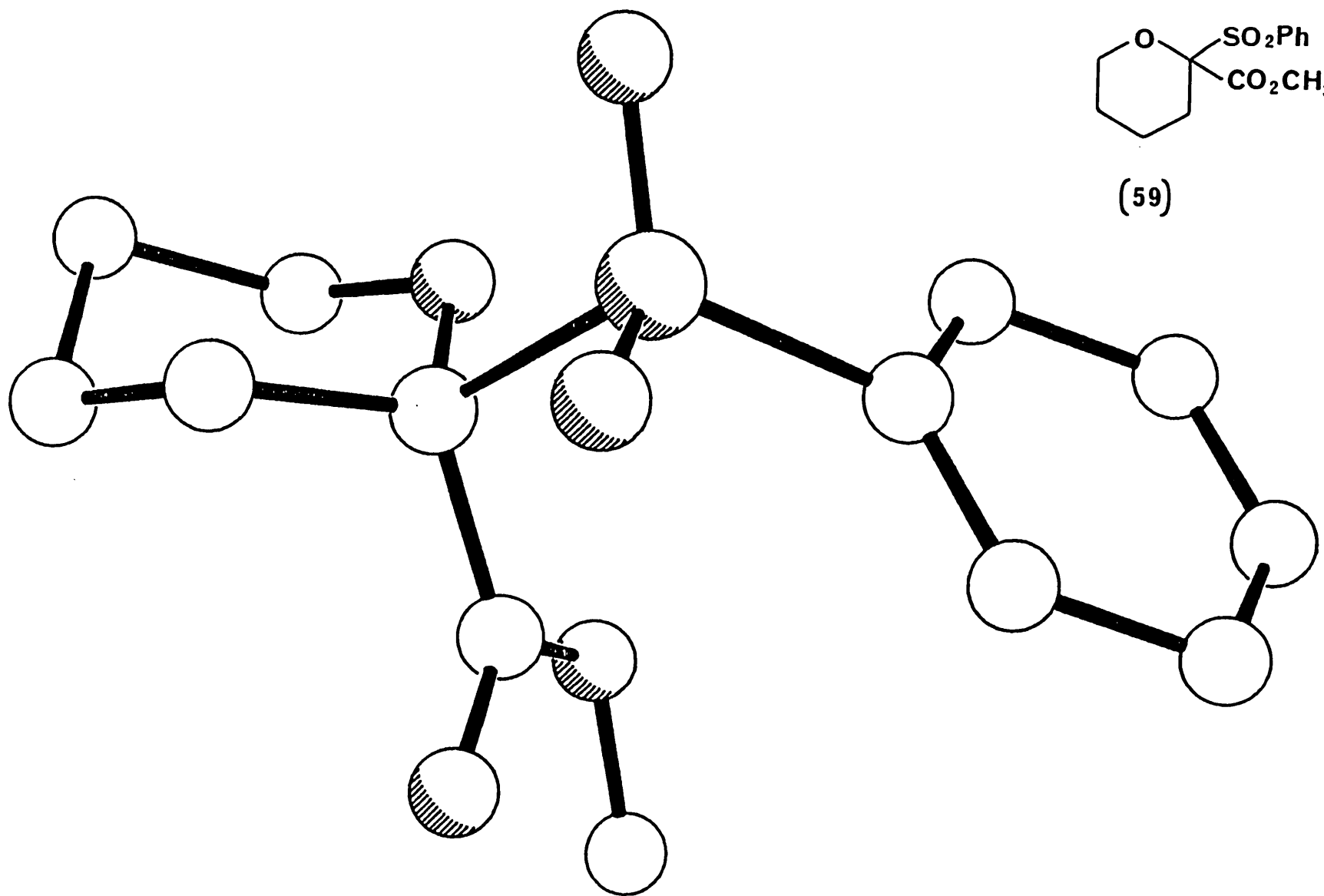


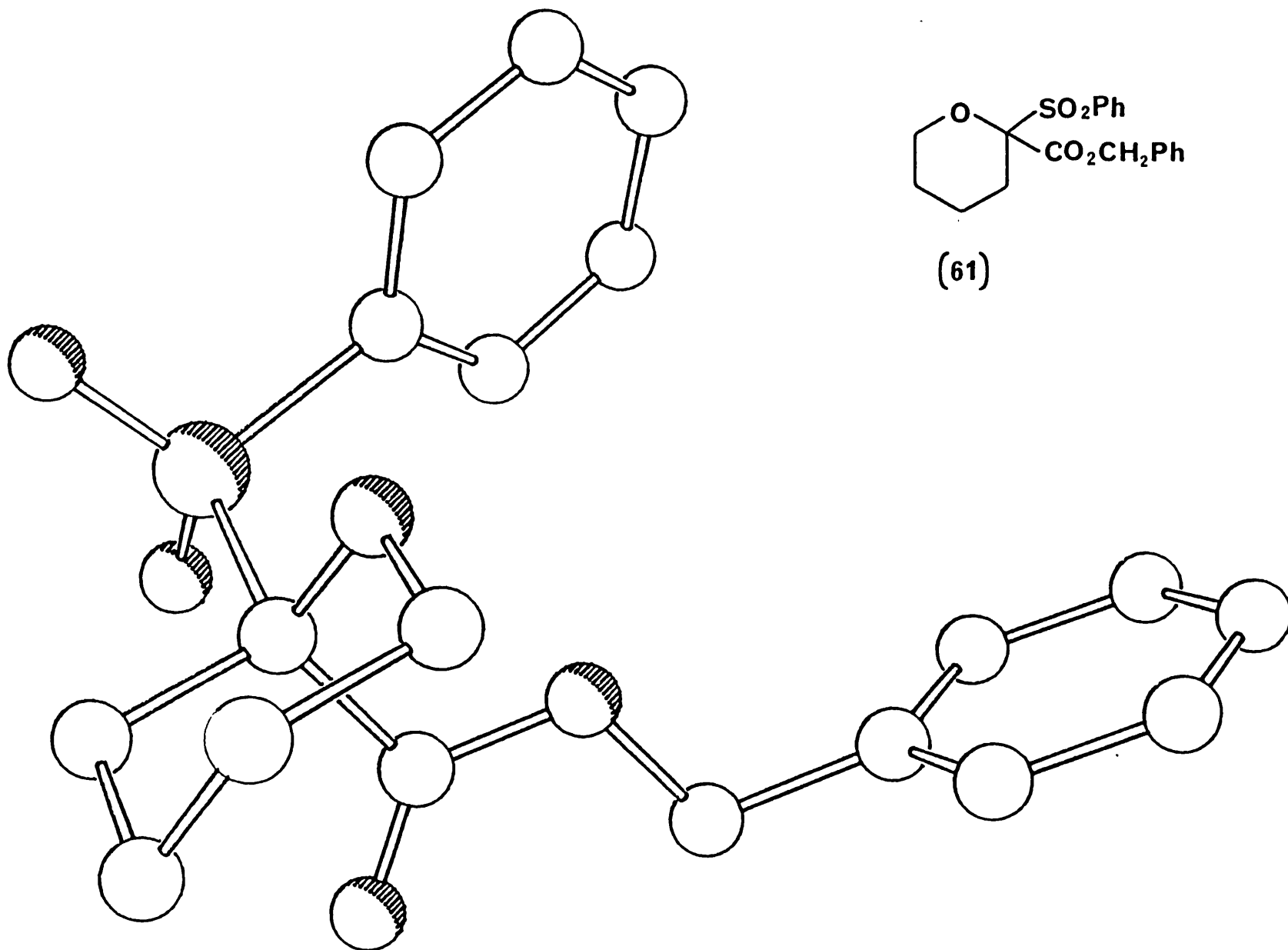
In the majority of examples with alkyl and aryl halides the endo isomer (confirmed by upfield resonance of the proton) was the only product isolated. However, with allyl bromide a mixture of *E* and *Z* isomers were obtained, the double bond having isomerised into conjugation with the double bond in the side chain. This product (51) was extremely volatile and rather difficult to purify. The same observation occurred with the reaction of benzyl bromide where the product was a mixture of *Z* and endo isomers (54), the double bond isomerising

into conjugation with the phenyl ring. The reaction with 1-iodopentane appeared to occur extremely poorly under the normal conditions, but if excess sulphone anion was available the reaction proceeded in reasonable yield. The excess reagent could be recovered after the reaction was worked up.

The reaction of the sulphone anion with ketones was very sluggish and optimum conditions were found to require 2.5 equivalents of sulphone.

The exception in this series was the reaction of the sulphone anion with alkyl or aryl chloroformates. No elimination of benzenesulphinate was observed, the acylated sulphone being recovered in good yields as crystalline solids. The only logical explanation of this reaction suggests the elimination is suppressed due to the ester function which destabilises any intermediate oxonium ion formation. X-ray crystallography structures of 2-methyl (2'-benzenesulphonyl tetrahydropyran-2-yl) formate (59) and the 2-benzyl derivative (61) showed the benzenesulphonyl group still occupied the equatorial position. Attempts to reductively desulphonylate these products by cooling a tetrahydrofuran solution to -78°C and treating with lithium naphthalenide were not successful on these substrates, although Sinaý²⁰ had achieved reductive desulphonylation of 2-methyl formate, 3,4,6-tri-O-*t*-butyldimethylsilyl-2-deoxy- α -glucopyranosyl phenylsulphone under identical conditions.

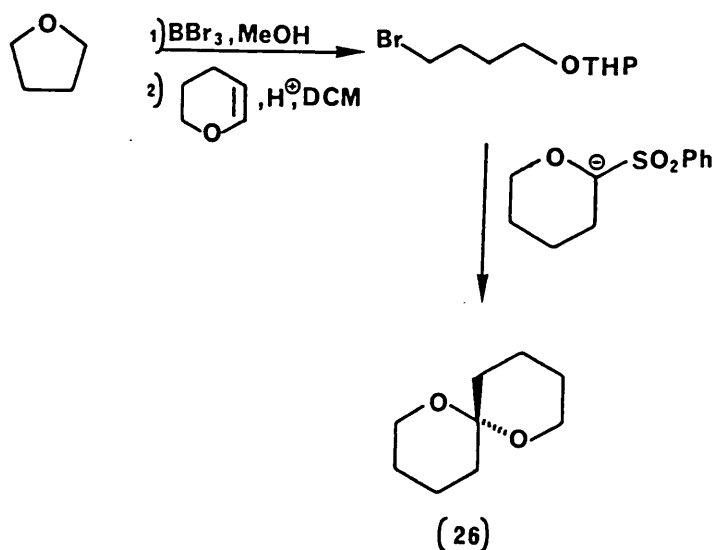




3.4 Application of the sulphone (38) in Spiroketal Synthesis

The synthetic utility of benzenesulphonyl- tetrahydro-pyrans in spiroketal synthesis was demonstrated by the preparation of the major and minor components of the Olive fly, Dacus oleae⁸ sex pheromones (26) and (68) and the common wasp, Paravespula vulgaris¹⁰ (62). The sulphone (38) anion was quenched with 1-((tetrahydro-2H-pyran-2-yl) oxy) 4- bromobutane.²¹ Elimination of the benzenesulphinate generated a sufficiently acidic media to cleave the protecting group, and directly cyclise the enol ether intermediate to the spiroketal (26) on work-up (Scheme 16).This one pot synthesis resulted in an excellent 77% yield of the pheromone, identical to the natural product.

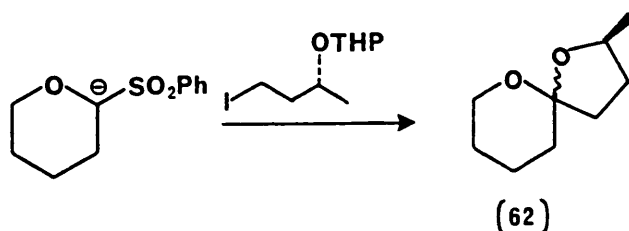
Scheme 16



The sulphone anion also reacted with 1-(^t-butyldimethylsilyl) oxy) 4- iodobutane. Here, the inter-

mediate enol ether was treated with aqueous hydrogen fluoride to afford the removal of the protecting group and cyclisation to yield the spiroketal (26) in 52% yield. Similarly, 2-methyl-1,7-dioxaspiro [5,5] undecane (30) and 1,6-dioxaspiro [4,5] decane (32) were prepared and characterised as previously. The sulphone anion was condensed with 1-iodo ((3-tetrahydro-2H-pyran-2-yl)oxy)butane²² which gave the spiroketal (62) in 79% yield (Scheme 17). This was identical to the natural product isolated from the common wasp, $[\alpha]_D^{22} = -12.1^\circ$ (c=2, hexane).

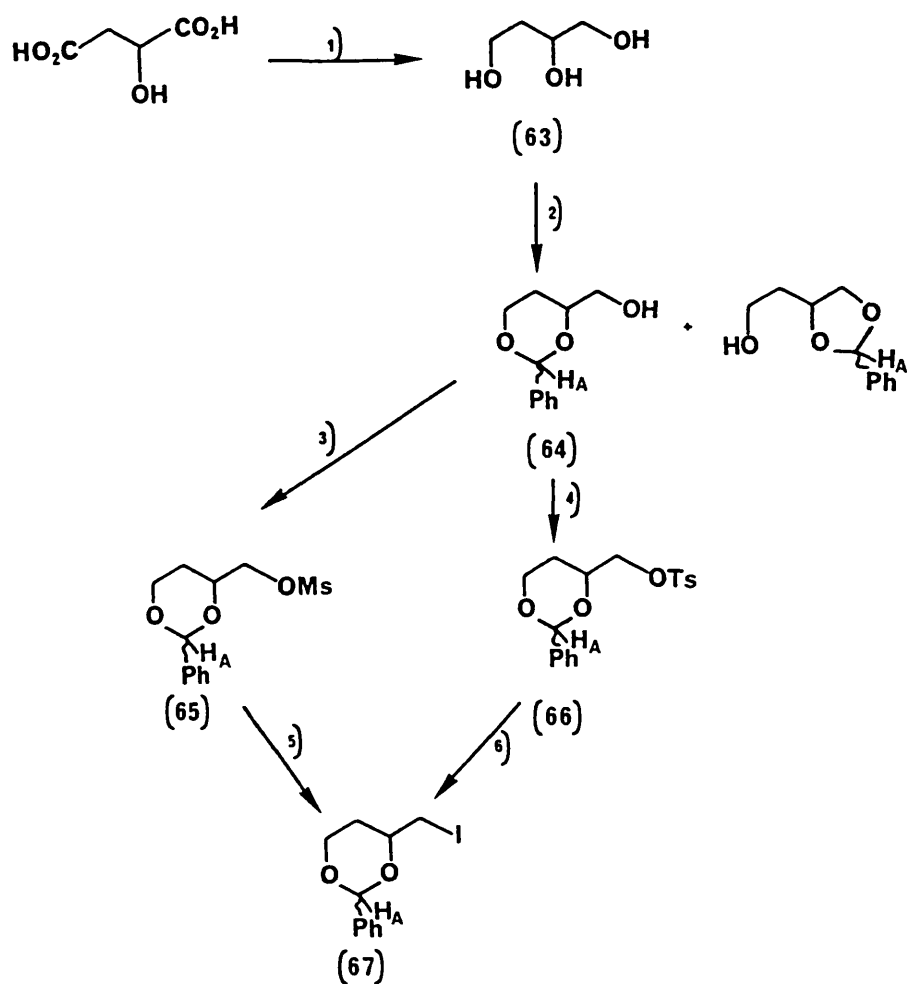
Scheme 17



The preparation of 2-phenyl-4-iodomethyl-1,3-dioxane (67) was achieved in four steps from dl-malic acid (Scheme 18).

Protection of the triol (63) with benzaldehyde dimethyl acetal gave a mixture of isomers (5 and 6 ring protection, the ratio was determined by the integral of H_A resonances in the ^1H nmr spectrum.), the major isomer being the desired product. Separation of isomers was not possible at this stage, so both isomers were treated with methanesulphonyl chloride to form

Scheme 18



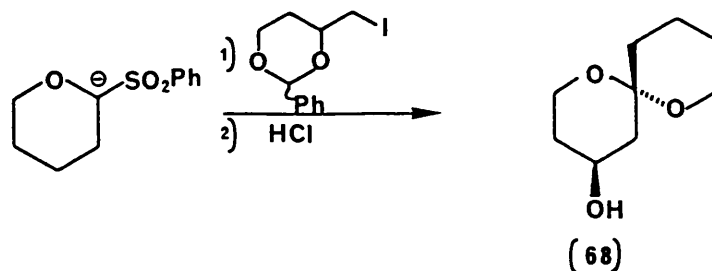
- 1) Borane dimethyl sulphide, THF.
- 2) Benzaldehyde dimethyl acetal, DMF.
- 3) Methanesulphonyl chloride, DCM.
- 4) Toluene-4-sulphonyl chloride, DCM.
- 5) Sodium iodide, DMF, 50°C.
- 6) Sodium iodide, acetone, reflux.

the mesylates (65). However, if the alcohols (64) were protected as the tosylate derivative (66), it was possible to separate the isomers. Treatment of (64) with toluene-4-sulphonyl chloride and a catalytic amount of pyridine over 2.5 days at -5°C gave exclusively the 6- ring isomer (66), confirmed by only one H_A resonance at 5.4 ppm. Loss of benzaldehyde suggested the 5- ring isomer was slowly deprotected under these conditions or was unstable and decomposed.

The tosylate (66) was then converted to the iodide (67) under the standard Finkelstein conditions. The mixture of mesylates (65) were also converted to the iodide (67) but the temperature needed to be held below 60°C , otherwise loss of the protecting group was observed. The two isomers were just separable by column chromatography, or the reaction could be worked up before completion, isolating mainly 5- ring isomer, and the recovered starting material resubjected to iodination.

Having prepared the iodide (67), it was added to a solution of the anion of the sulphone (38). The intermediate enol ether was subjected to 1M hydrochloric acid in a methanol solution to remove the protecting group, and cyclised to the spiroketal (68), a minor component of Dacus oleae sex pheromone ²³. (Scheme 19)

Scheme 19



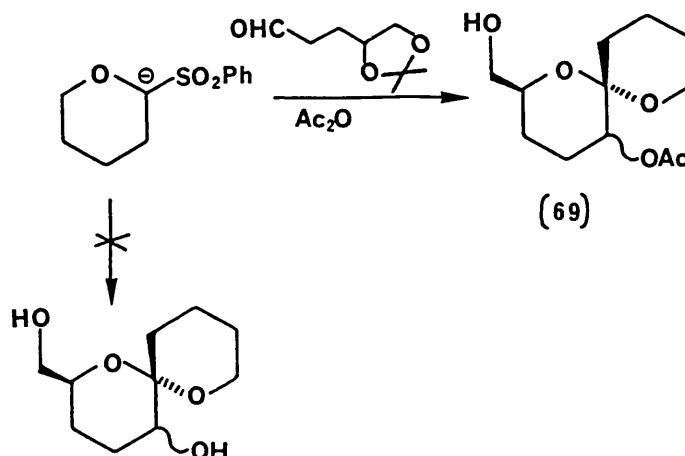
The spiroketal appeared to be a single isomer by high field ^1H nmr, the hydroxy group adopting the equatorial position. The signal of H_4 was deshielded by the 1,3-diaxial interaction with a ring oxygen (δ 4.08) and appeared as seven evenly spaced lines. The remaining four protons on the carbons adjacent to oxygen had similar chemical shifts. Thus, the ^1H nmr data indicated this isomer was the anomERICALLY stabilised conformation, as reported previously in the literature ^{23,24}.

This route could be modified to allow the enantio-selective synthesis of the spiroketal. Starting with 1- malic acid and converting it to the iodide as described previously and subsequent reaction with the sulphone anion gave the spiroketal (68) as the S-enantiomer, $[\alpha]_D = + 109^\circ$ ($c=2$, n-hexane), Ref $[\alpha]_D = + 121^\circ$ (n-pentane) ²⁴.

The anion of the sulphone (38) was condensed with 4,5-isopropylidene 4,5 dihydroxy pentanal. (Scheme 20) The intermediate hydroxy enol ether appeared relatively unstable and did not cleanly cyclise to the

desired spiroketal. It was postulated that the free hydroxy group α to the spirocentre was promoting ring opening of the spiroketal. Protection of the hydroxy group of the enol ether with benzoyl failed to cyclise but a reasonable yield of the spiroketal (69) was isolated when an acetyl protection was used. This suggested there were steric requirements influencing the reaction mechanism.

Scheme 20



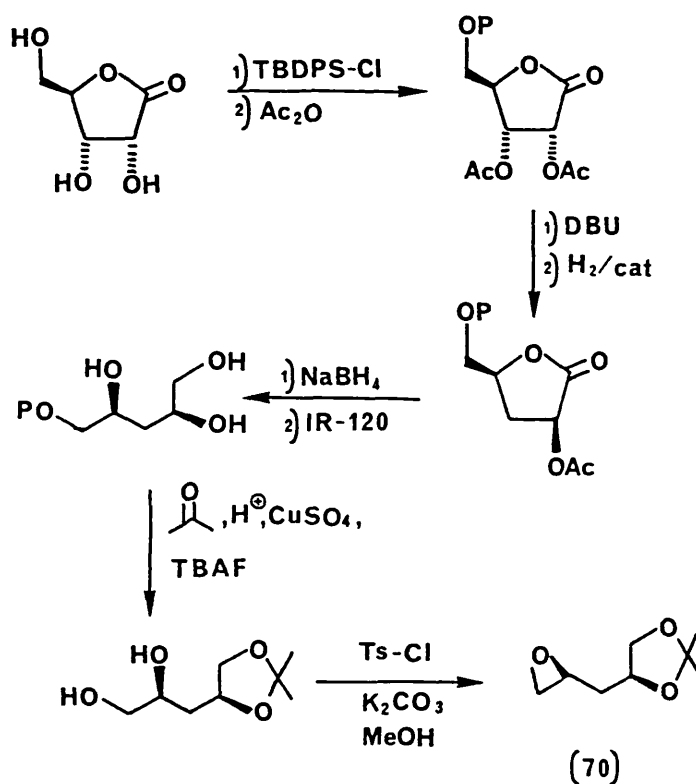
This compound appeared to be a single isomer by high field ^1H nmr data, the signal of H_5 was deshielded due to the acetyl group (δ 4.8). The acetyl group was observed as a singlet (δ 2.1), but assignment of whether the group was axial or equatorial was not determined.

The milbemycins are a family of potent antiparasitic agents isolated from Streptomyces B-41-146. The spiro-

ketal unit is common to most milbemycins and the application of the sulphone coupling strategy could provide a concise route to this moiety.

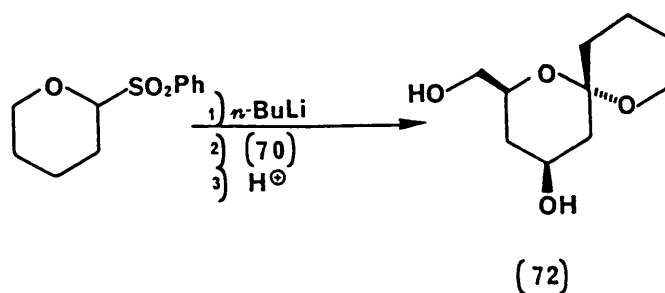
Although the anion of the sulphone (38) had failed to react with simple epoxides, the acetal epoxide (70), available in excellent yield from ribonolactone, (Scheme 21)²⁵ reacted with an excess of sulphone anion when stirred at -25°C overnight. (Scheme 22) The enol ether (71) was subsequently treated with acid and after work-up, the spiroketal (72) was isolated as a white crystalline solid.

Scheme 21



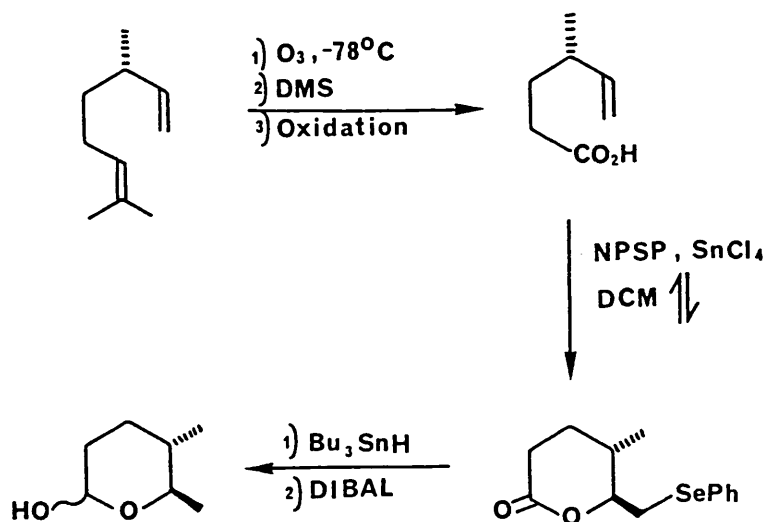
P = TBDPS

Scheme 22



The ^1H nmr data correlated well with previous data of the compound, and was confirmed to be a single isomer.²⁶ To create a better model for the milbemycin spiroketal moiety we required the introduction of methyl groups on the spiroketal. This could be achieved by preparing the functionalised sulphone (73), by treating the lactol derived from citronellene (Scheme 23)²⁷ with benzenesulphinic acid in dichloromethane and a catalytic amount of camphor sulphonic acid.

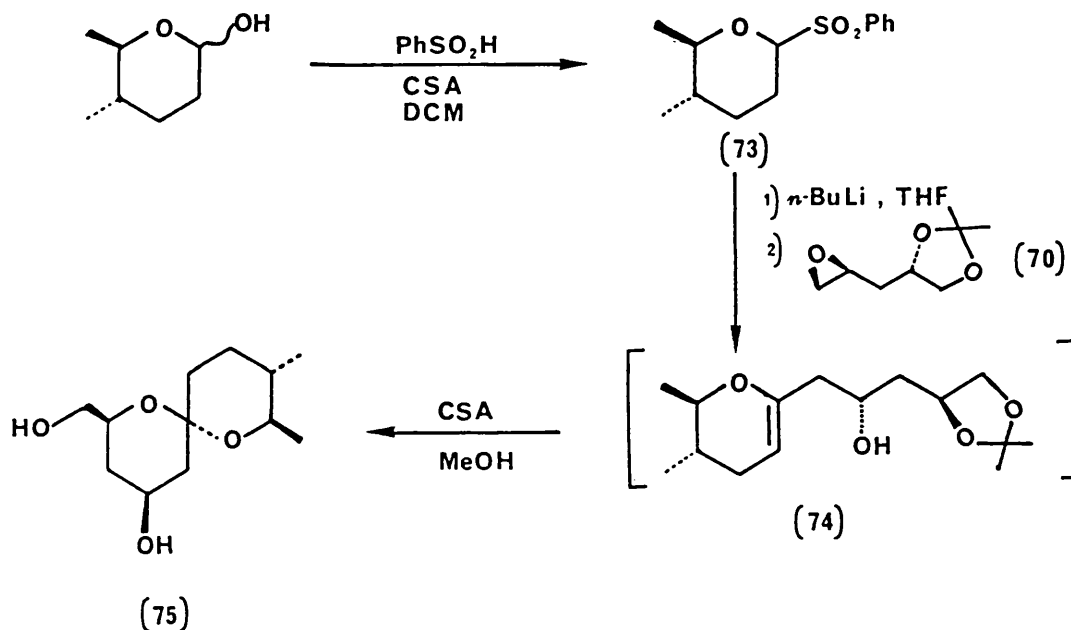
Scheme 23



The initial sulphone appeared to exist as a mixture of two isomers by ^1H nmr, as was clearly indicated by a doubling of the two methyl signals. However, recrystallation from ether- petrol gave colourless needles which were exclusively the axial isomer, confirmed by X- ray crystallographic analysis.

The sulphone (73) was deprotonated with n-butyllithium at -78°C and quenched with the acetal epoxide (70), stirring at -78°C for 4h before warming to room temperature. The enol ether (74) was immediately cyclised to the spiroketal (75) in 76% overall yield (Scheme 24), the desired model compound ²⁸.

Scheme 24

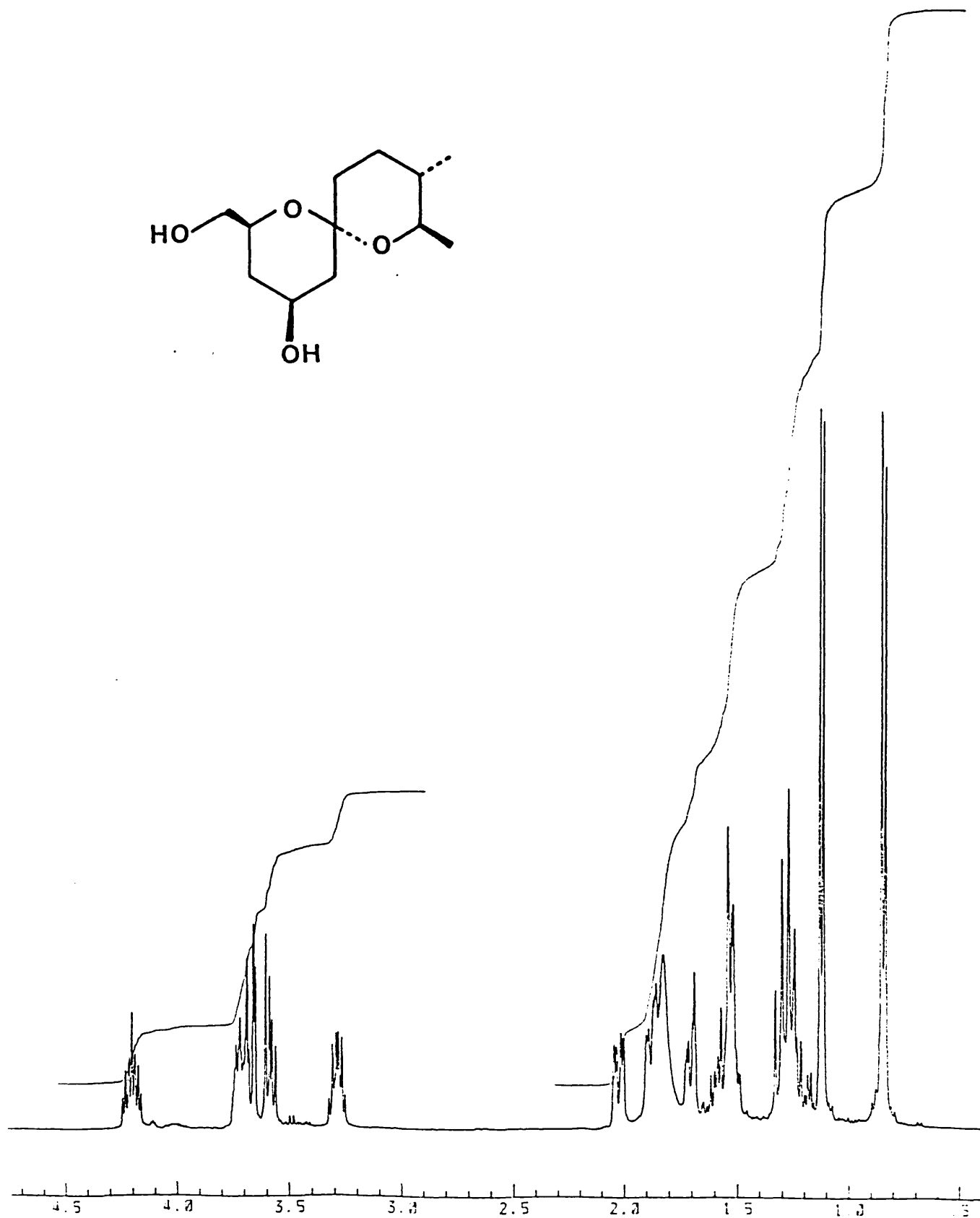
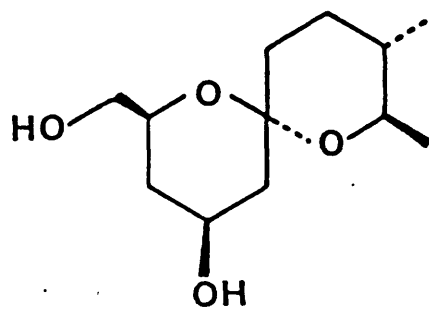


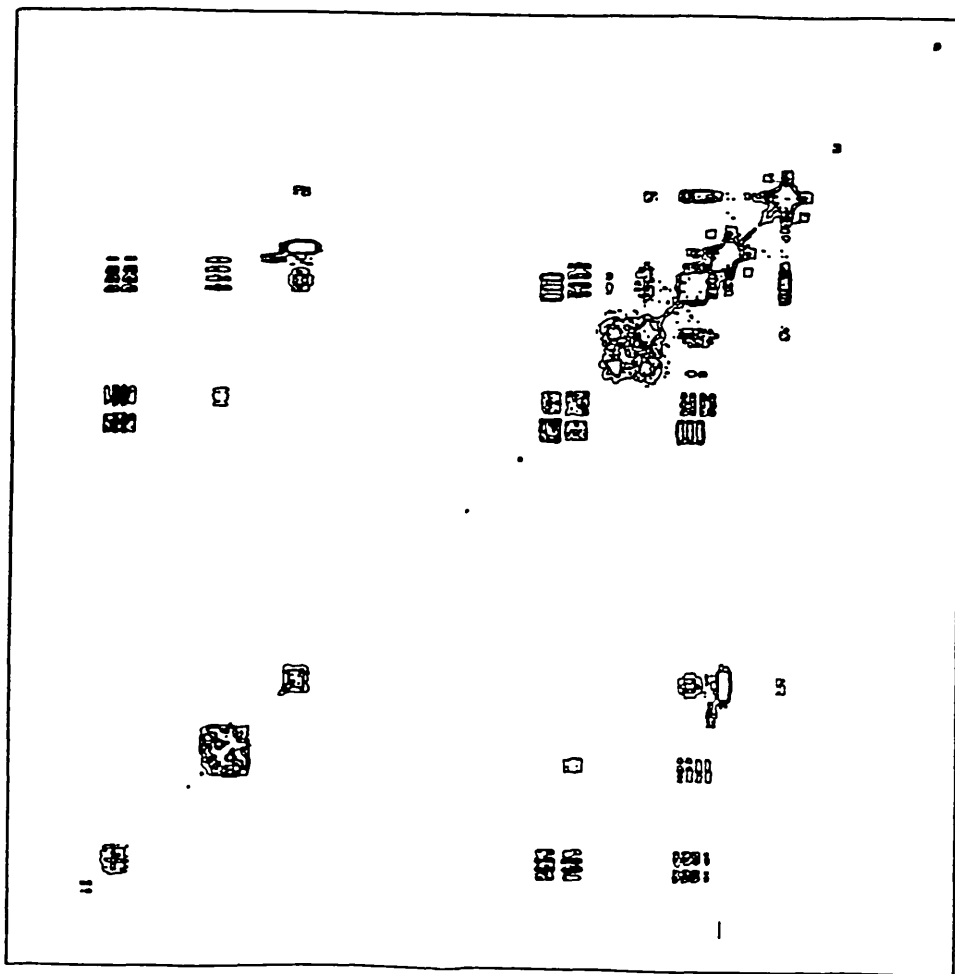
The ^1H nmr data showed the signal for H_4 was deshielded by 1,3- diaxial interaction with a ring oxygen

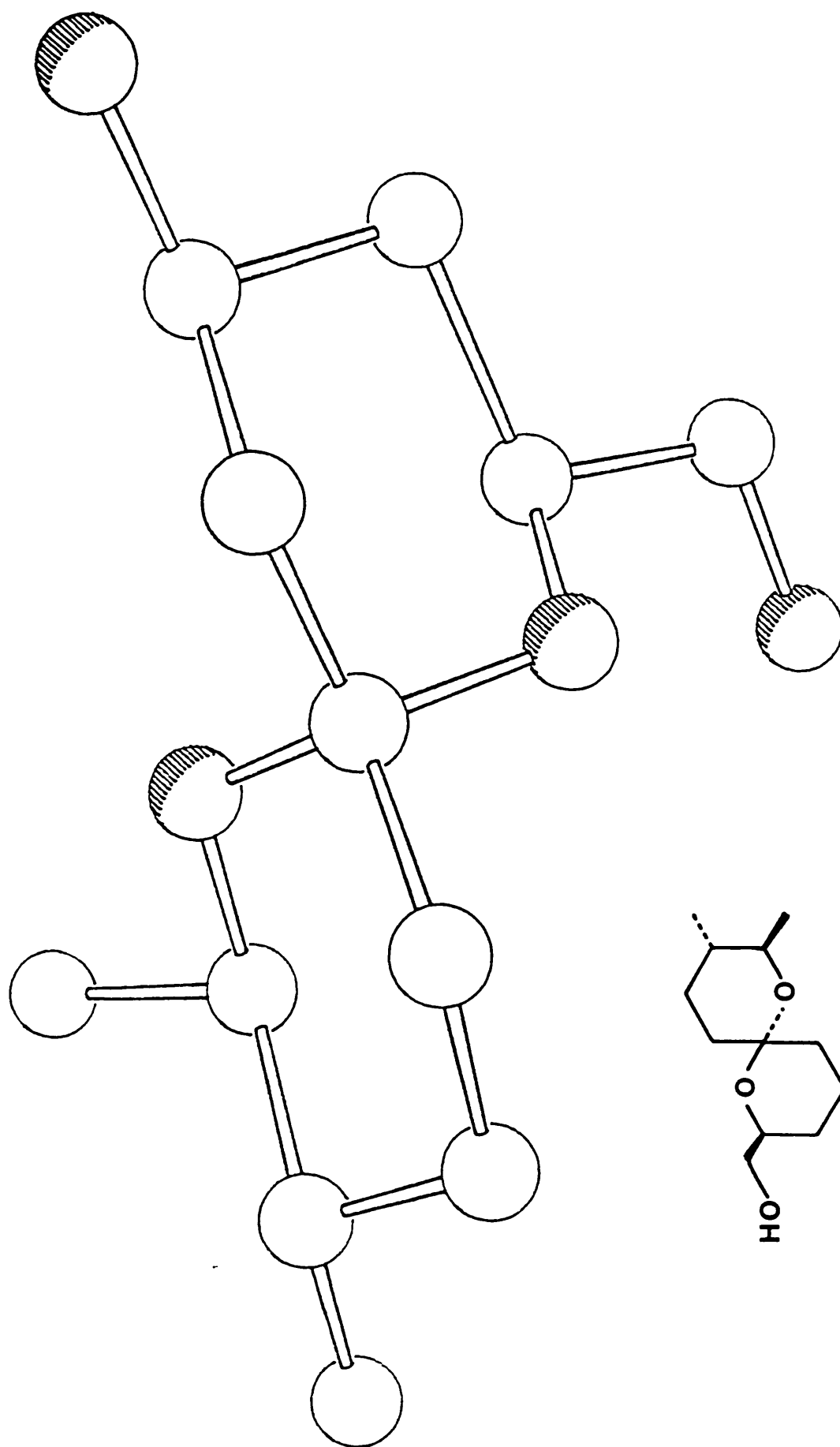
(δ 4.15) as observed in the other examples. A COSY spectrum of this material enabled a complete assignment of the ^1H nmr spectrum, showing the four protons on the carbons adjacent to oxygen had similar chemical shifts (H_1 , H_2 , δ 3.6 and H_8 δ 3.25). The equatorial protons H_5 and H_3 were distinct from the other ring protons, resonating further downfield by hyperconjugation. X- ray crystallography data confirmed the hydroxyl group was equatorial.

