

SYNTHETIC STUDIES TOWARDS
CLERODANE DITERPENES

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ABSTRACT

The review briefly describes the occurrence, constitution, and biological activity of the clerodane diterpenes, although the synthetic approaches to these natural products have been dealt with in more detail.

This thesis describes attempts to prepare a trans-decalin, suitably functionalised to investigate both the antifeedant activity and to develop strategies for the total synthesis of clerodane related diterpenes. 4 β -Formyl-4 α ,5 α -dimethylcyclohex-2-enone was prepared in 50% overall yield by reaction of tigaldehyde with Danishefsky's diene, followed by hydrolysis of the intermediate adduct. Methods for controlling the stereochemistry of conjugate addition to this enone, and related analogues, have been investigated, the most useful enone being 4 β -(2'-1',3'-dithiolan)-4 α ,5 α -dimethylcyclohex-2-enone. Addition of dialkyl cuprate reagents to this enone resulted in the formation of intermediates containing three of the six relative chiral centres present in the natural products.

In model studies, using 4,4-dimethylcyclohexenone as starting material, the preparation of a trans-decalin related to the clerodane type antifeedants has been achieved. The key step involved addition of divinyl cuprate to 5,5-dimethylbicyclo[4.4.0]dec-1,10-en-2-one, followed by trapping of the resultant regiospecific enolate with formaldehyde to give trans-1 α -hydroxymethyl-10 β -vinyl-5,5-dimethylbicyclo[4.4.0]decan-2-one, which was then transformed into spiro(trans-2 α -acetoxy-1 α -acetoxymethyl-5,5-dimethylbicyclo[4.4.0]decan-10,2' α -oxiran). This compound showed a 72% inhibition of feeding at 100 ppm, when tested against *Locusta migratoria*, comparable to that shown by related natural products.

Further examples of the selenium induced cyclisation reaction of alkenyl substituted β -dicarbonyl compounds have been investigated, and the complete

relative stereochemistry of decalin type products has been assigned.

A novel method for the conversion of enones into the corresponding α -bromo and α -chloro compounds, using the phenylselenium halide and pyridine has been developed.

ACKNOWLEDGEMENTS

I would like to thank Dr. S.V. Ley for his patient encouragement and supervision throughout this work, Bill Jackson who held my hand in the first year and Nigel Simpkins for being so helpful in the last year. Thanks are also due to Geoff Hawkes, Henry Rzepa, Dick Sheppard and David Neuhaus for the many superb NMR spectra.

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Special thanks go to everyone in the Whiffen Laboratory and in the Department for being there.

I express my gratitude to the S.R.C. and also to my parents for financial support.

Maria's patience and help in the preparation of this typescript is greatly appreciated.

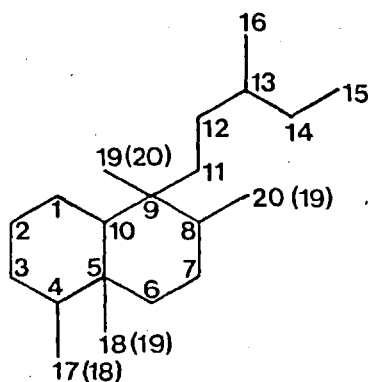
Last but not at all least, thank you to Lorraine.

INTRODUCTION

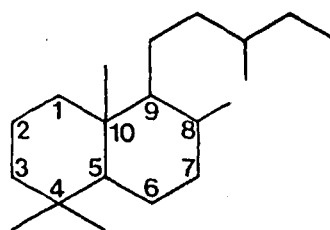
In this review a brief summary of the nature, occurrence and biological activity of the clerodane diterpenoids will be given. The synthetic approaches to these important natural products which have appeared so far will be discussed in more detail.

THE CLERODANES

Over the last few years, a large number of diterpenoids containing the clerodane skeleton (see below) have been isolated^{1,2}. Biosynthetically, the

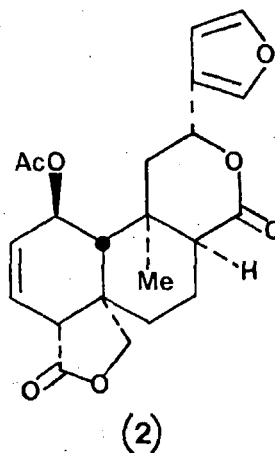
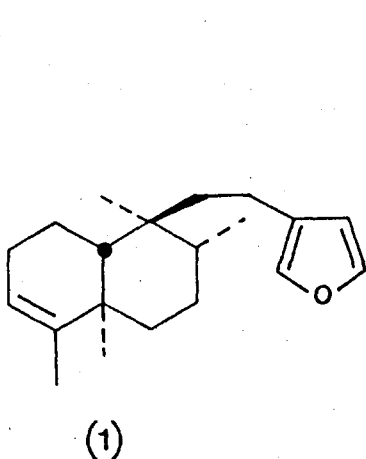


Clerodane Skeleton



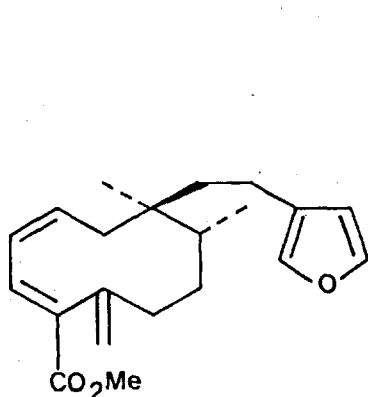
Labdane Skeleton

clerodanes appear to be derived from the labdanes, *via* sequential methyl and hydride shifts^{2a}, which are also widespread in nature. trans-Clerodanes alone are found in at least 21 different genera in 10 families of plants. They occur in various levels of oxidation, for example from the simple annonene* (1)³ to the highly oxygenated compound, splendidin (2)⁴.

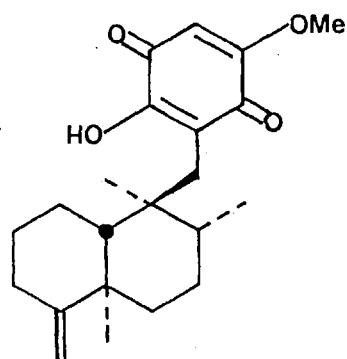


* Throughout this thesis, all structures, save for those representing natural products and compounds derived from natural products, represent racemates. Only that enantiomer bearing a direct relationship to the natural series is shown for convenience.

Also common to clerodane compounds is the huge variety of stereochemical arrangements of the various functional groups. The major distinction between different classes of clerodanes, however, is the particular ring junction stereochemistry of the decalin system, it being either cis or trans fused, although there are even examples such as strictic acid (3)⁵, where the central bond is missing. Some marine organisms are also



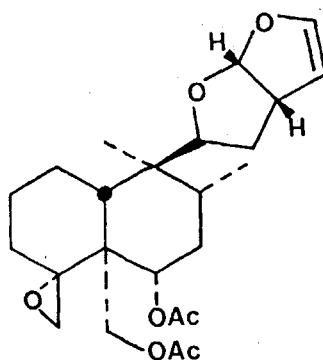
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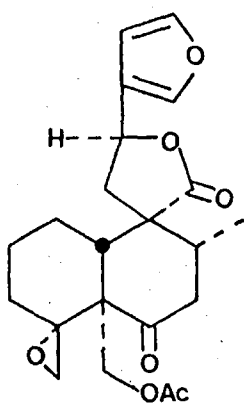
known to produce clerodane related compounds such as ilimaquinone (4)⁶.

There has been considerable confusion in the literature over the absolute stereochemistry of the various clerodane structures. Recently, the absolute configuration assigned to clerodin (5)⁷, the first member of the series, has been revised⁸. This reassignment meant that other structural assignments, such as 19-acetylgnaphlin (6), teucrin P₁ (7) and isofruticolone (8) (and thus fruticolone (10)), which have been shown⁹ to have the same

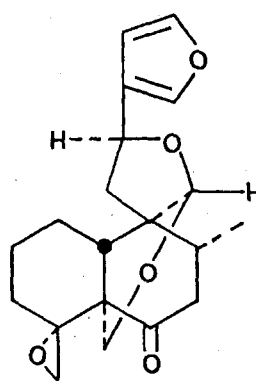


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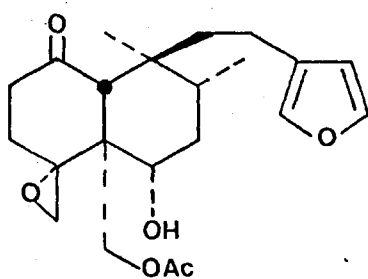
absolute configuration as clerodin, must now be termed neo-clerodanes⁸. Clerodanes, enantiomeric to clerodin, should therefore be now termed ent-neo-clerodanes. Almost all the trans-clerodanes whose absolute configuration has been unambiguously assigned belong to the neo-clerodane series. Unfortunately, this new nomenclature carries with it a risk of confusion as the neo-clerodanes appear to be related biogenetically to ent-labdanes, whilst the ent-neo-clerodanes appear to be related biogenetically to the normal labdanes⁹. Use of 6-oxo c.d.¹⁰ has also led to incorrect assignments¹¹, thereby further confusing the situation.



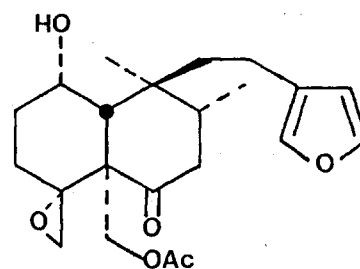
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(7)

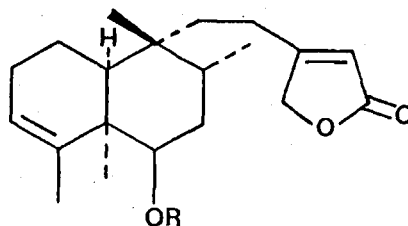


(8)



(9)

The stereostructures of several elongatolides and solidagolactones (eg. 10), have also recently been revised from trans- to cis-clerodanes¹².



(10)

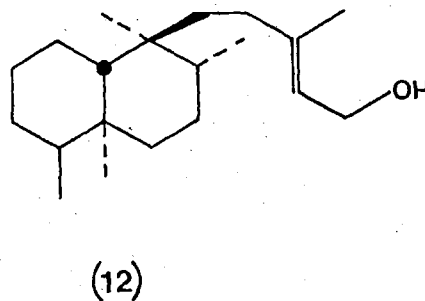
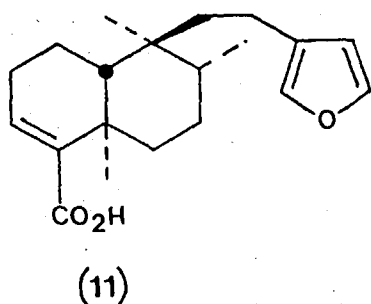
Interest in the clerodanes has been stimulated in recent years by the discovery of their biological activity¹³ as insect antifeedants¹⁴, and as antitumour¹¹, antimicrobial¹⁵, antifungal¹⁶, and anti-peptic ulcer¹⁷ agents. Despite their importance, however, only one successful total synthesis of a clerodane, that of annonene (1), has been reported¹⁸.

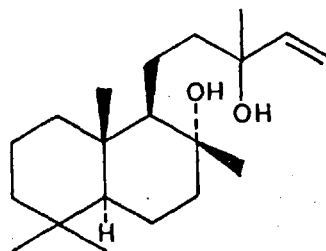
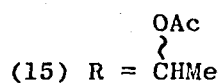
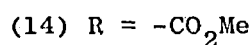
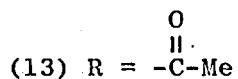
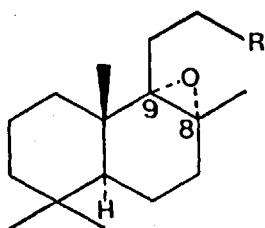
SYNTHETIC APPROACHES TO THE CLERODANE DITERPENOIDS

Although many clerodanes have been known for some twenty years, it is only recently that chemists have become interested in their synthesis, largely as a result of renewed interest in their biological activity. It is proposed to discuss the various approaches to these molecules in three parts: (a) those which lead to simple clerodanes, as exemplified by annonene (1); (b) those approaches aimed at solving the construction of the side-chains of the more complex polyoxygenated clerodanes, e.g. clerodine (5); and (c) those syntheses directed towards the total synthesis of the polyoxygenated clerodanes.

(a) Simple Clerodanes

In 1974, Hadley and Halsall¹⁹ published details of a biomimetic relay synthesis aimed at compounds such as (+) hardwickiic acid (11)²⁰ and kola-venol (12)²¹. They argued that if the clerodanes were in fact derived from labdanes by a series of methyl and hydride shifts, then the Lewis acid catalysed rearrangements of epoxides such as (13-15) might lead directly to the friedo-labdane, i.e. clerodane skeleton.

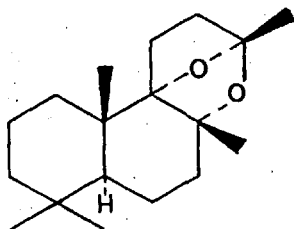




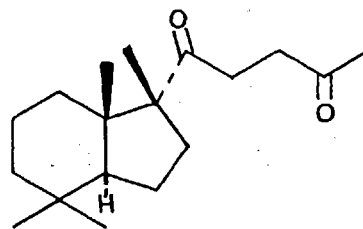
(16)

Unfortunately, because of the confusion over the absolute configuration of the natural products, these authors chose the epoxides (13-15), prepared from schareol (16), as their starting compounds. This would have led to the preparation of the antipodal forms of the natural products. In the event, however, the desired rearrangements did not take place and only multiple products were realised.

For example, on reaction with boron trifluoride etherate, the epoxide (13) gave mainly (17), formed by initial cleavage of the epoxide ring at either C-8 or C-9, followed by cis attack of the carbonyl group on the resulting positive carbanion. The only other significant product from this reaction was the diketone (18).

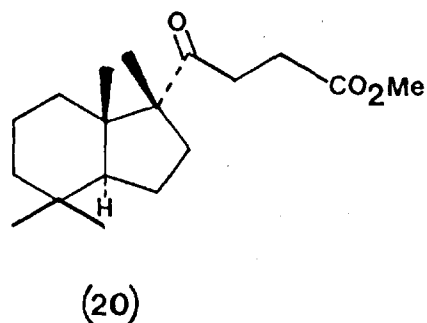
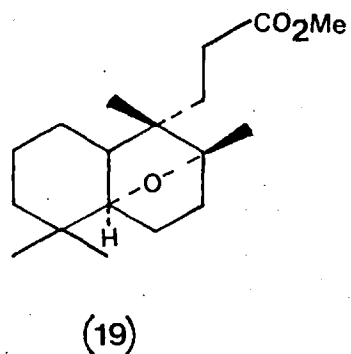


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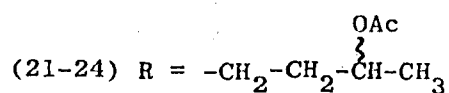
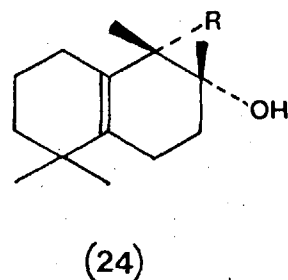
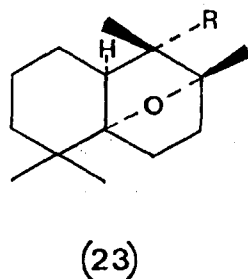
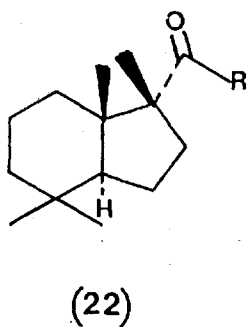
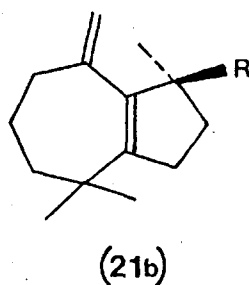
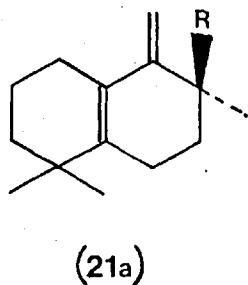


(18)

In a similar manner, rearrangement of (14) led to the formation of (19) and (20). It is worth noting that (19) is in fact the product of a C-10 to C-9 methyl and a C-6 to C-10 hydride shift - two of the four desired shifts.



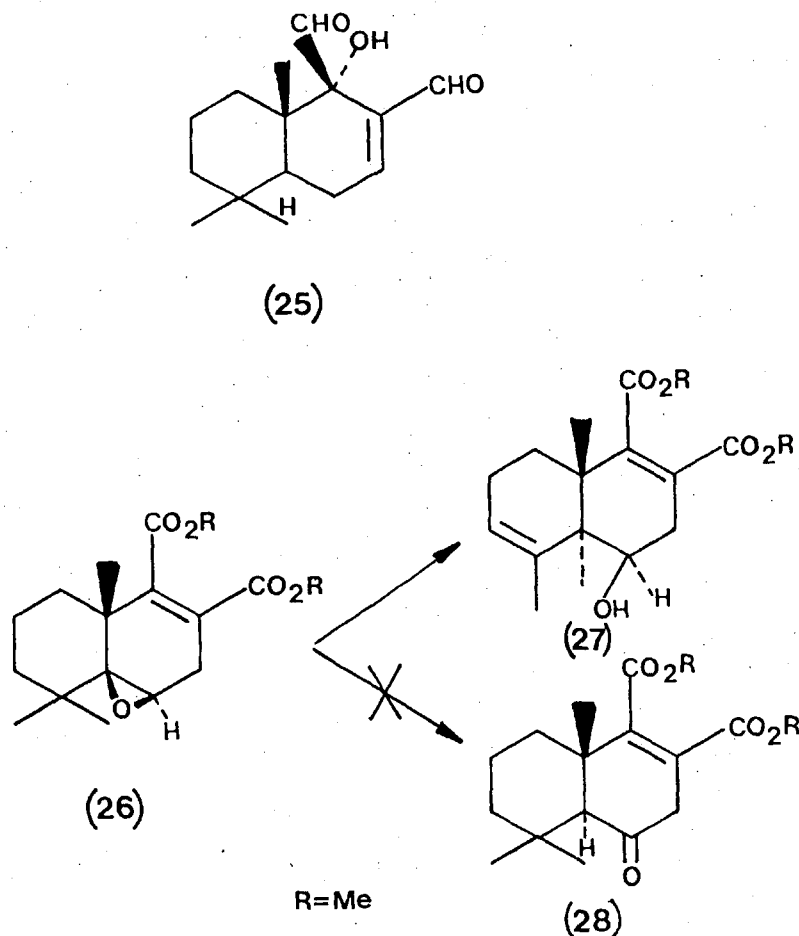
Finally, the rearrangement of the C-13 epimeric epoxides (15) led to the formation of four products (21-24) - the structure of one of which could not be totally assigned, but was proposed as either (21a) or (21b). Again,



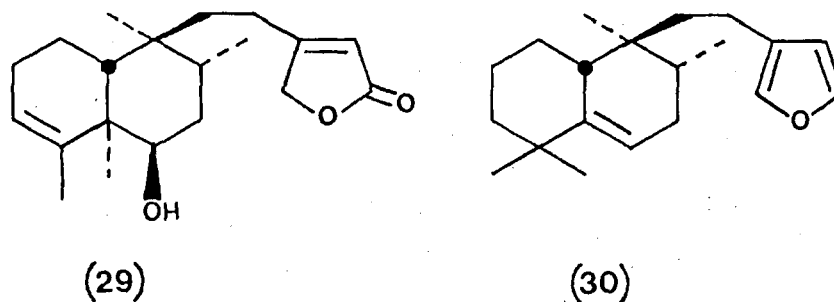
some of these products arise from useful C-10 to C-9 methyl and C-5 to C-10 hydride shifts.

Halsall encountered great difficulty in inducing the C-4 β -methyl group in (13-15) to migrate and attributed this to an inhibiting 1,3-diaxial interaction between C-5 and C-9 that would occur in the desired products. This observation, he considered, posed questions about how the C-4 methyl group migrates to C-5 in the biogenesis of the clerodanes and suggested that the pathway may be more complex than the simple series of methyl and hydride shifts proposed earlier.

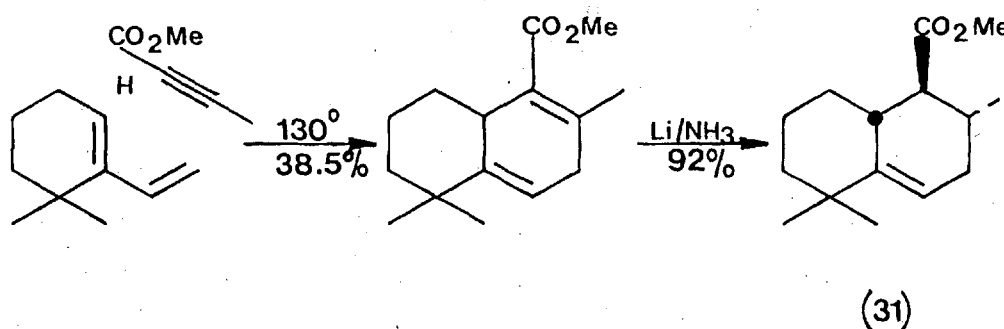
Interestingly, in 1979, Tanis²² reported an example of this type of methyl shift, discovered accidentally whilst working towards warburganal (25)²³, a drimane type antifeedant. He found that the epoxide (26) rearranged with boron trifluoride catalysis to give the alcohol (27) in 67% yield *via* a C-4 to C-5 methyl shift. The expected ketone (28) was not observed. As a consequence of this rearrangement, Tanis speculated upon



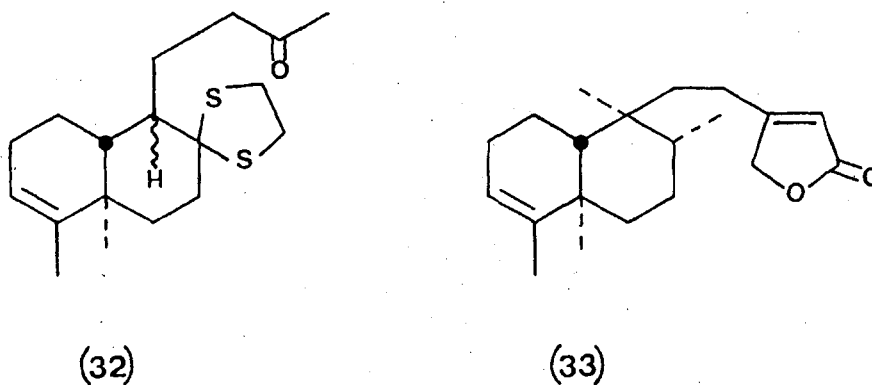
a synthesis of elongatolide A (29)²⁴, *via* the rearrangement of the β -epoxide from compound (30). However, although compound (31) was prepared, further



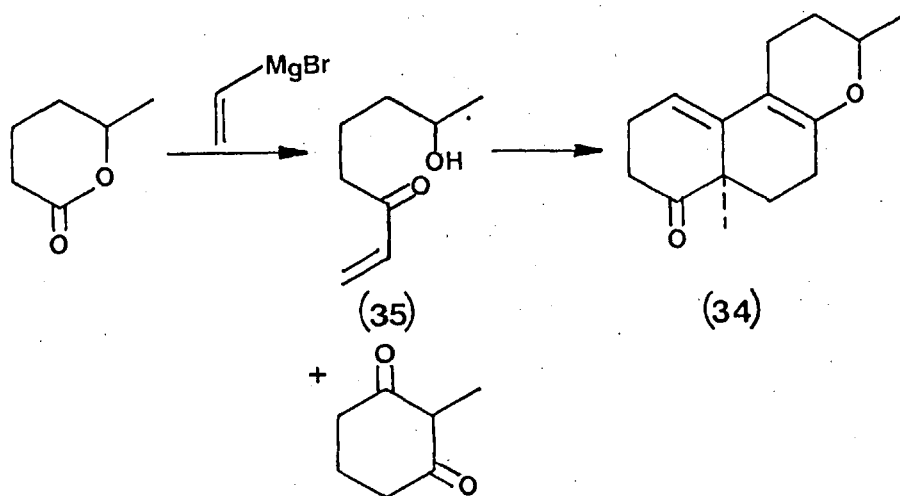
chemistry was not investigated.



The first published approach towards a total synthesis of simple clerodanes was that of ApSimon and Yamasaki^{25,26}. These authors suggested that compound (32) might be a useful synthon for the preparation of clerodanes such as hardwickiic acid (11)²⁰, kolavenol (12)²¹ and solidagolactone (33)²⁷. The key intermediate (34) was prepared using Saucy's method²⁸.

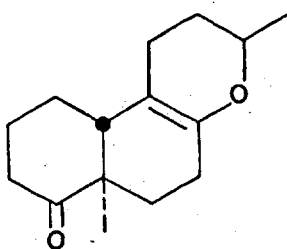


Thus, reaction between 2-methylcyclohexa-1,3-dione and the hydroxy α - β unsaturated ketone (35), itself the product of controlled addition of vinyl magnesium bromide to 5-methyl-5-pentanolide, gave (34) in 36% overall yield (Scheme 1).

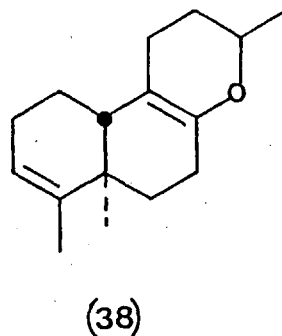
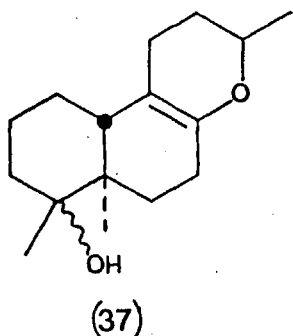


Scheme 1

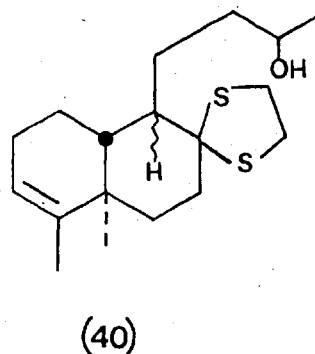
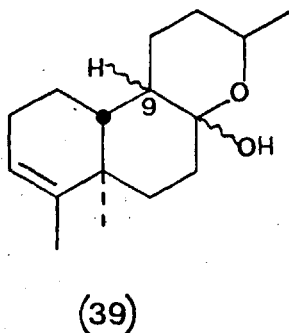
Hydrogenation of (34) to (36) was quantitative and moreover stereo-specific. Subsequent reactions of (36), as preliminary studies towards clerodane synthesis, were then investigated. Thus, addition of methyl Grignard to (36) gave the alcohols (37), which were dehydrated, albeit with difficulty to (38) in 30% yield. Hydration to (39) proceeded in 83%



(36)

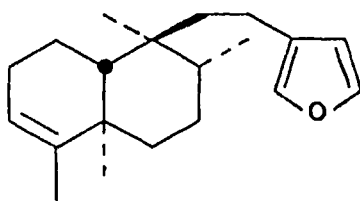


yield, although the product was unfortunately a mixture of epimers at C-9. The next step in the synthesis involved thioketalisation with ethylene-1,2-dithiol and boron trifluoride etherate to give (40) in 64% yield. This



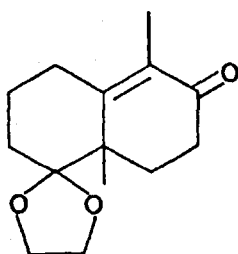
reaction enabled differentiation between the C-8 ketone and a subsequent C-13 ketone. Thus, Sarret oxidation of (40) gave the diketone equivalent (32). Although the yield of this step, at 45%, was not optimised, the earlier low yields and the non-stereospecific hydration meant that the yield of the desired isomer of (32) was between 1 and 2% for the eight steps and, therefore, this was not a useful synthetic sequence. This approach has since been abandoned²⁹.

The first reported and, so far, the only total synthesis of a clerodane was that of annonene (1), published in 1979 by Kakisawa¹⁸.

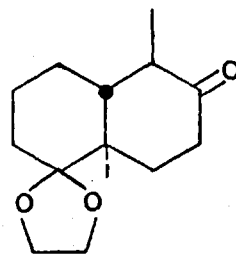


(1)

The starting material for this synthesis was the Wieland-Miescher ketone which was readily converted to the acetal (41). Birch reduction gave the trans-decalone (42), the ring junction stereochemistry being determined by comparison with known compounds³⁰. After the addition of

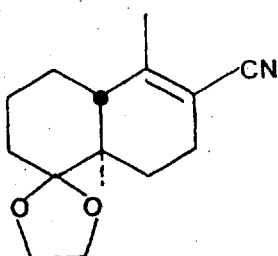


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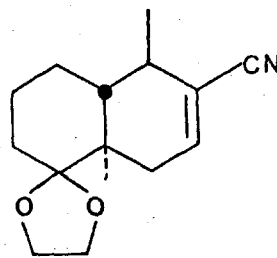


(42)

cyanide to (42), the resulting cyanohydrin was dehydrated to the nitriles (43) and (44) as a 1:1 mixture of regioisomers, in 84% overall yield from (42). The nitrile (43) was converted to the allylic alcohol (45) in 60%

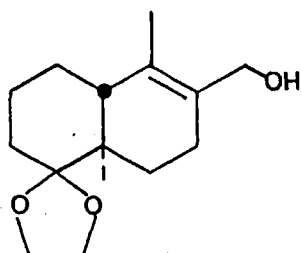


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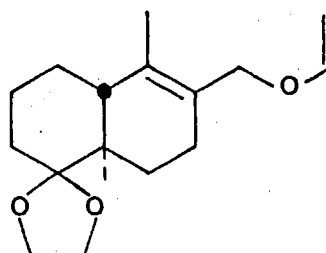


(44)

yield by sequential reduction with Dibal, and sodium borohydride. Vinylation of the alcohol (45) with ethyl vinyl ether and mercuric acetate next gave the key intermediate (46) in 44% overall yield from (43).

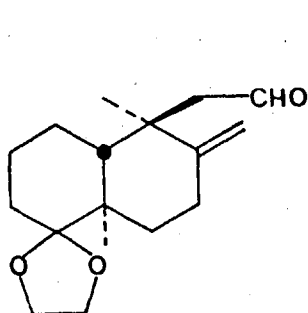


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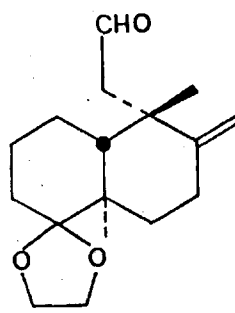


(46)

Clasien rearrangement of (46) gave a mixture of aldehydes (47) and (48) in 95% yield. The steric bulk of the axial C-5 methyl group hindered attack

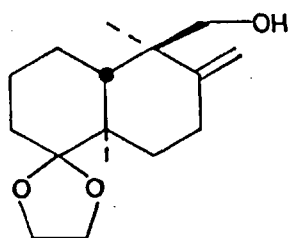


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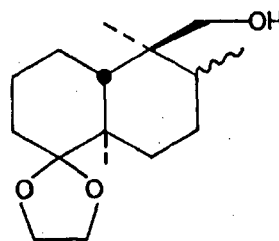


(48)

of the vinylic terminal from the α face, and so the β -formyl methyl compound (47) predominated over (48) by a ratio of 85:15. The desired aldehyde (47) was eventually isolated in 70% yield. Reduction to alcohol (49) followed, but hydrogenation to (50) proceeded from both sides to give a product that was found to be a 1:1 epimeric mixture at C-8. Separation of the isomers was not possible at this stage, and so after reoxidation to the aldehyde, reaction with 2-furyl lithium, followed by acetylation and reductive removal of the

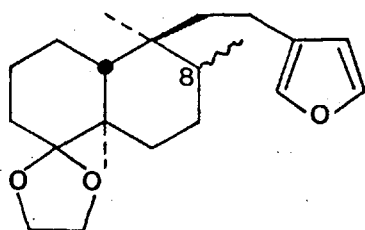


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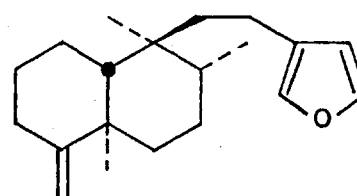


(50)

acetoxyl group, the furans (51) were obtained, again as a 1:1 C-8 epimeric mixture in 72% yield. Separation was possible and afforded a sample of pure



(51a) 8- α
(51b) 8- β

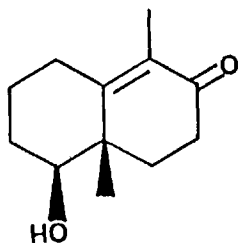


(52)

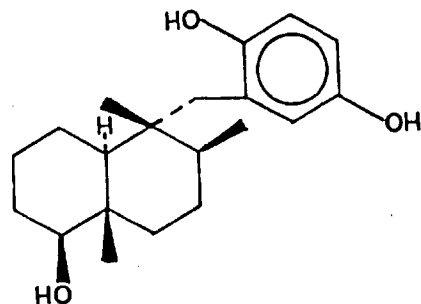
(51a). Conversion to (52) was achieved in 78% yield and using the known procedure³¹, (52) was eventually converted to racemic annonene.

Thus, in thirteen steps, two of which gave isomeric mixtures, a synthesis of racemic annonene was achieved in $\approx 3\%$ overall yield. Although successful, it is not a synthesis that could be applied to more complicated, polyoxygenated clerodanes.

A derivative (53) of the Wieland-Miescher ketone was the starting point for an alternative approach to clerodane systems, reported by Sarma³², although in this case the synthesis was directed towards avarol (54)³³, a marine sesquiterpenoid.

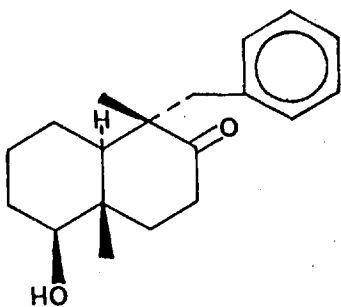


(53)

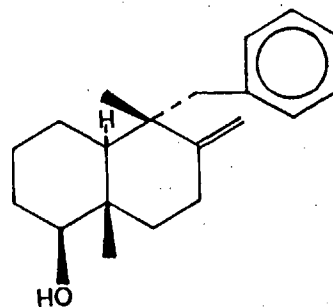


(54)

Thus reductive alkylation of (53) gave (55) in 40% yield, the stereochemistry of which was assumed. Wittig reaction of (55) then gave (56) in 80% yield. Catalytic hydrogenation gave a 4:1 mixture of products, the

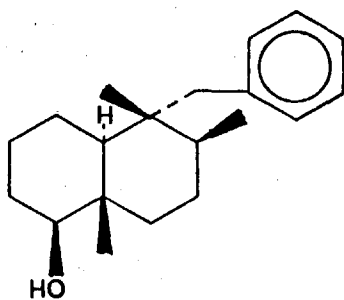


(55)

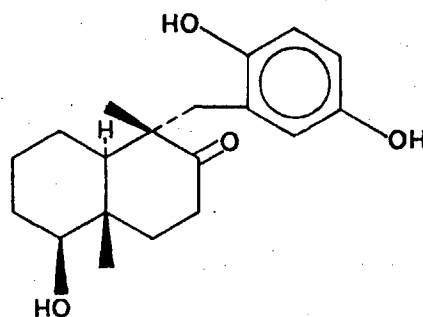


(56)

major isomer of which, after separation, was thought to be (57).



(57)



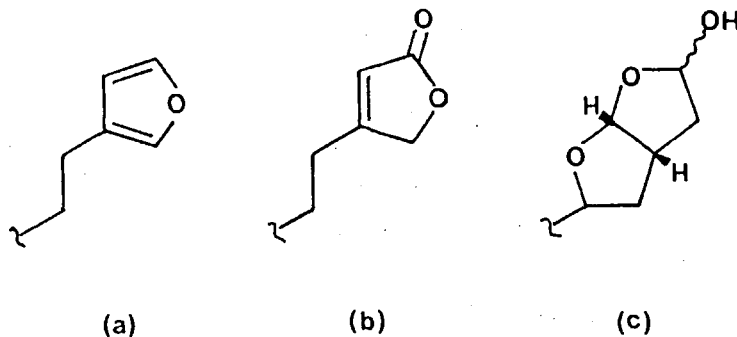
(58)

Attempts to selectively oxidize the aromatic ring in (57) failed, and so steps towards the synthon (58) as an intermediate in the synthesis of avarol (54) are currently being undertaken.

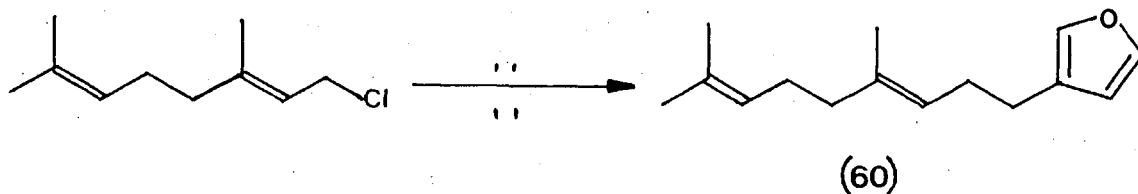
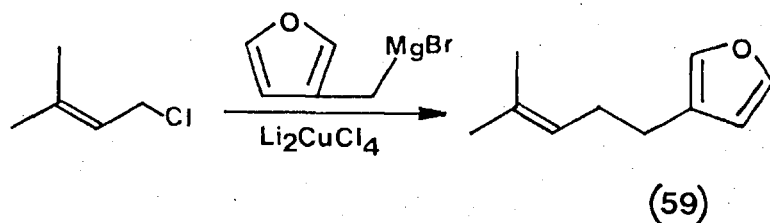
APPROACHES TO POLYOXYGENATED CLERODANES

(a) Synthesis of the oxygenated side-chain

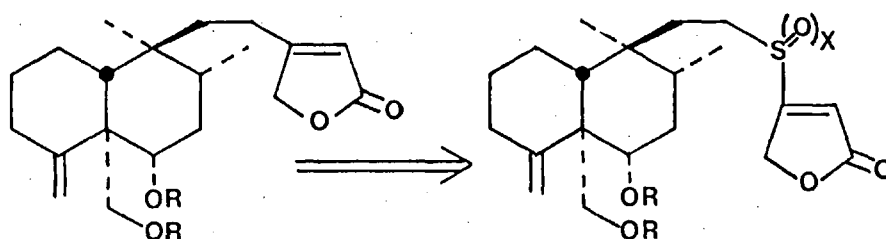
Three different side-chains are common to the clerodane diterpenoid natural products, namely (i) furan (a), (ii) the butenolide (b), and (iii) bis-hydrofuranyl systems (c).



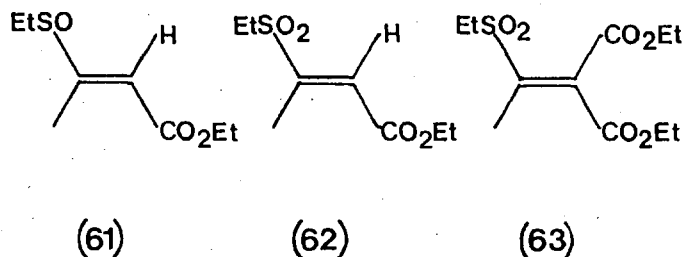
Tannis²² investigated methods of attaching a furan ring to model compounds and succeeded in preparing perillene (59)³⁴ and dendrolasin (60)³⁵ in high yield from the furano Grignard reagent and the corresponding allylic halide, in the presence of Kochi's³⁶ catalyst. No further examples were, however, reported.



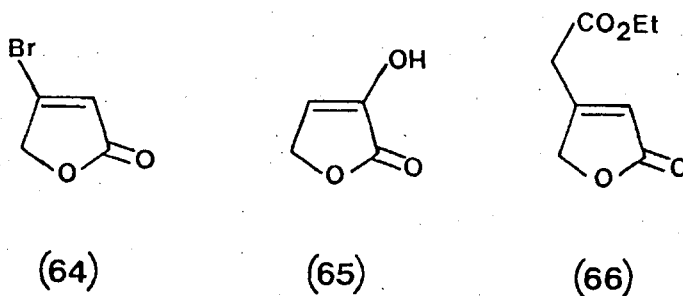
Lee³⁷ studied the possibility of using the Ramberg-Bäcklund rearrangement as a method of introducing the γ -lactone side-chain of the ajugarins³⁸.



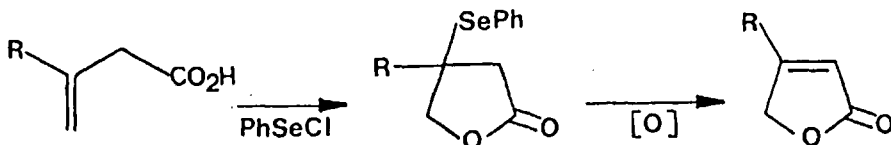
However, using the sulfoxide (61), and the sulphones (62) and (63) as models, he failed to observe the desired rearrangement products and thus the method was abandoned.



Similarly, Lee³⁷ also studied addition-elimination reactions to the lactone (64) and alkylations of the lactones (65) and (66), but without success.



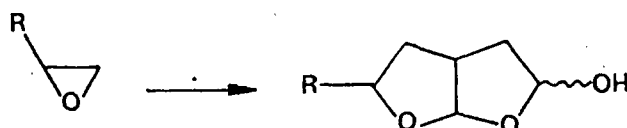
Together with Liotta's group, Goldsmith and Lee^{37,39} investigated the possibility of using the phenylselenolactonisation of β - γ unsaturated acids as a method of generating butenolides (Scheme 2). However, the reaction was



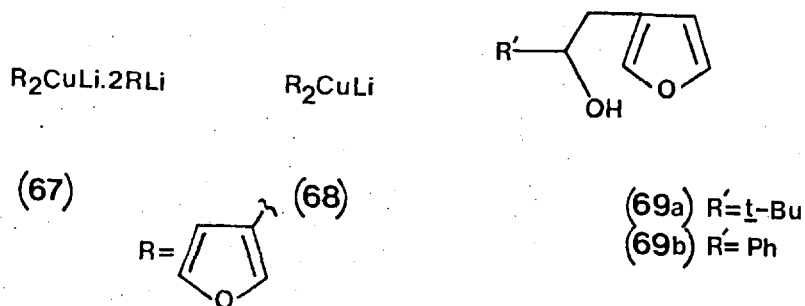
Scheme 2

not a general process and was not applicable to ajugarin synthesis.

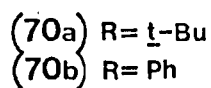
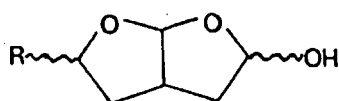
Kojima and Kato⁴⁰ have developed a method for the conversion of epoxides to perhydro[2,3-b]furans as probes for the biologically active centre, as these are common structural units for a number of natural systems. The method



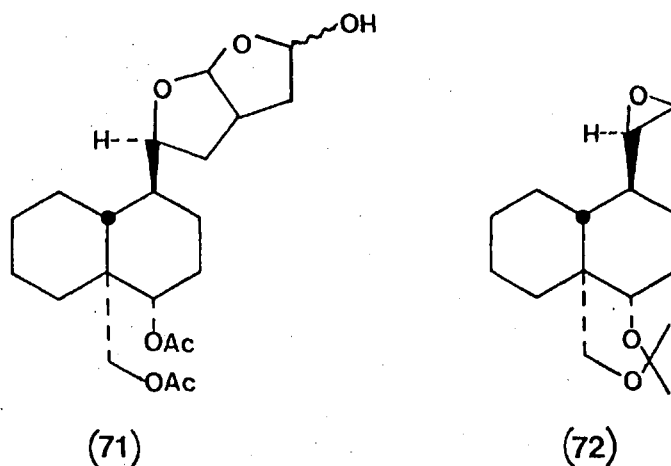
involves reaction of an epoxide with lithium di(3-furyl)cuprate, 2-furyl lithium complex (67)⁴⁰, or with lithium di(3-furyl)cuprate (68)^{40a,b} to give the furano alcohols (69). Reaction of (69) with (i) Br₂ in methanol



in the presence of potassium acetate, (ii) hydrogen in the presence of Raney-Nickel, and (iii) perchloric acid, according to the method of Finch⁴¹ led to the formation of a diastereoisomeric mixture of hemiacetals (70), in high yield. The product mixture could be equilibrated to give almost all the product with the natural relative stereochemistry. Unfortunately, neither (70a) nor (70b), nor simple derivatives of them, were found to be good



antifeedants against *Spodoptera litura* ^{40b}. This lack of activity, the authors reasoned, was due to the instability of the hemiacetals. However, these workers synthesised compound (71) *via* (72) in the hope that the decalin moiety would confer stability on the hemiacetal portion and, therefore, improve the antifeedant activity ^{40d,e}. The synthesis of (72) is shown

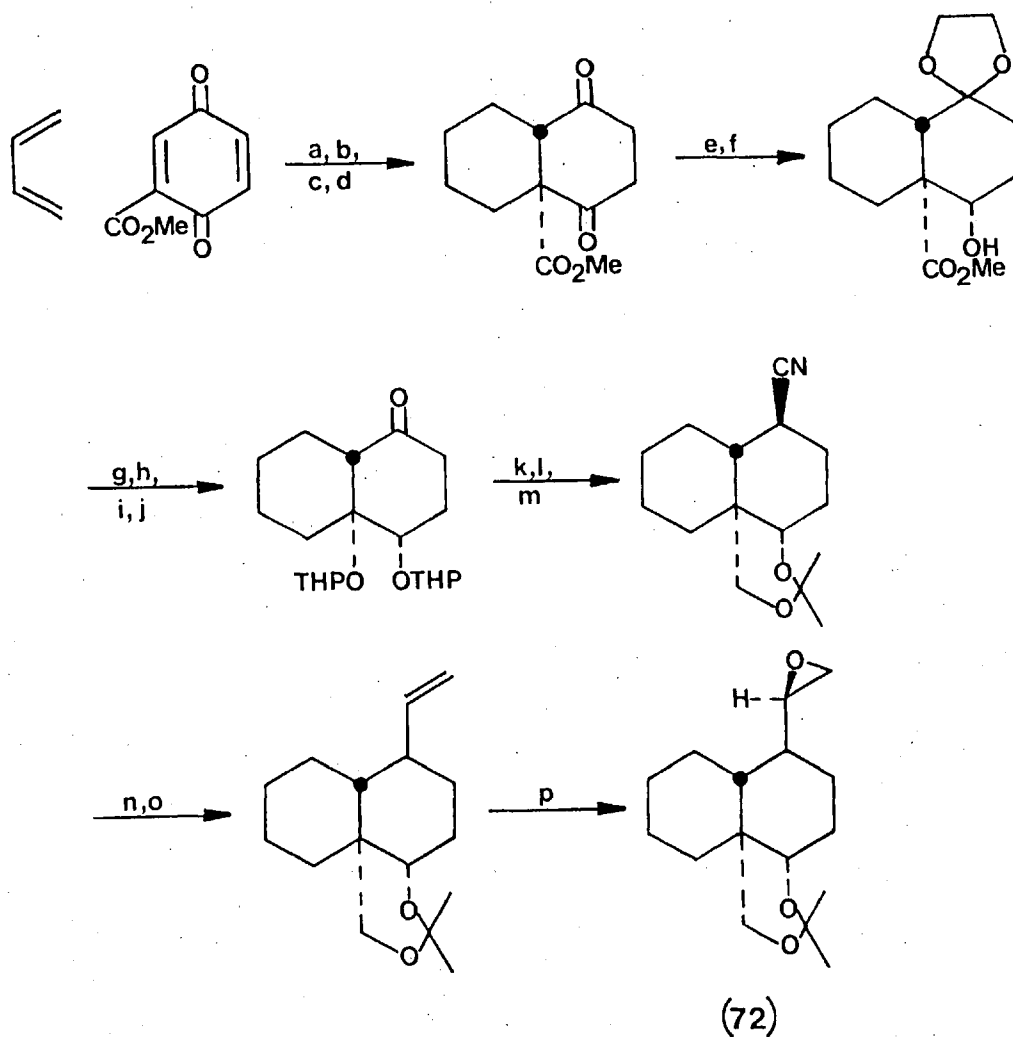


schematically below.

The epoxide (72) was then converted, as before to the hemiacetal diacetate (71) contaminated with a small amount of the C-11 isomer. Thus, in 18 steps the clerodin homologue (71) was prepared in 6% overall yield. These authors encountered severe problems in retaining the trans-nature of the ring junction which necessitated the replacement of protecting groups at several stages.

When tested against *S. litura* *F*, compound (71) and simple analogues showed similar (poor) activity to that shown by the previous compounds (70) ^{40e}.

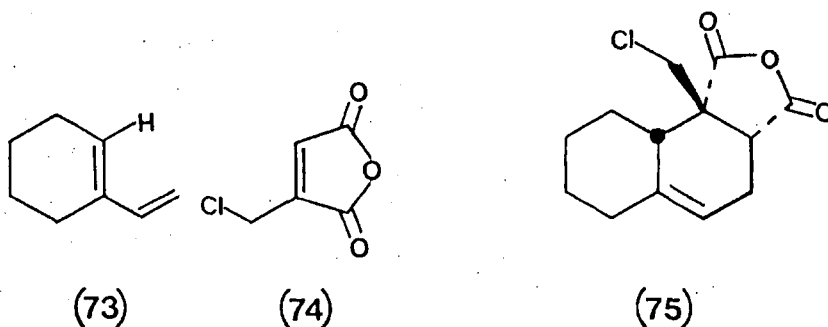
However, these workers still assert that the hemiacetal system is the active centre of antifeedant activity against *S. litura* F and are currently attempting to prepare analogues of (71) that are more closely related to the natural products.



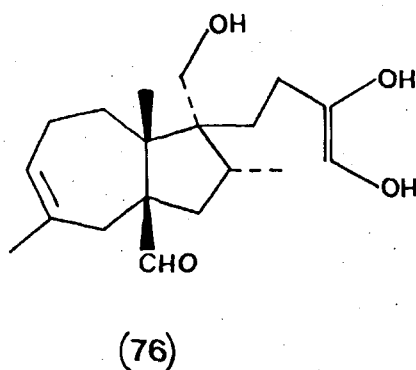
Reagents: (a) $\text{SnCl}_4/\text{R.T.}$; (b) Zn/HOAc ; (c) NaOMe ; (d) H_2 , 10% Pd/C ; (e) NaBH_4 ; (f) $\text{HO}-\text{CH}_2\text{CH}_2-\text{OH}/\text{pTSA}$; (g) LAH ; (h) $\text{pTSA}/80\% \text{ AcOH}-\text{H}_2\text{O}$; (i) KOH ; (j) $\text{Dihydropyran}/\text{pTSA}$; (k) $\text{TosMIC}/t\text{-BuOK}$; (l) pTSA/MeOH ; (m) $\text{X}(\text{OMe})_2/\text{pTSA}$; (n) Dibal ; (o) $\phi_3\text{P}=\text{CH}_2$; (p) $m\text{-CPBA}/\text{Na}_2\text{HPO}_4$.

(b) Approaches towards the total synthesis of polyoxygenated clerodanes

So far, there have appeared in the literature only five different approaches to the total synthesis of the polyoxygenated clerodanes. The earliest reported was that of Tokoroyama⁴², in which the Diels-Alder reaction between 1-vinylcyclohexene (73) and chloromethyl maleic anhydride (74) furnished an adduct (75) in 72% yield which contained some of the appropriate functionality and stereochemistry required for clerodane synthesis.

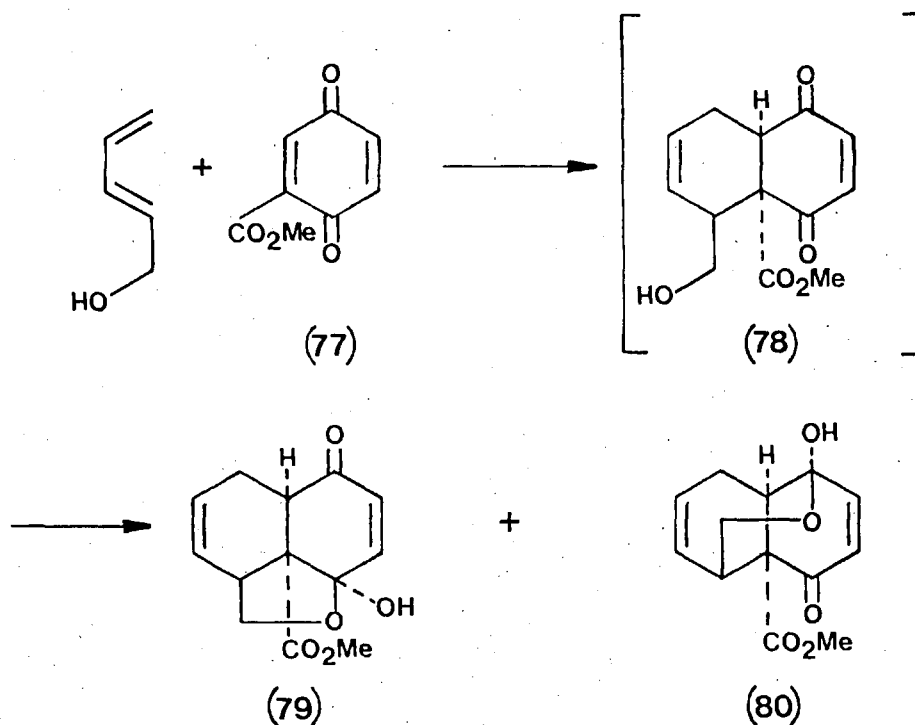


Most of Tokoroyama's early work in this field relates to proving the structure of the adduct (75), although in a later paper⁴³, this intermediate was used as the basis for a rather clever, if long-winded, synthesis of the unusual perhydroazulenoid portulal⁴⁴ (76). It is worth noting that this



diterpene is itself thought to be derived *via* the rearrangement of a labdane system, as are clerodanes. Unfortunately, the method for converting (75) to (76) cannot be applied to clerodane synthesis.

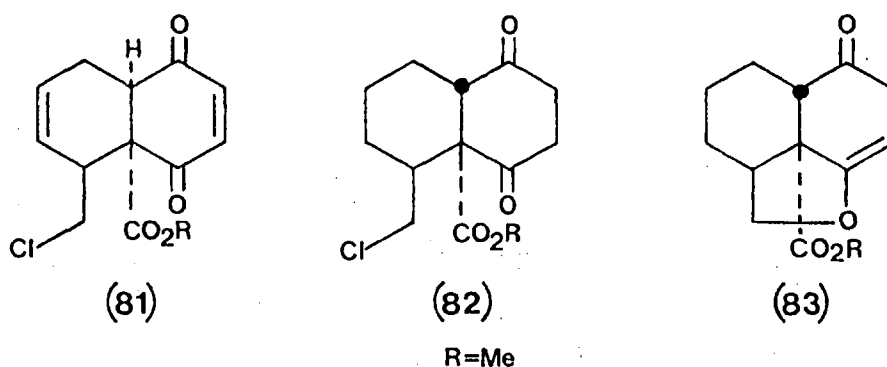
In 1978, Goldsmith's first approach⁴⁵ to the ajugarins began along similar lines to that used by Kojima and Kato^{40d,e} discussed above. Thus, the quinone (77) was reacted with 1-hydroxymethylbutadiene, however, the initial adduct (78) formed, under the reaction conditions, a mixture of isomeric hemiketals (79) and (80) (Scheme 3). Despite several further synthetic transformations,



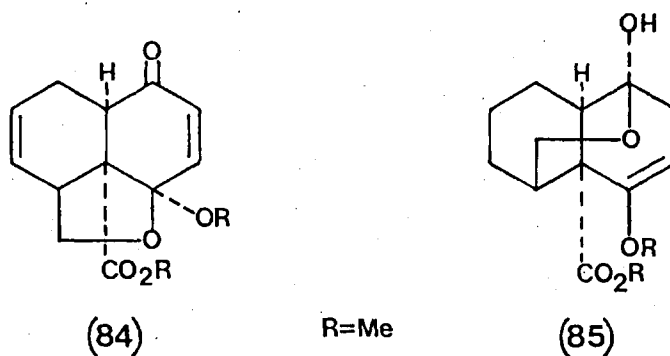
Scheme 3

it was at first found impossible to open the hemiketal rings to synthetically useful compounds. Instead, the initial diene was changed to 1-chloromethylbutadiene and the corresponding adduct (81) was obtained in 79% yield.

