APPROACHES TO THE SYNTHESIS OF CLERODANE DITERPENES

A thesis presented by

WILLIAM PAUL JACKSON

in partial fulfilment of the requirements for the award

of the degree of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

Whiffen Laboratory

Chemistry Department

Imperial College

London SW7 2AZ

December 1980

CONTENTS

	Page
ABSTRACT	i
ACKNOWLEDGEMENTS	ii
INTRODUCTION	1
REVIEW : INSECT ANTIFEEDANTS	
1) General Definition	2
2) Mode of Action	3
3) Methods of Testing	9
4) Organometallic Insect Antifeedants	12
5) Naturally Occurring Insect Antifeedants	12
CLERODANE DITERPENES	
Structure of clerodanes	38
i) Clerodanes which show, or might be expected to show, antifeeding activity	39
ii) Approaches to the synthesis of clerodane diterpenes	49
REFERENCES	53
RESULTS AND DISCUSSION	
Synthesis of Clerodane Diterpene Model Compounds	61
Preparation of a cis-Decalin with Potential Insect Antifeeding Properties	71
Lewis Acid Catalysed Conia Type Reaction	80
Attempts to Prepare a trans-Fused Epoxydiacetate Related to the Clerodanes and Ajugarins	83
Attempts to Prepare a trans-Fused Decalin by Radical Induced Ring Closure	86
Organo-Selenium Induced Cyclisations	89

Page

Mechanism of the Selenium Induced Cyclisation Reactions 105

Rearrangements of Oxygen-Cyclised Products to Carbon-Cyclised Products 108

EXPERIMENTAL 115

REFERENCES 143

Abstract

The biological testing and isolation of naturally occurring insect antifeedants has been reviewed. Special attention has been paid to the clerodane related antifeedants with regard to their structure/activity relationships and synthesis.

The thesis describes attempts to prepare a trans-decalin related to the clerodane antifeedants. Attempted ring closure of 2-carbomethoxy-4,4-dimethyl-3- [1- (pent-4-enyl)] -cyclohexanone (i) using phenylselenium chloride/antimony pentachloride afforded chlorinated products which were not fully characterised. Cyclisation took place when (i) was reacted with phenylselenium hexafluorophosphate (ii) or hexafluoroantimonate (iii) to afford a cis-fused decalin. Elimination of phenylselenenic acid afforded an olefin which was further elucidated to afford spiro (cis-2β-acetoxy-1α-acetoxymethyl-5,5-dimethyl bicyclo [4.4.0] decan-10,2'α-oxiran) (iv) which showed a 72% inhibition of feeding when tested against Locusta migratoria. Compound (iv) could also be prepared from the product of the Lewis acid catalysed cyclisation of 2-carbomethoxy-4,4-dimethyl-3- [1 (pent-4-ynyl)] cyclohexanone. Other cis-decalins were also prepared and their antifeeding properties studied.

The second part of the thesis describes a detailed investigation of the selenium induced cyclisation procedure described above. Several alkenyl substituted β-dicarbonyl compounds were reacted with (ii) and (iii) to afford products resulting from cyclisation via the enolic oxygen atom or via the carbon atom. It was found that the cyclisation reaction could be performed by using N-phenylselenophthalimide (v) in the presence of various catalysts. Again cyclisation took place via oxygen or carbon. It was determined that the first step in the reaction of β-dicarbonyl compounds with (v) involves phenylselenation between the dicarbonyl system. Subsequent rearrangement takes place to afford the observed products. Certain of the oxygen cyclised products were found to rearrange to their carbon cyclised counterparts when treated with strong Lewis acids.

ACKNOWLEDGEMENTS

I should like to thank Dr. S.V. Ley for his help, supervision, encouragement, friendship, Friday evenings and, moreover, for not accepting my many resignations! (although he had just cause).

I would also like to thank the staff of the Chemistry Department: Mr. John Bilton and Mrs. Lee for mass spectra; Mr. Jones and assistant for microanalyses; Dave Neuhouse for 250 MHz n.m.r.; and, finally, Mrs. B. Day for her prompt, friendly service in the organic stores.

Thanks go to Alan Whittle and Judith Morton for allowing me to include some of their results in the tables. Special thanks also go to all the other people who have made life in the Whiffen a memorable "experience".

Finally, thanks to my parents for support (moral and financial) and also the Science Research Council, whose grant made it all possible.

INTRODUCTION

The chemical composition of plants is the most important factor in the acceptance or rejection of plants as food for insects. This is also true in the selection of different parts of the plant as food. Quite often feeding deterrents are of major importance in determining which plants are eaten. Thus, the use of naturally occurring chemicals which inhibit feeding may be of considerable value in crop protection. These chemicals should also have the advantage that they are non toxic to other animal species and that they will not unduly disrupt the local ecology as they will only act upon those insects which feed on the treated plants.

This review will cover naturally occurring insect antifeedants which have been isolated over the past fifteen years, together with a short section on organometallic compounds which have been used as feeding deterrents.

INSECT ANTIFEEDANTS

1) General Definition

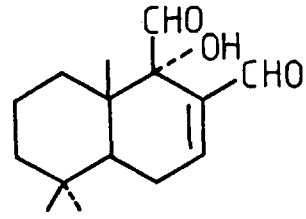
An antifeedant is a compound, either naturally occurring or synthetic, which inhibits feeding but does not kill the insect directly, the insect remaining near the treated leaves and dying of starvation[1] or becoming prey to other natural predators. Thus, so long as a crop is completely treated with an insect antifeedant the antifeedant should act as an efficient form of crop protection.

Many of the plants from which antifeedants have been isolated have been used for centuries in folk medicine and have little or no side effects. Crude extracts of some plants have actually been used to protect other plants in third world nations. Pure antifeedants, however, should be treated with respect as many show other biological properties including cytotoxicity and mutagenic activity. These other activities will be mentioned when relevant.

Kato and Munakata[2] have made an extensive survey of the factors influencing the antifeeding activity of compounds against Spodoptera litura. They found that there are two general types of insect antifeedant which they termed "relative" and "absolute". The laboratory method of testing antifeeding activity has a defined two hour period over which activity is observed and measured. However, when observations are carried out over a longer period, some antifeedants lose their activity, while others retain their activity indefinitely until the insects under test starve to death. The former are termed "relative" antifeedants, while the latter are "absolute".

It is interesting to note that even extremely powerful antifeedants, such as warburganal[3] (1), show activity only against certain insect species. For example, warburganal shows 100% inhibition at .1 ppm against S. exempta, while no activity is shown against the tobacco hornworm (Manduca sexta) or the vagrant grasshopper (Schistocerca vaga)[4]. Thus, antifeedants may also be species specific, which may or

may not be advantageous.



(1)

2) Mode of Action of Antifeedants

Antifeedants are not repellents. Repellents work by evaporation of the active principle into the atmosphere, while antifeedants work by contact between the leaf and insect.

The feeding behaviour of insects may be divided into four steps[5]; i) host plant recognition and orientation ii) initiation of feeding iii) maintenance of feeding, and iv) cessation of feeding. Antifeedants are concerned with steps (ii) and (iii).

The selection of the host plant is governed by the presence or absence of attractants and repellents. For example, some alkaloid glycosides from Solanaceae plants have been shown to be repellents[6] to the larvae of the Colorado beetle (Lepinotarse decemlineata Say) while others have shown feeding inhibition towards the tomato beetle[7]. Feeding stimulants present in the African corn leaf, the diet of S. exempta, have been shown to be sucrose, adenosine and an isomer of inositol[8].

Food selection in phytophargous insects[9] consists of finding a food source, sampling, followed either by feeding or rejection of the plant as a feeding source. Detection of the food source is carried out by visible and chemical means. The insect aims for certain shapes or colours coupled with the plant odour which the insect is able to detect with olefactory cells on the antennae. Once the insect

has alighted on the food source, testing then begins. Insect species with tarsal receptors detect chemicals on the surface of the food. In addition, locusts can detect chemicals, in free form, on the surface of the food by a characteristic "drumming behaviour", during which the labial and maxillary palpae appear to test possible food sources. The pegs on the tips of the palpae contain chemosensory cells reacting to various substances. For insects with sucking mouth parts, chemical stimulation takes place on proboscis setae-like structures which probably represent chemoreceptors. For example, cotton stainers (Dysdercus spp.) have twenty four sensilla at the end of the proboscis which function as contact chemoreceptors.

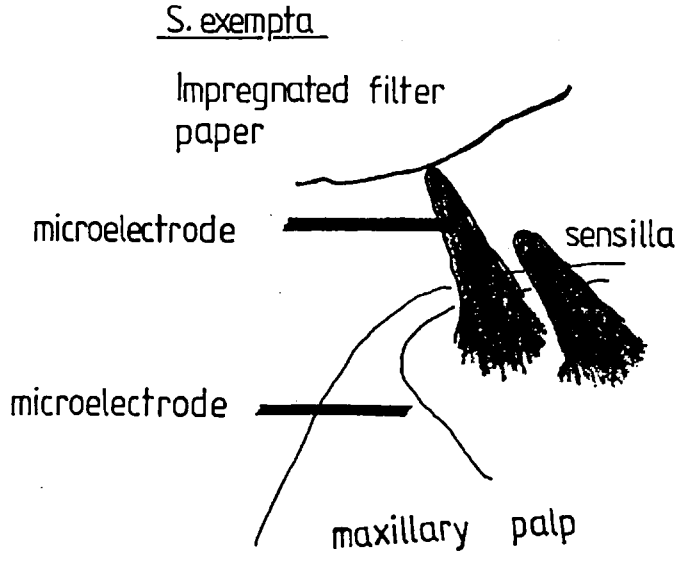
Once chemical contact with a possible food source has been made, the insect may take a test bite, which is usually smaller than any regular feeding bite and is chewed more carefully. If distasteful compounds are encountered at this stage insects not only stop the investigation, but may expel the material and often regurgitate some of the foregut contents as well. During feeding the chemical composition of the food is continuously monitored with different chemicals governing different phases of feeding behaviour. The larvae of the cabbage white (Pieris brassicae) are stimulated to bite by sinigrin, while sucrose promotes swallowing movements. Swallowing is controlled by a pair of sensilla on the epipharynx, which contain cells sensitive to sugars, salts and deterrents. In locusts there are other sensilla which control the exploratory biting procedure, and further activity, such as swallowing, only occurs when the first group is sufficiently stimulated.

In many insects specialised deterrent receptors detect unpalatable compounds which sometimes work in combination with the olefactory organs. The problem of which compounds affect the receptor is usually solved by electrophysiological analysis of the chemoreceptors[10]. Phytophargous insects have several taste cells which are stimulated by groups of chemically related compounds with the specificity

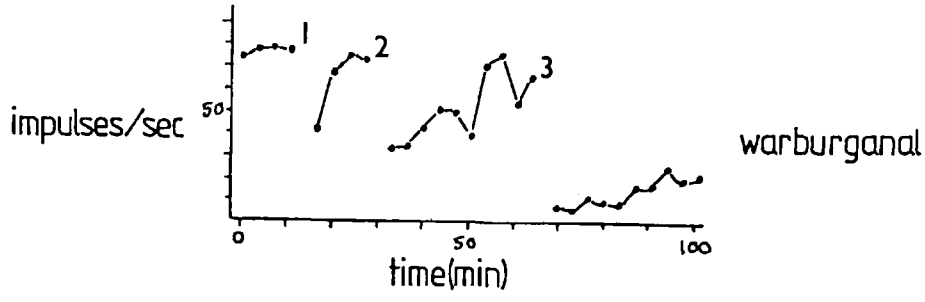
of the cells being quite high. Cells have been found which are sensitive to sugar, inositol, glucose, sorbitol, mustard oil, glycosides, amino acids and anthrocyanins. However, many chemicals affect several cells, either diminishing or increasing their sensitivity to other substances. Thus, complex reaction patterns are obtained with crude extracts from plants.

Receptor systems in different species of phytophargous insects show considerable differences with each species having developed a unique sensory apparatus (based on a common model), tuned so that optimal discrimination capacity is obtained for host versus non-host plant. Host selection occurs when the insect characterises a plant by its secondary plant substances. This occurs when the receptors detect these secondary substances either as deterrents or phargostimulants. Some insects have both classes of receptors, while others work by negative selection, i.e. they eat anything not containing deterrent secondary plant substances. Monophargous insects differ from polyphargous insects in that they will tolerate fewer secondary plant substances than the latter.

Many insect antifeedants have been detected by electrophysiological testing of Spodoptera littoralis or S. exempta[4], which is shown schematically below :-

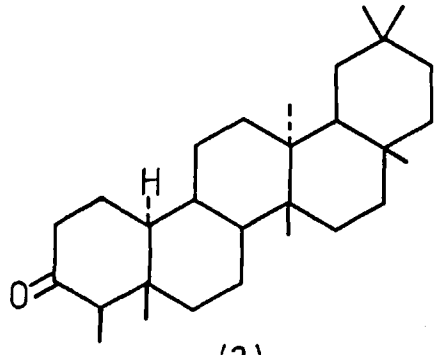


The larvae of S. exempta contain eight sensilla which are located at the tip of the maxillary palp. Two micro electrodes are inserted into the maxillary palp and the sensilla. The electrophysiological responses are then recorded with an oscilloscope as impulses per second by contacting the tips of the sensilla with filter paper impregnated with the test sample. The maximum number of impulses which can be evoked is in the order of two hundred. The function of all eight sensilla is not known, but it is known that certain ones respond to phargo stimulants and others to antifeedants. The mode of action of an antifeedant is exemplified by the response of the sensilla of S. exempta to warburganal, which is shown in the graph below :



This diagram shows the effect of prolonged exposure to warburganal; a filter paper which has been impregnated with a 1.0 m M solution of warburganal and a 50m M solution of phargostimulant (in this case meso-inositol) is brought into contact with the sensillum for three minutes (point 1). This leads to a 50% decrease in the taste sense, but recovery to normal level was fast. A second application (point 2) leads to a similar decrease in activity, but recovery is much slower. A third contact (point 3) results in a drastic reduction (almost to zero), with the response not recovering to the initial level. In practice, if an army worm is placed in contact with a treated corn leaf for one hour and then placed onto an untreated leaf it starves to death. However, in an excellent study on the antifeeding effect of friedelin [11] (2), it was shown in field tests

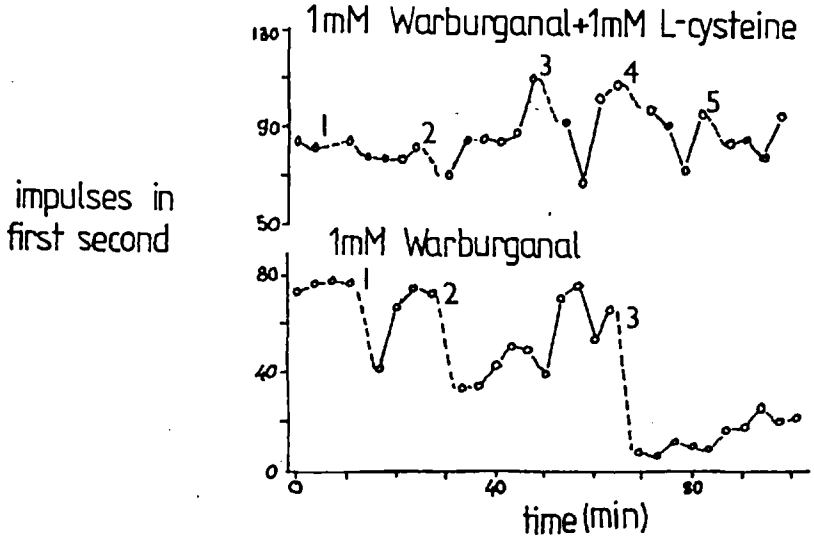
that larvae of S. littoralis, which had been exposed for six hours to leaves treated with a 0.5% solution, fed normally when offered untreated leaves. In this case,



(2)

then, the antifeedant did not irreversibly affect the taste receptors of the mouth or stomach.

In the graph below it can be seen that the antifeeding effect of warburganal is

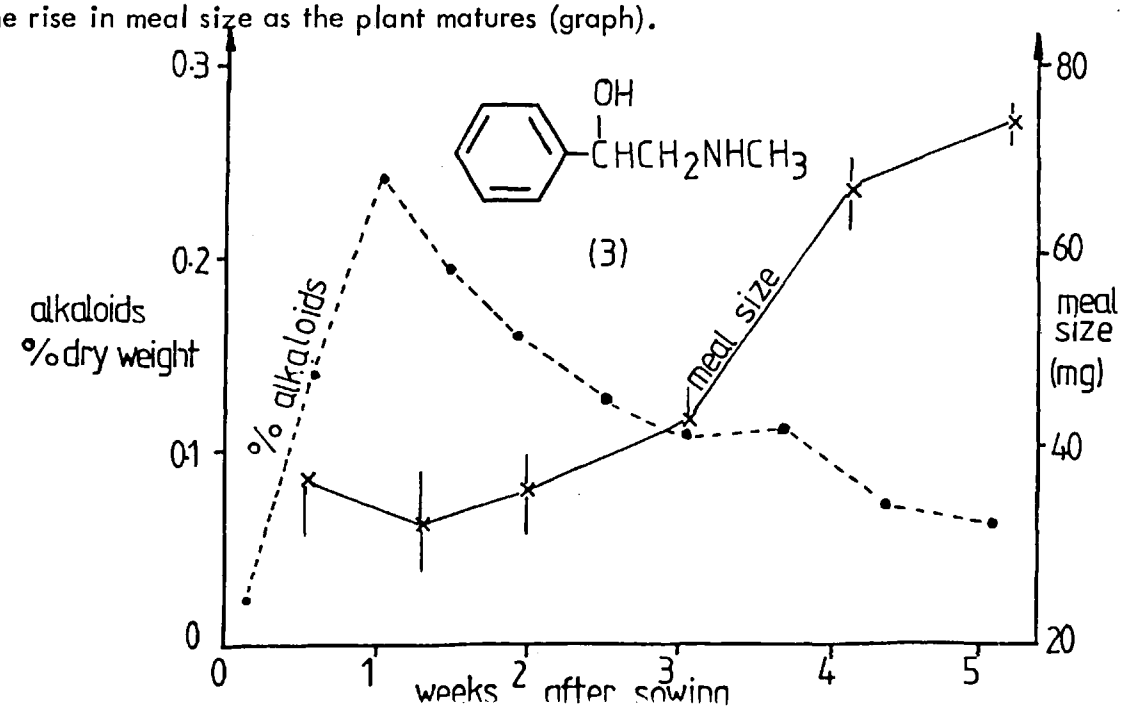


nullified by L-cysteine. In this case the filter paper was impregnated with phargostimulant, warburganal and an equimolar amount of L-cysteine. As can be seen, application of the filter paper leads to an increased response due to the feeding stimulant, indicating that the antifeeding effect of warburganal is destroyed by the

L-cysteine. This suggests that warburganal irreversibly interacts with thiol groups in certain enzymes and permanently blocks the response mechanism. It has also been suggested [12] that the antifeeding effect of quinones is due to nucleophilic attack of a thiol group into the enone system.

Undoubtedly, the reason why plants produce antifeedants is for self protection. This is often only necessary at certain times of the year, i.e. the growth periods when the new foliage is still maturing. Once the shoots have matured, then the antifeedants no longer need be produced in such large quantities. It has been shown [13] that the nymph of Locusta migratoria will eat up to nine times the amount of mature grasses as opposed to seedling grasses. The survey covered twenty grasses of the same species and all showed similar results. The seedling grasses are not eaten in normal quantity until a month or more after sowing. The same effect was observed with several species of insect, but not with S. exempta or S. littoralis (the latter actually showed a preference for the seedling grass).

It has been shown that seedling grasses produce larger quantities of alkaloids than the mature plant [14] and, in the seedling grasses of the Lolium species halostachine, (3), is known to be present in large quantities. This alkaloid shows antifeeding properties for Locusta, and its fall in production in the plant appears to be matched by the rise in meal size as the plant matures (graph).



Nakanishi and co-workers[15] isolated xylomolin from the unripe fruit of Xylocarpus moluscencis Roem. The bitter taste of the fruit is soon lost on ripening and the fruit becomes edible. Thus, it is probable that xylomolin serves to protect the fruit from attack while the seeds are still maturing.

Several extensive studies on the antifeeding properties of the foliage of juvenile Jack Pine, Pinus banksianc, have been conducted by Benjamin and All[16,17]. They have shown that the Swaine Jack Pine sawfly Neodiprion swainei Middleton and N. rugifrons Middleton exhibit extreme host specificity and show preferential feeding and enhanced survival on foliage aged one or two years, as compared to current season (juvenile) foliage. Furthermore, they have semipurified the extract of juvenile foliage and have shown that two ketonic components exhibit significant antifeeding activity at a level equivalent to 1g of pine needles per ml of solvent.

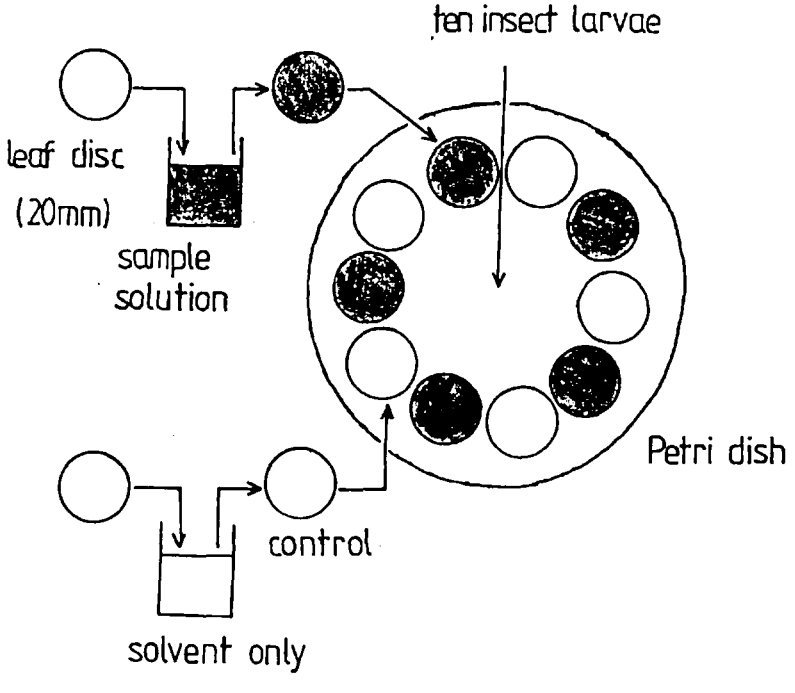
It appears, therefore that plants produce antifeedants at times of growth when the growing parts are not able to withstand insect attack as well as the mature parts of the plant.

3) Methods of Testing for Insect Antifeeding Activity

At the present time there is no standard method for measuring the insect antifeeding activity. However, certain guidelines are followed, the main one being that insects are only observed over an initial two hour feeding period. This short time, therefore, takes into account both "relative" and "absolute" antifeedants[2].

Initial testing for antifeedants is often carried out on S. exempta, as this is a monophargous insect and is thus much more susceptible to antifeedants. A much more sensitive insect is the Mexican bean beetle, Epilachna varivestis, which will respond to twenty times more substances than the Southern armyworm, S. eridania.

Although the best method of testing for antifeedant activity is electrophysiology (as described previously), the simplest method is treatment of leaves with an acetone solution of the antifeedant and measurement of the amount of the leaves eaten in the two hour period. Tests of this sort may be "choice" or "non-choice". In choice tests there are both treated and untreated leaves present. The insects are allowed to choose the treated or untreated leaves. In this case the 100% antifeeding effect is observed at that concentration of compound which causes none of the treated leaves to be consumed. The no choice test involves using a known weight of treated leaves; the amount eaten gives a direct measurement of the antifeeding effect when there is no other food source present. The 100% antifeeding effect occurs when none of the treated leaves have been eaten. A more sophisticated version of these tests is shown schematically below[18]. This test is known as the "leaf disc method" which may be either a "choice" or a "no choice" test.



Leaf discs are prepared with a 20 mm cork borer and are immersed for two seconds in an acetone solution of the compound under test (the immersion should not be carried out for more than two seconds or phargostimulants can be extracted from the leaves). The discs are placed in a petri dish with control leaf discs, and ten third instar larvae of S. exempta are allowed to feed (removal of the control leaves constitutes a "no choice" test). Observations may be carried out over a two day feeding period depending upon the potency of the antifeedant. However, in "no choice" tests the control discs are usually consumed within the two hour period. This test, then, allows both "absolute" and "relative" antifeedants to be studied.

In other tests[1] two identical groups of insects are allowed to feed separately, one on treated discs and the other on untreated discs as a control. The consumed areas of all the discs are measured using Dethier's method[19] and the consumed area of the treated discs as a percentage of the consumed area of the non treated discs is a measure of the antifeeding activity of the sample. With extremely voracious eaters, such as Locusta migratoria, it is possible to do away with plant material altogether and instead use discs of cellulose filter paper, which are impregnated with a phargostimulant such as sucrose.

Other, less common methods involve measuring the weight loss (or gain) of the insect[20] and measuring the uptake of radioactively labelled phosphorous from phosphoric acid which was included in the feeding solution under test[21].

Another factor in the determination of the antifeeding effect of compounds is the age of the insect under test. Most studies do quote the age and conditions under which the antifeeding tests were carried out. A recent paper, however, has shown that antifeedant activity may vary with the age of the insect larvae[22]. The active principles were extracted from the bastard indigo, Amorpha fruticosa L., and were treated with several orders of insects and mites. Tests were carried out on both

third and fourth instar larvae and adults of the Colorado beetle (Lepinotarse decemilineata). The third instar larvae left the treated leaves and did not return during the course of the experiment, while the control leaves were completely consumed. However, fourth instar larvae left the leaves after first nibbling and repeatedly returned to the leaves and attempted to feed on them, with 15% consumption after four hours, and 55% consumption after twenty four hours. Thus, the fourth instar larvae appear to be more voracious eaters and less susceptible to antifeeding compounds.

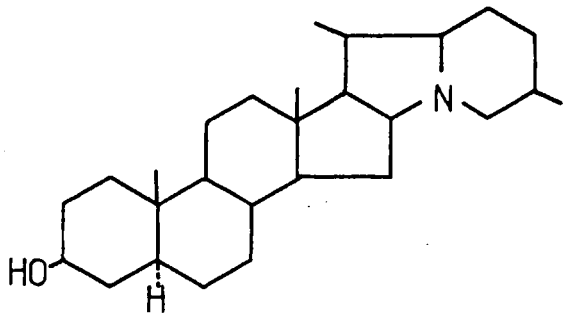
4) Organometallic Insect Antifeedants

Many organo tin compounds such as triphenyltin hydroxide and triphenyl-tin acetate have been used in field tests as insect antifeedants, and a comprehensive bibliography of the literature from the past fifteen years is available[23]. These compounds, however, are more often than not toxins, killing the insects within twenty four hours.

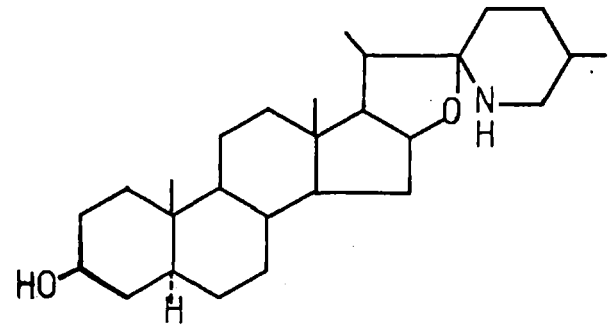
5) Naturally Occurring Insect Antifeedants

i) Alkaloids

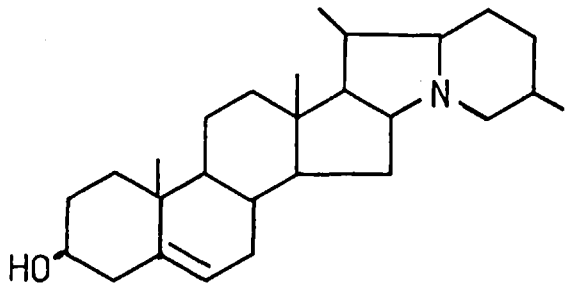
The most studied alkaloid insect antifeedants have been the glycoside alkaloids demissidine (4), tomatidine (5), solanidine (6), and Leptinine (7). Their effect on the larvae of the Colorado beetle (Leptinotarse decemlineata Say) has been the subject of a large number of papers[24-29]. Ma[30] has also shown that Solanine, tomatine and salts of quinine will inhibit the feeding of the larvae of the cabbage white (Pieris brassicae L.) when applied at very high concentrations. Isobolidine (8), which has been extracted from Cocculus trilobus, shows the 100% antifeeding activity at a concentration of 200 ppm against Abraxas miranda Butler and



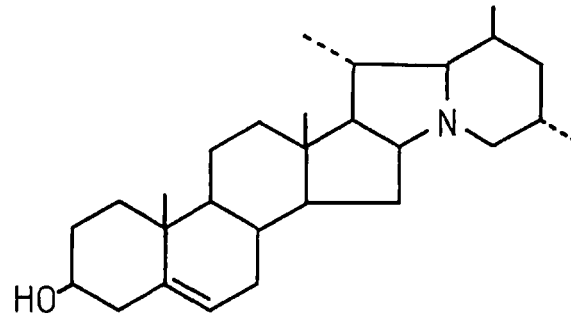
(4)



(5)

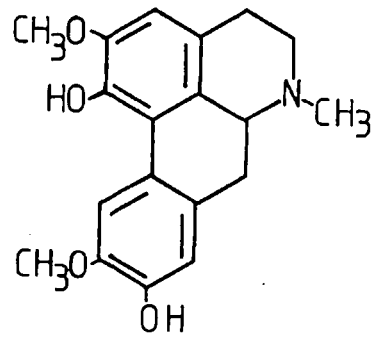


(6)



(7)

Spodoptera litura F., but shows no activity at all against Oraesia excavata Butler, and so is not a universal antifeedant[31, 5]. Isobolidine has also been isolated from

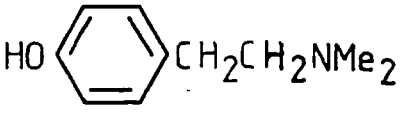


(8)

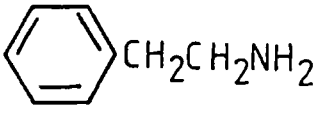
Nantina domestica Thurb.[32,33], Symplocos celastrinea M.[34], and from the leaves

of Beilschmieda elliptica C.T. White[35].

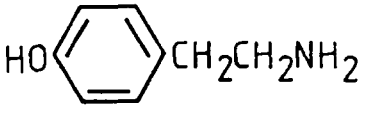
Several decarboxylated amino acids have been tested as insect antifeedants[36]. The most active of these are hordenine (9), phenethylamine (10) and tyramine (11) which all show 100% activity at 10 ppm against the brown plant hopper. The amino



(9)

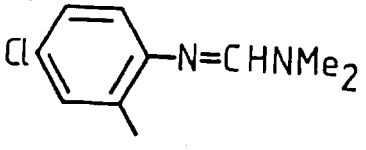


(10)



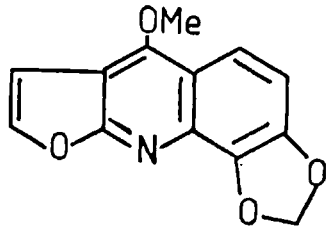
(11)

acids themselves were found to be much weaker. Chlorodimeform[37] (12) has been shown to be a quite general insect antifeedant, affecting phytophargous insects at concentrations down to 10 ppm.

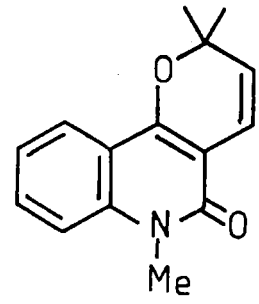


(12)

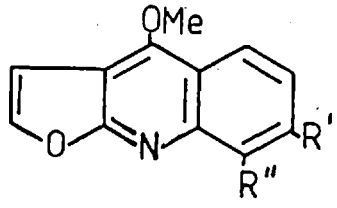
Kokusagin[38](13) and N-methylflindersine[39] (14) show the 100% antifeeding effect at 100 ppm against Spodoptera litura and S. exempta respectively. Evoxin (15) and japonin (16) were isolated together with kokusagin from extracts of Orixa japonica, but these showed much weaker activity with 50% inhibition occurring at 500 and 300 ppm respectively.

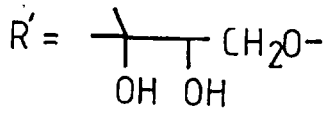


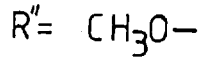
(13)



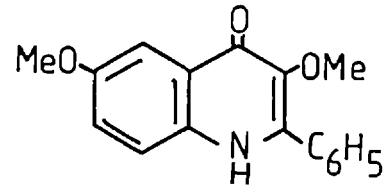
(14)







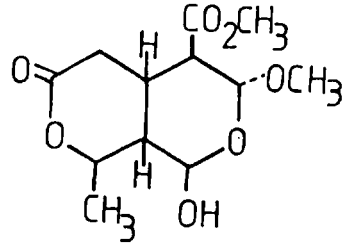
(15)



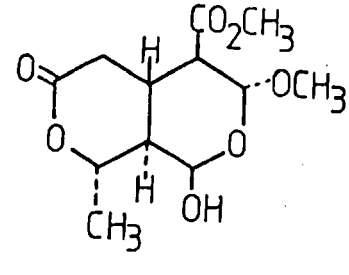
(16)

ii) Monoterpenes

Kubo and co-workers isolated[15] the bitter principle of the fruits of Xylocarpus Molluscensis M. Roem, which showed antifeeding activity against the caterpillars of S. exempta Walker, and was assigned structure (17). Other workers, however, showed by partial synthesis[40] that the true structure was actually (18).

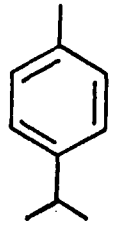


(17)

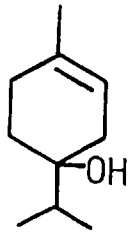


(18)

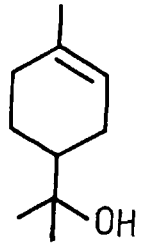
The crude extract of the bastard indigo (Amorpha fruticosa L.) has been semi-purified[22], and the active fraction has been shown to contain a variable mixture of three monoterpenes : p-cimol (19), terpinen-4-ol (20), and α-terpineol (21). This fraction showed antifeeding properties against a variety of insect and mites, as discussed previously.



(19)



(20)

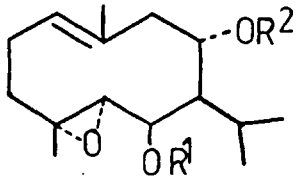


(21)

iii) Sesquiterpenes

a) Germacranes

During a systematic search for antifeedants in twelve families of plants it was found that three were not eaten at all[41]. Only the benzene extract of Parabenzoin trilobum, Nakai showed any activity at 5% concentration. This led to the isolation of three related compounds[42]: shiromodiol diacetate (22), shiromodiol (23), and shiromodiol monoacetate (24). The antifeeding effect against Spodoptera littoralis was similar with all three compounds : a 90% inhibition of feeding was observed at concentrations between .25 and .5%.



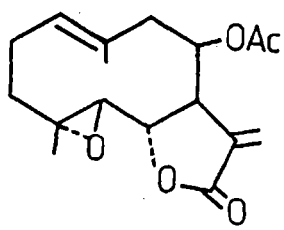
(22) $R^1 = R^2 = Ac$

(23) $R^1 = R^2 = H$

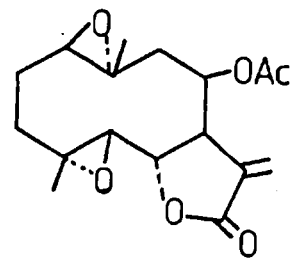
(24) $R^1 = H$ $R^2 = Ac$

When tested against Trimeresia miranda, the antifeeding activity of (22) was 100% at a concentration of .25%, while that of (24) was only 70% at the same concentration.

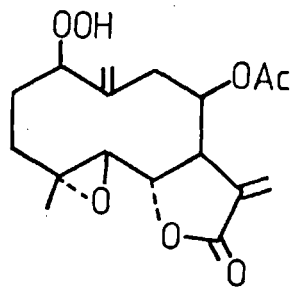
So far four antifeeding compounds have isolated from the ethanolic extract of the tulip poplar Liriodendron tulipifera L. These are lipiferolide (25), epitulipinolide diepoxide[43] (26), peroxyferolide (27)[44], and tulirinol[45](28).



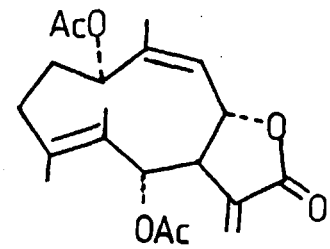
(25)



(26)



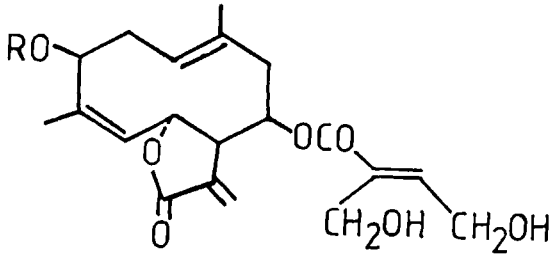
(27)



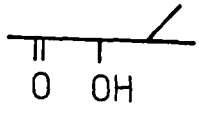
(28)

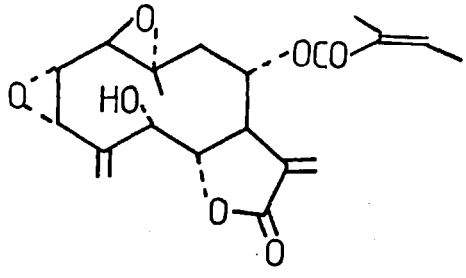
Peroxyferolide (27) is the first sesquiterpene hydroperoxide isolated from nature, and one of the few that are known from plant sources. Although the amount of peroxyferolide isolated from different plants varied considerably, it could be prepared in high yield from lipoferolide (25), by photooxygenation using methylene blue as sensitizer. All four compounds showed antifeeding activity against the larvae of the gipsy moth, Lymantria Dispar L., with tulirinol showing 69 and 53% activity at concentrations of 50 and 250 μg/ml, respectively.

Nakanishi and co-workers have isolated three other germacranolide insect antifeedants which show activity against S. exempta and Epilachna varivestis[46,4]. Schkuhrins I (29) and II (30) were obtained only after reverse phase HPLC of the crude extract of Schkuhria pinnata. Eriancorin (31) was obtained from the leaves of Eriangea cordifolia. Schkuhrins I and II both show in vitro cytotoxicity at 5.5 µg/ml and antimicrobial activity against certain gram positive bacteria. Eriancorin has been reported to inhibit ATP-ase[47].



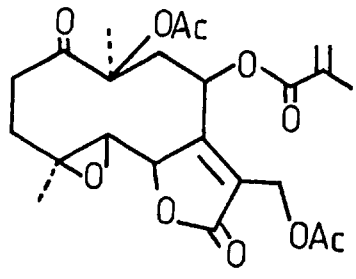
(29) R=Ac

(30) R= 



(31)

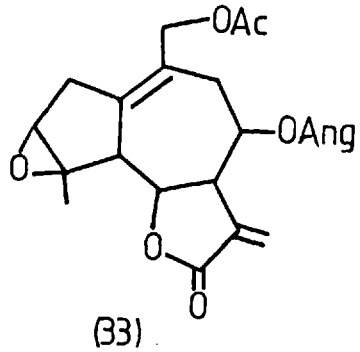
A butenolide containing sesquiterpene glaucolide A (32) has been isolated from the genus Veronia, and its antifeeding properties investigated[48]. The antifeedant was tested with several species of insect, but only gave positive results with the fall and southern armyworms, S. eridania and S. frugiperda, which are both polyphargous.



(32)

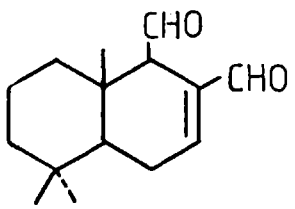
The yellow striped armyworm, S. ornithogalli actually preferred the treated leaves in a choice test and there was no apparent effect upon growth, even in concentrations up to .5%.

During a search for insect development inhibitors, it was found that the larvae of the fruit fly would not grow in a medium which contained the methanol extract of Eupatorium japonicum Thurb[49]. This suggested that either growth inhibitors and/or antifeedants were present. The active principle was found to be euponin,(33), which actually turned out to be a growth inhibitor, and not an anti-feedant.

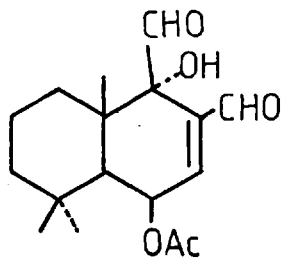


(33)

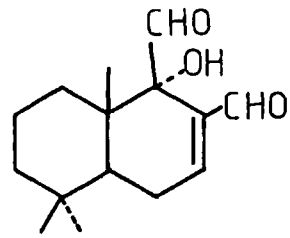
b) Polygodial Related Antifeedants



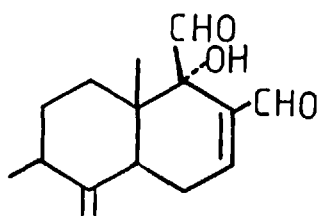
(34)



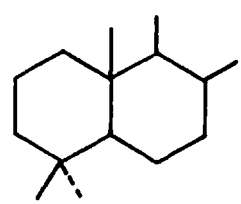
(35)



(1)



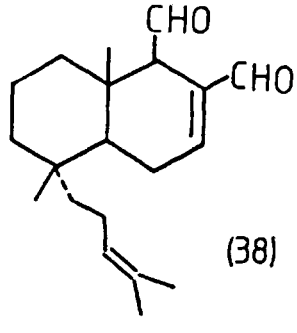
(36)



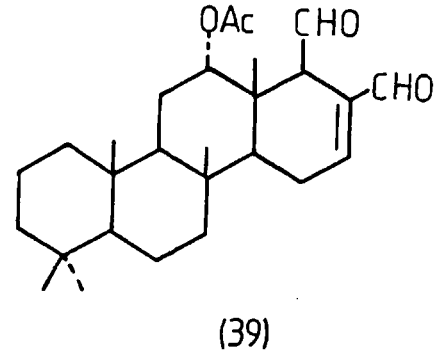
(37) Drimane

Polygodial (34) is a drimane sesquiterpene which was isolated[50] from Polygonum hydropiper L. by Barnes and Loder in 1962. Since then it has been isolated from Drimys lanceolata Baill.[51], Porella vernucosa[52], and Warburgia stuhlmannii[3]. Ugandensidial (35), muzigadial (36) and warburganal (I) were isolated[53] from a second plant of the Warburgia species, W. ugandensis Sprague. Ugandensidial had already[54] been isolated from this plant and also from Cinnamosma fragrans Baillon when it was called cinnamodial[55]. Canellal, isolated from Canella winterana L., has been shown[56] to be muzigadial.

Warburganal and muzigadial were obtained from the plant in low yield (.1%) but both are extremely potent biologically active molecules. Both of these compounds show the strongest insect antifeeding activity known against S. littoralis and S. exempta (.1 ppm shown 100% activity), but they show no activity at all against Manduca sexta Joh. or Schistocerca vaga Scudd. Their activity has been studied by electrophysiological methods, which have already been discussed. The antifeeding activity of warburganal and muzigadial is much greater than that of ugandensidial, which, in turn, is greater than that of polygodial. It has also been shown that the activity of these compounds is suppressed in the presence of an equivalent of L-cysteine. This suggests that nucleophilic attack of a thiol group plays an important part in the taste mechanism of the insect[57]. A further important fact is that if the aldehyde at the 9 position in polygodial is epimerized to the more stable 9α - configuration, by treatment with base, all activity is lost. All activity is again lost when the aldehydes are oxidised or reduced or even when only the 9β-aldehyde is reduced. Thus, for activity, the molecule requires i) the enal unit as a Michael acceptor, ii) the 9β-aldehyde (and, preferably, the 9α – hydroxy) as a means of hydrogen bonding to the substrate, and iii) an unblocked 6 position so that the Michael attack is unhindered. Two further compounds which contain the necessary functionality for antifeedant activity are (38)[58] and (39)[59]. However, these compounds have not been tested. Compound (38) does have a bitter taste which is some indication that it might show antifeedant activity.

