NEW METHODS FOR SPIROKETAL SYNTHESIS.

a thesis presented by

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Abstract.

Three novel methods for the construction of spiroketals, or as they are now more commonly known, spiroacetals, have been studied. The first of these makes use of an organoselenium-mediated cyclistation reaction, which cleanly allows conversion of alkenyl-substituted hydroxy ketones and hemiacetals into spiroacetal systems. The naturally occurring insect pheromones, 7-methyl-1,6-dioxaspiro[4.5]decane and 2-methyl-1,6-dioxaspiro[4.5]decane are synthesised in racemic form to illustrate application of this procedure. Extension of the reaction scope to effect cyclisation of alkenyl-substituted β-diketones is also examined and the stereochemical features of this process investigated, including crystallographic studies on a derivative of the product obtained.

Cyclisation processes employing sulphur are also investigated culminating in the development of a new reagent, phenylsulphenopyrrolidine, which is employed in the preparation of a cyclic ether, and the spiroacetals, 7-phenylsulphenomethyl-1,6-dioxaspiro[4.5]decane and 2-phenylsulphenomethyl-1,7-dioxaspiro[5.5]undecane.

The second method involves the development of Wittig and Horner-Wittig procedures for the preparation of spiroacetal systems, and this method is demonstrated by the synthesis of a variety of spiroacetals including the naturally occurring insect pheromones 7-methyl-1,6-dioxaspiro[4.5]decane and 1,7-dioxaspiro[5.5]undecane, in racemic form. This procedure is extended to the synthesis of the optically pure spiroacetal portion of milbemycin β_1. Studies towards the spiroacetal portion of avermectin A_{1b} are also presented.

The final method involves the development of sulphone coupling reactions employing the anion of 2-benzenesulphonyltetrahydropyran as a vinyl anion equivalent. Again the utility of this method is demonstrated by the synthesis of the insect pheromones 2-methyl-1,6-dioxaspiro[4.5]decane and 1,7-dioxaspiro-[5.5]undecane, the former being prepared in optically pure form.

List of Contents.

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1. SYNTHESIS OF SPIROACETALS.

1.1 INTRODUCTION.

The spiroacetal moiety has been recognised by organic chemists since the 1800's[1-5], however not until relatively recent times has it received much attention. This interest was stimulated by the characterisation of a wide variety of important natural products containing spiroacetal functions, ranging from simple insect pheromones[6,7], through plant metabolites, to the more complex classes of compounds such as steroids[8], polyether antibiotics[9], cytovaracins[10], and the milbemycin-avermectin family[11,12]. This latter class of compounds are particularly interesting since they exhibit extremely potent antiparasitic activity against a host of helminths and arthropods.

In this section the wide variety of methods reported for the preparation of spiroacetals will be presented, with emphasis on their generality and applicability to natural product synthesis. Owing to the vast amount of literature on this subject, only general strategies for the construction of the spiroacetal ring system will be discussed. However, included at the end of this section, there is a comprehensive listing of the different spiroacetal systems that have been prepared.

Spirolactones have not been included because although it is known that they can be reduced to spiroacetals[13], most methods employed in their preparation are derivative of methods that have been used to synthesise spiroacetals.

1.2 THE ANOMERIC EFFECT.

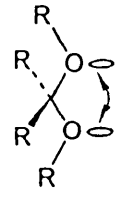
Before discussing synthetic methods directed towards spiroacetals, it is important to consider the stereoelectronic effects operating in the

structures presented. Recently an excellent monograph on this subject has appeared[14], however the relevent points will be reiterated here, in order to qualify the results presented later.

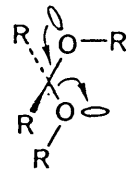
The influence of stereoelectronic effects on the conformation of acetals has long been recognised. Lemieux introduced the term *anomeric effect* in 1958[15], as a representation of the tendancy of an alkoxy group at the C-2 position of a pyranose ring to assume an axial rather than equatorial orientation.

Explanations for this phenomenon consider two possible effects, the first a destabilising effect due to repulsions between the lone-pair electrons on opposing oxygen atoms in conformations of type (1), and the second a stabilising effect due to the lone-pair σ-conjugation obtained in conformations of type (2)[16,17] (Scheme 1).

Scheme 1.



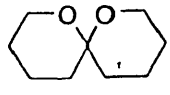
(1)



(2)

Deslongchamps has studied a variety of spiroacetal systems and found that by equating both anomeric and steric effects, it is possible to predict quite accurately, the equilibration isomer ratios of simple spiroacetals[14,18] (Scheme 2).

Scheme 2.



Three possible conformations:

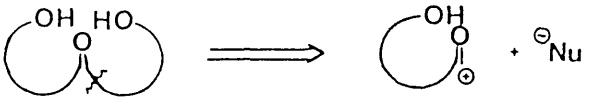
rel. stability KCal/mol	4.8 (only conformer that exists)	2.4	0.0

In the case of more complex systems other factors such as internal hydrogen bonding between substituents and ring oxygen atoms, etc.., further complicate the scene and predictions are of a more qualitative nature.

1.3 ADDITION OF CARBON-NUCLEOPHILES INTO LACTONES OR FORMATES.

In order to discuss the different methods employed in spiroacetal synthesis, it is important to realise that these molecules are latent dihydroxy ketones. Consideration of this form leads to the obvious disconnection shown below (Scheme 3).

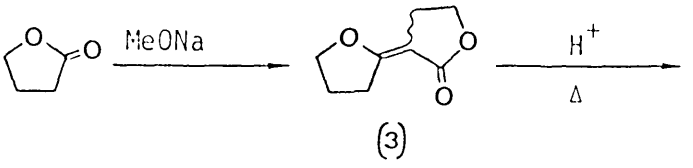
Scheme 3.



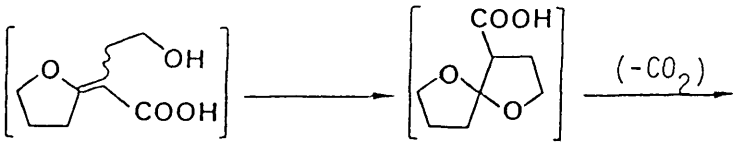
1.3.1 Treatment of Lactones with Base.

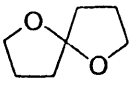
Historically this was the first method reported for the preparation of spiroacetals[1-5]. The example below is typical of the procedure and shows base catalysed dimerisation of γ-butyrolactone, to give the adduct (3). This intermediate then undergoes ring opening, cyclisation and

Scheme 4.



(3)

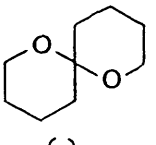




(4)

decarboxylation, on heating with acid to give the symmetrical spiroacetal (4) (Scheme 4).

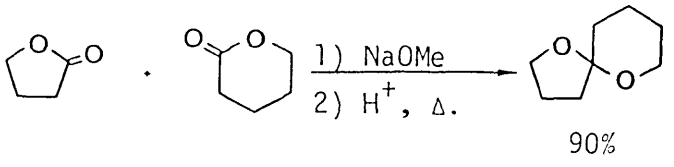
This method is excellent for the preparation of simple symmetric spiroacetals and has found much application in the literature, including a confirmatory synthesis of the natural product (5), isolated in 1980 from the Olive fly, *Dacus oleae*[19].



(5)

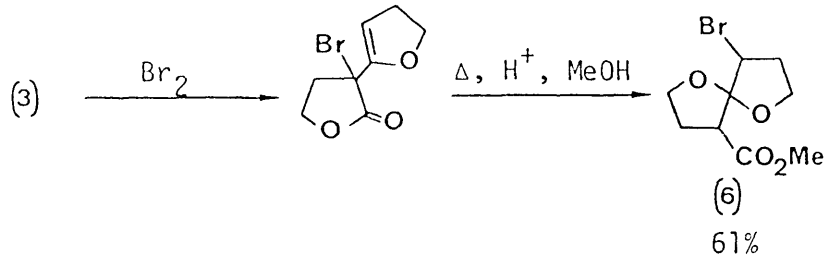
There has been one report in which this reaction was used to prepare unsymmetrical spiroacetals, however apart from the one example indicated (Scheme 5), no yields were presented[20]. The high yield obtained in this example must reflect the greatly increased tendency of δ-valerolactone to enolise on treatment with base compared with γ-butyrolactone.

Scheme 5.



The initial aldol adduct (3) has also been reacted with bromine[21], and reported to give the spiroacetal (6) on subsequent treatment with acid and methanol (Scheme 6), however the spectral data quoted was inconclusive for the assigned structure. Nevertheless, if this reaction does proceed as

Scheme 6.



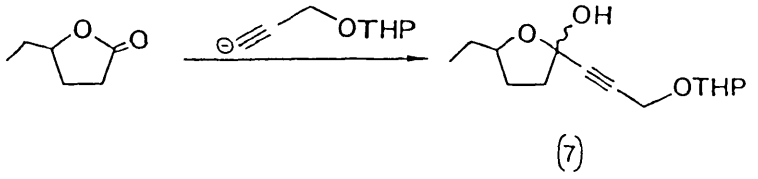
written it could be useful in the preparation of more complex spiro systems.

1.3.2 Addition of Acetylide Anions into Lactones and Formates.

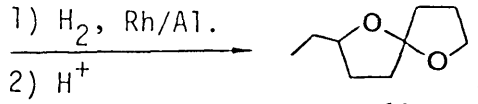
Acetylide anions have been shown to react cleanly with lactones, to give adducts of type (7)[18,22]. Hydrogenation of the acetylene bond followed by deprotection of the hydroxyl group and acid catalysed cyclisation of the resulting hydroxy hemiacetal, then gives the spiroacetal. The example

below[22a] shows application of this method in the synthesis of the natural product (8) isolated from *Pityogenes chalcographus L.*[23] (Scheme 7).

Scheme 7.



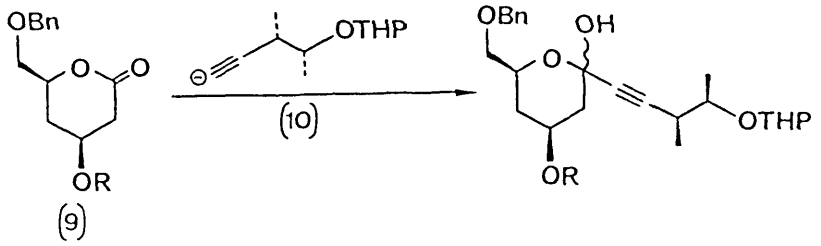
(7)



(8)

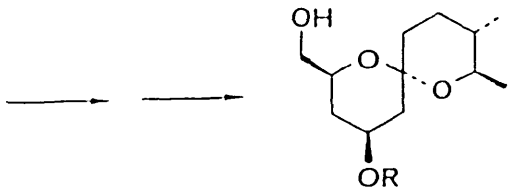
During the preparation of the milbemycin spiroacetal (11), Baker[24] made use of the acetylide (10) derived from addition of acetylide into *cis*-butene oxide. Addition into the laevoglucosan derivative (9) followed by hydrogenation and cyclisation, gave the spiroacetal (11) in 30% overall yield (Scheme 8). Despite the fact that the racemic acetylene (10) could only be partially resolved, this method did allow the preparation of optically active spiroacetal in good overall yield.

Scheme 8.



(9)

R= $Ph_2{}^tBuSi$

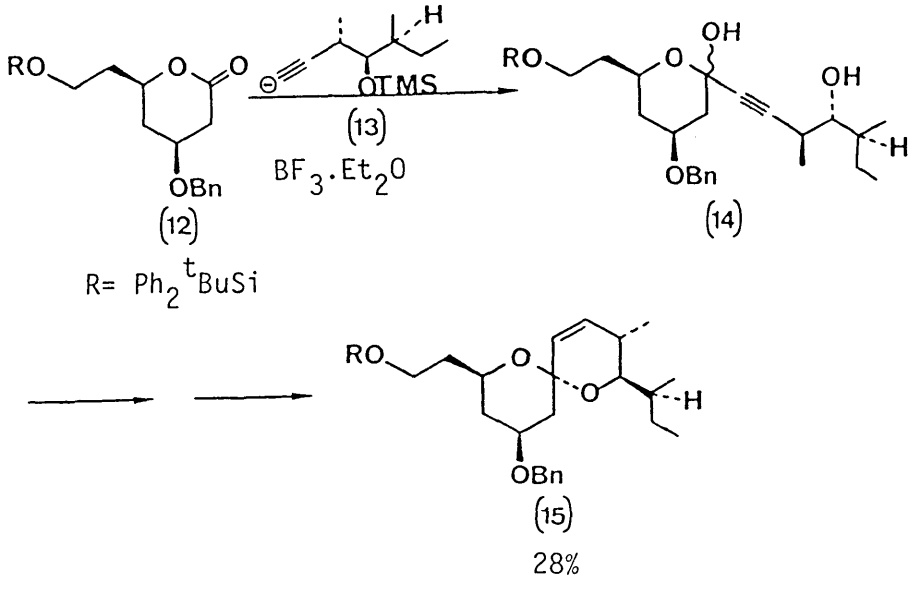


(11)

30%

Partial hydrogenation of the acetylene bond with quinoline poisoned palladium on barium sulphate catalyst to give the *cis*-olefin, allows access to unsaturated spiroacetal systems and this approach has been applied in the synthesis of the spiroacetal portion of avermectin B_{1a} (15)[25]. Here, Hanessian prepared both lactone (12) and acetylene (13) in their optically pure forms, by rather lengthy sequences from D-glucose. In this case it was necessary to use $BF_3.Et_2O$ in the anion addition reaction in order to

Scheme 9.



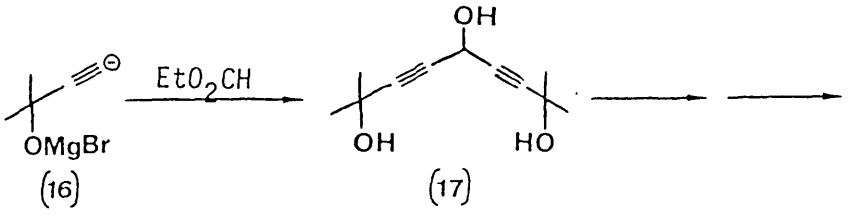
avoid β-elimination of benzyl alcohol from the lactone (12). This necessarily reduced the reactivity of the acetylide anion giving only a 38% yield of the adduct (14) (90% based on recovered starting material).

Partial hydrogenation followed by acid catalysed cyclisation then gave the spiroacetal (15) (Scheme 9).

A similar strategy is being applied by Deslongchamps in an approach to Erythronolide A[14].

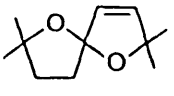
Acetylide anions of type (16) have also been reacted with ethyl formate [26], to give the diaddition product (17) in moderate yield, 33%. This material may be converted into the naturally occurring spiroacetal (18) isolated from hops[27], by a variety of oxidation and hydrogenation sequences (Scheme 10).

Scheme 10.



(16) (17)

33%



(18)

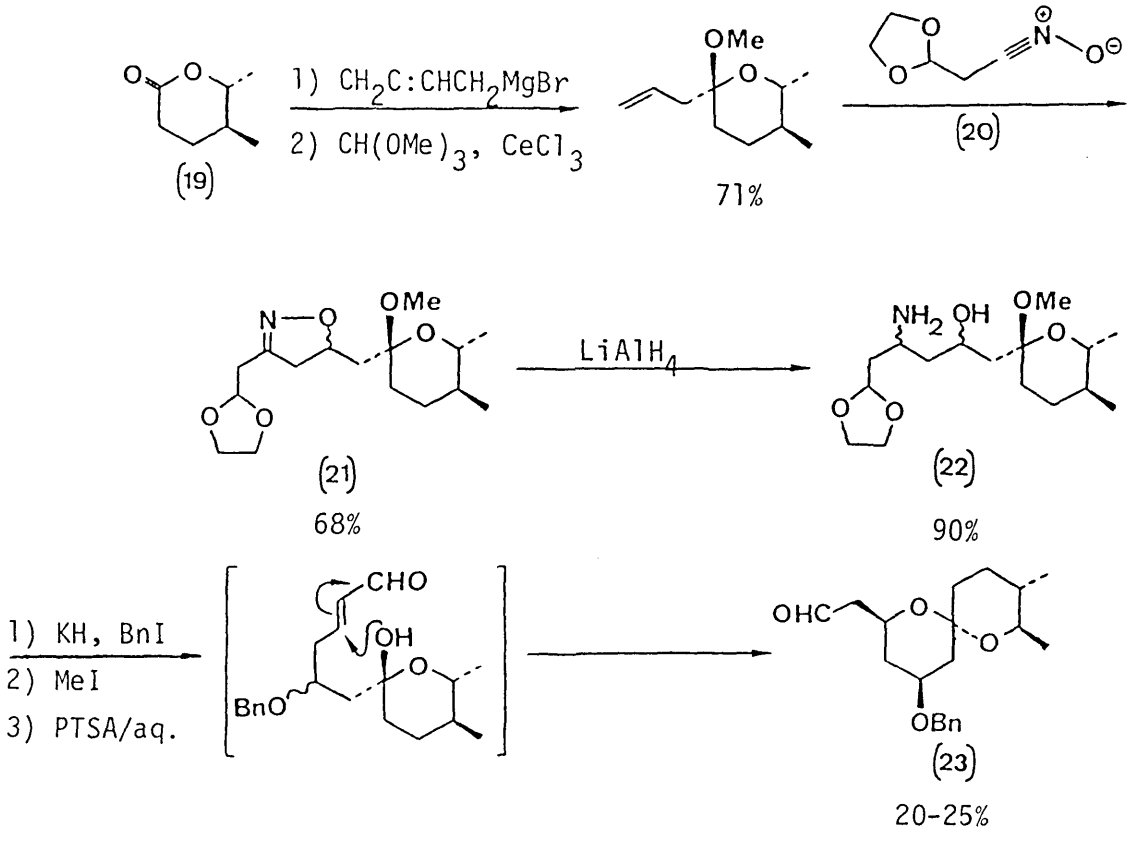
1.3.3 Addition of Grignard Reagents into Lactones and Formates.

As with the acetylide anions discussed above, additions of Grignard reagents into lactones have been used extensively in the preparation of spiroacetals. The Grignard reagents are however more reactive than the corresponding acetylide anions, and in some cases conditions have to be carefully controlled in order to ensure mono-addition. This is an especially difficult problem in the reaction with simple lactone

derivatives[28].

Smith[29] employed a Grignard reagent addition into lactone (19) during his synthesis of the milbemycin spiroacetal (23), although the key step involved reaction of the resulting alkene with nitrile oxide (20) to give the isoxazoline (21) as a mixture of isomers. Reduction to the aminol (22) further complicated the situation giving a mixture of all four possible

Scheme 11.

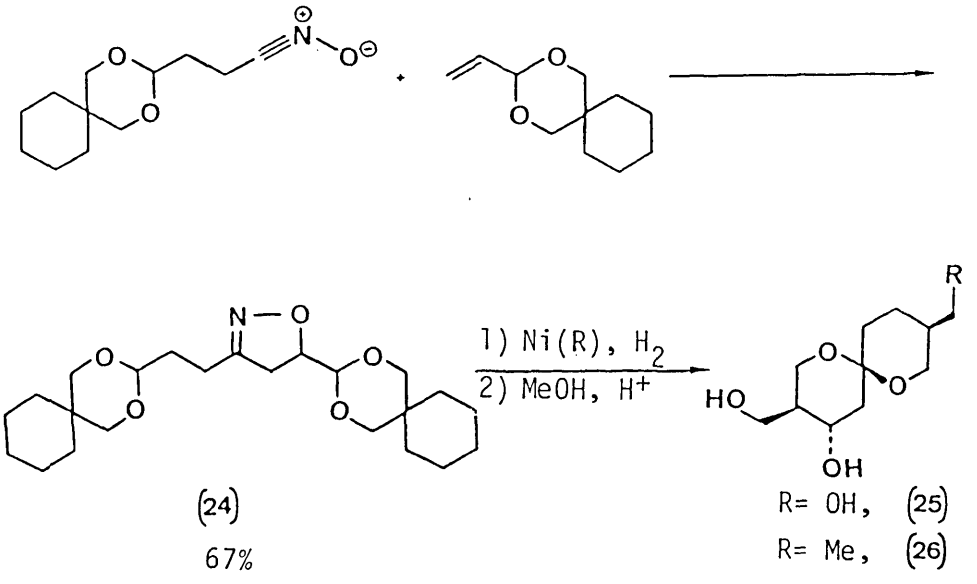


isomers. Fortunately protection of the hydroxyl group, Hoffmann elimination of the amino group, and liberation of the aldehyde moiety, followed by *in situ* Michael-type cyclisation resulted in only the desired isomer (23) crystallising from the reaction mixture (Scheme 11).

A similar nitrile oxide addition was employed by Kozikowski[30]

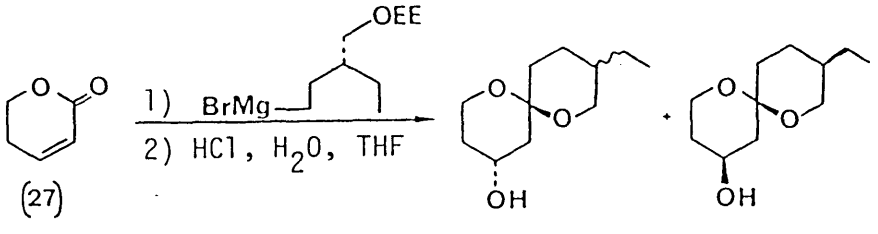
in the synthesis of talaromycin B (26). In this case the isoxazoline (24) produced was reduced with Raney nickel, to give a β-hydroxy ketone, which subsequently cyclised on treatment with acid (Scheme 12).

Scheme 12.



Smith[31] also made use of a Grignard reaction with lactone (27) in a recent synthesis of talaromycins A and B. In this case the strategy parallels that employing acetylide anions, since the hydroxyl group required for future cyclisation is carried in protected form, as part of the Grignard reagent. In this example, cyclisation was accompanied by hydration of the olefin bond, giving a mixture of three spiroacetals (Scheme 13). This mixture was then utilised in the preparation of both talaromycins A and B.

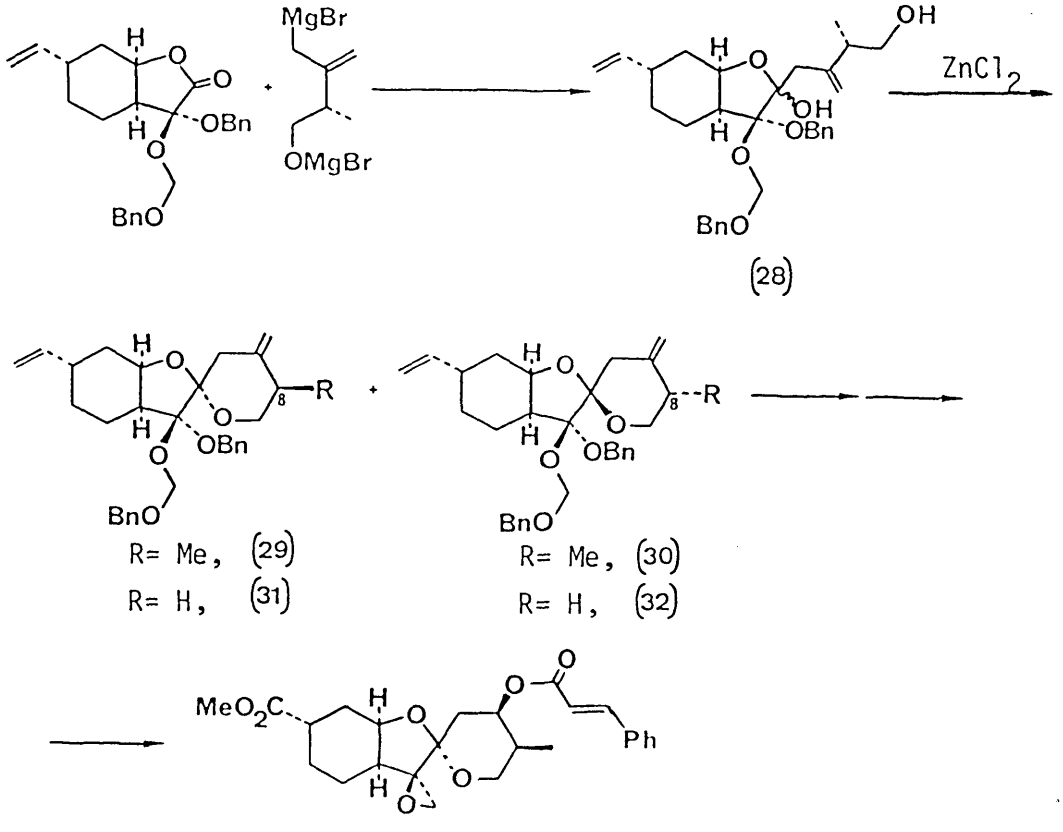
Scheme 13.



——→ ——→ Talaromycin A and B.

A Grignard reagent containing a hydroxyl substituent has also been incorporated in the synthesis of (+) phyllanthocin[32]. In this case, formal protection of the hydroxyl group was not necessary (Scheme 14). Cyclisation

Scheme 14.



(+)-Phyllanthocin.

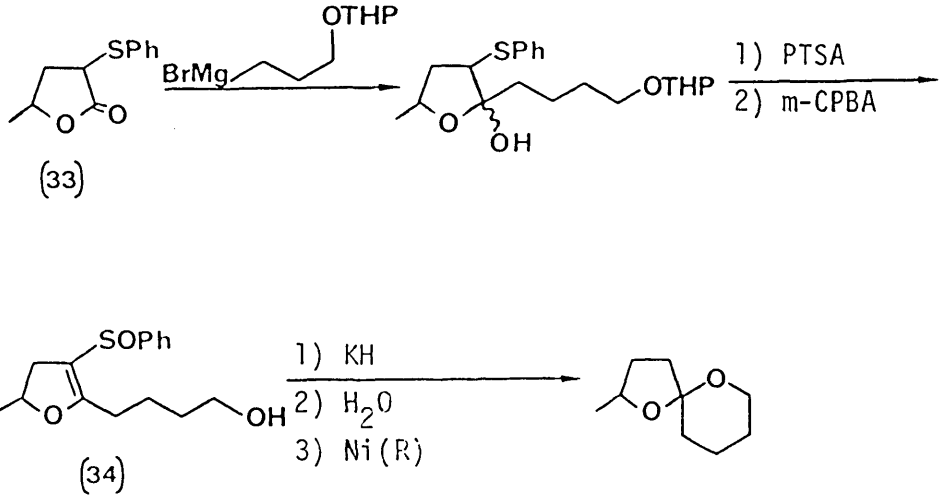
of the adduct (28) with zinc (II) chloride proved to be highly stereoselective giving the desired spiroacetal (29) in 68% yield, with only

trace amounts of the more hindered isomer (30).

A similar strategy was used in the synthesis of the related (+)-phyllanthocindiol[33]. Here the importance of the steric requirements of the C-8 methyl group in governing the stereoselectivity of the spiro cyclisation was illustrated by the observation that absence of this substituent led after cyclisation to a 1:1.5 mixture of spiroacetals (31) and (32), favouring the undesired isomer.

A recent report describes the addition of Grignard reagents into lactone (33), which contains an α-phenylsulpheno group[34]. Dehydration, oxidation, and removal of the hydroxyl protecting group then allows cyclisation *via* Michael addition into the unsaturated sulphoxide system (34). Finally, treatment with Raney nickel effects removal of the sulphoxide group (Scheme 15).

Scheme 15.

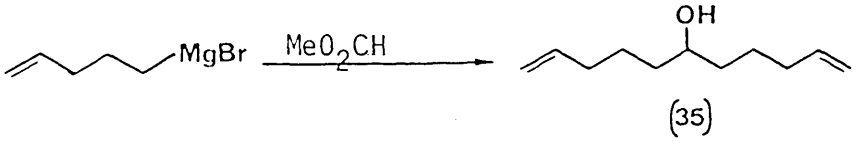


This method apparently allows selective preparation of either *cis* or *trans* spiroacetal isomers depending upon the configuration at sulphur, of the sulphoxide (34), however the authors make no reference to the stability of these compounds, which have been reported to equilibrate rapidly to *cis*-

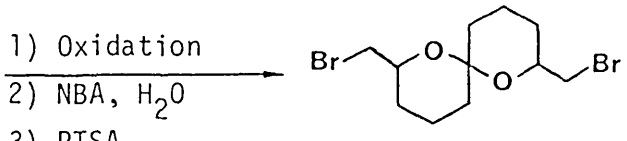
trans mixtures in a previous publication[35].

The diaddition of Grignard reagents into methyl formate has also been investigated as a means of preparing spiroacetals[36]. Oxidation of the initial adduct (35) followed by addition of HOBr across the olefin bonds and subsequent cyclisation, afforded the dibromo spiroacetal (36) (Scheme 16).

Scheme 16.



(35)

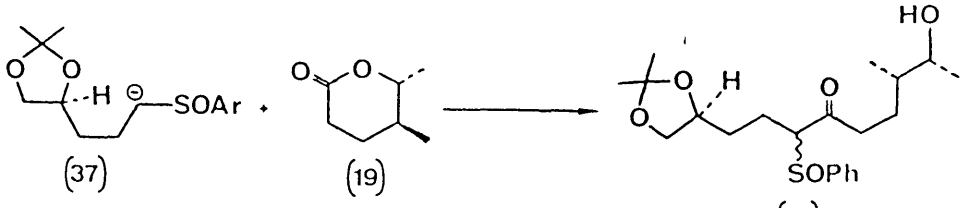


(36)

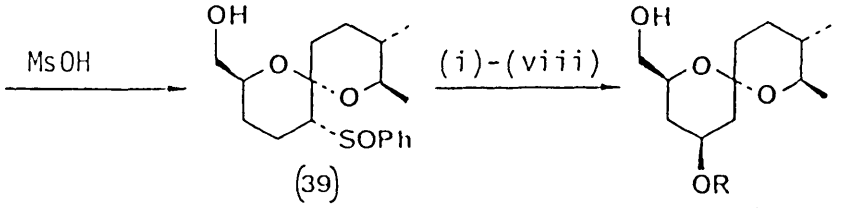
1.3.4 Addition of Sulphoxide Anions into Lactones.

A novel approach employing the addition of an optically active sulphoxide (37) into a lactone (19) was employed by Williams[37] in a synthesis of the milbemycin spiroacetal (11) (Scheme 17). The initial adduct (38) was cyclised under acidic conditions to the spiroacetal (39), these conditions also

Scheme 17.



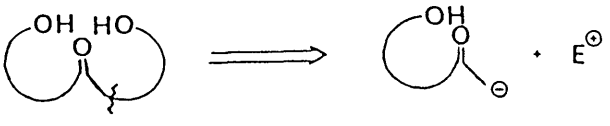
(37) (19) (38)



(i) BzCl; (ii) $P(OMe)_3$, Δ; (iii) ^tBuOCl;
(iv) $^nBu_3SnH$; (v) PCC; (vi) $NaBH_4$, DME;
(vii) $Ph_2{}^tBuSiCl$; (viii) LiOH.

equilibrating the sulphoxide group to the more stable equatorial position. *Syn*-elimination of the sulphoxide group followed by hydroxylation of the resulting double bond (Scheme 17), gave the desired spiroacetal (11).

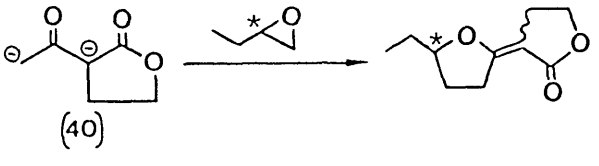
1.4 APPLICATION OF ENOLATE REACTIONS.



1.4.1 Mono- and Di-anions Derived from β-Dicarbonyl Compounds.

Dianions derived from β-keto esters have been used extensively in the synthesis of spiroacetals. Mori[38,39] utilised the dianion (40), which on reaction with an optically active epoxide led as shown (Sheme 18) to

Scheme 18.

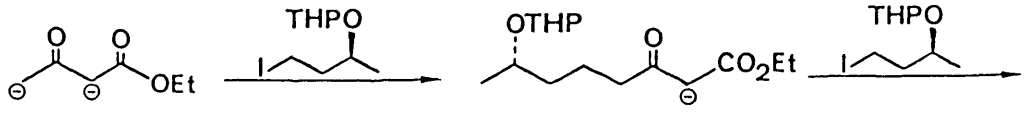


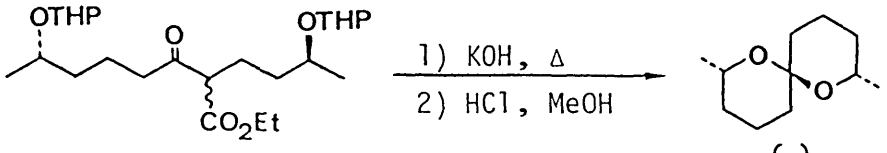
(8)

the natural product (8), an aggregation pheromone of *Pityogenes chalcographus L*[23]. Both 2-(R) and 2-(S) forms of the spiroacetal were prepared in this way.

Reaction with epoxides limited this method to the preparation of spiroacetals containing at least one five-ring, although this problem was overcome by employing alkyl iodides as electrophiles[35,40], as illustrated in the preparation of the isomers of the pheromone (41)[40a], isolated from Andrena Bees[41] (Scheme 19).

Scheme 19.



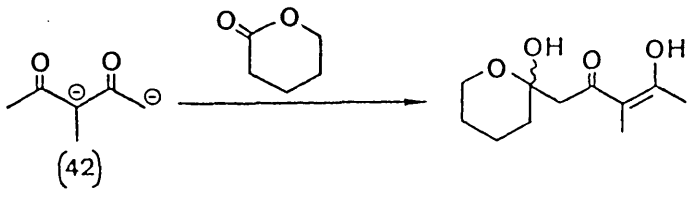


(41)

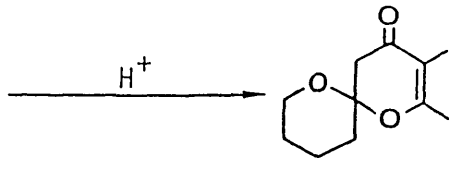
Dianions derived from β-diketones have been reported in the preparation of unsaturated spiroacetals. First reported by Barrett[42], the reaction of dianion (42) with δ-valerolactone, gave on cyclisation, the spiroacetal (43)

(Scheme 20). This work formed part of a model study towards the spiroacetal system contained in the milbemycins, however as yet no further results have been reported.

Scheme 20.



(42)

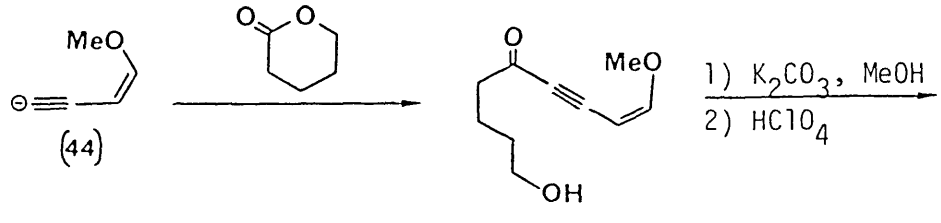


(43)

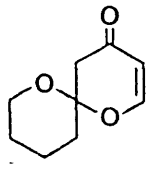
68%

Crimmins[43] considered a similar approach using the dianion of formyl acetone, but obtained disappointing results, finding that it was more useful to employ the formyl anion equivalent (44) (Scheme 21).

Scheme 21.



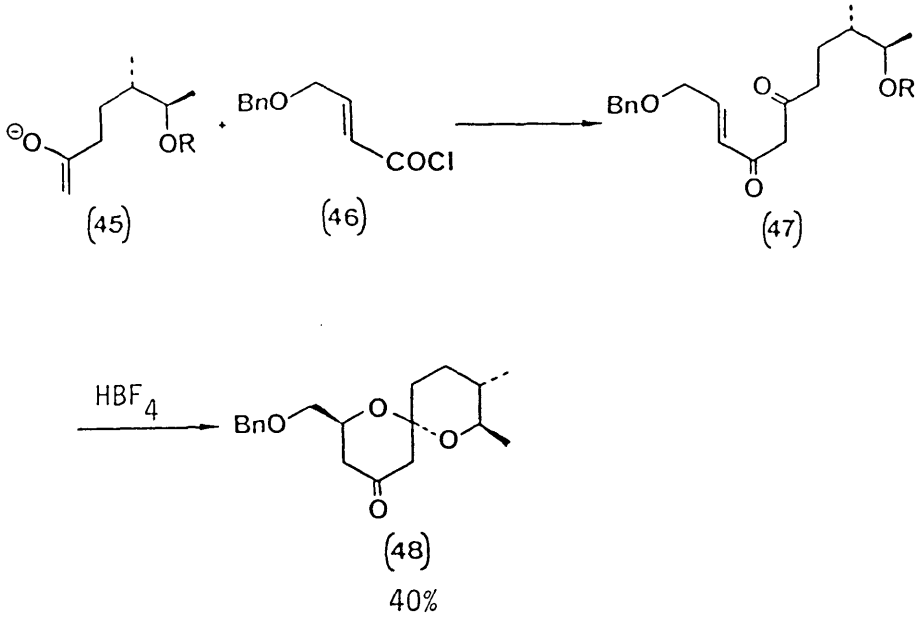
(44)



1.4.2 Enolates Derived from Ketones.

Williams[44] reported a reaction in which the enolate (45) was acylated with compound (46) leading to the enone (47). Hemiacetal formation followed by Michael-type cyclisation gave the spiroacetal (48), unfortunately as a

Scheme 22.

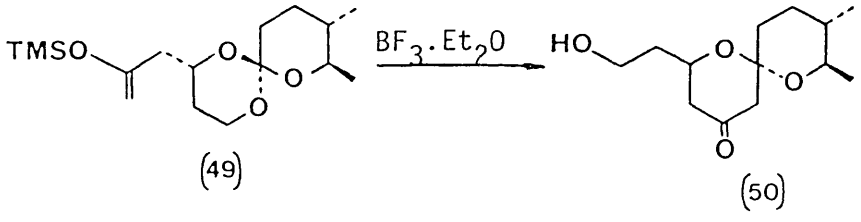


(45) (46) (47) (48)

40%

60:40 mixture of isomers (Scheme 22).

A recent report by Kocienski[45] makes use of a novel intramolecular Mukiyama reaction in an approach to the milbemycin spiroacetal (Scheme 23). Unfortunately this method suffers from a lack of stereospecificity in the formation of the acetal (49) and the cyclisation itself only gives moderate yields of the spiroacetal (50), due to the instability of the product to the



(49) (50)

Scheme 23.

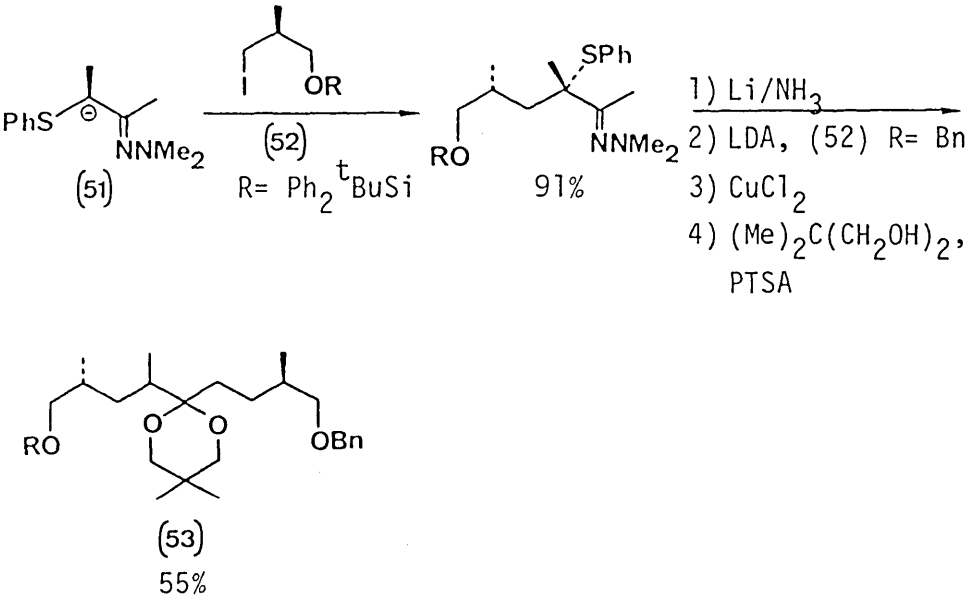
reaction conditions.

An aldol condensation was also the key step in the construction of the spiroacetal system of the polyether antibiotic monensin[46,47].

1.4.3 Enolate Equivalents.

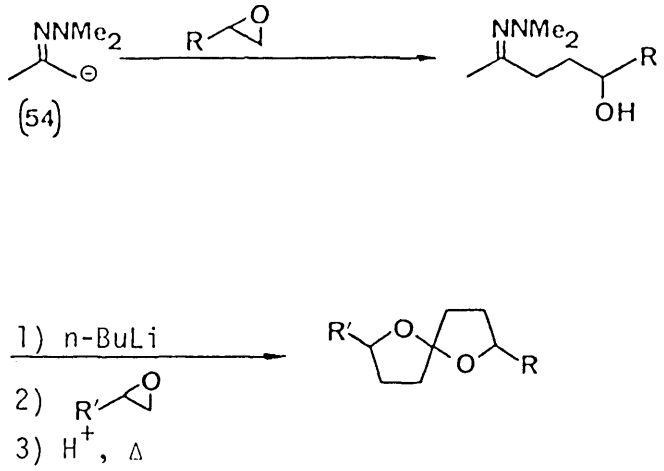
The anion (51) was alkylated with iodide (52) in the key step towards the preparation of the spiroacetal portion of the ionophore antibiotic calcimycin[48]. Further alkylation gave compound (53), containing all the essential elements required for cyclisation to the spiroacetal, which was one of the last steps in the synthesis (Scheme 24).

Scheme 24.

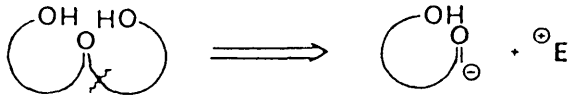


More recently, Enders[49] has made use of the anion (54) in reactions with optically active epoxides (Scheme 25). This method gives high overall yields of optically active spiroacetals and it should be possible to extend to reaction with alkyl halides, allowing access to other spiro systems.

Scheme 25.



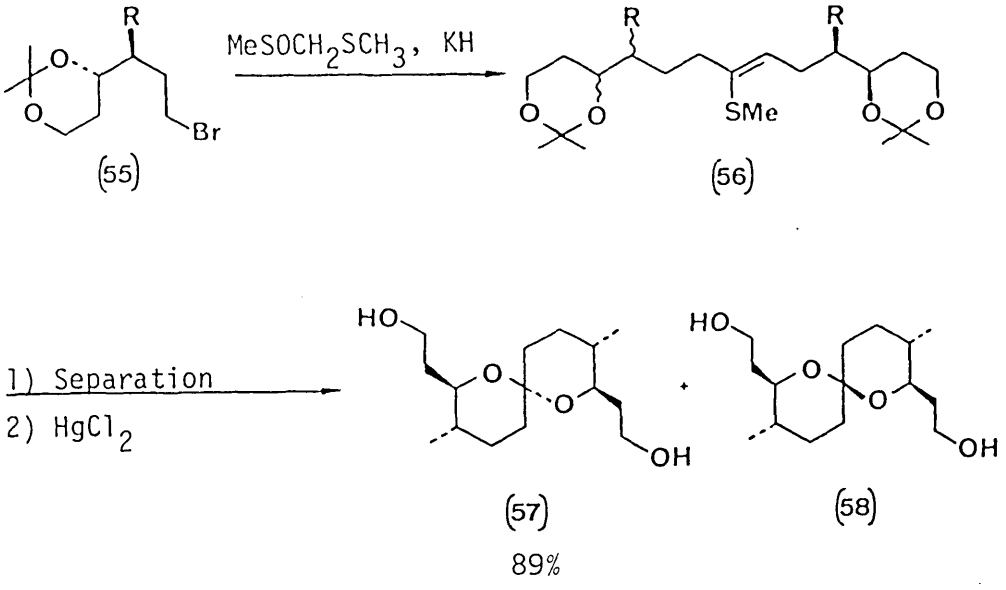
1.5 USE OF ACYL ANION EQUIVALENTS.



1.5.1 Formation of Vinyl Sulphides.

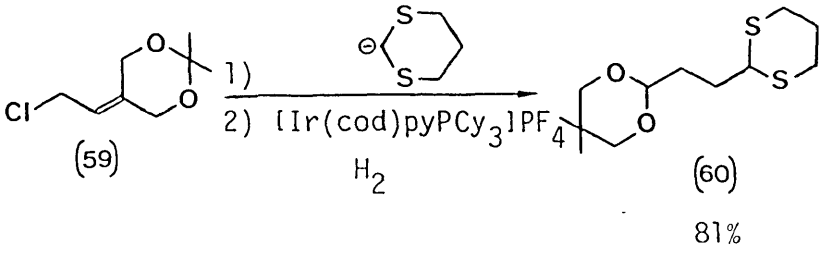
The first example of this strategy was reported by Evans[50], who prepared the vinyl sulphide (56), by coupling together two molecules of the bromide (55) (Scheme 26). Hydrolysis of compound (56) was accompanied by cyclisation to the spiroacetals (57) and (58) in high yield, the major product (57) being isolated in 89% yield. Attempts to utilise thioacetals instead of the vinyl sulphide led to only poor reaction.

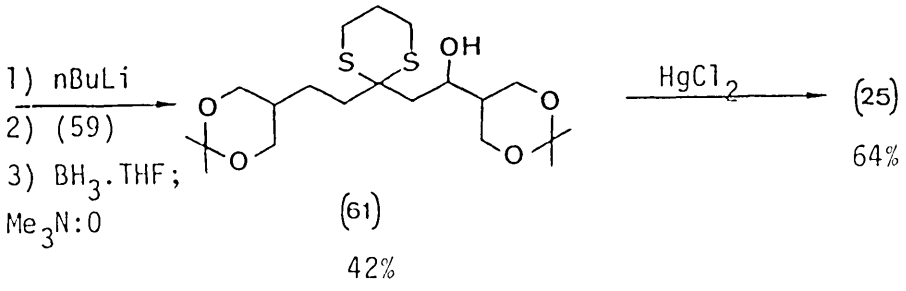
Scheme 26.



1.5.2 Use of 1,3-Dithiane Anions.

Double alkylation of 1,3-dithiane has been used as a method of preparing both symmetrical and unsymmetrical spiroacetals[51]. This method was nicely illustrated by Schreiber[51b] in a synthesis of racemic talaromycin B. Here the anion from 1,3-dithiane was reacted with allylic chloride (59), to give after hydrogenation of the olefin, adduct (60). Reaction with a further molecule of the chloride (59), followed this time by hydroboration of the olefin, gave compound (61). In this way two molecules of the allylic chloride (59) were efficiently used to prepare the unsymmetrical unit (61) required for cyclisation. Hydrolysis of compound (61) gave the spiroacetal





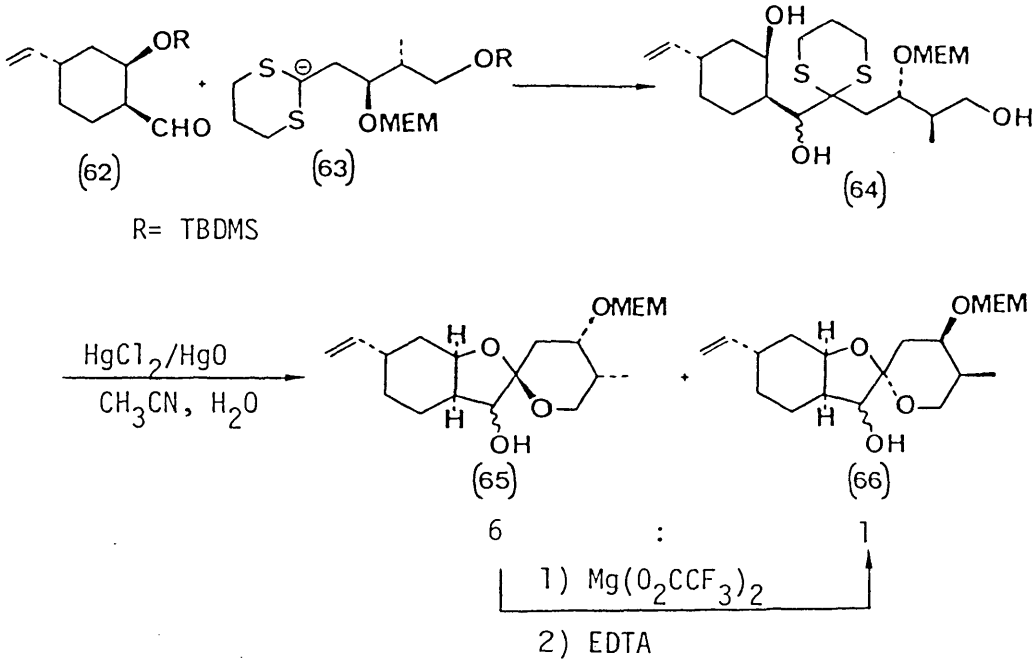
Scheme 27.

(25), a known precursor[30] for talaromycin B (Scheme 27).

Substituted 1,3-dithianes prepared from ring opening of carbohydrate derivatives have been employed in the synthesis of optically active insect pheromones[41,52]. Due to the simple substitution patterns present in these systems, rather lengthy sequences are required in order to prepare the dithiane unit and hence this method is not usually as efficient as others that are available.

This strategy was also employed by Williams[53] in a synthesis of phyllanthocin (Scheme 28). Stereoselective addition of the dithiane anion (63) into aldehyde (62) followed by desilylation, gave the adduct (64) as

Scheme 28.



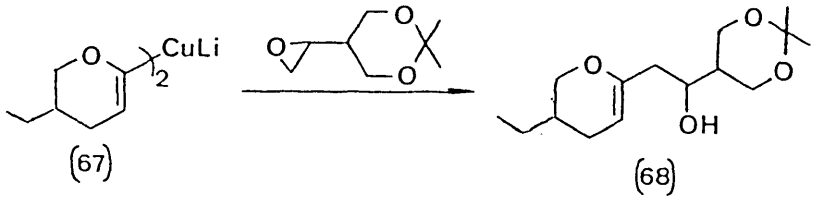
——→ ——→ Phyllanthocin.

a 3.5:1 mixture of alcohol epimers, which could be cyclised to a mixture of spiroacetals (65) and (66). Unfortunately, the protic conditions necessary for hydrolysis of the dithiane group favoured formation of the undesired spiroacetal (65). However it was shown that treatment of this material with magnesium trifluoroacetate gave a stable chelation complex, which on addition of EDTA gave the desired spiroacetal (66) almost exclusively. The observation that protic or aprotic conditions favour formation of different spiroacetals in this system highlights the problems in predicting the stereochemistry of products in such complex compounds.

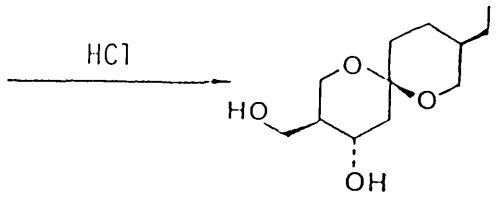
1.5.*3* Dihydropyran Anions.

The cuprate (67) has recently been used by Kocienski in the preparation of spiroacetals[54]. This reagent was found to react cleanly with epoxides as illustrated in a synthesis of talaromycin B[55] (Scheme 29).

Scheme 29



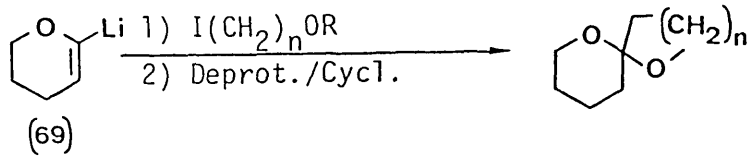
(67) (68)



23%

Amouroux[56] has also shown that the simple lithio anion (69) reacts cleanly with a variety of alkyl iodides, and can be used efficiently to prepare a range of simple spiroacetals (Scheme 30).

Scheme 30.



(69)

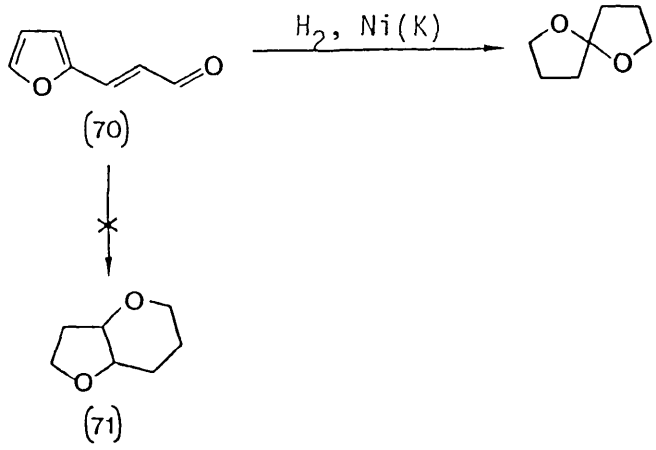
1.6 FROM FURANS.

1.6.1 Reductive Methods.

Hydrogenation of furan substituted enals of type (70) using a nickel on Kieselghur catalyst was found to give spiroacetals in poor to moderate yields[23, 27,57], although initially this reaction was thought to be producing the bicyclic compound (71)[58] (Scheme 31).

The reaction mechanism is thought to proceed as shown below (Scheme 32), the side chain hydrogenating first, followed by the less substituted furan double bond. The resulting enol ether then cyclises to a spiroacetal in preference to further hydrogenation. This proposed mechanism is

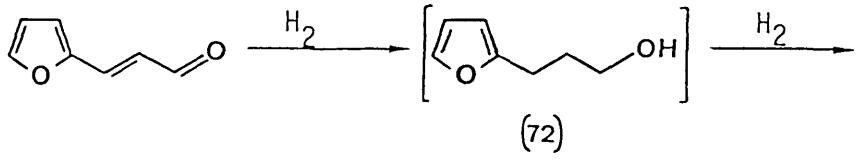
Scheme 31.



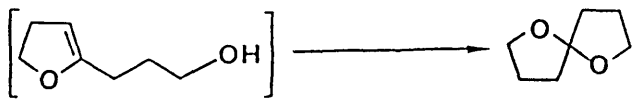
(70) (71)

substantiated by the observation that furans containing a saturated side-chain also react in the same manner, e.g. compound (72)[57b]. This would

Scheme 32.