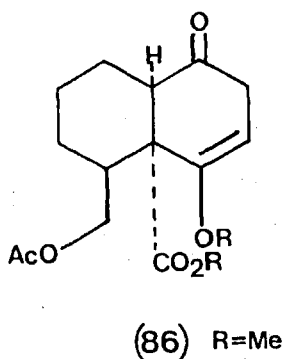
Reduction of (81) using zinc in acetic acid also epimerised C-10 and catalytic hydrogenation gave (82) in 88% yield. Unfortunately, attempted elimination (DBN) to the exomethylene compound failed, furnishing instead the enol ether



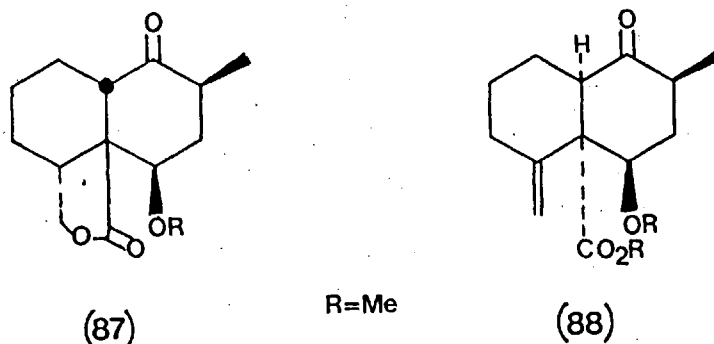
(83). Undeterred, they returned to the mixture of isomeric hemiketals (79) and (80) and converted them to a single ketal (84) using methanol and an acid catalyst. Zinc in acetic acid reduction cleaved the ketal, but again a hemiketal (85) was isolated. However, after hydrogenation, it was possible



to trap out the hydroxyketone form by acetylation, to give (86). A recent publication by Liotta⁵¹ gave details of how Goldsmith converted the decalin

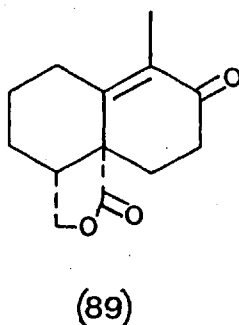


lactone (87) to the exomethylene decalin ester (88) *via* alkyl oxygen fission with PhSe^- , followed by reaction with diazomethane, oxidation and selenoxide elimination. Although no further details were given, it seems likely that



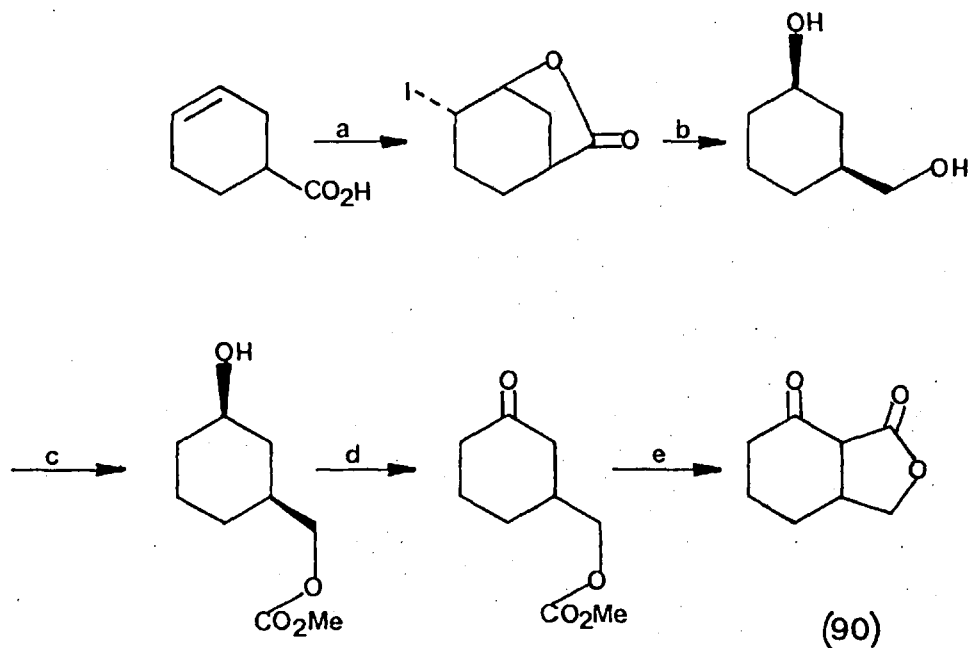
(87) could have been prepared from Goldsmith's published intermediate (86) *via* standard methodology. Again, this appears to be a relatively long synthetic approach and it is questionable as to whether or not (88) could serve as a useful intermediate in a clerodane synthesis.

Goldsmith's second approach⁴⁷ involved the preparation of a Robinson annulation product (89) which, he suggested, would be a useful synthon for clerodane synthesis. As shown in Scheme 4, straight forward chemistry



furnished the bicyclic lactone (90) and annulation with ethyl vinyl ketone gave (89) in about 13% overall yield from the olefinic acid. Further transformations of (89) have not yet been reported.

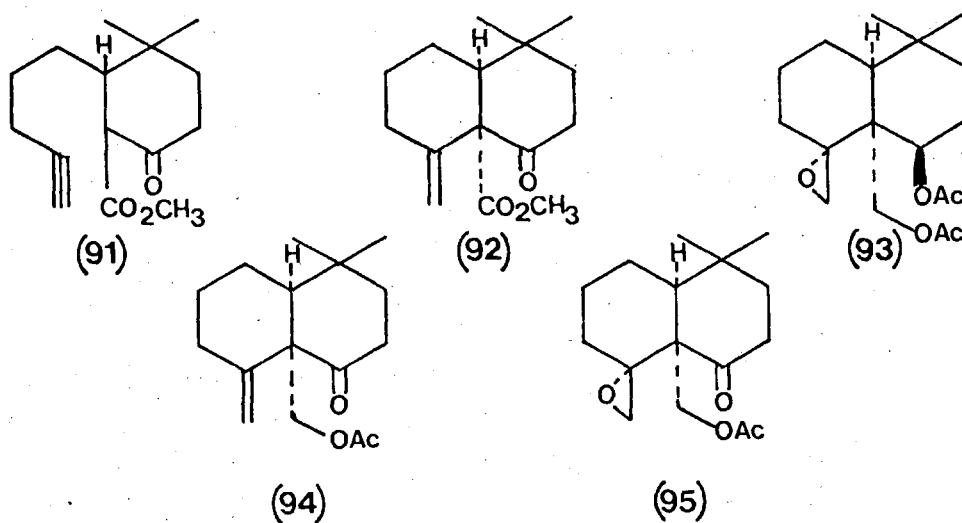
Of the two remaining approaches, one was carried out in these laboratories by Jackson and Ley⁴⁸. Using a completely novel strategy the acetylenic β -oxo-ester (91) (prepared using standard methodology from 4,4-dimethyl-



(a) KI/NaHCO_3 ; (b) LiAlH_4 ; (c) $\text{py}/\text{ClCO}_2\text{CH}_3$; (d) CrO_3 ; (e) NaH

Scheme 4

cyclohexenone) was thermally cyclised to give the cis-decalin (91) in 53% overall yield. Reduction, followed by hydroxyl directed epoxidation⁴⁹ and acetylation gave the cis-epoxydiacetate (93) (71%). Simple modification of the route provided other analogues such as (94) and (95).

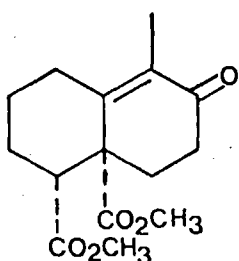


When tested against *S. littoralis* and *Heliothis virescens*, compounds (93) and (95) did not show significant activity. However, against *Locusta migratoria* at 1000 ppm, the diacetate (93) produced a 72% inhibition of feeding, while the ketone (95) was less than half as active. This result indicates that the epoxydiacetate functionality is a necessary prerequisite

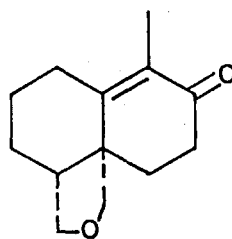
for antifeedant activity against *L. migratoria*.

The final method discussed is the continuing approach to the ajugarins by de Groot and co-workers⁵⁰. Although their route involves many steps, it is the best published route to date and should be applicable to the synthesis of the natural compounds.

Starting with the diester (96)⁵¹, ketone protection, ester reduction, dehydration and deprotection, gave the ether (97) in 84% overall yield. Reductive alkylation gave the trans-decalone (98) in 70-85% yield, thereby

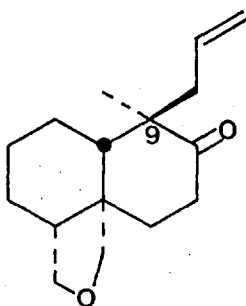


(96)

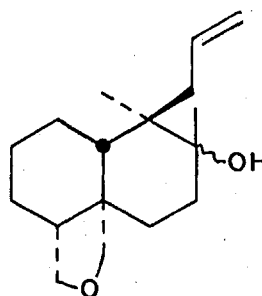


(97)

controlling both the stereochemistry of the ring junction and that at C-9. Unfortunately, the next step - addition of methyl lithium - did not proceed as expected. Instead, deprotonation was a major side-reaction and a 95% conversion of (98) to the alcohols (99) could only be achieved by a repeated addition, hydrolysis, addition cycle. Dehydration then gave the olefin (100)

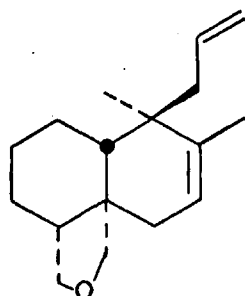


(98)

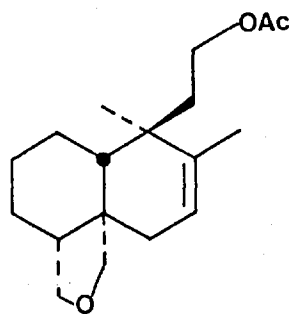


(99)

in quantitative yield. The terminal olefinic bond in (100) reacted preferentially with 9-BBN, and oxidative work up, followed by acetylation, gave the acetate (101) in 92% yield. C-6 functionality was introduced by allylic

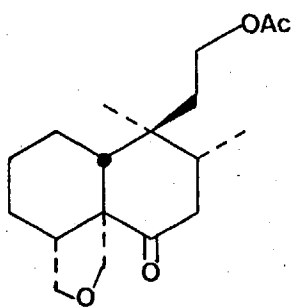


(100)

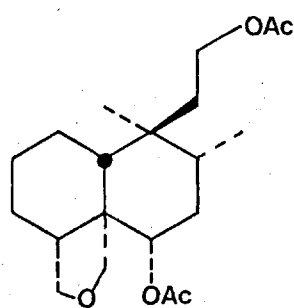


(101)

oxidation (CrO_3 in acetic acid, 55% yield), and catalytic hydrogenation of the intermediate proceeded stereospecifically to give (102) in 54% yield from (101). Borohydride reduction of (102) was not stereospecific (instead a 4:1 ratio of equatorial to axial alcohols was obtained), but after acetylation, the desired isomer (103) was obtained in 69% yield from (102). Thus, by this stage the



(102)



(103)

carbon nucleus necessary for clerodane synthesis had been assembled together with five out of six relative chiral centres, in 12 steps, with an overall yield of 19%. Further transformations of this system are expected⁵².

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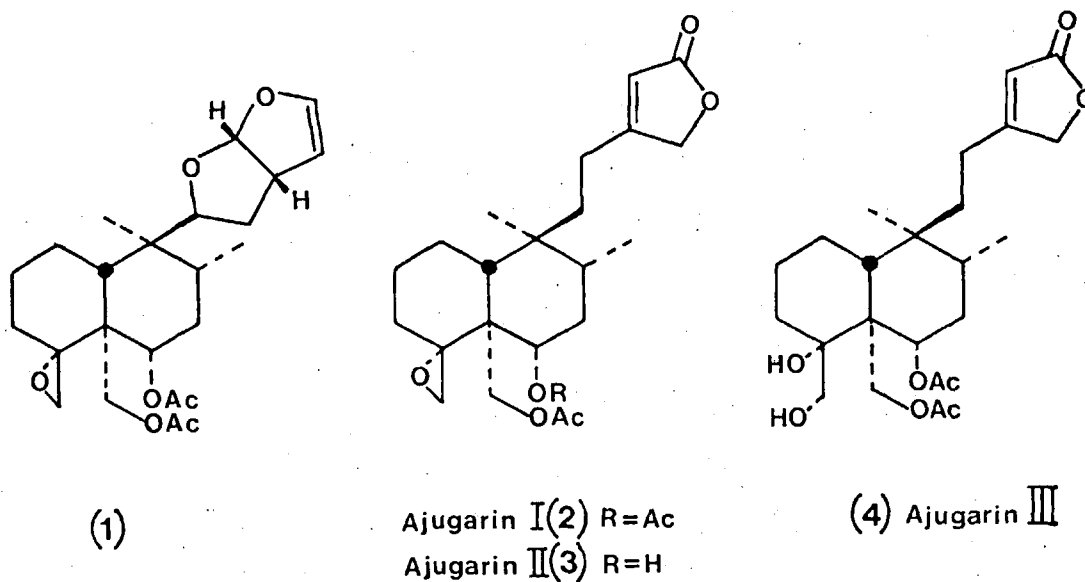
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RESULTS AND DISCUSSION

INTRODUCTION AND INITIAL APPROACHES

The biological activity associated with a number of polyoxygenated clerodane diterpenes such as clerodin (1) and the ajugarins (2-4) has stimulated considerable synthetic interest in recent years (see review).

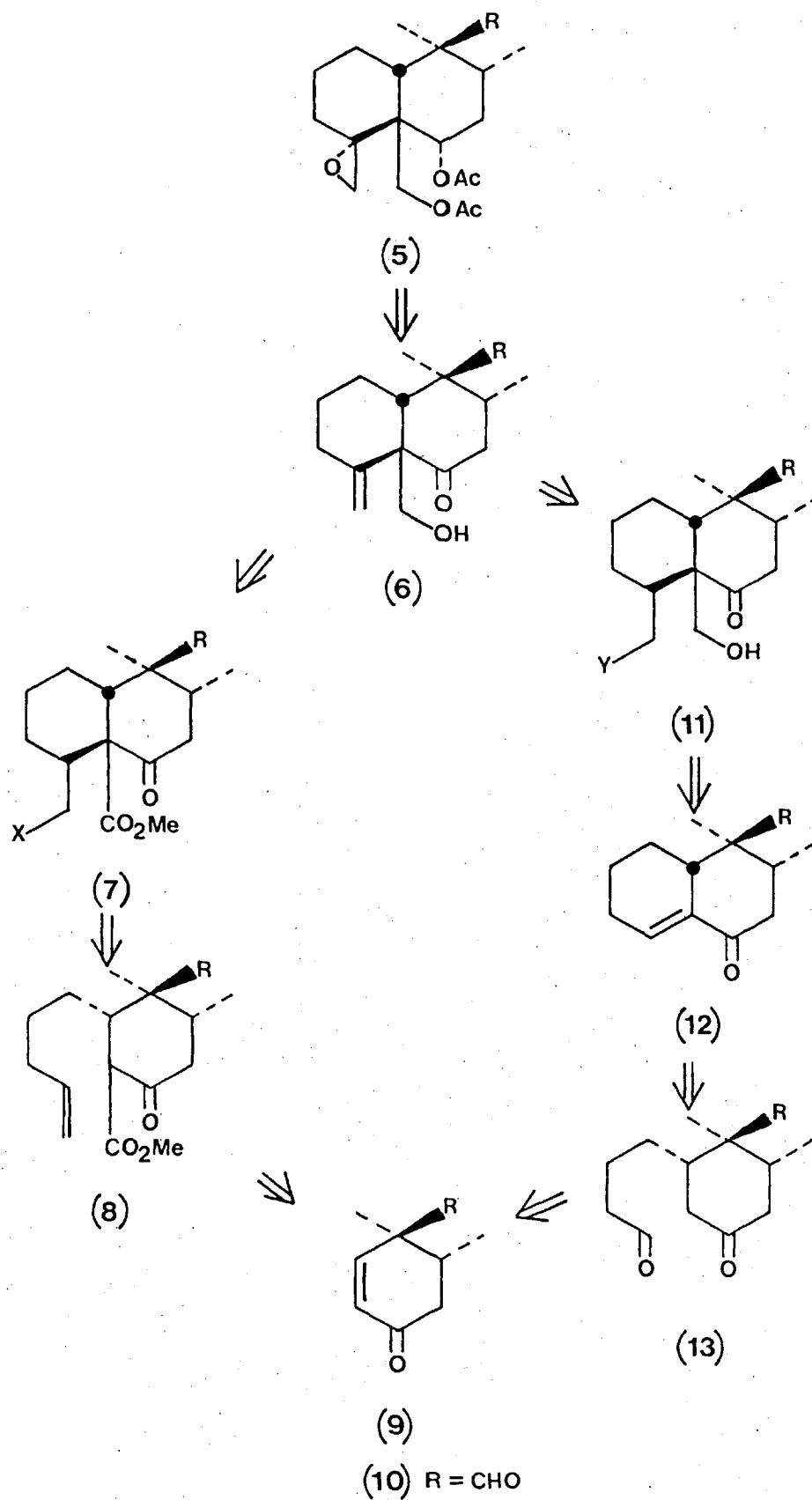


Despite this synthetic activity, no total synthesis of these important compounds has yet appeared. The initial approach to these molecules developed in our laboratories¹ has led to the discovery of new methods for the construction of ring systems some of which have been further developed and will be discussed later.

In overall terms, what we require in our synthetic approach are (a) methods by which we can control the six interconnecting chiral centres of the decalin moiety, and (b) versatility such that it would be possible to prepare related analogues so that the biological activity can be probed in more detail.

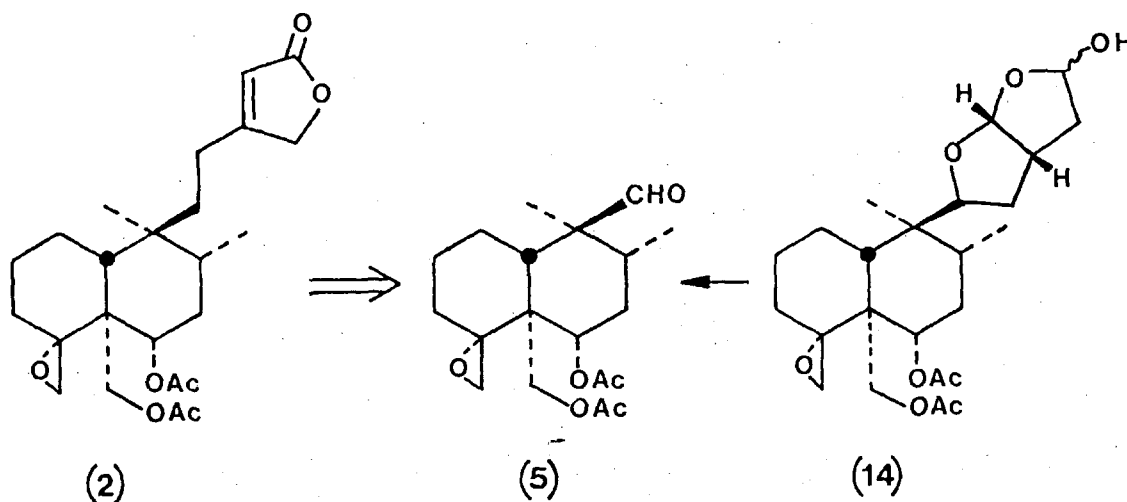
Retrosynthetically, therefore, two basic routes have been considered,

and are illustrated in broad outline in Scheme 1. These approaches can, of course, be further subdivided as subsequent chemistry will show.



Scheme 1

It was hoped that compound (5, R = CHO) would act both as an intermediate in the total synthesis of various polyoxygenated clerodanes, and as a relay compound in the conversion of clerodin hemiacetal (14) to ajugarin I (2), presently being attempted in these laboratories², Scheme 2.

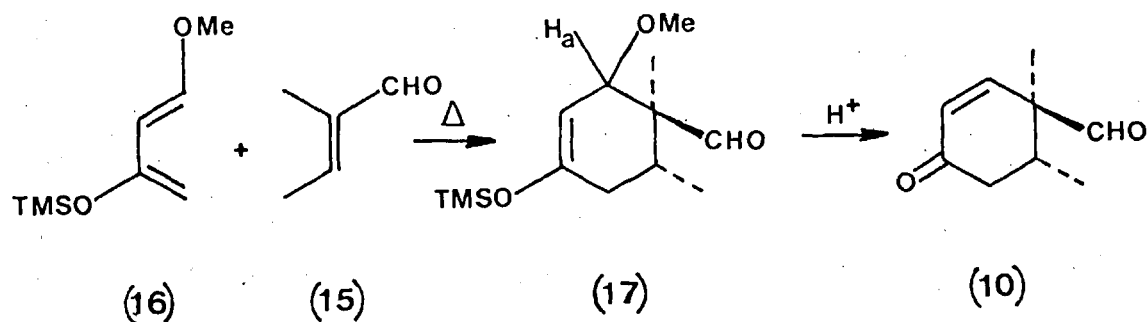


Scheme 2

Before going on to discuss the detailed synthetic steps, it should be pointed out that in this thesis while much of the early work did not provide a useful strategy for clerodane synthesis, a number of interesting and useful reactions were discovered. Towards the end of the thesis, however, a route was developed that, it is believed, can be applied to the total synthesis.

Despite all the possible variations, the basic premise of each of the synthetic routes discussed earlier was that the initial functionality required in (8) or (13) could be assembled *via* the conjugate addition of a suitable side-chain to a common enone (9). The choice of the R group in the synthesis is important as it must be capable of elaboration to the various side chains. R = CHO was therefore an obvious candidate as this could, in principle, be constructed stereo- and regio-specifically

by a Diels-Alder reaction between (E)-2-methyl-2-butenal (tigaldehyde, 15) and Danishefsky's diene (16), Scheme 3.

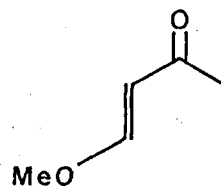


Scheme 3

The presence of the aldehyde moiety in this sequence would facilitate the initial reaction with the electron rich diene, while the 2-trimethylsilyloxy and 4-methoxy groups on the diene are known³ to be latent enone functionalities. Simple hydrolysis of (17) would produce the desired enone-aldehyde (10). Consequently, tigaldehyde (15) was prepared by pyrolysing isoprene monoepoxide (18), over alumina according to the literature procedure⁴. Danishefsky's diene (16) was prepared from 4-methoxy-3-buten-2-one (19) using an improved version of the literature method³.



(18)

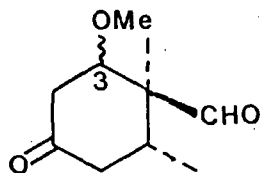


(19)

Initial hopes that the Diels-Alder reaction would occur under relatively mild conditions (for example, in refluxing toluene) were not realised - this was probably due to some steric interaction in the transition state caused by the methyl groups. Attempts to use conventional Lewis acid catalysis in the reaction led to decomposition of the diene. Eventually the desired reaction was observed when the neat reagents were heated together in a sealed, base-washed, Carius tube at 124°C for 14 h. ^1H NMR analysis of the reaction mixture showed, apart from the resonance due to excess tigaldehyde (15), two further aldehydic resonances at δ 9.58 and 9.50, in the ratio 5:2. After removal of all the volatile components in the mixture (primarily tigaldehyde (15) and 4-methoxy-3-buten-2-one (19), from decomposition of the diene), a more complete analysis of the ^1H NMR and IR spectra of the residue showed that it was composed of an epimeric mixture of isomers of the required adduct (17). The ^1H NMR showed resonances at δ 9.58 and 9.50 (CHO); 5.0 and 4.75 (olefinic); 4.05 and 3.55 ($\text{CH}-\text{OMe}$); and at 3.15 ($\text{O}-\text{CH}_3$). The rest of the spectrum was consistent with the structural assignment, thus the coupling constants for H_a in both isomers of (17) confirmed that they were indeed stereoisomers (caused by "endo" and "exo" attack) and not regioisomers, and is in accord with previous examples⁵. The IR spectrum showed absorptions at 2710, 1720, and 1660 cm^{-1} , again consistent with structure (17).

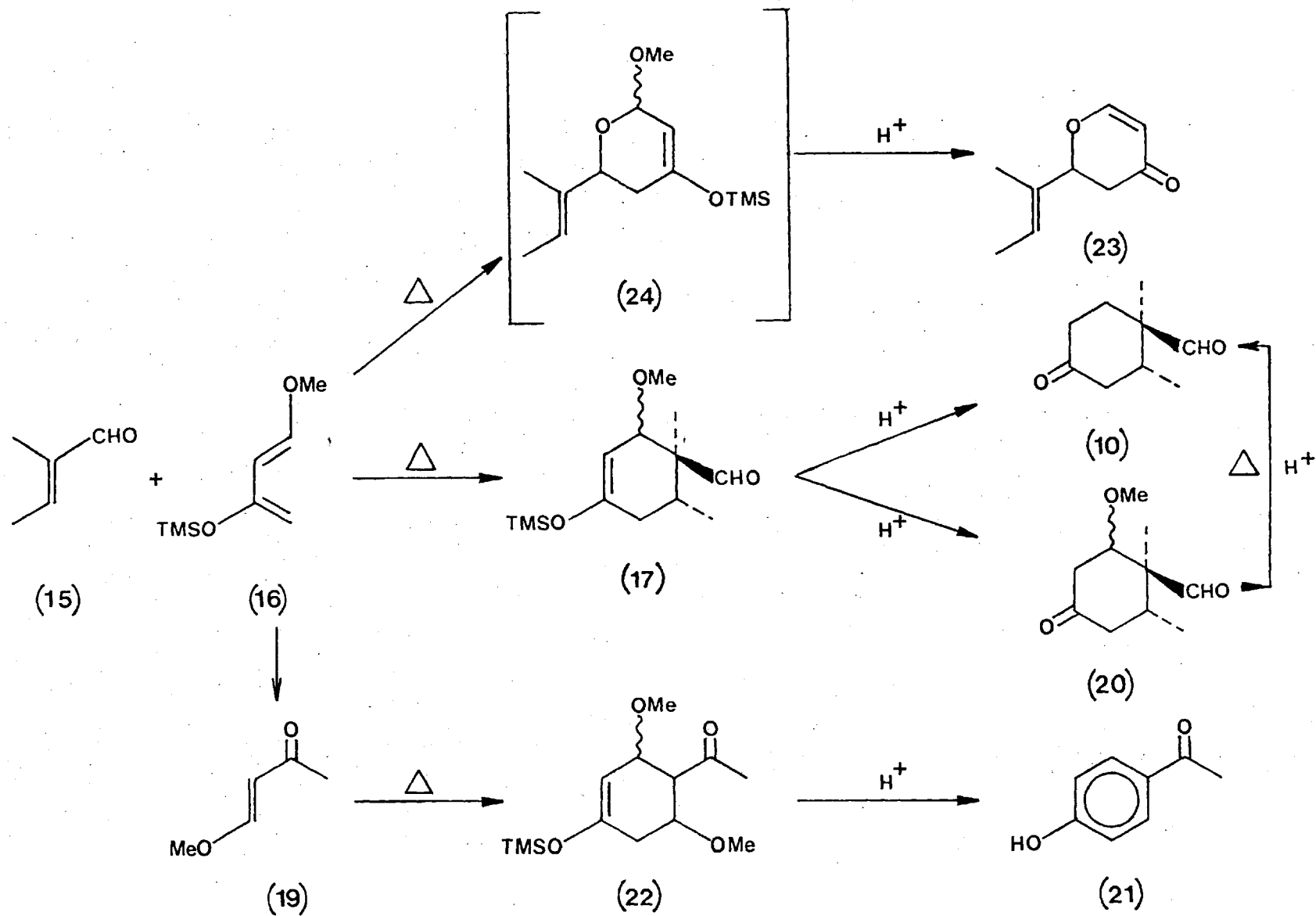
The crude mixture of silyl enolethers (17) was hydrolysed with dilute HCl and, after chromatography, gave the cyclohexenone (10) together with small, but appreciable quantities of the cyclohexanone methyl ethers (20).

The ^1H NMR of (10) additionally confirmed the regiochemistry of the initial Diels-Alder reaction.



(20a) 3-β
(20b) 3-α

After optimisation of the reaction conditions, distillation under high vacuum raised the yield of (10) to 35%, together with 20% of the methyl ethers (20). The distillation residue was shown to be predominantly 4-hydroxyacetophenone (21), formed by addition of the diene (16) to 4-methoxy-3-buten-2-one (19) (itself the product of diene decomposition), and hydrolysis of the intermediate adduct (22), Scheme 4. The methyl ethers (20) were formed as a result of protonation on the olefinic bond (as opposed to the methoxy group) during hydrolysis; analogous compounds have been observed by other workers⁶. On treating the ethers (20) with pTSA in refluxing benzene, however, smooth conversion to the enone (10) was achieved in 66% yield. Chromatography of this hydrolysate yielded, apart from (10), the pyranone (23) formed *via* (24) by the diene (16) adding across the carbonyl bond of tigaldehyde (15), Scheme 4. Although the yield of (23) was low (*ca.* 3% overall) its formation at all was considered surprising in view of the normal selectivity observed when using enals in Diels-Alder reactions⁷. Its formation is probably due to two factors: firstly, the lack of steric hindrance about the carbonyl bond; and secondly, the polarised nature of the diene, making addition across

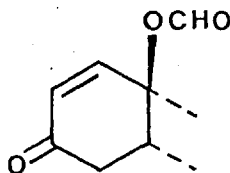


Scheme 4

the polar carbonyl bond more favourable than would normally be the case with an unheterosubstituted diene.

Several attempts were made to stop the decomposition of the diene (16) to (19) and thereby suppress the formation of (22) but without success.

It was not possible to prepare an analytically pure sample of the enone-aldehyde (10), even after using a combination of purification techniques, nor could a suitable 2,4-DNP, or a dimidone derivative be prepared. Prolonged exposure to atmospheric oxygen led to the conversion of (10) to the formate ester (25) as the Baeyer-Villiger product. Compound (25) gave characteristic resonances in the ^1H NMR spectrum at

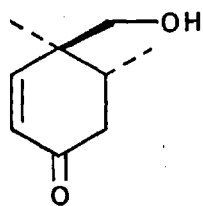


(25)

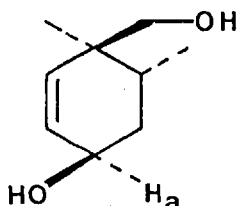
δ 8.00 (s, 1H), 7.10 (d, J 10 Hz, 1H), 5.90 (d, J 10 Hz, 1H), 1.50 (s, 3H), and 1.05 (d, J 7 Hz, 3H); together with absorbances in the IR at 1720, 1678, and 1185 cm^{-1} ; and peaks in the mass spectrum at m/e 168 (M^+), 140, 126, 123, and 122.

Having achieved a stereospecific synthesis of the enone-aldehyde (10) in reasonable yield (49.5% overall, based on diene), we then embarked upon a study of the reactivity of this key intermediate. Initially, attempts to protect the aldehyde moiety in (10), prior to carrying out conjugate additions to the enone, were considered. One obvious way of masking the aldehyde functionality was by selective reduction to the

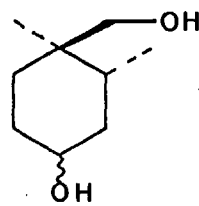
alcohol (26).



(26)



(27)



(28)

Not surprisingly, in view of the known⁸ ability of lithium aluminium hydride and sodium borohydride to reduce enones in a conjugate sense, the use of these reagents led to the formation of the diol (28) as the only product. The use of the more hindered reagent, di-*iso*-butylaluminium hydride (Dibal) was then considered, but as shown in Table 1, even using a variety of conditions we were still unable to achieve a high degree of selectivity in the formation of the enone-alcohol (26).

TABLE 1. Reductions of the enone-aldehyde (10)

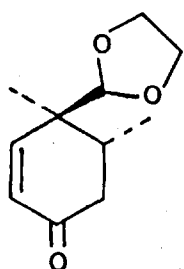
No. of equiv. of Hydride	Solvent	Reaction temperature °C	Product distribution %		
			(10)	(26)	(27)
2.8	Benzene	25	0	0	60
2.2	"	25	0	31	33
1.4	"	10	10	25	20
1.4	Toluene	-23	20	25	0

Attempts to oxidise the allylic alcohol (27) to (26) using active manganese dioxide⁹ did not seem promising, and therefore this reductive

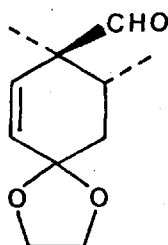
approach to protection of the aldehyde moiety in (10) was abandoned.

From a stereochemical point of view it was interesting to note that only the pseudo axial ring alcohol (27) (H_a , δ 4.20, dddd, J 6.0, 6.0, 1.5, and 1.5 Hz, 1H) was formed during reduction of the enone moiety. This result meant that the incoming hydride must have attacked from the underside of the molecule and so cannot have been influenced by the normal directing effect of the hydroxymethyl group¹⁰.

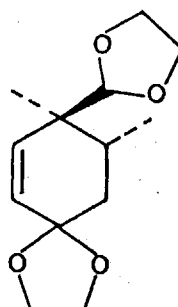
An alternative approach *via* selective protection of the CHO in the enone (10) as the dioxalane (29) was then investigated. However, when the formation of (29) was attempted under standard conditions (ethylene glycol, pTSA, refluxing benzene), then by following the course of the reaction by IR, it was clear that the enone group reacted faster than the aldehyde unit, suggesting that (30) was formed first. Work-up eventually gave predominantly the di-dioxalane (31). Similarly, when attempts were made using the dithiol (32) as a protecting group (which was known to be specific for aldehydes¹¹) the enone again reacted first, contrary to the literature.



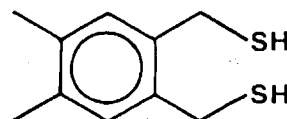
(29)



(30)



(31)

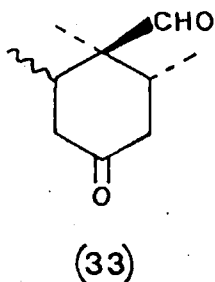


(32)

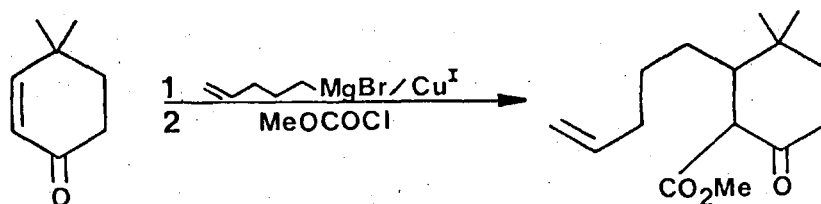
It became apparent therefore that the enone-aldehyde (10) was not going to behave with the selective reactivity normally associated with aldehydes versus enones. Undoubtedly this was due to steric hindrance about the aldehyde group caused by the neighbouring methyl group. Although this was a nuisance with respect to selective aldehyde protection, it

meant that conjugate addition into the unprotected enone-aldehyde (10) was a more viable proposition than had previously been thought.

As a model for the conjugate addition and also to facilitate structural proof of the products, it seemed reasonable to study the addition of methyl cuprates, which might lead directly to (33).

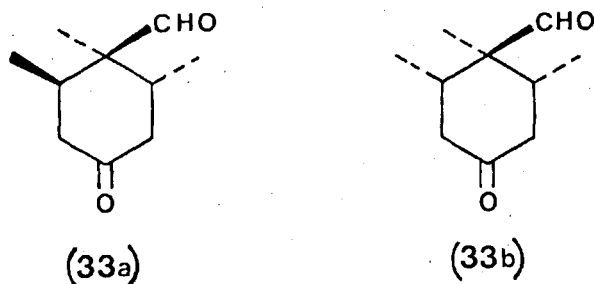


As described in the review, Jackson¹ had conjugately added a pentenyl side-chain to 4,4-dimethylcyclohexenone *via* the copper catalysed addition of the Grignard reagent, and was able to trap the resultant enolate on carbon, with an acylating agent - a notoriously difficult task¹².

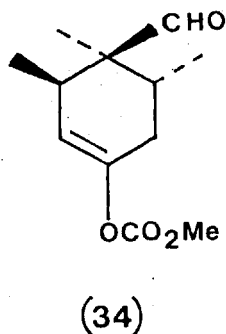


Unfortunately, in the case of the enone-aldehyde (10), a similar type of reaction failed despite numerous attempts. This annoying failure meant that we had to turn to stoichiometric cuprate reagents, which almost invariably led to quenching on oxygen by acylating agents. For

example, to lithiodimethyl cuprate formed from methyl lithium and the copper (I) bromide-dimethyl sulphide complex, according to House's¹³ procedure, was added the enone-aldehyde (10) at low temperature. The initial tan solution afforded an immediate precipitate of bright yellow methyl copper, indicating an instantaneous reaction. Work-up led to isolation of a single adduct, shown to be (33a) in 60% yield. The ¹H NMR spectrum of the adduct (33) showed, in the methyl region, one singlet and two distinct doublet methyl resonances - therefore the product of methyl addition must be (33a) and not the alternative (33b). (33b) is symmetrical and would therefore show only one doublet resonance. Attempted



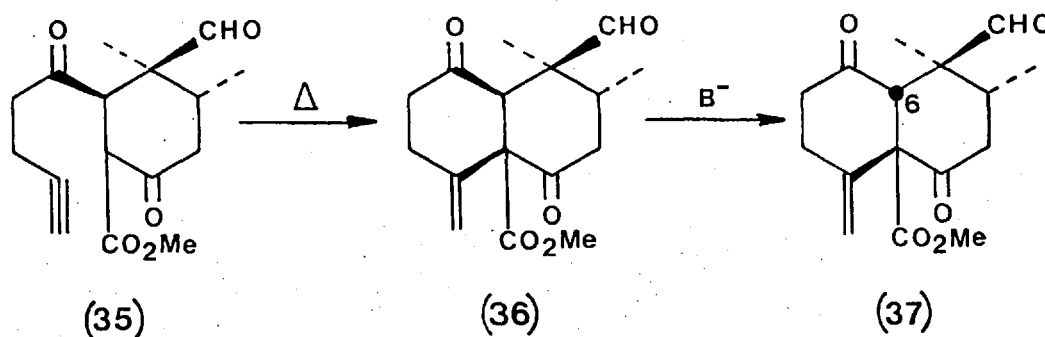
trapping of the resultant enolate in this reaction, using methyl chloroformate, gave the enol-carbonate (34) as the only product. Characteristic



of (34) and other "O" acylated products was an absorbance in the IR at 1780-1760 cm⁻¹. It was noted that the same "O" acylated product was formed irrespective of whether the cuprate was generated *via* the lithium

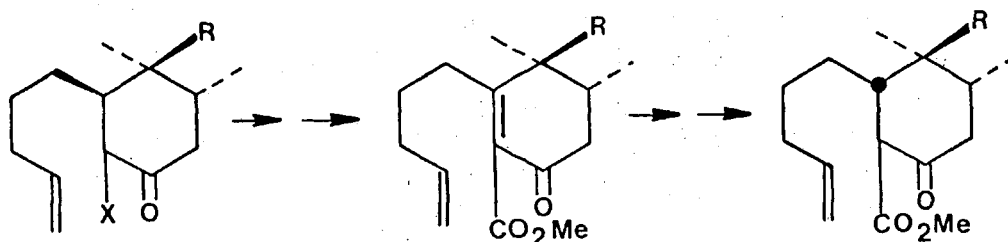
species or from the Grignard reagent, in ether or THF solutions.

In these reactions, therefore, it was clear that the incoming methyl group had attacked (10) from the β face, which of course was exactly opposite to the one we required if this process was to be eventually translated into a clerodin (1) or ajugarin (2-4) synthesis. Thus, we would need to find a way of reversing this stereochemistry. Three possible ways of doing this were considered. Firstly, a suitably modified side-chain could be allowed to attack (10) from the "wrong side" to give, for example, (35) which could then be cyclised to the cis decalin (36) using the methods of Jackson¹ or Conia¹⁴. Base epimerisation should then give the trans-decalin (37) with the desired C-6 stereochemistry, Scheme 5.



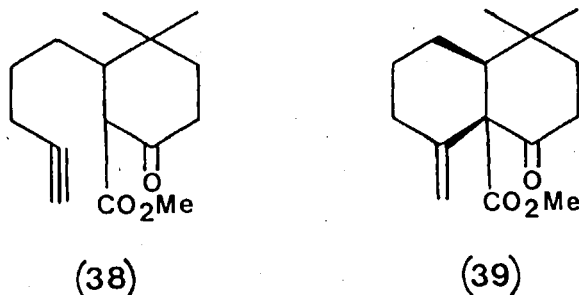
Scheme 5

Secondly, the incoming side-chain could be allowed to attack again from the "wrong side" and later be forced into the correct arrangement by a second incoming group (hydride) also attacking at C-3 as in Scheme 6.

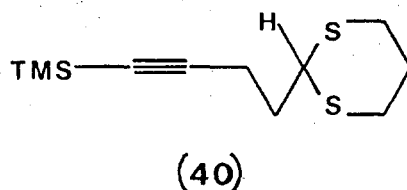


Scheme 6

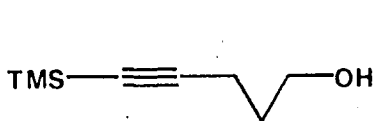
Lastly, the enone-aldehyde (10) could be modified such that the incoming side-chain was forced to approach from only the "correct" (α) face. Of these possibilities, the epimerisation route (Scheme 5) was first investigated as we had previously shown that the β -keto-ester (38) could be cyclised to the cis-decalin (39) in quantitative yield¹.



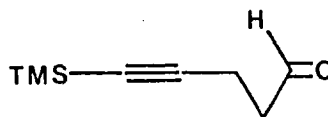
In order to follow this avenue, therefore, we required a side-chain that combined both a terminal acetylene unit, and a carbonyl equivalent that would add in a 1,4 sense to the enone-aldehyde (10). In view of the HMPA mediated conjugate addition of 2-lithio-1,3-dithians to enones¹⁵, it seemed likely that the substituted 1,3-dithian (40) would fulfil all our criteria.



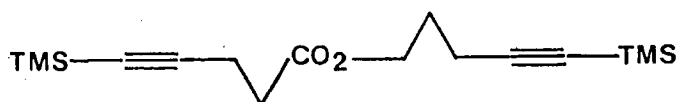
Thus, the anion of pent-4-yn-1-ol¹⁶ was formed in THF using ethyl magnesium bromide and quenched by the addition of two equivalents of chlorotrimethylsilane. Mild acid hydrolysis then gave the mono-protected acetylenic alcohol (41) in high yield. Previous authors¹⁷ had prepared this compound by a similar method, however, they had used ether as solvent



(41)



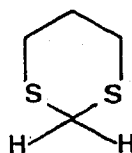
(42)



(43)

and had found that a catalyst had to be used in order to facilitate the quench. By carrying out the reaction in THF, the need for a catalyst was avoided. PCC Oxidation¹⁸ of the alcohol (41) gave the aldehyde (42) in 83% yield together with a small amount of the ester (43) formed by formation and oxidation of the hemiacetal¹⁹. The aldehyde (42) was then converted to the dithian (40), using standard conditions, in almost quantitative yield.

Prior to attempting any conjugative addition with this dithian, it was important to determine exactly under which conditions it could be deprotonated with various alkyl lithiums. Thus, both the 2-substituted-1,3-dithian (40) and the parent 1,3-dithian (44) were treated with methyl



(44)

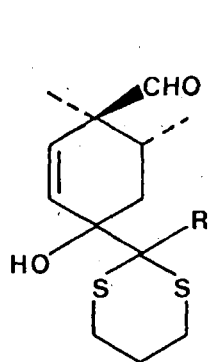
or t-butyl lithium in ether or THF at different temperatures for different periods of time. After quenching with D₂O and work-up, the degree of deuterium incorporation, and hence deprotonation, was measured from the integrals of the various resonances in the ¹H NMR spectrum. The results of the various experiments are shown in Table 2.

TABLE 2. Deprotonation of 1,3-diathians (40) and (44)

Dithian	Alkyl lithium	Solvent	Temperature °C	Time h	% D incorp.
44	1.4 M MeLi	Et ₂ O	0	1.0	0
"	"	DME	-10	1.0	50
"	"	THF	-23	1.0	100
"	2.0 M <i>t</i> -BuLi	Et ₂ O	-23	1.0	decomp.*
"	"	"	-78	1.75	100
40	1.6 M MeLi	"	-23	0.75	20
"	"	THF	-23	1.0	100
"	2.0 M <i>t</i> -BuLi	Et ₂ O	-23	0.75	100
"	"	"	-50	2.0	100
"	"	THF	-50	2.0	decomp.*

* Decomposition of the dithian was observed.

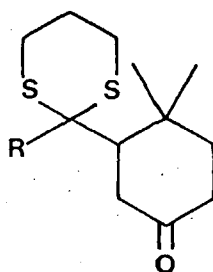
Although conditions to form the anions were found, disappointingly it proved impossible to add either of the dithians (40) or (44) to the enone-aldehyde (10) in a conjugate sense. The only product that was isolated was shown to be that of 1,2 addition, namely (45).



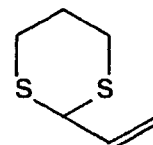
(45)

a) R=H

b) R=TMS—C≡C—CH₂CH₂CH₂CH₃



(46)



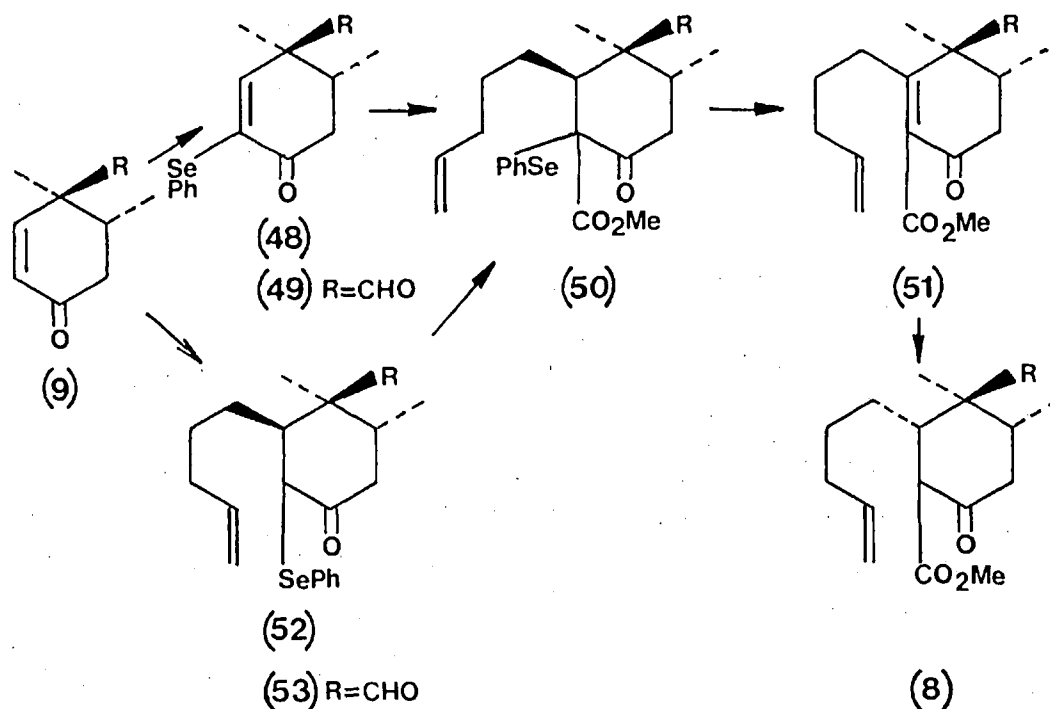
(47)

This failure was again attributed to the peculiar nature of the enone-aldehyde (10) as both the dithians (40) and (44) could be successfully added, in a conjugate sense, to 4,4-dimethylcyclohexenone, to give (46). It is perhaps significant that no successful 1,4-additions of lithiodithians to sterically hindered enones have been reported²⁰.

Since a fair amount of effort had been expended on this route, we decided to attempt the addition of the dithian (40) *via* the cuprate species, in spite of the absence of precedent at the time. Thus, using a similar procedure to that used for lithiodimethyl cuprate, the addition of the dithian (40) to 4,4-dimethylcyclohexenone was attempted and again led to the formation of a small amount of the 1,4 adduct (46b). Unfortunately, all attempts to raise the yield of the 1,4 adduct failed. No addition of the cuprate of (40) to (10) was also possible and therefore this approach to the synthesis of the trans-decalin (6) was abandoned.

Other workers²¹ have since published details of the successful cuprate induced 1,4 addition of the vinyl-substituted dithian (47) to enones. However, this appears to be a special case and as yet the method has not proven generally useful.

The second option for reversing the C-3 stereochemistry was then investigated, i.e. that of allowing the side-chain to attack from the "incorrect" face, and then forcing it into the correct orientation by a second incoming nucleophile (hydride) again attacking at C-3. The strategy for achieving this is shown in Scheme 7. We reasoned that if we could prepare the 3-substituted enone (51), conjugate reduction should result in the hydride moiety attacking from the β face, thereby pushing the pent-4-enyl side-chain onto the α face. The enone (51) should be easily prepared *via* the selenophenyl substituted cyclohexanone (50) which itself would be readily available *via* either conjugate addition to the



Scheme 7

selenophenyl enone (48) and subsequent trapping of the enolate with methyl chloroformate (the selenophenyl group, it was hoped, would help to stabilise the enolate on carbon, as opposed to oxygen); or *via* conjugate attack into the enone (9) followed by trapping of the enone with a phenylselenating agent to give (52). Subsequent anion formation and chloroform^{-ate} quench should give (50).

Obviously, the first step in this sequence was to develop a high yielding synthesis of the 2-selenophenyl enone (49). Thus, using the typical conditions developed by Liotta²², the enone-aldehyde (10) was reacted with 1.05 equivalents of phenylselenium chloride and 1.2 equivalents of dry pyridine in dry, distilled dichloromethane, at 35°C for 5 h, under argon. Work-up and chromatography gave a 21% yield of the 2-selenophenyl enone (49), together with 49% of the starting enone (10). Subsequent attempts to raise the yield of (49) are summarised in Table 3. From the Table it is apparent that as the number of equivalents of phenylselenium chloride and pyridine was increased, the novel formation of a second product - the 2-chloro-enone (54) - was noted.

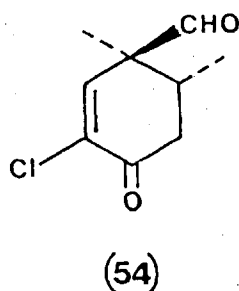


Table 3

No. eq. PhSeCl	No. eq. pyridine	reaction conditions °C	product yield %		
			(9)	(49)	(54)
1.05	1.2	DCM/5 h/35	49	21	-
1.10	DMAP/1.1	DCM/72h/25	N.R.	-	-
1.05	1.2	DCM/20h/40	N.R.	-	-
1.05	1.2	TCM/5 h/60	80	10	-
1.05	2.0	TCM/24h/25	N.R.	-	-
1.05	2.0	TCM/24h/54	N.R.	-	-
1.05	1.2	DCM/24h/45	50	31	-
4.00	4.3	DCM/14h/40	51	45	-
6.00	6.0	DCM/3 h/50 and 14h/25	-	17	6
1.70	1.8	DCM/12h/30	80	8	-
2.00	2.0	DCM/48h/40	-	39	35
3.30	4.2	DCM/72h/35	-	55	20

DMAP : use of 4-N,N-dimethylaminopyridine as base

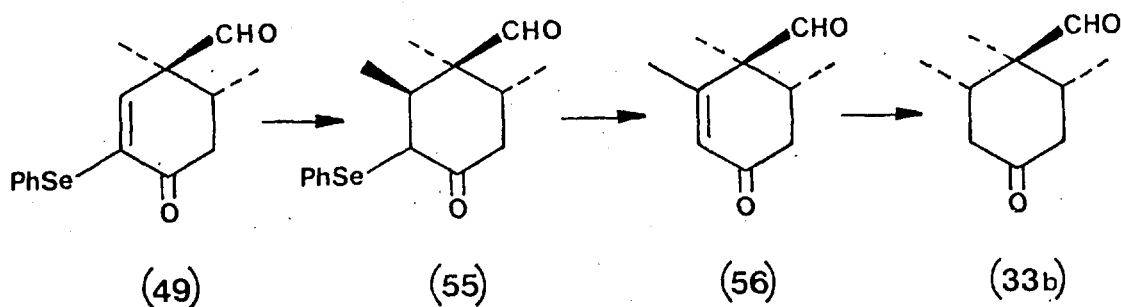
N.R. : no reaction observed, re-isolation of starting material

TCM : chloroform

The mechanism of formation of this new product is discussed later, together with further examples. In spite of this unexpected byproduct, it was possible to obtain reasonable quantities of the desired 2-selenophenyl enone (49) by using the appropriate conditions and recycling the recovered starting material.

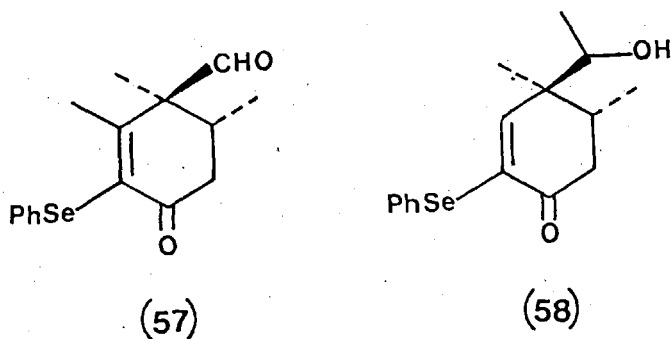
Before continuing with the total synthesis, we considered it important to prove that the C-3 group could be manipulated into the correct stereo-

chemical orientation in the manner that we had speculated upon. Therefore, we decided to attempt to prepare (33b) *via* the sequence shown in Scheme 8.



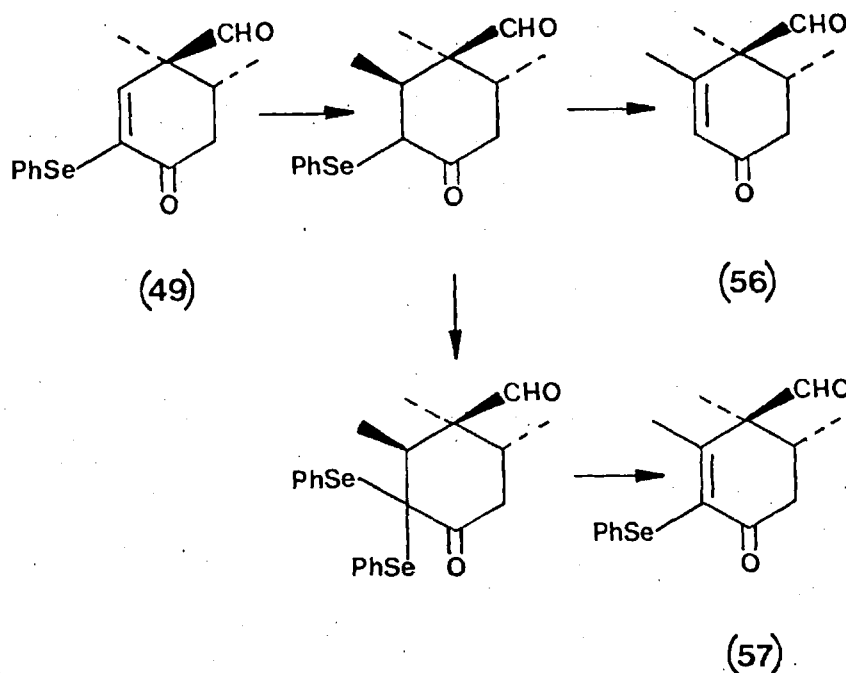
Scheme 8

Unfortunately, the addition of lithiodimethyl cuprate to the enone (49) was not tremendously successful. Although a 22% yield of the adduct (55) was obtained (as a mixture of C-2 isomers), a multitude of other compounds was formed, including (56), (57), possibly (58), and a mass of other unidentifiable products, all apparently lacking the selenophenyl group (^1H NMR). Attempts to limit the formation of these byproducts and so



increase the yield of (55) by, for example, varying the reaction conditions and the stoichiometry of the cuprate reagent, were not successful. This failure to obtain an acceptable yield of the adduct (55) was found surprising, especially in view of a later report²³ in which other workers described successfully carrying out such a cuprate addition (and subsequently trapping

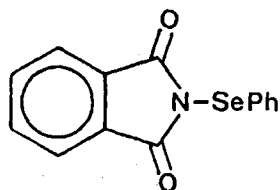
the enolate on carbon with an electrophile) in high yield. However, it is interesting to note that these authors only used simple, unhindered enones as starting materials. Mechanistically, the formation of the enones (56) and (57) is difficult to explain, but they may arise as in Scheme 9.