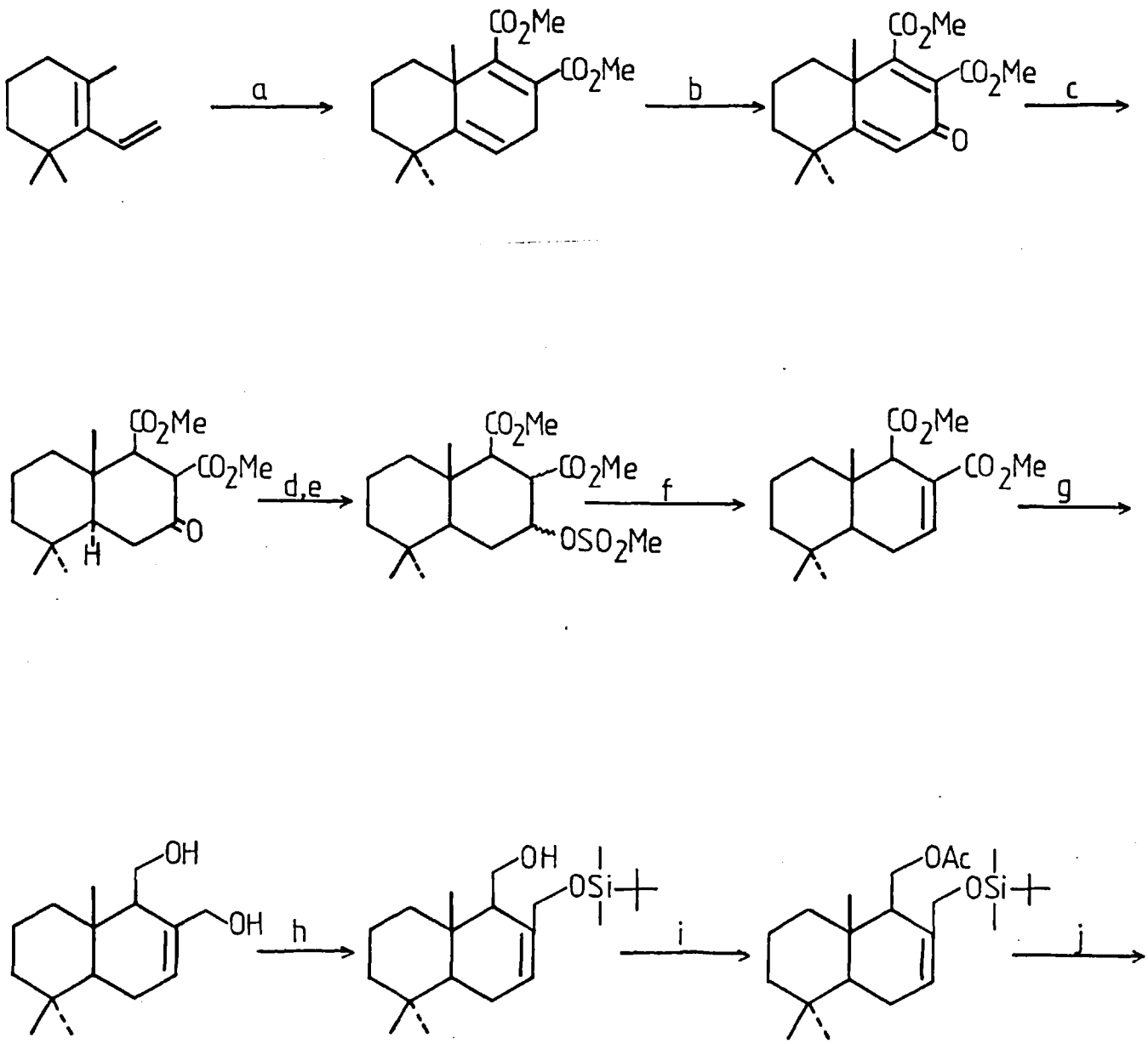


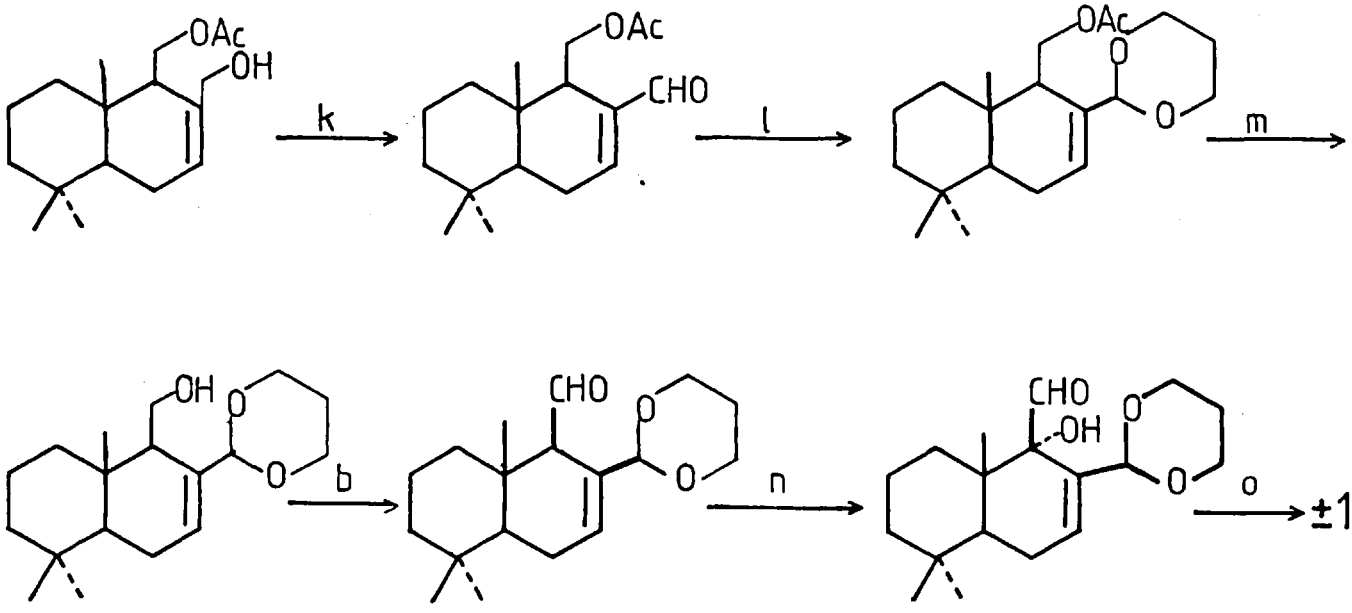
(38)



(39)

The broad range of biological activity shown by the polygodial group of compounds, coupled with the fairly simple structure has led to considerable work directed towards their synthesis. So far, four total syntheses of warburganal have been reported[60-63]. The most efficient of these[60], which resulted in a 15.7% overall yield of (±) warburganal, is outlined below.

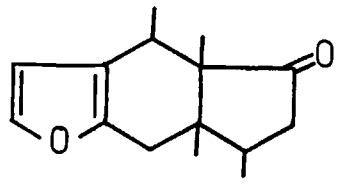




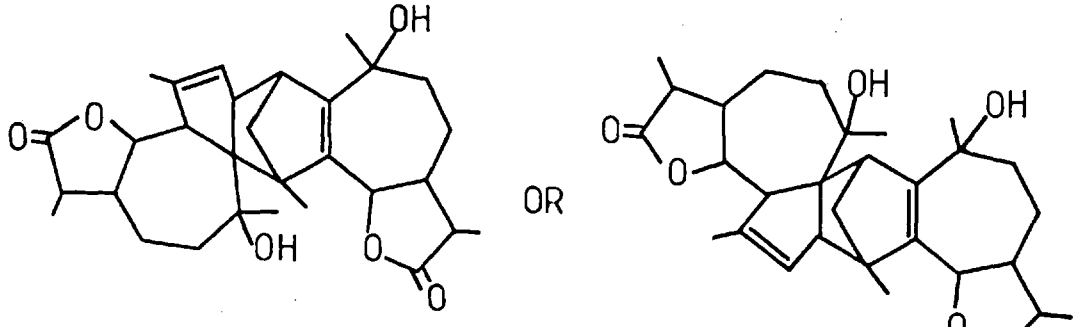
REAGENTS:- a) $CO_2Me-\equiv-CO_2Me$ b) $CrO_3.Py_2$ c) H_2, Pd/C d) $NaBH_4$, MeOH e) MsCl, Et_3N f) DBU g) LAH h) $-\overset{|}{\underset{|}{Si}}Cl$, imidazole, DMF i) Ac_2O/Py j) HOAc k) MnO_2 l) $HO(CH_2)_3OH$ m) KOH, MeOH n) LDA, MoO_5·Py·HMPA o) HCl, 

c) Pinguisone and absinthine

Both pinguisone[64](40), which was isolated from Aneura pinguis L., and absinthine[65], (41) (isolated from Artemisia absinthum L.) are compounds which are derived from sesquiterpenes. Munakata has shown[66] that both exhibit antifeeding activity against S. littoralis at concentrations greater than 0.125%. He also determined that there is no relationship between the bitterness of the compounds and the antifeeding activity.



(40)

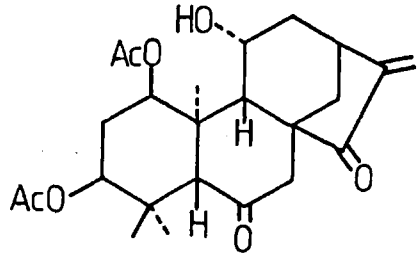


(41)

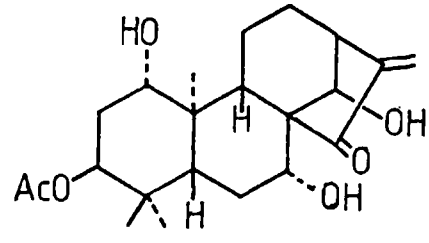
iv) Diterpenes

a) Ent-kaurene Antifeedants

Inflexin (42) was isolated[67] from the leaves of Isodon inflexus in 0.0003% yield and shows in vitro cytotoxicity (LD_{50} 5.4 µg/ml, KB test) and inhibitory activity on the respiratory reactions of the mitochondria from rat liver, as well as antifeedant activity against the American armyworm. The structure was determined by a number of nmr techniques. Isodomedin (43), isolated[68] from I. shikokianus var intermedius, also shows cytotoxic (LD_{50} 4.0 µg/ml) and antifeeding properties.

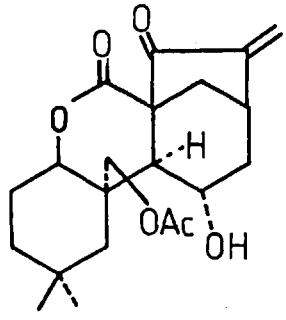


(42)

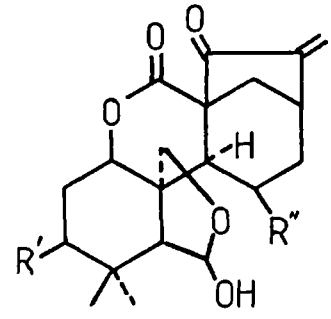


(43)

In an extensive study[69], again carried out by Kubo and co-workers, five Isodon ent-kaurenes (44 - 48) and their dihydro derivatives were examined with respect to their antifeeding activity. It has been found, in other studies, that the cyclopentenone moiety is necessary for biological activity (antimicrobial, cytotoxic, and inhibition of oxidative phosphorylation in rat liver mitochondria), due to its ability to add a thiol group in a Michael fashion.

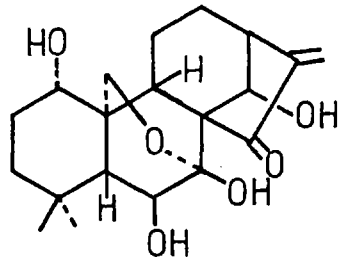


(44)

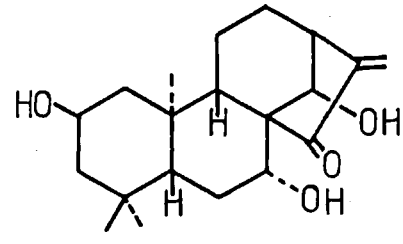


(45) R'=OH R"= H

(46) R'=H R"= OH



(47)



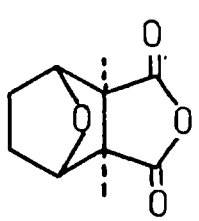
(48)

However, as both the unsaturated and di-hydro compounds have bitter taste, the a-methylene cyclopentanone moiety is not responsible for this. A theory has been proposed[70] that compounds in this series must contain a "bitter unit" to taste bitter.

This consists of a hard acid and a hard base moiety positioned so that they can form an intramolecular hydrogen bond. Consequently, all of the compounds in this series which taste bitter show antifeeding activity; in a "choice" test all prevented feeding for two hours at 100 ppm against S. exempta, but none showed antifeeding activity after twenty four hours in a "no-choice" test. Isodonal (44) and enemin (45) showed only 50% antifeeding activity at 1000 ppm after twenty four hours. These compounds may then be termed "relative" antifeedants. When the insects which had been fed on the unsaturated compounds were returned to a normal diet their growth was strongly inhibited and they eventually died. It was shown that these compounds are actually growth inhibitors and that the insects consume more than twenty times the lethal dose before they are unable to feed. Other insects which were tested, such as the house fly, Musca domestica, and the antesia bug, Antestiopsis spp., were unaffected.

b) Cantharidine

Cantharidine (49), as well as being a very strong poison (with a lethal dose of 0.5 mg/kg for humans) is also an insect antifeedant[71].



(49)

Tests were carried out on several species of ant, and it was shown that effective concentrations were in the order of 10^{-5}M. However, several species of insect were unaffected by cantharidine.

c) Clerodanes

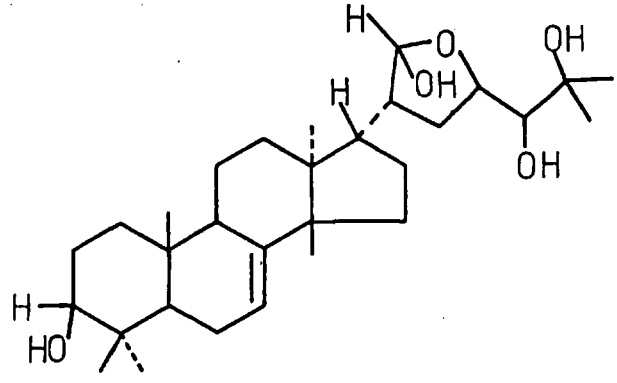
These compounds will be dealt with in a section of their own in a later part of this review.

v) Triterpenes

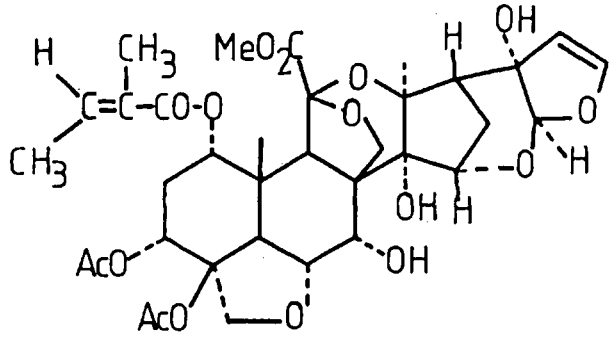
a) Meliantriol and azadirachtin

It has been known for a long time that plants of the Melia species are not attacked by a large number of insects, including Schistocerca gregaria Forsk., Locusta migratoria L., Anacridium aegypticum L., Calliptamus italicus L., and Dociustaurus maroccanus Thunb.[72-76] An extensive review[77] on the use of the crude extract of Melia azedarach L. as an antifeedant has recently been published.

Following these observations, Lavie and co-workers[78] isolated a compound from the chloroform extract of the fruit and seed oil of M. azedarach, which showed 100% antifeeding activity against crickets at a level of 3 $\gamma\ cm^{-2}$ on filter paper impregnated with .25 M sucrose solution (this corresponds to .8 $\mu g\ cm^{-2}$). The compound was called meliantriol and assigned structure (50), which was confirmed by partial synthesis from meliandiol, which had also been previously isolated from M. azedarach.



(50)



(51)

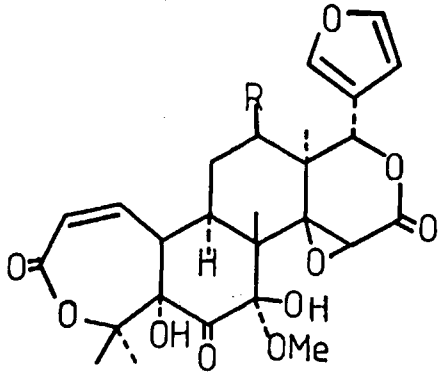
The crude leaf extract of M. azadirachta L., when applied to coffee leaves, caused morphological changes in Antestiopsis (coffee bug) stronger even than that of an equivalent weight of β-ecdysone[79] (insect moulting hormone). During attempts to isolate this active compound azadirachtin (51) was isolated[80], and its structure elucidated. The compound was first isolated by Butterworth and Morgan[81,82] from the seeds of M. azadirachta and M. azedarach and was shown[83] to be an effective antifeedant against Schistocerca gregaria (desert locust), causing 100% feeding inhibition at a concentration of 40 μg l^{-1} or on filter paper at 1 ng cm^{-2} (equivalent to .04 ppm.). Subsequently, the compound was shown to be an antifeedant against insects other than the desert locust, including[84,85] Heliothis virescens (tobacco bud worm) larvae, Pieris brassicae (cabbage moth) adults, Galleria mellonella larvae, and Teticuli termis (termite) larvae. However, it is not effective against other termites, aphids, or against Plutella xylostella L.[86] The most interesting and important property which azadirachtin shows is systemic activity[84]; it is absorbed by the roots of beans and distributed throughout the plant, effectively protecting new shoots from attack.

Although the structure is too complex to be usefully synthesised, the crude extract may be used as an antifeedant[77] due to the extremely potent effect, coupled with the fact that the compound appears to be harmless to humans and birds; birds actually consume the fruit and humans have used the twigs as chewing sticks to prevent tooth infection. Moreover, the dried seeds are readily available as their oil is used commercially in soap manufacture. Indeed, Volonsky[72] advocated the use of the Melia extract as an insecticide as long ago as 1937. He estimated that the extract from 400 kg of dried leaves could protect a vineyard of up to 60 hectares.

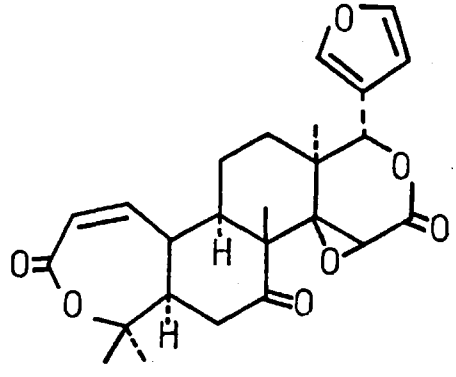
b) Harrisonin type compounds

Kubo and co-workers have recently isolated[87] Harrisonin (52a) from the East-African tree Harrisonia abyssinica Oliv, which has been used in folk medicine for many centuries. Later studies [4] revealed the presence of obacunone[88] (53) as well

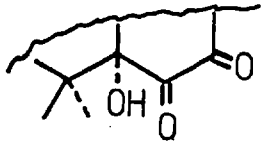
as the 12β-acetoxy (52b) and 6,7-diketone (54) derivatives of harrisonin. Harrisonin and the 12β-acetoxy derivative showed strong antifeeding activity towards S. exempta (100% activity being observed at 20 ppm) as well as antibiotic



(52) a R = H
b, R = OAc



(53)



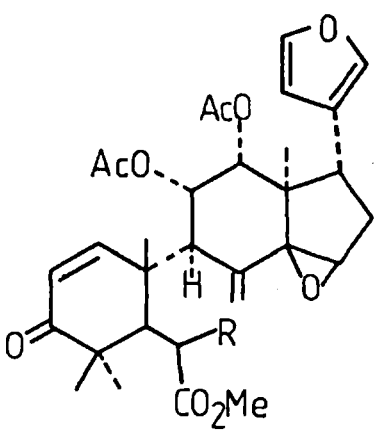
(54) R=H

activity (5 μg/ml against Bacillus subtilis) and cytotoxicity (KB test, 2.2 μg/ml). Obacunone showed no activity, while the diketone was obtained in too small a yield for bio-assay. It was expected that this, too, may show activity, due to the ease of hemiketal formation.

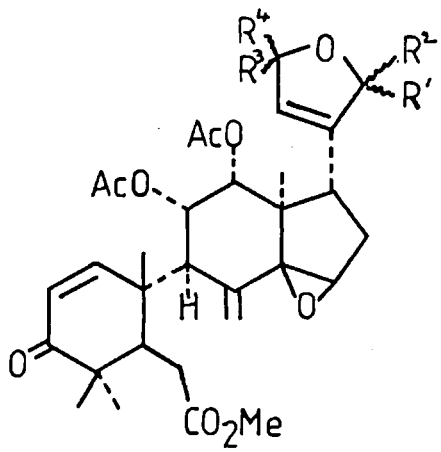
c) Toonacilins

Kraus and co-workers have isolated four compounds[89,90] from Toona ciliata which show antifeeding activity against the moth Hypsipyla grandella Zeller and the

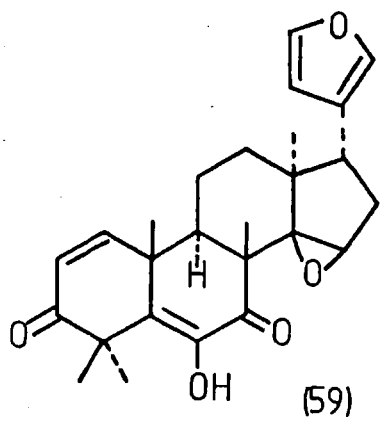
Mexican bean beetle Epilachna varivestis Muls., a virulent pest in the soybean plantations of America. Toonacilin (55) and 6-acetoxytoonacilin (56) are the first B-seco-tetranortriterperoids which are related to cedrelone (59). The 23- and 21- (R, S) hydroxy derivatives (57 and 58) were obtained in high yield from the more polar fractions of the extract. Moreover (57) has been prepared by photooxidation of toonacilin, and so these compounds may actually be artifacts of the isolation procedure.



(55) R=H
(56) R=OAc



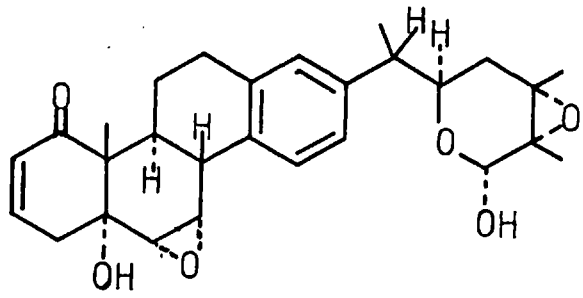
(57) R^1, R^2 = =O
R^3, R^4 = OH,H
(58) R^1, R^2 = OH,H
R^3, R^4 = =O



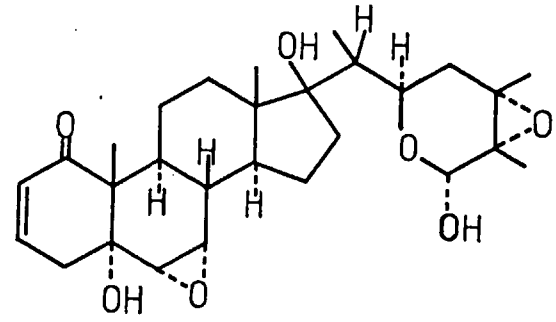
(59)

d) Triterpenoids from Nicandra physaloides

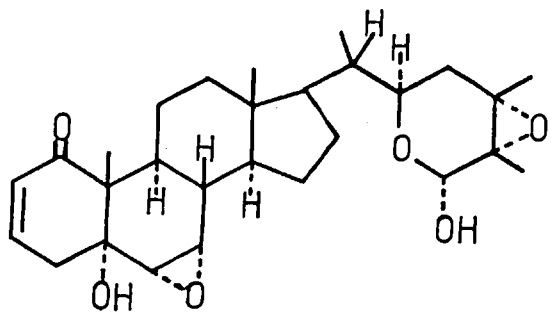
Many authors have noticed[91] that extracts of the Peruvian plant Nicandra physaloides Gaertn. show insect antifeeding properties and many triterpenes have been isolated and characterised[92]. The three major components (60, 61, 62) are shown below. Nicandrenone (60) prevents feeding by L. decemlineata at .01% concentration[29]. It is suspected, however, that these compounds may actually be repellants.



(60)



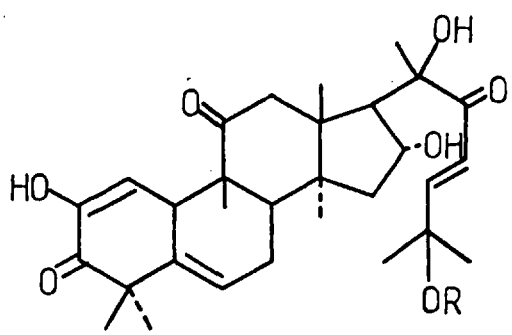
(61)



(62)

e) Cucurbitacines

It has been shown[93] that cucurbitacines E and I (63 and 64), which are isolated from the seeds and leaves of Iberis amara L., are effective antifeedants towards Phyllotreta nemorum L. Maximum inhibition of feeding is observed at 40 mg/l and 190 mg/l respectively. The same authors have shown that some feeding inhibition is also observed against P. undulata Kutsch., P. tetrastigma Com. and Phaedon cochlearidae F., while others[94,95] have noticed that the tree is not attacked by P. cruciferae Goeze or insects of the Pieris species.



(63) R = Ac
(64) R = H

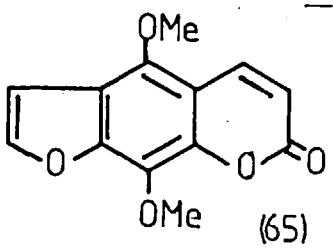
f) Friedelin

Friedelin (2) was isolated from the leaves of Acokanthera spectabilis Hook and was found to be an antifeedant against S. littoralis[11]. Its activity is similar to that of shiromodiol mono and diacetates and completely inhibits feeding at a concentration of 2,500 ppm.

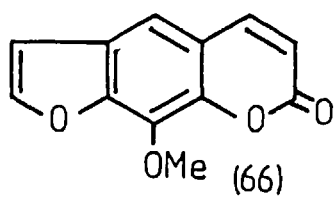
vi) Furocoumarins

A study[96] of forty two plants from twenty nine families revealed that nine showed quite strong antifeeding properties against S. litura. The strongest activity was observed

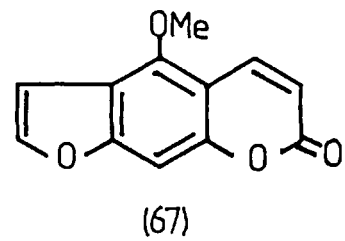
with the extract from Orixa japonica. Six active compounds were isolated; isopimpinellin (65), xanthotoxin (66), and bergapten (67), together with kokusagin (13), evoxin (15) and japonin (16), which have been discussed earlier. A feeding inhibition of 50% is observed against S. litura at concentrations of 5, 100 and 10 ppm respectively. Bergapten has also been isolated[97], together with xanthyletin (68) from the benzene extracts of Boenninghausenia albiflora Reichb. The antifeeding activity



(65)



(66)



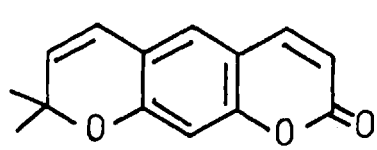
(67)

of xanthyletin is quite weak, showing 100% inhibition at a concentration of 2,500 ppm.

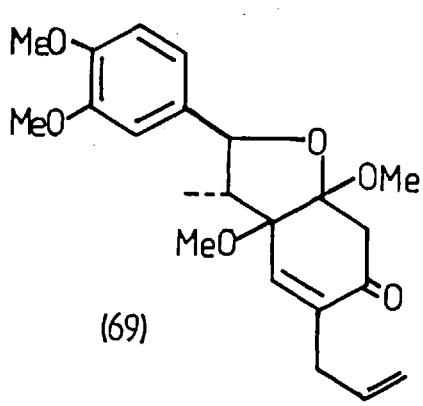
vii) Lignans and Derivatives

a) Compounds from Piper futokadzura

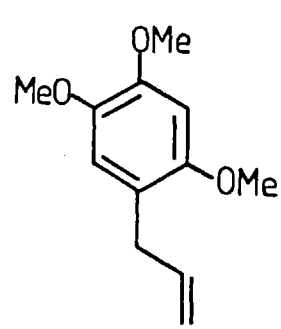
Piperenone (69) was isolated[98] from the benzene extract of the leaves of Piper futokadzura Sieb. and Zucc. The structure has since been confirmed by X-ray[99]. Piperenone shows 100% activity against S. Litura at a concentration of 0.005% while isoasarone (70), which was isolated[100] from the same source, shows a much weaker activity (100% inhibition at .5% concentration).



(68)



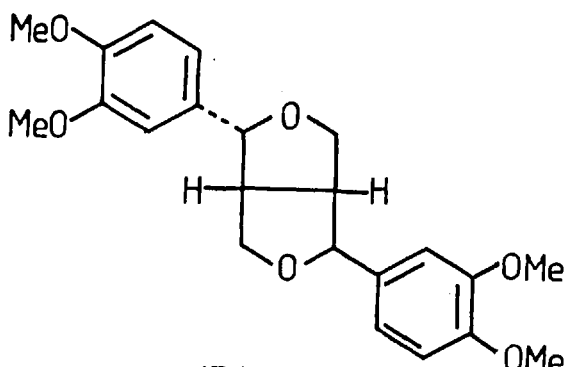
(69)



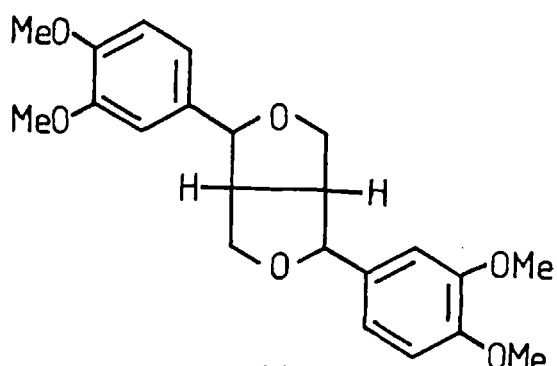
(70)

b) Compounds from Parabenzoin praecox Nakai

The benzene extract of Parabenzoin praecox Nakai yielded[100] two isomeric compounds, (+) epieudesmin (71) and (+) eudesmin (72) which showed quite different antifeeding properties against S. litura. Epieudesmin showed 100% inhibition at 0.05% while eudesmin showed 100% inhibition at 1%, indicating the important biological differences observed between epimers.



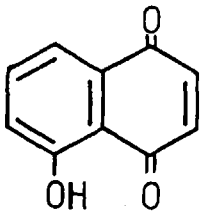
(71)



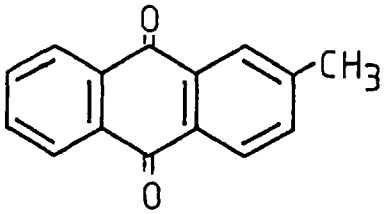
(72)

viii) Quinones

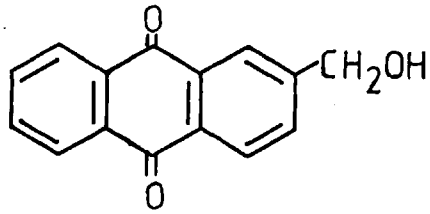
Norris[101] has shown that juglone (73) (from the bark of Carya ovata Mill) completely inhibits the feeding of Scolytus multistriatus at 0.5 mg/ml. However, no antifeeding activity is observed against Scolytus quadrispinosus. Other authors[102] investigated the effects of other anthraquinones (74 - 77) on termites. It is difficult, however, to determine whether these are actually antifeedants or repellants.



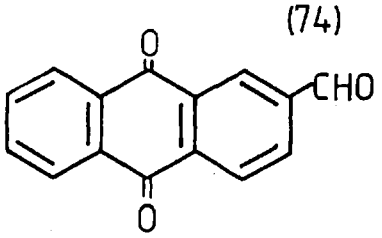
(73)



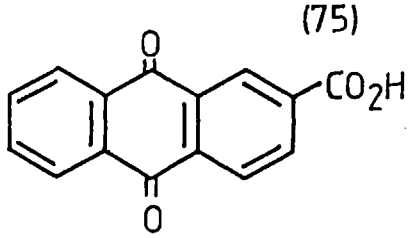
(74)



(75)



(76)

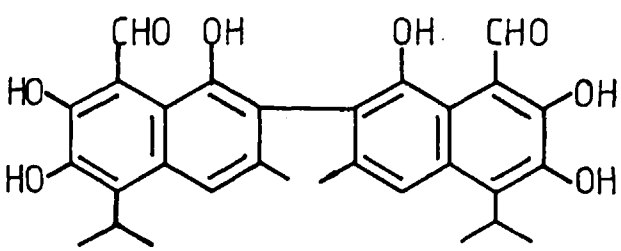


(77)

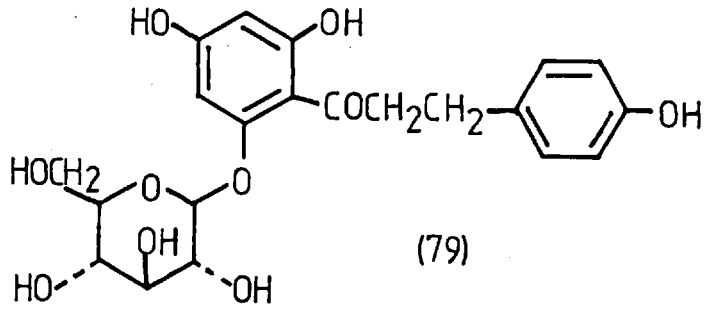
ix) Miscellaneous

a) Phenolic Compounds

Gossypol (78), which is present in all species of cotton, has been shown to be an antifeedant as well as a poison. A 1% solution strongly decreases the feeding of the larvae of Boarmia (Ascotis) selenaria Schiff. and S. littoralis[103]. Phlorizine (79), which is present in the apple trees of the genus Malus, exhibits antifeeding properties against the peach fly, Myzus persicae Sulzer, and against the fly Amphorophora agathonica Hottes, with complete inhibition being observed at 10^{-3}M concentration[104]. Unfortunately, it is much less effective against Aphis pomi De Geer which thrives on apple trees.



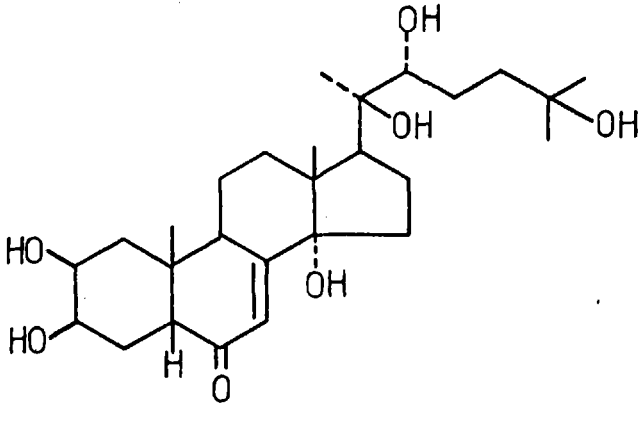
(78)



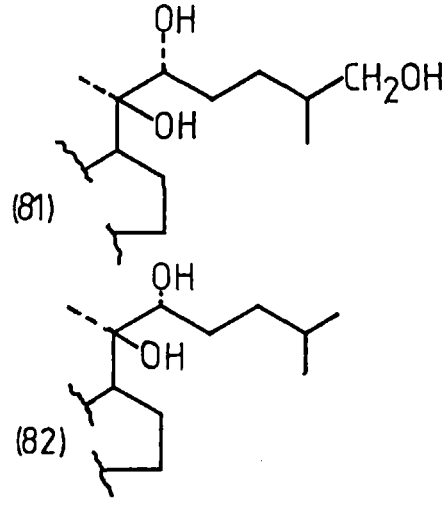
(79)

b) Steroids

Ecdysterone (80), inokosterone (81) and ponasterone A (82), which are hormones controlling the metamorphosis of insects, but which are also present in plants, have been shown to be insect antifeedants[105]. These compounds show antifeeding properties against the Cabbage White (Pieris brassicae L.) at all concentrations greater than 0.4×10^{-4}M, total inhibition being observed at 3×10^{-4}M.



(80)



(81)

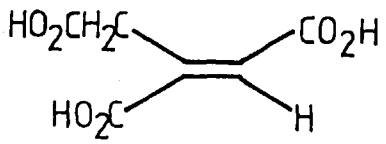
(82)

c) Others

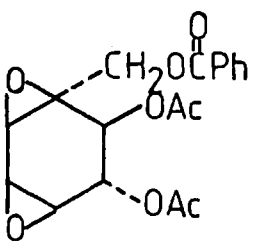
Trans-aconitic acid (83) has been isolated from barnyard grass (Echinochloa crus-galli var oryzicola) and has been shown to be the active antifeeding principle against the brown plant hopper[105] (Nilaparvata lugens Stal.). The calcium salt is active at 0.25% concentration, while the cis isomer is completely inactive.

The known[106] crotepoxide (84) which shows tumor inhibitory, antileukemic,

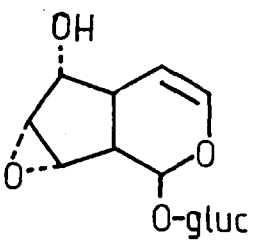
and antibiotic activity was isolated[4] from Croton macrostachys and shown to be the active antifeeding principle. Another epoxide was isolated as the active principle from the bark of Canthium euroides and was shown[4] to be unedoside (85) which had previously[107] been obtained from Arbutus unedo. Unedoside showed 100% feeding inhibition at 100 ppm against the African armyworm.



(83)



(84)

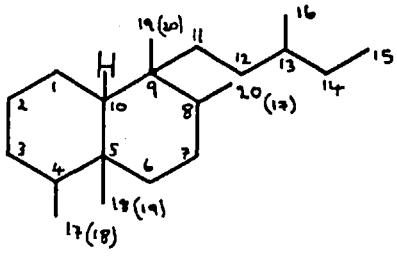


(85)

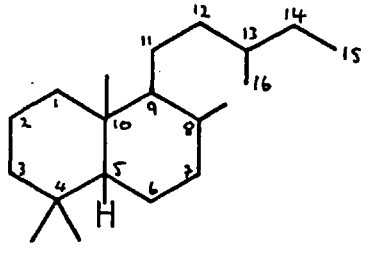
CLERODANE DITERPENES

Structures of clerodanes

Clerodanes have the basic skeleton shown below, and are derived from labdanes via a methyl shift from C4 to C5 and a methyl shift from C10 to C9. The numbering of



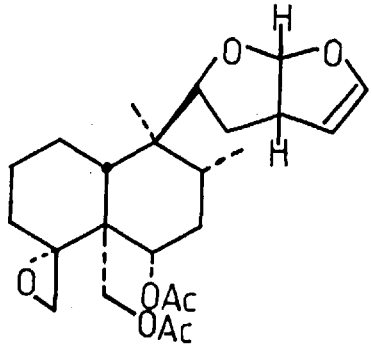
Clerodane skeleton



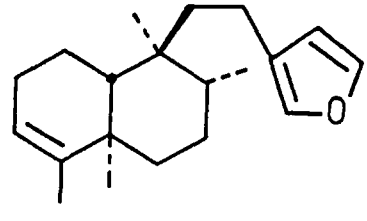
Labdane skeleton

the decalin portion and the side chain are consistent throughout the literature, however, the numbering of the other carbon atoms attached to the decalin portion varies as shown.

The first of the clerodanes isolated[108] was clerodin (83), from which the class takes its name. Although clerodin has a fairly complex, highly oxygenated structure many simpler, less functionalised clerodanes have been isolated, exemplified by annonene[109] (84).



(83)



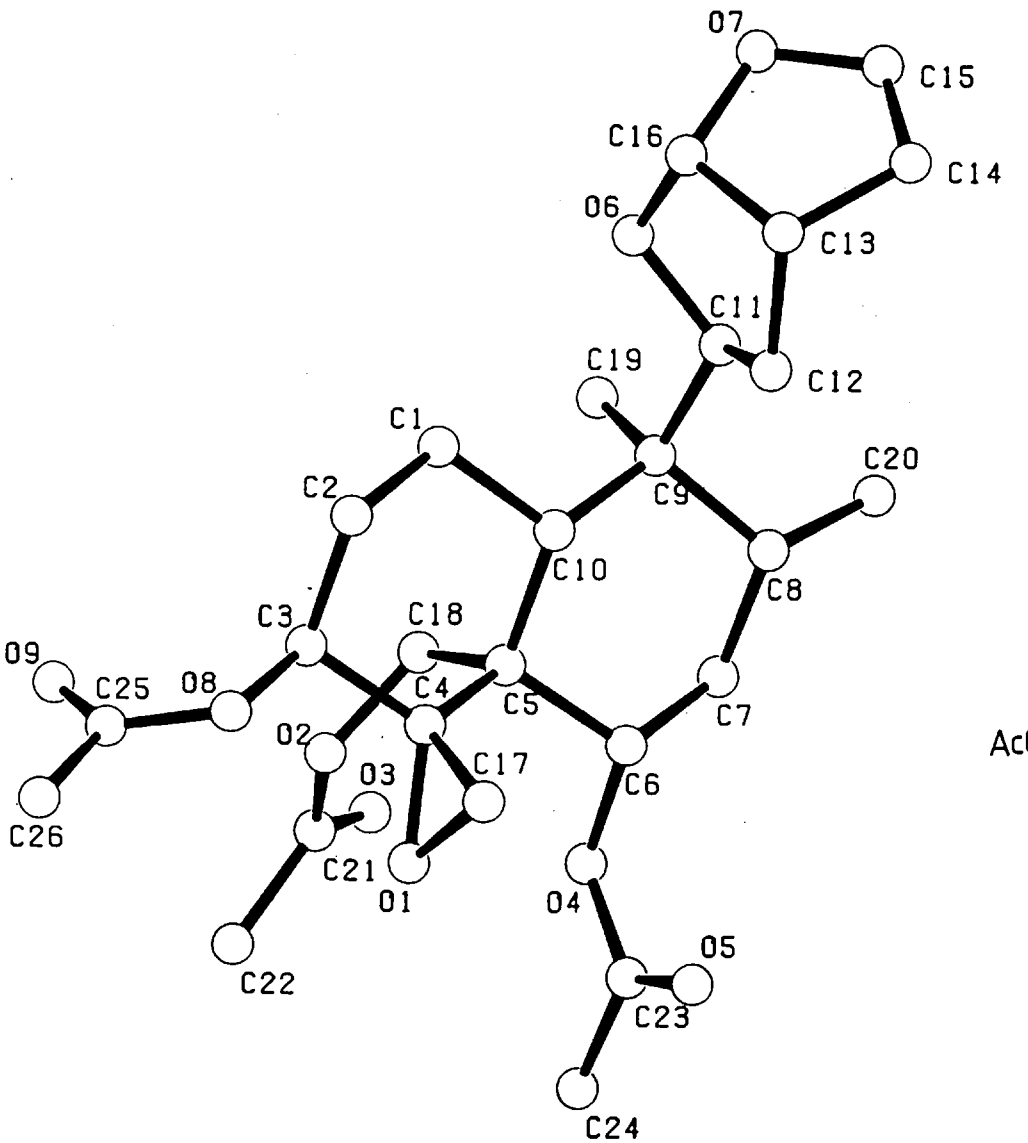
(84)

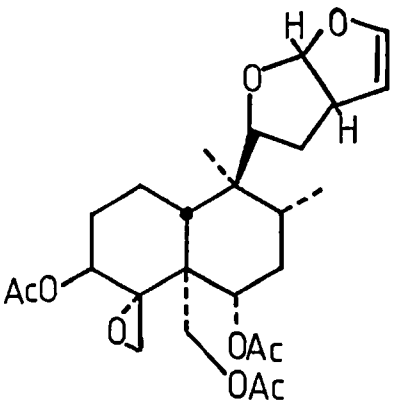
This section will be divided into two parts : i) clerodanes, which do show, or might be expected to show, antifeeding activity, and ii) synthetic approaches to the clerodanes.

i) Clerodanes which show, or might be expected to show, antifeeding activity

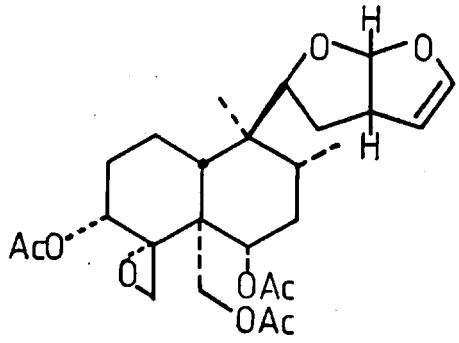
Since the isolation of clerodin in the late 1950's, there have been many highly oxygenated clerodanes isolated, but only recently have their biological properties been investigated. The absolute configuration of clerodin was determined by X-ray analysis of its bromohydrin by Sim and co-workers[110]. However, although the absolute configuration was correctly determined, there was an error which led to the wrong enantiomer being published as the absolute configuration. This error, however, was not discovered until recently[111] and so there is some confusion in the past literature. It has been suggested[111] that new nomenclature be adopted to indicate that authors have taken note of this revision. Thus, compounds which have the same absolute configuration as clerodin are now neo-clerodanes, while those which are still enantiomeric (if, indeed, they do exist) are termed ent-neo clerodanes. It now appears that all those compounds which show antifeeding activity should now be considered as neo-clerodanes.

Original assignments of the absolute stereochemistry of clerodanes was carried out by comparing the C.D. spectrum of a derivative of clerodin to that of a similar derivative of the compound under test. On this basis many compounds were designated as ent-clerodane and some, such as[112] caryoptin (85) and epi-caryoptin (86) (shown in neo-clerodane, absolute configuration), were thought to be exceptions to the general rules of determining absolute stereochemistry by Circular Dichroism spectroscopy. Recent X-ray and C.D. studies[111,113] of these compounds have shown that both have the same absolute stereochemistry as clerodin.

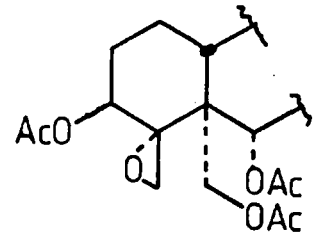

O7
C15
C16
C14
O6
C13
C11
C19
C12
C1
C20
C2
C9
C10
C8
C3
C18
O9
C25
O8
C4
C5
C7
O2
C17
O3
C6
C26
C21
O1
O4
O5
C22
C23
C24


H
O
O
H
AcO
O
OAc
OAc

(86)

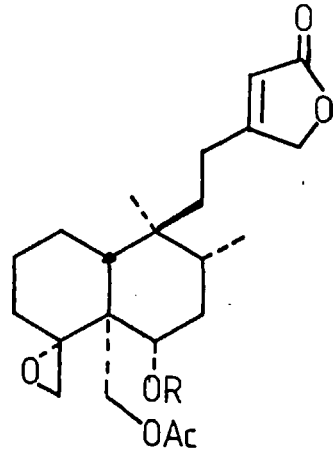


(85)



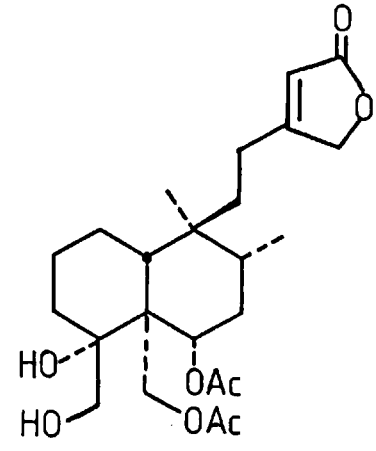
(86)

Although it has now been conclusively shown that those compounds showing antifeeding activity have the same absolute configuration as clerodin, Nakanishi has insisted[114], on the basis of C.D. work, that the ajugarins (87 - 89) are enantiomeric to clerodin. However, a recent X-ray study of an ajugarin derivative shows that the ajugarins are of the neo-clerodin absolute stereochemistry[115]



Ajugarin I (87) R=Ac

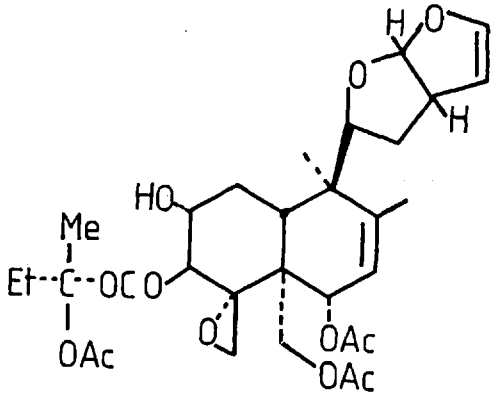
Ajugarin II (88) R=H



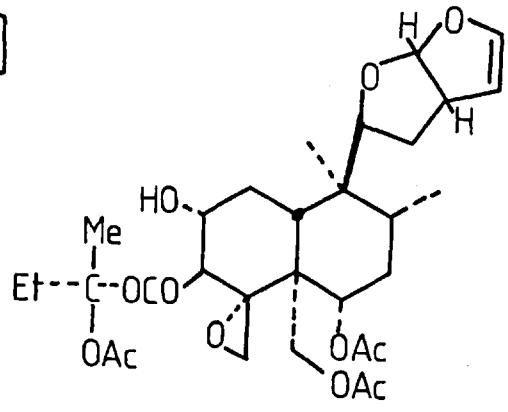
Ajugarin III (89)

Determination of the absolute stereochemistry of clerodendrins A (90) and B (91) was somewhat simplified[116] as hydrolysis had already shown that part of the molecule was the ester of R - (-) - 2 - hydroxy - 2 - methylbutyric acid. Thus, an X-ray of a

clerodendrin A derivative revealed the absolute stereochemistry immediately.