This provided a complimentary method to the Horner-Wittig method reported previously by our group, but with a much superior yield ²⁹.

The same strategy has now been applied by others in the group for the milbemycin northern hemisphere ³⁰.



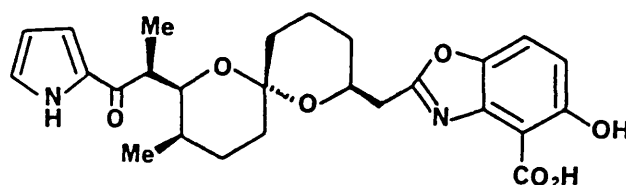




STUDIES TOWARDS THE SYNTHESIS OF CP-61,405

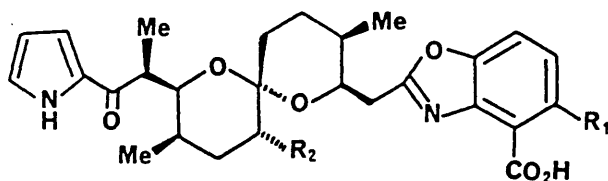
4.1 Introduction

CP-61,405 (Patent no. U.S. 4,547,523) was isolated by Pfizer in 1985 from the microorganism Streptomyces routienii (N 478-13). It is a new polyether antibiotic and used to control swine dysentery and to promote feed utilisation in swine and ruminants.



CP - 61, 405

Structurally, it is similar to Calcimycin³¹, (A-23187), the most well known compound in this class of pyrrole-ether ionophore antibiotics.



<u>R₁</u>	<u>R₂</u>	
NHMe	Me	A23187 (Calcimycin)
OH	H	X14885A
H	Me	Cezomycin

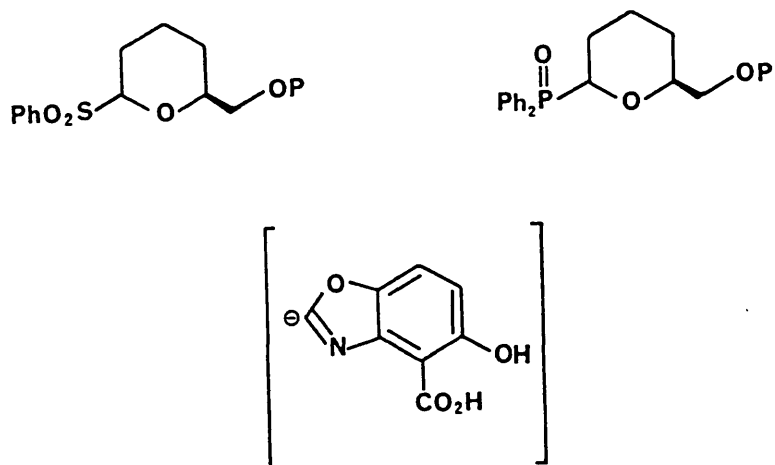
The structure consists of three basic units; the α - keto-pyrrole, a substituted benzoxazole and a 1,7- di-oxaspiro [5,5] undecane ring where the oxygen atoms are axial by the anomeric effect³² and the points of attachment of the rest of the molecular chain are equatorial.

The ends of the molecule are held in close proximity by hydrogen bonding between the pyrrole nitrogen atom and the carbonyl oxygen atoms on the benzoxazole.

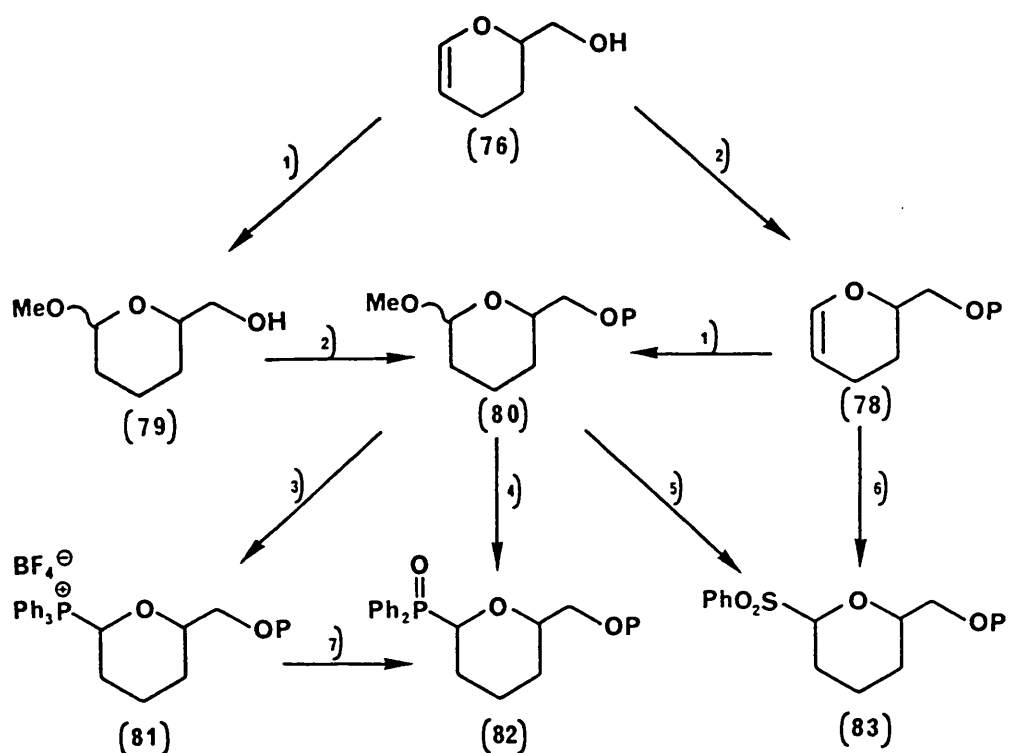
These compounds are specific for complexing and transporting divalent cations (Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+}).

Most syntheses of these type of compounds have made use of the basic units, coupling them together by known methodology. We proposed to use the sulphone or Horner-Wittig approach developed in our laboratories to construct the spiroketal moiety and couple the benzoxazole and pyrrole units by other chemistry previously developed in the group.

Sub- targets for the synthesis of CP-61,405



4.2 Model studies (Scheme 25)



- 1) MeOH, CSA. 2) *t*-BDPS-Cl, DMF, imidazole. 3) $\text{Ph}_3\text{P}^+\text{BF}_4^-$
 4) $\text{Ph}_2\text{P}(\text{O})\text{Cl}$, DCM 5) PhSO_2H , CaCl_2 . 6) PhSO_2H 7) NaOH .

P = *t*-BDPS

The commercially available 3,4-dihydro-2H-pyran-2-methanol (76) was treated with *t*-butyldimethylsilyl chloride to protect the free hydroxyl (77). This was a bad choice of protecting group as it was cleaved under the acidic conditions during methanolysis or sulphone formation. However, using *t*-butyldiphenylsilyl chloride instead, overcame this problem. Treatment of the enol ether (76) with acidic methanol

gave the methoxy compound (79), followed by protection of the primary hydroxyl with ^t-butyldiphenylsilyl chloride to give the desired compound (80). The protected enol ether (78) was also converted to (80), showing the reaction sequence was commutative.

The conversion of (80) to the phosphonium salt (81) by treatment with triphenylphosphonium hydrogen tetrafluoroborate gave a crystalline product in reasonable yield (70%). Nmr spectroscopic data indicated only one diastereoisomer was formed, presumably with both substituents being equatorial.

Saponification of the salt by refluxing in sodium hydroxide (3N) for 1h gave the phosphine oxide (82) in 85% yield. The product was very difficult to crystallise, nmr data suggesting two diastereoisomers were formed. The phosphine oxide (82) was also prepared by the Arbusov reaction ³. Treatment of the methoxy compound (80) with chlorodiphenylphosphine at 0°C gave the phosphine oxide (82) in 55% yield. The reaction was rather sluggish and recovery of starting material made the former route the method of preference.

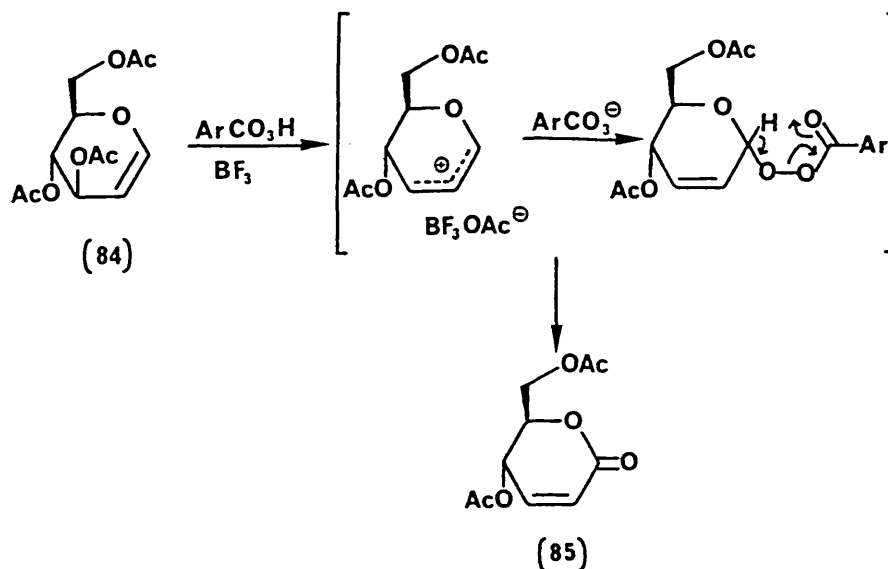
The sulphone (83) was prepared by treating the protected enol ether (78) or the methoxy derivative (80) with benzenesulphinic acid. The latter case proceeded very slowly, even with an excess of calcium chloride (used to absorb the methanol liberated). The sulphone was isolated as a sticky oil which failed to crystallise presumably owing to it being a mixture of two diastereoisomers.

Having prepared the model compounds it was now necessary to prepare the required chiral derivatives. A literature search showed the methoxy derivative (79) could be prepared in optically pure form by the Corey route ³³. Although this method was inelegant as it destroyed inherent chiral centres, the yields of the reaction steps were good and the starting material was cheap and readily available.

4.3 Synthesis of 6-methoxy-2-hydroxy, methyl tetrahydro- pyran (79)

Tri-O-acetyl-D-glucal (84) was oxidised to the corresponding lactone (85) by meta-chloroperbenzoic acid, catalysed by boron trifluoride ³⁴. In the presence of a Lewis acid catalyst an oxidative-elimination is observed. The boron trifluoride induces the removal of the allylic acetoxyl to form the allyl carboxonium ion which is prone to nucleophilic attack by the peroxyacid anion at the C-2 (Scheme 26).

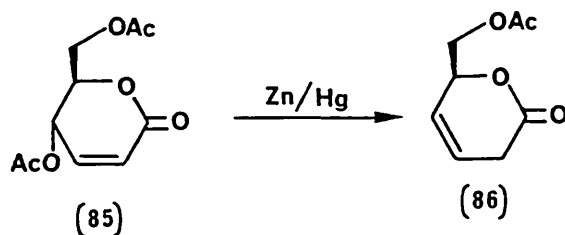
Scheme 26



The reaction proceeded in one pot and was complete within 30 mins in excellent yield (80%). Removal of the benzoic acid was best achieved by stirring the oil in a small volume of chloroform, the benzoic acid precipitated, and was filtered off.

Allylic acetates can be reductively cleaved by zinc amalgam with hydrochloric acid in ether ^{35,36}. The reaction proceeds to give exclusively the less stable isomer, that is the unconjugated position. It is assumed the reduction goes via an intermediate that behaves as an allylic metal halide which is protonated at the more substituted end of the allylic system (Scheme 27).

Scheme 27



The difficulty experienced by us with this reaction was the formation of over-reduced products, possibly due to radical formation as the reaction became "localised". Therefore, rapid stirring was essential to prevent accumulation of reactants in this heterogeneous system. Ultrasonification was not possible as the reaction temperature had to be maintained at 0°C. The optimum concentration of the hydrochloric acid in ethereal solution was 2.5-3M. Neutralisation of the

reaction after consumption of the starting material was essential, otherwise the residual acid and salts caused polymerisation of the product.

Although other methods of reduction were tried, (tin hydride, sodium borohydride and sodium amalgam) none gave the desired product (86). This step in the reaction sequence caused the most problems and was only successful on a small scale (66% on 1mmol scale).

On brief exposure to the base, diazobicyclo (5.4.0) undecane at room temperature, the double bond isomerised into conjugation with the carbonyl function (87).

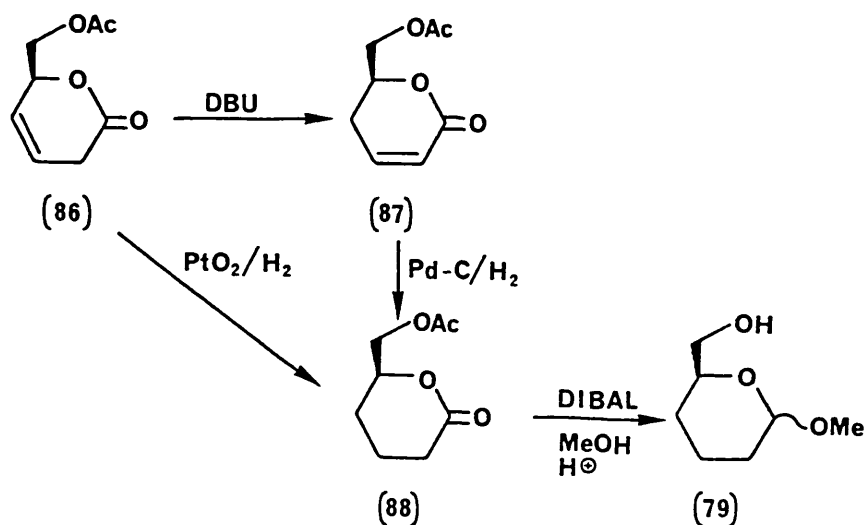
Palladium catalysed hydrogenation (1 atm- ethyl acetate) proceeded smoothly to give the lactone (88) in 55% yield.

Hydrogenation of the unconjugated lactone with Adams catalyst (1 atm- methanol) gave the lactone (88) directly ³⁷, ($[\alpha]_D^{20} = +78^{\circ}$ (c=1, CHCl₃)).

Treatment of the lactone (88) with two equivalents of diisobutylaluminium hydride (DIBAL) afforded removal of the acetoxy group and reduction of the lactone . The lactol was not isolated but converted to the methoxy compound (79) by immediate treatment with acidic methanol (Scheme 28).

Due to the difficulty of the reduction step, a new route to this chiral lactone using cyclopentanone and SAMP reagent ³⁸, (enantioselective reagent for forming carbon bonds) is to be studied. Also the ring opening of 1,6- anhydrohexopyranose ³⁹, with a suitable nucleophilic reagent is to be examined.

Scheme 28



4.4 Novel route to substituted aromatic compounds

(Scheme 29)

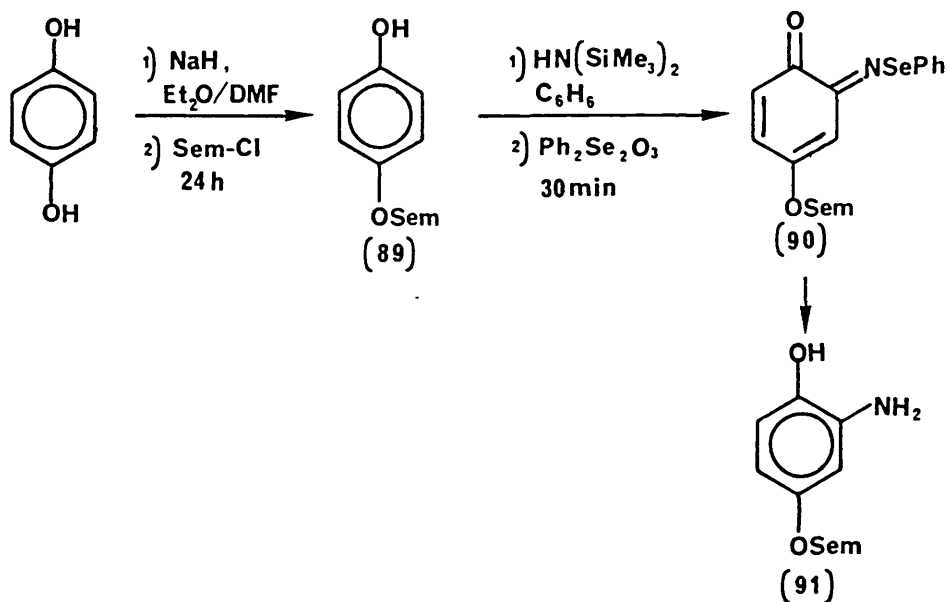
Attempts at the monoprotection of dihydroquinone with trimethylsilylethoxymethyl chloride⁴⁰ proved very poor under various conditions. However, further literature searching suggested a longer reaction time and excess of the protecting reagent were required⁴¹. Having optimised the conditions (NaH, ether/dimethyl formamide, room temperature, 24h), the monoprotected phenol (89) was obtained in 65% yield.

The reason for the choice of trimethylsilylethoxymethyl protection was twofold. Firstly, the pyrrole moiety of the natural product was to be protected by trimethylsilylethoxymethyl as this has been shown to enhance lithiation at the C-2 position⁴². Secondly, it was proposed to introduce the carboxylic acid on

the aromatic ring by ortho-lithiation,^{41,43} anticipating the choice of protection would coordinate with the lithiated intermediate, providing increased stabilisation. Finally, the protecting groups could be cleaved by lithium tetrafluoroborate⁴⁰ or anhydrous tetra-n-butylammonium fluoride,⁴⁴ at a latter stage in the synthesis.

The next step of the synthesis was to use some selenium chemistry which had been developed previously in the group⁴⁵. Treatment of the phenol (89) with hexamethyldisilazane and benzeneseleninic anhydride in benzene at room temperature gave the selenoimine (90) in 75% yield. The selenoimine was a dark red oil with the characteristic low infra-red stretch of the carbonyl at 1605cm^{-1} , attributed to some contribution of the cyclic selenoxazoline structure.

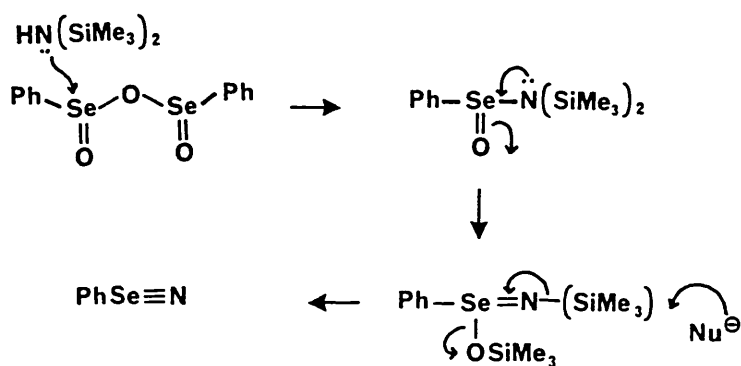
Scheme 29



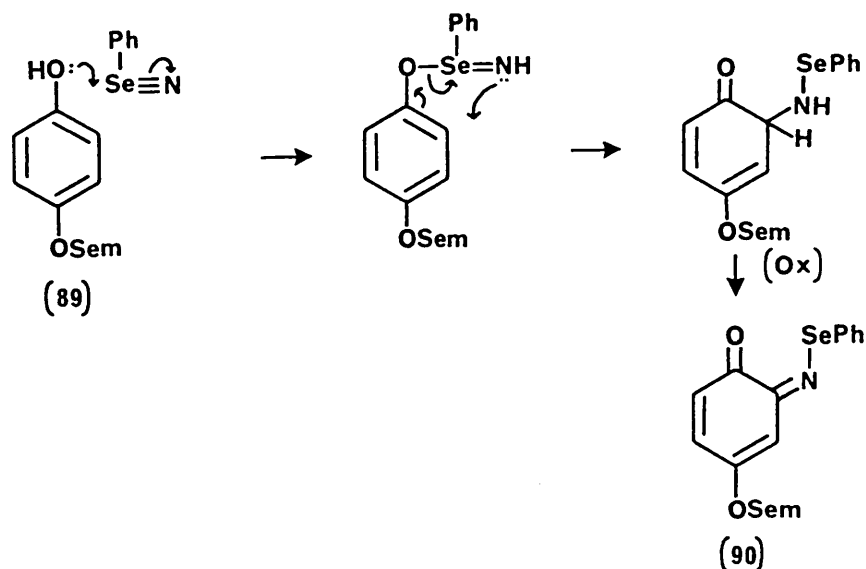
The high degree of ortho-selectivity observed during selenoimine formation suggested the mechanism involved initial reaction of the phenolic oxygen with a species in the reaction mixture, giving an intermediate which was capable of delivering functionality into the ortho-position.

The reactive species could possibly be generated from the reaction of the benzeneseleninic anhydride with hexamethyldisilazane (Scheme 30), which would then react with the phenol (Scheme 31). The selenium intermediate underwent a 2,3 sigmatropic shift (hence ortho-selectivity, then further oxidation to yield the selenoimine, (in this example in excellent 75% yield).

Scheme 30



Scheme 31



Reduction of the selenoimine to the aminophenol could be achieved by treating a benzene solution with thiophenol at room temperature for 5h. Unfortunately, these conditions also lead to the decomposition of the protecting group, giving a poor yield of the desired product, (91).

Attempts to reductively acetylate the selenoimine were equally unsuccessful.

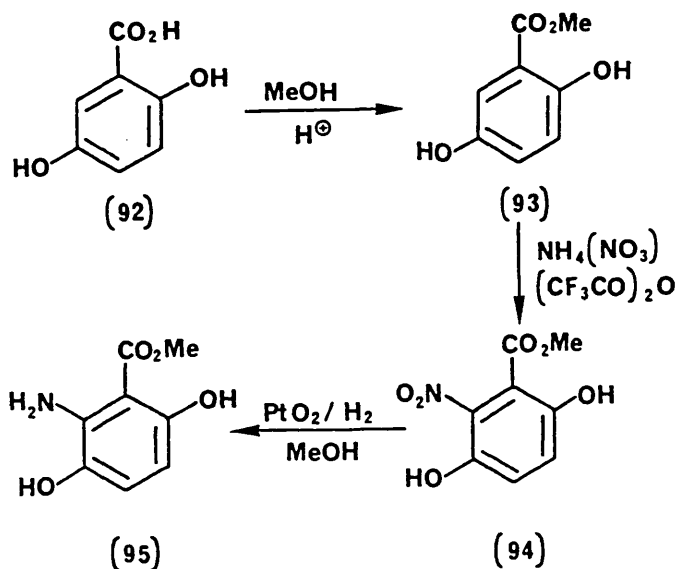
Preliminary attempts to deprotonate compound (89) proved sluggish with n-butyllithium in various solvents (ether, tetrahydrofuran, dimethoxyethane), but *t*-butyllithium proved too vigorous, cleaving the protecting group and effectively forming a trianion which was insoluble. In view of these unfavorable results and the difficulty in forming the aminophenol it was decided to abandon this approach.

4.5 Conventional route to substituted aromatic compounds

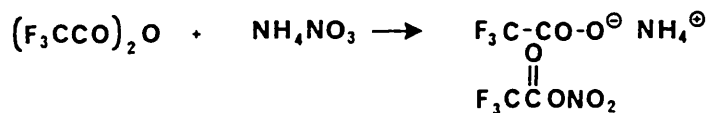
(Scheme 32)

The commercially available 2,5 dihydroxybenzoic acid (92) was converted to the methyl ester (93) by refluxing in acidic methanol. Nitration of activated aromatic systems requires some selectivity due to regioisomers and polysubstituted aromatics forming. Extensive substitution ortho to the ester was predicted by the activation at this position and possibly some stabilisation of the transition state by conjugation. The active species in classical nitration reagents (nitric acid/sulphuric acid) is the nitronium ion ($\text{NO}_2^{\oplus}$) and the nitric acidium ion ($\text{H}_2\text{O}-\text{NO}_2^{\oplus}$). Following the method of Evans et al.³¹, nitration (1eq. HNO_3 , ether, 25°C) gave a mixture of the regioisomers in the ratio 7:1 of the favoured isomer and were separated by chromatography. However, this reaction was not satisfactorily reproducible and an alternative method was sought. Many nitrating agents proved too vigorous, but the mild reagent of cupric nitrate with acetic anhydride was suitable⁴⁶. The active species was $\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{ONO}_2$, which reacted to give only the desired regioisomer. Removal of the acetic acid proved tedious and by using trifluoroacetic anhydride this was avoided. The yield was improved further by using ammonium nitrate (Scheme 33), where the active species was the trifluoroacetyl nitrate, which was a more powerful nitrating agent than acetyl nitrate⁴⁷.

Scheme 32



Scheme 33



The reaction was very fast and clean and the results reproducible.

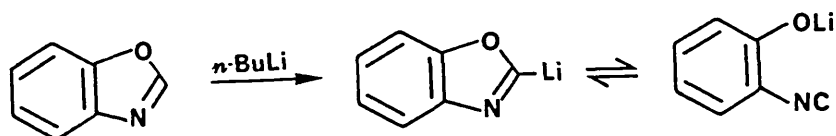
Hydrogenation of the nitro-compound (94) using platinum (IV) oxide as a catalyst gave the amino-phenol (95) in good yield (76%).

4.6 Benzoxazole formation

Attempted deprotonation at the C-2 position of benzoxazole with a variety of bases suggested this was not an efficient synthetic approach. Quenching the

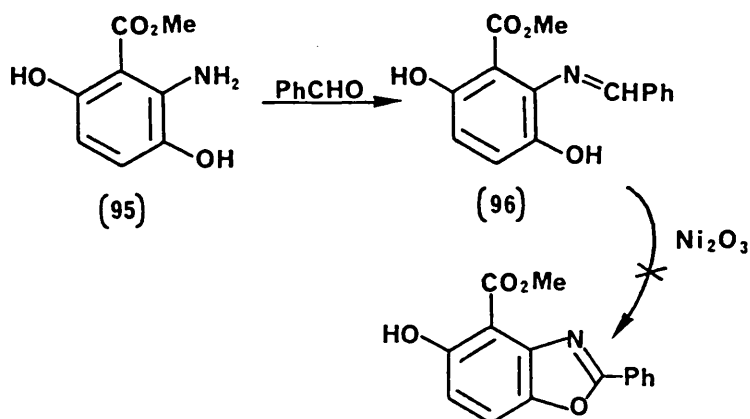
anion with deuterium oxide gave 38% recovered product with 70% deuterium incorporation (assigned by ^1H nmr data). The lithiation of an oxazole ring has been shown to give an equilibrium mixture of the C-2 anion and the open-chain isomer, the α -isocyano enolate ⁴⁸ (Scheme 34). There have been examples ⁴⁹ where the anion has been trapped and recycled but this procedure was not successful in our work.

Scheme 34



Schiff bases have been shown to cyclise to benzoxazoles in the presence of nickel peroxide at room temperature.⁵⁰ The model schiff base (96) was prepared by condensing the 2-aminophenol (95) with benzaldehyde and refluxing in ethanol for 6h. The reaction did not go to completion but some of the desired compound was recovered, confirmed by the characteristic resonance of the imine proton in the nmr at δ 8.5ppm, and was subjected to nickel peroxide. Unfortunately, the desired benzoxazole (Scheme 35) was not formed, a complex mixture of products were recovered. Obviously, the donation of a second electron to this system was more facile than the cyclisation.

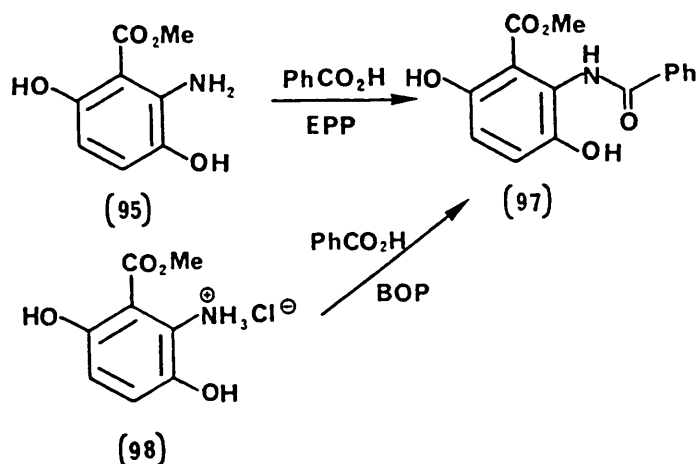
Scheme 35



Polyphosphate esters⁵¹ have also been used in the synthesis of 2-substituted benzoxazole by activating the carboxylic acid sufficiently so it couples with the 2-aminophenol⁵².

The 2-aminophenol (95) and benzoic acid were dissolved in chloroform with polyphosphate ester and refluxed. The intermediate amide (97) was isolated (Scheme 36), but seemed reluctant to cyclise, even after prolonged heating with 1-propanephosphonic acid cyclic anhydride.

Scheme 36



A novel reagent, requiring mild conditions that has been used in peptide coupling ~~reagent~~, is benzotriazolyl oxytris (dimethylamino) phosphonium hexafluorophosphate (BOP) ⁵³. Preparation of methyl-3,6- dihydroxy-anthranilate hydrochloride (98) by treating the aminophenol (95) with an ethereal solution saturated with anhydrous hydrogen chloride, and subsequent coupling of benzoic acid in the presence of BOP gave the intermediate amide (97) ⁵⁴. This was expected to cyclise to the benzoxazole by treating with ethyl polyphosphate, but as previously this proved impossible. Although this milder route is probably desirable in many peptide couplings, the former coupling with ethyl polyphosphate in this instance proved suitable for this reaction system, thereby eliminating one step - the preparation of the hydrochloride.

The reluctance of the amide(97) to cyclise could be due to some interactions of the free hydroxyl, and hopefully if it is protected this step will succeed.

4.7 Studies directed towards the other portion of the molecule⁵⁵

The target was to make the suitable chiral portion which would couple with the 2-benzenesulphonyl tetrahydropyran derivative or the corresponding phosphonium salt or phosphine oxide and then spirocyclise. This portion also had to incorporate suitable functionality for the subsequent addition of the SEM-pyrrole group.

Initially, a route starting with (R)-(-)-3-hydroxy-2-methylpropionate was chosen, involving a cycloaddition and Baeyer-Villiger reaction, finally opening the resulting lactone to give the required acyclic portion. However, racemization problems on a large scale and difficulty in separation led to the abandonment of this route in favour of another starting from (R)-(-)-citronellene.

The second route was shorter and used the resident chirality to control the formation of the other stereocentres via an aldol condensation.

At the present time studies on the aldol condensation are in progress.

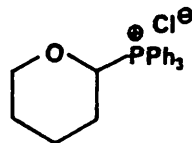
EXPERIMENTAL

^1H NMR spectra were obtained on Bruker WH-400, Bruker WH-250, Jeol FX-90Q and Varian EM-360A spectrometers in deuteriochloroform solutions with tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained on Jeol FX-90Q. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as liquid films or chloroform solutions. Mass spectra were obtained on a VG Micromass 7070B instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected.

Column chromatography was performed on MN-silica gel 60 (230-400 mesh) or BDH florisil (200-300 U.S. mesh), under pressure. Analytical thin layer chromatography was performed on precoated aluminium or glass backed plates (Merck silica 60 F₂₅₄).

Petrol refers to petroleum ether (bp 40-60°C) and was redistilled before use. Ether refers to diethyl ether and was dried by reflux over sodium/benzophenone and distilled before use, as were dimethoxyethane and tetrahydrofuran. Dichloromethane was dried by reflux over phosphorous pentoxide and distilled before use. Dimethylformamide was dried over 4Å molecular sieves and distilled under reduced pressure before use. All other reagents were purified by usual methods. Solutions were dried over anhydrous sodium sulphate or magnesium sulphate.