Scheme 9

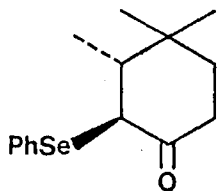
The low yield of adduct (55) obtained from the cuprate reaction was not sufficient to enable us to continue this approach easily and so we sought a more efficient synthesis of this compound. Using the method of Reich²⁴, lithiodimethyl cuprate was added to the enone (10) and the resultant regiospecific enolate was quenched by the addition of a mixture of phenylselenium bromide and diphenyldiselenide. Surprisingly, this again led to the formation of the adduct (55) in low yield (19%), although interestingly, the ratio of the isomers in (55) was now different to that previously observed.

In an attempt to find a better method of quenching the cuprate enolate, we investigated the possibility of using the recently discovered N-selenophenyl phthalimide²⁵ (59) as a source of "PhSe⁺".

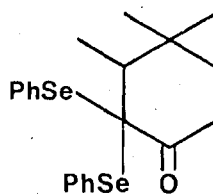


(59)

As a model, lithiodimethyl cuprate was added to 4,4-dimethylcyclohexenone and the enolate was further reacted with NPSP (59). In this way, it was possible to isolate the expected 2-selenophenylcyclohexanone (60) in 25% yield, together with some di-selenated adduct (61), formed in 24% yield. Although this method showed promise, it was not at this stage



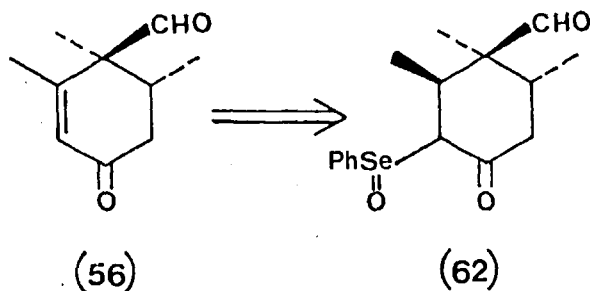
(60)



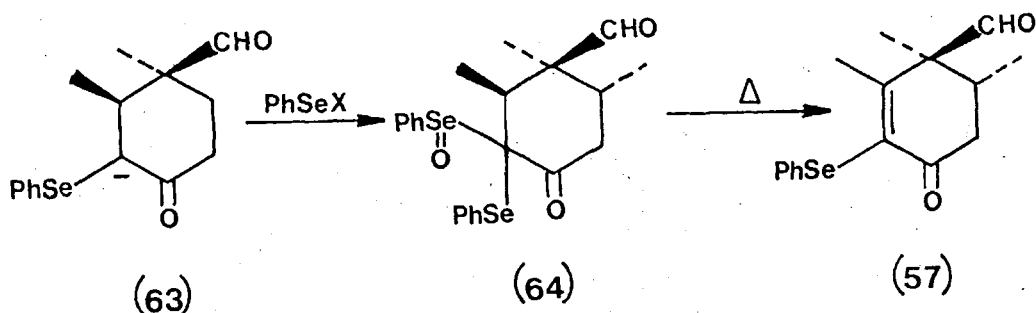
(61)

developed further because of the need to solve other more immediate problems.

Returning to the formation of the model 3-substituted enone (56), it was hoped that oxidation and fragmentation of the resultant selenoxide (62) would provide the enone in high yield. Unfortunately, this was not to be the case. Oxidation, using mCPBA, followed by thermolysis in refluxing

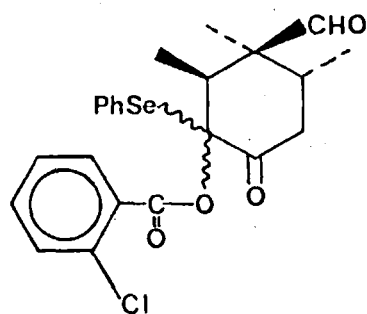


chloroform, led to the formation of the 3-methyl enone (56) in only 28% yield, together with 16% of the 2-selenophenyl-3-methyl enone (57). Compounds analogous to (57) have previously been observed and their formation has been explained in terms of the selenoxide enolate (63) reacting with a phenylselenating agent (most probably PhSeO-SePh, produced from PhSeOH), to give (64) which then syn-eliminated to give the observed product (57), Scheme 10.



Scheme 10

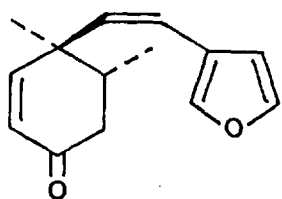
An attempt was made, therefore, to trap the intermediate selenating agent (PhSeX) using di-isopropylamine²⁴. However, only an 8% yield of the desired enone (56) was then obtained, together with 7% of the 2-selenophenyl enone (57), and 4% and 16% respectively of the two isomeric esters (65), formed *via* a Pummerer-type rearrangement and trapping of the intermediate selenonium species by *m*-chlorobenzoic acid.



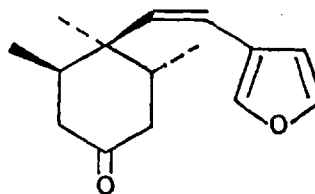
(65)

Combining the results of the two previous experiments, preparation of the selenoxide (62) by ozonolysis of the selenide (55), followed by thermolysis in refluxing carbon tetrachloride in the presence of di-isopropylamine, should have eliminated the byproducts in these reactions. Indeed, the crude product of such a reaction was, by TLC and ^1H NMR analysis, much cleaner than that of the previous experiments. However, after chromatography, the enone (56) was again obtained in low (30%) yield. And so, after three relatively poor steps, i.e. the formation of the selenophenyl enone (49), the conjugate addition to that enone and the selenoxide elimination, the overall yield of the 3-methylsubstituted enone (56) was less than 5%. This was unacceptable and in view of other developments, this approach to reversing the stereochemistry of the side-chain at C-3 was abandoned.

Having tried two of the three proposed methods of reversing the stereochemistry of the C-3 group with little success, modification of the enone (10) such that the incoming side-chain attacked only from the "correct" α face was attempted. Initial hopes that increasing the steric bulk of R in (9) would give the desired effect were not realised. Thus, when lithiodimethyl cuprate was added to the enone²⁶ (66), the incoming methyl group again attacked from the β side to give (67). By high-field ^1H NMR and TLC analysis of the crude reaction mixture no

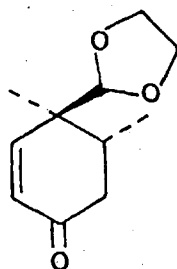


(66)

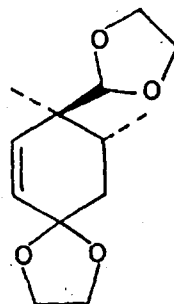


(67)

trace of the other isomer was observed. An alternative way of sterically hindering the β attack involved preparation of the dioxalane (29). (29) Was obtained selectively from (31) in 88% yield using the solid support acid hydrolysis methods of Conia²⁷. The addition of lithiodimethyl cuprate



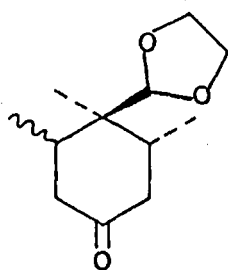
(29)



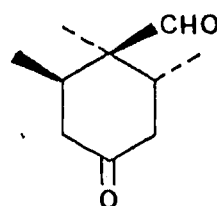
(31)

to (29) again gave an adduct (68). Unfortunately, the methyl group resonances in the ^1H NMR were not particularly well resolved and it was necessary to hydrolyse the dioxalane (68) before a spectral analysis and, therefore, the stereochemical assignment, could be made. The product of hydrolysis was shown to be (33a), again the unwanted isomer.

It became apparent therefore that steric bulk on the C-4 side-chain alone did not allow the correct stereoselective control. Instead, therefore, we chose a new group based upon the following argument: that is, as sulphur containing groups are known to bind strongly with organocopper species,



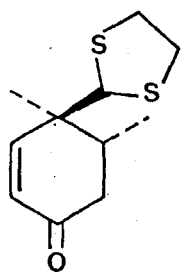
(68)



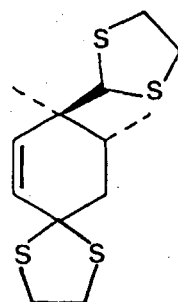
(33a)

then, if the dithiolan-enone (69) could be prepared, it might react with the cuprate firstly to form a huge and very bulky complex which would considerably hinder the β face and, therefore, addition of a second equivalent of cuprate might then attack from the desired α face.

In view of the earlier results, it was obvious that the enone (69) could not be prepared in a one-step process from the enone-aldehyde (10). However, it seemed likely that, in a way analogous to the conversion of the di-dioxalane (31) to the enone-dioxalane (29), it would be possible to convert the di-dithiolan (70) to the desired enone-dithiolan (69).

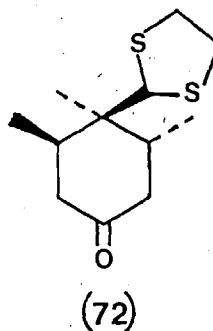
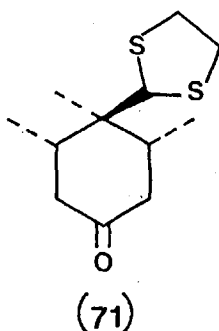


(69)



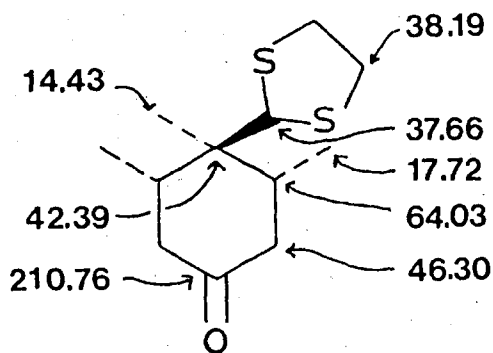
(70)

Consequently, (70) was prepared using standard methodology from the enone-aldehyde (10) and ethane-1,2-dithiol. The first attempts to selectively deprotect the di-dithiolan (70) were made using the alkylative procedure of Wang-Chang²⁸, which gave the enone-dithiolan (69), although in only 41% yield. Attempts to use benzeneseleninic anhydride (B.S.A.)²⁹ failed, as did several other standard methods³⁰. However, it was eventually found that when the crude benzene solution of (70) was vigorously stirred with mercuric acetate, cadmium carbonate and water, the enone-dithiolan (69) was formed in 55-60% yield from (10). The concentration and solubility of reagents was found to be crucial to the success of this particular reaction, and when for instance mercuric chloride was used instead of mercuric acetate, the deprotection reaction did not proceed at all well. With (69) to hand, the next step was to add the dimethyl cuprate. We had argued that the lower the temperature of addition, the greater the chance of reversing the direction of attack of the nucleophile. Consequently, the reaction was carried out using 1.25 equivalents of cuprate at -78°C , and slowly warmed to -20°C before quench and work-up in the usual manner. ^1H NMR and TLC analysis showed that a large amount of starting enone (69) was present in the reaction product, together with a small amount of an adduct. Separation gave a 61% yield of the starting material, and pleasingly, a 27% yield of the long-sought-after adduct (71), with all the methyl groups on the same (α) face of the molecule.



The high-field ^1H NMR spectrum of adduct (71) showed one singlet methyl resonance and one doublet methyl resonance, integrating to three and six protons respectively. At this stage, it was considered that the sole doublet methyl resonance could have been due to accidental equivalence of the two methyl doublet resonances of (72). However, in the course of optimising the reaction conditions, it was found that if the reaction was carried out at too high a temperature, then a second adduct was formed which did, in fact, show two distinct methyl doublets in the high field ^1H NMR - (72). It was also noted that by using 2.2 equivalents of cuprate a 90% yield of adduct (71) was obtained.

As a final check on the stereochemical assignment of (71), the ^{13}C NMR spectra of both adducts, (71) and the C-3 epimer (72), were obtained. As expected, (71) showed eight resonances, while compound (72) showed twelve. Again, the difference being due to the presence or absence of a plane of symmetry through the molecule. The ^{13}C assignments for (71) are shown in Figure 1 and were confirmed by SFORD experiments.

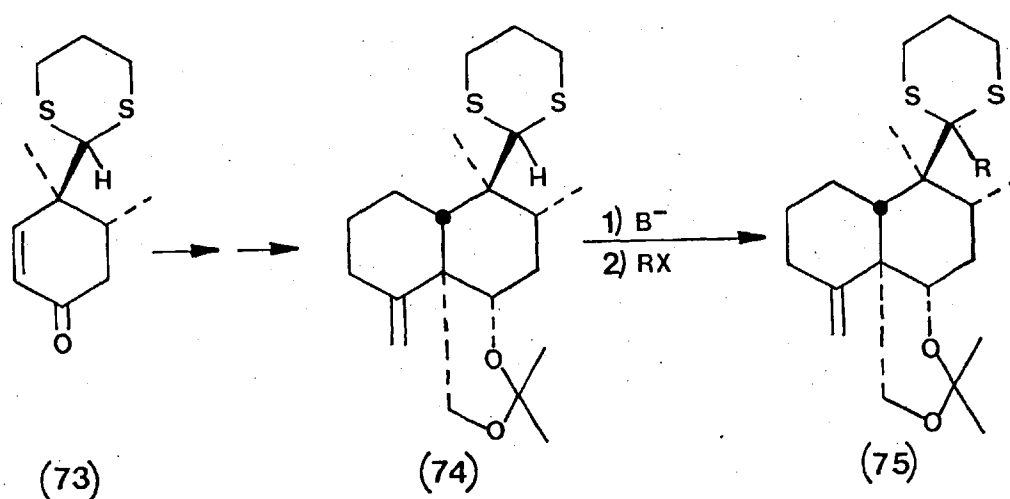


(δ ppm relative to TMS)

Figure 1

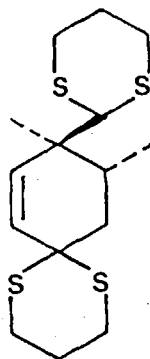
Thus, by this simple modification of the enone-aldehyde (10), it was now possible to achieve the desired asymmetric induction with remarkable efficiency. Mechanistically, the fact that 2.2 equivalents of cuprate are required for complete reaction of the enone (69), seems to indicate that one equivalent does in fact form the supposed complex with the dithiolan moiety and completely blocks access to that β face, thus making approach to the α face more favourable as predicted. Since this reaction was developed, Still has used a similar effect to control the addition of a cuprate to α -asymmetric aldehydes bearing β -oxygen substituents³¹.

With the knowledge that the basic principle of stereo-electronic control was, in this case at least, correct, it was decided to investigate whether such control could be achieved if the enone-dithian (73) was used instead of the dithiolan (69). This modification would give the added advantage that the "Umpluong" reactivity³² of the dithian could be exploited in the construction of, say, the γ -lactone side-chain of the ajugarins (2-4) as shown in Scheme 11.



Scheme 11

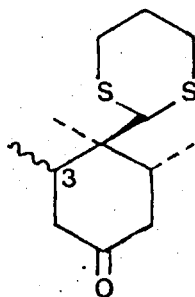
As before, the enone-dithian (73) was prepared by selective de-thioacetalisation of the di-dithian (76) which was itself prepared by the standard method.



(76)

Of the methods tried (MeI ²⁸, sulphuryl chloride/silica gel³³, and B.S.A.²⁹), benzeneseleninic anhydride proved to be the best and gave (73) in 55% yield from (76) (47% overall from the enone-aldehyde (10)).

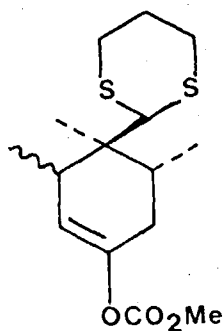
The addition of lithiodimethyl cuprate (2.2 eq.) was carried out, as before, at -78°C and, after slow warming to -23°C , work-up in the usual manner gave an adduct (77) in 85% yield. Unfortunately, the product proved

(77a) 3- β (77b) 3- α

to be a chromatographically unseparable mixture of C-3 epimers in the ratio 2:1 and it was impossible to show definitively which isomer predominated in the mixture. Luckily, the adducts were solid and after careful recrystallisation, two distinct crystalline forms were apparent. Manual separation of the major component (prisms) showed that the major isomer was in fact the undesired one (77a). As a result of this, we returned to

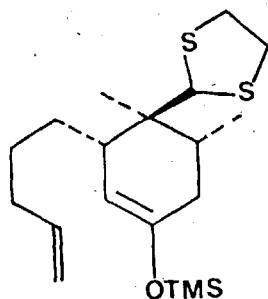
using the dithiolan (69) to control the C-3 stereochemistry.

Prior to continuing the synthesis, in order to avoid wasting valuable material, lithiodimethyl cuprate was added to the enone-dithian (73) and again attempts to trap the resulting enolate on carbon, using methyl chloroformate, gave only the "O" acylated product (78), again as a mixture of C-3 epimers.

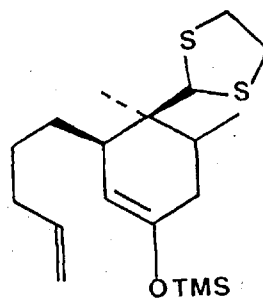


(78)

Since all attempts to trap on carbon the regiospecific enolate resulting from the addition of a stoichiometric cuprate to an enone had failed, it was decided to trap the enolate as the silyl enol ether (for example 79) and then use one of several methods³⁴ to acylate this particular intermediate. Using known methodology, compound (79a) was prepared by the addition of the cuprate derived from pent-4-enyl magnesium bromide³⁵ to the enone (69), and



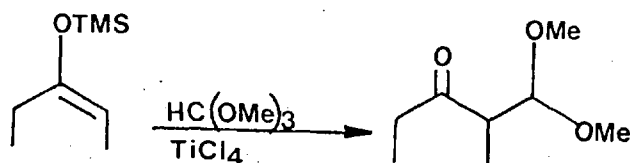
(79a)



(79b)

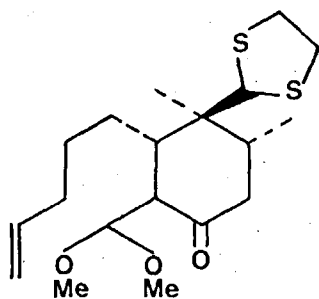
subsequent quench with purified (acid-free) chlorotrimethylsilane. The assignment of C-3 stereochemistry was at this stage only tentative, but the fact that only one isomer of (79) was formed when the reaction was carried out at -78°C , while two were formed at higher temperatures seemed to indicate that the assignment was correct. Correlations between the positions of the resonances in the ^1H NMR of the dithiolans (71) and (72), the dithians (77a) and (77b), and the enol ethers (79a) and (79b) provided further evidence for the assignment.

Of the methods considered for the "C" acylation of the enol-ether (79a), that of Mukiyama³⁶ (Scheme 12) seemed the most promising. Thus (79a)

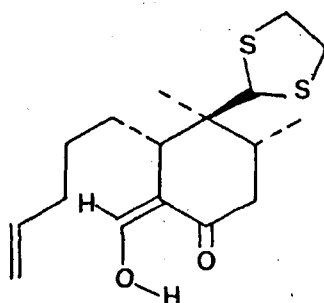


Scheme 12

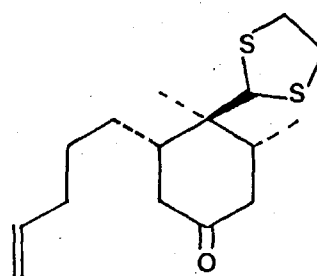
was reacted with trimethylorthoformate and TiCl_4 in dichloromethane at -78°C . However, the acetal (80) was not formed under these conditions. Instead, a small amount of the 2-formyl ketone (81) was isolated, together with the major product, the unsubstituted ketone (82). Many attempts to increase the yield of (80) or (81) were made, including using different Lewis acids,



(80)



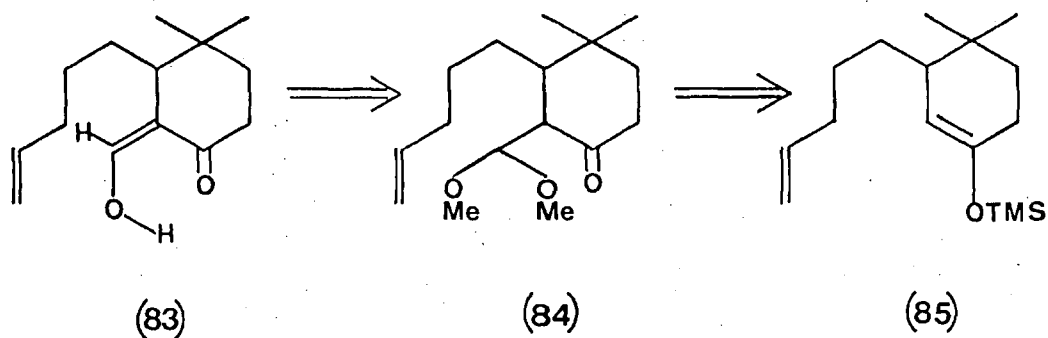
(81)



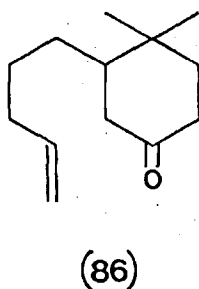
(82)

different ortho-esters, and different reaction conditions. None of these were very successful. In some reactions, a sulphurous smell was noted. Thus, it seems that the strong Lewis acids were probably destroying the dithiolan moiety in some way.

In order to investigate whether or not the olefinic side-chain was affecting the course of the reaction, it was proposed to study the preparation of (83) as a model compound. The trimethylsilyl enol ether (85) was



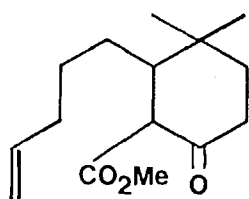
prepared in the usual manner and reacted with trimethylorthoformate and TiCl_4 , as before. Pleasingly, this gave the desired acetal (84) together with some of the 2-formyl ketone (83) and a small amount of the unsubstituted ketone (86). Hydrolysis of this mixture gave (83) in up to 65% yield from 4,4-dimethylcyclohexenone. It was apparent, therefore, that the dithiolan moiety in (79b) was indeed preventing the formation of the acetal (80).



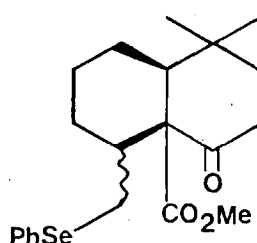
However, before other methods of acylation were fully investigated, realisation came that we were not going to be able to prepare the trans-decalin moiety of (7) using the approach that had initially been envisaged. This became apparent from a detailed study of the mechanism of the selenium mediated cyclisation reaction.

THE SELENIUM MEDIATED CYCLISATION REACTION

With the successful preparation of the alkenyl substituted 2-formyl ketone (83), the stage was set to attempt a cyclisation using the novel selenium based methodology¹. Jackson¹ had previously cyclised the β -keto ester (87) to cis-decalin (88) using a preformed mixture of phenylselenium chloride and silver hexafluoroantimonate, and in studies to define the scope

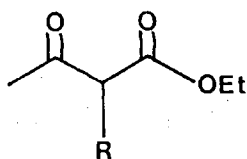


(87)



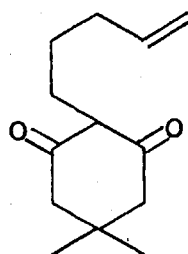
(88)

and limitations of this cyclisation reaction, several other alkenyl substituted β -keto esters and β -diketones were prepared³⁷. Thus, in this thesis, 6-carboethoxy-7-oxo-octene (90) and 4-carboethoxy-5-oxohexene (89) were prepared from ethyl acetoacetate and the appropriate alkenyl halide, using the method of Brieger³⁸, while the substituted dimidone (91) was prepared as described by Conia³⁹.



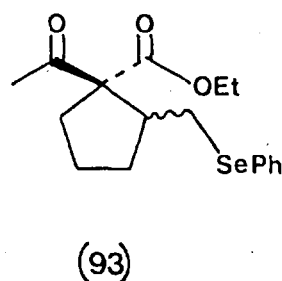
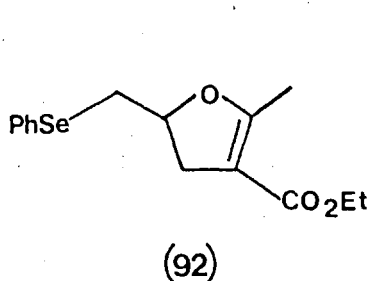
(89) R =

(90) R =

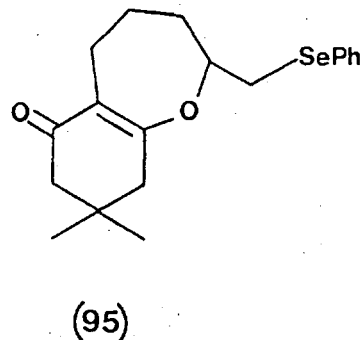
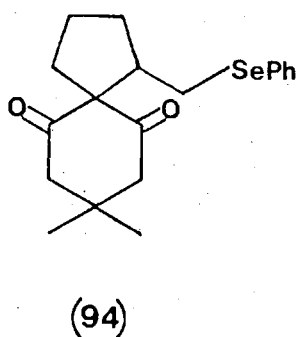


(91)

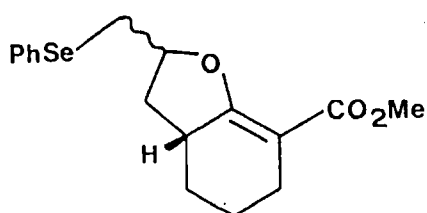
Compound (89) was then added to a cooled, preformed mixture of phenylselenium chloride and silver hexafluoroantimonate in dry dichloromethane under argon. After warming to room temperature, work up and chromatography gave the dihydrofuran (92) in 70% yield. Similarly, compound (90) gave the cyclopentane (93) in 81% yield as a 1:1 diastereoisomeric mixture.



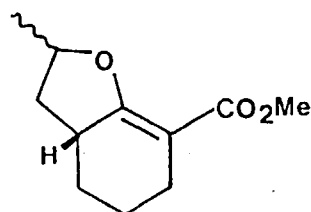
Obviously, the basic difference between these two cyclisation products is that (92) results from exclusive attack on the intermediate seleniranium ion *via* the oxygen atom of the enolic form (oxygen cyclisation) while (93) results from carbon cyclisation¹. Under similar conditions, the β -diketone (91) gave the carbon cyclised product (94) in 44% yield, but when reacted with a preformed mixture of phenylselenium chloride and silver hexafluorophosphate, it gave 27% of the carbon cyclised product (94) together with 30% of the benzoxepin (95); the product of oxygen cyclisation. The structures were assigned by a combination of spectral techniques, including high field



^1H NMR, together with further chemical transformations³⁷. For example, (96)¹ was converted to (97) using triphenyltinhydride according to the method of Clive⁴⁰. Whether one gets carbon or oxygen cyclisation was found to be



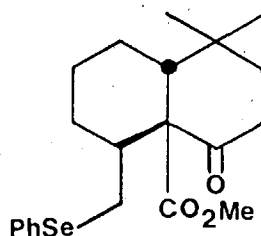
(96)



(97)

dependent on the nature of the acidic catalyst used. These effects have been more fully described elsewhere, together with further examples^{1,41}.

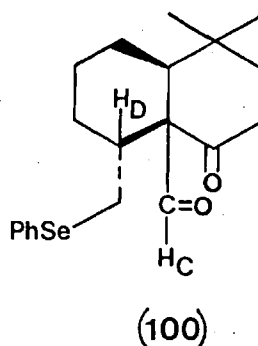
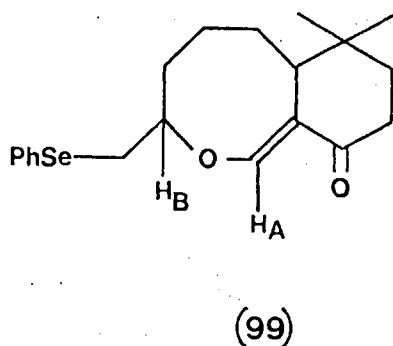
More important, with respect to the synthetic approaches towards the clerodanes, was the determination of the cis or trans nature of the ring junction in decalins prepared using this cyclisation procedure. As previously stated, Jackson¹ had formed the cis-decalin (88) from the β -keto ester (87) using phenylselenium chloride and silver hexafluoroantimonate. However, using a mixture of phenylselenium chloride and antimony pentachloride, a different product was formed that was thought tentatively to be the desired trans-decalin (98). Unfortunately, Jackson was not able to further prove



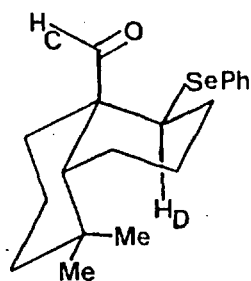
(98)

the structure of (98). Consequently, more work in this area was needed in order to properly determine the exact stereochemical course of the reaction.

Thus, the 2-formyl ketone (83) was added to a cooled preformed mixture of phenylselenium chloride and silver hexafluoroantimonate, as before. Work-up gave a compound that was totally unstable to silica gel chromatography, but whose spectral properties strongly indicated that it was the product of oxygen cyclisation (99). For example, the ^1H NMR spectrum showed resonances

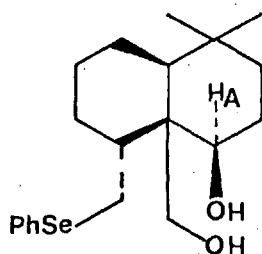


at δ 8.30 (H_A) and 3.95 (H_B), while the IR spectrum showed characteristic absorbances at 1670, 1585, and 690 cm^{-1} . Since it had been shown^{1,41} that other oxygen cyclised compounds could be rearranged to their corresponding carbon cyclised counterparts using various Lewis acids, (99) was treated with ZnCl_2 . Unfortunately, the rearrangement did not proceed with any degree of efficiency and eventually only 15% of (100) was isolated after chromatography. A tentative stereochemical assignment of the product was made when it was realised that the observed coupling constant between H_C and H_D could only be explained in terms of a four bond W-coupling⁴² in the structure (100) but could not be accommodated by a similar trans-fused compound. Obviously, this one spectral observation was insufficient to fully substantiate the structure and further chemical proof was required, which eventually led to the formation of a derivative suitable for X-ray spectral analysis.

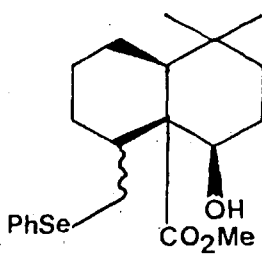


(100)

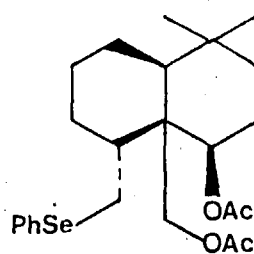
Reduction of (100) by lithium aluminium hydride gave a single diol product thought to be (101). The equatorial nature of the secondary OH in (101) was proven by the size of the coupling constants (11.5 and 6.3 Hz) to the adjacent (axial) proton H_A in the ^1H NMR spectrum.



(101)



(102)



(103)

The diol (101) was found to be identical to the product obtained when the hydroxy ester (102) (itself obtained by selective borohydride reduction of compound (88)¹) was further reduced with lithium aluminium hydride. Since both the cis nature of the ring junction and the equatorial position of the alcohol in (102) had been proven by a crystal structure determination on a later derivative¹, only the orientation of the selenophenylmethyl moiety in (101) remained to be determined. Unfortunately, high field ^1H NMR did not prove useful in this respect and so the diol (101) was converted to the diacetate (103) and an X-ray crystallographic analysis was undertaken. The result is shown in Figure 2 (over) together with the stereographic projection (Figure 3, below). Note that the antipodal enantiomer to that normally drawn has been illustrated in order to give a clearer indication of the stereo-

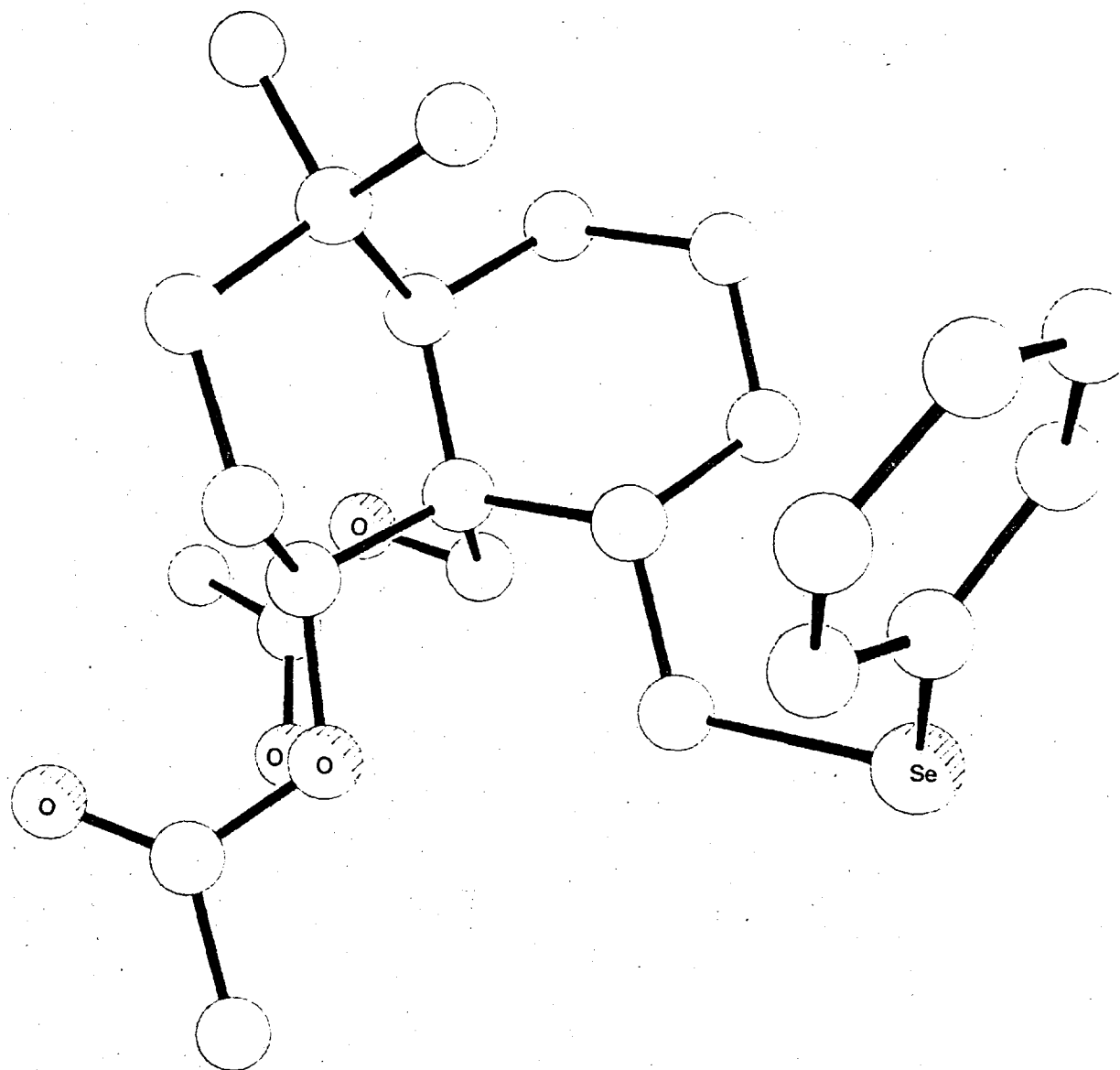


Figure 2

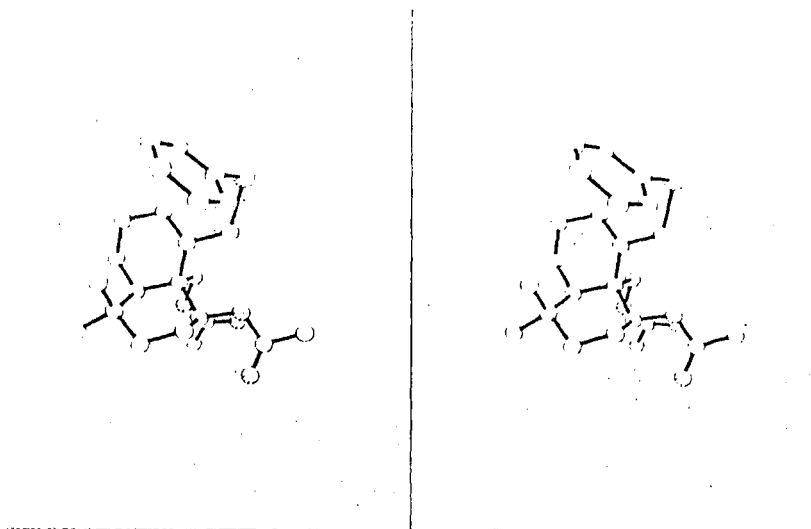
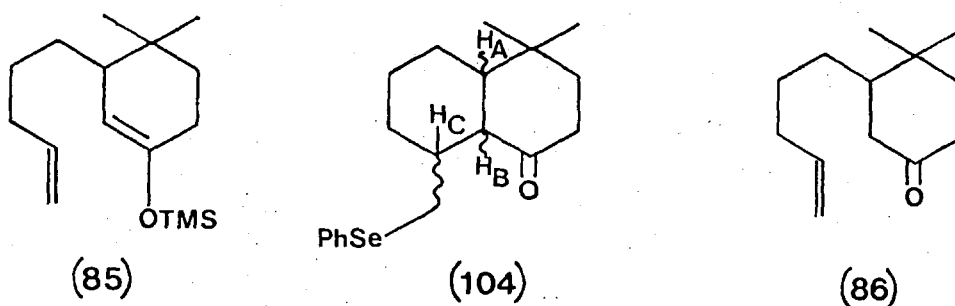


Figure 3

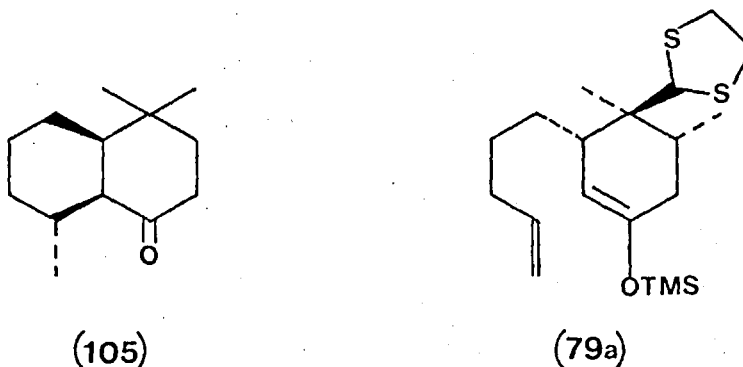
chemistry and minimise bond and atom overlay. Notable features of the structure include an angle of 121° between planes running through the two cyclohexane rings.

Also investigated was the possibility of cyclising the silyl enol ether (85), prepared earlier, to the decalin (104). Thus, the substrate was added to a cooled preformed mixture of phenylselenium chloride and silver



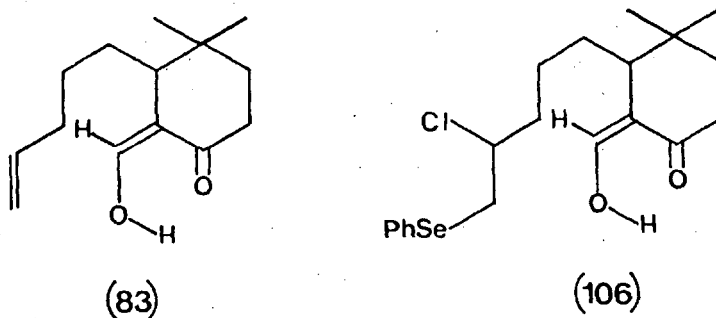
hexafluoroantimonate, and after warming to room temperature and work-up in the normal manner, careful chromatography gave the decalin (104) although in only 17% yield, together with the uncyclised alkenyl substituted cyclohexanone (86), in 30% yield. Despite the low yield of (104), the relative stereochemistry could, in theory, be defined simply by measuring the coupling constants H_A-H_B and H_B-H_C in the ^1H NMR spectrum. Unfortunately, even at 250 MHz, the ^1H NMR spectrum of this compound was too complex to analyse

completely, and so the stereochemical assignment of (109) was not possible at this stage. Consequently, (104) was deselenated to the trimethyl decalin (105) using triphenyltin hydride in the usual manner⁴⁰. As described later



(see Appendix), the relative stereochemistry of (105) and hence (104) was determined by extensive use of 400 MHz and 250 MHz ^1H NMR spectroscopy. Attempts to cyclise the silyl enol ether (79a) were unsuccessful.

Mechanistically, it is intriguing that only one isomer of each of the corresponding decalins is ever produced in these cyclisation reactions and this has been shown to be consistently the cis-fused ring system. The nominally more stable trans-decalins were never observed. When phenylselenium chloride was added to compound (83), compound (106) was obtained, thus showing that the selenating species preferentially attacks the olefinic bond rather than the β -dicarbonyl moiety.



The stereochemical outcome of the reaction can best be explained in terms of a transition state, in which, initially the enol form of the β -carbonyl cyclohexanone ring sits such that the alkenyl side-chain adopts an equatorial position. After formation of the seleniranium ion, attack occurs *via* the nucleophilic central carbon atom of the β -keto ester system (Figure 4). The new bond which develops therefore is axial to the original cyclohexanone ring and, in so doing, causes the selenophenyl methyl unit to

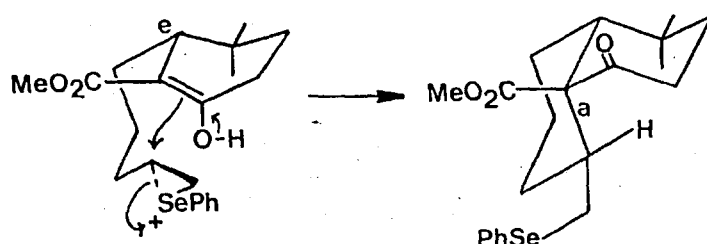
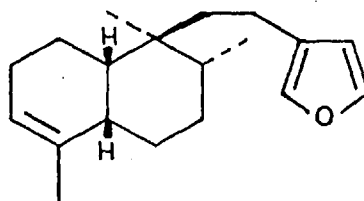


Figure 4

adopt an equatorial position. This is in accord with other literature examples⁴³.

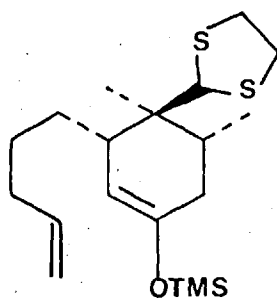
If this mechanism is indeed correct, then the likelihood of obtaining a trans-decalin (98) merely by changing the counter ion seems remote. Consequently, we abandoned the approach of using the selenium mediated cyclisation reaction as a method of forming the trans-fused decalin system of the clerodanes such as clerodin (1) and the ajugarins (2-4).

However, there are numerous cis-fused clerodanes, such as the furan (107)⁴⁴, and therefore, before we returned to the original synthesis, we investigated whether or not we could in fact develop an approach to these cis-clerodanes using the selenium methodology.



(107)

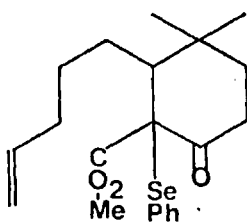
As described previously, it had not been possible to acylate the regio-specific enol ether (79a) using Mukiyama's method³⁶. Similarly, attempts to remove the silyl group with tertiary butyl ammonium fluoride, and then quench



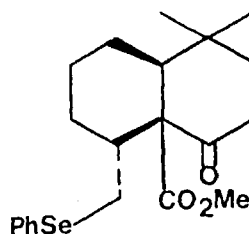
(79a)

the resultant enolate with an acylating agent, were not successful.

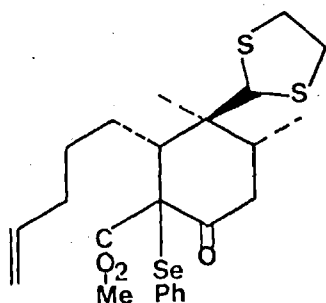
In view of developments in the selenium cyclisation reaction, made by other workers in these laboratories^{1,41} whereby compounds such as (108), with a selenophenyl moiety positioned between the ketone and ester functions, were rearranged to the decalin (109), using a mild Lewis acid catalyst, similar reaction with (110) might also be possible. Obviously, the preparation of (110) would require regiospecific acylation of the 2-selenophenyl ketone (111). Attempts to prepare (111) by the addition of pent-4-enyl cuprate to the enone-dithiolan (69), followed by quenching of the resultant enolate with a mixture of phenylselenium bromide and diphenyldiselenide²⁴ failed. Similarly, attempts



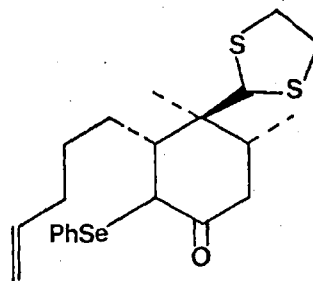
(108)



(109)

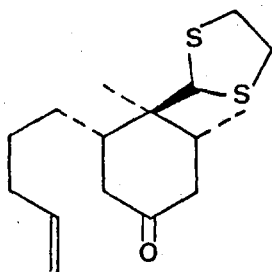


(110)



(111)

to use NPSP (59) to trap the enolate also failed. Presumably, this was due to the large excess of cuprate present which was necessary in order to get the 1,4-addition to proceed in high yield. The only recognisable products obtained from the reaction were the alkenyl substituted ketone (82) and the pentenyl phenyl selenide (112).

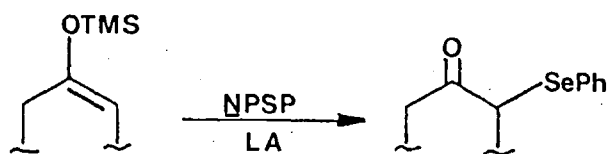


(82)



(112)

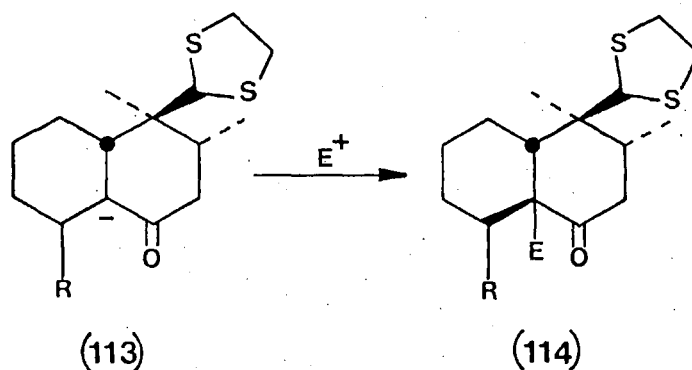
In one final attempt to prepare the selenide (111), use was made of a procedure developed by Simpkins⁴⁵, in these laboratories, which involved converting trimethylsilyl enol ethers into the corresponding 2-selenophenyl ketones, using NPSP (59) together with a trace of a Lewis acid catalyst. Thus, similarly with (79a) the reaction appeared to proceed with some degree



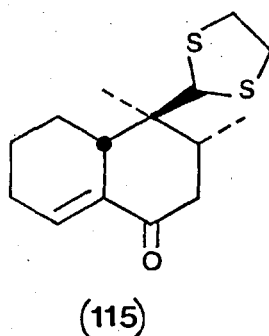
of success, providing a crude reaction mixture whose spectral and TLC properties were in accord with those expected for compound (111). Unfortunately, the product was unstable both on standing and to silica gel chromatography. Attempts to generate and subsequently acylate the enolate of the crude reaction mixture were unsuccessful. This route too was therefore abandoned in favour of more important work.

PREPARATION OF A TRANS-DECALIN WITH POTENTIAL INSECT ANTIFEEDING PROPERTIES

Having arrived at a conclusion as to why the selenium mediated cyclization reaction gave rise to only cis-decalins, a new strategy for the production of the desired trans ring junction was therefore required. From earlier results it was thought likely that if the decalin moiety was already intact then quenching of the bridgehead enolate, such as (113), might occur in an axial direction to the desired trans-decalin (114). An obvious entry to

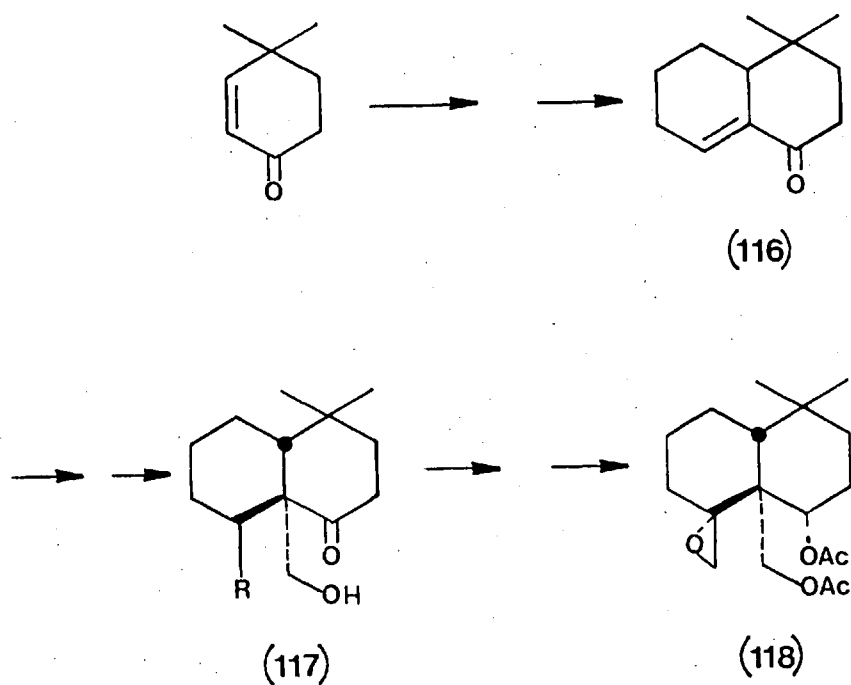


enolates of the type (113) would be via the conjugate addition of cuprates to an enone such as (115), as speculated on in the earlier retrosynthetic discussion. The incoming cuprate would, of course, have to be capable of



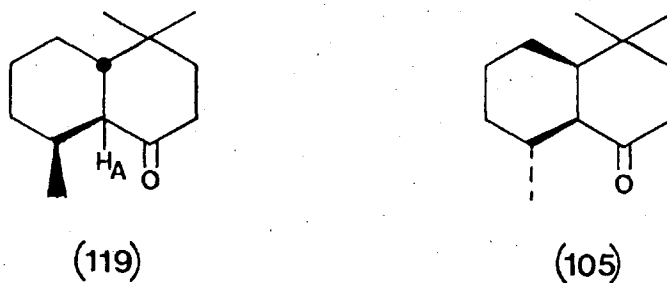
elaboration to an exomethylene moiety at a later stage. In order that this new strategy would best fit the desired clerodane synthesis, the enolate so formed by the cuprate addition would best be trapped by a formaldehyde

equivalent, thus leading to a hydroxy methylene unit which could then be readily modified. To test this strategy, the synthesis of the model compound (118), via the route shown in Scheme 13 was proposed.

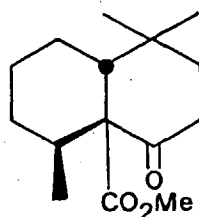


Scheme 13

The decalin-enone (116) was prepared from 4,4-dimethylcyclohexenone using standard methodology⁴⁵, and after addition of lithiodimethyl cuprate, followed by proton quench, at last gave a trans-decalin (119) in about 60% yield. In contrast to the cis-decalin (105), the 250 MHz ¹H NMR spectrum

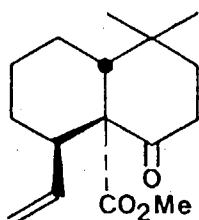


of (119) was readily interpretable and the coupling constants to H_A (12.0 and 4.0 Hz) provided strong evidence for the relative stereochemistry as shown. The axial nature of the secondary methyl group is in accord with previous examples⁴⁶. Also, upon quenching the enolate with methyl chloroformate (in ether), the "C"-acylated (trans ?) decalin (120) was obtained in 55% yield⁴⁵. However, addition of vinyl magnesium cuprate to (116), followed by

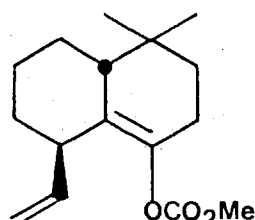


(120)

a chloroformate quench gave a product which was clearly that obtained by acylation on oxygen, i.e. compound (122). The trans compound (121) that we had hoped to form in this reaction was not observed. In view of previous results¹ that suggested that there was a delicate balance between "O" and "C"-acylation and that it could be tipped in favour of quench on oxygen by the presence of THF, it was thought that the small amount of this solvent present from the preparation of the vinyl Grignard reagent, had caused this dramatic change in reactivity. If this was indeed the case, then by using vinyl lithium in diethyl ether with which to prepare the cuprate, reversal of the reactivity



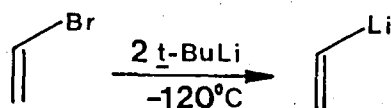
(121)



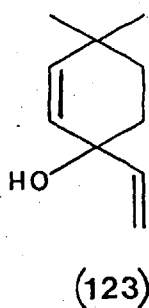
(122)

might result and thus give the desired keto-ester (121).

Seebach⁴⁷ had previously prepared vinyl lithium in THF by transmetalation of vinyl bromide using *t*-butyl lithium at -120°C , but he had not attempted to prepare it in diethyl ether. Thus, it was necessary to develop suitable conditions ourselves.

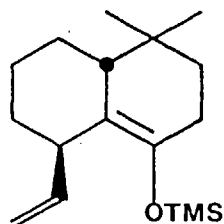


Different molar amounts of 1.4 M *t*-butyl lithium were therefore added to vinyl bromide in diethyl ether at -120°C . After varying lengths of time, the reaction was quenched by the addition of excess 4,4-dimethylcyclohexenone as the electrophile (benzyl bromide was also tried but was not particularly effective). From the amount of carbinol (123) obtained after work-up, the yield of vinyl lithium formed in the first place was determined (assuming complete reaction with the enone and that there was no enolisation). After suitable conditions



had been found, the decalin enone (116) was then added to lithiodivinyl cuprate and the resultant regiospecific enolate in ether was trapped with methyl chloroformate. The product of this reaction was again that of oxygen acylation (122).

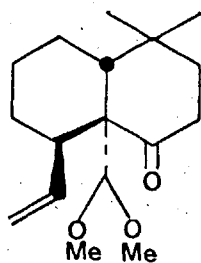
The use of Stork's methodology⁴⁸, whereby a silyl enol ether is reacted with methyl lithium to regenerate the lithium enolate was then attempted.



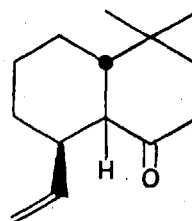
(124)

Thus, the silyl enol ether (124) was prepared in the usual manner and reacted with methyl lithium, in ether at 0°C until TLC indicated that the formation of the enolate was complete (i.e. by the absence of starting material). Quenching of the so formed enolate gave, not too surprisingly, the O-quenched material (122) again.

