RADICAL MACROCYCLISATIONS

IN CEMBRANOID SYNTHESIS

by

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N.J.G. COX

DECLARATION

I hereby declare that the substance of this thesis has not been submitted nor is being concurrently submitted in canditure for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and where work of other investigators has been used, this has been fully acknowledged in the text.

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(N.J.G. Cox)

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ABSTRACT

In recent years the cembranoid family of natural products has emerged as an interesting class of biologically active compounds. The origins and properties of these compounds are first outlined, and a summary of methods previously used to synthesise the 14-membered cembranoid ring system is then given.

In connection with a synthetic programme towards cembranoids, based on a radical macrocyclisation as the key step, a number of suitable radical precursors were prepared and their radical macrocyclisations were attempted. Cyclisation _via_ electropinacolisation of the α,ω-dialdehyde (69) was found to be an unsuitable method. Similarly, attempts at a reductive cyclisation of the acetylenic aldehyde (70) also proved unsuccessful. A modified precursor, the halo-enone (118) possessing an activated olefin function, was then chosen. This precursor also failed to cyclise on radical initiation. Ultimately it was found necessary to design the radical precursor such that the β-position of the activated olefin was unsubstituted in order to favour the required macrocyclisation. Thus the 14-membered cembranoid type ring was eventually prepared by radical cyclisation of the allylic iodo-dienone (127) to give the cyclic enone (132). This preparation then constituted a formal synthesis of the natural cembranolide (37). Despite other possible modes of cyclisation this particular allylic radical cyclisation was found to give selectively only the 14-membered product as a mixture of 10_E_- and 10_Z_-isomers. Attempts to extend this

methodology, to include an epoxide function in the substrate, proved unsuccessful. Finally a convenient synthesis of the natural cembranoid mukulol (41) is described, using a radical macrocyclisation of the iodo-dienone (149) to give the cyclic enone (148) as the key step.

In the appendix an investigation of low valent titanium mediated couplings as a means of preparing dihydrothiophenes and dihydrofurans is described. The diketo ether (184) was found not to cyclise under any conditions. Conversely the diketo thioether (176) was found to cyclise to give a cyclic diol (178). We were unable to subsequently convert the diol to the corresponding dihydrothiophene.

CONTENTS

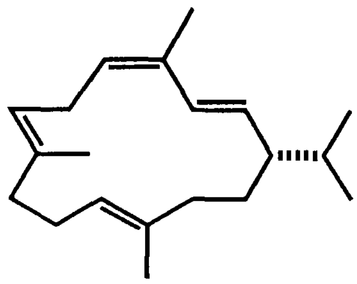
INTRODUCTION

(i) An Overview of Structures and Sources of Cembranoids

In recent years the cembranoid family of natural products has emerged as the largest subgroup of the diterpenes. Isolated from plants, insects and marine organisms these 14-membered carbocyclic isoprenoids have shown a wide range of structural diversity, and many exhibit interesting biological activities.

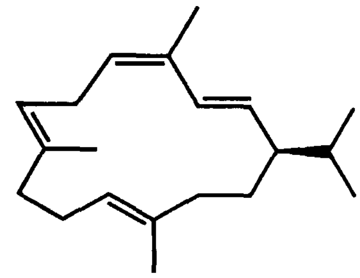
The first cembranoid, thunbergene, was isolated as early as 1931 as a crystalline solid from the Japanese black pine, *Pinus thunborgii*[1]. However it was not until 1963 that its structure was determined[2] and found to be identical to that of cembrene (1), a diterpene isolated from from the white bark pine, *Pinus albicaulis* of the group Cembrae, and from many other species of pine[3]. The structure of cembrene was determined by Dauben in 1962 and shown to be the first example of a diterpene containing a 14-membered ring[4]. Since then cembrene has been isolated from many other varieties of tree[5] and its antipode (2) has been isolated from the soft coral *Sinularia mayi*[6].