(72)



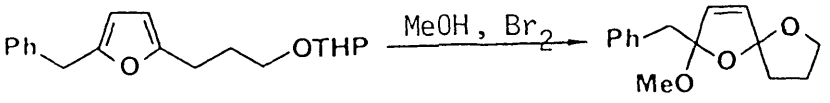
obviously not take place were the cyclisation occurring *via* a radical process on the nickel surface.

Best yields (20%- 40%) are obtained from furans containing bulky side-chains, since this favours hydrogenation of the unsubstituted furan double bond.

1.6.2 Oxidative Methods.

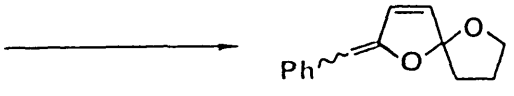
Oxidation of substituted furan derivatives using bromine in methanol has been employed in spiroacetal synthesis, as illustrated by the preparation of compound (74)[59] (Scheme 33).

Scheme 33.



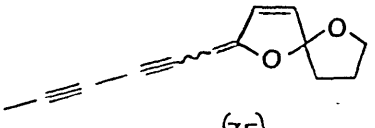
(73)

30%



(74)

The oxidation step giving intermediate (73) proceeds in only moderate yield, but does provide a useful variation on the above hydrogenation method and has been used in the preparation of quite sensitive spiroacetals such as compound (75).

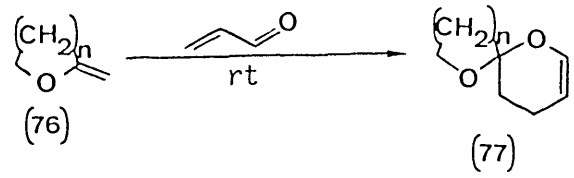


(75)

1.7 HETERO DIELS-ALDER REACTIONS.

Two variations on the preparation of spiroacetals *via* hetero Diels-Alder reactions have been reported, the most direct developed by Ireland[60], involves cycloaddition between an *exo*-methylene substituted cyclic ether of type (76) and an enal or enone, giving high yields of the versatile unsaturated spiroacetals (77) (Scheme 34).

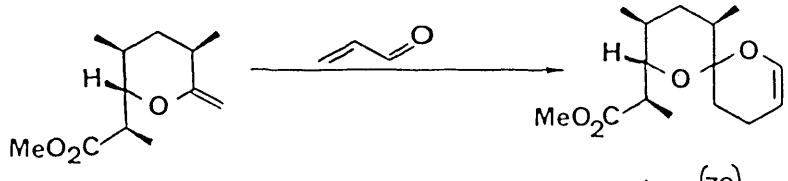
Scheme 34.



(76) (77)

This method was later applied to more complex systems[61], notably the cyclic ether (78), but gave only poor yields of the spiroacetal product (79) (Scheme 35).

Scheme 35.

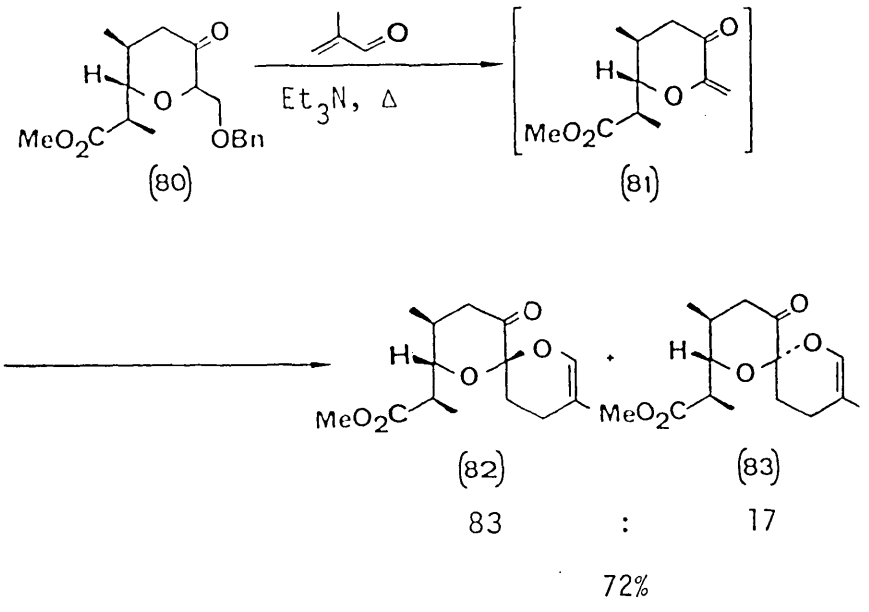


(78) (79)

19%

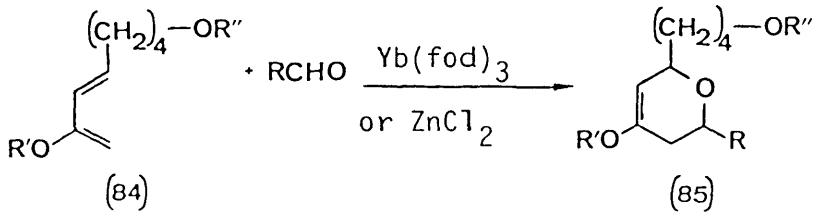
Reaction was improved by using the cyclic ether (81), which makes use of a keto group to prevent migration of the *exo*-methylene bond into the ring, the major side reaction in the above reaction. Compound (81) dimerises rapidly and it was found to be convenient to use the immediate precursor (80) in the Diels-Alder reaction, effecting elimination to the olefin *in situ* (Scheme 36). This resulted in a 72% yield of the two spiroacetals (82) and (83), the stereoselectivity observed indicating a small electronic

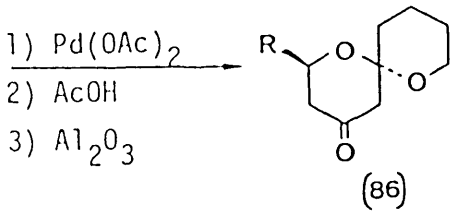
Scheme 36.



effect in the transition state of the cycloaddition.

The second approach to spiroacetals making use of a hetero Diels-Alder reaction was reported by Danishefsky[62], in which dienes of type (84) were reacted with aldehydes in the presence of a Lewis acid catalyst. Subsequent hydrolyses of the adduct (85) led to the spiroacetal (86) (Scheme 37). Again overall yields were quite good.

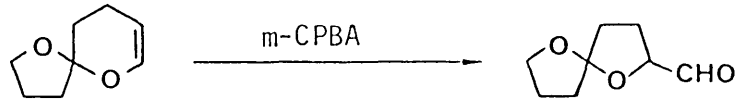




(86)

Scheme 37.

Both methods, as a consequence of the [4+2] nature of the Diels-Alder reaction, necessarily produce at least one six-membered ring in the initial spiroacetal structure, but as demonstrated by Ireland[60], this is not necessarily a limitation, since oxidation of the enol ether (87) is accompanied by ring contraction, to give the thermodynamic [4.4] dioxaspiro system (88) (Scheme 38).



(87) (88)

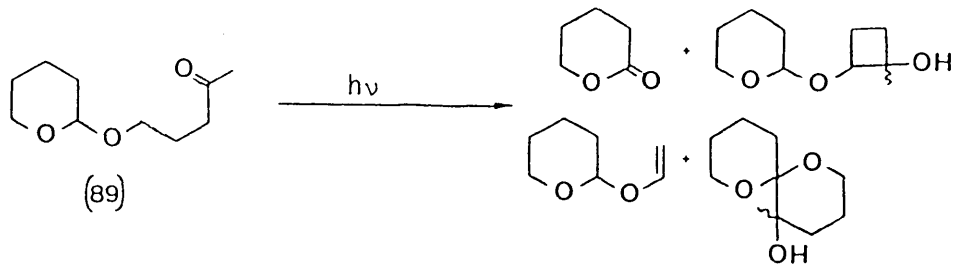
67%

Scheme 38.

1.8 RADICAL CYCLISATION REACTIONS.

It has been shown that photolysis of compounds of type (89) can produce amongst other products, spiroacetals[63] (Scheme 39). Generally, the

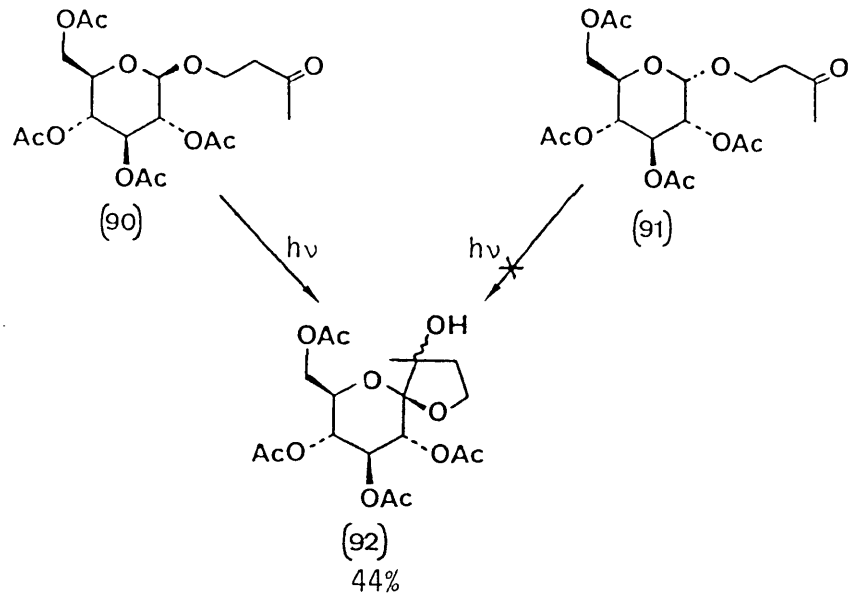
Scheme 39.



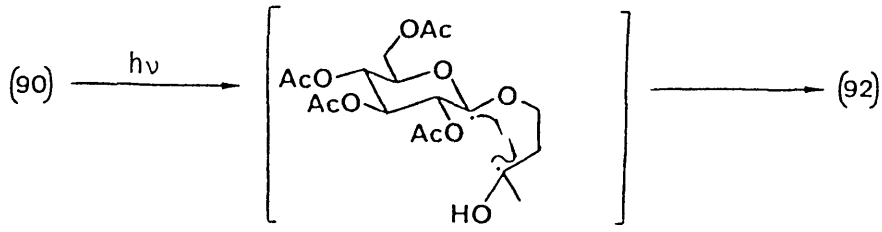
(89)

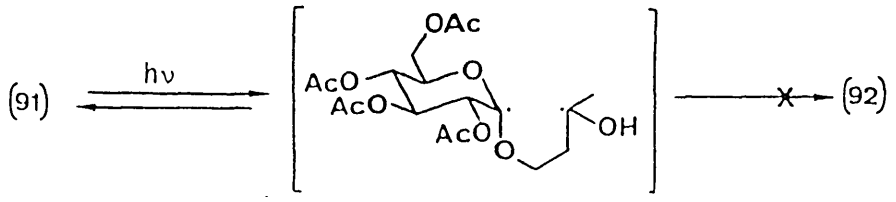
spiroacetal is the major product and in this case it can be isolated in 77% yield. This method does not appear to have any direct application in the synthesis of complex natural products, but has been studied in carbohydrate systems with interesting results[64] (Scheme 40).

Scheme 40.



The β-anomer (90) cyclises as before, to give a 44% yield of the spiroacetals (92), but the corresponding α-anomer (91) does not cyclise. This can be rationalised if the mechanism is represented as a Norrish type II process (Scheme 41). The greater stability of the axial radical[16,65], in this case allows differentiation in the reaction between the α- and β-forms.



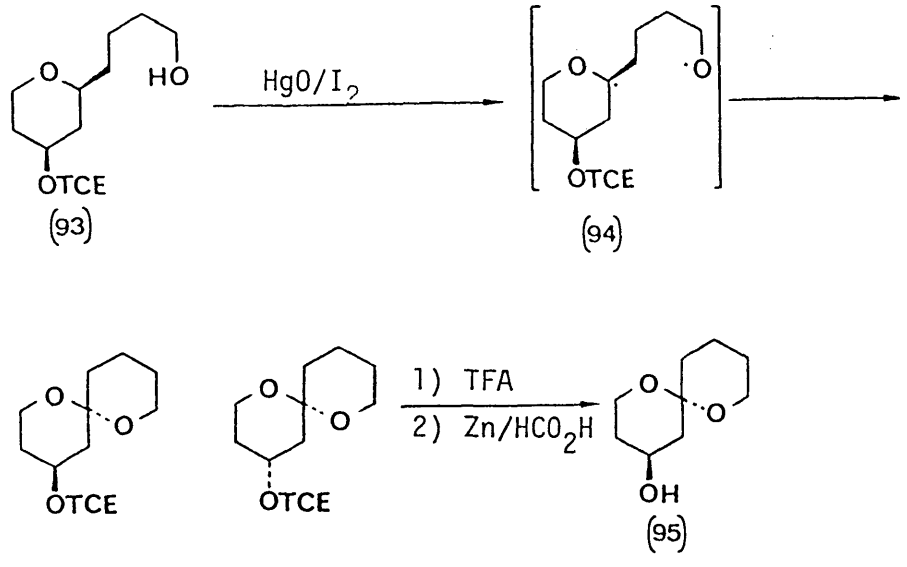


Scheme 41.

This observation is important since it clearly shows that other methods employing radical alkylation at the anomeric centre may provide a useful means for the stereospecific construction of *anti*-anomeric spiroacetals, since the alkyl group is necessarily introduced in the axial position.

Cyclisation of the hydroxy-substituted tetrahydropyran derivative (93) with HgO/I_2 has been reported[66] in the synthesis of compound (95), a naturally occurring spiroacetal isolated from the Olive fly, *Dacus Oleae*[22d] (Scheme 42). It seems likely that this process proceeds *via* the diradical

Scheme 42.

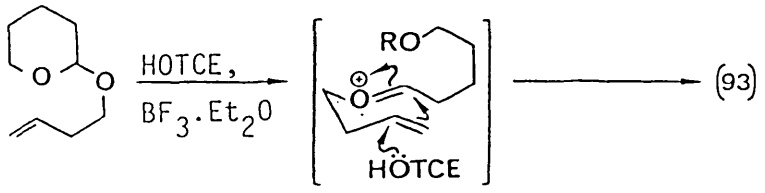


intermediate (94), although in this case cyclisation was not stereospecific, leading to a mixture of spiroacetals. This mixture isomerised to the

thermodynamic isomer on treatment with trifluoroacetic acid and subsequent removal of the hydroxyl protecting group gave the product (95).

The tetrahydropyran (93) was itself prepared by a novel cation-olefination cyclisation (Scheme 43).

Scheme 43.

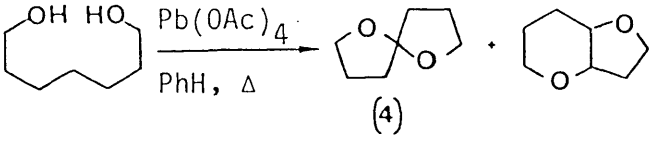


1.9 MISCELLANEOUS METHODS.

1.9.1 From Diols.

Several methods have been reported in which the key step for the preparation of the spiroacetal, is introduction of a keto group into a diol. These include oxidation of 1,7-heptane diol with lead tetraacetate[67] (Scheme 44), which gives low yields of the spiroacetal (4).

Scheme 44.



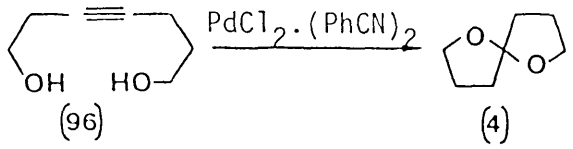
(4)

29%

The keto group has also been introduced *via* hydroboration of a olefin bond and this approach was employed by Grieco[68] in a synthesis of calcimycin.

A related reaction involves the cyclisation of the diol (96) onto an acetylene bond, using palladium catalysis[69] (Scheme 45).

Scheme 45.



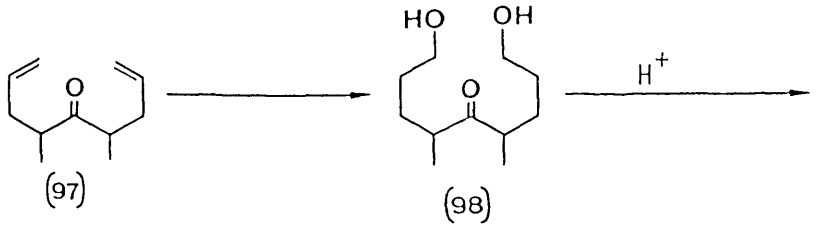
(96) (4)

1.9.2 From Ketones.

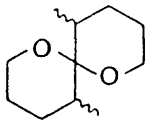
This approach is complimentary to method 9.1. In this case the diol moiety is introduced into a molecule already containing a keto group suitably disposed for cyclisation to the spiroacetal.

The diene (97) was converted *via* its dibromide, to the keto diol (98), which in turn could be cyclised to a mixture of spiroacetals (99) on treatment with acid[18] (Scheme 46).

Scheme 46.



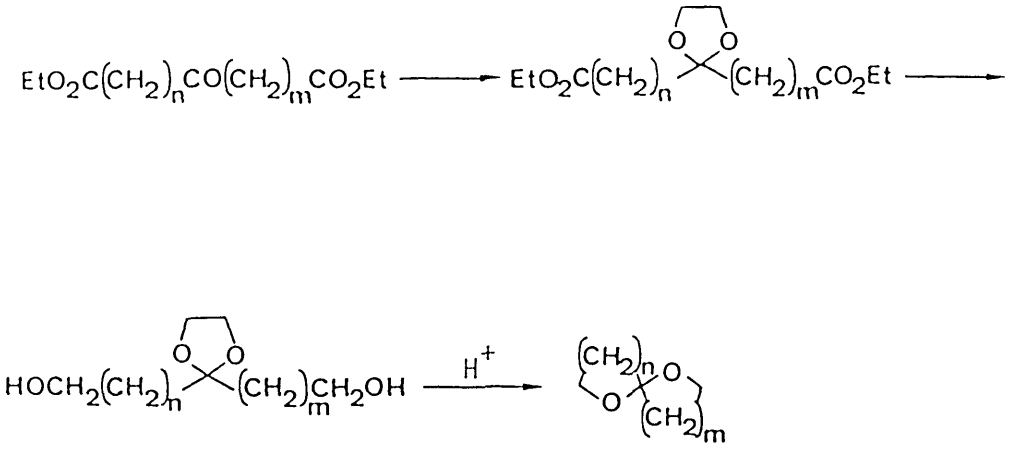
(97) (98)



(99)

The diol functionality has also been introduced by the reduction of diesters as shown in the example below[70] (Scheme 47). Subsequent treatment

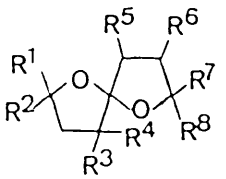
Scheme 47.



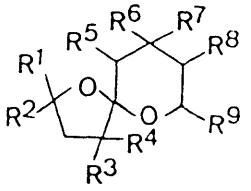
with acid effected removal of the dioxalane protecting group and cyclisation to the spiroacetal product. It has been noted that in the case of more hindered ketones, it is necessary to form the 1,3-dithiolane instead of the dioxalane[71].

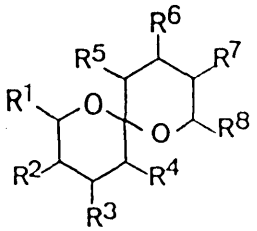
1.9.3 Cyclisation of Naturally Occurring Dihydroxy Ketones.

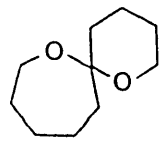
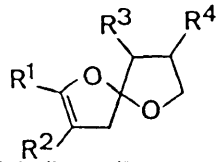
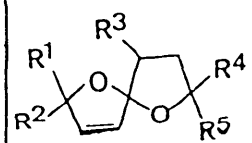
A few naturally occurring dihydroxy ketones have been shown to form spiroacetals on treatment with acid[72], including erythronolide A[14,72c] and tricoccin S_{10}[72b].

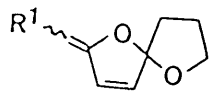
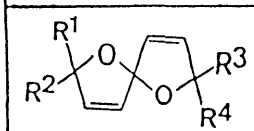
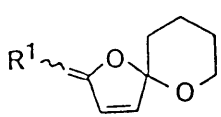
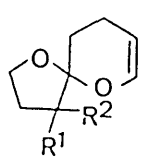
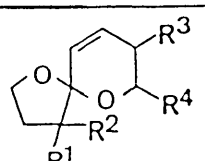
Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	-	-	-	-	-	-	-	-	-	3.1	3, 4, 27.
										4.1	73.
										4.3	49.
										6.1	57.
										9.1	69.
										9.3	70.
	Me	-	-	-	-	-	-	-	-	3.2	22b.
										4.1	39.
										4.3	49.
										5.2	51a.
										6.1	27, 57b.
	-	-	-	-	-	Me	-	-	-	6.1	27.
	Et	-	-	-	-	-	-	-	-	3.2	22a, b, c.
										4.1	38a, b, 39.
										4.3	49.
										5.2	51a, 52a, b.
										6.1	23, 27.
										7	60a, b.
	-	-	Et	-	-	-	-	-	-	6.1	27.
	-	-	-	-	-	Et	-	-	-	6.1	27.
	n-Pr	-	-	-	-	-	-	-	-	3.2	22b.
										6.1	27.
	n-Bu	-	-	-	-	-	-	-	-	3.2	22b.
	$n\text{-}C_5H_{11}$	-	-	-	-	-	-	-	-	3.2	22b.
	$n\text{-}C_6H_{13}$	-	-	-	-	-	-	-	-	3.2	22b.

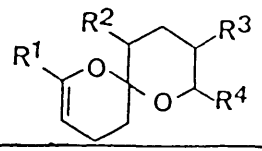
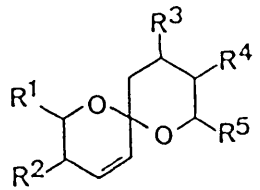
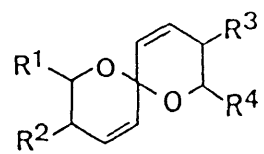
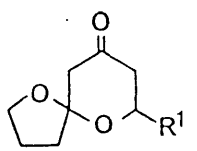
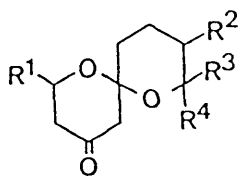
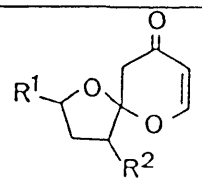
Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	Me	Me	-	-	-	-	-	-	-	4.1	39.
										6.1	57f.
	Me	-	Me	-	-	-	-	-	-	6.1	57g.
	Me	-	-	-	Me	-	-	-	-	6.1	23.
	Me	-	-	-	-	-	Me	-	-	3.1	3, 5, 27.
										4.3	39.
										4.1	49.
	-	-	-	-	-	Me	Me	-	-	6.1	27.
	Me	-	Et	-	-	-	-	-	-	6.1	57f, g.
	Me	i-Pr	-	-	-	-	-	-	-	6.1	57f.
	Me	-	i-Pr	-	-	-	-	-	-	6.1	57f, g.
	Me	t-Bu	-	-	-	-	-	-	-	6.1	57g.
	Me	-	-	-	-	-	CH_2CO_2H	-	-	3.3	22c.
	Et	-	-	-	-	-	Et	-	-	3.1	3.
										4.3	49.
	n-Pr	-	-	-	-	-	n-Pr	-	-	4.3	49.
	-	-	Br	-	CO_2Me	-	-	-	-	3.1	21.
	Me	Me	-	-	Me	-	-	-	-	3.2	22e.
	Me	Me	-	-	-	-	Me	-	-	3.3	22b.
										4.1	39.
	Me	Me	-	-	-	-	Et	-	-	3.2	22b.
	Me	Me	-	-	-	-	n-Bu	-	-	3.2	22b.
	Me	Me	-	-	-	-	$n\text{-}C_5H_{11}$	-	-	3.2	22b.
	Me	Me	-	-	-	-	$n\text{-}C_6H_{13}$	-	-	3.2	22b.
	Me	Et	Et	-	-	-	-	-	-	6.1	57g.

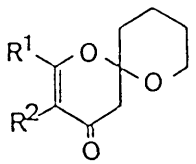
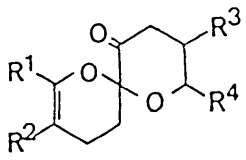
Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	Me	Et	i-Pr	-	-	-	-	-	-	6.1	57g.
	Me	Me	-	-	-	-	Me	Me	-	3.2	26.
										4.1	39.
	Me	Me	Me	Me	-	-	Me	-	-	6.1	20.
	-	-	-	-	-	-	-	-	-	3.1	20.
										3.2	22b
										5.3	56.
										7	60b.
										8	63c.
										9.1	67.
										9.2	70
	Me	-	-	-	-	-	-	-	-	3.2	22b.
										3.3	34.
										4.1	35.
										5.2	51a.
										7	60b.
										9.1	69.
	-	-	-	-	-	-	-	-	-	3.2	22b, c.
										4.1	35.
	Et	-	-	-	-	-	-	-	-	5.2	51a.
	-	-	OH	-	-	-	-	-	-	8	63c, d.
	Me	Me	-	-	-	-	-	-	-	3.2	22b.
	-	-	-	-	-	Me	Me	-	-	9.2	71.
	Me	-	-	-	-	-	-	-	Me	3.2	22b.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	Me	-	-	-	-	-	-	-	Et	3.1	20.
	Et	-	-	-	-	-	-	-	Me	3.1	20.
	-	-	Me	OH	-	-	-	-	-	8	63a, b.
	-	-	Me	OH	-	-	-	OAc	CH_2OAc	8	64a.
	-	-	Me	OH	OAc	OAc	-	OAc	CH_2OAc	8	64b, c.
	-	-	Me	OH	OH	OAc	-	OAc	CH_2OAc	8	64b.
	-	-	-	-	-	-	-	-	-	3.1	19.
										3.2	18.
										5.2	51c, 52c.
										5.3	56.
										7	60b.
										9.1	67.
										9.2	70.
	Me	-	-	-	-	-	-	-	-	3.1	20.
										3.2	18.
										5.3	56.
	-	OH	-	-	-	-	-	-	-	7	22d.
	-	-	OH	-	-	-	-	-	-	3.2	22d.
										5.3	54.
										8	66.
	Me	-	-	-	-	-	-	Me	-	3.1	20.
										4.1	40a, b, c.
										5.2	41.
	-	-	-	Me	Me	-	-	-	-	3.3	14, 18.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	Me	-	OH	-	-	-	-	-	-	5.1	41.
	Et	-	-	-	-	OH	-	-	-	3.3	31.
	-	$-C_4H_8-$		-	-	-	-	-	-	3.3	18.
	C_2H_4OH	-	-	-	-	-	-	C_2H_4OH	-	5.1	50.
	CH_2Br	-	-	-	-	-	-	CH_2Br	-	3.3	36.
	Et	-	-	-	-	OH	CH_2OH	-	-	3.3	30, 31.
										5.2	51b.
										5.3	55.
										8	77.
	C_2H_4OH	Me	-	-	-	-	Me	C_2H_4OH	-	5.1	50.
	CH_2OH	-	$OSiPh_2{}^tBu$	-	-	-	Me	Me	-	3.2	24.
										3.4	37.
	CH_2CHO	-	OBn	-	-	-	Me	Me	-	3.3	29.
	CH_2Br	-	-Ar-		OMEM	OH	-	Me	-	9.2	75.
	-	-	-	-	-	-	-	-	-	9.2	70.
	Me	CO_2Me			-	-	-	-	-	4.1	74.
	Me	Me	Me	-	-	-	-	-	-	3.2	22e.
	Me	Me	-	Me	Me	-	-	-	-	3.2	22c, 26.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
		-	-	-	-	-	-	-	-	6.2	59.
		-	-	-	-	-	-	-	-	6.2	59.
	Ph	-	-	-	-	-	-	-	-	6.2	59.
	CO_2R	-	-	-	-	-	-	-	-	6.1	57h.
										6.2	57h
	Me	Me	Me	Me	-	-	-	-	-	3.2	26.
		-	-	-	-	-	-	-	-	6.2	59.
	-	-	-	-	-	-	-	-	-	7 8	60a, b. 63b
	OH	Me	OAc	CH_2OAc	-	-	-	-	-	8	64a.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	-	-	-	-	-	-	-	-	-	7	60a, b.
	-	Me	Me	$CH(Me)CO_2Me$	-	-	-	-	-	7	61.
	Et	Me	Me	$CH(Me)CO_2Me$	-	-	-	-	-	7	61.
	CH_2OBz	-	-	Me	Me	-	-	-	-	3.4	37.
	i-Bu	Me	OBn	-	C_2H_4OH	-	-	-	-	3.2	25.
										9.3	72a.
	Me	-	-	-	-	-	-	-	-	7	62.
	Et	-	-	-	-	-	-	-	-	7	62.
	Ph	-	-	-	-	-	-	-	-	7	62.
	CH_2OBn	Me	Me	-	-	-	-	-	-	4.2	44.
	C_2H_4OH	Me	Me	-	-	-	-	-	-	4.2	45.
	-	-	-	-	-	-	-	-	-	4.1	43.
	Me	-	-	-	-	-	-	-	-	4.1	43.
	-	Me	-	-	-	-	-	-	-	4.1	43.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Method	Reference
	-	-	-	-	-	-	-	-	-	4.1	43.
	Me		-	-	-	-	-		-	4.1	42.
	Me	Me	-	-	-	-	-	-	-	4.1	42.
	-	Me	Me	$CH(Me)CO_2Me$	-	-	-	-	-	7	61.
	Et	Me	Me	$CH(Me)CO_2Me$	-	-	-	-	-	7	61.
Monensin										4.2	46, 47.
Calcimycin										4.3 5.2 9.1	48. 76. 68.
Phyllanthocin										3.3 5.2	32. 53.
Phyllanthocindiol										3.3	33.

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New Methods For Spiroketal Synthesis.

In this section, three novel methods for the construction of spiroketals, or as they are now more commonly known, spiroacetals, will be presented. The first involves the use of organoselenium-mediated cyclisation reactions of alkenyl hydroxyketones and includes the preparation of several naturally occurring insect pheromones.

The second section involves the development of Wittig and Horner-Wittig procedures for the preparation of spiroacetal systems, and this is again applied to pheromone syntheses. This section closes with a synthesis of the spiroacetal portion of Milbemycin β_1[1], and an approach towards the spiroacetal portion of Avermectin A_{1b}[2].

The final section involves the use of sulphone coupling reactions in the preparation of spiroacetals, and shows the development of an interesting vinyl anion equivalent. Again, the utility of this method is demonstrated by the synthesis of several insect pheromones.

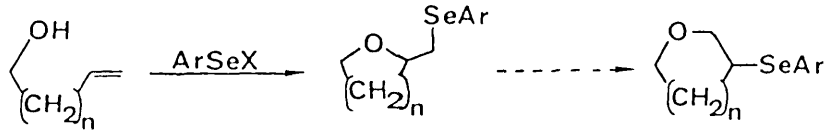
2. Preparation of Spiroacetals using Organoselenium-mediated Cyclisation Reactions.

2.1 Cyclisation of Alkenyl-substituted Hydroxy Ketones and Hemiacetals.

2.1.1 Introduction.

The use of organoselenium-mediated cyclisation reactions of hydroxy ketones in the preparation of cyclic ethers has received considerable attention recently[3].

Scheme 1.

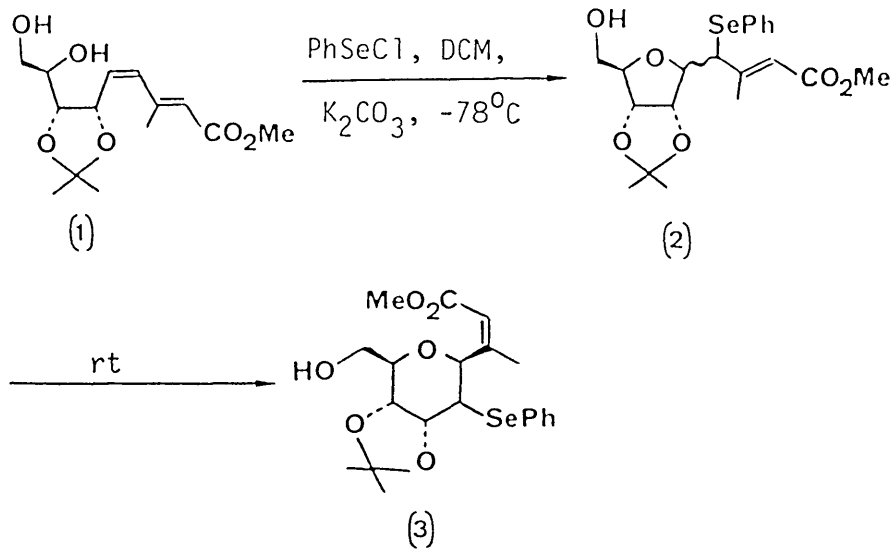


In most cases, these reactions have been shown to be highly regioselective, giving five-membered in preference to four- or six-membered rings and six-membered in preference to seven-membered rings. Exceptions to this rule are observed when steric interactions between the ring substituents favour a different ring size.

It is presumed that under the reaction conditions (usually ArSeX and in some cases a base), the initial cyclisation across the double bond proceeds in a Markownikoff fashion and that any subsequent rearrangement to a more thermodynamically stable isomer occurs cleanly under the reaction conditions (Scheme 1). In some cases it is possible to selectively isolate either product, depending upon the reaction conditions[4]. This was observed in the cyclisation of compound (1), where the initial product (2) could be isolated but rearranged slowly on standing, to the thermodynamic product (3) (Scheme

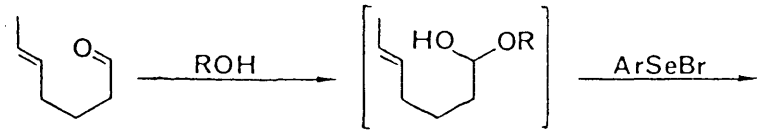
2).

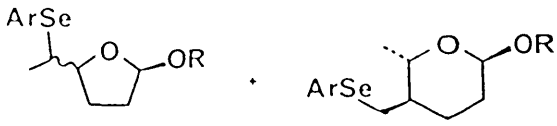
Scheme 2.



An interesting extension of this reaction was reported by Sharpless[5], in which an *in situ* formed hemiacetal provided the hydroxy substituent required for cyclisation (Scheme 3). In this study, it was possible to selectively prepare the kinetic product (4) under basic conditions, whilst in the absence of base and at higher temperatures, the thermodynamic product (5) predominated.

Scheme 3.

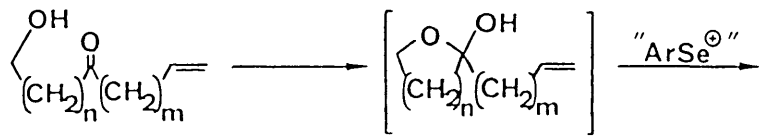


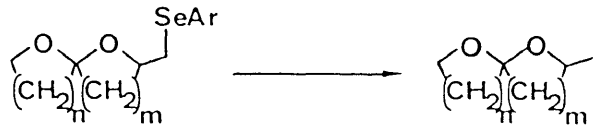


(4) (5)

These results prompted the idea that a similar intramolecular hemiacetal formation followed by cyclisation might provide a novel route to spiroacetals (Scheme 4). In this way, it should be possible to prepare several naturally occurring spiroacetal systems, for example compounds (6) and (7), which are recognition pheromones for the Common Wasp, *Paravespula vulgaris*[6].

Scheme 4.





n=2, m=3 (6)

n=3, m=2 (7)

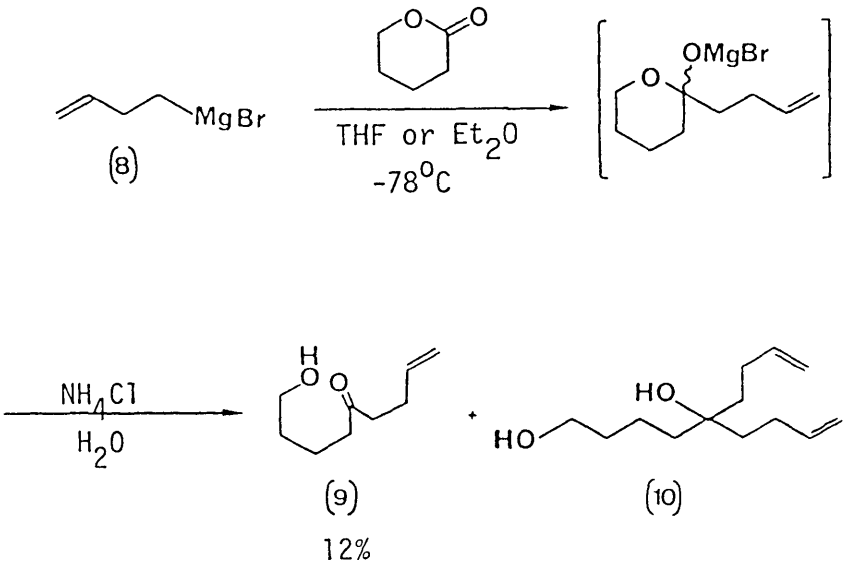
2.1.2 Preparation of Alkenyl-Substituted Hydroxy Ketones.

In order to investigate the proposed cyclisation reactions, it was first

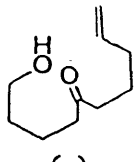
necessary to find a general method for the preparation of the alkenyl-substituted hydroxy ketone precursors.

A possible method involved the mono-addition of a alkenyl Grignard reagent into a lactone, since the initially formed magnesium alkoxide should be insoluble and its precipitation would inhibit further reaction. This was indeed the case for the addition of but-3-enylmagnesium bromide (8) into δ-valerolactone, although the desired product (9) was obtained in low yield along with the product of diaddition (10) (Scheme 5).

Scheme 5.



Compound (11) was also prepared by this route, in slightly higher yield 23%. Despite these low yields, reasonable quantities of compounds (9) and (11) could be prepared for further study.

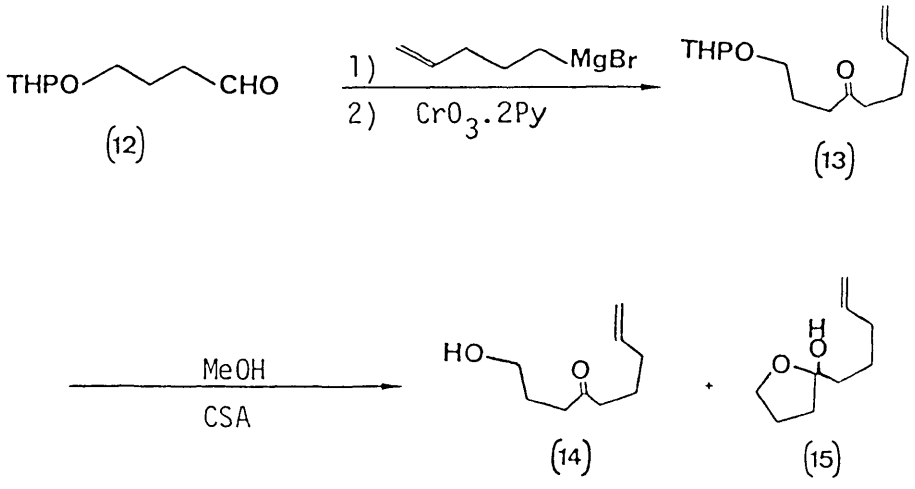


(11)

Unfortunately, in the case of Grignard reagent additions to γ-butyrolactone, the only product obtained was that of diaddition irrespective of the conditions employed. This observation is consistent with a recent report by Savonia[7] and is probably due to the insolubility of γ-butyrolactone in tetrahydrofuran at low temperatures, which counteracts any effect gained from precipitation of the initially formed alkoxide. Consequently a slightly longer route had to be employed for the preparation of these compounds.

To this end, the known aldehyde (12)[8] was reacted with pent-4-enylmagnesium bromide to give, after Collins oxidation[9], the protected alkenyl hydroxy ketone (13). Deprotection under standard conditions[10] furnished

Scheme 6.



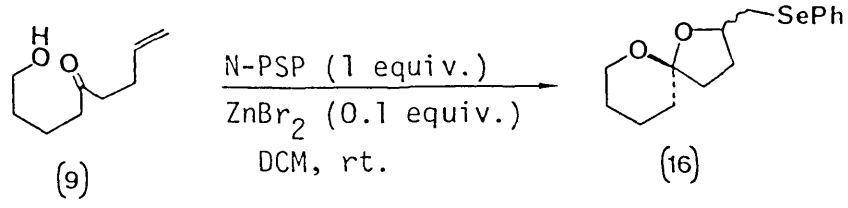
the desired compound as a mixture of hydroxy keto (14) and hemiacetal (15) forms in good overall yield, 87% (Scheme 6). These two compounds could be separated by silica gel chromatography and showed no tendency to interconvert on storage at $0^{o}C$.

2.1.3 The Selenium-Mediated Cyclisation.

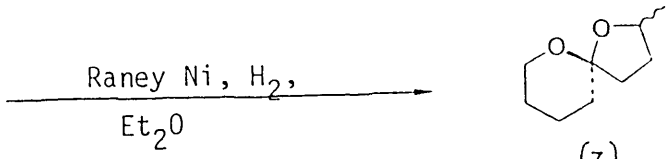
Initially the organoselenium-mediated cyclisation reactions of compound (9) were investigated. This material did not cyclise to give a spiroacetal on treatment with phenylselenyl chloride, the usual conditions employed for cyclic ether formation. Since Sharpless employed the more reactive *p*-chlorophenylselenyl bromide in his cyclisation reaction, it seems likely that the above conditions do not provide the acidic enviroment required for initial hemiacetal formation.

We next chose to investigate Lewis acid catalysed cyclisation reactions, using the readily available N-phenylselenophthalimide (N-PSP) as a selenium-transfer agent, by analogy with conditions used to cyclise unsaturated β-dicarbonyl compounds[11,12]. It was found that one equivalent of N-PSP and a catalytic amount of camphor sulphonic acid (CSA) in dry dichloromethane at room temperature, cyclised compound (9), giving the desired spiroacetal (16) in 20% yield. This yield could be improved to 78% if zinc (II) bromide (0.1 equivalents) was used instead of the CSA. Catalytic amounts of zinc (II) iodide and tin (IV) chloride also effected cyclisation, but gave lower yields.

Scheme 7.



(9) (16)



(7)

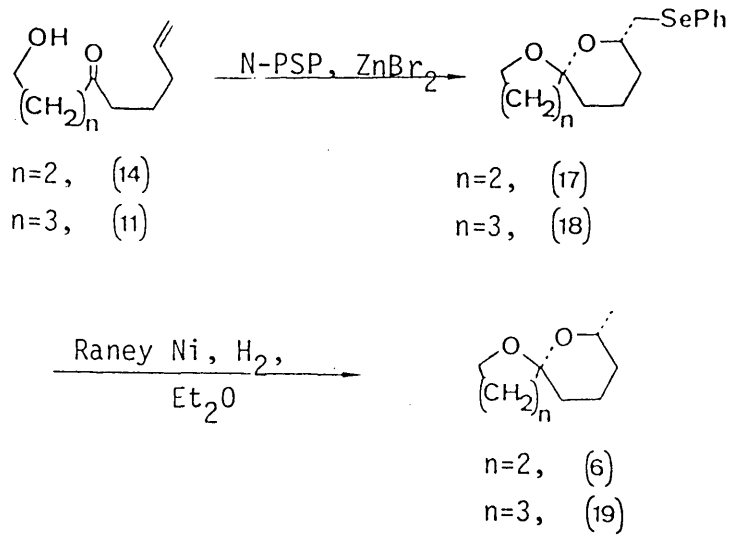
90%

Compound (16) was obtained as a 1:2 mixture of *cis*:*trans* isomers, this

being a direct consequence of anomeric control in the cyclisation reaction. The two isomers were assigned on the basis of their spectral data, especially their ^{1}H nmr parameters (see Table 1), which clearly show the chemical shifts of H_a and H_b to be further downfield in the *cis*-isomer . This is a consequence of their close proximity to the oxygen atom in the opposing ring.

Removal of the phenylseleno group in compound (16) was straightforward, using Raney nickel in diethyl ether at room temperature, under a hydrogen atmosphere (Scheme 7). Diethyl ether was preferred as solvent over the more usual ethanol or tetrahydrofuran because it is more easily removed from the volatile spiroacetal product. The resulting 2-methyl-1,6-dioxaspiro[4.5]undecane (7) was isolated as a 1:2 mixture of *cis:trans* isomers, both its spectral parameters, and its isomer ratio, being identical to those reported for the natural material obtained from the Common Wasp, *Paravespula vulgaris* [6,13]. No attempt was made to separate the two isomers, since it is known that they undergo equilibration within a few days[14].

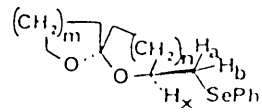
Scheme 8.



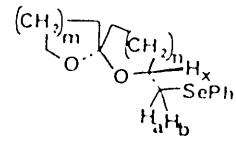
Compounds (14) and (11) were cyclised in a similar manner, to give the corresponding spiroacetals (17) and (18) in 81% and 77% respectivly. The

hemiacetal (15) could also be cyclised to compound (17) in similar yield. Both (17) and (18) appear to exist as single isomers, and were assigned as *trans* on the basis of stereoelectronic arguments. Removal of the phenylseleno

Table 1: 250 MHz ^{1}H nmr spectra of the phenylseleno spiroacetals.



TRANS



CIS

Compound	δH_a	δH_b	J_{ax}(Hz)	J_{bx}(Hz)	J_{ab}(Hz)
trans m= n= 1*	3.00	2.96	2.6	3.7	12.5
cis	3.26	3.11	5.9	4.7	12.5
trans m= 2, n= 1 (7)	3.08	2.96	5.8	7.8	11.7
cis (7)	3.29	3.13	5.8	5.0	11.7
trans m= 1, n= 2 (6)	3.04	2.90	6.9	4.7	12.0
trans m= n= 2 (19)	3.12	2.95	8.6	5.1	12.2

* see ref. 15.

group as before, cleanly gave the spiroacetals (6) and (19) (Scheme 8). Compound (6) had identical spectral properties to the *trans*-isomer (6) isolated from the Common Wasp[6,13], hence providing proof of its stereochemistry. Compound (19) also showed spectral data in full agreement with that reported for the previously prepared *trans*-isomer[16].

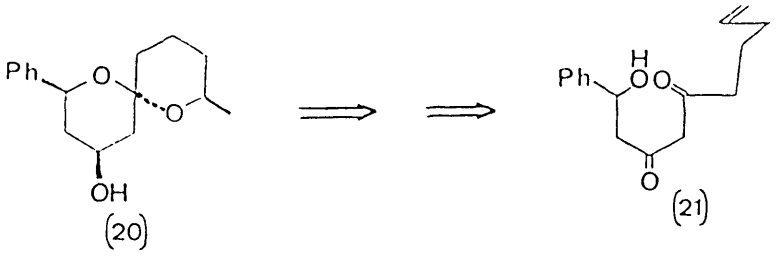
In conclusion, the cyclisation of alkenyl-substituted hydroxy ketones using the selenium-based methodology, appears to be quite general and can be

used to prepare methyl-[4.5] and [5.5] dioxaspiro systems including the two natural products (6) and (7), in overall yields that compare well with other literature routes. This method has since been extended to the synthesis of methyl- and ethyl-[4.4] dioxaspiro systems[15], including the natural product 2-ethyl-1,6-dioxaspiro[4.4]nonane an aggregation pheromone isolated from *Pityogenes calcographus*[17].

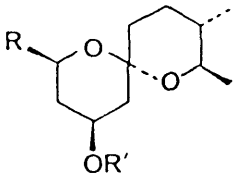
2.2 CYCLISATION STUDIES ON AN ALKENYL-SUBSTITUTED β-DIKETONE.

2.2.*1* Introduction.

In order to extend this methodology to more complex spiroacetal systems, a synthesis of compound (20) was undertaken.



(20) (21)



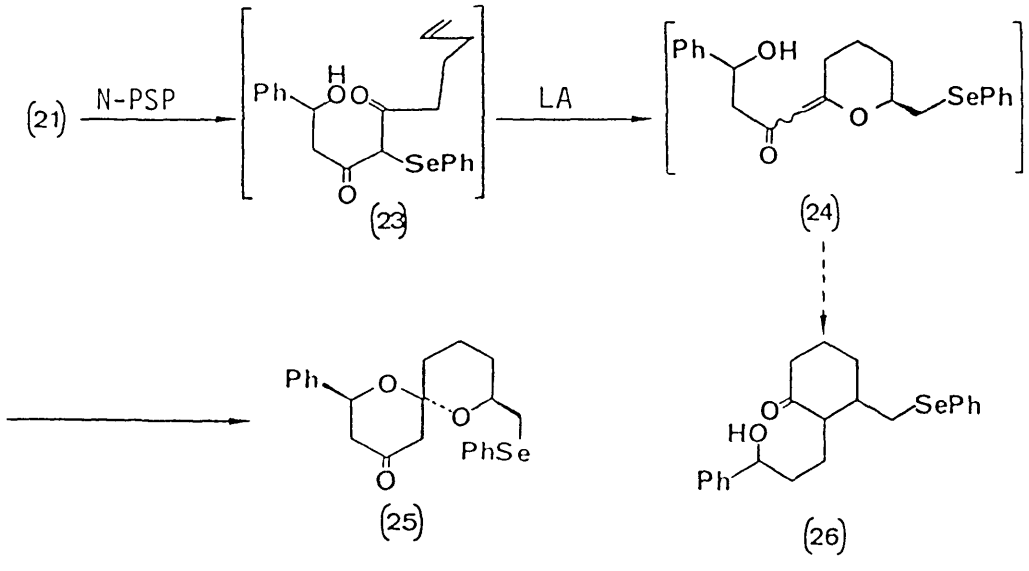
(22)

This particular target molecule provided an interesting model system for the spiroacetal portion (22) of the milbemycins which are potent antiparasitic agents isolated from *Streptomyces* B-41-146[1]. It was hoped that the phenyl substituent would provide a means of functionalising the C-2 position, *via*

oxidative cleavage to a carboxylic acid group[18].

Mechanistically, the organoselenium-mediated cyclisation of compound (21) is likely to be quite different from those discussed so far, since the highly enolised β-dicarbonyl system should prevent hemiacetal formation. In this case, the mechanism would be expected to parallel that reported for the cyclisation of alkenyl β-keto esters[12], namely initial formation of a 'α-selenide' intermediate (23) followed by oxygen cyclisation of the enolic ketone to give (24). This intermediate should subsequently cyclise, with anomeric control, to give the spiroacetal (25) (Scheme 9). It is anticipated

Scheme 9.



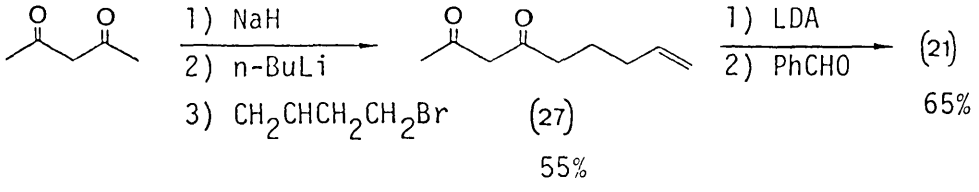
that if catalytic quantities of Lewis acid are employed in the reaction, this latter cyclisation will proceed in preference to rearrangement of (24) to the carbocycle (26).

2.2.2 Preparation of the Spiroacetal (20).

The dianion from pentane-2,4-dione was formed by sequential treatment with sodium hydride in tetrahydrofuran at $0^{o}C$, followed by n-butyllithium at

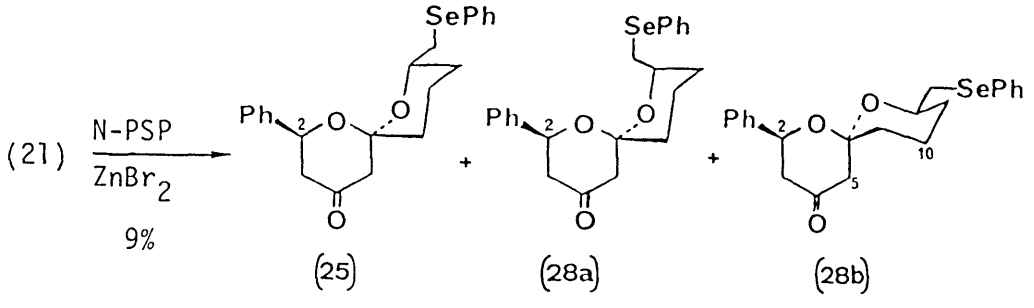
$-20^{o}C$[19]. Reaction with 4-bromo but-1-ene gave the kinetically quenched product (27). Reformation of the dianion from compound (27) using two equivalents of lithium diisopropylamide, followed by reaction with benzaldehyde at $-78^{o}C$, gave the necessary material (21) required for the cyclisation studies (Scheme 10).

Scheme 10.



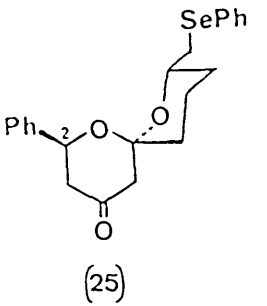
On treatment of compound (21) with N-PSP and zinc (II) bromide, a 1:1 mixture of two spiroacetal products was obtained in low yield, 18%, after stirring at room temperature for 120 h. Longer reaction times or increased amounts of Lewis acid did not improve the yield.

The two products were isolated and assigned the structures (25) and (28) on the basis of their spectral properties (Scheme 11). By ^{1}H nmr, one product appeared to exist as a mixture of conformers and therefore best



agreed with structure (28). This was clearly indicated by the proton at C-2 in the ^{1}H nmr, which occurred as a double-doublet at δ 5.33 and 5.09, in the ratio of approximately 2:1. This proton was apparently axial in both forms, as shown by the large axial-axial coupling constants (13 and 17 Hz respectivly) in both multiplets. Unfortunately, insufficient

Scheme 11.