Attempted reaction of the TMS enol ether (124) with trimethylorthoformate in the presence of TiCl_4 failed to yield any (125), giving instead only the ketone (126). Other workers have since shown that reaction of (127) with

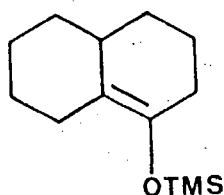


(125)

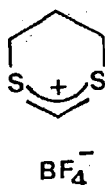


(126)

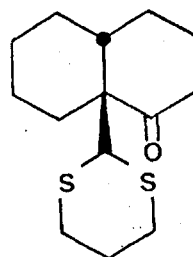
1,3-dithienium fluoroborate (128) gave a cis-fused decalone (129) as the sole product⁴⁹.



(127)

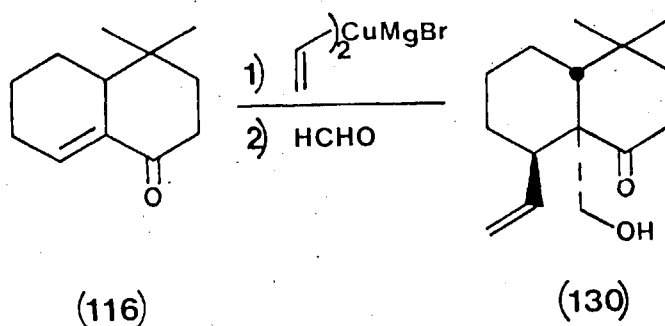


(128)



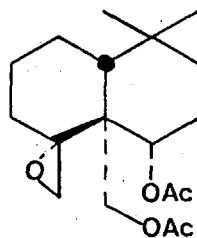
(129)

At this point, it was obvious that the enolate would have to be quenched by formaldehyde if reaction on carbon was going to occur. The use of paraformaldehyde together with Lewis acids was not successful. However, using an ethereal solution of formaldehyde formed by passing gaseous formaldehyde into dry ether (or THF) (see experimental), the long-sought-after reaction could be achieved. Thus, addition of this formaldehyde solution to the enolate resulted in the formation of the trans-vinyl hydroxymethyl decalone (130) in 63% yield (Scheme 14), together with a small amount ($\geq 5\%$) of another (cis ?) isomer. The relative stereochemistry of the functional groups in (130) was proven later. With the successful preparation of the hydroxymethyl ketone

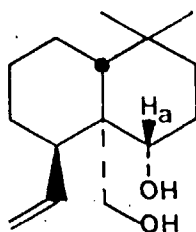


Scheme 14

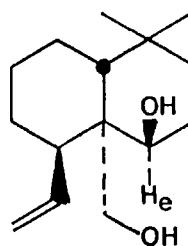
(130), it was only a matter of simple functional group manipulation before the synthesis of the trans-epoxydiacetate model (118) was realised. Consequently, the first step in the sequence was the stereospecific reduction of the keto-alcohol (130). Sodium borohydride reduction gave a 1:1 mixture of the epimeric



(118)



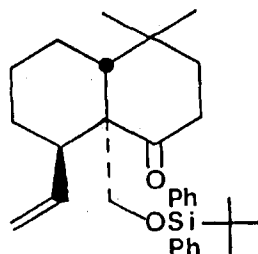
(131)



(132)

diols (131) and (132) as shown by the coupling constants in the ^1H NMR spectrum for the protons H_a and H_e (H_a , dd, J 11.6, 3.3 Hz; H_e , dd, J 3.0 and 3.0 Hz). This result was regarded as further evidence for the trans-nature of the ring junction as reduction of the cis-decalins (98) and (100) had led to the formation of only one isomer.

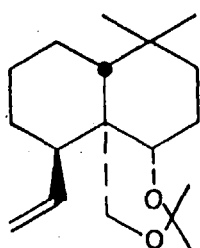
It was argued that if the steric bulk of the hydroxymethyl group was increased then hydride attack would be more likely to occur from the correct side to give only the equatorial alcohol (131). Thus, reaction of the alcohol (130) with *t*-butyldiphenylsilyl chloride, and imidazole in DMF, gave the silyl ether (133) in 98% yield. Attempted reduction of (133) with the hindered



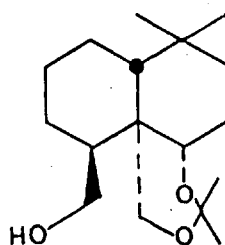
(133)

reagent K-selectride⁵⁰ failed to give any reaction. Similarly, sodium borohydride also failed to reduce (133). Lithium aluminium hydride, however, was successful giving the deprotected diol (131) directly on work-up in 63% yield (methods of improving this stereospecific reduction are currently being

investigated). Protection of the diol (131) as the acetonide (134) was achieved in almost quantitative yield using 2,2-dimethoxypropane and ozonolysis followed by reductive work-up with borohydride gave the alcohol (135) in 86% overall yield. Reaction of (135) with NPSP (59) and tri-n-butylphosphine according to

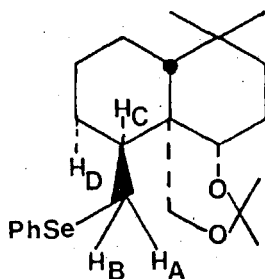


(134)



(135)

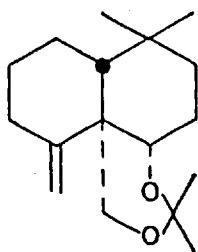
the method of Grieco and Nicolaou⁵¹ afforded smooth conversion to the selenide (136) in 89% yield. It was at this point that the high field ¹H NMR spectrum



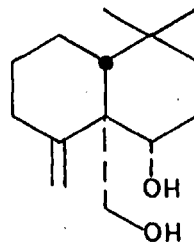
(136)

of (136) confirmed the original stereochemical assignment of the vinyl group in (130) as axial. In the selenide (136), the proton H_A alpha to selenium shows three coupling constants - one geminal (to H_B) of 11.8 Hz; one vicinal (to H_C) of 3.4 Hz; and one W-type⁴² (to H_D) of 1.7 Hz. This W-coupling can only occur if the selenophenylmethyl moiety [and hence the vinyl group in (130)] is an axial orientation.

The selenide (136) was converted to the selenoxide using ozone at -78°C in dichloromethane in the usual way, and thermolysis in refluxing carbon tetrachloride in the presence of di-isopropylamine, gave the exo-methylene



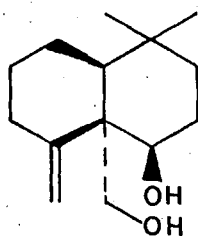
(137)



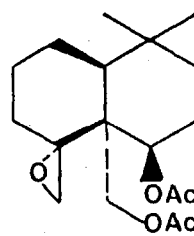
(138)

acetone (137) in 86% yield. Removal of the diol protecting group using trifluoroacetic acid proceeded in 89% yield to give the trans-exomethylene diol (138).

Jackson¹ had previously converted the cis-exomethylene diol (139) to the cis-epoxydiacetate (140) using the hydroxyl directed epoxydation reagent of Sharpless⁵² ($\text{VO}(\text{acac})_2/\text{t-BuOOH}$), followed by acetylation in a one-pot procedure. Thus, in a similar fashion, the diol (138) was converted to the

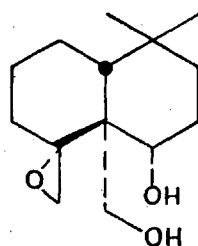


(139)

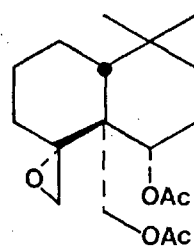


(140)

trans-epoxydiacetate (118) via (141) in 52% yield, so completing the synthesis of this model decalin.



(141)



(118)

Suitable crystals of (118) for X-ray analysis could not be obtained. However, the high field ^1H NMR spectrum, together with decoupling, and detailed nOe ^{53} experiments, completely confirmed the structural assignment.

Firstly, a comparison was made between the relevant portions in the 250 MHz ^1H NMR spectrum of the epoxy-diacetate (118) with the natural product ajugarin I (2) (see figure 5).

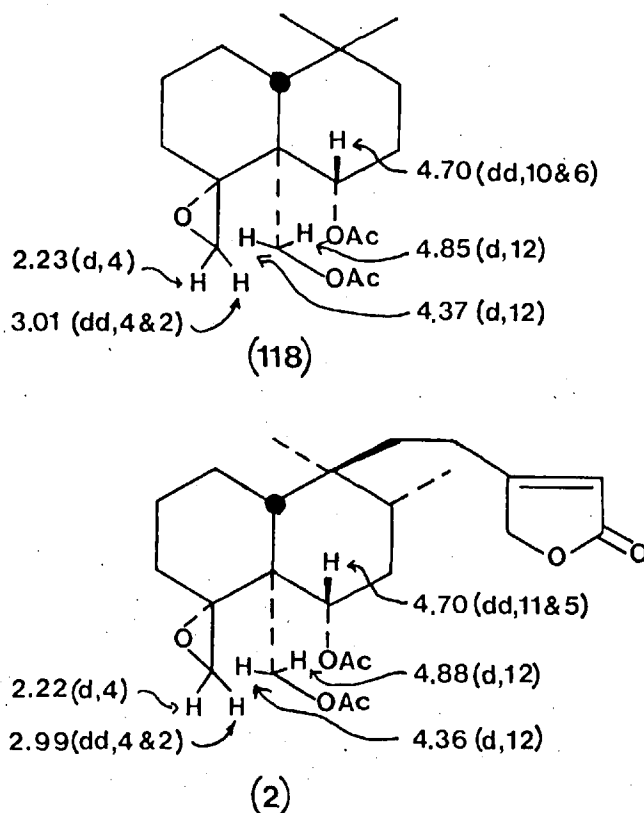


Figure 5: A comparison of ^1H NMR data between the model compound (118) and Ajugarin I (2). Chemical shifts in ppm, relative to TMS, (d = doublet, coupling constants in Hertz).

The proton assignment of the primary acetate follows from the existence (and removal by decoupling) of a small W-coupling ($> \frac{1}{2}$ Hz) to the proton adjacent to the secondary acetate. As is clear from Figure 5, the data of the two compounds are almost identical in the relevant spectral regions.

Several nOe difference spectra (nOeds) for compound (118) were obtained and are shown in spectra (1a, b, and c). It is now proposed to discuss these spectra in some detail.

Spectrum (1a) shows, in ascending order, apart from the normal high field ^1H spectrum (plotted with a twenty fold scaling factor), the nOeds obtained when the resonances at δ 4.88, 4.70 and 4.36 respectively (H_D , H_C and H_E respectively, Figure 6) are pre-irradiated. Spectra (1a, i) and (1a, iii) show an effect between the protons on the primary acetate group and very little else apart from one minor effect to the axial methyl group from H_D .

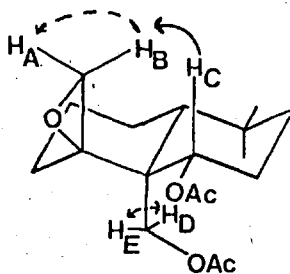


Figure 6

Spectrum (1a, ii) however, shows a large effect (7%) to the near epoxide proton H_B (Fig. 6) at δ 2.99, which itself then induces a secondary nOe in its neighbour, H_A , at δ 2.22 which consequently appears as a negative effect (it should be noted that the percentage nOe observed in FT type experiments need not be the same as that observed using conventional CW techniques). As yet, there appears to be no published examples of such an effect, probably because it will only occur in certain special cases and, if and when it does, because of its low intensity, its occurrence is only revealed by the difference technique with its inherent improved sensitivity.

Spectrum (1b, i) shows the nOeds obtained when the resonance at δ 2.99 (the epoxide proton H_B , Fig. 7) is partially saturated. Substantial effects are apparent both to the adjacent epoxide proton (H_A , Fig. 8, 17%) resonating

at δ 2.22 and to the axial proton H_C (Fig. 7, 14%) at δ 4.70.

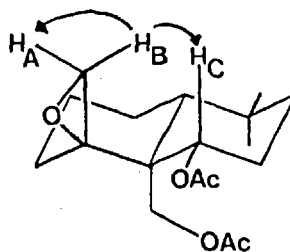


Figure 7

The apparent "roofing" effect on the resonance at δ 2.22 (H_A) is due to a combination of the nOe (through space) and an INDOR, through bond (see the Appendix) effect. Spectrum (1b, ii) shows the effect obtained when the proton H_A (Fig. 8) at δ 2.22 is pre-irradiated. This leads to a large effect (15%) to the adjacent epoxide proton (H_B) (although complicated by a smaller INDOR effect) which then induces a secondary "negative" nOe in the axial proton H_C at δ 4.70. H_A Also induces a nOe (again complicated by INDOR effects) to H_F at δ 1.05. However, the pre-irradiating frequency, nominally at δ 2.22, also partially saturated a resonance at δ 2.12, which had previously been shown,

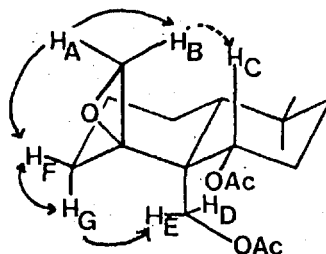
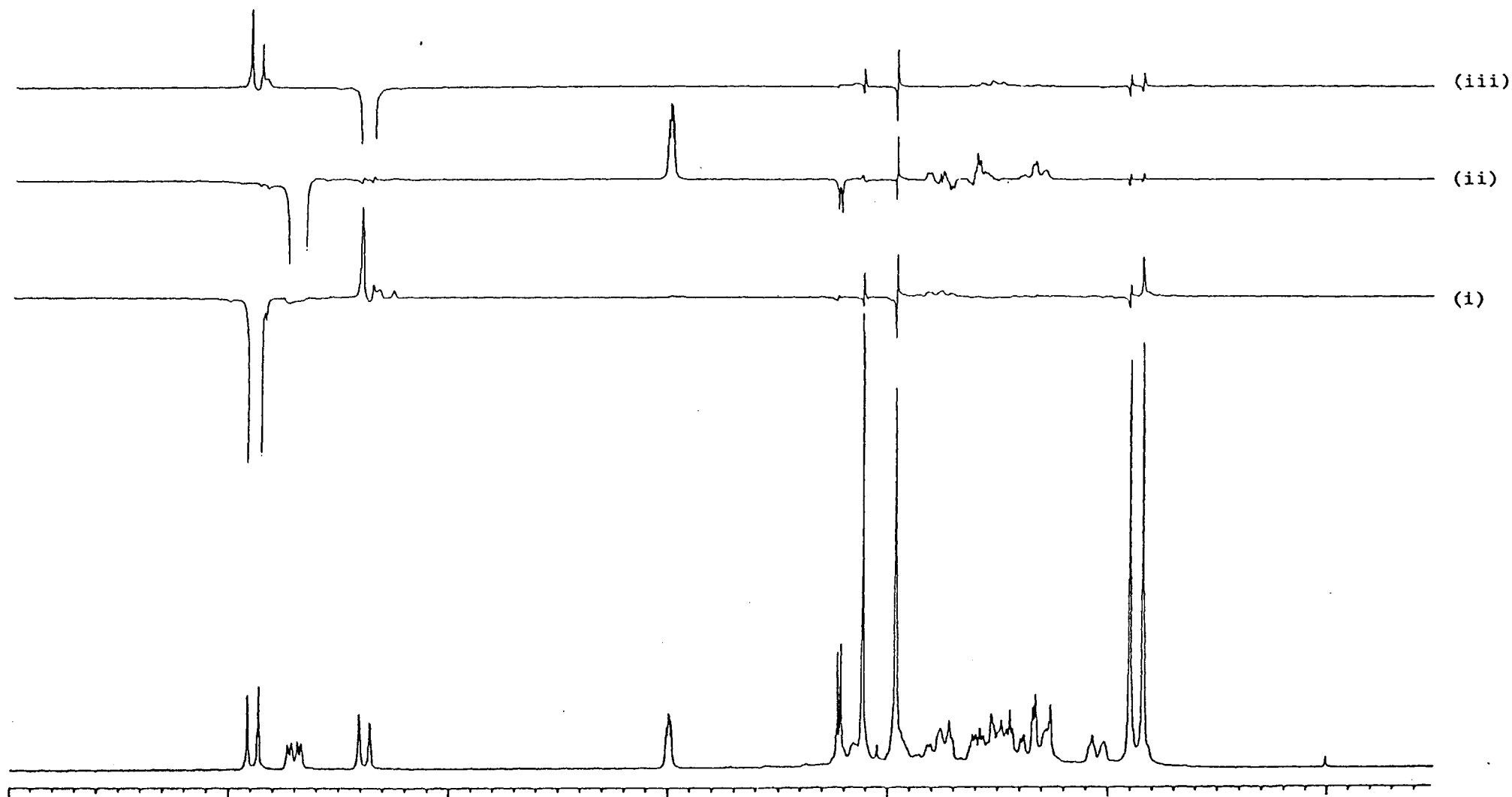
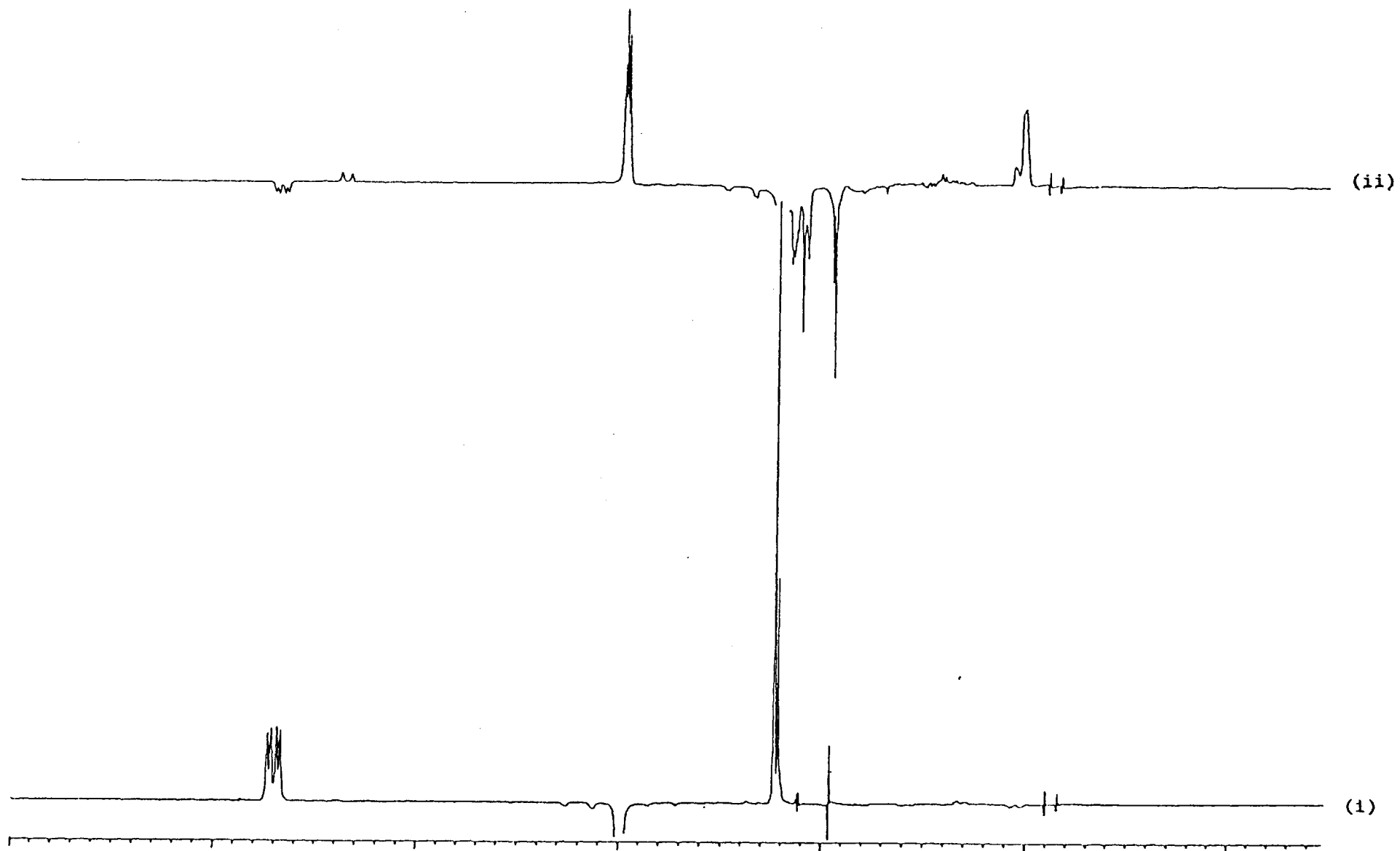


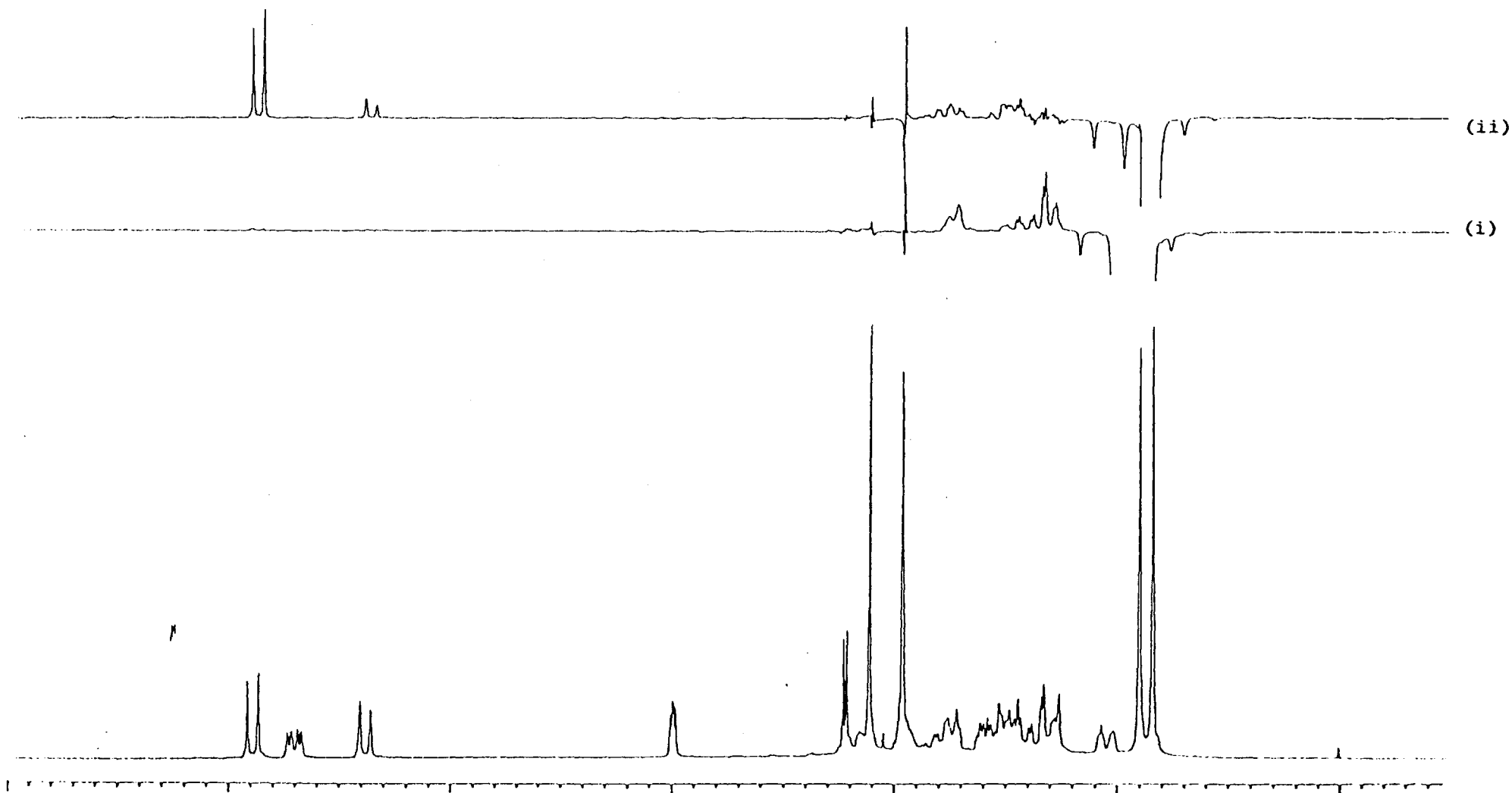
Figure 8



Spectrum 1a



Spectrum 1b



Spectrum 1c

by decoupling H_B , to be due to the W-coupled proton H_G . H_G Then induces a nOe to it's nearest neighbours, namely H_E and H_F .

Spectrum (1c) shows the effects of pre-irradiating the methyl groups. The equatorial group (Spec. 1c,i) does not induce any effect in the low field portion of the spectrum (although it does cause some minor and undecipherable effects to the high field, ring proton, resonances. Pre-irradiation of the axial methyl group (1c, ii) on the other hand, causes nOe to the H_D on the primary acetate (Fig. 9) together with smaller effects to H_E (Fig. 10) and to the high field, ring proton, resonances.

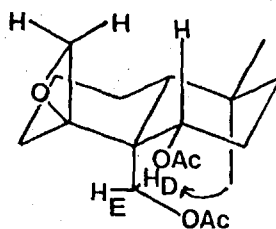
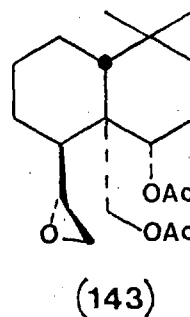
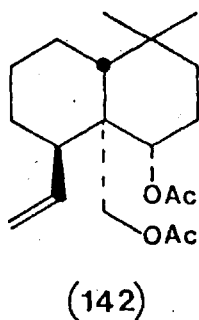


Figure 9

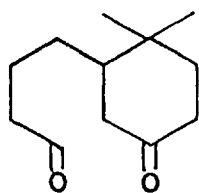
From these results, together with the comparison of chemical shifts (Fig. 5), the structural assignment of (118) is on firm ground. An X-ray crystallographic structure determination of the epoxide (143), prepared by m-CPBA oxidation of the vinyl diacetate (142)⁴⁵ has since provided proof of many of the relative structural assignments made earlier.



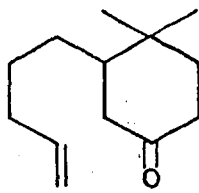
With the trans-epoxydiacetate (118) to hand, it's biological activity was investigated⁵⁴. At 1000 ppm against *Locusta migratoria*, a 95% inhibition of feeding was observed. For comparison, the cis-epoxydiacetate (140) and clerodin hemiacetal (14) were also tested. Compound (140) showed a 70% inhibition at 1000 ppm, while the natural product (14) induced a total cessation of feeding (100%). However, more importantly, on testing (118) at 100 ppm one still observed a 70% inhibition of feeding which compared very favourably to the natural product (82%). The cis-epoxydiacetate (140) at 100 ppm was totally inactive. When one considers that the model compound (118) is a racemic mixture, and that it is likely that only one enantiomer is biologically active, the activity shown is very significant. Several further analogues of (118) are currently being prepared⁴⁵ and will be tested at a later date.

ATTEMPTS TO PREPARE A C-5 FUNCTIONALISED TRANS-EPOXYDIACETATE

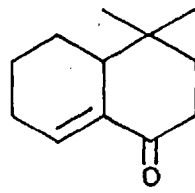
Having successfully prepared the model compound (118), approaches to the total synthesis of the natural products (1-4) were then investigated. In the model system, the crucial intermediate (116) had been prepared by the aldol cyclisation of compound (144) which had itself been prepared by ozonolysis of the alkenyl substituted cyclohexanone (86)⁴⁵. Obviously such a



(144)

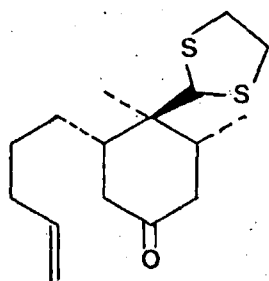


(86)

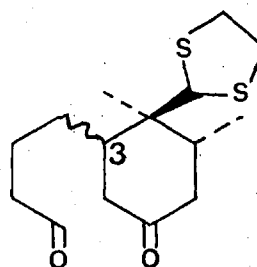


(116)

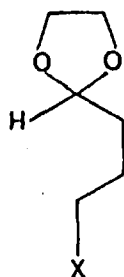
procedure would be impossible for the natural product using (79a) as the starting compound owing to complication by overoxidation of sulphur. Thus an



(79)

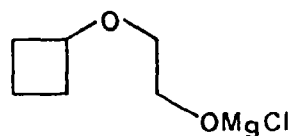
(145a) 3 α (145b) 3 β

alternative route for the preparation of the keto-aldehyde (145a) was required. Two possible ways of approaching this problem were considered. Firstly, a side-chain could be added to the enone-dithiolan (69) which was already at the oxidation state of aldehyde, i.e. an acetal. Or, secondly, a protected alcohol could be used and later oxidised to the aldehyde without affecting the dithiolan. Of the two, the former appeared to be the most attractive way.



(146a) X=Cl

(146b) X=Br

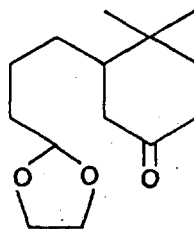


(147)

The required synthon for this approach was therefore the dioxalane (146). The chloride (146a) is known and has been used in similar transformations⁵⁵. However, both the Grignard reagent and the lithio derivative are difficult to prepare⁵⁵ and are known to rearrange on heating (45°C) to give (147). To avoid such side reactions, the bromide (146b) seemed more appropriate. 4-Bromopent-1-ene was ozonolysed to the aldehyde (148) which was immediately protected in the normal manner using ethylene glycol and a trace of pTSA in refluxing benzene. The Grignard reagent of (146b) was readily prepared in THF (attempts in ether failed) at 30°C. The derived cuprate from this Grignard reagent was first added to 4,4-dimethylcyclohexenone, as a model compound, which gave the expected product (149), in 62% yield. A one-pot acid catalysed hydrolysis and aldol condensation was then attempted using Helquist's method⁵⁶. In the cases of 5,5 and 6,5 ring systems, this has been shown to be quite successful. However, in this (6,6) example, the aldol reaction did not occur and only the

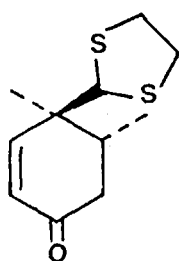


(148)

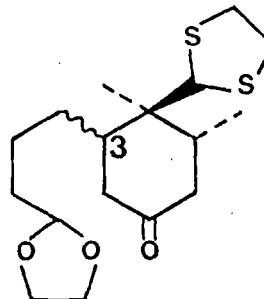


(149)

known⁴⁵ keto-aldehyde (144) was isolated. Having shown that the cuprate derived from (146b) was in fact useful, attempts to add it stereospecifically to the enone-dithiolan (69) were then made. Earlier, it had been found that



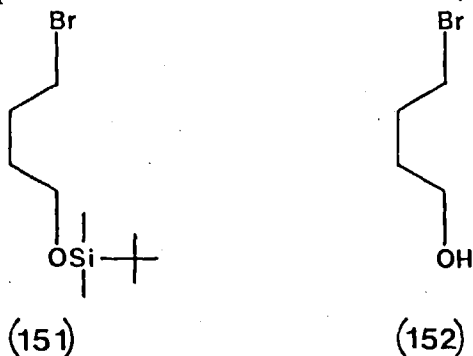
(69)

(150a) 3 α (150b) 3 β

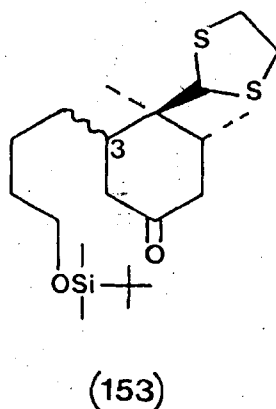
these cuprate reactions were best carried out by mixing at -78°C and allowing to warm slowly. However, in this example, an immediate colour change was observed (purple to yellow) indicating that the cuprate reacted instantaneously. On work-up, the adduct (150) was isolated as a mixture of isomers, chromatographic separation of which was not possible. Similarly, separation after hydrolysis to the aldehydes (145) was also not possible. By comparison with earlier examples, it was concluded that the major isomer was in fact the desired one, i.e. (145a), in a ratio of 7:3 with the minor one (145b).

In view of the previous stereospecific addition of both methyl and pent-4-enyl groups to the enone-dithiolan (69), this result was surprising but might be explained in terms of the apparent enhanced reactivity of this particular cuprate, or that it failed to complex first with the dithiolan moiety. Consequently, attempts were made to slow down the 1,4-addition process by carrying out the reaction at lower temperatures. However, even down to -125°C (where the reaction mixture began to freeze), the reaction appeared to occur instantaneously (colour change) and a mixture of isomers of (150) in the ratio 7:3 was again obtained.

As an alternative, therefore, the second approach discussed earlier was attempted. A suitable side-chain derivative was thought to be the t-butyldimethylsilyl protected 4-bromobutan-1-ol (151). Thus the alcohol



(152) was prepared by ozonolysis of 1-bromopent-4-ene, followed by reductive (sodium borohydride) work-up. Protection was achieved in the normal manner using t-butyldimethylsilyl (t-BDMS) chloride and imidazole in DMF⁵⁷. After formation of the Grignard reagent of (151) and subsequently the cuprate, as before, addition of the enone-dithiolan (69) gave a product (153) which was apparently a 50:50 mixture of 3 α and 3 β epimers. Lack of time prevented



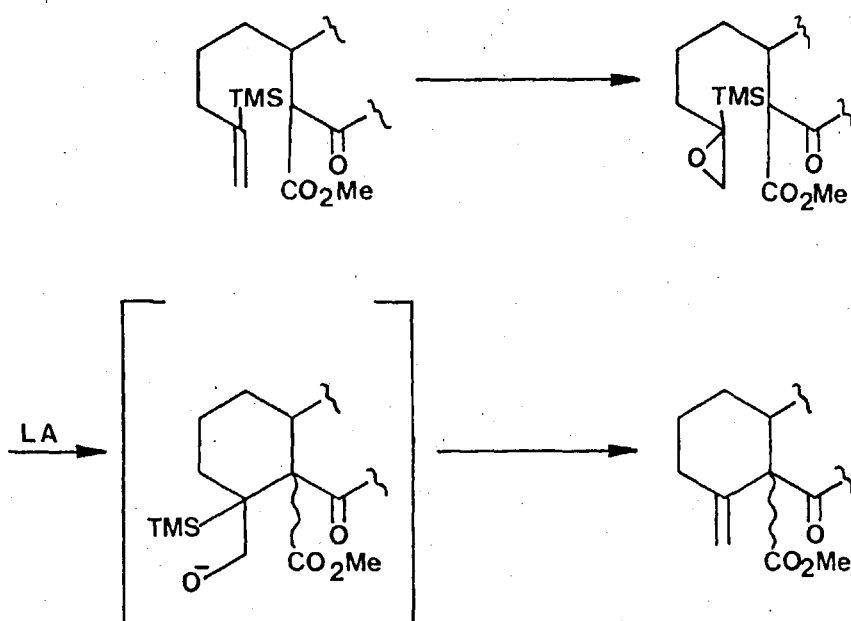
further investigation of this reaction. It does seem, however, that there are more subtle factors operating in the control of the direction of attack of cuprate nucleophiles on the enone-dithiolan (69) than were originally supposed. Further work, in progress in these laboratories, is being carried out in order to elucidate these reactions in more detail.

These results conclude the efforts made in attempts to develop a total

synthesis of the polyoxygenated clerodanes. Although not successful to date, it seems likely that given time, the present approach will be adaptable to a total synthesis. The preparation and biological testing of the model compound (118), together with analogues may be a significant contribution to defining the mode of action and usefulness of the clerodane type anti-feedants.

ATTEMPTS TO PREPARE A VINYLSILANE SIDE-CHAIN PRECURSOR FOR A NOVEL CYCLISATION PROCEDURE

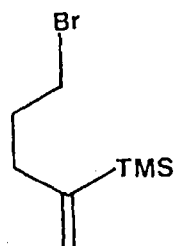
Towards the beginning of the project, an alternative idea for a novel cyclisation procedure based upon an intramolecular Peterson olefination, outlined in Scheme 15, was conceived.



Scheme 15

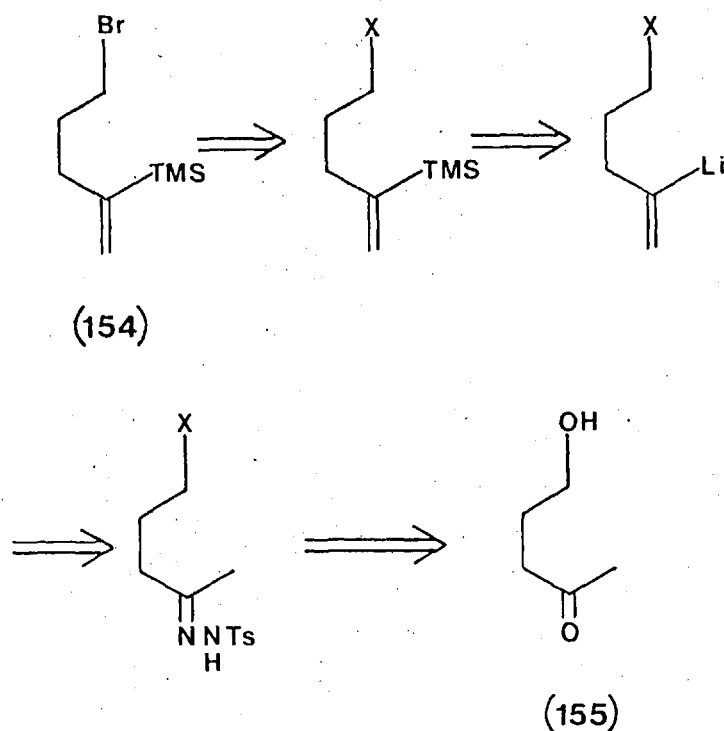
The method would have the advantage that an exo-methylene group (required in our strategy for an approach towards the synthesis of clerodane diterpenes) would be simultaneously introduced.

Taking account of the need to be able to add the requisite functionalised side-chain to an enone *via* the cuprate species, the ideal side-chain precursor seemed to be the bromo-vinylsilane (154). Of the methods for the preparation of vinylsilanes, it appeared that only one would give us the required regiochemistry, *i.e.* that *via* the vinyl lithium species derived by



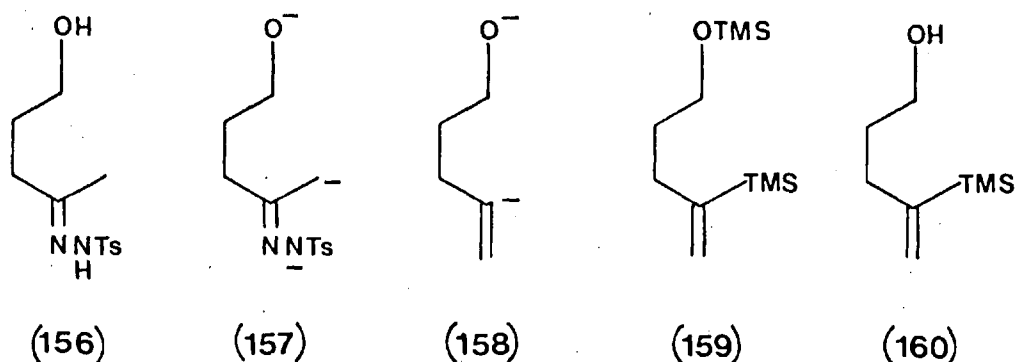
(154)

Shapiro reaction of the tosylhydrazone⁵⁸. The retrosynthetic scheme to (154) envisaged is shown in Scheme 16, leading to the starting material, 5-hydroxy-pentan-2-one (155). Initially, it was thought likely that the derived



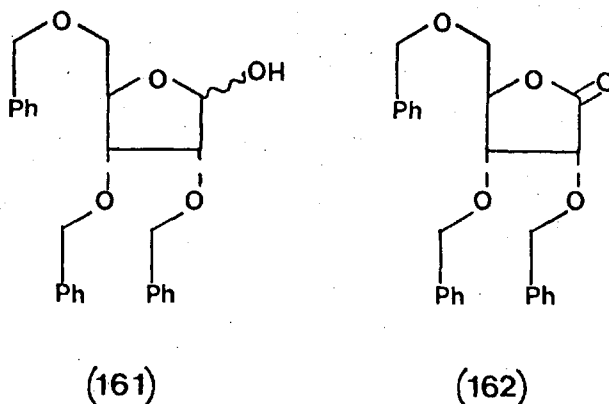
Scheme 16

hydroxy-tosylhydrazone (156) would, on reaction with a suitable alkyl lithium, give the trianion (157), which would decompose to the alkoxy vinyl dianion (158), and give after chlorosilane quench, the disilylated compound (159). Mild acid hydrolysis would then give the alcohol (160) which could easily be transformed into the desired bromo-vinylsilane (154).

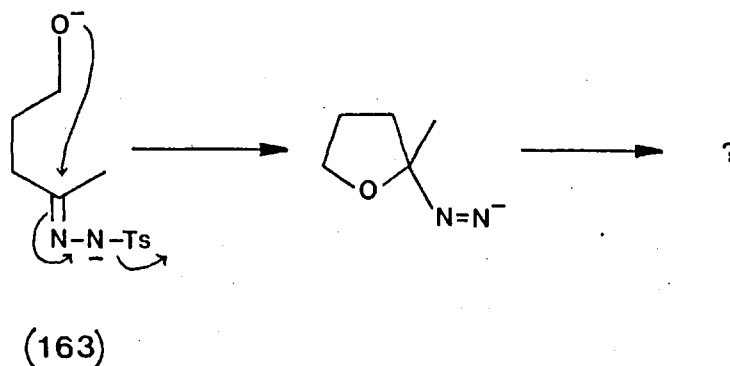


Thus, the hydroxy-tosylhydrazine (156) was prepared in high yield from the hydroxy-ketone (155), using tosylhydrazine and an acid catalyst in methanol. Unfortunately, when using the conditions of Paquette^{58b} (1.6 M *n*-butyl lithium, TMEDA, -50°C), the trianion (157) was not formed and when the experiment was carried to completion, none of the desired products (159) or (160) could be isolated. Repeating the experiment using a more concentrated solution of *n*-butyl lithium (6M) or *t*-butyl lithium, under different conditions and in different solvents, did not lead to any success.

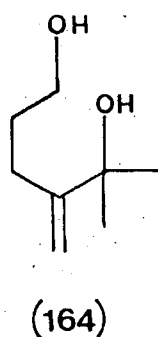
There are two possible explanations for this failure. Firstly, the insolubility of the tosylhydrazone (156) in the various solvents could lead to difficulty in forming the anion. Secondly, the occurrence of an unusual side-reaction, as described by Adlington⁵⁹ could lead to problems. While this work was in progress, Adlington found that the δ -hydroxy-2,4,6-tri-*iso*-propylbenzenesulphonyl hydrazone derived from *o*-benzyl-D-ribofuranose (161) decomposed *via* intramolecular attack of the hydroxyl function at the imine carbon atom, to give on work up, the ribofuranolactone (162). Therefore, it is possible that if the dianion (163) preceding the trianion (157) was



in fact formed, then it could rapidly cyclise leading to the formation of furano-type compounds. This reaction seems only to occur for δ -hydroxy- sulphonylhydrazones.



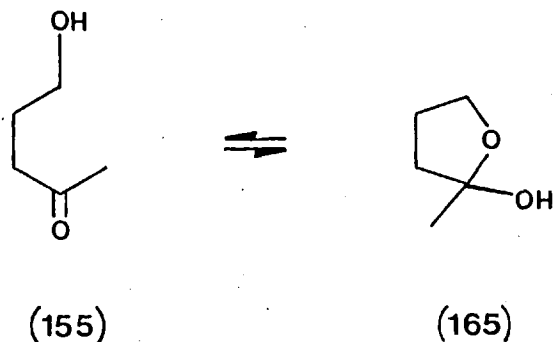
Two possible methods of avoiding this reaction were investigated. Firstly, the 2,4,6-tri-iso-propylbenzenesulphonylhydrazone of the hydroxy-ketone (155) was prepared in dry ether using a pTSA resin as catalyst⁵⁹. This was followed by rapid azeotropic removal of water and the crude hydrazone was then dissolved in dry dimethoxyethane and cooled to -78°C . After the addition of 3.5 equivalents of n-butyl lithium, the mixture was warmed to 0°C over 2 h so forming the alkoxy vinyl dianion (158) and then recooled to -78°C . Quenching with dry acetone and work up followed by careful column chromatography gave a small amount (21%) of the expected diol (164). Using this method then,



the yield of the alkoxy vinyl anion was not particularly good and, realistically, the reaction was therefore useless as an early step in a large synthetic scheme.

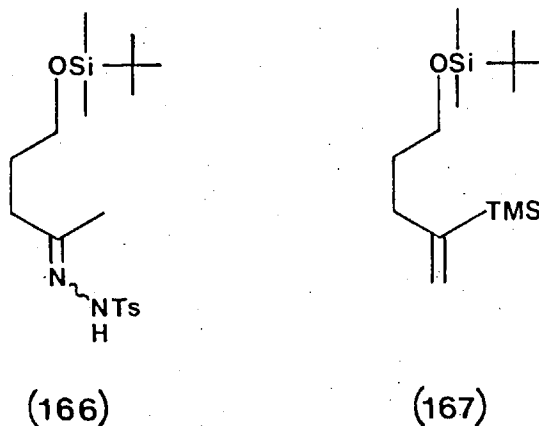
Protection of the hydroxyl function was therefore considered necessary. The protecting group obviously had to be stable to extremely strong basic and

nucleophilic conditions and, of the methods considered, the THP⁶⁰, MEM⁶¹, or t-BDMS⁵⁷ ethers seemed most appropriate. As the hydroxy-ketone (155) exists in equilibrium with its ketol form (165), conversion to the tosylhydrazone



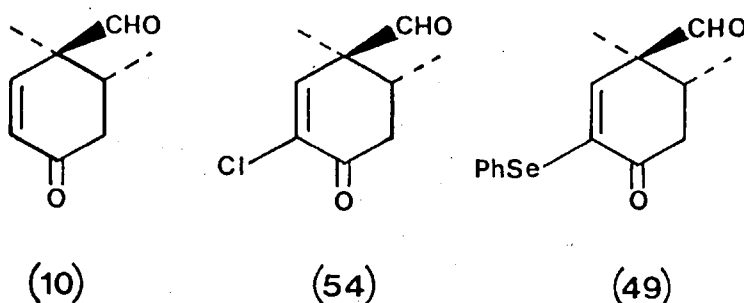
had to be carried out prior to protection of the alcohol. Unfortunately, the conditions required to form the THP ether resulted in partial decomposition (hydrolysis) of the hydrazone and a complex mixture was the result. Similarly, reaction of the hydroxy-hydrazone (156) with either MEM chloride and Hunig's base⁶¹ or the preformed salt of triethylamine and MEM chloride, led to partial decomposition of the hydrazone, and the subsequent isolation of a complex reaction mixture.

Finally, t-BDMS chloride and imidazole in DMF were tried. This resulted in the formation of the silyl ether (166) in high yield, as a 1:1 mixture of isomers. However, in view of other chemistry that was progressing at this time, the route from (166) to (167) was not investigated further.

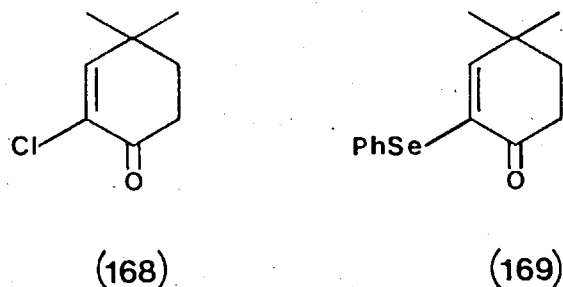


THE PREPARATION OF 2-HALO ENONES AND ENALS

The early observation that, on reaction of the enone-aldehyde (10) with several equivalents of phenylselenium chloride and pyridine, formation of the 2-chloro-enone (54) occurred, in addition to the expected 2-selenophenyl enone (49), prompted a further investigation of this novel process. Firstly, in

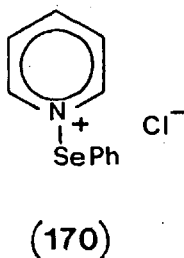


order to see whether this was a general reaction, the experiment was repeated using 4,4-dimethylcyclohexenone in place of (10). Thus, the enone was added to two molar equivalents of phenylselenium chloride and pyridine in dry dichloromethane, under argon, at room temperature. After 48 h, work up gave a mixture in a 2:1 ratio of the 2-chloro-enone (168) and the 2-selenophenyl enone (169) in high yield. This mixture was subsequently added to a solution of more phenylselenium chloride/pyridine and resulted in conversion to a single product shown to be the 2-chloro-enone (168) in 95% yield. Obviously, the 2-chloro



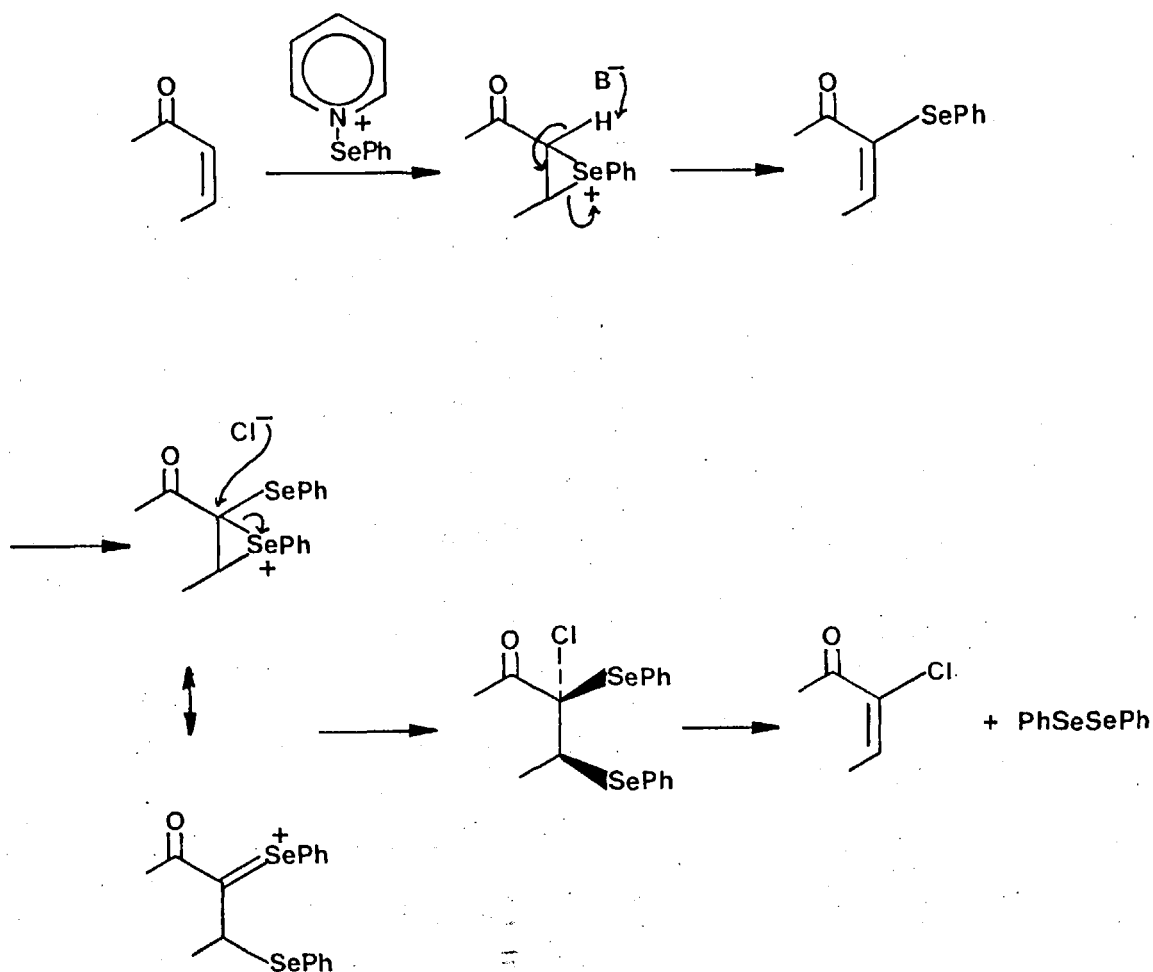
enone was formed *via* the 2-selenophenyl enone as intermediate and the only byproduct isolated was diphenyldiselenide, isolated in 91% yield.

Liotta²² suggests that the formation of the 2-selenophenyl enones from enones with the phenylselenating agent is caused by the Michael addition of pyridine to the enone, followed by alpha-selenation of the resulting enolate and subsequent loss of both pyridine and a proton. However, given that secondary amines are known to react with PhSeBr, PhSeCl, or PhSeOH to give N,N-dialkyl benzeneselenamides⁶², we believe that pyridine and phenylselenium chloride react to form a complex (170) which then acts as an electrophilic selenating agent.



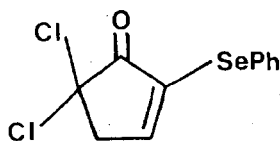
On adding pyridine to phenylselenium chloride in dichloromethane, there is an obvious change in colour (dark red to pale orange) and heat is evolved. The mechanism shown in Scheme 17, therefore, seems much more likely.

In order to extend the scope of the reaction, a variety of enones and enals were reacted with phenylselenium chloride and pyridine - the results of which are shown in Table 4. The products (171-5) were identified by their spectral data, their melting points and, where necessary, by conversion to a suitable derivative. As can be seen, the reaction generally gives high yields, however, the more hindered the enone, the slower the reaction.



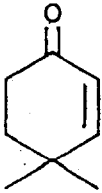
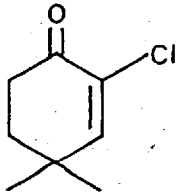
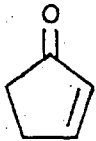
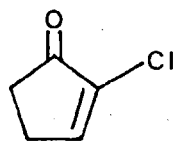
Scheme 17

On reaction of cyclopent-2-enone with phenylselenium chloride and pyridine in dichloromethane at 25°C (rather than the usual 37°C) another product was additionally formed in low (14%) yield. By a combination of spectral techniques, the best structural fit for this compound appears to be (176).



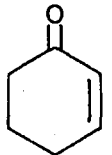
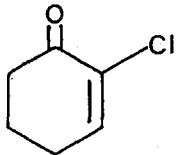
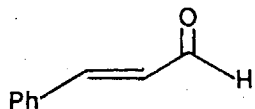
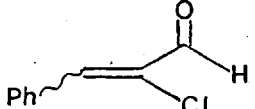
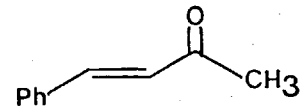
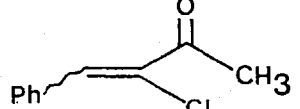
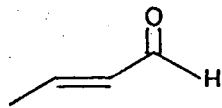
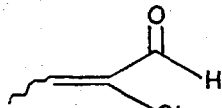
(176)

TABLE 4. Preparation of α -chloro-enones and enals

SUBSTRATE	PRODUCT	No. Eq. PhSeCl/Pyridine		Conditions Time/h Temp/°C		YIELD/%
	 (168)	3	3	72	37	92
	 (171)	3	3	72	37	52

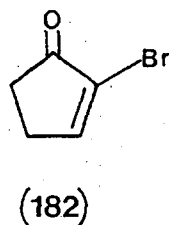
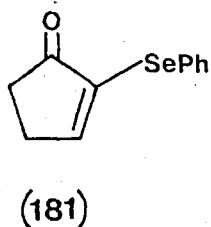
/continued...

TABLE 4/continued...

	 (172)	3	3	96	37	82
	 (173)	3	3	96	37	100
	 (174)	3	3	7days	37	85
	 (175)	2.5	2.5	60	25	95

Presumably, the formation of this compound occurs *via* the readily enolisable 2-selenophenylcyclopent-2-enone reacting with a positive chlorinating species, possibly Cl_2 or PhSeCl_3 .

It occurred to us that if the enones and enals were reacted with a mixture of phenylselenium bromide and pyridine, then the corresponding 2-bromo-compounds should be available. As shown in Table 5, this was indeed found to be the case. Once again, it was shown that the reaction proceeded *via* the 2-selenophenyl compound by reacting 2-selenophenylcyclopent-2-enone (181) with a further equivalent of phenylselenium bromide and pyridine, to give 2-bromocyclopent-2-enone (182) in 52% yield.



This new halogenating reaction appears to be quite useful, especially when compared with the literature routes to similar compounds which are inefficient or involve multistep sequences⁶³. In the new method, diphenyl-diselenide can be readily recovered and recycled.