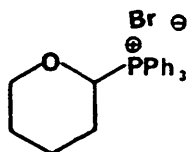
Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1)



3,4-Dihydro-2H-pyran (40.0g, 0.48mol) was added dropwise to a solution of triphenylphosphine (120g, 0.46mol) in dry benzene (1L), and dry hydrogen chloride bubbled through the resulting solution at room temperature for 5h.

The solvent was removed under reduced pressure to give a solid, which was semi-purified by recrystallisation from dichloromethane-ethyl acetate, to give tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (158g, 90%) as a white amorphous solid, mp 113-116°C. IR (CHCl₃) 3369, 1439, 1113, 691 cm⁻¹; NMR δ (90MHz): 8.95 (3.5H, br.s. impurity), 8.00-7.55 (15H, m, ArH), 6.15-5.85 (1H, m, H₂), 4.20-3.80 (2H, m, H₆), 2.20-1.50 (6H, m); m/z (no M⁺), 85.

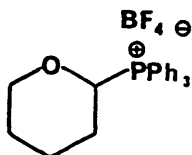
Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium bromide (2)



3,4-Dihydro-2H-pyran (27.0g, 0.32mol) was added dropwise to a solution of triphenylphosphine (83.8g, 0.32mol) in dry benzene (350 ml). Dry hydrogen bromide was bubbled through

the resulting solution at room temperature for 5h. The solvent was removed under reduced pressure and the product recrystallised from dichloromethane-ether to give tetrahydro-2H-pyran-2-yl triphenylphosphonium bromide (2) (109g, 80%) as a white crystalline solid, mp 173-175°C. IR (CHCl₃) 3396, 1438, 1112, 692 cm⁻¹; NMR δ (90MHz): 8.15-7.60 (15H,m,ArH), 6.65-6.40 (1H,m,H₂), 4.40-3.90 (2H,m,H₆), 2.50-1.50 (6H,m); m/z (FAB) 347 (M⁺), 263, 85, 57, 43. (Found: C, 64.44; H, 5.68; Br, 18.79; P, 6.83. C₂₃H₂₄BrOP requires C, 64.65; H 5.06; Br, 18.70; P, 7.25%).

Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3)



2-Methoxy tetrahydropyran (0.50g, 4.3mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.50g, 4.3mmol) in dry acetonitrile (5ml) at room temperature under argon, and stirred for 4h. Removal of the solvent under reduced pressure gave tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3) (1.78g, 96%) as a white crystalline solid, mp 171-173°C; IR (CHCl₃) 1321, 1056, 690 cm⁻¹; NMR δ (90MHz): 7.76 (15H,m,ArH), 5.61 (1H,m,H₂) 4.05 (2H,m,H₆), 2.10-1.50 (6H,m); m/z (FAB) 347 (M⁺), 263, 85, 43. (Found: C, 63.51; H, 5.50; P, 7.57; C₂₃H₂₄BF₄OP requires C, 63.62; H, 5.57; P, 7.13%).

General procedure for the Wittig reaction of
Tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1)

The phosphonium salt (1) was dissolved in dry tetrahydrofuran (10ml per mmol) under argon, cooled to -10°C and n-butyllithium (1.1 eq) added dropwise. The anion was stirred for 0.5h at -10°C , then a tetrahydrofuran solution of the aldehyde added and the solution warmed to room temperature. It was poured into saturated aqueous sodium chloride solution, extracted with ether (3x10 ml), dried and evaporated to give the crude product which was purified by Kugelrohr distillation.

Wittig reaction of (1) with Benzaldehyde

Following the general procedure, the anion of (1) (0.65g, 2mmol) was condensed with benzaldehyde (0.204ml, 2mmol). Distillation gave (14) (84mg, 24%) as a mixture of three alkene isomers, bp 110°C at 0.3mm Hg; IR (film) 2925, 1645, 1048, 694 cm^{-1} ; NMR δ (90MHz): 7.60-6.95 (5H,m,ArH), 5.98 (0.5H,s,C=CHPh, E-isomer), 5.27 (0.25H,s,C=CHPh, Z-isomer), 4.41 (0.25H,t,J=4Hz,C=CHPh, endo-isomer), 3.87 (2H,m,OCH₂), 3.25 (0.5H,s,CH₂Ph, endo), 2.60-1.55 (5.5H,m); m/z 174 (M^+), 91,90,83. (Found: C, 82.66; H, 8.31; C₁₂H₁₄O requires C, 82.72; H, 8.10%).

Wittig reaction of (1) with Dodecanal

Following the general procedure, the anion of (1) (0.65g, 2mmol) was condensed with dodecanal (0.442ml, 2mmol). Distillation gave (15) (25mg, 5%) as a mixture of three alkene isomers, bp 120°C at 0.1mm Hg. IR (film) 2925, 2854, 1677, 1069, 1047 cm^{-1} ; NMR δ (250MHz): 4.84 (0.5H, t, $J=8.3\text{Hz}$, C=CH, E-isomer), 4.41 (0.33H, t, $J=8.3\text{Hz}$, C=CH, Z-isomer), 4.05 (0.16H, t, $J=6.25\text{Hz}$, C=CH, endo-isomer), 3.85 (2H, m, OCH_2), 2.21 (0.32H, m, CH_2 endo), 1.65-1.55 (6H, m), 1.36-1.12 (23H, m); m/z 252 (M^+), 167, 85, 55. (Found M^+ 252.2448, $\text{C}_{17}\text{H}_{32}\text{O}$ requires 252.2453).

Wittig reaction of (1) with Furfural

Following the general procedure, the anion of (1) (0.32g, 1mmol) was condensed with furfural (0.083ml, 1mmol). Distillation gave (16) (19.6mg, 12%) as a mixture of three alkene isomers, bp 90°C at 0.08mm Hg. IR (film) 2943, 1663, 1493, 1051 cm^{-1} ; NMR δ (250MHz): 7.35 (1H, m, H_2), 6.32 (1H, m, H_4), 6.15 (1H, m, H_3), 5.85 (0.5H, s, C=CH, E-isomer), 5.45 (0.3H, s, C=CH, Z-isomer), 4.60 (0.2H, m, C=CH, endo-isomer), 4.0 (2H, m, OCH_2), 2.91 (0.4H, m, CH_2 endo), 1.98-1.72 (5.6H, m); m/z 164 (M^+), 85, 81, 55. (Found M^+ 164.0831, $\text{C}_{10}\text{H}_{12}\text{O}_2$ requires 164.0837).

General procedure for the Wittig reaction of Tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3)

The phosphonium salt (3) was dissolved in dry tetrahydrofuran under argon, cooled to -78°C and n-butyllithium (1.1eq) added dropwise. The anion was stirred for 1h at -78°C , then a tetrahydrofuran solution of the aldehyde added and the solution warmed to room temperature over 2h. It was poured into saturated aqueous sodium chloride solution, extracted with ether (3x10ml), dried and evaporated to give the crude product which was purified by Kugelrohr distillation.

Wittig Reaction of (3) with Benzaldehyde

Following the general procedure, the anion of (3) (0.87g, 2mmol) was condensed with benzaldehyde (0.204ml, 2mmol). Distillation gave (14) (280mg, 79%) as a colourless oil identical to that prepared above.

Wittig Reaction of (3) with Dodecanal

Following the general procedure, the anion of (3) (0.87g, 2mmol) was condensed with dodecanal (0.442ml, 2mmol). Distillation gave (15) (203mg, 40%) as a colourless oil, identical to that prepared previously.

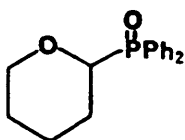
Wittig Reaction of (3) with Furfural

Following the general procedure, the anion of (3) (0.87g, 2mmol) was condensed with furfural (0.166ml, 2mmol). Distillation gave (16) (201mg, 60%) as a colourless oil, identical to that prepared previously.

Wittig Reaction of (3) with 3-Pyridinecarboxaldehyde

Following the general procedure, the anion of (3) (0.87g, 2mmol) was condensed with 3-pyridinecarboxaldehyde (0.188ml, 2mmol). Distillation gave (17) (140mg, 41%) as a mixture of three alkene isomers, bp 90°C at 0.03mm Hg. IR(film) 2927, 1673, 1061, 1047 cm^{-1} ; NMR δ (250MHz): 8.41 (1.6H,m, O-Pyr, endo-isomer), 8.22(0.4H,m,O-Pyr, E-isomer), 7.91 (1H, m,m-Pyr), 5.23 (0.4H,s,C=CH, E-isomer), 4.41(0.6H,t,J=11Hz, C=CH, endo-isomer), 3.95-3.87 (2H,m,OCH₂), 3.2 (1.2H,s,CH₂ endo), 2.3-1.72 (4.8H,m); m/z 175 (M⁺), 91, 85, 55, (Found M⁺ 175. 0994, C₁₁H₁₃NO requires 175.0997).

Preparation of Tetrahydro-2H-pyran-2-yl diphenylphosphine oxide (4)



Phosphonium salt (1) (36.3g, 95mmol) was dissolved in 3N aqueous sodium hydroxide (180ml, 540mmol) and the resulting solution heated under reflux for 30min. After cooling to room temperature, the mixture was extracted with chloroform (3x100ml) and the organic extracts dried and evaporated, to give a solid which was recrystallised from dichloromethane ethyl acetate to give tetrahydro-2H-pyran-2-yl diphenylphosphine oxide (4) (23.0g, 85%) as a white crystalline

solid, mp 154°C. IR(CHCl₃) 2939, 1437, 1183, 696 cm⁻¹;
NMR δ (90MHz): 8.10-7.70 (4H,m,ArH), 7.60-7.20 (6H,m,ArH),
4.40-3.90 (2H,m), 3.60-3.25 (1H,m), 2.15-1.30(6H,m);m/z (no
M⁺) 203, 202, 201, 155, 85, 77, 47. (Found: C,71.13; H,
6.70; P, 10.55; C₁₇H₁₉O₂P requires C,71.32; H, 6.69; P,
10.82%).

General procedure for the Horner-Wittig Reaction of
Tetrahydro-2H-pyran-2yl diphenylphosphine oxide.(4)

The phosphine oxide was dissolved in dry tetrahydrofuran under argon and added to a stirred solution of lithium diisopropyl-amide (from diisopropylamine (1.1eq) and n-butyllithium (1.1eq)) at -78°C in tetrahydrofuran under argon. The anion was stirred for 1h at -78°C, then a tetrahydrofuran solution of the aldehyde or lactol was added and the mixture warmed to room temperature. It was poured into saturated aqueous ammonium chloride solution, extracted with chloroform (3x10ml), dried and evaporated to give the crude adduct. This was dissolved in dry tetrahydrofuran and a solution of potassium t-butoxide (1eq) in tetrahydrofuran added dropwise. The resulting mixture was stirred at room temperature under argon for 1h, the solvent removed, the residue extracted with ether, filtered and evaporated under reduced pressure to give the crude product which was purified by Kugelrohr distillation.

Horner-Wittig Reaction of (4) with Dodecanal

Using the general procedure the anion of (4) (0.286g, 1mmol) was condensed with dodecanal (0.221ml, 1mmol). Distillation gave (15) (0.178g, 71%) as a colourless oil, identical to that prepared previously.

Horner-Wittig Reaction of (4) with Benzaldehyde

Using the general procedure, the anion of (4) (0.286g, 1mmol) was condensed with benzaldehyde (0.102ml, 1mmol). Distillation gave (14) (132mg, 76%) as a colourless oil, identical to that prepared previously.

Horner-Wittig Reaction of (4) with Cyclohexanecarboxaldehyde

Using the general procedure, the anion of (4) (0.286g, 1mmol) was condensed with cyclohexanecarboxaldehyde (0.121ml, 1mmol). Distillation gave (18) (0.122g, 68%) as a mixture of three alkene isomers, bp 90°C at 0.1mmHg. IR (film) 2925, 2850, 1676, 1076, 1048cm⁻¹; NMR δ (250MHz): 4.74 (0.45H, d, J=8.9Hz, C=CH, E-isomer), 4.28 (0.3H, t, J=8.9Hz, C=CH Z-isomer), 3.92 (0.25H, dd, J=5.3, 3.57Hz, C=CH, endo isomer), 3.82, (2H, m, OCH₂), 2.21 (0.5, H, m, CH₂ endo), 2.05 (0.75H, m), 1.68-1.49(16.25H, m, cyclic); m/z 180 (M⁺), 137, 96, 85, 83 and 55. (Found M⁺ 180.1511, C₁₂H₂₀O requires 180.1514).

Horner-Wittig Reaction of (4) with Cinnamylaldehyde

By the general procedure, the anion of (4) (0.286g, 1mmol) was condensed with cinnamylaldehyde (0.126ml, 1mmol).

Distillation gave (19) (0.156g, 78%) as a mixture of six isomers, bp 130°C at 0.08mm Hg. IR (film) 2947, 1643, 1594, 1273, 1044 cm^{-1} ; NMR δ (250MHz): 7.55-7.07 (5H, m, ArH), 6.72-6.58, 6.45-5.82, 5.25, 4.35 (3H, m, C=CH), 3.87-3.72 (2H, m, OCH_2), 2.56-2.22, 1.87-1.54 (6H, m); m/z 200 (M^+), 116, 85, 77, 55. (Found M^+ 200.1207, $\text{C}_{14}\text{H}_{16}\text{O}$ requires 200.1201).

Horner-Wittig Reaction of (4) with Phenylacetaldehyde

By the general procedure, the anion of (4) (0.286g, 1mmol) was condensed with phenylacetaldehyde (0.120g, 1mmol). Distillation gave (20) (0.127g, 68%) as a mixture of three isomers, bp 60°C at 0.005mm Hg. IR (film) 2939, 2867, 1676, 1087, 1045 cm^{-1} ; NMR δ (250MHz): 7.28-7.15 (5H, m, ArH), 5.15 (0.4H, t, $J=9.1\text{Hz}$, C=CH, E-isomer), 4.64 (0.4H, t, $J=9.1\text{Hz}$, C=CH, Z-isomer), 4.45 (0.2H, m, C=CH, endo-isomer), 3.85 (2H, m, OCH_2), 2.35-2.15 (2.4H, m, $-\text{CH}_2-\text{E}$, Z and endo-isomer), 1.85-1.7 (5.6H, m); m/z 188 (M^+), 104, 97, 91, 55. (Found M^+ 188.1203, $\text{C}_{13}\text{H}_{16}\text{O}$ requires 188.1201).

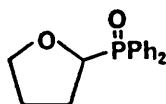
Horner-Wittig Reaction of (4) with Furfural

By the general procedure the anion of (4) (0.286g, 1mmol) was condensed with furfural (0.083ml, 1mmol). Distillation gave (16) (0.067g, 41%) as a colourless oil, identical to that prepared previously.

Horner-Wittig Reaction of (4) with 3-Pyridinecarboxaldehyde

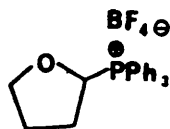
By the general procedure, the anion of (4) (0.286g, 1mmol) was condensed with 3-pyridinecarboxaldehyde (0.094ml, 1mmol). Distillation gave (17) (0.112g, 64%) as a colourless oil, identical to that prepared previously.

Preparation of Tetrahydrofuran-2-yl diphenylphosphine oxide (9)



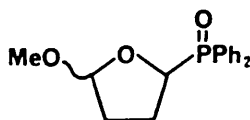
The phosphonium salt (prepared by bubbling hydrogen chloride through a solution of triphenylphosphine and 3,4 dihydrofuran in benzene) (10.0g, 27mmol) was dissolved in 3N aqueous sodium hydroxide solution (60ml, 180mmol) and the solution refluxed for 30 min. After cooling to room temperature, the mixture was extracted into chloroform (3x50ml) and the organic layers dried and evaporated to leave a solid which was recrystallised from dichloromethane-ethyl acetate to give tetrahydrofuran-2-yl diphenylphosphine oxide (9) (6.1g, 82%) as a white amorphous solid, mp 115°C. IR (CHCl₃) 1437, 1120, 697 cm⁻¹; NMR δ (90MHz): 8.10-7.70 (4H, m, ArH), 7.60-7.20 (6H, m, ArH), 4.70 (1H, q, J=7 Hz, H₂), 4.00-3.50 (2H, m), 2.45-1.50 (4H, m); m/z (no M⁺), 202, 155, 77, 71, 43. (Found: C, 70.50; H, 6.31; P, 11.30; C₁₆H₁₇O₂P requires C, 70.56; H, 6.29; P, 11.38%).

Preparation of Tetrahydrofuran-2-yl triphenylphosphonium tetrafluoroborate (7)



2-Methoxy-tetrahydrofuran(0.51g, 5mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.75g, 5mmol) in dry acetonitrile (10ml) at room temperature under argon and stirred for 4h. Removal of the solvent under reduced pressure gave tetrahydrofuran-2-yl triphenylphosphonium tetrafluoroborate (7) (1.89g, 88%) as a white crystalline solid, mp 130°C. IR (CHCl₃) 1438, 1287, 1052, 665 cm⁻¹; NMR δ (250MHz): 7.85-7.6 (15H, m, ArH), 5.85 (1H, dt, J=11.5, 8.6Hz H₂), 3.95 (1H, m, H₅), 3.55 (1H, m, H₅), 2.87 (1H, m), 2.18-1.95 (2H, m), 1.65 (1H, m); m/z (no M⁺), 333, 71. (Found: C, 62.67; H, 5.37; C₂₂H₂₂BF₄OP requires C, 62.88; H, 5.27%).

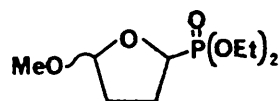
Preparation of 5-Methoxy tetrahydrofuran-2-yl diphenylphosphine oxide (11)



Chlorodiphenylphosphine (1.795ml, 10mmol) was added dropwise to a solution of 2,5-dimethoxy tetrahydrofuran (1.295ml, 10mmol) at 0°C in dry dichloromethane (3ml) under argon. The reaction was left to warm to room temperature and stirred for 12h. The solvent was removed under reduced pressure to give an oil which could be purified by dissolving in toluene and trituration of the solution with petroleum ether giving 5-methoxy tetrahydrofuran-2-yl diphenylphosphine oxide (11)

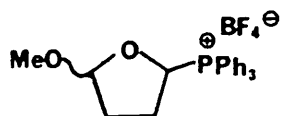
(2.02g, 67%) as a white amorphous solid, mp 98°C . IR (CHCl_3) 2862, 1442, 1298 cm^{-1} ; NMR δ (250MHz): 7.85 (4H, m, ArH), 7.50 (6H, m, ArH), 5.05 (1H, d, $J=6.25\text{Hz}$, H_5), 4.9 (1H, br.q, $J=8.3\text{Hz}$, H_2), 3.35 and 3.10 (3H, s, OMe), 2.5-1.5 (4H, m); m/z 302 (M^+), 202, 101. (Found: C, 67.27; H, 6.26; $\text{C}_9\text{H}_{18}\text{O}_5\text{P}$ requires C, 67.54; H, 6.26%).

Preparation of 5-Methoxytetrahydrofuran-2-yl diethoxyphosphine oxide (21)



Diethylchlorophosphite (0.714ml, 5mmol) was added dropwise to a stirred solution of 2,5-dimethoxy tetrahydrofuran (0.65ml, 5mmol) at 0°C in dichloromethane under argon. The solution was stirred for 12h at room temperature, concentrated and purified by Kugelrohr distillation to give (21) (0.475g, 48%) as a colourless oil, bp 120°C at 0.03mm Hg. IR (film) 2862, 1252 and 1032 cm^{-1} ; NMR δ (250MHz): 5.1 (1H, dd, $J=4.2\text{Hz}$, 16.6Hz, H_5), 4.32-4.20 (5H, m, OCH_2 , H_2), 3.3 (3H, d, $J=4.2\text{Hz}$ OMe), 2.3-1.9 (4H, m), 1.3 (6H, t, $J=6.94\text{Hz}$, Me); m/z 237 (M^+) 207, 138 and 101. (Found: C, 45.41; H, 7.97; $\text{C}_9\text{H}_{18}\text{O}_5\text{P}$ requires C, 45.57; H, 7.65%).

Preparation of 5-Methoxy-tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (22)



2,5-dimethoxytetrahydrofuran (0.648ml, 5mmol) was added to triphenylphosphonium tetrafluoroborate (1.75g, 5mmol) in dry acetonitrile (10ml) at room temperature under argon and stirred for 4h. Removal of the solvent under reduced pressure yielded 5-methoxy-tetrahydro-2H-furan-2-yl-triphenylphosphonium tetrafluoroborate (22) (1.57g, 68%) as a white amorphous solid, mp 50°C. IR (CHCl₃) 2839, 1438, 1286, 1063, 665 cm⁻¹; NMR δ (250MHz): 7.85-7.6 (15H, m, ArH), 6.05-5.85 (1H, m, H₂), 5.05 (1H, m, H₅), 3.35 (1.5H, s, OMe) 2.80 (1.5H, s, OMe), 2.30-1.75 (4H, m); m/z (no M⁺) 363, 101. (Found: C, 61.35; H, 5.43; C₂₃H₂₄BF₄O₂P requires C, 61.35; H, 5.37%).

Horner-Wittig Reaction of (9) with Benzaldehyde

Using the general procedure the anion of (9) (0.271g, 1mmol) was condensed with benzaldehyde (0.102ml, 1mmol) and the resulting solution stirred at room temperature for 15h. Distillation gave (23) (86.5mg, 54%) as a mixture of alkene isomers, bp 80°C at 0.02mm Hg. IR (film) 3023, 2926, 1672, 1595, 1077, 1028cm⁻¹; NMR δ (250MHz): 7.55-7.20 (5H, m, ArH), 5.23 (0.33H, s, C=CH E or Z isomer) 4.65 (0.67H, m, C=CH endo isomer), 3.90-3.75 (2H, m, OCH₂) 2.05-1.70 (4H, m); m/z 160 (M⁺), 91, 77, 71. (Found M⁺ 160.0887, C₁₁H₁₂O requires 160.0888).

Horner-Wittig Reaction of (11) with Benzaldehyde

Using the general procedure, the anion of (11) (0.302g,

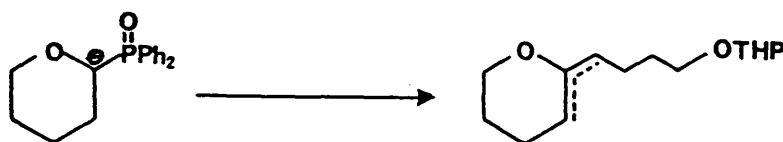
1mmol) was condensed with benzaldehyde (0.102ml, 1mmol) and stirred at room temperature for 15h. Distillation gave (24) (115mg, 60.5%) as a mixture of alkene isomers, bp 90°C at 0.02mm Hg. IR (film) 3383, 2926, 1674, 1599, 1025, 695cm⁻¹; NMR δ (250MHz) 7.55-7.20 (5H, m, ArH), 5.30 (0.5H, s, C=CH, E or Z-isomer), 4.72 (0.5H, m, C=CH, endo-isomer) 4.41 (1H, m, OCHOMe), 3.35 (3H, s, OMe), 2.0-1.65 (4H, m); m/z 190 (M⁺), 159, 91, 77, 71. (Found M⁺ 190.1002. C₁₂H₁₄O₂ requires 190.0994).

Horner-Wittig Reaction of (21) with Benzaldehyde

Using the general procedure, the anion of (21) (0.237g, 1mmol) was condensed with benzaldehyde (0.102ml, 1mmol) and stirred at room temperature for 15h. Distillation gave (24) (98mg, 51%) as a mixture of alkene isomers identical to those prepared above.

PREPARATION OF SPIROKETAL COMPOUNDS

Horner-Wittig Reaction of (4) with 4-((tetrahydro-2H-pyran-2-yl) oxy)-Butanal



Following the general procedure, the anion of (4) (1.40g, 4.9mmol) was condensed with 4-((tetrahydro-2H-pyran-2-yl) oxy) butanal (0.84g, 4.9mmol). Distillation gave 2-(4-

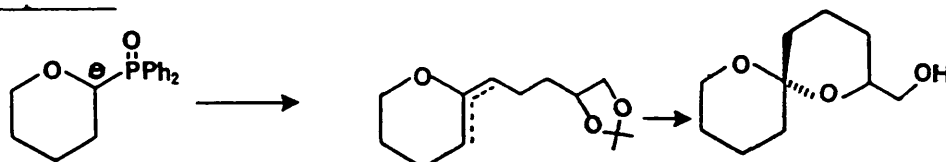
(tetrahydro-2H-pyran-2yl) oxy butan)-5, 6-dihydro-4H-pyran (25) (0.73g, 65%), bp 120°C at 0.04mm Hg .IR (film) 2938, 1675, 1114, 1050 cm^{-1} ; NMR δ (250MHz): 4.59 (1H, br.s.OCH₀), 4.08 (1H, t, J=6.5Hz, C=CH), 3.91-3.71 (4H, m), 3.57-3.37 (2H, m), 2.42 (1H, br.t), 1.99-1.25 (15H, m); m/z 240 (M^+), 155, 101, 98, 85, 55. (Found: C, 70.11; H, 10.17; $\text{C}_{14}\text{H}_{24}\text{O}_3$ requires C, 69.96; H, 10.07%).

Preparation of 1,7-dioxaspiro [5,5] undecane (26)



The compound (25) (0.49g, 2.0mmol) was dissolved in dry methanol (3ml) with camphor sulphonic acid and stirred at room temperature for 5h. Removal of solvent under reduced pressure followed by Kugelrohr distillation of the crude product gave 1,7-dioxaspiro [5,5] undecane (26) (0.29g, 93%) as a colourless oil, bp 100°C at 28mm Hg. IR (film) 2940, 1171, 1045, 984 cm^{-1} ; NMR δ (250MHz): 3.77-3.55 (4H, m, OCH₂), 1.95-1.73 (2H, m) and 1.68-1.36 (10H, m); m/z 156 (M^+), 101, 100, 98, 83, 55, 41 and was identical to the natural product.

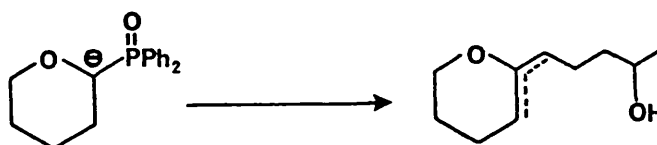
Horner-Wittig Reaction of (4) with 4,5-isopropylidene, 4,5-dihydroxy, pentanal



Following the general procedure, the anion of (4) (0.36g, 1.25mmol) was condensed with the aldehyde (26) (0.198g, 1.25 mmol). Distillation gave the enol ether (27) (183mg, 65%)

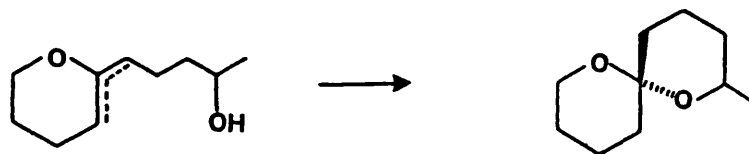
which was converted directly to the spiroketal by treatment with camphor-sulphonic acid (2mg) in methanol (5ml) and stirred for 5h at room temperature. The solvent was evaporated and the residue was purified by chromatography (ether-petrol) to give (E)-2-hydroxymethyl-1,7-dioxaspiro [5.5] undecane (28) (70mg, 61%) as a colourless oil. IR (film) 3430, 2930, 1045, 990 cm^{-1} ; NMR δ (250MHz): 3.82-3.47 (5H, m), 2.21 (1H, br.s OH), 1.99-1.74 (2H, m), 1.69-1.18 (10H, m); m/z 186 (M^+), 155, 111, 101, 55. (Found: C, 64.49; H, 9.68; $\text{C}_{10}\text{H}_{18}\text{O}_3$ requires C, 64.34; H, 9.94%).

Horner-Wittig Reaction of (4) with 2-hydroxy, 5-methyl tetrahydrofuran



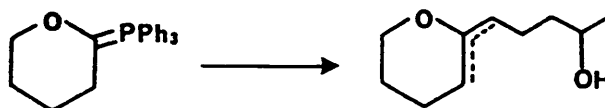
Following the general procedure, the anion of 2-hydroxy, 5-methyl-tetrahydrofuran (0.102g, 1mmol) (generated from n-butyllithium at 0°C in tetrahydrofuran) was added to a solution of the anion of (4) (0.286g, 1mmol). Purification by Kugelrohr distillation gave the enol ethers (29) (0.101mg, 58.5%) as a colourless oil and mixture of isomers, bp 100°C at 0.005 mm Hg. IR (film) 3358, 2931, 1679, 1066 cm^{-1} ; NMR δ (90 MHz): 4.88 (0.3H, t, J=8Hz, C=CH, Z-isomer), 4.42 (0.7H, t, J=7Hz, C=CH, endo-isomer), 4.10-3.50 (3H, m, OCH_2), 2.40-1.10 (14H, m); m/z 170 (M^+), 111, 98, 85, 55. (Found M^+ 170.1305, $\text{C}_{10}\text{H}_{18}\text{O}_2$ requires 170.1307).

Preparation of 2-methyl-1,7-dioxaspiro [5,5] undecane (30)



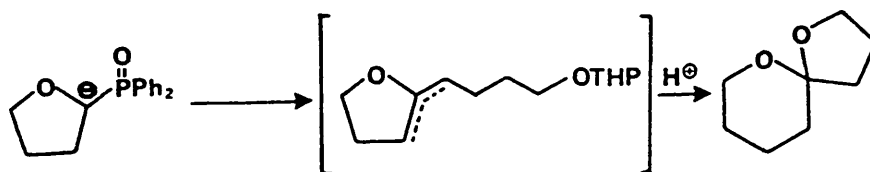
The compound (29) (138mg, 0.81mmol) was dissolved in dry methanol (5ml) with a catalytic amount of camphor sulphonic acid and the resulting solution stirred overnight. The solution was filtered through a silica pad and evaporated under reduced pressure to give (30) (113mg, 82%) as a colourless oil. IR (film) 2932, 1058cm⁻¹. NMR δ (90MHz): 3.8-3.55 (3H, m, OCH₂), 1.92-1.35 (12H, m), 1.15 (3H, d, J=6.3Hz, Me). m/z 170 (M⁺), 101, 85. (Found M⁺ 170.1303, C₁₀H₁₈O₂ requires 170.1307).

Wittig Reaction of (3) with 2-hydroxy, 5-methyl tetrahydrofuran



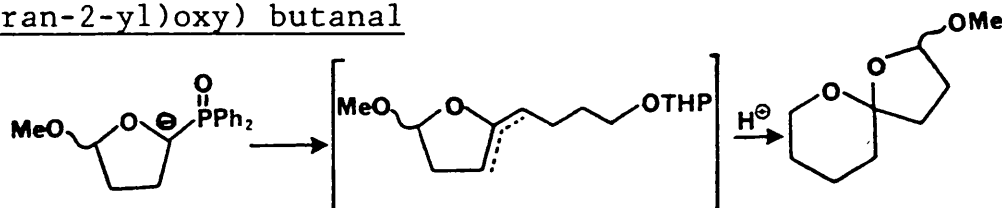
Following the general procedure, the anion of 2-hydroxy, 5-methyl tetrahydrofuran (0.102g, 1mmol) was added to a solution of the anion (3) (0.435g, 1mmol). The solution was stirred at room temperature for 5h. Purification by Kugelrohr distillation gave the enol ether (29) (56mg, 33%) as a colourless oil identical to that prepared above.

Horner-Wittig Reaction of (9) with 4-((tetrahydro-2H pyran-2-yl) oxy) butanal



Following the general procedure, the anion of (9) (0.271g, 1mmol) was condensed with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal (0.172g, 1mmol). Distillation gave (31) (159mg, 70%) as a colourless oil, bp 80°C at 0.02mm Hg, which was converted directly to the spiroketal by treatment with camphor sulphonic acid (2mg) in dichloromethane (5ml) and stirred overnight. Purification by chromatography (ether-Petrol) gave 1,6-dioxaspiro [4.5] decane(32) (83mg, 83%) as a pale yellow oil. IR (film) 2940, 1079, 1035cm⁻¹; NMR δ (250MHz): 3.95-3.35 (4H, m, OCH₂), 2.05-1.45 (10H, m); m/z 142 (M⁺), 85, 71, 55. (Found M⁺ 142.0996, C₈H₁₄O₄ requires 142.0994).

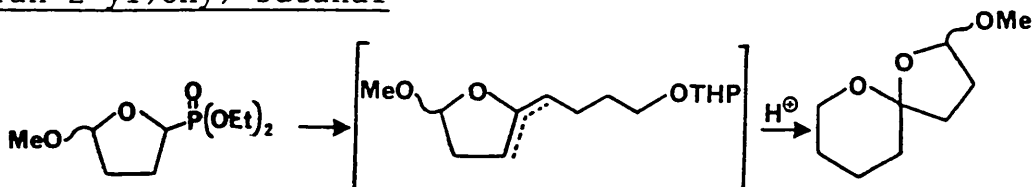
Horner-Wittig Reaction of (11) with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal



Following the general procedure, the anion of (11) (0.302g, 1mmol) was condensed with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal (0.172g, 1mmol). Distillation gave (33) (96mg, 37%) as a colourless oil, bp 90°C at 0.02mm Hg, which was converted directly to the spiroketal by treatment with camphor sulphonic acid (2mg) in dichloromethane (5ml) and stirred overnight. Purification by chromatography (ether-petrol) gave (E)-2-methoxy, 1,6-dioxaspiro [4,5] decane (34) (51mg, 79%) as a colourless oil. IR (film) 2927, 1452, 1369, 1065cm⁻¹; NMR δ (250MHz): 4.50 (1H, m, OCH), 3.95-3.55 (2H, m, OCH₂), 3.35 (3H, s, OMe), 1.95-1.45 (10H, m); m/z

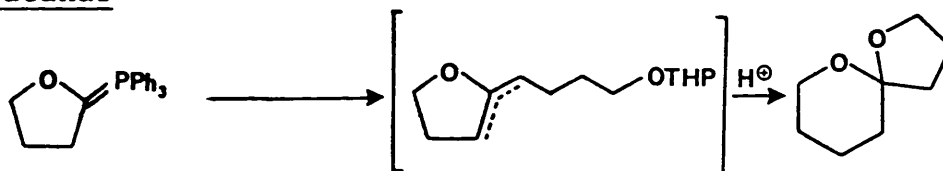
172 (M^+), 141, 101, 85, 71. (Found M^+ 172.1094, $C_9H_{16}O_3$ requires 172.1099).

Horner-Wittig Reaction of (21) with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal



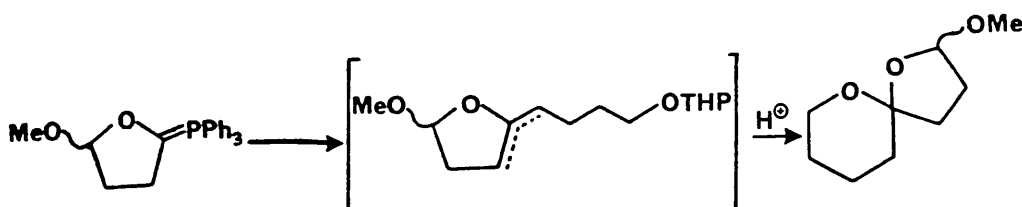
Following the general procedure, the anion of (21) (0.237g, 1mmol) was condensed with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal (0.172g, 1mmol). Distillation gave (33) (83mg, 32%) which was converted to (34) (49.5mg, 77%) as above.