(25)

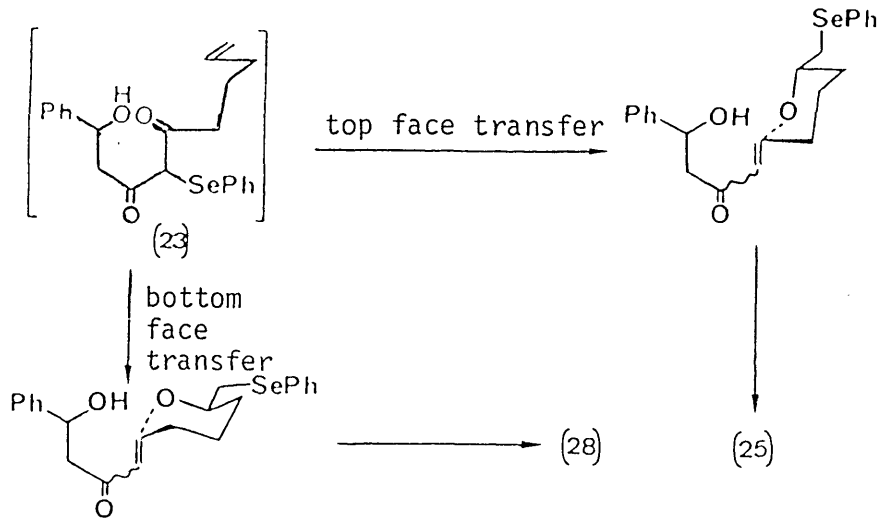
material was prepared to enable a thorough examination of the multiplicities of the C-8 proton resonances, in order to establish the stereochemistry at that centre in the two conformers. Since this material was considered relatively unimportant this problem was not pursued further.

Compound (28) would best fit these observations because the two forms (28a) and (28b) may exist in equilibrium as a consequence of steric interactions. Both forms have anomeric stabilisation, however (28a) has severe steric buttressing between the C-5 and C-10 hydrogen atoms. Conformer (28b) on the other hand has steric crowding resulting from the axial disposition of the bulky phenylselenomethyl substituent. Ring flipping of the other ring in (28a), to give an axial phenyl substituent presumably does not occur.

It is unlikely that compound (25) would exist as a mixture of conformers since it has anomeric stabilisation and does not suffer from such severe steric interactions.

The mixture of products arises as a consequence of intermediate (23)

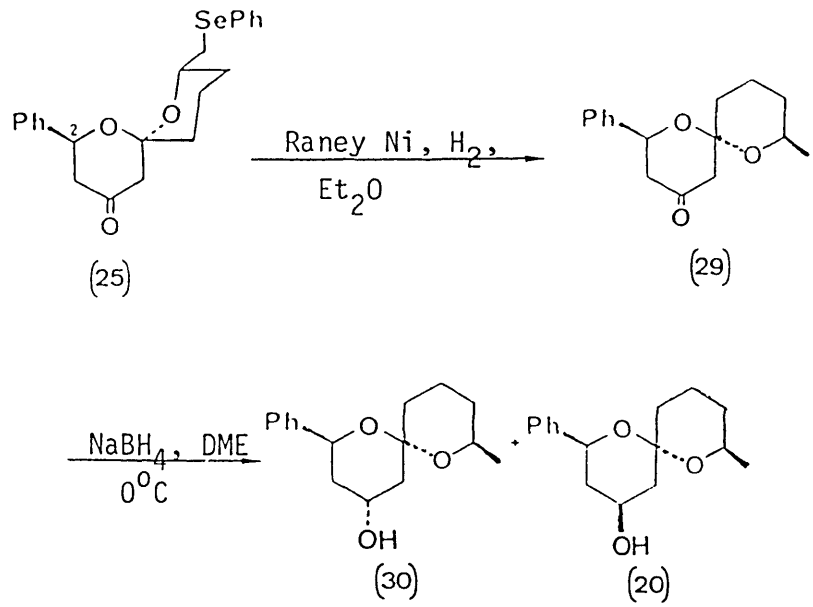
Scheme 12.



being able to transfer the phenylseleno group to either face of the double bond. Top face transfer leads to the desired product (25), while bottom face transfer gives (28) (Scheme 12). Due to the greater strain in compound (28), equilibrating conditions should favour formation of compound (25).

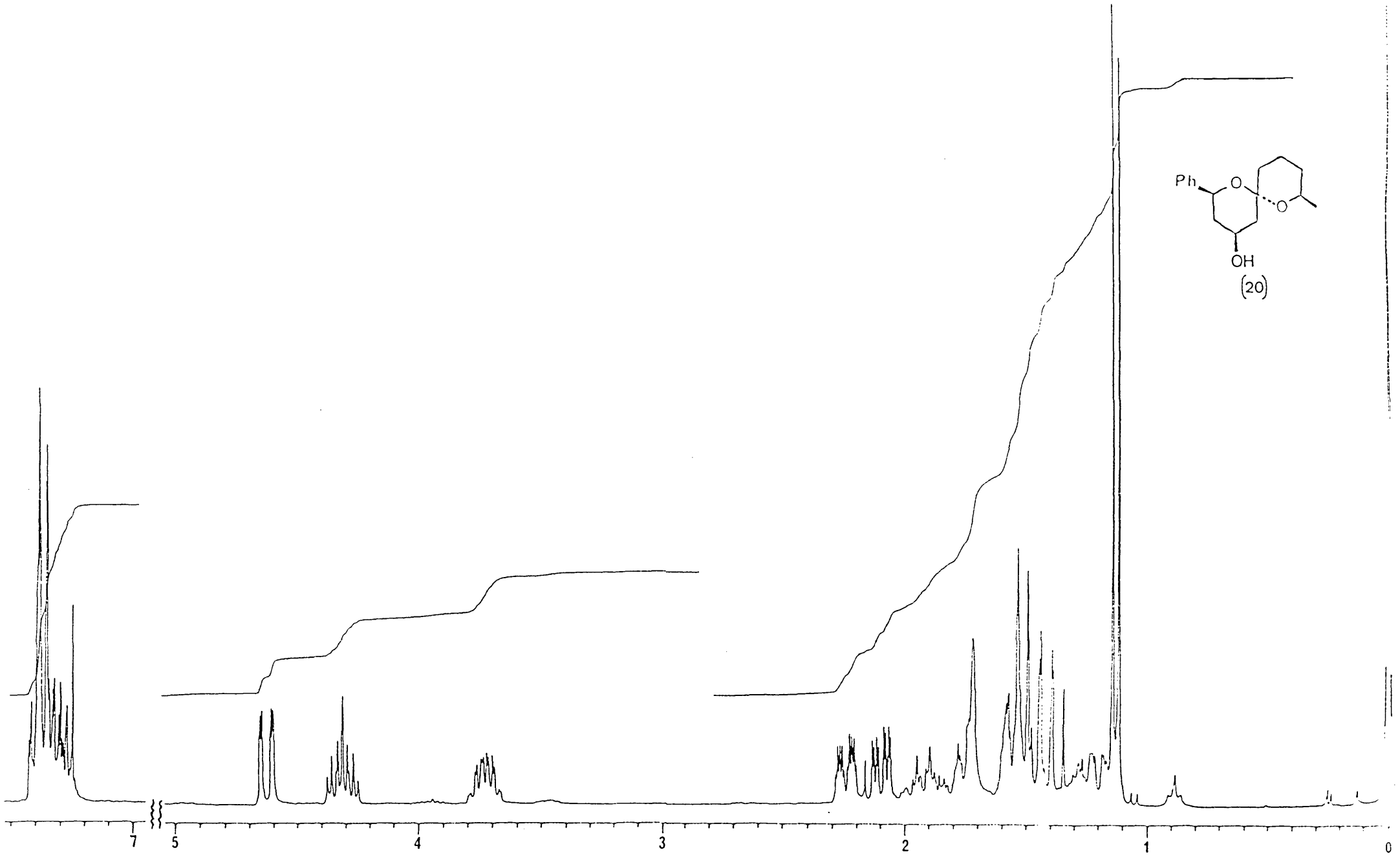
To this end, other Lewis acid catalysts were investigated and it was found that more vigorous conditions, namely tin (IV) chloride (0.1 equiv.) and N-PSP (1.0 equiv.) gave only the diastereoisomer assumed to be (25). In this case reaction was complete after 96 h at room temperature and the product was isolated in a respectable 50% yield.

Scheme 13.

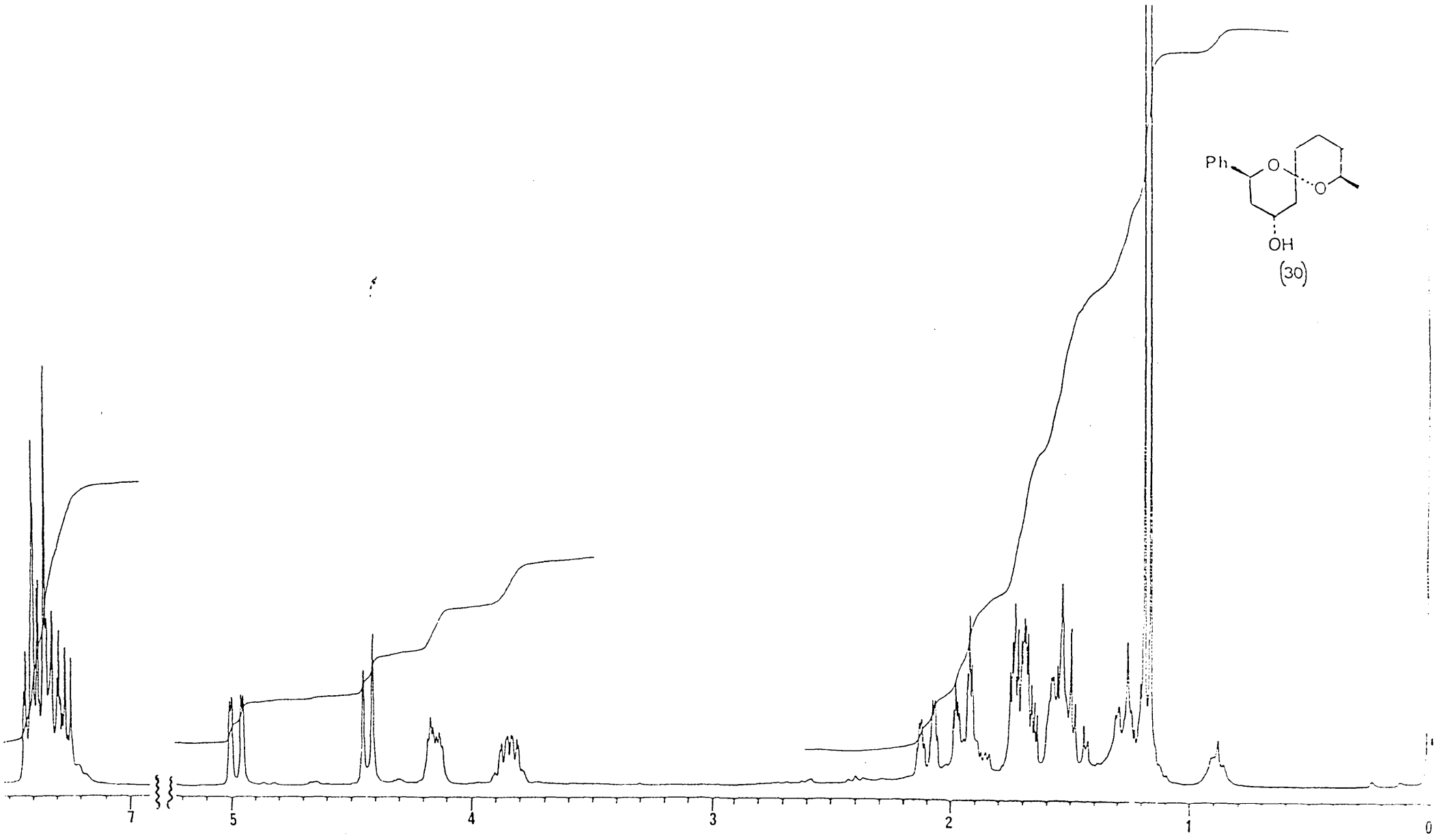


Deselenation as before with Raney nickel, gave the reduced product (29) in 94% yield. Finally, reduction of the carbonyl group in compound (29) was achieved using sodium borohydride in dimethoxyethane at $0^{o}C$[20], to give a separable mixture of the alcohols (20) and (30) in 61 and 32% yield respectively (Scheme 13). Many other reducing systems investigated gave a less favourable yield of the desired isomer (20) (Table 2)

Unambiguous proof for the spiroacetal structure was derived from X-ray crystallographic analysis of the minor isomer (30) (Scheme 14) confirming

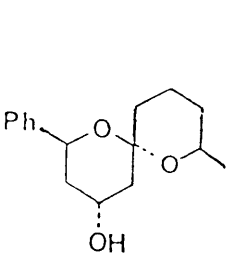


(20)

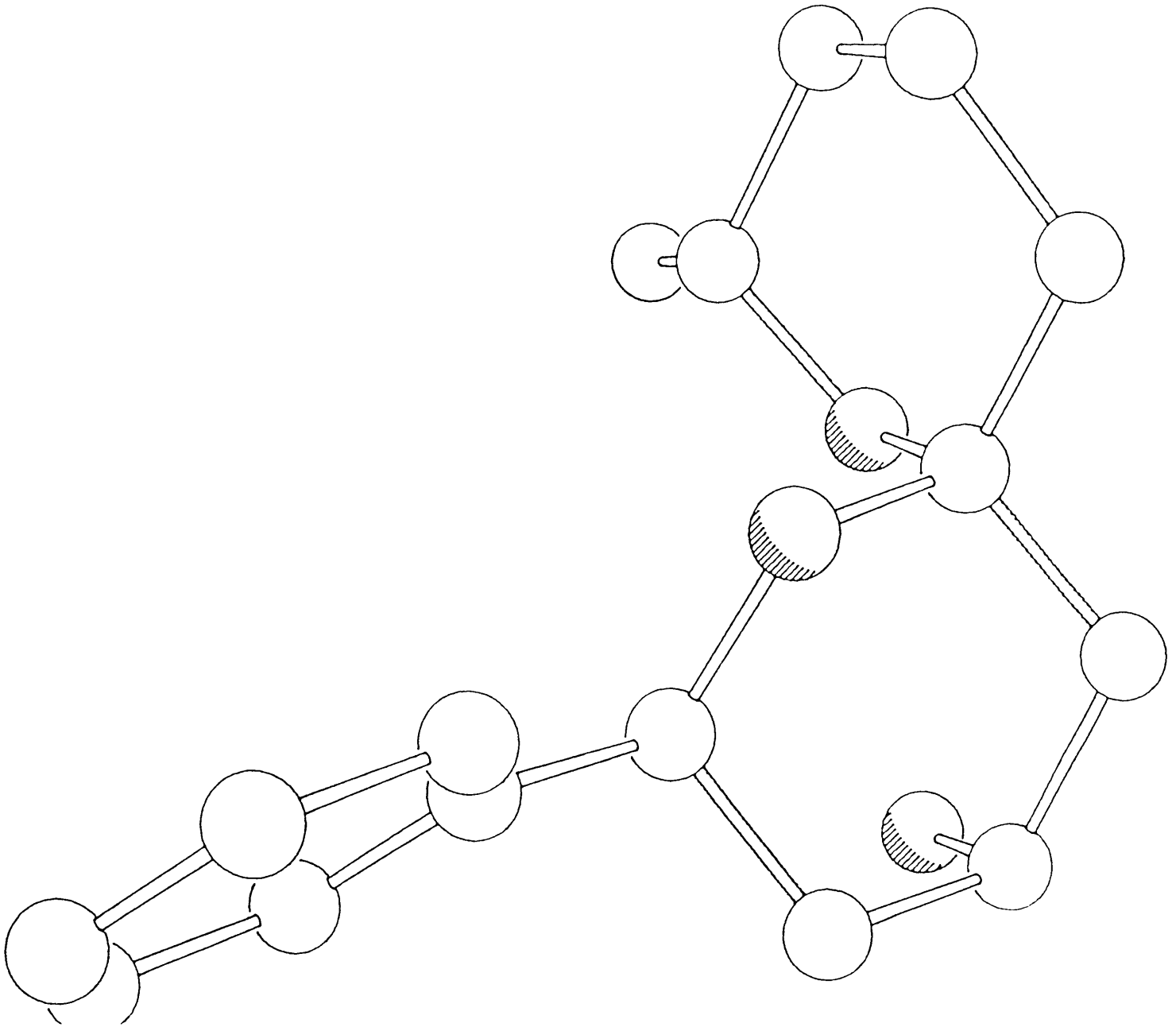


(30)

Scheme 14.



(30)



the product of cyclisation was indeed compound (25).

Table 2: Reduction of Compound (29)

Conditions	Ratio of products* (20) : (30)
Raney Ni, H_2	0 : 100
$NaBH_4$, DME, 0°C	2 : 1
$Zn(BH_4)_2$, Et_2O, 0°C	1 : 1
$Zn(BH_4)_2$, DME, 0°C	2 : 1
$^nBu_4NBH_4$, THF, 0°C	1 : 1
$^nBu_4NBH_4$, DME, 0°C	2 : 1
$LiBH_3Me$, Et_2O, rt	1 : 1
$BH_3.SMe_2$, rt	2 : 3
Red-al	1 : 3
K-selectride	0 : 100

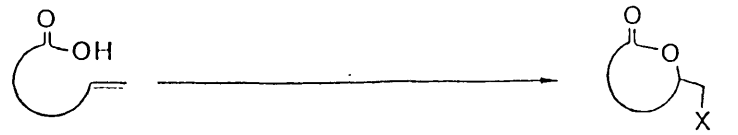
* estimated by ^1H nmr

Unfortunately all attempts to oxidatively cleave the C-2 phenyl substituent to a carboxylic acid were unsuccessful. Attempts to incorporate a more highly oxygenated aromatic ring in the synthesis were also unsuccessful, therefore further modifications of the spiroacetal (20) were not undertaken. Nevertheless this work does demonstrate that selenium-mediated cyclisation reactions can be used efficiently to prepare relatively complex spiroacetal systems.

2.3 Miscellaneous Cyclisation Reactions.

It is known that unsaturated carboxylic acids can be cyclised with phenylsulphenyl chloride[21] or molecular iodine[22] as well as with selenium reagents[3], to give lactones (Scheme 15). Only in the case of the sulphur

Scheme 15.



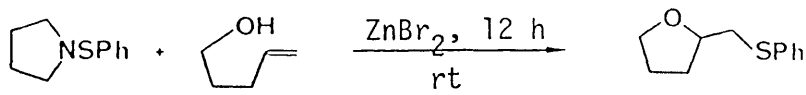
X= SPh, I,
SePh.

electrophile has this reaction not been extended to the preparation of cyclic ethers. If these sulphur cyclisation reactions could be applied to the preparation of spiroacetals, it would further enhance the utility of the method and give potentially useful products.

Not surprisingly, the alkenylhydroxy ketone (14) did not cyclise when treated with phenylsulphenyl chloride, but more unexpectedly reaction with N-phenylsulpheno phthalimide and a Lewis acid also failed to work. This result was thought to be a consequence of the increased N-S bond strength compared with that of the N-Se bond[23]. The readily available N-phenylsulpheno pyrrolidine (31)[24] seemed an attractive alternative reagent, because compared with the phthalimide derivative, a Lewis acid should complex more strongly to the nitrogen atom, thus weakening the N-S bond and effecting transfer of the phenylsulpheno group.

This concept was initially tested using 1-penten-4-ol, which cleanly cyclised on treatment with compound (31) (1.0 equiv.) and zinc (II) bromide (1.0 equiv.) to give the cyclic ether (32) in an excellent 88% yield (Scheme 16).

Scheme 16.

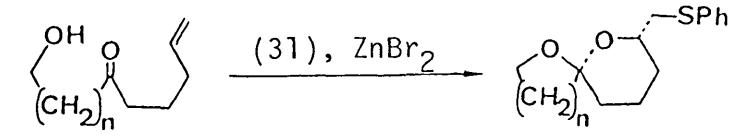


(31) (32)

88%

Reaction of the alkenylhydroxy ketone (14) under the same conditions, afforded the desired sulphur-substituted spiroacetal (33) as a single isomer, assumed to be *trans* by stereoelectronic considerations (Scheme 17). Unfortunately the yield was only a moderate 43%. This was a consequence of the liberated pyrrolidine by-product, which also reacted with compound (14) giving an enamine, subsequently destroyed on work-up.

Scheme 17.



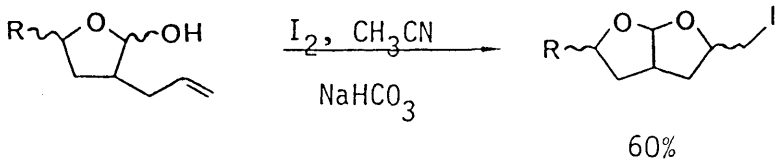
n= 1, (14) n= 1, (33), 43%
n= 2, (11) n= 2, (34) 46%

Compound (11) was cyclised in a similar manner, again giving exclusively the *trans* product, this time in 46% yield.

It may be possible to suppress the competing enamine formation by employing a more hindered amine, for instance 2,2',6,6'-tetramethyl piperidine but such a modification was not investigated.

Cyclisation reactions with iodine as the electrophile did not prove successful. This observation is in agreement with the results of Lallemande who recently published a related reaction[25] (Scheme 18), but was unable to extend this to spiroacetal synthesis[26].

Scheme 18.



60%

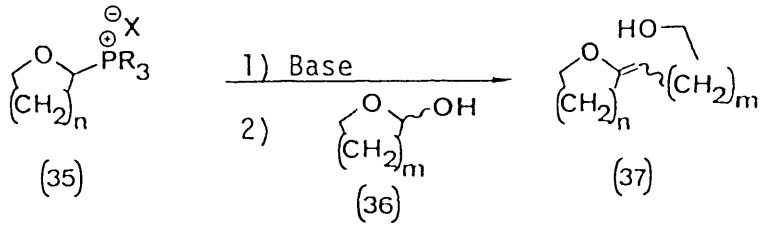
3. Preparation of Spiroacetals using Wittig-type Coupling Reactions.

3.1 INTRODUCTION.

Although the organoselenium-mediated cyclisation reactions presented in section 2 provide an interesting and novel approach to the synthesis of spiroacetal systems, the method has its limitations. Most notably, it cannot be readily applied to the preparation of optically active compounds due to the non-availability of the precursors for cyclisation. Also, problems may arise in the synthesis of highly substituted systems, where other functional groups could have a profound effect upon the mode of cyclisation.

Due to our interest in the synthesis of the spiroacetal portions of the milbemycins[1] and avermectins[2], a novel strategy that would overcome the above problems was sought. A possible solution would be a Wittig coupling between a phosphonium salt of type (35) and a lactol (36). This should result in an intermediate hydroxy-substituted enol ether (37), which could be cyclised under acidic conditions to give a spiroacetal (38) under anomeric control[27] (Scheme 19). If the phosphonium salt (35) could be prepared from a lactol system, it would allow both partners for the Wittig reaction to be derived from carbohydrates, overcoming the problems associated with the selenium-based methodology.

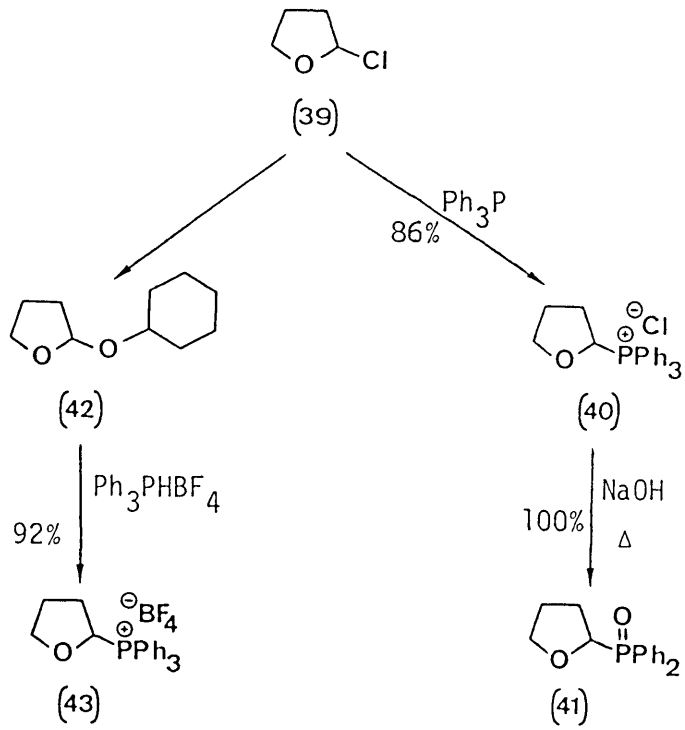
Scheme 19.



(38)

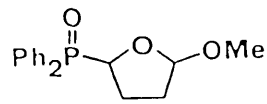
At the outset, little was known about compounds of type (35). One report described the preparation of phosphonium salts (40) and (43) from the corresponding anomeric chloride (39) and the acetal (42) respectivly[28] (Scheme 20). Hydrolysis of salt (40) to its phosphine oxide (41) was also studied.

Scheme 20.



Surprisingly however, no Wittig reactions of these materials had apparently been investigated prior to our work.

The phosphine oxide (44), prepared by the action of chlorodiphenyl phosphine on 2,5-dimethoxy tetrahydrofuran, has also been reported[29]. Again however, no Wittig couplings of this material have been examined.



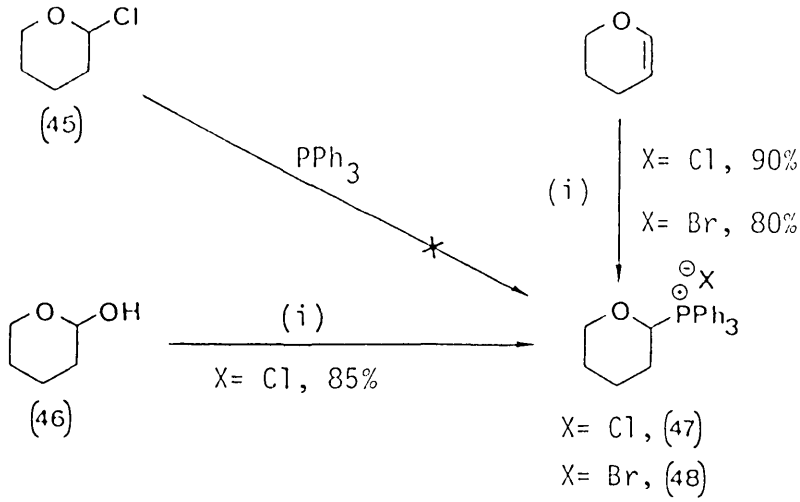
(44)

3.2 PREPARATION OF THE PHOSPHONIUM SALTS.

Initially it was decided to investigate routes to the simple phosphonium salt (47). Reaction of triphenylphosphine with the requisite anomeric chloride (45) resulted in poor yields of the desired compound due to instability of the starting material. This problem could be circumvented by employing conditions that formed compound (45) *in situ*. Thus treatment of a solution of lactol (46) and triphenylphosphine in benzene, with hydrogen chloride gas gave, after 5 h at room temperature, the salt (47) in good yield, 85% (Scheme 21).

Even more convenient was the reaction of 2,3-dihydro-4H-pyran under the same conditions, this time providing the salt (47) in 90% yield. In all cases the phosphonium salt (47) could not be purified to acceptable microanalytical levels. This parallels observations reported for the phosphonium chloride (40)[28], and so other methods for preparing this material were not sought at this time. If gaseous hydrogen bromide was used in the above reaction however, the resulting phosphonium bromide (48) could be easily recrystallised from dichloromethane-diethyl ether mixtures, to give the pure compound.

Scheme 21.

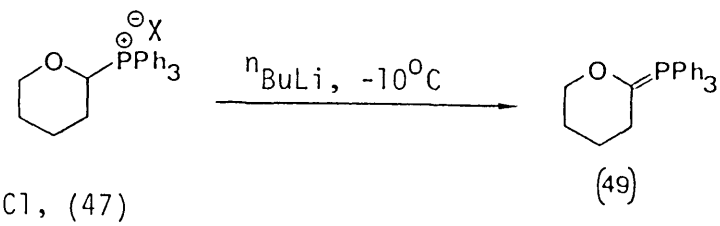


(i) Ph_3P, HX, PhH, rt.

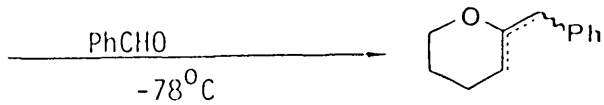
3.3 STUDIES ON THE WITTIG REACTION WITH ALDEHYDES AND LACTOLS.

Both the phosphonium chloride (47) and bromide (48) could be deprotonated with n-butyllithium at -10°C over 30 min, to give the deep red phosphorane (49). However, Wittig reactions of this material with aldehydes were poor, giving only low yields of the adducts, even with benzaldehyde (Scheme 22). In all cases investigated, a mixture of all three possible olefin isomers (50) was obtained, the *endo*-isomer probably arising as a consequence of isomerisation on work-up.

Scheme 22.



X= Cl, (47)
X= Br, (48)

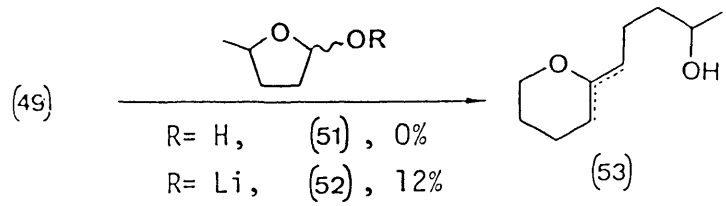


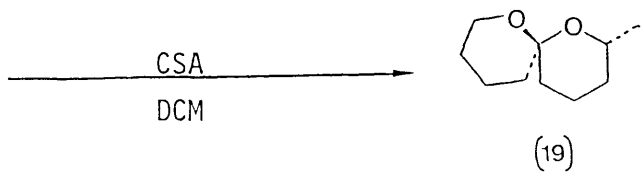
(50)

X= Cl, 24%

X= Br, 31%

The attempted coupling of compound (48) with lactol (51), employing a two-fold excess of the phosphorane (one equivalent deprotonates the lactol hydroxyl group) failed, however it was found that if the lactol was deprotonated first, using lithium diisopropylamide or n-butyllithium, and a solution of the lithio salt in tetrahydrofuran added to the phosphorane, then reaction did take place giving the adduct (53) in 12% yield. Both *endo* and *Z-exo* olefin isomers were obtained but these were not separated, since cyclisation with catalytic amounts of camphor sulphonic acid in dichloromethane cleanly afforded the *trans*-only spiroacetal (19) (Scheme 23).





Scheme 23.

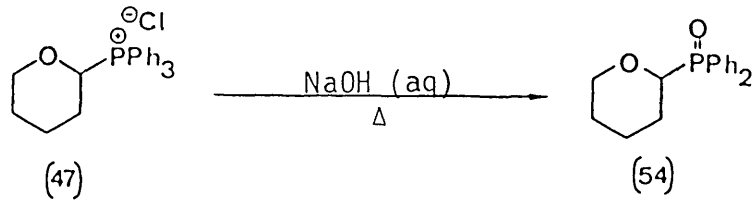
This material was identical to the previously prepared compound.

3.4 STUDIES ON THE HORNER-WITTIG REACTION WITH ALDEHYDES AND LACTOLS.

It is known that in many cases, phosphoranes with an α-oxygen substituent are thermally unstable and do not react particularly well in the Wittig reaction. The corresponding phosphine oxide anions however, provide a more stable alternative often leading to improved reaction[30].

Compound (47) was converted into the phosphine oxide (54) by treatment with aqueous sodium hydroxide at reflux (Scheme 24) in 83% yield. Treatment

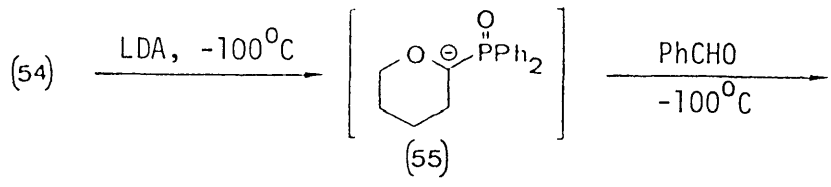
Scheme 24.



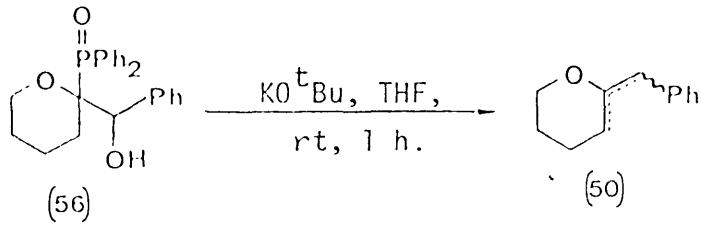
(47) (54)

of the oxide (54) with lithium diisopropylamide rapidly formed the deep red anion (55), even at -100°C and this in turn reacted instantaneously with benzaldehyde at low temperature, to give the adduct (56). Treatment of crude (56) with potassium t-butoxide in tetrahydrofuran at room temperature for 1 h[31], effected elimination of diphenylphosphinic acid, to give the coupled product (50), as a mixture of olefin isomers, in 76% combined yield (Scheme 25). This indeed represented a great improvement upon the normal Wittig

Scheme 25.



(55)

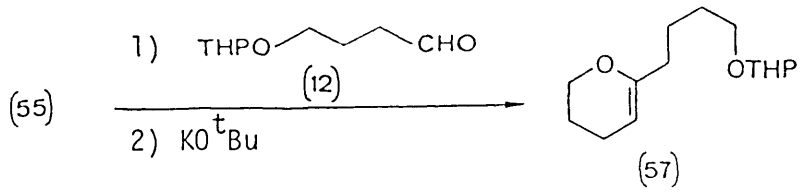


(56) (50)

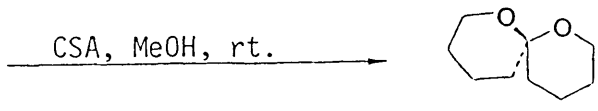
reaction.

Reaction of the anion (55) with aldehydes was next applied to the preparation of spiroacetals. Thus reaction with compound (12), followed by treatment with potassium t-butoxide and distillation, gave the adduct (57). This material could be deprotected and cyclised using catalytic amounts of

Scheme 26.



(57)



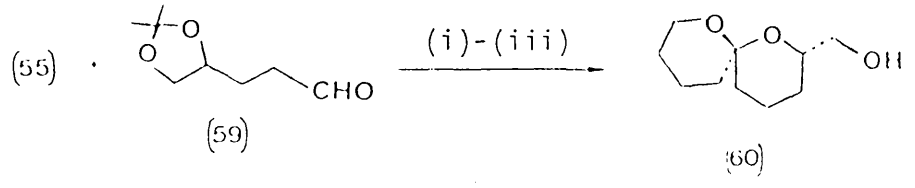
(58)

camphor sulphonic acid in methanol, to give the naturally occurring spiroacetal (58), a sex pheromone constituent from the Olive Fly, *Dacus oleae*[32] (Scheme 26).

Similarily, reaction with aldehyde (59) gave, after elimination and cyclisation, the spiroacetal (60) apparently as the *trans*-isomer only, which

provided a useful model for related studies on the elaboration of the 2-position in spiroacetals[33] (Scheme 27)

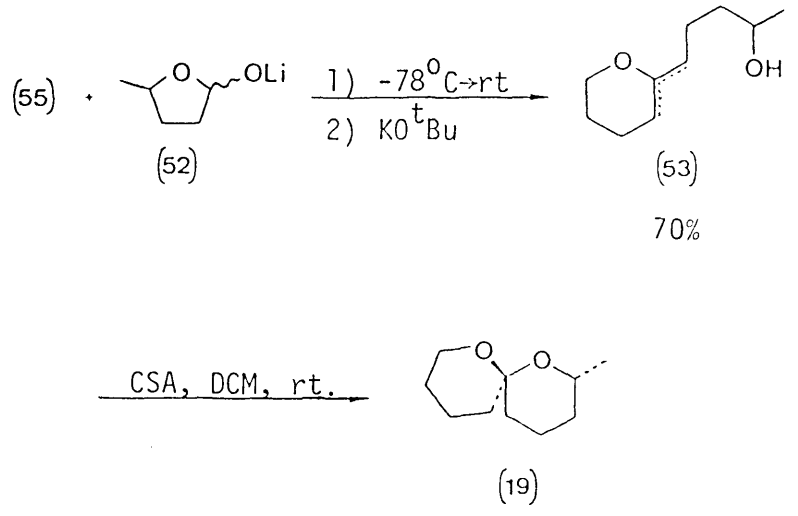
Scheme 27.



(i) -78°C; (ii) KO^{t}Bu, THF, rt; (iii) MeOH, CSA, rt.

Reaction of anion (55) with lactols was next considered and as before, best results were obtained when a solution of the lactol anion was employed, rather than relying upon excess (55) to effect deprotonation. Hence reaction of anion (55) with the lactol anion (52) gave, after elimination with potassium t-butoxide, adduct (53). This reaction was considerably slower than those observed with aldehydes, requiring higher temperatures for complete reaction. Treatment of the adduct (53) with catalytic amounts of camphor sulphonic acid in dichloromethane as before, gave the spiroacetal (19),

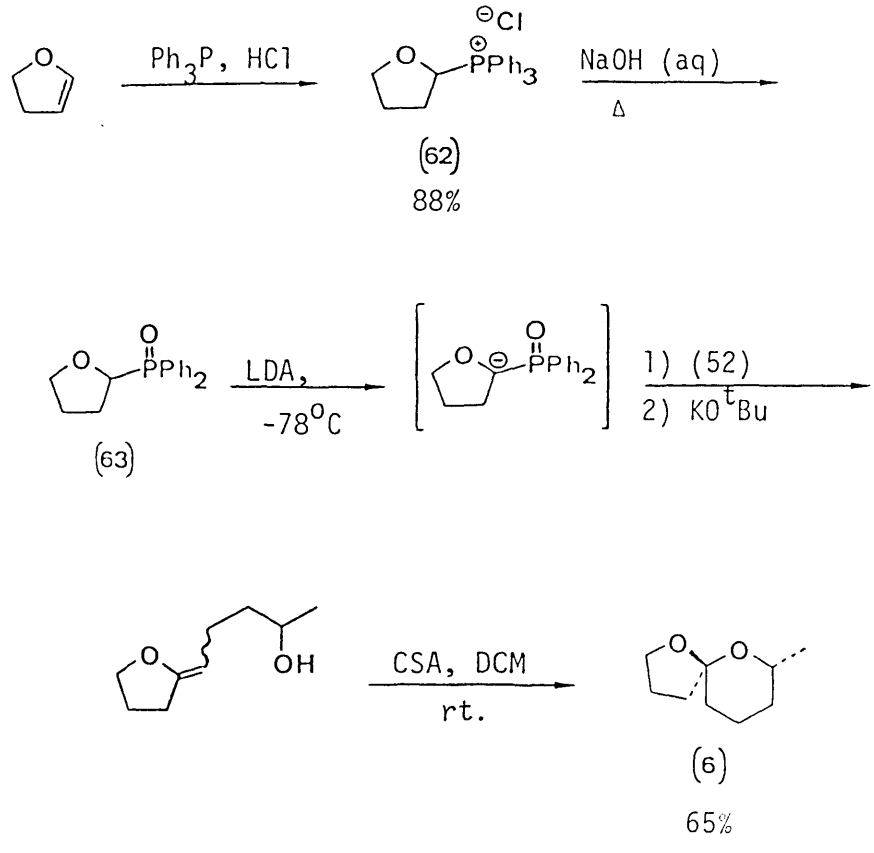
Scheme 28.



identical to the material prepared by the Wittig reaction, but this time in 57% yield (Scheme 28).

In order to illustrate application of this methodology to 5-ring systems, a recognition pheromone of the Common Wasp, *Paravespula vulgaris*[6] was synthesised (Scheme 29). Treatment of 2,3-dihydrofuran with triphenylphosphine and gaseous hydrogen chloride gave phosphonium salt (62). Again this material could not be purified completely, but did hydrolyse on treatment with aqueous sodium hydroxide at reflux, to give the phosphine oxide (63). Deprotonation with lithium diisopropylamide at -100°C produced a deep red anion, which quenched on addition of the lactol anion (52) and subsequent warming to room temperature. Elimination as before, followed by immediate treatment with

Scheme 29.



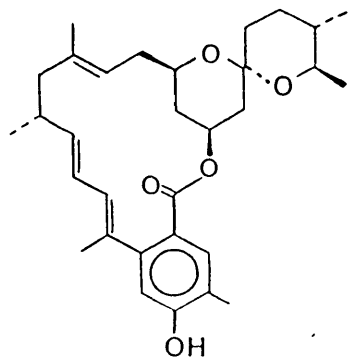
camphor sulphonic acid, gave the desired spiroacetal (6) as the *trans*-isomer only, in 65% overall yield. This compound was identical in all respects to that prepared earlier.

These results clearly demonstrate that the use of phosphine oxides instead of the analogous phosphonium salts, leads to greatly improved reaction, thus providing a powerful method for the construction of spiroacetal units from lactols.

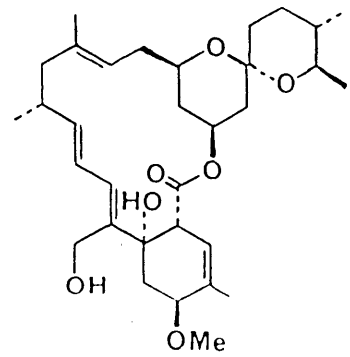
3.5 SYNTHESIS OF THE SPIROACETAL PORTION OF MILBEMYCIN β_1.

3.5.*1* Introduction.

The milbemycins are a family of potent antiparasitic agents isolated from *Streptomyces* B-41-146[1]. To date, only the simplest member of this family, milbemycin β_3 (64) has yielded to total synthesis[34,35]. The spiroacetal unit

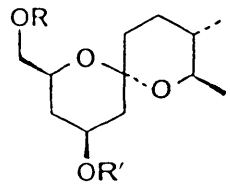


(64)



(65)

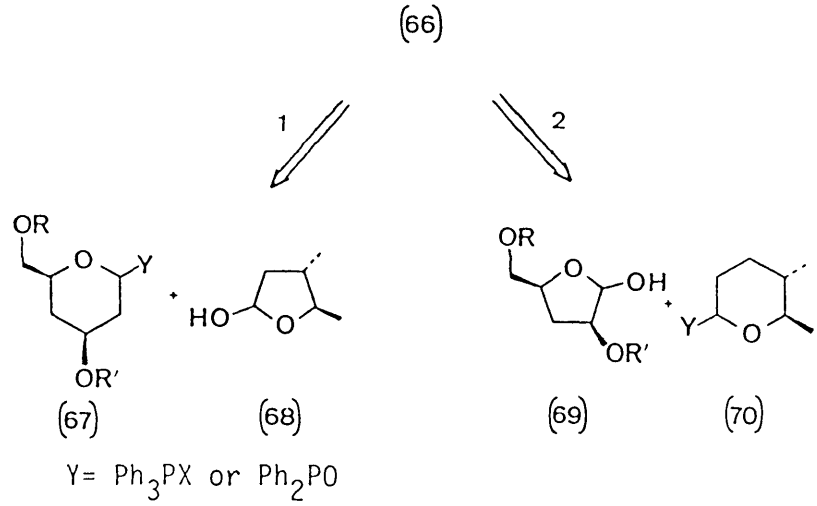
(66), which is common to most milbemycins, has however received more attention[36,37].



(66)

As part of a programme directed towards the synthesis of milbemycin β_1 (65), it was sought to apply the newly developed Wittig-type coupling strategy to the preparation of the spiroacetal portion (66).

Scheme 30.



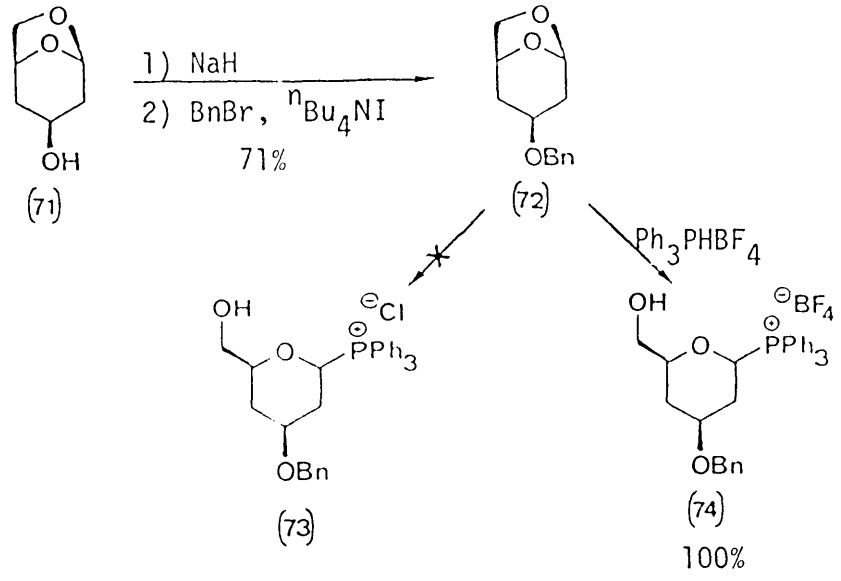
In principle, the coupling reaction could be approached in two different ways (Scheme 30), and an examination of both alternatives was undertaken.

3.5.2 Strategy 1.

The known alcohol (71)[38] was benzylated using standard conditions[39], to give the anhydro-derivative (72). Unfortunately, treatment of this material

with triphenylphosphine and gaseous hydrogen chloride in benzene, gave the crude phosphonium salt in very low yield (Scheme 31). All attempts to purify this material were unsuccessful, so a more reliable method of preparation was sought.

Scheme 31.

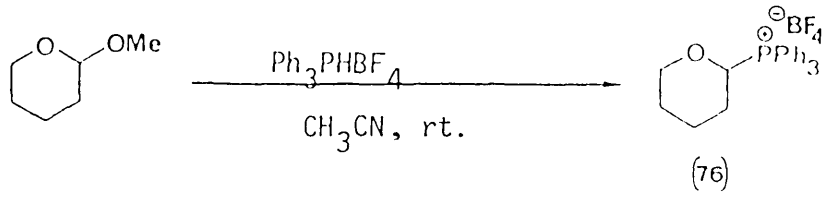


As mentioned earlier, it was known that treatment of 2-cyclohexoxy tetrahydrofuran with triphenylphosphonium tetrafluoroborate cleanly gave the corresponding phosphonium tetrafluoroborate salt[28]. Similar reaction of compound (72) gave, after stirring at room temperature in acetonitrile for 4 h, a quantitative yield of the analytically pure phosphonium salt (74).

Because of the ease of preparing salt (74) in high purity, this procedure was attempted with methoxy acetal (75) and again, on removal of the solvent from the reaction mixture, the pure salt (76) was obtained (Scheme 32).

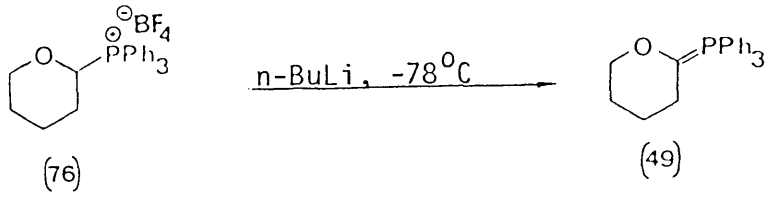
The phosphonium tetrafluoroborate (76) appeared to be more stable to heat than either the corresponding chloride (47) or bromide (48). Interestingly, despite being insoluble in the reaction medium, compound (76) formed a deep red phosphorane on treatment with n-butyllithium at -78^{o}C, compared with a temperature of -10^{o}C required for the deprotonation of the

Scheme 32.

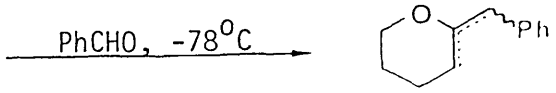


(76)

chloride (47) or bromide (48). This phosphorane was reacted with benzaldehyde giving a high yield of the adduct (50) (Scheme 33). The yield of 79% was far better than that obtained previously when the phosphorane was derived from the chloride (47) or bromide (48) salt, and compared with that obtained in the Horner-Wittig modification. This was probably a consequence of the lower



(76) (49)



(50)

79%

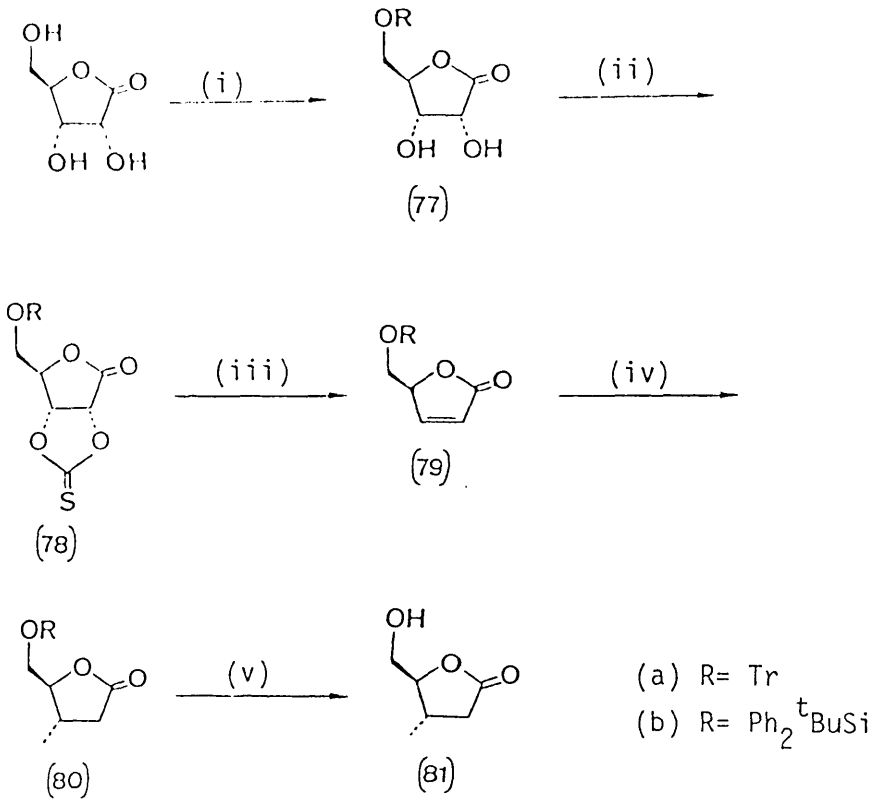
Scheme 33.

temperature required for formation of the phosphorane, resulting in far less decomposition.

With phosphonium salt (74) in hand, synthesis of the lactol unit (68) required for coupling, was undertaken. Hydroxy lactone (81) was known and

could be prepared in an optically pure form from ribonolactone following the Ireland protocol[40] (Scheme 34). Deoxygenation of the C-5 position in

Scheme 34



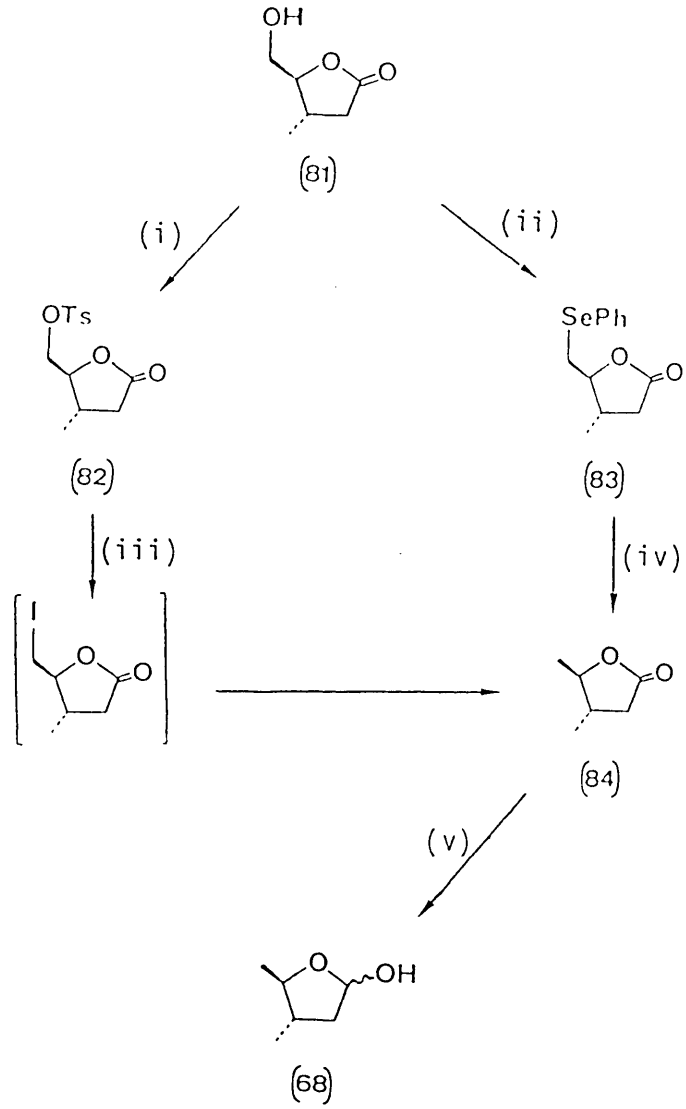
(i) TrCl, Py. or $Ph_2{}^tBuSiCl$, Imidazole, DMF; (ii) TCDI; (iii) Raney Ni; (iv) Me_2CuLi; (v) Pd-C, H_2 or $^tBu_4NF$.

compound (81), followed by reduction with diisobutylaluminium hydride should lead to the required lactol (68).

The reported synthesis of hydroxy lactone (81) employed the trityl protecting group for the C-5 hydroxy group, presumably for economic reasons. However it was found that the more stable t-butyldiphenylsilyl protection gave an improved overall yield of the final product. Deoxygenation at C-5 was achieved by converting the hydroxyl group into either the tosylate (82)[41] or the selenide (83)[42], followed by reduction with tri-n-butyltin hydride and AIBN[43] in dimethoxyethane at 80°C. In the case of tosylate (82), it was

necessary to include sodium iodide to effect *in situ* iodide formation, before the reduction could take place. Treatment of the resulting lactone (84) with

Scheme 35.