TABLE 5. Preparation of α -bromo-enones and enals

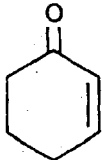
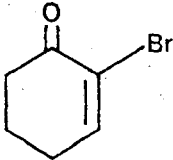
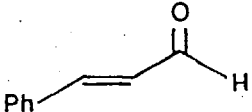
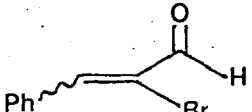
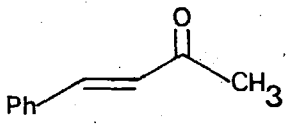
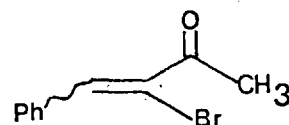
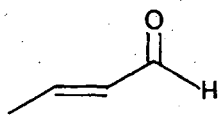
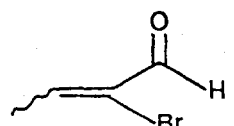
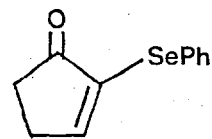
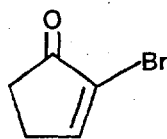
SUBSTRATE	PRODUCT	No. Eq. PhSeBr/Pyridine		Conditions Time/h Temp/°C		YIELD/%
	 (177)	2.5	2.5	24	25	100
	 (178)	3	3	7days	37	85

TABLE 5/continued...

	 (179)	3	3	65	37	51
	 (180)	2.5	2.5	24	25	95
 (181)	 (182)	15	15	72	37	52

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer 298 or 157G grating infra-red spectrophotometer. NMR spectra were recorded on a Bruker WH 400, a Bruker WM 250, a Varian XL 100, or on a Perkin Elmer R 32 spectrometer where the field strength is stated. Otherwise a Varian EM 360A spectrometer was used. Tetramethylsilane was used as internal reference, and the spectral data is given using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad.

Analytical thin layer chromatography (TLC) was performed on Merck precoated GF₂₅₄ silica gel plates. Preparative layer chromatography (PLC) was performed on GF₂₅₄ silica gel plates. Medium pressure chromatography was carried out on Merck Kieselgel H or on Merck Kieselgel 60 silica gel.

Solvents were purified as follows: benzene, diethyl ether - dried over sodium wire; dichloromethane - redistilled from phosphorus pentoxide; chloroform, ethyl acetate - redistilled; dioxan, tetrahydrofuran - redistilled from sodium/benzophenone ketyl; N,N-dimethylformamide - redistilled at reduced pressure from 4A molecular sieves onto 4A molecular sieves; ethanol, methanol - AnalaR reagents; pet. ether - redistilled b.p. 40-60°C fraction; pyridine - redistilled from, and stored over, potassium hydroxide; triethylamine - stored over potassium hydroxide.

Organic solutions were routinely dried over anhydrous sodium or magnesium sulphate. Solvents were evaporated at reduced pressure using a rotary evaporator at or below 40°C unless otherwise stated.

Mass spectral measurements were carried out on a V.G. micromass 7070B instrument in the mass spectral laboratory, and microanalyses were carried out by the microanalysis laboratory, both at Imperial College.

(1) Improved procedure for the preparation of 4-Methoxy-2-trimethylsilyloxy-1,3-butadiene (16)³

Anhydrous powdered zinc chloride (1.6 g) was added to dry triethylamine (92 g, 0.9 mol), and the mixture was stirred for 1 h at room temperature until the salt was suspended in the amine. To this mixture was added 4-methoxy-3-buten-2-one (19) (40 g, 0.4 mol) in dry benzene (120 ml) followed by trimethylchlorosilane (84 g, 0.8 mol) in one portion. A slight exothermic reaction ensued. After 30 min the reaction temperature was raised to 40°C and stirring continued overnight. On cooling, the reaction mixture was added to dry ether (1 l) and filtered through a pad of celite. The filtrate and combined ethereal washings were concentrated, *in vacuo*, to a volume of $\approx$ 100 ml. The brown reaction mixture was rediluted with dry ether (200 ml) and again filtered through celite. The cycle was repeated twice until no more solid precipitated when the oil was diluted. Distillation through a 12 cm Vigreux column (middle cut) gave 4-methoxy-2-trimethylsilyloxy-1,3-butadiene (16) (52 g, 76%), b.p. 32°C/2 mmHg (lit.,³ 54-55°C/5 mmHg); δ (CDCl₃) 6.81 (d, J 12 Hz, 1H), 5.36 (d, J 12 Hz, 1H), 4.03-4.17 (broad d, J 1 Hz, 2H), 3.57 (s, 3H), and 0.23 (s, 9H); $\nu_{\max}$ (CHCl₃) 1656, 1618, 1597, 1567, 1538, 1300, 1234, 1010, and 950 cm⁻¹.

(2) Preparation of (E)-2-Methyl-2-butenal(tigaldehyde, 15) using the method of Re⁴

To isoprene (80.1 g, 1.33 mol) in CH₂Cl₂ (1 l) under N₂, in a 3 l. 3-necked flask, fitted with a condenser, mechanical stirrer, pressure equalising dropping funnel and nitrogen inlet, was added anhydrous sodium carbonate (300 g, 2.7 mol) and 2,6-di-tert-butyl-4-methylphenol (100 mg).

The stirred suspension was cooled to 0°C and 38% peracetic acid (240 ml, 1.55 M) was added dropwise over 6 h. After an additional 18 h during which period the stirred reaction mixture was allowed to slowly warm to room temperature, the suspension was filtered and the residue extracted with CH₂Cl₂ (3 x 300 ml). The combined solution of isoprene monoepoxide (18) thus prepared was pyrolysed over alumina at 130-140°C by dropwise addition to the top of a heated packed column using nitrogen as carrier gas. The pyrolysate was collected at the bottom of the column (cardice/acetone) and, after removal of the solvent by distillation at atmospheric pressure, gave the crude product. Distillation under reduced pressure then gave (E)-2-methyl-2-butenal (15) (62 g, 55%), b.p. 61-2°C/100 mmHg (lit.,⁴ 62.5-65°C/119 mmHg); δ (CDCl₃) 8.8, (s, 1H), 6.1 (qq, J 8 and 1 Hz, 1H), 1.4 (d, J 8Hz, 3H), and 1.15 (d, J 1Hz, 1H); $\nu_{\max}$ (film) 2680, 1680, and 1650 cm⁻¹.

(3) Preparation of 4 β -Formyl-4 α ,5 α -dimethylcyclohex-2-enone (10)

Into a carefully base-washed and dried 12 oz glass bomb, was placed 4-methoxy-2-trimethylsilyloxy-1,3-butadiene (16) (22 g, 0.123 mol), tigaldehyde (15) (13 g, 0.154 mol) and hydroquinone (5 mg). The bomb was sealed, evacuated and placed in a hot Wood's metal bath (140°C) for 14-18 h. During the course of the reaction, the initial pale yellow colour of the mixture changed to a golden brown. After cooling, the crude adducts of three such runs were combined, dissolved in THF (450 ml) and hydrolysed by the addition of 2N HCl (1 ml). After 30 min the reaction mixture was carefully neutralised (aqueous sodium bicarbonate) and the product extracted into pet. ether (3 x 400 ml). The combined organic layers were dried, filtered and the solvent removed *in vacuo* to give the crude enone-aldehyde (10). Excess tigaldehyde (15) and 4-methoxy-3-buten-2-one (19) were

removed *in vacuo* (0.5 mmHg, 12 h) and the residue distilled under high vacuum through a 5 cm Vigreux column to give, firstly, 4 β -formyl-4 α ,5 α -dimethylcyclohex-2-enone (10) (20.94 g, 35%), b.p. 60-62 $^{\circ}$ /2.2 x 10 $^{-3}$ mmHg; 90 MHz (CDCl $_3$); δ 9.55 (s, 1H), 6.72 (d, J 10Hz, 1H), 6.06 (d, J 10 Hz, 1H), 2.77-2.03 (m, 3H), 1.25 (s, 3H), and 1.08 (d, J 8Hz, 3H); $\nu_{\max}$ (film) 2720, 1735, and 1695 cm $^{-1}$; m/e 152.0838 (M $^{+}$), 137, and 123 (Calculated for C $_9$ H $_{12}$ O $_2$: 152.0837). Next, a mixture of what was predominantly the two methyl ethers (20a) and (20b) (in a 1:1 ratio), distilled over (14.34 g (19.5%), b.p. 70-72 $^{\circ}$ C/5 x 10 $^{-3}$ mmHg. A small amount was separated chromatographically (silica gel, 50:50 ether/pet. ether), to give (i) 4 β -formyl-3 α -methoxy-4 α ,5 α -dimethylcyclohexanone (20b); δ (CDCl $_3$) 9.32 (s, 1H), 3.62 (dd, J 12, and 5 Hz, 1H), 3.20 (s, 3H), 2.80-2.00 (m, 5H), 1.15 (s, 3H), and 0.85 (d, J 6 Hz, 1H); $\nu_{\max}$ (film) 2830, 2710, 1720, and 1095 cm $^{-1}$; m/e 184.1100 (M $^{+}$) 168, 156, and 124 (Calculated for C $_{10}$ H $_{16}$ O $_3$: 184.1099); and (ii) the C-3 epimer - namely 4 β -formyl-3 β -methoxy-4 α ,5 α -dimethylcyclohexanone (20a); δ (CDCl $_3$) 9.51 (s, 1H), 3.65 (dd, J 4, and 4 Hz, 1H), 3.20 (s, 3H), 2.80-2.00 (m, 5H), 1.01 (s, 3H), and 0.89 (d, J 6 Hz, 3H), $\nu_{\max}$ (film) 2830, 2710, 1720 and 1095.

(4) Conversion of the epimeric methyl ethers (20a) and (20b) into 4 β -Formyl-4 α ,5 α -dimethylcyclohex-2-enone (10) according to the method of Danishefsky⁶

The mixture of ethers (20a) and (20b) (7.6 g, 41.3 mmol) obtained above was dissolved in benzene (400 ml), together with pTSA (1 g) and was heated to reflux for 45 min. After cooling, the reaction mixture was diluted with ether (500 ml) and washed sequentially with aqueous sodium bicarbonate (2 x 50 ml), aqueous ammonium chloride (50 ml) and brine (100 ml). The combined aqueous layers were extracted into ethyl acetate (100 ml) and the combined organic layers were dried and filtered.

Removal of the solvents *in vacuo* gave the crude enone-aldehyde (10) which was distilled, as above, or subjected to column chromatography (silica gel, 50:50, ether/petroleum ether), to give (i) 5,6-dihydro-4H,6(E-2'-but-2'-ene)-pyran-4-one (23) (0.56 g, 9%); δ 100 MHz (CDCl_3) 7.26 (d, J 5 Hz, 1H), 5.58 (m, 1H), 5.23 (dd, J 5, and 1.5 Hz, 1H), 4.67 (dd, J 12, and 4 Hz, 1H), 2.75 (dd, J 14, and 12 Hz, 1H), 2.30 (ddd, J 14, 4, and 1.5 Hz, 1H), and 1.72 (m, 6H); ν_{max} (film) 3065, 1680, 1593, 1405, and 1276 cm^{-1} ; m/e 152.0846 (M^+), 137, 124, and 97 (Calculated for $\text{C}_9\text{H}_{12}\text{O}_2$: 152.0837); and (ii) 4 β -formyl-4 α ,5 α -dimethylcyclohex-2-enone (10) (7.6 g, 66%) as before.

(5) Attempted reduction of 4 β -Formyl-4 α ,5 α -dimethylcyclohex-2-enone (10)

(a) Using Dibal. The reaction conditions were as described in Table 1. Typically, the enone-aldehyde (10) (0.2 g, 1.3 mmol) was dissolved in dry benzene (20 ml) under an atmosphere of dry argon. The stirred solution was cooled to 10 $^{\circ}\text{C}$, and a solution of Dibal (1.82 mmol) in dry benzene (8 ml) was added slowly. After stirring for 2 h, water (0.2 ml) was added followed by anhydrous sodium sulphate (5 g). The reaction mixture was vigorously shaken before being extracted with ether (3 x 50 ml), dried, filtered, and the solvent removed *in vacuo*. PLC (silica gel, 50:50 acetone/ CH_2Cl_2) gave three identifiable products: (i) the starting enone-aldehyde (10) (20 mg, 10%); (ii) 4 β -hydroxymethyl-4 α ,5 α -dimethylcyclohex-2-enone (26) (50 mg, 25%); δ (CDCl_3) 6.65 (d, J 10 Hz, 1H), 5.75 (d, J 10 Hz, 1H), 3.34 (broad s, 2H), 2.5-2.0 (m, 4H, 1H D_2O exch.), and 1.0-0.8 (m, 6H); ν_{max} (film) 3450 and 1690 cm^{-1} ; m/e 154 (M^+), 124, 109, and 98; and (iii) 4 β -hydroxymethyl-4 α ,5 α -dimethylcyclohex-2-en-1 β -ol (27) (40 mg, 20%); δ (CDCl_3) 5.72 (dd, J 9 and 1.5 Hz, 1H), 5.35 (dd, J 9 and 1.5 Hz, 1H), 4.2 (dddd, J 6, 6, 1.5, and 1.5 Hz, 1H), 3.34 (broad s, 2H), 2.1-1.0 (m, 5H, 2H D_2O exch.) 0.82 (d, J 7 Hz, 3H), and 0.75 (s, 3H); ν_{max} (CHCl_3)

3600, 3450 and 1650 cm^{-1} ; m/e 138 ($M-H_2O$) and 125 ($M-CH_2OH$).

(b) Using lithium aluminium hydride. Lithium aluminium hydride (15 mg, 0.39 mmol) was added to a stirred solution of the enone-aldehyde (10) (100 mg, 0.66 mmol) in dry ether (10 ml). After 4 h the reaction was quenched by the addition of water (1 ml) followed by anhydrous sodium sulphate (5 g). The mixture was then vigorously stirred before being extracted into ether (3 x 20 ml). The combined organic layers were dried, filtered and the solvent removed *in vacuo* to leave an oil which by ^1H NMR and TLC showed the absence of (26) or (27) and was discarded.

(6) Reaction of 4 β -Formyl-4 α ,5 α -cyclohex-2-enone (10) with 1,2-Dimethyl-4,5-di(mercaptomethyl)benzene (32)

(a) A mixture of the enone-aldehyde (10) (0.2 g, 1.3 mmol), 1,2-dimethyl-4,5-di(mercaptomethyl)benzene (32) (0.26 g, 1.3 mmol), (prepared by the method of Shahak and Bergmann¹¹) and 35% aqueous HCl (0.5 ml) were stirred together in dioxan (5 ml) for 7 min. Water (7 ml) was added and the mixture extracted into ether (3 x 25 ml). The combined ethereal layers were dried, filtered and the solvent removed *in vacuo* to give the crude product, δ ($CDCl_3$), 9.6 (CHO); ν_{max} (film) 1740. Both the ^1H NMR and the IR spectra showed the absence of an enone moiety.

(b) A mixture of the enone-aldehyde (10) (0.2 g, 1.3 mmol), the dithiol (32) (0.26 g, 1.3 mmol) and pTSA (5 mg) in benzene (25 ml) was heated to reflux for 24 h. After cooling, the solution was poured into ether (50 ml) and washed with aqueous sodium bicarbonate (2 x 10 ml), water (2 x 10 ml) and, finally, brine (2 x 10 ml). Drying, filtration and removal of the solvent *in vacuo* gave an oil the spectral data of

which again showed the absence of an enone, but did show the presence of an aldehyde-moiety.

(7) Preparation of 4 β -Formyl-3 β ,4 α ,5 α -trimethylcyclohexanone (33a)
using Lithiodimethyl cuprate

An oven dried, 3-necked, 50 ml round-bottomed flask was fitted with a dry three-way tap that was itself fitted with a (dry) argon filled balloon. The flask also contained a new, clean dry suba-seal, a dry magnetic follower and a stopper. The apparatus was charged with cuprous bromide-dimethyl sulphide complex¹³ (220 mg, 1.07 mmol) and all joints were sealed with Parafilm and the apparatus was evacuated and refilled from the balloon four times. The apparatus was then placed in an ice-water bath at 0°C and dry ether (4 ml) was added by syringe. 1M Methyl lithium (2.05 ml, 2.05 mol) was added dropwise, by syringe, to the stirred slurry over 5 min. The reaction mixture immediately went bright yellow and then, after the addition of all the alkyl lithium, colourless. Stirring for 5 min completed the formation of the cuprate giving a totally clear (occasionally tan coloured) solution. After slow cooling to -45°C, the enone-aldehyde (10) (0.152 g, 1.0 mmol) in dry ether (5 ml) was added dropwise over 10 min, leading to the immediate formation of a bright yellow precipitate. After stirring for a further 10 min at -45°C to -40°C, the reaction was quenched by the addition of dry methanol (0.5 ml) and the mixture was allowed to warm to R.T. After pouring into saturated aqueous ammonium chloride (30 ml) and ether (50 ml) vigorous shaking gave a pale yellow organic layer, over a blue aqueous one. (Occasionally, the copper salts did not break-down completely - this was avoided by blowing air through the extraction mixture). Separation, followed by further extraction of the aqueous layer into ether (2 x 50 ml), combination of the organic layers, drying,

filtration and removal of the solvent *in vacuo* gave the crude product as a yellow oil. Chromatography (silica gel 50:50 ether/pet. ether) gave 4 β -formyl-3 β ,4 α ,5 α -trimethylcyclohexanone (33a) (0.10 g, 60%), δ 100 MHz (CDCl₃) 9.52 (s, 1H), 2.70-1.65 (m, 6H), 1.22 (s, 3H), 1.02 (d, J 3.5 Hz, 3H), and 0.93 (d, J 3.5 Hz, 3H); $\nu_{\max}$ (film) 2960, 2932, 2880, 2690, and 1720 cm⁻¹; m/e 168.1149, 140, 124, and 109 (Calculated for C₁₀H₁₆O₂: 168.1150).

(8) Preparation of 1-(Methoxycarbonyloxy)-4 β -formyl-3 β ,4 α ,5 α -trimethylcyclohexene (34)

The enone-aldehyde (10) (0.152 g, 1 mmol) in dry ether (10 ml) was added dropwise to a solution of lithiodimethyl cuprate (1 mmol, prepared as described above) at -45°C. Again, a yellow precipitate was immediately produced and after warming to -23°C over 10 min the enolate thus formed was quenched by the dropwise addition of neat methyl chloroformate (0.15 ml, 4 mmol). After warming to R.T. the reaction mixture was poured onto saturated aqueous ammonium chloride solution (25 ml) and extracted into ether (3 x 50 ml). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which by ¹H NMR was predominantly the title enol carbonate (34). Attempted chromatography (silica gel, 50:50 ether/pet. ether), however, resulted in the decomposition of a substantial portion of the product, consequently only 23 mg (10%) of the product - 1-(methoxycarbonyloxy)-4 β -formyl-3 β ,4 α ,5 α -trimethylcyclohexene (34) - was obtained completely pure; δ (CDCl₃) 9.5 (s, 1H), 5.25 (broad d, J 5Hz, 1H), 3.70 (s, 3H), 3.25 (m, 1H), 2.40-2.00 (m, 3H), and 1.20-0.80 (m, 9H); $\nu_{\max}$ (CHCl₃) 2720, 1758, 1725, 1620, and 1264 cm⁻¹.

(9) Preparation of 5-Trimethylsilylpent-4-yn-1-ol (41)

To a cooled stirred solution of ethyl magnesium bromide, prepared from ethyl bromide (32.8 g, 0.3 mol) and magnesium (5.76 g, 0.34 mol) in dry THF (75 ml) under argon, was added pent-4-yn-1-ol¹⁶ (8.4 g, 0.14 mol) in dry THF (75 ml). A vigorous reaction occurred and a gas was given off. After the addition was complete, stirring was continued until the evolution of gas had stopped, whereupon chlorotrimethylsilane (40.3 g, 0.37 mol) was added, and the mixture was again stirred for 2 h at room temperature. 2N HCl (25 ml) was then carefully added, and stirring was continued for a further $\frac{1}{2}$ h. The crude product was extracted into ether (400 ml), dried and filtered. After removal of the solvent *in vacuo* the residue was distilled under reduced pressure to give 5-trimethylsilylpent-4-yn-1-ol (41) (19.4 g, 87%), b.p. 64-65°C/1.5 mmHg (lit.,¹⁷ 66°C/1.5 mmHg); δ (CDCl₃) 3.7 (t, J 6 Hz, 2H), 2.5-1.4 (m, 5H) and 0.2 (s, 9H); $\nu_{\max}$ (film) 3350, 2190, and 1250 cm⁻¹.

(10) Preparation of 5-Trimethylsilylpent-4-yn-1-al (42)

To a stirred solution of the alcohol (41) (5 g, 32 mmol) prepared as above, in dichloromethane (200 ml) was added pyridinium chlorochromate¹⁸ (14.0 g, 45 mmol), the reaction being followed by TLC (ether eluent) to completion. The reaction mixture was diluted with ether (200 ml) and the triturated mixture was filtered through a plug of magnesium sulphate, followed by a short silica column, to give a colourless solution. The solvent was removed *in vacuo* and the crude product distilled under reduced pressure to give pure 5-trimethylsilylpent-4-yn-1-al (42) (4.1 g, 83%), b.p. 49°C/1 mmHg; δ (CDCl₃) 9.78 (broad s, 1H), 3.0-2.0 (m, 4H), and 0.25 (s, 9H); $\nu_{\max}$ 2930, 2890, 2880, 2870, 2170, 1735, and 1235 cm⁻¹.

Analysed as the 2,4-dinitrophenylhydrazone, m.p. 151-153°C (from ethanol) (found: C, 50.11; H, 5.45; N, 16.67. $C_{14}H_{18}N_4O_4Si$ requires: C, 50.28; H, 5.43; N, 16.47%). The distillation residue was chromatographed (silica gel, 25:75 ether/pet. ether) to give 5'-trimethylsilylpent-4'-yn-5-trimethylsilylpent-4-yn-1-oate (43) (0.5 g, 10%); δ ($CDCl_3$) 4.2 (t, J 6 Hz, 2H), 2.5 (broad s, 4H), 2.4-1.4 (m, 4H), and 0.15 (s, 18H); ν_{max} (film) 2190, 1744, and 1250 cm^{-1} ; m/e 308 (M^+), 293, 279, 264, 251, 235, 155, 147, and 123. (Found: C, 62.19; H, 9.15. $C_{16}H_{28}O_2Si_2$ requires: C, 62.28; H, 9.29%).

(11) Preparation of 4'-Trimethylsilylbut-3'-yn-1,3-dithian (40)

Redistilled propan-1,3-dithiol (64.7 ml, 65 mmol) was added to a solution of 5-trimethylsilylpent-4-yn-1-al (42) (5 g, 32.5 mmol) prepared as above, in benzene (400 ml). pTSA (50 mg) was added and the mixture was refluxed through a Dean-Stark apparatus for 14 h. After cooling, the reaction mixture was diluted with ether (400 ml) and washed sequentially with aqueous sodium bicarbonate (2 x 50 ml), water (50 ml) and brine (50 ml). Drying, filtration and removal of the solvent by distillation at atmospheric pressure gave a mixture of the desired 1,3-dithian and excess propan-1,3-dithiol. Heating the stirred mixture under reduced pressure (60°C, 0.5 mmHg, 24h) gave 4'-trimethylsilylbut-3'-yn-1,3-dithian (40) (7.6 g, 96%); δ ($CDCl_3$) 4.15 (t, J 7 Hz, 1H), 3.08-2.85 (m, 4H), 2.80-2.38 (m, 3H), 2.30-1.85 (m, 3H), and 0.25 (s, 9H); ν_{max} (film) 2170, 1248, 845, and 639; m/e 244 (M^+), 239, 171, 170, 156, and 132. PLC (silica gel, ether) provided a sample for analysis (Found: C, 53.77; H, 8.44; S, 26.30. $C_{11}H_{20}S_2Si$ requires: C, 54.04; H, 8.26; S, 26.22%).

(12) Formation of the 2-Lithio-1,3-dithians of (40) and (44)

The experiments, the results of which are shown in Table 2, were all conducted in a similar manner. Typically, 1,3-dithian (44) (0.12 g, 1 mmol) was dissolved in dry ether (5 ml) under dry nitrogen and cooled to -23°C . 2N *tert*-Butyl lithium (0.5 ml, 1 mmol) was added dropwise to the stirred solution over 5 min. After stirring for a further 1 h, deuterium oxide (0.25 ml) was added and the mixture was allowed to warm to room temperature. The solution was diluted with ether, dried, filtered and gave, after removal of the solvent *in vacuo*, the 2-deuterio-1,3-dithian (0.12 g, 99%); δ (CDCl_3) 3.64 (broad s, 1H), 2.70 (t, J 5Hz, 4H), and 2.20-1.75 (m, 2H).

(13) Preparation of 4,4-Dimethyl-3-[2'-1',3'-dithian-2'-(4-l-trimethylsilylbut-1-yne)]-cyclohexanone (46b)

(a) Using HMPA as co-solvent. A solution of the dithian (40) (0.976 g, 4 mmol) in dry THF (20 ml) was cooled to -23°C , and 1.5M ethereal methyl lithium (2.7 ml, 4.05 mmol) was added dropwise. After 1 h, the lithio-dithian solution thus generated was cooled to -78°C , and dry HMPA (1.75 ml, 8.5 mmol) was added. 4,4-Dimethylcyclohexenone⁶⁶ (0.45 g, 4 mmol) in THF (10 ml) was then slowly added and the mixture was stirred for a further 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 ml) and, after warming to R.T., the solvent was removed *in vacuo*. The residue was dissolved in ether (50 ml) washed with water (5 x 50 ml) and brine (50 ml). The organic layer was dried, filtered, and the solvent removed *in vacuo* to give an oil. This was separated by repeated PLC (silica gel, 50:50 ether/pet. ether) to give a small amount of 4,4-dimethyl-3-[2'-1',3'-dithian-2'-(4-l-trimethylsilylbut-1-yne)]-cyclohexanone (46b); δ (CDCl_3) 2.95-1.35 (m, 17H), 1.22 (s, 3H), 1.15 (s, 3H), and 0.18 (s, 9H); ν (CHCl_3) 2775, 2165, 1715, _{max}

1385, 1360, 1244, and 840 cm^{-1} ; m/e 368.1660 (M^+), 243, 197, 169, and 125 (Calculated for $C_{19}H_{32}S_2SiO$: 368.1664).

(b) via The Cuprate method. A solution of the dithian (40) (0.53 g, 2.15 mmol) in dry ether (10 ml) under nitrogen, was cooled to -23°C , and 1.4 M *t*-butyl lithium (1.55 ml, 2.20 mmol), in hexane, was added dropwise. After 1 h the white solution thus generated was transferred, by catheter, to a stirred suspension of purified copper (I) iodide⁶⁴ (0.2 g, 1.06 mmol) in ether (15 ml) at 0°C . After stirring for 2 h, the mixture was cooled to -15°C and a solution of 4,4-dimethylcyclohexenone (0.25 g, 2 mmol) in ether (5 ml) was added. After 3 h, the reaction mixture was poured into saturated aqueous ammonium chloride (25 ml) and extracted into ether (3 x 50 ml). The combined organic layers were dried, filtered and the solvent removed *in vacuo* to give an oil which, after extensive chromatography (silica gel, 50:50 ether/pet. ether), gave a small amount of a product that appeared to be identical to the 4,4-dimethyl-3-[2'-1',3'-dithian-2'-(4-1-trimethylsilylbut-1-yne)]-cyclohexanone (46b) obtained above.

(14) Preparation of 4 β -Formyl-4 α ,5 α -dimethyl-2-selenophenylcyclohex-2-enone (48) using the method of Liotta²²

The reaction conditions set out in Table 3 were used. Typically dry pyridine (0.16 ml, 2 mmol) was added dropwise to a solution of phenyl-selenium chloride⁶⁵ (0.385 g, 2 mmol) in dry distilled CH_2Cl_2 (10 ml), under dry argon. The enone-aldehyde (10) (0.152 g, 1 mmol) in CH_2Cl_2 (3 ml) was added and the stirred mixture was warmed to 40°C . After 14 h the cooled reaction mixture was poured into ether (50 ml) and washed with 0.5 N HCl (2 x 25 ml), followed by brine (20 ml). After drying, filtration and removal of the solvent *in vacuo*, chromatography (silica gel, 25:75 ether/

pet. ether) gave (i) 4 β -formyl-4 α ,5 α -dimethyl-2-selenophenylcyclohex-2-enone (49) (0.12 g, 39%), m.p. 86.5–87^oC (ether/pet. ether); δ 250 MHz (CDCl₃) 9.63 (s, 1H), 7.57 (m, 2H), 7.40 (m, 3H), 5.95 (s, 1H), 2.70–2.40 (m, 3H), 1.10 (s, 3H), and 0.98 (d, J 3 Hz, 1H); $\nu_{\max}$ (KBr) 3070, 3055, 2700, 1725, 1675, 1590, 1578, 740, and 692 cm⁻¹; m/e 308 (M⁺), 279 and 157 (Found: C, 58.62; H, 5.32. C₁₅H₁₆SeO₂ requires: C, 58.64; H, 5.32%); and (ii) 4 β -formyl-4 α ,5 α -dimethyl-2-chlorocyclohex-2-enone (54), (65 mg, 35%); δ 250 MHz (CDCl₃) 9.56 (s, 1H), 6.84 (s, 1H), 2.75–2.40 (m, 3H), 1.30 (s, 3H), and 1.04 (d, J 3Hz, 3H); $\nu_{\max}$ (film) 3030, 2700, 1725, 1670, 1620, and 740 cm⁻¹; m/e 186.0448 (M⁺), 157, 151, 129, and 93 (Calculated for C₉H₁₁ClO₂: 186.0447).

(15) Preparation of 4 β -Formyl-3 β ,4 α ,5 α -trimethyl-2-selenophenylcyclohex-anone (55)

(a) By the addition of lithiodimethyl cuprate to 4 β -formyl-4 α ,5 α -dimethyl-2-selenophenylcyclohex-2-enone (49). To a preformed solution of lithiodimethyl cuprate (2.2 mol prepared as above) at -45^oC was added a solution of 4 β -formyl-4 α ,5 α -dimethyl-2-selenophenylcyclohex-2-enone (49) (0.50 g, 1.75 mmol) in dry ether (10 ml) over 10 min. After stirring for 30 min, the reaction mixture was poured into saturated aqueous ammonium chloride and worked-up in the usual manner. Chromatography of the resultant oil (silica gel, 40:60 ether/pet. ether) gave (i) 4 β -formyl-3 β ,4 α ,5 α -trimethyl-2-selenophenylcyclohexanone (55) as a mixture of isomers (80 mg, 14%); δ (CDCl₃) 9.39 (s, 1H), 7.50–7.00 (m, 5H), 4.16 (d, J 4 Hz, 0.25 H), 3.53 (d, J 6 Hz, 0.75 H), 2.65–2.00 (m, 4H), and 1.30–0.70 (m, 9H); $\nu_{\max}$ (film) 3070, 3050, 2710, 1720, 1678, 790, 760, 690, and 670 cm⁻¹; (ii) 4 β -formyl-3,4 α ,5 α -trimethyl-2-selenophenylcyclohex-2-enone (57) (20 mg, 3.6%); δ (CDCl₃) 9.53 (s, 1H), 8.00–7.10 (m, 5H), 2.60–2.40 (m, 4H), 1.73 (s, 3H), 1.26 (s, 3H), and 0.98 (d, J 6 Hz, 3H); $\nu_{\max}$ (film) 3070, 2710, 1735,

1692, 1645, 1575, 740, 690, and 670 cm^{-1} ; m/e 322 (M^+), 292, 153, and 139; and (iii) 4 β -formyl-3,4 α ,5 α -trimethylcyclohex-2-enone (56), (18 mg, 6%); δ (CDCl_3) 9.28 (s, 1H), 5.82 (q, J 1Hz, 1H), 2.50-2.10 (m, 3H), 1.85 (d, J 1Hz, 3H), 1.19 (s, 3H), and 0.90 (d, J 6 Hz, 3H); ν_{max} (film) 3030, 2705, 1725, 1670, 1624, and 740 cm^{-1} ; m/e 166.0994, (M^+), 153, 137, 123, 119, 117, 109, and 96 (Calculated for $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0992).

(b) By the addition of lithiodimethyl cuprate to 4 β -formyl-4 α ,5 α -dimethylcyclohex-2-enone (10), and subsequent trapping of the enolate according to the method of Reich²⁴. To a preformed solution of lithiodimethyl cuprate (4.4 mmol, prepared as above) at -40°C , was added a solution of the enone-aldehyde (10) (0.50 g, 3.3 mmol) in dry ether (15 ml) over 15 min. After stirring for a further 30 min and gradual warming to -30°C , the reaction was quenched by the addition of phenylselenium bromide²⁴ (0.57 g, 2.4 mmol) and diphenyldiselenide (0.63 g, 3.17 mmol) in THF (4 ml). The reaction mixture was warmed to R.T., poured into pet. ether (50 ml) and worked up in the usual manner. Chromatography of the resultant oil (silica gel, 40:60 ether/pet. ether) gave 4 β -formyl-3 β ,4 α ,5 α -trimethyl-2-selenophenylcyclohexanone (55) again as a mixture of isomers (0.20 g, 19%).

(16) Preparation of 3 α ,4 α ,4 β -Trimethyl-2 β -selenophenylcyclohexanone (60)

To a preformed solution of lithiodimethyl cuprate (3.0 mmol, prepared as above) at -40°C was added a solution of 4,4-dimethylcyclohex-2-enone (0.25 g, 2 mmol) in THF (5 ml), over 5 min. The stirred reaction mixture was warmed to -23°C over a period of 30 min whereupon a suspension of *N*-selenophenylphthalimide²⁵ (1.8 g, 6 mmol) in THF (40 ml) was added. The stirred reaction mixture was warmed to R.T., poured into saturated aqueous ammonium chloride solution (50 ml), and extracted into

pet. ether (3 x 100 ml). The combined organic layers were dried, filtered, and the solvent removed *in vacuo* to give a yellow slurry. The slurry was extracted into carbon tetrachloride (25 ml), filtered and the residue triturated with more carbon tetrachloride (3 x 10 ml). The combined filtrates were concentrated *in vacuo* and chromatography of the residue (silica gel, 70:30 ether/pet. ether) gave (i) 3,4,4-trimethyl-2,2-diselenophenylcyclohexanone (61) (0.22 g, 24%), m.p. 110-111°C (pet. ether); δ 250 MHz (CDCl₃) 7.75-7.20 (m, 10H), 3.23 (ddd, J 14.7, 14.7, and 5.1 Hz, 1H), 2.28 (ddd, J 14.7, 3.7 and 3.7 Hz, 1H), 1.88 (q, J 6.9 Hz, 1H), 1.64 (ddd, J 13.6, 5.1, and 3.7 Hz), 1.48 (d, J 6.9 Hz, 1H), 1.30 (s, 3H), 1.27 (ddd, J 14.2, 13.6 and 3.7 Hz, 1H), and 0.77 (s, 3H); $\nu_{\max}$ (CHCl₃) 3050, 1950, 1880, 1800, 1695, 1578, and 1140 cm⁻¹; m/e 452 (M⁺), 392, 374, 295, and 225. (Found: C, 56.15; H, 5.41. C₂₁H₂₁Se₂O requires C, 56.00; H, 5.37%); and (ii) 3 α ,4 α ,4 β -trimethyl-2 β -selenophenylcyclohexanone (60) (0.15 g, 25%); δ 7.60-6.90 (m, 5H), 3.25 (d, J 10 Hz, 1H), 2.80-1.22 (m, 5H), 1.04 (d, J 6Hz, 3H), 1.01 (s, 3H), and 0.80 (s, 3H); $\nu_{\max}$ (film) 3078, 3058, 1710, 1580, 792, 692, and 670 cm⁻¹; m/e 296 (M⁺), 157, and 139.

(17) Preparation of 4 β -Formyl-3,4 α ,5 α -trimethylcyclohex-2-enone (56) from the Selenide (55) using the Methods of Reich²⁴

(a) Using mCPBA as oxidant, followed by thermolysis in refluxing chloroform. 85% mCPBA (44 mg, 0.24 mol) was added to a stirred solution of 4 β -formyl-3 β ,4 α ,5 α -trimethyl-2-selenophenylcyclohexanone (55) (70 mg, 0.2 mmol) in CH₂Cl₂ (2 ml) at room temperature. After TLC (35:65 ether/pet. ether) showed the absence of starting material, the reaction mixture was poured into ether (25 ml) and washed with saturated aqueous sodium bicarbonate (2 x 25 ml). The organic layer was dried, filtered and the solvent removed *in vacuo* to give the crude selenoxide (62) which

was dissolved in chloroform (10 ml) and heated to reflux for 35 min. After cooling and removal of the solvent *in vacuo*, the crude product was chromatographed (silica gel, 55:45 ether/pet. ether) to give (i) 4 β -formyl-3,4 α ,5 α -trimethyl-2-selenophenylcyclohex-2-enone (57) (11 mg, 16%) identical to the previous sample; and (ii) 4 β -formyl-3,4 α ,5 α -trimethylcyclohex-2-enone (56) (10 mg, 28%), again identical to the previous sample.

(b) Using mCPBA as oxidant followed by thermolysis in refluxing carbon tetrachloride in the presence of di-isopropylamine. The selenoxide (62) was prepared as above using mCPBA (0.10 g, 0.69 mmol) and the selenide (55) (0.15 g, 0.46 mmol) in CH₂Cl₂ (3 ml). Removal of the solvent *in vacuo* gave a solid which was dissolved in ether (15 ml) and washed with saturated aqueous sodium bicarbonate (2 x 10 ml). The organic layer was dried, filtered, and the solvent again removed *in vacuo* to afford the crude selenoxide. The latter was then dissolved in carbon tetrachloride (10 ml). After the addition of di-isopropylamine (0.2 ml) this solution was added to a refluxing mixture of carbon tetrachloride (25 ml) and di-isopropylamine (0.1 ml). After 5 min, the reaction mixture was allowed to cool and the solvent removed *in vacuo* to give a crude product which was chromatographed (silica gel, 40:60 ether/pet. ether) to give (i) 4 β -formyl-3 β ,4 α ,5 α -trimethyl-2-selenophenyl-2-(m-chlorobenzoate)-cyclohexanone (65) as two isomers: (a) (9 mg, 4%), δ 9.98 (s, 1H), 7.80-7.10 (m, 9H), 3.00-2.00 (m, 4H), 1.50 (d, J 7Hz, 3H), 1.15 (s, 3H), and 1.15 (d, J 7Hz, 3H); $\nu_{\max}$ (film) 3080, 2730, 1735, 1730, 1712, 1598, 1578, 1252, 772, 740, 710 and 690 cm⁻¹; m/e 477 (M⁺), 321, 296, 293, 267 (M⁺ 321-293), 249, and 232; and (b) (35 mg, 16%), m.p. 138-139.5°C (ether/pet. ether), δ 9.70 (s, 1H), 7.63-6.90 (m, 9H), 2.95-2.30 (m, 4H), 1.42 (d, J 7Hz, 3H), 1.18 (s, 3H), and 0.92 (d, J 7Hz, 3H); $\nu_{\max}$ (CHCl₃) 3079, 3060, 2718, 1730, 1720, 1598, 1575, and 1255 cm⁻¹; m/e 477 (M⁺),

321, 296, 293, 267 (M^* 321-293), 249, and 232 (Found: C, 57.53; H, 4.80. $C_{23}H_{23}SeClO_4$ requires: C, 57.81; H, 4.85); (ii) 4 β -formyl-3,4 α ,5 α -trimethyl-2-selenophenylcyclohex-2-enone (57) (10 mg, 7%), as above; and finally, the desired 4 β -formyl-3,4 α ,5 α -trimethylcyclohex-2-enone (56) (6 mg, 8%) as above.

(c) Using ozone as oxidant, followed by thermolysis in refluxing carbon tetrachloride, in the presence of di-isopropylamine. Ozone was passed through a stirred solution of the selenide (55) (80 mg, 0.25 mmol) in CH_2Cl_2 (4 ml) at $-78^\circ C$, until a blue colouration persisted. Nitrogen was then bubbled through the selenoxide (62) solution until all the excess ozone had been removed, and the remaining solution was very pale yellow. The still cold solution was subsequently added by catheter to a refluxing solution of carbon tetrachloride (15 ml) and di-isopropylamine (0.2 ml). After 5 min, the cooled reaction mixture was washed with 1N HCl (2 x 5 ml), followed by saturated aqueous sodium bicarbonate (5 ml) and finally brine. The organic phase was dried, filtered and, after removal of the solvent *in vacuo*, the residue was chromatographed (silica gel, 40:60 ether/pet. ether) to give 4 β -formyl-3,4 α ,5 α -trimethylcyclohex-2-one (56) (15 mg, 36%), as above.

(18) Preparation of 4 β -1'-E-Vinylene-2'(3-furyl)-3 β ,4 α ,5 α -trimethyl-cyclohexanone (67)

To a preformed solution of lithiodimethyl cuprate (1.3 mmol, prepared as above) at $-23^\circ C$, was added a solution of 4 β -1'-E-vinylene-2'(3-furyl)-4 α ,5 α -dimethylcyclohex-2-enone²⁶ (66) (0.14 g, 0.65 mmol) in dry ether (5 ml) over 5 min. A yellow precipitate formed immediately and after 20 min, the reaction was quenched (dry methanol, 0.5 ml) and worked-up in the usual way. Chromatography (silica gel, 55:45 ether/pet. ether) gave

4 β -1'-E-vinylene-2'-(3-furyl)-3 β ,4 α ,5 α -trimethylcyclohexanone (67), 0.12 g (83%); δ 250 MHz (CDCl₃) 7.39 (ddd, J 1.8, 1.6, and 0.5 Hz, 1H), 7.30 (d, J 1.8 Hz, 1H), 6.32 (d, J 1.6 Hz, 1H), 6.29 (dd, J 8.0, and 0.5 Hz, 1H), 5.82 (d, J 8Hz, 1H), 2.55-2.30 (m, 3H), 2.25-2.04 (m, 3H), 1.20 (s, 3H), 1.00 (d, J 7Hz, 3H), and 0.92 (d, J 7 Hz, 3H); $\nu_{\max}$ (film) 1712, 1500, 1022, 870, 800, 762, and 725 cm⁻¹; m/e 252 (M⁺), 161, 148, 119, and 117.

(19) Preparation of 4 β -(2'-1',3'-Dioxolan)-4 α ,5 α -cyclohex-2-enone (29)

A mixture of the enone-aldehyde (10) (1.0 g, 6.6 mmol) ethylene glycol (0.3 g, 31 mmol) and pTSA (50 mg) in benzene (100 ml) was heated to reflux through a Dean-Stark apparatus for 24 h. After cooling, the mixture was diluted with pet. ether (200 ml), washed with water (2 x 25 ml) dried, filtered and the solvent removed *in vacuo*, to give the crude di-dioxalan (31); δ (CDCl₃) 5.57 (d, J 10 Hz, 1H), 5.32 (d, J 10 Hz, 1H), 4.48 (s, 1H), 3.72 (br, s, 8H), 2.20-1.15 (m, 3H), 0.82 (d, J 6 Hz, 3H), and 0.75 (s, 3H); m/e 240 (M⁺).

This crude di-ketal was then selectively deprotected using the method of Conia²⁷. Thus, a mixture of Kieselgel H (5 g), 10% aqueous oxalic acid (16 drops) and dichloromethane (8 ml) was stirred until it was homogeneous whereupon a solution of the di-ketal (31) in CH₂Cl₂ (2 ml) was added. After 1 h, sodium bicarbonate (0.25 g) was added and the slurry was stirred for a further 15 min. Filtration, followed by re-extraction of the residue with ether (5 x 25 ml), combination of the organic layers and removal of the solvent *in vacuo*, gave the crude enone. Chromatography (silica gel, 65:35 ether/pet. ether) gave 4 β -(2'-1',3'-dioxalan)-4 α ,5 α -cyclohex-2-enone (29) (0.84 g, 88%); δ (CDCl₃) 6.65 (d, J 10 Hz, 1H), 5.76 (d, J 10 Hz, 1H), 4.68 (s, 1H), 3.80 (br, s, 4H), 2.40-1.70 (m, 3H), 1.03 (s, 3H), and 0.98 (d, J 5 Hz, 3H); $\nu_{\max}$ (film) 1680 cm⁻¹; m/e 196 (M⁺), 168, 86, and 73.

(20) Preparation of 4 β -(2'-1',3'-Dioxalan)-3 β ,4 α ,5 α -trimethylcyclohexanone (68)

To a preformed solution of lithiodimethyl cuprate (0.75 mmol, prepared as above) at -23°C , was added a solution of 4 β -(2'-1',3'-dioxalan)-4 α ,5 α -dimethylcyclohex-2-enone (29) (0.15 g, 0.75 mmol) in dry ether (4 ml) over 10 min. After stirring for a further 15 min the reaction mixture was quenched by pouring into saturated aqueous ammonium chloride (25 ml) and worked up in the usual manner. The crude product was subjected to chromatography (silica gel, 65:35 ether/pet. ether) to give (i) 4 β -(2'-1',3'-dioxalan)-3 β ,4 α ,5 α -trimethylcyclohexanone (68) (60 mg, 37%); δ (CDCl_3) 4.70 (s, 1H), 3.80 (m, 4H), 2.50-1.50 (m, 6H), 1.00 (s, 3H), and 0.92 (m, 6H); ν_{max} (film) 1714 and 1090 cm^{-1} ; and (ii) the starting enone-dioxalan (29) (60 mg, 40%), as above.

(21) Deacetalisation of 4 β -(2'-1',3'-Dioxalan)-3 β ,4 α ,5 α -trimethylcyclohexanone (68) using the method of Conia²⁷

The dioxalan (68) (60 mg, 0.3 mmol) was added to a stirred homogeneous mixture of Kieselgel H (0.6 g), 15% H_2SO_4 (4 drops) and CH_2Cl_2 (3 ml). After 1 h, the reaction mixture was quenched by the addition of sodium bicarbonate (0.2 g). The semi-hydrolysed product was isolated by filtration, careful re-extraction (CH_2Cl_2 , 5 x 20 ml), and removal of the solvent *in vacuo*. The hydrolysis cycle was repeated to give 4 β -formyl-3 β ,4 α ,5 α -trimethylcyclohexanone (33a) (40 mg, 84%) identical to the previous sample.

(22) Preparation of 8 β -(2'-1',3'-Dithiolan)-8 α ,9 α -dimethyl-1,4-dithia[4.5]dec-6-ene (70)

A solution of the enone-aldehyde (10) (0.15 g, 1 mmol), redistilled ethane-1,2-dithiol (0.3 ml) and pTSA (10 mg) in benzene (30 ml) was re-

fluxed through a Dean-Stark apparatus until no more water was collected. After cooling, the solution was filtered through a pad of MFC silica gel, and the solvent was removed *in vacuo* to give an oil which, upon crystallisation (ether/pet. ether), gave 8β -(2'-1',3'-dithiolan)- 8α , 9α -dimethyl-1,4-dithia[4.5]dec-6-ene (70) (0.20 g, 66%), m.p. $85.5-86^\circ\text{C}$; δ (CDCl_3) 5.70 (d, J 10 Hz, 1H), 5.65 (d, J 10 Hz, 1H), 4.67 (s, 1H), 3.30 (br, s, 4H), 3.15 (s, 4H), 2.15-1.95 (m, 3H), 1.00 (s, 3H), and 0.95 (d, J 6 Hz, 3H); ν_{max} (KBr) 3020, 1425, 1275, 825, 778, and 688 cm^{-1} ; m/e 304 (M^+), 199, 139, and 105 (Found: C, 51.42; H, 6.76; S, 41.82. $\text{C}_{13}\text{H}_{20}\text{S}_4$ requires C, 51.27; H, 6.76; S, 42.11%). The mother liquor was concentrated *in vacuo* and the residue was chromatographed (silica gel, 4:96 ether/pet. ether) to give a further sample of the di-dithiolan (70) (72 mg, 23%) as above.

(23) Preparation of 4β -(2'-1',3'-Dithiolan)- 4α , 5α -dimethylcyclohex-2-enone (69)

(a) From 8β -(2'-1',3'-dithiolan)- 8α , 9α -dimethyl-1,4-dithia[4,5]dec-6-ene (70) using the method of Wang-Chang²⁸. A mixture of the di-dithiolan (70) (0.14 g, 0.46 mmol) and methyl iodide (0.4 ml, 6.4 mmol) was heated in refluxing methanol (15 ml) for 7 h. After cooling, the solvent was removed *in vacuo*, and the residue was dissolved in ether (25 ml) and washed with 1 N aqueous sodium hydroxide (10 ml), followed by brine (5 ml). The organic layer was dried, filtered and the solvent removed *in vacuo* to give an oil which on chromatography (silica gel, 50:50 ether/pet. ether) gave (i) starting 8β -(2'-1',3'-dithiolan)- 8α , 9α -dimethyl-1,4-dithia[4,5]dec-6-ene (70) (43 mg, 31%), as above; and (ii) the desired 4β -(2'-1',3'-dithiolan)- 4α , 5α -dimethylcyclohex-2-enone (69) (25 mg, 23%), m.p. $63-64^\circ\text{C}$ (ether/pet. ether); δ 250 MHz (CDCl_3) 7.13 (d, J 10 Hz, 1H), 6.02 (d, J 10 Hz, 1H), 4.91 (s, 1H), 3.30-3.20 (m, 4H), 2.45-2.20 (m, 3H), 1.18 (s, 3H) and 1.02 (d, J 5Hz, 3H); ν_{max} (CHCl_3) 3014 and 1678 cm^{-1} ;

m/e 228.0641 (M^+) 213, 123, and 105 (Calculated for $C_{11}H_{16}S_2O$: 228.0643)
 (Found: C, 57.60; H, 7.18; S, 27.77. $C_{11}H_{16}S_2O$ requires C, 57.85; H, 7.06;
 S, 28.08%).

(b) By a one-step procedure from 3 β -formyl-4 α ,5 α -dimethylcyclohex-2-enone (10). A solution of the enone-aldehyde (10) (3.04 g, 20 mmol), redistilled ethane-1,2-dithiol (5 ml, 58 mmol) and pTSA (100 mg) in benzene (250 ml) was refluxed through a Dean-Stark apparatus, under nitrogen, for 12 h. After cooling, the solution was diluted with ether (200 ml) and washed with saturated aqueous sodium bicarbonate (2 x 50 ml), followed by brine (50 ml). The organic phase was then vigorously stirred with a mixture of mercury (II) acetate (18 g, 56 mmol), and cadmium carbonate (3 g, 28 mmol), added in portions, and water (50 ml). After 14 h, sodium chloride (25 g) was added and the organic phase separated. The aqueous phase was re-extracted into ether/benzene (1:1, 3 x 200 ml) and the combined organic layers were dried and filtered through celite. Removal of the solvent *in vacuo*, followed by chromatography (silica gel, 50:50 ether/pet. ether) gave (i) 8 β -(2'-1',3'-dithiolan)-8 α ,9 α -dimethyl-1,4-dithia[4,5]dec-6-ene (70) (0.4 g, 6.6%), as above; (ii) the desired 4 β -(2'-1',3'-dithiolan)-4 α ,5 α -dimethylcyclohex-2-enone (69) (2.6 g, 55%), identical to the previous sample, and (iii) 3 β -formyl-4 α ,5 α -dimethylcyclohex-2-enone (10) (0.3 g, 10%) again identical to the previous sample.

(24) Preparation of 4 β -(2'-1',3'-Dithiolan)-3 α ,4 α ,5 α -trimethylcyclohexanone (71)

To a preformed solution of lithiodimethyl cuprate (4.6 mmol, prepared as above) at -78°C , was added a solution of 4 β -(2'-1',3'-dithiolan)-4 α ,5 α -

dimethylcyclohex-2-enone (69) (0.456 g, 2 mmol), in dry ether (20 ml), dropwise over 20 min. The stirred reaction mixture was slowly warmed to -30°C over 4 h after which it was poured into saturated aqueous ammonium chloride (20 ml) and worked-up in the usual manner. Chromatography (silica gel, 50 : 50 ether/pet. ether) of the resultant oil gave 4 β -(2'-1',3'-dithiolan)-3 α ,4 α ,5 α -trimethylcyclohexanone (71) (0.40 g, 82%); δ 250 MHz (CDCl_3) 5.50 (s, 1H), 3.30-3.15 (m, 4H), 2.45-2.10 (m, 6H), 1.10 (s, 3H), and 1.05 (d, J 6 Hz, 6H); ^{13}C , 62.9 MHz, 210.76 (s), 64.03 (d), 46.30 (t), 42.39 (s), 38.19 (t), 37.66 (d), 17.23 (q), and 14.43 (q); ν_{max} (CHCl_3) 1720 cm^{-1} ; m/e 244.0951 (M^+), 139, 138, 119, 117, and 105 (Calculated for $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}$: 244.0956) (Found: C, 58.74; H, 8.18; S, 26.24. $\text{C}_{12}\text{H}_{20}\text{S}_2\text{O}$ requires: C, 58.97; H, 8.25; S, 26.23%).

(25) Preparation of 9 β -(2'-1',3'-Dithian)-9 α ,10 α -dimethyl-1,5-dithia-[5,5]undec-7-ene (76)

A solution of 4 β -formyl-4 α ,5 α -dimethylcyclohex-2-enone (10) (1.52 g, 10 mmol), redistilled propane-1,3-dithiol (3 ml, 30 mmol) and pTSA (50 mg) was refluxed through a Dean-Stark apparatus for 4 h under nitrogen. After cooling, the reaction mixture was diluted with ether (200 ml), washed with saturated aqueous sodium bicarbonate (2 x 50 ml), dried, filtered and the solvent removed *in vacuo*. Excess dithiol was removed *in vacuo* (0.5 mmHg/12 h) and the residue was chromatographed (silica gel, 25:75 ether/pet. ether) to give 9 β -(2'-1',3'-dithian)-9 α ,10 α -dimethyl-1,5-dithia[5,5]undec-7-ene (76) (2.82 g, 85%), δ 5.66 (br, s, 2H), 4.03 (s, 1H), 2.95-2.55 (m, 8H), 2.25-1.64 (m, 7H), 1.00 (s, 3H), and 0.90 (d, J 7 Hz, 3H); ν_{max} (film), 3020, 1420, 1275, 910, 682, and 658 cm^{-1} .

(26) Preparation of 4 β -(2'-1',3'-Dithian)-4 α ,5 α -dimethylcyclohex-2-enone (73)

Benzeneseleninic anhydride²⁹ (0.45 g, 1.24 mmol) was added to a solution of 9 β -(2'-1',3'-dithian)-9 α ,10 α -dimethyl-1,5-dithia[5,5]undec-7-ene (76) (0.40 g, 1.2 mmol) in dry THF (20 ml) at 0°C. The stirred reaction mixture was slowly warmed to room temperature, then poured into saturated aqueous sodium bicarbonate (20 ml) and extracted into ether/pet. ether (1:1, 3 x 50 ml). The combined organic layers were dried, filtered and the solvent removed *in vacuo* to give an oil which was chromatographed (silica gel, 50:50 ether/pet. ether) to give 4 β -(2'-1',3'-dithian)-4 α ,5 α -dimethylcyclohex-2-enone (73) (0.15 g, 55%), δ 250 MHz (CDCl₃) 7.07 (d, J 10 Hz, 1H), 5.98 (d, J 10 Hz, 1H), 4.35 (s, 1H), 2.98-2.75 (m, 4H), 2.45-2.23 (m, 2H), 2.20-2.05 (m, 2H), 1.90-1.75 (m, 1H), 1.20 (s, 3H), and 1.00 (d, J 7Hz, 3H); $\nu_{\max}$ (film) 3022, 1678, 778, 735 and 690 cm⁻¹.