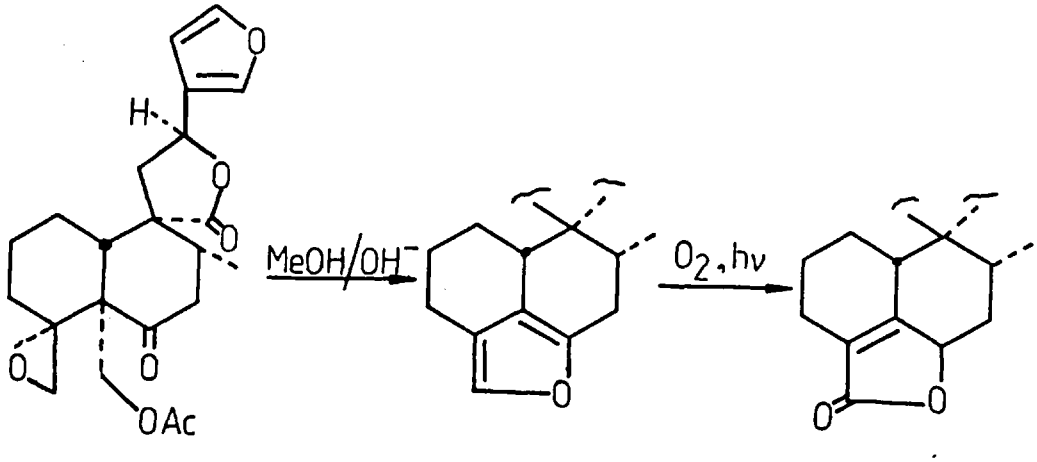


(90)



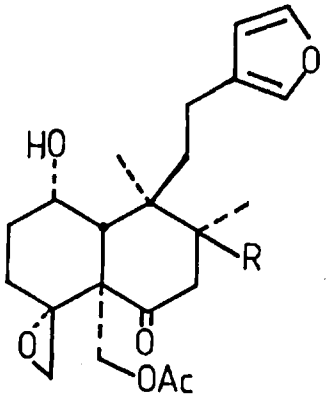
(91)

Many other clerodanes have a γ-lactone in the side chain, resulting from oxygenation at the 20 position. An example typical of this series is[117] 19-acetylgnaphalin (92) previously isolated[118] from a different Teucrium species and called teucrin H3. Treatment of (92) with base or chromatography of the 19-hydroxy derivative (gnaphalin) over silica led to (93) via a retro aldol reaction with loss of formaldehyde. This compound had already[119] been converted to teucvin (94) whose absolute stereochemistry had been determined. The fruiticolone series of clerodanes (95 - 97) (isolated[120] from Teucrium fruiticans) have a less oxygenated sidechain, but a more highly oxygenated decalin system.



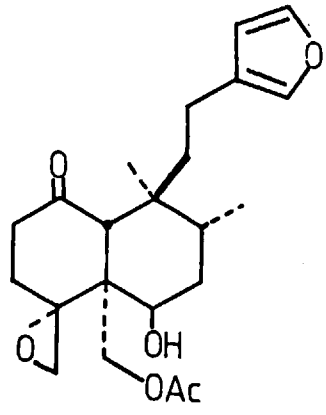
(92) (93) (94)

A further example of clerodanes which have been isolated are those in which a hemiacetal bridge is formed between C 19 and C 20. A representative example of this type is teucrin P_1 (98), which was isolated along with four other clerodanes from the bitter fraction of Teucrium polium L.[121].

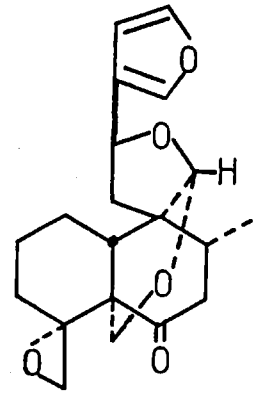


(95) Fruticolone R=H

(96) 8-Hydroxy fruticolone R=HO

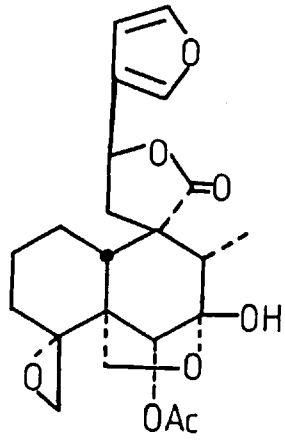


(97) iso-Fruticolone

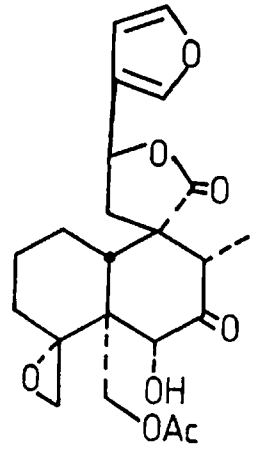


(98)

Other clerodanes showing hemiacetal linkages within the molecule are illustrated by compound (99), isolated[122] from T. polium. These result from hemiacetal formation between 19-hydroxy derivatives of those compounds which contain a ketone at position 7, such as picropolin (100)[122].



(99)



(100)

Antifeeding activity of clerodane compounds

Although a very large number of clerodane compounds have been isolated from nature, very few have been tested with respect to their insect antifeeding activity. The majority of the work carried out by Kato and Munakata[1,2,5,97,123] has involved derivatives of clerodin (83), caryoptin (85), epi-caryoptin (86) and clerodendrins A (90) and B (91). The majority of their work has concentrated on studying the effect of side chain modifications on the insect antifeeding properties (with respect to S. litura) as they claim that this is the site of activity. Their results are summarised in table 1, with the compound name referring to the decalin portion of the molecule. Their argument, however, should be considered with some scepticism considering that ajugarins I and II (87 and 88), which contain a butenolide side chain, also show strong antifeeding activity, with limiting concentrations of 100 and 300 ppm against S. exempta and S. littoralis respectively.

The most noticeable effect on antifeeding activity is observed when the decalin portion of the molecule is modified; both caryoptin and epicaryoptin, which have a 3-acetoxy substituent, show highly reduced antifeeding activity when compared to clerodin. The most noticeable difference occurs with the ethanol adducts of the hemiacetal derivatives; the caryoptin derivative shows only 50% inhibition of feeding at a concentration of 1,000 ppm, while the clerodin derivative completely inhibits feeding at 200 ppm. Thus, there appears to be a sinurgistic effect between substituents on the decalin ring (and especially in the 3-position, as can be observed with clerodendrins A and B) and substituents on the side chain (in this case the methanol adduct of clerodendrin A hemiacetal shows much enhanced antifeeding activity. This result, however, may not be correct).

It is also possible to compare compounds in which the decalin portion of the molecule has been varied, and the side chain has been kept constant. This variation

TABLE 1

CONCENTRATION FOR 100% FEEDING INHIBITION . AGAINST S. LITURA (ppm)

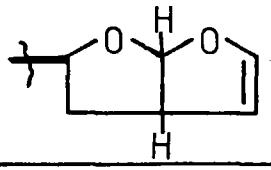
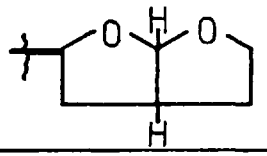
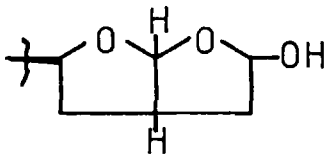
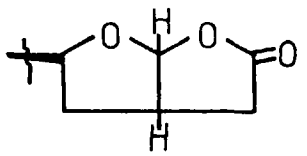
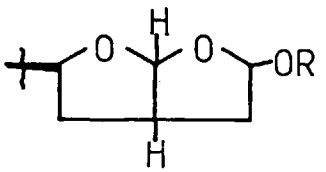
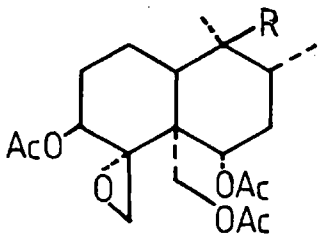
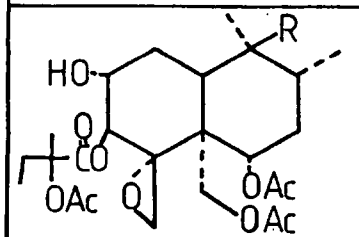
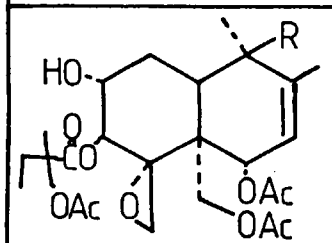
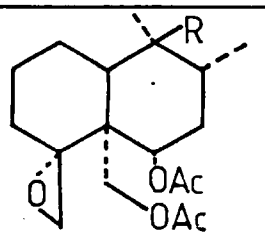
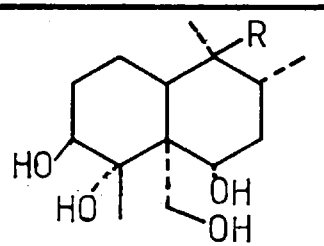
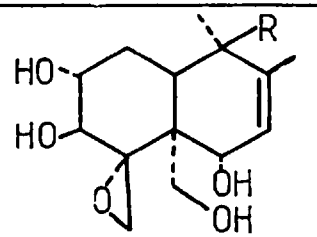
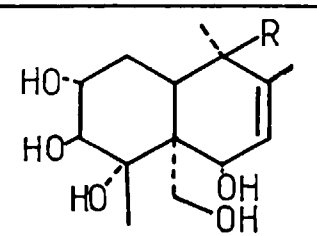
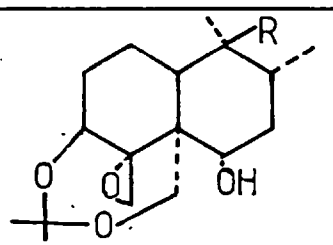
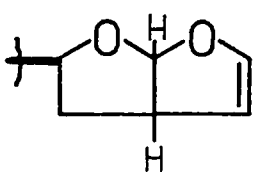
SIDE CHAIN	DECALIN SYSTEM				
	Clerodin	Caryoptin	3-Deacetyl caryoptin	Clerodendrins A	Clerodendrins B
	50	200	200	300	200
	50	80	100	500	—
	50	200	—	—	—
	50	500	—	—	—
	200 R = Et	>1,000 R=Et	15 R = Me	—	—

TABLE 2 VARIATION OF ANTIFEEDING EFFECT WITH DECALIN PORTION OF MOLECULE

DECALIN SYSTEM	ACTIVITY*
	200
	200
	300
	50

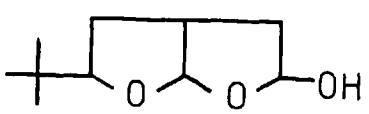
DECALIN SYSTEM	ACTIVITY*
	>1000
	>1000
	>1000
	>1000

R= 

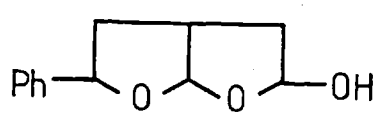
*CONCENTRATION FOR 100% FEEDING INHIBITION (ppm)

of the decalin portion is shown in table 2. One of the most important observations which has been made with regard to antifeeding activity is that ajugarin III, which does not contain an epoxide, is not an antifeedant, while ajugarins I and II are. This seems to suggest that the epoxide is necessary for antifeeding activity. This argument seems to have been completely ignored by Kato and Munakata. If this argument is true, then the only compound in table 2 which ought to show activity, but does not, is the last compound, caryoptin acetonide. However, the environment of the epoxide is so hindered that there is little chance of nucleophilic attack at C18, and so this example could also agree with the proposed argument.

Kato has recently tried to justify his theory that the perhydrofuro [2,3-b] furan ring is the centre of activity towards S. litura by preparing the simplified derivatives (101) and (102)[124]. These compounds were prepared according to scheme 2,



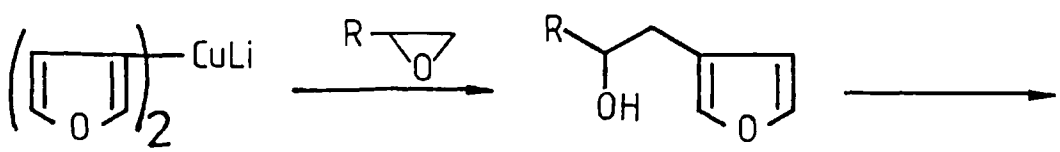
(101)

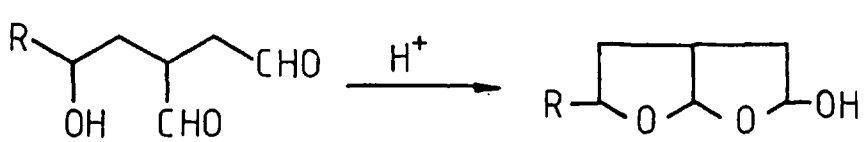


(102)

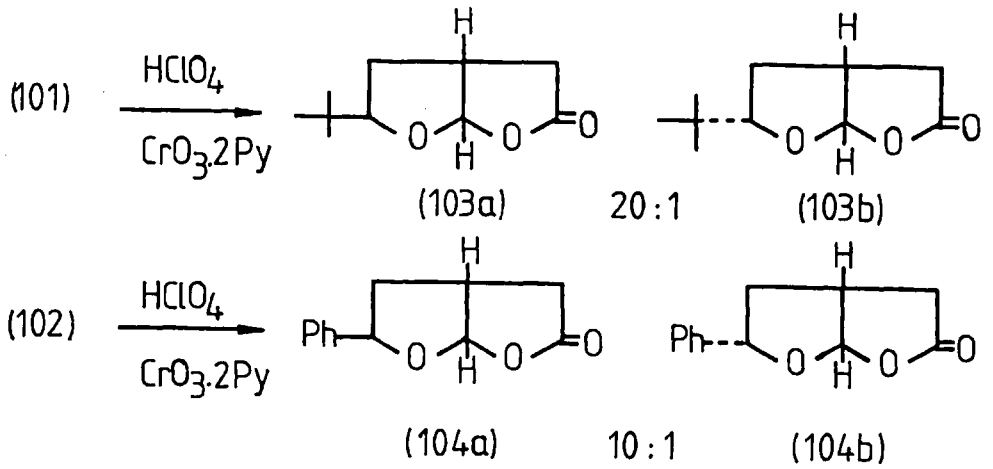
and they could be oxidised to the lactones, yielding a diastereomeric mixture. The lactols (101) and (102) could be equilibrated with $HClO_4$ to give, after oxidation, the lactones (103) and (104) in the ratios shown. After separation the major isomers

Scheme 2

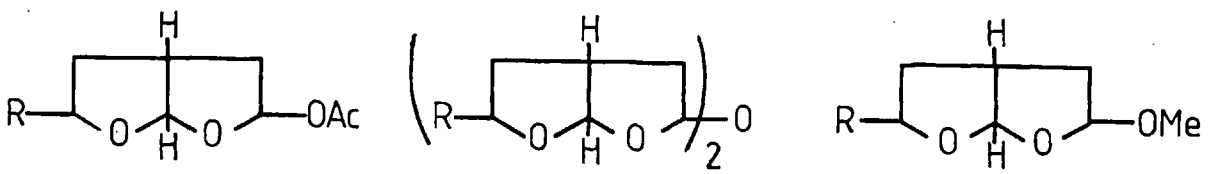




were converted to derivatives (105) to (110), which were tested for antifeeding

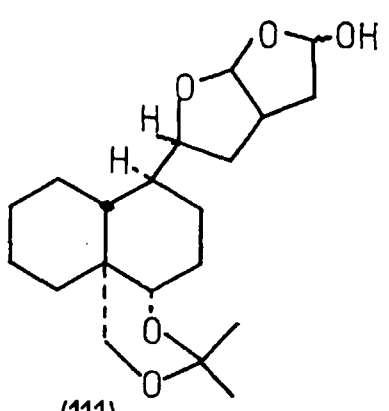


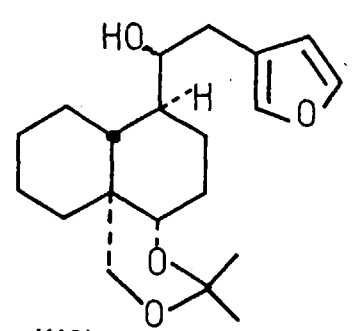
activity. Compounds (106), (108) and (110) all showed 100% inhibition of feeding



(105) R= t-Bu
(106) R = Ph
(107) R= t-Bu
(108) R= Ph
(109) R= t-Bu
(110) R= Ph

at 1000 ppm while little activity was observed with the t-butyl derivative. Considering that there is such a difference in activity between the phenyl substituted compounds, the t-butyl substituted compounds and the natural products suggests that this is not, after all, the centre of activity. A much better example to test the theory is compound (111), the precursor to which, (112), has recently been prepared[125] by the authors.





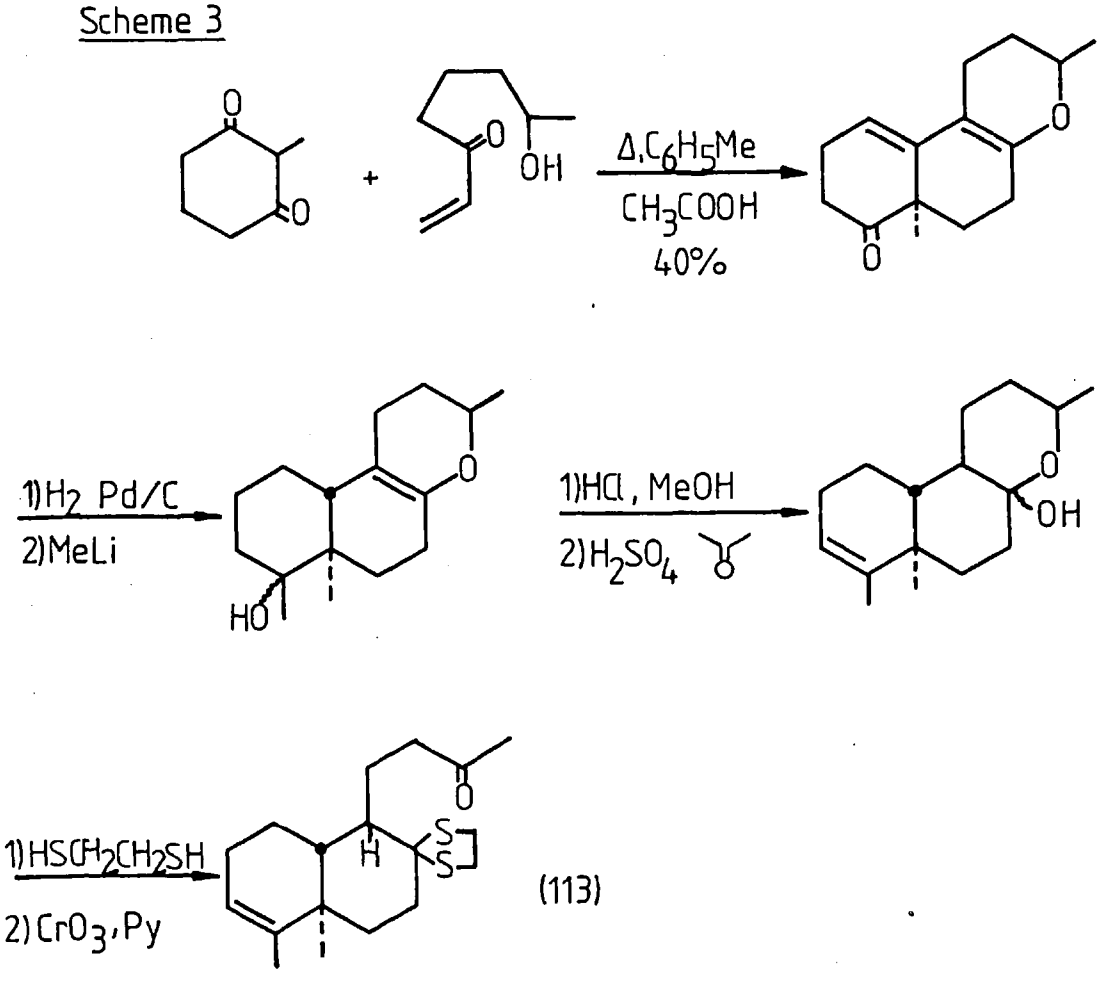
ii) Approaches to the synthesis of clerodane diterpenes

Although the first clerodane was isolated twenty years ago, there have been very few attempts to synthesise these compounds. Only since the discovery of their antifeeding properties have these compounds become the object of synthetic investigations.

The few approaches so far reported have concentrated on preparing suitable intermediates or models for the synthesis of less functionalised clerodanes. ApSimon's approach[126] suggested that (113) might be used as a suitable precursor to the clerodanes. This was prepared according to scheme 3, giving the final compound (113) in low overall yield. The approach is limited as (113) is a mixture of isomers at C-9 and it would be difficult to introduce the methyl at C-8 stereoselectively.

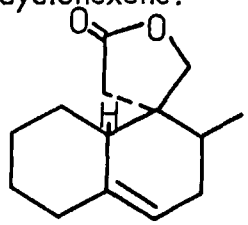
A second approach[127] suggested that (114) might be considered as a suitable

Scheme 3



(113)

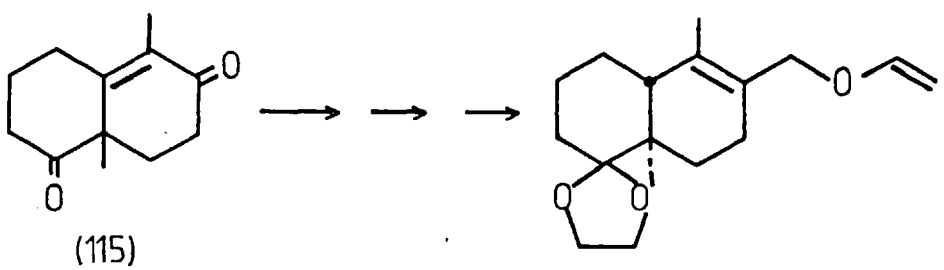
model for the clerodanes as it contains the correct stereochemistry at C-8, C-9 and C-10. The compound was prepared from the Diels-Alder adduct of a substituted maleic anhydride with 1-vinylcyclohexene.



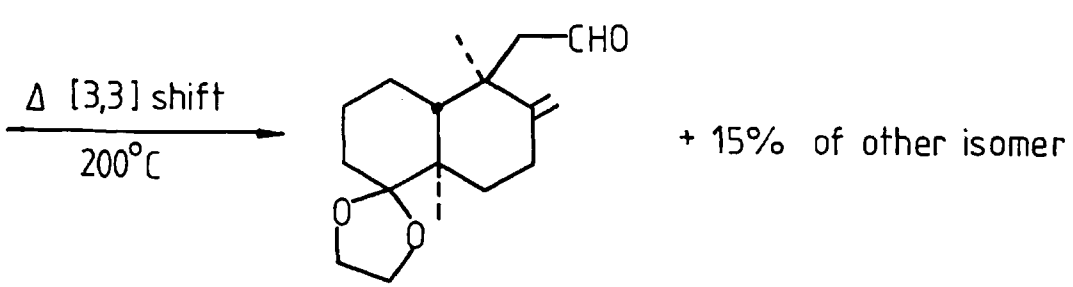
(114)

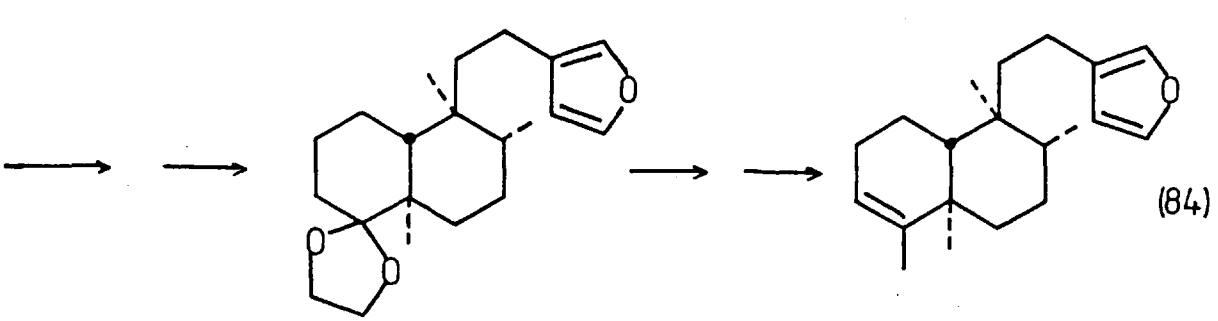
The first total synthesis of a clerodane has recently been achieved[128]. Annonene (8) was prepared from the Wieland-Mischer ketone (115) in a large number of steps, many of which gave a mixture of isomers (scheme 4). The drawback to this route is that it is not flexible enough to allow the synthesis of more highly oxygenated clerodanes.

Scheme 4



(115)

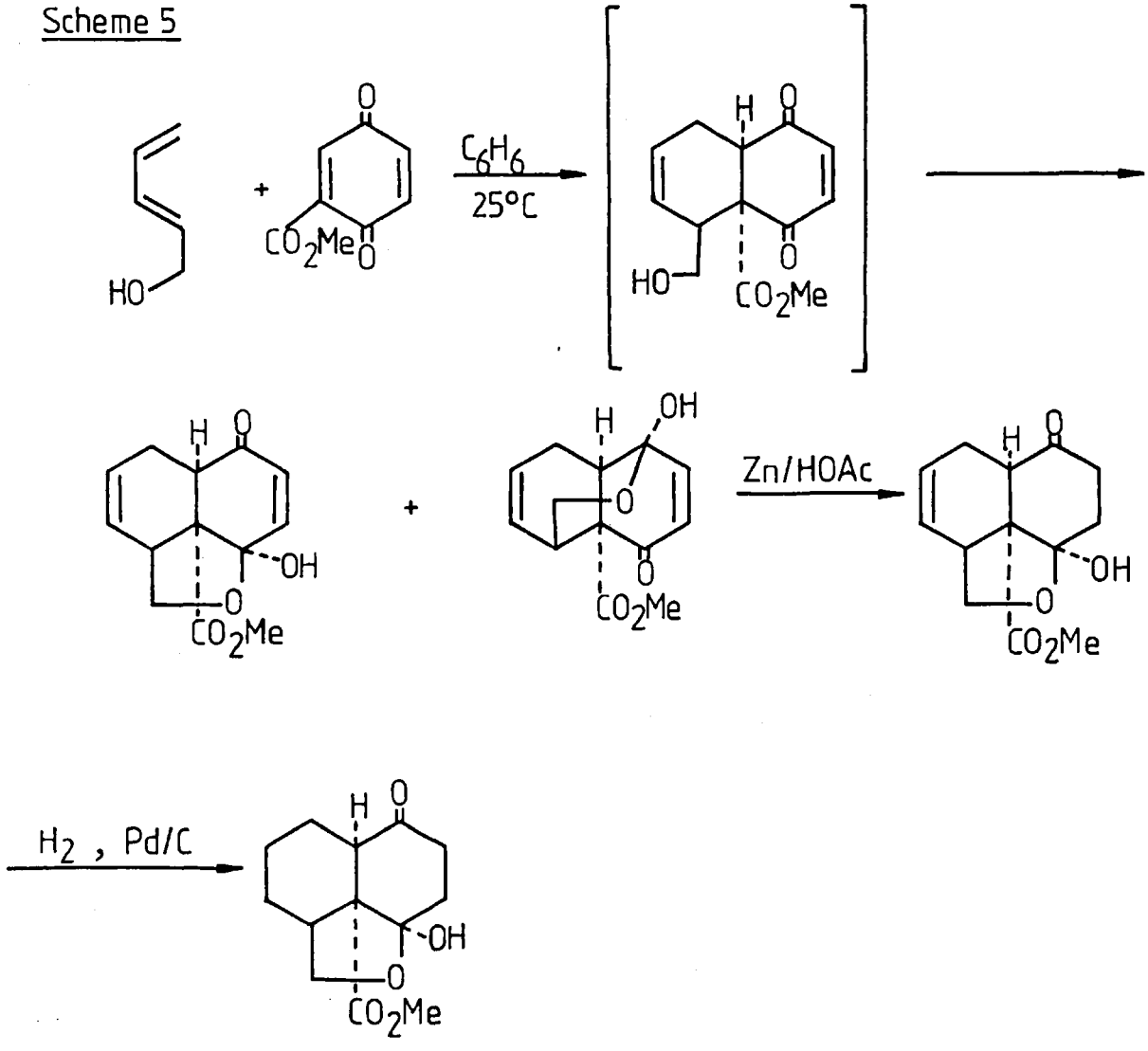




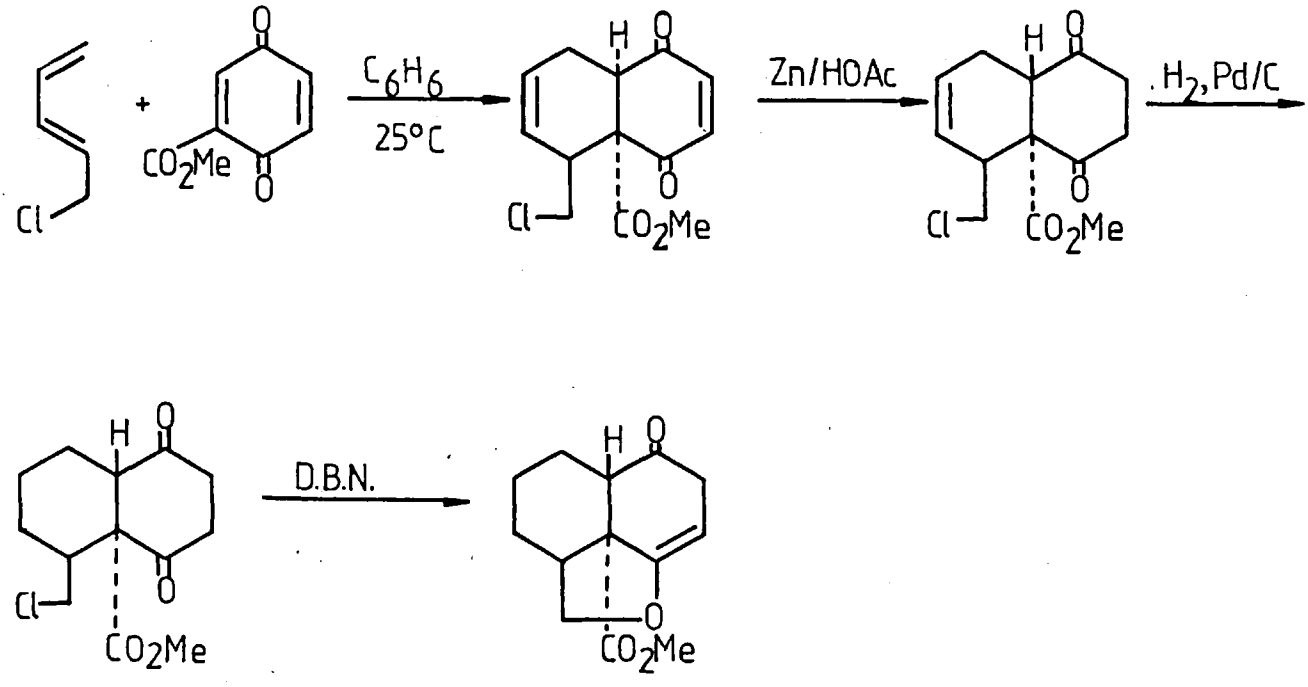
(84)

So far there has only been one study directed towards the synthesis of more highly oxygenated clerodanes. Goldsmith's approach[129] was to prepare an appropriately substituted decalin which may be converted to a clerodane. The decalin was prepared by a Diels-Alder reaction (scheme 5) between a substituted diene and a substituted quinone. However, the reaction was marred by the fact that a mixture of bridged hemiacetals was formed under the conditions of the Diels-Alder reaction and further reactions were not possible. His second approach (scheme 6) also failed because the chloro-decalin underwent substitution rather than elimination under basic conditions. This second approach was marred by the fact that the ring junction was alpha to a ketone; this was necessary so that the initially formed cis-decalin could be converted to trans . However, in a different series of reactions, isomerisation again took place, leading to a cis ring junction.

Scheme 5



Scheme 6



References

1) K. Munakata, A.C.S. Symposium on Host Plant Resistance to Pests, 1977, 62, 185

2) S. Hosozawa, N. Kato and K. Munakata, Agric. Biol. Chem., 1974, 38, 823

3) I. Kubo, Y-W. Lee, M.J. Pettei, F. Pilkiewicz and K. Nakanishi, J.C.S. Chem. Comm. , 1976, 1013

4) I. Kubo and K. Nakanishi, Advances in Pesticide Science, part 2, Zurich,1978

5) K. Munakata, Pure Appl. Chem., 1975, 42, 57

6) H. Buhr, R. Toball and K. Schreiber, Ent. Exp. Appl., 1958, 1, 209

7) T. Jermy, Ent. Exp. Appl., 1966, 9, 1

8) W.C. Ma and I. Kubo, Ent. Exp. Appl., 1977, 22, 107

9) R.F. Chapman, Bull. Entomol. Res., 1974, 64, 339

10) W.C. Ma, Physiol. Entomol., 1977, 2, 199

11) M.A. Abbassy, A. El-Shazli and F. El-Gayar, Z. Ang. Ent., 1977, 83, 317

12) D.M. Norris and H.M. Chu, J. Insect. Phys., 1974, 20, 1687

13) E.A. Barnays and R.F. Chapman, Symp. Biol. Hung., 1976, 16, 41

14) A.J. Aasen, C.C.J. Culvenor, E.P. Finnie, A.W. Kellock and L.W. Smith, Aust. J. Agric. Res., 1969, 20, 71

15) I. Kubo, I. Miura and K. Nakanishi, J. Amer. Chem. Soc.,1976, 98, 6704

16) J. N. All, D.M. Benjamin and F. Matsumura, Ann. Ent. Soc. Amer., 1975, 68, 1095

17) J.N. All and D.M. Benjamin, Canadian Entomologist, 1976, 108, 1137, and references therein

18) I. Kubo and K. Nakanishi, A.C.S. Symposium on Host Plant Resistance to Pests, 1977, 62, 165

19) V.G. Dethier, Chemical Insect Attractants and Repellants, 1974, p.210, Blakistan, Philadelphia

20) M.S. Chan and N.G. Patel, Indian J. Entomol., 1975, 35, 174

21) M. Hirata and K. Sogawa, Appl. Ent. Zoo., 1976, 11, 94

22) M.A. Gombos and K. Gasko, Acta. Phyto. Acad. Sci. Hung., 1977, 12, 349

23) K.R.S. Ascher, Phytoparasitica, 1979, 7, 117

24) R. Kuhn and A. Gauhe, Z. Naturf., 1947, 2B, 407

25) R. Kuhn, I. Löw and A. Gauhe, Chem. Ber., 1950, 83, 448

26) R. Kuhn and I. Low, in Origins of Resistance to Toxic Agents, Ed. M.G. Sevag, R.D. Reid and O.E. Reynolds, p. 122, Academic Press, New York

27) H. Buhr, R. Toball and K. Schreiber, Ent. Exp. Appl., 1958, 1, 209

28) B. Sturckow and I. Low, Ent. Exp. Appl., 1961, 4, 133

29) T.H. Hsiao and G. Fraenkel, Ann. Ent. Soc. Amer., 1968, 61, 485; 493

30) W. Ma, Meded. Landhoogesch. Wageningen, 1972, 72, 162

31) K. Wada and K. Munakata, J. Agr. Food. Chem., 1968, 16, 471

32) H. Chikamatsu and M.M. Tomita kotake, J. Chem. Soc. Japan, 1961, 82, 1708

33) M. Tomita and M. Fujie, J. Chem. Soc. Japan, 1962, 82, 1457

34) R. Tschesche, P. Welzel, R. Moll and G. Legler, Tetrahedron, 1964, 20, 1435

35) P.S. Clezy, E. Gellert, D.Y.K. Lau and A.W. Nichol, Aust. J. Chem., 1966, 19, 135

36) K. Sogawa, Appl. Ent. Zool., 1971, 6, 215

37) M. Hirata and K. Sogawa, Appl. Ent. Zool., 1976, 11, 53

38) T. Yajima, N. Kato and K. Munakata, Agric. Biol. Chem., 1977, 41, 1263

39) F.Y. Chou, K. Hostettmann, I. Kubo, K. Nakanishi and M. Taniguchi, Heterocycles, 1977, 7, 969

40) M. Nakane, C.R. Hutchinson, D. Van Engen and J. Clardy, J. Amer. Chem. Soc., 1978, 100, 7079

41) K. Wada, K. Matsui, Y. Enomoto, O. Ogiso and K. Munakata, Agric. Biol. Chem., 1970, 34, 941

42) K. Wada, Y. Enomoto and K. Munakata, Agric. Biol. Chem., 1970, 34, 946

43) R.W. Doskotch, S.L. Keely Jr., C.D. Hufford, and F.S. El-Feraly, Phytochemistry, 1975, 14, 769

44) R.W. Dos kotch, F.S. El-Feraly, E.H. Fairchild and C-T. Huang, J. Org. Chem., 1977, 42, 3614

45) R.W. Doskotch, E.H. Fairchild, C-T. Huang, J.H. Wilton, M.A. Beno and G.G. Christoph, J. Org. Chem., 1980, 45, 1441

46) M.J. Pettei, I. Miura, I. Kubo and K. Nakanishi, Heterocycles, 1978, 11, 471

47) N.J. Mugo, Agressologie, 1977, 18, 143

48) T.J. Mabry, J.E. Gill, W.C. Burnett, Jr., and S.B. Jones, Jr., A.C.S. Symposium on Host Plant Resistance to Pests, 1977, 62, 179

49) S. Nakajima and K. Kazuyoshi, Heterocycles, 1978, 10, 117

50) C.S. Barnes and J.W. Loder, Aust. J. Chem., 1962, 15, 322

51) J.W. Loder, Aust. J. Chem., 1962, 15, 389

52) Y. Asakawa and T. Aratani, Bull. Soc. Chim. France B, 1976, 1469

53) I. Kubo, I. Miura, M.J Pettei, Y-W Lee, F. Pilkiewicz and K. Nakanishi, Tetrahedron Letters, 1977, 4553

54) C.J.W. Brooks and G.H. Draffan, Tetrahedron, 1969, 25, 2887

55) L. Canonica, A. Corbella, G. Jommi and J. Křepinský, Tetrahedron Letters, 1967, 2137

56) F.S. El-Faraly , A.T. McPhail and K.D. Onan, J.C.S. Chem. Comm., 1978, 75

57) K. Nakanishi and I. Kubo, Israel J. Chem., 1977, 16, 28

58) Y. Asakawa, T. Takemoto, M. Toyota and T. Aratani, Tetrahedron Letters, 1977, 1407

59) C. Cimino, S. De Stefano and A. Di Luccia, Experientia, 1979, 35, 1277

60) S.P. Tanis and K. Nakanishi, J. Amer. Chem. Soc., 1979, 101, 4398

61) T. Nakata, H. Akita, T. Naito and T. Oishi, J. Amer. Chem. Soc., 1979, 101, 4400

62) A. Ohsuka and A. Matsukawa, Chem. Letters, 1979, 635

63) A.S. Kenda and T.J. Blacklock, Tetrahedron Letters, 1980, 3119

64) V. Benesova, Z. Zamek, V. Herout and F. Sorm, Collect. Czech. Chem. Comm., 1969, 34, 582

65) K. Vokáč, Z. Samek, V. Herout and F. Sorm, Tetrahedron Letters, 1968, 3855

66) K. Wada and K. Munakata, Agric. Biol. Chem., 1971, 35, 115

67) I. Kubo, K. Nakanishi, T. Kamikawa, T. Isobe and T. Kubota, Chem. Letters, 1977, 99

68) I. Kubo, I. Miura, K. Nakanishi, T. Kamikawa, T. Isobe and T. Kubota, J.C.S. Chem. Comm., 1977, 555

69) M. Taniguchi, M. Yamaguchi, I. Kubo and T. Kubota, Agric. Biol. Chem., 1979, 43, 71

70) T. Kubota and I. Kubo, Nature, 1969, 223, 97

71) J.E. Carrel and T. Eisner, Science, 1974, 183, 755

72) M. Volonsky, C.R. Soc. Biol. Paris, 1937, 127, 417; Arch. Inst. Pasteur. Alger., 1937, 15, 427

73) B. Krishnamurti and D.S. Rao, Bull. Agric. Coll. Research Inst. Mysore, Entomology ser., 1950, 14, 1

74) R.M. Shopra, 1958, in "Indigenous drugs of India", 2nd Ed., p.360, Dhur, Calcutta

75) F.R. Irvine, Woody Plants of Ghana, p. 512 and 525, Oxford University Press, 1961, London

76) J.M. Watt and M.G. Breyer-Brandwijk, in The Medicinal and Poisonous Plants of Southern and Eastern Africa, p.745 (2nd Ed.), E. & S. Livingstone Ltd., London

77) J.D. Warther, Jr., Agricultural Reviews and Manuals, Science and Education Administration, U.S. Department of Agriculture, 1979

78) D. Lavie, M.K. Jain and S.R. Shpan-Gabrielith, J.C.S. Chem. Comm., 1967, 910

79) K. Nakanishi, Recent Advances in Phytochemistry, Volume 9, Plenum Press, London, 1975

80) P.R. Zanno, I. Miura, K. Nakanishi and D.L. Elder, J. Amer. Chem. Soc., 1975, 97, 1975

81) J.H. Butterworth and E.D. Morgan, J.C.S. Chem. Comm. , 1968, 23

82) E.D. Morgan and M.D. Thornton, Phytochemistry, 1973, 12, 391

83) J.H. Butterworth and E.D. Morgan, J. Insect. Physiol., 1971, 17, 969

84) J.S. Gill and C.T. Lewis, Nature, 1971, 232, 402

85) C.N.E. Ruscose, Nature, New Biol., 1972, 236, 156

86) J.S. Gill, Ph.D. Thesis, University of London, 1972

87) I. Kubo, S.P. Tanis, Y-W. Lee, I. Miura, K. Nakanishi, and A. Chapya, Heterocycles, 1976, 5, 485

88) T. Kubota, T. Matsuura, T. Tokoroyama, T. Kamikawa, and T. Matsumoto, Tetrahedron Letters, 1961, 325; and references therein

89) W. Kraus, W. Grimminger and G. Sawitzki, Agnew. Chem. Internat. Ed., 1978, 17, 452

90) W. Kraus, W. Grimminger and G. Sawitzki, Proc. 11th Int. Sym. Chem. Nat. Prods., I.U.P.A.C., Bulgaria,1978, 115

91) G. Fraenkel, J. Nayar, O. Nalbandov and R.T. Yamamoto, Verh. XI. int. kongr. Ent., Wein., 1960, 3, 122 ; O. Nalbandov, R.T. Yamamoto and G. Fraenkel, J. Agr. Food Chem., 1964, 12, 55 ; F.V. Gizycki and G. Kotitschke, Arch. Pharm., 1951, 284, 129

92) M.J. Begley, L. Crombie, P.J. Ham and D.A. Whiting, J.C.S. Chem. Comm., 1972, 1108 ; M.J. Begley, L. Crombie, P.J. Ham and D.A. Whiting, J.C.S. Chem. Comm., 1972, 1250 ; R.B. Bates and S.R. M orehead, J.C.S. Chem. Comm., 1974, 125

93) J.K. Nielsen, L.M. Larsen and H. Sorensen, Phytochemistry, 1977, 16, 1519

94) P. Feeny, K.L. Paauwe and N.J. Demong, Ann. Ent. Soc. Amer., 1970, 63, 832

95) F. Terofal, Mitt. Muenchner Entomol. Ges., 1965, 55, 1

96) T. Yajima, N. Kato and K. Munakata, Agric. Biol. Chem., 1977, 41, 1263

97) S. Hosozawa, N. Kato, K. Munakata and Y.L. Chen, Agric. Biol. Chem., 1974, 38, 1045

98) K. Matsui and K. Munakata, Tetrahedron Letters, 1975, 1905

99) K. Matsui, K. Fukuyama, K. Tsukihara, I. Katsube and K. Munakata, Bull. Chem. Soc. Japan, 1976, 49, 62

100) K. Matsui, K. Wada and K. Munakata, Agric. Biol. Chem., 1976, 40, 1045

101) D.M. Norris, Ann. Ent. Soc. Amer., 1970, 63, 476

102) P. Rudman and F.J. Gay, Holzforschung, 1963, 17, 21

103) J. Meisner, M. Wysokim and L. Telzak, J. Econ. Entomol., 1976, 69, 683 ; J. Meisner, K.R.S. Ascher and M. Zur, J. Econ. Entomol., 1977, 70, 149