Wittig Reaction of (7) with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal



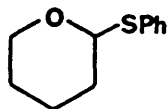
Following the general procedure, the anion of (7) (0.420g, 1mmol) was condensed with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal (0.172g, 1mmol). The solution was stirred at room temperature for 6h. Distillation gave (31) (161mg, 71%) as a mixture of ring open and ring closed products, which were converted to (32) (65mg, 65%) as previously.

Wittig Reaction of (22) with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal



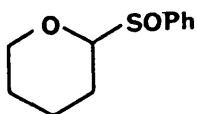
Following the general procedure, the anion of (22) (0.69g, 1.53mmol) was condensed with 4-((tetrahydro-2H-pyran-2-yl)oxy) butanal (0.263g, 1.5mmol). Distillation gave (33) (166mg, 65%) as a mixture of ring open and ring closed products, which were converted to (34) (72mg, 42%) as previously.

Preparation of 2-benzenesulphenyl tetrahydro-2H-pyran (35)



Thiophenol (5.12ml, 0.05mol) was added to a stirred solution of 3,4 dihydro-2H-pyran (4.2g, 0.05mol) in dichloromethane with a catalytic amount of camphor sulphonic acid. Stirring was continued for 15h, then the solution filtered through a florisil pad and evaporated to leave a crude oil, which was purified by Kuglerohr distillation to give (35) (8.03g, 83%) as a colourless oil, bp 140°C at 3mm Hg. IR (film) 2940, 1437, 1035 cm^{-1} ; NMR δ (90MHz): 7.55-7.00 (5H, m, ArH), 5.13 (1H, dd $J=4,5\text{Hz}$, H_2), 4.35-3.90 (1H, m, H_6), 3.75-3.40 (1H, m, H_6), 2.17-1.35 (6H, m); m/z 194 (M^+), 110, 85.

Methods of Oxidation of (35) to 2-benzenesulphoxyl tetrahydro-2H-pyran (37)



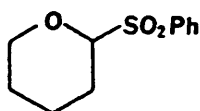
The sulphide (35) (0.194g, 1mmol) was added to a stirred solution of sodium periodate (0.22g, 1.05mmol) (buffered with potassium carbonate) in methanol/water (25ml) at 0°C and stirred at 0°C for 12h. The solution was filtered and the filtrate extracted with dichloromethane (3x10ml) dried and concentrated. Purification by chromatography (ether-petrol) gave (37) (169mg, 80.5%) as pale yellow crystals, mp 40-41°C. IR (film) 2940, 1100, 1075, 730 cm^{-1} ; NMR δ (250MHz): 7.65-7.40 (5H, m, ArH),

4.90 (0.9H, t, J=5 Hz, H₂ major), 4.80 (0.1H, t, J=5Hz, H₂ minor), 3.95-3.55 (2H, m, H₆), 1.80-1.60 (6H, m); m/z No (M⁺), 125, 85. (Found: C, 62.56; H, 6.78; C₁₁H₁₄O₂S requires C, 62.82; H, 6.71%).

The sulphide (35) (0.388g, 2mmol) was added to a stirred solution of meta-chloroperbenzoic acid (0.528g, 1.2eq) (buffered with sodium acetate) in dichloromethane (25ml) at -10°C and stirred for 3h. The solution was washed with sodium bicarbonate, dried and concentrated to leave a yellow oil. This was purified by chromatography (ether-petrol) to give crystals (37) (0.32g, 79%) identical to that prepared above.

The sulphide (35) (0.194g, 1mmol) was dissolved in methanol (4ml) at 0°C (buffered with sodium acetate) and oxone (0.74g, 1.2mmol) added in water (4ml) and stirred for 1h at -10°C. The slurry was diluted with water (10ml) extracted into ether (3x10ml), dried and concentrated. Chromatography of the crude oil (ether-petrol) gave (37) (191mg, 91%) identical to that prepared above.

Oxidation of (35) to 2-benzenesulphonyl tetrahydro-2H-pyran
(38)



The sulphide (35) (0.97g, 5mmol) was dissolved in methanol (20ml) at 0°C (buffered with sodium acetate) and oxone (9.22g, 15mmol) added in water (20ml) and the slurry stirred at 0°C

for 4h. The slurry was diluted with water (10ml), extracted into ether (3x20ml), dried and concentrated to leave a white solid. Recrystallisation from ether-petrol gave 2-benzenesulphonyl tetrahydropyran (38) (0.82g, 72.5%) as white crystals, mp 76°C. IR (CHCl₃) 1315, 1150, 1084, 692cm⁻¹; NMR δ (90MHz): 7.91 (2H, m, ArH), 7.58 (3H, m, ArH), 4.39 (1H, dd J=3.1, 10Hz, H₂), 4.11 (1H, m, H₆), 3.45 (1H, m, H₆), 2.18-1.46 (6H, m); m/z no (M⁺) 142 and 85. (Found: C, 58.24; H, 6.14; C₁₁H₁₄O₃S requires C, 58.39; H, 6.24%).

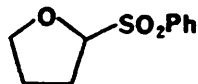
Preparation of benzenesulphinic acid

Sodium benzene sulphonate was added to 7% sulphuric acid at 0°C and stirred for 30mins at room temperature. The solution was extracted with ether, dried and concentrated to leave a white solid.

Preparation of 2-benzenesulphonyl tetrahydro-2H-pyran (38)

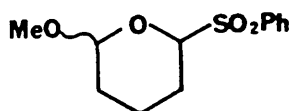
3,4 dihydro-2H-pyran (1.11g, 13.2mmol) was added dropwise to a stirred solution of freshly prepared benzenesulphinic acid (1.88g, 13.2mmol) in dry dichloromethane (50ml) at room temperature under argon. Stirring was continued for 2h, and the solvent removed under reduced pressure. Recrystallisation of the crude product from ether-petrol gave 2-benzenesulphonyl tetrahydro-2H-pyran (38) (2.45g, 82%) as white needles identical to the material prepared above.

Preparation of 2-benzenesulphonyl tetrahydrofuran (39)



Dihydrofuran (0.378ml, 5mmol) was added to a stirred solution of benzenesulphinic acid (0.72g, 5mmol) in dry dichloromethane (20ml) at room temperature under argon. Stirring was continued for 2h, then the solvent removed under reduced pressure. Recrystallisation of the crude product from ether-petrol gave 2-benzenesulphonyl tetrahydrofuran (39) (0.89g, 84%) as white needles, mp 55-56°C. IR (CHCl₃) 1310, 1150, 692 cm⁻¹; NMR δ (250MHz): 7.95 (2H, m ArH), 7.60 (3H, m, ArH), 4.85 (1H, dd, J=4.2, 8.3Hz, H₂), 4.11-3.95 (2H, m, H₆), 2.56 (1H, m), 2.32-1.95 (3H, m); m/z No (M⁺), 141, 71. (Found: C, 56.67; H, 5.66; C₁₀H₁₂O₃S requires C, 56.58; H, 5.69%).

Preparation of 2-benzenesulphonyl, 6-methoxy tetrahydropyran (40)



6-Methoxy, dihydro-2H-pyran (0.64g, 5.6mmol) was added to a stirred solution of benzenesulphinic acid (0.8g, 5.6mmol) in dry dichloromethane (20ml) and stirred at room temperature for 2h. The solvent was removed under reduced pressure and recrystallisation from ether-petrol gave 2-benzenesulphonyl, 6-methoxy tetrahydropyran (40) (1.06g, 74%) as white crystals, mp 59.5°C. IR (mull) 2863, 2806, 1326, 1153, 692cm⁻¹; NMR δ (250Hz): 7.92-7.55 (5H, m, ArH), 4.72 (1H, t, J=4.4Hz, H₆), 4.64 (1H, dd, J=4.4, 12Hz, H₂), 3.21 (3H, s, OMe), 1.75-1.60

(6H, m); m/z No (M^+), 225, 142, 115. (Found: C, 56.02; H, 6.01; $C_{12}H_{16}O_4S$ requires C, 56.23; H, 6.29%).

General procedure for condensation of the anion of 2-benzene-sulphonyl tetrahydro-2H-pyran with electrophiles

The sulphone (1eq) was dissolved in dry tetrahydrofuran (10ml) at -78°C under argon. n-Butyllithium(1.1eq) was added dropwise and the mixture stirred at -78°C for 15mins, then the electrophile (1eq) added and the solution warmed to room temperature over 1.5-2h. Extraction into ether, washing with sodium bicarbonate solution, drying and removal of the solvent under reduced pressure gave the crude product. This was purified by chromatography on florisil (ether-petrol) or by Kugelrohr distillation.

Using the general procedure the following enol ethers were prepared:-

Preparation of 2-(1'-hydroxy-2'-methyl-propyl)-5,6 dihydro-4H-pyran (42)

Isobutyraldehyde (0.091ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (42) (102mg, 65%) as a colourless oil. IR (film) $3446, 2955, 1675, 1062\text{cm}^{-1}$; NMR δ (90MHz): 4.70 (1H, t, $J=3.7$ Hz, H_3), 4.00 (2H, t, $J=5.2\text{Hz}$, H_6), 3.50 (1H, br, m, H_1), 2.15-1.05 (6H, m), 0.9 (6H, d, $J=5.2\text{Hz}$, H_3); m/z 156 (M^+), 113, 85, 55. (Found M^+ 156, 1154, $\text{C}_9\text{H}_{16}\text{O}_2$ requires 156.1150).

Preparation of 2-(1'-hydroxy-heptyl) 5,6 dihydro-4H-pyran (43)

Heptanal (0.134ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (43) (122mg,

62%) as a colourless oil. IR (film) 3407, 2926, 1675, 1063 cm^{-1} ; NMR δ (90MHz): 4.70 (1H, t, $J=3.6\text{Hz}$, H_3), 4.00 (2H, t, $J=5.1\text{Hz}$, H_6), 3.85 (1H, br, d, $J=7.2\text{Hz}$, H_1), 2.10-1.70 (15H, m), 0.9 (3H, t, $J=3.6\text{Hz}$, Me); m/z 198 (M^+), 114, 85, 83, 55. (Found: C, 72.69; H, 11.45; $\text{C}_{12}\text{H}_{22}\text{O}_2$ requires C, 72.68; H, 11.18%).

Preparation of 2-(1'-hydroxy-pentyl) 5,6 dihydro-4H-pyran (44)

Pentanal (0.106ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (44) (101mg, 59%) as a colourless oil. IR (film) 3422, 2955, 1675, 1062 cm^{-1} ; NMR δ (90MHz): 4.75 (1H, t, $J=3.6\text{Hz}$, H_3), 4.00 (2H, t, $J=5.2\text{Hz}$, H_6), 3.85 (1H, br.d. $J=6.9\text{Hz}$, H_1), 2.25 (1H, m, OH), 2.10-1.2 (10H, m), 0.9 (3H, t, $J=3.7\text{Hz}$, Me); m/z 170 (M^+), 114, 113, 85, 57. (Found M^+ 170.1305, $\text{C}_{10}\text{H}_{18}\text{O}_2$ requires 170,1306).

Preparation of 2-(1'-hydroxy-dec-4',5'enyl) 5,6 dihydro-4H-pyran (45)

Decan 4,5 en-al (0.154g, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (45) (152mg, 64%) as a colourless oil. IR (film) 3384, 2926, 1675, 1066 cm^{-1} ; NMR δ (90MHz): 5.35 (2H, t, $J=3.6\text{Hz}$, H_4' H_5'), 4.75 (1H, t, $J=3.9\text{Hz}$, H_3), 4.00 (2H, t, $J=5.4\text{Hz}$ H_6), 3.85 (1H, m, H_1'), 2.25-1.35 (17H, m), 0.9 (3H, t, $J=3.6\text{Hz}$, Me); m/z 238 (M^+), 183, 114, 85, 57. (Found M^+ 238.1931, $\text{C}_{15}\text{H}_{26}\text{O}_2$ requires 238.1932).

Preparation of 2-(1'-hydroxy-2'furfuryl) 5,6 dihydro-4H-pyran
(46)

2-Furaldehyde (0.082ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (46) (89mg, 50%) as a slightly yellow oil. IR (film) 3426, 2929, 1675, 1499, 1062 cm^{-1} ; NMR δ (90MHz): 7.35 (1H, s, H_5), 6.30 (2H, s, H_4 , H_3), 5.00 (1H, br.d. $J=5.1\text{Hz}$, H_1), 4.85 (1H, t, $J=3.8\text{Hz}$, H_3), 4.05 (2H, t, $J=5.4\text{Hz}$, H_6), 2.6 (1H, br.d. $J=15\text{Hz}$, OH), 2.1-1.6 (4H, m); m/z 180 (M^+), 163, 97, 85, 55. (Found 180.0794, $\text{C}_{10}\text{H}_{12}\text{O}_3$ requires 180.0786).

Preparation of 2-(1'-hydroxy-but-2',3' enyl) 5,6 dihydro-4H-pyran (47)

2-Butenal (0.083ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (47) (77mg, 50%) as a colourless oil. IR (film) 3446, 2930, 1675, 1628, 1064 cm^{-1} ; NMR δ (90MHz): 5.75 (2H, m, H_2 , H_3), 4.75 (1H, t, $J=3.6\text{Hz}$, H_3), 4.45 (1H, m, H_1), 4.99 (2H, t, $J=5.2\text{Hz}$, H_6), 2.05-1.35 (8H, m); m/z 154 (M^+), 130, 85, 69. (Found M^+ 154.0989, $\text{C}_9\text{H}_{14}\text{O}_2$ requires 154.0994).

Preparation of 2-(α -hydroxy-benzyl) 5,6 dihydro-4H-pyran (48)

Benzaldehyde (0.102ml, 1mmol) was added to a stirred solution of the anion of (38) (1.5mmol). Kugelrohr distillation gave (48) (87mg, 46%) as a colourless oil, bp 90°C at 0.1mm Hg. IR (film) 3422, 2927, 1674, 1086 cm^{-1} ; NMR δ (90MHz): 7.6-7.2

(5H, m, ArH), 5.05 (0.7H, br.s H_1), 4.79 (1H, t, $J=4.1\text{Hz}$, H_3), 4.00 (2H, t, $J=4.9\text{Hz}$, H_6), 3.75 (0.3H, s, H_1), 2.5 (1H, br.s. OH), 2.00-1.60 (4H, m); m/z 190 (M^+), 106, 105, 85, 77. (Found M^+ 190.0985, $C_{12}H_{14}O_2$ requires 190.0993).

Preparation of 2-(α -hydroxy- para-nitrobenzyl) 5,6-dihydro-4H-pyran (49)

para-Nitrobenzaldehyde (0.150g, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (49) (56mg, 25%) as yellow crystals. IR ($CHCl_3$) 3580, 3400, 1675, 1151, 1058cm^{-1} ; NMR δ (90MHz): 8.30-8.20 (2H, m ArH), 7.70-7.55 (2H, m, ArH), 5.10 (1H, d, $J=5\text{Hz}$, H_1), 4.85 (1H, t, $J=3.9\text{Hz}$, H_3), 4.0 (2H, t, $J=5.4\text{Hz}$, H_6), 2.55 (1H, d, $J=5\text{Hz}$, OH), 2.2-0.8 (6H, m); m/z 235 (M^+), 156, 150, 101, 85, 83, 77, 55. (Found M^+ 235.0847, $C_{12}H_{13}NO_4$ requires 235.0844).

In situ Reductive desulphonylation

Preparation 2-(1'-hydroxy-2'-methyl-propyl) tetrahydropyran (50)

The sulphone (38) (0.226g, 1mmol) was dissolved in tetrahydrofuran under argon. *n*-Butyllithium (0.70ml, 1.1eq) was added dropwise at -78°C , stirred for 15min, then isobutyraldehyde (0.091ml, 1mmol) added. After 15min at -78°C , a 1M solution of freshly prepared lithium naphthalenide (5mmol) in tetrahydrofuran was added. After a further 0.5h at -78°C , anhydrous methanol (0.40ml, 10mmol) was added and the solution warmed to rt over 2h, poured into water (10ml), extracted with ether

(3x20ml), dried and evaporated. Chromatography (petrol/ether) gave (50) (44mg, 27%). IR (film) 3470, 1465, 1207, 1087, 1000, 733cm^{-1} ; NMR δ (250MHz): 4.03 (1H, ddd, $J=11.3, 1.9, 1.9\text{Hz}$, H_6), 3.55-3.22 (2.3H, m, H_6, H_2, H_1 , (minor)), 3.22-3.11 (0.7H, ddd, $J=6.3, 4.8, 3.8\text{Hz}$, H_1 , (major)), 2.46 (0.7H, d, $J=3.8\text{Hz}$, OH (major)), 2.00-1.05 (7.3H, m), 1.05-0.81 (6H, m); m/z 159 (MH^+), 157, 141, 115, 85. (Found M^+ 141.1277, $\text{C}_9\text{H}_{17}\text{O}$ requires 141.1279 (calculated for MH^+-OH)).

Preparation of 2-(propenylidene) 5,6 dihydro-4H-pyran

(51)

Allyl bromide (0.085cm^3 , 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Chromatography gave (51) (63mg, 51%) as a slightly yellow oil. IR (film) 3077, 2938, 2870, 1713, 1638, 1069cm^{-1} ; NMR δ (90MHz): 6.0-5.6 (1H, m, H_2 ,), 5.2-4.9 (3H, m, H_3, H_1 ,), 3.7-3.3 (3H, m, H_6, H_3), 3.15 (1H, m, H_3), 1.9-1.7 (4H, m); m/z 125 (M^+H), 124 (M^+), 101, 84, 57. (Found 124.0884, $\text{C}_8\text{H}_{12}\text{O}$ requires 124.0888).

Preparation of 2-(4'-fur-2-yl butyl) 5,6 dihydro-4H-pyran (52)

1-Iodo-4-fur-2ylbutane (0.25g, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Kugelrohr distillation gave (52) (118mg, 57%) as a pale yellow oil, bp 100°C at 0.2mm Hg. IR (film) 2934, 1673, 1626, 1064cm^{-1} ; NMR δ (90MHz): 7.35 (1H, br.s. H_2 ,), 6.32 (1H, m, H_4 ,), 6.05 (1H, m, H_3 ,), 4.55 (1H, m, H_3), 4.05 (2H, m, H_6), 2.61 (4H, m), 1.98-1.56 (8H, m); m/z 206 (M^+), 123, 83, 81, 67, 55. (Found M^+ 206.1302, $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires 206.1306).

Preparation of 2-(2'-phenyl ethyl) 5,6 dihydro-4H-pyran (53)

Phenylethyl bromide (0.136ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Kugelrohr distillation gave (53) (100mg, 53%) as a colourless oil, bp 60°C at 0.005mm Hg. IR (film) 2933, 1675, 1088, 1063cm⁻¹; NMR δ (90MHz): 7.30-7.15 (5H, m, ArH), 4.65 (1H, m, H₃), 3.80 (2H, m, OCH₂), 2.85 (2H, m, CH₂Ph), 1.85-1.5 (6H, m); m/z 188 (M⁺), 104, 91, 85, 55. (Found M⁺ 188.1203, C₁₃H₁₆O requires 188.1201).

Preparation of 2-(α - benzyl) 5,6 dihydro-4H-pyran (54)

Benzyl bromide (0.109ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Kugelrohr distillation gave (54) (51mg, 29%) as a colourless oil, bp 80°C at 0.05mm Hg. IR (film) 3029, 1673, 1068, 692cm⁻¹; NMR δ (90MHz): 7.60-7.25 (5H, m, ArH), 5.21 (0.3H, s, Z-isomer), 4.45 (0.7H, t, J=4.5Hz, endo-isomer), 3.75 (2H, m, OCH₂), 3.20 (1.4H, s, CH₂ endo), 2.1-1.85 (4.6H, m); m/z 174 (M⁺), 91, 90, 83 and 55. (Found C, 82.66; H, 8.31; C₁₂H₁₄O requires C, 82.72; H, 8.10%).

Preparation of 2- pentyl 5,6 dihydro-4H-pyran (55)

1-Iodopentane (0.131ml, 1mmol) was added to a stirred solution of the anion of (38) (2.5mmol). Chromatography gave (55) (83mg, 56.1%) as a colourless oil. IR (film) 3042, 1674, 1465, 1068cm⁻¹; NMR δ (90MHz): 4.45 (1H, t, J=3.8Hz, H₃), 3.95 (2H, t, J=5.1Hz, H₆), 2.2-1.2 (12H, m), 0.9 (3H, t, J=3.1Hz, Me); m/z 154 (M⁺), 111, 101, 98, 83. (Found M⁺ 154.1356 C₁₀H₁₈O requires 154.1358).

Preparation of 2-(1'-hydroxy-1'-ethyl-propyl) 5,6, dihydro-4H-pyran (56)

Pentan-3-one (0.050ml, 0.5mmol) was added to a stirred solution of the anion of (38) (1.25mmol). Chromatography gave (56) (49mg, 58%) as a colourless oil. IR (film) 3478, 2930, 1670, 1058 cm^{-1} ; NMR δ (90MHz): 4.78 (1H, t, $J=3.6\text{Hz}$, H_3), 3.95 (2H, t, $J=4.3\text{Hz}$, H_6), 2.15-1.25 (9H, m), 0.95-0.85 (6H, m); m/z 170 (M^+), 141, 113, 83, 57. (Found 170.1310, $\text{C}_{10}\text{H}_{18}\text{O}_2$ requires 170.1306).

Preparation of 2-(1'-hydroxy- cyclopentyl) 5,6 dihydro-4H-pyran (57)

Cyclopentanone (0.088ml, 1mmol) was added to a stirred solution of the anion of (38) (2.5mmol). Chromatography gave (57) (111mg, 66%) as a colourless oil. IR (film) 3422, 2947, 1670, 1066 cm^{-1} ; NMR δ (90MHz): 4.8 (1H, t, $J=3.6\text{Hz}$, H_3), 4.00 (2H, t, $J=5.4\text{Hz}$, H_6), 2.2-1.55 (13H, m); m/z 168 (M^+), 151, 137, 111, 85, 83. (Found M^+ 168.1151, $\text{C}_{10}\text{H}_{16}\text{O}_2$ requires 168.1150).

Preparation of 2-(1'-hydroxy, phenyl ethyl.) 5,6 dihydro-4H-pyran (58)

Acetophenone (0.116ml, 1mmol) was added to a stirred solution to the anion of (38) (2.5mmol). Chromatography gave (58) (83mg, 42%) as a colourless oil. IR (film) 3446, 2930, 1670, 1599, 1087, 766 cm^{-1} ; NMR δ (90MHz): 7.6-7.3 (5H, m, ArH), 5.00 (1H, t, $J=3.75\text{Hz}$, H_3), 4.00 (2H, t, $J=5.4\text{Hz}$, H_6), 2.95 (1H, br.

s. OH), 2.2-2.05 (2H, m), 1.95-1.75 (2H, m), 1.65 (3H, s, Me);
m/z 204 (M^+), 189, 111, 105, 84, 77. (Found M^+ 204.1146.
 $C_{13}H_{16}O_2$ requires 204.1150).

Preparation of 2-Methyl (2'-benzenesulphonyl tetrahydropyran-
2-yl)formate (59)

Methyl chloroformate (0.077ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Recrystallisation of the solid from ether-petrol gave (59) (230mg, 81%) as white crystals, mp 52°C. IR ($CHCl_3$) 1744, 1078, 689 cm^{-1} ; NMR δ (90MHz): 7.88-7.28 (5H, m, ArH), 4.35-3.30 (5H, m, including 3.75, s, Me), 2.70-1.20 (6H, m); m/z No (M^+), 143, 141, 125, 109, 77, 59. (Found: C, 54.81; H, 5.65; $C_{13}H_{16}O_5S$ requires C, 54.91; H, 5.65%).

Preparation of 2- Ethyl (2'-benzenesulphonyl tetrahydropyran -
2-yl)formate (60)

Ethyl chloroformate (0.095ml, 1mmol) was added to a stirred solution of the anion (38) (1mmol). Recrystallisation of the solid obtained from petrol-ether gave (60) (223mg, 74%) as white crystals, mp 59°C. IR ($CHCl_3$) 2948, 2871, 1733, 1325, 1155, 1085, 1039, 605 cm^{-1} ; NMR δ (90MHz): 7.91 (2H, m, ArH), 7.65-7.52 (3H, m, ArH), 4.2-4.05 (3H, m, OCH_2), 3.75-3.55 (1H, m, OCH_2), 2.60-2.45 (1H, m), 2.15-1.45 (5H, m), 1.15 (3H, t, $J=7$ Hz, Me); m/z No (M^+) 156, 127, 142, 83. (Found: C, 56.35; H, 6.37; $C_{14}H_{18}O_5S$ requires C, 56.36; H, 6.09%).

Preparation of 2-Benzyl (2'-benzenesulphonyl tetrahydropyran-2-yl) formate (61)

Benzyl chloroformate (0.143ml, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Recrystallisation of the solid obtained from petrol-ether gave (61) (172mg, 48%) as white crystals, mp 68-69°C. IR (CHCl₃) 2948, 2868, 1736, 1325, 1156, 1085cm⁻¹; NMR δ (90MHz): 7.85-7.75 (2H, m, ArH), 7.60-7.30 (8H, m, including 7.35, s, Ph), 5.15 (2H, s, CH₂Ph), 4.20-4.00 (1H, m, OCH₂), 3.75-3.50 (1H, m, OCH₂), 2.70-2.45 (1H, m), 1.40-1.15 (5H, m); m/z No (M⁺), 218, 142, 91, 77. (Found: C, 63.11; H, 5.57; C₁₅H₂₀O₅S requires C, 63.32; H, 5.59%).

PREPARATION OF SPIROKETALS

Preparation of 1,7-dioxaspiro [5,5] undecane (26)



Using the general procedure, 1-((tetrahydro-2H-pyran-2-yl)oxy) 4-bromobutane (0.52g, 2.2mmol) was added to a stirred solution of the anion of (38) (2.2mmol). Kugelrohr distillation gave (26) (265mg, 77%) as a colourless oil, identical to that prepared previously, and the natural product.

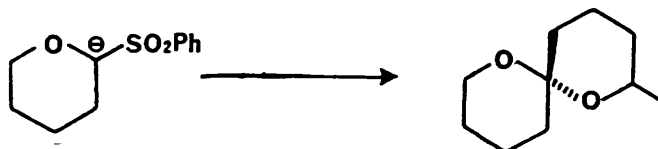
Preparation of 1,7-dioxaspiro [5,5] undecane (26)



Using the general procedure, 1-((tertiary-butyl(dimethylsilyl)oxy) 4-iodobutane (0.314g, 1mmol) was added to a stirred solution

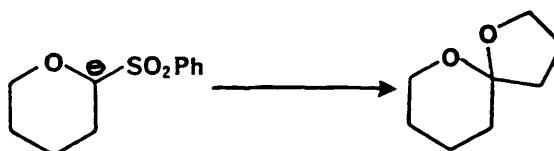
of the anion of (38) (1mmol). Treatment of the intermediate enol ether with hydrogen fluoride, followed by chromatography (ether-petrol) gave (26) (81mg, 52%) as a colourless oil, identical to that prepared previously.

Preparation of 2-methyl-1,7-dioxaspiro [5,5] undecane (30)



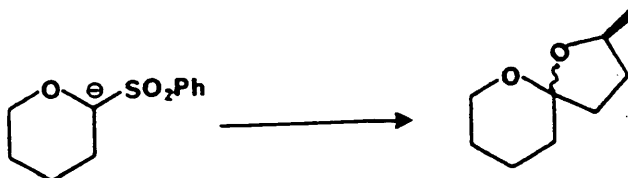
Using the general procedure, 1-((tertiary-butyl (dimethylsilyl) oxy, methyl) 4-iodobutane (0,329g, 1mmol) was added to a stirred solution of the anion of (38) (1mmol). Treatment of the intermediate enol ether with hydrogen fluoride, followed by chromatography (ether-petrol) gave (30) (79mg, 47%) as a colourless oil, identical to that prepared previously.

Preparation of 1,6-dioxaspiro [4,5] decane (32)



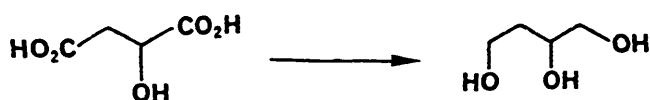
Using the general procedure, 1-((tetrahydro-2H-pyran-2-yl) oxy) 3-bromopropane (0.22g, 1mmol) was added to a solution of the anion of (38) (1mmol). Kugelrohr distillation gave (32) (81mg, 57%) as a colourless oil, identical with that prepared previously.

Preparation of 2-methyl-1,6-dioxaspiro [4,5] decane (62)

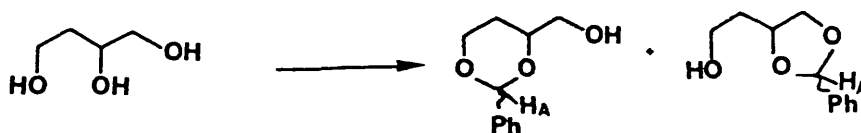


Using the general procedure, 1-iodo ((3-tetrahydro-2H-pyran-2-yl) oxy)butane (0.279g, 1mmol) was added to a solution of the anion of (38) (1mmol). Kugelrohr distillation gave (62) (123mg, 79%) as a colourless oil, bp 75°C at 10mm Hg. IR (film) 2940, 1050cm⁻¹; NMR δ (250MHz): 3.92-3.60 (3H, m), 2.07-1.21 (10H, m), 1.11 (3H, d, J=6.3Hz, Me); m/z 156 (M⁺), 141, 91 and was identical with the natural product.

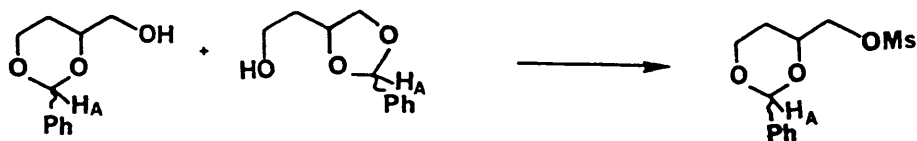
Preparation of 2-phenyl-4-iodomethyl-1,3-dioxane (67)



Borane dimethyl sulphide (11.2ml, 6 equiv) was added to a stirred solution of dl-malic acid (2g, 14.9mmol) in dry tetrahydrofuran under argon at 0°C. The solution was warmed to room temperature and stirred for 3 days. The reaction was quenched with methanol (10ml), the solvent removed under reduced pressure and the residue redissolved in tetrahydrofuran (40ml), the precipitate filtered and the resulting filtrate concentrated under reduced pressure. The sticky oil was purified by chromatography (methanol-chloroform) then distilled by Kugelrohr to give (63) (1.23g, 77.7%) as a colourless oil bp 130°C and 0.6mm Hg. IR (CHCl₃) 3360, 2940, 2880, 1650, 1420, 1060cm⁻¹; NMR δ (90MHz): 4.52-4.33 (3H, m, OCH₂,OH), 3.60-3.22 (5H, m, OCH₃, OH), 1.60 (1H, m, CH₂), 1.38 (1H, m, CH₂).



The triol (63) (0.83g, 7.8mmol) was warmed in dry dimethylformamide (8ml) with benzaldehyde dimethyl acetal (1.185g, 1.1eq) and a catalytic amount of camphor sulphonic acid. Stirring was continued for 1.5h, the mixture poured into water (15ml), extracted with ether (3x20ml), dried and the solvent removed under reduced pressure. Purification by chromatography (ethyl acetate-petrol) gave (64) (0.89g, 60%) as a colourless oil and mixture of isomers (5 and 6 ring protection). IR (film) 3450, 2940, 2860, 1450, 1310, 1210, 1050 cm^{-1} ; NMR δ (90MHz): 7.38 (5H, m, ArH), 5.84 and 5.70 (0.25H, s, $\text{H}_{\text{A}5}$), 5.50 (0.75H, s, $\text{H}_{\text{A}6}$), 4.5-3.60 (5H, m, OCH_2 , CH_2OH , CHOH), 2.50 (1H, br.s. OH), 2.3-1.4 (2H, m, CH_2); m/z 194 (M^+), 193, 163, 105.



The protected alcohols (64) (150mg, 0.78mmol) in dichloromethane (5ml) at -10°C under argon were treated with triethylamine (0.163ml, 1.17mmol, 1.5eq) followed by methanesulphonyl chloride (0.065ml, 0.87mmol, 1.1eq) with rapid stirring. The reaction was stirred for 15min, then poured into ice water/dichloromethane and the aqueous layer extracted with dichloromethane (3x10ml). The combined organic phases were dried and concentrated under reduced pressure to give an oil which was purified by chromatography (ethyl acetate-petrol) to give (65) (197mg, 94%) as a colourless oil and mixture of isomers. IR (film) 3080, 2860, 1450, 1350, 1100, 970 cm^{-1} . NMR δ (90MHz): 7.40 (5H, m, ArH), 5.84 and 5.70 (0.25H, s, $\text{H}_{\text{A}5}$), 5.54 (0.75H, s,

H_{A6}), 3.88-4.35 (5H, m, OCH₂, OCH, CH₂OMe), 3.00 (3H, s, Me), 1.9-1.1 (2H, m, CH₂); m/z 272 (M⁺), 271, 193, 163, 105.



The protected alcohols (64) (0.192g, 1mmol) were added to a stirred solution of toluene-4-sulphonyl chloride (0.209g, 1.1mmol) at -5°C in dichloromethane (25ml) under argon. Pyridine (0.12ml, 1.5mmol) was added dropwise and the reaction stirred for 2.5 days maintaining the temperature at -5°C. Loss of benzaldehyde was observed during product formation. The reaction was washed with CuSO₄ solution, followed by brine, dried and the solvent removed under reduced pressure. The oil was purified by chromatography (petrol-ether) to give (66) (0.205g, 58.9%) as pale yellow crystals mp 73-74°C. IR (mull) 2979, 2880, 1446, 1380, 1295, 1251cm⁻¹; NMR δ (250MHz): 7.8 (2H, d, J=9Hz, ArH), 7.4-7.2 (7H, m, ArH), 5.4 (1H, s, H_A), 4.3-3.9 (5H, m, CH₂O), 2.4 (3H, s, -Me), 1.9-1.4 (2H, m); m/z 348 (M⁺), 163, 155, 91.

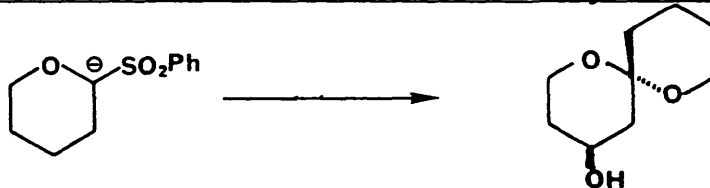
The tosylate (66) (0.162g, 0.46mmol) was added to a stirred solution of sodium iodide (excess) in acetone (10ml) and refluxed for 5h. The solution was cooled and filtered to remove the solid residues. The filtrate was concentrated to leave a white solid which was redissolved in dichloromethane (15ml), washed with sodium thiosulphate, brine and dried. Removal of the solvent under reduced pressure and purification by chromatography (petrol/ether) gave (67) (0.139g, 73%) as a colourless oil (light sensitive). IR (film) 3060,

2850, 1450, 1390, 1020, 750 cm^{-1} ; NMR δ (90MHz): 7.5 (2H, m, ArH), 7.38 (3H, m, ArH), 5.52 (1H, s, H_A), 4.30 (1H, m, OCH), 4.02-3.88 (2H, m, OCH₂), 3.33 (1H, dd $J=6.2, 10.5\text{Hz}$), 3.24 (1H, dd, $J=6.4, 10.5\text{Hz}$) 1.90-1.70 (2H, m, CH₂); m/z 304 (M^+), 303, 181, 123, 105, 56. (Found: C, 43.65; H, 4.50; $\text{C}_{11}\text{H}_{13}\text{O}_2$ I requires C, 43.44; H, 4.31%).