(27) Preparation of 4 β -(2'-1',3'-Dithian)-3(α + β), 4 α ,5 α -trimethylcyclohexanone (77)

To a preformed solution of lithiodimethyl cuprate (1.95 mmol, prepared as above) at -78°C, was added a solution of the enone-dithian (73) (0.22 g, 0.91 mmol) in dry ether (5 ml) dropwise over 5 min. The stirred solution was warmed to -23°C over 3 h after which it was poured into saturated aqueous ammonium chloride (20 ml), and worked up in the usual manner. Chromatography (silica gel, 40:60 ether/pet. ether) gave a 2:1 mixture of the C-3 epimeric cyclohexanones - 4 β (2'-1',3'-dithian)-3(α + β),4 α ,5 α -trimethylcyclohexanone (77) (0.20 g, 83%); δ 250 MHz (CDCl₃) 4.39 (s, 1/3H), 4.18 (s, 2/3H), 3.00-2.73 (m, 4H), 2.65-2.42 (m, 2H), 2.38-2.05 (m, 4H), 1.96-1.73 (m, 2H), 1.35 (s, 2H), 1.21 (d, J 6 Hz, 2H), 1.08 (d, J 6 Hz, 2H),

1.06 (s, 1H), and 1.00 (d, J 6 Hz, 2H); $\nu_{\max}$ (CHCl_3) 1710 cm^{-1} ; m/e 258.1107 (M^+), 172, and 119 (Calculated for $\text{C}_{13}\text{H}_{22}\text{S}_2\text{O}$: 258.1112).

Careful recrystallisation (ether/pet. ether) of the mixture resulted in the formation of two different types of crystal. Manual separation of the major component (prisms) gave an isomerically pure sample of 4 β -(2'-1',3'-dithian)-3 β ,4 α ,5 α -trimethylcyclohexanone (77a), m.p. $128-130^\circ\text{C}$; δ 4.18 (s, 1H), 3.00-2.65 (m, 4H), 2.50-1.70 (m, 8H), 1.35 (s, 3H), 1.20 (d, J 6 Hz, 3H), and 1.00 (d, J 6 Hz, 3H) (Found: C, 60.60; H, 8.64; S, 24.95. $\text{C}_{13}\text{H}_{22}\text{S}_2\text{O}$ requires: C, 60.43; H, 8.53; S, 24.84%).

(28) Preparation of 1-(Methoxycarbonyloxy)-4 β -(2'-1',3'-dithian)-3(α + β)-(1'-pent-4'-enyl)-4 α ,5 α -dimethylcyclohexene (78)

Pent-4-enyl magnesium bromide (6.0 mmol, prepared from 1-bromopent-4-ene³⁵, 0.92 g, 6.0 mmol, and magnesium, 0.15 g, in dry ether) was added dropwise to a suspension of copper (I) bromide dimethyl sulphide complex (0.60 g, 3 mmol) in dry ether (3 ml) at -10°C under argon. After stirring for a further 5 min, the mixture was slowly cooled to -60°C . A solution of the enone-dithian (73) (0.34 g, 1.4 mmol) in ether (10 ml) was added dropwise over 10 min and the stirred reaction mixture was warmed to -23°C , over $1\frac{1}{2}$ h. Neat methyl chloroformate (0.6 ml, 7.7 mmol) was added in one portion. The mixture was warmed to room temperature and worked up in the usual manner. Chromatography (silica gel, 15:85 ether/pet.ether) gave 1-(carbonyldioxymethyl)-4 β -(2'-1',3'-dithian)-3-(1'-pent-4'-enyl)4 α ,5 α -dimethylcyclohexene (78), as a mixture of 3 α and 3 β isomers (0.22 g, 42%); δ (CDCl_3) 6.00 - 5.15 (m, 2H), 5.10-4.70 (m, 2H), 4.03 (s, 1H), 3.83 (s, 3H), 3.00-2.65 (m, 4H), and 2.60-0.80 (m, 18H); $\nu_{\max}$ (film) 3075, 1760, 1700, 1640, 1250, and 785 cm^{-1} ; m/e 370.1634^(M), 295, 263, 251, 235.5 (M^+ 370-295), 219, 207, and 174 (Calculated for $\text{C}_{19}\text{H}_{30}\text{S}_2\text{O}_3$: 370.1636).

(29) Purification of Chlorotrimethylsilane

Dry pyridine (5 ml) was added to chlorotrimethylsilane (100 ml) and the well stirred mixture was rapidly filtered through a pad of celite. The chlorosilane was distilled under nitrogen (middle cut, b.p. 57°C), and stored under argon.

(30) Preparation of 1-Trimethylsilyloxy-4 β -(2'-1',3'-dithiolan)-3 α -(1'-pent-4'-enyl)-4 α ,5 α -dimethylcyclohexene (79b)

Pent-4-enyl magnesium cuprate (2 mmol) was prepared in the usual manner, in ether and cooled to -75°C. A solution of the enone-dithiolan (69) (0.288 g, 1.0 mmol) in ether (10 ml) was added dropwise over 10 min and the reaction mixture was then slowly warmed to -30°C over 4 h. A preformed mixture of purified chlorotrimethylsilane (2 ml) and dry triethylamine (2 ml) in THF (10 ml) was added and the reaction mixture was warmed to room temperature over 3 h. After pouring into pet. ether (100 ml), rapid washing by water (2 x 50 ml), ice-cold 2.5% HCl (2 x 25 ml), saturated aqueous sodium bicarbonate (2 x 50 ml) and brine (50 ml), followed by drying, filtration and removal of the solvent *in vacuo* gave the crude trimethylsilyl enol ether. Ordinarily, purification of this crude material was not attempted as it tended to decompose on silica gel. However, rapid chromatography (silica gel, 70:30 CH₂Cl₂/pet. ether) gave (i) 1-trimethylsilyloxy-4 β -(2'-1',3'-dithiolan)-3 α -(1'-pent-4'-enyl)-4 α ,5 α -dimethylcyclohexene (79b) (0.17 g, 43%); δ 250 MHz (CDCl₃) 5.90-5.73 (m, 1H), 5.05-4.93 (m, 2H), 5.03 (s, 1H), 4.82 (d, J 4 Hz, 1H), 3.28-3.12 (m, 4H), 2.30-1.10 (m, 10H), 1.03 (d, J 7 Hz, 3H), 1.00 (s, 3H), and 0.20 (s, 9H); $\nu_{\max}$ (film) 3078, 1675, 1640, 1195, 755, and 735 cm⁻¹; m/e 370 (M⁺), 277, 265, 192, 187, 168, 159, 141, 119, and 105; and (ii) 4 β -(2'-1',3'-dithiolan)-3 α -(1'-pent-4-enyl)-4 α ,5 α -dimethylcyclohexanone (82), (30 mg, 10%); δ 250 MHz (CDCl₃) 5.90-5.73 (m, 1H), 5.09 (s, 1H), 5.05-4.93 (m, 2H), 3.30-3.15 (m, 4H), 2.62-

2.30 (m, 3H), 2.20-2.00 (m, 5H), 1.90-1.86 (m, 1H), 1.55-1.40 (m, 1H), 1.35-1.20 (m, 1H), 1.08 (s, 3H), and 1.04 (d, J 7 Hz, 3H); $\nu_{\max}$ (film) 3078, 1715, 1642, 915, and 735 cm^{-1} .

(31) Preparation of 2-Formyl-4 β -(2'-1',3'-dithiolan)-3 α -(1'-pent-4'-enyl)-4 α , 5 α -dimethylcyclohexanone (81) using the method of Mukiyama³⁶

A mixture of the trimethylsilylenol ether (79b) (0.16 g, 0.43 mmol) and trimethylorthoformate (0.1 ml, 0.9 mmol) in CH_2Cl_2 (1 ml) was cooled to -78°C under argon. 10% Titanium tetrachloride in CH_2Cl_2 (1 ml, 0.86 mmol) was added dropwise and the mixture was stirred for a further 3.5 h, after which time it was poured into saturated aqueous ammonium chloride (5 ml) and extracted with ether (2 x 25 ml). The combined organic extracts were dried, filtered, and after removal of the solvent *in vacuo*, the residue was chromatographed (silica gel 30:70 ether/pet. ether) to give 2-formyl-4 β -(2'-1',3'-dithiolan)-3 α -(1'-pent-4'-enyl)-4 α ,5 α -dimethylcyclohexanone (81) (10 mg, 7%); δ 250 MHz (CDCl_3) 14.2 (br, s, 1H), 7.95 (s, 1H), 5.75 (m, 1H), 5.1-4.9 (m, 2H), 4.80 (s, 1H), 3.2 (m, 4H), 2.6-1.3 (m, 10H), 1.18 (s, 3H), and 1.08 (d, J 6 Hz, 3H); $\nu_{\max}$ 2860, 1715, 1645, 1595, and 912 cm^{-1} ; m/e 326 (M^+), 298, 272.4 (M^* 326-298), 221, 192, 175, and 151.

(32) Preparation of 4,4-Dimethyl-1-trimethylsilyloxy-3-(1'-pent-4'-enyl)-cyclohexene (85)

To a preformed solution of pent-4-enyl magnesium cuprate (50 mmol, prepared in the usual manner) in ether (50 ml) at -35°C , was added a solution of 4,4-dimethylcyclohexenone⁶⁶ (2.5 g, 20 mmol) in ether (10 ml) over 10 min. After stirring for a further 20 min, a preformed mixture of purified chlorotrimethylsilane (7 ml, 55 mmol) and dry triethylamine (7 ml, 50 mmol) in dry THF (40 ml) was added, and the reaction mixture was warmed to room

temperature over 2.5 h. After pouring into pet. ether (500 ml) and washing in the usual manner (water, ice-cold 2.5% HCl, saturated aqueous sodium bicarbonate and brine), the solution was dried, filtered and the solvent removed *in vacuo* to give the crude 4,4-dimethyl-1-trimethylsilyloxy-3-(1'-pent-4'-enyl)-cyclohexene (85) (5.3 g); δ (CDCl₃) 6.10-4.75 (m, 4H), 2.25-1.80 (m, 4H), 1.75-1.04 (m, 7H), 0.90 (s, 3H), 0.75 (s, 3H), and 0.20 (s, 9H); $\nu_{\max}$ (film) 3078, 1665, 1640, 1190, 845, 755, and 640 cm⁻¹; m/e 266 (M⁺), 265, 251, 223, 210, and 197. Purification of this compound was not attempted as it rapidly decomposed both thermally and on silica gel.

(33) Preparation of 2-(1',1'-Dimethoxymethyl)-4,4-dimethyl-3-(1'-pent-4'-enyl)-cyclohexanone (84) using the method of Mukiyama³⁶

To a mixture of the crude trimethylsilylenol ether (85), 0.16 g (ca. 0.6 mmol), and trimethylorthoformate (0.15 ml, 0.6 mmol) in CH₂Cl₂ (10 ml), under argon at -78°C, was added 10% titanium tetrachloride in CH₂Cl₂ (1.5 ml, 1.3 mmol), dropwise over 5 min. After 2 h, the reaction mixture was poured into saturated aqueous ammonium chloride (25 ml) and extracted into pet. ether (2 x 70 ml). The combined organic layers were dried, filtered and concentrated *in vacuo* to give an oil which was chromatographed (silica gel, 10:90 ether/pet. ether) to give (i) 2-formyl-4,4-dimethyl-3-(1'-pent-4'-enyl)-cyclohexanone (83) (63 mg, 45%); δ 250 MHz (CDCl₃) 14.46 (d, J 4 Hz, 1H, D₂O exch.) 8.34 (d, J 4 Hz, 1H), 6.00-4.65 (m, 3H), 2.50-1.10 (m, 11H), 1.00 (s, 3H), and 0.94 (s, 3H); $\nu_{\max}$ (film) 3080, 1640, 1590, and 810 cm⁻¹; m/e 222.1616 (M⁺), 204, 194, 189, 166, 153, and 137 (Calculated for C₁₄H₂₂O₂: 222.1620) (Found: C, 75.70; H, 10.09. C₁₄H₂₂O₂ requires C, 75.60; H, 9.97%); (ii) 4,4-dimethyl-3(1'-pent-4'-enyl)-cyclohexanone (86) (33 mg, 30%); δ (CDCl₃) 5.90-4.65 (m, 3H), 2.50-1.10 (m, 13H), 1.02 (s, 3H), and 0.99 (s, 3H); $\nu_{\max}$ (film) 3080, 1715, 1640,

910, and 735 cm^{-1} and finally, (iii) 2-(1',1'-dimethoxymethyl)-4,4-dimethyl-3-(1'-pent-4'-enyl)-cyclohexanone (84), (37 mg, 21%); δ 250 MHz (CDCl_3), 5.92-5.70 (m, 1H), 5.04-4.90 (m, 2H), 4.56 (d, J 5.1 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.44 (dd, J 5.9 and 5.1 Hz, 1H), 2.32 (m, 2H), 2.05-0.80 (m, 9H), 1.00 (s, 3H), and 0.80 (s, 3H); ν_{max} (film) 3080, 1710, 1642, 1110, 1072, and 910 cm^{-1} ; m/e 268 (M^+), 253, 273, 236, 205, and 143.

(34) Preparation of 2-Formyl-4,4-dimethyl-3(1'-pent-4'-enyl)-cyclohexanone (83), using the method of Conia²⁷

The mixture of 2-formyl-ketone (83), ketone (86), and 2(1',1'-dimethoxymethyl)ketone (84) (prepared as above) in CH_2Cl_2 (1 ml) was added to a stirred homogeneous slurry of Kieselgel-H (1 g), CH_2Cl_2 (2 ml), and 15% H_2SO_4 (4 drops). After 2 h, the mixture was quenched by the addition of sodium bicarbonate (0.5 g), and after filtration and re-extraction (ether 5 x 10 ml), chromatography (silica gel, 10:90 ether/pet. ether) of the concentrated product gave (i) 2-formyl-4,4-dimethyl-3(1'-pent-4'-enyl)-cyclohexanone (83) (91 mg, 65%), identical to the previous sample, and (ii) 4,4-dimethyl-3(1'-pent-4'-enyl)-cyclohexanone (86) (33 mg, 30%) as above.

(35) Preparation of 6-Carboethoxy-7-oxo-octene (90) using the method of Brieger³⁸

Ethyl acetoacetate (3.25 g, 25 mmol), 1-iodopent-4-ene¹ (5 g, 25 mmol), and anhydrous potassium carbonate (4.9 g, 37.5 mmol) were heated to 100°C in DMF (50 ml) for 1.5 h. After cooling, the reaction mixture was poured into water (100 ml) and extracted with ether (250 ml). The ethereal layer was washed with more water (2 x 50 ml) followed by brine (50 ml), dried, filtered and concentrated *in vacuo*. The crude product was distilled under

reduced pressure to give 6-carboethoxy-7-oxo-octene (90) (3.5 g, 70%), b.p. $84^{\circ}\text{C}/1.5\text{ mmHg}$; δ (CCl_4) 6.1-5.3 (m, 1H), 5.2-4.75 (m, 2H), 4.18 (q, J 7 Hz, 2H), 3.37 (t, J 7 Hz, 1H), 2.19 (s, 3H), 2.17-1.40 (m, 6H), and 1.25 (t, J 7 Hz, 3H); ν_{max} (film) 3080, 1743, 1725, 1640, 1140, and 912 cm^{-1} ; m/e 198 (M^+), 169, 156, and 143.

(36) Preparation of 4-Carboethoxy-5-oxo-hexene (89) using the method of Brieger³⁸

A mixture of ethyl acetoacetate (6.5 g, 50 mmol), dry allyl bromide (6.0, 50 mmol) and anhydrous potassium carbonate (14.0 g, 100 mmol) in dry DMF (90 ml) was vigorously stirred and heated to 60°C for 16 h. After cooling, the mixture was poured into water (250 ml) and extracted with ether (300 ml). The organic layer was washed with water (2 x 100 ml), followed by brine, dried and filtered. After removal of the solvent *in vacuo*, distillation under reduced pressure gave 4-carboethoxy-5-oxo-hexene (89) (6.0 g, 70%), b.p. $44-46^{\circ}\text{C}/1\text{ mmHg}$; δ (CCl_4) 6.00-5.30 (m, 1H), 5.20-4.75 (m, 2H), 4.12 (q, J 7 Hz, 2H), 3.32 (t, J 7 Hz, 1H), 2.60-2.30 (m, 2H), 2.15 (s, 3H), and 1.25 (t, J 7 Hz, 3H); ν_{max} (film) 3425 (enol), 3040, 1740, 1715, 1642, 1621, and 920 cm^{-1} .

(37) Preparation of 3-Carboethoxy-2-methyl-5-(selenophenylmethyl)-4H-dihydrofuran (92)

Phenylselenium chloride (0.21 g, 1.1 mmol) in dry, distilled CH_2Cl_2 (10 ml) was added to a suspension of silver hexafluoroantimonate (0.25 g, 1.1 mmol) in CH_2Cl_2 (10 ml) under argon at room temperature. The mixture was cooled to -78°C and 4-carboethoxy-5-oxo-hexene (89) (0.20 g, 1.1 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, poured into saturated aqueous sodium

bicarbonate (25 ml) and extracted with more CH_2Cl_2 (2 x 20 ml). After drying and filtration, removal of the solvent *in vacuo* gave a residue which was chromatographed (silica gel, 50:50 CH_2Cl_2 /pet. ether) to give 3-carboethoxy-2-methyl-5-(selenophenylmethyl)-4H-dihydrofuran (92) (0.26 g, 70%); δ 250 MHz (CDCl_3) 7.54 (m, 2H), 7.27 (m, 3H), 4.76 (dddd, J 9.5, 7.0, 7.0, and 5.5 Hz, 1H), 4.17 (q, J 7 Hz, 2H), 3.19 (dd, J 12.0, and 5.5 Hz, 1H), 3.04 (ddq, J 15.0, 9.5, and 1.5 Hz, 1H), 3.025 (dd, J 12.0, and 7.0 Hz, 1H), 2.70 (ddq, J 15.0, 7.0, and 1.5 Hz, 1H), 2.13 (dd, J 1.5, and 1.5 Hz, 3H), and 1.27 (t, J 7 Hz, 3H); ν_{max} (film), 3070, 3050, 1695, 1646, 1578, 1222, 1079, 760, 735, 690, and 665 cm^{-1} ; m/e 326.0421 (M^+), 281, 169, 157, and 123 (Calculated for $\text{C}_{15}\text{H}_{18}\text{O}_3^{80}\text{Se}$:326.0425).

(38) Preparation of 2-Acyl-2-carboethoxy-(selenophenylmethyl)cyclopentane
(93)

Phenylselenium chloride (0.21 g, 1.1 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of silver hexafluoroantimonate (0.38 g, 1.1 mmol) in CH_2Cl_2 (10 ml) under argon, at R.T. The mixture was cooled to -78°C and 6-carboethoxy-7-oxo-octene (90) (0.22 g, 1.1 mmol) in CH_2Cl_2 (10 ml) was added over 10 min. The mixture was warmed to room temperature, poured into saturated aqueous sodium bicarbonate (25 ml) and extracted into CH_2Cl_2 (2 x 25 ml). After drying, filtration and removal of the solvent *in vacuo*, gave a residue which was chromatographed (silica gel, CH_2Cl_2) to afford 2-acyl-2-carboethoxy-(selenophenylmethyl)cyclopentane (93), as a mixture of isomers (0.39 g, 81%); δ 250 MHz (CDCl_3) 7.52 (m, 2H), 7.25 (m, 3H), 4.18 (m, 2H), 3.18 (m, 1H), 2.95-2.35 (m, 3H), 2.30-2.05 (m, 2H), 2.12 (br, s, 3H), 1.88-1.45 (m, 4H), 1.26 (t, J 5.5 Hz, 1.5H), and 1.24 (t, J 5.5 Hz, 1.5 H); ν_{max} (film) 3070, 3050, 1745, 1710, 1578, 1245, 735, 690, 668, and 645 cm^{-1} ; m/e 354.0735 (M^+), 309, 265, 242, 197, and 169 (Calculated for $\text{C}_{17}\text{H}_{22}\text{O}_3^{80}\text{Se}$:354.0735).

(39) Preparation of (94) and (95) from 3,3-Dimethyl-6-(1'-pent-4'-enyl)-1,5-dioxocyclohexane (91)

Phenylselenium chloride (0.21 g, 1.1 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of silver hexafluorophosphate (0.284 g, 1.1 mmol) in CH_2Cl_2 (10 ml) under argon at R.T. The mixture was cooled to -78°C and 3,3-dimethyl-6-(1'-pent-4'-enyl)-1,5-dioxocyclohexane³⁹ (91) (0.21 g, 1.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise over 10 min. The mixture was warmed to room temperature and worked up in the usual manner. Chromatography (silica gel, CH_2Cl_2) then gave (i) 4,4-dimethyl-2,6-dioxocyclohexan-spiro-1',2'-(selenophenylmethyl)-cyclopentane (94) (97 mg, 27%), m.p. $86-87^\circ\text{C}$ (pet. ether); δ 250 MHz (CDCl_3) 7.52 (m, 2H), 7.27 (m, 3H), 2.82 (m, 2H), 2.71 (m, 1H), 2.55 (m, 2H), 2.46 (m, 1H), 2.35 (m, 1H), 2.15 (m, 1H), 2.00-1.70 (m, 5H), 0.99 (s, 3H), and 0.93 (s, 3H); ν_{max} (CHCl_3) 2890, 1725, 1690, 1580, and 1475 cm^{-1} ; m/e 364.0945 (M^+), 270, and 157 (calculated for $\text{C}_{19}\text{H}_{24}\text{O}_2^{80}\text{Se}$: 364.0941); and (ii) 8,8-dimethyl-6-oxo-2-(selenophenylmethyl)-[3,4,5,7,9H]-benzoxepin (95) (111mg, 30%); δ 250 MHz (CDCl_3) 7.51 (m, 2H), 7.26 (m, 3H), 4.41 (m, 1H), 3.16 (dd, J 13.0 and 8.0 Hz, 1H), 2.99 (dd, J 13.0 and 5.0 Hz, 1H), 2.62 (ddd, J 18.0, 4.7 and 4.7 Hz, 1H), 2.19 (d, J 1 Hz, 2H), 2.35-2.08 (m, 3H), 1.77-1.73 (m, 4H), 1.04 (s, 3H), and 0.98 (s, 3H); ν_{max} (film) 3070, 3050, 1655, 1620, 1578, 1225, 739, and 690 cm^{-1} ; m/e 364.0945 (M^+), 207, and 157 (Calculated for $\text{C}_{19}\text{H}_{24}\text{O}_2^{80}\text{Se}$: 364.0941).

(40) Preparation of (94) from 3,3-Dimethyl-6-(1'-pent-4'-enyl)-1,5-dioxocyclohexane (91)

Phenylselenium chloride (0.21 g, 1.1 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of silver hexafluoroantimonate (0.38 g, 1.1 mol) in CH_2Cl_2 (10 ml) under argon at R.T. The mixture was cooled to -78°C and 3,3-dime-

thyl-6-(1'-pent-4'-enyl)-1,5-dioxocyclohexane³⁹ (91) (0.21 g, 1.0 mmol) in CH_2Cl_2 (10 ml) was added over 15 min. The reaction mixture was warmed to R.T. and worked up in the usual manner. Chromatography (silica gel, 30:70 ether/pet. ether) gave 4,4-dimethyl-2,6-dioxocyclohexanspiro-1'-2'-(selenophenylmethyl)-cyclopentane (94), 0.16 g, 44%, identical to the previous sample.

(41) Preparation of 7-Carbomethoxy-2-methyl-[3,4,5,6,9H]-benzofuran (97)
using the method of Clive⁴⁰

A mixture of 7-carbomethoxy-2-(selenophenylmethyl)-[3,4,5,6,9H]-benzofuran¹ (96) (0.147 g, 0.42 mmol), triphenyltin hydride (0.44 g, 1.2 mmol), and AIBN (10 mg) were heated to reflux in toluene (10 ml) under argon for 3.5 h. After cooling, the solvent was removed *in vacuo* and the residue was chromatographed (silica gel, 7:93 ether/pet. ether) to give 7-carbomethoxy-2-methyl-[3,4,5,6,9H]-benzofuran (97) (55 mg, 67%); δ (CDCl_3) 4.65 (m, 1H), 3.70 (s, 3H), 2.40-1.70 (m, 9H), and 1.45 (d, J 6 Hz, 3H); ν_{max} 3070, 1690, 1660, 910, and 698 cm^{-1} .

(42) Preparation of 9,9-Dimethyl-4-(selenophenylmethyl)-3-oxabicyclo[6.4.0]dodec-1,2-en-12-one (99)

Phenylselenium chloride (0.105 g, 0.55 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of silver hexafluoroantimonate (0.19 g, 0.55 mmol) in CH_2Cl_2 (5 ml) under argon at R.T. The mixture was cooled to -78°C and 2-formyl-4,4-dimethyl-3-(1'-pent-4'-enyl)-cyclohexanone (83) (0.11 g, 0.5 mmol) in CH_2Cl_2 (5 ml) was added over 5 min. The mixture was warmed to R.T., poured into saturated aqueous ammonium chloride (15 ml) and extracted into CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried, filtered and the solvent removed *in vacuo* to give the crude 9,9-dimethyl-4-(seleno-

phenylmethyl)-3-oxabicyclo[6.4.0]-dodec-1,2-ene-12-one (99) as a mixture of isomers (160 mg, 85%); δ 250 MHz (CDCl_3) 8.30 (s, 1H), 7.50 (m, 2H), 7.23 (m, 3H), 3.95 (m, 1H), 1.00 (br, s, 3H), 0.97 (s, 1.5H), and 0.88 (s, 1.5H), *inter alia*; ν_{max} (film) 1670, 1585, and 690 cm^{-1} . This compound could not be purified as it decomposed rapidly on silica gel.

(43) Preparation of cis-1 α -Formyl-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]decan-2-one (100)

The crude 'O'-cyclised selenide (99) obtained above was dissolved in CH_2Cl_2 (10 ml) and treated with ZnI_2 (0.32 g, 1 mmol). The rearrangement reaction was followed by TLC (25:75 ether/pet. ether) and after 48 h, the reaction mixture was filtered and washed with 5% aqueous sodium metabisulphite (2 x 5 ml) followed by brine (5 ml). The organic layer was dried, filtered and the solvent removed *in vacuo* to give the crude product which, by TLC and ^1H analysis, was composed of a mixture of both the starting "O" cyclised material (99) and the rearranged "C" cyclised product (100). Chromatography (silica gel, pet. ether to 20:80 ether /pet. ether) gave cis-1 α -formyl-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]-decan-2-one (100) (55 mg, 15%); δ 250 MHz (CDCl_3) 9.70 (d, J 1Hz, 1H), 7.50 (m, 2H), 7.25 (m, 3H), 3.07 (dd, J 12.5 and 3.8 Hz, 1H), 2.96 (dd, J 12.5 and 11.0 Hz, 1H), 2.41 (m, 1H), 2.30-2.04 (m, 2H), 1.93 (m, 1H), 1.73 (ddd, J 13.75, 7.5 and 6 Hz, 1H), 1.64-1.40 (m, 7H), 1.06 (s, 3H), and 1.02 (s, 3H); ν_{max} (film) 2875, 1728, 1700, 1580, 1392, 1370, and 693; m/e 378.1097 (M^+), 360, 350, 221, 193 and 195 (Calculated for $\text{C}_{20}\text{H}_{26}\text{O}_2^{80}\text{Se}$ 378.1097). The 'O' cyclised material decomposed on the silica gel and was not isolated.

(44) Preparation of cis-1 α -Hydroxymethyl-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]decan-2 β -ol (101)

(a) From cis-1 α -Formyl-5,5-dimethyl-10 α -(selenophenylmethyl)bicyclo[4.4.0]-decan-2-one (100). The 1 α -formylselenide (100) (36 mg, 0.095 mmol) was dissolved in methanol (1 ml) and sodium borohydride (36 mg, 0.94 mmol) was added in one portion. After 30 min, water (1 ml) was added and the product was extracted into CH₂Cl₂ (2 x 25 ml). The combined organic layers were dried, filtered and concentrated *in vacuo* and the residue was chromatographed (silica gel, 75:25 ether/pet. ether) to give cis-1 α -hydroxymethyl-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]decan-2 β -ol (101), 30 mg, (82%), m.p. 159-160°C (EtOAc); δ 250 MHz (CDCl₃) 7.55 (m, 2H), 7.23 (m, 3H), 4.40 (dd, J 11.5 and 6.3 Hz, 1H), 4.32 (dd, J 12.0 and 3 Hz, 1H), 3.78 (dd, J 10.8 and 2.0 Hz, 1H), 3.60 (br, d, J 10.8 Hz, 1H), 2.86 (dd, J 12.0 and 10.0, 1H), 2.73 (br, s, 1H), 2.58 (br, s, 1H), 2.30 (m, 1H), 2.17 (m, 1H), 1.04 (m, 1H), 1.60-1.25 (m, 9H), 0.90 (s, 3H), and 0.87 (s, 3H); $\nu_{\max}$ (KBr) 3380, 2860, 1575, 1475, 728, and 689 cm⁻¹; m/e 382.1411 (M⁺), 225, 207, and 189 (calculated for C₂₀H₃₀O₂⁸⁰Se:382.1410) (Found: C, 63.17, H, 7.94. C₂₀H₃₀SeO₂ requires: C, 62.98; H, 7.93%).

(b) From cis-1 α -carbomethoxy-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]-decan-2 β -ol (102)¹. The alcohol-ester (102)¹ (140 mg, 0.34 mmol) was dissolved in dry ether (2 ml) and lithium aluminium hydride (20 mg, 0.53 mmol) was added in one portion. After 1 h, water ($\frac{1}{2}$ ml) was added, followed by anhydrous sodium sulphate (2 g). The crude diol was extracted into CH₂Cl₂ (2 x 25 ml) and, after removal of the solvent, *in vacuo*, chromatographed (silica gel, 75:25 ether/pet. ether) to give cis-1 α -hydroxymethyl-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]decan-2 β -ol (101) (124 mg, 95%), m.p. 159-160°C (EtOAc) identical to the previous sample.

(45) Preparation of cis-2 β -Acetoxy-1 α -acetoxymethyl-10 α -(selenophenylmethyl)-5,5-dimethylbicyclo[4.4.0]decane (103)

A mixture of diol (101) (27 mg, 0.07 mmol), pyridine (0.1 ml), acetic anhydride (0.05 ml) and 4-N,N-dimethylaminopyridine (1 mg) was stirred at R.T. for 3 h. Excess reagents were removed *in vacuo* and the residue was chromatographed (silica gel, 50:50 ether/pet. ether) to give cis-2 β -acetoxy-1 α -acetoxymethyl-10 α -(selenophenylmethyl)-5,5-dimethylbicyclo[4.4.0]decane (103) (28 mg, 85%), m.p. 76.5–78.5^oC (MeOH); δ 250 MHz (CDCl₃) 7.55 (m, 2H), 7.25 (m, 3H), 4.83 (dd, J 5.5 and 5.5 Hz, 1H), 4.28 (d, J 11.5 Hz, 1H), 4.24 (d, J 11.5 Hz, 1H), 3.98 (dd, J 12.0 and 2.5 Hz, 1H), 2.54 (dd, J 12.0 and 12.0 Hz, 1H), 2.38 (m, 1H), 2.15 (m, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.70–1.25 (m, 10H), 0.98 (s, 3H), and 0.95 (s, 3H); $\nu_{\max}$ (CHCl₃) 3075, 2850, 1740, and 910 cm⁻¹. (Found: C, 61.95; H, 7.47. C₂₄H₃₄SeO₄ requires, C, 61.93; H, 7.36%).

Crystals of (103) are monoclinic, $a = 8.339(1)$, $b = 16.871(3)$, $c = 16.472(3)$ Å, $\beta = 92.39(1)^{\circ}$, $V = 2315$ Å³ space group $P2_1/a$, $Z = 4$, $D_c = 1.34$ gcm⁻³. Data were measured using monochromatised Cu-K α radiation (graphite monochromator) on a Nicolet R3m diffractometer. A total of 2382 independent reflections were measured ($\theta \leq 50^{\circ}$) using the omega scan measuring routine, and of these 180 had $F_o < 3\sigma(F_o)$ and were classed as unobserved. The structure was solved by the heavy-atom method and the non-hydrogen atoms refined anisotropically. The hydrogen atoms, with the exception of the methyl groups which were refined as rigid bodies, were placed at calculated positions and allowed to ride on their parent carbon atoms. 17 Reflections which had $|F_o| < |F_c|$ were suspected of being affected by extinction and therefore removed. Refinement was terminated at a final $R = 0.055$. (Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.)

(46) Preparation of cis-1 α -H-5,5-Dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]decan-2-one (104)

Phenylselenium chloride (0.21 g, 1.1 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of silver hexafluoroantimonate (0.25 g, 1.1 mmol) in CH_2Cl_2 (10 ml) under argon at R.T. The mixture was cooled to -78°C and the crude 4,4-dimethyl-1-trimethylsilyloxy-3-(1'-pent-4'-enyl)-cyclohexene (85) (0.25 g, ca. 1.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 5 min. The mixture was kept at -78°C for 1 h before being warmed to room temperature and worked up in the usual manner. The crude product was carefully chromatographed (silica gel, pet. ether to 15:85 ether/pet. ether), to give (i) cis-1 α -H-5,5-dimethyl-10 α -(selenophenylmethyl)-bicyclo[4.4.0]decan-2-one (104) (60 mg, 17%); δ 250 MHz (CDCl_3) 7.45 (m, 2H), 7.25 (m, 3H), 3.01 (dd, J 12.0 and 6.7 Hz, 1H), 2.95 (dd, J 12.0 and 9.0 Hz, 1H), 2.55 (m, 1H), 2.41 (ddd, J 14.5, 13.0, and 6.0 Hz, 1H), 2.23 (ddd, J 14.5, 5.0, and 2.0 Hz, 1H), 1.81 (ddd, J 13.0, 13.0, and 5.0 Hz, 1H), 1.74-1.62 (m, 4H), 1.58-1.43 (m, 3H), 1.30 (dddd, J 13.0, 13.0, 13.0, 3.0, and 3.0 Hz, 1H), 1.20 (s, 3H), 0.96 (s, 3H), and 0.92 (dddd, J 12.5, 12.5, 12.5, and 4Hz, 1H); ν_{max} (film) 3075, 3055, 2862, 1710, 1580, 1480, 1390, 1370, 910, 692, and 670 cm^{-1} ; m/e 350 (M^+), 272, 228, 193, 175, and 107 (M^+ 350-193); and (ii) 4,4-dimethyl-3-(1'-pent-4'-enyl)cyclohexanone (86), (60 mg, 30%) identical to the previous sample.

(47) Preparation of cis-1 α -H-10 α ,5,5-Trimethylbicyclo[4.4.0]decan-2-one (105)

A mixture of the selenide (104) (30 mg, 0.085 mmol), triphenyltinhydride⁴⁰ (53 mg, 0.17 mmol), and AIBN (5 mg) were heated to reflux in toluene (7 ml) under argon for 2 h. After cooling, the residue was chromatographed (silica gel, pet. ether to 10:90 ether/pet. ether) to give cis-1 α -H-10 α ,5,5-trimethylbicyclo[4.4.0]decan-2-one (105) (9 mg, 55%);

δ 400 MHz (CDCl_3) 2.51 (m, 2H), 2.38 (dddd, J 14.75, 13.5, 6.75, and 1.0 Hz, 1H), 2.23 (ddd, J 14.75, 5.0, and 2.0 Hz, 1H), 1.81 (ddd, J 13.5, 13.5, and 5.0 Hz, 1H), 1.77 (ddd, J 13.0, 5.0, and 2.75 Hz, 1H), 1.70 (dddd, J 13.0, 3.25, 3.25, 3.25, and 1.5 Hz, 1H), 1.66 (dddd, J 13.25, 13.25, 4.75, and 4.75 Hz, 1H), 1.50 (dddd, J 13.5, 6.75, 2.0, and 2.0 Hz, 1H), 1.50 (m, J 13.25, 4.0, 3.0, and 3.0 Hz, 1H), 1.38 (dddd, J 13.0, 13.0, 13.0, 4.0, and 4.0 Hz, 1H), 1.26 (m, J 13.25, 4.0, 2.6, and 1.5 Hz, 1H), 1.24 (s, 3H), 0.98 (s, 3H), 0.96 (d, J 7.5 Hz, 3H), and 0.85 (dddd, J 13.0, 13.0, 13.0, and 3.75 Hz, 1H); ν_{max} (CHCl_3) 1708 cm^{-1} ; m/e 194.1671 (M^+), 179, 165, 151, and 138 (Calculated for $\text{C}_{13}\text{H}_{22}\text{O}$: 194.1666).

(48) Reaction of 2-Formyl-4,4-dimethyl-3(1'-pent-4'-enyl)-cyclohexanone (83) with Phenylselenium chloride

A mixture of the 2-formyl ketone (83) (0.444 g, 2 mmol), phenylselenium chloride (0.404 g, 2.1 mmol), and pyridine (0.24 ml, 3 mmol) was stirred at R.T. overnight. The mixture was washed with 5% HCl (2 x 15 ml) and brine (5 ml), and after drying, filtration, and removal of the solvent *in vacuo*, it gave 2-formyl-4,4-dimethyl-3(5'-2'-chloro-1'-selenophenylpentane)-cyclohexanone (106) (0.8 g); δ (CDCl_3) 16.5 (br, s, 1H), 8.23 (s, 1H), 7.5-7.00 (m, 5H), 3.88 (m, 1H), 3.20 (m, 2H), 2.25 (m, 2H), 1.95-1.05 (m, 9H), 0.98 (s, 3H), and 0.76 (s, 3H); ν_{max} (film) 2870, 1635, 1580, 1480, 1438, 755, 740, 690, and 688 cm^{-1} . This material could not be further purified as it decomposed on silica gel.

(49) Preparation of 1-Vinyl-4,4-dimethylcyclohex-2-en-1-ol (123)

A solution of vinyl bromide (0.175 ml, 2.5 mmol) in dry ether (3 ml), under argon, was cooled to -120°C (methylcyclohexane/liq. N_2) and 1.4 M *t*-butyl lithium in hexane (3.1 ml, 4.4 mmol) was added dropwise over 15 min.

After a further 3 h, neat 4,4-dimethylcyclohexenone (0.6 g, 5 mmol) was added and the reaction mixture was warmed to R.T. The mixture was then poured into saturated aqueous ammonium chloride (10 ml), extracted into ether (3 x 15 ml) and the combined organic layers were dried, filtered, and the solvent was removed *in vacuo*. Excess enone was removed *in vacuo* and the residue was chromatographed (silica gel, 50:50 ether/pet. ether to ether), to give 1-vinyl-4,4-dimethylcyclohex-2-en-1-ol (123) (0.388 g, 67%); δ (CDCl₃) 6.15-4.80 (m, 5H), 2.40 (br, s, 1H, D₂O exch.), 2.00-1.40 (m, 4H), 1.00 (s, 3H), and 0.95 (s, 3H).

(50) Preparation of 5,5-Dimethyl-2-(methoxycarbonyloxy)-10-vinylbicyclo[4.4.0]dec-1,2-ene (122)

An ethereal solution of vinyl lithium was prepared as before from vinyl bromide (2.5 mmol) and *t*-butyl lithium (4.4 mmol) at -120°C for 3h. The cold solution was added dropwise to a slurry of copper (I) bromide-dimethyl sulphide complex (0.20 g, 1 mmol) in dry ether (5 ml) at -10°C under argon. After the addition was complete, stirring for a further 10 min completed the formation of the cuprate as a dark blue solution. This was cooled to -30°C, and a solution of 5,5-dimethylbicyclo[4.4.0]dec-1,10-en-2-one⁴⁵ (116) (0.11 g, 0.61 mmol) in ether (2 ml) was added. After stirring for 45 min, neat methyl chloroformate (0.3 ml, 2 mmol) was added in one portion, and the reaction mixture was warmed to room temperature. Work-up in the normal manner gave crude 5,5-dimethyl-2-(methoxycarbonyloxy)-10-vinylbicyclo[4.4.0]dec-1,2-ene (122); δ (CDCl₃) 6.00-4.70 (m), 3.80 (s), 1.00 (s), and 0.90 (s), *inter alia*; $\nu_{\max}$ (film) 2860, 1760, 1440 and 1260 cm⁻¹. This compound could not be purified as it rapidly decomposed on silica gel.

(51) Preparation of 2-Trimethylsilyloxy-10-vinyl-5,5-dimethylbicyclo[4.4.0]dec-1,2-ene (124)

Vinyl magnesium bromide (1.1 mmol, prepared in the usual way) in dry THF (3 ml) was added to a stirred slurry of copper (I) bromide-dimethyl sulphide complex (0.11 g, 0.55 mmol) in ether (10 ml) at -50°C under argon. Stirring for a further 30 min completed the formation of the green cuprate, and a solution of 5,5-dimethylbicyclo[4.4.0]dec-1,10-en-2-one (116) (86 mg, 0.5 mmol) in dry ether (2 ml) was then added dropwise. The reaction mixture immediately went black and, after a further 30 min, a preformed mixture of purified chlorotrimethylsilane (1 ml) and dry triethylamine (1 ml) was added in one portion. After warming to R.T., work-up in the normal manner afforded 2-trimethylsilyloxy-10-vinyl-5,5-dimethylbicyclo[4.4.0]dec-1,2-ene (124) (0.127 g, 91%); δ (CDCl_3) 6.00-4.60 (m, 3H), 2.10-1.10 (m, 12H), 0.90 (s, 3H) 0.80 (s, 3H), and 0.15 (s, 9H); ν_{max} (film) 3080, 2855, 1675, 1250, 840, and 750 cm^{-1} .

(52) Attempted preparation of trans-1 α -Carbomethoxy-10-vinyl-4,4-dimethylbicyclo[4.4.0]decan-2-one (121)

To a solution of the silyl enol ether (124) (70 mg, 0.25 mmol) in ether (2 ml) under argon at 0°C was added ethereal 1.2 M methyl lithium (0.25 ml, 0.3 mmol). The stirred mixture was warmed to R.T. and the disappearance of the starting material was followed by TLC (25:75 ether/pet. ether). After 2 h, neat methyl chloroformate (0.2 ml) was added, resulting in the immediate formation of a white precipitate. The reaction mixture was then poured into saturated aqueous ammonium chloride (2 ml) and worked up in the usual manner to give only 5,5-dimethyl-2-(methoxycarbonyloxy)-10-vinylbicyclo[4.4.0]dec-1,2-ene (122) as above.

(53) Preparation of an Ether solution of Formaldehyde

Dry paraformaldehyde was placed in a glass boat in a pyrex tube and a gentle stream of nitrogen was passed over it and through dry ether (or THF) cooled to -78°C . Gentle heating decomposed the polymer and the monomeric formaldehyde was trapped in solution. Provided the solution was kept at -78°C , the monomer was stable for up to a week.

(54) Preparation of trans-1 α -Hydroxymethyl-10 β -vinyl-5,5-dimethylbicyclo[4.4.0]decan-2-one (130)

A solution of vinyl magnesium bromide [prepared from vinyl bromide (0.79 ml, 11.0 mmol) in THF (12 ml)] was added dropwise to a slurry of copper (I) bromide-dimethyl sulphide complex (1.1 g, 5.5 mmol) in ether (15 ml), under argon at -50°C . Stirring for a further 30 min gave a green/brown suspension to which was added 5,5-dimethylbicyclo[4.4.0]dec-1,10-en-2-one (116) (0.89 g, 5 mmol) in ether (10 ml). After 20 min, an ethereal solution of formaldehyde was added - the quench being followed by TLC (50:50 ether/pet. ether) - and the reaction mixture was warmed to R.T. The mixture was poured into saturated aqueous ammonium chloride (30 ml) and worked up in the usual manner to give the crude product. Chromatography (silica gel, 50:50 ether/pet. ether) gave trans-1 α -hydroxymethyl-10 β -vinyl-5,5-dimethylbicyclo[4.4.0]decan-2-one (130) (0.743g, 63%); δ 250 MHz (CDCl_3) 5.87 (ddd, J 17.7, 9.9, and 8.8 Hz, 1H), 5.10 (m, 1H), 5.05 (m, 1H), 4.01 (dd, J 12.0 and 12.0 Hz, 1H), 3.74 (d, J 12.0 Hz, 1H), 3.19 (m, 1H), 2.70 (d, J 12.0 Hz, 1H, D_2O exch.), 2.35 (ddd, J 14.5, 14.5, and 4.0 Hz, 1H), 2.28 (ddd, J 14.5, 5.0, and 5.0 Hz, 1H), 1.93 (dd, J 12.5, and 3.0 Hz, 1H), 1.85-1.35 (m, 8H), 1.05 (s, 3H), and 0.88 (s, 3H); ν_{max} (film) 3450, 3078, 2763, 1698, 1630, 1390, 1370, 1040, and 918 cm^{-1} ;

m/e 236 ($M^+ - H_2O$), 206, 205, 150, and 149.

(55) Reduction of trans-1 α -Hydroxymethyl-10 β -vinyl-5,5-dimethylbicyclo[4.4.0]decan-2-one (130) with sodium borohydride

The keto-alcohol (130) (17.5 mg, 0.075 mmol) was dissolved in methanol (1 ml) and sodium borohydride (8 mg, 0.21 mmol) was added in one portion. After 30 min, water (0.1 ml) was added and the product was extracted into CH_2Cl_2 (2 x 25 ml). The combined organic layers were dried, filtered and, after the removal of the solvent *in vacuo*, chromatographed (silica gel, 25:75 EtOAc/ CH_2Cl_2) to give trans-1 α -hydroxymethyl-5,5-dimethyl-10 β -vinylbicyclo[4.4.0]decan-2-ol (131) and (132) (15 mg, 85%) as a 1:1 mixture of 2 α and 2 β isomers; δ 250 MHz ($CDCl_3$) 6.71 (ddd, J 17.0, 10.0 and 10.0 Hz, 0.5 H), 6.24 (ddd, J 17.0, 10.0 and 10.0 Hz, 0.5 H), 5.23 (m, 0.5H), 5.17 (m, 0.5H), 5.13 (dd, J 17.0 and 1.6 Hz, 0.5H), 5.05 (dd, J 17.0 and 1.6 Hz, 0.5H), 4.30 (d, J 11.3 Hz, 0.5H), 4.09 (dd, J 3.0 and 3.0 Hz, 0.5H), 3.98 (d, J 11.25, 0.5H), 3.93 (d, J 11.25 Hz, 0.5H), 3.86 (d, J 10.8 Hz, 0.5H), 3.67 (dd, J 11.6 and 3.3 Hz, 0.5H), 3.18 (m, 0.5H), 3.07 (br, s, 0.5H, D_2O exch.), 2.87 (ddd, J 10.0, 3.75, and 2.0 Hz, 0.5H), 2.48 (br, s, 0.5H, D_2O exch.), 2.07 (br, s, 0.5H, D_2O exch.), 2.00-1.05 (m, 11.5H, 0.5H, D_2O exch.), 0.94 (s, 1.5H), 0.88 (s, 1.5H), 0.82 (s, 1.5H), and 0.78 (s, 3H); ν_{max} (film) 3350, 3075, 1660, 1390, 1360, 1108, and 910 cm^{-1} .

(56) Preparation of trans-1 α -t-Butyldiphenylsilyloxymethyl-5,5-dimethyl-10 β -vinylbicyclo[4.4.0]decan-2-one (133) using the method of Hanessian and Lavallee ⁶⁷

A solution of the keto-alcohol (130) (80 mg, 0.31 mmol), t-butyl-diphenylsilylchloride (0.33 ml, 0.37 mmol) and imidazole (46 mg, 0.62 mmol)

in dry DMF (1 ml) was stirred overnight at R.T. The reaction mixture was poured into ether (50 ml) and washed with water (3 x 10 ml), followed by brine (10 ml). After drying, and removal of the solvent *in vacuo*, the residue was chromatographed (silica gel 10:90 ether/pet. ether) to give trans-1 α -t-butyldiphenylsilyloxymethyl-5,5-dimethyl-10 β -vinylbicyclo[4.4.0]decan-2-one (133) (0.145 g, 98%); δ 250 MHz (CDCl₃), 7.65 (m, 4H), 7.40 (m, 6H), 5.85 (ddd, J 16.7, 10.8, and 5.8 Hz, 1H), 5.12 (ddd, J 16.7, 2.6, and 2.6 Hz, 1H), 5.11 (ddd, J 10.8, 2.6, and 2.6 Hz, 1H), 4.02 (d, J 6.8 Hz, 1H), 3.95 (d, J 6.8 Hz, 1H), 3.28 (m, 1H), 2.27 (ddd, J 15.0, 11.25 and 4.6 Hz, 1H), 2.10 (ddd, J 15.7 and 4.6 Hz, 1H), 1.73 (dd, J 12.1 and 3.2 Hz, 1H), 1.67-1.45 (m, 6H), 1.40-1.25 (m, 2H), 1.05 (s, 9H), 0.93 (s, 3H), and 0.76 (s, 3H); $\nu_{\max}$ (film) 3065, 3040, 2855, 1960, 1895, 1820, 1720, 1630, 1585, 1425, 1008, 995, 904, 820, 739, and 700 cm⁻¹; m/e 474 (M⁺), 459, 416, 387, 337, 267, 200 and 199.

(57) Preparation of trans-1 α -Hydroxymethyl-5,5-dimethyl-10 β -vinylbicyclo[4.4.0]decan-2 α -ol (131)

Lithium aluminium hydride (18 mg, 0.47 mmol) was added, in portions, to a stirred solution of the silyl protected keto-alcohol (133) 0.22 g, 0.47 mmol) in dry ether (10 ml) at R.T. After stirring for 1 h (whilst following the course of the reaction by TLC, 10:90 ether/pet.ether) water (0.5 ml) was added, followed by anhydrous sodium sulphate (5 g) and the crude diol was extracted into CH₂Cl₂ (4 x 25 ml). After removal of the solvent *in vacuo*, the residue was chromatographed (silica gel, 90:10 ether pet. ether to ether) to give trans-1 α -hydroxymethyl-5,5-dimethyl-10 β -vinylbicyclo[4.4.0]decan-2 α -ol (131) (70 mg, 63%); δ 250 MHz (CDCl₃) 6.24 (ddd, J 16.7, 10.0 and 10.0 Hz, 1H), 5.23 (dd, J 16.7 and 1.6 Hz, 1H), 5.13 (dd, 10.0 and 1.6 Hz, 1H), 4.30 (d, J 11.3 Hz, 1H), 3.86 (dd, J 11.3 and 10.8 Hz, 1H), 3.67 (ddd, J 11.6, 3.3 and 1.7 Hz, 1H), 3.18 (m, 1H),

3.07 (d, J 10.8 Hz, 1H, D₂O exch.), 2.04 (d, J 3.3 Hz, 1H, D₂O exch.), 1.95-1.80 (m, 2H), 1.70-1.20 (m, 9H), 0.88 (s, 3H), and 0.78 (s, 3H); $\nu_{\max}$ (film) 3350, 3075, 1660, 1390, 1360, 1108, and 910 cm⁻¹; m/e 238 (M⁺) 220, and 189.

(58) Preparation of trans-5,5-Dimethyl-10 β -vinyl[(1 α -hydroxymethyl-2 α -hydroxy)acetone]bicyclo[4.4.0]decane (134)

A solution of the diol (131) (70 mg, 0.29 mmol), 2,2-dimethoxypropane (45 mg, 0.5 mmol) and pTSA (5 mg) in benzene (25 ml) was heated to reflux in a Dean-Stark apparatus for 2 h. After cooling, the solution was diluted with ether (50 ml) and washed with saturated aqueous sodium bicarbonate (2 x 50 ml) followed by brine (5 ml). The organic layer was dried, filtered and the solvent removed *in vacuo* to give the crude acetone. Chromatography (silica gel, 5:95 ether/pet. ether) gave trans-5,5-dimethyl-10 β -vinyl[(1 α -hydroxymethyl-2 α -hydroxy)acetone]bicyclo[4.4.0]decane (134) (81 mg, 99%); δ (CDCl₃) 6.3-5.6 (m, 1H), 5.25-4.80 (m, 2H), 4.20-3.50 (m, 3H), 2.95 (m, 1H), 2.30-1.00 (m, 17H), and 0.85 (s, 6H); $\nu_{\max}$ (film), 3078, 1632, 1460, 1370, 1230, and 915 cm⁻¹; m/e 263 (M⁺-CH₃) and 203.

(59) Preparation of trans-5,5-Dimethyl-10 β -hydroxymethyl[(1 α -hydroxymethyl-2 α -hydroxy)acetone]bicyclo[4.4.0]decane (135)

The vinyl acetone (134) (81 mg, 0.29 mmol) was dissolved in methanol (2 ml) and cooled to 0°C. Ozone was bubbled through the stirred solution and the disappearance of the starting material was followed by TLC (10:90 ether/pet. ether). After the formation of the ozonide was complete, the ozone source was removed and sodium borohydride was added in small (5 mg) portions until the reduction was complete (TLC). Water (0.25 ml) was added

and after the removal of the solvent *in vacuo* the residue was extracted into ether (3 x 10 ml). The combined extracts were dried and filtered and the solvent removed *in vacuo*. The crude product was chromatographed (silica gel, 40:60 ether/pet. ether) to give trans-5,5-dimethyl-10 β -hydroxymethyl-[(1 α -hydroxymethyl-2 α -hydroxy)acetonide]bicyclo[4.4.0]decane (135), (70 mg, 86%); δ 250 MHz (CDCl₃) 4.20 (d, J 11.5 Hz, 1H), 3.90 (dd, J 11.0 and 6.25 Hz, 1H), 3.85 (dd, J 10.0 and 6.0 Hz, 1H), 3.83 (d, J 11.5 Hz, 1H), 3.62 (dd, J 11.0 and 5.0 Hz, 1H), 2.65 (m, 1H), 2.25 (dddd, J 12.5, 11.0, 11.0 and 3.0 Hz, 1H), 2.15 (br, s, 1H, D₂O exch.), 1.80-1.50 (m, 6H), 1.47 (s, 3H), 1.40 (s, 3H), 1.30-1.05 (m, 4H), and 0.87 (s, 6H); ν_{max} (film) 3470, 1460, 1380, 1370, and 1230; m/e 282 (M⁺), 267, 224, and 207.

(60) Preparation of trans-5,5-Dimethyl-10 β -selenophenylmethyl[(1 α -hydroxymethyl-2 α -hydroxy)acetonide]bicyclo[4.4.0]decane (136) using the method of Grieco and Nicolau⁵¹

A solution of the hydroxymethyl acetonide (135) (70 mg, 0.25 mmol), N-selenophenylphthamide (59) (0.15 g, 0.5 mmol) and tri-n-butylphosphine (0.125 ml, 0.5 mmol) in dry THF (3 ml) was stirred at R.T. for 2 h. The solvent was removed *in vacuo* and the residue was chromatographed (silica gel, pet. ether to 5:95 ether/pet. ether) to give (i) a small amount of diphenyldiselenide, and (ii) trans-5,5-dimethyl-10 β -selenophenylmethyl-[(1 α -hydroxymethyl-2 α -hydroxy)acetonide]bicyclo[4.4.0]decane (136) (93 mg, 89%); δ 250 MHz (CDCl₃) 7.55 (m, 2H), 7.25 (m, 3H), 4.06 (d, J 11.8 Hz, 1H), 3.82 (d, J 11.8 Hz, 1H), 3.80 (dd, J 8.5 and 4.2 Hz, 1H), 3.15 (ddd, J 11.8, 3.4, and 1.7 Hz, 1H), 2.93 (dd, J 11.8, and 11.8 Hz, 1H), 2.60 (m, 1H), 2.15-1.88 (m, 2H), 1.80-1.20 (m, 9H), 1.39 (s, 3H), 1.17 (s, 3H), 0.87 (s, 3H), and 0.86 (s, 3H); ν_{max} (film) 3075, 3055, 2876, 1580, 908 and 690 cm⁻¹; m/e 422 (M⁺) 407, 364, 265, and 207.