104) M.E. Montgomery and H. Arn, J. Insect Physiol., 1974, 20, 413

105) M. Kim, H. Koh, T. Obata, H. Fukami and S. Ishii, Appl. Ent. Zoo., 1976, 11, 53

106) S.M. Kupchan, R.J. Hemingway and R.M. Smith, J. Org. Chem., 1969, 34, 3898; K. Oda, A. Ichihara and S. Sakamura, Tetrahedron Letters, 1975, 3187; M.R. Demuth, P.E. Garrett and J.D. White, J. Amer. Chem. Soc., 1976, 98, 634

107) T.A. Geisman, W.F. Knaack, Jr., and J.O. Knight, Tetrahedron Letters, 1966, 1245

108) D.H.R. Barton, H.T. Cheung, A.D. Cross, L.M. Jackman and M. Martin Smith, J. Chem. Soc., 1961, 5061

109) M. Ferrari, F. Pelizzoni and G. Ferrari, Phytochemistry, 1971, 10, 3267

110) I.C. Paul, G.A. Sim, T.A. Hamor and J.M. Robertson, J. Chem. Soc., 1962, 4133

111) D. Rogers, G.G. Unal, D.J. Williams, S.V. Ley, G.A. Sim, B.S. Joshi and K.R. Ravindranath, J.C.S. Chem. Comm., 1979, 97

112) S. Hosozawa, N. Kato and K. Munakata, Tetrahedron Letters, 1974, 3753

113) N. Harada and H. Uda, J. Amer. Chem. Soc., 1978, 100, 8022

114) G. Trivedi, H. Komura, I. Kubo, K. Nakanishi, and B.S.Joshi, J.C.S. Chem. Comm., 1979, 885

115) K. Nakanishi, private communication

116) N. Kato, M. Shibayama and K. Munakata, J.C.S. Perkin I, 1973, 712

117) G. Savona, M. Paternostro, F. Piozzi and B. Rodriguez, Tetrahedron Letters, 1979, 379

118) E. Gacs-Baitz, L. Radics, G.B. Oganessian and V.A. Mnatsakanian, Phytochemistry, 1978, 17, 1967

119) E. Fujita, I. Uchida and T. Fujita, J.C.S. Perkin I, 1974, 1547

120) G. Savona, S. Passannanti, M.P. Paternostro, F. Piozzi, J.R. Hanson, P.B. Hitchcock and M. Siverns, J.C.S. Perkin I, 1978, 356;

G. Savona, S. Passannanti, M. Paternostro, F. Piozzi, J.R. Hanson and M. Siverns, Phytochemistry, 1978, 17, 320

121) P.Y. Malakov, G.Y. Papanova and N.M. Mollov, Z. Naturforsch., 1979, 34b, 1570

122) C.H. Brieskorn and T. Pfeuffer, Chem. Ber., 1967, 100, 1998

123) N. Kato, M. Takahashi, M. Shibayama and K. Munakata, Agric. Biol. Chem., 1972, 36, 2582 ; S. Hosozawa, N. Kato and K. Munakata, Phytochemistry, 1973, 12, 1833

124) Y. Kojima and N. Kato, Agric. Biol. Chem., 1980, 44, 855 ; Y. Kojima, N. Kato and Y. Terada, Tetrahedron Letters, 1979, 4667

125) Y. Kojima and N. Kato , Tetrahedron Letters, 1980, 4365

126) J. ApSimon and K. Yamasaki, Polish J. Chem., 1979, 53, 107; J. ApSimon and K. Yamasaki, Chem. Letters, 1977, 1453

127) T. Tokoroyama, K. Matsuo and T. Kubota, Tetrahedron, 1978, 34, 1907

128) S. Takahashi, T. Kusumi and H. Kakisawa, Chem. Letters, 1979, 515

129) D.J. Goldsmith, G. Srouji and C. Kwong, J. Org. Chem., 1978, 43, 3182

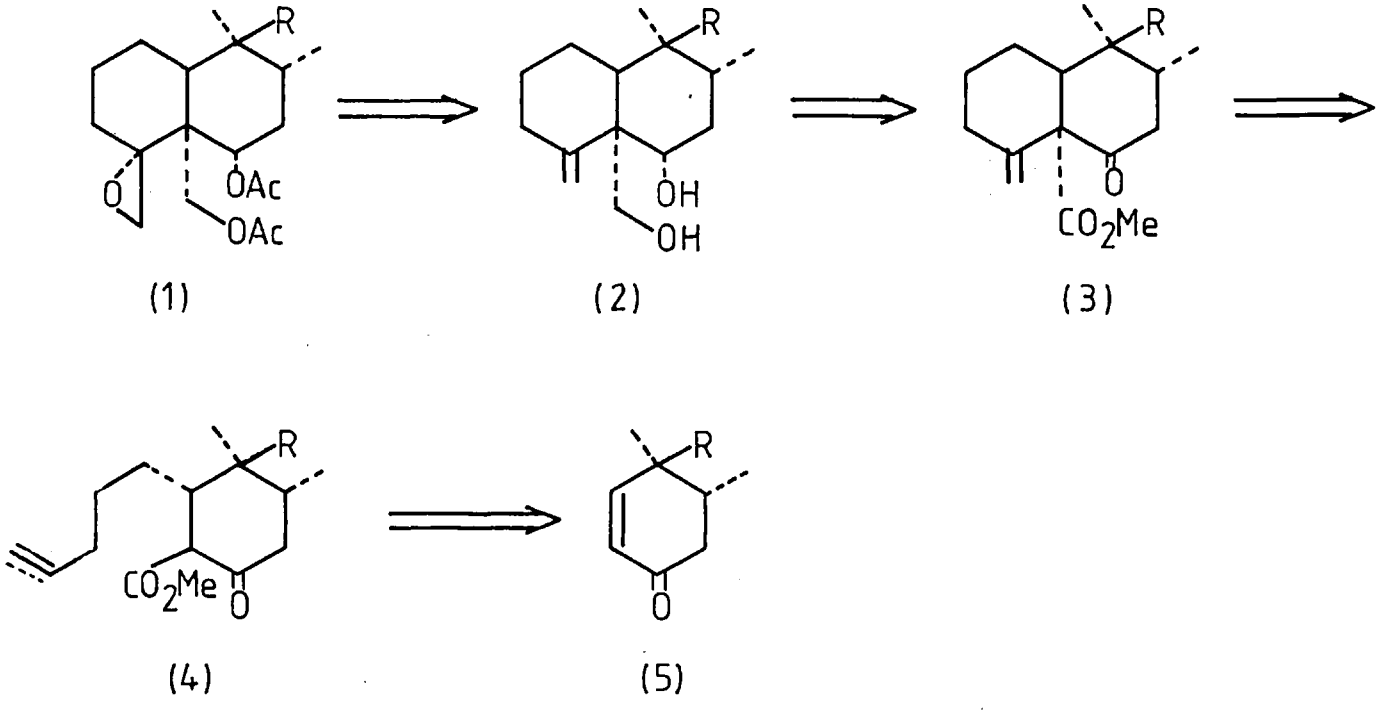
RESULTS AND DISCUSSION

Synthesis of Clerodane Diterpene Model Compounds

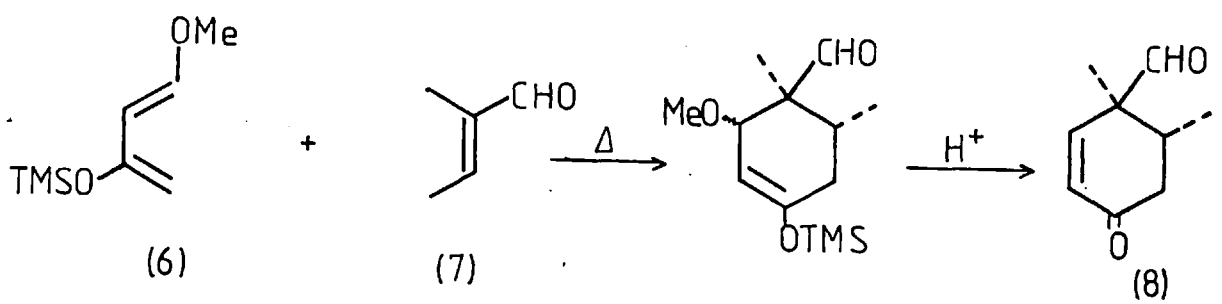
At the start of this project there had been no synthetic approaches to any of the clerodane diterpenes, oxygenated or otherwise. Due to the lack of specific knowledge of the functionality responsible for the insect antifeeding properties of certain clerodanes, we required a synthetic approach which was highly flexible and would allow us to modify the decalin ring system and the oxygenated side chain separately. Retro synthetic analysis (scheme 1) suggested that appropriately substituted cyclohexenones (5) might prove to be suitable starting materials.

It was argued that the final clerodane compound (1) could quite readily be prepared by a hydroxyl group directed[1] epoxydation of the methylene diol (2) and

Scheme 1



acetylation of the primary and secondary alcohols. The methylene diol (2) could, in theory, be quite easily prepared from the ketoester (3) by hydride reduction. We chose the β - keto ester (4) to function not only as a precursor to the required diol but also that it might assist in the cyclisation onto a suitable side chain to form the second six membered ring of the decalin unit. Compound (4) therefore becomes our initial synthetic target. This compound should be most reasonably obtained by a 1,4-conjugate addition of a copper species to the enone (5) and trapping of the intermediate regio-specific enolate with something which would afford the β - keto ester (4). The "R" group in the scheme should be such that it is easily transformed into the desired side chain. For this reason it was decided that enone (5) with "R" = CHO (8) should be easily prepared by Diels-Alder reaction between Danishefski's diene[2] (6) and tigaldehyde (7). The aldehyde function in (8) should serve as a useful group for

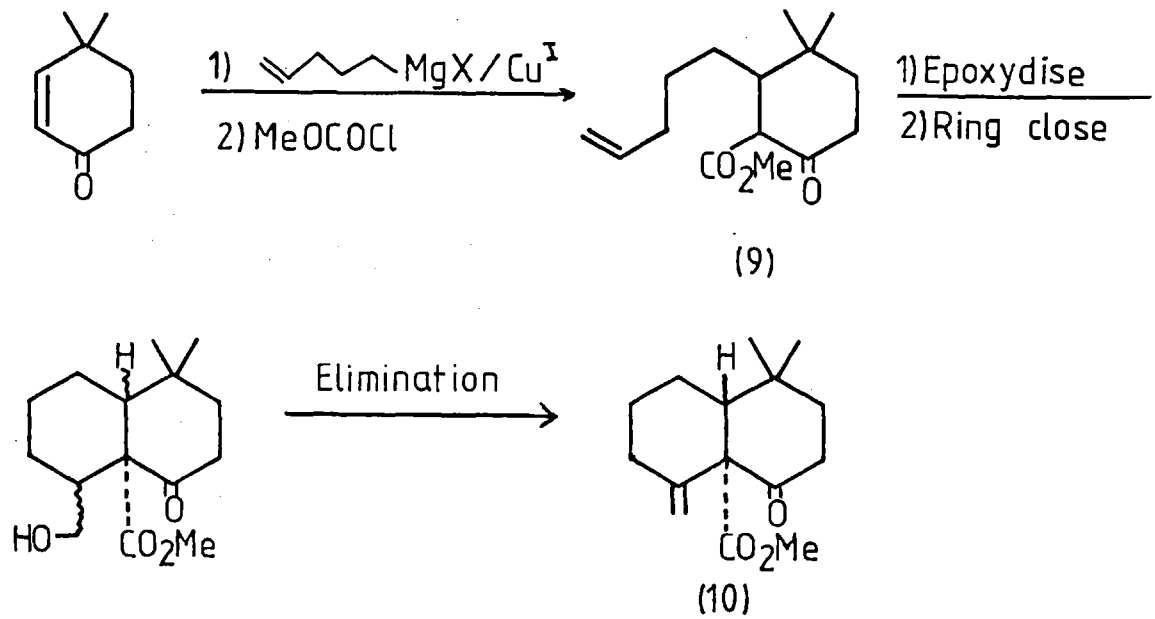


the preparation of a variety of side chains. Compound (8) has subsequently been prepared in these laboratories[3].

As we wished to probe the factors which determine insect antifeeding activity and also to develop methods for closing the β - keto ester onto the unsaturated side-chain we chose the symmetrical and cheap 4,4 - dimethylcyclohexenone[4] as the starting enone. Our initial route is outlined in scheme 2. We hoped that we might

be able to close the β-keto ester onto an epoxide (in the presence of a catalyst),

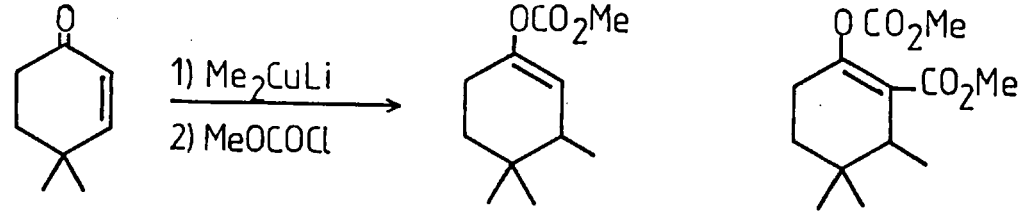
Scheme 2



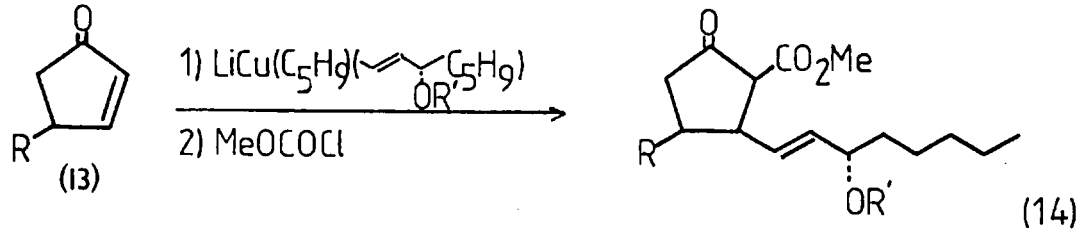
which, after elimination of water, would give the desired exo-methylene decalin system (10).

It had been shown previously[5] that when lithio-cuprates were added conjugatively to enones the resulting enolates often react via the oxygen atom when treated with acylating agents to form enol derivatives. For example, conjugate addition of lithium dimethyl cuprate to 4,4-dimethylcyclohexenone, in tetrahydrofuran, leads to a mixture of mono- and di-quenched products (11) and (12) on acylation with methyl chloroformate. In these reactions eleven equivalents of methyl chloroformate were used, and the reaction run overnight. Other authors[6] found that similar reactions could be modified to yield the product arising from quenching of the enolate on carbon. For example, addition of the mixed cuprate in tetrahydrofuran/H.M.P.A. to the substituted cyclopentenone (13) and quenching

with 1.5 equivalents of methyl chloroformate gave a mixture resulting from reaction on carbon (14, 55%) and a diacylated product (15, 15%).



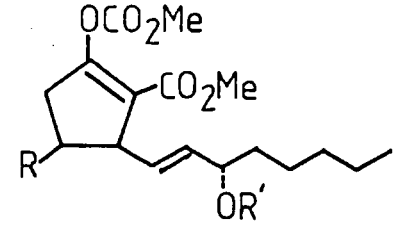
(11) 9% (12) 51%



(14)

R = OTHP

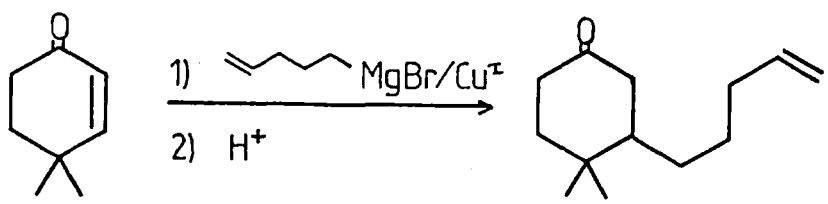
R' = ^{t}BuSiMe$_2$



(15)

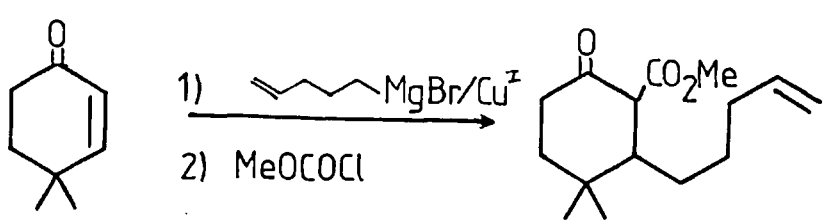
As pent-4-enyl lithium has been prepared twice before[7], it seemed that (9) might be fairly readily prepared. After several attempts to prepare the alkenyl lithium (and, therefore, the cuprate) had failed, reaction with pent-4-enylmagnesium

bromide and a copper (I) catalyst was studied. It was found that the copper (I) catalysed Michael addition of this Grignard reagent proceeded smoothly, in ether, at 0°C, to afford the 1,4 adduct (16) in 85% yield. The reaction was carried out by inverse addition of the Grignard to the enone and catalyst as recommended by Posner[8]. The i.r. spectrum of (16) showed a stretching frequency at 1715 cm^{-1} and the n.m.r. spectrum showed that the AB quartet of the enone double bond had been lost, both of which are consistent with structure (16). Stork has shown[9] that magnesium



(16)

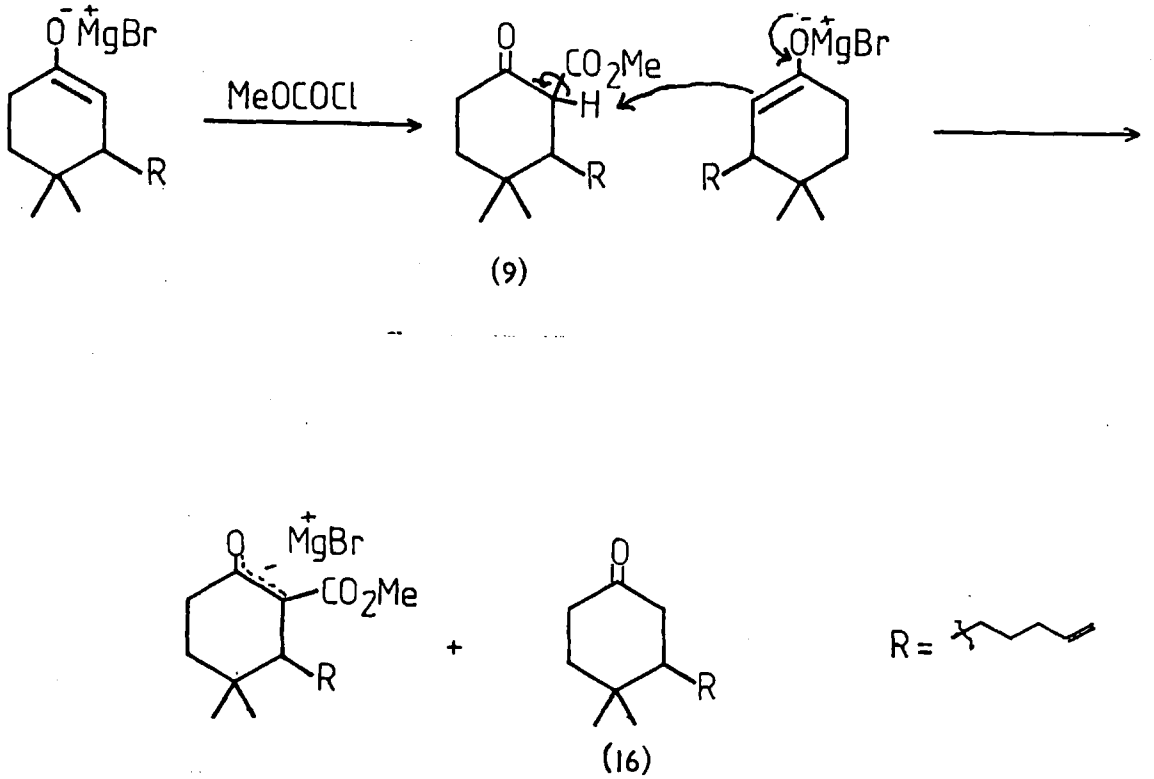
enolates do not equilibrate below -10°C, and as we wished to trap the regiospecific enolate, the conditions were modified such that the reaction was carried out at -23°C. Copper (I) catalysed addition of pent-4-enylmagnesium bromide and quenching of the regiospecific enolate with methyl chloroformate afforded the desired β-keto ester (9) in reasonable yield (50-65%). The main by-product of the reaction was the H^{+}



(9)

quenched product (16). This presumably results from some equilibration taking place (scheme 3). A much quicker and easier method of preparing the β - keto ester was via

Scheme 3

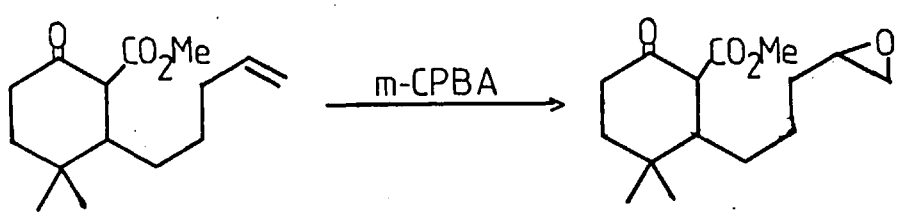


the homo-cuprate, i.e. addition of two equivalents of Grignard reagent to one of copper (I) iodide results in the formation of the homo-cuprate, $R_2CuMgBr$. Rapid addition of the enone at -78°C and quenching with methylchloroformate (at higher temperatures)again afforded the β- keto ester (9) in about 50% yield . The only other product is that from proton quench of the enolate.

From the i.r. spectrum of the β-keto ester (9) it could be seen that the compound existed almost entirely in the enolised form [ν_{max} 1755 (weak), 1715 (weak), 1660 (strong) and 1615 (strong) cm^{-1}] and thus increased our chances of effecting a cyclisation onto the neighbouring epoxide in compound (17). The epoxide

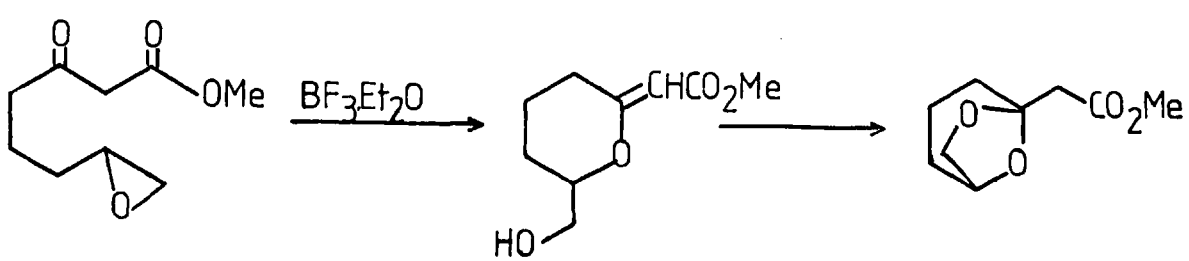
(17) was prepared from (9) in 50 - 60% yield, by treatment with m-CPBA in the normal manner. Longer reaction times gave a more polar product, which was not identified.

With (17) to hand we were now in the position to study its ring closure. Weiler[10] has recently shown that it is possible to perform an intra-molecular



(9) (17)

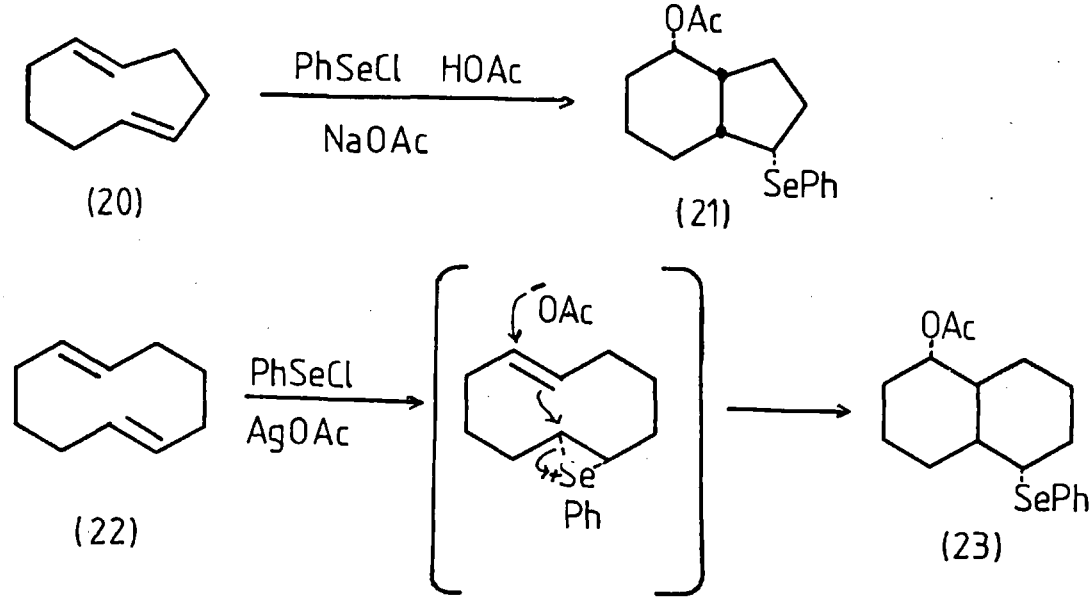
cyclisation of a β-keto ester onto an epoxide. In his example, cyclisation of the β-keto ester (18) afforded the hemiacetal (20), as opposed to the expected alcohol (19). We, however, attempted cyclisation of (17), under a variety of acid and Lewis acid conditions, without success. Also, under basic conditions no cyclised



(18) (19) (20)

product was observed, possibly due to the stability of the anion between the β-keto ester. What was apparently required, then, was a more electrophilic species than the

epoxide. Consequently, the idea of using intermediate seleniranium ions was investigated. Clive has shown[11] that dienes (20) and (22) may be cyclised to the bicyclic compounds (21) and (23) respectively via the intermediacy of a seleniranium species. Encouraged by these observations, phenyselenium chloride was reacted with



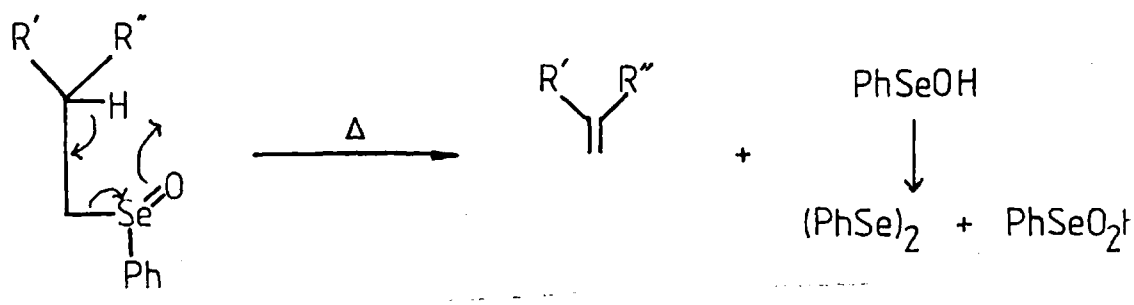
the unsaturated β-keto ester (9) under a variety of conditions - even at reflux in pyridine ! - but no cyclisation was observed. The product was that due to simple addition of phenylselenium chloride across the double bond. It appears that the counter anion of the selenium species (in this case Cl^-) is too nucleophilic compared to the β-keto ester. What was therefore required was a non-nucleophilic counter anion. Garratt and Schmidt have shown[12] that species such as $PhSe^+PF_6^-$ and $PhSe^+SbF_6^-$ may be prepared by reaction of phenylselenium chloride with the respective silver salts in dichloromethane and that these species form stable seleniranium and selenerenium salts with olefins and acetylenes respectively,

provided that no other nucleophiles are present.

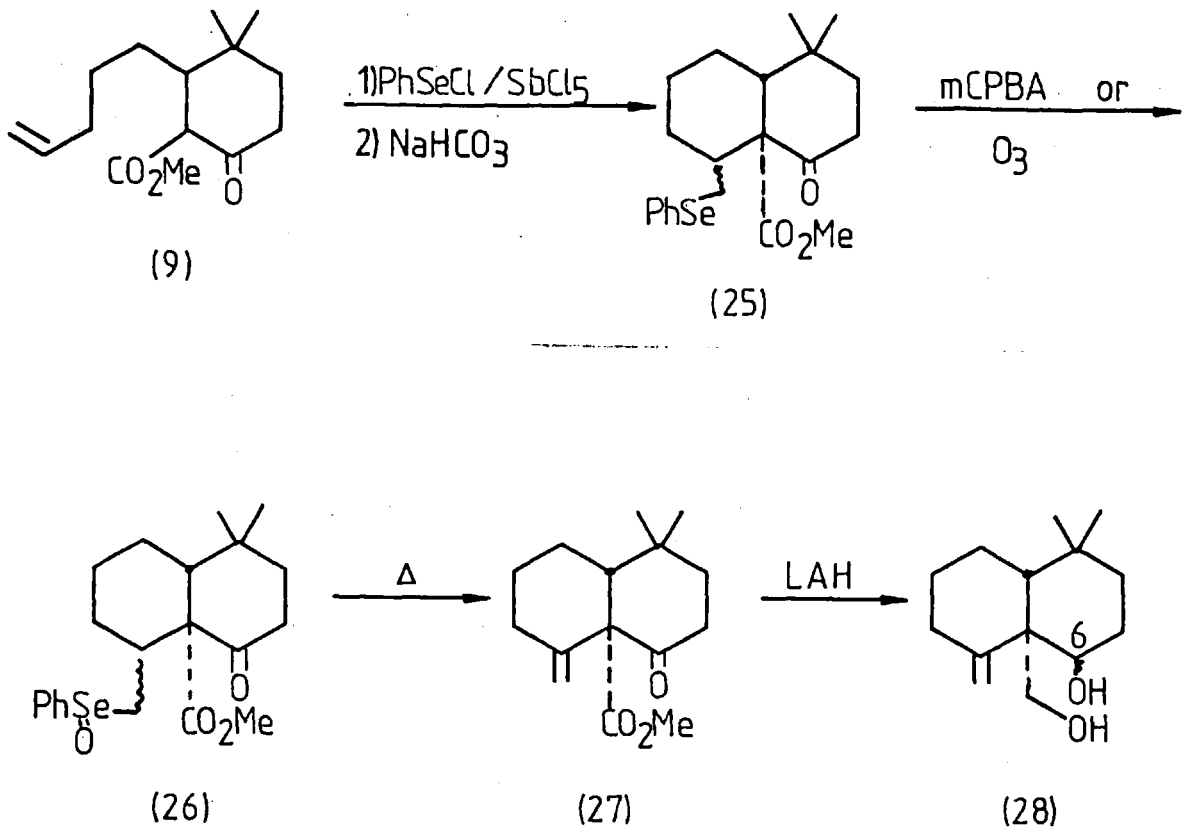
As these silver salts were not initially available to us, we hoped that phenylselenium chloride plus Lewis acid might serve a similar purpose. Use of a mixture of phenylselenium chloride with either tin tetrachloride, boron trichloride or phosphorous pentachloride failed to give any cyclised products (as determined by i.r. of the reaction mixtures). However, when the unsaturated β-keto ester (9) was added to a mixture of phenylselenium chloride and antimony pentachloride (a much more halophilic Lewis acid) at -23°C, a rapid reaction took place, affording, after p.l.c., what appeared to be selenide (25). The compound was obtained in about 30% yield and was characterised by its spectral properties. The ^{1}H n.m.r. spectrum showed that the olefinic protons of (9) had disappeared and that there was a two proton multiplet at δ 2.8 to 3.4 which is expected for protons on the carbon to which the selenophenyl group is connected. The i.r. spectrum was also consistent with structure (25), the ketone and ester groups showing absorptions at 1710 and 1740 cm^{-1} respectively.

An additional reason for using an organo-selenium species in our strategy lies in the fact that selenoxides (which are easily prepared from selenides) undergo a thermal syn-elimination to afford olefins (scheme 4). Conversion of selenide (25) to the

Scheme 4



selenoxide (26) was cleanly achieved using either m-chloroperbenzoic acid or ozone. A solution of this selenoxide was heated at reflux for 17h in methylene chloride to afford an olefin (38%) to which structure (27) was assigned. The methylene protons



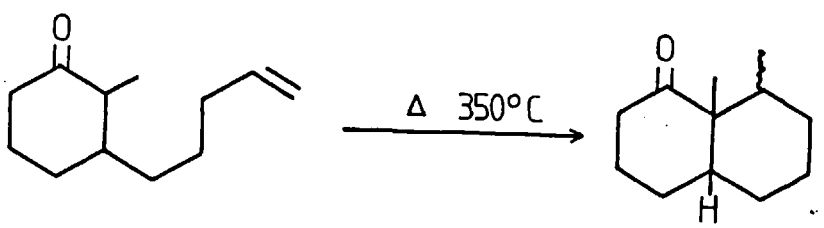
appeared as a two proton broad singlet at δ 5.1 ppm in the ^{1}H n.m.r. spectrum. The i.r. spectrum showed an absorption band at 1635 cm^{-1} which is consistent with the exo-methylene double bond. Reduction of (27) with lithium aluminium hydride gave two products, which were almost identical by ^{1}H n.m.r. These compounds were diols which were presumably epimers about C-6 (28).

Subsequently, the cyclisation of (9) was attempted, using $PhSe^+PF_6^-$, as the silver salt was now available to us. The reaction was much cleaner and gave a higher yield of product (48%). The compound showed some slight differences from (25) in the ^{1}H n.m.r. spectrum. It was found that thermal elimination of the resulting selenoxide afforded a different olefin. The ^{1}H n.m.r. of this compound showed that the olefin

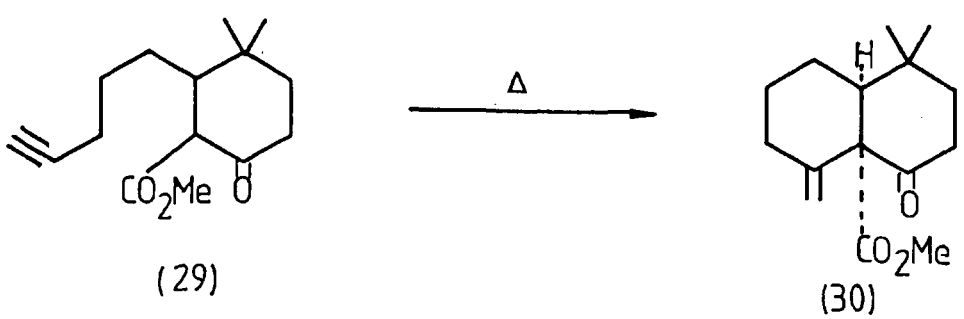
protons occurred as two, one proton singlets at δ 4.30 and δ 4.90. It appeared, therefore, that we were obtaining either cis or trans fused decalins, selectively, depending upon the reaction conditions. As it was not possible to determine unequivocally which olefin was cis or trans by spectroscopic methods, it was decided to synthesise the cis isomer by an unambiguous route. This route was also aimed at producing novel cis fused compounds which could also show insect anti-feeding activity.

Preparation of a cis-Decalin with Potential Insect Antifeeding Activity

Conia[13] has shown that it is possible to intramolecularly thermally cyclise either alkenyl or alkynyl ketones and diketones to afford cis fused products. It was



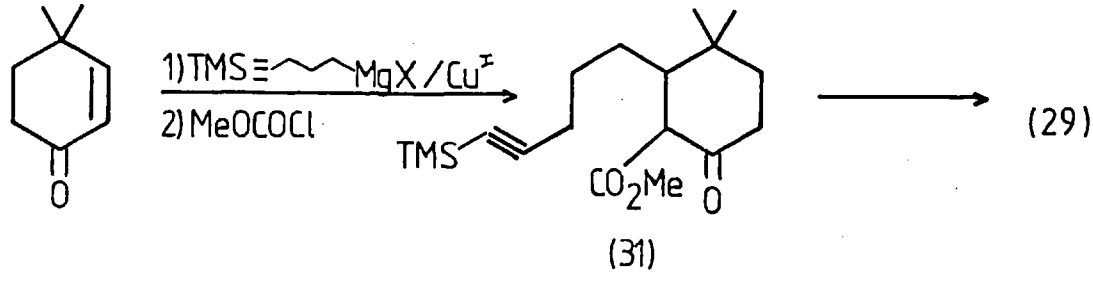
hoped that thermal cyclisation of acetylene (29), in a similar manner, would lead to the cis-decalin (30), directly, and would allow us to assign the stereochemistry of the decalins obtained by the selenium cyclisation routes. It was assumed that (29)



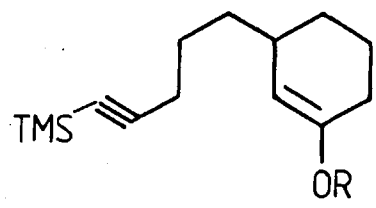
(29) (30)

could be prepared quite readily by a similar strategy to that used previously for the preparation of (9), i.e. as shown in scheme 5.

Scheme 5



Thus, the trimethylsilyl protected 5-chloropentyne was obtained in high yield by a literature route[14]. However, it was found that the corresponding Grignard reagent could only be prepared in boiling tetrahydrofuran. Copper catalysed Michael addition of the chloro-Grignard reagent in tetrahydrofuran was carried out similarly to the previous route, but on trapping of the enolate with methylchloroformate reaction occurred solely on oxygen to give the enol carbonate (32). The reaction was repeated several times with modifications, but none of the desired C-quenched product (31) was obtained. It was decided that the enolate should be trapped with trimethylsilyl chloride to afford the silyl-enol ether (33). Hopefully, regeneration of the enolate from (33) would afford the C-quenched product. The crude silyl-enol ether was easily obtained, but regeneration of the lithium enolate proved quite difficult; only in glyme at 0°C did regeneration occur with any ease, and trapping with methyl chloroformate afforded exclusively the O-quenched product (32). As it looked as

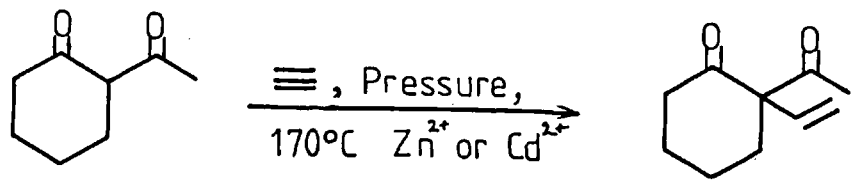


(32) R = CO_2Me

(33) R = TMS

though the chloro-Grignard reagent would not be suitable for quenching on carbon when tetrahydrofuran was used as solvent, we decided to prepare the iodo-Grignard in the hope that it could be prepared in ether and could subsequently be used for the addition and quench reaction. The required iodo-trimethylsilyl-protected acetylene was first prepared from the chloro-derivative with sodium iodide in acetone[15] or better, by displacement of the corresponding tosylate by iodide anion[16]. The iodo-Grignard reagent was readily formed in diethyl ether, at reflux, and pleasingly, afforded the desired C-quenched product (31) after conjugate addition and trapping of the regiospecific enolate in 60% yield. Deptrotection of the acetylene proved more difficult than expected; using the standard conditions[17] of $KF.2H_2O$ in DMF or the modified conditions of Conia[14(b)]- $KF.10H_2O$ in DMF - resulted in the formation of a polar product which was not identified but was presumably the product from self condensation of the highly enolised β-keto ester system[18]. The trimethylsilyl group was finally removed by treating the compound (31) with silver nitrate followed by potassium cyanide[19]. In this manner the trimethylsilyl group could be removed, affording (29) in up to 89% yield.

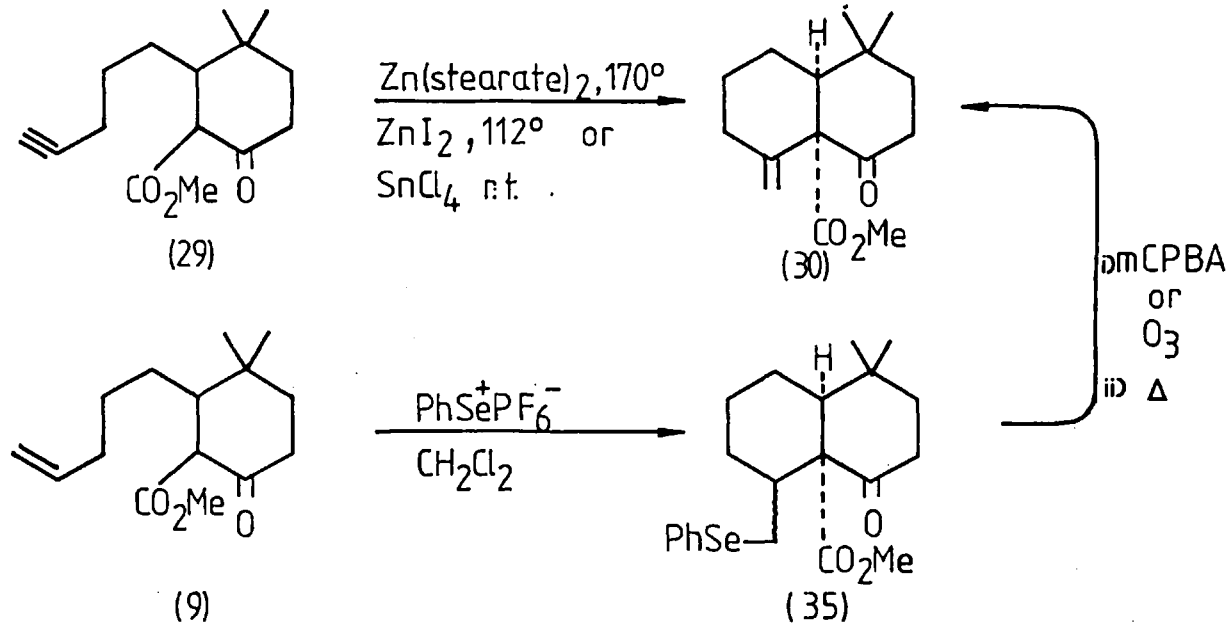
Typical conditions[13] used by Conia for the cyclisation of compounds such as (29) would involve heating of the compound at temperatures $>250^{\circ}C$. Hence, (29) could be cyclised at $270^{\circ}C$ in a decalin solution (decarboxylation occurred when heated neat). As these high temperatures would preclude efficient reaction if the substrate contained more sensitive functionality, we sought lower temperature reaction conditions. It has been shown[20] that β-keto esters, such as carbomethoxycyclohexanone (34) will react with acetylene provided that a Zn^{2+} or Cd^{2+} catalyst is present. In our hands we found that zinc stearate catalysed the cyclisation of (29), reaction taking place at $170^{\circ}C$ in a decalin solution. In an attempt to lower the reaction temperature further, Lewis acid catalysis was investigated. Heating (29)



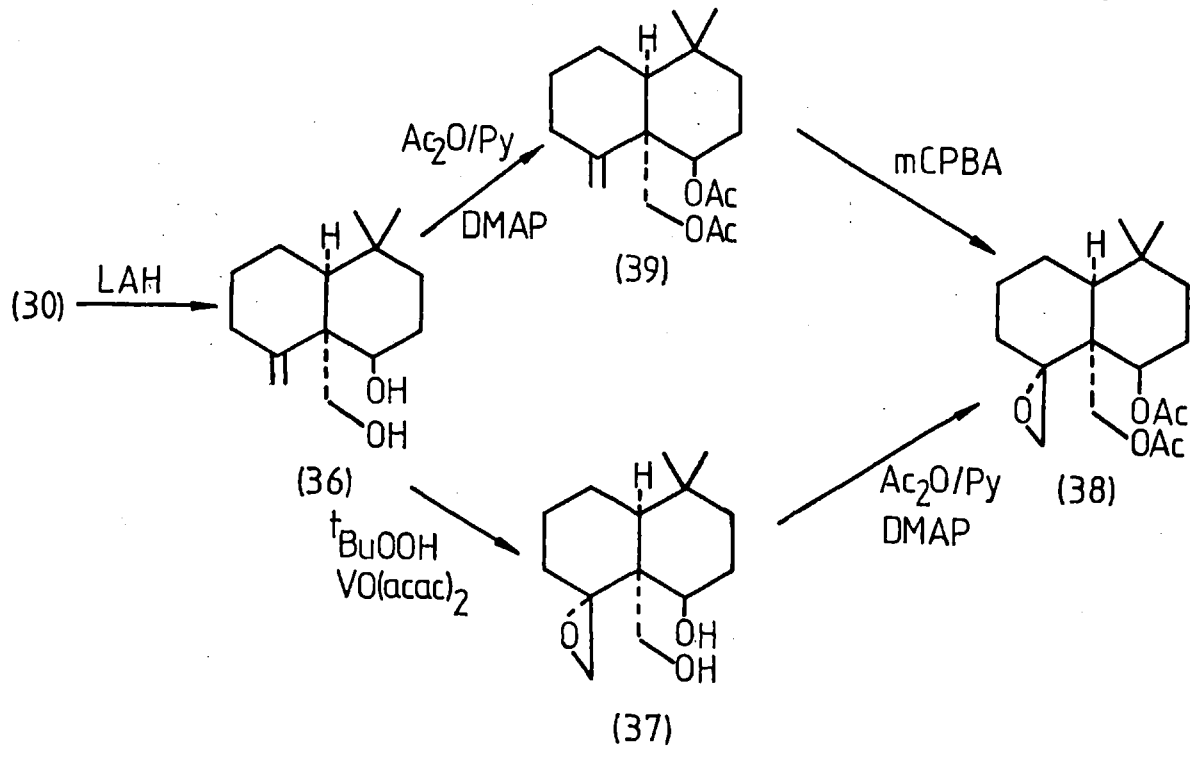
(34)

at reflux in toluene with a trace of zinc iodide, or at room temperature with tin tetrachloride (one equivalent) in methylene chloride, gave (30) in quantitative yield. The method of choice being the former as (30) could be obtained by simple filtration and removal of solvent. This olefin was found to correspond to that formed from elimination of the selenoxide obtained by the $PhSe^{+}PF_6^{-}$ route.