A mixture of mesylates (0.107g, 0.4mmol) was dissolved in dry dimethyl formamide (5ml) and added to a saturated solution of sodium iodide in dry dimethyl formamide (20ml) at room temperature. The solution was heated to 60°C and stirred for 24h. The iodide formed was isolated and the unreacted mesylate stirred for a further 48h. The reaction was poured into water (20ml), extracted into ether (3x20ml), dried and concentrated under reduced pressure. Chromatography (petrol-ether) gave (67) (0.120g, 74%) as a colourless oil, identical to that prepared above.

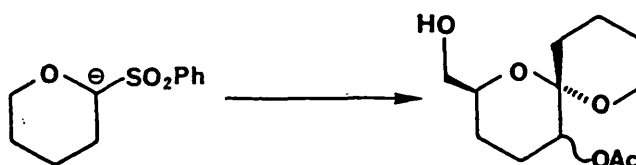
Preparation of 4-hydroxy-1,7-dioxaspiro [5,5] undecane (68)



Using the general procedure, 2-phenyl-4-iodomethyl-1,3-dioxane (67) (71mg, 0.23mmol) was added to a solution of the anion of (38) (0.13g, 0.58mmol). Treatment of the intermediate enol ether with HCl (1M) in methanol, followed by chromatography (ether) gave (68) (19.3mg, 49%) as a waxy solid. IR (CHCl_3)

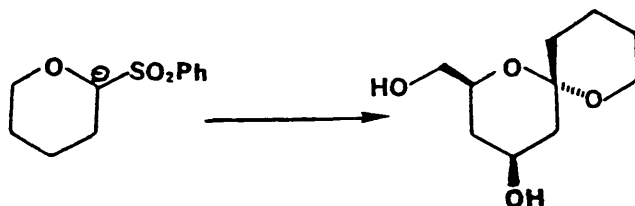
3446, 2946, 2870, 1449, 1380, 1058, 1045, 982 cm^{-1} ; NMR δ (400 MHz): 4.08 (1H, tt, $J=11.5$ Hz, H_4), 3.75-3.47 (4H, m, H_2 , H_8), 2.01 (1H, ddd, $J=11.5$, 5, 2Hz, H_{5e}), 1.89 (1H, ddd, $J=12$, 5, 2Hz, H_{3e}), 1.81 (1H, tt, $J=12.5$ Hz, H_{10a}), 1.71 (1H, br.s, OH), 1.68-1.44 (6H, m) 1.29 (1H, dd, $H=11.5$, 11 Hz, H_{5a}); ^{13}C (22.51MHz): 18.5, 25.1, 35.0, 35.6, 45.2, 58.8, 60.4, 64.1, 97.3; m/z 172 (M^+), 155, 117, 101, 83, 55. (Found M^+ 172.1099, $\text{C}_9\text{H}_{16}\text{O}_3$ requires 172.1099).

E-2-hydroxymethyl 5-acetoxy-1,7-dioxaspiro [5,5] undecane (69)



Using the general procedure, 4,5-isopropylidene 4,5-dihydroxy pentanal (0.159g, 1mmol) was added to a solution of the anion of (38) (1mmol). The intermediate hydroxy enol ether was trapped with acetic anhydride (0.142ml, 2mmol) then subsequently treated with camphor sulphonic acid (catalytic) in methanol. Chromatography (ether-petrol) gave (69) (62mg, 33%) as a pale yellow oil. IR (film) 3456, 1634, 1373, 1180, 1078, 1046 cm^{-1} ; NMR δ (90MHz): 4.8 (1H, m, HCOAc), 3.9-3.5 (5H, m, OCH), 2.25 (1H, m), 2.10 (3H, s, OAc), 1.85-1.4 (10H, m); m/z 244 (M^+) 213, 153, 85, 55. (Found M^+ 244.1310, $\text{C}_{12}\text{H}_{20}\text{O}_5$ requires 244.1310).

Preparation of E-2-hydroxymethyl, 4-hydroxy-1,7-dioxaspiro [5,5] undecane (72)



A solution of the anion (38) (0.186g, 0.825mmol) was treated with the epoxide (70) (0.052g, 0.33mmol). The reaction was stirred at -25°C overnight. Chromatography (petrol/ether) gave (71) (0.052g, 65%) as a colourless oil. IR (film) 3482, 2934, 1675, 1063cm⁻¹; NMR δ (90MHz): 4.71 (1H, t, J=4.1Hz, H₃), 4.2-3.8 (5H, m, OCH₂), 3.5-3.4 (1H, m, OCH₂), 2.3-1.95 (5H, m), 1.65-1.30 (4H, m), 1.25 (6H, d, J=4.5Hz, Me); m/z 242 (M⁺), 227, 127, 87, 85. (Found M⁺-Me 227.1276. C₁₂H₁₉O₄ requires 227.1283).

The enol ether (71) was dissolved in methanol (2ml) containing camphor sulphonic acid (2mg), and stirred for 2h. Purification by chromatography (isopropyl alcohol/petrol) gave (72) (42mg, 70%) as a white crystalline solid mp 141-3°C. IR (mull) 3342, 1070, 1045cm⁻¹; NMR δ (250MHz): 4.16 (1H, tt, J=11, 5Hz), 3.82-3.50 (5H, m), 2.08-1.44 (12H, m), 1.36 (2H, m); ¹³C (22.51MHz): 18.6, 25.0, 35.2, 36.3, 44.9, 60.5, 64.2, 65.8, 68.7, 97.3. m/z 202 (M⁺), 184, 171, 153, 101. (Found: C, 59.27; H, 9.11; C₁₀H₁₈O₄ requires C, 59.39; H, 8.97%).

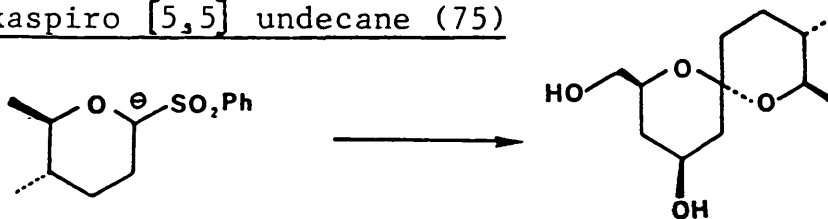
Preparation of 5(S), 6(R) dimethyl, 2-benzenesulphonyl tetrahydropyran (73)



The lactol (800mg, 6.15mmol) was added to a stirred solution of benzenesulphinic acid (1.25, 1.5eq) in dichloromethane (10ml) with a catalytic amount of camphor sulphonic acid. The reaction

was stirred for 2h, the excess acid washed out with water, extracting the sulphone into ether (3x15ml). Evaporation left a white solid which was recrystallised from petrol/ether to give (73) (0.76g, 72%) as colourless needles, mp 96-7°C. IR (CHCl₃) 1302, 1291, 1150, 1082, 644, 604cm⁻¹; NMR δ(250MHz): 7.9 (2H, m, ArH), 7.7-7.5 (3H, m, ArH), 4.65 (1H, br.d. J=6.2Hz, H₂), 4.20 (1H, dq, J=16.6, 7.5Hz, H₆), 2.61 (1H, md, J=13.3Hz, H₄), 2.05-1.6 (4H, m), 1.1 (3H, d, J=7.3Hz, Me), 0.9 (3H, d, J=7.3Hz, Me); m/z 255 (MH⁺), 142, 113, 95, 69. (Found: C, 61.52; H, 7.19; C₁₃H₁₈O₃S requires C, 61.39; H, 7.13%).

Preparation of 2(S)-hydroxy methyl, 4(S)-hydroxy- 8(R), 9(S) dimethyl-1,7-dioxaspiro [5,5] undecane (75)

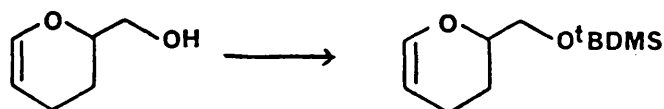


A solution of the anion (73) (0.210g, 0.825mmol) was treated with the epoxide (70) (0.052g, 0.33mmol). The reaction was stirred at -78°C for 4h, then warmed to rt. Chromatography after work-up gave (74) (72mg, 81%) which was immediately dissolved in methanol (3ml) with a catalytic amount of camphor sulphonic acid (2mg) and stirred overnight. Purification by chromatography (isopropyl alcohol/petrol) gave (75) (57mg, 76%) as a white crystalline solid, mp 152-154°C. IR (mull) 3342, 2970, 1093, 1050cm⁻¹; NMR δ(250MHz): 4.15 (1H, tt, J=4.95, 10.7 Hz, H₄), 3.6 (3H, m, H₁, H₂), 3.25 (1H, dq, J=6.6, 9.9Hz, H₈), 2.25 (2H, br.s, OH), 2.00 (1H, ddd, J=1.95, 4.95, 12.3Hz, H_{5eq}), 1.85 (1H, sym.m, J=2.05, 4.95, 12.3Hz, H_{3eq}),

1.70-1.40 (4H, m), 1.30 (3H, m, H_{3ax} , H_{5ax} , H_9), 1.05 (3H, d, $J=4.2\text{Hz}$, Me), 0.85 (3H, d, $J=4.2\text{Hz}$, Me); ^{13}C (22.51MHz): 17.8, 19.3, 27.8, 35.6, 36.2, 36.4, 44.7, 64.2, 65.7, 68.6, 71.3, 97.6; m/z 231 (MH^+), 213, 199, 186, 144, 126. (Found: C, 62.85; H, 9.64; $\text{C}_{12}\text{H}_{22}\text{O}_4$ requires C, 62.58; H, 9.63%).

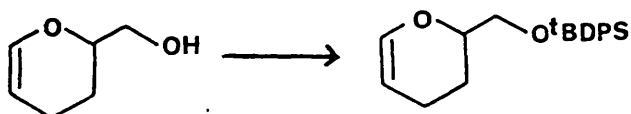
MODEL STUDIES

Preparation of 2-t-butyldimethylsilyloxymethyl-3,4-dihydro-2H-pyran (77)



The alcohol (1.04ml, 10mmol) was dissolved in dimethyl formamide (4ml) and imidazole (1.70g, 25mmol) added. The solution was cooled at 0°C and t-butyldimethylsilylchloride (1.88g, 12mmol) added. The reaction was warmed to rt and stirred for 4h. An aqueous workup, extracting the product into ether, evaporation and chromatography (petrol/ether) gave (77) (2.03g, 89%). IR (film) 3061, 2930, 1647, 1470, 1096, 909, 837cm⁻¹; NMR δ (90MHz): 6.35 (1H, d, J=5.2Hz, H₆), 4.75 (1H, m, H₅), 3.85 (1H, m, H₂), 3.70 (2H, m, H₁), 2.10-1.4 (4H, m), 0.9 (9H, s, t-butyl); m/z 229 (M⁺+1), 171, 115, 97, 85, 73. (Found: C, 63.15; H, 10.82; C₁₂H₂₄O₂Si requires C, 63.10; H, 10.59%).

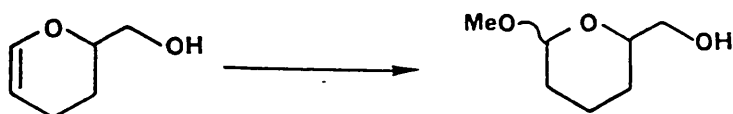
Preparation of 2-t-butyldiphenylsilyloxymethyl-3,4-dihydro-2H-pyran (78)



The alcohol (0.52 ml, 5mmol) was dissolved in dimethyl formamide (2ml) and imidazole (0.85g, 12.5mmol) was added. The solution was cooled to 0°C and t-butyldiphenylsilylchloride (1.56ml, 6mmol) added. The reaction was allowed to warm to rt and stirred overnight. An aqueous workup, extracting the product into ether, evaporation and Kugelrohr distillation gave (78) (1.62g, 92%)

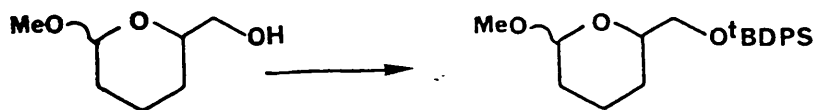
as a colourless oil, bp 160°C at 0.02mm Hg. IR (film) 3067, 2928, 1646, 1470, 1113, 1070, 908, 823cm⁻¹; NMR δ (250MHz): 7.8-7.7 (4H, m, ArH), 7.5-7.4 (6H, m, ArH), 6.45 (1H, d, J=7.1Hz, H₆) 4.75 (1H, m, H₅), 4.0 (1H, m, H₂), 3.8 (2H, dm, J=17.8Hz, OCH₂), 2.15-1.95 (3H, m), 1.80 (1H, m), 1.15 (9H, s, t-butyl); m/z No M⁺, 295, 199, 183, 84. (Found: C, 74.95; H, 8.27; C₂₂H₂₈O₂Si requires C, 74.95; H, 8.00%).

Preparation of 6-methoxy-2-hydroxy, methyl tetrahydropyran (79)



The enol ether (0.52ml, 5mmol) was dissolved in methanol (5ml) with a little camphor sulphonic acid and stirred at rt for 1h. Filtration, evaporation and chromatography (petrol/ether) gave (79) (0.53g, 92%) as a colourless oil. IR (film) 3462, 2942, 1439, 1368, 1068, 1034cm⁻¹; NMR δ (90MHz): 4.65 (0.75H, s, H₆), 4.25 (0.25H, br.d, J=9Hz H₆ (minor isomer)), 3.85-3.40 (3H, m, H₂, H₁, and 0.75H, s, Me (minor isomer)), 3.35 (2.25H, s, Me), 2.8-2.7 (1H, br.s OH), 1.80-1.25 (6H, m); m/z 146 (M⁺), 115, 97, 71, 58. (Found: C, 57.66; H, 9.89; C₇H₁₄O₃ requires C, 57.51; H, 9.65%).

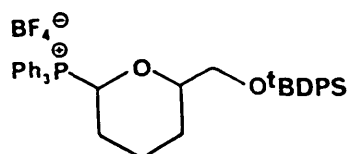
Preparation of 2-t-butyldiphenylsilyloxymethyl, 6-methoxy tetrahydropyran (8C)



The alcohol (79) (0.292g, 2mmol) was dissolved in dimethylformamide (2ml) and imidazole (0.34g, 2.5eq) added. The solution

was cooled to 0°C and t-butyldiphenylsilylchloride (0.62ml, 1.2eq) added. The reaction was stirred overnight at rt. An aqueous work-up, extracting the product into ether, evaporation and Kugelrohr distillation gave (80) (0.52g, 68%) as a colourless oil, bp 170°C at 0.02mm Hg. IR (film) 3069, 2931, 2856, 1470, 1112, 1030, 823cm⁻¹; NMR δ (250MHz): 7.7 (4H, m, ArH), 7.4 (6H, m, ArH), 4.75 (0.6H, br.s. H₆), 4.32 (0.4H, br.d J=10.7 Hz, H₆ (minor isomer)), 3.9-3.55 (3H, m, OCH) 3.5 (1.2H, s, OMe (minor isomer)), 3.35 (1.8H, s, OMe) 1.9-1.5 (6H, m), 1.1 (9H, s, t-butyl); m/z 383 (M⁺-H), 353, 327, 295, 199, 105, 77. (Found: C, 71.64; H, 8.65; C₂₃H₃₂O₃Si requires C, 71.83; H, 8.38%).

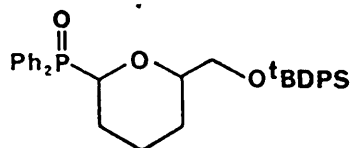
Preparation of 6-t-butyldiphenylsilyloxymethyl tetrahydro-pyran-2-yl triphenylphosphonium tetrafluoroborate (81)



(80) (0.382g, 1mmol) was added to a stirred solution of triphenylphosphonium hydrogen tetrafluoroborate (0.350g, 1mmol) in acetonitrile (4ml) under argon, and stirring continued for 4h. Evaporation of solvent left a white solid which was recrystallised from ether/dichloromethane to give (81) (0.56g, 80%) as white needles mp 144°C. IR (mull) 3066, 2938, 2857, 1438, 1066, 935, 823, 690cm⁻¹; NMR δ (250MHz): 7.85-7.5 (18H, m, ArH), , 7.45-7.20 (7H, m, ArH), 5.82 (1H, d, J=10.7Hz, H₆), 4.15 (1H, dd, J=5.35, 8.6Hz, H₁), 4.00 (1H, m, H₂) 3.80 (1H,

dd, $J=5.35, 8.8\text{Hz}$, H_1 ,), 2.10-1.70 (6H, m), 1.05 (9H, s, t-butyl); m/z (FAB) 615 (cation), 461, 369, 185. (Found: C, 68.50; H, 6.08; $C_{40}H_{44}O_2SiPBF_4$ requires C, 68.37; H, 6.31%).

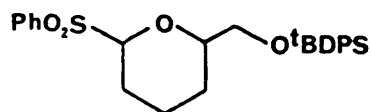
Preparation of 6-t-butyldiphenylsilyloxymethyl tetrahydropyran-2-yl diphenylphosphine oxide (82)



The phosphonium salt (81) (700mg, 1mmol) was dissolved in 3N sodium hydroxide and refluxed for 0.5h. The benzene phase was separated and the aqueous phase extracted with chloroform (3x 10ml), washed, dried and evaporated to leave a white foam which was recrystallised from dichloromethane/ether to give (82) (471mg, 85%) as white needles, mp 131°C . IR (mull) 2955, 1589, 1435, 1113, 1046, 823, 664cm^{-1} ; NMR δ (250MHz): 8.00-7.78 (4H, m, ArH), 7.7-7.55 (4H, m, ArH), 7.5-7.3 (12H, m, ArH), 4.62 (1H, br.d. $J=8.4\text{Hz}$, H_2), 4.35-4.2 (1H, m, H_6), 3.55 (2H, m, H_1 ,), 2.12-1.85 (3H, m), 1.75-1.5 (3H, m), 1.05 (9H, 2s, tBu); m/z (FAB) 554, 400, 308, 124. (Found: C, 73.83; H, 7.33, $C_{34}H_{39}O_3SiP$ requires C, 73.61; H, 7.08%).

Chlorodiphenylphosphine (0.18ml, 1mmol) was added dropwise to a solution of (8C) (0.38g, 1mmol) at 0°C under argon. The reaction was warmed to rt and stirring continued for a further 36h. Evaporation of solvent left a white foam which was recrystallised from dichloromethane/ether to give (82) (0.33g, 55%) as prepared above.

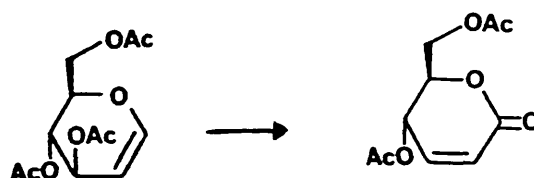
Preparation of 6-t-butylldiphenylsilyloxymethyl, 2-benzenesulphonyl tetrahydropyran (83)



The enol ether (0.350g, 1mmol) was dissolved in dichloromethane (10ml) and added to a stirred solution of benzenesulphinic acid (0.142g, 1mmol) under argon. Stirring was continued for 2h, the solvent evaporated and chromatography (petrol/ether) gave (83) (0.327g, 68%) as a viscous oil. IR (film) 3067, 2930, 1470, 1306, 1147, 1113, 1048, 823cm⁻¹; NMR δ (250MHz): 7.9-7.8 (2H, m, ArH), 7.7-7.5 (5H, m, ArH), 7.45-7.2 (8H, m, ArH), 4.70-4.55 (2H, m, H₂, H₆), 3.55 (2H, dd, J=2.1, 5.2Hz, H₁,) 2.65 (1H, br.d. J=12.5 Hz), 2.35-2.1 (1H, m), 1.95-1.7 (4H, m), 1.05 (9H, 2s, t-butyl); m/z No M⁺, 295, 256, 199, 77. (Found: C, 67.99; H, 6.87; C₂₈H₃₄O₄SiS requires C, 67.98; H, 6.93%).

(80) (0.343g, 0.9mmol) was added to a stirred solution of benzene sulphinic acid (0.130g, 0.9mmol) in dichloromethane (5ml) with a catalytic amount of camphor sulphonic acid. Stirring was continued overnight then the solution filtered, evaporated and chromatographed (petrol/ether) to give (83) (117mg, 24%) as prepared above and starting material (156mg).

Preparation of 5-(S)-acetoxy-6-(S)-(acetoxymethyl) 5,6-dihydro-2H-pyran-2-one (85)



m-Chloroperbenzoic acid (0.95g, 5.5mmol) was added to a stirred solution of tri-O-acetyl-D-glucal (84) (1.36g, 5mmol) in dichloromethane (20ml) at -5°C . Then boron trifluoride etherate (0.61ml, 5mmol) was added dropwise and the reaction warmed to room temperature and stirred for 20min. The mixture was then poured into sodium bicarbonate solution, extracted with dichloromethane, the solvent removed under reduced pressure. The crude residue was stirred in chloroform (10ml) and filtered to remove the benzoic acid, then distilled by Kugelrohr to yield (85) (1.01g, 88%) as a colourless oil, bp 120°C at 0.02mm Hg. IR (film) 1741, 1639, 1225cm^{-1} ; NMR δ (90MHz): 6.75 (1H, dd, $J=9.3, 3.0\text{Hz}$, H_4), 6.10 (1H, dd, $J=9.3, 1.5\text{Hz}$, H_3), 5.50 (1H, dp, $J=7.2, 2.0, 1.5\text{Hz}$, H_5), 4.65 (1H, m, H_6), 4.25 (2H, m, CH_2), 2.15 (3H, s, OAc), 2.10 (3H, s, OAc); m/z 229 (M^+), 186, 155, 113, 96. (Found: C, 52.48; H, 5.44; $\text{C}_{10}\text{H}_{12}\text{O}_6$ requires C, 52.63; H, 5.30%) $[\alpha]_{\text{D}}^{20} = +128^{\circ}$ ($c=2$, CHCl_3) (lit $[\alpha]_{\text{D}} = +129^{\circ}$ ($c=1$, CHCl_3)).

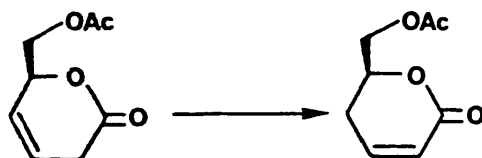
Preparation of 6-(S)-acetoxymethyl 3,6 - dihydro-2H-pyran-2-one (86)



The ene-lactone (85) (0.23g, 1mmol) was stirred with freshly prepared zinc amalgam (Zn(1g), HgCl(0.2g), HCl(0.1ml), H_2O (3ml)) in dry ether (10ml) with sodium sulphate at 0°C . Hydrogen chloride dissolved in dry ether (1ml, 2mmol) was added dropwise over 2h with rapid stirring, maintaining the temperature at 0°C .

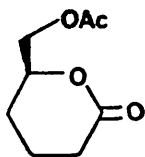
The solution was poured into ether, saturated with sodium hydrogen carbonate to neutralise, then filtered through a silica pad and concentrated under reduced pressure to leave a yellow oil. Purification by chromatography (petrol/ether) gave (86) 0.113g, 66%) as a colourless oil. IR (film) 2957, 1735, 1220 cm^{-1} ; NMR δ (250MHz): 5.95 (1H, m, H_4), 5.80 (1H, dq $J=10$, Hz, H_5), 5.15 (1H, m, H_6), 4.25 (2H, m, CH_2), 3.12 (2H, m, H_3), 2.05 (3H, s, OAc); m/z No (M^+), 140, 110, 98, 43. (Found: C, 56.37; H, 5.81; $\text{C}_8\text{H}_{10}\text{O}_4$ requires C, 56.47; H, 5.92%). $[\alpha]_{\text{D}}^{20} = -107^\circ$ ($c=1$, CHCl_3) (lit $[\alpha]_{\text{D}} = -113^\circ$ ($c=1.25$, CHCl_3)).

Preparation of 6-(S)-acetoxymethyl 5,6 - dihydro-2H-pyran-2-one (87)



The unconjugated lactone (124mg, 0.73mmol) was dissolved in tetrahydrofuran (5ml) and 1,8-diazobicyclo (5.4.0) undec-7-ene (DBU) (0.011ml, 0.1eq) added at 25 $^\circ\text{C}$. Stirring was continued for 1h, then the solution filtered through a short silica pad and evaporated under reduced pressure to leave a slightly yellow oil. Purification by chromatography (ether) gave (87) (116mg, 93.5%) as a colourless oil. IR (film) 2957, 1735, 1220 cm^{-1} ; NMR δ (90MHz): 6.90 (1H, m, H_4), 6.05 (1H, dt, $J=10.8$, 1.8Hz, H_3), 4.70 (1H, m, H_6), 4.25 (2H, d, $J=5.4\text{Hz}$, CH_2), 2.40 (2H, m, H_5), 2.05 (3H, s, OAc); m/z No (M^+), 140, 110, 98, 43. (Found: C, 56.29; H, 5.82; $\text{C}_8\text{H}_{10}\text{O}_4$ requires C, 56.47; H, 5.92%).

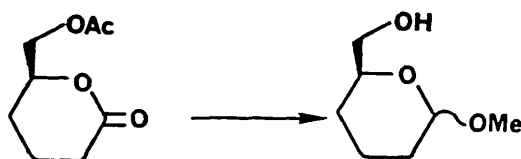
Preparation of 6-(S)-acetoxymethyl tetrahydropyran-2-one (88)



The conjugated lactone (87) (100mg, 0.59mmol) was dissolved in ethyl acetate (8ml) and palladium on active carbon (10%) (20mg) added. The reaction was stirred under a hydrogen atmosphere for 12h. The catalyst was filtered off, the solvents evaporated under reduced pressure and chromatography gave (88) (56mg, 55%) as a colourless oil. IR (film) 2950, 1740, 1230 cm^{-1} ; NMR δ (90MHz): 4.40 (1H, m, H_6), 4.25 (2H, d, $J=5.2\text{Hz}$, CH_2), 2.05 (3H, s, OAc), 1.92-1.65 (6H, m); m/z 173 (MH^+), 131, 113, 99, 55, 43. (Found: C, 55.70; H, 7.15; $\text{C}_8\text{H}_{12}\text{O}_4$ requires C, 55.81; H, 7.02%).

The unconjugated lactone (86) (58mg, 0.34mmol) was dissolved in methanol (4ml) and platinum (IV) oxide (12mg) added. The reaction was stirred under a hydrogen atmosphere until the orange colour had changed to black (1h). The catalyst was filtered off, the solvents evaporated under reduced pressure and chromatography (ether) gave (88) (42mg, 72%) as a colourless oil and identical to that prepared above.

Preparation of 6-methoxy-2-hydroxy,methyl tetrahydropyran (79)



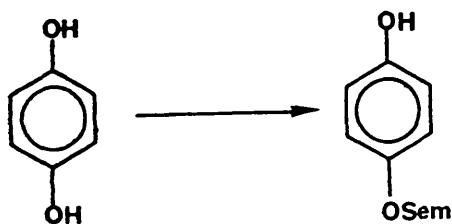
The lactone (42mg, 0.25mmol) was dissolved in tetrahydrofuran (3ml) and added to a stirred solution of diisobutylaluminium hydride (0.77ml , 3.2eq) in tetrahydrofuran (3ml) at -78°C . Stirring was continued at -78°C for 2h, water (0.10ml) added, the reaction warmed to 0°C , solid sodium hydrogen carbonate added with rapid stirring and the reaction warmed to room temperature. Filtration through a silica pad, and evaporation left a sticky oil which was immediately dissolved in methanol (3ml) with camphor sulphonic acid and stirred for 0.5h at room temperature. The solution was filtered through a silica pad, evaporated and column chromatography (ether/petrol) gave (79) (25mg, 68%) as a colourless oil, and identical to that prepared previously.

Deprotonation of Benzoxazole

Benzoxazole (0.124g, 1mmol) was dissolved in ether (5ml) and n-butyllithium (0.76ml, 1.1eq) added at -78°C . The red coloured anion formed immediately and was quenched with deuterium oxide (0.018ml, 1mmol) after 5mins and allowed to warm to rt. The reaction was quenched with ammonium chloride solution, extracted into ether and the ethereal fractions washed with brine and dried. Concentration and purification by chromatography (ether/petrol) gave (44.6mg, 38%) as a waxy white solid. (69% product

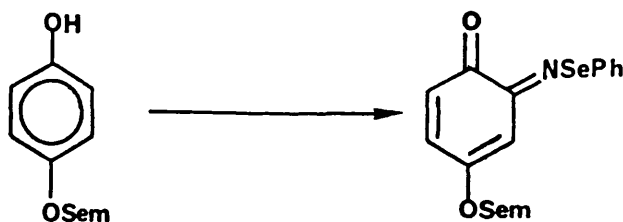
deuterated) NMR δ (250MHz): 8.1 (0.31H, s, H₁), 7.8 (1H, m) 7.62 (1H, m), 7.4 (2H, m); m/z 128 (M⁺) (deuterated), 127 (M⁺), 92, 64.

Preparation of 4-(2'-trimethylsilylethoxymethyl) phenol
(89)



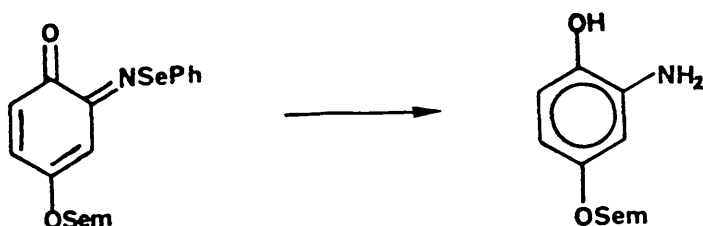
Hydroquinone (1.10g, 10mmol) was dissolved in ether (4ml)/dimethylformamide (2ml) and added dropwise to a suspension of sodium hydride (0.44g, 1.1eq) in ether (20ml)/dimethylformamide (7ml) under argon at 25°C. A green slurry developed and was stirred for 10min, then a solution of 2-trimethylsilylethoxy methyl chloride (1.76ml, 10mmol) in ether (4ml) was added and stirring continued for 15h. The reaction was poured into water (20ml) extracted into ether, washed with sodium hydroxide (10%), water and brine, dried and evaporated. Chromatography (petrol/ether) gave (89) (1.49g, 62%) as a pale yellow oil. IR (film) 3398, 1507, 1249, 1088, 860, 833, 759cm⁻¹; NMR δ (250MHz): 6.9 (2H, m, ArH), 6.75 (2H, m, ArH), 5.15 (2H, s, OCH₂O), 4.75 (1H, br.s, OH), 3.75 (2H, t, J=8Hz, CH₂O), 0.95 (2H, t, J=8Hz, CH₂Si), 0.0 (9H, s, SiMe); m/z 240 (M⁺), 210, 167, 110, 93, 75, 73. (Found: C, 59.85; H, 8.24; C₁₂H₂₀O₃Si requires C, 59.96; H, 8.39%).

Preparation of 4-(2'-trimethylsilylethoxymethyl) 1,2
benzoquinone - 2-phenylselenoimine (90)



The phenol (89) (1.20g, 5mmol) was dissolved in dry benzene (30ml) and hexamethyl disilazane (1.16ml, 1.1eq) and benzene seleninic anhydride (1.80g, 1eq) added. The reaction was stirred at rt for 0.5h. A deep red colour developed immediately. The reaction was diluted with chloroform (10ml) and filtered. Evaporation and chromatography (petrol/ether) gave (90) (1.51g, 73%) as a blood red oil. IR (film) 1633, 1601, 1541, 1248, 1090, 859, 832, 737 cm^{-1} ; NMR δ (90MHz): 8.0-7.1 (6H, m, ArH), 6.85-6.70 (2H, m, ArH), 5.15 (2H, s, OCH_2O), 3.75 (2H, t, $J=8\text{Hz}$, OCH_2), 0.95 (2H, t, $J=8.2\text{Hz}$ CH_2Si), 0.0 (9H, s, SiMe); m/z 409 (M^+), 407, 351, 336, 314, 157, 73. (Found C, 52.79; H, 5.63; N, 3.34; $\text{C}_{18}\text{H}_{23}\text{O}_3\text{NSiSe}$ requires C, 52.93; H, 5.67; N, 3.42%).

Preparation of 2-amino-4-(2'-trimethylsilylethoxymethyl)
phenol (91)

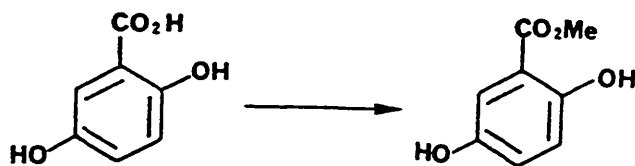


The selenoimine (90) (100mg, 0.25mmol) was dissolved in benzene (10ml) and benzenethiol (1.5ml) added. Stirring was continued until the deep red colour had disappeared (approx 5h). Evaporation of solvent and chromatography (petrol/ether) gave (91) (10mg, 15%) as a pale yellow oil. IR (film) 3450, 2954, 1479, 1250, 734 cm^{-1} ; NMR δ (250MHz): 7.21 (1H, m, ArH), 6.65 (1H, d, J=6.3Hz, ArH), 6.55 (1H, d, J=6.2Hz, ArH), 6.15 (1H, br.s. OH), 5.15 (2H, s, OCH₂O), 3.82 (2H, br.s. NH₂), 3.75 (2H, m, CH₂O), 0.95 (2H, m, CH₂Si), 0.0 (9H, s, SiMe₃); m/z 255 (M⁺), 240, 225, 182, 167, 110, 73.

Method for Reductive Acetylation of Selenoimine

The selenoimine (90) (41mg, 0.1mmol) was dissolved in acetic anhydride (2ml), zinc dust (60mg) added, then acetic acid (3 drops) and pyridine (1 drop) added. (The reaction flask was kept in an ice-bath). The solution was stirred for 1h, extracted into ether, dried and evaporated under reduce pressure. None of the desired product was recovered.

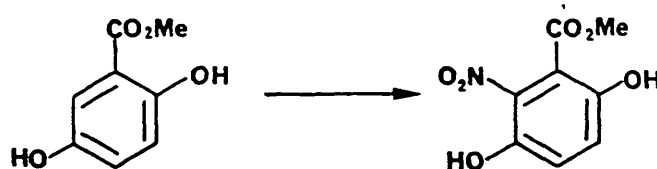
Preparation of methyl 2,5-dihydroxybenzoate (93)



2,5 Dihydroxybenzoic acid (92) (2.10g, 15mmol) was dissolved in methanol (40ml) with 3% hydrochloric acid and refluxed for

3h. The solution was diluted with water, neutralised with sodium hydrogen carbonate, extracted into ether, dried and evaporated to leave a white solid. Recrystallisation from chloroform/petrol gave (93) (2.26g, 90%) as fine colourless needles. IR (CHCl_3) 3592, 3256, 1684, 1618, 1309, 1080cm^{-1} ; NMR δ (90MHz): 10.30 (1H, s, OH), 7.35-6.90 (3H, m, ArH), 4.80 (1H, br.s, OH), 3.95 (3H, s, Me); m/z 168 (M^+) 136, 108, 80.