(61) Preparation of trans-5,5-Dimethyl[(1 α -hydroxymethyl-2 α -hydroxy) acetonide]bicyclo[4.4.0]dec-10,1'-ene (137)

The selenide (136) (93 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (2 ml) and cooled to -78°C . Ozone was bubbled through the stirred solution until it showed a persistent blue colouration and TLC (5:95 ether/pet. ether) showed the absence of starting material. Nitrogen was then blown through the solution until it was once more colourless and, after dilution with CCl_4 (15 ml), diethylamine (10 drops) was added and the mixture was heated to reflux. After 30 min, the solution was cooled, the solvent removed *in vacuo* and the residue was chromatographed (silica gel, 5:95 ether/pet. ether) to give trans-5,5-dimethyl[(1 α -hydroxymethyl-2 α -hydroxy) acetonide]-bicyclo[4.4.0]dec-10,1'-ene (137), (50 mg, 86%); δ 250 MHz, (CDCl_3) 5.06 (br, s, 1H), 4.90 (br, s, 1H), 4.24 (d, J 11.5 Hz, 1H), 4.03 (dd, J 11.5 and 4.7 Hz, 1H), 3.94 (dd, J 11.5 and 1.0 Hz, 1H), 3.40-3.18 (m, 3H), 2.95-2.75 (m, 2H), 1.65-1.60 (m, 1H), 1.55-1.45 (m, 1H), 1.47 (s, 3H), 1.45-1.15 (m, 3H), 1.32 (s, 3H), 1.04 (m, 1H), 0.93 (s, 3H), and 0.86 (s, 3H); ν_{max} (film) 3090, 1639, 1375, 1365, and 1240 cm^{-1} ; m/e 264 (M^+) 249, 189, and 176.

(62) Preparation of trans-5,5-Dimethyl-2 α -hydroxy-1 α -hydroxymethylbicyclo[4.4.0]dec-10,1'-ene (138)

The exomethylene acetonide (137) (40 mg, 0.18 mmol) was dissolved in acetonitrile (2 ml) together with water (0.25 ml) and trifluoroacetic acid (1 drop). After 30 min, sodium bicarbonate (0.5 g) was added, followed by ether (5 ml) and magnesium sulphate (1 g). After filtration and re-extraction of the residue (ether, 2 x 5 ml), the combined ethereal extracts were concentrated *in vacuo* to give trans-5,5-dimethyl-2 α -hydroxy-1 α -hydroxymethylbicyclo[4.4.0]dec-10,1'-ene (138) (30 mg, 89%); δ 250 MHz (CDCl_3)

5.10 (br, s, 1H), 4.95 (br, s, 1H), 4.15 (dd, J 8.3 and 2.0 Hz, 1H), 3.99 (ddd, J 7.3, 4.2, and 2.6 Hz, 1H), 3.92 (dd, J 8.3 and 6.25 Hz, 1H), 3.79 (d, J 2.6, 1H, D₂O exch.), 3.33 (dd, J 6.25 and 2.0 Hz, 1H, D₂O exch.), 2.40-2.18 (m, 2H), 2.0-1.60 (m, 4H), 1.50-1.20 (m, 4H), 1.10 (m, 1H), 0.83 (s, 3H), and 0.77 (s, 3H); $\nu_{\max}$ (film) 3345, 3090, and 1639 cm^{-1} ; m/e 224 (M^+) 206, 176, and 120.

(63) Preparation of spiro(trans-2 α -Acetoxy-1 α -acetoxymethyl-5,5-dimethylbicyclo[4.4.0]dec-10,2' α -oxiran) (118)

To a stirred solution of the exo-methylenediol (138) (30 mg, 0.13 mmol) and VO (acac)₂⁵² (10 mg) in benzene (2 ml) was added 8% *t*-butylhydroperoxide in benzene (0.5 ml, 0.39 mmol). After 4 h, the solvent was removed *in vacuo* and pyridine (0.1 ml), acetic anhydride (0.05 ml), and *N,N*-dimethylaminopyridine (5 mg) were added. After 10 h, excess reagents were removed *in vacuo* and the residue chromatographed (silica gel, pet. ether to 50:50 ether/pet. ether), to give spiro(trans-2 α -acetoxy-1 α -acetoxymethyl-5,5-dimethylbicyclo[4.4.0]decan-10, 2' α -oxiran) (118) (32 mg, 53%), m.p. 105.5-106°C (ether/pet. ether); δ 250 MHz (CDCl₃) 4.88 (d, J 12.3 Hz, 1H), 4.70 (dd, J 11.4 and 4.75 Hz, 1H), 4.36 (d, J 12.3 Hz, 1H), 2.99 (dd, J 4.0 and 2.4 Hz, 1H), 2.22 (d, J 4.0 Hz, 1H), 2.12 (m, 1H), 2.11 (s, 3H), 1.96 (s, 3H), 1.80-1.25 (m, 9H), 1.04 (m, 1H), 0.90 (s, 3H), and 0.84 (s, 3H); $\nu_{\max}$ (CHCl₃) 2780, 2760, 1730, 1725, 1365, 1260, and 1038 cm^{-1} ; m/e 295 (M^+ -CHO), 282, 251, 221, 209, 204, 191, 179, and 174.6 (M^+ , 209-191) (Found: C, 66.94; H, 8.75; C₁₈H₂₈O₅ requires: C, 66.64; H, 8.75%).

(64) Preparation of 4-Bromobutanal (148)

5-Bromopent-1-ene³⁵ (15 g, 101 mmol) was dissolved in CH₂Cl₂ (200 ml)

cooled to -75°C , and ozone was passed through the solution until a persistent blue colouration was apparent. Excess ozone was removed by flushing with nitrogen and the solution of ozonide thus generated was added dropwise to a stirred mixture of 50% acetic acid (100 ml) and powdered zinc (25 g). After TLC (50:50 ether/pet. ether) showed the absence of ozonide, the reaction mixture was filtered and the residue re-extracted with ether (3 x 150 ml). The combined organic layers were then washed with water (5 x 200 ml), saturated aqueous sodium bicarbonate (care! sufficient to cause neutralisation) and finally, brine (100 ml). Drying, filtration and removal of the solvent *in vacuo* gave 4-bromobutanal (148) (12.1 g, 79%); δ (CDCl_3) 9.80 (t, J 1Hz, 1H), 3.48 (t, J 6 Hz, 2H), 2.60 (m, 2H), and 2.15 (m, 2H); ν_{max} (film) 2812, 2713, 1713, and 1245 cm^{-1} .

(65) Preparation of 2-(1'-3'-Bromopropane)-1,3-dioxalan (146b)

A mixture of 4-bromobutanal (148) (8 g, 53 mmol), ethylene glycol (8 g, 130 mmol) and pTSA (50 mg) were heated to reflux in benzene (140 ml) through a Dean-Stark apparatus until no more water was collected. After cooling, the solution was diluted with ether (200 ml) and washed with saturated aqueous sodium bicarbonate (2 x 50 ml) followed by brine (50 ml). After drying, filtration and removal of the solvent *in vacuo*, the crude dioxalan was distilled, under reduced pressure, to give 2-(1'-3'-bromopropane)-1,3-dioxalan (146 b) (8.8 g, 85%), b.p. $68-70^{\circ}\text{C}/5\text{ mmHg}$; δ (CDCl_3) 4.84 (t, J 4Hz, 1H), 3.82 (m, 4H), 3.40 (t, J 6.5 Hz, 2H), and 1.85 (m, 4H); ν_{max} (film) 2890 and 1135 cm^{-1} ; m/e 194 (M^+), 121, 85, and 73.

(66) Preparation of 4,4-Dimethyl-3-[1'-propane-3'-(2-1,3-dioxalan)]-cyclohexanone (149)

Magnesium (0.22 g, 9.2 mmol) was covered with dry THF (2 ml) under

argon and activated by the addition of 1,2-dibromoethane (80 mg, 0.4 mmol). After the initial vigorous reaction had subsided, 2-(1'-3'-bromopropyl)-1,3-dioxolane (146b) (0.6 g, 3.1 mmol) in dry THF (5 ml) was added dropwise at such a rate that the internal reaction temperature of 30°C was maintained. After all the bromide had been added, the reaction temperature was maintained at 30°C for a further 10 min before being allowed to cool to room temperature. The Grignard solution thus formed was added dropwise to a slurry of copper (I) bromide-dimethylsulphide complex (0.2 g, 1 mmol) in dry ether (6 ml) at -8°C, under argon. After all the Grignard had been added, stirring for a further 5 min completed the formation of the cuprate, as a purple suspension. After cooling to -45°C, a solution of 4,4-dimethylcyclohexanone (0.12 g, 1 mmol) in ether (3 ml) was added. The immediate formation of a yellow precipitate was apparent and after warming to -10°C, the reaction mixture was poured into saturated aqueous ammonium chloride (10 ml) and worked up in the usual manner. Chromatography (silica gel, 40:60 ether/pet. ether) of the crude product gave 4,4-dimethyl-3-[1'-propyl-3'-(2-1,3-dioxolanyl)]-cyclohexanone (149), (0.15 g, 62%); δ 250 MHz (CDCl₃) 4.83 (t, J 9 Hz, 1H), 4.00-3.80 (m, 4H), 2.50-2.32 (m, 2H), 2.27 (m, 1H), 2.05 (dd, J 13.5 and 12.5 Hz, 1H), 1.77-1.40 (m, 7H), 1.35-1.03 (m, 2H), 1.03 (s, 3H), and 1.00 (s, 3H); $\nu_{\max}$ (film) 2862, 1714, 1390, 1368, and 1140 cm⁻¹; m/e 240.1727 (M⁺), 197, 178, 125, 99, 81, and 73 (Calculated for C₁₄H₂₄O₃: 240.1725).

(67) Attempted formation of 5,5-Dimethylbicyclo[4.4.0]dec-1,10-en-2-one (116) using the method of Helquist⁵⁶

A mixture of the acetal (149) (0.1 g, 0.42 mmol), 2.5% HCl (6 drops) and water (0.5 ml) was stirred in THF at R.T. for 10 days. The reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate (3 drops) and the product was extracted into pet. ether (3 x 25 ml). The

combined organic layers were dried, filtered and following removal of the solvent *in vacuo* gave only the known⁴⁵ 4,4-dimethyl-3-(4'-butanal)-cyclohexanone (144), identical by NMR, IR, and TLC to the previous sample.

(68) Preparation of 4 β -(2'-1',3'-Dithiolan)-3-[1'-propane-3'(2-1,3-dioxalan)]-4 α ,5 α -dimethylcyclohexanone (150)

The cuprate derived from the Grignard reagent of 2-(1'-3'-bromopropane)-1,3-dioxalan (146b) (0.6 g, 3.1 mmol), magnesium (0.2 g, 8.3 mmol), and copper (I) bromide-dimethyl sulphide complex (0.2 g, 1 mmol) was prepared in the usual manner at -10°C under argon. After 15 min, the mixture was cooled to -105°C and the enone-dithiolan (69) (0.114 g, 0.5 mmol) in ether (4 ml) was added dropwise over 5 min. An instantaneous colour change (purple to yellow) was apparent and, after slow warming to R.T., the reaction mixture was quenched and worked up in the usual manner. Chromatography of the residue (silica gel, 50:50 ether/pet. ether) gave 4 β -(2'-1',3'-dithiolan)-3-[1'-propane-3'(2-1,3-dioxalan)]-4 α ,5 α -dimethylcyclohexanone (150) (71 mg, 41%) as a 3:7 mixture of 3 β and 3 α isomers; δ 250 MHz (CDCl₃) 5.08 (s, 0.7H), 4.96 (s, 0.3H), 4.84 (t, J 8Hz, 1H), 4.00-3.80 (m, 4H), 3.25-3.15 (m, 4H), 2.60-1.10 (m, 12H), 1.50 (s, 0.9H), 1.08 (s, 2.1H), 1.03 (d, J 6Hz, 2.1H), and 1.02 (d, J 6Hz, 0.9H); $\nu_{\max}$ (film) 1712, 1140, 1030, and 941 cm⁻¹; m/e 344.1478 (M⁺), 316, 271, 238, 105, and 73 (Calculated for C₁₇H₂₈S₂O₃:344.1480).

(69) Preparation of 4 β -(2'-1',3'-Dithiolan)-3-(4'-butan-1-al)-4 α ,5 α -dimethylcyclohexanone (145)

A mixture of the acetal (150) (12.1 mg, 0.035 mmol), 2.5% HCl (2 drops) and water (drops) was stirred in THF at R.T. for 6 days. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (3 drops)

and the product was extracted with pet. ether (3 x 10 ml). The combined organic layers were dried, filtered and, after removal of the solvent *in vacuo*, gave 4 β -(2'-1',3'-dithiolan)-3-(4'-butan-1-yl)-4 α ,5 α -dimethylcyclohexanone (145) (9 mg, 85%) as a 3:7 mixture of 3 α and 3 β isomers, δ 250 MHz (CDCl₃) 9.77 (m, 1H), 4.06 (s, 0.7H), 3.92 (s, 0.3H), 3.25 (m, 4H), 2.6-1.4 (m, 12H), 1.28 (s, 0.3H), 1.07 (s, 0.7H), and 1.03 (d, J 6Hz, 3H); $\nu_{\max}$ (film) 2720 and 1714 cm⁻¹.

(70) Preparation of 4-Bromobutan-1-ol (152)

Ozone was bubbled through a solution of 1-bromopent-4-ene (3 g, 2 mmol) in ethanol (50 ml) at 0°C until TLC (50:50 ether/pet. ether) showed the absence of starting material. The still cold solution was dropped onto a cooled solution of sodium borohydride (0.5 g, 1.33 mmol) in ethanol (25 ml). After the initial vigorous reaction had ceased, the mixture was stirred for a further 5 min, poured into 5% HCl (25 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried and filtered, and removal of the solvent *in vacuo* gave 4-bromobutan-1-ol (152) (2.52 g, 92%); δ (CDCl₃) 3.68 (t, J 6 Hz, 2H), 3.45 (t, J 7Hz, 2H), 3.20 (br, s, 1H, D₂O exch.) and 2.1-1.55 (m, 2H); $\nu_{\max}$ (film) 3340, 1420, 1335, 1250, and 1060 cm⁻¹.

(71) Preparation of 4-Bromo-1-*t*-butyldimethylsilyloxybutane (151) using the method of Corey⁵⁷

A mixture of the alcohol (152) (1.37 g, 10 mmol), *t*-butyldimethylsilylchloride (1.8 g, 12 mmol) and imidazole (1.7 g, 27 mmol) in DMF (3 ml) was stirred at R.T. for 6 h. The reaction mixture was poured into water (10 ml) and extracted with ether (2 x 50 ml). The combined ethereal extracts were washed with water (2 x 20 ml), brine (20 ml) and dried, filtered, and concentrated *in vacuo*. Chromatography (silica gel, pet. ether to 25:75 ether/

pet. ether) of the resultant oil gave 4-bromo-1-t-butyldimethylsilyloxybutane (151) (2.5 g, 94%); δ 3.60 (t, J 6 Hz, 2H), 3.40 (t, J 6 Hz, 2H), 1.95-1.20 (m, 4H), 0.89 (s, 9H), and 0.05 (s, 6H); $\nu_{\max}$ (film) 1470, 1461, 1255, 1100, 835, 775, 710, and 660 cm^{-1} .

(72) Preparation of 4 β -(2'-1',3'-Dithiolan)-3-(4'-1'-t-butyldimethylsilyloxybutane)-4 α ,5 α -dimethylcyclohexanone (153)

The Grignard reagent prepared from the bromide (151) (0.53 g, 2 mmol) and magnesium (62 mg, 2.6 mmol) in ether (10 ml) was added to a stirred suspension of copper (I) bromide-dimethylsulphide complex (0.20 g, 1 mmol) in ether (4 ml) at -10°C under argon. The mixture was stirred for a further 10 min to give a dark brown suspension which was then cooled to -90°C . The enone-dithiolan (69) (0.114, 0.5 mmol) in ether (4 ml) was added dropwise to the cuprate mixture and the reaction was allowed to warm to R.T. over 4 h. After quench and work up in the normal manner, chromatography of the residue (silica gel, 25:75 ether/pet. ether), gave (i) 4 β -(2'-1',3'-dithiolan)-3-(4'-1'-t-butyldimethylsilyloxybutane)-4 α ,5 α -dimethylcyclohexanone (153) (18 mg, 9%) as a 1:1 mixture of 3 α and 3 β isomers; δ 250 MHz (CDCl_3) 5.08 (s, 0.5H), 4.95 (s, 0.5H), 3.60 (t, J 6 Hz, 2H), 3.20 (m, 4H), 2.60-2.05 (m, 5H), 1.90-1.35 (m, 7H), 1.25 (s, 1.5H), 1.08 (s, 1.5H), 1.04 (d, J 6Hz, 1.5H), 1.03 (d, J 6Hz, 1.5H), 0.90 (s, 9H), and 0.05 (s, 6H); $\nu_{\max}$ (film) 2850, 1712, 1250, 1095, 835, and 770 cm^{-1} ; m/e 359 (M^+ - t-butyl), 317, 255, 199, and 159; and (ii) 4 β -(2'-1',3'-dithiolan)-4 α ,5 α -dimethylcyclohex-2-enone (69) (92 mg, 80%), identical to the previous sample.

(73) Preparation of 5-Hydroxypentan-2-one tosylhydrazone (156)

Tosyl hydrazine⁶⁸ (10 g, 54 mmol) was added to a solution of 5-hydroxypentan-2-one (155) (5.5 g, 54 mmol) in methanol (200 ml). 2N HCl (1 drop)

was added and the mixture stirred for 3 h and cooled overnight. The crystalline mass that precipitated was collected and recrystallised from methanol to give 5-hydroxypentan-2-one tosylhydrazone (156) as white needles (13.1 g, 90%), m.p. 119-121°C; ν_{max} (Nujol) 3500, 3050, and 1640 cm^{-1} . (Found: C, 53.19; H, 6.83; N, 10.39; S, 11.51. $\text{C}_{12}\text{H}_{18}\text{N}_2\text{SO}_3$ requires: C, 53.31; H, 6.71; N, 10.36; S, 11.86%).

(74) Preparation of 5-Methyl-4-methylenhexan-1,5-diol (164) using the method of Adlington⁵⁹

A catalytic amount of dry pTSA resin was added to a stirred mixture of 5-hydroxypentan-2-one (155) (0.102 g, 1 mmol) and tri-iso-propylbenzene-sulphonyl hydrazine^{58c} (0.300 g, 1 mmol) in dry ether (10 ml) at R.T. The formation of the hydrazone was followed to completion by TLC (50:50 ether/pet. ether) and after 2 h, the pTSA resin was removed by filtration through a dry sinter. After removal of the solvent *in vacuo*, at R.T., dry toluene (5 ml) was added and again removed *in vacuo* (to azeotrope off water). This cycle was repeated once more to give a yellow oil which was rapidly dissolved in dry 1,2-dimethoxyethane (5 ml). The flask was fitted with a suba-seal, flushed with and subjected to a positive pressure of dry argon and cooled to -78°C. 1.54 M n-Butyl lithium (2.5 ml, 3.85 mmol) was added dropwise to the stirred mixture and after 1.5 ml had been added, a pale yellow colouration (the trianion, 157) began to appear. The reaction mixture was allowed to warm to 0°C over a period of 2 h after which it was recooled to -78°C. The alkoxyvinyl dianion (158) thus formed was quenched by the addition of dry, distilled acetone (0.3 ml, 4 eq.), the reaction mixture then being allowed to warm to R.T. The mixture was poured onto water (20 ml) and extracted into ether (2 x 50 ml). The combined ethereal layers were dried, filtered and the solvent removed *in vacuo* to give a white gum, chromatography of which (silica gel, 50:50 ether/pet. ether) gave, as the slowest

running component, 5-methyl-4-methylenehexan-1,5-diol (164) as a thin oil (30 mg, 21%); δ 4.95 (br, s, 1H), 4.67 (br, s, 1H), 3.50 (t, J 6 Hz, 2H), 3.13 (br, s, 2H, D₂O exch.), 2.35-1.95 (m, 2H), 1.90-1.50 (m, 2H), and 1.32 (s, 6H); $\nu_{\max}$ (film) 3640, 3095, 1640, 1145, and 1058 cm⁻¹; m/e 129 (M⁺-CH₃) and 126 (M⁺-H₂O).

(75) Preparation of 5-t-Butyldimethylsilyloxypentan-2-one tosylhydrazone (166) using the method of Corey⁵⁷

A solution of 5-hydroxypentan-3-one tosylhydrazone (155) (0.54 g, 2 mmol) t-butyldimethylsilyl chloride (0.31 g, 2 mmol), and imidazole (0.14 g, 2 mmol) in dry DMF (4 ml) was stirred at 0°C for 3 h. After pouring into water (10 ml), the product was extracted into ether (2 x 25 ml), dried filtered and the solvent removed *in vacuo*. Recrystallisation (pet. ether) gave 5-t-butyldimethylsilyloxypentan-2-one tosylhydrazone (166) as a mixture of isomers (197 g, 91%), m.p. 82.5-83.5°C; δ (CDCl₃) 8.80 (br, s, 1H), 8.15-7.30 (m, 4H), 3.85-3.45 (m, 2H), 2.65-2.30 (m, 2H), 2.10 (s, 1.5H), 2.00 (s, 1.5H), 2.15-1.70 (m, 2H), 1.20 (s, 4.5H), 1.10 (s, 4.5H), 0.35 (s, 3H), and 0.25 (s, 3H); $\nu_{\max}$ (CHCl₃) 3210, 3170, 1640, 1596, 1255, 1160, 835, 772, and 670 cm⁻¹ (Found: C, 56.23; H, 8.52; N, 7.41. C₁₈H₃₂N₂Si requires: C, 56.21; H, 8.38; N, 7.28%).

(76) Preparation of 2-Chloro-4,4-dimethylcyclohex-2-enone (168)

(a) From 4,4-Dimethylcyclohexenone. A mixture of phenylselenium chloride (0.76 g, 3.95 mmol), pyridine (0.4 ml, 4 mmol) and 4,4-dimethylcyclohexenone (0.124 g, 1 mmol) in dry CH₂Cl₂ (10 ml) under argon, was heated to 37°C for 72 h. After cooling, the reaction mixture was poured into ether (150 ml) and washed with 2.5% HCl (2 x 25 ml), followed by

brine (20 ml). After drying, filtration and removal of the solvent *in vacuo*, the residue was chromatographed (silica gel, pet. ether to 25:75 ether/pet. ether) to give (i) diphenyldiselenide and, (ii) 2-chloro-4,4-dimethylcyclohex-2-enone (168) (0.145 g, 92%), δ (CDCl₃) 6.65 (s, 1H), 2.60-2.50 (m, 2H), 2.00-1.70 (m, 2H), and 1.20 (s, 6H); $\nu_{\max}$ (film) 3010, 1700, 1605, 835, 750, 730, 690, and 650 cm⁻¹; m/e 158.0500 (M⁺), 143, 123, 116, and 81. (Calculated for C₈H₁₁³⁵ClO : 158.0498).

(b) From a mixture of the 2-chloro- and 2-selenophenyl-enones (168) and (169). A 4:3 mixture of the 2-chloro- and 2-selenophenyl²² enones (168) and (169) (100 mg, 0.272 mmol and 0.204 mmol) together with phenylselenium chloride (0.5 g, 2.6 mmol) and dry pyridine (0.3 ml, 3 mmol) in dry CH₂Cl₂ (15 ml) under argon, was stirred at R.T. for 60 h. Work up as above, followed by chromatography (silica gel, pet. ether to 25:75 ether/pet. ether) gave (i) diphenyldiselenide and (ii) 2-chloro-4,4-dimethylcyclohex-2-enone (168) (71.4 mg, 95%) identical to the previous sample.

(77) Preparation of 2-Chlorocyclopent-2-enone (171)

(a) A mixture of phenylselenium chloride (0.76, 3.95 mmol), pyridine (0.4 ml, 4 mmol) and cyclopent-2-enone⁶⁹ (82 mg, 1 mmol) in dry CH₂Cl₂ (10 ml), under argon, was stirred at R.T. for 4 days. Work up as before, followed by chromatography (silica gel, pet. ether to 30:70 ether/pet. ether) gave (i) 4,4-dichloro-2-selenophenylcyclopent-2-enone (176) (41 mg, 14%); δ 250 MHz (CDCl₃) 7.65 (m, 2H), 7.48 (m, 1H), 7.38 (m, 2H), 7.25 (t, J 3Hz, 1H), and 3.32 (d, J 3Hz, 2H); $\nu_{\max}$ (film) 3070, 1734, 1595, 1575, 1338, 1275, 988, 835, 800, 742, and 690 cm⁻¹; m/e 306.9111 (M⁺) 271, 258, 157, 149, and 121 (Calculated for C₁₁H₈O³⁵Cl₂⁸⁰Se: 306.9117) and (ii) 2-chloro-cyclopent-2-enone (171) (42 mg, 36%); δ (CDCl₃) 7.60 (t, J 3Hz, 1H) and 2.75-2.42 (m, 4H); $\nu_{\max}$ (film) 3075, 2912, 1720, 1600, 1570, 1392, 959,

785, 751, and 736 cm^{-1} ; m/e 116 (M^+), 88, 81, and 53.

(b) The reaction was carried out as described above using phenylselenium chloride (0.58 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and cyclopent-2-enone (82 mg, 1 mmol) in CH_2Cl_2 (10 ml), except that the reaction mixture was warmed to 37°C for 48 h. After cooling, work up as before, followed by chromatography (silica gel, pet. ether to 35:65 ether/pet. ether) gave (i) diphenyldiselenide (0.43 g, 91%), and (ii) 2-chlorocyclopent-2-enone (171) (60 mg, 52%) identical to the previous sample.

(78) Preparation of 2-Chlorocyclohex-2-enone (172)

The reaction was carried out in the usual way using phenylselenium chloride (0.58 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and cyclohex-2-enone (96 mg, 1 mmol) at 37°C for 96 h. Work up as before and chromatography (silica gel, pet. ether to 30:70 ether/pet. ether) gave (i) diphenyldiselenide and (ii) 2-chlorocyclohex-2-enone (172) (0.115 g, 88%), m.p. $71\text{--}72^\circ\text{C}$ (pet. ether) (lit., ^{63d} $67\text{--}72^\circ\text{C}$); δ (CDCl_3) 7.12 (t, J 4.5 Hz, 1H), 2.75–2.35 (m, 4H), and 2.30–1.80 (m, 2H); ν_{max} (CHCl_3) 1690, 1609, 1326, 1122, 1008, 970, and 905 cm^{-1} ; m/e 130 (M^+) 102, and 95.

(79) Preparation of 2-Chloro-3-phenyl-2-propenal (173)

The reaction was carried out in the usual manner using phenylselenium chloride (0.58 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and 3-phenyl-2-propenal (0.132 g, 1 mmol) at 37°C for 96 h. Work up and chromatography (silica gel, pet. ether to 30:70 ether/pet. ether) gave (i) diphenyldiselenide and (ii) 2-chloro-3-phenyl-2-propenal (173) (0.166 g, 100%); δ 250 MHz (CDCl_3) 9.47 (s, 1H), 7.92 (m, 2H), 7.53 (s, 1H), and 7.45 (m, 3H); ν_{max} (film) 2840, 1695, 1610, 1575, 1492, 1450, 1121, 760, 690, and 651 cm^{-1} ; m/e

166.0184 (M^+), 165, 138, 135, 103, and 77 (Calculated for $C_9H_7^{35}ClO$: 166.0185).

(80) Preparation of 3-Chloro-4-phenyl-3-butene-2-one (174)

The reaction was carried out in the usual manner using phenylselenium chloride (0.58 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and 4-phenyl-3-butene-2-one (0.149 g, 1 mmol) at 37°C for 7 days. Work-up and chromatography (silica gel, pet. ether to 30:70 ether/pet. ether) gave 3-chloro-4-phenyl-3-butene-2-one (174) (152 mg, 84%); δ 250 MHz ($CDCl_3$) 7.85 (m, 2H), 7.76 (s, 1H), 7.43 (m, 3H), and 2.56 (s, 3H); ν_{max} (film) 1686, 1608, 1596, 1574, 1490, 1448, 1360, 1230, 758, and 690 cm^{-1} ; m/e 180.0346 (M^+) 179, 165, 145, 137, and 102 (Calculated for $C_{10}H_9^{35}ClO$: 180.0342). DNP (ethanol) m.p. 217-218°C (lit., ^{63}C 218-219°C).

(81) Preparation of 2-Chloro-2-butenal (175)

The reaction was carried out in the usual manner using phenylselenium chloride (0.58 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and 2-butenal (70 mg, 1 mmol) at R.T. for 12 h. After work up in the normal manner, complete reaction was indicated by TLC, NMR, and IR. However, after chromatography (silica gel, pet. ether to 25:75 ether/pet. ether) only a small amount of 2-chloro-2-butenal (175) (15.6 mg, 15%) was isolated; δ ($CDCl_3$) 9.32 (s, 1H), 6.90 (q, J 7 Hz, 1H), and 2.10 (d, J 7 Hz).

(82) Preparation of 2-Bromocyclopent-2-enone (182)

The reaction was carried out in the usual manner using phenylselenium bromide²⁴ (0.345 g, 1.5 mmol), pyridine (0.3 ml, 3 mmol) and 2-selenophenylcyclopent-2-enone (181) (50 mg, 0.6 mmol) at 37°C for 72 h. Work up and

chromatography (silica gel, petrol to 50:50 ether/pet. ether) gave (i) diphenyldiselenide and (ii) 2-bromocyclopent-2-enone (182) (37 mg, 52%), m.p. $38.5-39^{\circ}\text{C}$ (pet. ether) (lit.^{63a} $38.5-39^{\circ}\text{C}$); δ (CDCl_3) 7.65 (t, J 3Hz, 1H) and 2.65-2.40 (m, 4H); $\nu_{\text{max}}(\text{film})$ 1720, 1590, 1390, 935, 782 and 745 cm^{-1} .

(83) Preparation of 2-Bromocyclohex-2-enone (177)

The reaction was carried out in the usual manner using phenylselenium bromide (0.575 g, 2.5 mmol), pyridine (0.25 ml, 2.5 mmol) and cyclohex-2-enone (96 mg, 1 mmol) at R.T. for 24 h. Work up in the usual way and chromatography (silica gel, pet. ether to 50:50 ether/pet. ether) gave (i) diphenyldiselenide and (ii) 2-bromocyclohex-2-enone (177) (0.175 g, 100%) m.p. $75-76^{\circ}\text{C}$ (pet. ether) (lit.^{63b} 74°C); δ (CDCl_3) 7.23 (t, J 4.5 Hz, 1H), and 2.70-1.95 (m, 6H).

(84) Preparation of 2-Bromo-3-phenyl-2-propenal (178)

The reaction was carried out in the normal manner using phenylselenium bromide (0.69 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and 3-phenyl-2-propenal (0.132 g, 1 mmol). Work up and chromatography (silica gel, pet. ether to 30:70 ether/pet. ether) gave (i) diphenyldiselenide and (ii) 2-bromo-3-phenyl-2-propenal (178) (0.180 g, 85%), m.p. $71.5-72^{\circ}\text{C}$ (pet. ether/ether) (lit.^{63e} $72-73^{\circ}\text{C}$); δ 250 MHz (CDCl_3) 9.23 (s, 1H), 7.98 (m, 2H), 7.89 (s, 1H), and 7.48 (m, 3H); ν_{max} (KBr) 2810, 2760, 2700, 1680, 1600, 1441, 1284, 1105, 871, 755, 690, and 680 cm^{-1} .

(85) Preparation of 3-Bromo-4-phenyl-3-buten-2-one (179)

The reaction was carried out in the usual manner using phenylselenium bromide (0.69 g, 3 mmol), pyridine (0.3 ml, 3 mmol) and 4-phenyl-3-buten-2-

one (0.149 g, 1 mmol) at 37°C for 6 days. Work up in the usual way and chromatography (silica gel, pet. ether to 25:75 ether/pet. ether) gave (i) diphenyldiselenide, (ii) 3-bromo-4-phenyl-3-buten-2-one (179) (0.116 g, 52%); δ (CDCl₃) 7.92 (s, 1H), 7.75 (m, 2H), 7.30 (m, 3H), and 2.52 (s, 3H); $\nu_{\max}$ 1680, 1600, 1588, 1220, 1695, 750, and 690 cm⁻¹; m/e 224 (M⁺), 223, 209, 181, 145, and 102; and (iii) 3-selenophenyl-4-phenyl-3-buten-2-one (61 mg, 20%); δ (CDCl₃), 7.80 (s, 1H), 7.75-7.00 (m, 10H), and 2.30 (s, 3H).

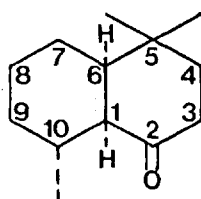
(86) Preparation of 2-Bromo-2-butenal (180)

The reaction was carried out in the usual manner using phenylselenium bromide (0.575 g, 2.5 mmol), pyridine (0.25 ml, 2.5 mmol) and 2-butenal (70 mg, 1 mmol) at R.T. for 24 h. After work up in the normal manner, complete reaction was indicated by TLC, NMR, and IR. However, after chromatography (silica gel, pet. ether to 25:75 ether/pet. ether) only a small amount of 2-bromo-2-butenal (180) was isolated (8 mg, 5%); δ (CDCl₃) 9.15 (s, 1H), 7.2 (q, 6Hz,) and 2.15 (d, J 6 Hz, 3H); $\nu_{\max}$ (film) 2815, 2712, 1700, 1611, 1160, 815 and 640 cm⁻¹.

APPENDIX

THE USE OF INDOR IN STRUCTURE DETERMINATION

The analysis of structure (105) by high field NMR



(105)

In order to provide a greater insight into the exact mechanism of the selenium-mediated cyclisation reaction⁷¹, it was of considerable importance to discover both the stereochemical nature of the ring junction and the relative stereochemistry of the 10-methyl group in the rigid substituted decalone (105). Prior to obtaining the high field (250 MHz) ¹H NMR spectrum, it was hoped that protons H₁, H₆, and H₁₀ would all give separate, well defined resonances and thus merely by a determination of the coupling constants, J_{1,6} and J_{1,10}, it would prove possible to define the complete relative stereochemistry.

However, at 250 MHz, the spectrum indicated that the resonances due to protons H₁ and H₁₀ were superimposed and consequently the coupling constant between them could not be determined by simple means. Even more of a problem was that the resonance due to proton H₆ was buried in an envelope of other resonances. Simple proton-proton decoupling experiments did not provide much useful information and we did not anticipate that nOe techniques⁵³ or lanthanide shift reagents⁷² would prove particularly successful. Consequently we resorted to higher field ¹H NMR in the hope that, at 400 MHz, a simplification of the problem might occur.

The full ^1H 400 MHz spectrum is shown in spectrum 2 together with the expansions, spectra 3 (a, b, and c). It was disappointing to note that once again two protons gave overlapping resonances at δ 2.51 (spectrum 3a), corresponding to H_1 and H_{10} . Equally annoying was the absence of any clear resonance assignable to H_6 . In fact, of thirteen ring protons, only four show resonances completely independent of other signals. Of these, the two at δ 2.38 and 2.23 (spectrum 3a) were assignable on the basis of chemical shift to the methylene protons alpha to the carbonyl group, $\text{H}_{3\alpha}$ and $\text{H}_{3\beta}$. The resonance centered at δ 2.38 shows two large coupling constants of (ignoring the relative signs) 14.75 and 13.75 Hz, together with one medium coupling constant of 6.75 Hz and a small one of 1.0 Hz. The longest coupling constant (14.75 Hz) can be assigned to a geminal interaction. In fact, here the sign should be negative but its amplitude is indicative of geminal coupling alpha to a carbonyl moiety⁴². Thus, the next largest constant, 13.75 Hz, must be due to an axial-axial interaction⁴² and the medium constant (6.75 Hz) is most reasonably due to an axial-equatorial interaction⁴². Hence the resonance at δ 2.38 must be due to the proton $\text{H}_{3\text{ax}}$. For the moment, the small coupling constant must be regarded as a long range effect with no apparent use in the structural assignment. However, it does become important later.

Similarly, the resonance centered at δ 2.23 (spectrum 3a) can only be due to $\text{H}_{3\text{eq}}$. The large coupling constant being (-) 14.75 Hz (to $\text{H}_{3\text{ax}}$), followed by an equatorial-axial coupling constant (5.0 Hz) and, finally, by one due to an equatorial-equatorial arrangement (2.0 Hz)⁴². Simple decoupling at 250 MHz confirmed that the resonances at δ 2.38 and 2.23 were mutually coupling with $J = (-) 14.75$ Hz.

Of the two remaining non-overlapping resonances, only one at δ 1.38 (spectrum 3b) was immediately assignable. The signal appears as a quartet of triplets with coupling constants of 13.0 Hz and 4.0 Hz respectively and thus, the proton involved must be coupled to five other protons within 2

or 3 bonds - 4 bond interactions would not in this system be so large⁴². The proton responsible must therefore be on carbon-8. Of the two possible protons, only the axial one can show three large coupling constants (one geminal and two axial-axial) and two small (axial-equatorial) coupling constants. Thus, the resonance at δ 1.38 can only be due to H_{8ax} .

The final non-overlapping resonance, at δ 0.85 (spectrum 3c) was at this stage unassignable, however, coupling constants of 13.0, 13.0, 13.0 and 3.75 Hz were apparent.

In summary, so far only three out of the thirteen ring protons could be assigned on the basis of the simple 400 MHz spectrum, none of which helped in the determination of the relative configurations.

In view of recent advances in the technique of FT INDOR spectroscopy^{73,74} it seemed likely that this method might prove useful. Since the technique has not been extensively used and its theory is not commonly understood, some exploration of method and its theory is necessary before the results can properly be discussed.

Continuous wave INDOR (INternuclear DOuble Resonance) spectroscopy has been used since the late 1960s^{75,76} and the theory behind it has been well defined^{77,78}. However the Fourier Transform (FT) equivalent of this technique has only recently been described^{73,74}. Moreover, it is only with the most modern commercial FT spectrometers that the method can be used to its fullest potential and consequently, very few examples have been described in the literature^{73,74,79}. The basic theory is similar to that for CW INDOR spectroscopy^{77,78} but a definitive treatment is highly complex and far beyond the scope of what is required here. Instead a simple visualisation of the INDOR effect should suffice.

If one considers a coupled, 2-spin AX system, then the transformed spec-

trum shows four lines corresponding to the four transitions between the four different spin states. Diagrammatically, this is shown in Figure 10 (below) where P_1 to P_4 are the equilibrium (Boltzmann) populations and A_1 , A_2 , X_1 and X_2 are the transitions between the spin states.

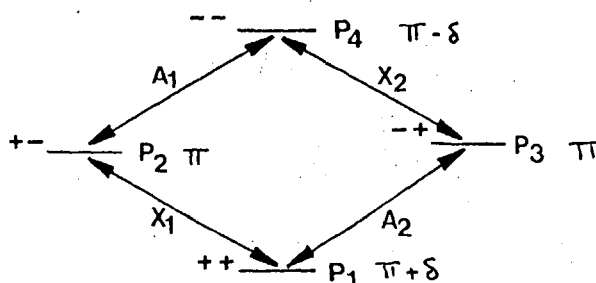


Figure 10

In the unperturbed situation, $P_2 \approx P_4$ and so we can write the spin populations as $P_2 = P_3 = \Pi$, $P_1 = \Pi + \delta$ and $P_4 = \Pi - \delta$ (where δ corresponds to some fraction of Π). Since the intensity of a transition is proportional to the population difference between the two spin states involved, then initially all four transition intensities are proportional to δ and the spectrum observed is as shown in Figure 10a, where all lines are equal in intensity.

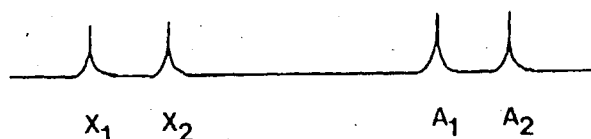


Figure 10a

If a second selective radiofrequency now saturates the transition X_1 , for example, it equalises the population P_1 and P_2 and, in the absence of other effects, the population diagram would become:

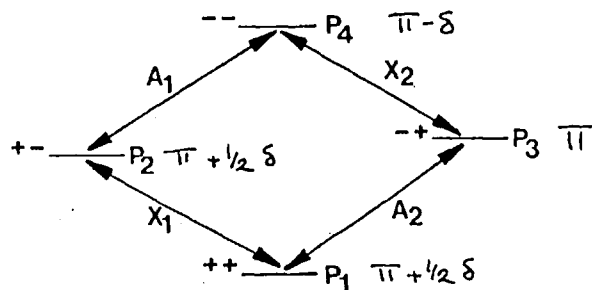


Figure 11

and so the transformed spectrum would appear as shown in Fig. 11a.

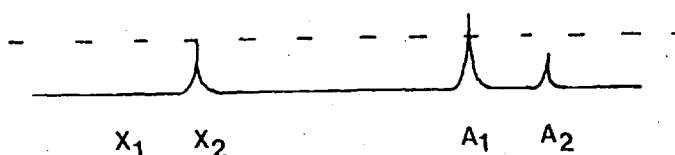


Figure 11a

In fact, this is not what is observed, instead, the system tries to regain it's equilibrium (Boltzmann) population ratio by "leakage" of spin population between the different spin states. This cannot occur for P_1 and P_2 (as X_1 is saturated). However, it can to some extent occur for P_3 and P_4 . Since the saturating pulse decreases P_1 , then P_3 will be decreased by leakage (into P_1), and similarly as P_2 has been increased, P_4 will also increase. The net effect is that the observed spectrum would be as shown in Figure 12a.

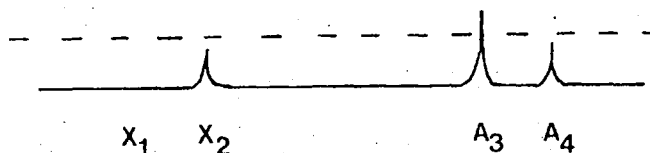


Figure 12a

This simple treatment is complicated by P_3 and P_4 trying to maintain the Boltzmann population distribution between themselves, but overall, there is a decrease in the intensity of X_2 . Thus, in the difference mode, when the unperturbed spectrum is subtracted from the INDOR spectrum, what

is observed in shown in Figure 13a.

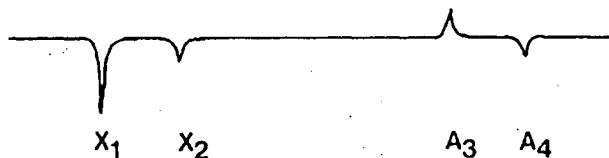


Figure 13a

If the whole experiment is now repeated for X_2 , the the difference mode spectrum becomes:

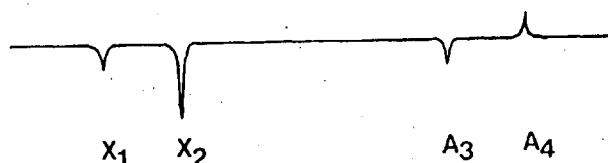


Figure 14a

Thus, the phase change between the two experiments can be used to help separate real INDOR effects from those merely due to incomplete cancellation of unrelated resonances when the difference spectrum is obtained.

The use of the technique is now apparent. If two protons are mutually coupled, but one of the resonances is enveloped (and consequently undefinable) in a complex multiplet which is not coupled to the observable resonance, then by setting a weak radio frequency to impinge upon one transition of the observable resonance, then the FT INDOR difference spectrum will show only the coupled resonances. Thus, the overall effect is similar to the conventional decoupling difference spectrum, in that the FT INDOR spectrum shows only transitions connected (*via* the coupling constant) to the selectively irradiated transition. However, FT INDOR has the added advantage that only one line of multiplet need be irradiated instead of the whole multiplet. This special feature was used with effect in the final assignment of compound (105).

An excellent example of the FT INDOR technique was provided by placing

the saturating field on one of the transitions in the resonance centered at δ 2.23. Irradiation of the high-field transition leads to the FT INDOR spectra shown in 4(a, b, and c). Thus, the resonance at δ 2.38 appears (4a) and it is possible to measure all four coupling constants directly. The power of the technique is highlighted by further examples. For instance, spectrum 4c shows nothing but signals due to incomplete cancellation effects (see below), but spectrum 4b shows resonances at δ 1.81 and 1.50 (together with a signal at δ 1.24, again due to incomplete cancellation effects). Again, not all the transitions appear and, in this case, not all the coupling constants can be measured. However, spectra 4(a, b, and c) together show that the resonance at δ 2.23 is coupled to the resonances at δ 2.38, 1.81 and one of the resonances at δ 1.50 and no others.

In the next experiment, the selective irradiating frequency was placed at the low field transition of the same resonance. Consequently, although the same resonances show up in the FT INDOR difference spectrum, the INDOR effect is confirmed by the change in phase within those resonances genuinely involved.

When the selective pulse was placed on a transition of what had now been shown to be a multiplet at δ 1.81, the resultant FT INDOR spectrum (this time using a 90° non-selective pulse) (spectra 5) shows resonances at (5a) δ 2.38 and 2.23, with all transitions present and thus all the coupling constants can be obtained. Similarly, 5b shows apart from the position of the original resonance at δ 1.81, a resonance at 1.50 and again all the coupling constants are apparent. However, it is interesting that this resonance appeared as a doublet of doublets of triplets. This resonance had been assigned to proton H_{4eq} (with three expected coupling constants). Thus, three were readily assigned as geminal to H_{4ax} (J (-)13.5 Hz), equatorial-axial to J_{3ax} (J 6.75 Hz) and equatorial-equatorial to J_{3eq} (J 2.0 Hz), leaving one unexplained coupling constant of 2.0 Hz. The reason for this coupling was not immediately apparent and only later became clear, when the structural assignment had been completed.

By means of the two illustrated FT INDOR spectra, together with several others, all the chemical shifts and coupling constants assignable to protons on carbons 3 and 4 had been found and assigned as shown in Fig. 15 and Table 6.

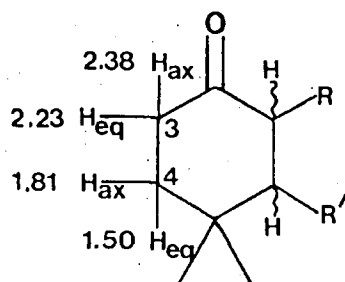


Figure 15

TABLE 6

PROTON	RESONANCE POSITION	COUPLING CONSTANTS (Hz, ($\pm$) 0.125)
H _{3ax}	2.38	(-) 14.75, 13.75, 6.75, 1.0
H _{3eq}	2.23	(-) 14.75, 5.0, 2.0
H _{4ax}	1.81	(-) 13.5, 13.5, 5.0
H _{4eq}	1.50	(-) 13.5, 6.75, 2.0, 2.0

It was noticed that, in contrast to previous observations⁴², the equatorial protons appeared to resonate at higher field than the axial ones. Consequently a note of caution had to be introduced at this stage.

When beginning the assignment of the protons on ring B, the lack of heteroatom functionality meant that little could be predicted in terms of expected chemical shift. In view of the number of overlapping resonances, extensive use of the FT INDOR technique, together with several decoupling experiments, had to be employed in order to determine the correct assignment.

The resonance due to H₁₀ can readily be shown free of overlap from the

H_1 resonance by means of an FT INDOR spectrum with the selective saturation pulse impinging on the doublet methyl resonance at δ 0.94 (spectrum 3c). The spectrum thus generated shows only the H_{10} resonance at δ 2.51 while spectrum 6 shows this response in its original form together with a resolution enhanced signal and a 'power spectrum' of the 'resolution enhanced' signal. Unfortunately, due to the complexity of this signal, a complete analysis of the coupling constants was not possible and thus, its assignment as axial or equatorial was not yet possible.

Having now confirmed that the low field multiplet was due to H_1 and H_{10} , simultaneous decoupling of both these protons was possible and, in theory (ignoring small long range effects) the only protons on ring B which should have been affected were therefore those on C-6 and C-9, together with those of the doublet methyl resonance at δ 0.94. Thus, when the experiment was carried out, it was observed that the resonances at δ 1.77, 1.66, 1.26 and possibly that at δ 1.50 (together with those of the doublet methyl group at δ 0.94) became simplified. Unfortunately, it was not possible to use the "difference decoupling" technique which would have made the interpretation of these results much easier. Instead, a careful visual comparison with the undecoupled spectrum had to be employed. It was noted that any change in the resonance at δ 1.50 was only minor. Again, the meaning of this became clear later. Now, FT INDOR, with the selective pulse placed on the resonance at δ 1.38 (H_{8ax}) should show only protons on C-7,8 and 9 and combining the results of several such spectra with the selective pulse placed on different transitions of the multiplet, it was clear that H_{8ax} was coupled to the protons resonating at δ 1.66, 1.50 (only one of the two protons resonating here, the other being H_{4eq}), 1.26, 0.85 and probably also to the proton whose resonance position was at δ 1.70. Comparing the results of the decoupling and FT INDOR experiments the resonance at δ 1.77 must therefore be due to H_6 .

An additional bonus of the FT INDOR technique then began to emerge. As described earlier, selective irradiation of one transition in a resonance alters the intensity of transitions in other coupled resonances. However, it also alters the intensities of the transitions in the original resonance. Thus, by irradiating one clear transition that shows through superimposed resonances and then inverting the usual FT INDOR difference spectra (at a higher attenuation), it is possible to show only the resonance of which the selective irradiated transition is a part. Spectrum 7 shows the result of such a process. The upper trace shows part of the normal spectrum, while the lower trace shows the inverted FT INDOR difference spectrum caused as a result of placing the selective pulse as shown. It should be noted, of course, that the protons coupled to H_6 are shown, but at this attenuation they are of a much smaller intensity. Spectrum 8, shows the H_6 resonance after resolution enhancement, together with the high field (δ 1.1-0.70) portion of the normal spectrum for comparison. It is possible to measure each of the four coupling constants on H_6 and, taken together with the usual FT INDOR spectrum, assignments can be made.

That this proton shows on one large (vicinal) coupling constant must mean that the decalone is cis-fused. If it were trans-fused then H_6 would show 2 large (≈ 13 Hz) coupling constants, one to H_{7ax} (as here) and one to H_1 . Thus, the ring junction can now be properly assigned as cis-leaving only the stereochemistry of the secondary methyl group to be determined.

The normal FT INDOR spectrum corresponding to spectrum 7 shows that the coupling constant to H_1 was 5 Hz, and also that H_6 was coupled to the proton resonating at δ 0.85. This meant that this high field resonance must be due to a proton on C_7 . From spectrum 3(c), if one ignores the small impurity peaks, it is clear that the coupling constants are 13.0, 13.0, 13.0, and 3.75 Hz. Hence this resonance can only be due to H_{7ax} .

FT INDOR at this high field resonance showed interactions with the resonances at δ 1.77 (H_6), 1.70, 1.50, and 1.38 (H_{8ax}). Similarly, decoupling the resonance at δ 0.85 showed significant simplifications at δ 1.77 (H_6), 1.70 and 1.38 (H_{8ax}). The absence of any noticeable simplification of the resonance at δ 1.50 suggested that this interaction was much smaller than the other three, that is, axial-equatorial, rather than axial-axial (to H_6 and H_{8ax}) or geminal (to H_{7eq}). Hence, the resonance at δ 1.50 is probably due to H_{8eq} . This was confirmed by other FT INDOR experiments. For example, the resonance at δ 1.50 showed up when the selective pulse was placed at δ 1.38 (H_{8ax}). This meant that the resonance at δ 1.70 could now be definitely assigned to H_{7eq} .

The result so far then is that all the ring proton resonances except the two at δ 1.66 and 1.26 can be assigned and that these two must be due to either H_{9ax} or H_{9eq} . As before, inversion of the normal FT INDOR spectrum as shown in spectrum 9, with the selective pulse on one of the transitions in the resonance at δ 1.66, showed only this resonance (together with the small but still apparent interproton effects at δ 1.50, 1.38, and 1.26). Measurement of the coupling constants gave values of $J = 13.0, 13.0, 4.75$, and 4.75 Hz. Thus, this resonance must therefore be due to H_{9ax} , and what is more, the presence of only a geminal and one axial-axial interaction (to H_{8ax}) shows that H_{10} must be equatorial and so defines the orientation of the C-10 methyl group as axial.

The assignment of the resonance at δ 1.26 as being due to H_{9eq} follows, and was confirmed by other FT INDOR experiments. Most of the coupling constants on this proton could be measured from the resolution enhanced spectrum obtained with the multiplet at δ 2.51 decoupled.

Several further FT INDOR difference and decoupled spectra were recorded and aided the confirmation of the assignments as did a partially relaxed

spectra, which because of the differential relaxation rate of methylene and methine protons in a rigid system⁸⁰, showed only the methine proton resonances at δ 2.51 and 1.77.

A complete list of the connectivities shown by FT INDOR and decoupling spectra are given below, together with the complete spectral assignment.

CONNECTIVITIES SHOWN BY FT INDOR

RESONANCE OF IRRADIATED TRANSITION	RESONANCES APPARENT IN THE FT INDOR SPECTRUM
2.23	2.38, 1.81, 1.50*
1.81	2.38, 2.23, 1.50*
1.77	2.51, 0.85, 1.26 [†]
1.66	2.51, 1.50 [†]
1.38	1.66, 1.50*, 1.26, 0.85
1.26	1.66, 1.50, 1.38, 1.70 [†]
0.96	2.51*
0.85	1.77, 1.70, 1.50, 1.38

* Only one of two overlapping resonances showing

[†] Possible intraction

CONNECTIVITIES SHOWN BY DECOUPLING

POSITION OF DECOUPLER	RESONANCES DECOUPLED
2.51	1.77, 1.60, 1.50, 1.26, 0.96
1.70	2.51, 1.26, 0.84
1.66	
0.85	1.77, 1.70, 1.38

ASSIGNMENT

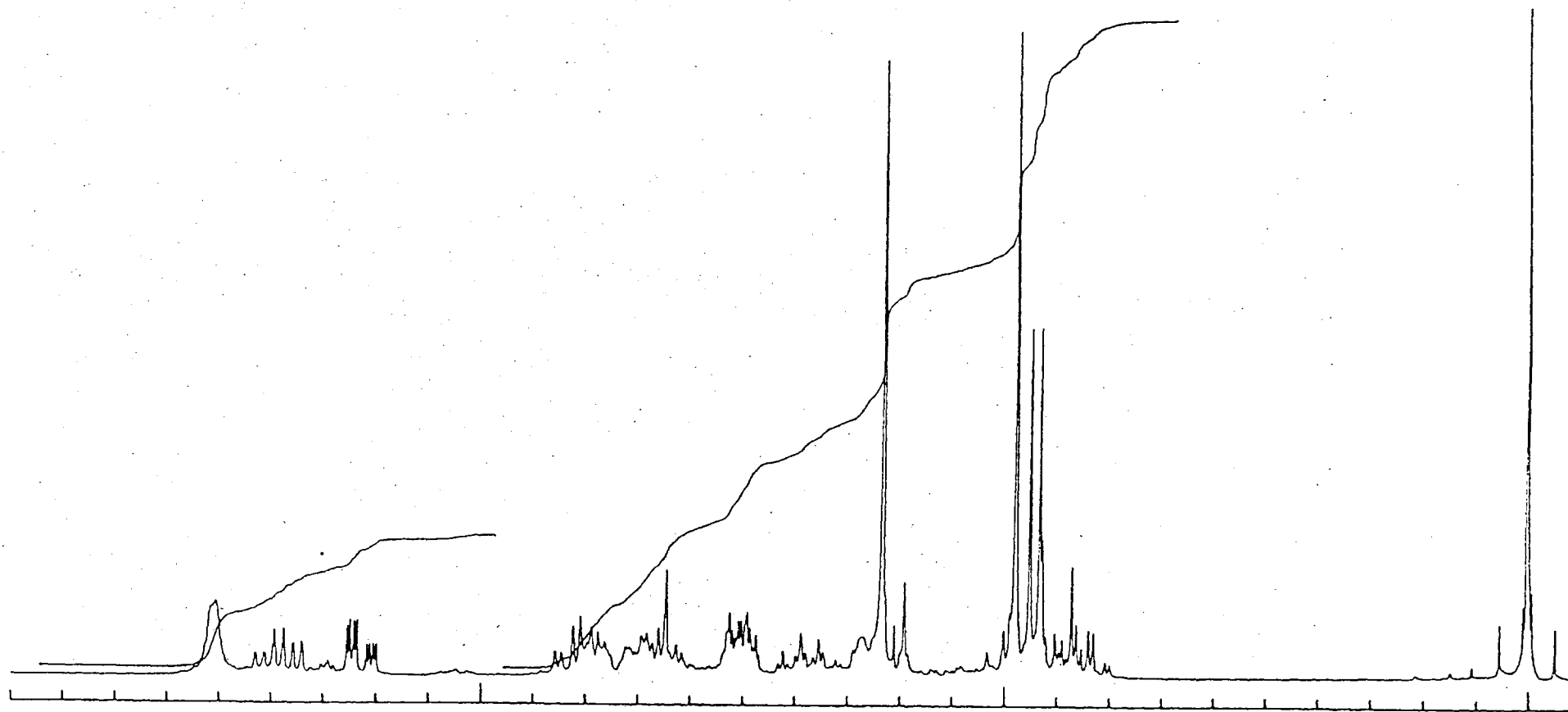
PROTON	RESONANCE	COUPLING CONSTANT
1	2.51	5.0, ?
3 _{ax}	2.38	(-) 14.75, 13.5, 6.75, 1.0
3 _{eq}	2.23	(-) 14.75, 5.0, 2.0
4 _{ax}	1.81	(-) 13.5, 13.5, 5.0
4 _{eq}	1.50	(-) 13.5, 6.75, 2.0, 2.0
6	1.77	13.0, 5.0, 2.75
7 _{ax}	0.85	(-) 13.0, 13.0, 13.0, 3.75
7 _{eq}	1.70	(-) 13.0, 3.25, 3.25, 3.25, 1.5
8 _{ax}	1.38	(-) 13.0, 13.0, 13.0, 4.0, 4.0
8 _{eq}	1.50	(-) 13.25, 4.0, 3.0, 3.0, ?
9 _{ax}	1.66	(-) 13.25, 13.25, 4.75, 4.75
9 _{eq}	1.26	(-) 13.25, 4.0, 2.6, 1.5, ?
10	2.51	7.5, 7.5, 7.5, 4.75, ?, ?, ?