Scheme 6



(29) (30) (9) (35)



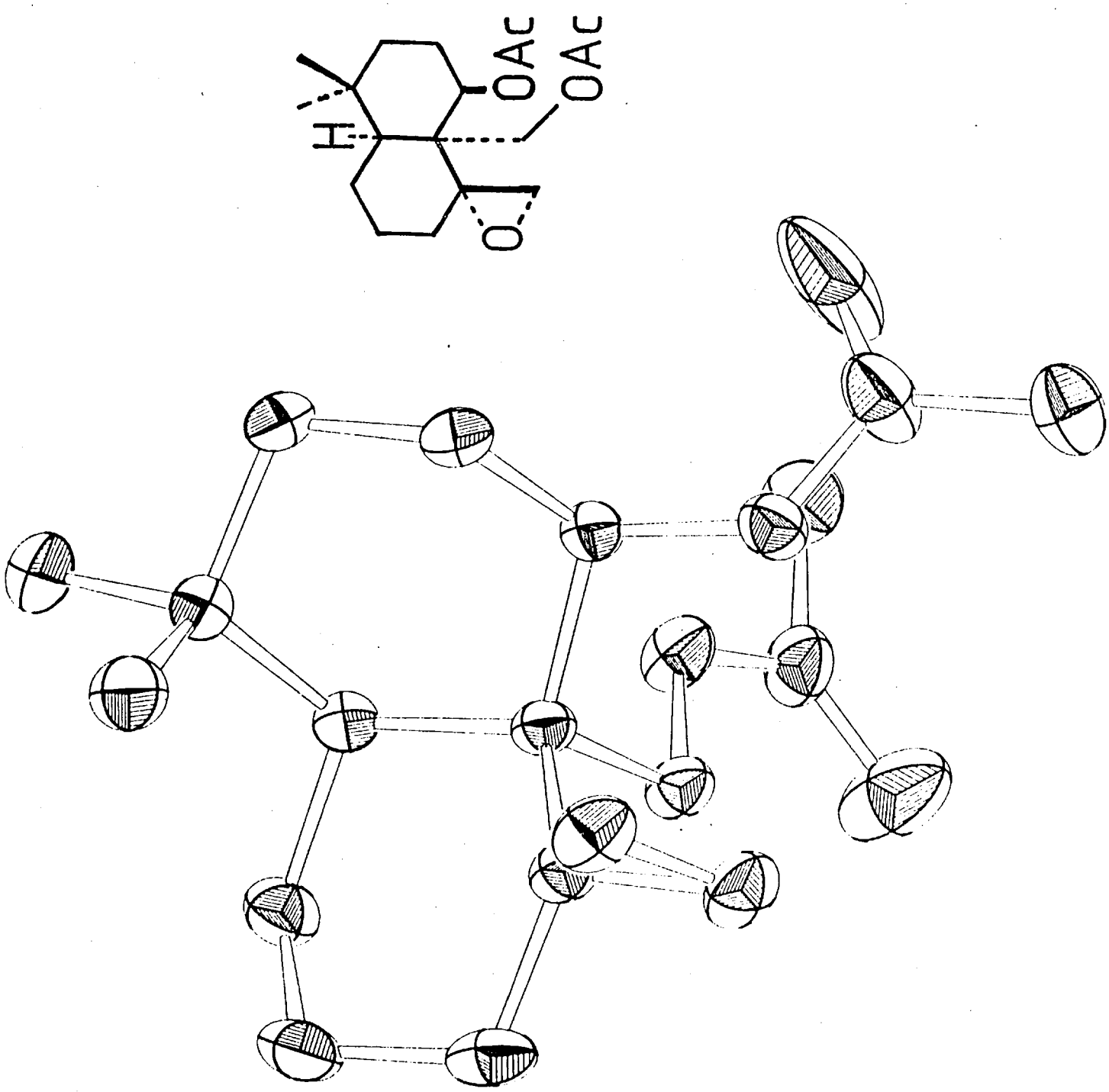
With the cis-decalin (30) now readily available, its conversion to a corresponding cis-epoxydiacetate (38) was studied. Reduction of β-keto ester (30) gave a single crystalline diol to which structure (36) was assigned. Although the stereochemistry at C-6 could not be determined by ^{1}H n.m.r., molecular models suggested that this was the most likely configuration and this was later confirmed by X-ray crystallographic determination of the cis-epoxydiacetate (38). Epoxydation of the diol (36) under Henbest[1] conditions gave a single epoxide (37) which decomposed on standing in the reaction mixture. Attempted work-up of the reaction by the addition of aqueous sodium bicarbonate also resulted in decomposition to several compounds. Attempted purification on Florisil again led to extensive decomposition. The compound was eventually used, without purification, and gave the epoxydiacetate (38) by treatment with acetic anhydride/pyridine using 4-N,N-dimethylamino pyridine as catalyst. Compound (38) crystallised and, as its structure was not fully assignable by spectroscopic methods, was subjected to an X-ray crystallographic study (figure 1). The epoxydiol (37) could be better prepared from the methylene diol (36) by the Sharpless procedure[21] using t-butyl hydroperoxide and VO(acac)$_2$. When prepared in this way the epoxydiol (37) could be isolated but was usually converted through to the cis-epoxydiacetate (38),

as before, in up to 79% yield. The epoxydiacetate (38) could also be prepared by epoxydation of the diacetate (39) with m-chloroperbenzoic acid in 89% yield. The ^{1}H n.m.r. spectrum of (39) was typical of natural products which contain the epoxydiacetate functionality; the acetates appeared as three proton singlets at δ 1.97 and 2.02. The hydrogens on C-13 appeared as doublets at δ 2.33 and 3.05 with a coupling constant of 4 Hz. The hydrogens on C-14, as expected, appeared as an AB quartet with a coupling constant of 12 Hz.

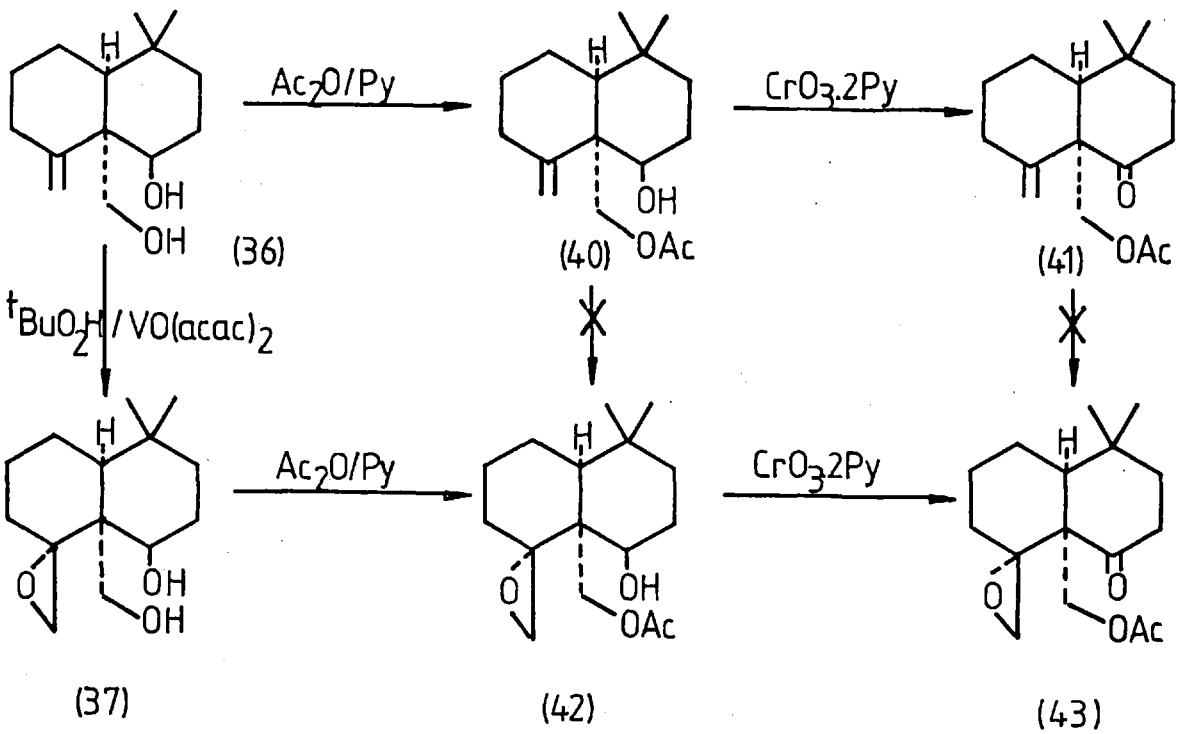
It was noticed that, in the X-ray structure determination of (38), the oxygen atoms of the epoxide and the diacetate showed similar positioning to that observed for 3-epicaryoptin[22]. We hoped, therefore, that (38) would show insect antifeeding properties. However, when (38) was tested against Spodoptera littoralis and Heliothis virescens on cotton leaves at a concentration of 1,000 ppm, no appreciable antifeeding effect was observed. To our delight, when (38) was tested against Locusta migratoria on GF/A disks (filter paper) impregnated with 5% sucrose solution, a 70% inhibition of feeding was observed at 1,000 ppm. This is quite a marked effect when it is considered that the material is racemic and that many naturally occurring antifeedants do not show 100% feeding inhibition below a concentration of 2,500 ppm. Having determined that (38) did show activity, we decided to prepare the 6-hydroxy and 6-keto derivatives as there are many naturally occurring compounds which have these groups at C-6. These compounds were prepared as outlined in scheme 7.

We were not able to epoxidise either (40) or (41) to directly give (42) and (43) respectively, as complex reaction mixtures ensued. It was possible, however, to monoacetylate the epoxydiol (37). The monoacetate (42) could be easily oxidised with Collins' reagent[23] to afford the 6-keto derivative (43).

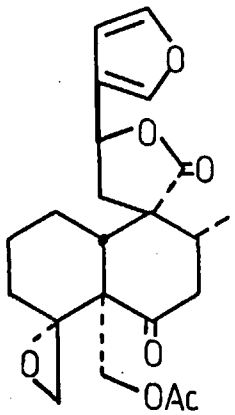
When (43) was tested against Locusta migratoria, under the same conditions as the diacetate (38), less than half the antifeeding activity was observed. Although there


OAc
OAc
H
O

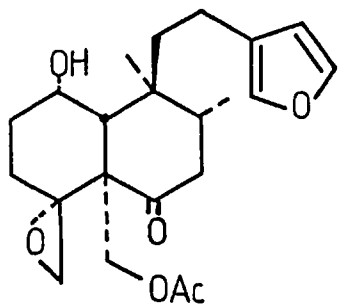
Scheme 7



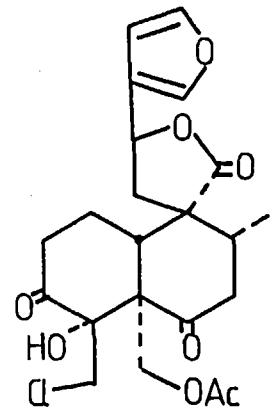
are many naturally occurring compounds with a 6-keto function, none appears to have been tested for antifeeding activity. If these compounds also showed reduced antifeeding activity compared to their corresponding 6-hydroxy or 6-acetoxy derivatives we would have a clear indication that the 6-acetoxy or 6-hydroxy group is required in order to produce the full antifeeding effect. Fortunately some of these naturally occurring trans-clerodanes were available to us. Antifeeding testing[24] was carried out at a concentration of 1,000 ppm on GFA disks plus 5% sucrose solution, and was a "no choice" test. Montanin C (44) showed only 38% feeding inhibition while fruiticolone (45), which differs only by the 1-hydroxy group, showed 70% inhibition of feeding. The chloro-hydrins (46) and (47), which have recently been isolated from a Teucrium species[25] were similarly tested in the hope that they might be converted in vivo to the epoxide and so show some antifeeding activity. Indeed, compound (47) showed almost total inhibition of feeding (95%), while the 6-keto



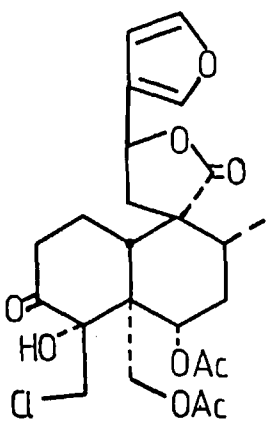
(44)



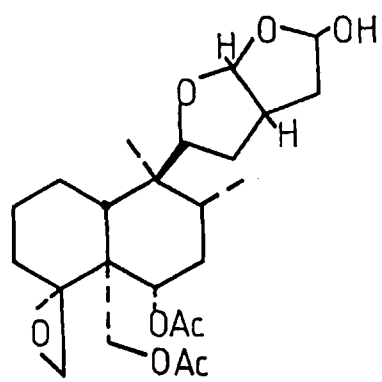
(45)



(46)



(47)



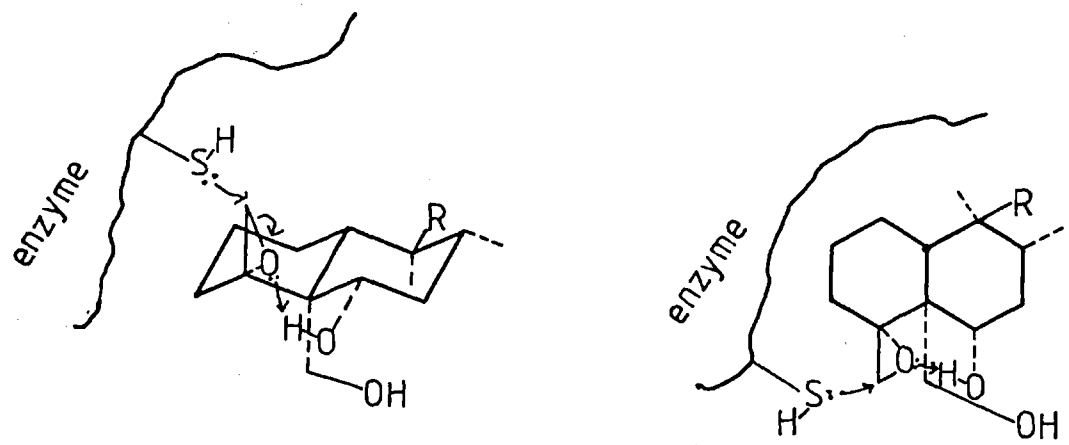
(48)

derivative (46) showed only 38% inhibition of feeding. This result highlights the need to have a 6-acetoxy group in order to produce strong insect antifeeding activity. Throughout the testing clerodin hemiacetal (48) was used as a control and showed 95 - 100% inhibition of feeding at 1,000 ppm.

In view of these results, we can speculate about the mode of action of the polyoxygenated clerodane diterpenes as antifeedants against the species Locusta migratoria. It appears that the diacetate is required, presumably for biological transport to the active site as the corresponding diols are, generally, inactive. On reaching the active site the acetates could be lost, leaving the so formed 6-hydroxy group to strongly hydrogen bond with the epoxide, thus allowing easy

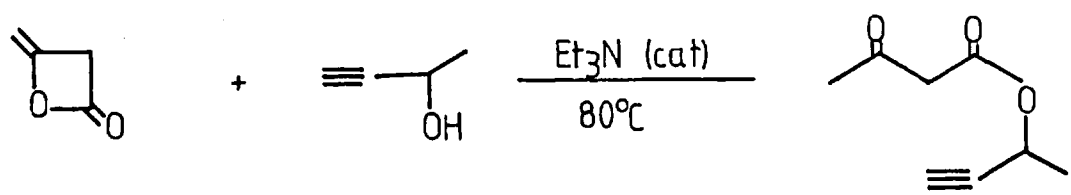
nucleophilic opening by, possibly, a thiol group on an enzyme. It is known[26] that thiol groups and other antifeedants interact to cause the antifeeding effect.

Possible mode of action of clerodane antifeedants

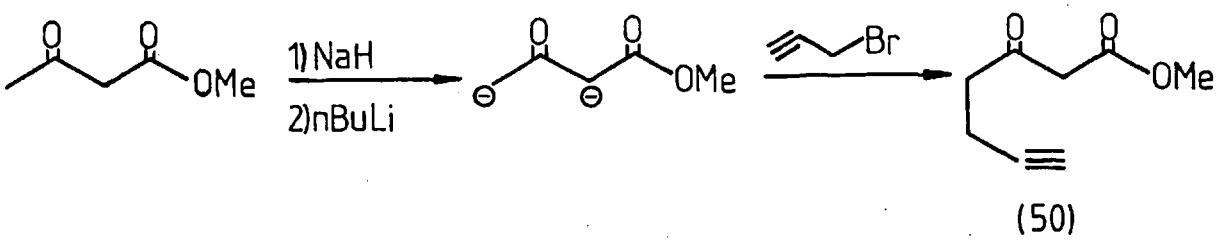


Lewis Acid Catalysed Conia Type Cyclisations

In order to determine whether or not the Lewis acid mediated cyclisation of acetylenic β-keto esters such as (29) is a generally useful synthetic reaction, cyclisation of (49) and (50) was also studied. The acetylenic ester (49) was readily available from diketene and the acetylenic alcohol according to the literature procedure[27]. The acetylene (50) was obtained by quenching the dianion of methyl acetoacetate with propargyl bromide again according to the literature procedure[28].

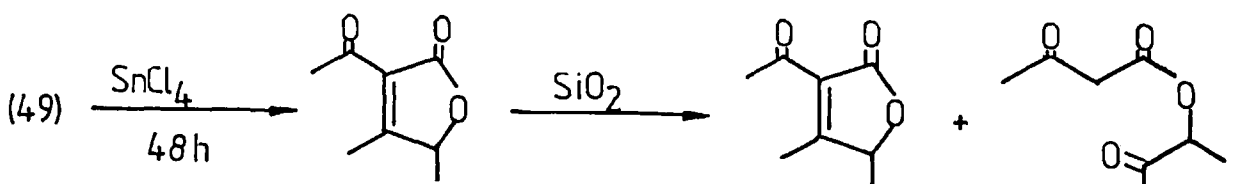


(49)



(50)

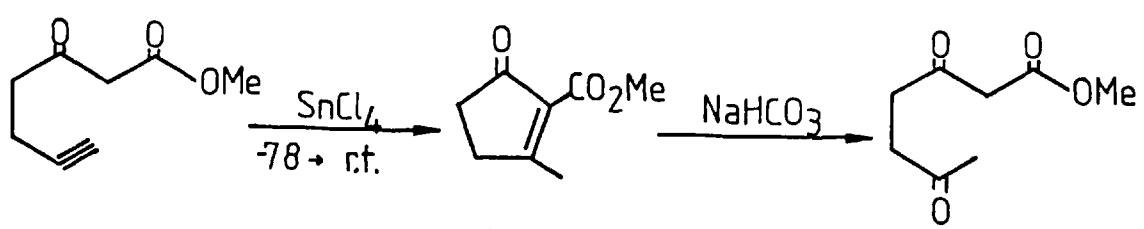
It was found that the ester (49) reacted slowly in the presence of tin tetrachloride, giving the butenolide (51) after two days at room temperature. The butenolide (51), which results from cyclisation and conjugative rearrangement of the double bond into the ring, was obtained in 80% yield after removal of base line material by passage through a pad of silica. Attempts to purify (51) further by column chromatography lead to partial decomposition to the retro-aldol product (52). Reaction of (50) with tin tetrachloride at room temperature proceeded rapidly, giving a complex mixture of products.



(51) 80%

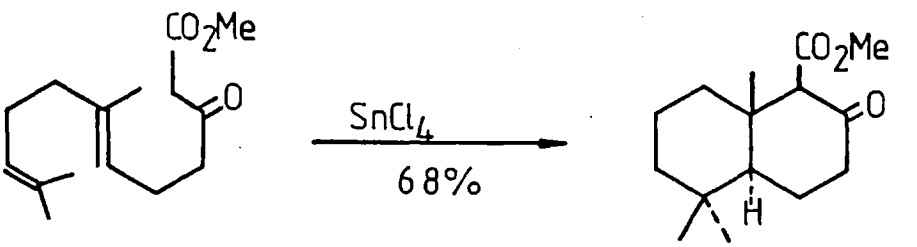
(52)

However, if the tin tetrachloride was added at -78°C and the reaction mixture allowed to warm to room temperature, a single product was obtained after bicarbonate work up.

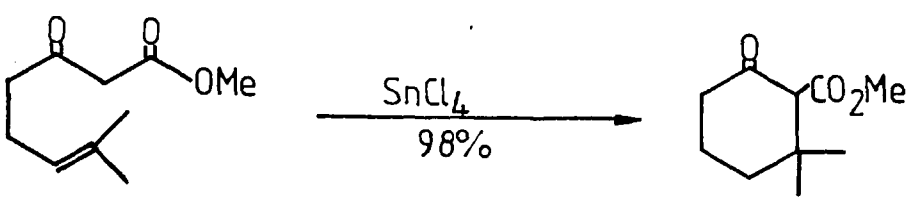


(53) (54) >80%

The product was shown to be the 5-keto β-keto ester (54), which obviously results from a retro-aldol opening of enone (53). Work up with water gave an approximate 1 : 1 mixture of (53) and (54) by ^{1}H n.m.r. Attempted chromatography of the mixture resulted in complete conversion to (54). Workers in prostaglandin synthesis have attempted[29] to prepare (53) from (54) by an acid catalysed condensation. They were, however, unsuccessful and dimeric products resulted. When a larger side chain was present the condensation readily took place to give an isolable product. White[30] and Weiler[31] have recently cyclised the highly substituted olefins (55) and (56) with tin tetrachloride to afford (57) and (58) respectively.

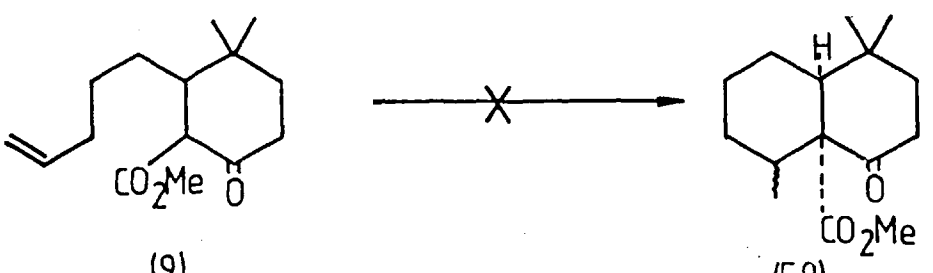


(55) (57)



(56) (58)

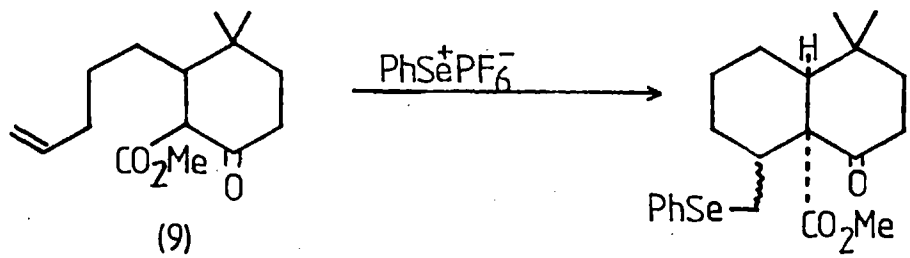
Our attempts to cyclise (9) in a similar fashion failed to give any of the desired product (59), although it could be prepared by an alternative route which is discussed later.



(9) (59)

Attempts to Prepare a trans-Fused Epoxydiacetate Related to the Clerodanes and Ajugarins

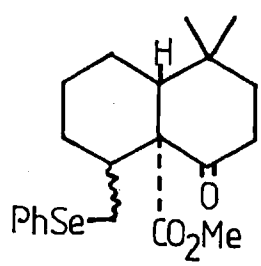
Having found that reaction of the alkenyl β-keto ester (9) with $PhSe^{+}PF_6^{-}$ gave the cis-fused selenide (35) it was decided to reinvestigate the reaction conditions discussed earlier that had apparently afforded a trans fused system.



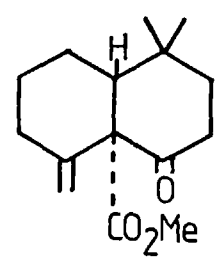
(9) (35)

The reaction conditions were slightly modified compared with the previous experiment in that a 1 : 1 mixture of phenylselenium chloride and antimony pentachloride were now added to a solution of (9) in dichloromethane at - 78°C. Analytical t.l.c. indicated the formation of a single product. Attempted purification of this product, however, resulted in severe decomposition affording some starting material (9) and diphenyl diselenide as the only isolable products. A product could be isolated, however, by low temperature (- 78°C) chromatography. This product could be smoothly oxidised (to the corresponding selenoxide) but attempted syn elimination gave a mixture of products, the main one being the re-reduced selenide and an olefinic product which co-ran on t.l.c.

These results were somewhat disappointing as the desired trans-selenide (25),



(25)



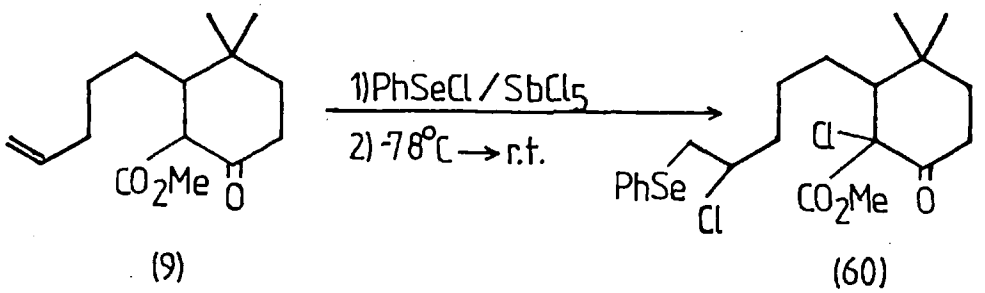
(27)

which had been produced previously, was apparently stable to p.l.c. and the olefin (27) was clearly different by t.l.c. to the new olefinic material. In an attempt to improve the quantity of this new olefin the crude selenide, obtained as above, was first oxidised with ozone, then excess t-butyl hydroperoxide was added to the mixture (to prevent re-reduction back to the selenide). After heating at 60°C for three days repeated chromatography gave the olefin which was practically free from the contaminating starting selenide. This olefin showed some similarity to (27) by ^{1}H n.m.r., with a two proton broad singlet occurring at δ 5.15 ppm.

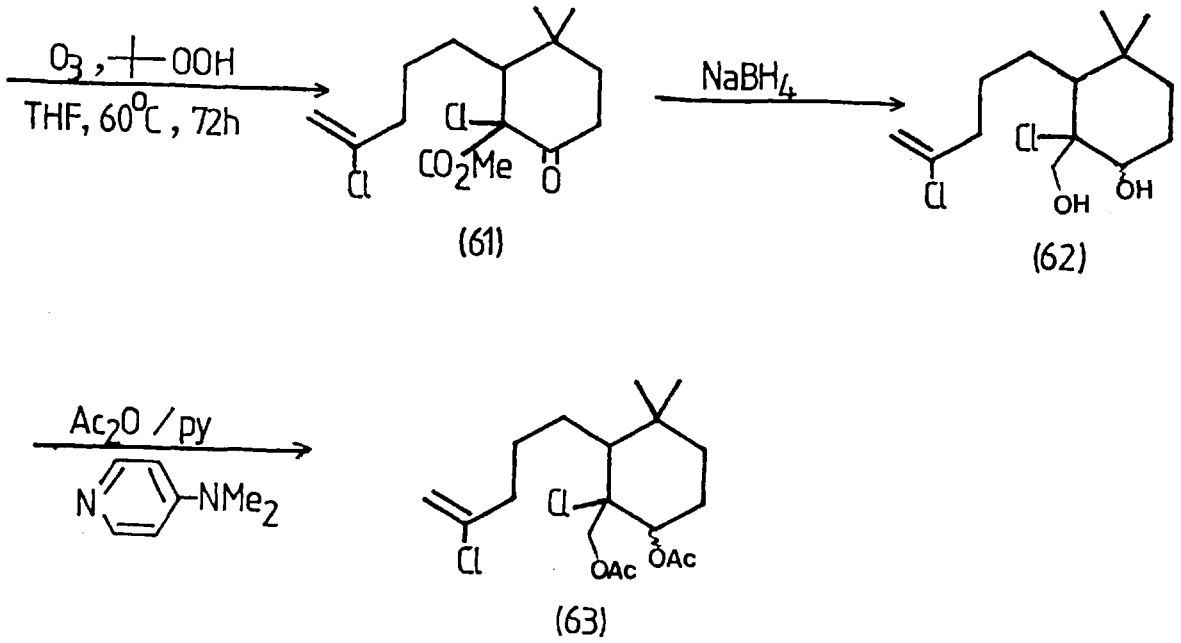
Reduction of this new olefin (61) with lithium aluminium hydride gave a complex reaction mixture by t.l.c. However, borohydride reduction was much cleaner. Examination of the i.r. and ^{1}H n.m.r. spectra showed that both the ketone and ester had been reduced. The crude product from this reaction was acetylated with acetic anhydride/pyridine/4-NN-dimethylamino pyridine to give a diacetate which could be properly purified. The mass spectrum indicated that two chlorine atoms were present. The ^{1}H n.m.r. spectrum showed an AB quartet corresponding to a $-CH_2OAC$ group in which the two protons were non-equivalent.

We propose, then, that a sequence of reactions takes place as shown in scheme 8. Final structural proof of diol (62) will be completed after X-ray crystallographic determination of a suitable derivative, which is now under way.

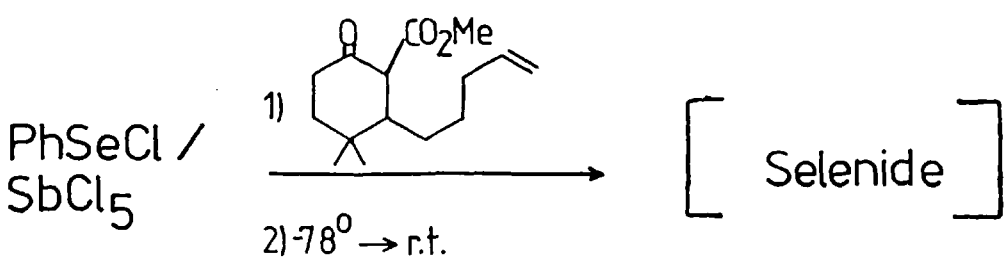
Scheme 8

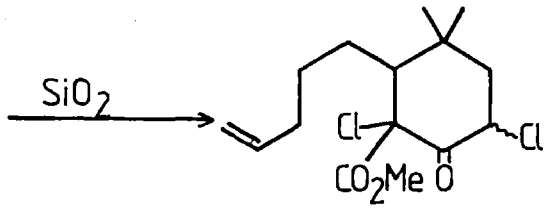


(9) (60)



In view of the above observations cyclisation of (9) was attempted under different reaction conditions. Consequently, on adding (9) to a mixture of phenylselenium chloride and antimony pentachloride at -78°C a clean reaction again took place, affording a single product which decomposed on attempted purification by p.l.c. Decomposition of the product was apparently more rapid than the previous experiment, thus suggesting that yet another product was being formed. The mass spectrum suggested that two chlorine atoms were again present. One chlorine atom was clearly between the β-keto ester as "normal" i.r. stretching frequency was observed for separate ketone and ester functions (ν_{max} 1760, 1740 and 1720 cm^{-1}). The ^1H n.m.r. spectrum indicated that the pentenyl side chain was intact. Although the position of the other chlorine atom is still not known for certain, it can most reasonably be placed alpha to the carbonyl group, as shown in (64) below.

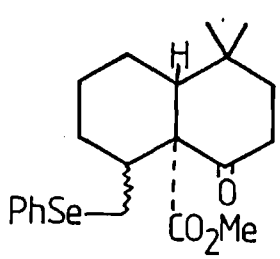




(64)

In order to determine whether or not the antimony pentachloride was simply acting as a chlorinating agent (9) was mixed with one equivalent of antimony pentachloride in CH_2Cl_2 and stirred at room temperature for several hours. On re-isolation (9) was found to be free of any chlorine atom incorporation. It appears, therefore, that on reacting phenylselenium chloride with antimony pentachloride a chlorinating species must be produced. No further work was done to discover the nature of this species.

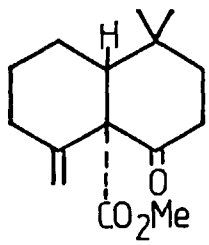
In conclusion, therefore, it seems that methods to (25) involving phenylselenium chloride and $SbCl_5$ are complicated by a number of side reactions and that, so far, it has not been possible to reproduce some of the earlier studies in that the trans-fused selenide (25) cannot now be obtained.



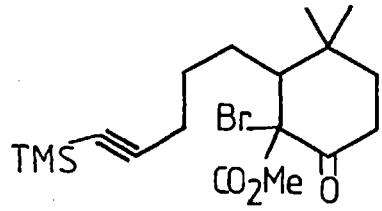
(25)

Attempts to Prepare a trans-fused Decalin by Radical Induced Ring Closure

As our efforts to prepare the trans-fused decalin (27) by a selenium induced ring closure could not be fully realised, other methods of ring closure were studied.



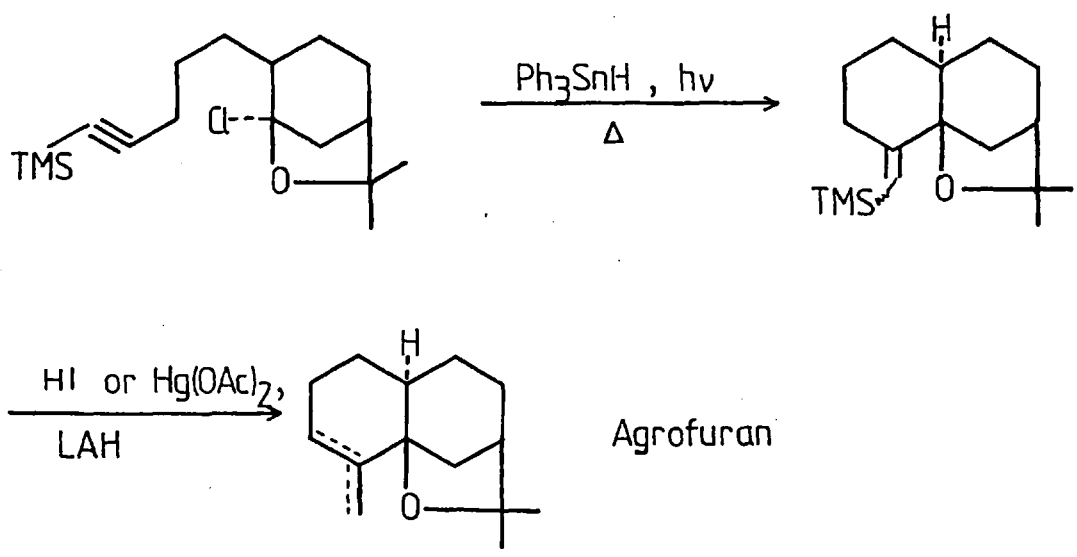
(27)



(65)

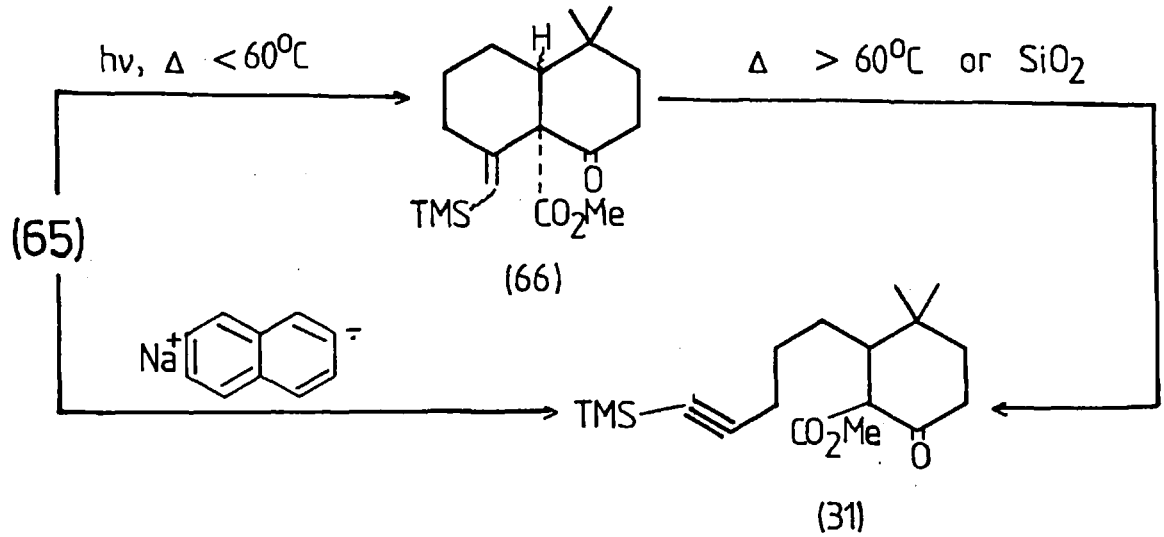
Buchi's recent synthesis of agrofuran [15] (scheme 9) suggested to us that it might be possible to prepare (27) from a precursor such as (65) by an analogous radical induced ring closure. The bromide (65) was prepared in high yield (> 95%) from (31) by reaction with anhydrous magnesium bromide and m-chloroperbenzoic acid [32]. Attempts to cyclise (65) are summarised in scheme 10. For example, it was found that

Scheme 9



reaction of (65) with triphenyl tin hydride and a trace of AIBN at reflux in cyclohexane gave a mixture of (31) and a more polar product which was assigned structure (66). Extended heating of the mixture gave (31) as the only product. Irradiation of (65) with

Scheme 10



triphenyltin hydride and AIBN at 60°C (± 5°C) gave (66) as the only product. As (66) appeared to be thermally labile we attempted to generate the radical intermediate by reaction of (65) and sodium naphthalide at room temperature. The reaction was clean and rapid, but unfortunately gave (31) as the only product.

It was also noted that chromatography of the crude mixture from reduction of (65) with triphenyl tin hydride resulted in decomposition of (66) to (31). Low temperature chromatography at -78°C prevented decomposition, but (66) could still not be isolated pure due to contaminating organotin residues.

Further reactions in this series were not pursued due to more important work.

Organo-selenium Induced Cyclisations

Although organo-selenium reagents have been used extensively by Clive and Nicolaou to effect the heterocyclic ring closure[33] of a large number of unsaturated acids, alcohols, thiols, thioesters, phenols, and urethanes, their use in the construction of rings *via* the formation of new carbon-carbon bonds has been very limited[11].

Our discovery, presented earlier in this thesis, that alkenyl substituted β-keto esters could be cyclised using organo-selenium reagents in which the counter anion was non-nucleophilic suggested that a more detailed investigation was required. We were particularly hopeful that the process could become a useful general reaction for the formation of rings in which new carbon-carbon bonds are formed.

A number of alkenyl substituted β-keto esters and diketones were, therefore, prepared by standard methods; compounds (67), (68) and (69) were prepared by alkylation of the β-keto ester with the alkyl halide (preferably the iodide) in the presence of potassium carbonate in D.M.F.[34]. Compounds (55), (70) and (71) were prepared from the dianion of the β-keto ester and the respective alkyl halides[28,30,31]. The dimedone derivative (72) was prepared in low yield according to the literature procedure[35].

The results of the organo-selenium induced cyclisations of the above alkenyl substituted β-dicarbonyl compounds with $PhSe^{+}X^{-}$ ($X = PF_6$ or SbF_6) are summarised in Table 1[36]. Most of the reactions shown proceeded smoothly, giving only one product.

The table shows that the β-keto esters and diketones can cyclise either *via* the oxygen of the enol form or *via* the carbon of the enol form (scheme 11). The reasons why the compounds cyclise as they do will be discussed later. However, it is first proposed to discuss how each of the products was characterised.

Compound (73) showed significant absorptions in the i.r. spectrum at 1690 and 1645 cm^{-1} which are typical of the unsaturated ester and the conjugated, cyclic vinyl ether. In this example, as in others, the carbon-carbon bonds of the phenyl

TABLE 1 REACTION OF UNSATURATED β-DICARBONYL COMPOUNDS WITH $PhSe^{\oplus}X^{\ominus}$

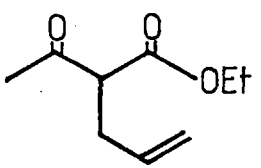
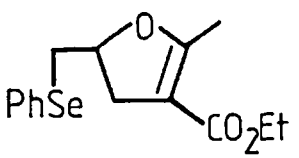
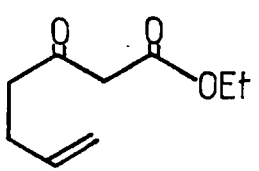
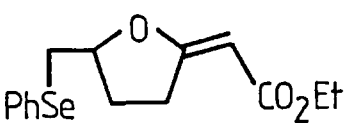
SUBSTRATE	PRODUCT(S)	ANION	YIELD + COMMENTS
 (67)	 (73)	$SbF_6^{\ominus}$	70% reference 3
 (70a)	 (74a)	$PF_6^{\ominus}$	60%

TABLE 1 (CONT.)

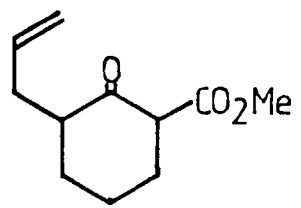
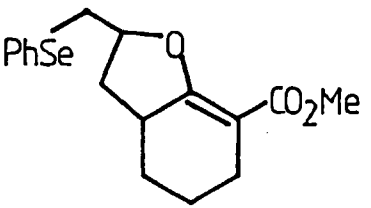
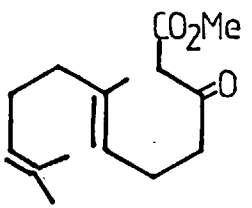
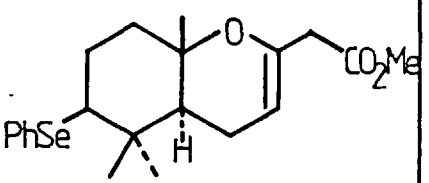
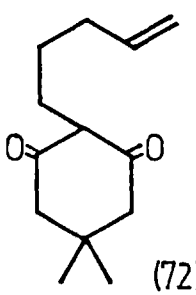
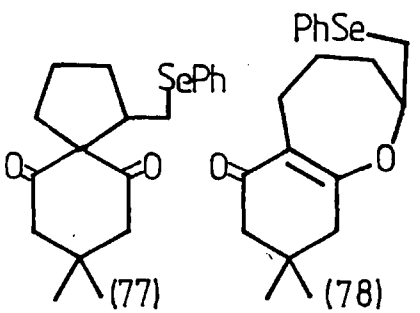
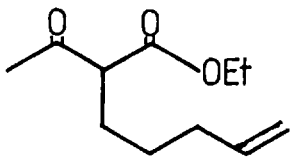
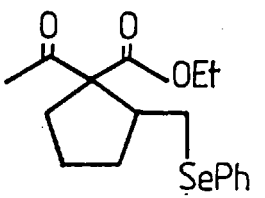
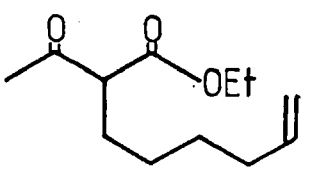
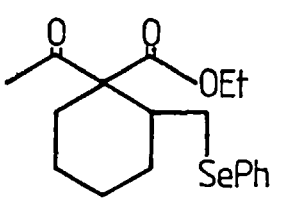
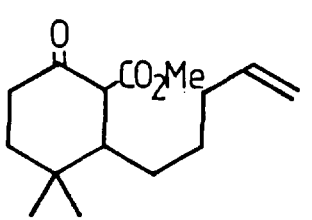
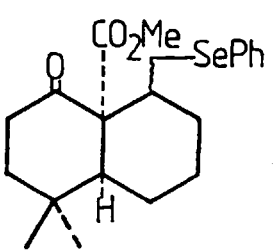
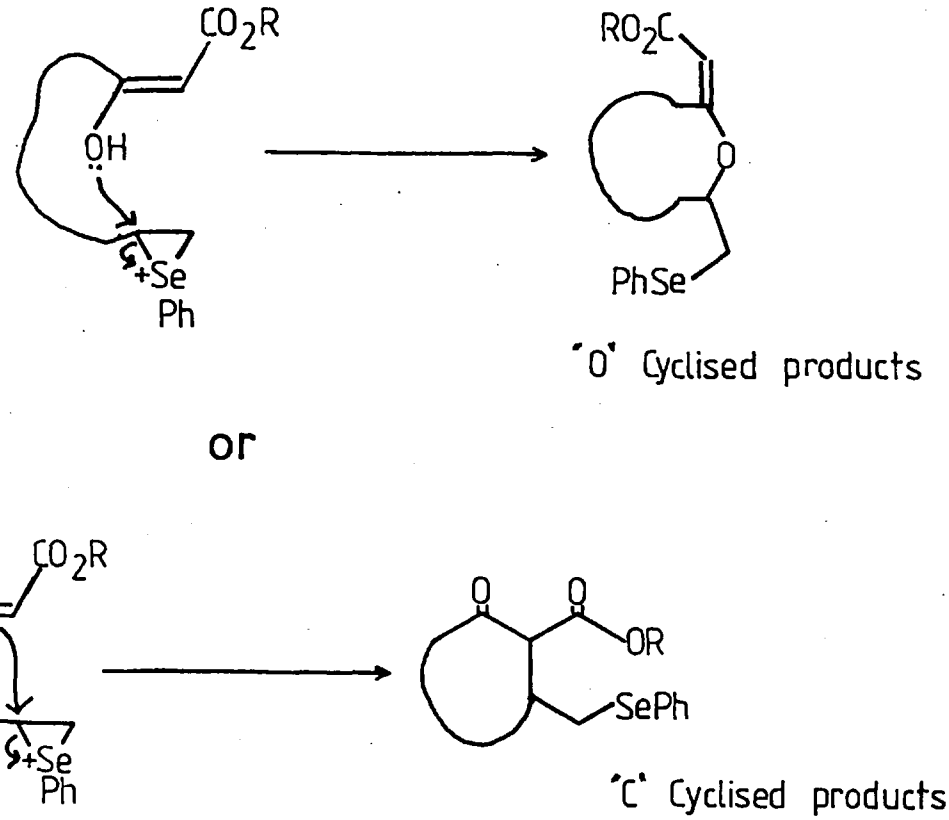
 (71)	 (75)	$PF_6^{\ominus}$	70%
 (55)	 (76)	$PF_6^{\ominus}$	58% inverse addition
 (72)	 (77) (78)	$SbF_6^{\ominus}$ $PF_6^{\ominus}$	(78) 42% (77) 30% (78) 27% reference 3

TABLE 1 (CONT.)