Preparation of methyl-3,6-dihydroxy-2-nitrobenzoate (94)



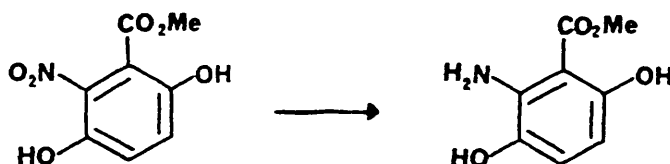
Nitration methods:-

1. The ester (0.2g, 1.2mmol) was dissolved in chloroform (3ml) and cupric nitrate (0.36g, 1.2mmol) added. Trifluoroacetic anhydride (3ml) was added dropwise and the reaction stirred at room temperature for 1h. The resulting solution was diluted with dichloromethane (10ml), and poured into ice/water (25ml). The aqueous layer was separated and extracted with dichloromethane (2x20ml). The combined organic layers were washed with sodium hydrogen carbonate (1%), water, brine, dried and evaporated. Purification by recrystallisation from benzene or column chromatography (ether/petrol) gave (94) (160mg, 62%) as pale orange crystals, mp 124°C . IR (CHCl_3) 3242, 1685, 1620, 1530, 1310cm^{-1} ; NMR δ (250MHz): 10.80 (1H, br.s. OH), 10.08 (1H, v.br.s. OH),

7.55 (1H, d, J=7.5Hz, ArH), 7.45 (1H, d, J=7.5Hz, ArH), 3.90 (3H, s, OMe); m/z 213 (M^+), 181, 151, 107, 53.

2. The ester (0.4g, 2.3mmol) was dissolved in chloroform (3ml) and ammonium nitrate (0.184g, 2.3mmol) added. Trifluoroacetic anhydride (3ml) was added dropwise and the reaction stirred at room temperature for 1h. Work-up and purification as above gave (94) (361mg, 73.5%), identical to that prepared before.
3. The ester (0.4g, 2.4mmol) was dissolved in acetic anhydride (3ml) and finely ground cupric nitrate (0.72g, 3.0mmol, 1.25eq) added slowly, maintaining the reaction temperature below 50°C. When addition was complete the reaction was stirred for 1h at room temperature. Work-up and purification as previously gave (94) (260mg, 51%), identical to that prepared before.
4. The ester (0.336g, 2mmol) was dissolved in ether (4ml) and nitric acid (0.085ml, 2mmol) added at 25°C. Stirring was continued for 0.5h, the solution became dark brown. Dilution with ether (10ml), filtration through a silica pad, evaporation and chromatography (ether/ethyl acetate) gave (94) (298mg, 70%), identical to that prepared above.

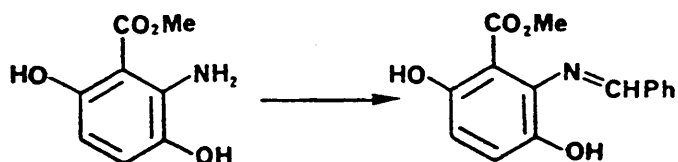
Preparation of methyl-3,6-dihydroxy-2-aminobenzoate (95)



Reduction Methods:-

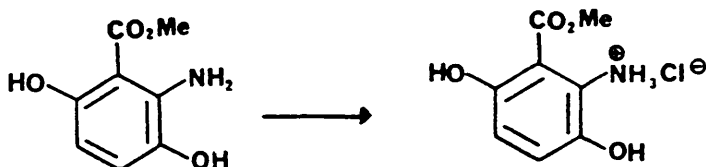
1. The nitro ester (94) (200mg, 0.94mmol) was dissolved in methanol (5ml) and platinum (IV) oxide (15mg) added. The reaction was stirred under a hydrogen atmosphere for 0.5h, the catalyst filtered off, the solvents evaporated and purification by chromatography (ether/petrol) gave (95) (131mg, 76%) as pale yellow crystals mp 162-163°C IR (mull) 3318, 1670, 1609, 1441, 1340, 756cm⁻¹; NMR δ (250MHz): 9.70 (1H, br.s.OH), 7.80 (1H, br.s.OH), 6.60 (1H, d, J=7.2Hz, ArH), 6.52 (1H, d, J=7.2Hz, ArH), 4.56 (2H, br.s. NH₂), 3.88 (3H, s, OMe); m/z 183(M⁺), 151, 123, 95.
2. The nitro ester (94) (80mg, 0.37mmol) was dissolved in methanol (3ml) and palladium on activated carbon (10%) (5mg) added. The reaction was stirred under a hydrogen atmosphere for 15h, then worked up as previously to yield (95) (51mg, 75%), identical to that prepared before.
3. The nitro ester (94) (100mg, 0.47mmol) was dissolved in ethanol (5ml) with calcium chloride (excess) and zinc (10mg) The resulting slurry was refluxed for 2h, filtered through a silica pad, evaporated and purified by column chromatography (ether/petrol) to yield (95) (22mg, 25.5%), identical to that prepared before.

Preparation of methyl-3,6-dihydroxy-2-(benzylideneamino) benzoate (96)



The aminophenol (95) (100mg, 0.55mmol) was dissolved in ethanol (5 ml) and a solution of benzaldehyde (0.053ml, 0.95eq) in ethanol (1 ml) added. The solution was refluxed overnight, cooled, filtered through a silica pad and evaporated to yield the Schiff base (96) (68mg, 45.5%) as yellow crystals. IR (mull) 3363, 1670, 1477, 1215, 756cm⁻¹; NMR δ (90MHz): 10.30 (1H, s, OH), 9.95 (1H, s, OH), 8.50 (1H, s, =CHPh), 7.95-7.80 (2H, m, ArH), 7.60-7.55 (3H, m, ArH), 7.15 (1H, d, J=5.2Hz, ArH) 6.85 (1H, d, J=5.2Hz, ArH), 3.90 (3H, s, OMe); m/z 271 (M⁺), 239, 211, 183, 108, 89. (Found M⁺ 271.0837, C₁₅H₁₃NO₄ requires 271.0844).

Preparation of methyl-3,6-dihydroxy-anthranilate hydrochloride
(98)



The aminophenol (95) (200mg, 1.1mmol) was dissolved in ether. Dry ether (5ml) was saturated with dry hydrogen chloride, and this solution was added dropwise with stirring to the aminophenol solution. A fine white precipitate formed almost immediately. The ether was decanted off, the precipitate washed several times with ether, dried and recrystallised from hot methanol and ether to yield (98) (207mg, 85%) as fine cream crystals. IR (mull) 3325, 1670, 1600, 1450, 750cm⁻¹; NMR δ (90MHz): 9.70 (1H, br.s. OH), 7.90 (1H, br.s. OH), 6.85 (1H, d,

$J=7.5\text{Hz}$, ArH), 6.50 (1H, d, $J=7.5\text{Hz}$, ArH), 4.05 (2H, br.s. NH_2), 3.90 (3H, s, OMe); m/z 183 (M^+) 151, 123, 95, 36. (Found C, 43.52; H, 4.77; N, 6.18; $\text{C}_8\text{H}_{10}\text{O}_4\text{NCl}$ requires C, 43.75; H, 4.59; N, 6.37%).

Preparation of ethyl polyphosphate

Phosphorus pentoxide (22g), chloroform (22ml) and ether (45ml) were refluxed for 35h. The mixture was filtered and evaporated to leave a viscous pale yellow syrup which was used immediately.

Attempted cyclisations

The aminophenol (95) (91.5mg, 0.5mmol) and benzoic acid (61mg, 0.5mmol) were dissolved in chloroform (5ml). Triethylamine (0.21ml, 1.5mmol, 3eq) and ethyl polyphosphate (950mg) were added and the mixture refluxed for 12h. The solvent was removed, ice, water and solid sodium bicarbonate added and the reaction stirred for a further hour to decompose the excess ethyl polyphosphate. The mixture was then extracted into ethylacetate, washed, dried and evaporated. The residual oil was chromatographed (petrol/ether) to yield (97) (72mg, 51%) as a white solid. m/z 287 (M^+), 269, 255, 168, 136, 105 confirming the amide had failed to cyclise.

Benzoic acid (69mg, 0.57mmol, 1.2eq) was dissolved in dimethylformamide (20ml), triethylamine (0.23ml) and (98) (100mg, 0.45mmol) added followed by benzotriazol-1-yl-oxy-tris (dimethylamino) phosphonium hexafluorophosphate (200mg).

The reaction was stirred at 50°C for 12h, poured into water, extracted into chloroform, dried and evaporated. The residual oil was chromatographed (petrol/ether) to give (97) (95mg, 74%) as a white solid.

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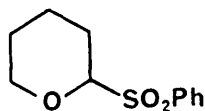
PREPARATION AND REACTIONS OF 2-BENZENESULPHONYLTETRAHYDROPYRAN

Steven V. Ley*, Barry Lygo and Anne Wonnacott

Department of Chemistry, Imperial College, London SW7 2AY.

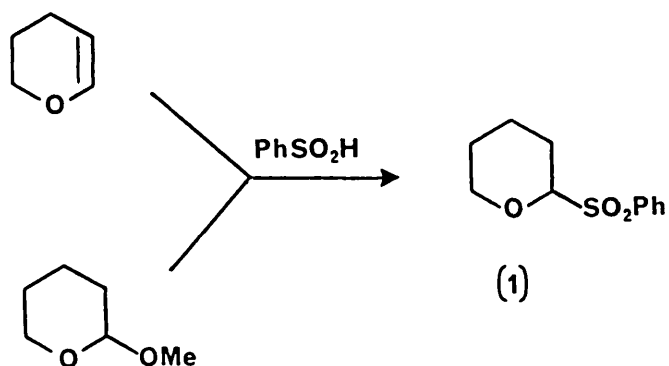
Summary: The anion derived from 2-benzenesulphonyltetrahydropyran (1) reacts with various electrophiles to give alkylated or acylated products some of which are useful precursors for spiroketal synthesis.

Methods for forming carbon-carbon bonds at the 2-position of cyclic ethers are currently of importance in synthesis.¹ Our recent observation that 2-diphenylphosphinoxy cyclic ethers undergo the Wittig-Horner reaction with aldehydes or lactols is one solution to this problem.² These results, however, prompted the idea that similar 2-benzenesulphonyl derivatives might provide an alternative and potentially more flexible approach. Here we report preliminary observations upon the use of the anion derived from 2-benzenesulphonyltetrahydropyran (1).

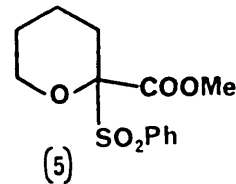
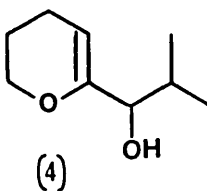
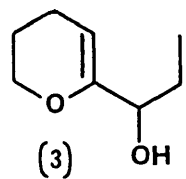
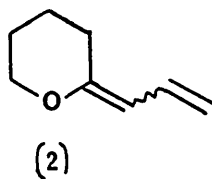


(1)

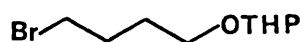
The crystalline and easily handled sulphone (1) was obtained by reaction of either 3,4-dihydro-2H-pyran or 2-methoxytetrahydropyran with benzenesulphinic acid. During this last process the reaction rate was noticeably enhanced by the addition of calcium chloride.



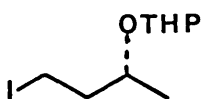
Deprotonation of (1) was readily achieved using one equivalent of *n*-butyllithium at -78°C in tetrahydrofuran. The resulting anion was subsequently reacted with a variety of electrophilic species. For example with allylbromide the volatile exocyclic diene (2) was obtained in 55% yield; directly upon work-up with saturated ammonium chloride, there being no need to eliminate benzenesulphonic acid in a separate step. Similarly reaction of the anion with aldehydes such as acrolein or iso-butylaldehyde afforded (3) and (4) in 76% and 77% yields respectively again by simultaneous loss of benzenesulphonic acid. Reaction with methylchloroformate produced the acylated derivative (5) (81%).



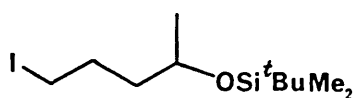
Application of the chemistry to the preparation of spiroketals is also possible. Reactions of the anion from (1) with the bromide (6) affords an intermediate which on protic work-up with camphor sulphonic acid gave the naturally occurring spiroketal pheromone (7) previously isolated from *Dacus oleae*.³ In a similar way reaction of the optically active iodide (8) provides the natural product (9)⁴ (79%) in its optically pure form ($[\alpha]^{20} - 12.1^\circ$). Alkylation of the anion with (10) gave the spiroketal (11) (47%) after protonation. The anion from (1) also reacts with the dimethyl *t*-butylsilyl protected iodide (12) to give (7) (52%) on acidic work-up.



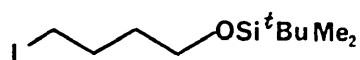
(6)



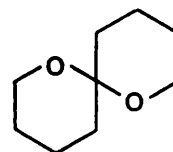
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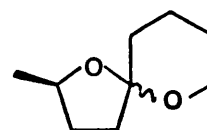
(10)



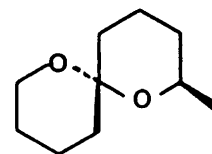
(12)



(7)



(9)



(11)

Reactions of anions α to both oxygen and the phenylsulphonyl group have so far found limited use in the literature.⁵ We believe these new results will promote further applications in a variety of useful transformations.

We thank the SERC, Pfizer Central Research, Sandwich, Kent and the Wolfson Foundation for generous financial support.

Footnotes.

All new compounds were fully characterised by spectroscopic microanalytical and/or accurate mass data.

Later reactions showed that the addition of camphor sulphonic acid was not necessary owing to the concomitant formation of phenylsulphinic acid during the neutralisation of reaction mixture.

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WITTIG AND HORNER-WITTIG COUPLING REACTIONS OF 2-SUBSTITUTED CYCLIC ETHERS AND THEIR APPLICATION TO SPIROKETAL SYNTHESIS

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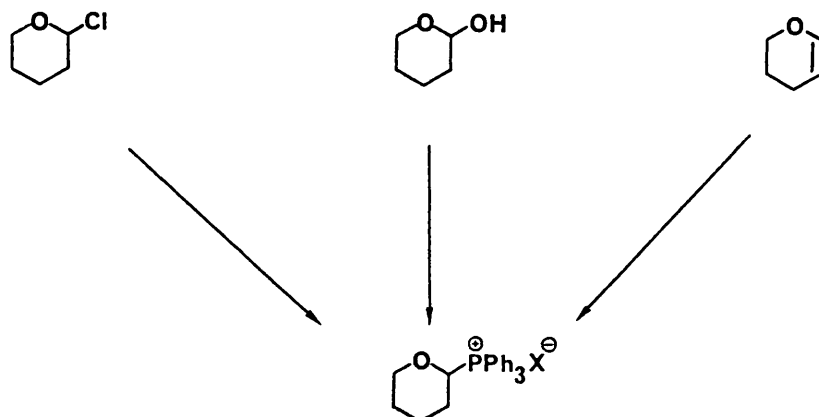
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Abstract: Wittig and Horner-Wittig coupling reactions of tetrahydropyran or tetrahydrofuran 2-triphenylphosphonium salts or 2-diphenylphosphine oxides with aldehydes and lactols affords good yields of the corresponding enol ethers. In selected examples these enol ether products may be further converted to spiroketals some of which are natural pheromones derived from *Dacus oleae* and *Paravespula vulgaris*.

The preparation of enol ethers using Wittig related procedures is of course well known and is an important synthetic transformation.¹ Remarkably however, the use of phosphoranes or diphenylphosphinoxy carbanions at the 2-position of cyclic ethers has not been exploited.² In view of the developing interest, for natural product synthesis, in being able to form new carbon-carbon bonds at this position, we have undertaken a more detailed study of these potentially very versatile systems.^{3,4}

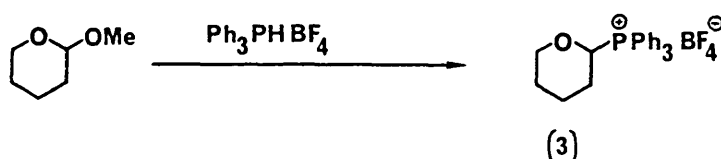
The preparation of the initially required tetrahydro-2H-pyran-2-yl triphenylphosphonium salt (1) by reaction of PPh_3 with the corresponding anomeric chloride resulted in a poor chemical yield, probably due to the instability of the starting material. However this problem was overcome by using conditions which formed the anomeric chloride *in situ*, either by treating the lactol with PPh_3 in benzene with gaseous hydrogen chloride for 5 h which gave the salt in 85% yield, or alternatively by reacting 2,3-dihydropyran under the same conditions give the salt in 90% yield. (Scheme 1)



- (1) $\text{X} = \text{Cl}$
 (2) $\text{X} = \text{Br}$

Scheme 1

Owing to the fact that the phosphonium chloride (1) could not be purified to acceptable microanalytical levels alternative methods to more stable salts were investigated. For example, when the same starting materials were subjected to gaseous hydrogen bromide under the previous conditions, the pure phosphonium salt (2) was obtained in 80% yield. Although the best procedure involved treating 2-methoxy tetrahydropyran with triphenylphosphonium tetrafluoroborate in acetonitrile for 4 h which gave the salt (3) in essentially quantitative yield. (Scheme 2) In this case compound (3) was easily purified by recrystallisation and appeared much more stable to heat than the corresponding chloride or bromide.

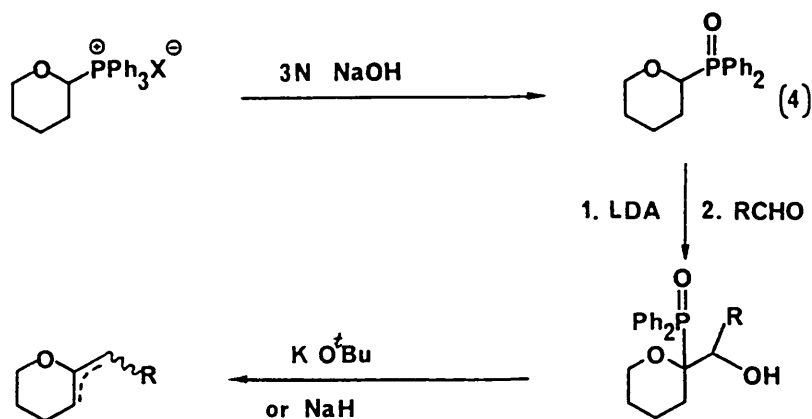


Scheme 2

The phosphonium chloride and bromide salts were readily deprotonated with *n*-butyllithium in THF at -10°C over 30 min to generate the deep red phosphorane although subsequent Wittig coupling reactions of the phosphorane with either aldehydes or lactols afforded only low yields of product (Table 1). This was probably due to other by-products being formed which were derived from ring opening of the tetrahydropyran unit. It is also possible that the reaction with *n*-butyllithium at -10°C leads to some decomposition of the salt. Attempts to improve the reaction by adding HMPA as a cosolvent were not successful. On the other hand results using the phosphonium tetrafluoroborate salt (3) were much better. Generation of the phosphorane by treating the salt (3) with *n*-butyllithium at -78°C and quenching with an aldehyde or lactol at this temperature, gave after work-up, the desired enol ethers in good yields (Table 1). Elimination of the triphenylphosphine oxide during these reactions was rapid as the mixture was warmed to room temperature and gave a mixture of three possible isomers (*E*, *Z* and *endo*) which were not separable by chromatography but could be identified by their NMR data.

Since it was known that phosphoranes with a β -oxygen substituent are thermally unstable and do not react particularly well in the Wittig reaction,⁵ the use of phosphine oxide anions [Horner-Wittig couplings] have been recommended in some cases.^{1c} This modification has also been applied to this work.

The triphenylphosphonium salt (1) was first converted to the corresponding diphenylphosphine oxide (4) by treatment with aqueous sodium hydroxide at reflux in 80% yield. Subsequent deprotonation of the diphenylphosphine oxide was achieved with lithium diisopropyl amide at -78°C , to form a deep red anion which reacted rapidly with the aldehyde or lactol. Treatment of the crude phosphine oxide adduct with either potassium *t*-butoxide in tetrahydrofuran at room temperature for 1 h or sodium hydride in dimethylformamide for 2 h at 50°C , resulted in the elimination of the diphenylphosphinic acid to give the coupled product again as a mixture of isomers (*E*, *Z* and *endo*) as in the previous Wittig method (Table 1) (Scheme 3).



Scheme 3

We have also studied the related Wittig and Horner-Wittig coupling reactions of the corresponding tetrahydrofuran derivatives. Treatment of 2,3-dihydrofuran with triphenylphosphine and gaseous hydrogen chloride gave the tetrahydrofuran-2-yl-triphenylphosphonium chloride (25) in 88% yield. As this salt could not be satisfactorily purified the deprotonation studies were not investigated. However, hydrolysis with aqueous sodium hydroxide at reflux gave the tetrahydrofuran-2-yl diphenylphosphine oxide (26) in 82% yield. Deprotonation with lithium diisopropylamide at -78°C produced a deep red anion which could be quenched by various aldehydes and lactols. (Table 2)[†]

Other phosphine oxides were similarly studied, these included 5-methoxytetrahydrofuran-2-yl diphenylphosphine oxide, (27) prepared by adding chlorodiphenylphosphine to 2,5 dimethoxy tetrahydrofuran at 0°C in dichloromethane (67%) and 5-methoxy-tetrahydrofuran-2-yl diethoxy phosphine oxide (28) prepared by treating 2,5-methoxy tetrahydrofuran with diethylchlorophosphite under the same conditions (48%). These salts carry additional functionality which could be usefully elaborated at a later stage in a synthetic scheme.

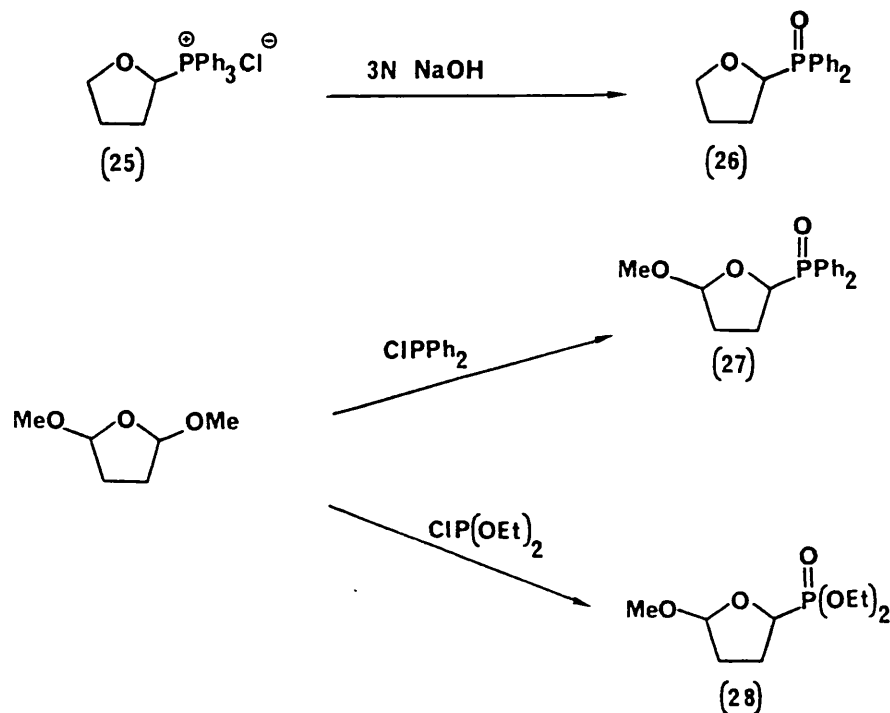
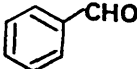
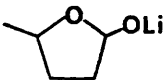
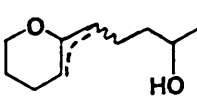
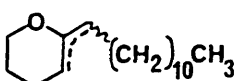
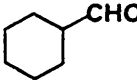
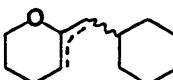
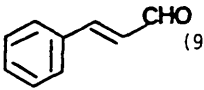
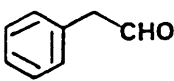
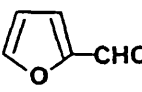
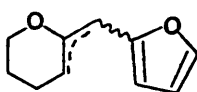
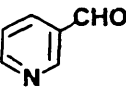
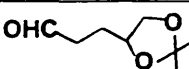
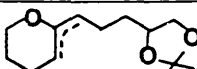
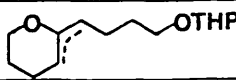
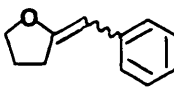
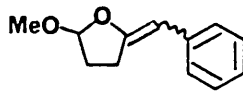
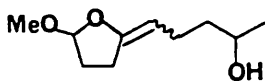


Table 1

Phosphonium salt/ Phosphine oxide	Aldehyde or Lactol	Product	Yield%
(1)	 (5)	 (15)	24*
(2)	(5)	(15)	31
(3)	(5)	(15)	79
(4)	(5)	(15)	76
(2)	 (6)	 (16)	12
(3)	(6)	(16)	33
(4)	(6)	(16)	59.5
(1)	$\text{CH}_3(\text{CH}_2)_{10}\text{CHO}$ (7)	 (17)	0
(2)	(7)	(17)	0
(3)	(7)	(17)	40
(4)	(7)	(17)	71
(1)	 (8)	 (18)	0
(3)	(8)	(18)	53
(4)	(8)	(18)	68
(3)	 (9)	 (19)	0
(4)	(9)	(19)	78
(3)	 (10)	 (20)	0
(4)	(10)	(20)	68
(3)	 (11)	 (21)	60
(4)	(11)	(21)	41
(3)	 (12)	 (22)	41
(4)	(12)	(22)	64
(4)	 (13)	 (23)	65
(4)	$\text{OHC}(\text{CH}_2)_4\text{OTHP}$ (14)	 (24)	62

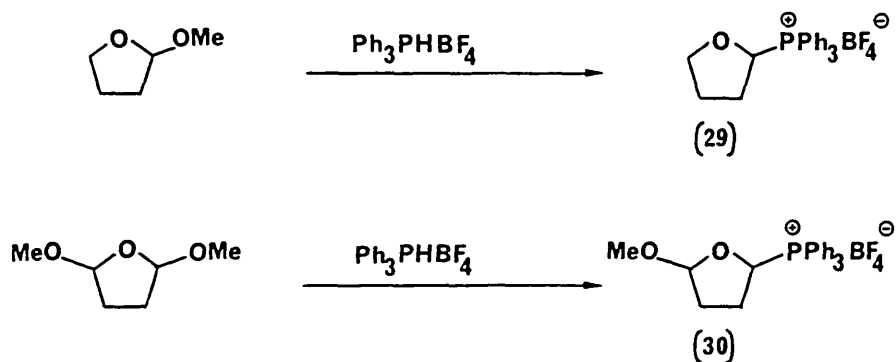
* All yields are of pure products, purified by Kugelrohr distillation

Table 2

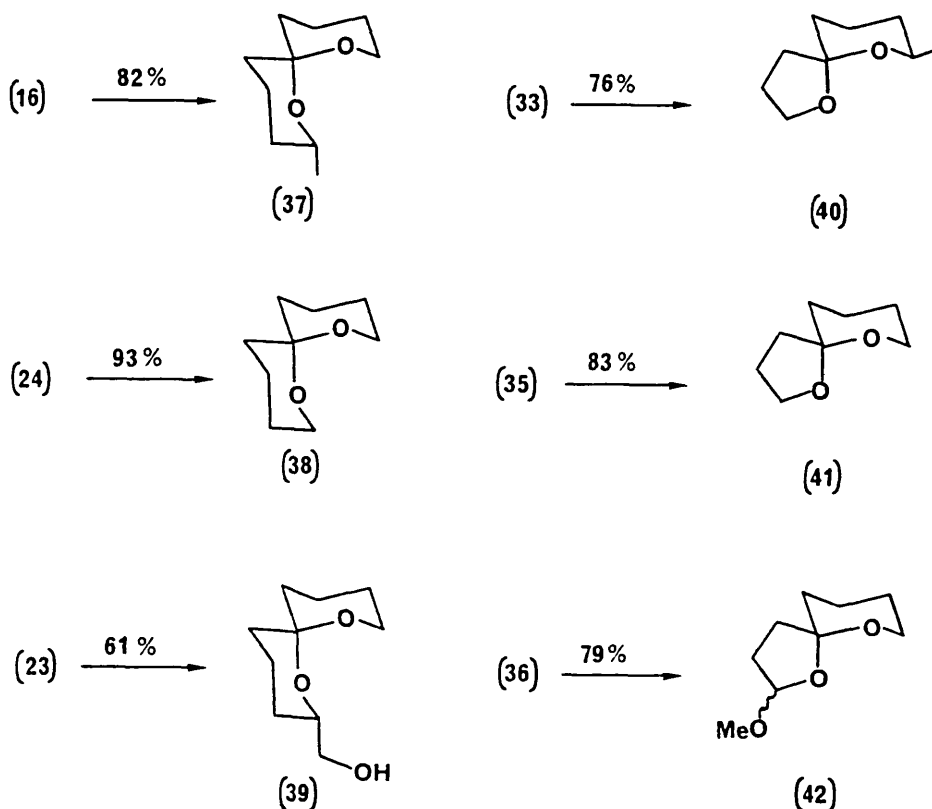
Phosphine oxide Phosponium salt	Aldehyde or Lactol	Product	Yield%
(26)	(5)	 (31)	54
(29)	(5)	(31)	0
(27)	(5)	 (32)	60.5
(28)	(5)	(32)	51
(30)	(5)	(32)	0
(26)	(6)	 (33)	86
(27)	(6)	 (34)	0
(26)	(14)	 (35)	70
(29)	(14)	(35)	71
(27)	(14)	 (36)	37
(28)	(14)	(36)	32
(30)	(14)	(36)	65

As before the phosphine oxides were deprotonated at -78°C in THF using diisopropylamide and reacted with several aldehydes and lactols to give coupled products (Table 2). These enol ether products were extremely hygroscopic and are best used rapidly after preparation.

The phosphonium tetrafluoroborate salts (29) and (30) were also prepared and could be readily purified by recrystallisation. These salts too could be deprotonated and coupled to aldehydes and lactols to give a range of enol ether products. (Table 2) Attempted isolation of the enol ethers derived from condensation with benzaldehyde suggested that some ring opening of the tetrahydrofuran unit had also occurred.



A key objective behind the above study is that many of the enol ethers which have been prepared are useful precursors for spiroketal synthesis. The spiroketal functional group occurs in many natural products, ranging from simple insect pheromones to complex ionophore antibiotics. In the examples we have investigated the enol ethers (16) (24) (23) (33) (35) and (36) upon treatment with camphor sulphonic acid in methanol or dichloromethane gave excellent yields of the corresponding spirocyclic products (37)–(42) respectively.⁶ The spiroketal (38) being identical to the natural pheromone derived from the olive fly *Dacus oleae*⁷ while (40) was equivalent to the pheromone from the common wasp *Paravespula vulgaris*.⁸ Enol ethers derived by these Wittig strategies should find many further applications in organic synthesis.



Experimental

¹H NMR spectra were obtained on Bruker WH-250, Jeol FX90Q and Varian EM-360A spectrometers in deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as liquid films or chloroform solutions. Mass spectra were obtained on a VG Micromass 7070B instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on MN-silica gel 60 230-400 mesh, under pressure. Light petroleum refers to the fraction boiling in the range 40°-60°C and ether to diethyl ether. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods.

Preparation of Tetrahydro-2-H-pyran-2-yl triphenyl phosphonium chloride (1) - (Method A)
2-Hydroxytetrahydropyran (128mg, 1.27mmol) was added dropwise to a solution of triphenylphosphine (334 mg, 1.27 mmol) in dry benzene (4 cm³) at room temperature. Dry hydrogen chloride was bubbled through the solution for 3 h, and the solvent removed to give a white solid, which could be semi-purified from dichloromethane-ethyl acetate, to give tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (413 mg, 85%) as a white amorphous solid, mp 113-116°C; IR (CHCl₃) 3369, 1439, 1113, and 691 cm⁻¹; NMR δ (90 MHz): 8.95 (3.5H, br. s, impurity), 8.00-7.55 (15H, m, Ar H), 6.15-5.85 (1H, m, H₂), 4.20-3.80 (2H, m, H₆), and 2.20-1.50 (6H, m); m/z (no M⁺), 85.

Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (Method B)
2,3-Dihydro-4H-pyran (40.0 g, 0.48 mol) was added dropwise to a solution of triphenylphosphine (120 g, 0.46 mol) in dry benzene (11), and dry hydrogen chloride bubbled through the resulting solution at room temperature for 5 h. The solvent was removed under reduced pressure to give a solid, which could be semi-purified by recrystallisation from dichloromethane-ethyl acetate, to give tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (1) (158g, 90%) identical to the material prepared earlier.

Preparation of Tetrahydro-2H-pyran-2-yl triphenyl phosphonium bromide (2)
2,3-Dihydro-4H-pyran (27.0 g, 0.32 mol) was added dropwise to a solution of triphenylphosphine (83.8 g, 0.32 mol) in dry benzene (350 cm³). Dry hydrogen bromide was bubbled through the resulting solution at room temperature for 5 h. The solvent was removed under reduced pressure and the product recrystallised from dichloromethane-ether to give tetrahydro-2H-pyran-2-yl triphenylphosphonium bromide (2) (109 g, 80%) as a white crystalline solid, mp 173-175°C; IR (CHCl₃) 3396, 1438, 1112, and 692 cm⁻¹; NMR δ (90 MHz): 8.15-7.60 (15H, m, ArH), 6.65-6.40 (1H, m, H₂), 4.40-3.90 (2H, m, H₆), and 2.50-1.40 (6H, m); m/z (FAB) 347 (M⁺), 263, 85, 57 and 43. (Found: C, 64.44; H, 5.68, Br, 18.79; P, 6.83. C₂₃H₂₄BrOP requires C, 64.65; H, 5.66; Br, 18.70; P, 7.25%).

General Procedure for the Wittig-Reaction of Tetrahydro-2H-pyran- 2-yl Triphenylphosphonium salts with aldehydes or lactols

The phosphonium salt was dissolved in dry THF at -10°C under argon. n-Butyllithium was added dropwise, the mixture stirred at -10°C for 30 min, then a THF solution of the aldehyde or lactol added and the solution warmed to room temperature. It was poured into saturated aqueous sodium chloride solution, and extracted with diethyl ether (3 X 10 cm³). The ether extracts were dried and evaporated to give the crude adduct which was purified by Kugelrohr distillation.

Preparation of Enol Ethers (15).

To a solution of the anion of (1) (2.0 mmol) was added benzaldehyde (5) (0.204 cm³, 2 mmol). Distillation after work up gave (15) (84 mg, 24%) as a mixture of three alkene isomers, bp. 110°C/0.3 mmHg; IR 2925, 1645, 1048, and 694 cm⁻¹; NMR δ (60 MHz): 7.60-6.93 (5H, m, ArH), 5.98 (0.5H, s, C=CHPh E isomer), 5.23 (0.25H, s, C=CHPh Z isomer), 4.41 (0.25H, t, J = 4Hz, C=CH endo), 3.87 (2H, m, OCH₂), 3.25 (0.5H, s, CH₂Ph endo), and 2.60-1.53 (5.5H, m). m/z 174 (M⁺) 91, 90, 83 and 55 (Found: C, 82.66; H, 8.31; C₁₂H₁₄O requires C, 82.72; H, 8.10%).

To a solution of the anion of (2) (2.0 mmol) was added benzaldehyde (5) (0.204 cm³, 2 mmol). Distillation after workup gave (15) (108 mg, 31%) identical to the material prepared above.

Preparation of Enol Ethers (16).