Biosynthetically the cembranoids can be considered to result from bond formation between the terminal double bond and the C_1 carbon of geranylgeranyl pyrophosphate (Scheme 1). Biogenetically, the simplest cembranoid is therefore neocembrene (3). Neocembrene occurs widely in nature being found in spruce and hinoki trees (both members of the pine family)[7], in a gum resin from *Comiphora mukul* (known as Guggulu oil and used in folk medicine)[8] as well as being used by the Australian termite, *Nasutitermes exitiosus*, as a trail pheromone[9] and occurring in a number of soft corals[10]. Because of their biosynthetic origin the carbon atoms of cembranoids are usually numbered as for



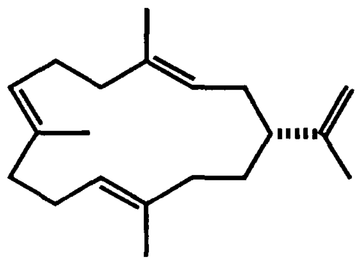
(1)

R(+)-Cembrene



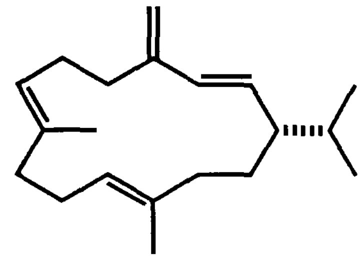
(2)

S(-)-Cembrene



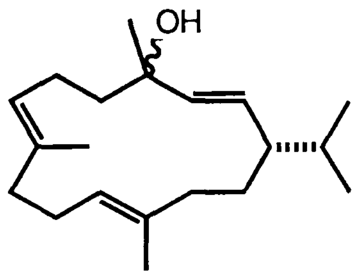
(3)

R(-)-Neocembrene



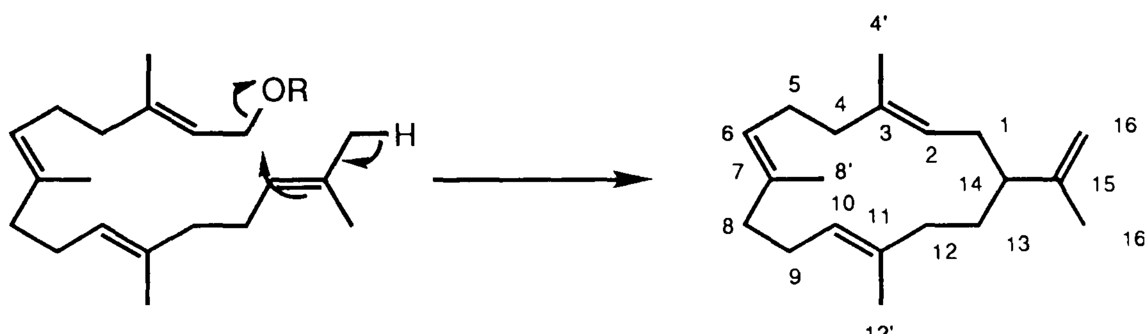
(4)

Isocembrene



(5)

Thunbergol



R = H, OPP

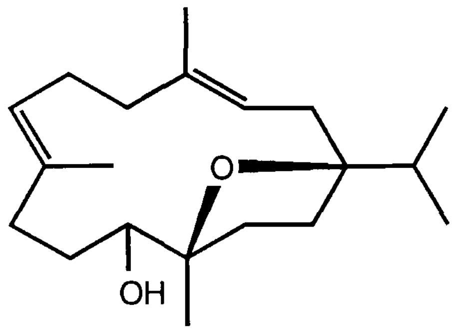
Scheme 1

geranylgeraniol (Scheme 1).

Other cembranoids from the pine family include isocembrene (4), isolated from the Siberian pine, Pinus sibirica, and the Korean pine, Pinus koraiensis[11], and thunbergol (5), a constituent of pocket resin from the Douglas fir, Pseudotsuga menziesii[12].

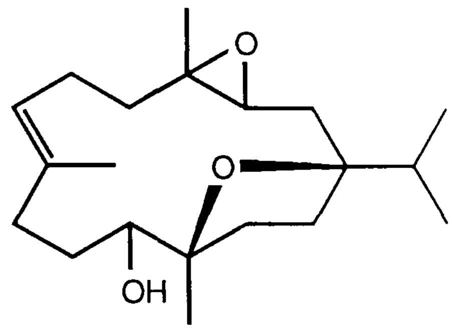
Cembranoids can possess highly oxygenated structures as exemplified by incensole (6), incensole oxide (7) and isoincensole oxide (8) which are constituents of frankincense resin (from the tree Boswellia curteri)[13]. Many cembranoids contain an α-methylene lactone structure and these have been given the name cembranolides. An example is ovatodiolide (9) which was isolated in 1965 from the grass Anisomeles ovata found on the high plateaus of Vietnam[14]. It has also been isolated, along with its epimer isoovatodiolide (10), from the leaves of Anisomeles indica, a plant used for treating stomach ailments in Trinidad[15], and also, along with anisomelic acid (11), from Anisomeles malabarica, a plant used medicinally in South India[16].