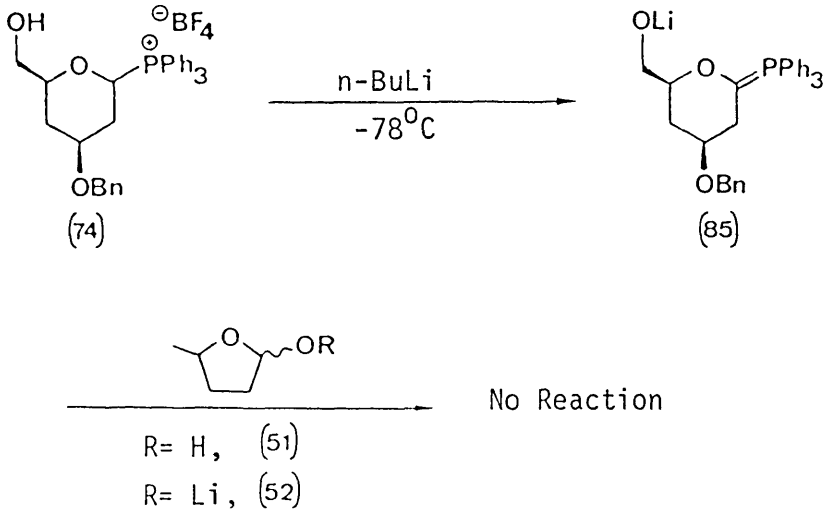


(i) TsCl, Py, DMAP; (ii) N-PSP, $^{n}Bu_3P$; (iii) NaI, $^{n}Bu_3SnH$, AIBN, DME, 80°C; (iv) $^{n}Bu_3SnH$, AIBN, DME, 80°C; (v) DIBAL-H.

diisobutylaluminium hydride cleanly gave the desire lactol (68) (Scheme 35). Crude yields of both lactone (84) and lactol (68) were high and the moderate

yields obtained after purification reflect losses occurring during the distillation of relatively small amounts of these materials. Other routes to this optically active lactol (68) are currently under investigation in this laboratory.

Having prepared both the phosphonium salt (74) and lactol (68), Wittig couplings of these two fragments were next examined. The deep red phosphorane (85) could be readily generated from compound (74) by treatment with two equivalents of n-butyllithium in tetrahydrofuran at -78°C, however disappointingly this material did not react with either lactol (68) or its lithio anion, even after several hours at room temperature (Scheme 36).



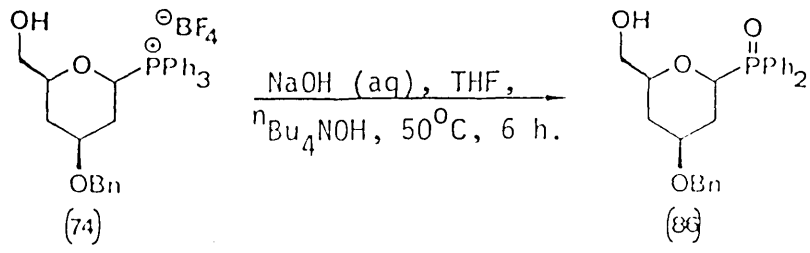
Scheme 36.

Prolonged reaction times simply lead to decomposition of the phosphorane (85).

Conversion of phosphonium salt (74) into the corresponding phosphine oxide (86) was not straigtforward, since the salt was insoluble in aqueous sodium hydroxide. A two phase system had to be employed, where phosphonium salt (74) was dissolved in tetrahydrofuran containing 10 mol % of tetra-n-butylammonium hydroxide as phase transfer catalyst, and this mixture was heated at 50°C with 3N aqueous sodium hydroxide for 6 h. Phosphine oxide (86) could still only be

isolated in a poor 38% yield (Scheme 37).

Scheme 37.

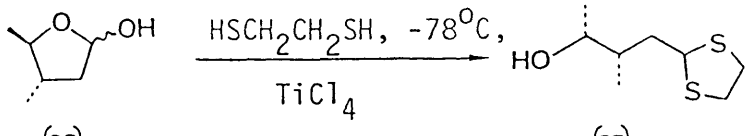


(74) (86)

38%

Reaction of the phosphine oxide anion, generated by treatment of compound (86) with two equivalents of n-butyllithium at -78°C, with the lithio anion of lactol (68) was again unsuccessful.

At this point in the synthesis, it was decided to attempt to trap the lactol in its open hydroxy aldehyde form, in order to utilise the more reactive aldehyde function in the coupling reaction. Hence, treatment of lactol (68) with four eqivalents of 1,2-ethanedithiol and one equivalent of titanium (IV) chloride at -78°C[44], gave the hydroxy dithiolane (87) (Scheme 38).



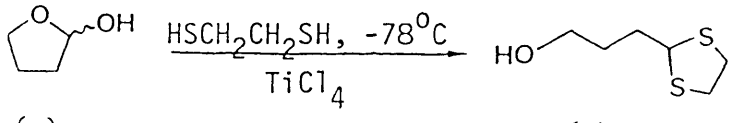
(68) (87)

67%

Scheme 38.

Shortage of material necessitated the investigation of subsequent reactions using the model system (89), which could be prepared as above from the lactol

Scheme 39.

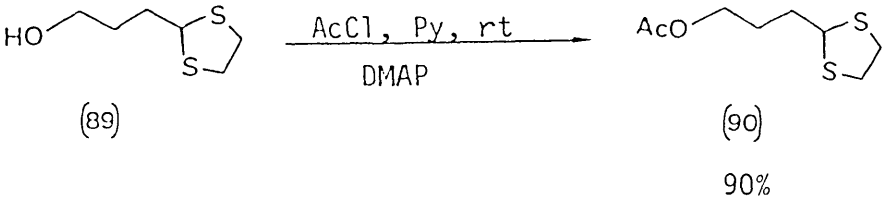


(88) (89)

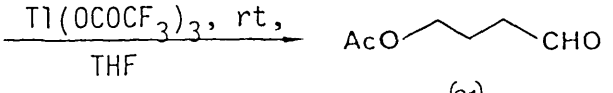
76%

(88) (Scheme 39). Tetrahydropyranyl[45] and t-butyldiphenylsilyl[46] protecting groups were investigated for the hydroxy group in compound (89), both proving unstable to the conditions necessary for hydrolysis of the dithiolane group. The acetate (90) however, could be prepared in high yield[47], and allowed rapid, clean removal of the dithiolane function with thallium (III) trifluoroacetate[48] to give the aldehyde (91) (Scheme 40).

Scheme 40.



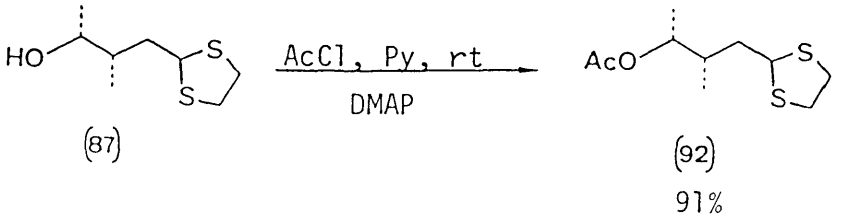
(89) (90) 90%



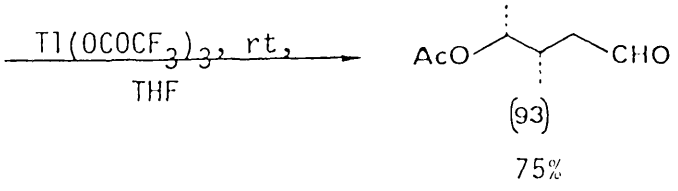
(91) 70%

Application of this method to compound (87), gave the optically pure aldehyde (93) required for Wittig coupling (Scheme 41).

Scheme 41.

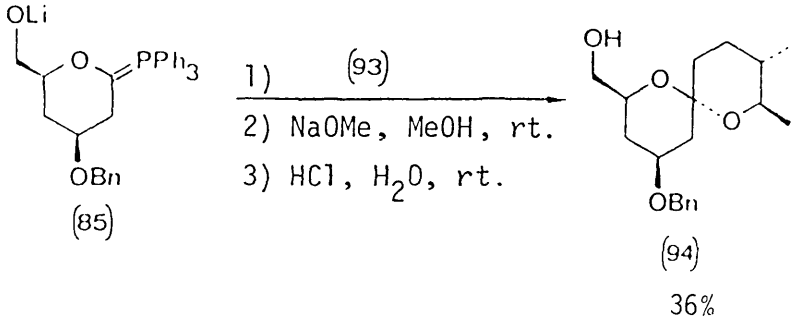


(87) (92) 91%



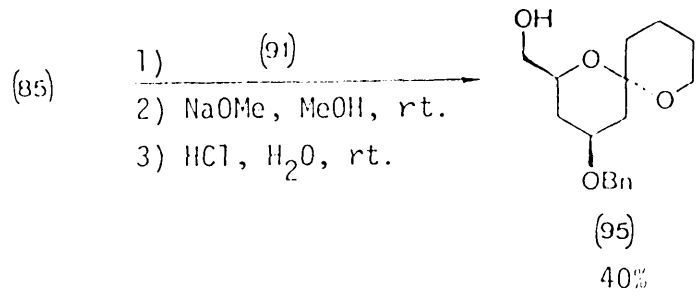
This time aldehyde (93) reacted smoothly with the phosphorane (85) to give the Wittig adduct. This material was not isolated, but treated immediately with sodium methoxide in methanol[49], to remove the acetate protecting group. After treatment of the reaction mixture with acid for 30 min, the desired spiroacetal (94) was isolated, in 36% overall yield (Scheme 42). Compound (94) appeared to be a single isomer by high field ^{1}H nmr (Scheme 44), and this data compared well with the literature reported spectrum of a related derivative[36].

Scheme 42.



Reaction of the aldehyde (91) with the phosphorane (85) was also investigated and under the same conditions gave spiroacetal (95) in 40% overall yield (Scheme 43). This compound again appeared to be a single isomer, its structure being in accord with the high field ^{1}H nmr data (Scheme 45). A COSY spectrum of this material confirmed these findings and enabled almost complete assignment of the ^{1}H nmr spectrum (Scheme 45).

Scheme 43.

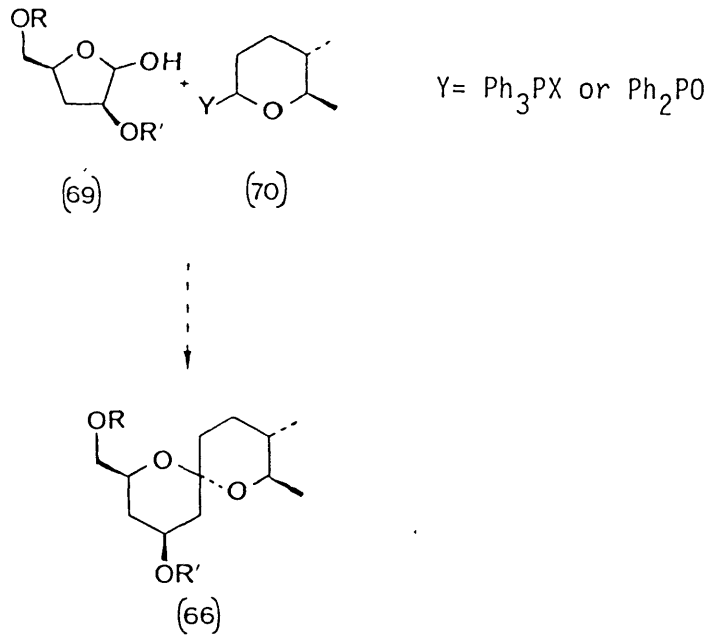


(95)

40%

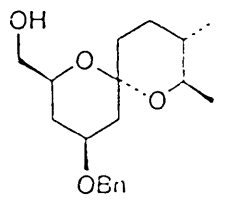
3.5.3 Strategy 2.

As mentioned earlier, this strategy involves a proposed coupling of the two fragments (69) and (70), to give the spiroacetal (66).



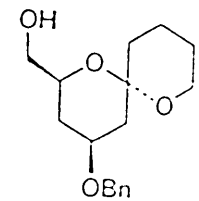
The optically active lactone (98), from which it should be possible to prepare phosphonium salt (70) has been obtained from citronellene (96) by the route outlined below (Scheme 46)[35]. Unfortunately, in our hands the iodo-lactonisation step was found to be low yielding, giving material that was difficult to purify, hence preventing the use of this reaction on a large

Scheme 44.

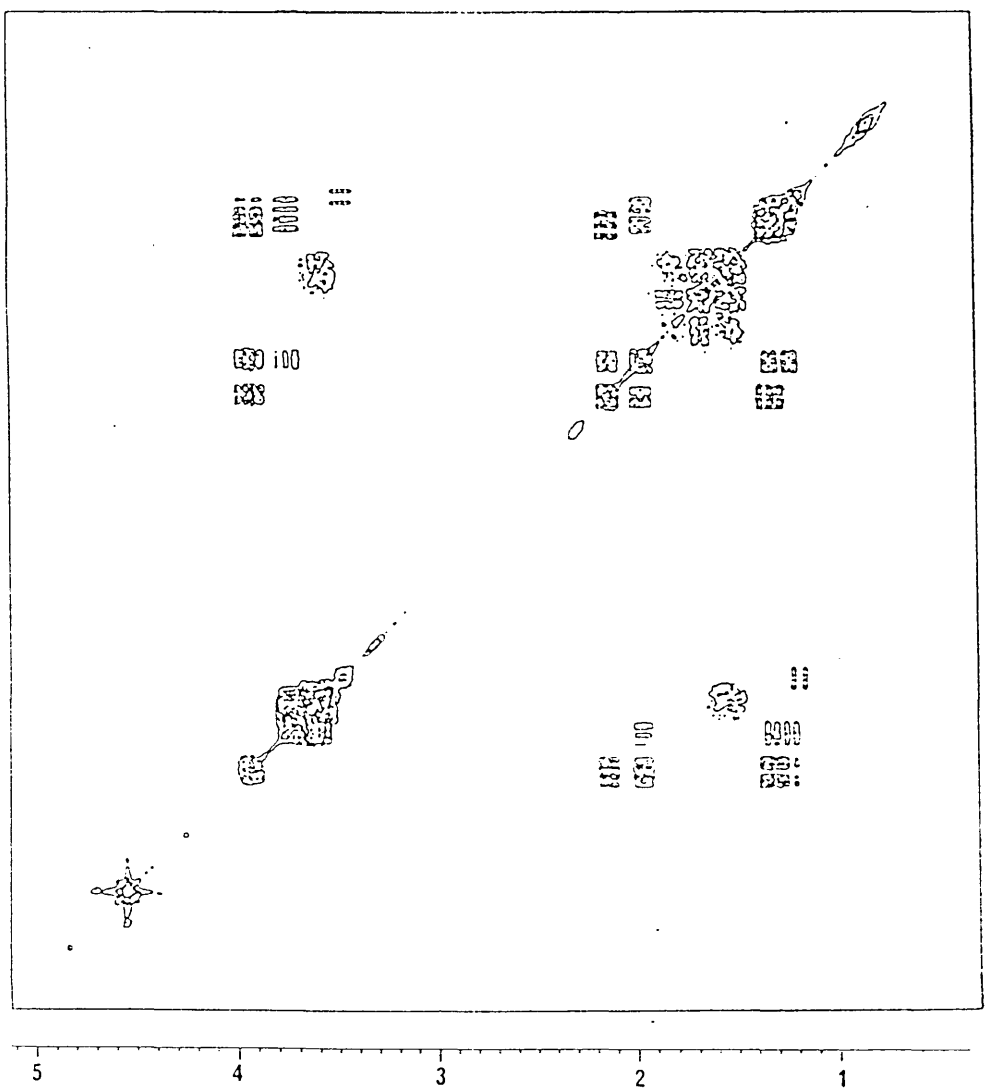


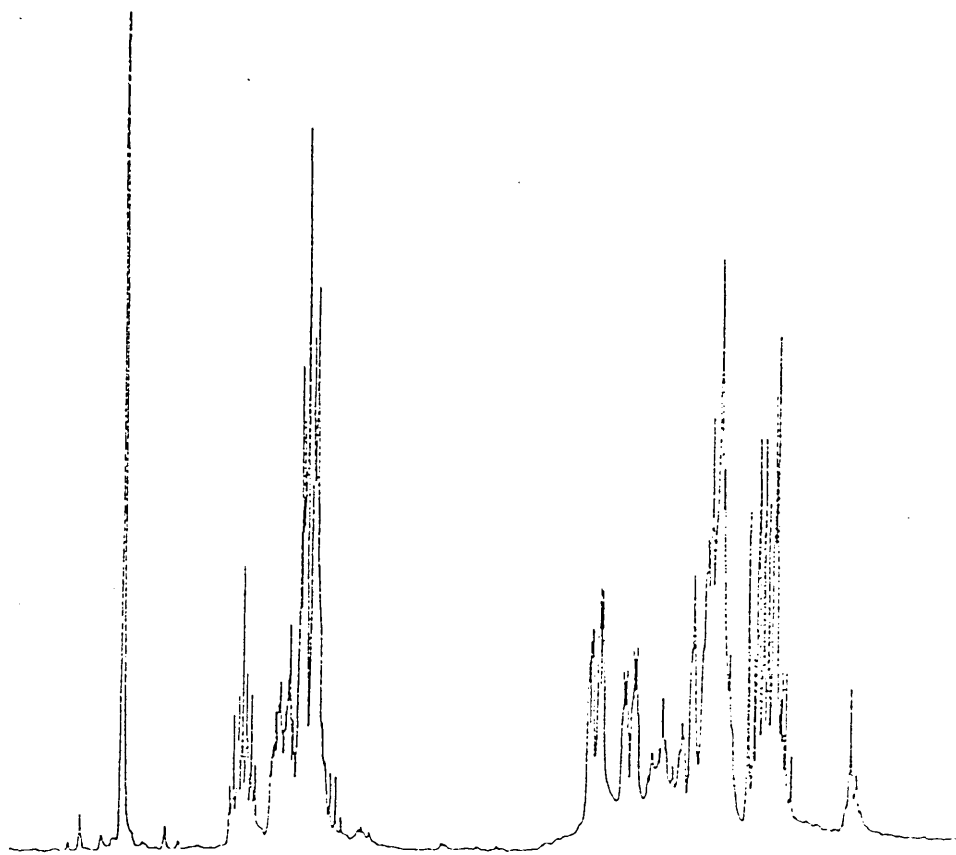
(94)

Scheme 45.

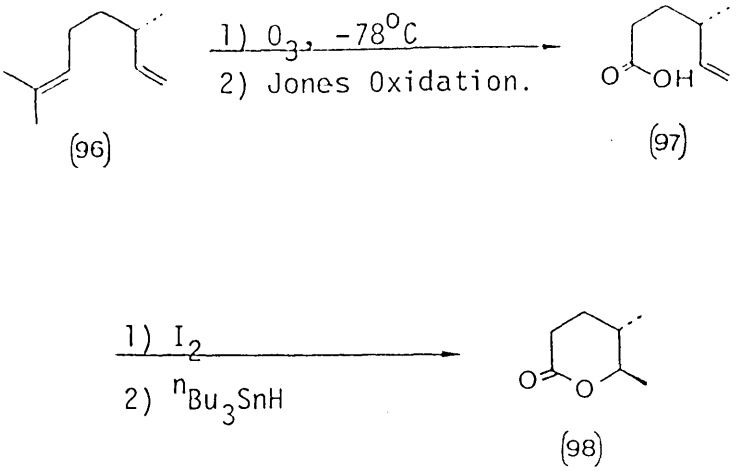


(95)





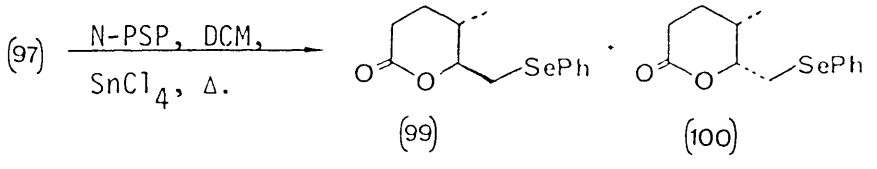
Scheme 46.



(96) (97) (98)

scale. A related phenylseleno lactonisation procedure[3] with N-PSP and tin (IV) chloride however, gave an excellent yield of the required *trans* phenylseleno lactone (99), contaminated with only trace amounts of the *cis*-isomer (100) (Scheme 47). Crystallisation of the crude reaction mixture from

Scheme 47.



(99) (100)

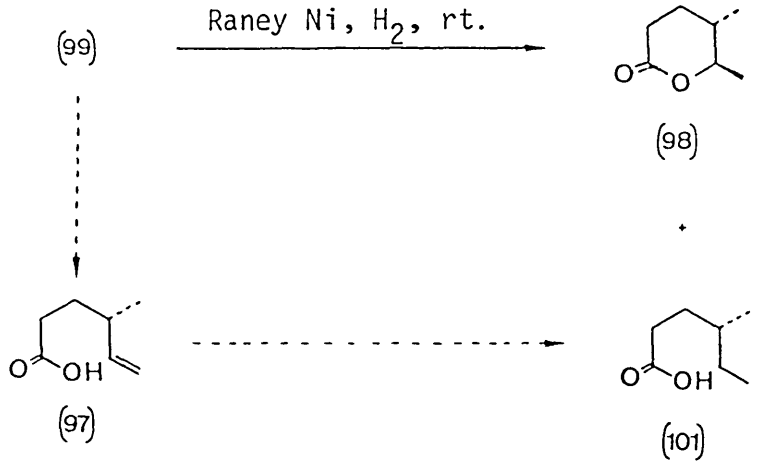
78%

dichloromethane-petrol gave the pure *trans* lactone in 78% yield. To the best of our knowlege, this is the first example of a phenylseleno lactonisation under thermodynamic conditions, and it was found to be necessary to add the N-PSP as a solution in dichloromethane to an already refluxing mixture of the unsaturated acid (97) and tin (IV) chloride, otherwise poor yields resulted. At lower temperatures, less of the desired thermodynamic product was obtained. The ^1H nmr spectrum of compound (99) clearly showed a 9.2 Hz axial-axial

coupling constant between the protons at C-5 and C-4, thus indicating a *trans* disposition of the two substituents.

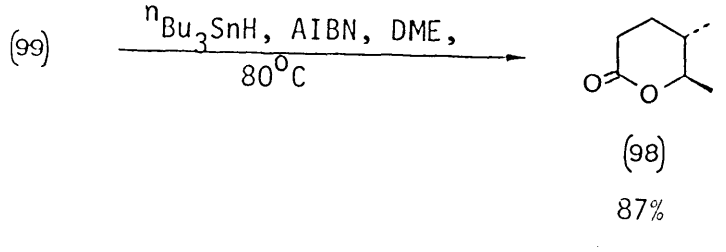
Removal of the phenylseleno group using Raney nickel[50] proved to be unreliable, often giving mixtures of the desired lactone (98) and another product that appeared from its spectral properties to be 4(R)-methyl hexanoic acid (101) (Scheme 48). Compound (101) may arise as a consequence of base

Scheme 48.



catalysed reversal of the cyclisation step, followed by hydrogenation of the resulting olefin. It is unlikely that this ring opening proceeds *via* a radical process on the surface of the nickel catalyst, since reduction of compound (99) with tri-n-butyltin hydride and AIBN[43] gave only the desired lactone (98) in a high 87% yield (Scheme 49). This material was identical to

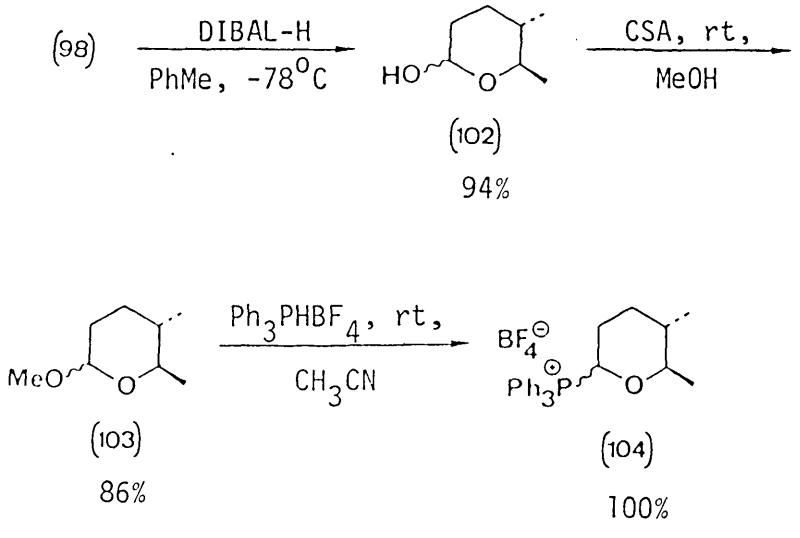
Scheme 49.



the reported compound[34,35], confirming the *trans* nature of the substituents.

Reduction of compound (98) with diisobutylaluminium hydride gave the lactol (102) in 94% yield. Subsequent conversion to the methoxyacetal (103) followed by treatment with triphenylphosphonium tetrafluoroborate again proved to be the best method for the preparation of the phosphonium salt (104) (Scheme 50).

Scheme 50.

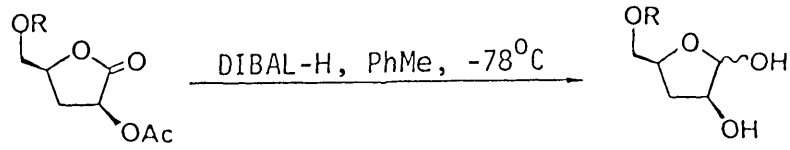


Phosphonium salt (104) was isolated in quantitative yield, as a stable white amorphous solid and as with the other tetrafluoroborate salts prepared, did not require further purification. This material appeared to exist as a mixture of two isomers by ^1H nmr, as was clearly indicated by a doubling of the two methyl signals. Since it is unlikely that any epimerisation of the two methyl centres would have occurred under the reaction conditions employed, this result is probably due to the phosphonium group being able to adopt both axial and equatorial positions as a consequence of the relatively long C-P bond. This observation echoes those obtained with other substituted phosphonium salts prepared in the course of this work.

For the synthesis of fragment (69), the readily available lactone (105)[51]

was chosen as starting material. Treatment of this material with diisobutylaluminium hydride gave the hydroxy lactol (106). Unfortunately it was not possible to selectively reduce the lactone function without also reducing, and hence removing, the acetate substituent (Scheme 51).

Scheme 51.



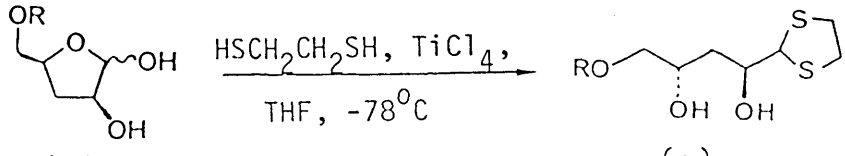
(105) (106)

R= $Ph_2{}^tBuSi$ 61%

All attempts to couple the phosphorane obtained by treatment of phosphonium salt (104) with n-butyllithium at -78°C, with the preformed dilithio dianion of hydroxy lactol (106) were unsuccessful. By analogy with the previous strategy, it was therefore decided to trap open the lactol in its more reactive hydroxy aldehyde form.

Treatment of compound (106) with 1,2-ethanedithiol and titanium (IV) chloride as before, gave the dihydroxy dithiolane (107) in good yield, 94% (Scheme 52). Several protecting groups for the diol were examined, namely

Scheme 52.

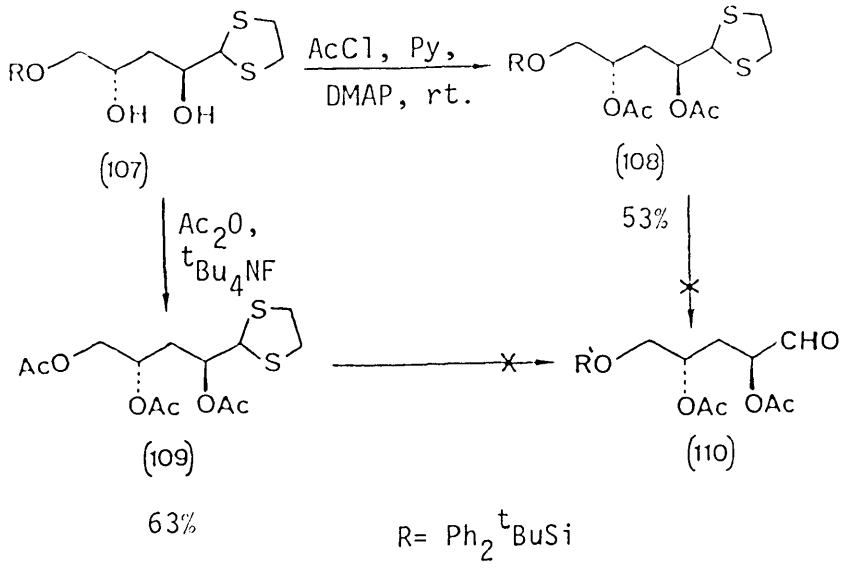


(106) (107)

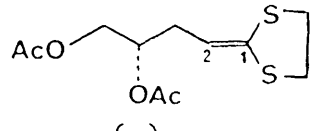
94%

tetrahydropyranyl[45], acetonide[52], and t-butyldimethylsilyl[46], however all proved unstable to the conditions required for hydrolysis of the dithiolane group. Formation of the diacetate[47] (108) (Scheme 53) this time did not solve the problem. This was thought to be a consequence of the instability of the t-butyldiphenylsilyl group present in the molecule. Reaction of compound

Scheme 53.



(107) with acetic anhydride and tetra-n-butylammonium fluoride[53], conditions known to acetylate both free hydroxyl groups and those protected with silyl groups, gave the triacetate (109) as expected (Scheme 53). Again a wide variety of conditions reported for dithiolane removal[54] were examined, all failing to give the desired aldehyde (110). It is not clear exactly why these reactions were not successful. In most cases ^{1}H nmr indicated the loss of an acetate group from one of the secondary hydroxyl groups, but the products could not be identified. Conditions employing the use of a base (e.g. methyl iodide in refluxing aqueous acetone, with potassium carbonate as a buffer) caused elimination of acetic acid, giving compound (111) as the



(111)

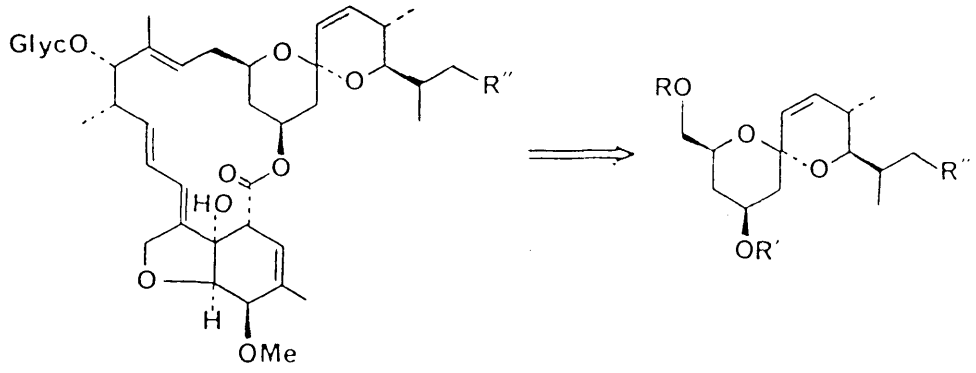
only product. This was clearly evident from the ^1H nmr spectrum, which showed loss of the C-2 acetate group and the C-1 proton resonance, in addtion to the presence of a one proton triplet at δ 5.5 , assumed to correspond to the newly formed olefinic proton.

Unfortunately it was not possible to investigate further protecting groups, or other modifications to this strategy, due to lack of time. This work is however continuing in these laboratories.

3.6 SYNTHETIC STUDIES TOWARDS THE SPIROACETAL PORTION OF AVERMECTIN A_{1b}.

3.6.1 Introduction.

The avermectins are a family of potent antiparasitic agents[2] structurally very similar to the milbemycins. As yet, none of the avermectins have yielded to total synthesis, although the spiroacetal portion has been prepared [55]. As part of our studies in this area, it was sought to apply the Wittig

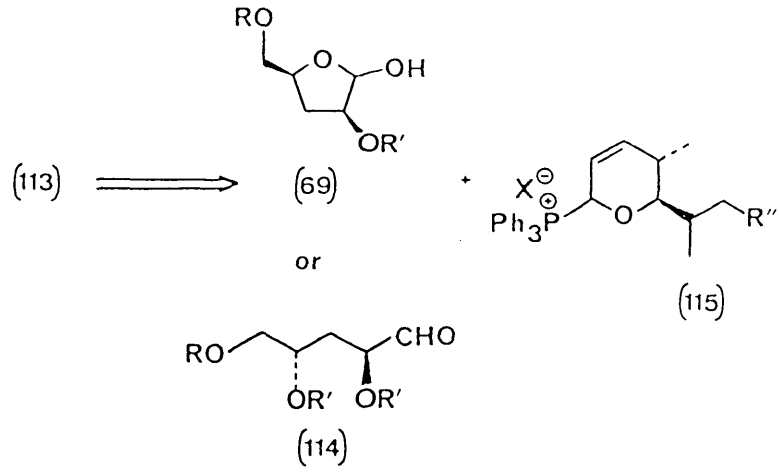


R"=H, (112) R"=H, (113)

coupling reaction to the preparation of the spiroacetal unit of avermectin A_{1b} (112). By analogy to the retroanalysis proposed earlier for the

milbemycin spiroacetal portion, it is obvious that compound (113) can only be prepared by the disconnection outlined below (Scheme 54).

Scheme 54.



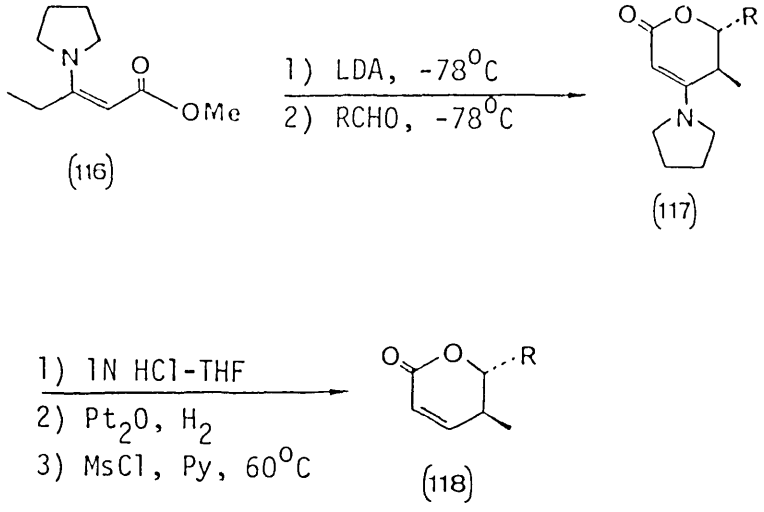
Since a phosphonium salt of type (115) on treatment with base, would give a partially stabilised, and hence less reactive phosphorane, it seemed likely that the aldehyde (114) would again be necessary for the coupling reaction.

3.6.2 Preparation of the Phosphonium Salt.

In order to develop a route to the phosphonium salt (115), two main factors had to be considered. The route had to allow variation in the R''-substituent, in order that it could be applied to other avermectin systems, and it was also necessary to be able to prepare the product in optically active form.

A synthesis of 2-pentenolides (118), from which it should be possible to prepare compound (115), had been reported using an enamine alkylation reaction [56] (Scheme 55), although no experimental details were published. Such a route

Scheme 55.



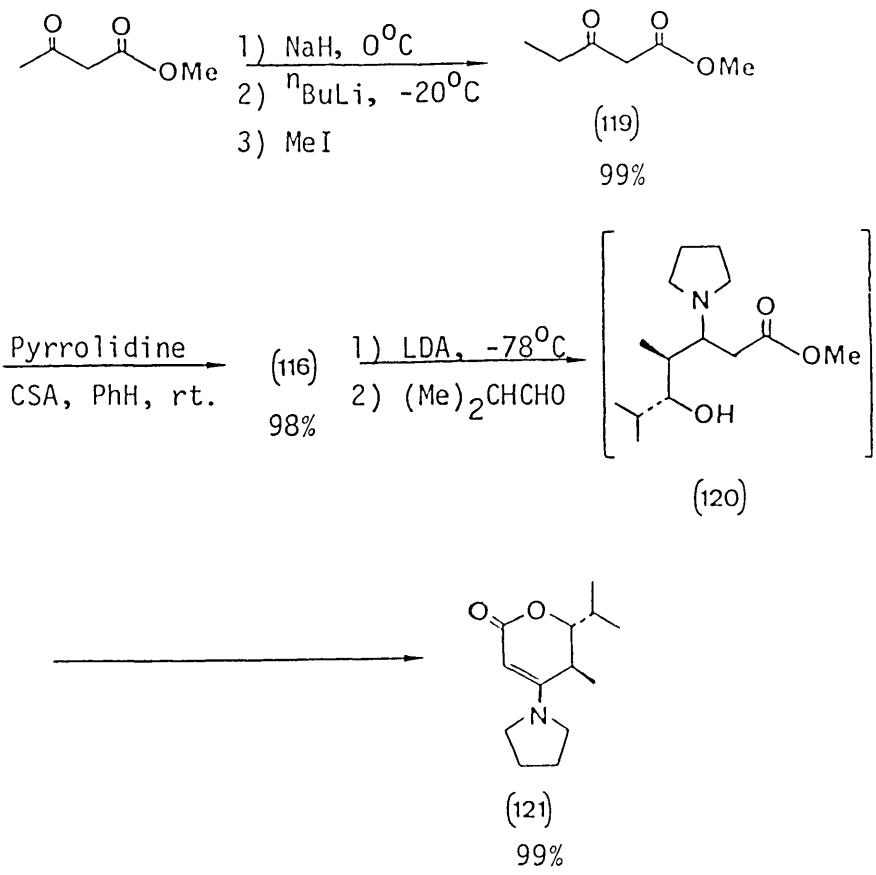
(116) (117) (118)

clearly allows variation in the R-group and also should, with the use of a chiral enamine[57], be amenable to the preparation of optically active material. However, the proposed synthesis was initially investigated using racemic materials in order to establish optimum reaction conditions.

Formation of the dianion from methyl acetoacetate, by treatment with one equivalent of sodium hydride at 0°C, followed by one equivalent of n-butyl-lithium at -20°C[19] and kinetic quenching with methyl iodide, gave the β-keto-ester (119) in 99% yield. This compound (119) was reacted with pyrrolidine and a catalytic amount of camphor sulphonic acid in benzene at room temperature to give the enamine (116), 98%. Deprotonation of this material with lithium diisopropylamide at -78°C, followed by addition of iso-butyraldehyde, gave the kinetically quenched adduct (120), which lactonised under the reaction conditions to yield the crystalline enamine-lactone (121) (Scheme 56). All attempts to hydrolyse compound (121) to the keto-lactone as reported, were unsuccessful. Fortunately, compounds similar to (121) had been converted to the corresponding 2-pentenolides *via* reduction of the

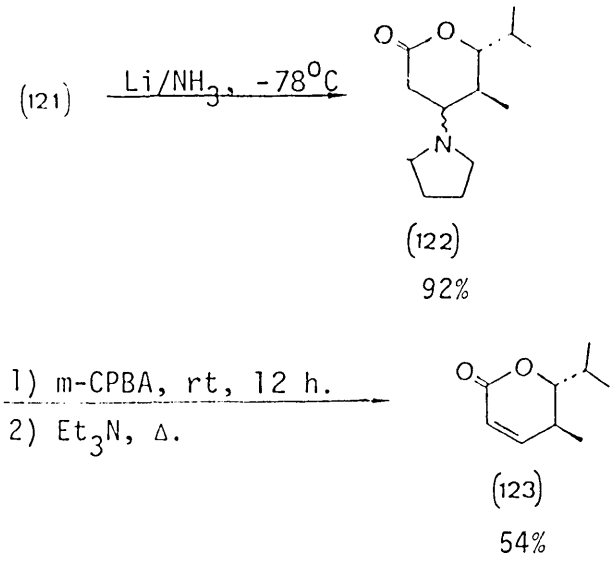
enamine double bond, followed by Cope elimination of the resulting amine[56].

Scheme 56.



Application of this method to compound (121) provided a solution to the problem. Hence, dissolving metal reduction of compound (121) with lithium in liquid ammonia, gave the amine (122) as a mixture of epimers in 92% yield. Oxidation to the N-oxide with m-CPBA followed by elimination on heating with triethylamine, gave the desired 2-pentenolide (123) (Scheme 57) as a single isomer. Elimination of the N-oxide towards the C-4 methyl position would have led to the 3-pentenolide, but none of this product was detected. In addition, epimerisation of the C-4 methyl group could have occurred had the 3-pentenolide formed and the double bond subsequently migrated into conjugation with the lactone. No such epimerisation was observed.

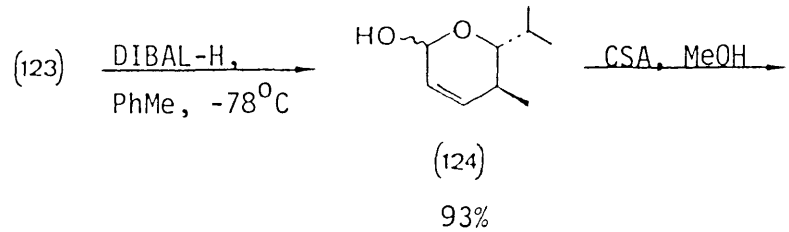
Scheme 57.

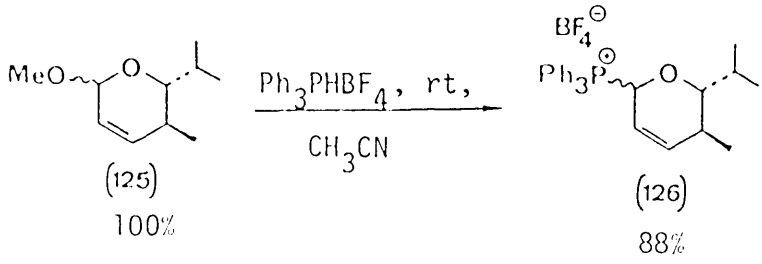


Diisobutylaluminium hydride reduction of compound (123) to the lactol (124) proceeded well, and subsequent treatment with methanol and camphor sulphonic acid gave the methoxy acetal (125) in 93% overall yield. This compound appeared to be rather unstable, turning bright red on standing at room temperature, and therefore was immediately reacted with triphenylphosphonium tetrafluoroborate, to give the required phosphonium salt (126) (Scheme 58).

Compound (126) was isolated as a mixture of isomers, as indicated by a doubling of the methyl and iso-propyl resonances in the ^{1}H nmr spectrum. As with the other salts studied, these were presumed to be phosphonium anomers,

Scheme 58.





(125)
100%

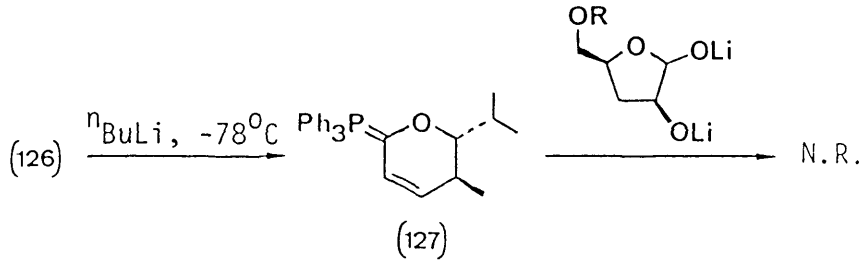
(126)
88%

although it was not possible to prove this conclusively.

Application of this route to the preparation of optically active phosphonium salts could not be studied in the time available, but will be the source of future work in this laboratory.

3.6.3 Synthetic Studies towards the Wittig Coupling Reaction.

Unfortunately as mentioned earlier, the aldehyde (114) required for Wittig coupling could not be produced in the time available, to allow investigation of this reation. The condensation of the phosphorane (127) derived from



(127)

Scheme 59.

phosphonium salt (126) on treatment with n-butyllithium at -78°C, with the dilithio dianion of hydroxy lactol (106), was however examined. As before, this reaction failed to produce the desired adduct underlining the necessity for aldehyde (114) (Scheme 59).

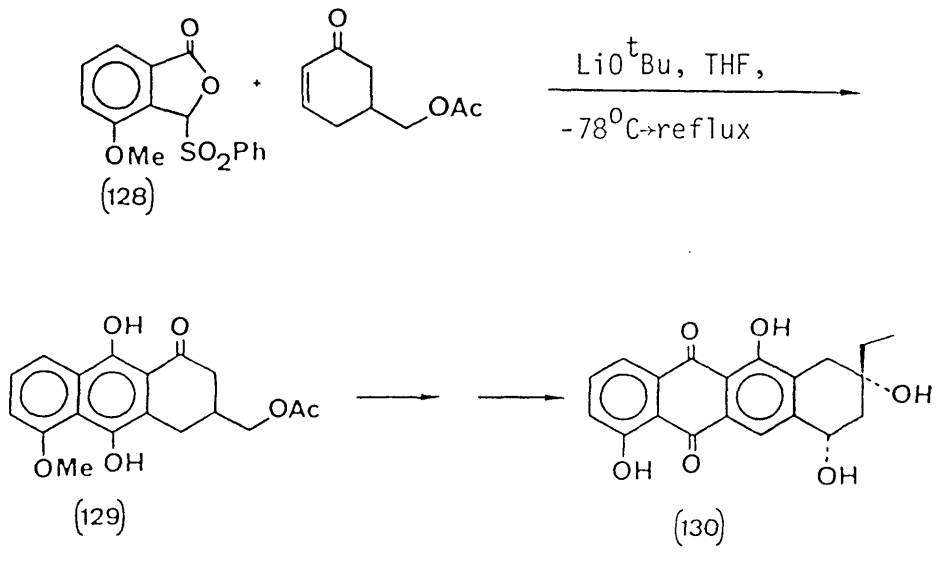
4. PREPARATION OF SPIROACETALS USING SULPHONE COUPLING REACTIONS.

4.1 INTRODUCTION.

With the success of the Wittig and Horner-Wittig couplings in the preparation of a variety of spiroacetal systems, it was decided to investigate the related sulphone coupling reactions, since they may offer a complementary reactivity profile.

At the start of this work, carbohydrates substituted at the anomeric position by a sulphone group were known. All such compounds had been prepared by oxidation of the corresponding sulphide by either potassium permanganate in acetic acid[58], or hydrogen peroxide in acetic acid[59], but attempts to deprotonate these compounds had not been reported. Compounds of type (128) had also been reported, and their derived anions used in the preparation of tetracyclic systems , such as (±)-γ-citromycin[60] (130) (Scheme 60).

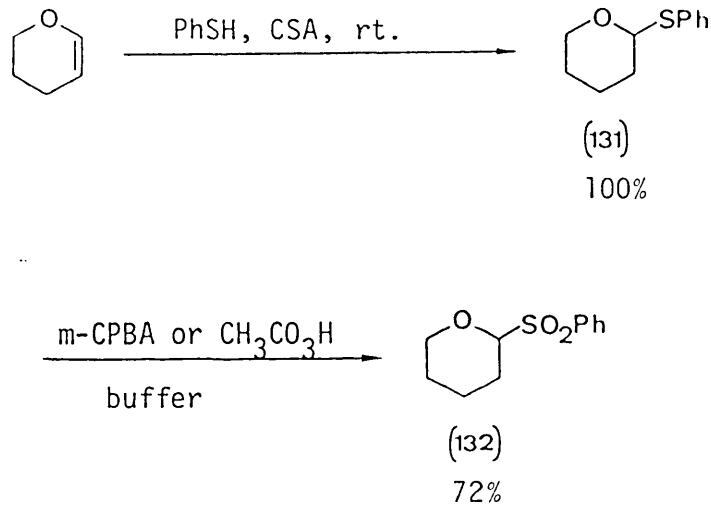
Scheme 60.



4.2 PREPARATION OF THE SULPHONE.

For the purposes of this study, the simple 2-benzenesulphonyl tetrahydropyran (132) system was examined. This could be prepared in reasonable yield from the corresponding sulphide (131) by oxidation with either m-CPBA or peracetic acid. In both cases buffered conditions were required to prevent the acid catalysed elimination of benzenesulphinate (Scheme 61). Literature

Scheme 61.



reported oxidative methods for the related carbohydrate systems, were unsuccessful because of the ease of this elimination. The sulphide (131) was prepared from 2,3-dihydro-4H-pyran by treatment with benzenethiol and a trace of camphor sulphonic acid.

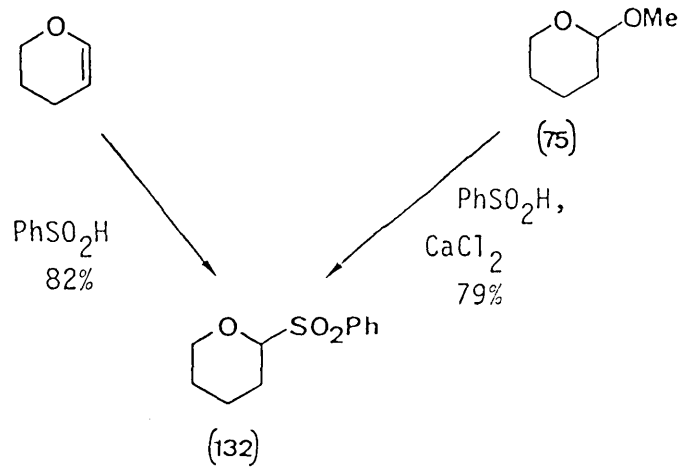
This sulphone was a stable crystalline solid and ^1H nmr clearly showed it to be one isomer, with the benzenesulphonyl group occupying an equatorial position. However this material did decompose to a certain extent on silica gel chromatography, possibly due to the acid catalysed elimination process mentioned. This made purification of the compound difficult and time consuming, therefore an alternative method of preparation was sought.

The use of sodium benzenesulphinate as a sulphur nucleophile in the preparation of sulphones from alkyl halides is well known[61]. It was

considered that the corresponding acid, benzenesulphinic acid, should react with 2,3-dihydro-4H-pyran in a similar manner. Its acidity would be expected to catalyse the initial oxonium ion formation and the benzenesulphinate species should then capture this intermediate to give the sulphone.

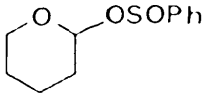
Benzenesulphinic acid can be prepared by treatment of the sodium salt with hydrochloric acid[62] but is relatively unstable, decomposing to a variety of sulphur compounds over several days at ambient temperatures. However as postulated, it did react with 2,3-dihydro-4H-pyran giving the required sulphone (132) in high yield, 82%, after stirring at room temperature for 2 h, without any appreciable decomposition of the reagents (Scheme 62). The

Scheme 62.



material from this reaction was free of by-products requiring only simple recrystallisation, to give the pure product.

It is known that in the preparation of sulphones using sodium benzenesulphinate, small amounts of product derived from oxygen attack of the reagent are obtained, however no evidence of the corresponding sulphinate ester (133) was detected in this reaction. This may simply be a consequence of the instability of compound (133) to isolation.



(133)

Application of this method to 2-methoxy tetrahydropyran (75) was less successful because reaction was slow, leading only to decomposition of the sulphinic acid. Addition of molecular sieves to remove methanol, and hence accelerate the reaction did not help, however powdered calcium chloride was useful, giving the sulphone (132) in 79% yield after 1 h at room temperature. Small amounts of methyl benzenesulphinate (134) and 2-hydroxy tetrahydropyran were also obtained from this reaction. These by-products could have resulted from reaction of the sulphinate ester (133) with liberated methanol (Scheme

Scheme 63.

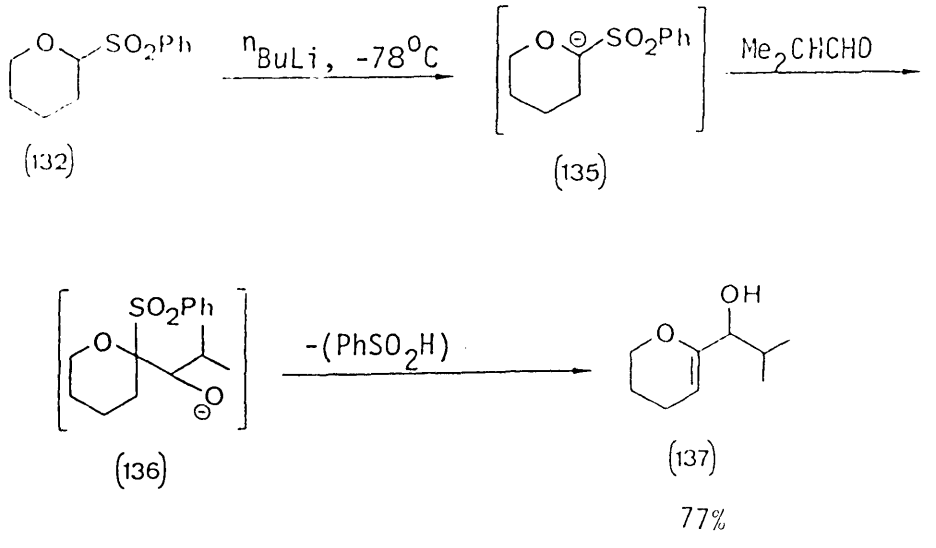
63). Despite these contaminents recrystallisation of the sulphone was still possible.

4.3 REACTIONS OF THE SULPHONE.

Sulphone (132) was readily deprotonated by n-butyllithium at -78°C in tetrahydrofuran, to give a pale yellow anion solution, which after quenching with deuterium oxide led to complete incorporation at the 2-position.

Reaction of the sulphone anion (135) with iso-butyraldehyde at -78°C proceeded cleanly to give a single product in 77% yield, identified as the cyclic enol ether (137). This product must have resulted from elimination of benzenesulphinate from the initial adduct (136), which suggests that once

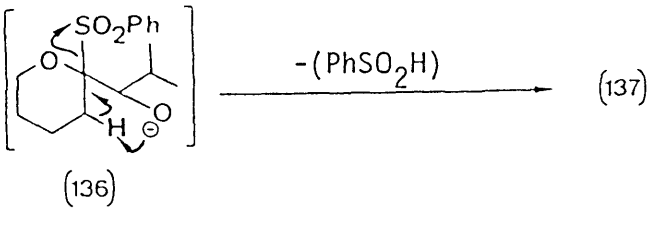
Scheme 64.



the 2-position is substituted, elimination becomes a very facile process.

The possibility of this elimination process only occurring as a consequence of intramolecular proton transfer (Scheme 65) was discounted

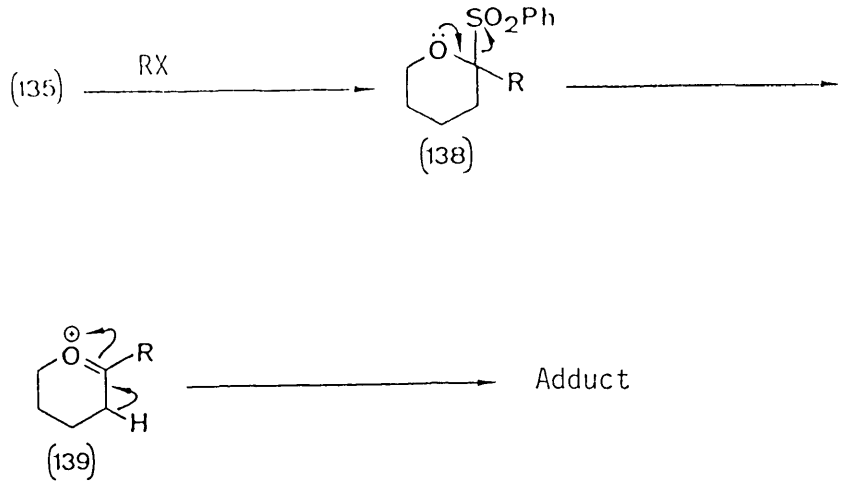
Scheme 65.



because as will be discussed later, the reaction of anion (135) with alkyl halides, also gives rise to enol ether products. It seems likely that steric strain at the anomeric position may be responsible for the observed

elimination, the mechanism at least in the case of the alkyl halide adducts,

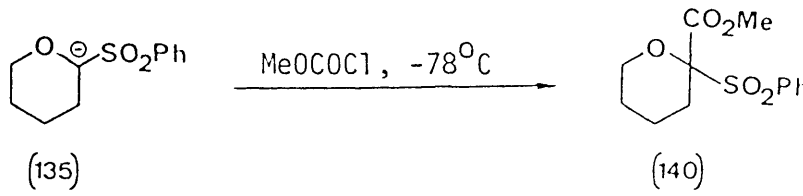
Scheme 66.



proceeding *via* a oxonium ion intermediate (139) (Scheme 66).