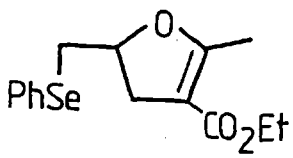
 (68)	 (79)	$SbF_6^{\ominus}$	82% reference 3
 (69)	 (80)	$PF_6^{\ominus}$	56%
 (9)	 (35)	$SbF_6^{\ominus}$ $PF_6^{\ominus}$	48% 75%

Scheme 11

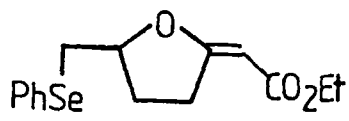


group absorb at 1580 cm^{-1}. The 250 M Hz ^1H n.m.r. spectrum of (73) shows a signal at δ2.13 as a finely coupled triplet ($J < 1$ Hz) which corresponds to the methyl group attached to the double bond. The signal corresponding to the proton alpha to the oxygen in the ring appears as a multiplet centred at δ 4.65. This resonance also occurred in many later examples in which cyclisation had taken place via oxygen. The signals corresponding to the protons on the carbon next to selenium appear as doublets at δ 3.02 (J 6Hz) and δ3.20 (J 4Hz) ppm. Finally, the phenyl protons resonate as two distinct multiplets at δ 7 to 8 ppm; the downfield resonance usually integrates to two protons (ortho protons) while the upfield multiplet usually integrates to three protons (two meta and the para protons).

Compound (74a) showed absorptions in the i.r. spectrum at 1700, 1640 and 1580 cm^{-1} which are consistent with the furanoid structure shown. The proton on the double

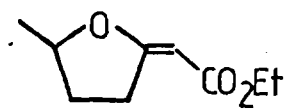


(73)



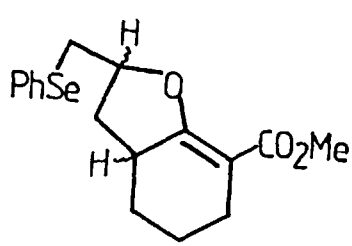
(74a)

bond resonates as a finely coupled (allylic) triplet in the ^1H n.m.r. spectrum at δ 5.25 ppm while the proton in the ring alpha to oxygen is once again responsible for the multiplet centred at δ 4.55 ppm. Although it is not possible, from spectral data alone, to state whether (74a) is in the Z or E form, it is, by comparison with other literature examples, most likely to exist in the E form[37]. Selenide (74a) has since been deselenated[38] to the known compound (81)[37]. The complete structural assignment of (81) was made after careful shift reagent studies.



(81)

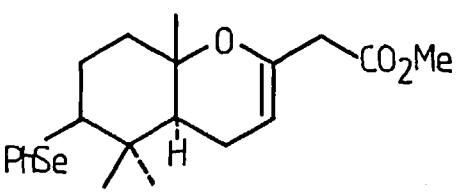
6-Allyl-2-carbomethoxycyclohexan-1-one (71) also cyclises via oxygen to afford (75). The i.r. data (1685, 1655 and 1580 cm^{-1}) is again consistent with the furanoid structure of (75). The 250 M Hz ^1H n.m.r. spectrum clearly shows (75) to be a mixture of two isomers. The ring proton alpha to oxygen resonates at δ 4.57 ppm for the major isomer, and at δ 4.63 ppm for the minor isomer. Integration of these



(75)

peaks gave a 4 : 1 ratio of the isomers.

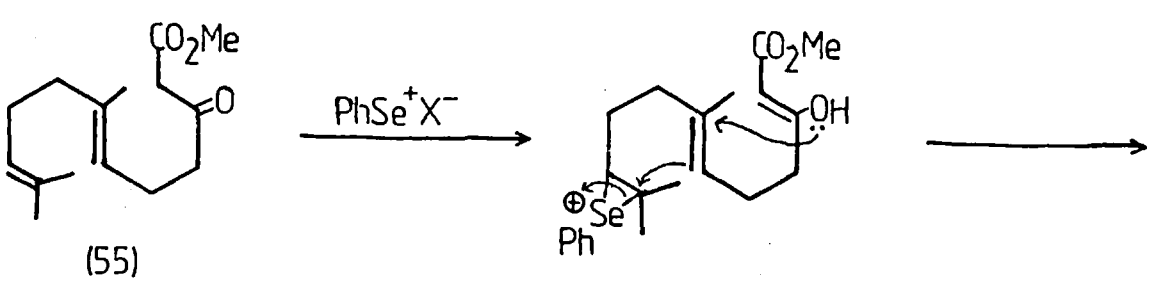
The product from the reaction of the geranyl β-keto ester (55) with $PhSe^{+}X^{-}$ showed absorptions at 1740 and 1685 cm^{-1}, in the i.r. spectrum, which are typical of a saturated ester function and an enol ether respectively. The ^{1}H n.m.r. spectrum of (76) showed that the allylic protons (alpha to the ester group) resonate at δ 2.90 ppm as a two proton broad singlet. The one proton double doublet at δ4.66 ppm is the absorption due to the vinylic proton. Compound (76) arises from addition of $PhSe^{+}$



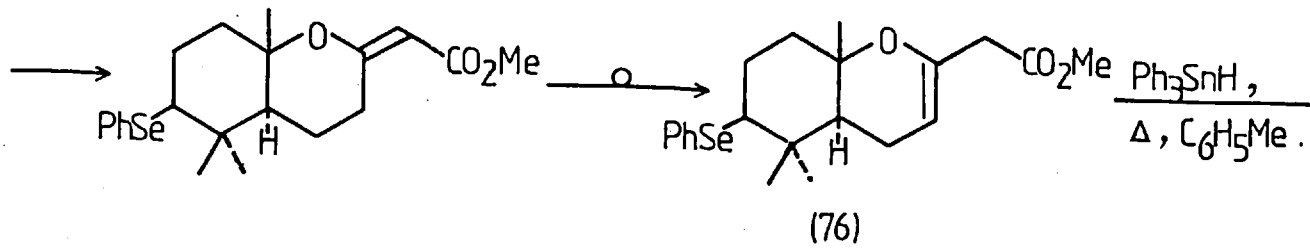
(76)

onto the more reactive (terminal) double bond. Cyclisation then occurs by attack of the oxygen of the enol form onto the central double bond, with concomitant opening of the seleniranium ion. Finally, rearrangement of the exo-cyclic double bond takes place[39] to afford (76) (scheme 12). Although it is not possible to absolutely assign the stereochemistry of the phenylselenide moiety, similar cyclisations are well documented[40] and we, therefore, assign it as a β-substituent by analogy. Deselenation of (76) with triphenyl tin hydride[41] gave a 76% yield of (82).

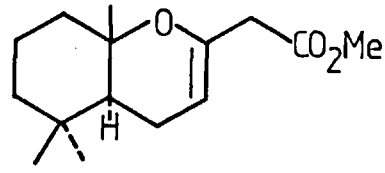
Scheme 12



(55)

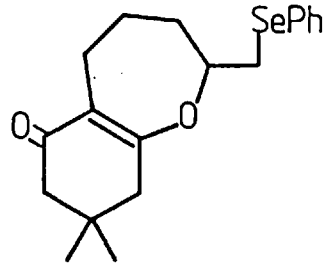


(76)

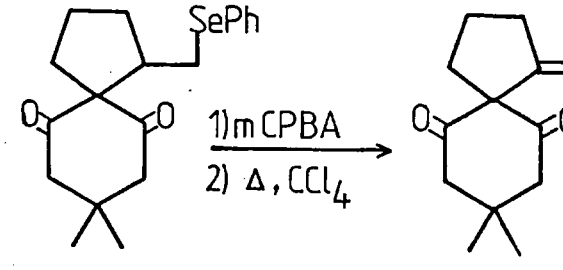


(82)

Reaction of (72) with $PhSe^{+}SbF_6^{-}$ gave a 42% yield of (78) whose structure was consistent with the i.r. and ^1H n.m.r. spectral data (1655, 1620 and 1580 cm^{-1} for the conjugated ketone, vinyl ester and phenyl groups respectively, and δ 4.40 ppm [one proton multiplet] corresponding to the ring proton alpha to oxygen). Reaction of (72) with $PhSe^{+}PF_6^{-}$, however, gave, as well as (78), a less polar product. This other product, m.p. 86-87°C, showed carbonyl stretching frequencies at 1725 and 1690 cm^{-1}. The ^1H n.m.r. spectrum was consistent with it being the spiro-selenide (77). This selenide was converted to the corresponding known[35] olefin (83) by oxidation to the selenoxide and thermolysis in carbon tetrachloride.



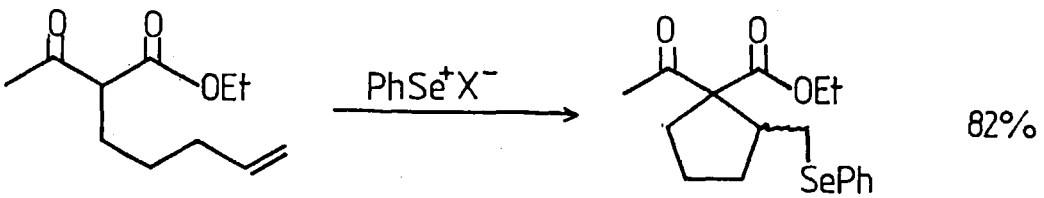
(78)



(77) (83)

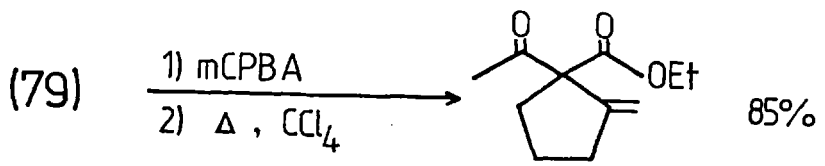
Compound (68) was expected to cyclise via carbon to give the five membered ring selenide (79) as, indeed, turned out to be the case. The i.r. spectrum showed

absorptions at 1740 and 1710 cm^{-1}, which are consistent with ester and ketone functions. The ^1H n.m.r. spectrum was complicated by the fact that (79) was a



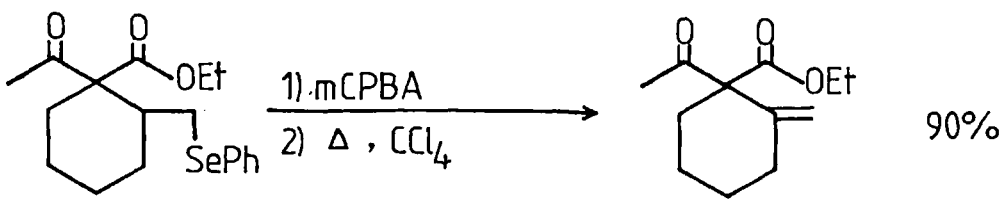
(68) (79)

1 : 1 mixture of isomers, as shown. The structure was confirmed by conversion to the olefin (84) by oxidation and syn elimination of the intermediate selenoxide.



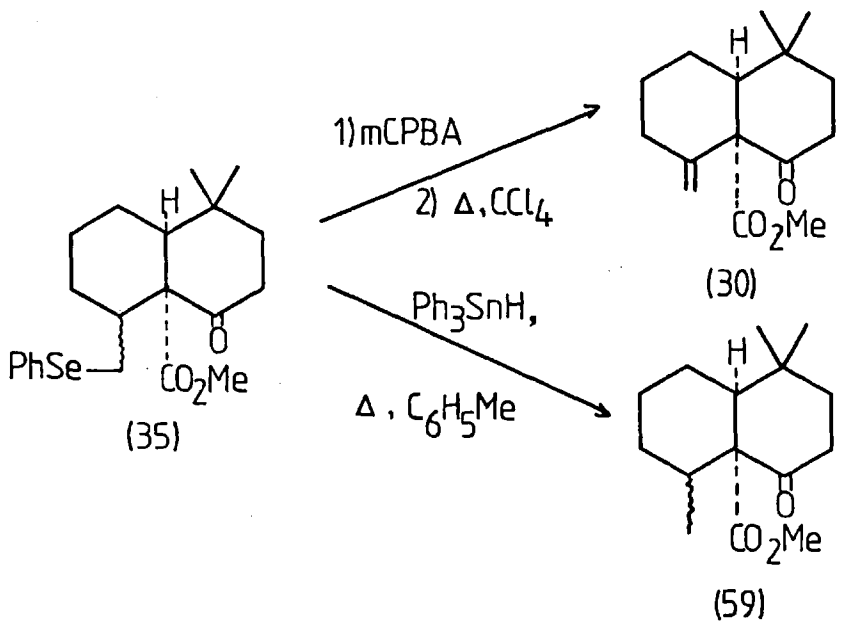
(84)

The hexenyl β-keto ester (69) cyclised similarly to afford the 6-ring selenide (80) in 56% yield. Conversion to the selenoxide (with m-chloroperbenzoic acid) and thermolysis in carbon tetrachloride gave the corresponding olefin, (85), in 90% yield. The signals due to the olefinic hydrogens appeared as broad singlets at δ5.07 and δ4.70 ppm in the ^1H n.m.r. spectrum.



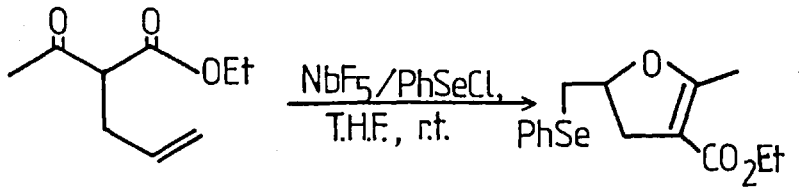
(80) (85)

Cyclisation of (9) with $PhSe^+ SbF_6^-$ gave (35) in 75% yield, which was identical to the previous sample. Oxidation (to the selenoxide) and syn-elimination gave (30) in 82% yield[42]. Reduction of the selenide (35) with triphenyl tin hydride[41] afforded (59) as a single isomer in 73% yield. The methyl group resonates as a doublet at δ 0.78 (J 7Hz) in the ^{1}H n.m.r. spectrum. The orientation of this methyl group will be determined by X-ray crystallographic analysis of the corresponding diol.

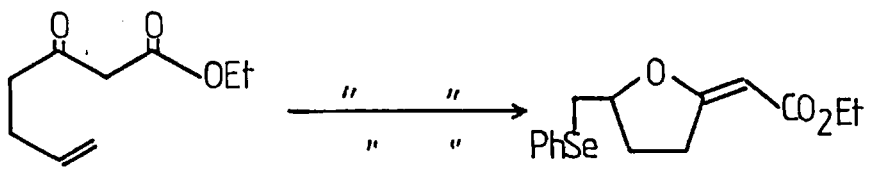


In a previous section it had been noted that a mixture of phenylselenium chloride and antimony pentachloride reacted with (9) to afford chlorinated products. However, it was found that certain cyclisations could be effected without halogenation using phenylselenium chloride and niobium pentafluoride. Consequently, (67) could be cyclised to (73) in 53% yield, while (70a) could be cyclised to (74a) in 70% yield, using this system. In many other cases studied cyclisation did not occur, although the niobium pentafluoride did cause extensive polymerisation of the tetrahydrofuran which

was used as solvent.



(67) (73)



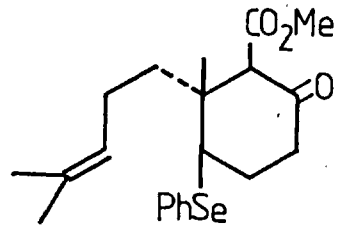
(70a) (74a)

While we have shown that $PhSe^{+}SbF_6^{-}$ and $PhSe^{+}PF_6^{-}$ are effective cyclising agents for alkenyl β-dicarbonyl compounds they are prepared from silver salts[12] and are, therefore, expensive. Cheaper alternatives would consequently be attractive.

Nicolaou has recently reported[43] that N-phenylselenophthalimide (N-PSP) has a number of advantages over phenylselenium chloride as a phenylselenating agent. For example, N-PSP will not add to a double bond unless a nucleophile (internal or external) and catalyst are present also, N-PSP in the presence of excess water can serve as a "PhSe OH" equivalent and, finally, N-PSP can induce macrolide formation, which is not possible with phenylselenium chloride. As phthalimide, which is produced as a by-product in the reaction, is non-nucleophilic, we hoped that this reagent might also be able to effect the cyclisation of alkenyl substituted β-dicarbonyl compounds.

The results of the reaction of various alkenyl substituted β-dicarbonyl species

with N-PSP in the presence of catalysts are shown in table 2[44,38]. Points of special interest from this table are : i) that the geranyl β-keto ester (55) gave an unknown product in low (<20%) yield, and ii) that β-keto esters (68), (69) and (9) failed to react. All of the other alkenyl compounds gave the same products as in the previous cyclisation procedure in comparable yield. It was disappointing, though, that four compounds failed to react. In an effort to increase the amount of carbon-carbon bond formation in the reaction of (72) with N-PSP, zinc iodide catalyst was added instead of para-toluene sulphonic acid. The reaction proceeded smoothly to give (77) as the only product. Encouraged by this observation we repeated the reactions using zinc iodide as catalyst. Compounds (68), (69) and (9) once again failed to react, and only decomposition of N-PSP was observed. Compounds (67), (70a) and (71) gave the oxygen-cyclised products in reasonable yield. Reaction of the geranyl β-keto ester (55) with N-PSP/zinc iodide was quite complex. The t.l.c. indicated that a single non-polar product was initially formed, which breaks down to afford another product after prolonged reaction. This product was assigned structure (86) as a result of its



(86)

spectral data. The ^{1}H n.m.r. spectrum showed a signal corresponding to the terminal double bond proton (δ 5.02 ppm) as well as resonances for the vinylic methyl groups (δ 1.58 and δ 1.68 ppm, singlets, integrating to three hydrogens each). A three hydrogen singlet resonance was observed at δ 1.21 ppm corresponding to the other methyl group. The proton on the carbon to which the phenylseleno group is attached

TABLE 2 REACTION OF ALKENYL SUBSTITUTED β-DICARBONYL COMPOUNDS WITH N-PSP IN THE PRESENCE OF CATALYSTS

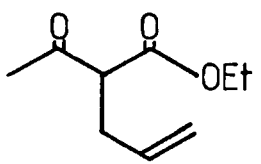
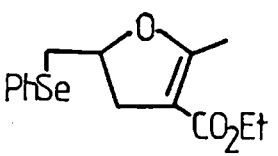
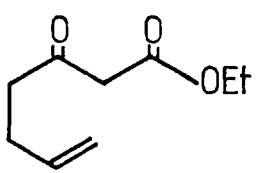
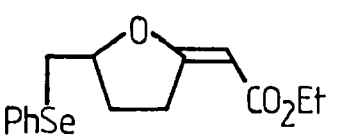
SUBSTRATE	PRODUCT	CATALYST	YIELD + COMMENTS
 (67)	 (73)	$H^{\oplus}$	80%
		ZnI_2	81%
 (70a)	 (74a)	$H^{\oplus}$	68%
		ZnI_2	82% (THF) 73% (CH_2Cl_2)

TABLE 2 (CONT.)

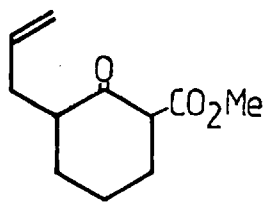
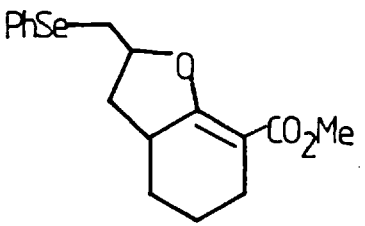
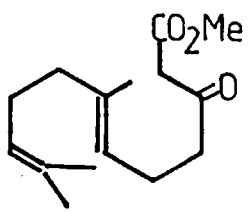
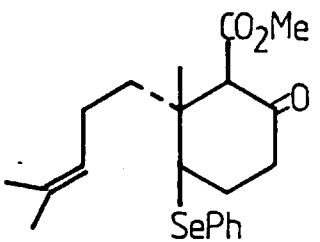
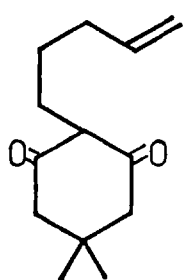
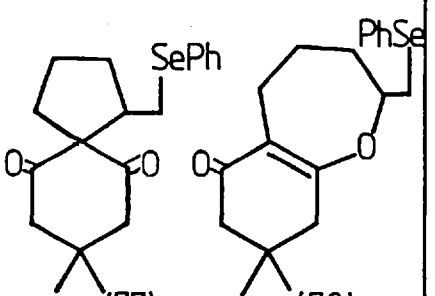
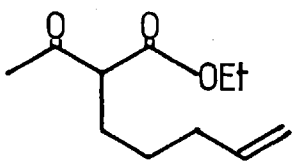
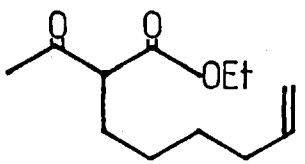
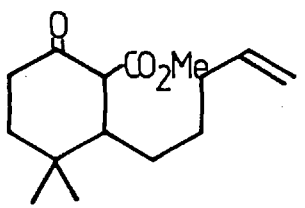
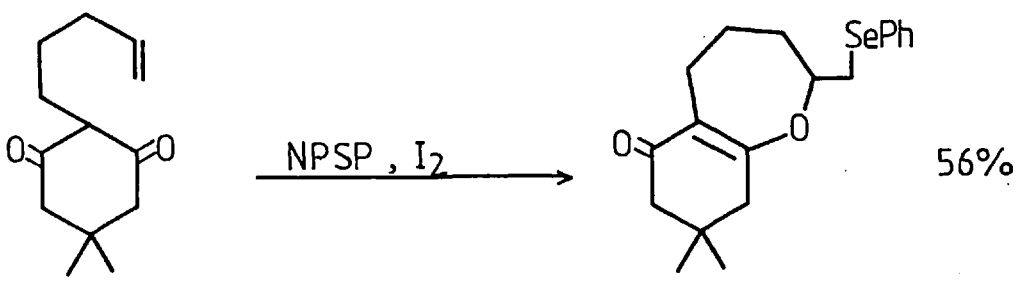
 (71)	 (75)	$H^{\oplus}$ ZnI_2	66 % 44%
 (55)	 (86)	$H^{\oplus}$ ZnI_2	unknown product 67%
 (72)	 (77) (78)	$H^{\oplus}$ ZnI_2	(77) 42% (78) 49% (77) 67%

TABLE 2 (CONT.)

 (68)	———	$H^{\oplus}$ ZnI_2	NO REACTION REAGENT DECOMPOSED
 (69)	———	$H^{\oplus}$ ZnI_2	NO REACTION REAGENT DECOMPOSED
 (9)	———	$H^{\oplus}$ ZnI_2	NO REACTION REAGENT DECOMPOSED

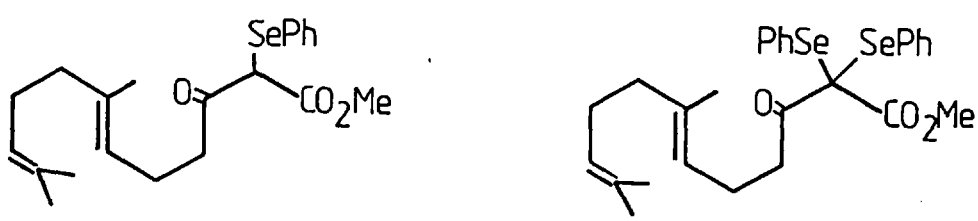
resonated as a multiplet at δ 3.50 ppm, while the hydrogen between the β-keto ester occurred as a singlet at δ 3.63 ppm. A similar monocyclic product has recently been observed in a mercuric acetate induced cyclisation[45].

The above cyclisations can also be achieved with N-PSP when iodine is used as catalyst. The reactions were generally lower yielding. Cyclisation of the dimedone derivative (72) affords (78) as the only product.[38] Reaction of the geranyl β-keto ester



(72) (78)

(55) with N-PSP and iodine catalyst produced (87) as the major product, together with a small amount of (88) (by n.m.r. and t.l.c.). Both these products, however, were unstable to column chromatography.

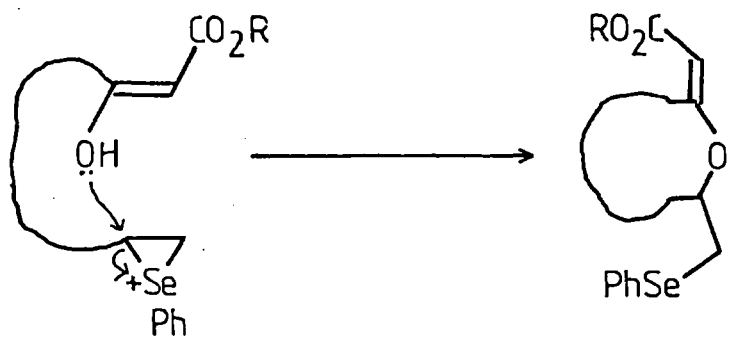


(87) (88)

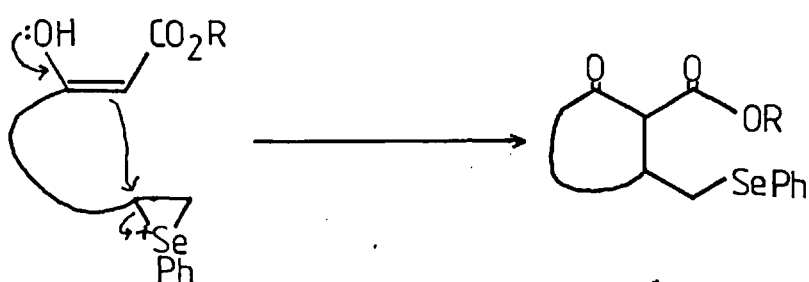
Mechanism of the Selenium Induced Cyclisation Reactions

The cyclisation of alkenyl β-dicarbonyl compounds with $PhSe^{+}X^{-}$ reagents most reasonably occurs by nucleophilic attack of the β-dicarbonyl compound onto an intermediate seleniranium species, as shown previously in scheme 11 . However, the case with N-PSP is not so clear cut, as other intermediates appear to be formed

Scheme 11



"O" Cyclised products

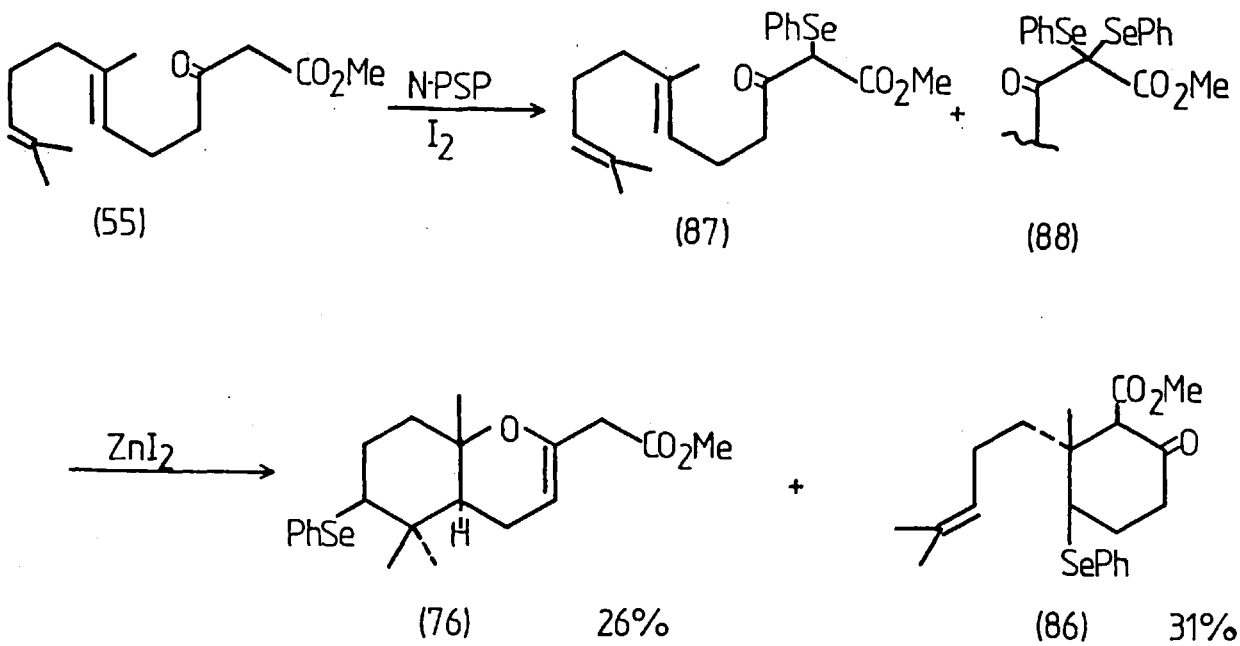


"C" Cyclised products

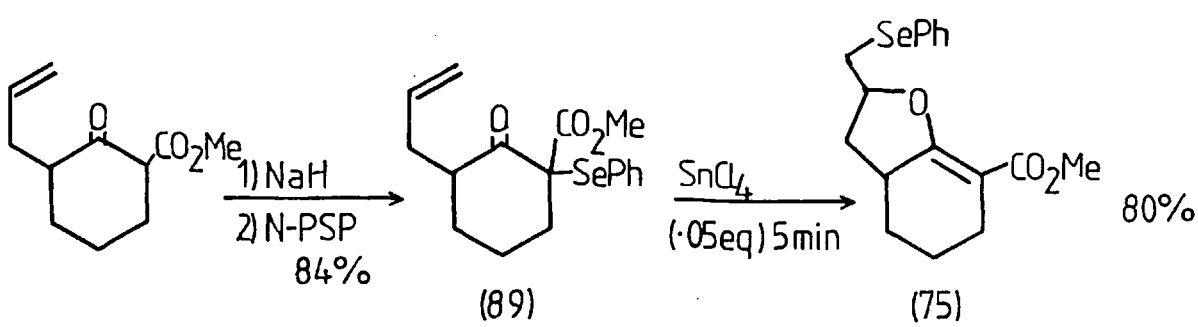
in the reaction. For example, reaction of the geranyl β-keto ester (55) with N-PSP and zinc iodide catalyst initially lead to a fast running spot by t.l.c. which disappeared gradually, to be replaced by other spots which were eventually replaced by a spot corresponding to (86).

We had previously noted that reaction of the β-dicarbonyl compounds with N-PSP and no catalyst was slow and afforded a product resulting from phenylselenation between the β-dicarbonyl system. In order to determine whether or not phenyl-

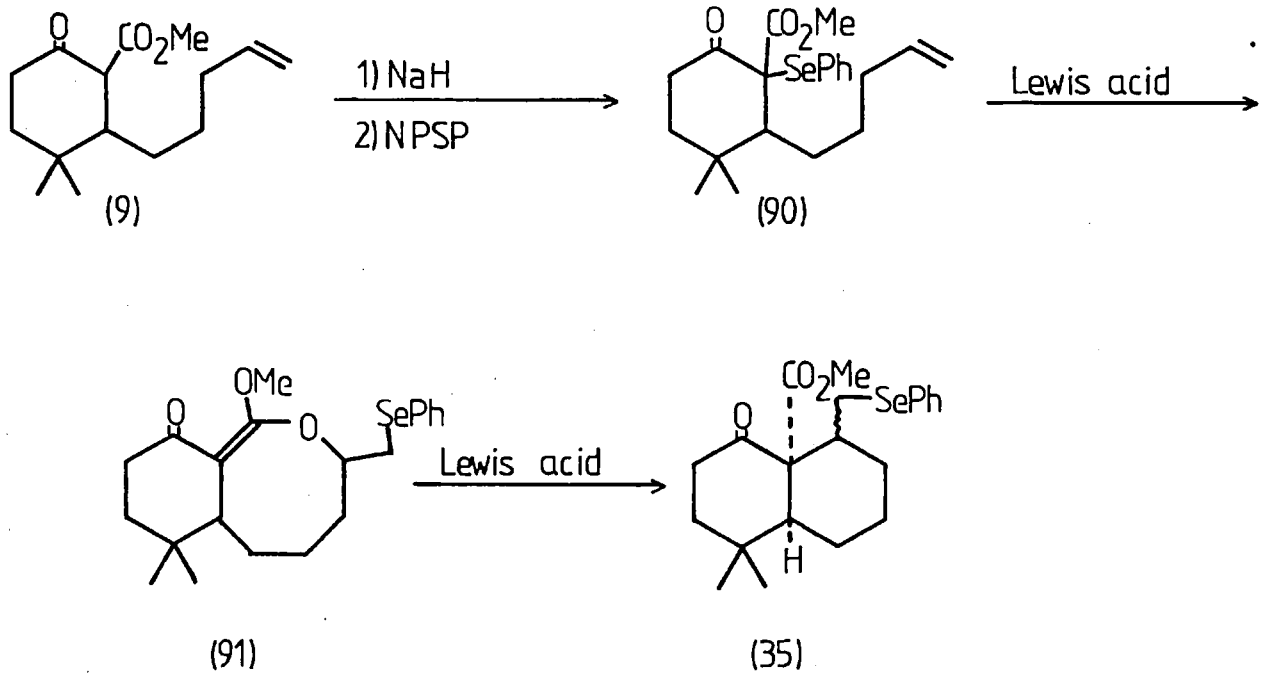
selenation between the β-dicarbonyl system was the initial step in the catalysed reactions the crude reaction mixture from (55) with N-PSP/iodine, which we knew produces (87) and (88), was treated with zinc iodide. Rearrangement took place to give (76) and (86) as products.



Products resulting from phenylselenation between the β-keto ester unit could be independently prepared by reaction of the mono-anion of the β-keto ester with N-PSP[46]. For example, the mono-anion of 6-allyl-2-carbomethoxycyclohexanone with N-PSP gave (89) in 84% yield. Treatment of (89) with a trace of tin tetrachloride gave (75) in 80% yield. Comparative rearrangement of (89) with zinc iodide required much longer reaction times.



The selenide (90) was similarly prepared from the mono-anion of (9) and N-PSP. When treated with various Lewis acids (ZnI_2, $AlCl_3$, $FeCl_3$, etc.), the selenide (90) smoothly reacted to afford a product which was not (35)! Although unstable to



(9) (90) (91) (35)

chromatography, the product could be obtained reasonably pure (> 90% by ^{1}H n.m.r.) and was assigned structure (91) on the basis of its spectral data. The i.r. spectrum of (91) showed absorptions at 1650, 1610 and 1575 cm^{-1}, which correspond to the enone system and the phenyl group. In the ^{1}H n.m.r. spectrum the methoxy group signal appears downfield shifted by 0.2 ppm relative to (90), again consistent with the methoxy group being enolic. The protons on the carbon adjacent to selenium resonate as a multiplet at δ 3.17 ppm. The two methyl signals occur at δ 0.91 and 0.96 ppm, which is some indication that cyclisation has occurred. Prolonged reaction of (91) with zinc iodide caused further rearrangement to the cis-decalin (35)[47].

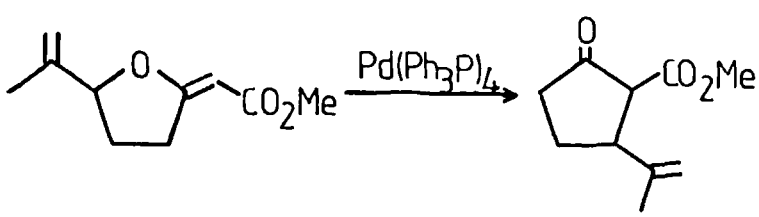
Thus, it is possible that the reason why compounds (9), (68) and (69) did not cyclise with N-PSP was due to the lack of phenylselenation between the β-keto ester system. We hoped that, by using a stronger Lewis acid (such as tin tetrachloride) in combination with N-PSP, cyclisation might take place. Indeed, in a number of cases, this turned out to be possible (table 3), although (9) could still not be cyclised using tin tetrachloride as catalyst. However, cyclisation of (9) was possible using boron trifluoride etherate as catalyst, albeit in low yield (20%). Further work in these laboratories[38] has since shown that (70b) and N-PSP reacted in the presence of tin tetrachloride to afford (92) in 74% yield. Compound (92) would obviously be a useful precursor for prostaglandin synthesis. In a similar manner the diester (93), which had failed to cyclise under all other previous conditions, now reacted with N-PSP/$SnCl_4$ to afford (94) in 50% yield[38].

From these results it can be seen that the scope of the selenium mediated cyclisation has now been substantially improved.

Rearrangements of Oxygen-Cyclised Products to Carbon-Cyclised Products

As the formation of carbon-carbon bonds is of prime importance in organic synthesis methods by which the oxygen-cyclised products, reported earlier in this thesis, could be rearranged to their carbon-cyclised counterparts were investigated.

Trost[48] and Tsuji[49] have recently shown that oxygen-cyclised compounds, such as (95) and (97), may be rearranged to their carbon-cyclised counterparts using Pd^0 catalysts.



(95) (96)

TABLE 3 REACTION OF VARIOUS β-DICARBONYL COMPOUNDS WITH N-PSP AND STRONG LEWIS ACIDS

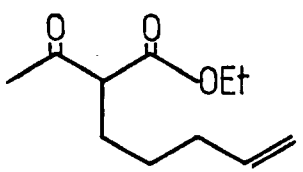
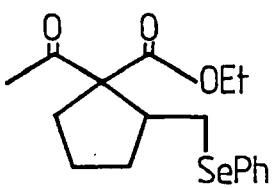
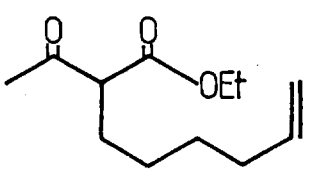
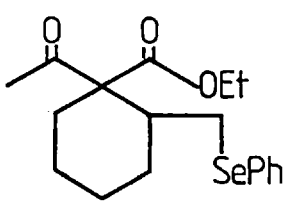
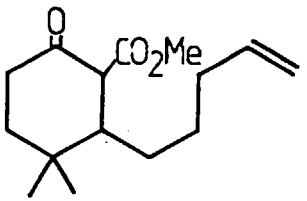
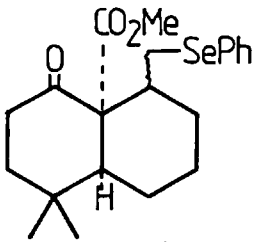
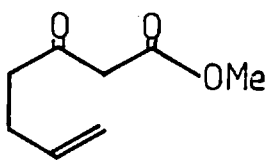
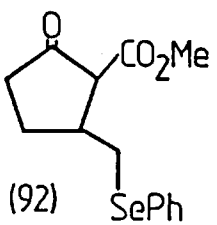
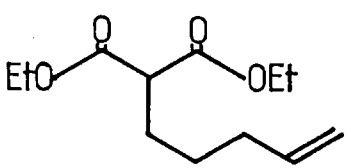
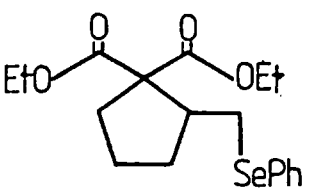
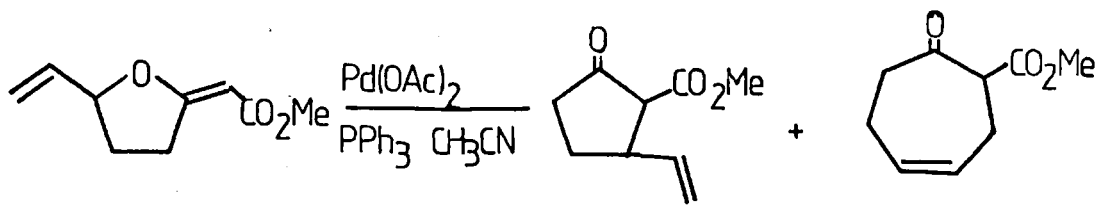
SUBSTRATE	PRODUCT	CATALYST	YIELD + COMMENTS
 (68)	 (79)	$SnCl_4$	73%
 (69)	 (80)	$SnCl_4$	49%

TABLE 3 (CONT.)

 (9)	 (35)	$BF_3.Et_2O$	20%
 (70b)	 (92)	$SnCl_4$	74% ref. 38
 (93)	 (94)	$SnCl_4$	50% ref. 38

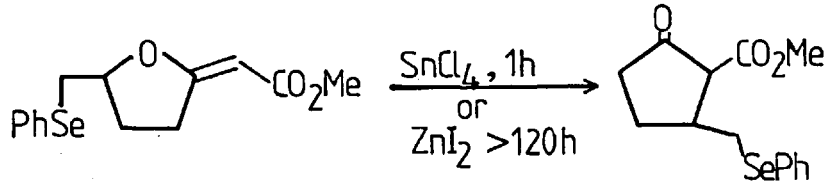


(97) (98) 19 : 1 (99)

72%

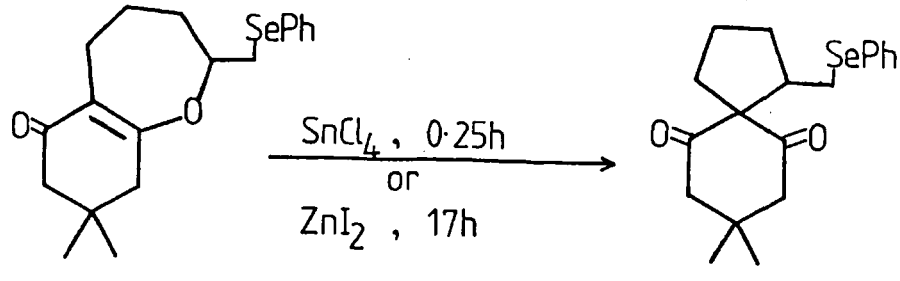
Some evidence suggested that the oxygen-cyclised selenides might be rearranged to the carbon-cyclised counterparts by the use of strong Lewis acids, such as tin tetrachloride.

Indeed, treatment of (74b) with 0.5 equivalents of tin tetrachloride gave (92) in essentially quantitative yield after 1 hour. The same rearrangement was possible



(74b) (92)

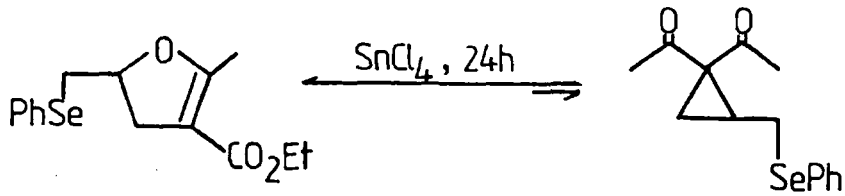
using zinc iodide, although it was extremely slow and required several days for any significant reaction to occur. Compound (78), in a similar way, could be rearranged to (77) using either 0.5 equivalents of tin tetrachloride or one equivalent of zinc iodide. In both cases (77) was obtained in very high yield. Attempts to rearrange (73)



>90%

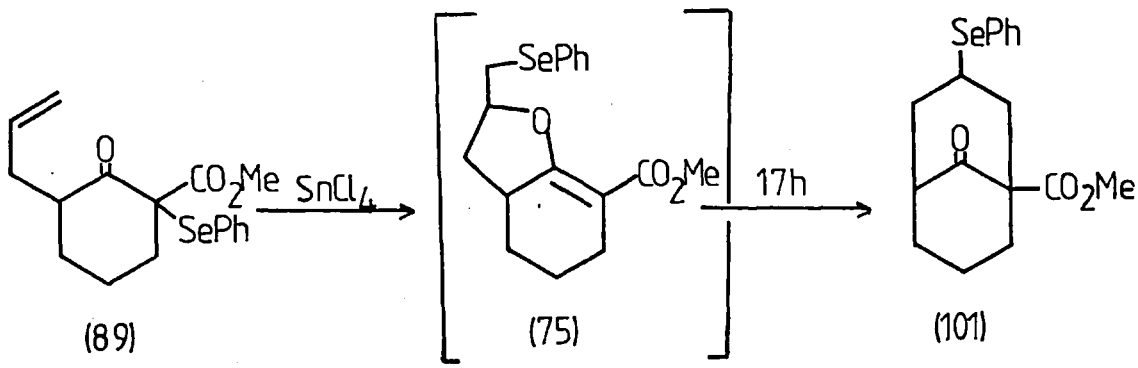
(78) (77)

to the corresponding cyclopropyl derivative (100) failed. This result, of course, was not too surprising, considering that (100) would be thermodynamically very much less stable than (73).