Clearly, it was not possible to measure all the coupling constants, although those that are missing are not crucial to the assignment of stereochemistry.

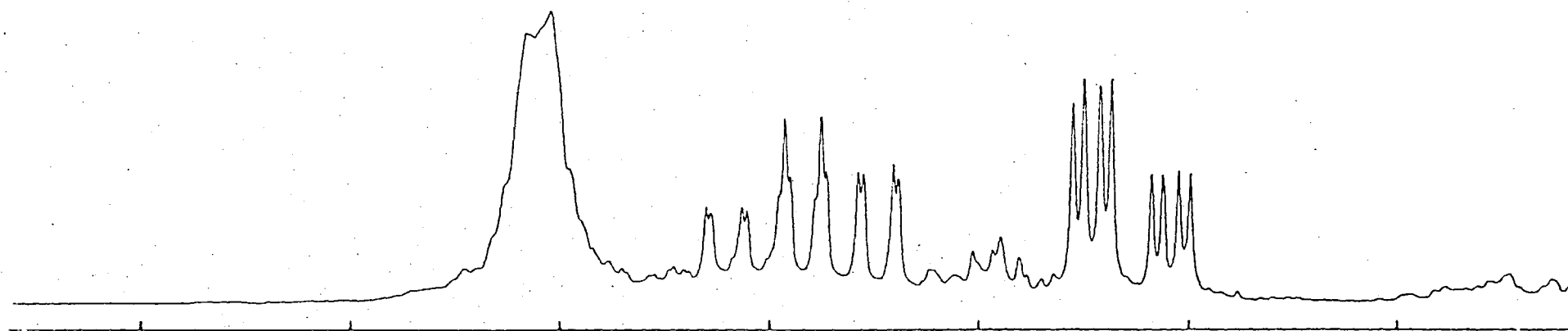
From a study of a molecular model of the compound (105), it was possible to explain some of the coupling connectivities that had until this stage proven misleading. For example, it had not been expected that FT INDOR with the selective pulse at δ 1.26 (H_{9eq}) would show a connectivity to the resonance at δ 1.70 (H_{7eq}), while similarly, decoupling at δ 2.51 had not been expected to cause a simplification at δ 1.50 (H_{8eq}). From the model, it is apparent that these effects are due to long range, W-type, coupling⁴², of which there are at least two ($H_{4eq}-H_6$ and $H_{7eq}-H_{9eq}$) and possibly two more ($H_{8eq}-H_{10}$ and $H_{9eq}-H_1$) ! The "extra" coupling constant on

H_{3ax} is probably due to a 4-bond coupling through the carbonyl system to H_1 . Such effects are known⁴² and explanations have been given. The large number of couplings into protons H_1 and H_{10} explain the complexity of the resonances due to these protons.

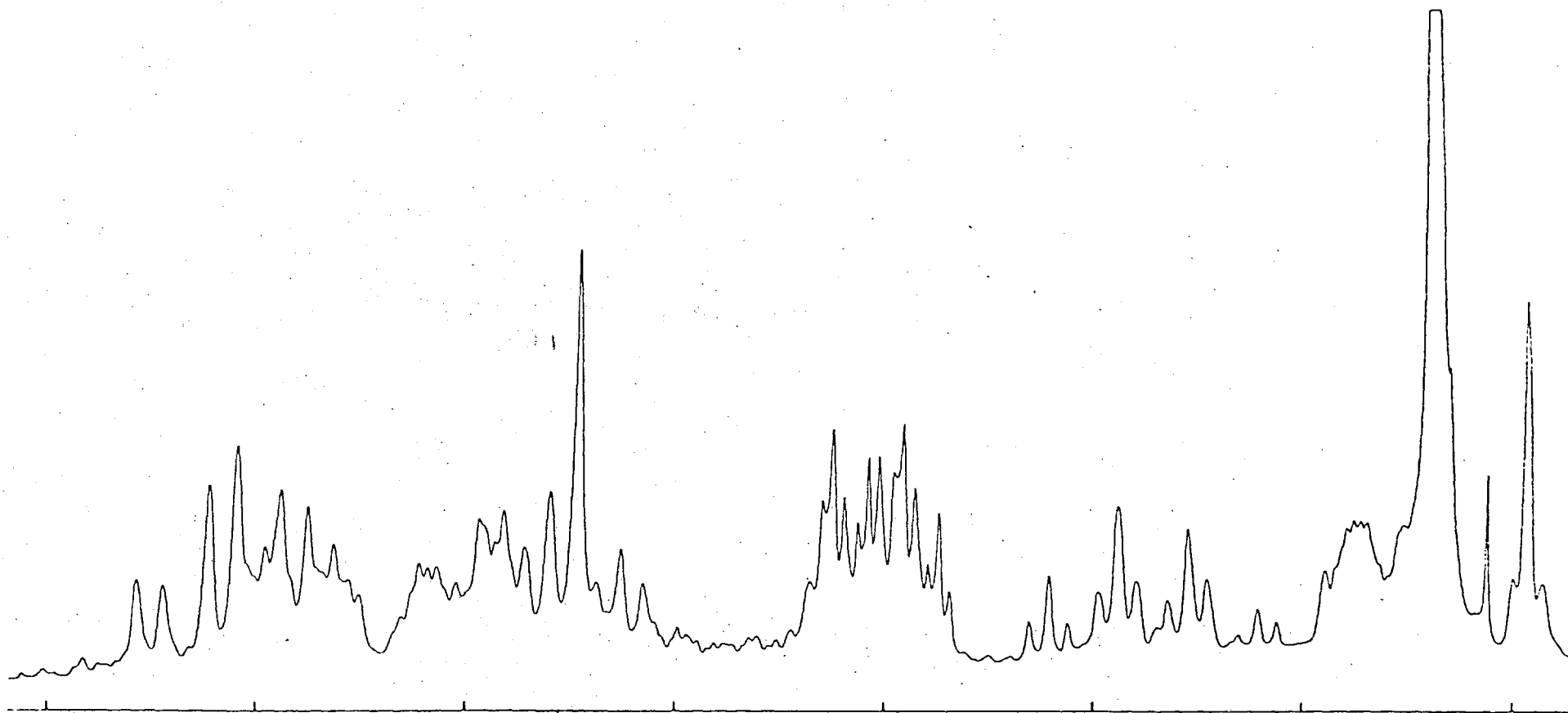
Finally, extensive use was made of computer-aided spectral simulation techniques and while the spectra thus generated are not reproduced here, they provided a useful confirmation of the final assignments.



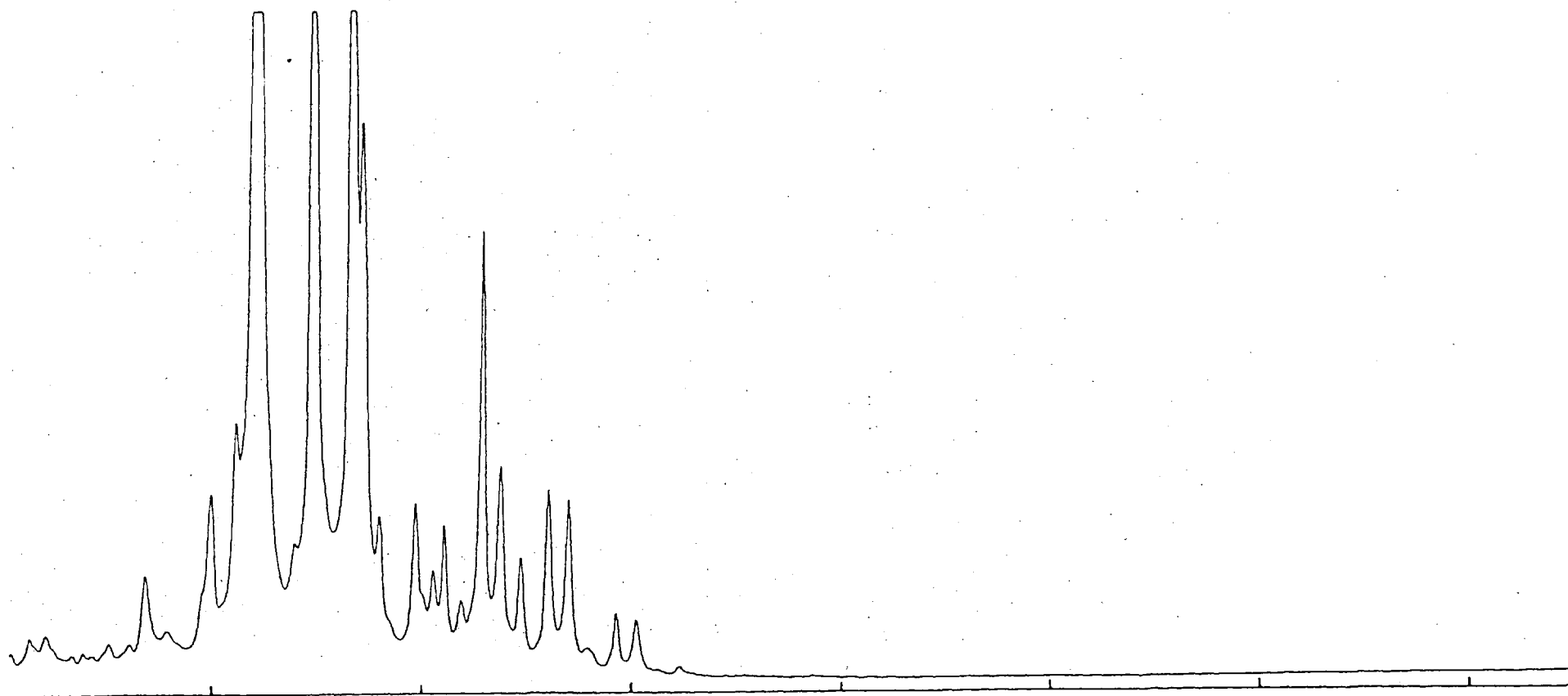
Spectrum 2



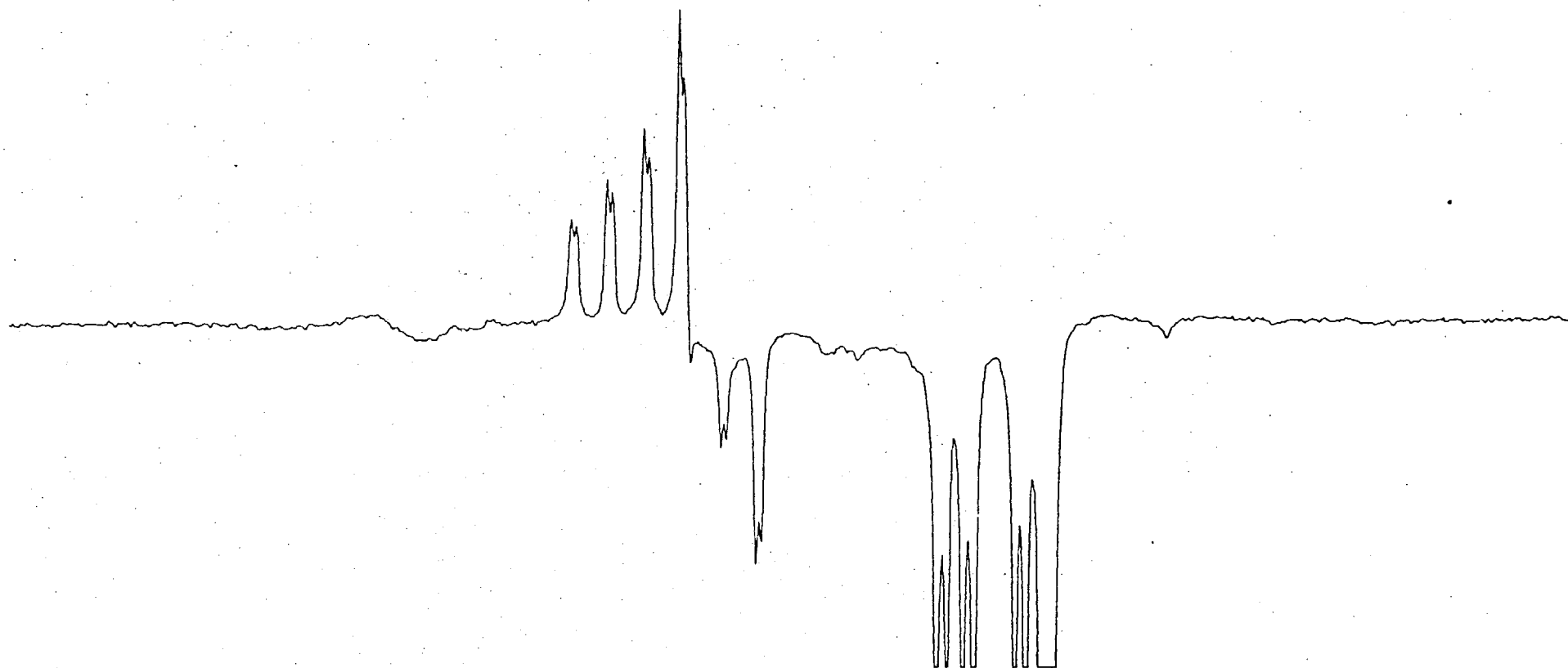
Spectrum 3a



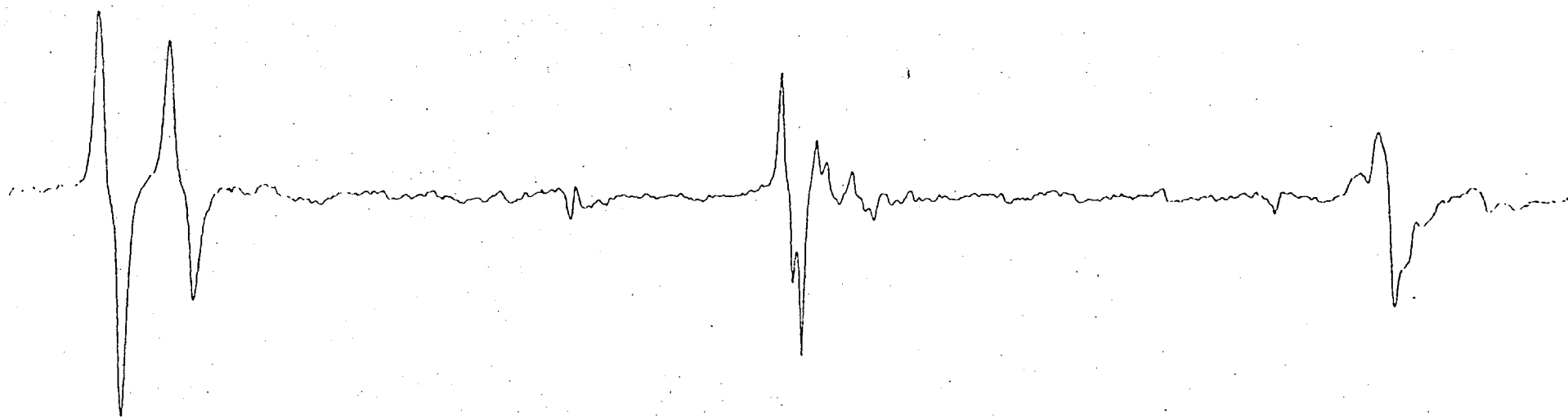
Spectrum 3b



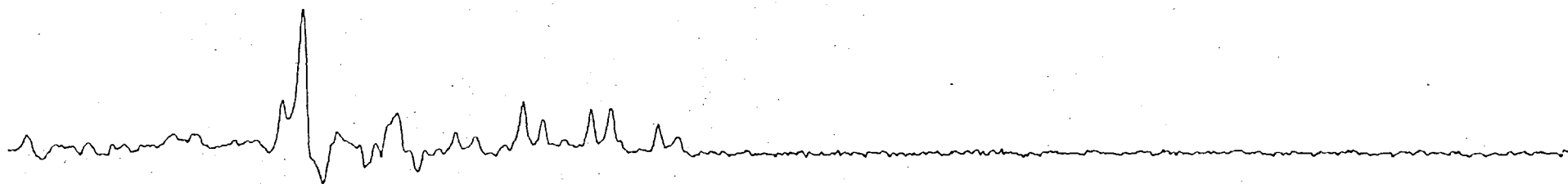
Spectrum 3c



Spectrum 4a



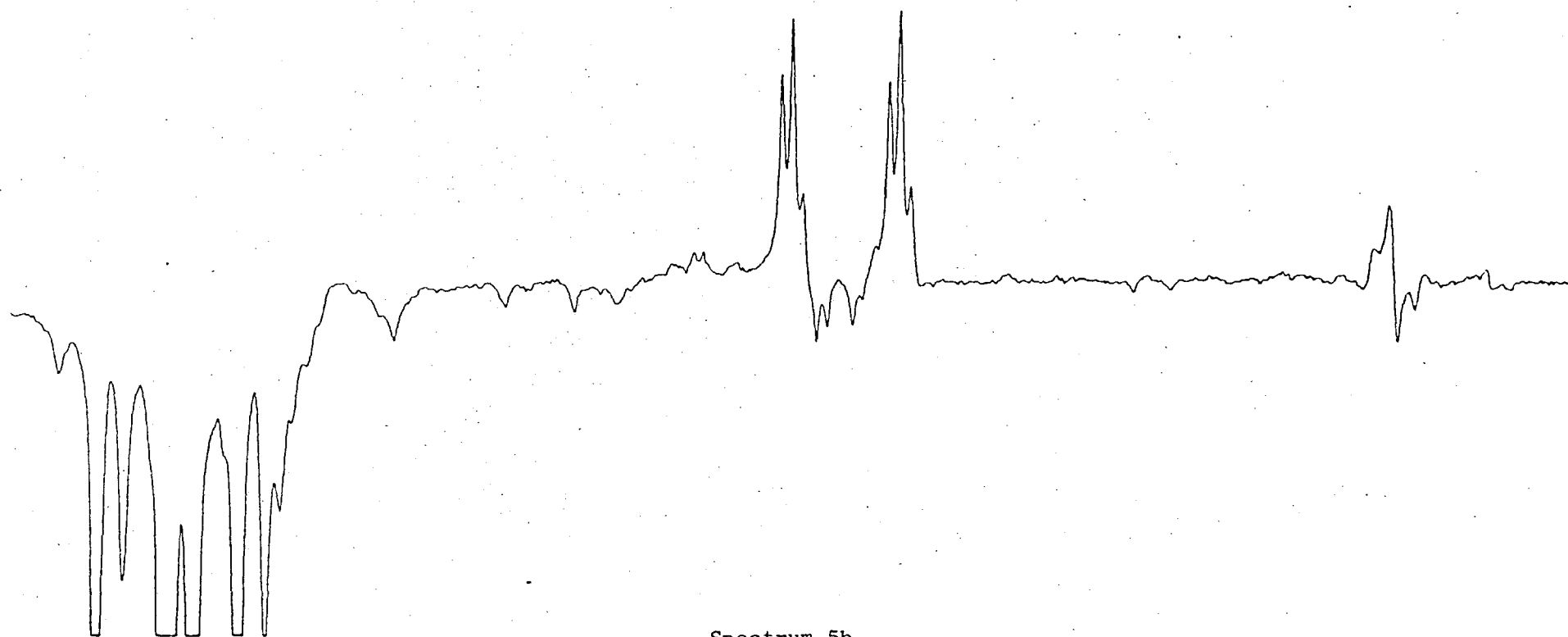
Spectrum 4b



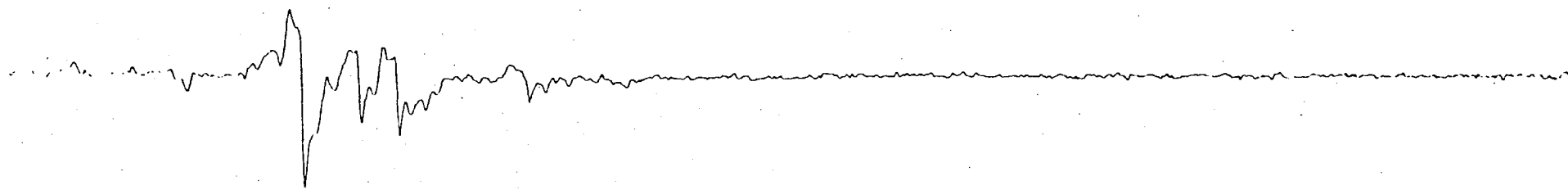
Spectrum 4c



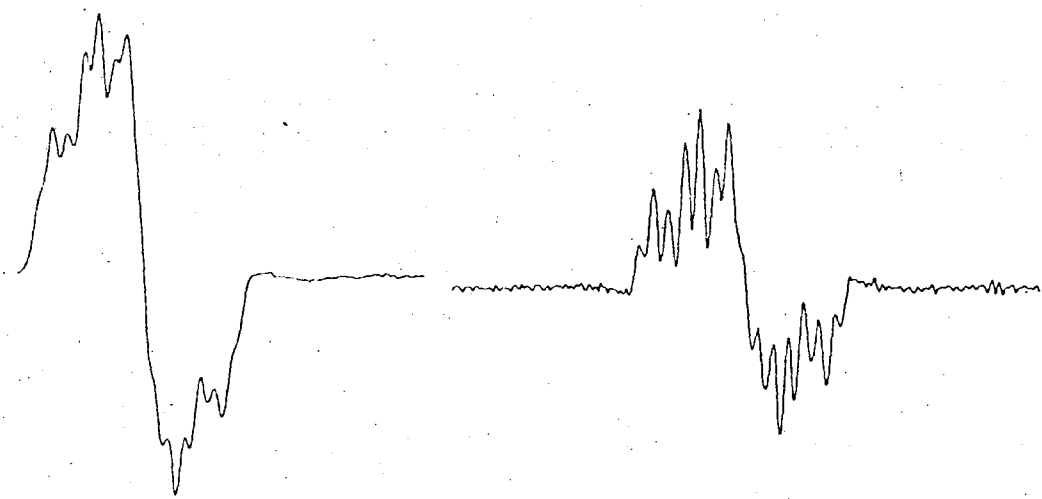
Spectrum 5a



Spectrum 5b

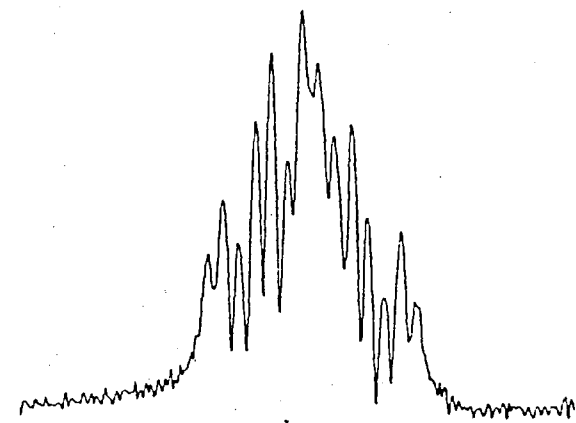


Spectrum 5c



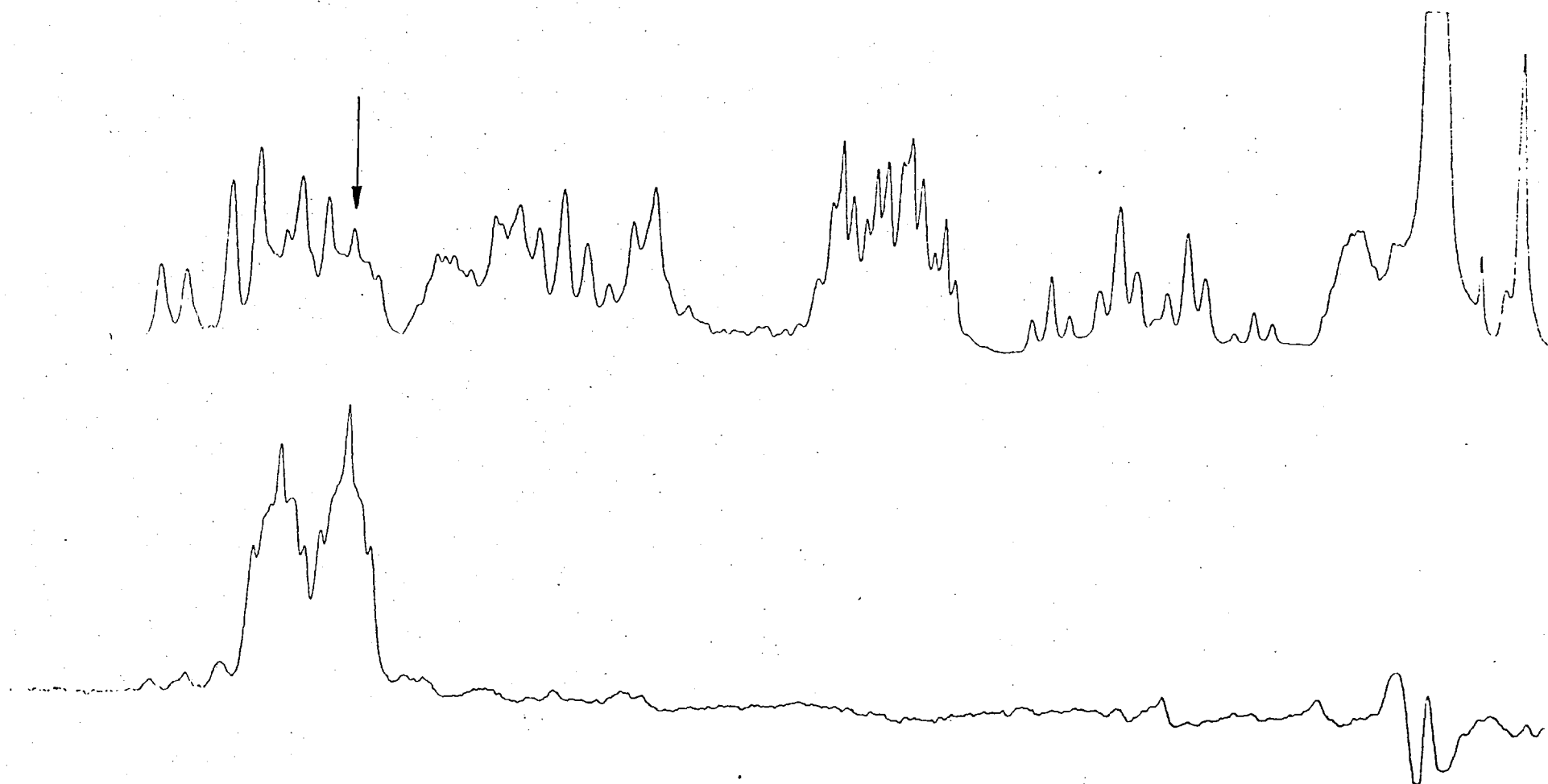
original

resolution enhanced

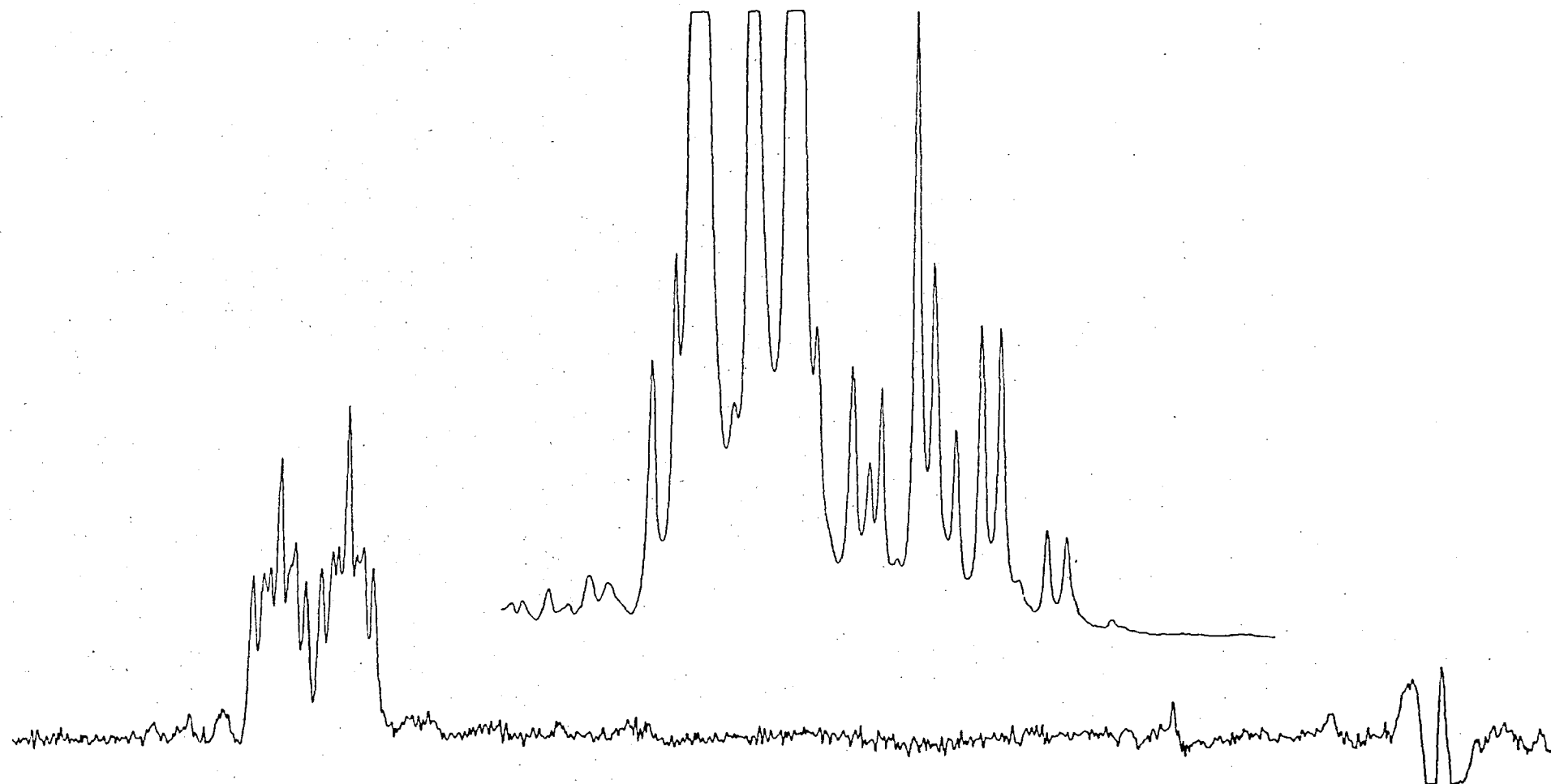


power spectrum

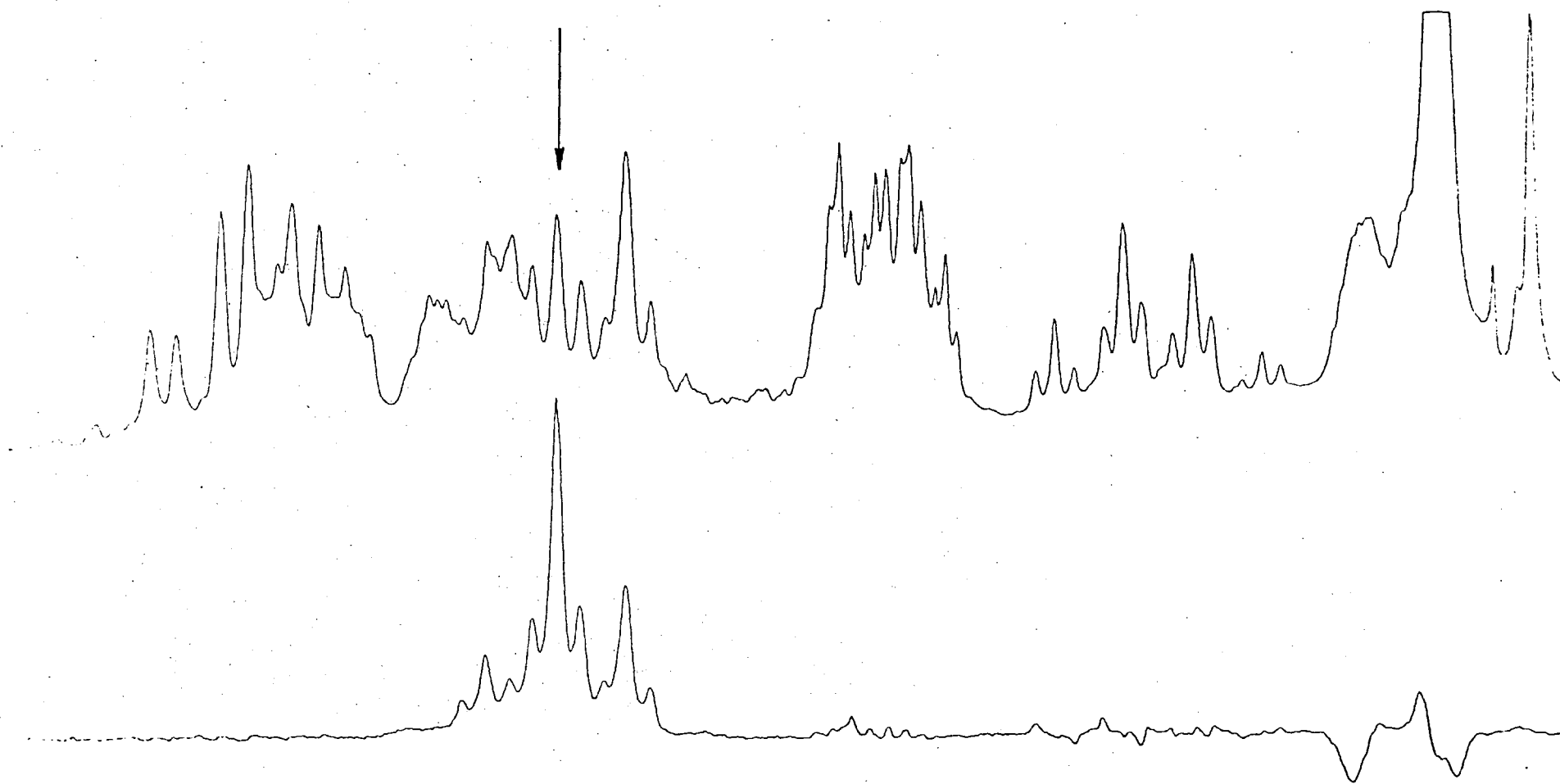
Spectrum 6



Spectrum 7



Spectrum 8



Spectrum 9

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Synthesis of a trans-Decalin as a Potential Insect Antifeedant

by

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Summary:

In a model study for the synthesis of clerodane related insect anti-feedants the trans-decalin (3) was prepared and shown to inhibit feeding of Locusta migratoria.

THE synthesis of clerodane related diterpenes has recently attracted considerable attention.¹ However none of the approaches reported so far have achieved the construction the desired epoxy diacetate functional group arrangement common to the natural products such as clerodin(1)² and ajugarin I (2)³ and known to be important for insect antifeedant activity⁴.

Here we report a synthesis of a suitable model compound (3) which allows us to both probe the biological activity and develop a strategy which could potentially be applied to the total synthesis of natural compounds.

The readily available enone⁵(4) reacted with a vinyl cuprate to form a regiospecific enolate which was trapped with formaldehyde in ether solution to afford the trans-decalin ketoalcohol (5)[†] in 65% overall yield. Methylene equivalents other than the vinyl cuprate with the enone (4) were unsuccessful. The stereochemical assignment of (5) was expected on mechanistic grounds and was entirely consistent with a detailed high field ¹H n.m.r. spectral analysis.

In order to obtain the stereospecific reduction of (5) removal of the directing effect of the primary hydroxy group was necessary by prior treatment with t-butyltrimethylsilyl chloride. Subsequent reaction with excess lithium aluminium hydride gave the diol (6) in 77% yield [δ 3.7 (dd, J 11.6 and 1.7 Hz >CH-OD after D₂O exchange)].

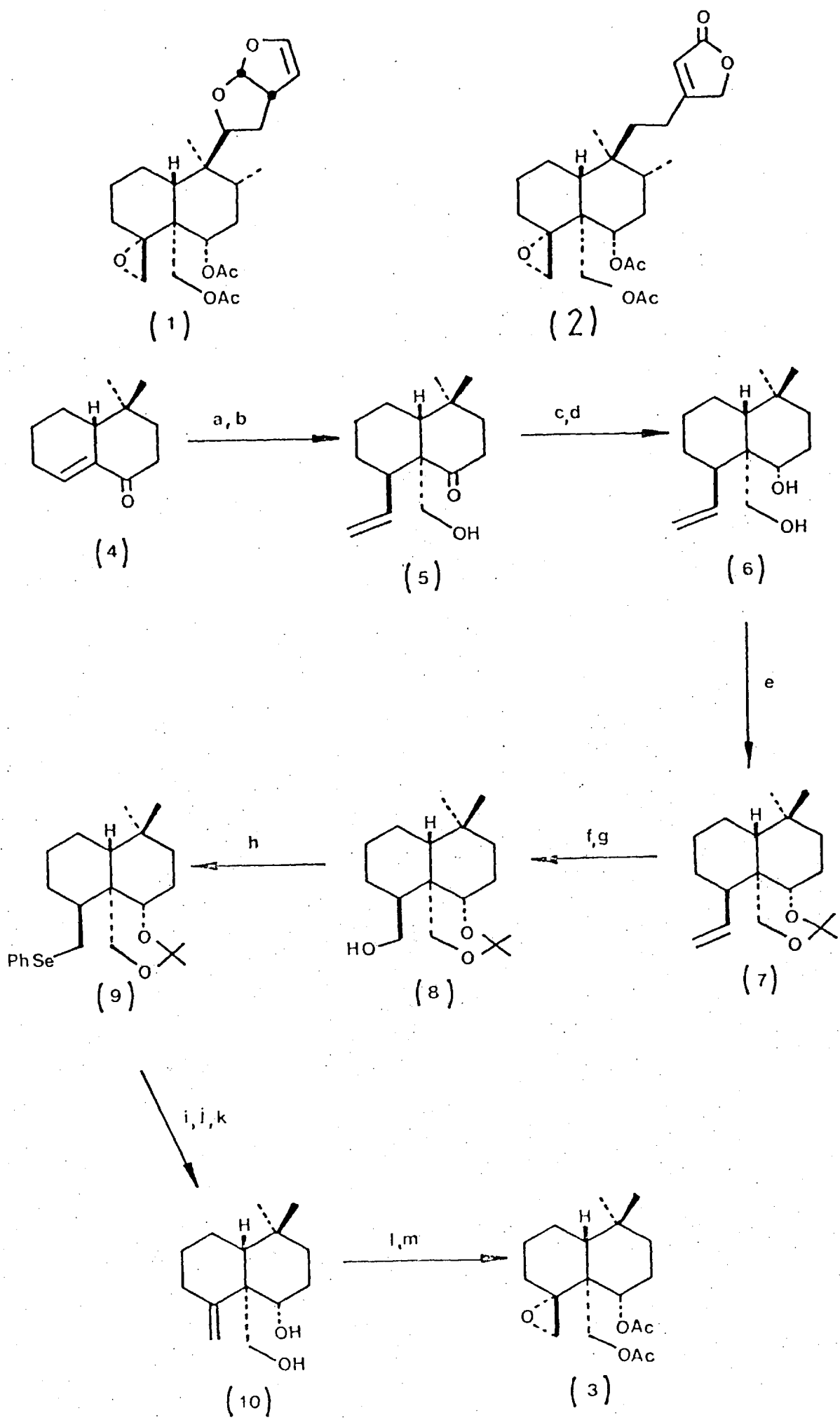
Protection of the 1,3-diol unit by acetone dimethylacetal gave (7) in essentially quantitative yield. The vinyl group was elaborated by ozonolysis and reductive work-up with Na BH_4 to give the alcohol (8) in 86% yield.

This alcohol was smoothly converted to the selenide (9) using N-phenylselenophthalimide $/\text{nBu}_3\text{P}^6$ in high yield (89%) and subsequently oxidised, syn-eliminated and deprotected with aqueous trifluoroacetic acid to give (10) (m.p. $122-124^\circ\text{C}$) (92%).

Directed epoxidation of (10) using $t\text{BuOOH}/\text{VO}(\text{acac})_2$ gave an intermediate epoxydiol which was rapidly acetylated to the final epoxydiacetate (3) in 52% yield (m.p. $105-106^\circ\text{C}$). The ^1H n.m.r. spectrum of (3) showed characteristic resonances at δ 4.88 (d, J 12.3 Hz 1H), 4.7 (dd, J 11.4 and 4.75 Hz 1H), 4.36 (d, J 12.3 Hz 1H) 2.99 (dd, J 4 and 2.4 Hz 1H) and 2.22 (d. J. 4 Hz 1H) these data being identical to equivalent resonances in the natural products. Additionally the structure of (3) is supported by the observation of strong N. O. E.'s between the secondary acetate methine proton and one methine proton on the epoxide ring and between the axial methyl group and one of the methylene protons of the primary acetate unit.

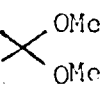
- On testing compound (3) for insect anti-feeding properties with Locusta migratoria a 95% inhibition of feeding was obtained at 1000 ppm. on GF/A discs containing 5% sucrose as the food source.

We thank the S.R.C. for financial support and the Royal Society for an equipment grant.



Scheme

To accompany scheme

- a) ()₂ CuMg X 1.2eq, -50°;
 b) H.CHO in ether warm to RT;
 c) ^tBuMe₂SiCl, Imidazole, DMF, RT, 12h;
 d) Li AlH₄, Et₂O, RT;
 e) , p-TSA, benzene, Δ, 45 min;
 f) O₃, O°, MeOH;
 g) NaBH₄;
 h) N-PSP 2eq, nBu₃P, T.H.F. 2h;
 i) O₃, -78°, CH₂Cl₂;
 j) Δ, CCl₄, Et₂NH;
 k) T.F.A. CH₃CN/H₂O 30 min RT;
 l) ^tBuOOH 1.5 equiv., VO(acac)₂, 1h;
 m) Ac₂O, py, 4-N, N-dimethylaminopyridine, RT, 12h.

Footnotes

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

* We thank Dr. M. A. Bernays, Centre for Overseas Pest Research, London, for this result.

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Selenium-mediated Cyclization Reactions of Alkenyl-substituted β -Ketoesters

By WILLIAM P. JACKSON, STEVEN V. LEY,* and ALAN J. WHITTLE
(Department of Chemistry, Imperial College, London SW7 2AY)

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Summary Phenylselenating agents, in which the counter ion is non-nucleophilic, react with certain alkenyl-substituted β -ketoesters to afford cyclized products, some of which can be further rearranged using SnCl_4 .

We have recently shown that a number of alkenyl-substituted β -dicarbonyl compounds can be cyclized using *N*-phenylselenophthalimide.¹ However, as this approach was not applicable in all cases, we sought alternative methods.

Consequently, it was found that by allowing the compounds (1)—(8) to react with a phenylselenating agent which has a non-nucleophilic counter ion, such as SbF_6^- or PF_6^- ,² cyclization can be achieved in reasonable yield and in examples where the previous route had failed (Table).

Cyclization of compounds (1)—(3) occurred *via* the oxygen atom of enolic forms of the β -ketoester to form the heterocyclic products (9)—(11)† in a fashion similar to our previous method. However, reaction of (4) led to the formation of

† All compounds were fully characterised by spectroscopic methods and accurate mass and/or microanalysis.

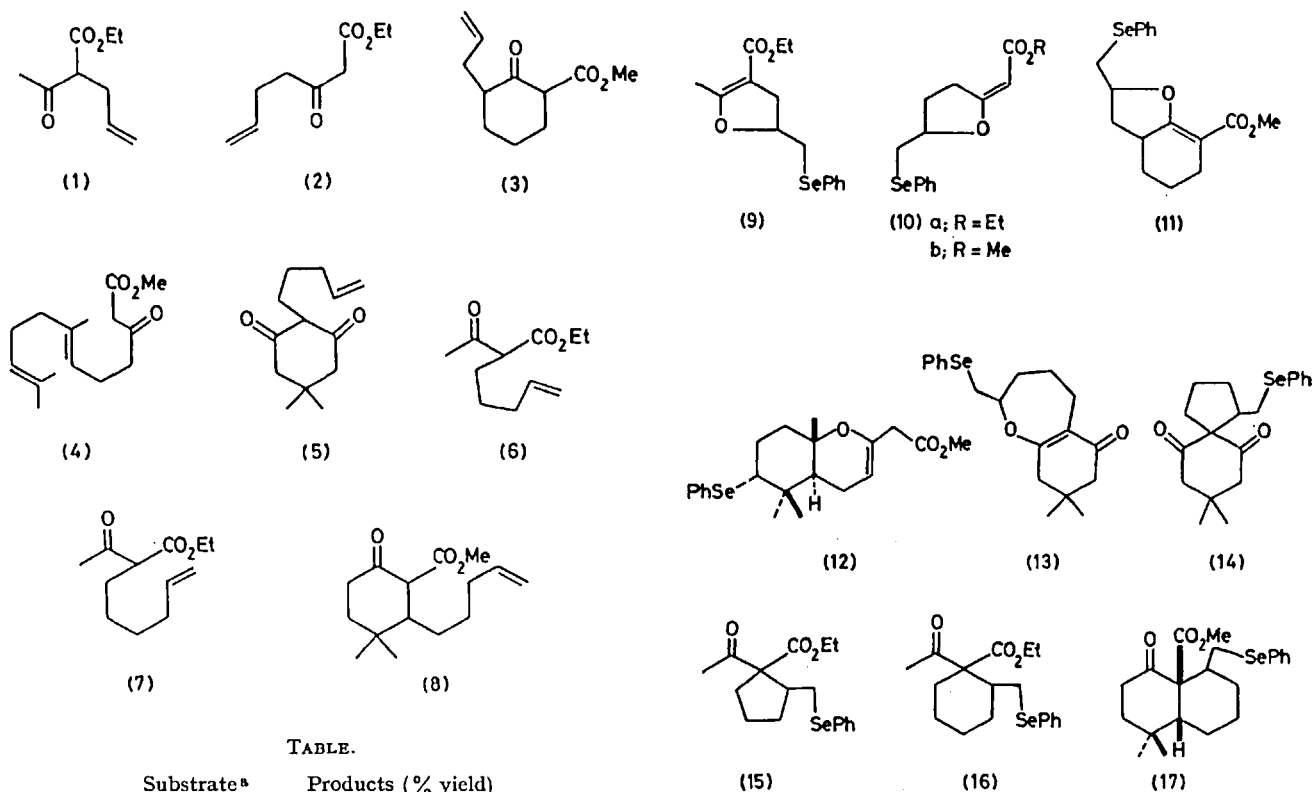


TABLE.

Substrate ^a	Products (% yield)
(1) ^b	(9) (70)
(2) ^c	(10a) (60)
(3) ^c	(11) (70)
(4) ^{c,d}	(12) (58)
(5) ^c	(13) (27) and (14) (30)
(6) ^b	(15) (82)
(7) ^c	(16) (57)
(8) ^b	(17) (76)

^a Substrate (1 mmol) in CH_2Cl_2 (10 ml) was added over 30 min to a solution of PhSeX (1.1 mmol) in CH_2Cl_2 (15 ml) at -78°C under argon, warmed to room temp. and worked-up by the addition of aqueous sodium hydrogen carbonate. ^b Using SbF_6^- salt. ^c Using PF_6^- salt. ^d By inverse addition.

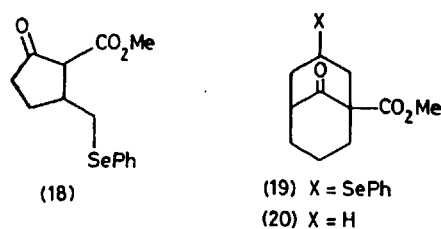
the bicyclic compound (12) as the only characterisable product; the reason for this change in reactivity will be discussed at a later date.

Treatment of the β -dicarbonyl species (5) with $\text{PhSe}^+\text{PF}_6^-$ gave products resulting from both oxygen and carbon cyclization, compounds (13) and (14) respectively.

In a similar way, the β -ketoesters (6)–(8) cyclized via carbon only, affording the products (15)–(17). Previously,¹ these three starting materials had failed to react with *N*-phenylselenophthalimide in the presence of H^+ , I_2 , or ZnI_2 .

As the formation of new carbon–carbon bonds is of prime importance in organic synthesis, ways of converting the oxygen-cyclized compounds into the corresponding carbon-cyclized counterparts were investigated.³ The best

of these methods involves treatment of oxygen-cyclized products with SnCl_4 (0.5–1 equiv.) in methylene dichloride at room temperature. In this way (10b) gave (18) in essentially quantitative yield after 1 h. Similarly, (13) could be rearranged to (14), again in very high yield. Compound (11) however required a much longer reaction time (17 h) although it too gave a new product (79%) to which the structure (19) was assigned on the basis of its spectroscopic



properties [δ 7.15–7.62 (m, 5H), 3.75–4.3 (m, 1H), 3.81 (s, 3H), and 1.5–2.75 (m, 11H); ν_{max} 1735 and 1715 cm^{-1}] and from the fact that it could be reduced to the known compound (20)⁴ using triphenyltin hydride.⁵

We thank the S.R.C. for research studentships (to W.P.J. and A. J. W.).

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¹ W. P. Jackson, S. V. Ley, and J. A. Morton, *J. Chem. Soc., Chem. Commun.*, in the press.

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³ For a similar rearrangement in related examples using a Pd^0 species, see B. M. Trost, T. A. Runge, and L. N. Jungheim, *J. Am. Chem. Soc.*, 1980, **102**, 2840.

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A CONVENIENT PREPARATION OF 2-HALOENONES FROM ENONES USING PHENYLSELENIUM HALIDES

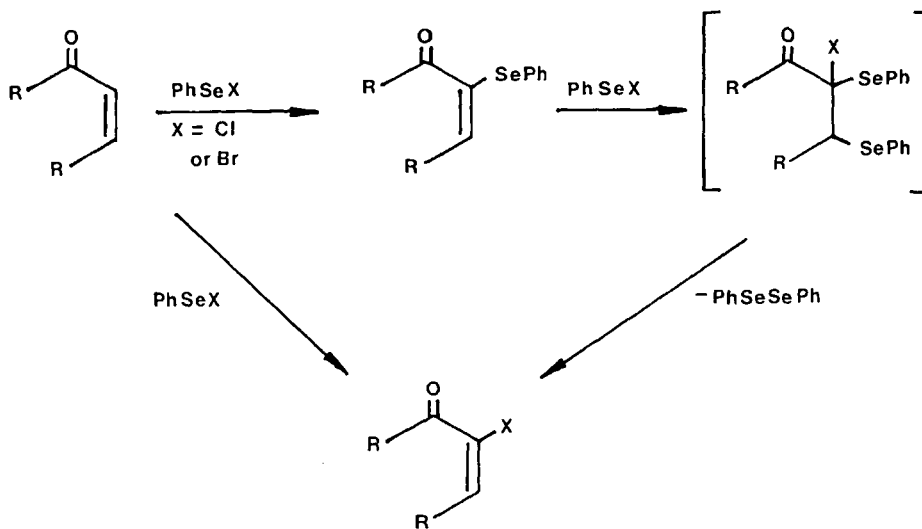
Steven V. Ley* and Alan J. Whittle

(Department of Chemistry, Imperial College, London SW7 2AY)

SUMMARY: Enones can be converted in high yield to their corresponding 2-halo analogues by treatment with an excess of phenylselenium halide in methylene chloride/pyridine at 37°C.

In connection with other work we needed supplies of 2-haloenones. As the literature methods¹ to these compounds are inefficient or involve a multistep sequence, we sought a more convenient alternative procedure.

Enones are known to react with phenylselenium chloride to give 2-phenylselenoenones² and it seemed reasonable to us that these derivatives might react further with a selenating agent to give adducts which would rapidly disproportionate by loss of diphenyldiselenide³ to afford the desired halo compounds. Direct halogenation should also be possible by using increased quantities of the phenylselenium halide (Scheme).



SCHEME

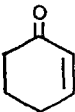
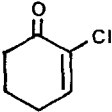
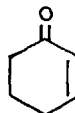
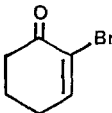
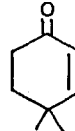
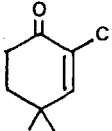
Consequently, by treating a number of enones (or enals) with an excess of phenylselenium chloride (1) or bromide (2) in dry methylene dichloride at 37°C, smooth conversion to the corresponding 2-substituted halo derivative can be achieved in high yield (Table). The products of the reaction were worked up by quenching the cooled reaction mixtures with water and washing the organic phase with dilute hydrochloric acid and water in the usual way. Flash chromatography subsequently separated the desired halo compounds from the faster running diphenyldiselenide. The recovered diselenide could be readily transformed back to the starting phenylselenium halides by standard methods.

By following the reactions by t.l.c. one can clearly see that these reactions proceed via the prior formation of the 2-phenylseleno enone species.² In two experiments (entries 12 and 13 in the Table) 2-phenylseleno substituted enones were separately converted to 2-halo-enones by reaction with the appropriate selenium halide.

The lower yields of halo compounds in entries 4 and 7 in the Table were due to the fact that the corresponding 2-phenylseleno derivatives were additionally isolated in 39 and 20% yields respectively and thus indicated incomplete reaction in these examples.

2-Haloenones are potentially useful synthetic intermediates.⁴

TABLE

STARTING MATERIAL	REAGENTS	PRODUCT ^{a, b}	TIME h at 37°C	PROPERTIES m.p. °C	YIELD %
1. 	(1) 3 equiv. py 3 equiv.		96	71-72	82
2. 	(2) 2.5 equiv. py 2.5 equiv.		24 ^d	75-76	100
3. 	(1) 3 equiv. py 3 equiv.		72	oil	92

/continued...

TABLE/continued...

STARTING MATERIAL	REAGENTS	PRODUCT ^{a, b}	TIME h at 37°C	PROPERTIES m.p. °C	YIELD %
4.	(1) 3 equiv. py 3 equiv.		48	oil	35
5.	(1) 3 equiv. py 3 equiv.		72	oil	52
6. PhCH=CH.CO.CH ₃	(1) 3 equiv. py 3 equiv.		7 days	oil DNP 218-219°	85
7. PhCH=CH.CO.CH ₃	(1) 3 equiv. py 3 equiv.		65	30	51
8. PhCH=CH.CHO	(1) 3 equiv. py 3 equiv.		96	oil	100
9. PhCH=CH.CHO	(2) 3 equiv. py 3 equiv.		7 days	71.5-72	85
10. MeCH=CH.CHO	(1) 3 equiv. py 3 equiv.		12	oil	90
11. MeCH=CH.CHO	(2) 2.5 equiv. py 2.5 equiv.		24 ^d	oil	95
12.	(1) 4 equiv. py 3 equiv.		60 ^d	oil	95
13.	(2) 1.5 equiv. py 1.5 equiv.		72	38.5-39°	52

/continued...

TABLE/continued...

- a All new compounds were fully characterised by spectroscopic methods and acc. mass and/or microanalysis.
- b In view of Wender's findings,⁴ these compounds should be handled with care owing to their potential vesicant properties. We however have not noticed these unpleasant side-effects with compounds prepared by the above method.
- c Z/E geometry of these compounds is not yet known.
- d At room temperature.

*We thank the S.R.C. for a research studentship
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