To a solution of the anion of (2) (2.0 mmol) was added the anion of 2-hydroxy 5-methyltetrahydrofuran (6) (0.204 g, 2.0 mmol) [generated from n-butyllithium at 0°C in THF] and after workup gave the adduct (16) (0.10 g, 12%) as a mixture of alkene isomers, bp 100°C/0.005 mmHg, IR 3400, 2928, 1625 and 1059 cm⁻¹; NMR δ (60 MHz): 4.87 (0.3H, t, J = 8Hz C=CH Z isomer), 4.42 (0.7H, t, J = 7 Hz, C=CH endo), 4.10-3.20 (3H, m) and 2.40-0.80 (14H, m); m/z 170 (M⁺), 111, 98, 85 and 55, (Found M⁺ 170.1305, C₁₀H₁₈O₂ requires 170.1307).

Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3)

2-Methoxy tetrahydropyran (0.50 g, 4.3 mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.50 g, 4.3 mmol) in dry acetonitrile (5 cm³) at room temperature under argon, and stirred for 4 h. Removal of the solvent under reduced pressure gave tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (3), (1.87 g 100%) as a white crystalline solid, mp 171-173°C; IR (CHCl₃) 1321, 1056 and 690 cm⁻¹; NMR δ (90 MHz): 7.76 (15H, m, ArH), 5.61 (1H, m, H₂), 4.05 (2H, m, H₆), and 2.10-1.50 (6H, m); m/z (FAB) 347 (M⁺), 263, 85 and 43 (Found: C, 63.51; H, 5.50; P, 7.57. C₂₃H₂₄BF₄OP requires C, 63.62; H, 5.57; P, 7.13%).

General Procedure for the Wittig reaction of tetrahydro-2H-pyran- 2-yl triphenylphosphonium tetrafluoroborate (3) with aldehydes and lactols

The phosphonium salt (3) was suspended in dry THF at -78°C under argon, *n*-Butyllithium was added dropwise and the solution stirred at -78°C for 1 h, then the aldehyde or lactol in a THF solution added and the solution warmed to room temperature over 2 h, then poured into a saturated aqueous sodium chloride, and extracted with diethyl ether ($3 \times 10 \text{ cm}^3$). The ether extracts were dried and evaporated to give the crude adduct which was purified by Kugelrohr distillation.

Preparation of the Enol Ethers (15)

To a solution of the anion of (3) (0.87 g, 2 mmol) was added benzaldehyde (5) (0.204 cm^3 , 2 mmol). Distillation gave (15) (280 mg, 79%) identical to that prepared above.

Preparation of the Enol Ethers (18)

To a solution of the anion of (3) (0.87 g, 2 mmol) was added cyclohexanecarboxaldehyde (8) (0.242 cm^3 , 2.0 mmol). Distillation gave (18) (184 mg, 53%) as a mixture of three alkene isomers, bp $90^{\circ}\text{C}/0.1 \text{ mmHg}$: IR 2925, 2850, 1676, 1067 and 1048 cm^{-1} ; NMR δ (250 MHz): 4.74 (0.45 H, d, $J = 9.8 \text{ Hz}$, C=CH E isomer), 4.41 (0.33 H, t, $J = 8.3 \text{ Hz}$, C=CH Z isomer), 4.05 (0.16 H, t, $J = 6.25 \text{ Hz}$, C=CH endo), 3.85 (2H, m, OCH_2), 2.21 (0.32 H, m, CH_2 endo), 1.65-1.55 (6H, m), 1.36-1.12 (23 H, m), m/z 180 (M^+), 137, 96, 85, 83 and 55. (Found M^+ 180.1511, $\text{C}_{12}\text{H}_{20}\text{O}$ requires 180.1514).

Preparation of the Enol Ethers (17)

To a solution of the anion of (3) (0.87 g, 2 mmol) was added dodecanal (7) (0.442 cm^3 , 2.0 mmol). Distillation gave (17) (203 mg, 40%) as a mixture of three alkene isomers, bp $120^{\circ}\text{C}/0.1 \text{ mmHg}$; IR 2925, 2854, 1677, 1069 and 1047 cm^{-1} ; NMR δ (250 MHz): 4.84 (0.5 H, t, $J = 8.3 \text{ Hz}$, C=CH E isomer), 4.41 (0.33 H, t, $J = 8.3 \text{ Hz}$, C=CH Z isomer), 4.05 (0.16 H, t, $J = 6.25 \text{ Hz}$, C=CH endo), 3.85 (2H, m, OCH_2), 2.21 (0.32 H, m, CH_2 endo), 1.65-1.55 (6H, m), 1.36-1.12 (23 H, m); m/z 252 (M^+), 167, 85 and 55. (Found M^+ 252.2448, $\text{C}_{17}\text{H}_{32}\text{O}$ requires 252.2453).

Preparation of Enol Ethers (21)

To a solution of the anion of (3) (0.87 g, 2.0 mmol) was added furfural (11) (0.166 cm^3 , 2.0 mmol). Distillation gave (21) (203 mg, 62%) as a mixture of three alkene isomers, bp $90^{\circ}\text{C}/0.08 \text{ mmHg}$; IR 2943, 1663, 1493 and 1051 cm^{-1} ; NMR δ (250 MHz): 7.35 (1H, m, H_3), 6.32 (1H, m, H_4), 6.15 (1H, m, H_5), 5.85 (0.5 H, s, C=CH E-isomer), 5.45 (0.3 H, s, C=CH Z isomer), 4.60 (0.2 H, m, C=C endo), 4.0 (2H, m, OCH_2), 2.91 (0.4 H, m, CH_2 endo), 1.98-1.72 (5.6H, m); m/z 164 (M^+) 85, 81 and 55. (Found M^+ 164.0831, $\text{C}_{10}\text{H}_{12}\text{O}_2$ requires 164.0837).

Preparation of the Enol Ethers (22)

To a solution of the anion of (3) (0.87 g, 2.0 mmol) was added 3-Pyridinecarboxaldehyde (12) (0.188 cm^3 , 2.0 mmol). Distillation gave (22) (140 mg, 41%) as a mixture of three alkene isomers, bp $90^{\circ}\text{C}/0.03 \text{ mmHg}$; IR 2927, 1673, 1061 and 1047 cm^{-1} ; NMR δ (250 MHz): 8.41 (1.6H, m, σ -Pyr), 8.22 (0.4H, m, σ -Pyr E-Isomer), 7.91 (0.4 H, dt, $J = 10, 7.5 \text{ Hz}$, p -Pyr, E isomer), 7.48 (0.6 H, dt, $J = 10, 7.5 \text{ Hz}$, p -Pyr endo isomer), 7.1 (1H, m, m -Pyr), 5.23 (0.4 H, s, C=CH E isomer), 4.41 (0.6 H, t, $J = 11 \text{ Hz}$, C=CH endo), 3.95-3.87 (2H, m, OCH_2), 3.2 (1.2 H, s, CH_2 endo), 2.3-1.72 (4.8 H, m); m/z 175 (M^+), 91, 85 and 55 (Found M^+ 175.0994, $\text{C}_{11}\text{H}_{13}\text{NO}$ requires 175.0997).

Preparation of the Enol Ethers of (16)

To a solution of the anion of (3) (0.435 g, 1.0 mmol) was added the anion of 2-hydroxy-5-methyl-tetrahydrofuran [generated as previously]. The solution was stirred at room temperature for 5 h. Distillation gave (16) (56 mg, 33%) identical to that prepared earlier.

Preparation of Tetrahydro-2H-pyran-2-yl diphenyl phosphine oxide (4)

Phosphonium salt (1) (36.3 g, 94.9 mmol) was dissolved in 3N aqueous sodium hydroxide (180 cm^3 , 540 mmol) and the resulting solution heated under reflux for 30 min. After cooling to room temperature, the mixture was extracted with chloroform ($3 \times 100 \text{ cm}^3$) and the organic extracts dried and evaporated, to give a solid which was recrystallised from dichloromethane-ethyl acetate to give tetrahydro-2H-pyran-2-yl diphenylphosphine oxide (4) (23.0 g, 85%) as a white crystalline solid, mp 154°C , IR (CHCl_3) 2939, 1437, 1183 and 696 cm^{-1} ; NMR δ (90 MHz): 8.10-7.70 (4H, m, ArH), 7.60-7.20 (6H, m, ArH), 4.40-3.90 (2H, m), 3.60-3.25 (1H, m) and 2.15-1.30 (6H, m); m/z (no M^+) 203, 202, 201, 155, 85, 77, and 47 (Found: C, 71.13; H, 6.70; P, 10.55; $\text{C}_{17}\text{H}_{19}\text{O}_2\text{P}$ requires C, 71.32; H, 6.69; P, 10.82%).

General Procedure for the Horner-Wittig Reaction of the Compound (4) with aldehydes and lactols

The phosphine oxide was dissolved in dry THF under argon and added to a stirred solution of lithium diisopropylamide [from diisopropylamine (1.1 eq.) and *n*-Butyllithium (1.1 eq.)] at -78°C in THF under argon. The anion was stirred for 1 h at -78°C , then a THF solution of the aldehyde or lactol was added and the solution warmed to room temperature. It was poured into saturated aqueous ammonium chloride solution, and extracted with chloroform ($3 \times 10 \text{ cm}^3$). The organic extracts were dried and evaporated to give the crude adduct. This was immediately dissolved in dry THF and a solution of potassium *t*-butoxide (1 eq) in THF added and stirred at room temperature for 1 h. The solvent was removed and the residue dissolved in dichloromethane, then extracted with diethylether, filtered through a celite pad and the solvent removed under reduced pressure to give the crude product which was purified by Kugelrohr distillation.

Preparation of the Enol Ethers (15)

To a solution of the anion of (4) (1.40 g, 4.9 mmol) was added benzaldehyde (5) (0.50 cm³, 4.9 mmol). Distillation gave (15) (650 mg, 76%) identical to that prepared above.

Preparation of Enol Ethers (16)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added the anion of 2-hydroxy, 5-methyl-tetrahydrofuran (6) (0.102 g, 1 mmol). Distillation gave the adduct (16) (101 mg, 59.5%), identical to that prepared above.

Preparation of Enol Ethers (17)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added dodecanal (7) (0.221 cm³, 1 mmol). Distillation gave the adduct (17) (178 mg, 71%) as above.

Preparation of Enol Ethers (18)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added cyclohexane carboxaldehyde (0.121 cm³, 1 mmol). Distillation gave (18) (122 mg, 68%) identical to that prepared above.

Preparation of Enol Ethers (19)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added cinnamylaldehyde (0.126 cm³, 1 mmol). Distillation gave (19) (156 mg, 78%) as a mixture of six isomers, bp 130°C/0.08 mmHg; IR 2947, 1643, 1594, 1273 and 1044 cm⁻¹; NMR δ (250 MHz): 7.55-7.07 (5H, m, ArH), 5.15 (0.4 H, t, J = 9.1 Hz, C=CH E-isomer), 4.65 (0.4 H, t, J = 9.1 Hz, C=CH Z isomer), 4.45 (0.2 H, m, C=CH endo), 3.85 (2H, m, OCH₂), 2.35-2.15 (2.4 H, m, -CH₂- E, Z and endo isomer), 1.85-1.7 (5.6H, m). m/z 200 (M⁺), 116, 85, 77 and 55. (Found M⁺ 200.1207, C₁₄H₁₆O requires 200.1201).

Preparation of the Enol Ethers (20)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added phenylacetaldehyde (10) (0.120 g, 1.0 mmol). Distillation gave (20) (127 mg, 68%) as a mixture of isomers, bp 60°C/0.005 mmHg; IR 2939, 2861, 1676, 1087 and 1045 cm⁻¹; NMR δ (250 MHz): 7.28-7.15 (5H, m, ArH), 5.15 (0.4 H, t, J = 9.1 Hz, C=CH E-isomer), 4.65 (0.4 H, t, J = 9.1 Hz, C=CH Z isomer), 4.45 (0.2 H, m, C=CH endo), 3.85 (2H, m, OCH₂), 2.35-2.15 (2.4 H, m, -CH₂- E, Z and endo isomer), 1.85-1.7 (5.6H, m). m/z 188 (M⁺), 104, 97, 91 and 55. (Found M⁺ 188.1203, C₁₃H₁₆O requires 188.1201).

Preparation of the Enol Ethers (21)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added furfural (11) (0.083 cm³, 1 mmol). Distillation gave (21) (67 mg, 41%) as prepared before.

Preparation of the Enol Ethers (22)

To a solution of the anion of (4) (0.286 g, 1 mmol) was added 3-pyridinecarboxaldehyde (12) (0.094 cm³, 1 mmol). Distillation gave (22) (112 mg, 64%) as prepared before.

Preparation of Enol Ether (23)

To a solution of the anion of (4) (0.36 g, 1.25 mmol) was added (13) (0.198 g, 1.25 mmol). Distillation gave (23) (183 mg, 65%). This was converted directly to the spiroketal (39).

Preparation of Enol Ether (24)

To a solution of the anion of (4) (1.40 g, 4.9 mmol) was added 1-[(tetrahydro-2H-pyran-2-yl)oxy]-butanal (14) (0.84 g, 4.9 mmol). Distillation gave 2-[4'-(tetrahydro-2H-pyran-2-yl)oxy butan]-5,6-dihydro-4H-pyran (24) (0.73 g, 62%), bp. 120°C/0.04 mmHg; IR 2938, 1675, 1114 and 1050 cm⁻¹; NMR δ (250 MHz): 4.59 (1H, br. s OCHO), 4.08 (1H, t, J = 6.5 Hz, C=CH), 3.91-3.71 (4H, m) 3.57-3.37 (2H, m), 2.42 (1H, br. t), and 1.99-1.25 (15 H, m); m/z 240 (M⁺), 155, 101, 98, 85 and 55. (Found: C, 70.11; H, 10.17. C₁₄H₂₄O₃ requires C, 69.96, H, 10.07%).

Preparation of Tetrahydrofuran-2-yl triphenylphosphonium chloride (25)

2,3-Dihydrofuran (20.0 g, 0.29 mmol) was added dropwise to a solution of triphenylphosphine (74.9 g, 0.29 mmol) in dry benzene (300 cm³). Dry hydrogen chloride was bubbled through the solution for 3 h at room temperature. The solvent was removed under reduced pressure to give a solid, which could be semi-purified by dissolving in dichloromethane and trituration of the solution with ethyl acetate giving tetrahydrofuran-2-yl triphenylphosphonium chloride (25) (94 g, 88%) as a white amorphous solid, IR (CHCl₃) 3358, 1438, 1113, and 691 cm⁻¹; NMR δ (90 MHz): 8.90-8.30 (1.5 H, br. s. impurity), 8.00-7.50 (15 H, m, ArH), 6.50-6.15 (1H, m, H₂), 4.15-3.85 (1H, m), 3.70-3.45 (1H, m), 3.30-2.70 (1H, m) and 2.50-1.40 (3H, m); m/z (no M⁺), 71.

Preparation of Tetrahydrofuran-2-yl diphenylphosphine oxide (26)

The phosphonium salt (25) (10.0 g, 27.1 mmol) was dissolved in 3N aqueous sodium hydroxide solution (60 cm³, 180 mmol) and the solution was heated at reflux for 30 min. After cooling to room temperature, the mixture was extracted with chloroform (3 X 50 cm³) and the organic layers dried and evaporated to leave a solid. Recrystallisation from dichloromethane-ethyl acetate gave tetrahydrofuran-2-yl diphenylphosphine oxide (26) (6.1 g, 82%) as a white amorphous solid, mp 115°C; IR (CHCl₃) 1437, 1120 and 697 cm⁻¹; NMR δ (90 MHz): 8.10-7.70 (4H, m, ArH), 7.60-7.20 (6H, m, ArH), 4.70 (1H, q, J = 7 Hz, H₂), 4.00-3.50 (2H, m) and 2.45-1.50 (4H, m); m/z (no M⁺), 202, 155, 77, 71 and 43 (Found: C, 70.50; H, 6.31; P 11.30. C₁₆H₁₇O₂P requires C, 70.56; H, 6.29; P, 11.38%).

Preparation of Tetrahydrofuran-2-yl triphenylphosphonium tetrafluoroborate (29)

2-Methoxytetrahydrofuran (0.51 g, 5 mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.75 g, 5 mmol) in dry acetonitrile (10 cm³) at room temperature under argon and stirred for 4 h. Removal of the solvent under reduced pressure gave tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (29) (1.89 g, 88%) as a white crystalline solid, mp 130°C; IR (CHCl₃) 1438, 1287, 1052, 665 cm⁻¹; NMR δ (250 MHz): 7.85-7.6 (15 H, m, ArH), 5.85 (1H, dt, J = 11.5 Hz, H₂), 3.95 (1H, m, H₅), 3.55 (1H, m, H₃), 2.87 (1H, m), 2.18-1.95 (2H, m), 1.65 (1H, m) m/z (no M⁺), 333, 71 (Found: C, 62.67; H, 5.37. C₂₂H₂₂BF₄OP requires C, 62.88; H, 5.27).

Preparation of 5-methoxy tetrahydrofuran-2-yl diphenylphosphine oxide (27)

Chlorodiphenylphosphine (1.795 cm³, 10 mmol) was added dropwise to a solution of 2,5-dimethoxytetrahydrofuran (1.295 cm³, 10 mmol) at 0°C in dry dichloromethane (3 cm³) under argon. The reaction was left to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure to give an oil which could be purified by dissolving in toluene and trituration of the solution with petroleum ether giving 5-methoxy tetrahydrofuran-2-yl diphenylphosphine oxide (27) (2.02 g, 67%) as a white amorphous solid, mp. 98°C IR (CHCl₃) 2862, 1442, 1298 cm⁻¹; NMR δ (250 MHz): 7.85 (4H, m, ArH), 7.50 (6H, m, ArH), 5.05 (1H, d, J = 6.25 Hz, H₂), 4.9 (1H, br. q, J = 8.3 Hz, H₅), 3.35 and 3.10 (3H, s, OCH₃), 2.5-1.5 (4H, m); m/z 302 (M⁺) 202, 101. (Found: C, 67.27; H, 6.26. C₁₇H₁₉O₃P requires C, 67.54; H, 6.26%).

Preparation of 5-methoxy tetrahydrofuran-2-yl diethoxyphosphine oxide (28)

Diethylchlorophosphite (0.714 ml, 5 mmol) was added dropwise to a stirred solution of 2,5-dimethoxytetrahydrofuran (0.65 ml, 5 mmol) at 0°C in dichloromethane under argon. The solution was stirred for 12 h at room temperature, concentrated and purified by Kugelrohr distillation to give (28) (0.475 g, 48%) as a colourless oil, bp 120°C/0.03 mmHg. IR 2862, 1252 and 1032 cm⁻¹; NMR δ (250 MHz): 5.1 (1H, dd, J = 4.2 Hz, 16.6 Hz, H₂), 4.3-4.2 (5H, m, -OCH₃, H₅), 3.3 (3H, d, J = 4.2 Hz, OCH₃), 2.3-1.9 (4H, m), 1.3 (6H, t, J = 6.94 Hz, -CH₃). m/z 237 (M⁺), 207, 138, and 101. (Found: C, 45.41; H, 7.97; C₉H₁₈O₅P requires C, 45.57; H, 7.65).

Preparation of 5-Methoxy-tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (30)

2,5-dimethoxy tetrahydrofuran (0.648 cm³, 5 mmol) was added to triphenylphosphonium tetrafluoroborate (1.75 g, 5 mmol) in dry acetonitrile (10 cm³) at room temperature under argon and stirred for 4 h. Removal of the solvent under reduced pressure gave 5-methoxy-tetrahydro-2H-furan-2-yl triphenylphosphonium tetrafluoroborate (30) (1.57 g, 68%) as a white amorphous solid mp 50°C; IR (CHCl₃) 2839, 1438, 1286, 1063, 665 cm⁻¹; NMR δ (250 MHz): 7.85-7.6 (15H, m, ArH), 6.05-5.85 (1H, m, H₂), 5.05 (1H, m, H₅), 3.35 (1.5H, s, OCH₃), 2.30-1.75 (4H, m). m/z (no M⁺) 363, 101. (Found: C, 61.35; H, 5.43%. C₂₃H₂₄BF₄O₂P requires C, 61.35; H, 5.37%).

Following the general Horner-Wittig procedure the following enol ethers were prepared.

Preparation of Enol Ethers (31)

To a solution of the anion of (26) (0.271 g, 1 mmol) was added benzaldehyde (0.102 cm³, 1 mmol) stirring the resulting solution for 15 h at room temperature. Distillation gave (31) (86.5 mg, 54%) as a mixture of alkene isomers, bp: 80°C/0.02 mmHg, IR 3023, 2926, 1672, 1595, 1077 and 1028 cm⁻¹; NMR δ (250 MHz): 7.55-7.20 (5H, m, ArH), 5.23 (0.33 H, s, E or Z isomer), 4.65 (0.67, m, endo), 3.90-3.75 (2H, m, OCH₃), 2.05-1.70 (4H, m); m/z 160 (M⁺), 91, 77, and 71. (Found M⁺ 160.0887, C₁₁H₁₂O requires 160.0888).

Preparation of Enol Ethers (32)

To a solution of the anion of (27) (0.302 g, 1 mmol) was added benzaldehyde (0.102 cm³, 1 mmol) and stirred for 15 h at room temperature. Distillation gave (32) (115 mg, 60.5%) as a mixture of alkene isomers, bp: 90°C/0.02 mmHg; IR 3383, 2926, 1674, 1599, 1025 and 695 cm⁻¹; NMR δ 7.55-7.20 (5H, m, ArH), 5.30 (0.5H, s, C=CH E or Z isomer), 4.72 (0.5H, s, C=CH endo), 4.41 (1H, m, OCH₃), 3.35 (3H, s, OCH₃), 2.0-1.65 (4H, m); m/z 190 (M⁺), 159, 91, 77 and 71. (Found: M⁺ 190.1002, C₁₂H₁₄O₂ requires 190.0994).

Preparation of Enol Ethers (32)

To a solution of the anion of (28) (0.237 g, 1 mmol) was added benzaldehyde (0.102 cm³, 1 mmol) and stirred for 15 h at room temperature. Distillation gave (32) (98 mg, 51%) as prepared previously.

In the following examples the enol ether was prepared following the general Wittig-Horner procedure and the crude product cyclised directly to the spiroketal.

Preparation of Enol Ether (33)

To a solution of the anion of (26) (3.09 g, 11.4 mmol) was added the anion of (6) (1.16 g, 11.4 mmol) and the reaction stirred over 15 h. Distillation gave (33) (1.53 g, 86%).

Preparation of Enol Ethers (35)

To a solution of the anion of (26) (0.271 g, 1 mmol) was added (13) (0.172 g, 1 mmol) and the reaction stirred over 15 h. Distillation gave (35) (159 mg, 70.3%) bp. 80°C/0.02 mmHg.

Preparation of Enol Ethers (36)

To a solution of the anion of (27) (0.302 g, 1 mmol) was added (13) (0.172 g, 1 mmol) and the reaction stirred over 15 h. Distillation gave (36) (96 mg, 37%) bp. 90°C/0.02 mmHg.

Preparation of Enol Ethers (36)

To a solution of the anion of (28) (0.237 g, 1 mmol) was added (13) (0.172 g, 1 mmol) and the reaction stirred over 15 h. Distillation gave (36) (83 mg, 32%) as prepared above.

Following the general procedure for Wittig type reactions.

Preparation of Enol Ethers (35)

To a solution of the anion of (29) (0.420 g, 1 mmol) was added (13) (0.172 g, 1 mmol) and the reaction stirred over 6 h. Distillation gave (35) (161 mg, 71%) as a mixture of ring open and ring closed products.

Preparation of Enol Ethers (36)

To a solution of the anion of (30) (0.69 g, 1.53 mmol) was added (13) (0.263 g, 1.53 mmol). Distillation gave (36) (166 mg, 65%) as a mixture of ring open and ring closed products.

Preparation of 2-Methyl-1,7-dioxaspiro[5.5]undecane (37)

The compound (16) (138 mg, 0.81 mmol) was dissolved in dry dichloromethane (2 cm³) containing camphor sulphonic acid (2 mg), and the resulting solution stirred overnight. After passing through a silica pad (to remove the CSA), the solvent was evaporated to give 2-methyl-1,7-dioxaspiro[5.5]undecane (37) (113 mg, 82%). IR 2932 and 1058 cm⁻¹. NMR δ (90 MHz): 3.8-3.55 (3H, m, OCH₂), 1.92-1.35 (12 H, m), 1.15 (3H, d, J = 6.3 Hz, CH₃) m/z 170 (M⁺), 101, 85. (Found: M⁺ 170.1303, C₁₀H₁₈O₂ requires 170.1307).

Preparation of 1,7-Dioxaspiro[5.5]undecane (38)

Compound (24) (0.49 g, 2.0 mmol) was dissolved in dry methanol (3 cm³) with camphor sulphonic acid (2 mg), and the solution stirred at room temperature for 5 h. Removal of the solvent under reduced pressure followed by Kugelrohr distillation of the crude product gave 1,7-dioxaspiro[5.5]undecane (38) (0.29 g, 93%) as a colourless oil, bp 100°C at 28 mmHg, IR 2940, 1171, 1045 and 984 cm⁻¹; NMR δ (250 MHz): 3.77-3.55 (4H, m, OCH₂), 1.95-1.73 (2H, m) and 1.68-1.36 (10H, m); m/z 156 (M⁺), 101, 100, 98, 83, 55 and 41 and was identical to the natural product.

E-2-Hydroxymethyl-1,7-dioxaspiro[5.5]undecane (39)

The enol ether (23) (0.14 g, 0.65 mmol) was added to a solution of CSA (2 mg) in methanol and stirred at room temperature for 6 h. The residue was purified by chromatography to give (39) (70 mg, 61%) as a colourless oil; IR 3430, 2930, 1045 and 990 cm⁻¹; NMR δ (250 MHz): 3.82-3.47 (5H, m), 2.21 (1H, br s, OH) 1.99-1.74 (2H, m), and 1.69-1.18 (10H, m); m/z 186 (M⁺), 155, 111, 101 and 55 (Found: C, 64.49; H, 9.68; C₁₀H₁₈O₃ requires C, 64.34; H, 9.94).

(E)-7-methyl-1,6-dioxaspiro[4.5]decane (40)

The enol ether (33) (1.53 g, 9.8 mmol) was dissolved in dry dichloromethane containing CSA (5 mg) and stirred at room temperature for 5 h. Removal of solvent and Kugelrohr distillation gave (40) (1.16 g, 76%) as a colourless oil; IR 2940 and 1050 cm⁻¹; NMR δ (250 MHz): 3.92-3.60 (3H, m), 2.07-1.21 (10H, m) and 1.11 (3H, d, J = 6.3 Hz Me); m/z 156 (M⁺), 141 and 97, which was identical with the natural product.

1,6-dioxaspiro[4.5]decane (41)

The enol ether (35) (159 mg, 0.70 mmol) was dissolved in dry dichloromethane containing CSA and stirred overnight. Removal of solvent and purification by chromatography gave (41) (83 mg, 83%) as a pale yellow oil; IR 2940, 1079 and 1035 cm⁻¹; NMR δ (250 MHz): 3.95-3.35 (4H, m, OCH₂), 2.05-1.45 (10H, m). m/z 142 (M⁺) 85, 71 and 55. (Found: M⁺ 142.0996 C₈H₁₄O₄ requires 142.0994).

(E)-2-methoxy-1,6-dioxaspiro[4.5]decane (42)

The enol ether (36) (96 mg, 0.375 mmol) was dissolved in dry dichloromethane containing CSA and stirred overnight. Purification by chromatography gave (42) (51 mg, 79%) as a colourless oil; IR 2927, 1452, 1369 and 1065 cm⁻¹; NMR δ (250 MHz): 4.50 (1H, m, OCH OCH₂), 3.95-3.55 (2H, m, OCH₂), 3.35 (3H, s, OCH₃), 1.95-1.45 (10H, m); m/z 172 (M⁺), 141, 101, 85 and 71. (Found M⁺ 172.1094, C₉H₁₆O₃ requires 172.1099).

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Footnotes

The enol ethers generated are labile and rapidly add water to give hemiethers, consequently they should be used soon after preparation.

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ALKYLATION REACTIONS OF ANIONS DERIVED FROM 2-BENZENESULPHONYL TETRAHYDROPYRAN AND THEIR
APPLICATION TO SPIROKETAL SYNTHESIS

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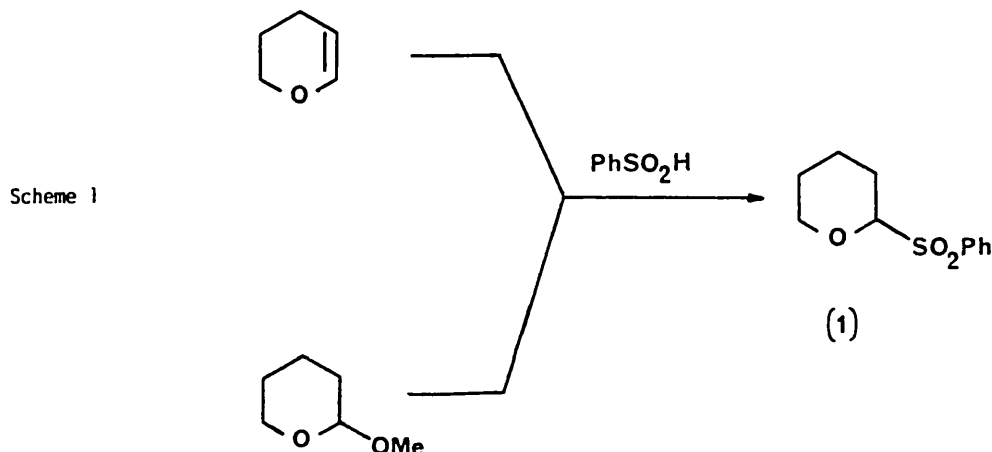
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Abstract: Reaction of 3,4-dihydro-2H-pyran or 2-methoxytetrahydropyran with benzenesulphinic acid gave 2-benzenesulphonyl tetrahydropyran (1). Deprotonation of (1) followed by alkylation with carbonyl compounds or halides gave cyclic enol ether addition products by spontaneous elimination of benzenesulphinic acid. Interception of the initial addition products with aldehydes by reductive desulphonylation to give alkylated tetrahydropyran derivatives proceeded in moderate yield using sodium naphthalenide. Several of the cyclic enol ether addition products were further converted to spiroketals including syntheses of natural product pheromones from *Dacus oleae* and *Paravespula vulgaris*.

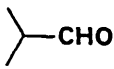
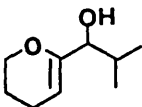
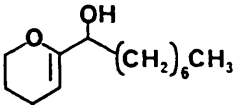
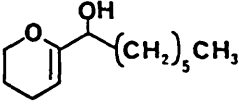
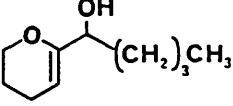
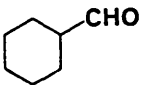
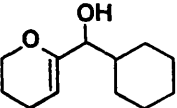
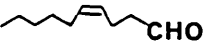
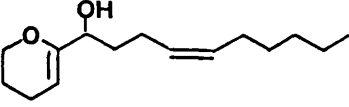
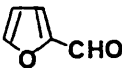
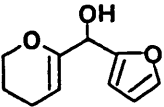
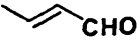
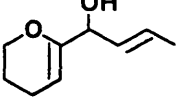
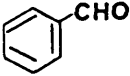
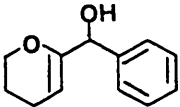
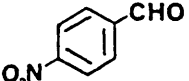
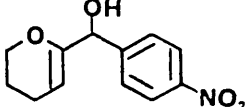
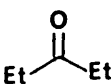
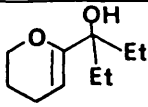
New methods of forming carbon-carbon bonds at the 2-position of cyclic ethers are of increasing importance in the total synthesis of many natural products. Here we report a detailed study on the preparation and alkylation reactions of anions derived from 2-benzenesulphonyl tetrahydropyran. This approach provides an alternative method for the formation of carbon-carbon bonds at the 2-position of cyclic ethers and is complementary to recently reported routes using Wittig or Horner-Wittig strategies.^{2,5} Other groups have also recently disclosed reactions of 2-deoxy-D-glucopyranosyl sulphones for C-glucoside synthesis.⁶

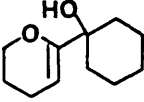
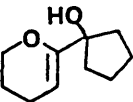
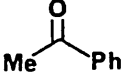
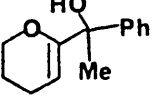
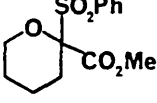
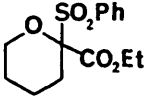
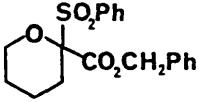
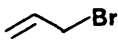
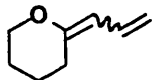
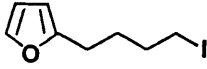
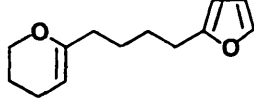
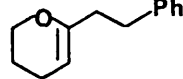
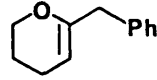
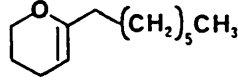
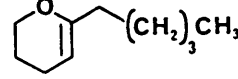
The crystalline sulphone 1 was prepared by reaction of either 3,4-dihydro-2H-pyran or 2-methoxy tetrahydropyran with benzenesulphinic acid in dichloromethane at room temperature for 2 h (Scheme 1). Deprotonation of (1) was achieved with n-butyl lithium or lithium diisopropyl amide at -78°C in tetrahydrofuran. The pale yellow anion formed could be quenched with a variety of electrophiles (Table 1) and after aqueous work-up the endo-enol ethers were obtained in reasonable yields, although many of these products were rather volatile and hydroscopic. Benzenesulphinic acid was spontaneously eliminated from the intermediate alkylated products as the reaction warmed to room temperature presumably due to the slightly basic media and the inherent leaving ability of the benzenesulphonyl group. The only exception to this was the reaction with alkyl and aryl chloroformates, where the acylated sulphones were isolated. X-ray crystal structure determination showed the sulphone adopted the equatorial position in all examples.



By quenching the anion from (1) with deuterium oxide, assignment of the anomeric proton could be made by nmr spectroscopy, from which it was determined that the sulphone moiety was also equatorial.

Table 1

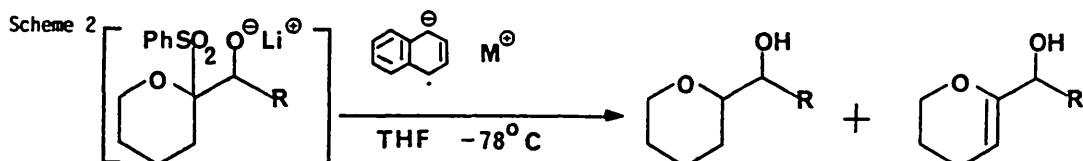
Electrophile	Product	Yield, %
	 (2)	65
$\text{CH}_3(\text{CH}_2)_6\text{CHO}$	 (3)	58
$\text{CH}_3(\text{CH}_2)_5\text{CHO}$	 (4)	62
$\text{CH}_3(\text{CH}_2)_4\text{CHO}$	 (5)	59
	 (6)	88
	 (7)	64
	 (8)	50
	 (9)	50
	 (10)	46
	 (11)	25
	 (12)	58

	 (13)	70
	 (14)	66
	 (15)	42
ClCO_2Me	 (16)	81
ClCO_2Et	 (17)	74
$\text{ClCO}_2\text{CH}_2\text{Ph}$	 (18)	48
	 (19)	51
	 (20)	57
$\text{PhCH}_2\text{CH}_2\text{Br}$	 (21)	53
PhCH_2Br	 (22)	29
$\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{I}$	 (23)	37
$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{I}$	 (24)	49.