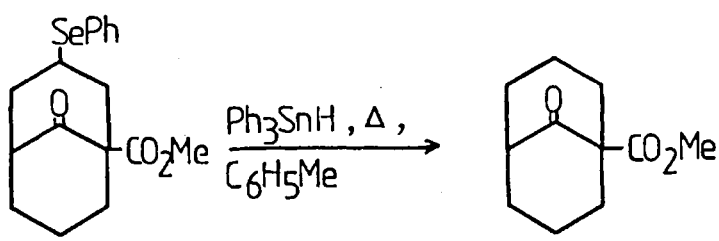
(73) (100)

It has been shown previously that (89), on treatment with tin tetrachloride, afforded (75). Consequently, its further rearrangement to the carbon cyclised compound (101) was expected to be slow. In practice it was found that (89), on treatment with one equivalent of tin tetrachloride for 17 hours at room temperature, afforded an 88% yield of (101). The i.r. spectrum of (101) shows ester and ketone absorptions at 1735 and



(89) (75) (101)

1715 cm^{-1} respectively. The ^1H n.m.r. spectrum shows an absorption at δ 4.15 ppm resulting from the methine proton alpha to the phenylseleno moiety. Reduction of (101) with triphenyltin hydride[41] gave (102), which has been prepared previously by an

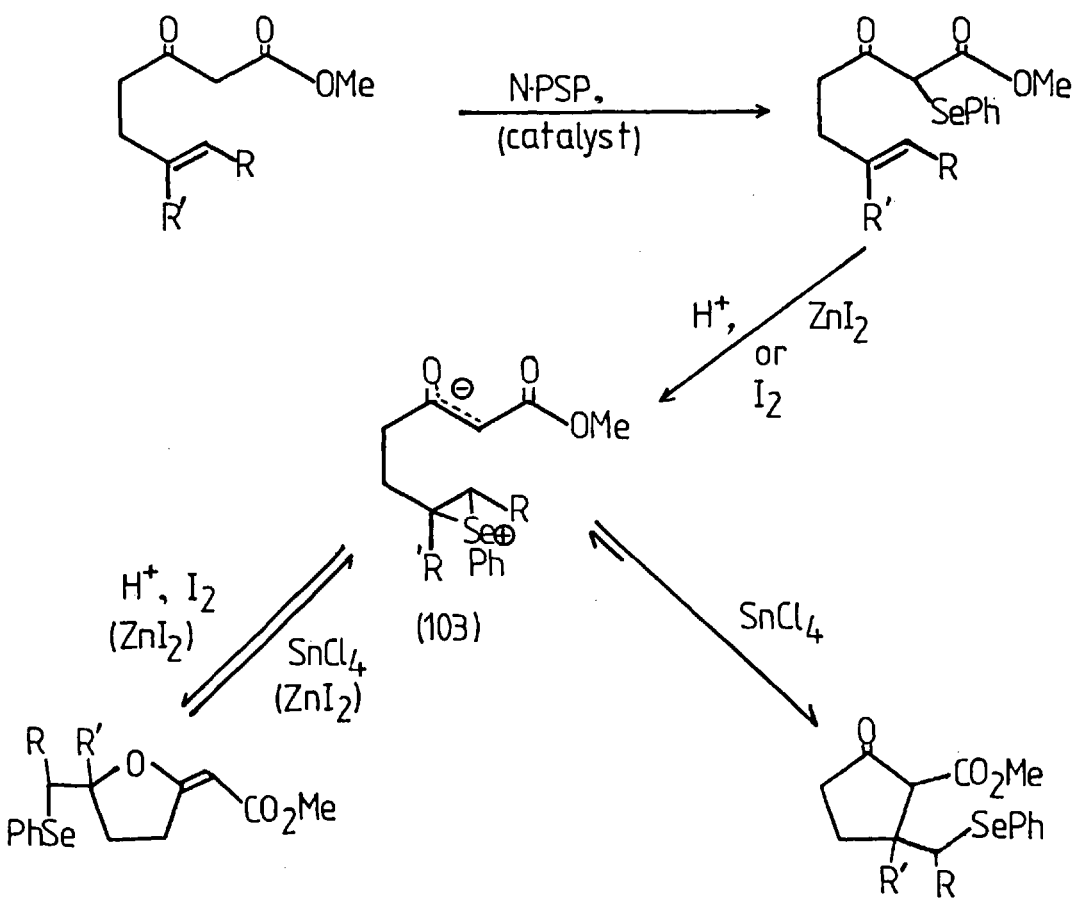


(101) (102)

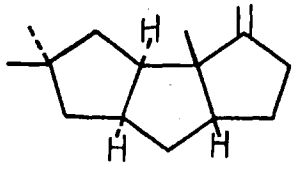
alternative route[50].

In view of the above results it is now possible to speculate that the mechanism for the cyclisation reaction using N-PSP follows a pathway as outlined in scheme 13. Initial reaction appears to be one of phenylselenation between the β-keto ester which subsequently rearranges to the oxygen or carbon cyclised products. If strong Lewis acids are used the carbon cyclised (thermodynamic) product can be obtained most likely via an intermediate Zwitter ionic species (103). Similar intermediates have been evoked by Trost[48] to explain the Pd^{o} catalysed reactions briefly discussed earlier.

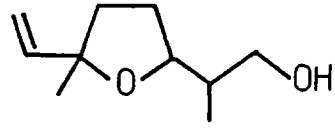
Scheme 13



In conclusion, then, it can be seen that these selenium induced cyclisations form the basis for a useful new synthetic method for constructing carbo- and heterocyclic ring systems. The selenophenyl group which has also been introduced is extremely synthetically versatile[51]. Further work in our laboratories will make use of these new selenium induced cyclisation reactions for the synthesis of a number of natural products including hirsutene (104)[52] and lilac alcohol (105).



(104)



(105)

Experimental

Melting points were determined on a Kofler block and are uncorrected. I.R. spectra were recorded with Perkin-Elmer 237 and 298 grating spectrometers. ^{1}H n.m.r. spectra were recorded with a Varian EM 360A or XL 100 spectrometer. High field ^{1}H n.m.r. spectra were obtained on a Bruker WH-250 F.T. spectrometer with 16k transforms. Spectra were obtained for solutions in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. Apparent J values and multiplicities are quoted throughout. Reaction solvents were purified and dried by literature methods, product solutions being dried over sodium sulphate unless otherwise stated. Chromatography was performed on Merck-Kieselgel 60H and p.l.c. carried out on Merck-Kieselgel GF 254.

Preparation of compound (16) :- To a solution of 4,4-dimethylcyclohexenone (0.4 g, 3.2 mmol) and CuCN (20 mg) in diethyl ether (25 ml) was added a solution of pent-4-enylmagnesium bromide (from the bromide [1 g, 6.6 mmol] and magnesium [0.2 g]) in diethyl ether (20 ml), at 0°C, under argon, over 0.5 h. After 1 h, the reaction was quenched with 2 M hydrochloric acid (50 ml) and the organic phase separated and dried. After removal of solvent the residue was subjected to p.l.c. (15% ether/pet ether) to afford 4,4-dimethyl-3-(1-pent-4-enyl)-cyclohexan-1-one (16) (0.53 g, 85%); δ 1.00 (3H, s), 1.03 (3H, s), 1.2-1.7 (7H, m), 1.8-2.3 (6H, m), and 4.7-6.0 (3H, m); ν_{max} 2900, 1710, and 1640 cm^{-1} (Found : C, 80.07; H, 11.56. $C_{13}H_{22}O$ requires C, 80.41; H, 11.35%)

Preparation of compound (9) :- a) To a solution of 4,4-dimethylcyclohexenone (0.4 g, 3.2 mmol) and CuCN (20 mg) in diethyl ether (25 ml) at -23°C, under argon,

was added pent-4-enylmagnesium bromide (from the bromide [1 g, 6.6 mmol] and magnesium [0.2 g]) in diethyl ether (25 ml) over 0.25 h. Methylchloroformate (0.5 ml, 0.61 g, 6.4 mmol) was added in a single portion after 0.5 h, and the mixture was allowed to warm to room temperature. 2M Hydrochloric acid (50 ml) was added and the organic phase extracted and dried. The solvent was removed and the residue subjected to p.l.c. (5% ether/light petrol) to afford 2-carbomethoxy-4,4-dimethyl-3-(1- [pent-4-enyl])-cyclohexanone (9) (0.49 g, 60%) ; δ 0.88(3H,s), 0.97(3H,s), 1.2-2.4 (11H, m), 3.72 (3H, m) and 4.75-6.0 (3H, m); ν_{max} 2940, 1755, 1710, 1610, 1440, and 1205 cm^{-1} (Found : C, 71.14 ; H, 9.73 . $C_{15}H_{24}O_3$ requires C, 71.43; H, 9.52%)

b) A solution of pent-4-enyl magnesium iodide (from the iodide [4 g, 20 mmol] and magnesium [0.75 g]) in diethyl ether (20 ml) was transferred by double tipped needle to a suspension of copper(I) iodide (2.2 g, 11.6 mmol) in diethyl ether (30 ml) at 0°C, under argon. After 1 h the mixture was cooled to -78°C and 4,4-dimethylcyclohexenone (1.2 g, 9.7 mmol) in diethyl ether (8 ml) was added over 0.1 h. The mixture was warmed to -23°C and methylchloroformate (1.2 ml, 1.5 g, 16 mmol) was added in a single portion. After 0.5 h at -23°C the mixture was allowed to warm to room temperature and 2 M hydrochloric acid (50 ml) was added. The organic phase was separated and dried. The solvent was removed and the residue purified by column chromatography (1% ether/pet ether) to afford 2-carbomethoxy-4,4-dimethyl-3-(1- [pent-4-enyl])-cyclohexanone (9) (1·2 g, 49%) identical to the previous sample.

Preparation of compound (17) :- A mixture of 2-carbomethoxy-4,4-dimethyl-3-(1- [pent-4-enyl])-cyclohexanone (250 mg, 1 mmol) and m-chloroperbenzoic acid (190 mg, 85%) were stirred until starting material was consumed, as indicated by t.l.c. analysis. The

organic phase was washed with saturated aqueous bicarbonate solution and distilled water. After drying the solvent was removed and the residue purified by p.l.c. (15% ether/pet. ether) to afford 2-carbomethoxy-4,4-dimethyl-3-(1- [4,5-epoxypentyl])-cyclohexanone (17) (147 mg, 54%) ; δ 0.93 (3H, s), 1.0 (3H, s), 1.1-1.7 (8H, m), 2.1-2.3 (4H, m), 2.5-2.9 (2H, m), and 3.74 (3H, s); ν_{max} 2800, 1750, 1710, 1640, and 1600 cm^{-1}. (Found : C, 66.93 ; H, 9.02 . $C_{15}H_{24}O_4$ requires C, 67.16; H, 8.96%).

Preparation of 1-trimethylsilyl-5-iodopent-1-yne

a) A solution of 5-hydroxypentyne (16.8 g, 0.2 mol) in tetrahydrofuran (50 ml) was added, with external cooling, to a solution of ethylmagnesium bromide (from the bromide [50 g, 47.5 mmol] and magnesium [12 g]) in tetrahydrofuran (500 ml). After all evolution of gas had ceased, trimethylsilyl chloride (65 ml) was added with cooling. The mixture was stirred overnight and pet.ether (0.5 l) was added, and the mixture filtered. The solid residue was washed several times with pet.ether. The solvent was removed, replaced with pet.ether and filtered. After removal of solvent crude 1-trimethylsilyl-5-trimethylsiloxypentyne was obtained (43.8 g, 96%) which was >99% pure by g.l.c.

b) To a mixture of 1-trimethylsilyl-5-trimethylsiloxypentyne (20.5 g, 90 mmol) and pyridine (5 drops) at 0°C was added thionyl chloride (12 g, 0.1 mol) over 0.25 h. The mixture was stirred overnight and distilled at atmospheric pressure to afford trimethylsilyl chloride (8.3 g, 85%). The mixture was heated to 140°C for 0.5 h, cooled and distilled to afford 1-trimethylsilyl-5-chloropentyne (12.8 g, 82%) b.p. 63°C at 5 mm Hg.

c) A mixture of 1-trimethylsilyl-5-chloropentyne (17.4 g, 0.1 mol) and sodium iodide (23 g, 0.15 mol) were heated at reflux for 15 h in acetone (150 ml). Pet.ether (300 ml) was added and the mixture filtered. Removal of solvent and distillation afforded 1-trimethylsilyl-5-iodopent-1-yne (23.6 g, 88%), b.p. 74-75°C at 4 mm Hg.

Preparation of compound (31) :- To a mixture of 4,4-dimethylcyclohexenone (6.25 g, 50 mmol) and CuCN (0.5 g) in diethyl ether (400 ml) at -23°C, under argon, was added a solution of 5-trimethylsilylpent-4-ynylmagnesium iodide (from the iodide [20 g, 75 mmol] and magnesium [3.5 g, 145 mmol]), in diethyl ether (100 ml) over 4 h. Methylchloroformate (8 ml, 100 mmol) was added and stirring continued for 1 h at -23°C and 0.5 h at room temperature. 2M Hydrochloric acid (100 ml) was added and the organic phase separated and dried. The solvent was removed and the residue chromatographed (pet. ether then 5% ether/pet. ether) to give 2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] - 4,4-dimethylcyclohexan-1-one (31) (9.7g, 60%) ; δ 0.13 (9H, s), 0.93 (3H, s), 1.02 (3H, s), 1.2-2.3 (11H, m), and 3.74 (3H, s) ; ν_{max} 2900, 2140, 1755, 1715, 1660, 1615, 1440, 1280, 1250, 1225, 1205, and 845 cm^{-1} (Found : C, 67.08 ; H, 9.64. $C_{18}H_{30}O_3Si$ requires C, 67.05 ; H, 9.39%).

Preparation of compound (32) :- To a mixture of 4,4-dimethylcyclohexenone (1 g, 8 mmol) and CuCN (0.1 g) in tetrahydrofuran (50 ml) at -23°C, under argon, was added 5-trimethylsilylpent-4-ynylmagnesium chloride (from the chloride [3 g, 17 mmol] and magnesium [0.5 g, 21 mmol] at reflux) in tetrahydrofuran (50 ml) over 0.5 h. After 1 h methylchloroformate (0.95 ml, 12 mmol) was added in a single portion and stirring continued for 1 h at -23°C and 0.5 h at room temperature. 2M Hydrochloric acid (100 ml) was added and the mixture extracted with diethyl ether (2 x 100 ml). After drying, the solvent was removed to afford 1-methoxycarbonyloxy-3- [1-(5-trimethylsilylpent-4-ynyl)] - 4,4-dimethylcyclohex-1-ene (32) as an oil which was unstable to chromatography; δ 0.12 (9H, s) , 0.84 (3H, s) , 0.98 (3H, s) , 1.4 - 2.3 (11H, m) , 3.71 (3H, s) , and 5.29 (1H, br s) ; ν_{max} 2930, 2150, 1760, 1250, and 850 cm^{-1}. (Found M^{+}; 322.1968 . $C_{18}H_{30}O_3Si$ requires 322.1964).

Preparation of compound (33) :- To a mixture of 4,4-dimethylcyclohexenone (0.5 g, 4 mmol) and CuCN (0.05 g) in tetrahydrofuran (25 ml) at -23°C, under argon, was added 5-trimethylsilylpent-4-ynylmagnesium chloride (from the chloride [1.5g,8.5 mmol] and magnesium [0.25 g, 10.5 mmol] at reflux) in tetrahydrofuran (20 ml) over 0.5 h. After 0.5 h, trimethylsilyl chloride (2.5 ml) was added and the mixture allowed to warm to room temperature. After removal of the solvent, the resulting oil was triturated with pet. ether. Removal of solvent gave crude 1-trimethylsilyloxy-3-[1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohex-1-ene (33) (3 g) which was unstable to chromatography ; δ 0.13 (9H, s) , 0.16 (9H, s) , 0.80 (3H, s) , 0.95 (3H, s), 1.2-2.3 (11H, m),and 4.77 (1H, br s) ; ν_{max} 2800, 2165, 1670, 1250,and 1050 cm^{-1}. (Found : $M^{+\cdot}$ 336.2296. $C_{19}H_{36}OSi_2$ requires 336.2305).

Preparation of compound (29) :- To a solution of silver nitrate (8 g) in ethanol/water (150 ml, 3:1) was added 2-carbomethoxy-3-[1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (8.5 g, 26 mmol) in ethanol (120 ml) over 0.75 h, with vigorous stirring. After 0.5 h, potassium cyanide (20 g) was added in ethanol/water (180 ml, 1 : 1). The mixture was stirred for 3 h, poured into water (500 ml) and extracted with CH_2Cl_2 (2 x 200 ml). The solvent was removed, water (250 ml) added, and the organic components extracted with CH_2Cl_2 (2 x 150 ml). After drying and removal of solvent, the residue was subjected to chromatography (5% ether/pet. ether) to afford 2-carbomethoxy-3-[1-(pent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (29) (4.56 g, 60%) ; δ 0.90 (3H, s), 0.99 (3H, s), 1.2-2.3 (12H, m), and 3.70 (3H, s) ; ν_{max} 2900, 1750, 1710, 1650, 1615, 1440, 1280, 1225,and 1205 cm^{-1} (Found : C, 71.87 ; H, 9.14 . $C_{15}H_{22}O_3$ requires C , 71.95 ; H , 8.86%).

Preparation of compound (30) :- (a) 2-Carbomethoxy-3-[1-(pent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (29) (4.35 g, 17.5 mmol) was boiled in toluene (60 ml)

with zinc iodide (200 mg) until the reaction was complete, as shown by t.l.c. analysis (ca. 5 h). The mixture was filtered and the solvent removed under reduced pressure to afford cis-1a-carbomethoxy-5,5-dimethylbicyclo [4.4.0] dec-10,1'-en-2-one (30) (4.35 g, 100%) ; δ 1.06 (3H, s), 1.13 (3H, s) , 1.25-2.8 (11H, m) , 3.70 (3H, s) , 4.30 (1H, s) , and 4.79 (1H, s) ; ν_{max} 2900 , 1720 (broad) , 1635 , and 1230 cm^{-1} (Found : C, 71.98; H, 9.04 . $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

(b) 2-Carbomethoxy-3- [1-(pent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (29) (100 mg, 0.4 mmol) was stirred at room temperature with tin tetrachloride (0.8 ml of a 0.5 M solution in CH_2Cl_2) in CH_2Cl_2 (8 ml) for 2.5 h. The mixture was washed with saturated aqueous sodium bicarbonate solution and the organic phase separated and dried. Removal of solvent gave cis-1a-carbomethoxy-5,5-dimethylbicyclo [4.4.0] dec-10,1'-en-2-one (30) (95 mg, 95%) identical to the above sample.

Preparation of compound (36) :- A solution of cis-1a-carbomethoxy-5,5-dimethylbicyclo [4.4.0] dec-10,1'-en-2-one (4.1 g, 16.4 mmol) in diethyl ether (50 ml) was added dropwise to a suspension of lithium aluminium hydride (1.5 g) in diethyl ether (50 ml) at room temperature. After 3 h water (7 ml) was added cautiously until evolution of hydrogen ceased, and then solid sodium sulphate (25 g) was added. The mixture was filtered and the solid washed several times with ether. Removal of solvent gave cis-5,5-dimethyl-2β-hydroxy-1a-hydroxymethylbicyclo [4.4.0] dec-10,1'-ene (36) (3.27 g, 89%), m.p. 132-133°C (from cyclohexane) ; δ 0.88 (3H, s) , 1.05 (3H , s) , 1.25-2.2 (11H, m) , 3.25 (1H , d , J 11 Hz) , 3.50 (1H , d) , 3.81 (2H , br s) , 4.19 (1H , d , J 11 Hz) , 5.0 (1H , s) , and 5.45 (1H , d) ; ν_{max} 3400 , 2950 , 1635 , 1440 , and 1090 cm^{-1} (Found : C , 75.08 ; H , 10.87 . $C_{14}H_{24}O_2$ requires C , 74.94 ; H , 10.79%).

Preparation of compound (38) :- To a solution of cis-5,5-dimethyl-2β-hydroxy-1a-hy-

droxymethyl bicyclo [4.4.0] dec-10,1'-ene(36) (0.83 g , 3.7 mmol) and $VO(acac)_2$ (50 mg) in benzene (4 ml) was added t-butylhydroperoxide (0.6 g, 90%) in benzene (5 ml). After 17 h, the solvent was removed and pyridine (15 ml) , acetic anhydride (5 ml) , and 4-N,N-dimethylaminopyridine (50 mg) added. Excess reagents were removed under high vacuum after 7 h and the residue chromatographed on Florisil (eluting with 5% pet. ether/CH_2Cl_2) to afford spiro (cis-2β-acetoxy-1α-acetoxymethyl-5,5-dimethyl-bicyclo [4.4.0] decan-10,2'α-oxiran) (38) (0.945 g, 79%), m.p. 64°C (from pet. ether) ; δ 1.04 (3H, s), 1.05 (3H , s) , 1.24-1.80 (11H , m) , 1.97 (3H , s) , 2.02 (3H , s) , 2.33 (1H , d , J 4 Hz) , 3.05 (1H , d , J 4 Hz) , 3.82 (1H , d , J 12 Hz) , 4.18 (1H , d , J 12 Hz) , and 4.76 (1H , t) ; ν_{max} 2900 , 1745 , 1240 , and 1045 cm^{-1} (Found : C , 66.70 ; H , 8.67 . $C_{18}H_{28}O_5$ requires C , 66.62 ; H , 8.70%).

Preparation of compound (39) :- A mixture of cis-5,5-dimethyl-2β-hydroxy- 1α-hydroxy-methylbicyclo [4.4.0] dec - 10,1'-ene (36)(120 mg , 0.54 mmol) pyridine (1 ml), acetic anhydride (0.5 ml) and 4-N,N-dimethylaminopyridine (5 mg) were stirred at room temperature for 1.5 h. Excess reagents were removed with high vacuum. The residue was purified by p.l.c. (1 : 1 ether/pet. ether) to afford cis-2β-acetoxy-1α-acetoxymethyl-5,5-dimethyl-bicyclo [4.4.0] dec-10,1'-ene (39) (152 mg, 96%) m.p. 56-57°C ; δ 0.97 (3H , s) , 1.08 (3H , s) , 1.35-2.20 (11H , m) , 2.0 (3H , s) , 2.02 (3H , s) , 3.98 (1H , d J 12Hz), 4 70 (1H , d) , 5.02 (1H , br s) , and 5.28 (1H , s) ; ν_{max} 2950, 1750, 1640, 1240, and 1050 cm^{-1} (Found : C , 70.10 ; H , 9.28 . $C_{18}H_{28}O_4$ requires C, 70.08; H, 9.16%).

Alternative preparation of compound (38) :- A mixture of cis-2β-acetoxy-1α-acetoxy-methyl-5,5-dimethyl bicyclo [4 . 4. 0] dec-10, 1' - ene (39) (185 mg, 0.6 mmol) and m-chloroperbenzoic acid (130 mg , 85%) were stirred overnight in CH_2Cl_2 (10 ml). The organic phase was washed successively with sodium metabisulphite solution, sodium

bicarbonate solution, and water. After drying the solvent was removed to afford spiro (cis-2β-acetoxy-1α-acetoxymethyl-5,5-dimethylbicyclo [4.4.0] decan-10,2'α-oxiran) (38) (173 mg, 89%) identical to the previous sample.

Preparation of compound (40) :- A mixture of cis-5,5-dimethyl-2β-hydroxy-1α-hydroxymethylbicyclo [4.4.0] dec-10,1'-ene (36) (0.5 g, 2.2 mmol), pyridine (5 ml) and acetic anhydride (2.5 ml) were stirred for 1 h at room temperature. Excess reagents were removed under high vacuum and the residue subjected to p.l.c. (25% pet. ether/ether) to afford cis-1α-acetoxymethyl-5,5-dimethyl-2β-hydroxybicyclo [4.4.0] dec-10,1'-ene (40) (0.56, 94%) m.p. 68-70°C (from pet. ether); δ 0.93 (3H, s), 1.00 (3H, s), 1.2-2.2 (11H, m), 2.01 (3H, s), 2.87 (1H, br s), 3.48 (1H, dd, J 11Hz 4Hz), 4.00 (1H, d, J 11Hz), 4.35 (1H, d, J 11Hz), 4.94 (1H, br s), and 5.45 (1H, br s); ν_{max} 3500, 2930, 1740, 1635, 1240 and 735 cm^{-1}.

Preparation of compound (41) :- A solution of cis-1α-acetoxymethyl-5,5-dimethyl-2β-hydroxybicyclo [4.4.0] dec-10,1'-ene (40)(0.134 g, 0.5 mmol) in CH_2Cl_2 (10 ml) was stirred overnight with Collins reagent (1.3 g). The mixture was diluted with ether (50 ml) and filtered through a pad of celite. The solvent was removed and the residue subjected to p.l.c. (1 : 1 ether/pet. ether) to afford cis-1α-acetoxymethyl-5,5-dimethylbicyclo [4.4.0] dec-10,1'-en-2-one (41) (0.125 g, 95%) ; δ 1.05 (3H, s), 1.20 (3H, s), 1.6-1.26 (9H, m), 1.98 (3H, s), 2.2-2.5 (2H, m), 4.08 (1H, J 10Hz), 4.53 (1H, d, J 10Hz), 4.43 (1H, s), and 4.87 (1H, s); ν_{max} 2920, 1750, 1720, 1230, and 1040 cm^{-1} (Found : C, 72.46 ; H, 9.31. $C_{16}H_{24}O_3$ requires C, 72.67 ; H, 9.16%).

Preparation of compound (42) :- The epoxydiol (37) was prepared from cis-5,5-dimethyl-2β-hydroxy-1α-hydroxymethylbicyclo [4.4.0] dec-10,1'-ene (36) (225 mg, 1 mmol) as

previously described. The solvent was removed and replaced by pyridine (3 ml) and acetic anhydride (1 ml). The mixture was stirred for 0.5 h and the excess reagents removed under high vacuum. The residue was chromatographed on Florisil (CH_2Cl_2) to afford spiro (cis-1a -acetoxymethyl-5,5-dimethyl-2β-hydroxybicyclo [4.4.0] decan-10,2'a -oxiran) (42) (130 mg, 46%) m.p, 96-98°C ; δ 0.97 (3H, s), 1.05 (3H, s), 1.2-1.8 (11H, m), 2.07 (3H, s), 2.57 (1H, d), 3.4-3.6 (3H, m), and 4.41 (2H, d) ; ν_{max} 3450, 2940, 1750, 1235,and 1080 cm^{-1}. (Found : C, 67.83 ; H, 9.23. $C_{16}H_{26}O_4$ requires C, 68.05 ; H, 9.28%).

Preparation of compound (43) :- Spiro (cis-1a-acetoxymethyl-5,5-dimethyl-2β-hydroxybicyclo [4.4.0] decan-10,2'a -oxiran) (42) (130mg, 0.46mmol) was stirred overnight with Collins reagent (1.3 g) in CH_2Cl_2 (10 ml). Ether (50 ml) was added and the mixture filtered through a pad of celite. Purification on Florisil (eluting with CH_2Cl_2) gave spiro (cis-1a -acetoxymethyl-5,5-dimethylbicyclo [4.4.0] decan-2-one-10,2'a -oxiran) (43) (85 mg, 66%), m.p. 101-103°C (from cyclohexane) ; δ 1.20 (6H, s), 1.50-1.85 (9H, m), 1.97 (3H, s), 2.25-2.62 (4H, m), 4.08 (1H, d, J 11Hz),and 4.62 (1H, d, J 11Hz) ; ν_{max} 2930, 1750, 1715, 1240,and 1045 cm^{-1} (Found : C, 68.63 ; H, 8.80. $C_{16}H_{24}O_4$ requires C, 68.53 ; H, 8.63%).

Preparation of compound (49) :- A mixture of 1-butyn-3-ol (7g, 100 mmol) and triethylamine (3 drops) were heated at 60°C and diketene (9 g, 107 mmol) was added slowly, allowing the temperature to rise to 80°C, with external cooling. The mixture was distilled to afford butyn-3-acetoacetate (49) (13.4 g, 84%) b.p. 65-66°C at 2.5 mm Hg ; δ 1.47 (3H, d), 2.21 (3H, s), 2.47 (1H, d, J 2Hz), 3.40 (2H, s),and 5.34 (1H, dq) ; ν_{max} 3280, 2985, 1740, 1715,and 1635 cm^{-1}.

Preparation of compound (51) :- A solution of butyn-3-acetoacetate (51) (260 mg, 1.7 mmol) and tin tetrachloride (4 ml of a 0.5M solution in CH_2Cl_2) in CH_2Cl_2 (6 ml) was stirred for two days at room temperature. Saturated aqueous sodium bicarbonate solution was added and the mixture extracted with CH_2Cl_2 (2 x 10 ml). After drying and removal of solvent the residue was filtered through a pad of silica to afford 4-acyl-2,3-dimethyl-4-buten-3-olide (51) (210 mg, 81%) as an oil ; δ 1.50 (3H, d), 2.37 (3H, s), 2.52 (3H, s),and 4.90 (1H, q) ; ν_{max} 2985, 2935, 1760, 1690, 1630,and 1020 cm^{-1}.

The compound could not be purified by chromatography due to decomposition to 2-oxo-butan-3-acetoacetate (52).

Preparation of compound (50) :- To a suspension of sodium hydride (0.1 g, 50% washed free of oil with light petrol) in tetrahydrofuran (10 ml) was added methyl acetoacetate (240 mg, 2 mmol) in tetrahydrofuran (2 ml) at 0°C, under argon. n Butyl lithium (1.5 ml, 1.5 M solution in hexane) was added, followed by propargyl bromide (300 mg, 2.5 mmol) in tetrahydrofuran (2 ml). After 0.1 h saturated aqueous ammonium chloride solution was added and the mixture extracted with pet. ether (2 x 30 ml). After drying and removal of solvent the residue was subjected to chromatography (40% pet. ether/ CH_2Cl_2) to afford 6-carbomethoxy-5-oxo-hexyne (50) (300 mg, 94%) as an oil; δ 1.92 (1H, t, J 2Hz), 2.23-3.23 (4H, m), 3.45 (2H, s),and 3.70 (3H, s); ν_{max} 3280, 2955, 1750, 1720,and 1435 cm^{-1}. (Found : C, 62.40 ; H, 6.59. $C_8H_{10}O_3$ requires C, 62.33 ; H 6.54%).

Preparation of compound (54) :- A solution of 6-carbomethoxy-5-oxohexyne (50) (310 mg,

2 mmol) in CH_2Cl_2 (3 ml) was cooled to -78°C and tin tetrachloride (4 ml of a 0.5 M solution in CH_2Cl_2) was added. The mixture was allowed to warm to room temperature and saturated sodium bicarbonate solution added after 0.75 h. The mixture was extracted with CH_2Cl_2 (2 x 10 ml) and dried. After removal of solvent the residue was filtered through a pad of silica to afford 6-carbomethoxy-2,5-dioxohexane (54) (260 mg, 80%) identical to the known compound.

Preparation of compound (61) :- To a solution of 2-carbomethoxy-4,4-dimethyl-3-(1-pent-4-enyl)-cyclohexanone (5.2 g, 20 mmol) in CH_2Cl_2 (200 ml) at -78°C was added a solution of phenylselenium chloride (4.4 g, 24 mmol) and antimony pentachloride (3 ml, 25 mmol) in CH_2Cl_2 (400 ml). The mixture was allowed to warm to room temperature and aqueous sodium bicarbonate solution was added. After extraction and drying, the crude mixture was reacted with excess m-chloroperbenzoic acid (3.3 g) until all of the selenide had been oxidised. The solvent was removed and replaced by tetrahydrofuran (400 ml) and t-butyl hydroperoxide (10 ml) was added. The mixture was heated at 60°C for three days. Removal of solvent and chromatography (5 times) gave 2-carbomethoxy-2-chloro-3- [1-(4-chloropent-4-enyl)] -4,4-dimethylcyclohexan-1-one (61) (3.85 g, 60%); δ 1.03 (3H, s), 1.16 (3H, s), 1.3 - 2.6 (10H, m), 2.7 - 3.1 (1H, m), 3.76 (3H, s),and 5.08 (2H, s); ν_{max} 2955, 1760, 1740, 1720,and 1630 cm^{-1}.

Preparation of compound (63) :- A solution of (61) (155 mg, 0.48 mmol) in ethanol (4 ml) was stirred with $NaBH_4$ (150 mg) for 1.5 h. Water was added and the product extracted with CH_2Cl_2 (2 x 20 ml). After drying the solvent was removed to afford diol (62) (139 mg). The crude reaction mixture was stirred with pyridine (2 ml), acetic anhydride (0.2 ml) and 4-N,N-dimethylaminopyridine (5 mg) for 1.5 h. After washing successively with 2M hydrochloric acid, aqueous sodium bicarbonate and water, the mixture was dried.

The solvent was removed and the residue subjected to chromatography (25% pet. ether/CH_2Cl_2) to afford 1-acetoxy-2-acetoxymethyl-2-chloro-3-[1-(4-chloropent-4-enyl)] -4,4-dimethylcyclohexane (63) (133 mg, 70%); δ 0.96 (3H, s), 1.05 (3H, s), 1.26-2.0 (9H, m), 2.07 (3H, s), 2.08 (3H, s), 2.35 (2H, m), 3.85 (1H, d, part ABq, J 12Hz), 4.43 (1H, d, part ABq, J 12Hz), 4.93 (1H, dd), and 5.17 (2H, br s); ν_{max} 2950, 1750,and 1630 cm^{-1}.

Preparation of compound (64) :- To a solution of phenylselenium chloride (200 mg, 1.05 mmol) and $SbCl_5$ (2.1 ml of a 0.5 M solution in CH_2Cl_2) in CH_2Cl_2 at -78°C was added 2-carbomethoxy-4,4-dimethyl-3-(1-[pent-4-enyl])-cyclohexanone (252 mg, 1 mmol) in CH_2Cl_2 (4 ml). The mixture was allowed to warm to room temperature and poured on to saturated aqueous sodium bicarbonate solution. After extraction and drying the solvent was removed and the residue chromatographed on acidic alumina (5% ether/pet. ether) to afford 2-carbomethoxy-2,6-dichloro-4,4-dimethyl-3-(1-[pent-4-enyl])-cyclohexanone (64), (230 mg, 72%); δ 1.04 (3H, s), 1.16 (3H, s), 1.35 - 3.20 (10H, m), 3.80 (3H, s),and 4.8 - 6.0 (3H, m); ν_{max} 2950, 1760, 1740, 1720, 1640,and 910 cm^{-1}. (Found : C, 55.64; H, 7.23. $C_{15}H_{22}O_3Cl_2$ requires C, 55.91 ; H, 7.19%).

Preparation of compound (65) :- m-Chloroperbenzoic acid (200 mg, 85%) was added to a solution of 2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (350 mg, 1.08 mmol) and anhydrous magnesium bromide : tetrahydrofuran complex (480 mg, 1 mmol), in ether (10 ml). After 0.2 h saturated aqueous sodium bicarbonate was added and the organic phase separated and dried. After removal of solvent the residue was chromatographed (30% Pet.ether/CH_2Cl_2) to afford 2-bromo-2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one

(65) (410 mg, 94%) ; δ 0.08 (9H, s) 1.03 (3H, s), 1.20 (3H, s), 1.2-2.5 (11H, m), and 3.70 (3H, s); ν_{max} 2960, 2170, 1760, 1735, 1720, 1250, 1220,and 840 cm^{-1}. (Found : C, 53.48 ; H, 7.33. $C_{18}H_{29}O_3BrSi$ requires C, 53.84; H, 7.29%).

Attempted preparation of compound (66) :- i) A solution of 2-bromo-2-carbomethoxy-3- [1-(5-trimethylsilyl(pent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (0.63 g, 1.57 mmol) and triphenyltin hydride (1.5 g, 4.3 mmol) in cyclohexane (20 ml) was heated at reflux, under irradiation (tungsten lamp) for 0.5 h. Analysis of the mixture by t.l.c. and 'H n.m.r. showed the product to be 2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (31).

ii) A solution of sodium naphthalide [from sodium (0.1 g, xs) and naphthalene (.15 g, 1.17 mmol)] in tetrahydrofuran (20 ml) was transferred by double tipped needle to a solution of 2-bromo-2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (0.457 g, 1.14 mmol) in tetrahydrofuran (10 ml). Analysis by t.l.c. and 'H n.m.r. showed the only product to be 2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (31).

iii) A mixture of 2-bromo-2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (0.4 g, 1 mmol), triphenyltin hydride (1.05 g, 3 mmol) and AIBN (trace) were irradiated (tungsten lamp) with warming in cyclohexane (40 ml). The temperature was kept below 60°C until the analysis showed that starting material had reacted to produce a more polar product. Removal of solvent and chromatography on Florisil resulted in decomposition affording only 2-carbomethoxy-3- [1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (31) (210 mg, 65%).

iv) The reaction was repeated as in (iii), but the product was chromatographed at -78°C on Florisil. The mixture could not be separated, but no decomposition was observed.

Attempted preparation of (27) from (66) :- The crude mixture from (iv) above (110 mg) was stirred with hydriodic acid (35 mg of a 50% solution) in benzene (2 ml) for 1 h. A further amount of hydriodic acid (35 mg of a 50% solution) was added and the mixture stirred for 1 h. Saturated aqueous sodium bicarbonate solution was added and the mixture extracted with pet.ether (2 x 10 ml) and dried. Analysis of the mixture by t.l.c. and ^{1}H n.m.r. showed the product to be 2-carbomethoxy-3-[1-(5-trimethylsilylpent-4-ynyl)] -4,4-dimethylcyclohexan-1-one (31).

Preparation of compound (71) :- To a suspension of sodium hydride (3 g, 50%, 62.5 mmol, washed free of oil with pet. ether) in tetrahydrofuran (100 ml) was added 2-carbomethoxycyclohexanone (9 g, 58 mmol) in tetrahydrofuran (25 ml) at 0°C. n-Butyllithium (40 ml, 1.63 M solution in hexane) was added over 0.2 h. The mixture was stored at 0°C for a further 0.5 h, and allyl bromide (7.0g, 58 mmol) was added in tetrahydrofuran (15 ml). After 0.5 h saturated aq. ammonium chloride was added, and the mixture was extracted with ether (3 x 100 ml). After drying and removal of solvent, the mixture was distilled to give 6-allyl-2-carbomethoxycyclohexanone (71) (5 g, 44%), b.p. 90-92°C at 2 mm Hg; δ 1.4-2.5 (9H, m), 3.72 (3H, s),and 4.95 - 5.70 (3H, m) ; ν_{max} 2950, 1745, 1710, 1655, 1610,and 1440 cm^{-1} (Found : C, 66.95 ; H 8.52 . $C_{11}H_{16}O_3$ requires C, 66.98; H, 8.18%).

Preparation of compound (69) :- 6-Bromohex-1-ene (2.2 g, 90%, 12.1 mmol) was stirred with ethylacetoacetate (1.8 g, 13.8 mmol) and anhydrous potassium carbonate (3 g, 21 mmol) in dimethylformamide (20 ml) at 100°C for 2 h. The mixture was poured onto water (100 ml) and extracted with ether (3 x 50 ml). After drying and removal of solvent the residue was subjected to column chromatography (10% ether/light petrol) to give 7-carboethoxy-8-oxo-nonene (69) (1.86 g, 73%); δ 1.30 (3H, t J 6 Hz),

1.5-2.0 (8H, m), 2.22 (3H, s), 3.38 (1H, t), 4.17 (2H, q, J 6 Hz), and 4.8-6.0 (3H, m); ν_{max} 2930, 1740, 1715, 1640, and 1240 cm^{-1}. (Found : C, 67.67; H, 9.45. $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%).

Preparation of compound (75) from (71) :- To a solution of silver hexafluoroantimonate (380 mg, 1.1 mmol) in CH_2Cl_2 (20 ml) was added phenylselenium chloride (210 mg, 1.1 mmol) in CH_2Cl_2 (20 ml), under argon, at room temperature. The mixture was cooled to -78°C and 6-allyl-2-carbomethoxycyclohexanone (196 mg, 1 mmol) was added dropwise in CH_2Cl_2 (15 ml) over 0.5 h. The mixture was allowed to warm to room temperature, poured onto saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was subjected to column chromatography (eluting with 30% pet. ether/CH_2Cl_2) to yield 7-carbomethoxy-2-(selenophenylmethyl)- [3,4,5,6,9- H] -benzofuran (75) as an oil (245 mg, 70%);

δ (major isomer) 1.1-2.75 (9H, m), 3.01 (1H, dd, J 8 and 12 Hz), 3.44 (1H, dd, J 5 and 12 Hz), 3.70 (3H, s), 4.57 (1H, m), 7.26 (3H, m), and 7.54 (2H, m); ν_{max} 2940, 1710, 1680, 1650, 1580, and 1480 cm^{-1}. (Found : C, 58.12; H, 5.98. $C_{17}H_{20}O_3Se$ requires, C, 58.12; H, 5.74%).

Preparation of (74a) from (70a) :- Phenylselenium chloride (200 mg, 1.05 mmol) in CH_2Cl_2 (10 ml) was added to a solution of silver hexafluorophosphate (250 mg, 1.1 mmol) in CH_2Cl_2 (10 ml), under argon, at room temperature. The mixture was cooled to -78°C and 6-carboethoxy-5-oxo-hexene (170 mg, 1 mmol) in CH_2Cl_2 (5 ml) added dropwise over 0.2 h. The mixture was allowed to warm to room temperature, poured onto saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of the solvent the residue was subjected to column chromatography (eluting with 30% pet. ether/CH_2Cl_2) to give 5-(carboethoxy-methylene)-2-(seleno-

phenylmethyl)-tetrahydrofuran (74a) as an oil (195 mg, 60%), identical (i.r., n.m.r., t.l.c.) to the previously prepared sample.[38]

Preparation of compound (80) from (69) :- Phenylselenium chloride (210 mg, 1.1 mmol) in CH_2Cl_2 (10 ml) was added to a solution of silver hexafluorophosphate (250 mg, 1.1 mmol) in CH_2Cl_2 (10 ml), under argon, at room temperature. The mixture was cooled to -78°C and 7-carboethoxy-8-oxo-nonene (214 mg, 1 mmol) in CH_2Cl_2 (5 ml) added dropwise over 0.2 h. The mixture was allowed to warm to room temperature, poured onto saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was subjected to column chromatography (30% pet. ether/CH_2Cl_2) to give 2-acyl-2-carboethoxy-(selenophenylmethyl)-cyclohexane (80) as an oil (210 mg, 56%); δ 1.00 (3H, t, J 7 Hz), 1.2-1.5 (9H, m), 1.78 (3H,s), 2.75 (1H, d, J 6 Hz), 2.77 (1H, d, J 7 Hz), 3.93 (2H, q, J 7 Hz), and 6.90 - 7.40 (5H, m); ν_{max} 3060, 1735, 1710, 1580, 1475, and 1435cm^{-1}(Found : C, 58.89; H, 6.68. $C_{18}H_{24}O_3Se$ requires C, 58.69; H, 6.57%).

Preparation of compound (35) from (9) :- Phenylselenium chloride (210 mg, 1.1 mmol) in CH_2Cl_2 (15 ml) was added over 0.2 h to a solution of silver hexafluoroantimonate (380 mg, 1.1 mmol) in CH_2Cl_2 (15 ml), under argon, at room temperature. The mixture was cooled to -78°C and 2-carbomethoxy-4,4-dimethyl-3(1-pent-4-enyl)-cyclohexanone (252 mg, 1 mmol) in CH_2Cl_2 (15 ml) added over 0.5 h. The mixture was allowed to warm to room temperature, poured onto saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of the solvent, the residue was subjected to column chromatography (50% pet. ether/CH_2Cl_2) to give cis- 1a-carbomethoxy-5,5-dimethyl-10-(selenophenylmethyl)bicyclo [4.4.0] decan-2-one, (35) as an oil (310 mg, 75%); δ 0.90 (3H, s), 1.03 (3H, s), 1.5-1.85 (10H, m), 2.3-2.8 (2H, m), 2.90-3.15

(2H, m), 3.68 (3H, s), and 7.0 - 7.6 (5H, m); ν_{max} 3060, 2940, 1740, 1710, 1580, 1480, and 1435 cm^{-1}. (Found : C, 62.28; H, 7.06 . $C_{21}H_{28}O_3Se$ requires C, 61.93; H, 6.93%).

Preparation of compound (73) from (67) :- To a solution of 4-carboethoxy-5-oxohexene (180 mg, 1.05 mmol) in tetrahydrofuran (6 ml) was added NbF_5 (220 mg, 1 mmol) followed quickly by phenylselenium chloride (220 mg, 1.15 mmol) in THF (2 ml). The mixture was added to a solution of saturated sodium bicarbonate and the mixture extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was chromatographed (20% pet. ether/CH_2Cl_2) to afford 3-carboethoxy-2-methyl-5-(selenophenylmethyl)-4 H-dihydrofuran (73) (190 mg, 53%) identical (n.m.r., i.r., t.l.c.) to the previous sample.[3]

Preparation of selenide (74a) from (70a) :- To a solution of 6-carboethoxy-5-oxohexene (170 mg, 1 mmol) in tetrahydrofuran (3 ml) was added NbF_5 (220 mg, 1 mmol) followed quickly by phenylselenium chloride (200 mg, 1.05 mmol) in tetrahydrofuran (2 ml). After 0.1 h the mixture was poured onto saturated aqueous sodium bicarbonate solution and the mixture extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was subjected to column chromatography (30% pet. ether/CH_2Cl_2) to afford 5-(carbo ethoxymethylene)-2-(selenophenylmethyl) tetrahydrofuran (74a) (230 mg, 70%) identical (n.m.r., i.r., t.l.c.) to the previous sample.

Preparation of compound (73) from (67) :- A solution of N-phenylselenophthalimide (330 mg, 1.1 mmol), 4-carboethoxy-5-oxo-hexene (180 mg, 1.05 mmol), and a trace of tosic acid were stirred in CH_2Cl_2 (8 ml) until phthalimide precipitated (1 h). Pet. ether (20 ml) was added and the mixture filtered. After removal of solvent the residue

was subjected to column chromatography (20% pet. ether/CH_2Cl_2) to give 3-carboethoxy-2-methyl-5-(selenophenylmethyl)-4H-dihydrofuran (73) as an oil (300 mg, 84%) ; δ 1.24 (3H, t, J 8Hz), 2.10 (3H, t, J 1Hz), 2.5 - 2.9 (2H, m), 3.03 (1H, d, J 6Hz), 3.12 (1H, d, J 6Hz), 4.14 (2H, q, J 8Hz), 4.4 - 4.9 (1H, m), 7.20 (3H, m), and 7.50 (2H, m) ; ν_{max} 2980, 1690, 1645, 1580, 1475, and 1435 cm^{-1}. (Found : C, 55.41 ; H, 5.61 . $C_{14}H_{18}O_3Se$ requires C, 55.39 ; H, 5.58%).

Preparation of compound (75) from (71) :- A mixture of 6-allyl-2-carbomethoxycyclohexanone (196 mg, 1 mmol), N-phenylselenophthalimide (330 mg, 1.1 mmol) and a trace of tosic acid were stirred in CH_2Cl_2 (5 ml) until phthalimide precipitated (0.5 h). Pet. ether (20 ml) was added and the mixture filtered. After removal of solvent the residue was subjected to column chromatography to give 7-carbomethoxy-2-(selenophenylmethyl)-[3,4,5,6,9 H] -benzofuran (75) as an oil (230 mg, 66%) identical to the previous sample (n.m.r., i.r., t.l.c.).