Indeed, reaction of the sulphone anion with methyl chloroformate cleanly gave the sulphone (140) (Scheme 67). In this case elimination of benzene-

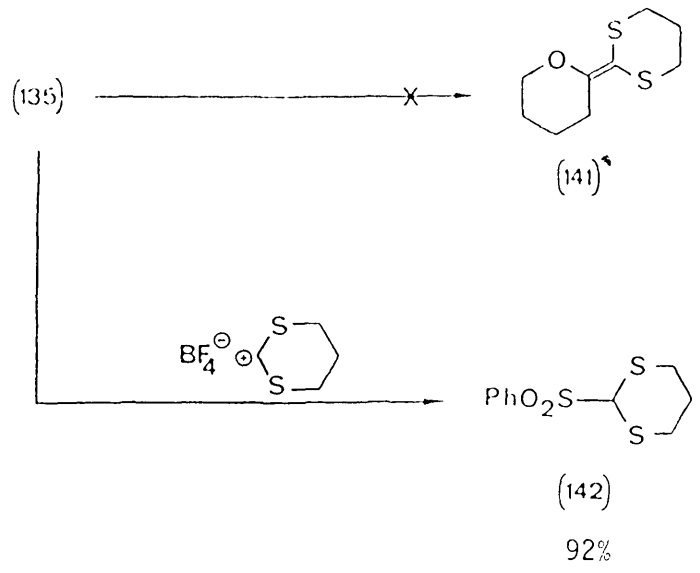
Scheme 67.



sulphinate is suppressed presumably due to the ester function destabilising any intermediate oxonium ion formation.

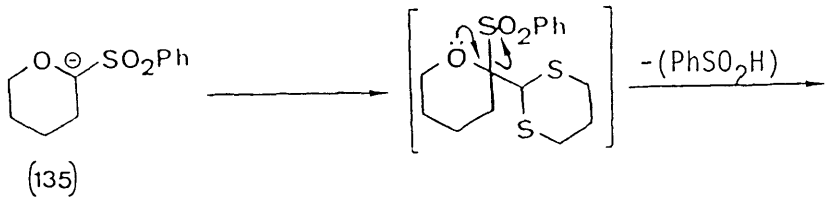
A rather anomolous product was obtained on reaction of anion (135) with 1,3-dithienium tetrafluoroborate[63]. It was hoped that this reaction would provide access to the ketene thioacetal (141), but the only product obtained was the sulphone (142) (Scheme 68).

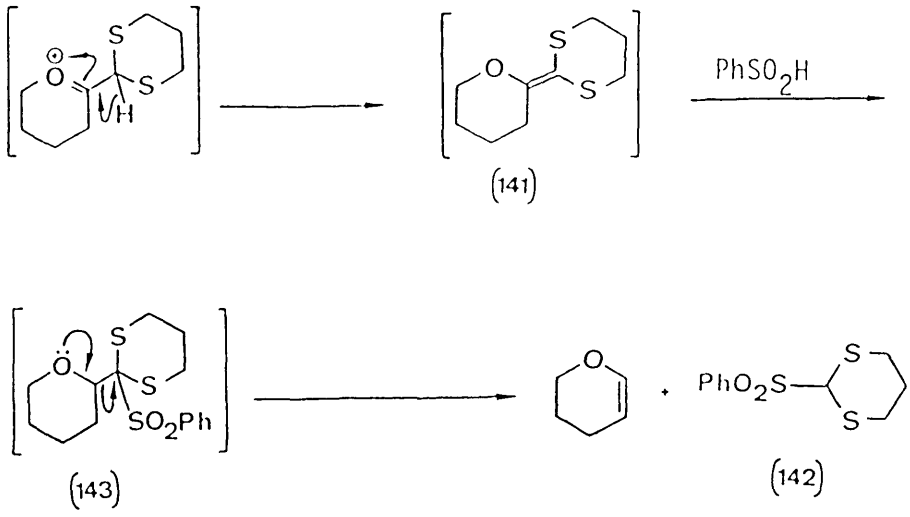
Scheme 68.



The formation of compound (142) can be rationalised by the mechanism shown below (Scheme 69). It is thought that reaction proceeds as expected to give the desired ketene thioacetal (141), but under the reaction conditions benzenesulphinic acid adds across the very reactive olefin bond, giving

Scheme 69.





(141)

(143)

(142)

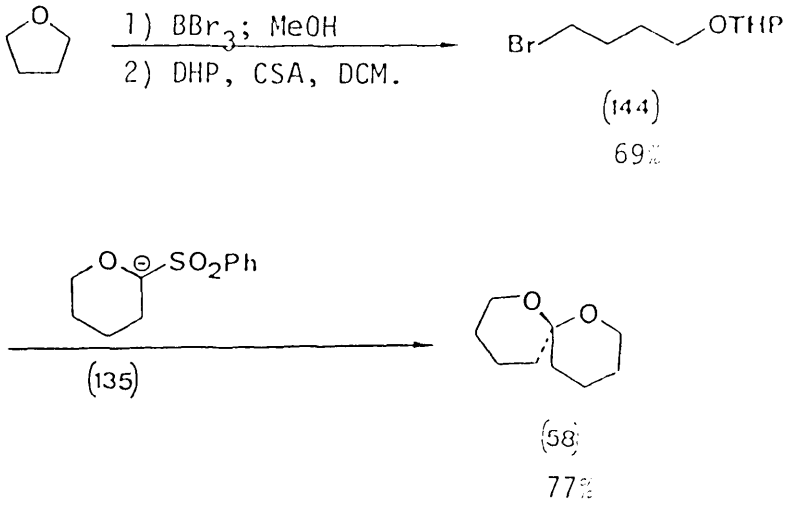
intermediate (143). Elimination of the stabilised 2-benzenesulphonyl-1,3-dithiane anion, followed by protonation, would then lead to the observed product (142).

The sulphone anion (135) was found to be unreactive towards alkyl chlorides and epoxides.

4.4 APPLICATION OF SULPHONE (132) IN SPIROACETAL SYNTHESIS.

The utility of the sulphone (132) in spiroacetal synthesis was demonstrated by the preparation of the major component of the Olive Fly, *Dacus oleae* sex pheromone (58)[32]. Thus treatment of tetrahydrofuran with boron tribromide[64], followed by protection of the resulting bromo alcohol as the tetrahydropyranyl ether[45], gave the bromide (144) required for coupling. This reacted smoothly with the sulphone anion (135) at -30°C, to give the spiroacetal (58) (Scheme 70), which was identical to the previously prepared material. This reaction is particularily useful for the preparation

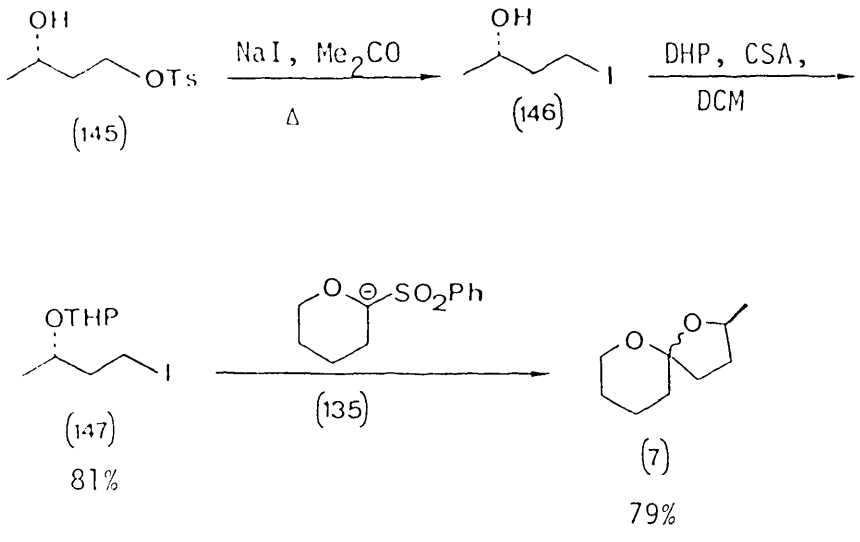
Scheme 70.



of spiroacetals, since the benzenesulphinic acid produced effects removal of the tetrahydropyranyl protecting group and subsequent cyclisation of the enol ether intermediate, to give the product directly, without the need for a separate deprotection step. The overall yield of compound (58) from tetrahydropyran was a respectable 53%, and this procedure could easily be carried out in a day.

This new sulphone methodology was also applied in the synthesis of the optically active 2(S)-methyl-1,6-dioxaspiro[4.5]decane (7) a natural product isolated from the Common Wasp, *Paravespula vulgaris*[6]. The iodide (147) required for coupling with the sulphone (132) was prepared from (S)-butane-1,3-diol, by conversion of the more reactive primary hydroxyl group to a iodide (146) *via* the tosylate (145), and protection of the remaining secondary hydroxyl group as a tetrahydropyranyl ether. Reaction of this iodide (147) with the sulphone anion (135) proceeded rapidly at -78°C, to give on work-up, the optically active spiroacetal (7) in 46% overall yield from the diol (Scheme 71).

Scheme 71.



This spiroacetal was obtained as a 2:1 mixture of *trans*:*cis* isomers, identical in all respects except optical rotation, to the racemic material prepared earlier.

These two syntheses clearly demonstrate the utility of this sulphone coupling reaction in the preparation of spiroacetals, and show the sulphone to be a useful 2,3-dihydro-4H-pyran anion equivalent.

5. EXPERIMENTAL.

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotation measurements were conducted using a Perkin-Elmer 141 polarimeter at ambient temperature. Infrared spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer or a Perkin-Elmer 983 G infrared spectrophotometer. ^{1}H n.m.r. spectra were recorded at 60 MHz on a Varian EM-360A, at 90 MHz on a Jeol FX 90 Q, at 250 MHz on a Bruker WM-250, and at 400 MHz on a Bruker WH-400 machine, and are quoted for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were determined with a VG micromass 7070 B instrument. Elemental microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory.

Analytical thin layer chromatography was performed on precoated aluminium- or glass-backed plates (Merck Kieselgel 60 F_{254}) and preparative chromatography was conducted under low pressure using either MN Kieselgel 60 (230-400 mesh) or BDH Florisil (200-300 mesh). Silica refers to the Kieselgel.

Petrol refers to petroleum ether (bp 40-60^{o}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 4 Å molecular sieves and distilled under reduced pressure before use. All other reagents were purified by usual methods.

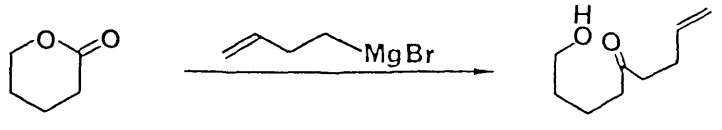
Solutions were dried over anhydrous sodium sulphate.

General Procedure for the Addition of Grignard Reagents to δ-Valerolactone.

A solution of the appropriate Grignard reagent (2.0 mmol) in ether (2 ml) was added dropwise to a stirred suspension of δ-valerolactone (2.0 mmol) in dry tetrahydrofuran (6 ml) under argon at -78°C, over a period of 3 h, *via* a motorised syringe.

Stirring was continued for a further 1 h, after which time aqueous saturated ammonium chloride (2 ml) was added, and the mixture allowed to warm to room temperature. The aqueous phase was extracted with ether (3 x 2 ml), and the combined organic extracts dried and evaporated. The residue was subjected to chromatography on silica (30% ether- 70% petrol) to give the pure hydroxy keto alkene.

(1) Preparation of 9-Hydroxy-1-nonen-5-one (9).

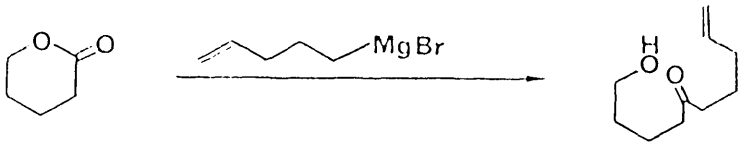


(9)

Using the above procedure, but-3-enylmagnesium bromide was reacted with δ-valerolactone to give 9-hydroxy-1-nonen-5-one (9) (38 mg, 12%), as a colourless oil, ν_{max} (film) 3476, 2927, 2872, 1708, and 1634 cm^{-1}; δ (60 MHz) 6.09-4.73 (3H, m), 3.56 (2H, ≈t), and 2.62-1.43 (11H, m); *m/z* 156 (M^+), 87, 69, 58, 55, and 41; and the product of double Grignard addition 5-but-3-enylnon-8-ene-1,5-diol (10) (34 mg, 8%), as a colourless oil, ν_{max} (film) 3370, 2923, 2859, and 1637 cm^{-1}; δ(60 MHz) 6.16-4.67 (6H, m), 3.57 (2H, ≈t), and 2.17-1.31 (16H, m); *m/z* (no M^+), 195, 157, 139, 83,

51, and 41.

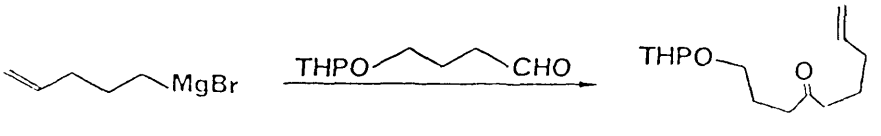
(2) Preparation of 1-Hydroxy-9-decen-5-one (11).



(11)

Using the above general procedure, pent-4-enylmagnesium bromide was reacted with δ-valerolactone to give 1-hydroxy-9-decen-5-one (11) (77 mg, 23%) as a colourless oil, ν_{max} (film) 3398, 2930, 1705, and 1639 cm^{-1}; δ (60 MHz) 6.03-4.67 (3H, m), 3.53 (2H, m), and 2.53-1.27 (13H, m); *m/z* 170 (M^+), 116, 101, and 98. (Found: M^+ 170.1312, $C_{10}H_{18}O_2$ requires 170.1307), and the product of double Grignard addition 5-pent-4-enyldec-9-ene-1,5-diol (29 mg, 6%) as a colourless oil, ν_{max} (film) 3360, 2929, 2858, and 1638 cm^{-1}; δ(60 MHz) 6.15-4.74 (6H, m), 3.59 (2H, br.t), 2.70 (2H, br.s D_2O exch.), and 2.20-1.20 (18H, m); *m/z* (no M^+), 222, 171, 84, and 69.

(3) Preparation of 1-[(Tetrahydro-2H-pyran-2-yl)oxy]8-nonen-4-one (13).

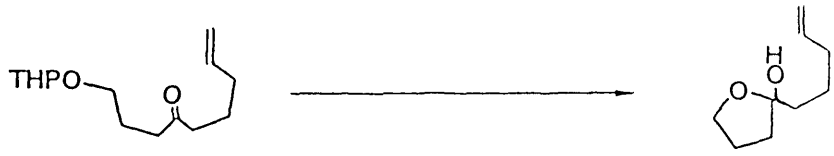


(13)

To a stirred solution of 4[(tetrahydro-2H-pyran-2-yl)oxy]butanal (12) (0.35 mg, 2.0 mmol) in ether (7 ml) at 0^oC under argon, was added a solution of pent-4-enylmagnesium bromide (2.0 mmol) in ether (5 ml).

After the addition, stirring was continued for 30 min at room temperature. Saturated ammonium chloride (7 ml) was added, and the mixture extracted with ether (3 x 5 ml). The organic extracts were dried and the solvent removed under reduced pressure, to give the crude alcohol which was added directly, as a solution in dichloromethane (2 ml) to Collins reagent[9] (12.0 mmol) in dichloromethane (7 ml) under argon. The reaction mixture was stirred at room temperature for 2 h, diluted with ether (10 ml) and the solution decanted off. The residue was extracted further with ether (5 x 5 ml) and the combined organics filtered through a pad of Florisil. Removal of the solvent under reduced pressure and chromatography on silica (50% ether- 50% petrol) gave *1-[(tetrahydro-2H-pyran-2-yl)oxy]8-nonen-4-one* (13) (0.46 g, 97%) as a colourless oil, ν_{max} (film) 2933, 1710, 1635, 1112, and 1028 cm^{-1}; δ(60 MHz) 6.17-4.70 (3H, m), 4.54-4.36 (1H, m), 4.02-3.12 (4H, m), and 2.36-1.13 (16H, m); *m/z* (no M^+), 155, 139, 97, 85, 84, and 41. (Found: C, 69.76; H, 10.19. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.07%)

(4) Preparation of 2-Hydroxy, 2-pent-4'-enyl tetrahydrofuran (15).



(13) (15)

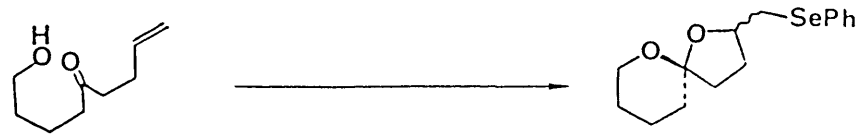
The tetrahydropyranyl derivative (13) (0.36 g, 1.5 mmol) was dissolved in methanol (3 ml) containing camphor sulphonic acid (CSA) (2 mg) and the resulting solution stirred at 50°C for 30 min. After cooling to room temperature, the reaction mixture was passed through a pad of silica (to remove the CSA) and the solvent evaporated to give crude hemiacetal (15)

(0.21 g, 90%) as a colourless oil, ν_{max} (film) 3410, 2950, 2389, 1635, and 913; δ(60 MHz) 6.00-4.69 (3H, m), 3.98-3.61 (2H, ≈t), and 2.53-1.28 (11H, m); *m/z* 156 (M^+), 71, 51, and 41.

General Procedure for the Selenium-mediated Cyclisation.

To a solution of the appropriate hydroxy keto alkene (1.0 mmol) and N-phenylselenophthalimide (N-PSP) (0.33 g, 1.1 mmol) in dry dichloromethane (3 ml) under argon at room temperature, was added anhydrous zinc (II) bromide (12 mg, 0.01 equiv.). The mixture was stirred for 1-2 h, diluted with petrol (4 ml), filtered (to remove precipitated phthalimide), washed with saturated aqueous sodium bicarbonate (1 ml) and dried. The solvent was removed under reduced pressure and the residue subjected to chromatography on silica (10% ether- 90% petrol) to afford the product.

(5) Cyclisation of 9-Hydroxy-1-nonen-5-one (9).

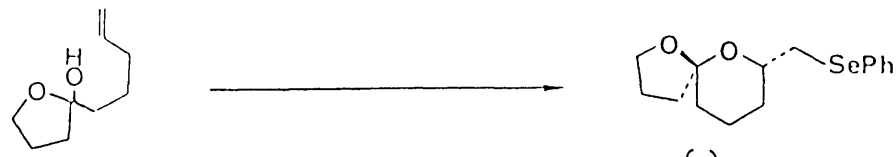


(9) (16)

Treatment of compound (9) (0.16 g, 1.0 mmol) with N-PSP and zinc (II) bromide gave *2-phenylselenomethyl-1,6-dioxaspiro[4.5]decane* (16) (0.25 g, 78%) as a colourless oil, and a 2:1 mixture of *trans*:*cis* isomers, ν_{max} ($CHCl_3$) 2920, 2875, and 984 cm^{-1}; δ(250 MHz) 7.54 (2H, m, Ar*H*), 7.24 (3H, m, Ar*H*), 4.40-3.52 (3H, m), 3.29 (0.3H, dd, J_{ax} 5.8, J_{ab} 11.7 Hz, H_a *cis*-isomer), 3.13 (0.3H, dd, J_{bx} 5.0, J_{ab} 11.7 Hz, H_b *cis*-isomer), 3.08 (0.7H, dd, J_{ax} 5.8, J_{ab} 11.7 Hz, H_a *trans*-isomer), 2.96 (0.7H, dd, J_{bx} 7.8, J_{ab}

11.7 Hz, H_b *trans*-isomer), and 2.24-1.48 (10H, m); *m/z* 312 (M^+, ^{80}Se), 141, and 85. (Found: C, 58.04; H, 6.60. $C_{15}H_{20}O_2Se$ requires C, 57.88; H, 6.48%)

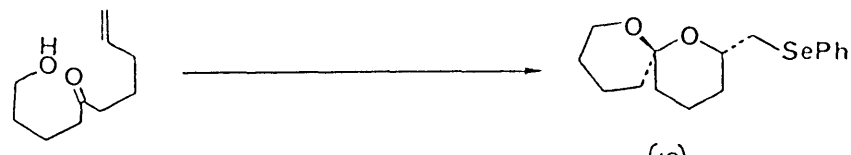
(6) Cyclisation of 2-Hydroxy, 2-pent-4-enyl tetrahydrofuran (15).



(15) (17)

Treatment of compound (15) (0.16 g, 1.0 mmol) with N-PSP and zinc (II) bromide gave *(E)-7-phenylselenomethyl-1,6-dioxaspiro[4.5]decane* (17) (0.26 g, 81%) as a colourless oil, ν_{max} ($CHCl_3$) 2936, 1574, and 1431 cm^{-1}; δ(250 MHz) 7.50 (2H, m, Ar*H*), 7.22 (3H, m, Ar*H*), 4.07-3.93 (1H, m, H_x), 3.92-3.34 (2H, m), 3.04 (1H, dd, J_{ax} 6.9, J_{ab} 12.0 Hz, H_a), 2.90 (1H, dd, J_{bx} 4.7, J_{ab} 12.0 Hz, H_b), and 2.09-1.59 (10H, m); *m/z* 312 (M^+,^{80}Se), 241, and 97. (Found: C, 57.95; H, 6.56. $C_{15}H_{20}O_2Se$ requires C, 57.88; H, 6.48%)

(7) Cyclisation of 1-Hydroxy-9-decen-5-one (11).



(11) (18)

Treatment of compound (11) (0.17 g, 1.0 mmol) with N-PSP and zinc (II) bromide gave *(E)-2-phenylselenomethyl-1,7-dioxaspiro[5.5]undecane* (18) (0.25 g, 77%) as a colourless oil, ν_{max} ($CHCl_3$) 2930 and 978 cm^{-1}; δ(250 MHz) 7.52 (2H, m, Ar*H*), 7.23 (3H, m, Ar*H*), 3.94-3.50 (3H, m), 3.12 (1H, dd,

J_{ax} 8.6, J_{ab} 12.2 Hz, H_a), 2.95 (1H, dd, J_{bx} 5.1, J_{ab} 12.2 Hz, H_b), and 1.89-1.21 (12H, m); *m/z* 326 (M^+, ^{80}Se), 155, and 111. (Found: C, 58.81; H, 6.81. $C_{16}H_{22}O_2Se$ requires C, 59.07; H, 6.82%).

General Procedure for Deselenation using Raney-nickel.

The phenylselenomethyl spiroacetals (1.0 mmol) were added to a stirred mixture of W4 Raney-nickel (5 wt. equiv.) in ether (2 ml) under a hydrogen atmosphere (maintained by a hydrogen filled balloon) at room temperature. After the reduction was complete (3-5 h), the mixture was filtered through a pad of silica and the solvent removed under reduced pressure to give the deselenated product. Generally further purification was not necessary.

(8) Deselenation of 2-Phenylselenomethyl-1,6-dioxaspiro[4.5]decane (16).

(16) (7)

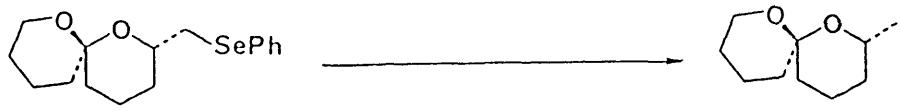
By the above general procedure, compound (16) (0.31 g, 1.0 mmol) after reduction, afforded 2-methyl-1,6-dioxaspiro[4.5]decane (7) (0.14 g, 90%) as a colourless oil, and a 1:2 mixture of *cis*:*trans* isomers, ν_{max} (film) 2929, 1435, and 1367 cm^{-1}; δ(250 MHz) 4.28-3.25 (3H, m), 2.20-1.40 (10H, m), 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.

(9) Deselenation of (E)-7-Phenylselenomethyl-1,6-dioxaspiro[4.5]decane (17).

(17) (6)

By the above general method, compound (17) (0.31 g, 1.0 mmol) after reduction afforded (E)-7-methyl-1,6-dioxaspiro[4.5]decane (6) (0.14 g, 92%) as a colourless oil, ν_{max} ($CHCl_3$) 2940 and 1050 cm^{-1}; 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.

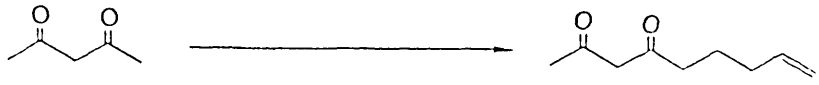
(10) Deselenation of (E)-2-Phenylselenomethyl-1,7-dioxaspiro[5.5]undecane (18).



(18) (19)

By the above general method, compound (18) (0.33 g, 1.0 mmol) after reduction, gave (E)-2-methyl-1,7-dioxaspiro[5.5]undecane (19) (0.15 g, 88%) as a colourless oil, ν_{max} (film) 2932 and 1058 cm^{-1}; δ(250 MHz) 3.79-3.50 (3H, m), 1.93-1.33 (12H, m), and 1.15 (3H, d, J 6.3 Hz, *Me*); *m/z* 170 (M^+), 155, and 101. (Found M^+ 170.1303, $C_{10}H_{18}O_2$ requires 170.1307), and was identical to the previously reported compound.

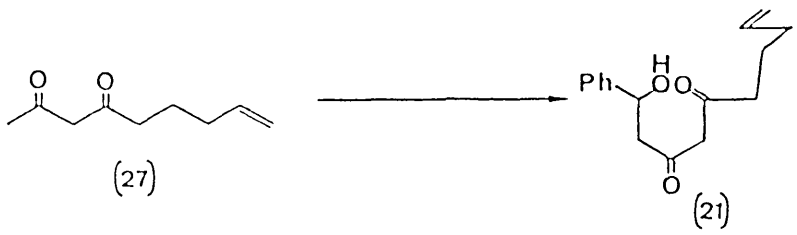
(11) Preparation of 8-Nonen-2,4-dione (27).



(27)

Pentane-2,5-dione (5.13 ml, 50.0 mmol) was added dropwise to a stirred solution of sodium hydride (2.4 g of a 50% dispersion in oil, washed twice with petrol and once with tetrahydrofuran, 50.0 mmol) in dry tetrahydrofuran (100 ml) at 0°C under argon. The resulting mixture was stirred for 10 min at 0°C, cooled to -20°C, and n-butyllithium (34.3 ml of a 1.46M solution in hexane, 50.0 mmol) was added, to form a pale yellow solution. After 30 min at -20°C, 1-bromo but-3-ene (6.75 g, 50.0 mmol) was added and the mixture stirred at 0°C for 3 h, then at room temperature for 2 h. The solution was then poured into saturated aqueous ammonium chloride (50 ml) and ether (50 ml). The layers were separated and the aqueous phase extracted with ether (2 x 50 ml). The combined organic extracts were dried, concentrated under reduced pressure, and the residue distilled to give 8-nonen-2,4-dione (27) (4.2 g, 55%) as a colourless oil, bp 67-68°C at 0.9 mmHg; ν_{max} (film) 3420, 2941, 1710, 1607, and 1421 cm^{-1}; δ(60 MHz) 6.04-4.71 (3.7H, m, including 5.38, s, enolic C*H*), 3.48 (0.6H, s, keto CH_2), and 2.48-1.48 (9.7H, m, including 2.01, s, *Me*); *m/z* 154 (M^+), 100, and 85.

(12) Preparation of 1-Hydroxy-1-phenyldec-9-en-3,5-dione (21).



(27) (21)

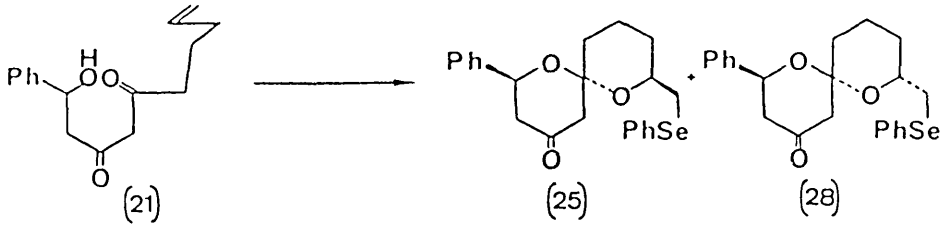
The dione (27) (0.2 g, 1.3 mmol) was added dropwise to a stirred solution of lithium diisopropylamide [from diisopropylamine (0.38 ml, 2.1 equiv.) and n-butyllithium (1.70 ml of a 1.61M solution in hexane, 2.1 equiv.) at $0^{o}C$] in dry tetrahydrofuran (5 ml) at $-78^{o}C$ under argon. The resulting solution was stirred at $-78^{o}C$ for 3 h, benzaldehyde (0.13 ml, 1.3 mmol) added, and the mixture allowed to warm to room temperature over 3 h. The solution was poured into saturated aqueous ammonium chloride (5 ml) and the layers separated. After extraction of the aqueous layer with ether (3 x 5 ml), the organic layers were dried and the solvent removed under reduced pressure, to give a residue which was subjected to chromatography on silica (20% ether- 80% petrol) giving 1-hydroxy-1-phenyldec-9-en-3,5-dione (21) (0.22 g, 65%) as a colourless oil, ν_{max} (film) 3402, 2917, 1709, and 1603 cm^{-1}; δ(60 MHz) 7.29 (5H, s, Ar*H*), 6.09-4.72 (4.7H, m, including 5.40, s, enolic C*H*), 3.47 (0.6H, s, keto CH_2), and 2.88-1.45 (9.7H, m); *m/z* 260 (M^+), 113, 107, and 85. (Found M^+ 260.1404, $C_{16}H_{20}O_3$ requires 260.1412).

General Procedure for the Cyclisation of 1-Hydroxy-1-phenyldec-9-en-3, 5-dione (21) using N-PSP and a Lewis acid.

To a solution of compound (21) (0.2 mmol) in dry dichloromethane (2 ml) containing N-PSP (66.2 mg, 0.2 mmol) at room temperature under argon, was

added the appropriate Lewis acid. The resulting mixture was stirred at room temperature until reaction was complete, diluted with petrol (2 ml) and filtered (to remove precipitated phthalimide). The solution was washed with saturated aqueous sodium bicarbonate (2 ml) and dried. Solvent was removed under reduced pressure to leave a residue which was subjected to chromatography to give the products.

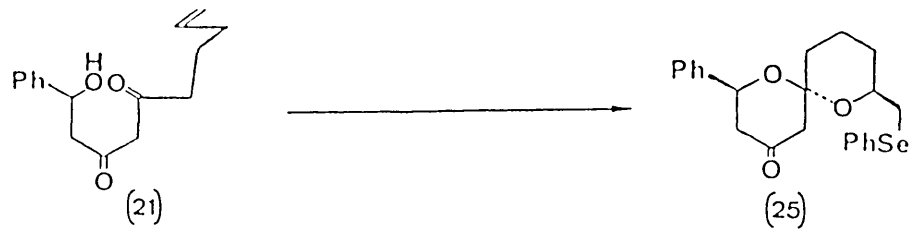
(13) Cyclisation using Zinc (II) Bromide as the Lewis acid.



(21) (25) (28)

According to the above general procedure, compound (21) was treated with N-PSP and zinc (II) bromide (0.1 equiv.), to give after 120 h at room temperature (±) *2(S)-phenyl,8(S)-phenylselenomethyl-1,7-dioxaspiro-[5.5]undecan-4-one* (25) (7 mg, 9%) as a colourless low melting solid, ν_{max} ($CHCl_3$) 2932, 1716, and 1190 cm^{-1}; δ(250 MHz) 7.50-7.17 (10H, m, Ar*H*), 5.09 (1H, dd, J 4.8 and 15.6 Hz, H_2), 4.83 (1H, m, H_8), 3.02 (1H, dd, J_{ax} 7.6, J_{ab} 12.9 Hz, CH_aH_bSePh), 2.89 (1H, dd, J_{bx} 4.5, J_{ab} 12.9 Hz, CH_aH_bSePh), 2.58 (4H, m), and 1.99-1.47 (6H, m); *m/z* 416 (M^+,^{80}Se), 155, and 111. (Found: C, 63.53; H, 5.78. $C_{22}H_{24}O_3Se$ requires C, 63.61; H, 5.82%); and (±) 2(S)-phenyl,8(R)-phenylselenomethyl-1,7-dioxaspiro[5.5]-undecan-4-one (28) (7 mg, 9%) as a colourless oil, ν_{max} (film) 2930, 1690, and 1130 cm^{-1}; δ(250 MHz) 7.68-7.14 (10H, m, Ar*H*), 5.33 (0.6H, dd, J 2.1 and 13.1 Hz, H_2 major conformer), 5.09 (0.4H, dd, J 2.1 and 16.9 Hz, H_2 minor conformer), 3.53-3.33 (1H, m, H_8), 3.21-2.10 (6H, m), and 1.87-1.00 (6H, m).

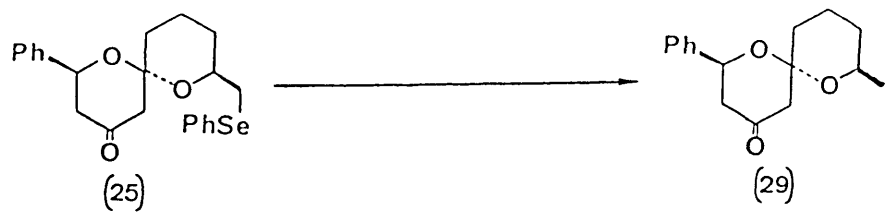
(14) Cyclisation using Tin (IV) Chloride as the Lewis acid.



(21) (25)

According to the above general procedure, compound (21) was treated with N-PSP and tin (IV) chloride (0.1 equiv.), to give after 96 h at room temperature (±) 2(S)-phenyl,8(S)-phenylselenomethyl-1,7-dioxaspiro[5.5]-undecan-4-one (25) (46 mg, 50%), identical with the previously prepared material.

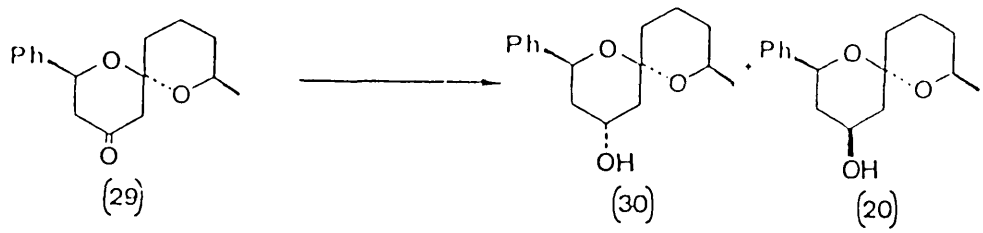
(15) Deselenation of (±) 2(S)-Phenyl,8(S)phenylselenomethyl-1,7-dioxaspiro[5.5]undecan-4-one (25).



(25) (29)

Compound (25) (0.46 g, 1.1 mmol) was deselenated using Raney-nickel as in the general procedure, to give (±) 8(R)-methyl,2(S)-phenyl-1,7-dioxaspiro[5.5]undecan-4-one (29) (0.27 g, 94%) as a colourless oil, ν_{max} (film) 2928 and 1720 cm^{-1}; δ(60 MHz) 7.32 (5H, m, Ar*H*), 4.84 (1H, dd, J 5.0 and 9.5 Hz, H_2), 3.64 (1H, m, H_8), 2.55 (4H, m), 2.29-1.23 (6H, m), and 1.12 (3H, d, J 6.0 Hz, *Me*); *m/z* 260 (M^+), 154, and 112. (Found M^+ 260.1417, $C_{16}H_{20}O_3$ requires 260.1412).

(16) Reduction of (±) 8(R)-Methyl,2(S)-phenyl-1,7-dioxaspiro[5.5]undecan-4-one (29).



(29) (30) (20)

To a solution of compound (29) (0.19 g, 0.73 mmol) in dry dimethoxyethane (20 ml) at 0°C under argon, was added sodium borohydride (30.5 mg, 0.80 mmol). The mixture was stirred at 0°C for 1 h, then poured into saturated aqueous sodium chloride solution (20 ml) and ether (50 ml). The layers were separated, the organics dried and evaporated. Chromatography on silica (20% ether- 80% petrol) gave (±) *4(S)-hydroxy,8(R)-methyl,2(S)-phenyl-1,7-dioxaspiro[5.5]undecane* (30) (61.4 mg, 32%) as a white crystalline solid, mp 63°C; ν_{max} ($CHCl_3$) 3500, 2930, and 1039 cm^{-1}; δ(250 MHz) 7.35 (5H, m, Ar*H*), 4.98 (1H, dd, J 2.5 and 12.0 Hz, H_2), 4.43 (1H, br. d, O*H*), 4.15 (1H, m, H_4), 3.84 (1H, m, H_8), 2.26-1.24 (10H, m), and 1.18 (3H, d, J 7.0 Hz, *Me*); *m/z* 262 (M^+), 244, and 122. (Found: C, 73.25; H, 8.40. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%); and (±) *4(R)-hydroxy,8(R)-methyl,2(S)-phenyl-1,7-dioxaspiro[5.5]undecane* (20) (0.12 g, 61%) as a colourless oil, ν_{max} (film) 3335, 2924, and 948 cm^{-1}; δ(250 MHz) 7.33 (5H, m, Ar*H*), 4.63 (1H, dd, J 2.2 and 11.8 Hz, H_2), 4.32 (1H, m, H_4), 3.74 (1H, m, H_8), 2.30-1.22 (11H, m), and 1.13 (3H, d, J 6.3 Hz, *Me*); *m/z* 262 (M^+), 244, and 156. (Found: C, 73.09; H, 8.69. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

General Procedure for the Sulphur-mediated Cyclisation.

To a solution of the appropriate hydroxy alkene (0.50 mmol) and N-phenylsulphenopyrrolidine (107 mg, 0.55 mmol), in dry dichloromethane (2 ml) under argon at room temperature, was added anhydrous zinc (II) bromide (113 mg, 1.0 equiv.). The mixture was stirred at room temperature for 2 h, poured into saturated aqueous sodium bicarbonate (2 ml) and extracted with ether (3 x 2 ml). The organic extracts were dried and evaporated, to give a residue which was subjected to chromatography on silica (5% ether- 95% petrol) to afford the product.

(17) Preparation of 2-Phenylsulphenomethyl tetrahydrofuran (32).

(32)

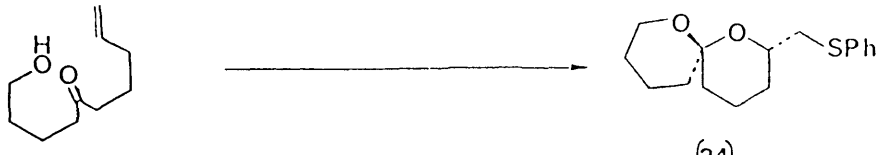
According to the above general procedure, 1-hydroxy pent-4-ene (36 mg, 0.42 mmol) was cyclised to give, after chromatography, *2-phenylsulphenomethyl tetrahydrofuran* (32) (71.7 mg, 88%) as a colourless oil, ν_{max} (film) 2940, 2850, 1475, 1045, and 735 cm^{-1}; δ(60 MHz) 7.60-6.80 (5H, m, Ar*H*), 4.20-3.50 (3H, m), 3.13 (1H, dd, J 6 and 12 Hz, CH_aH_bSPh), 2.83 (1H, dd, J 7 and 12 Hz, CH_aH_bSPh), and 2.25-1.40 (4H, m); *m/z* 194 (M^+), 124, 71, and 43. (Found: C, 68.01; H, 7.47. $C_{11}H_{14}OS$ requires C, 68.00; H, 7.26%).

(18) Preparation of (E)-7-Phenylsulphenomethyl-1,6-dioxaspiro[4.5]decane (33).

(15) (33)

Treatment of compound (15) (78 mg, 0.50 mmol) with N-phenylsulphenopyrrolidine and zinc (II) bromide according to the above general procedure, gave (E)-7-phenylsulphenomethyl-1,6-dioxaspiro[4.5]decane (33) (57 mg, 43%) as a colourless oil, ν_{max} (film) 2938 and 1008 cm^{-1}; δ(250 MHz) 7.38-7.11 (5H, m, Ar*H*), 4.03-3.80 (3H, m, including 3.98, t, J 6.9 Hz), 3.07 (1H, dd, J 6.9 and 13.2 Hz, CH_aH_bSPh), 2.91 (1H, dd, J 6.9 and 13.2 Hz, CH_aH_bSPh), and 2.08-1.59 (10H, m); *m/z* 264 (M^+), 141, 97, 55, and 41. (Found M^+ 264.1182, $C_{15}H_{20}O_2S$ requires 264.1184).

(19) Preparation of (E)-2-Phenylsulphenomethyl-1,7-dioxaspiro[5.5]undecane (34).

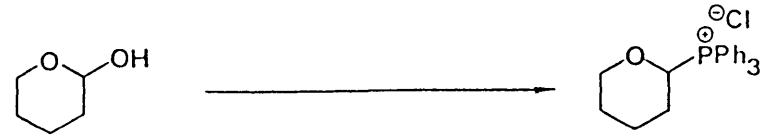


(11) (34)

Treatment of compound (11) (85 mg, 0.50 mmol) with N-phenylsulphenopyrrolidine and zinc (II) bromide according to the above general procedure, gave *(E)-2-phenylsulphenomethyl-1,7-dioxaspiro[5.5]undecane* (34) (64 mg, 46%) as a colourless oil, ν_{max} (film) 2932 and 1040 cm^{-1}; δ(250 MHz) 7.39-

7.11 (5H, m, Ar*H*), 3.90-3.68 (2H, m), 3.59-3.50 (1H, m), 3.12 (1H, dd, J 7.5 and 13.1 Hz, C*H*$_a$H$_b$SPh), 2.95 (1H, dd, J 5.0 and 13.1 Hz, CH$_a$*H*$_b$SPh), and 1.89-1.18 (12H, m); *m/z* 278 (M^+), 155, 111, 71, 55, and 41. (Found: C, 68.92; H, 8.14. $C_{16}H_{22}O_2S$ requires C, 69.03; H, 7.97%).

(20) Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (47)-Method A.



(47)

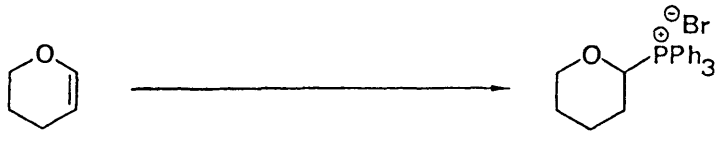
2-Hydroxytetrahydropyran (46) (128 mg, 1.27 mmol) was added dropwise to a solution of triphenylphosphine (334 mg, 1.27 mmol) in dry benzene (4 ml) at room temperature. Dry hydrogen chloride was bubbled through the resulting solution for 3 h, and the solvent removed to give a white solid, which could be semi-purified by recrystallisation from dichloromethane-ethyl acetate, to give tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (47) (413 mg, 85%) as a white amorphous solid, mp 113-116^{o}C; ν_{max} ($CHCl_3$) 3369, 1439, 1113, and 691 cm^{-1}; δ(90 MHz) 8.95 (≈3.5H, br.s, *impurity*), 8.00-7.55 (15H, m, Ar*H*), 6.15-5.85 (1H, m, H$_2$), 4.20-3.80 (2H, m, H$_6$), and 2.20-1.50 (6H, m); *m/z* (no M^+), 85.

(21) Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium chloride (47)-Method B.

(47)

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 (1000 ml), 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 triphenyl-phosphonium chloride (47) (158 g, 90%), identical to the material prepared earlier.

(22) Preparation of Tetrahydro-2H-pyran-2-yl triphenyl phosphonium bromide (48).



(48)

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 ml). 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 (48) (109 g, 80%) as a white crystalline solid, mp 173-175°C; ν_{max} ($CHCl_3$) 3396, 1438, 1112, and 692 cm^{-1}; δ(90 MHz) 8.15-7.60 (15H, m, Ar*H*), 6.65-5.40 (1H, m, H_2), 4.40-3.90 (2H, m, H_6), 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. $C_{23}H_{24}BrOP$ 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 triphenyl phosphonium salts with benzaldehyde.

The phosphonium salt (2.0 mmol) was dissolved in dry tetrahydrofuran (10 ml) at -10°C, under argon. n-Butyllithium (2.0 mmol) was added dropwise, and the mixture stirred at -10°C for 30 min to give a clear red solution. Benzaldehyde (0.2 ml, 2.0 mmol) in tetrahydrofuran (2 ml), was added, immediately quenching the red colouration. After warming to room temperature, the solution was poured into saturated aqueous sodium chloride (5 ml) and extracted with diethyl ether (3 x 10 ml). The ether extracts were dried and evaporated, and the crude residue distilled, to give the adduct.

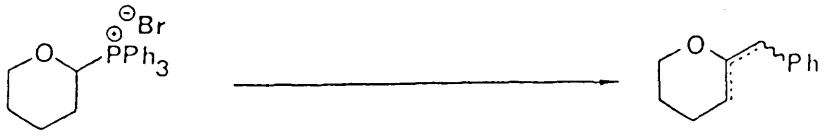
(23) Wittig reaction of the Phosphonium chloride (47) with Benzaldehyde.

(47) (50)

Phosphonium chloride (47) was reacted with benzaldehyde as in the

general procedure to give, after Kugelruhr distillation, the adduct (50) (84 mg, 24%) as a mixture of three olefin isomers, bp 110°C at 0.3 mmHg; ν_{max} (film) 2925, 1645, 1048, and 694 cm^{-1}; δ(60 MHz) 7.60-6.93 (5H, m, Ar*H*), 5.98 (0.5H, s, C=C*H*Ph E-isomer), 5.23 (0.25H, s, C=C*H*Ph Z-isomer), 4.41 (0.25H, t, J 4 Hz, C=C*H* endo-isomer), 3.87 (2H, m, OCH_2), 3.25 (0.5H, s, CH_2Ph endo-isomer), and 2.60-1.53 (5.5H, m) *m/z* 174 (M^+), 91, 90, 83, and 55. (Found: C, 82.66; H, 8.31. $C_{12}H_{14}O$ requires C, 82.72; H, 8.10%).

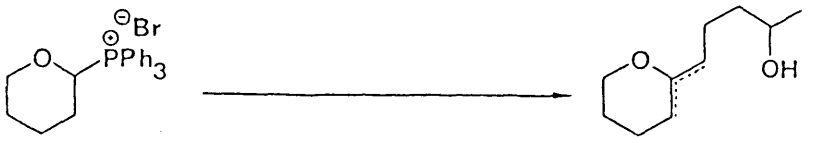
(24) Wittig reaction of the Phosphonium bromide (48) with Benzaldehyde.



(48) (50)

Phosphonium bromide (48) was reacted with benzaldehyde as in the above general procedure to give, after Kugelruhr distillation, the adduct (50) (108 mg, 31%) as the same mixture of isomers as obtained above.

(25) Wittig reaction of Phosphonium bromide (48) with Lactol anion (52).

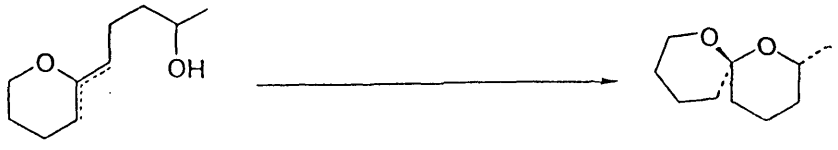


(48) (53)

Phosphonium salt (48) (2.10 g, 4.9 mmol) was dissolved in dry tetrahydrofuran (25 ml) and the resulting solution cooled to -10°C, under

argon. n-Butyllithium (4.05 ml of a 1.33M solution in hexane, 5.4 mmol) was added dropwise, rapidly generating the deep red phosphorane. After stirring at -10°C for 30 min, a solution of the lactol anion (52) [from 2-hydroxy,5-methyl tetrahydrofuran (0.50 g, 4.9 mmol) and n-butyllithium (4.05 ml, 5.4 mmol) at 0°C] in tetrahydrofuran (2 ml) was added slowly. The resulting mixture was warmed to room temperature over 1 h, and stirred for 5 h, before pouring into saturated aqueous sodium chloride (10 ml). Extraction with ether (3 x 15 ml) followed by drying of the organic layer and removal of the solvent under reduced pressure, gave the crude product. Kugelruhr distillation gave the adduct (53) (0.10 g, 12%) as a mixture of olefin isomers, bp 100°C at 0.005 mmHg; ν_{max} (film) 3400, 2928, 1625, and 1059 cm^{-1}; δ(60 MHz) 4.87 (0.3H, t, J 8 Hz, C=C*H* Z-isomer), 4.42 (0.7H, t, J 7 Hz, C=C*H* endo-isomer), 4.10-3.20 (3H, m), and 2.40-0.80 (14H, m); *m/z* 170 (M^+), 111, 98, 85, 55, 43, and 41. (Found M^+ 170.1305, $C_{10}H_{18}O_2$ requires 170.1307).

(26) Preparation of 2-Methyl-1,7-dioxaspiro[5.5]undecane (19).

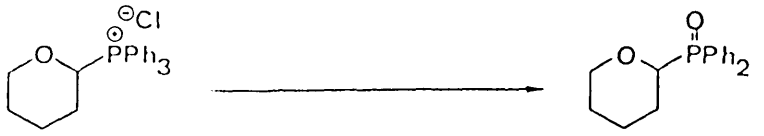


(53) (19)

The compound (53) (138 mg, 0.81 mmol) was dissolved in dry dichloromethane (2 ml) 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 (19) (113 mg, 82%) identical to the material prepared

earlier.

(27) Preparation of Tetrahydro-2H-pyran-2-yl diphenyl phosphine oxide (54).



(47) (54)

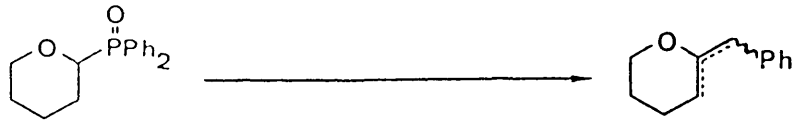
Phosphonium salt (47) (36.3 g, 94.9 mmol) was dissolved in 3N aqueous sodium hydroxide (180 ml, 540 mmol) and the resulting solution heated under reflux for 30 min. After cooling to room temperature, the mixture was extracted with chloroform (3 x 100 ml) and the organic extracts dried and evaporated, to give a solid. Recrystallisation from dichloromethane-ethyl acetate gave *tetrahydro-2H-pyran-2-yl diphenyl phosphine oxide* (54) (23.0 g, 85%) as a white crystalline solid, mp 154°C; $\nu_{max}(CHCl_3)$ 2939, 1437, 1183, and 696 cm^{-1}; δ(90 MHz) 8.10-7.70 (4H, m, Ar*H*), 7.60-7.20 (6H, m, Ar*H*), 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. $C_{17}H_{19}O_2P$ requires C, 71.32; H, 6.69; P, 10.82%).

General Procedure for the Horner-Wittig Reaction of Compound (54) with Aldehydes and Lactol anions.

A solution of the phosphine oxide (4.9 mmol) in dry tetrahydrofuran (20 ml) was added to a stirred solution of lithium diisopropylamide [from diisopropylamine (0.76 ml, 5.4 mmol) and n-butyllithium (5.4 mmol) at 0°C] in tetrahydrofuran (5 ml) at -100°C under argon. The resulting deep red

anion solution was diluted with ether (20 ml), and the aldehyde (or lactol anion) (4.9 mmol) in tetrahydrofuran (5 ml) added. After quenching of the anion colouration was complete, the mixture was warmed to room temperature and poured into saturated aqueous sodium chloride solution (20 ml). Extraction with chloroform (3 x 20 ml), drying of the organics, and evaporation of the solvent, gave the crude adduct. This was immediately dissolved in dry tetrahydrofuran (20 ml), and a solution of potassium t-butoxide (0.60 g, 5.4 mmol) in tetrahydrofuran (20 ml) was added dropwise. The resulting mixture was stirred at room temperature under argon for 1 h, the solvent removed, and the residue extracted with ether-petrol (5 x 10 ml of a 1:2 mixture). Evaporation of the extracts gave the crude product which was purified by Kugelruhr distillation.

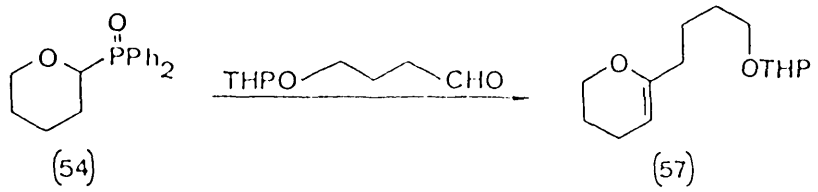
(28) Horner-Wittig Reaction of Compound (54) with Benzaldehyde.



(54) (50)

Using the above general procedure, compound (54) was condensed with benzaldehyde (0.50 ml, 4.9 mmol) at -100°C over 30 min. Treatment of the crude adduct with potassium t-butoxide gave after distillation, the adduct (50) (0.65 g, 76%) as a colourless oil, identical to that prepared earlier.

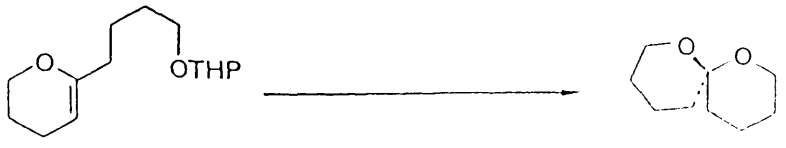
(29) Horner-Wittig Reaction of Compound (54) with 1-[(Tetrahydro-2H-pyran-2-yl)oxy]butanal (12).