* All yields of pure products prepared under optimized conditions and purified by Kugelrohr distillation or column chromatography on florisil.

In an effort to extend this sulphone-based methodology, ways of reductively removing the sulphone group at low temperature prior to sulphinic acid elimination were investigated. In this way it was hoped that simple alkylation at the 2-position of tetrahydropyrans could be achieved.

In situ reductive desulphonylation of the intermediate alkylated species at -78°C with 5 equivalents of lithium or sodium naphthalenide (generated by ultrasonic methods) was moderately successful, affording good yields of mixtures of the required ether and enol ether which could be separated by chromatography. (Scheme 2) (Table 2).

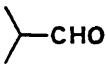
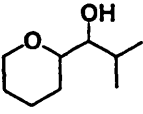
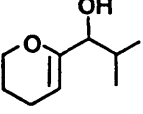
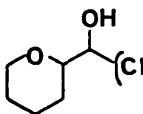
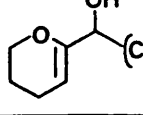
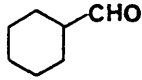
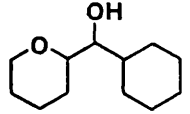
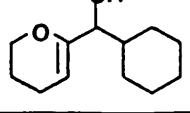


A degree of diastereoselectivity was observed in the formation of the cyclic ether products. Although this was low for condensation with isobutyraldehyde (7 : 3) and cyclohexanecarboxaldehyde (3:1), the adduct with octanal was formed with apparent complete stereoselectivity.

Unfortunately, treatment of the acyl sulphones (16), (17) and (18) with lithium and sodium naphthalenide or sodium amalgam did not afford the desired reductively desulphonylated tetrahydropyran products.

Ethers (25) and (27) could also be prepared by catalytic hydrogenation (H_2 , Pd/C) of (2) and (6) respectively, with different diastereoselection from that observed for reductive desulphonylation.

Table 2

Electrophile	Products	Yields	
		$\text{Li}^+[\text{C}_{10}\text{H}_8]^-$	$\text{Na}^+[\text{C}_{10}\text{H}_8]^-$
	 (25)	47	53
	 (2)	36	26
$\text{CH}_3(\text{CH}_2)_5\text{CHO}$	 (26)	-	57
	 (3)	-	16
	 (27)	27	50
	 (6)	25	24

* All yields of pure products purified by column chromatography on silica.

Many of the intermediate enol ethers prepared in the initial study readily underwent acid catalysed cyclisation to spiroketals (See table 3). The spiroketal group is an important functional arrangement in many natural products and this new method therefore provides a short synthetic pathway to several insect pheromongs derived from the olive fly *Dacus oleae* (29) (33) and the common wasp *Paravespula vulgaris* (32)*.

Table 3

Electrophile	Product	Yield %
	 (29)	71
	 (29)	52
	 (30)	47
	 (31)	57
	 (32)	79
	 (33)	48
	 (34)*	33

* After Ac₂O trapping of intermediate hydroxy enol ether.

EXPERIMENTAL

^1H NMR spectra were obtained on Bruker WH-400, Bruker WH-250, Jeol FX90Q and Varian EM-360A spectrometers in deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as liquid films or chloroform solutions. Mass spectra were obtained on a VG Micromass 7070B instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on MN-silica gel 60 230-400 mesh or florisil 200-300 U.S. mesh., under pressure. Light petroleum refers to the fraction boiling in the range $40^\circ\text{--}60^\circ\text{C}$ and ether to diethyl ether. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods.

Preparation of 2-Benzenesulphonyltetrahydro-2H-pyran (1) (Method A).— 3,4-Dihydro-2H-pyran (1.11 g, 13.2 mmol) was added dropwise to a stirred solution of benzenesulphonic acid (1.88 g, 13.2 mmol) in dry dichloromethane at room temperature under argon. Stirring was continued for 2 h, then the solvent removed under reduced pressure and the product recrystallised from ether-petrol to give 2-benzenesulphonyl tetrahydro-2H-pyran (2.45 g, 82%) as white needles, m.p. 78°C ; IR (CHCl_3) 1315, 1150, 1084, 692 cm^{-1} ; NMR δ (90 MHz): 7.91 (2H, m, ArH), 7.58 (3H, m, ArH), 4.39 (1H, dd, $J = 3.1, 10\text{ Hz}$, H2), 4.11 (1H, m, H6), 3.45 (1H, m, H6), 2.18–1.46 (6H, m); m/z 142 and 85, (Found C 58.24; H 6.14. $\text{C}_{11}\text{H}_{14}\text{O}_3\text{S}$ requires C 58.39; H 6.24%).

(Method B)

2-Methoxytetrahydropyran (1.54 g, 13.3 mmol) was added dropwise to a stirred solution of benzenesulphonic acid (2.83 g, 19.9 mmol) in dry dichloromethane at room temperature under argon with a suspension of calcium chloride. After 4 h, the solution was washed with water, dried and evaporated and the product recrystallised from ether-petrol to give 2-benzenesulphonyl-tetrahydro-2H-pyran (2.38 g, 79%) identical to the material prepared above.

General Procedure for condensation of the anion of 2-Benzenesulphonyltetrahydro-2H-pyran with electrophiles.

The sulphone was dissolved in dry THF at -78°C under argon. *n*-Butyllithium was added dropwise and the mixture stirred at -78°C for 15 min, then the electrophile added and the solution warmed to room temperature over $\frac{1}{2}$ –2 h. It was poured into sodium bicarbonate solution and extracted with ether (2 x 20 cm^3). The ethereal extracts were dried and evaporated to give the crude adduct which was purified by column chromatography on florisil eluting with petrol-ether mixtures or by kugelrohr distillation.

Preparation of enol ether (2).— Isobutyraldehyde (0.09 cm^3 , 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work up gave (2), 2-(1'-hydroxy-2'-methyl-propyl)-5,6-dihydro-4H-pyran (102 mg, 65%). IR 3446, 2955, 1675, and 1062 cm^{-1} ; NMR δ (90 MHz): 4.70 (1H, t, $J = 3.7\text{ Hz}$, H3), 4.00 (2H, t, $J = 5.2\text{ Hz}$, H6), 3.50 (1H, br. m, H1'), 2.15–1.05 (6H, m), 0.9 (6H, d, $J = 5.2\text{ Hz}$, H3'); m/z 156 (M^+), 113, 85, 55. (Found M^+ 156.1154, $\text{C}_9\text{H}_{16}\text{O}_2$ requires 156.1150).

Preparation of enol ether (3).— Octanal (0.174 cm^3 , 1.11 mmol) was added to a solution of the anion of (1) (1.112 mmol). Chromatography after work-up gave (3), 2-(1'-hydroxy-octyl)-5,6-dihydro-4H-pyran (137 mg, 58%). IR 3422, 2926, 1675, 1465, and 1064 cm^{-1} ; NMR δ (90 MHz): 4.70 (1H, t, $J = 3.85\text{ Hz}$, H3), 4.00 (2H, m, H6), 3.85 (1H, br. t, $J = 6.4\text{ Hz}$, H1'), 2.6 (1H, br, $J = 7.7\text{ Hz}$, OH), 2.4–1.1 (16H, m), 0.9 (3H, t, $J = 3.9\text{ Hz}$, CH_3). m/z 212 (M^+), 114, 85, 55. (Found M^+ 212.1771, $\text{C}_{13}\text{H}_{24}\text{O}_2$ requires 212.1776).

Preparation of enol ether (4).— Heptanal (0.134 cm^3 , 1 mmol) was added to a solution of the anion of (1), (1 mmol). Chromatography after work-up gave (4) 2-(1'-hydroxy-heptyl)-5,6-dihydro-4H-pyran. (122 mg, 62%). IR 3407, 2926, 1675 and 1063 cm^{-1} ; NMR δ (90 MHz): 4.70 (1H, t, $J = 3.6\text{ Hz}$, H3), 4.00 (2H, t, $J = 5.1\text{ Hz}$, H6), 3.85 (1H, br. d, $J = 7.2\text{ Hz}$, H1'), 2.10–1.1 (15H, m) 0.9 (3H, t, $J = 3.6\text{ Hz}$, CH_3). m/z 198 (M^+), 114, 85, 83, 55 (Found: C 72.69; H 11.45. $\text{C}_{12}\text{H}_{22}\text{O}_2$ requires C, 72.68, H 11.48%).

Preparation of enol ether (5).— Pentanal (0.106 cm^3 , 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (5), 2-(1'-hydroxy-pentyl)-5,6-dihydro-4H-pyran (101 mg, 59%). IR, 3422, 2955, 1675 and 1062 cm^{-1} ; NMR δ (90 MHz): 4.75 (1H, t, $J = 3.6\text{ Hz}$, H3), 4.00 (2H, t, $J = 5.2\text{ Hz}$, H6), 3.85 (1H, br. d, $J = 6.9\text{ Hz}$, H1'), 2.25 (1H, m, OH), 2.10–1.2 (10H, m) 0.9 (3H, t, $J = 3.7\text{ Hz}$, CH_3). m/z 170 (M^+), 114, 113, 85, 57. (Found: M^+ 170.1305, $\text{C}_{10}\text{H}_{18}\text{O}_2$ requires 170.1306)

Preparation of enol ether (6).— Cyclohexanecarboxaldehyde (0.134 cm^3 , 1.108 mmol) was added to a solution of the anion of (1) (1.1 mmol). Chromatography after work-up gave (6), 2-(1'-hydroxy-cyclohexyl)-5,6-dihydro-4H-pyran (191 mg, 88%). IR, 3431, 1675, 1448 and 1060 cm^{-1} . NMR δ (90 MHz), 4.65 (1H, t, $J = 3.8\text{ Hz}$, H3), 4.00 (2H, m, H6), 3.5 (1H, dd, $J = 5.1\text{ Hz}$, 5.1 H1'), 2.10–0.6 (16H, m). m/z 196 (M^+), 114, 113, 85. (Found: M^+ 196.1467 $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires 196.1463).

Preparation of enol ether (7).— Dec-4,5-enal (0.154 g, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (7), 2-(1'-hydroxy-non-4',5'-enol)5,6-dihydro-4H-pyran (152 mg, 64%). IR 3384, 2926, 1675 and 1066 cm^{-1} . NMR δ (90 MHz): 5.35 (2H, t, $J = 3.6$ Hz, H4' H5'), 4.75 (1H, t, $J = 3.9$ Hz, H3), 4.00 (2H, t, $J = 5.4$ Hz, H6), 3.85 (1H, m, H1') 2.25-1.35 (17H, m), 0.9 (3H, t, $J = 3.6$ Hz, CH₃). m/z 238 (M^+), 183, 114, 85, 57. (Found: M^+ 238.1931, C₁₅H₂₆O₂ requires 238.1932).

Preparation of enol ether (8).— 2-Furaldehyde (0.082 cm^3 , 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (8), 2-(1'-hydroxy-2'-furfuryl) 5,6-dihydro-4H-pyran (89 mg, 50%). IR 3426, 2929, 1675, 1499 and 1062 cm^{-1} . NMR δ (90 MHz): 7.35 (1H, s, H5'), 6.30 (2H, s, H4' H3'), 5.00 (1H, br.d $J = 5.1$ Hz, H1'), 4.85 (1H, t $J = 3.8$ Hz, H3), 4.05 (2H, t, $J = 5.4$ Hz, H6), 2.6 (1H, br.d $J = 15$ Hz, OH), 2.1-1.6 (4H, m). m/z 180 (M^+), 163, 97, 85, 55. (Found: 180.0794, C₁₀H₁₂O₃ requires 180.07867).

Preparation of enol ether (9).— Trans-2-Butenal (0.083 cm^3 , 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (9), 2-(1'-hydroxy-but-2',3'-enyl)5,6-dihydro-4H-pyran (77 mg, 50%). IR 3446, 2930, 1675, 1628 and 1064 cm^{-1} . NMR δ (90 MHz): 5.75 (2H, m, H2' H3'), 4.75 (1H, t, $J = 3.6$ Hz, H3), 4.45 (1H, m, H1'), 4.00 (2H, t, $J = 5.2$ Hz, H6), 2.05-1.35 (8H, m). m/z 154 (M^+) 130, 85, 69. (Found: M^+ 154.0989. C₉H₁₄O₂ requires 154.0994)

Preparation of enol ether (10).— Benzaldehyde (0.102 cm^3 , 1 mmol) was added to a solution of the anion of (1) (1 mmol). Distillation after work-up gave (10), 2-(1'-hydroxy-phenyl)5,6-dihydro-4H-pyran (87 mg, 46%) b.p. 90°C at 0.1 mmHg. IR 3422, 2927, 1674 and 1086 cm^{-1} . NMR δ (90 MHz): 7.6-7.2 (5H, m, Ar H), 5.05 (0.7H, br.s H1'), 4.75 (1H, t, $J = 4.1$ Hz, H3), 4.00 (2H, t, $J = 4.9$ Hz, H3), 3.75 (0.3H, s, H1') 2.5 (1H, br.s, OH), 2.2-0.8 (4H, m). m/z 190 (M^+), 106, 105, 85, 77. (Found: M^+ 190.0985 C₁₂H₁₄O₂ requires 190.0993).

Preparation of enol ether (11).— Paranitrobenzaldehyde (0.150g, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (11) 2-(1'-hydroxy-1'-paranitrobenzaldehyde)5,6-dihydro-4H-pyran, (59 mg, 25%). IR (CHCl₃) 3580, 3400, 1675, 1151, 1058 cm^{-1} . NMR δ (90 MHz): 8.3-8.2 (2H, m, ArH), 7.7-7.5 (2H, m, ArH), 5.1 (1H, d, $J = 5$ Hz, H1'), 4.85 (1H, t, $J = 3.9$ Hz, H3), 4.0 (2H, t, $J = 5.4$ Hz, H6), 2.55 (1H, d, $J = 5$ Hz, OH), 2.2-0.8 (4H, m). m/z 235 (M^+) 156, 150, 101, 85, 83, 77, 55. (Found M^+ 235.0547, C₁₂H₁₃NO₄ requires 235.0844).

Preparation of enol ether (12).— Pentan-3-one (0.050 cm^3 , 0.5 mmol) was added to a solution of the anion of (1), (1.25 mmol). Chromatography after work-up gave (12), 2-(1'-hydroxy-1'-ethyl-propyl)5,6-dihydro-4H-pyran (0.049 g, 58%). IR 3478, 2930, 1670, 1058 cm^{-1} . NMR δ (90 MHz): 4.78 (1H, t, $J = 3.6$ Hz, H3), 3.95 (2H, t, $J = 4.3$ Hz, H6), 2.15-1.25 (9H, m), 0.95-0.85 (6H, m), m/z 170 (M^+), 141, 113, 83, 57. (Found: 170.1310, C₁₀H₁₈O₂ requires 170.1306).

Preparation of enol ether (13).— Cyclohexanone (0.125 cm^3 , 1.21 mmol) was added to a solution of the anion of (1) (3.02 mmol). Chromatography after work-up gave (13) 2-(1'-hydroxy-1'-cyclohexyl) 5,6-dihydro-4H-pyran (153 mg, 70%). IR 3398, 2926, 1667, 1448, 1235, 1150, 1067 cm^{-1} . NMR δ (90 MHz): 4.80 (1H, t, $J = 3.9$ Hz, H3), 4.00 (2H, t, $J = 5.1$ Hz, H6), 2.3-1.0 (14H, m). m/z 182 (M^+), 139, 55 (Found: M^+ 182.1303, C₁₁H₁₈O₂ requires 182.1307).

Preparation of enol ether (14).— Cyclopentanone (0.088 cm^3 , 1 mmol) was added to a solution of (1) (2.5 mmol). Chromatography after work-up gave (14), 2-(1'-hydroxy-1'-cyclopentyl)5,6-dihydro-4H-pyran (111 mg, 66%). IR 3422, 2947, 1670 and 1066 cm^{-1} . NMR δ (90 MHz) 4.8 (1H, t, $J = 3.6$ Hz, H3), 4.00 (2H, t, $J = 5.4$ Hz, H6), 2.2-1.55 (13H, m). m/z 168 (M^+), 151, 137, 111, 85, 83. (Found: M^+ 168.1151, C₁₀H₁₆O₂ requires 168.1150).

Preparation of enol ether (15).— Acetophenone (0.116 cm^3 , 1 mmol) was added to a solution of the anion of (1) (2.5 mmol). Chromatography after work-up gave (15) 2-(1'-hydroxy-1'-methyl-phenyl)-5,6-dihydro-4H-pyran (83 mg, 42%). IR 3446, 2930, 1670, 1599, 1087 and 766 cm^{-1} . NMR δ (90 MHz): 7.6-7.3 (5H, m, ArH), 5.00 (1H, t $J = 3.750$ (1H, m, OCH₃), 3.75-3.50 (1H, m, OCH₃), 2.70-2.45 (1H, m), 1.40-1.15 (5H, m). m/z No M^+ , 218, 142, 91, 77. (Found C 63.11; H, 5.57; C₁₉H₂₀O₅ requires C 63.32; H 5.59%).

Preparation of the acylated sulphone (16).— Methyl chloroformate (0.077 cm^3 , 1 mmol) was added to a solution of the anion of (1) (1 mmol). Recrystallisation of the solid obtained after work-up from ether-petrol gave (16) as a white solid, 2-methyl(benzenesulphonyl) tetrahydropyran-2-yl)formate (230 mg, 81%), m.p. 52°C. IR (CHCl₃), 1744, 1073, 689 cm^{-1} . NMR δ (90 MHz): 7.88-7.28 (5H, m, ArH), 4.35-3.30 (5H, m, including 3.75 s, Me), 2.70-1.20 (6H, m). m/z no M^+ , 143, 141, 125, 1.09, 77 and 59. (Found: C 54.81; H, 5.65. C₁₃H₁₆O₅S requires C 54.91; H, 5.65%).

Preparation of the acylated sulphone (17).— Ethyl chloroformate (0.095 cm^3 , 1 mmol), was added to a solution of the anion of (1) (1 mmol). Recrystallisation of the solid obtained after work-up from petrol-ether gave (17) as white solid, 2-ethyl(benzenesulphonyl) tetrahydropyran-2-yl)formate (223 mg, 74%) m.p. 59°C. IR (CHCl₃) 2948, 2871, 1733, 1325, 1155, 1085, 1039 and 605 cm^{-1} . NMR δ (90 MHz): 7.91 (2H, m, ArH), 7.65-7.52 (3H, m, ArH), 4.25-4.05 (3H, m, OCH₂), 3.75-3.55 (1H, m, OCH₂), 2.60-2.45 (1H, m), 2.15-1.45 (5H, m), 1.15 (3H, t, $J = 20$ Hz). m/z No (M^+), 156, 127, 142, 83. (Found: C, 56.35, H, 6.37. C₁₄H₁₈O₅S requires C 56.36, H 6.09%).

Preparation of the acylated sulphone (18).— Benzyl chloroformate (0.143 cm³, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Recrystallisation of the solid from petrol-ether gave (18) as a white solid, 2-benzyl-(benzenesulphonyl, tetrahydropyran-2-yl)formate (172 mg, 48%). m.p. 68–69°C. IR (CHCl₃), 2948, 2868, 1736, 1325, 1156, and 1085 cm⁻¹. NMR δ (90 MHz): 7.85–7.75 (2H, m, ArH), 7.60–7.30 (8H, m, including 7.35, s, Ph), 5.15 (2H, s, CH₂ Ph), 4.20–4.00 (1H, m, OCH₂), 3.75–3.50 (2H, m, OCH₂), 2.70–2.45 (1H, m), 1.40–1.15 (5H, m). ⁻m/z No M⁺, 218, 142, 91, 77. (Found C 63.11; H, 5.57; C₁₉H₂₀O₅ requires C 63.32; H 5.59%).

Preparation of enol ether (19).— Allyl bromide (0.0865 cm³, 1 mmol) was added to a solution of the anion of (1) (1.5 mmol). Chromatography after work-up gave (19) (63 mg, 51%). IR 3077, 2938, 2870, 1713, 1638 and 1069 cm⁻¹. NMR δ (90 MHz): 6.0–5.6 (1H, m, H^{2'}) 5.2–4.9 (3H, m, H₃, H^{1'}), 3.7–3.3 (3H, m, H₆, H₃) 3.15 (1H, m, H₃) 1.9–1.7 (4H, m). m/z 125 (M⁺), 124 (M⁺), 101, 84, 57. (Found: 124.0884, C₈H₁₂O requires 124.0888).

Preparation of enol ether (20).— 1-Iodo-4-furyl butane (0.25 g, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Distillation after work-up yielded (20) 2-(4' furyl butyl)5,6-dihydro-4H-pyran (118 mg, 57%) b.p. 100°C/0.2 mm Hg. IR 2934, 1673, 1626 and 1064 cm⁻¹. NMR δ (90 MHz): 7.35 (1H, br.s, H^{2'}), 6.32 (1H, m, H^{4'}), 6.05 (1H, m, H^{3'}), 4.55 (1H, m, H₃), 4.05 (2H, m, H₆), 2.61 (4H, m). 1.98–1.56 (8H, m). m/z 206 (M⁺) 123, 83, 87, 67, 55. (Found: M⁺ 206.1302, C₁₃H₁₈O₂ requires 206.1306).

Preparation of enol ether (21).— Bromo ethyl phenyl (0.136 cm³, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Distillation after work-up gave (21), 2-(2'phenylethyl)5,6-dihydro-4H-pyran (100 mg, 53%) b.p. 60°C/0.005 mmHg. IR 2933, 1675, 1088, 1063 cm⁻¹. NMR δ (90 MHz): 7.30–7.15 (5H, m, Ar), 4.65 (1H, m, H₃), 3.00 (2H, m, OCH₂), 2.25 (2H, m, CH₂-Ph), 1.85–1.5 (6H, m). m/z 188 (M⁺), 104, 91, 85, 55. (Found: M⁺ 188.1203, C₁₃H₁₆O requires 188.1201).

Preparation of enol ether (22).— Benzylbromide (0.109 cm³, 1 mmol) was added to a solution of the anion of (1) (1 mmol) (deprotonated using lithium diisopropylamide). Distillation after work-up yielded (22), 2(1'phenylmethyl)5,6-dihydro-4H-pyran (51 mg, 29%) b.p. 80°C/0.05 mmHg. IR 3029, 1673, 1068 and 692 cm⁻¹. NMR δ (90 MHz): 7.60–7.25 (5H, m, ArH), 5.21 (0.3H, s, Z isomer), 4.45 (0.7H, Z, J = 4.5 Hz, endo isomer), 3.75 (2H, m, OCH₂), 3.20 (1.4H, s, CH₂ endo), 2.1–1.85 (4.6H, m). m/z 174 (M⁺), 91, 90, 83 and 55. (Found: C 82.66; H 8.31. C₁₂H₁₄O requires C 82.72, H 8.10%).

Preparation of enol ether (23).— 1-Iodoheptane (0.113 cm³, 0.690 mmol) was added to a solution of the anion of (1) (2.07 mmol). Chromatography after work-up gave (23), 2-(heptyl) 5,6-dihydro-4H-pyran (46.5 mg, 37%). IR 2930, 2853, 1678, 1463, 1207, 1098, 1067, 898 cm⁻¹. NMR δ (60 MHz): 4.75 (1H, t, J = 3.9 Hz, H₃), 4.0 (2H, t, J = 5. Hz, H₆), 2.2–0.7 (19H, m). m/z 183 (M⁺ + 1⁺), 182, 101, 86, 84. (Found: M⁺ 182.1671, C₁₂H₂₂O requires 182.1671).

Preparation of enol ether (24).— 1-Iodopentane (0.126 cm³, 0.965 mmol) was added to a solution of the anion of (1) (2.983 mmol). Chromatography after work-up gave (24), 2-pentyl 5,6-dihydro-4H-pyran (72.5 mg, 49%). IR 3042, 1674, 1465, 1234, and 1066 cm⁻¹. NMR δ (90 MHz): 4.45 (1H, t, J = 3.9 Hz, H₃), 3.95 (2H, t, J = 5.1 Hz, H₆), 2.2–1.1 (12H, m), 0.9 (3H, t, J = 3.2 Hz, H₃). m/z 155, 154 (M⁺), 111, 101, 981, 83, 55, 41, 29. (Found: M⁺ 154.1356, C₁₀H₁₈O requires 154.1358).

Preparation of sodium or lithium naphthalenide solution.

A mixture of the metal and naphthalene (1:1 molar equivs.) in dry THF at room temperature under argon was ultrasonified for 1h to afford a dark green solution.

General Procedure for condensation of the anion of 2-Benzenesulphonyltetrahydro-2H-pyran with electrophiles and in situ reductive desulphonylation.

The sulphone was dissolved in anhydrous THF at -78°C under argon. n-Butyllithium was added dropwise, the mixture stirred at -78°C for 15 min and then the electrophile added. After stirring for 15 min at -78°C, a 1 M solution of freshly prepared lithium or sodium naphthalenide in THF was added then, after a further 1 h at -78°C, anhydrous methanol. The solution was warmed to room temperature over 2–3 h, poured into water (10 cm³) and extracted with ether (3 x 30 cm³). The ethereal extracts were dried and evaporated to give the crude adduct which was purified by column chromatography on silica, eluting with petrol-ether mixtures.

Preparation of ether (25).— A solution of the anion of (1) (1.001 mmol) was treated with isobutyraldehyde (0.091 cm³, 1.001 mmol), sodium naphthalenide (5.01 cm³ of 1 M solution, 5.01 mmol, 5 eq) and methanol (0.40 cm³, 10 mmol, 10 eq) according to the general procedure. Chromatography after work-up (elution gradient 10:1 → 4:1 petrol-ether) gave (25), 2-(1'-hydroxy, 2'-methyl-propyl)-tetrahydropyran, (83.8 mg, 53%). IR 3470, 1465, 1207, 1087, 1003, 733 cm⁻¹. NMR δ (250 MHz): 4.03 (1H, ddd, J = 11.3, 1.9, 1.9 Hz, H₆), 3.55–3.22 (2.3H, m, H₆, H₂, H^{1'} (minor diastereomer), 3.22–3.11 (0.7H, ddd, J = 6.3, 4.8, 3.8 Hz, H^{1'} (major diastereomer), 2.46 (0.7 H, d, J = 3.8 Hz, OH (major diastereomer), 2.00–1.05 (7H, m, H₃, H^{4'}, H^{5'}, H^{2'}), 1.05–0.81 (6H, m, H₃). m/z 159 (M⁺), 157, 141, 115, 113, 85, 84. (Found: 141.1277, C₉H₁₇O requires 141.1279 (calculated for (M⁺ - OH)). Continued elution gave (2), (41.1 mg, 26%), identical to the material prepared above.

Preparation of ether (26).- A solution of the anion of (3) (1.016 mmol) was treated with octanal (0.159 cm³, 1.016 mmol), sodium naphthalenide (5.08 cm³ of 1 M solution, 5.08 mmol, 5 eq) and methanol (0.41 cm³, 10.1 mmol, 10 eq) according to the general procedure. Chromatography after work-up (elution gradient 10:1 → 7:1 → 4:1 petrol-ether) gave (26) 2-(1'-hydroxy, octyl)-tetrahydropyran (124 mg, 57%). IR 3462, 1465, 1207, 1091, and 1045 cm⁻¹. NMR δ (400 MHz): 4.03 (1H, ddd, J = 11.5, 2.1, 1.8 Hz, H₆), 3.41 (2H, m, H_{1'}, H₆), 3.10 (1H, ddd, J = 11.5, 6.5, 2 Hz, H₂), 2.56 (1H, br.s, OH), 1.86 (1H, br.d, J = 12 Hz), 1.60-1.20 (17H, m), 0.85 (3H, t, J = 7 Hz, Me). m/z 215 (M⁺), 213, 197 (M⁺-H₂O), 1.69, 130, 115, 111, 85. (Found: 197.1900, C₁₃H₂₆O requires 197.1905 (calculated for (M⁺-H₂O)). Continued elution gave (3) (35 mg, 16.1%), identical to the previously prepared material.

Preparation of ether (27).- A solution of the anion of (1) (1.002 mmol) was treated with cyclohexanecarboxaldehyde (0.121 cm³, 1.002 mmol), sodium naphthalenide (5.0 cm³ of 1 M solution, 5.0 mmol, 5 eq) and methanol (0.40 cm³, 9.9 mmol, 9.9 eq) according to the general procedure. Chromatography after work-up (elution gradient 10:1 → 7:1 → 4:1 petrol-ether) gave (27), 2-(1'-hydroxy, cyclohexyl)tetrahydropyran. (100 mg, 50%). IR 3462, 1448, 1085, 1048 cm⁻¹. NMR δ (250 MHz): 4.00 (1H, ddd, J = 11.6, 1.8, 1.8 Hz, H₆), 3.52-3.20 (2.4H, m, H₆, H₁, H_{1'}, (minor diastereomer), 3.18-3.06 (0.6H, ddd, J = 4.6, 4.6, 4.6 Hz, H₁, (major diastereomer), 2.40 (0.67H, d, J = 4.6 Hz, OH (major diastereomer), 2.20 (0.22H, br.s, OH (minor diastereomer), 2.06-0.82 (17H, m). m/z 197 (M⁺-H), 179, 115, 112, 85, 84. (Found: 197.1545, C₁₂H₂₀O₂ requires 197.1541 (calculated for M⁺-H). Continued elution gave (6) (46 mg, 24%), identical to the material prepared previously.

General Procedure for catalytic hydrogenation of enol ethers.

The enol ether in dry methanol was stirred with palladium on activated carbon (25% catalyst system) under a H₂ atmosphere for 16-64 h. The catalyst was filtered off and the solvents evaporated to afford the pure ether.

Hydrogenation of (2).- (2) (100 mg, 0.64 mmol) was hydrogenated for 16 h according to the general procedure to provide (25) (90 mg, 89%) as a diastereomeric mixture (data as above).

Hydrogenation of (6).- (6) (46 mg, 0.23 mmol) was hydrogenated for 64 h according to the general procedure to afford (27) (41 mg, 90%) as a diastereomeric mixture (data as above).

Preparation of Spiroketals

1,7-Dioxaspiro[5.5]undecane (29).- A solution of the anion of (1) (2.2 mmol) was treated with 1-[(t-butylidimethylsilyl)oxy]-4-bromobutane (0.52 g, 2.2 mmol). Work-up and distillation gave (29) (265 mg, 77%) as a colourless oil, b.p. 100°C/25 mmHg. IR 2940, 1171, 1045 and 948 cm⁻¹. NMR δ (250 MHz): 3.77-3.55 (4H, m, OCH₂), 1.95-1.73 (2H, m) and 1.68-1.36 (10H, m); m/z 156 (M⁺), 101, 100, 98, 83, 55 and 41 and was identical to the natural product.

1,7-Dioxaspiro[5.5]undecane (29).- A solution of the anion of (1) (1 mmol) was treated with 1-[(t-butylidimethylsilyl)oxy]-4-iodobutane (0.314 g, 1 mmol). Work-up, immediate treatment of the intermediate with hydrogen fluoride and chromatography gave (29) (81 mg, 52%) identical to that prepared above.

2-Methyl-1,7-dioxaspiro[5.5]undecane (30).- A solution of the anion of (1) (1 mmol) was treated with 1-[(t-butylidimethylsilyl)oxy, methyl]-4-iodobutane (0.329 mg, 1 mmol). Work-up, immediate treatment of the intermediate with hydrogen fluoride and chromatography gave (30) (79 mg, 47%). IR 2932 and 1058 cm⁻¹. NMR δ (90 MHz): 3.8-3.55 (3H, m, OCH₂), 1.92-1.35 (12H, m), 1.15 (3H, d, J = 6.3 Hz, CH₃). m/z 170 (M⁺), 101, 85 (Found: M⁺ 170.1303, C₁₀H₁₈O₂ requires 170.1307).

1,6-dioxaspiro[4.5]decane (31).- A solution of the anion of (1) (1 mmol) was treated with 1-[(t-butylidimethylsilyl)oxy]-3-bromopropane (0.22 g, 1 mmol). Work-up and distillation gave (31) (81 mg, 57%) as a colourless oil. IR 2940, 1079 and 1035 cm⁻¹. NMR δ (250 MHz): 3.95-3.35 (4H, m, OCH₂), 2.05-1.45 (10H, m). m/z 142 (M⁺), 85, 71 and 55. (Found: M⁺ 142.0996 C₈H₁₄O₄ requires 142.0994).

2-Methyl-1,6-dioxaspiro[4.5]decane (32).- A solution of the anion of (1) (11.1 mmol) was treated with 1-iodo[3-tetrahydro-2H-pyran-2-yl]oxybutane (3.1 g, 11 mmol). Work-up and distillation gave (32) (1.37 g, 79%) as a colourless oil (1:2 mixture cis:trans isomers), b.p. 75°C/10 mmHg. $[\alpha]_D^{25}$ -21.1°. IR 2929, 1435 and 1367 cm⁻¹. δ (250 MHz): 4.28-3.25 (3H, m), 2.20-1.40 (10H, m), 1.31 (1H, d, J = 5.4 Hz, Me cis isomer) and 1.24 (2H, d, J = 5.8 Hz, Me trans isomer). m/z 156 (M⁺), 85, 67, and 53 which was identical with the natural product.

4-Hydroxy 1,7-dioxaspiro[5.5]undecane (33).- A solution of the anion of (1) (0.13 g, 0.58 mmol) was treated with 2-phenyl-1,3-dioxolane-4-iodomethane (71 mg, 0.23 mmol). Work-up, immediate treatment with HCl (1M) in MeOH and chromatography gave (33) (19.3 mg, 49%) as waxy solid. IR (film) 3446, 2946, 2870, 1449, 1380, 1058, 1045 and 982 cm⁻¹. NMR (400 MHz) 4.08 (1H, tt, J = 11, 5 Hz, H₄) 3.75-3.47 (4H, m, H₂, H₈), 2.01 (1H, ddd, J = 11.5, 5, 2 Hz, H_{5e}), 1.89 (1H, ddd, J = 12, 5.2 Hz, H_{3e}), 1.81 (1H, tt, J = 12, 5 Hz, H_{10a}), 1.71 (1H, br.s OH), 1.68-1.44 (6H, m), 1.29 (1H, dd, J = 11.5, 11 Hz H_{5a}). ¹³C (22.51 MHz) 18.5, 25.1, 35.0, 35.6, 45.2, 58.8, 60.4, 64.1, 97.3. m/z 172 (M⁺), 155, 117, 101, 83, 55 and was identical to the natural product.

E-2-hydroxymethyl-5-acetoxy-1,7-dioxaspiro[5,5]undecane (34).- A solution of the anion of (1) (1 mmol) was treated with 2,2-dimethyl-1,3-dioxolane-4-propanal (0.159 g, 1 mmol). The intermediate was trapped with acetic anhydride (0.142 cm³, 2 mmol) then subsequently treated with CSA in MeOH. Chromatography gave (35) (62 mg 33%) as a pale yellow oil. IR 3456, 1734, 1373, 1180, 1078 and 1046 cm⁻¹. NMR δ (90 MHz): 4.8 (1H, m, H-OCOCH₃), 3.9-3.5 (5H, m, OCH), 2.25 (1H, m), 2.10 (3H, s, OCH₃) 1.85-1.4 (10H, m). m/z 244 (M⁺), 213, 153, 85, 59, (Found M⁺ 244.1310 C₁₂H₂₀O₅ requires 244.1310).

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