Preparation of compound (76) from (55) :- To a solution of geranyl β-keto ester (55) (0.5 g, 2 mmol) in CH_2Cl_2 (10 ml) at -78°C, under argon, was added phenylselenium hexafluoroantimonate [2.1 mmol, from phenylselenium chloride (0.4 g) and silver hexafluoroantimonate (0.5 g)] in CH_2Cl_2 (40 ml), over 0.5 h. The mixture was allowed to warm to room temperature, poured onto saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (2 x 40 ml). After drying and removal of the solvent, the residue was subjected to column chromatography (eluting with 50% pet. ether/CH_2Cl_2) to give trans-2-(carbomethoxymethyl)-5,5,9 β -trimethyl-6 β -selenophenyl- [4,7,8, 10H] -chromene (76) as an oil (490 mg, 60%) ; δ 0.92 (3H, s), 1.20 (3H, s), 1.24 (3H, s), 1.42 - 2.12 (7H, m), 2.98 (2H, s), 3.05 (1H, dd, J 5 and 13 Hz), 3.67 (3H, s), 4.66 (1H, dd), 7.26 (3H, m), and 7.56 (2H, m) ; ν_{max} 3060, 2940, 1740,

1680, 1580, 1435,and 1130 cm^{-1}. (Found : C, 61.79; H, 7.00; $C_{21}H_{28}O_3Se$ requires C, 61.93 ; H, 6.93%).

Preparation of (77) and (78) from (72) :- A solution of N-phenylselenophthalimide (330 mg, 1.1 mmol), 3,3-dimethyl-6-(1-pent-4-enyl)-1,5-dioxocyclohexane (208 mg, 1 mmol) and a trace of tosic acid in CH_2Cl_2 (6 ml) were stirred until phthalimide precipitated (0.1 h). Pet. ether (20 ml) was added and the mixture filtered. After removal of solvent the residue was subjected to column chromatography (30% pet. ether/CH_2Cl_2 then CH_2Cl_2) to give 4,4-dimethyl-2,6-dioxocyclohexanespiro-1'-2'-(selenophenylmethyl)-cyclopentane (77) (160 mg, 42%) m.p. 86-87°C (pet. ether); δ_{CCl_4} 0.92 (3H, s), 0.96 (3H, s), 1.6-2.25 (7H, m), 2.3-2.5 (4H, m), 2.6 - 2.8 (2H, br s),and 7.1-7.6 (5H, m); ν_{max} 2890, 1725, 1690, 1580,and 1475 cm^{-1}. (Found : C, 62.90 ; H, 6.72 . $C_{19}H_{24}O_2Se$ requires C, 62.82 ; H, 6.66%) ; and 8,8-dimethyl-6-oxo-2-(selenophenylmethyl)-[3,4,5,7,9 H] -benzoxepin (78) as an oil (183 mg, 49%);

δ 0.98 (3H, s) 1.04 (3H, s), 1.73-1.97 (4H, m), 2.08-2.35 (3H, m), 2.19 (2H, d, J 1Hz), 2.57-2.70 (1H, dt), 2.99 (1H, dd, J 5 and 13 Hz), 3.16 (1H, dd, J 8 and 13 Hz), 4.41 (1H, m), 7.26 (3H, m),and $7.51_{\lambda}^{(2H,m)}$; ν_{max} 2950, 1655, 1620, 1580, 1480, 1380,and 1225 cm^{-1}.(Found : M^+, 364.0945.$C_{19}H_{24}O_2Se$ requires 364.0941).

Preparation of selenide (74a) from (70a) :- i) To a mixture of 6-carboethoxy-5-oxohexene (170 mg, 1 mmol) and zinc iodide (320 mg, 1 mmol) in tetrahydrofuran (4 ml) was added N-phenylselenophthalimide (330 mg, 1.1 mmol) in portions. After 0.1 h pet. ether (30 ml) was added and the mixture filtered. After removal of solvent the residue was subjected to chromatography (30% pet. ether/CH_2Cl_2) to give 5-(carboethoxymethylene)-2-(selenophenyl methyl)-tetrahydrofuran (74a) as an oil (268 mg, 82%) identical (n.m.r., i.r., t.l.c.) with the previous sample.

ii) To a mixture of 6-carbo ethoxy-5-oxo-hexene (110 mg, 0.65 mmol) and zinc iodide (200 mg, 0.63 mmol) in CH_2Cl_2 (6 ml) was added N-phenylselenophthalimide (210 mg, 0.69 mmol) in portions. After 0.5 h pet. ether (10 ml) was added and the mixture filtered. After removal of the solvent the residue was subjected to column chromatography (30% pet. ether/CH_2Cl_2) to give 5-(carboethoxymethylene)-2-(selenophenyl methyl)-tetrahydrofuran (74a) an oil (150 mg, 71%) identical (n.m.r., i.r., t.l.c.) to the previous sample.

Preparation of selenide (77) from (72) :- To a mixture of 3,3-dimethyl-6-(1-pent-4-enyl)-1,5-dioxocyclohexane (0.31 mmol) and zinc iodide (0.37 mmol) in CH_2Cl_2 (4 ml) was added N-phenylselenophthalimide (120 mg, .39 mmol) in portions. After 0.1 h pet. ether (10 ml) was added and the mixture filtered. After removal of solvent the residue was purified by column chromatography (30% pet. ether/CH_2Cl_2) to give 4,4-dimethyl-2,6-dioxocyclohexanespiro-1'-2'-(selenophenylmethyl)-cyclopentane (77) (75 mg, 66%) identical (n.m.r., i.r., t.l.c., m.p.) to the previous sample.

Preparation of selenide (86) from (55) :- To a mixture of geranyl β-keto ester (55) (252 mg, 1 mmol) and zinc iodide (320 mg, 1 mmol) in CH_2Cl_2 (6 ml) was added N-phenylselenophthalimide (330 mg, 1.1 mmol) in portions. After 0.5 h the mixture was washed with 10% aqueous sodium metabisulphite and dried. After removal of solvent the residue was subjected to column chromatography (20% pet. ether/CH_2Cl_2) to give 2β-carbomethoxy-3β-methyl-4β-selenophenyl-3α(1-[4-methyl-pent-3-enyl])-cyclohexanone (86) as an oil (274 mg, 67%); δ 1.21 (3H, s), 1.58 (3H, s), 1.67 (3H, s), 1.85 - 2.1 (4H, m), 2.24 - 2.48 (4H, m), 3.44 - 3.56 (1H, m) 3.62 (1H, s), 3.72 (3H, s), 5.03 (1H, br t), 7.31 (3H, m), and 7.63 (2H, m); ν_{max} 3060, 2930, 1740, 1715, 1630, 1575, and 1435 cm^{-1}. (Found : C, 62.05; H, 7.15.

$C_{21}H_{28}O_3Se$ requires C, 61.93; H, 6.93%).

Preparation of selenide (79) from (68) :- To a mixture of 6-carboethoxy-7-oxo-octene (200 mg, 1 mmol) and N-phenylselenophthalimide (350 mg, 1.15 mmol) in CH_2Cl_2 (6 ml) was added tin tetrachloride (0.25 ml of a 0.5M solution in CH_2Cl_2). Saturated aqueous sodium bicarbonate was added after 0.25 h and the mixture extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was chromatographed (30% pet. ether/CH_2Cl_2) to give 2-acyl-2-carboethoxy-(selenophenylmethyl)cyclopentane (79) as an oil (260 mg, 73%); δ 1.26 (3H, dt), 1.45 - 1.9 (6H, m), 2.12 (3H, s), 2.2-2.9 (2H, m), 3.19 (1H, m), 4.18 (2H, m), and 7.2-7.6 (5H, m); ν_{max} 3060, 2970, 1735, 1710, 1575, 1475, and 1435 cm^{-1}. (Found : C, 57.79; H, 6.44 . $C_{17}H_{22}O_3Se$ requires C, 57.47 ; H, 6.24%).

Preparation of selenide (80) from (69) :- To a solution of 7-carboethoxy-8-oxononene (210 mg, 1 mmol) and N-phenylselenophthalimide (350 mg, 1.15 mmol) in CH_2Cl_2 (6 ml) was added tin tetrachloride (1 ml of a 0.5 M solution in CH_2Cl_2). After 0.1 h saturated aqueous sodium bicarbonate solution was added and the mixture extracted with CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was subjected to chromatography (30% pet. ether/CH_2Cl_2) to afford 2-acyl-2-carboethoxy-(selenophenyl methyl) cyclohexane (80) (180 mg, 49%) identical (n.m.r., i.r., t.l.c.) to the previous sample.

Preparation of (35) from (9) :- To a solution of 2-carbomethoxy-4,4-dimethyl-3(1-pent-4-enyl) cyclohexanone (252 mg, 1 mmol) and boron trifluoride etherate (48%, 5 drops) was added N-phenylselenophthalimide (400 mg, 1.33 mmol) in portions. Saturated aqueous sodium bicarbonate solution was added after 1 h and the mixture extracted with

CH_2Cl_2 (2 x 20 ml). After drying and removal of solvent the residue was subjected to chromatography (50% pet. ether/CH_2Cl_2) to afford cis-1a -carbomethoxy-5,5-dimethyl-10-(selenophenylmethyl) bicyclo [4.4.0] decan-2-one as an oil (84 mg, 20%) identical (n.m.r., i.r., t.l.c.) to the previous sample.

Preparation of (86) and (76) from (55) :- To a solution of geranyl β-keto ester (55) (252 mg, 1 mmol) and a trace (0.05 eq) of I_2 in CH_2Cl_2 (6 ml) was added N-phenyl-selenophthalimide (340 mg, 1.12 mmol) in portions over 0.1 h. After 0.2 h, zinc iodide (320 mg, 1mmol) was added. Pet. ether (20 ml) was added after 0.75 h and the mixture filtered. The solution was washed with 10% aqueous sodium metabisulphite solution and dried. After removal of the solvent the residue was purified by chromatography (50%, then 20% pet. ether/CH_2Cl_2) to give trans-2-(carbomethoxymethyl)-5,5-dimethyl-9β -methyl-6β -selenophenyl- [4,7,8,10 H] -chromene (76) (105 mg, 26%) and 2β -carbomethoxy-3β -methyl-4β -selenophenyl-3a-(1-[4-methylpent-3-enyl])-cyclohexanone (86) (125 mg, 31%) which were both identical (n.m.r., i.r., t.l.c.) to the previous samples.

Preparation of selenide (89) :- To a suspension of sodium hydride (0.06 mg, 50% washed free of oil with light petrol) in tetrahydrofuran (10 ml) was added 6-allyl-2-carbomethoxy-cyclohexanone (400 mg, 2 mmol) in tetrahydrofuran (4 ml). After 0.2 h N-phenylseleno-phthalimide (610 mg, 2 mmol) in tetrahydrofuran (15 ml) was added in one portion. Dilute hydrochloric acid was added after 0.2 h and the mixture extracted with pet. ether (2 x 50 ml). Solvent was removed, replaced by pet. ether and filtered. After drying and removal of solvent crude 6-allyl-2-carbomethoxy-2-selenophenylcyclo-hexanone (89) was obtained as an oil (600 mg, 84%); δ 1.2-2.7 (9 H, m), 3.68 (3 H, s), 4.82 (1H, t), 5.06 (1 H, d), 5.4-6.1 (1 H, m), and 7.2-7.7 (5 H, m); ν_{max} 3070, 2940, 1735, 1710, 1640, 1575, 1335, 1225, and 915 cm^{-1}. (Found : C, 58.65;

H, 5.97 . $C_{17}H_{20}O_3Se$ requires C, 58.12 ; H, 5.74%).

Preparation of (75) from (89) :- To a solution of crude 6-allyl-2-carbomethoxy-2-selenophenylcyclohexanone (89) (250 mg) in CH_2Cl_2 (4 ml) was added tin tetrachloride (0.1 ml of a 0.5 M solution in CH_2Cl_2). After 0.1 h saturated aqueous sodium bicarbonate was added and the mixture extracted with CH_2Cl_2 (2 x 10 ml). After drying and removal of solvent the residue was chromatographed (40% ether/pet. ether) to give 7-carbomethoxy-2-(selenophenyl methyl)- [3,4,5,6,9H] -benzofuran (75) (200 mg, 80%) identical (n.m.r., i.r., t.l.c.) to the previous sample.

Preparation of compound (90) :- To a suspension of sodium hydride (0.5 g, 50% washed free of oil with pet. ether) in tetrahydrofuran (30 ml) was added 2-carbomethoxy-4,4-dimethyl-3-(1- [pent-4-enyl]) cyclohexanone (2.02 g, 8 mmol) in tetrahydrofuran (10 ml). After 0.25 h the solution was transferred by double tipped needle to a solution of N-phenylselenophthalimide (2.7 g, 9 mmol) in tetrahydrofuran (30 ml). After 0.1 h dilute hydrochloric acid was added and the mixture extracted with pet. ether. Solvent was removed, replaced by pet. ether and filtered. After drying, the solvent was removed to give crude 2-carbomethoxy-4,4-dimethyl-3 (1- [pent-4-enyl])-2-selenophenylcyclohexanone (90) (3.82 g, c 120%) as a viscous oil which was unstable to chromatography; δ 1.0 (3H, s), 1.76 (3H, s), 1.45 - 2.70 (c.11H, m), 3.50 (3H, s), 4.77 (1H, t), 5.0 (1H, d), 5.37 - 5.90 (1H, m), and 7.1 - 7.7 (5H, m); ν_{max} 3060, 1745, 1725, 1700, 1640, 1580, 1435 and 1210cm^{-1} (Found : M^+ 408.1203 . $C_{21}H_{28}O_3Se$ requires 408.1203).

Preparation of compound (35) from (90) :- a) A mixture of zinc iodide (330 mg, 1.1

mmol) and crude 2-carbomethoxy-4,4-dimethyl-3 (1- [pent-4-enyl])-2-selenophenyl-cyclohexanone (90) (410 mg) was stirred in CH_2Cl_2 (10 ml) until the reaction was complete by t.l.c. The mixture was filtered and, after removal of solvent, the residue subjected to chromatography (50% pet. ether/CH_2Cl_2) to give cis-1a -carbomethoxy-5,5-dimethyl-10-(selenophenylmethyl) bicyclo [4.4.0] decan-2-one (35) as an oil (214 mg, 55%) identical (i.r., n.m.r., t.l.c.) to the previous sample.

b) Tin tetrachloride (0.2 ml of a 0.5 M solution in CH_2Cl_2) was added to a solution of crude 2-carbomethoxy-4,4-dimethyl-3-(1- [pent-4-enyl])-2-selenophenylcyclo-hexanone (35) (205 mg) in CH_2Cl_2 (4 ml) at room temperature. After complete reaction, as indicated by t.l.c., saturated sodium bicarbonate solution was added and the mixture extracted with CH_2Cl_2 (2 x 10 ml) to give the intermediate of the above reaction (172 mg, 84%) which was unstable to chromatography; δ 0.91 (3H, s), 0.96 (3H, s), 1.17 - 2.35 (11H, m), 3.0 - 3.4 (2H, m), 3.77 (3H, s), 3.70 - 4.0 (1H, m), and 7.0 - 7.5 (5H, m); ν_{max} 2940, 1650, 1610, 1575, and 1435 cm^{-1}.

Preparation of (77) from (78) :- a) To a solution of 8,8-dimethyl-6-oxo-2-(seleno-phenyl methyl)- [3,4,5,7,9H] -benzoxepin (78) (38 mg, 0.1 mmol) in CH_2Cl_2 (2 ml) was added tin tetrachloride (0.1 ml of a 0.5 M solution in CH_2Cl_2). After 1 h saturated aqueous sodium bicarbonate solution was added and the mixture extracted with CH_2Cl_2 (2 x 10 ml). Drying and removal of solvent gave 4,4-dimethyl-2,6-dioxocyclohexanespiro-1'-2'-(selenophenylmethyl)-cyclopentane (77) (35 mg, 92%) identical (n.m.r., i.r., t.l.c.) to the previous sample.

b) A mixture of 8,8-dimethyl-6-oxo-2-(selenophenylmethyl)- [3,4,5,7,9H] -benzoxe-pin (78) (100 mg, 0.27 mmol) and zinc iodide (90 mg, 0.28 mmol) were stirred for 24 h at room temperature. Filtration and removal of solvent gave 4,4-dimethyl-2,6-dioxocyclo-hexanespiro-1'-2'-(selenophenylmethyl)-cyclopentane (77) (98 mg, 98%) identical (i.r.,

n.m.r., t.l.c., m.p.) to the previous sample.

Preparation of selenide (92) from (74b) :- To a solution of 5-(carbomethoxy-methylene)-2-(selenophenyl methyl)-tetrahydrofuran (74b) (330 mg, 1.1 mmol) in CH_2Cl_2 (4 ml) was added tin tetrachloride (1 ml of a 0.5 M solution in CH_2Cl_2). After 1 h saturated aqueous sodium bicarbonate solution was added and the mixture extracted with CH_2Cl_2 (2 x 20 ml). After drying the solvent was removed to give 2-carbomethoxy-3-(selenophenyl methyl)-cyclopentanone (92) (330 mg, 100%) which was pure by t.l.c. and identical (n.m.r., i.r., t.l.c.) to the known compound[38] ; δ 1.8-2.7 (7H, m), 3.2-3.45 (1H, m), 3.70 (3H, s), 7.2 (3H, m), and 7.5 (2H, m); ν_{max} 2740, 1745, 1715, 1660, 1620, 1580, 1440, and 910 cm^{-1}

Preparation of selenide (101) from (89) :- To a solution of 6-allyl-2-carbomethoxy-2-selenophenylcyclohexanone (100 mg, 0.284 mmol) in CH_2Cl_2 (5 ml) was added tin tetrachloride (0.6 ml of a 0.5 M solution in CH_2Cl_2). After 17 h at room temperature the mixture was poured onto saturated aqueous sodium bicarbonate solution and extracted with CH_2Cl_2 (2 x 10 ml). After drying and removal of solvent the residue was purified by p.l.c. (CH_2Cl_2) to give 1-carbomethoxy-3-selenophenyl-9-oxo-bicyclo [3.3.1] nonane (101) (88 mg, 88%) as an oil identical (n.m.r., i.r., t.l.c.) to the known[38] compound; δ 1.70-2.70 (11H, m), 3.70 (3H, s), 3.90 - 4.30 (1H, m), and 7.1-7.6 (5H, m); ν_{max} 3060, 1735, 1715, 1575, 1430 and 1250 cm^{-1}.

Preparation of compound (83) :- A solution of 4,4-dimethyl-2,6-dioxocyclohexane spiro-1'-2'-(selenophenylmethyl)-cyclopentane (77) (120 mg, 0.32 mg) was converted to the selenoxide with m-chloroperbenzoic acid (60 mg, 85%) at room temperature in CH_2Cl_2 (5 ml). The mixture was washed with saturated aqueous sodium bicarbonate

solution and dried. Solvent was removed and replaced by carbon tetrachloride (5 ml) and the mixture heated at reflux for 1 h. After removal of solvent the residue was subjected to chromatography to afford 4,4-dimethyl-2,6-dioxocyclohexanespiro-1'-2'-methylene-cyclopentane (50 mg, 71.5%) m.p. 86-87°C (lit.[36], 89-90°C), which was identical (n.m.r., i.r.) with the known[36] compound.

Preparation of compound (84) :- A solution of 2-acyl-2-carboethoxy-(selenophenyl-methyl) cyclopentane (79) (170 mg, 0.45 mmol) in CH_2Cl_2 (5 ml) was oxidised to the selenoxide with m-chloroperbenzoic acid (80 mg, 85%). The mixture was washed with saturated aqueous sodium bicarbonate solution and dried. The solvent was replaced by carbontetrachloride (10 ml) and the mixture heated at reflux for 0.5 h. The solvent was removed and the residue purified by column chromatography (20% pet. ether/CH_2Cl_2) to afford 2-acyl-2-carboethoxymethylenecyclopentane (84) (80 mg, 85%); δ 1.27 (3H, t), 1.55-2.0 (4H, m), 2.17 (3H, s), 2.30-2.60 (2H, m), 4.20 (2H, q),and 5.23 (2H, q); ν_{max} 2980, 1740, 1715, 1650, 1355,and 1235 cm^{-1}. (Found : C, 66.89; H, 8.42. $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%).

Preparation of compound (85) :- A solution of 2-acyl-2-carboethoxy-(selenophenyl methyl) cyclohexane (200 mg, 0.54 mmol) in CH_2Cl_2 (6 ml) was oxidised to the selenoxide with m- chloroperbenzoic acid (100 mg, 85%). The mixture was washed with saturated aqueous sodium bicarbonate solution and dried. Solvent was removed and replaced by carbon tetrachloride (10 ml). The mixture was heated at reflux for 0.5 h. After removal of solvent the residue was chromatographed (20% pet. ether/CH_2Cl_2) to afford 2-acyl-2-carbo ethoxy-methylenecyclohexane (85) (103 mg, 90%); δ 1.0 (3H, t), 1.2-1.47 (6H, m), 1.97 (3H, s), 1.72-2.10 (2H, m), 3.97 (2H, q), 4.39 (1H, s),and 4.70 (1H, s) ; ν_{max} 2940, 1740, 1715, 1640, 1450,and 1230 cm^{-1}.

(Found : C, 68.35; H, 8.53 . $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.63%).

Preparation of compound (30) :- A solution of cis-1a -carbomethoxy-5,5-dimethyl-10-(selenophenylmethyl)bicyclo [4.4.0] decan-2-one (35) (280 mg, 0.69 mmol) in CH_2Cl_2 (5 ml) was oxidised to the selenoxide with m-chloroperbenzoic acid (120 mg, 85%). The mixture was washed with saturated aqueous sodium bicarbonate solution and the mixture dried. The solvent was removed and replaced with carbon tetrachloride (10 ml) and heated at reflux for 2 h. After removal of solvent the residue was purified by column chromatography (10% pet. ether/CH_2Cl_2) to afford cis-1a -carbomethoxy-5,5-dimethylbicyclo [4.4.0] dec-10,1'-en-2-one (30) (141 mg, 82%) identical (n.m.r., i.r., t.l.c.) to the previously prepared compound.

Preparation of compound (59) :- A mixture of cis-1a-carbomethoxy-5,5-dimethyl-10-(selenophenyl methyl)-bicyclo [4.4.0] decan-2-one (35) (220 mg, 0.54 mmol) and triphenyl tin hydride (350 mg, 1 mmol) and a trace of AIBN were heated at reflux in toluene (10 ml) for 5 h. Solvent was removed and the residue subjected to chromatography and p.l.c. to afford cis-1a -carbomethoxy-5,5,10-trimethylbicyclo [4.4.0] decan-2-one (59) (90 mg, 73%); δ 0.78 (3H, d), 0.91 (3H, s), 1.08 (3H, s), 1.25-1.87 (8H, m), 2.20-2.65 (4H, m),and 3.63 (3H, s) ; ν_{max} 2940, 1740, 1710, 1480,and 1435 cm^{-1}. (Found : C, 71.25; H, 9.68 . $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%).

Preparation of compound (82) :- A solution of trans-2-(carbomethoxymethyl)-5,5,9β -trimethyl-6β -selenophenyl- [4,7,8,10H] -chromene (140 mg, 0.34 mmol) was heated in toluene (10 ml) with triphenyltin hydride (0.5 g, 1.35 mmol) and a trace of AIBN for 2 h. Solvent was removed and, after addition of pet. ether, the mixture was filtered. After removal of solvent the filtrand was chromatographed (10% CH_2Cl_2/pet. ether, then 30% pet. ether/CH_2Cl_2) to afford trans-2-(carbomethoxymetheyl)-5,5,9β -trimethyl-

[4,7,8,10H] -chromene (82) (65 mg, 75%); δ 0.83 (3H, s), 0.92 (3H, s), 1.13 (3H, s), 1.24-2.0 (9H, m), 2.77 (2H, s), 3.56 (3H, s), and 4.41 (1H, t); ν_{max} 2940, 1740, 1680, 1435, and 1130 cm^{-1}. (Found : C, 71.14; H, 9.56. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%).

REFERENCES

1. H.B. Henbest and R.A.L. Wilson, J. Chem. Soc., 1957, 1958
2. S. Danishefsky, T. Kitahara, C.F. Yan, and J. Morris, J. Amer. Chem. Soc., 1979, 101, 6996
3. A.J. Whittle, Ph.D. Thesis, 1981, University of London
4. H.O. Krabbenhoft, J. Org. Chem., 1979, 44, 4050; Y. Chan, and W.W. Epstein, Org. Synth., 1973, 53, 48
5. R.G. Salomon and M.F. Salomon, J. Org. Chem., 1975, 40, 1488
6. T. Toru, S. Kurozumi, T. Tanaka, M.Kobayashi and S.Ishimoto, S. Miura, Tetrahedron Letters, 1976, 4087
7. From Li wire, 0°C; E.J. Corey and R.D. Balanson, J. Amer. Chem. Soc., 1974, 96, 6516; from Li dispersion, -30°C; Y. Yamamoto, K. Kondo, and I. Moritani, J. Org. Chem., 1975, 40, 3644
8. G.H. Posner, Organic Reactions, 1972, 19, Chapter 1
9. G. Stork and P.F. Hudrlik, J. Amer. Chem. Soc., 1968, 90, 4462
10. P.E. Sum and L. Weiler, Can. J. Chem., 1979, 57, 1475
11. D.L.J. Clive, Aldrichimica Acta., 1978, 11, 43; D.L.J. Clive, G. Chittattu, and C.K. Wong, J.C.S. Chem. Comm., 1978, 441
12. G.H. Schmid and D.G. Garratt; Tetrahedron Letters, 1975, 3991
13. J.M. Conia and P. La Perchec, Synthesis, 1975, 1
14. (a) Prof. J. Drouin, personal communication; (b) J. Drouin, F. Leyendecker, and J.M. Conia, Tetrahedron Letters, 1975, 4053
15. G. Büchi and H. Wüest, J. Org. Chem., 1979, 44, 546
16. G. Eglinton and M.C. Whiting, J. Chem. Soc., 1950, 3650
17. E.J. Corey, G.W.J. Fleet, and M. Kato, Tetrahedron Letters, 1973, 3963
18. e.g. J.H. Clark and J.M. Miller, Tetrahedron Letters, 1977, 139
19. E.J. Corey, H.A. Kirst, and J.A. Katzenellenbogen, J. Amer. Chem. Soc., 1970, 92, 6314

20. M. Seefelder, Annalen, 1962, 652, 107

21. S. Tanaka, H. Yamamoto, H. Nozaki, K.B. Sharpless, R.C. Michaelson, and J.D. Cutting, J. Amer. Chem. Soc., 1974, 96, 5254

22. D.Rogers, G.G. Unal, D.J. Williams, S.V. Ley, G.A. Sim, B.S. Joshi, and K.R. Ravindranath, J.C.S. Chem. Comm., 1979, 97

23. J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Letters, 1968, 3363

24. We thank E.A. Bernays of the Overseas Centre for Pest Research for these results

25. We thank Dr. J.R. Hanson, University of Sussex, for these compounds

26. See review section

27. O. Mauz, Annalen, 1974, 345

28. S.N. Huckin and L. Weiler, J. Amer. Chem. Soc., 1974, 96, 1082

29. N. Finch, J.J. Fitt, and I.H.C. Hsu, J. Org. Chem., 1971, 36, 3191

30. R.W. Skeean, G.L. Trammell, and J.D. White, Tetrahedron Letters, 1976, 525

31. F.W. Sum and L. Weiler, J. Amer. Chem. Soc., 1979, 102, 4401

32. N. Inukai, H. Iwamoto, T. Tamura, I. Yanagisawa, Y. Ishii, and M. Murakami, Chem. Pharm. Bull., 1976, 24, 820

33. Alcohols, thiols, thioesters; K.C. Nicolaou, R.L. Magolda, W.J. Sipio, W.E. Barnette, Z. Lysenko, and M.M. Joulie, J. Amer. Chem. Soc., 1980, 102, 3784; phenols, D.L.J. Clive, G. Chittattu, N.J. Curtis, W.A. Kiel, and C.K. Wong, J.C.S. Chem. Comm., 1977, 725; acid, K.C. Nicolaou, S. Seitz, W.J. Sipio, and J.F. Blount, J. Amer. Chem. Soc., 1979, 101, 3884; urethanes, D.L.J. Clive, V. Farina, A. Singh, C.K. Wong, W.A. Kiel, and S.M. Menchen, J. Org. Chem., 1980, 45, 2120

34. G. Brieger and W.M. Pelletier, Tetrahedron Letters, 1965, 3555

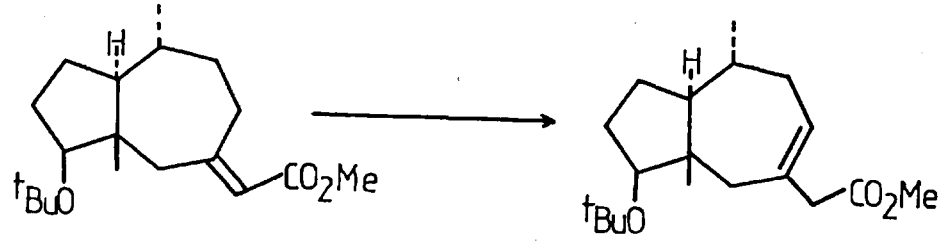
35. G. Mandville, F. Leyendecker, and J.M. Conia, Bull. Soc. ChimFr., 1973, 963

36. W.P. Jackson, S.V. Ley, and A.J. Whittle, J.C.S. Chem. Comm., in press

37. T.A. Bryson, J. Org. Chem., 1973, 38, 3428

38. J.A. Morton, Ph.D. Thesis, 1981, University of London

39. The rearrangement (106) to (107) has been achieved via proton quench of the anion of (106)



(106) (107)

P.T. Lansbury, D.G. Hangauer, Jr., and J.P. Vacca, J. Amer. Chem. Soc., 1980, 102, 3964

40. R.M. Coates, Progress in the Chemistry of Natural Products, 1976, 33, 73

41. D.L.J. Clive, G.T. Chittattu, V. Farina, W.A. Kiel, S.M. Menchen, C.G. Russell, A. Singh, C.K. Wong, and N.J. Curtis, J. Amer. Chem. Soc., 1980, 102, 4438

42. W.P. Jackson and S.V. Ley, J.C.S. Chem. Comm., 1979, 732; W.P. Jackson and S.V. Ley, J.C.S. Perkin I, submitted for publication

43. K.C. Nicolaou, D.A. Claremon, W.E. Barnette, and S.P. Seitz, J. Amer. Chem. Soc., 1979, 101, 3704

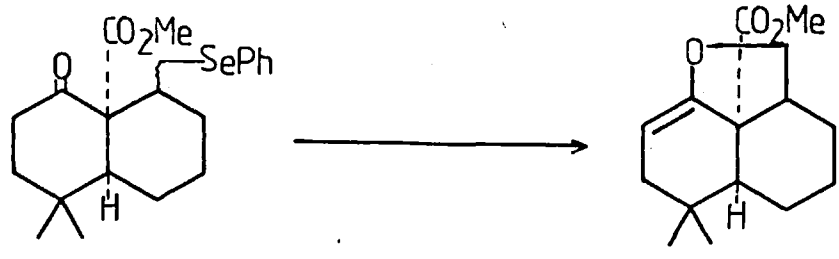
44. W.P. Jackson, S.V. Ley, and J.A. Morton, J.C.S. Chem. Comm., 1980, 1028

45. E.J. Corey, M.A. Tius, and J. Das, J. Amer. Chem. Soc., 1980, 102, 1742

46. S.J. Falcone and M.E. Munk, Syn. Comm., 1979, 9, 719. The authors have reported the rearrangement of (108) to (109) via the enolate or the enamine of (108)

(108) (109)

47. Use of $SnCl_4$ as catalyst in the reaction led to the formation of a small amount of (35). The major product was (110) which results from displacement of the phenylseleno moiety by the enolic form of (35)



(35) (110)

48. B.M. Trost, R.A. Runge, and L.N. Jungheim, J. Amer. Chem. Soc., 1980, 102, 2840

49. J. Tsuji, Y. Kobayashi, H. Kataoka, and T. Takahasi, Tetrahedron Letters, 1980, 1475

50. K.H. Baggaley, W.H. Evans, S.H. Graham, D.A. Jonas, and D.H. Jones, Tetrahedron, 1968, 24, 3445

51. D.L.J. Clive, Tetrahedron, 1978, 34, 1049; H.J. Reich, Oxidation in Organic Chemistry, Part C, Academic Press, 1978, p.1

52. Syntheses; A.E. Greene, Tetrahedron Letters, 1980, 3059; T. Hurdlicky, T.M. Kutchan, S.R. Wilson, and D.T. Mao, J. Amer. Chem. Soc., 1980, 102, 6351 and references therein.

Synthesis of a Substituted *cis*-Decalin as a Potential Insect Antifeedant

By William P. Jackson and Steven V. Ley*
(*Department of Chemistry, Imperial College, London* SW7 2AY)

Reprinted from

Journal of The Chemical Society
Chemical Communications
1979

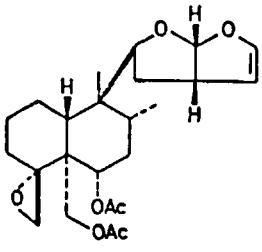
The Chemical Society, Burlington House, London W1V 0BN

Synthesis of a Substituted *cis*-Decalin as a Potential Insect Antifeedant

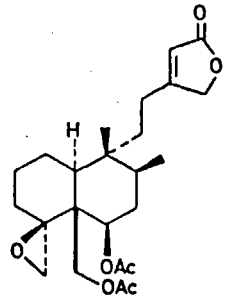
By WILLIAM P. JACKSON and STEVEN V. LEY*
(*Department of Chemistry, Imperial College, London* SW7 2AY)

Summary A *cis*-decalin containing epoxydiacetate functions has been synthesised as a potential insect antifeedant.

IN order to probe the insect antifeedant activity of a number of clerodane diterpenes such as clerodin (**1**)[1] and ajugarin I (**2**),[2] we have begun a programme of synthesis of a number of model compounds. Here we report the stereospecific synthesis of a *cis* fused derivative (**7**) by a route which allows sufficient flexibility to prepare other analogues.

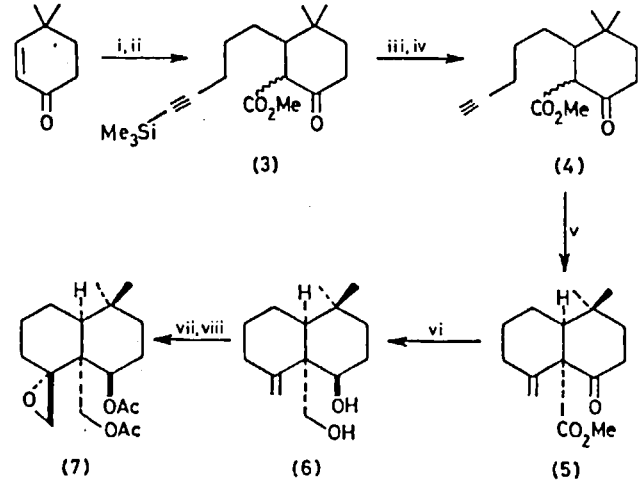


(1)



(2)

Copper(I) catalysed addition of trimethylsilyl protected pentynylmagnesium iodide to 4,4-dimethylcyclohex-2-enone and subsequent trapping of the intermediate regiospecific enolate with methyl chloroformate gave (**3**) in 60% yield. Deprotection[3] of (**3**) proceeded smoothly to give (**4**) in 89% yield. Cyclisation of (**4**) to (**5**) could be accomplished by a variety of methods. Firstly, under typical conditions used by Conia,[4] *i.e.* at 300 or at 170 °C in the presence of zinc stearate,[5] good conversion was achieved. As these high temperatures were not suitable for more highly substituted derivatives of (**4**) we sought milder conditions. Thus (**4**), in toluene at reflux with a trace of ZnI_2 or in methylene chloride at room temperature with $SnCl_4$ as catalyst, gave quantitative formation of (**5**) over a similar period of time. Reduction of (**5**) with lithium aluminium hydride gave the corresponding diol (**6**) (89%), m.p. 132—133 °C, as the only observable product. Although it was not possible to



SCHEME. i, Me_3Si-C≡C-$[CH_2]_3MgI$, Cu^I, Et_2O, − 23 °C; ii, $ClCO_2Me$; iii, $AgNO_3$; iv, KCN; v, heat and ZnI_2-toluene or $SnCl_4$-CH_2Cl_2 at room temperature; vi, $LiAlH_4$; vii, MCPBA or $VO(acac)_2$-Bu^tOOH; viii, Ac_2O-pyridine then 4-*NN*-dimethylaminopyridine.

assign the ring junction and reduction stereochemistry from spectral data they can be derived from a knowledge of the relative configurations of the final epoxydiacetate (7).

The synthesis was completed by epoxidation of (6) by either *m*-chloroperbenzoic acid (MCPBA) or $VO(acac)_2$–Bu^tOOH[6] to give the epoxydiol which was converted directly into the diacetate (7) using Ac_2O–pyridine–4-*NN*-dimethylaminopyridine in 79% overall yield (Scheme). Compound (7) was also obtained on epoxidation of the diacetate of (6) with MCPBA in 89% yield.

The structure of (7), m.p. 64 °C, follows from its spectral and *X*-ray crystallographic properties.† For example, ^{1}H n.m.r. spectroscopy shows characteristic absorptions at δ 1·04 (s, 3H), 1·05 (s, 3H), 1·24—1·8 (m, 11H), 1·97 (s, 3H), 2·02 (s, 3H), 2·33 (d, 1H, *J* 4 Hz), 3·05 (d, 1H, *J* 4 Hz), 3·82 (ABq, 1H, *J* 12 Hz), 4·18 (ABq, 1H, *J* 12 Hz), and 4·76 (t, 1H, *J* 6 Hz). Compound (7) did not show any appreciable antifeedant activity against *Spodoptera Littoralis* and *Heliothis Virescens* when sprayed on *Gosypium Hirsatum* δ-pine (cotton leaves). However, when tested against *Locusta Migratoria* on GF/A discs +5% sucrose and 1000 p.p.m. of (7) a 72% inhibition of feeding was observed.‡ The stereospecific preparation of the *trans*-isomer of (7) and other analogues by another route will be reported later. Satisfactory microanalyses were obtained for all new compounds.

We thank the S.R.C. for a Research Studentship (to W. P. J.).

(*Received*, 1*st June* 1979; *Com.* 577.)

† We thank Professor D. Rogers and Dr. M. A. A. F. de C. T. Carrondo for these results, details of which will be reported in the full paper.

‡ We thank Dr. P. A. Worthington, I.C.I. Plant Protection, Jealotts Hill, and Dr. E. A. Bernays, Centre for Overseas Pest Research, London, for these and other results which we will report later.

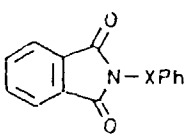
[1] For a recent discussion see D. Rogers, G. G. Unal, D. J. Williams, S. V. Ley, G. A. Sim, B. S. Joshi, and K. R. Ravindranath, *J.C.S. Chem. Comm.*, 1979, 97.
[2] I. Kubo, Y-W. Lee, V. Balog-Nair, K. Nakanishi, and A. Chapya, *J.C.S. Chem. Comm.*, 1976, 949; now shown in *ent-neo*-formulation, K. Nakanishi, personal communication.
[3] E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, 1970, **92**, 6314.
[4] R. Block, P. Le Perchec, F. Rouessac, and J. M. Conia, *Tetrahedron*, 1968, 5971.
[5] M. Seefelder, *Annalen*, 1962, **652**, 107.
[6] S. Tanaka, H. Yamamoto, H. Nozaki, K. B. Sharpless, R. C. Michealson, and J. D. Cutting, *J. Amer. Chem. Soc.*, 1974, **96**, 5254.

New Cyclization Procedure for Alkenyl-substituted β-Dicarbonyl Compounds using *N*-Phenylselenophthalimide

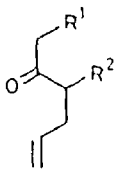
By WILLIAM P. JACKSON, STEVEN V. LEY,* and JUDITH A. MORTON
(*Department of Chemistry, Imperial College, London* SW7 2AY)

Summary *N*-Phenylselenophthalimide can be used as an effective cyclizing reagent for certain alkenyl-substituted β-dicarbonyl compounds to give a number of polyfunctionalised products.

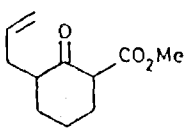
N-PHENYLTHIOPHTHALIMIDE[1] (1) and more recently *N*-phenylselenophthalimide[2] (2) have been shown to be useful reagents for effecting a variety of synthetic transformations. Here we discuss the use of (2) as a suitable cyclizing reagent for certain alkenyl-substituted β-dicarbonyl compounds (3)—(7). At room temperature, with CH_2Cl_2 as solvent, the compounds (3)—(7) were treated with (2) under



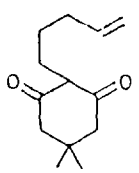
(1) X = S
(2) X = Se



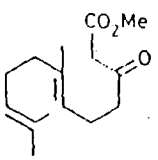
(3) R^1 = H, R^2 = CO_2Et
(4) R^1 = CO_2Et, R^2 = H



(5)

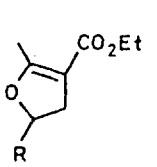


(6)

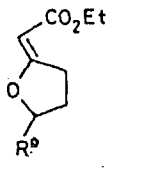


(7)

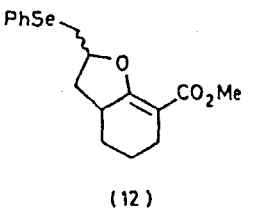
different catalytic conditions and, on work-up, gave the cyclized products (8), (10), (12), (13), (15), and (16) (Table). In most cases, cyclization took place *via* the oxygen atom of the enolic form of the dicarbonyl system with a presumed intermediate seleniranium ion. While seleno-moderated cyclizations involving alcohols and phenols are known,[3] the present work constitutes the first examples of reaction of alkenyl-substituted β-dicarbonyl species.



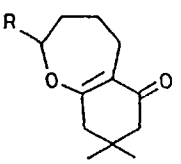
(8) R = CH_2SePH
(9) R = Me



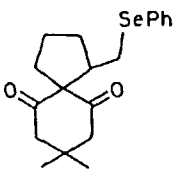
(10) R = CH_2SePh
(11) R = Me



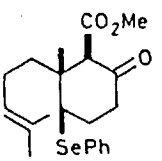
(12)



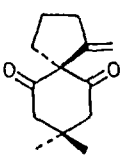
(13) R = CH_2SePh
(14) R = Me



(15)



(16)



(17)

The cyclized products were fully characterised by the usual methods (^1H n.m.r., i.r., acc. mass, and/or microanalysis) and in certain cases were additionally characterised by reduction of the phenylseleno-group with triphenyltin hydride (Table).[4]

Interestingly, when the pentenyl-substituted dimedone compound (6) was treated with (2) in the presence of a catalytic amount of iodine the oxygen-cyclized product (13) was obtained. However, under acidic conditions both the

TABLE. Reaction of β-dicarbonyl compounds with 1·1 equiv. of *N*-phenylselenophthalimide in CH_2Cl_2.

Substrate	Product (% yield) I_2[a]	*p*-$MeC_6H_4SO_3H$[a]	ZnI_2[b]	Reduced product[c] (% yield)
(3)	(8) (76)	(8) (80)	(8) (81)	(9) (92)
(4)	(10) (61)	(10) (68)	(10) (82)[e]	(11) (91)
(5)	(12) (33)	(12) (66)	(12) (44)	—
(6)	(13) (56)	(13) (49)	—	(14) (91)
	—	(15) (42)	(15) (66)	—
(7)	—[d]	—[d]	(16) (67)	—

[a] 0·05 Equiv. of catalyst. [b] 1 Equiv. of catalyst. [c] Tetrahydrofuran as solvent. [d] Complex reaction mixtures. [e] Ph_3SnH (3 equiv.), heat, toluene, azobis-isobutyronitrile.

oxygen- and carbon-cyclized products (13) and (15) were produced, while in the presence of ZnI_2, (15) appeared to be the only product. The reasons for these changes in the reaction pathway are not yet fully understood. Compound (16) can also be converted into the known methylene derivative (17)[5] in 72% yield by treatment with *m*-chloroperbenzoic acid followed by *syn* elimination of the intermediate selenoxide. It should be noted that an attempted biomimetic cyclization of (7)[6] to afford decalins failed and that only during the ZnI_2-catalysed reaction did cyclization *via* carbon take place, giving (16) as the major product.

The above cyclization procedure can be compared with other literature methods which give similar compounds,[7] although the incorporation of the highly flexible phenylseleno-group[8] into the product could provide distinct synthetic advantages.

We thank the S.R.C. for Research Studentships (to W.P.J. and J.A.M.).

(*Received*, 30*th July* 1980; *Com.* 837.)

[1] D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, W. F. Van Horn, and J. P. Snyder, *Tetrahedron Lett.*, 1970, 3551; D. N. Harpp and T. G. Back., *J. Org. Chem.*, 1971, **36**, 382; D. N. Harpp and T. G. Back., *Tetrahedron Lett.*, 1971, 4953; Y. Abe and J. Tsurgi., *Chem. Lett.*, 1972, 441.

[2] K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.*, 1979, **101**, 3704.

[3] K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko, and M. M. Joullie, *J. Am. Chem. Soc.* 1980, **102**, 3784 and references therein; D. L. J. Clive, G. Chittattu, and C. K. Wong, *Can. J. Chem.*, 1977, **55**, 3894; D. L. J. Clive, G. Chittattu, N. J. Curtis, W. A. Kiel, and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 1977, 725.

[4] D. L. J. Clive, G. J. Chittattu, V. Farina, W. A. Kiel, S. A. Menchen, C. G. Russell, A. Singh, C. K. Wong, and N. J. Curtis, *J. Am. Chem. Soc.*, 1980, **102**, 4438.

[5] G. Mandville, F. Leyendecker, and J. M. Conia, *Bull. Soc. Chim. Fr.*, 1973, 963.

[6] R. W. Skeean, G. L. Trammell, and J. D. White, *Tetrahedron Lett.*, 1976, 525 and references therein; F. W. Sum and L. Weiler, *J. Am. Chem. Soc.*, 1979, **101**, 4401.

[7] J. Tsuji, Y. Kobayashi, H. Kataoka, and T. Takahashi, *Tetrahedron Lett.*, 1980, 1475; B. M. Trost, T. A. Runge, and L. N. Jungheim, *J. Am. Chem. Soc.*, 1980, **102**, 2840.

[8] H. Reich in 'Oxidation in Organic Chemistry,' Part C, Ch. 1, ed. W. S. Trahanovsky, Academic Press, London, 1978, p. 1; D. L. J. Clive, *Tetrahedron*, 1978, **34**, 1049.