(54) (57)

Using the above procedure, compound (54) was condensed with 1-[(tetrahydro-2H-pyran-2-yl)oxy]butanal (0.84 g, 4.9 mmol) at -100°C over 30 min. Treatment of the crude adduct with potassium t-butoxide followed by distillation gave *2-[4'-(tetrahydro-2H-pyran-2-yl)oxy butan]-5,6-dihydro-4H-pyran* (57) (0.73 g, 62%) as a colourless oil, bp 120°C at 0.04 mmHg; ν_{max} (film) 2938, 1675, 1114, and 1050 cm^{-1}; δ(250 MHz) 4.59 (1H, br.s, OC*H*O), 4.08 (1H, t, J 6.5 Hz, C=C*H*), 3.91-3.71 (4H, m), 3.57-3.37 (2H, m), 2.42 (1H, br.t), and 1.99-1.25 (15H, m); *m/z* 240 (M^+), 155, 101, 98, 85, and 55. (Found: C, 70.11; H, 10.17. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.07%).

(30) Preparation of 1,7-Dioxaspiro[5.5]undecane (58).



(57) (58)

Compound (57) (0.49 g, 2.0 mmol) was dissolved in methanol (3 ml) containing camphor sulphonic acid (2 mg), and the resulting solution was stirred at room temperature for 5 h. Removal of the solvent under reduced pressure followed by Kugelruhr distillation of the crude product gave 1,7-dioxaspiro[5.5]undecane (58) (0.29 g, 93%) as a colourless oil, bp

100°C at 28 mmHg (lit.[32] 193°C at 750 mmHg); ν_{max} (film) 2940, 1171, 1045, and 984 cm^{-1}: δ(250 MHz) 3.77-3.55 (4H, m, OCH_2), 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.

(31) Horner-Wittig Reaction of Compound (54) with Aldehyde (59).

(54) (60)

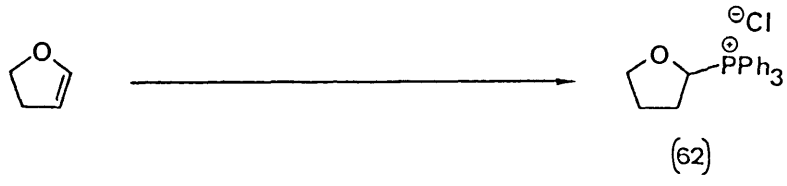
Using the general procedure, compound (54) (0.30 g, 1.05 mmol) was condensed with aldehyde (59) (0.15 g, 0.95 mmol) at -100°C over 30 min. Treatment of the crude adduct with potassium t-butoxide gave adduct (53) (0.14 g, 65%), which was added directly to a solution of camphor sulphonic acid (2 mg) in methanol. After stirring at room temperature for 6 h, the solvent was evaporated and the residue subjected to chromatography on silica (40% ether- 60% petrol) to give (E)-2-hydroxymethyl-1,7-dioxaspiro-[5.5]undecane (60) (70 mg, 61%) as a colourless oil, ν_{max} (film) 3430, 2930, 1045, and 990 cm^{-1}; 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.

(32) Horner-Wittig Reaction of Compound (54) with Lactol (51).

(54) (53)

Using the general procedure, compound (54) (1.40 g, 4.9 mmol) was condensed with the anion (52) [from lactol (51) (0.50 g, 4.9 mmol) and n-butyllithium (3.27 ml of a 1.5M solution in hexane, 4.9 mmol) at $0^{o}C$] by warming the reaction mixture to room temperature over 3 h, and stirring for a further 3 h. Treatment of the crude adduct with potassium t-butoxide followed by distillation of the crude material gave adduct (53) (0.56 g, 67%) identical to the previously prepared sample.

(33) Preparation of Tetrahydrofuran-2-yl triphenylphosphonium chloride (62).

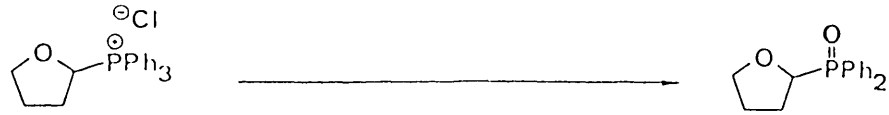


(62)

2,3-Dihydrofuran (20:0 g, 0.29 mol) was added dropwise to a solution of triphenylphosphine (74.9 g, 0.29 mol) in dry benzene (300 ml). Dry hydrogen chloride was bubbled through the resulting solution at room temperature for 3 h. The solvent was removed under reduced pressure to give a solid, which could be semi-purified by dissolving in dichloromethane and titration of the resulting solution with ethyl acetate giving tetrahydrofuran-2-yl triphenylphosphonium chloride (62) (94 g, 88%) as a

white amorphous solid, ν_{max} ($CHCl_3$) 3358, 1438, 1113, and 691 cm^{-1}; δ(90 MHz) 8.90-8.30 (≈1.5H, br.s, *impurity*), 8.00-7.50 (15H, m, Ar*H*), 6.50-6.15 (1H, m, H_2), 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.

(34) Preparation of Tetrahydrofuran-2-yl diphenylphosphine oxide (63).



(62) (63)

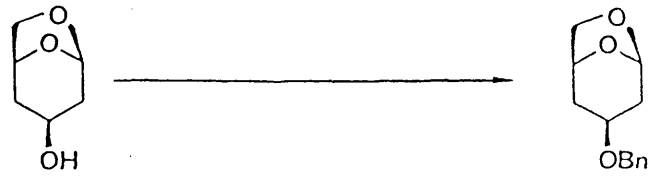
Phosphonium salt (62) (10.0 g, 27.1 mmol) was dissolved in 3N aqueous sodium hydroxide solution (60 ml, 180 mmol) and the resulting solution was heated at reflux for 30 min. After cooling to room temperature, the mixture was extracted with chloroform (3 x 50 ml) and the organic layers dried and evaporated to leave a solid. Recrystallisation from dichloromethane-ethyl acetate gave *tetrahydrofuran-2-yl diphenylphosphine oxide* (63) (6.1 g, 82%) as a white amorphous solid, mp 115°C; ν_{max} ($CHCl_3$) 1437, 1120, and 697 cm^{-1}; δ(90 MHz) 8.10-7.70 (4H, m, Ar*H*), 7.60-7.20 (6H, m, Ar*H*), 4.70 (1H, q, J 7 Hz, H_2), 4.00-3.50 (2H, m), and 2.45-1.50 (4H, m); *m/z* (no M^+), 202 (Ph_2POH), 155, 77, 71, and 43. (Found: C, 70.50; H, 6.31; P, 11.30. $C_{16}H_{17}O_2P$ requires C, 70.56; H, 6.29; P, 11.38%).

(35) Horner-Wittig Reaction of Compound (63) with Lactol (51).

(63) (6)

Using the standard procedure, compound (63) (3.09 g, 11.4 mmol) was condensed with the anion (52) [from lactol (51) (1.16 g, 11.4 mmol) and n-butyllithium (8.60 ml of a 1.45M solution in hexane, 12.5 mmol) at $0^{o}C$] by slowly warming the reaction mixture to room temperature over 15 h. Treatment of the crude adduct with potassium t-butoxide gave the coupled product (1.53 g, 86%). This material was immediately dissolved in dry dichloromethane (25 ml) containing camphor sulphonic acid (5 mg) and stirred at room temperature for 5 h. Removal of the solvent under reduced pressure followed by Kugelruhr distillation of the residue gave (E)-7-methyl-1,6-dioxaspiro[4.5]decane (6) (1.16 g, 76%) as a colourless oil, identical to the material prepared earlier.

(36) Preparation of (1S, 3S, 5R)-3-Benzyloxy-6,8-dioxabicyclo[3.2.1]octane (72).



(71) (72)

Alcohol (71) (1.0 g, 7.7 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred suspension of sodium hydride (0.36 g of a 57%

dispersion in oil, washed twice with petrol and once with tetrahydrofuran, 8.5 mmol) in dry tetrahydrofuran (25 ml) at room temperature under argon and the mixture stirred at room temperature for 30 min until clear. Benzyl bromide (0.9 ml, 7.7 mmol) was then added, followed by a solution of tetra-n-butylammonium iodide (5 mg) in tetrahydrofuran (0.1 ml) and the resulting solution stirred for 12 h. Water (25 ml) was added, and the mixture extracted with ether (3 x 25 ml). The organic extracts were dried and evaporated under reduced pressure to give, after chromatography on silica (20% ether- 80% petrol), *(1S, 3S, 5R)-3-benzyloxy-6,8-dioxabicyclo-[3.2.1]octane* (72) as a colourless solid, mp 36-37°C; $[\alpha]_D^{22}$ -60.3°; ν_{max} 2949, 1123, and 862 cm^{-1}; δ(60 MHz) 7.30 (5H, s, Ar*H*), 5.50 (1H, br.s, H_1), 4.50 (2H, s, CH_2Ph), 4.35 (2H, d, J 7 Hz, H_7), 3.65 (2H, m, H_3, H_5), and 2.40-1.50 (4H, m); *m/z* 202 ($M^+ - H_2O$), 163, 146, and 91. (Found: C, 70.67; H, 7.52. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%).

(37) Preparation of [4(S)-Benzyloxy, 6(S)-hydroxymethyl tetrahydropyran-2-yl]triphenylphosphonium tetrafluoroborate (74).

(72) (74)

Compound (72) (0.79 g, 3.6 mmol) was dissolved in dry acetonitrile (20 ml) containing triphenylphosphonium tetrafluoroborate (1.25 g, 3.6 mmol) and the resulting solution was stirred at room temperature under argon for 4 h. Removal of the solvent under reduced pressure gave *[4(S)-benzyloxy, 6(S)-hydroxymethyl tetrahydropyran-2-yl]triphenylphosphonium tetrafluoroborate* (74) (2.04 g, 100%) as a colourless glass, mp 68°C;

ν_{max} ($CHCl_3$) 1439, 1060, and 751 cm^{-1}; δ(90 MHz) 7.95-7.15 (20H, m, Ar*H*), 6.01-5.50 (1H, m, H_2), 4.70-3.30 (6H, m), 2.75 (1H, br.s, O*H*), and 2.40-1.10 (4H, m); *m/z* (FAB) 483 (M^+), 279, 263, 75, 57, and 45. (Found: C, 65.06; H, 5.73. $C_{31}H_{32}BF_4O_3P$ requires C, 65.28; H, 5.65%).

(38) Preparation of Tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate (76).

(76)

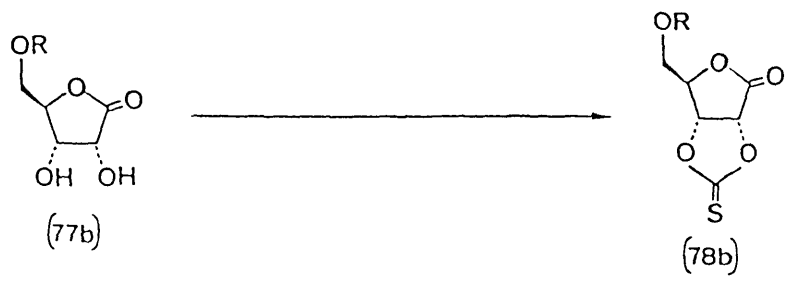
2-Methoxy tetrahydropyran (0.50 g, 4.3 mmol) was added dropwise to a solution of triphenylphosphonium tetrafluoroborate (1.50 g, 4.3 mmol) in dry acetonitrile (5 ml) at room temperature under argon, and the resulting solution was stirred for 4 h. Removal of the solvent under reduced pressure gave *tetrahydro-2H-pyran-2-yl triphenylphosphonium tetrafluoroborate* (76), (1.87 g, 100%) as a white crystalline solid, mp 171-173°C; ν_{max} ($CHCl_3$) 1321, 1056, and 690 cm^{-1}; δ(90 MHz) 7.76 (15H, m, Ar*H*), 5.61 (1H, m, H_2), 4.05 (2H, m, H_6), 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. $C_{23}H_{24}BF_4OP$ requires C, 63.62; H, 5.57; P, 7.13%).

(39) Wittig Reaction of Compound (76) with Benzaldehyde.

(76) (50)

Phosphonium salt (76) (0.87 g, 2.0 mmol) was suspended in dry tetrahydrofuran (10 ml) at -78°C under argon. n-Butyllithium (1.25 ml of a 1.60M solution in hexane, 2.0 mmol) was added and the mixture stirred at -78°C for 1 h, until a clear red solution was obtained. Benzaldehyde (0.20 ml, 2.0 mmol) in dry tetrahydrofuran (2 ml) was added dropwise, immediately quenching the reaction colour. The mixture was warmed to room temperature over 1 h, poured into saturated aqueous sodium chloride (5 ml) and extracted with ether (3 x 10 ml). The ether extracts were dried and evaporated to give a residue, which on Kugelruhr distillation gave the adduct (50) (0.28 g, 79%) as a colourless oil, identical to that prepared earlier.

(40) Preparation of 5-O-(t-Butyldiphenylsilyl)-2,3-O-(thiocarbonyl)-D-ribono-1,4-lactone (78b).

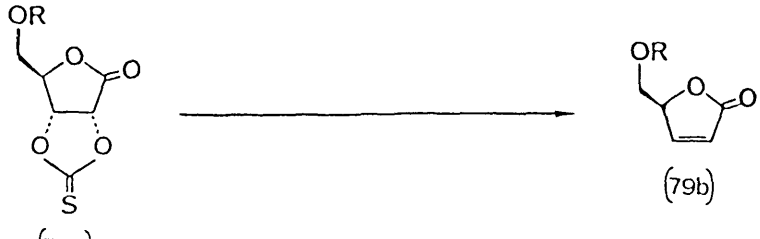


(77b) (78b)

Compound (77b)[51] (7.8 g, 20.2 mmol) was dissolved in dry acetone (1000 ml) containing thiocarbonyl diimidazole (5.0 g, 28.1 mmol) and the solution was

heated at reflux under argon for 4 h. After cooling, the mixture was concentrated to *ca* 750 ml, poured into water (750 ml) and extracted with dichloromethane (3 x 500 ml). The organic extracts were washed with saturated aqueous sodium bicarbonate solution (500 ml), dried, and the solvent removed under reduced pressure. The crude product was passed through a Florisil pad with ether, and the solvent evaporated to give *5-O-(t-butyldiphenylsilyl)-2,3-O-(thiocarbonyl)-D-ribono-1,4-lactone* (78b) (7.1 g, 82%) as a pale yellow solid, ν_{max} ($CHCl_3$) 1801, 1319, and 1113 cm^{-1}; δ(90 MHz) 7.75-7.30 (10H, m, Ar*H*), 5.42 (2H, s, H_2, H_3), 4.90 (1H, t, J 1.8 Hz, H_4), 4.00 (1H, dd, J 1.8 and 12.0 Hz, H_5), 3.78 (1H, dd, J 1.8 and 12.0 Hz, H_5), and 1.05 (9H, s, ^tBu); *m/z* 371 ($M^+ - {}^tBu$), 254, 199, 164, and 115. (Found: C, 61.39; H, 5.79. $C_{22}H_{24}O_5SSi$ requires C, 61.66; H, 5.64%).

(41) Preparation of 5-(t-Butyldiphenylsilyloxy), 4(S)-hydroxy-2-pentenoic Acid-1,4-lactone (79b).

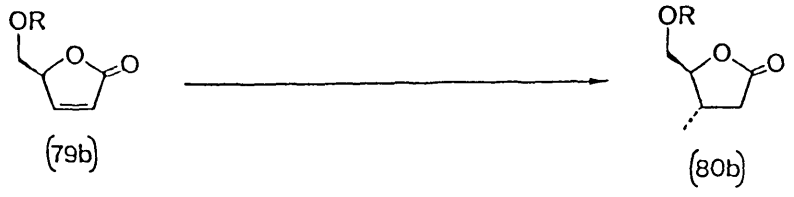


(78b) (79b)

Compound (78b) (7.1 g, 16.6 mmol) was dissolved in dry tetrahydrofuran (700 ml) containing Raney nickel (35 g, previously refluxed overnight in acetone) and the resulting mixture was stirred vigorously at reflux under argon for 16 h. After cooling to room temperature, the solution was filtered through a pad of silica and the solvent removed under reduced pressure. The residue was subjected to chromatography on silica (50% ether- 50% petrol) to give *5-(t-butyldiphenylsilyloxy), 4(S)-hydroxy-2-*

pentenoic acid-1,4-lactone (79b) (5.3 g, 91%) as a white solid, mp 78°C; $[\alpha]_D^{22}$ - 51.7°; ν_{max} ($CHCl_3$) 2932, 1751, 1101, and 706 cm^{-1}; δ(60 MHz) 7.77-7.23 (11H, m, Ar*H*, H_3), 6.09 (1H, dd, J 1.5 and 6.0 Hz, H_2), 5.00 (1H, m, H_4), 3.91 (2H, d, J 4.4 Hz, H_5), and 1.07 (9H, s, ^tBu); *m/z* 295 (M^+ - ^tBu), 199, 77, and 45. (Found: C, 71.47; H, 6.87. $C_{21}H_{24}O_3Si$ requires C, 71.55; H, 6.86%).

(42) Preparation of 5-(t-Butyldiphenylsilyloxy), 4(S)-hydroxy, 3(S)-methyl-pentanoic Acid-1,4-lactone (80b).

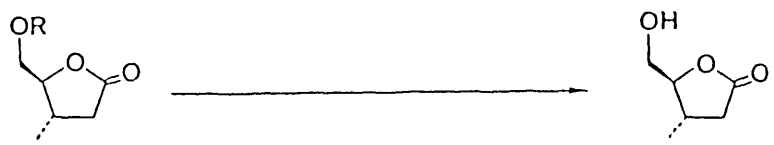


(79b) (80b)

Compound (79b) (4.0 g, 11.4 mmol) in dry ether (50 ml) was added dropwise to a stirred solution of dimethylcopper lithium [from methyllithium (90.7 ml of a 1.2M solution in ether, 108.8 mmol) and copper (I) bromide-dimethylsulphide complex (11.6 g, 56.4 mmol)] in ether (50 ml) at -30°C under argon, and the resulting mixture was stirred at -30°C for 12 h. Saturated aqueous ammonium chloride solution (50 ml) was added, followed by ether (100 ml). The organic layer was washed with saturated aqueous ammonium chloride (3 x 50 ml), dried, and evaporated under reduced pressure. Chromatography on silica (50% ether- 50% petrol) gave *5-(t-butyldiphenylsilyloxy), 4(S)-hydroxy, 3(S)-methyl-pentanoic acid-1,4-lactone* (80b) (3.9 g, 93%) as a colourless oil, $[\alpha]_D^{22}$ +23.7°; ν_{max} (film) 2931, 1782, 1113, and 703 cm^{-1}; δ(250 MHz) 7.66 (4H, m, Ar*H*), 7.42 (6H, m, Ar*H*), 4.11 (1H, dt, J 3.7 and 5.6 Hz, H_4), 3.87 (1H, dd, J 3.7 and 11.5 Hz, H_5), 3.71 (1H, dd, J 3.7 and 11.5 Hz, H_5), 2.82 (1H, dd, J 8.8 and 16.9 Hz, H_2), 2.59 (1H, m, H_3),

2.17 (1H, dd, J 6.9 and 16.9 Hz, H_2), 1.14 (3H, d, J 6.6 Hz, *Me*), and 1.06 (9H, s, ^{t}Bu); *m/z* 311 ($M^{+}-{}^{t}Bu$), 199, 111, 75, and 57. (Found: C, 71.49; H, 7.86. $C_{22}H_{28}O_3Si$ requires C, 71.70; H, 7.66%).

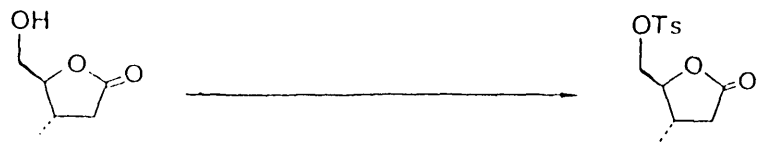
(43) Preparation of 4(S), 5-Dihydroxy, 3(S)-methyl-pentanoic Acid-1,4-lactone (81).



(80b) (81)

Tetra-n-butylammonium fluoride (11.9 ml of a 1M solution in tetrahydrofuran, 11.9 mmol) was added dropwise to a stirred solution of compound (80b) (4.0 g, 10.8 mmol) in dry tetrahydrofuran (150 ml) at room temperature under argon and the resulting solution was stirred for 30 min. Removal of the solvent under reduced pressure followed by chromatography of the residue on silica (30% ethylacetate- 70% petrol) and Kugelruhr distillation gave 4(S), 5-dihydroxy, 3(S)-methyl-pentanoic acid-1,4-lactone (81) (1.32 g, 93%) as a colourless oil, bp 135°C at 0.07 mmHg (lit.[40] bp 90°C at 0.01 mmHg); ν_{max} (film) 3550, 2948, 1790, 1113, and 1030 cm^{-1}; δ(60 MHz) 4.20-3.30 (4H, m, 1H D_2O exchangeable), 3.00-1.90 (3H, m), and 1.15 (3H, d, J 6 Hz, *Me*), and was identical to the reported material .

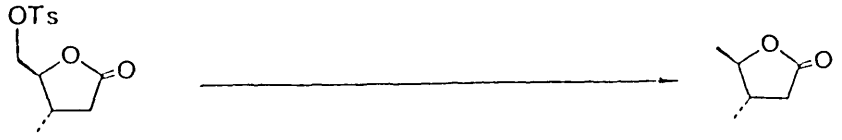
(44) Preparation of 4(S)-Hydroxy, 3(S)-methyl, 5-(tosyloxy)-pentanoic Acid-1,4-lactone (82).



(81) (82)

Compound (81) (1.22 g, 9.4 mmol) was dissolved in dry pyridine (15 ml) containing 4,4'-dimethylaminopyridine (10 mg) and the solution cooled to $0^{o}C$ under argon. Tosyl chloride (1.79 g 9.4 mmol) was added and the resulting mixture stirred at room temperature for 18 h, poured into ether (75 ml) and washed with 1N hydrochloric acid (5 x 25 ml). The organic layer was dried and the solvent removed under reduced pressure. Chromatography on silica (50% ether- 50% petrol) gave *4(S)-hydroxy, 3(S)-methyl, 5-(tosyloxy)-pentanoic acid-1,4-lactone* (82) (1.99 g, 75%) as a low melting solid, $[\alpha]_D^{22} + 43.2^{o}$; ν_{max} (film) 1785, 1361, 1177, and 663 cm^{-1}; δ(250 MHz) 7.75 (2H, m, Ar*H*), 7.34 (2H, m, Ar*H*), 4.21-4.05 (3H, m), 2.69 (1H, dd, J 9.0 and 17.1 Hz, H_2), 2.44 (1H, m, H_3), 2.42 (3H, s, Ar*Me*), 2.15 (1H, dd, J 8.2 and 17.1 Hz, H_2), and 1.12 (3H, d, J 7.1 Hz, *Me*); *m/z* 284 (M^+), 138, 99, 71, and 43. (Found: C, 54.84; H, 5.68. $C_{13}H_{16}O_5S$ requires C, 54.92; 5.67%).

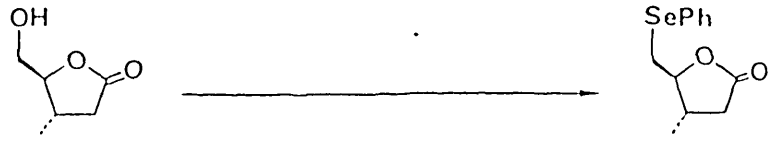
(45) Preparation of 4(R)-Hydroxy, 3(S)-methyl-pentanoic Acid-1,4-lactone (84).



(82) (84)

A solution of compound (82) (1.81 g, 6.4 mmol), tri-n-butyltin hydride (2.8 g, 9.6 mmol), sodium iodide (1.9 g, 12.7 mmol), and AIBN (10 mg), in dry dimethoxyethane (50 ml) was heated at 80°C for 1h under argon. After cooling to 0°C, carbon tetrachloride (35 ml) was added and the mixture stirred at room temperature for 2 h, poured into saturated aqueous potassium fluoride solution (20 ml), and filtered. The organic layer was washed with saturated aqueous potassium fluoride (2 x 20 ml), dried, and the solvent removed under reduced pressure. Chromatography on Florisil (petrol→ 50% ether- 50% petrol) followed by Kugelruhr distillation gave 4(R)-hydroxy, 3(S)-methyl-pentanoic acid-1,4-lactone (84) (0.40 g, 55%) as a colourless oil, bp 100°C at 10 mmHg; ν_{max} (film) 2972, 1781, 1225, 1180, and 1058 cm^{-1}; δ(250 MHz) 4.08 (1H, dq, J 6.3 and 7.3 Hz, H_4), 2.69-2.00 (2H, m, H_2), 1.82 (1H, m, H_3), 1.33 (3H, d, J 6.3 Hz, Me_4), and 1.07 (3H, d, J 6.8 Hz, Me_3); *m/z* 114 (M^+), 70, 55, 45, and 42.

(46) Preparation of 4(S)-Hydroxy, 3(S)-methyl, 5-(phenylseleno)-pentanoic Acid-1,4-lactone (83).



(81) (83)

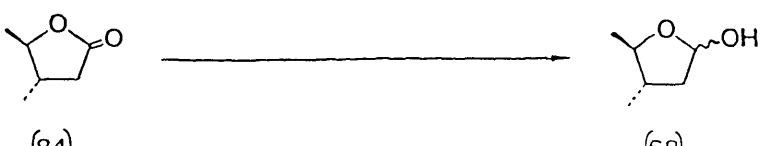
Compound (82) (344 mg, 2.6 mmol) was dissolved in dry tetrahydrofuran (15 ml) containing N-phenylselenophthalimide (1.60 g, 5.3 mmol) and the resulting solution was treated with tri-n-butylphosphine (1.44 ml, 5.3 mmol) at room temperature under argon. After stirring for 4 h at room temperature the solvent was removed under reduced pressure and the residue subjected to chromatography on silica (petrol→ 50% ether- 50% petrol) to give *4(S)-hydroxy, 3(S)-methyl, 5-(phenylseleno)-pentanoic acid-1,4-lactone* (83) (488 mg, 70%) as a low melting solid, $[\alpha]_D^{22} + 27.1^o$; ν_{max} (film) 2960, 1778, 1579, and 1175 cm^{-1}; δ(250 MHz) 7.53 (2H, m, Ar*H*), 7.28 (3H, m, Ar*H*), 4.23 (1H, q, J 5.9 Hz, H_4), 3.18 (1H, dd, J 5.9 and 13.1 Hz, H_5), 3.10 (1H, dd, J 5.9 and 13.1 Hz, H_5), 2.74 (1H, dd, J 8.1 and 17.3 Hz, H_2), 2.41 (1H, m, H_3), 2.20 (1H, dd, J 8.4 and 17.3 Hz, H_2), and 1.14 (3H, d, J 7.1 Hz, *Me*); *m/z* 270 (M^+, ^{80}Se), 99, 71, 43, 41, and 40. (Found: C, 53.55; H, 5.44. $C_{12}H_{14}O_2Se$ requires C, 53.54; H, 5.24%).

(47) Preparation of 4(R)-Hydroxy, 3(S)-methyl-pentanoic Acid-1,4-lactone (84).

(83) (84)

A solution of compound (83) (426 mg, 1.6 mmol), tri-n-butyltin hydride (550 μl, 2.0 mmol) and AIBN (3 mg) in dry dimethoxyethane (10 ml) was heated at 80°C under argon for 1 h. After cooling to 0°C, carbon tetrachloride (10 ml) was added and the mixture stirred at room temperature for 2 h, poured into saturated aqueous potassium fluoride solution (5 ml), and filtered. The organic layer was washed with saturated aqueous potassium fluoride (2 x 5 ml), dried, and the solvent removed under reduced pressure. Chromatography on Florisil (petrol→ 50% ether- 50% petrol) followed by Kugelruhr distillation gave 4(R)-hydroxy, 3(S)-methyl-pentanoic acid-1,4-lactone (84) (109 mg, 60%) as a colourless oil, identical to the previously prepared material.

(48) Preparation of 2-Hydroxy, 4(S), 5(R)-dimethyl-tetrahydrofuran (68).

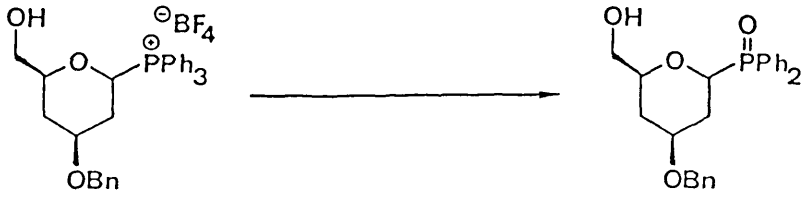


(84) (68)

Lactone (84) (0.40 g, 3.5 mmol) in dry toluene (2 ml) was added dropwise to a stirred solution of diisobutylaluminium hydride (3.50 ml of a 1.5M solution in toluene, 5.3 mmol) at -78°C under argon. The mixture was

stirred at -78°C for 3 h, then acetic acid (0.71 ml, 12.4 mmol) added dropwise over 30 min. After warming to room temperature, water (0.21 ml, 11.7 mmol) was added, followed by solid sodium bicarbonate (1.41 g, 16.8 mmol). The resulting alum was extracted with ethyl acetate (5 x 30 ml), and the extracts evaporated under reduced pressure. The crude product was passed through a Florisil pad with ether, then Kugelruhr distilled to give 2-hydroxy, 4(S), 5(R)-dimethyl-tetrahydrofuran (68) (0.22 g, 54%) as a colourless oil (mixture of anomers), bp 100°C at 4 mmHg, ν_{max} (film) 3410, 2964, 1104, and 995 cm^{-1}; δ(60 MHz) 5.67-5.37 (1H, m, H_2), 4.43 (1H, br.s, O*H*), 3.70 (1H, m, H_5), and 2.53-0.93 (9H, m).

(49) Preparation of [4(S)-Benzyloxy, 6(S)-hydroxymethyl tetrahydropyran-2-yl]diphenylphosphine oxide (86).



(74) (86)

Compound (74) (270 mg, 0.47 mmol) was dissolved in tetrahydrofuran (6 ml) containing tetra-n-butylammonium hydroxide (31 µl of a 1.54M solution in water, 0.05 mmol), and this mixture was added to 3N aqueous sodium hydroxide (2 ml). The resulting mixture was stirred vigorously at 50°C for 6 h, cooled, and extracted with chloroform (3 x 7 ml). The organic extracts were dried and the solvent removed under reduced pressure. Chromatography of the residue on silica (ethyl acetate) gave [4(S)-benzyloxy, 6(S)-hydroxymethyl tetrahydropyran-2-yl]diphenylphosphine oxide (86) (75 mg, 38%) as a white solid, ν_{max} ($CHCl_3$) 3363, 2920, 1588, and 1116 cm^{-1}; δ(250 MHz) 7.97-7.74 (4H, m, Ar*H*), 7.58-7.38 (6H, m, Ar*H*), 7.36-

7.20 (5H, m, Ar*H*), 4.51 (2H, m, C*H*$_2$Ph), 4.23 (1H, br.dd, J 7.9 and 11.8 Hz, H$_2$), 3.72-3.45 (4H, m), 2.70 (1H, br.s, O*H*), 2.45 (1H, br.d, J 10.6 Hz), 1.98 (1H, br.d, J 10.6 Hz), and 1.60-1.22 (2H, m).

(50) Preparation of 4(R)-Hydroxy, 3(S)-methyl-pentanal-1,3-dithiolane (87).

(68) (87)

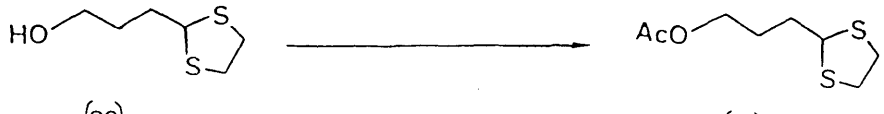
Compound (68) (171 mg, 1.47 mmol) was dissolved in dry dichloromethane (10 ml) containing 1,2-ethanedithiol (488 µl, 5.82 mmol) and the resulting solution cooled to -78^{o}C under argon. Titanium (IV) chloride (163 µl, 1.48 mmol) was added, and the mixture stirred for 1h, before warming to room temperature. Saturated aqueous ammonium chloride was added, and the mixture extracted with dichloromethane (3 x 10 ml). The organic extracts were dried and the solvent evaporated under reduced pressure. Chromatography on silica (20% ether- 80% petrol) gave *4(R)-hydroxy, 3(S)-methyl-pentanal-1,3-dithiolane* (87) (189 mg, 67%) as a colourless oil, $[\alpha]_D^{22}$ -35.8^o; ν_{max} (film) 3391, 2967, 2927, and 1096 cm^{-1}; δ(250 MHz) 4.55 (1H, dd, J 4.5 and 9.0 Hz, H$_1$), 3.61 (1H, m, H$_4$), 3.28-3.09 (4H, m, SC*H*$_2$C*H*$_2$S), 2.20-1.83 (2H, m, H$_3$, O*H*), 1.70-1.54 (2H, m, H$_2$), 1.09 (3H, d, J 6.1 Hz, *Me*$_4$), and 0.89 (3H, d, J 6.1 Hz, *Me*$_3$); *m/z* 192 (M^+), 118, 105, and 45. (Found: C, 49.72; H, 8.31. $C_8H_{16}OS_2$ requires C, 49.96; H, 8.38%).

(51) Preparation of 4-Hydroxy-butanal-1,3-dithiolane (89).

(88) (89)

2-Hydroxy-tetrahydrofuran (88) (5.35 g, 60.8 mmol) was dissolved in dry dichloromethane (50 ml) containing 1,2-ethanedithiol (20.1 ml, 245 mmol) and the resulting solution cooled to -78°C under argon. Titanium (IV) chloride (6.7 ml, 60.8 mmol) was added dropwise and the mixture stirred for 1 h, before warming to room temperature. Saturated aqueous ammonium chloride (50 ml) was added, and the mixture extracted with dichloromethane (3 x 50 ml). The organic extracts were dried and the solvent evaporated under reduced pressure. Chromatography on silica (20% ether- 80% petrol) gave 4-hydroxy-butanal-1,3-dithiolane (89) (7.55 g, 76%) as a colourless oil, ν_{max} (film) 3349, 2925, and 1055 cm^{-1}; δ(60 MHz) 4.38 (1H, t, J 6 Hz, H_1), 3.53 (2H, t, J 5 Hz, H_4), 3.18 (4H, s, SCH_2CH_2S), and 2.08-1.40 (5H, m); *m/z* 164 (M^+), 105, 71, 61, and 45.

(52) Preparation of 4-Acetoxy-butanal-1,3-dithiolane (90).



(89) (90)

Compound (89) (1.00 g, 6.1 mmol) was dissolved in dry pyridine (20 ml)

containing 4,4'-dimethylaminopyridine (5 mg), and the resulting solution cooled to $0^{o}C$ under argon. Acetyl chloride (0.65 ml, 9.1 mmol) was added dropwise and the mixture stirred at room temperature for 1 h, then poured into 3N aqueous hydrochloric acid (25 ml) and ether (100 ml). The organic layer was washed with 3N hydrochloric acid (3 x 50 ml), dried, and the solvent removed under reduced pressure. Chromatography of the residue on silica (20% ether- 80% petrol) gave *4-acetoxy-butanal-1,3-dithiolane* (90) (1.13 g, 90%) as a colourless oil, ν_{max} (film) 2924, 1734, 1240, and 1043 cm^{-1}; δ(60 MHz) 4.58-3.98 (3H, m, H_1, H_4), 3.20 (4H, s, SCH_2CH_2S), and 2.20-1.60 (7H, m, including 2.03, s, *Me*); *m/z* 206 (M^+), 118, 105, and 43. (Found: C, 46.65; H, 6.98. $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%).

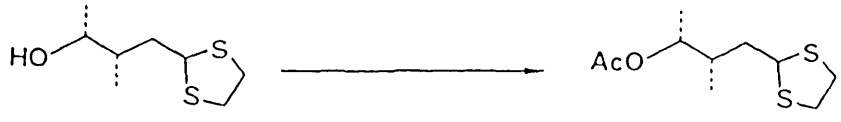
(53) Preparation of 4-Acetoxy-butanal (91).

(90) (91)

Compound (90) (340 mg, 1.65 mmol) in dry tetrahydrofuran (2 ml) was added dropwise to a stirred solution of thallium (III) trifluoroacetate (1.35 g, 2.48 mmol) in tetrahydrofuran (10 ml) at room temperature under argon. The resulting orange solution was stirred for 30 min, then saturated aqueous sodium bicarbonate solution (10 ml) was added. Extraction with ether (3 x 25 ml), followed by drying of the organic layers and evaporation of the solvent, gave the crude product. Chromatography on silica (50% ether- 50% petrol) gave 4-acetoxy-butanal (91) (150 mg, 70%) as a colourless oil, ν_{max} (film) 2962, 1737, 1241, and 1050 cm^{-1}; δ(60 MHz) 9.70 (1H, t, J 1 Hz, H_1), 4.06 (2H, t, J 7 Hz, H_4), and 3.50-1.70 (7H, m, including 2.03,

s, *Me*); *m/z* 87 (M^+ - *Ac*), 61, and 43.

(54) Preparation of 4(R)-Acetoxy, 3(S)-methyl-pentanal-1,3-dithiolane (92).



(87) (92)

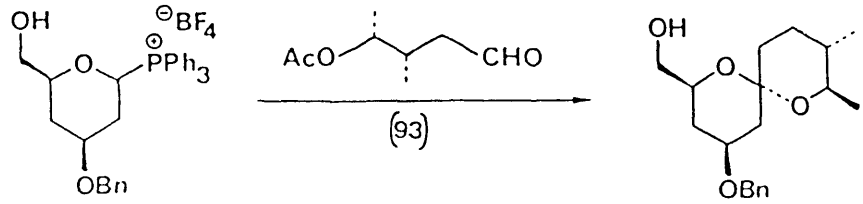
Compound (87) (190 mg, 0.99 mmol) was dissolved in dry pyridine (5 ml) containing 4,4'-dimethylaminopyridine (1 mg) and the resulting solution cooled to 0°C under argon. Acetyl chloride (211 µl, 2.97 mmol) was added and the mixture stirred at room temperature for 1 h, then poured into 3N hydrochloric acid (5 ml) and ether (25 ml). The organic layer was washed with 3N hydrochloric acid (3 x 10 ml), dried, and the solvent removed under reduced pressure. Chromatography of the residue on silica (10% ether- 90% petrol) gave *4(R)-acetoxy, 3(S)-methyl-pentanal-1,3-dithiolane* (92) (210 mg, 91%) as a colourless oil, $[\alpha]_D^{22}$ - 13.2°; ν_{max} (film) 2928, 1731, and 1245 cm^{-1}; δ(60 MHz) 5.02-4.37 (2H, m, H_1, H_4), 3.23 (4H, s, SCH_2CH_2S), 2.40-1.70 (6H, m, including 2.05, s, *Me*), 1.15 (3H, d J 6 Hz, Me_4), and 0.98 (3H, d, J 6 Hz, Me_3); *m/z* 175 (M^+ - *OAc*), 146, 118, 105, and 43. (Found: C, 51.22; H, 7.91. $C_{10}H_{18}O_2S_2$ requires C, 51.25; H, 7.74%).

(55) Preparation of 4(R)-Acetoxy, 3(S)-methyl-pentanal (93).

(92) (93)

Compound (92) (200 mg, 0.85 mmol) in dry tetrahydrofuran (1 ml) was added dropwise to a stirred solution of thallium (III) trifluoroacetate (690 mg, 1.27 mmol) in tetrahydrofuran (4 ml) at room temperature under argon. The resulting orange solution was stirred for 30 min, then saturated aqueous sodium bicarbonate solution (5 ml) added. Extraction with ether (3 x 10 ml), followed by drying of the organic layers and removal of the solvent under reduced pressure, gave the crude product. Chromatography on silica (30% ether- 70% petrol) gave 4(R)-acetoxy, 3(S)-methyl-pentanal (93) (101 mg, 75%) as a colourless oil, $[\alpha]_D^{22}$ - 18.3°; ν_{max} (film) 2980, 1721, 1374, 1244, and 1047 cm^{-1}; δ(60 MHz) 9.70 (1H, t, J 2 Hz, H_1), 4.57 (1H, m, H_4), 3.10-1.80 (6H, m, including 2.00, s, *Me*), 1.19 (3H, d, J 6 Hz, Me_4), and 0.98 (3H, d, J 7 Hz, Me_3).

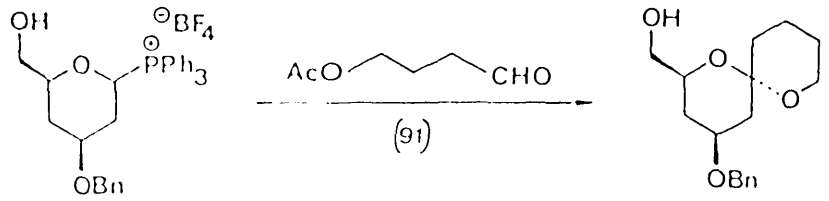
(56) Preparation of 4(S)-Benzyloxy, 2(S)-hydroxymethyl, 8(R), 9(S)-dimethyl-1,7-dioxaspiro[5.5]undecane (94).



(74) (93) (94)

n-Butyllithium (1.02 ml of a 1.24M solution in hexane, 1.26 mmol) was added dropwise to a stirred solution of phosphonium salt (74) (343 mg, 0.60 mmol) in dry tetrahydrofuran (10 ml) at -78°C under argon, to generate a deep red phosphorane. After 10 min at -78°C, aldehyde (93) (95 mg, 0.60 mmol) in tetrahydrofuran (1 ml) was added, and the mixture allowed to warm slowly to room temperature over 6 h. Water (5 ml) was added, and the mixture extracted with chloroform (3 x 20 ml). The extracts were dried, and the solvent removed under reduced pressure. The residue was dissolved in methanol (1 ml) and added to a solution of sodium methoxide (86 mg, 1.80 mmol) in methanol (1 ml) at room temperature. After stirring for 30 min, the reaction mixture was acidified with 3N hydrochloric acid, and stirred for a further 30 min. Water (5 ml) was added, and the mixture extracted with chloroform (3 x 10 ml). The organic extracts were dried, and the solvent removed under reduced pressure. Chromatography of the residue on silica (20% ether- 80% petrol) gave 4(S)-benzyloxy, 2(S)-hydroxymethyl, 8(R), 9(S)-dimethyl-1,7-dioxaspiro[5.5]undecane (94) (69 mg, 36%) as a colourless oil, $[\alpha]_D^{22}$ + 46.7°; ν_{max} (film) 3453, 2929, 2876, and 1076 cm^{-1}; δ(400 MHz) 7.35-7.25 (5H, m, Ar*H*), 4.56 (2H, d, J 1.0 Hz, CH_2Ph), 4.00 (1H, tt, J 4.7 and 11.0 Hz, H_4), 3.75-3.68 (1H, m, H_2), 3.67 (1H, dd, J 3.2 and 11.3 Hz, C*H*HOH), 3.59 (1H, dd, J 7.0 and 11.3 Hz, CH*H*OH), 3.30 (1H, dq, J 6.0 and 9.8 Hz, H_8), 2.16 (1H, ddd, J 1.7, 4.7, and 12.5 Hz, H_{5e}), 2.05 (1H, br.s, O*H*), 2.01 (1H, symmetrical m, 10 lines, J 1.7, 4.7, and 12.1 Hz, H_{3e}), 1.75-1.69 (1H, m, H_{11a}), 1.63-1.49 (3H, m, H_{10a}, H_{10e}, H_{11e}), 1.38 (1H, dd, J 11.0 and 12.5 Hz, H_{5a}), 1.30 (1H, dd, J 11.0 and 12.1 Hz, H_{3a}), 1.27 (1H, m, H_9), 1.13 (3H, d, J 6.0 Hz, *Me*$_8$), and 0.85 (3H, d, J 6.0 Hz, *Me*$_9$); *m/z* 320 (M^+), 289, 128, 91, and 70.

(57) Preparation of 4(S)-Benzyloxy, 2(S)-hydroxymethyl-1,7-dioxaspiro[5.5]-undecane (95).



(74) (95)

n-Butyllithium (1.47 ml of a 1.46M solution in hexane, 2.15 mmol) was added dropwise to a stirred solution of phosphonium salt (74) (585 mg, 1.03 mmol) in dry tetrahydrofuran (15 ml) at -78°C under argon, to generate a deep red phosphorane. After 10 min at -78°C, aldehyde (91) (133 mg, 1.02 mmol) in tetrahydrofuran (1 ml) was added and the mixture warmed slowly to room temperature over 6 h. Water (10 ml) was added and the mixture extracted with chloroform (3 x 40 ml). The extracts wre dried and the solvent removed under reduced pressure. The residue was dissolved in methanol (2 ml) and added dropwise to a solution of sodium methoxide (147 mg, 3.06 mmol) in methanol at room temperature. The resulting mixture was stirred at room temperature for 30 min, then acidified with 3N hydrochloric acid, and stirred for a further 30 min. Water (10 ml) was added and the mixture extracted with chloroform (3 x 40 ml). The organic extracts were dried and the solvent removed under reduced pressure. Chromatography of the residue on silica (50% ether- 50% petrol) gave *4(S)-benzyloxy, 2(S)-hydroxymethyl-1,7-dioxaspiro[5.5]undecane* (95) (119 mg, 40%) as a colourless oil, $[\alpha]_D^{22}$ + 57.1°; ν_{max} (film) 3458, 2940, 1072, and 993 cm^{-1}; δ(400 MHz) 7.36-7.24 (5H, m, Ar*H*), 5.55 (2H, s, CH_2Ph), 3.95 (1H, tt, J 4.7 and 11.0 Hz, H_4), 3.76 (1H, m, H_2), 3.70-3.53 (4H, m), 2.16 (1H, ddd, J 1.7, 4.7, and 12.5 Hz, H_{5e}), 2.08 (1H, br.s, O*H*), 1.99 (1H, symmetrical m, 10 lines, J 1.7, 4.7, and 12.0 Hz, H_{3e}), 1.85 (1H, m), 1.70 (1H, m), 1.66-

1.48 (4H, m), 1.36 (1H, dd, J 11.0 and 12.5 Hz, H_{5_α}), and 1.31 (1H, dd, J 11.0 and 12.0 Hz, H_{3_α}); *m/z* 292 (M^+), 261, 201, 186, 137, 101, and 91. (Found: C, 69.76; H, 8.49. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27%).

(58) Preparation of 5(S)-Hydroxy, 4(S)-methyl, 6-phenylseleno-hexanoic Acid-1,5-lactone (99).

(99)

4(S)-Methyl-hexenoic acid (9.0 g, 70.3 mmol) and tin (IV) chloride (7.0 ml of a 1M solution in dichloromethane, 7.0 mmol) were dissolved in dry dichloromethane (75 ml) under argon and the resulting solution was heated to reflux. N-Phenylselenophthalimide (23.4 g, 77.5 mmol) in dry dichloromethane (250 ml) was added at such a rate as to maintain reflux. The mixture was heated at reflux for 1.5 h, then cooled to room temperature and washed with 1N aqueous sodium hydroxide (3 x 75 ml). The organic layer was dried, and the solvent removed under reduced pressure to give a solid. Recrystallisation from dichloromethane-petrol gave *5(S)-hydroxy, 4(S)-methyl, 6-phenylseleno-hexanoic acid-1,5-lactone* (99) (15.5 g, 78%) as a white solid, mp 106°C; $[\alpha]_D^{22}$ + 62°; ν_{max} ($CHCl_3$) 2955, 1728, and 842 cm^{-1}; δ(250 MHz) 7.56 (2H, m, Ar*H*), 7.27 (3H, m, Ar*H*), 4.21 (1H, symmetrical m, 7 lines, J 3.4, 5.5, and 9.2 Hz, H_5), 3.29 (1H, dd, J 3.4 and 12.5 Hz, C*H*HSe), 3.15 (1H, dd, J 5.5 and 12.5 Hz, CH*H*Se), 2.62 (1H, ddd, J 4.5, 11.2, and 17.5 Hz, H_2), 2.49 (1H, ddd, J 6.7, 9.5, and 17.5 Hz, H_2), 2.08-1.83 (2H, m), 1.55 (1H, m), and 0.95 (3H, d, J 6.7 Hz, *Me*); *m/z* 284 (M^+,

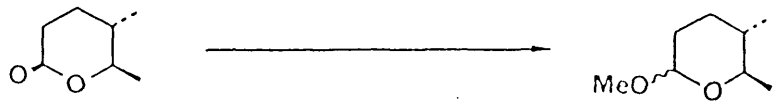
^{80}Se), 113, 85, 55, and 43. (Found: C, 54.88; H, 5.71. $C_{13}H_{16}O_2Se$ requires C, 55.13; H, 6.69%).

(59) Preparation of 5(R)-Hydroxy, 4(S)-methyl-hexanoic Acid-1,5-lactone (98).

(99) (98)

A solution of compound (99) (0.50 g, 1.8 mmol), tri-n-butyltin hydride (0.77 g, 2.7 mmol) and AIBN (8 mg) in dry dimethoxyethane (10 ml) was heated at 80°C under argon for 10 min, cooled to 0°C, and carbon tetrachloride (10 ml) added. After stirring at room temperature for 2 h, the mixture was poured into saturated aqueous potassium fluoride solution (5 ml) and filtered. The organic layer was washed with saturated aqueous potassium fluoride (2 x 5 ml), dried, and the solvent removed under reduced pressure. Chromatography on silica (petrol 50% ether- 50% petrol) gave 5(R)-hydroxy, 4(S)-methyl-hexanoic acid-1,5-lactone (98) (0.20 g, 87%) as a colourless oil, $[\alpha]_D^{22}$ + 12.6°; ν_{max} (film) 3550, 1785, and 1030 cm^{-1}; δ(250 MHz) 4.07 (1H, dq, J 6.0 and 9.5 Hz, H_5), 2.48 (1H, ddd, J 7.0, 9.5, and 17.5 Hz, H_2), 2.64 (1H, ddd, J 4.0, 7.0, and 17.5 Hz, H_2), 1.91 (1H, m, H_4), 1.75-1.44 (2H, m, H_3), 1.37 (3H, d, J 6.0 Hz, Me_5), and 1.01 (3H, d, J 6.0 Hz, Me_4), and was identical to the literature prepared material .

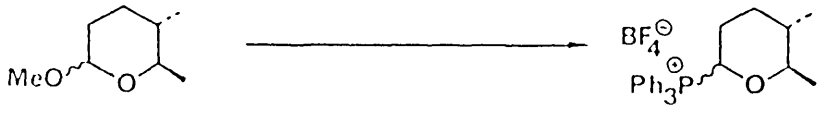
(60) Preparation of 5(S), 6(R)-Dimethyl, 2-methoxy-tetrahydropyran (103).



(98) (103)

Lactone (98) (461 mg, 3.6 mmol) in dry toluene (2 ml) was added dropwise to a stirred solution of diisobutylaluminium hydride (4.5 ml of a 1M solution in toluene, 4.5 mmol) at -78°C under argon. The mixture was stirred at -78°C for 3 h, then water (250 µl) added and the solution warmed to room temperature. Solid sodium bicarbonate (3.8 g) was added, and the resulting mixture extracted with ethyl acetate (5 x 10 ml). The extracts were filtered through a Florisl pad and the solvent removed under reduced pressure to give lactol (102) (440 mg, 94%). This was dissolved in methanol (10 ml) containing camphor sulphonic acid (5 mg) and the resulting solution stirred at room temperature under argon for 12 h. Removal of the solvent under reduced pressure and chromatography of the residue on silica (5% ether- 95% petrol) gave 5(S), 6(R)-dimethyl, 2-methoxy-tetrahydropyran (103) (420 mg, 86%) as a colourless oil, ν_{max} (film) 2932 and 1075 cm^{-1}; δ(250 MHz) 4.69 (1H, br.d, J 2 Hz, H_2), 3.45 (1H, dq, J 6.0 and 9.0 Hz, H_6), 3.35 (3H, s, O*Me*), 1.77-1.67 (2H, m), 1.56-1.42 (2H, m), 1.40-1.24 (1H, m), 1.16 (3H, d, J 6.0 Hz, Me_6), and 0.84 (3H, d, J 6.0 Hz, Me_5); *m/z* 144 (M^+), 113, 95, 69, 58, 56, 43, and 41.

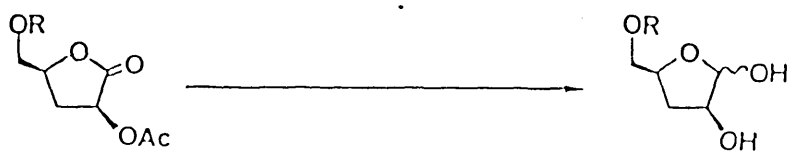
(61) Preparation of [5(S), 6(R)-Dimethyl-tetrahydropyran-2-yl]triphenly-phosphonium tetrafluoroborate (104).



(103) (104)

Compound (103) (103 mg, 0.72 mmol) was dissolved in dry acetonitrile (3 ml) containing triphenylphosphonium tetrafluoroborate (252 mg, 0.72 mmol) and the resulting mixture was stirred at room temperature under argon for 4 h. Removal of the solvent under reduced pressure at room temperature gave *[5(S), 6(R)-dimethyl-tetrahydropyran-2-yl]triphenyl-phosphonium tetrafluoroborate* (104) (333 mg, 100%) as a white amorphous solid (1:1 mixture of anomers), ν_{max} ($CHCl_3$) 2967, 1438, 1057, and 691 cm^{-1}; δ(90 MHz) 7.95-7.45 (15H, m, Ar*H*), 5.90-5.45 (1H, m, H_2), 3.95-3.45 (1H, m, H_6), 2.40-1.45 (5H, m), 1.42 (1.5H, d, J 6.9 Hz, Me_6 α-anomer), 1.18 (1.5H, d, J 6.4 Hz, Me_6 β-anomer), 0.92 (1.5H, d, J 6.9 Hz, Me_5 β-anomer), and 0.82 (1.5H, d, J 6.4 Hz, Me_5 α-anomer). (Found: C, 64.96; H, 5.94. $C_{25}H_{28}BF_4OP$ requires C, 64.96; H, 6.11%).

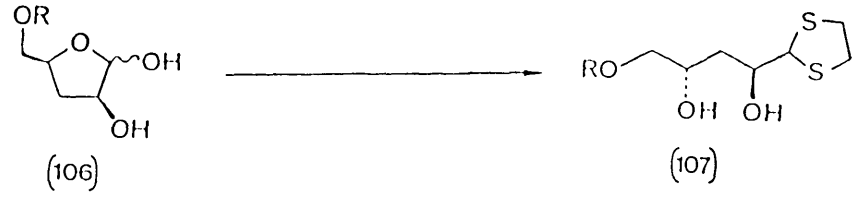
(62) Preparation of 4(S)-(t-Butyldiphenylsilyloxy), 2, 3(S)-dihydroxy-tetrahydrofuran (106).



(105) (106)

Compound (105)[51] (1.5 g, 3.6 mmol) in dry toluene (10 ml) was added dropwise to a solution of diisobutylaluminium hydride (12.0 ml of a 1M solution in toluene, 12.0 mmol) at -78°C under argon. The mixture was stirred at -78°C for 4 h, then acetic acid (3.3 ml, 57.7 mmol) added dropwise over 30 min. After warming to room temperature, water (1.0 ml, 55.6 mmol) was added followed by solid sodium bicarbonate (6.7 g, 79.8 mmol). The alum was extracted with ethyl acetate (5 x 50 ml) and the solvent removed under reduced pressure. Chromatography of the residue on Florisil (ether) gave 4(S)-(t-butyldiphenylsilyloxy)methyl, 2, 3(S)-dihydroxy-tetrahydrofuran (106) (0.82 g, 61%) as a colourless oil (mixture of anomers), ν_{max} (film) 3412, 2933, 1113, and 704 cm^{-1}; δ(250 MHz) 7.69 (4H, m, Ar*H*), 7.42 (6H, m, Ar*H*), 5.41 (0.7H, d, J 1.9 Hz, H_2 β-anomer), 5.18 (0.3H, dd, J 3.0 and 10.0 Hz, H_2 α-anomer), 4.45-3.39 (4H, m), 2.63-1.77 (4H, m, 2H D_2O exchangeable), 1.08 (6.3H, s, ^tBu β-anomer), and 1.05 (2.7H, s, ^tBu α-anomer); *m/z* (no M^+), 241, 199, 181, and 163.

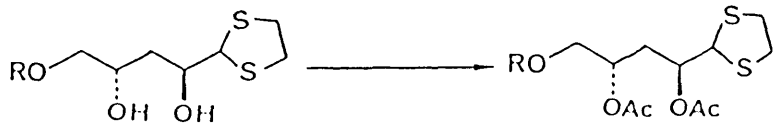
(63) Preparation of 5-(t-Butyldiphenylsilyloxy), 2(S), 4(S)-dihydroxypentanal-1,3-dithiolane (107).



(106) (107)

Compound (106) (1.1 g, 2.9 mmol) was dissolved in dry dichloromethane (25 ml) containing 1,2-ethanedithiol (0.96 ml, 11.5 mmol) and the resulting solution cooled to -78°C under argon. Titanium (IV) chloride (0.32 ml, 2.9 mmol) was added dropwise to the stirred solution and the mixture stirred at -78°C for 1 h, before warming to room temperature. Saturated aqueous ammonium chloride (20 ml) was added and the mixture extracted with dichloromethane (3 x 20 ml). The organic extracts were dried and the solvent removed under reduced pressure. Chromatography of the residue on silica (50% ether- 50% petrol) gave *5-(t-butyldiphenylsilyloxy), 2(S), 4(S)-dihydroxy-pentanal-1,3-dithiolane* (107) (1.22 g, 94%) as a colourless oil, $I\alpha I_D^{22}$ - 6.7°; ν_{max} (film) 3438, 2930, 1427, 1113, and 704 cm^{-1}; δ(250 MHz) 7.70 (4H, m, Ar*H*), 7.40 (6H, m, Ar*H*), 4.50 (1H, d, J 6.5 Hz, H_1), 4.11 (1H, m), 3.89 (1H, m), 3.73 (1H, dd, J 3.8 and 9.6 Hz, H_5), 3.61 (1H, dd, J 6.5 and 9.6 Hz, H_5), 3.56 (2H, br.s, O*H*), 3.30-3.00 (4H, m, SCH_2CH_2S), 1.84 (1H, m), 1.68 (1H, m), and 1.12 (9H, s, ^tBu); *m/z* 412 (M^+-^tBu), 241, 199, and 105. (Found: C, 60.50; H, 7.32. $C_{23}H_{32}S_2SiO_3$ requires C, 61.56; H, 7.19%).

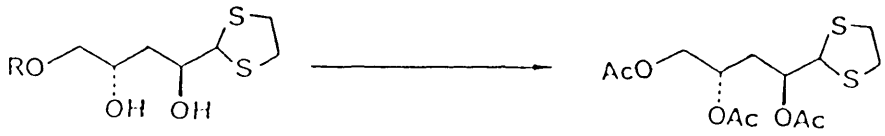
(64) Preparation of 2(S), 4(S)-Diacetoxy, 5-(t-butyldiphenylsilyloxy)-pentanal-1,3-dithiolane (108).



(107) (108)

Compound (107) (570 mg, 1.3 mmol) was dissolved in dry pyridine (20 ml) containing 4,4'-dimethylaminopyridine (5 mg) and the resulting solution was cooled to $0^{o}C$ under argon. Acetyl chloride (574 µl, 8.1 mmol) was added and the mixture stirred at room temperature for 12 h, poured into 3N hydrochloric acid (20 ml) and ether (100 ml). The organic layer was washed with 3N hydrochloric acid (3 x 30 ml), dried and the solvent removed under reduced pressure. Chromatography of the residue on silica (20% ether- 80% petrol) gave 2(S), 4(S)-diacetoxy, 5-(t-butyldiphenylsilyloxy)-pentanal-1,3-dithiolane (108) (347 mg, 53%) as a colourless oil, $[\alpha]_D^{22}$ - 13.8°; ν_{max} (film) 2929, 1744, 1238, and 1113 cm^{-1}; δ(250 MHz) 7.64 (4H, m, Ar*H*), 7.40 (6H, m, Ar*H*), 5.09-4.95 (2H, m, H_2, H_4), 4.57 (1H, d, J 6.8 Hz, H_1), 3.68 (2H, d, J 4.7 Hz, H_5), 3.31-3.12 (4H, m, SCH_2CH_2S), 2.22 (1H, m, H_3), 2.05 (3H, s, *Me*), 2.01 (3H, s, *Me*), 1.91 (1H, m, H_3), and 1.05 (9H, s, ^{t}Bu); *m/z* (no M^+), 475 ($M^+ - {}^{t}Bu$), 241, 199, 157, and 43.

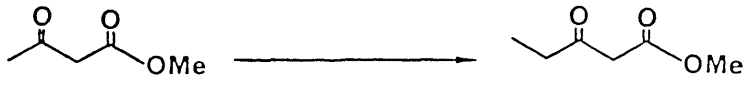
(65) Preparation of 2(S), 4(S), 5-Triacetoxy-pentanal-1,3-dithiolane (109).



(107) (109)

Compound (107) (200 mg, 0.47 mmol) was dissolved in dry tetrahydrofuran (10 ml) and the solution cooled to 0°C under argon. Acetic anhydride (2.23 ml, 23.58 mmol) was added, followed by tetra-n-butylammonium fluoride (9.43 ml of a 1M solution in tetrahydrofuran, 9.43 mmol). The resulting mixture was stirred at room temperature for 12 h, the solvent removed under reduced pressure, and the residue subjected to chromatography on silica (20% ether- 80% petrol) to give 2(S), 4(S), 5-triacetoxy-pentanal-1,3-dithiolane (109) (100 mg, 63%) as a colourless oil, ν_{max} (film) 2925, 1741, 1366, and 1223 cm^{-1}; δ(250 MHz) 5.10 (1H, m, H_4), 5.03 (1H, ddd, J 2.7, 6.8, and 10.2 Hz, H_2), 4.50 (1H, d, J 6.8 Hz, H_1), 4.27 (1H, dd, J 4.1 and 11.5 Hz, H_5), 4.01 (1H, dd, J 6.1 and 11.5 Hz, H_5), 3.32-3.14 (4H, m, SCH_2CH_2S), 2.17 (1H, ddd, J 2.7, 10.6, and 14.0 Hz, H_3), 2.08 (6H, s, *Me*), 2.05 (3H, s, *Me*), and 1.88 (1H, ddd, J 3.0, 10.2, and 14.0 Hz, H_3).

(66) Preparation of Methyl, 3-oxo-pentanoate (119).



(119)

Methyl acetoacetate (10.0 ml, 92.8 mmol) was added dropwise to a stirred suspension of sodium hydride (4.9 g of a 50% dispersion in oil, washed twice with petrol and once with tetrahydrofuran, 102.1 mmol) in dry tetrahydrofuran (150 ml) at $0^{o}C$ under argon. The resulting mixture was stirred at $0^{o}C$ for 10 min, before cooling to $-20^{o}C$, and formation of the pale yellow dianion with n-butyllithium (67.0 ml of a 1.52M solution in hexane, 101.8 mmol). After 5 min at $-20^{o}C$, methyl iodide (5.8 ml, 93.1 mmol) was added dropwise and the mixture warmed to room temperature, stirred for 3 h, then poured into saturated aqueous ammonium chloride (100 ml). Extraction with ether (3 x 100 ml) followed by drying of the organic layers and removal of the solvent under reduced pressure gave a residue which was distilled to give methyl, 3-oxo-pentanoate (119) (11.9 g. 99%) as a colourless oil, bp $75^{o}C$ at 10 mmHg; ν_{max}(film) 2972, 2939, 1741, and 1709 cm^{-1}; δ(60 MHz) 3.73 (3H, s, OMe), 3.45 (2H, s, H_2), 2.54 (2H, q, J 7 Hz, H_4), and 1.07 (3H, t, J 7 Hz, Me_4); *m/z* 130 (M^+), 101, 59, 57, and 43.

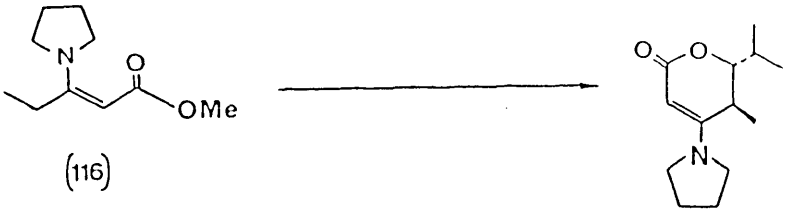
(67) Preparation of Methyl, 3-pyrrolidyl-pent-2-enoate (116).

(119) (116)

Compound (119) (10.0 g, 76.9 mmol) was dissolved in dry benzene (500 ml) containing camphor sulphonic acid (10 mg) to give a clear solution. Pyrrolidine (7.0 ml, 84.0 mmol) was added to the stirred solution at room temperature, and the mixture stirred for 96 h. The solvent was removed under reduced pressure and the crude product passed through a Florisil pad with ether (to remove the CSA). Evaporation of the solvent and distillation

of the residue gave *methyl, 3-pyrrolidyl-pent-2-enoate* (116) (13.8 g, 98%) as a pale yellow oil, bp 110°C at 0.001 mmHg; ν_{max} (film) 2972, 1680, and 789 cm^{-1}; δ(60 MHz) 4.30 (1H, s, H_2), 3.58 (3H, s, O*Me*), 3.25 (4H, m, CH_2NCH_2), 2.88 (2H, q, J 7 Hz, H_4), 1.92 (4H, m), and 1.15 (3H, t, J 7 Hz, Me_4); *m/z* 183 (M^+), 168, 152, 124, and 70. (Found: C, 65.59; H, 9.40; N, 7.64. $C_{10}H_{17}NO_2$ requires C, 65.54; H, 9.53; N, 7.64%).

(68) Preparation of (±) 4(S), 6-Dimethyl, 5(R)-hydroxy, 3-pyrrolidyl, 2-heptenoic Acid-1,5-lactone (121).

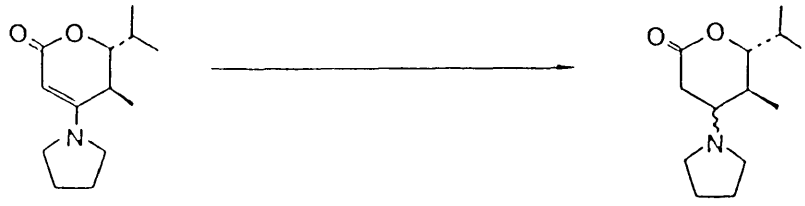


(116) (121)

Enamine (116) (10.0 g, 54.6 mmol) in dry tetrahydrofuran (60 ml) was added dropwise to a solution of lithium diisopropylamide [from diisopropylamine (8.5 ml, 60.8 mmol) and n-butyllithium (40.0 ml of a 1.52M solution in hexane, 60.8 mmol) at 0°C] in dry tetrahydrofuran (60 ml) at -78°C under argon, and the resulting solution stirred at -78°C for 30 min. Isobutyraldehyde (4.9 ml, 55.6 mmol) was added and the mixture warmed to room temperature over 1 h. After 30 min at room temperature, the reaction mixture was poured into saturated aqueous ammonium chloride (100 ml) and ether (50 ml), and the aqueous layer was extracted with ether (3 x 50 ml). The organic extracts were dried and the solvent removed under reduced pressure to give a solid. Recrystallisation from dichloromethane-petrol gave (±) *4(S), 6-dimethyl, 5(R)-hydroxy, 3-pyrrolidyl, 2-heptenoic acid-1,5-lactone* (121) (12.1 g, 99%) as a pale yellow crystalline solid, ν_{max} ($CHCl_3$) 1665 and 1583 cm^{-1}; δ(250 MHz) 4.40 (1H, s, H_2) 3.63 (1H, d, J 10.7

Hz, H_5), 3.38 (2H, m, NCH_2), 3.12 (2H, m, NCH_2), 2.57 (1H, q, J 7.0 Hz, H_4), 1.94 (5H, m), 1.25 (3H, d, J 7.0 Hz, Me_4), 0.98 (3H, d, J 7.0 Hz, Me_6), and 0.80 (3H, d, J 7.0 Hz, Me_6); *m/z* 223 (M^+), 152, 124, 85, and 83. (Found: C, 69.70; H, 9.59; N, 6.22. $C_{13}H_{21}NO_2$ requires C, 69.92; H, 9.48; N, 6.27%).

(69) Preparation of (±) 4(S), 6-Dimethyl, 5(R)-hydroxy, 3-pyrrolidyl-heptanoic Acid-1,5-lactone (122).

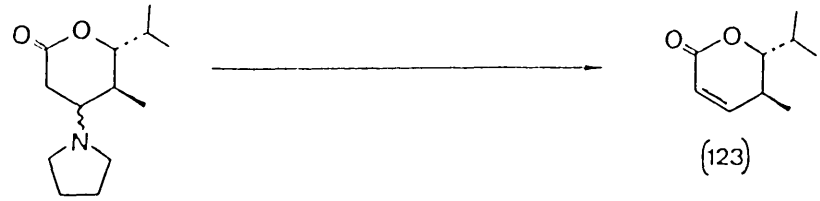


(121) (122)

Freshly cut lithium metal (0.3 g, 43.2 mmol) was added to a mixture of liquid ammonia (100 ml), dry tetrahydrofuran (15 ml), and t-butanol (1 ml), at -78°C under argon. After 15 min at -78°C, a solution of compound (121) (3.0 g, 13.5 mmol) in dry tetrahydrofuran (15 ml) was added to the deep blue solution. The resulting mixture was stirred at -78°C for 5 min, then warmed to room temperature, allowing the ammonia to evaporate off. Saturated aqueous ammonium chloride (50 ml) was added and the solution extracted with ethyl acetate (3 x 75 ml). The organic extracts were dried and the solvent removed under reduced pressure. The crude product could be purified by dissolving in 3N hydrochloric acid (50 ml), extracting with ether (3 x 50 ml), neutralising the aqueous layer with 3N sodium hydroxide solution, and extracting with ethyl acetate (3 x 50 ml). The ethyl acetate extracts were dried and evaporated to give (±) *4(S), 6-dimethyl, 5(R)-hydroxy, 3-pyrrolidyl-heptanoic acid-1,5-lactone* (122) (2.8 g, 92%) as a pale yellow oil (mixture of epimers at C-3), ν_{max} (film) 2940, 1730, and 1000 cm^{-1}; δ(250 MHz) 5.48 (0.5H, m, H_5 β-isomer), 4.71 (0.5H, dd, J 2.5

and 9.0 Hz, H_5 α-isomer), 3.83 (0.5H, dd, J 3.0 and 9.5 Hz, H_3), 3.75 (0.5H, dd, J 3.0 and 10.7 Hz, H_3), and 3.03-0.75 (21H, m); *m/z* 225 (M^+), 142, 97, 69, and 44. (Found: C, 69.58; H, 10.65; N, 6.01. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.29; N, 6.22%).

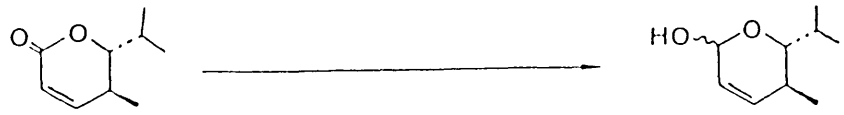
(70) Preparation of (±) 4(S), 6-Dimethyl, 5(R)-hydroxy-2-heptenoic Acid-1,5-lactone (123).



(122) (123)

m-Chloroperoxybenzoic acid (2.2 g, 12.7 mmol) was added in batches to a solution of compound (122) (1.5 g, 6.7 mmol) in dry toluene (15 ml) at 0°C under argon. The resulting mixture was stirred at 0°C for 30 min, then at room temperature for 24 h. Triethylamine (2.8 ml, 20.1 mmol) was added and the mixture heated at 100°C for 30 min. After cooling to room temperature, the solvent was removed under reduced pressure and the residue subjected to chromatography on silica (5% ether- 95% petrol) to give (±) 4(S), 6-dimethyl, 5(R)-hydroxy-2-heptenoic acid-1,5-lactone (123) (0.56 g, 54%) as a colourless oil, bp 80°C at 0.1 mmHg; ν_{max} (film) 2950, 1706, and 1230 cm^{-1}; δ(250 MHz) 6.65 (1H, dd, J 2.8 and 9.4 Hz, H_3), 5.94 (1H, dd, J 2.8 and 9.4 Hz, H_2), 4.92 (1H, dd, J 3.1 and 9.4 Hz, H_5), 2.59 (1H, m, H_4), 1.98 (1H, m, H_6), 1.10 (3H, d, J 6.9 Hz, Me_4), 1.08 (3H, d, J 6.3 Hz, Me_6), and 0.97 (3H, d, J 6.3 Hz, Me_6); *m/z* 153 ($M^+ - H$), 110, 82, and 70.

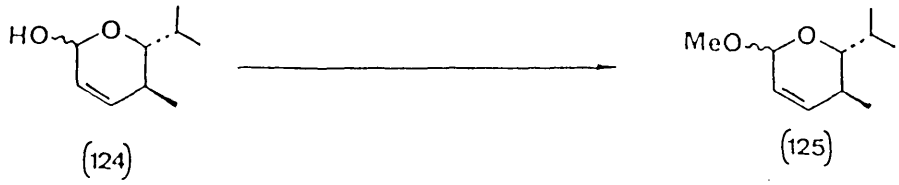
(71) Preparation of (±) 2-Hydroxy, 6(R)-isopropyl, 4(S)-methyl-5,6-dihydro-2H-pyran (124).



(123) (124)

Compound (123) (371 mg, 2.4 mmol) in dry toluene (2 ml) was added dropwise to a stirred solution of diisobutylaluminium hydride (3.6 ml of a 1M solution in toluene, 3.6 mmol) at -78°C under argon. The resulting solution was stirred at -78°C for 3 h, water (0.2 ml) added, and the mixture warmed to room temperature. Solid sodium bicarbonate (2.5 g) was added and the mixture thoroughly extracted with ethyl acetate (5 x 10 ml). Removal of the solvent under reduced pressure, followed by Kugelruhr distillation of the residue gave (±) 2-Hydroxy, 6(R)-isopropyl, 4(S)-methyl-5,6-dihydro-2H-pyran (124) (348 mg, 93%) as a colourless oil, bp 90°C at 0.1 mmHg; ν_{max} (film) 3380, 2958, 2873, and 1000 cm^{-1}; δ(250 MHz) 5.81-5.60 (2H, m, H_3, H_4), 5.36 (0.8H, br.s, H_2 β-anomer), 5.28 (0.2H, br.s, H_2 α-anomer), 3.41 (0.8H, dd, J 2.0 and 10.4 Hz, H_6 β-anomer), 3.13 (0.2H, dd, J 2.4 and 9.1 Hz, H_6 α-anomer), 2.22 (1H, m, H_5), 1.90 (1H, m, H_7), 1.01 (3H, d, J 7.5 Hz, Me_5), 0.91 (3H, d, J 6.9 Hz, Me_7), and 0.86 (3H, d, J 6.9 Hz, Me_7); *m/z* 139 ($M^+ - OH$), 55, 43, and 41.

(72) Preparation of (±) 6(R)-Isopropyl, 5(S)-methyl, 2(S)-methoxy-5,6-dihydro-2H-pyran (125).



(124) (125)

Compound (124) (203 mg, 1.3 mmol) was dissolved in methanol (3 ml) containing camphor sulphonic acid (2 mg) and the resulting solution was stirred overnight at room temperature. Removal of the solvent under reduced pressure gave the crude product which was passed through a silica pad with ether (to remove the CSA). Removal of the ether under reduced pressure gave (±) 6(R)-isopropyl, 5(S)-methyl, 2(S)-methoxy-5,6-dihydro-2H-pyran (125) (221 mg, 100%) as a colourless oil, δ(60 MHz) 5.66 (2H, br.s, H_3, H_4), 4.77 (1H, br.s, H_2), 3.50-3.10 (4H, m, including 3.33, s, O*Me*, H_6), and 2.50-0.70 (12H, m, including 1.07, d, J 6 Hz, Me_5, and 0.90, d, J 7 Hz, Me_7), this material decomposed on storage and so was used immediately.

(73) Preparation of (±) [6(R)-Isopropyl, 5(S)-methyl-5,6-dihydro-2H-pyran-2-yl]triphenylphosphonium tetrafluoroborate (126).

(125) (126)

Compound (125) (167 mg, 0.98 mmol) was dissolved in dry acetonitrile (3 ml) containing triphenylphosphonium tetrafluoroborate (344 mg, 0.98 mmol)

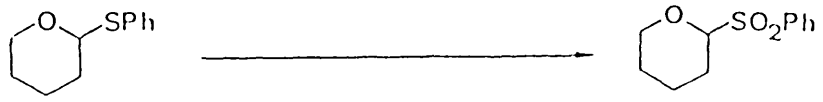
and the resulting solution was stirred at room temperature under argon for 6 h. Removal of the solvent under reduced pressure gave (±) *[6(R)-isopropyl, 5(S)-methyl-5,6-dihydro-2H-pyran-2-yl] triphenylphosphonium tetrafluoroborate* (126) (421 mg, 88%) as a pale yellow solid, mp 70-73°C; ν_{max} ($CHCl_3$) 2967, 1637, 1439, 1060, and 725 cm^{-1}; δ(90 MHz) 8.20-7.30 (15H, m, Ar*H*), 6.70-5.60 (3H, m, H_2, H_3, H_4), 3.35 (1H, m, H_6), and 3.00-0.45 (11H, m, including: 1.05, d, J 7.2 Hz, Me_5 major anomer; 0.92, d, J 7.2 Hz, Me_7 major anomer; 0.55, d, J 7.2 Hz, Me_7 major anomer). (Found: C, 66.55; H, 6.18. $C_{27}H_{30}BF_4OP$ requires C, 66.41; H, 6.19%).

(74) Preparation of 2-Phenylsulphenyl tetrahydropyran (131).

(131)

2,3-Dihydro-4H-pyran (5.4 g, 59.5 mmol) was added dropwise to a stirred solution of benzenethiol (6.1 g, 59.5 mmol) and camphor sulphonic acid (25 mg) in dry dichloromethane (100 ml) at 0°C under argon. The resulting solution was stirred at 0°C for 30 min, then at room temperature for 1 h. Removal of the solvent under reduced pressure gave a residue which was distilled to give 2-phenylsulphenyl tetrahydropyran (131) (11.5 g, 100%) as a colourless oil, bp 140°C at 3 mmHg; ν_{max} (film) 2940, 1437, 1035, and 742 cm^{-1}; δ(60 MHz) 7.55-7.00 (5H, m, Ar*H*), 5.13 (1H, br.dd, J 4 and 5 Hz, H_2), 4.35-3.80 (1H, m, H_6), 3.75-3.30 (1H, m, H_6), and 2.17-1.35 (6H, m); *m/z* 194 (M^+), 110, 85, 67, 57, 43, and 41.

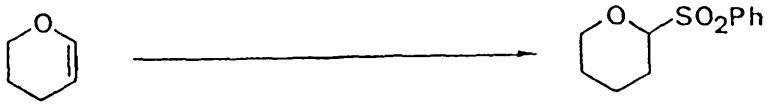
(75) Preparation of 2-Benzenesulphonyl tetrahydropyran (132):- Method 1.



(131) (132)

A solution of compound (131) (1.0 g, 5.2 mmol) in dichloromethane (10 ml) at $0^{o}C$ was treated with peroxyacetic acid (3.85 ml of a 3.95M solution in water, 15.2 mmol) buffered with sodium acetate (0.5 g, 6.1 mmol). The resulting mixture was stirred at $0^{o}C$ for 1 h, water (10 ml) added and the mixture extracted with dichloromethane (3 x 20 ml). The organic extracts were washed with 3N aqueous sodium hydroxide solution (10 ml), dried, and the solvent removed under reduced pressure. Chromatography of the residue on Florisil (30% ether- 70% petrol) gave *2-benzenesulphonyl tetrahydropyran* (132) (0.85 g, 72%) as a white crystalline solid, mp $78^{o}C$; ν_{max} ($CHCl_3$) 1315, 1150, 1084, 728, 692, and 608 cm^{-1}; δ(250 MHz) 7.91 (2H, m, Ar*H*), 7.58 (3H, m, Ar*H*), 4.39 (1H, dd, J 3.1 and 10.0 Hz, H_2), 4.11 (1H, m, H_6), 3.45 (1H, m, H_6), and 2.18-1.46 (6H, m); *m/z* 85 ($M^+ - SO_2Ph$), 84, 77, 55, 41, and 39. (Found: C, 58.24; H, 6.14; S, 14.41. $C_{11}H_{14}O_3S$ requires C, 58.39; H, 6.24; S, 14.17%).

(76) Preparation of 2-Benzenesulphonyl tetrahydropyran (132):- Method 2.



(132)

2,3-Dihydro-4H-pyran (1.11 g, 13.2 mmol) was added dropwise to a stirred solution of benzene sulphinic acid (1.88 g, 13.2 mmol) in dry dichloromethane (20 ml) at room temperature under argon. After stirring for 2 h at room temperature, the solvent was removed under reduced pressure, and the crude product recrystallised from ether-petrol to give 2-benzenesulphonyl tetrahydropyran (132) (2.45 g, 82%), identical to the material prepared above.

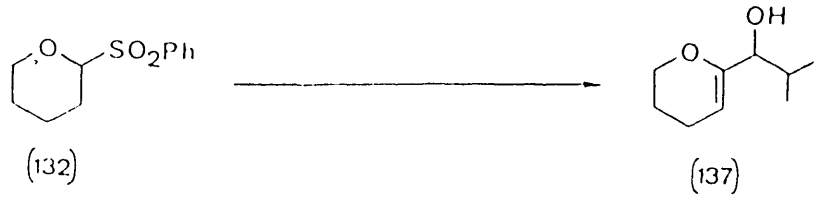
(77) Preparation of 2-Benzenesulphonyl tetrahydropyran (132):- Method 3.

(75) (132)

2-Methoxy tetrahydropyran (75) (1.54 g, 13.3 mmol) was added dropwise to a stirred mixture of benzene sulphinic acid (2.83 g, 19.9 mmol) and calcium chloride (4.36 g, 39.6 mmol), in dry dichloromethane (40 ml) at room temperature under argon. The resulting mixture was stirred at room temperature for 1 h, filtered, and the solvent removed under reduced pressure. Recrystallisation of the crude product from ether-petrol gave

2-benzenesulphonyl tetrahydropyran (132) (2.38 g, 79%) identical to the previously prepared material.

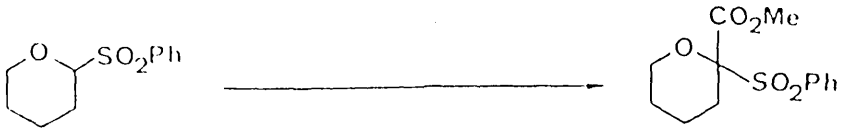
(78) Reaction of the anion of 2-Benzenesulphonyl tetrahydropyran (132) with Isobutyraldehyde.



(132) (137)

n-Butyllithium (1.53 ml of a 1.53M solution, 2.4 mmol) was added to a stirred solution of compound (132) (500 mg, 2.2 mmol) in dry tetrahydrofuran (10 ml) at -78°C under argon. The resulting pale yellow anion solution was stirred at -78°C for 10 min, then isobutyraldehyde (200 µl, 2.2 mmol) added. The mixture was warmed slowly to room temperature over 2 h, poured into saturated aqueous sodium bicarbonate (20 ml) and extracted with ether (3 x 30 ml). The organic extracts were dried and the solvent removed under reduced pressure, to give the crude adduct. Chromatography on Florisil (20% ether- 80% petrol) gave 2-(1'-hydroxy, 2'-methyl-propyl)-5,6-dihydro-4H-pyran (137) (260 mg, 77%) as a colourless oil, ν_{max} (film) 3454, 2958, 1675, and 1065 cm^{-1}; δ(90 MHz) 4.70 (1H, t, J 3.9 Hz, H_3), 4.00 (2H, t, J 5.1 Hz, H_6), 3.50 (1H, br.d, J 7.7 Hz, $H_{1'}$), 2.20-1.00 (6H, m); *m/z* 156 (M^+), 113, 73, 55, and 43.

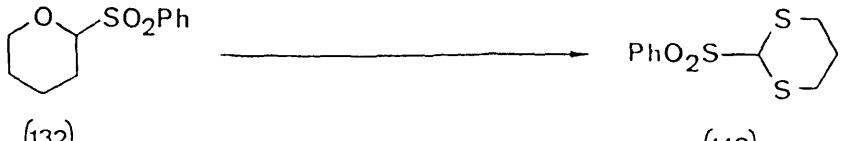
(79) Reaction of the anion of 2-Benzenesulphonyl tetrhydropyran (132) with Methyl chloroformate.



(132) (140)

n-Butyllithium (316 µl of a 1.5M solution in hexane, 0.47 mmol) was added dropwise to a stirred solution of compound (132) (100 mg, 0.44 mmol) in dry tetrahydrofuran (5 ml) at -78°C under argon. The resulting solution was stirred at -78°C for 10 min, then methyl chloroformate (34 µl, 0.44 mmol) was added and the mixture warmed slowly to room temperature over 1 h. Water (5 ml) was added and the mixture extracted with dichloromethane (3 x 5 ml). The organic extracts were dried and the solvent removed under reduced pressure to give a solid. Recrystallisation from dichloromethane-petrol gave *methyl(2'-benzenesulphonyl tetrahydropyran-2-yl)formate* (140) (105 mg, 84%) as a white crystalline solid, ν_{max} ($CHCl_3$) 1744, 1078, and 689 cm^{-1}; δ(60 MHz) 8.00-7.27 (5H, m, Ar*H*), 4.35-3.30 (5H, m, including 3.75, s, *Me*), and 2.70-1.20 (6H, m); *m/z* 141 (*SO_2Ph*), 125, 109, 77, and 59. (Found: C, 54.81; H, 5.65. $C_{13}H_{16}O_5S$ requires C, 54.91; H, 5.65%).

(80) Preparation of 2-Benzenesulphonyl-1,3-dithiane (142).



(132) (142)

n-Butyllithium (325 μl of a 1.5M solution in hexane, 0.49 mmol) was added dropwise to a stirred solution of compound (132) (100 mg, 0.44 mmol) in dry tetrahydrofuran (3 ml) at -78°C under argon. The resulting solution was warmed to room temperature, then added dropwise to a stirred suspension of 1,3-dithienium tetrafluoroborate (91 mg, 0.44 mmol) in tetrahydrofuran (2 ml) at -78°C. The resulting solution was warmed to room temperature over 30 min, poured into water (3 ml), and extracted with dichloromethane (3 x 5 ml). The organic extracts were dried and the solvent removed under reduced pressure to give a solid. Recrystallisation from ether-petrol gave *2-benzenesulphonyl-1,3-dithiane* (142) (105 mg, 92%) as a white solid, mp 168°C; ν_{max} ($CHCl_3$) 1302, 1138, and 868 cm^{-1}; δ(250 MHz) 7.95 (2H, m, Ar*H*), 7.70-7.50 (3H, m, Ar*H*), 4.38 (1H, s, H_2), 3.65 (2H, dt, J 10.4 and 13.5 Hz, H_3, H_5), 2.53 (2H, dt, J 3.8 and 13.5 Hz, H_3, H_5), 2.22 (1H, m, H_4), and 2.02 (1H, m, H_4); *m/z* 119 ($M^+ - SO_2Ph$), 77, and 45. (Found: C, 45.87; H, 4.67. $C_{10}H_{12}O_2S_2$ requires C, 46.13; H, 4.65%).

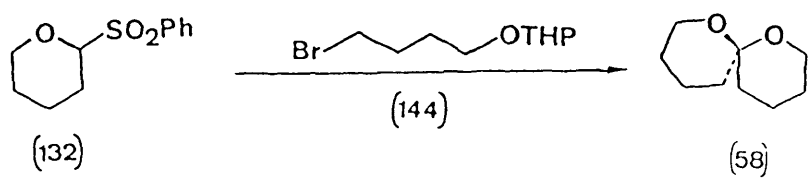
(81) Preparation of 4-Bromo, 1-[(tetrahydro-2H-pyran-2-yl)oxy]butane (144).

(144)

Dry tetrahydrofuran (633 μl, 7.8 mmol) was added dropwise to a stirred solution of boron tribromide (246 μl, 2.6 mmol) in dry dichloromethane (5 ml) at 0°C under argon. The resulting solution was heated at reflux for 1 h, cooled to room temperature, and the solvent removed under reduced pressure. The residue was dissolved in methanol (5 ml) and heated at reflux

for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure leaving 4-bromo butan-1-ol, which was added directly to a stirred solution of 2,3-dihydro-4H-pyran (710 µl, 7.8 mmol) and camphor sulphonic acid (5 mg) at room temperature. This mixture was stirred for 30 min, the solvent removed, and the residue subjected to chromatography on silica (10% ether- 90% petrol) to give 4-bromo, 1-[(tetrahydro-2H-pyran-2-yl)oxy]butane (144) (1.27 g, 69%) as a colourless oil, ν_{max} (film) 2942, 2870, and 1035 cm^{-1}; δ(60 MHz) 4.50 (1H, br.s, $H_{2'}$), 4.00-3.25 (6H, m), and 2.13-1.35 (10H, m); *m/z* 237 ($M^+ - H$, ^{81}Br), 137, 85, and 55.

(82) Preparation of 1,7-Dioxaspiro[5.5]undecane (58).



(132) (144) (58)

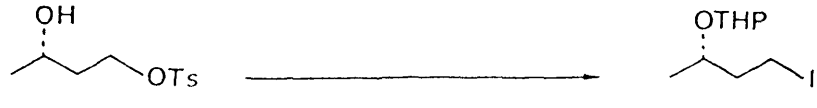
n-Butyllithium (1.62 ml of a 1.5M solution in hexane, 2.4 mmol) was added dropwise to a stirred solution of compound (132) (0.50 g, 2.2 mmol) in dry tetrahydrofuran (7 ml) at -78°C under argon. The resulting pale yellow anion solution was stirred at -78°C for 10 min, then bromide (144) (0.52 g, 2.2 mmol) added. The mixture was warmed slowly to room temperature over 4h, poured into water (10 ml). Extraction with ether (3 x 20 ml) followed by drying of the extracts, and removal of the solvent under reduced pressure gave the crude product. Kugelruhr distillation gave 1,7-dioxaspiro[5.5]undecane (58) (265 mg, 77%) as a colourless oil, identical to the material prepared earlier.

(83) Preparation of 3(S)-Hydroxy, 1-(tosyloxy)butane (145).

(145)

(S)-Butane-1,3-diol (2.0 g, 22 mmol) was dissolved in dry dichloromethane (25 ml) containing tosyl chloride (4.3 g, 23 mmol). The resulting solution was cooled to $0^{o}C$ under argon and pyridine (2.0 ml, 25 mmol) added dropwise. After stirring at room temperature for 12 h, the solution was poured into 1N hydrochloric acid (20 ml) and dichloromethane (25 ml). The organic layer was washed with 1N hydrochloric acid (3 x 20 ml), dried, and the solvent removed under reduced pressure. Chromatography of the residue on silica (50% ether- 50% petrol) gave 3(S)-hydroxy, 1-(tosyloxy)butane (145) (4.1 g, 76%) as a colourless oil, $[\alpha]_D^{22}$ + 10.7°; ν_{max} (film) 3405, 2970, 1354, 1176, and 663 cm^{-1}; δ(90 MHz) 7.80 (2H, m, Ar*H*), 7.35 (2H, m, Ar*H*), 4.40-3.60 (3H, m, H_1, H_3), 2.47 (3H, s, Ar*Me*), 2.00-1.50 (3H, m, H_2, O*H*), and 1.22 (3H, d, J 6.1 Hz, *Me*); *m/z* 244 (M^+), 172, 91, 72, and 43.

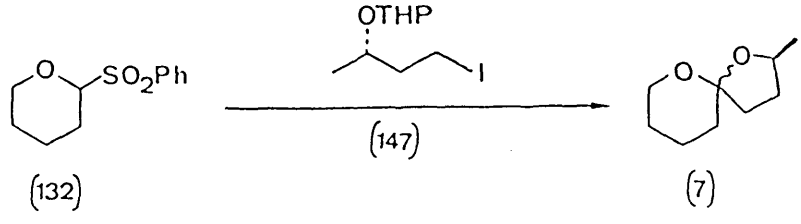
(84) Preparation of 1-Iodo, 3(S)-[(tetrahydro-2H-pyran-2-yl)oxy]butane (147).



(145) (147)

Compound (145) (4.0 g, 16.4 mmol) was dissolved in dry acetone (100 ml) containing sodium iodide (20 g, 133.3 mmol) and the resulting mixture was heated at reflux for 5 h under argon. The solvent was removed under reduced pressure and the residue dissolved in water (70 ml). Extraction of this mixture with ether (3 x 75 ml) followed by drying of the extracts and removal of the solvent under reduced pressure gave the crude 3(S)-hydroxy, 1-iodo butane (3.25 g, 99%). This material was dissolved in dry dichloromethane (30 ml) containing 2,3-dihydro-4H-pyran (1.63 ml, 17.8 mmol) and camphor sulphonic acid, and the resulting mixture stirred at room temperature for 30 min. Removal of the solvent under reduced pressure followed by chromatography of the residue on silica (2% ether- 98% petrol) gave *1-iodo, 3(S)-[(tetrahydro-2H-pyran-2-yl)oxy]butane* (147) (3.74 g, 81%) as a colourless oil (mixture of isomers at C-2'), $[\alpha]_D^{22}$ + 33.2°; ν_{max} (film) 2940 and 1033 cm^{-1}; δ(90 MHz) 4.57 (1H, br.s, $H_{2'}$), 4.10-3.40 (3H, m), 3.27 (2H, q, J 7.2 Hz, H_1), 2.20-1.40 (8H, m), 1.25 (1.2H, d, J 7.2 Hz, *Me* one diastereoisomer), and 1.12 (1.8H, J 6.1 Hz, *Me* one diastereoisomer); *m/z* 283 ($M^+ - H$), 183, 85, and 55. (Found: C, 38.08; H, 6.05. $C_9H_{17}IO_2$ requires C, 38.04; H, 6.03%).

(85) Preparation of 2(S)-Methyl-1,6-dioxaspiro[4.5]decane (7).



(132) (147) (7)

n-Butyllithium (7.9 ml of a 1.54M solution in hexane, 12.2 mmol) was added dropwise to a stirred solution of compound (132) (2.5 g, 11.1 mmol) in dry tetrahydrofuran (50 ml) at -78°C under argon. The resulting pale

yellow anion solution was stirred at -78°C for 10 min, then iodide (147) (3.1 g, 11.0 mmol) was added. The mixture was warmed to room temperature over 1 h, poured into water (30 ml), and extracted with ether (3 x 50 ml). The extracts were dried and the solvent removed under reduced pressure to give the crude product. Kugelruhr distillation gave 2(S)-methyl-1,6-dioxa-spiro[4.5]decane (7) (1.37 g, 79%) as a colourless oil (1:2 mixture of *cis*: *trans* isomers), bp 75° at 10 mmHg; $[\alpha]_D^{22}$ - 12.1°, and had identical spectra to the racemic material prepared earlier.

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PUBLICATIONS.

Synthesis of (*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid Involving the Use of an Organoselenium-mediated Cyclization Reaction

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A short stereospecific synthesis of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (1) has been achieved from readily available starting materials using a novel organoselenium-mediated cyclization of alkenyl-substituted β-oxoesters.

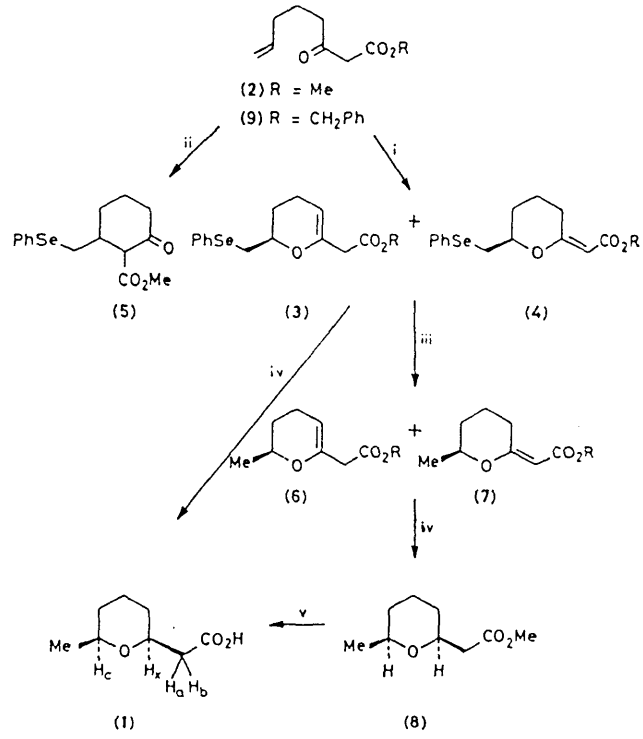
The use of organoselenium-mediated cyclizations to construct both hetero[1]- and carbo[2]-cyclic ring systems is now well recognised. Here we show how methodology developed in our laboratories[3] can be used efficiently to synthesise (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (1), a natural product recently isolated from *Viverra civetta*.[4]

The readily available alkenyl-substituted β-oxoester[5] (2) reacts at room temperature with *N*-phenylselenophthalimide (NPSP),[6] and trace amounts (0.01 equiv.) of tin tetrachloride to give a 9:1 mixture of compounds (3, R=Me) and (4, R=Me) in 84% combined yield. This mixture can be used directly in the next reaction; however, if conventional flash chromatography is used to purify the products, (4) is seen to rearrange to (3) which can be isolated in a pure form.† Treatment of (2) with NPSP and greater quantities of $SnCl_4$ (1 equiv.) results in the rapid formation of the carbocyclic product (5) in 83% yield.

Reduction of (3) and (4) with tri-n-butyltin hydride[7] proceeds well, without ring opening, to give (6, R=Me) and (7, R=Me) in 64% yield. Upon similar treatment, pure (3) gave (6) in comparable yield.

Hydrogenation of (6) and (7) using Raney-nickel as a catalyst gave a single compound shown to be methyl (*cis*-6-methyltetrahydropyran-2-yl)acetate (8) in 71% yield. This ester was identical with the previously synthesised material.[4] Hydrolysis of (8) gave a 92% yield of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (1)[4,8] [m.p. 51—52 °C; ^{1}H n.m.r. δ 10.1 (1H, br.s, CO_2H), 3.84—3.72 (1H, m, H_x), 3.53 (1H, m, H_c), 2.9 (1H, q, H_b, J_{ab} 15, J_{bx} 7.5 Hz), 2.48 (1H, q, H_a, J_{ab} 15 Hz), 1.9—1.15 (6H, m), and 1.19 (3H, d, *J* 6.3 Hz)].

In an effort to simplify this route further we chose to combine the two reduction steps with a final deprotection reaction.



Scheme 1. *Reagents and conditions:* i, NPSP–$SnCl_4$ (1.1:0.01), room temp., CH_2Cl_2, 2 h; ii, NPSP–$SnCl_4$ (1.1:1.0), room temp., CH_2Cl_2, 30 min; iii, Bu^n_3SnH, azoisobutyronitrile, toluene, heat, 1 h; iv, H_2–Raney-nickel, 100 atm, EtOH, 60 °C, 20 h; v, 10% NaOH, MeOH–H_2O, heat, 15 min.

Thus, when the benzyl-substituted compound (9) was treated with NPSP–$SnCl_4$ (1.1:0.01 equiv.) as before, a 4:1 mixture of (3, R=CH_2Ph) and (4, R=CH_2Ph) was obtained in 57%

† All new compounds were fully characterised by spectroscopic and microanalytical methods.

yield. This mixture, on reduction with H_2–Raney-nickel, afforded (1) in one step in an unoptimised 47% yield.

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SYNTHESIS OF METHYL-1,6-DIOXASPIRO[4.5]DECANES USING ORGANOSELENIUM MEDIATED CYCLIZATION REACTIONS

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SUMMARY:- Three naturally occurring methyl-1,6-dioxaspiro[4.5]decanes have been prepared in good yield using organoselenium mediated reactions during the crucial cyclization process.

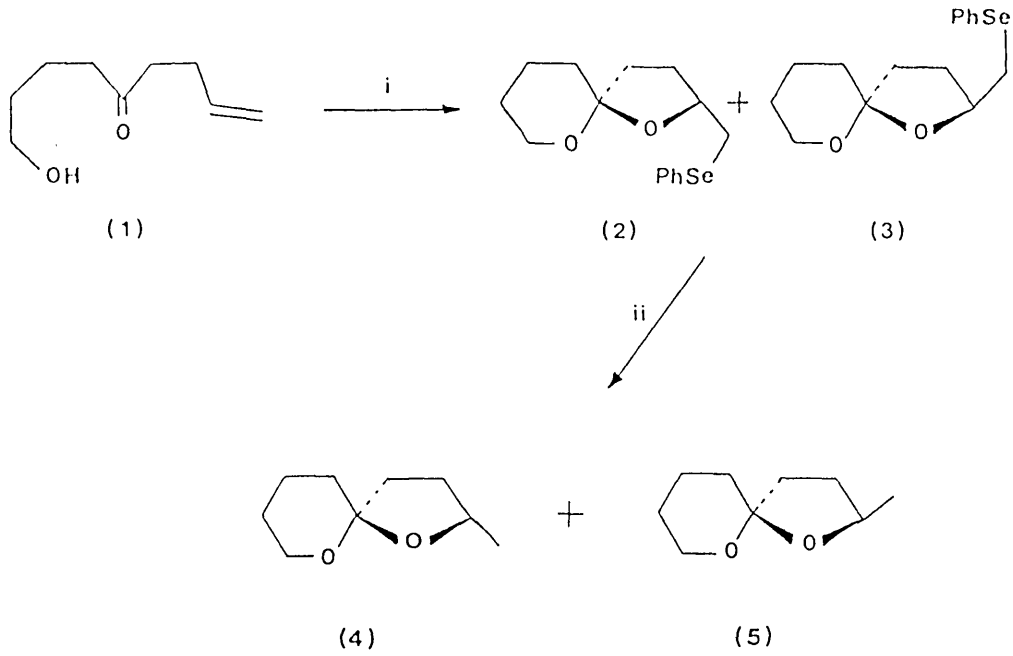
The spiro-ketal moiety occurs in many biologically active natural products including insect pheromones[1], polyether antibiotics[2] and the extremely potent antiparasitic agents, the avermectins[3]. Consequently new methods for their preparation are becoming increasingly important.

The use of organoselenium mediated cyclization reactions to synthesise oxygen containing heterocyclic species is known[4] however, application to natural product synthesis has so far been limited to only a few examples.[4e,h,5] In this Letter we show how natural 1,6-dioxaspiro-[4.5]decanes can be prepared using organo-selenium based methodology. In principle this route could be applied to many other related spiro-ketal systems.

In the first of these syntheses the alkenylhydroxy ketone[6] (1) was treated with N-phenyl-selenophthalimide[7], NPSP, and zinc bromide (0.1 eq) in dichloromethane at room temperature for 1.5h to give a *Z:E* mixture (1:2) of the phenylseleno-spiroketals (2) and (3) in 78.3% yield. These were not isolated separately but were reduced with Raney-nickel in ethanol at 50°C to afford the methyl-1,6-dioxaspiro[4.5]decanes (4) and (5) in the same ratio in 90% yield(Scheme 1) These compounds were identical to the pheromone components isolated recently from the common wasp *P. vulgaris*[8]. No attempt was made to separate these materials,although this is possible, as it is known that these *Z:E*-diastereomers undergo equilibration at 5°C within a few days.[8c]

During the cyclization reaction of (1) it was not possible to detect by ^{1}H n.m.r. spectroscopy any intermediate formation of the related dioxaspiro[5.5]analogues that one may expect to be the kinetic cyclization product.

Scheme 1

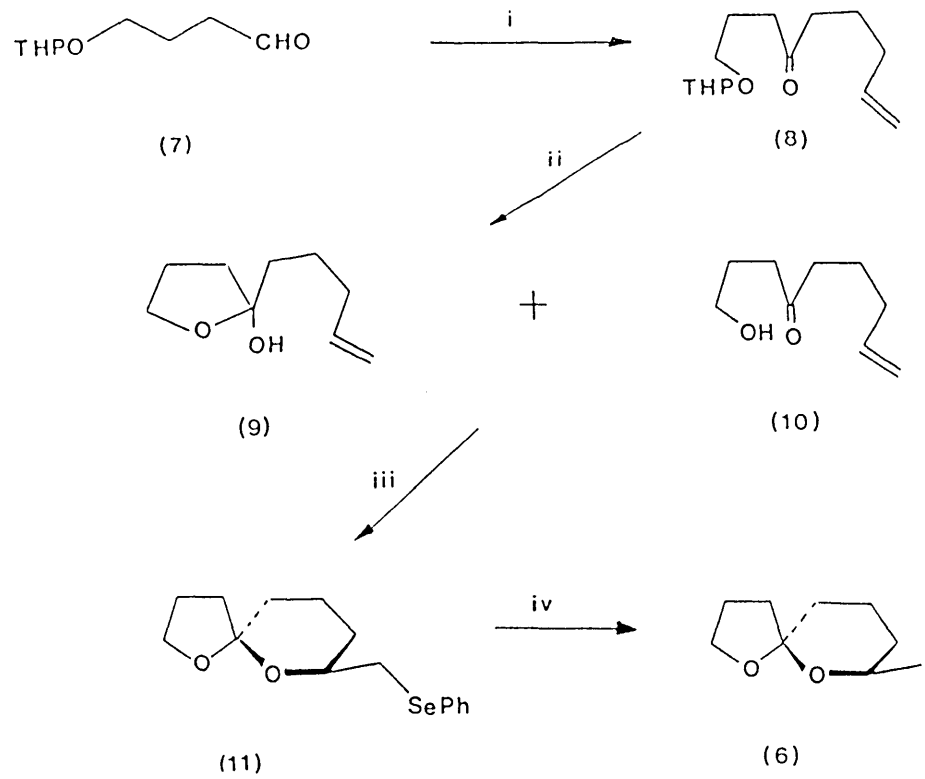


i) NPSP(1.1eq), $ZnBr_2$(0.1eq), CH_2Cl_2, 1.5h, RT; ii) Raney-nickel, EtOH, 50^0, 1h.

For the synthesis of the remaining methyl-1,6-dioxaspiro[4.5]decane (6) a somewhat longer synthetic sequence was necessary. The tetrahydropyranyl protected hydroxyaldehyde (7) was reacted with pent-4-enyl magnesium bromide to give (8) on oxidation work-up with Collins reagent in greater than 96% yield. Deprotection of (8) with camphor sulphonic acid / methanol at 40-50^0C for 30 min gave a mixture of the lactol (9) and the uncyclized ketoalcohol (10) in 70 and 19% yields respectively. Treatment of either (9) or (10) with NPSP / $ZnBr_2$ (1.0:0.1 equiv) in dichloromethane at room temperature gave a single phenylselenospiro-ketal(11) as a colourless oil in 80% yield. Reduction of this ketal with Raney-nickel as before gave exclusively *E*-methyl-1,6-dioxaspiro[4.5]decane (6) (92%) (Scheme 2).

The mechanistic implications of these reactions, together with other examples will be discussed at a later date.

Scheme 2



i) Pent-4-enyl magnesium bromide, -10°C, Ether; CrO_3.2py; ii) Camphor sulphonic acid/ methanol, 40-50°C, 30 min; iii) NPSP(1.1eq), $ZnBr_2$(0.1eq); iv) Raney-nickel, EtOH, 50°, 1h.

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^{1}H N.m.r. data (250 M Hz δ $CDCl_3$)

Compound 4: 3.32-4.21 (3H,m), 2.15-1.43 (10H,m), 1.31 (3H,d J=5.5Hz).

Compound 5. 3.32-4.21 (3H,m), 2.15-1.43 (10H,m), 1.24 (3H,d J=5.5Hz)

Compound 6. 3.92-3.60 (3H,m), 2.07-1.21 (10H,m), 1.11 (3H,d J=6.3Hz)

Compound 11:7.50 (2H,m), 7.22(3H,m), 4.07-3.93(1H,m,H_x), 3.92-3.34 (2H,m,H_c,H_d), 3.04 (1H,dd,H_a $J_{H_aH_b}$=12Hz, $J_{H_aH_x}$=6.9Hz), 2.90(1H,dd,H_b, $J_{H_aH_b}$=12Hz, $J_{H_bH_x}$=4.7Hz), 2.09-1.59(10H,m).

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A NEW ROUTE TO SPIRO-KETALS USING THE HORNER-WITTIG REACTION OF 2-DIPHENYLPHOSPHINOXY CYCLIC ETHERS

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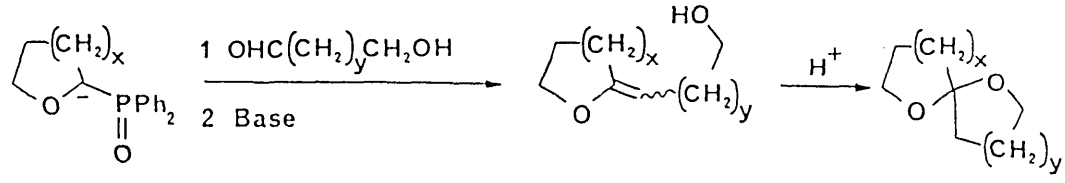
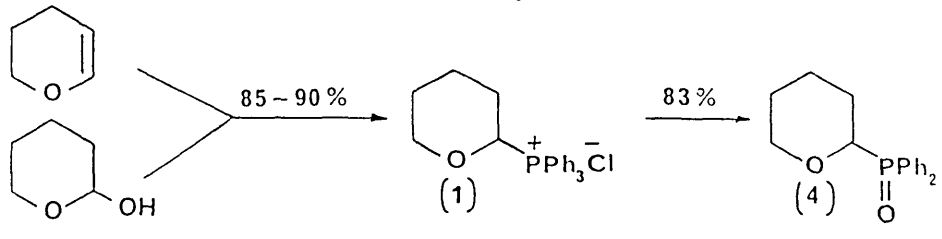
Summary: Two insect pheromones along with other spiro-ketals have been synthesised by a new route which involves Horner-Wittig coupling of 2-diphenylphosphinoxy cyclic ethers with aldehydes and lactols followed by acid catalysed cyclisation.

Owing to the increased interest in the formation of spiro-ketals,[1] we report here a new method which is potentially very general and applicable to a wide range of compounds. The method relies upon the Horner-Wittig coupling of cyclic ethers with either aldehydes or lactols, followed by acid catalysed spiro-ketal formation (Scheme).

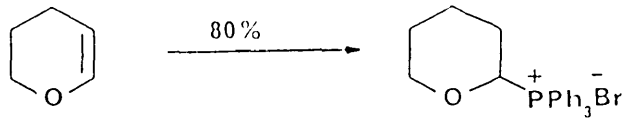


Scheme

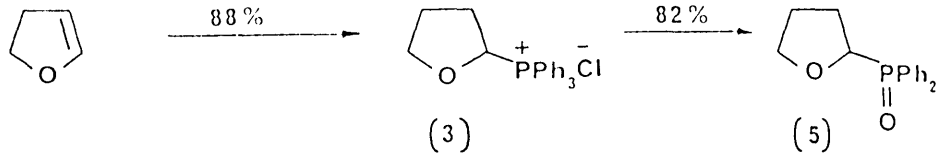
The cyclic ether phosphonium salt[2] (1) was readily prepared by treatment of a benzene solution of either 5-hydroxypentanal lactol or 3,4-dihydro-2H-pyran and triphenylphosphine with gaseous hydrogen chloride over a period of 5-10 h at ambient temperature (eq. 1). The phosphonium salt (1) was difficult to purify to acceptable microanalytical levels, however similar preparation of the bromide (2) using HBr (eq. 2) gave analytically pure material[3]. Preparation of (3) was achieved from dihydrofuran by an analogous method (eq. 3). The salts (1) and (3) were subsequently converted to the corresponding diphenylphosphine oxides (4) and (5) by brief (30 min) treatment with 3N sodium hydroxide under reflux[4].



eq.1

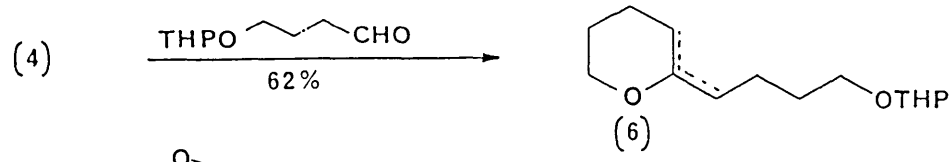


(2) eq.2

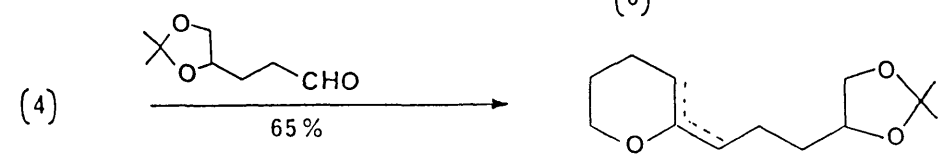


(3) (5) eq.3

With the 2-diphenylphosphinoxy cyclic ethers to hand, their reactions with various aldehydes and lactols under Horner-Wittig conditions[5] were next examined. In a typical experiment the diphenylphosphine oxides were deprotonated with lithium diisopropylamide (LDA) at -78°C in THF to give a deep red anion which was diluted with diethyl ether. To this mixture was added the appropriate aldehyde (or the lithio salt of the lactol) and, upon loss of the red colour, was quenched by the addition of water.[5] After separation and evaporation of solvent, the residue was dissolved in THF and potassium tert-butoxide (1 eq.) was added to effect the elimination of diphenylphosphinic acid. This elimination was normally complete after 1 h at room temperature. THF was removed and replaced by a small amount of dichloromethane followed by extraction with ether. Removal of the ether afforded the crude enol ethers which could be further purified by Kugelruhr distillation. It was not necessary to separate the various enol ethers formed as they could be used directly in the next reaction. Following the above procedure enol ethers (6) to (9) were prepared (eq. 4-7).

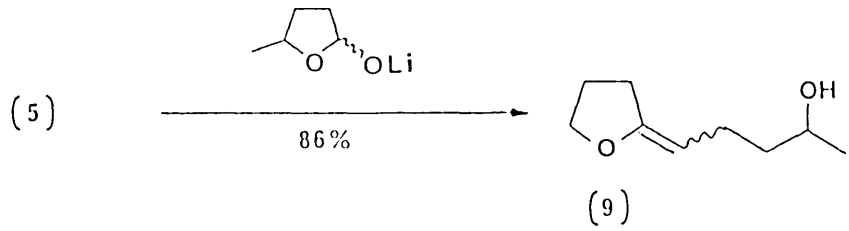


(6) eq.4



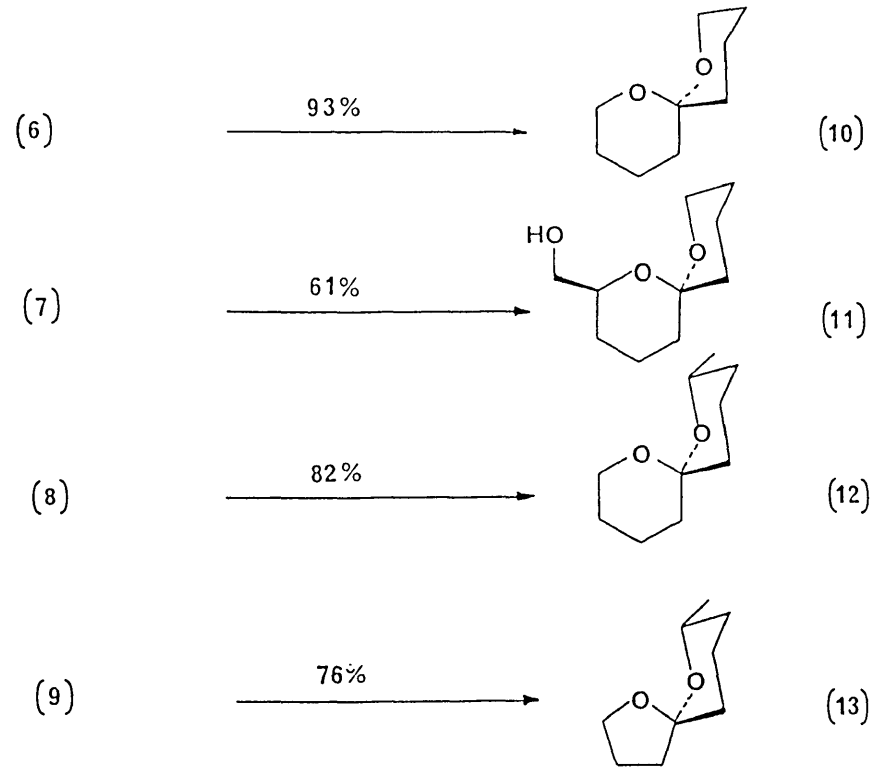
(7) eq.5

(8) eq.6



(5) (9)

Cyclisation of the enol ethers (6)-(9) to the corresponding spiro-ketals (10)-(13) was straightforward using a trace of camphor sulphonic acid in methanol, over a period of several hours (6-12) with concomitant removal of tetrahydropyranyl or acetonide protecting groups in relevant examples.



(6) (10)

(7) (11)

(8) (12)

(9) (13)

The spiro-ketal (10) was identical to the major sex pheromone isolated from the olive fly Dacus oleae, while (13) was identical to a common wasp pheromone from Paravespula vulgaris (L).[8]

The above method is clearly very general and its application to the construction of more biologically important spiro-ketal containing natural products, such as the avermectins and milbemycins,[9] is obvious and will be reported at a later date.

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Synthesis of Spiroacetals using Organoselenium-mediated Cyclisation Reactions. *X*-Ray Molecular Structure of (2*S*,8*R*)-8-Methyl-2-phenyl-1,7-dioxaspiro-[5.5]undecan-4(*R*)-ol

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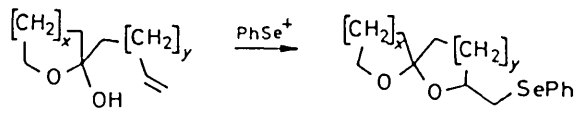
Department of Chemistry, Imperial College, London SW7 2AY

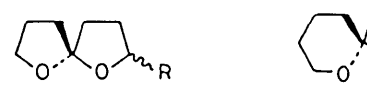
Alkenyl hydroxyketones undergo cyclisation *via* their hemiacetal form, in the presence of *N*-phenylselenophthalimide (NPSP) and a Lewis acid, to give the corresponding phenylseleno-substituted spiroacetals. Using this methodology the synthesis of *trans*- and *cis*-2-methyl-1,6-dioxaspiro-[4.4]nonane (**1**), *trans*- and *cis*-2-ethyl-1,6-dioxaspiro[4.4]nonane (chalcogran) (**2**), *trans*- and *cis*-2-methyl-1,6-dioxaspiro[4.5]decane (**3**), *trans*-7-methyl-1,6-dioxaspiro[4.5]decane (**4**), *trans*-2-methyl-1,7-dioxaspiro[5.5]undecane (**5**), and (2*S*,8*R*)-8-methyl-2-phenyl-1,7-dioxaspiro[5.5]undecane-4-one (**6**) has been achieved, after reductive removal of selenium using Raney-nickel in diethyl ether. Compound (**2**) is the principal aggregation pheromone from *Pityogenes chalcographus* (L), whilst compounds (**3**) and (**4**) constitute the pheromone components of the common wasp, *Paravespula vulgaris*. The structure of the spiroacetal (**6**) was determined as a result of *X*-ray crystallography of a later derivative, obtained by sodium borohydride reduction of (**6**).

The spiroacetal functional group is common to a wide range of natural products, notably insect pheromones,[1] oxygenated terpenoids,[2] polyether antibiotics,[3] the cytovaricins,[4] and the recently isolated potent antiparasitic agents, the milbemycins and avermectins.[5] We report here a new spiroacetal-forming reaction[6] which could prove useful in the preparation of such molecules and their structural analogues.

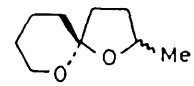


Scheme 1.

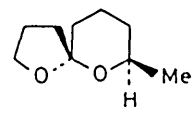
Conceptually the reaction involves the organoselenium-mediated intramolecular trapping of a hemiacetal by a suitably disposed carbon–carbon double bond[7] (Scheme 1). The use of organoselenium-mediated cyclisation reactions in the preparation of oxygen-containing heterocyclic compounds is a rapidly developing and important synthetic strategy;[8] however, application to natural product synthesis has so far been limited.[9] In this work the synthesis of the spiroacetals (**1**)—(**6**) is described. Compound (**2**) is the principal aggregation pheromone from *Pityogenes chalcographus* (L),[10] compounds (**3**) and (**4**) are pheromone components of the common wasp *Paravespula vulgaris*,[11] and compound (**6**) is a useful precursor for avermectin/milbemycin analogues. For the preparation of the spiroacetal (**1**), but-3-enylmagnesium bromide was treated, at 0 °C in diethyl ether, with the known tetrahydropyranyl-protected aldehyde (**7**)[12] to give an adduct, which was oxidised with Collins' reagent to provide the enone (**8**) in 75% yield. Deprotection of (**8**) with camphorsulphonic acid in methanol gave a mixture of the hydroxyketone (**9**) and the hemiacetal (**10**) in 94% combined yield. Treatment of this mixture with one equivalent of *N*-phenylselenophthalimide (NPSP),[13] and a trace of zinc(II) bromide (0.1 equiv.), in dichloromethane at room temperature gave a 1:1 *cis*:*trans* mixture of the spiroacetals (**11**) in 52% yield. The reaction was conveniently followed by t.l.c. and/or by ^{1}H n.m.r. spectroscopy. Reductive removal of the phenylseleno substituent was achieved by treatment with Raney-nickel in diethyl ether, at room temperature under hydrogen, to give an excellent yield of compound (**1**) as a 1:1 mixture of *cis*:*trans* isomers. No attempt



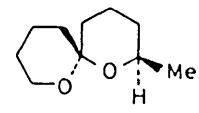
(**1**) R = Me *cis* and *trans*
(**2**) R = Et *cis* and *trans*



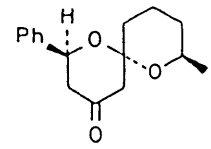
(**3**) *cis* and *trans*



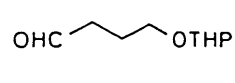
(**4**) *trans*



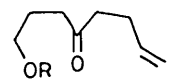
(**5**) *trans*



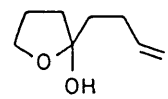
(**6**)



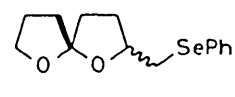
(**7**)



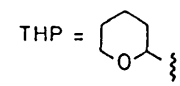
(**8**) R = THP
(**9**) R = H



(**10**)



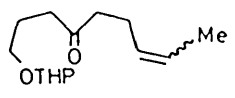
(**11**)



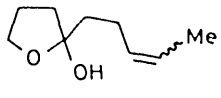
was made to separate these isomers as similar systems are known to undergo equilibration at 5 °C over a period of a few days.[11]

Synthesis of the natural product (2) was achieved in a similar fashion, namely reaction of pent-3-enylmagnesium bromide with (7) which gave enone (12) after Collins' oxidation. This, upon hydrolysis to (13) and selenium-mediated cyclisation, gave the spiroacetals (14). Reduction with Raney-nickel afforded compound (2) in 34% overall yield.

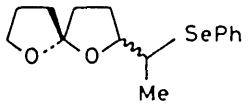
Preparation of the spiroacetals (3) was accomplished by a slightly different strategy, in that starting materials were prepared by an alternative route. Accordingly, but-3-enylmagnesium bromide was treated with δ-valerolactone at −78 °C, to give the enone (15) in low yield after separation from the other product, that of diaddition of the Grignard reagent to the lactone. Cyclisation of (15) with NPSP gave a 1:2 mixture of *cis*:*trans* isomers of compound (16) in 78% yield, which after Raney-nickel reduction gave (3), again as a 1:2 mixture of *cis*:*trans* isomers in 90% yield. This equilibration ratio was identical with that observed for the natural material.[14]



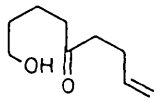
(12)



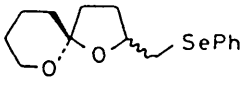
(13)



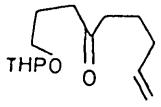
(14)



(15)



(16)



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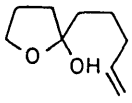
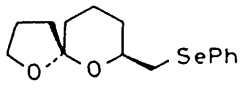
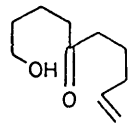


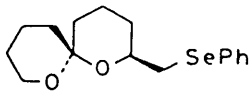
(18)



(19)



(20)

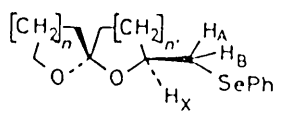


(21)

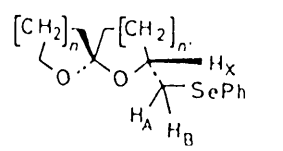
However, during the synthesis of the spiroacetals (4) and (5) only single *trans* isomers were obtained. Reaction of pent-4-enylmagnesium bromide with the protected aldehyde (7) gave the enone (17), after Collins' oxidation, in 96% overall yield. Hydrolysis afforded compound (18), which upon subsequent selenium-mediated cyclisation gave the *trans*-phenylselenospiroacetal (19) in 73% yield. Finally, Raney-nickel reduction afforded the natural spiroacetal (4).

For the synthesis of (5), pent-4-enylmagnesium bromide was treated with δ-valerolactone at −78 °C to provide the hydroxyketone (20) in poor (22%) yield, after separation by silica gel chromatography from the diaddition product. Compound (20) was cyclised with NPSP in the normal way to provide the *trans*-spiroacetal (21) (77%) which was reduced to compound (5) using Raney-nickel (88%).

Table 1. 250 MHz ^{1}H n.m.r. spectra of the phenylseleno-spiroacetals



trans



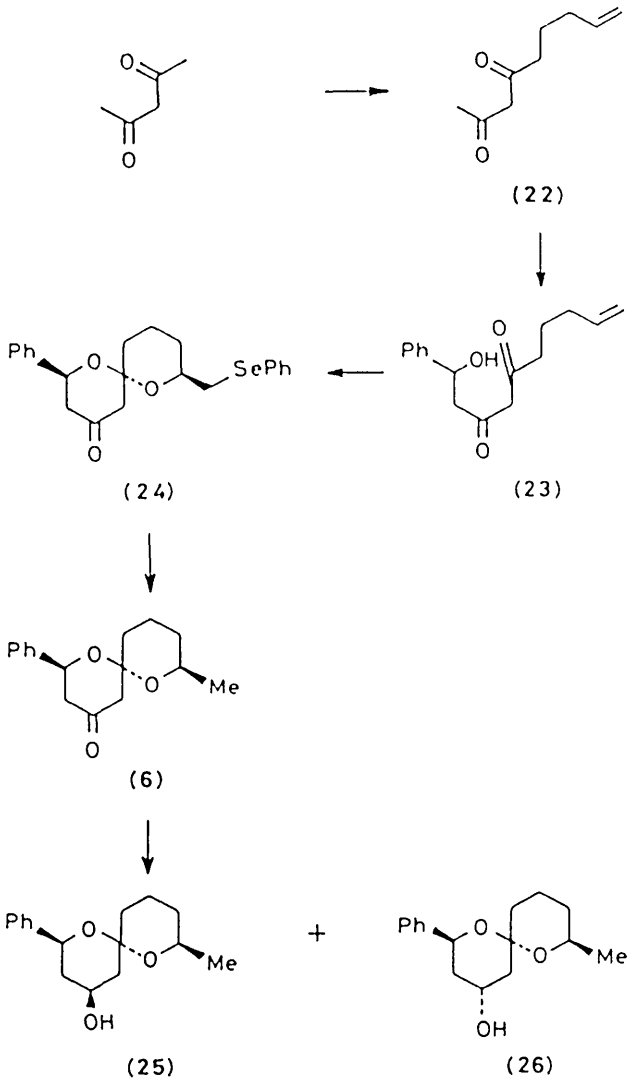
cis

Compound	δ H_A	δ H_B	J_{AX}(Hz)	J_{BX}(Hz)	J_{AB}(Hz)
(11) *trans* $n = n' = 1$	3.00	2.96	2.6	3.7	12.5
cis	3.26	3.11	5.9	4.7	12.5
(16) *trans* $n = 2$, $n' = 1$	3.08	2.96	5.8	7.8	11.7
cis	3.29	3.13	5.8	5.0	11.7
(19) *trans* $n = 1$, $n' = 2$	3.04	2.90	6.9	4.7	12.0
(21) *trans* $n = n' = 2$	3.12	2.95	8.6	5.1	12.2

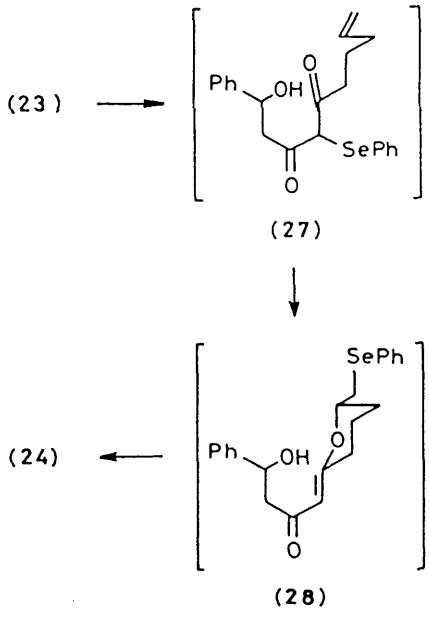
The structural proof of the initially formed phenylseleno-spiroacetals follows from their spectral data, especially their high-field ^{1}H n.m.r. parameters, some key features of which are noted in Table 1.

The last spiroacetal to be studied, (6), was designed as a suitable model compound for avermectins/milbemycins. The dianion from pentane-2,4-dione was formed by sequential treatment with sodium hydride in tetrahydrofuran (THF) at 0 °C, followed by n-butyl-lithium at −20 °C. This dianion was treated with 4-bromobut-1-ene to give the kinetically quenched adduct (22). Re-formation of the dianion using 2 equivalents of lithium di-isopropylamide followed by reaction with benzaldehyde at −78 °C gave the necessary starting material (23) for cyclisation studies. Treatment of (23) with NPSP (1.1 equiv.) and $SnCl_4$ (0.1 equiv.) in dichloromethane afforded the spiroacetal (24) as the major product (50%) after 96 h at room temperature. The high-field 250 MHz ^{1}H n.m.r. spectrum of (24) is entirely in accord with the proposed structure, which was confirmed by *X*-ray crystallographic determination of a later derivative. The phenylseleno group in compound (24) was removed by Raney-nickel to give compound (6) as a colourless oil in 94% yield. Finally reduction of the carbonyl group in (6) was achieved using $NaBH_4$ in dimethoxyethane at 0 °C, to give a separable mixture of the alcohols (25) and (26) in 61 and 32% yield respectively (Scheme 2). Use of other reducing systems gave a less favourable ratio of the desired isomer (25). During the organoselenium-mediated cyclisation of (23) to the spiroacetal (24), organoselenium-containing intermediates were noticed by means of t.l.c. and ^{1}H n.m.r. spectroscopy, but were not isolated. We propose that the first formed intermediate was that of seleniation on the central carbon of the dicarbonyl system, *i.e.* (27), and this then undergoes Lewis acid-catalysed rearrangement, with migration of the phenylseleno group, to form the monocyclic intermediate (28). This intermediate subsequently cyclises with anomeric control[15] to give the final product (24) (Scheme 3). Evidence for the phenylseleno group migration and the proposed intermediates is based upon our earlier studies on related systems.[16] While the spectroscopic data for the two alcohols (25) and (26) agree with their structure assignment, unambiguous proof was derived from *X*-ray crystallographic analysis of the minor isomer (26) (Figure).

From the above studies, the new selenium-based methodology



Scheme 2.



Scheme 3.

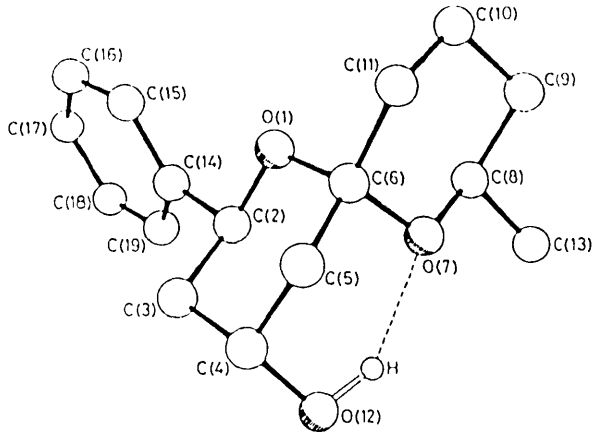


Figure. The molecular structure of (26)

can be used effectively to afford methyl- [4.4]-, [4.5]-, and [5.5]-dioxaspiro systems and compares favourably with current methods of spiroacetal formation.[17]

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 298 spectrophotometer and ^{1}H n.m.r. spectra with a Varian EM 360A, or Brucker WH250 spectrometer, for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were obtained using a V.G. Micromass 7070 spectrometer. Light petroleum refers to the fraction boiling in the range 40—60 °C. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods. Chromatography was performed on MN-Silica gel 60, 230—400 mesh, under pressure.

General Procedure for the Reaction of Grignard Reagents with 4-(Tetrahydropyran-2-yloxy)butanal (7) *and Subsequent Oxidation.*—To a solution of compound (7) (2 mmol) in diethyl ether (7 ml) at 0 °C under argon was added a solution of the Grignard reagent (1—2 equiv.) in diethyl ether (5 ml). After the addition, the mixture was stirred for 30 min at room temperature. Saturated aqueous ammonium chloride (7 ml) was added and the organic phase was separated and dried. The solvent was removed under reduced pressure to give the crude product, which was added directly to a solution of Collins' reagent (6—10 equiv.) in dichloromethane (7 ml). The reaction mixture was stirred at room temperature for 2 h, diluted with diethyl ether (60 ml), and filtered through a pad of Celite. The solvent was removed under reduced pressure and the crude product subjected to chromatography (50% diethyl ether–light petroleum) to provide the pure compounds.

Reaction with but-3-enylmagnesium bromide. Reaction of compound (7) with but-3-enylmagnesium bromide [from but-3-enyl bromide (0.41 g, 3.0 mmol) and magnesium (0.08 g)] followed by oxidation and chromatography gave 1-(*tetrahydropyran-2-yloxy*)*oct-7-en-4-one* (8) (0.47 g, 75%), δ (250 MHz) 5.80 (1 H, m), 5.00 (2 H, m), 4.53 (1 H, t, *J* 3.0 Hz), 3.83—3.40 (4 H, m), 2.50 (4 H, m), and 2.10—1.10 (10 H, m); $\nu_{max.}$(film) 1 710, 1 630, and 1 120 cm^{-1}; *m/z* 226, 208, 141, and 85 (Found: C, 69.0; H, 10.05. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%).

Reaction with pent-3-enylmagnesium bromide. Reaction of compound (7) with pent-3-enylmagnesium bromide [from pent-3-enyl bromide (0.45 g, 3.0 mmol) and magnesium (0.08 g)] followed by oxidation and chromatography gave 1-(*tetrahy-*

dropyran-2-yloxy)non-7-en-4-one (**12**) (0.50 g, 74%) as an oil, δ (250 MHz) 5.42 (2 H, m), 4.55 (1 H, t, *J* 3.1 Hz), 3.83—3.40 (4 H, m), 2.48 (4 H, m), and 2.30—1.45 (13 H, m); $\nu_{max.}$(CHCl$_3$) 1 717, 1 630, and 1 120 cm^{-1}; *m/z* 240, 155, 139, and 85 (Found: C, 69.85; H, 10.25. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.06%).

Reaction with pent-4-enylmagnesium bromide. Reaction of compound (**7**) with pent-4-enylmagnesium bromide [from pent-4-enyl bromide (0.33 g, 2.2 mmol) and magnesium (0.06 g)] followed by oxidation and chromatography gave 1-(*tetrahydropyran-2-yloxy)non-8-en-4-one* (**17**) (0.48 g, 97%), δ (60 MHz) 6.17—4.70 (3 H, m), 4.54—4.36 (1 H, m), 4.02—3.12 (4 H, m), and 2.63—1.13 (16 H, m); $\nu_{max.}$(film) 2 933, 1 710, 1 635, 1 112, and 1 028 cm^{-1}; *m/z* no M^+ peak, 155, 139, 97, 85, 84, and 41 (Found: C, 69.75; H, 10.2%).

General Procedure for the Removal of the Tetrahydropyran-2-yl Protecting Group.—The tetrahydropyranyl derivative (1.5 mmol) was added dropwise to a stirred solution of camphorsulphonic acid (CSA) (2 mg) in methanol (3 ml). After 30 min at 50 °C the mixture was cooled and filtered through a pad of Celite. Removal of the solvent under reduced pressure gave the crude product which contained the alkenyl-substituted hemiacetal as the major product, together with a small amount of the corresponding open-form hydroxyketone. This mixture, however, could be used directly in the next reaction.

Deprotection of compound (**8**). By the above general method, compound (**8**) (0.24 g, 1.1 mmol) gave the crude hemiacetal (**10**) (0.15 g, 95%), δ (250 MHz) 5.83 (1 H, m), 5.09—4.92 (2 H, m), 3.87 (1 H, m), 3.39 (1 H, m), 2.50 (2 H, m), and 2.35—1.61 (7 H, m).

Deprotection of compound (**12**). By the above general method compound (**12**) (0.34 g, 1.5 mmol) gave the crude hemiacetal (**13**) (0.19 g, 81%).

Deprotection of compound (**17**). By the above general method, compound (**17**) (0.34 g, 1.5 mmol) gave the crude hemiacetal (**18**) (0.21 g, 90%), δ (60 MHz) 6.00—4.69 (3 H, m), 3.98—3.61 (2 H, t), and 2.53—1.28 (11 H, m); $\nu_{max.}$ (film) 3 410, 2 950, 2 389, 1 635, and 913 cm^{-1}; *m/z* 156, 71, 51, and 41.

General Procedure for the Addition of Grignard Reagents to δ-Valerolactone.—A solution of the appropriate Grignard reagent (2.0 mmol) in diethyl ether (2 ml) was added dropwise to a suspension of δ-valerolactone (2.0 mmol) in dry THF (6 ml) under argon at −78 °C during 3 h, *via* a motorised syringe. The mixture was stirred for a further 1 h, after which time saturated aqueous ammonium chloride (2 ml) was added and the mixture was allowed to warm to room temperature. The organic phase was separated, dried, and the solvent was removed under reduced pressure. The residue was subjected to rapid chromatography (30% diethyl ether–light petroleum) to give the product, the hydroxyketo alkene.

Reaction of δ-valerolactone with but-3-enylmagnesium bromide. Using the above procedure, but-3-enylmagnesium bromide [from but-3-enyl bromide (0.27 g, 2.0 mmol) and magnesium (0.06 g)] was treated with δ-valerolactone (2.0 mmol) to give 9-hydroxynon-1-en-5-one (**15**) (38 mg, 12%), δ (60 MHz) 6.09—4.73 (3 H, m), 3.56 (2 H, t), and 2.62—1.43 (11 H, m); $\nu_{max.}$(CHCl$_3$) 3 476, 2 927, 2 872, 1 708, and 1 634 cm^{-1}; *m/z* 156, 87, 69, 58, 55, and 41; and the product of diaddition, 5-but-3-enylnon-8-ene-1,5-diol (34 mg, 8%), δ (60 MHz) 6.16—4.67 (6 H, m), 3.57 (2 H, t), and 2.17—1.31 (16 H, m); $\nu_{max.}$(film) 3 370, 2 923, 2 859, and 1 637 cm^{-1}; *m/z* no M^+ peak, 195, 157, 139, 83, 51, and 41.

Reaction of δ-valerolactone with pent-4-enylmagnesium bromide. Using the above procedure, pent-4-enylmagnesium bromide [from pent-4-enyl bromide (0.3 g, 2.0 mmol) and magnesium (0.06 g)] was treated with δ-valerolactone (2.0 mmol) to give 1-hydroxydec-9-en-5-one (**20**) (77 mg, 23%), δ (60 MHz) 6.03—4.67 (3 H, m), 3.53 (2 H, t), and 2.53—1.27 (13 H, m); $\nu_{max.}$(film) 3 398, 2 930, 1 705, and 1 639 cm^{-1}; *m/z* 170, 116, 101, and 98 (Found: M^+, 170.1312. $C_{10}H_{18}O_2$ requires *M*, 170.1307); and the product of diaddition, 5-pent-4-enyldec-9-ene-1,5-diol (29 mg, 6%), δ (60 MHz) 6.15—4.74 (6 H, m), 3.59 (2 H, br t), 2.70 (2 H, br, exch. D_2O), and 2.20—1.20 (18 H, m); $\nu_{max.}$(film) 3 360, 2 929, 2 858, and 1 638 cm^{-1}; *m/z* no M^+ peak, 222, 171, 84, and 69.

General Procedure for the Selenium-mediated Cyclisation.—To a solution of the appropriate hydroxyalkene (1 mmol) and NPSP (0.33 g, 1.1 mmol) in dry dichloromethane (3 ml) under argon at room temperature was added dry zinc(II) bromide (16 mg, 0.1 equiv.).

The mixture was stirred for 1—2 h, diluted with light petroleum (4 ml), filtered (to remove precipitated phthalimide), washed with saturated aqueous sodium hydrogen carbonate (1 ml), and dried. The solvent was removed under reduced pressure and the residue subjected to chromatography to afford the product.

Cyclisation of compound (**10**). Treatment of compound (**10**) (0.14 g, 0.98 mmol) with NPSP and zinc(II) bromide gave 2-phenylselenomethyl-1,6-dioxaspiro[4.4]nonane (**11**) (0.17 g, 58%) as a 1:1 mixture of diastereoisomers, δ (250 MHz) 7.52 (2 H, m), 7.24 (3 H, m), 4.34 (0.5 H, m, *cis* isomer), 4.22 (0.5 H, m, *trans* isomer), 3.88 (2 H, m), 3.26 (0.5 H, dd, J_{AB} 12.5, J_{AX} 5.9 Hz), 3.11 (0.5 H, dd, J_{AB} 12.5, J_{BX} 4.7 Hz), 3.00 (0.5 H, dd, $J_{A'B'}$ 12.5, $J_{A'X'}$ 2.6 Hz), 2.96 (0.5 H, dd, $J_{A'B'}$ 12.5, $J_{B'X'}$ 3.7 Hz), and 2.31—1.67 (8 H, m); $\nu_{max.}$(CHCl$_3$) 2 940, 1 580, and 1 440 cm^{-1}; *m/z* 298, 141, and 127 (Found: M^+, 298.0466. $C_{14}H_{18}O_2Se$ requires *M*, 298, 0471).

Cyclisation of compound (**13**). Treatment of compound (**13**) (0.16 g, 1 mmol) with NPSP and zinc(II) bromide gave 2-(1-*phenylselenoethyl*)-1,6-*dioxaspiro*[4.4]*nonane* (**14**) (0.14 g, 45%) as a mixture of diastereoisomers, δ (250 MHz) 7.58 (2 H, m), 7.26 (3 H, m), 4.25—3.20 (4 H, m), and 2.20—1.35 (11 H, m, including Me doublets at 1.47 and 1.39); $\nu_{max.}$(film) 2 920, 2 875, and 1 580 cm^{-1}; *m/z* 312, 155, and 127 (Found: C, 57.65; H, 6.4. $C_{15}H_{20}O_2Se$ requires C, 57.88; H, 6.48%).

Cyclisation of compound (**15**). Treatment of compound (**15**) (0.16 g, 1 mmol) with NPSP and zinc(II) bromide gave 2-*phenylselenomethyl*-1,6-*dioxaspiro*[4.5]*decane* (**16**) (0.24 g, 78%) as a 2:1 mixture of *E*:*Z* isomers, δ (250 MHz) 7.54 (2 H, m), 7.24 (3 H, m), 4.40—3.52 (3 H, m), 3.29 (0.3 H, dd, J_{AX} 5.8, J_{AB} 11.7 Hz, H_A *cis* isomer), 3.13 (0.3 H, dd, J_{BX} 5.0, J_{AB} 11.7 Hz, H_B *cis* isomer), 3.08 (0.7 H, dd, J_{AX} 5.8, J_{AB} 11.7 Hz, H_A *trans* isomer), 2.96 (0.7 H, dd, J_{BX} 7.8, J_{AB} 11.7 Hz, H_B *trans* isomer), and 2.24—1.48 (10 H, m); $\nu_{max.}$(CHCl$_3$) 2 920, 2 875, and 984 cm^{-1}; *m/z* 312, 141, and 85 (Found: C, 58.05; H, 6.6. $C_{18}H_{20}O_2Se$ requires C, 57.88; H, 6.48%).

Cyclisation of compound (**18**). Treatment of compound (**18**) (0.16 g, 1 mmol) with NPSP and zinc(II) bromide gave trans-7-*phenylselenomethyl*-1,6-*dioxaspiro*[4.5]*decane* (**19**) (0.25 g, 81%) as an oil, δ (250 MHz) 7.50 (2 H, m), 7.22 (3 H, m), 4.07—3.93 (1 H, m, H_X), 3.92—3.34 (2 H, m), 3.04 (1 H, dd, J_{AB} 12, J_{AX} 6.9 Hz, H_A), 2.90 (1 H, dd, J_{AB} 12, J_{BX} 4.7 Hz, H_B) and 2.09—1.59 (10 H, m); $\nu_{max.}$(CHCl$_3$) 2 936, 1 574, and 1 431 cm^{-1}; *m/z* 312, 241, and 97 (Found: C, 57.95; H, 6.55. $C_{15}H_{20}O_2Se$ requires C, 57.88; H, 6.48%).

Cyclisation of compound (**20**). Treatment of compound (**20**) (0.17 g, 1 mmol) with NPSP and zinc(II) bromide gave trans-2-*phenylselenomethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**21**) (0.25 g, 77%) as an oil, δ (250 MHz) 7.52 (2 H, m), 7.23 (3 H, m), 3.94—3.50 (3 H, m), 3.12 (1 H, dd, J_{AX} 8.6, J_{AB} 12.2 Hz, H_A), 2.95 (1 H, dd, J_{BX} 5.1, J_{AB} 12.2 Hz, H_B), and 1.89—1.21 (12 H, m); $\nu_{max.}$(CHCl$_3$) 2 930 and 978 cm^{-1}; *m/z* 326, 155, and 111 (Found: C, 58.8; H, 6.8. $C_{16}H_{22}O_2Se$ requires C, 59.07; H, 6.82%).

General Procedure for Deselenation using Raney-nickel.—The phenylseleno spiroacetal (1 mmol) were added to a stirred mixture of W-Raney-nickel (5 mass equiv.) in diethyl ether (2 ml) under hydrogen (maintained by a hydrogen-filled balloon) at room temperature. After reduction was complete (3—5 h), the mixture was filtered through a pad of silica gel and the solvent was removed under reduced pressure to give the deselenated product. In most cases no further purification was necessary.

Reduction of compound (**11**). By the above method compound (**11**) (0.145 g, 0.5 mmol) after reduction afforded 2-methyl-1,6-dioxaspiro[4.4]nonane (**1**) (50 mg, 72%) as a 1:1 *cis*:*trans* mixture of isomers, δ (250 MHz) 4.30—3.80 (3 H, m), 2.21—1.40 (8 H, m), 1.34 (1.5 H, d, *cis* isomer CH_3), and 1.25 (1.5 H, d, *trans*-isomer CH_3); $\nu_{max.}$(film) 1 450, 1 380, and 1 180 cm^{-1}; *m/z* 142, 141, and 127, which was identical with the previously reported compound.

Reduction of compound (**14**). By the above general method compound (**14**) (0.25 g, 0.8 mmol) after reduction afforded 2-ethyl-1,6-dioxaspiro[4.4]nonane (chalcogran) (**2**) (0.11 g, 90%) as a 1:1 *cis*:*trans* mixture of isomers, δ (250 MHz) 4.10—3.30 (3 H, m), 2.15—1.70 (10 H, m), and 0.90 (3 H, m); $\nu_{max.}$(film) 2 926, 2 870, and 1 440 cm^{-1}; *m/z* 156, 155, and 127, which was identical with the natural product.

Reduction of compound (**16**). By the above general method compound (**16**) (0.31 g, 1 mmol) after reduction afforded 2-methyl-1,6-dioxaspiro[4.5]decane (**3**) (0.14 g, 90%) as a 1:2 *cis*:*trans* mixture, δ (250 MHz) 4.28—3.25 (3 H, m), 2.20—1.40 (10 H, m), 1.31 (1 H, d, *J* 5.4 Hz, *cis* isomer), and 2.24 (2 H, d, *J* 5.8 Hz, *trans* isomer); $\nu_{max.}$(film) 2 929, 1 435, and 1 367 cm^{-1}; *m/z* 156, 85, 67, 65, and 53.

Reduction of compound (**19**). By the above general method compound (**19**) (0.31 g, 1 mmol) after reduction afforded *trans*-7-methyl-1,6-dioxaspiro[4.5]decane (**4**) (0.14 g, 92%), δ (250 MHz) 3.92—3.60 (3 H, m), 2.07—1.21 (10 H, m), and 1.11 (3 H, d, *J* 6.3 Hz); $\nu_{max.}$($CHCl_3$) 2 940 and 1 050 cm^{-1}; *m/z* 156, 141, and 97.

Reduction of compound (**21**). By the above general method compound (**21**) (0.33 g, 1 mmol) after reduction afforded *trans*-2-methyl-1,7-dioxaspiro[5.5]undecane (**5**) (0.15 g, 88%) as a single isomer, δ (250 MHz) 3.79—3.50 (3 H, m), 1.93—1.33 (12 H, m), and 1.15 (3 H, d, *J* 6.3 Hz); $\nu_{max.}$(film) 2 932 and 1 058 cm^{-1}; *m/z* 170, 155, and 101 (Found: M^+, 170.1303. $C_{10}H_{18}O_2$ requires *M*, 170.1307).

Preparation of Compound (**22**).—Pentane-2,4-dione (5.13 ml, 50 mmol) was added dropwise to a stirred solution of sodium hydride (2.4 g of a 50% dispersion in oil, washed twice with light petroleum and once with THF) in THF (100 ml) at 0 °C under argon. The resulting mixture was stirred for 10 min at 0 °C, cooled to −20 °C, and n-butyl-lithium (34.3 ml of a 1.46M solution in hexane) was added dropwise to form a pale yellow solution. After 30 min at −20 °C the mixture was treated with 4-bromobut-1-ene (6.75 g, 50 mmol) and the mixture was stirred at 0 °C for 3 h, then at room temperature for 2 h. The mixture was poured into a mixture of saturated aqueous ammonium chloride (50 ml) and diethyl ether (50 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (2 × 20 ml). The combined organic layers were dried, concentrated under reduced pressure, and the residue was distilled to give non-8-ene-2,4-dione (**22**) (4.2 g, 55%), b.p. 67—68 °C at 0.9 mmHg; δ (60 MHz) 6.04—4.71 (3.7 H, m including δ 5.38 s, enolic C–H), 3.48 (0.6 H, s, $OCCH_2CO$), and 2.48—1.48 (9.7 H, m, including δ 2.01 s); $\nu_{max.}$(film) 3 420, 2 941, 1 710, 1 607, and 1 421 cm^{-1}; *m/z* 154, 100, and 85.

Preparation of Compound (**23**).—The dione (**22**) (0.2 g, 1.3 mmol) was added dropwise to a stirred solution of lithium di-isopropylamide [from di-isopropylamine (0.382 ml, 2.1 equiv.) and n-BuLi (1.7 ml of a 1.61M solution in hexane, 2.1 equiv.)] at 0 °C) in THF (5 ml) at −78 °C, under argon. The resulting solution was stirred at −78 °C for 3 h, benzaldehyde (0.132 ml, 1.3 mmol) was added, and the mixture was allowed to warm to 0 °C over 3 h and was then poured into saturated aqueous ammonium chloride (5 ml) and the layers were separated. After extraction of the aqueous layer with diethyl ether (3 × 2 ml), the organic layers were combined, dried, and after concentration under reduced pressure gave a residue which was subjected to chromatography to give 1-hydroxy-1-phenyldec-9-ene-3,5-dione (**23**) (0.22 g, 65%), δ (60 MHz) 7.29 (5 H, s), 6.09—4.72 (4.7 H, m including δ 5.4, s, enolic C–H), 3.47 (0.6 H, s, $COCH_2CO$), and 2.88—1.45 (9.7 H, m); $\nu_{max.}$(film) 3 402, 2 917, 1 709, and 1 603 cm^{-1}; *m/z* 260, 113, 107, and 85 (Found: M^+, 260.1404. $C_{16}H_{20}O_3$ requires *M*, 260.1412).

Selenium-mediated Cyclisation of Compound (**23**).—To a solution of compound (**23**) (56.5 mg, 0.22 mmol) in dry dichloromethane (2 ml) containing NPSP (72.2 mg, 1.1 equiv.) at room temperature, under argon, was added tin tetrachloride (22 μl of a 1M solution in dichloromethane, 0.1 equiv.).

The resulting mixture was stirred at room temperature for 96 h, diluted with light petroleum (2 ml), and filtered to remove phthalimide. The solution was washed with saturated aqueous sodium hydrogencarbonate (2 ml) and dried. The solvent was removed under reduced pressure to leave a residue which was subjected to chromatography (10% diethyl ether–light petroleum) to give (2S,8S)-2-*phenyl*-8-*phenylselenomethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*one* (**24**) (46 mg, 50%) as a low melting solid, δ (250 MHz) 7.50—7.17 (10 H, m), 5.09 (1 H, dd, *J* 4.8, 15.6 Hz), 4.83 (1 H, m, H_X), 3.02 (1 H, dd, J_{AX} 7.6, J_{AB} 12.9 Hz, H_A), 2.89 (1 H, dd, J_{BX} 4.5, J_{AB} 12.9 Hz, H_B), 2.58 (4 H, m), and 1.99—1.47 (6 H, m); $\nu_{max.}$($CHCl_3$) 2 932, 1 716, and 1 190 cm^{-1}; *m/z* 416, 155, and 111 (Found: C, 63.55; H, 5.8. $C_{22}H_{24}O_3Se$ requires C, 63.61; H, 5.82%).

Deselenation of Compound (**24**).—Deselenation of compound (**24**) (0.46 g, 1.1 mmol) with Raney-nickel as in the general procedure (above) gave (2*S*,8*R*)-8-methyl-2-phenyl-1,7-dioxaspiro[5.5]undecan-4-one (**6**) (0.27 g, 94%) as an oil, δ (60 MHz) 7.32 (5 H, m), 4.84 (1 H, dd, *J* 5.0, 9.6 Hz), 3.64 (1 H, m), 2.55 (4 H, m), 2.29—1.23 (6 H, m) and 1.12 (3 H, d, *J* 6.0 Hz); $\nu_{max.}$(film) 2 928 and 1 720 cm^{-1}; *m/z* 266, 154, and 112 (Found: M^+, 260.1417. $C_{16}H_{20}O_3$ requires *M*, 260.1412).

Reduction of Compound (**26**) *with Sodium Borohydride.*—To a solution of compound (**26**) (0.19 g, 0.73 mmol) in dry dimethoxyethane (20 ml) at 0 °C under argon was added sodium borohydride (30.5 mg, 4.4 equiv.). The mixture was stirred at 0 °C for 1 h, then poured into a mixture of saturated aqueous sodium chloride (20 ml) and diethyl ether (50 ml). The layers were separated and the organic layer was washed with saturated aqueous sodium chloride, dried, and evaporated to leave an oil. This oil was subjected to chromatography (20% diethyl ether–light petroleum ⟶ 40% diethyl ether–light petroleum) to give (2S,8R)-8-*methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4(S)-*ol* (**25**) (0.117 g, 61%) as an oil, δ (250 MHz) 7.33 (5 H, m), 4.63 (1 H, dd, *J* 2.2, 11.8 Hz), 4.32 (1 H, m), 3.74 (1 H, m), 2.30—1.12 (11 H, m), and 1.13 (3 H, d, *J* 6.3 Hz); $\nu_{max.}$ (film) 3 335, 2.924, and 984 cm^{-1}; *m/z* 262, 244, and 156 (Found: C, 73.1; H, 8.7. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%) and (2S,8R)-8-*methyl*-2-*phenyl*-1,7-*dioxaspiro*[5.5]*undecan*-4(R)-*ol* (**26**) (61.4 mg, 32%), δ (250 MHz) 7.35 (5 H, m), 4.98 (1 H, dd, *J* 2.5, 12.0 Hz), 4.43 (1 H, br d, exch. D_2O), 4.15 (1 H, m), 3.84 (1 H, m), 2.26—1.24 (10 H, m), and 1.18 (3 H, d, *J* 7.0 Hz); $\nu_{max.}$(film) 3 500, 2 930, and 1 039 cm^{-1}; *m/z* 262, 244, and 112 (Found: C, 73.25; H, 8.4%).

Table 2. Atomic co-ordinates ($\times 10^4$) and temperature factors ($Å^2 \times 10^3$)

Atom	x	y	z	U
O(1)	−2 107(2)	4 131(1)	1 722(1)	51(1)*
C(2)	−3 359(3)	4 270(1)	1 935(1)	49(1)*
C(3)	−4 828(4)	4 418(2)	1 751(1)	65(1)*
C(4)	−5 160(4)	3 685(2)	1 530(1)	67(1)*
C(5)	−3 783(4)	3 509(2)	1 329(1)	64(1)*
C(6)	−2 313(4)	3 422(1)	1 520(1)	52(1)*
O(7)	−2 515(2)	2 681(1)	1 705(1)	51(1)*
C(8)	−1 234(3)	2 469(2)	1 906(1)	67(1)*
C(9)	181(4)	2 352(2)	1 702(1)	88(1)*
C(10)	501(4)	3 117(2)	1 506(1)	87(1)*
C(11)	−905(4)	3 357(2)	1 317(1)	71(1)*
O(12)	−5 638(3)	2 956(1)	1 703(1)	77(1)*
C(13)	−1 719(5)	1 699(2)	2 089(1)	98(1)*
C(14)	−2 986(3)	4 991(1)	2 149(1)	49(1)*
C(15)	−2 025(4)	5 637(1)	2 062(1)	60(1)*
C(16)	−1 796(4)	6 313(2)	2 266(1)	73(1)*
C(17)	−2 503(4)	6 334(2)	2 555(1)	77(1)*
C(18)	−3 452(5)	5 694(2)	2 642(1)	80(1)*
C(19)	−3 674(4)	5 026(2)	2 442(1)	69(1)*

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 3. Bond lengths (Å)

O(1)-C(2)	1.436(3)	O(1)-C(6)	1.426(2)
C(2)-C(3)	1.521(4)	C(2)-C(14)	1.499(3)
C(3)-C(4)	1.521(4)	C(4)-C(5)	1.501(4)
C(4)-O(12)	1.434(3)	C(5)-C(6)	1.524(4)
C(6)-O(7)	1.428(2)	C(6)-C(11)	1.506(4)
O(7)-C(8)	1.445(3)	C(8)-C(9)	1.519(5)
C(8)-C(13)	1.510(4)	C(9)-C(10)	1.501(5)
C(10)-C(11)	1.517(5)	C(14)-C(15)	1.378(3)
C(14)-C(19)	1.381(3)	C(15)-C(16)	1.392(3)
C(16)-C(17)	1.372(4)	C(17)-C(18)	1.364(5)
C(18)-C(19)	1.372(4)		

Crystal Data.—(**26**) $C_{16}H_{22}O_3$, orthorhombic, a = 8.749(2), b = 15.916(4), c = 42.316(11) Å, U = 5 892 Å^3, space group $F2dd$, Z = 16, M = 262.3, D_c = 1.19 g cm^{-3}. Refined unit-cell parameters were obtained by centering 18 reflections on a Nicolet R3m diffractometer. 1 071 Independent reflections were measured ($\sigma \leq 58°$) with Cu-K_α radiation (graphite monochromator) using the omega-scan measuring routine. Of these, 1 045 had $|F|_o > 3\sigma(|F|_o)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors. No absorption correction was applied.

Initial attempts at fully automatic solution of the structure by direct methods were unsuccessful. This was surprising as the structure contains only 19 non-hydrogen atoms. Increasing the size of the starting set did not improve the figures of merit. Incorporation into the starting set of the 4 principal contributers to the list of negative quartets also resulted in very poor figures of merit. However, 3 cycles of automatic ΔE-map recycling for the best solution from this phase expansion (N_{quest}[18] −0.11, R_{alpha}[19] 0.25) gave the positions of all the non-hydrogen atoms.

The non-hydrogen atoms were refined anisotropically. The hydroxy hydrogen atom was clearly located in a ΔF-map and refined isotropically. The positions of the other hydrogen atoms were idealised (C–H 0.96 Å), assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. Refinement was by block-cascade least-squares to R 0.030, R_w 0.035, [$w^{-1} = \sigma^2(F) + 0.000\,27F^2$]. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[20]

Table 4. Bond angles (°)

C(2)-O(1)-C(6)	113.7(2)	O(1)-C(2)-C(3)	110.3(2)
O(1)-C(2)-C(14)	109.4(2)	C(3)-C(2)-C(14)	112.0(2)
C(2)-C(3)-C(4)	110.9(2)	C(3)-C(4)-C(5)	109.7(2)
C(3)-C(4)-O(12)	111.3(2)	C(5)-C(4)-O(12)	111.8(2)
C(4)-C(5)-C(6)	113.2(2)	O(1)-C(6)-C(5)	110.6(2)
O(1)-C(6)-O(7)	109.8(1)	C(5)-C(6)-O(7)	105.2(2)
O(1)-C(6)-C(11)	107.0(2)	C(5)-C(6)-C(11)	113.2(2)
O(7)-C(6)-C(11)	111.0(2)	C(6)-O(7)-C(8)	114.8(2)
O(7)-C(8)-C(9)	109.1(2)	O(7)-C(8)-C(13)	105.7(3)
C(9)-C(8)-C(13)	114.8(3)	C(8)-C(9)-C(10)	111.5(3)
C(9)-C(10)-C(11)	110.2(3)	C(6)-C(11)-C(10)	112.3(2)
C(2)-C(14)-C(15)	122.9(2)	C(2)-C(14)-C(19)	118.6(2)
C(15)-C(14)-C(19)	118.4(2)	C(14)-C(15)-C(16)	120.0(2)
C(15)-C(16)-C(17)	120.4(3)	C(16)-C(17)-C(18)	119.8(2)
C(17)-C(18)-C(19)	119.9(3)	C(14)-C(19)-C(18)	121.5(3)

Table 2 lists the fractional atomic co-ordinates. Tables 3 and 4 give the bond lengths and valence angles, respectively. The anisotropic thermal parameters, the structure factors, and the hydrogen co-ordinates and temperature factors have been treated as a Supplementary Publication [SUP No. 23898 (11 pp.)]*.

The structure (Figure) shows the molecule (**26**) to have the spiro configuration with the C(2) Ph and C(8) Me equatorial and the C(4) OH axial. There is an intramolecular hydrogen bond (2.77 Å, O–H···O angle 139°) between O(12) and O(7). The structures is loosely packed with only 1 intermolecular contract of less than 3.4 Å.

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