A large number of cembranoids have been isolated from tobacco plants[17] and most prominent amongst these are the duvatrienediols (12 and 13). These are found in most tobacco varieties but were first isolated by Roberts and Rowland in 1962 from burley tobacco (Nicotiana tabacum) and Turkish tobacco[18,19]. These diols, present in the cuticular wax of the leaf and flower, have been shown to possess plant growth inhibiting activity and insect resistance properties[19]. Biosynthetically it is probable that they are derived from



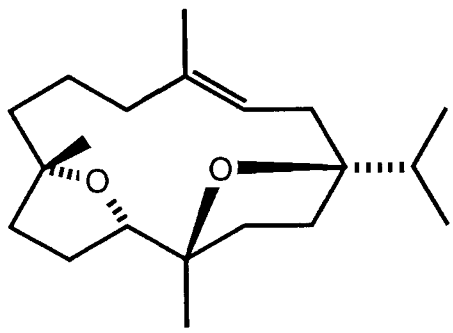
(6)

Incensole



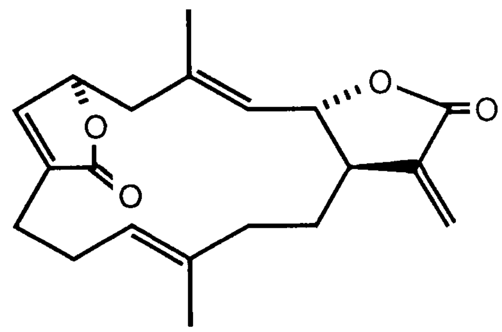
(7)

Incensole oxide



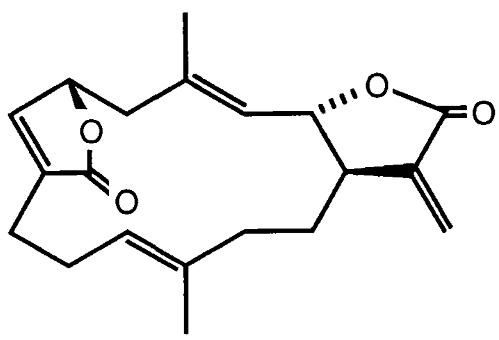
(8)

Isoincensole oxide



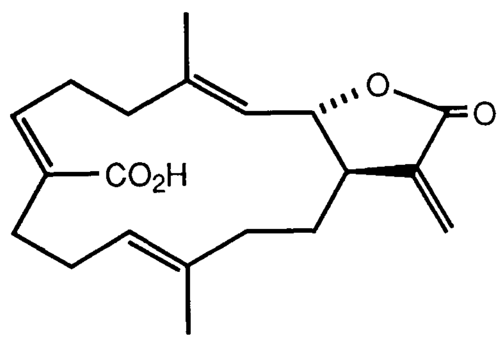
(9)

Ovatodiolide



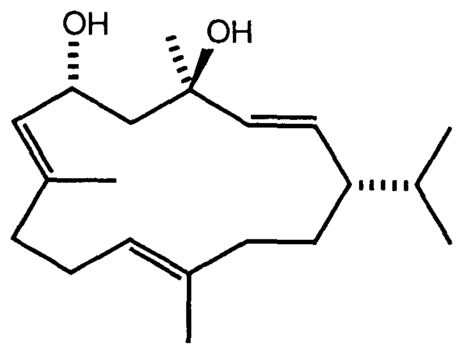
(10)

Isoovatodiolide



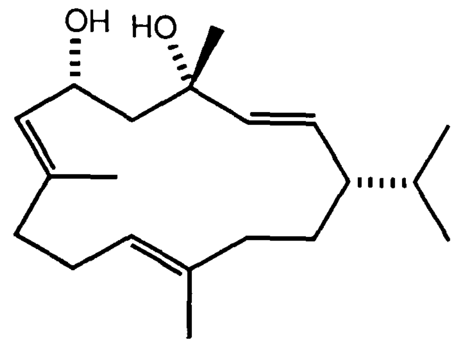
(11)

Anisomelic acid



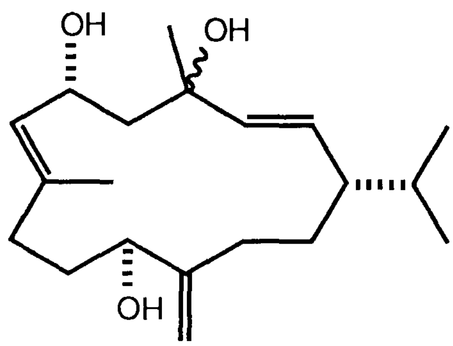
(12)

4R-Duvatrienediol

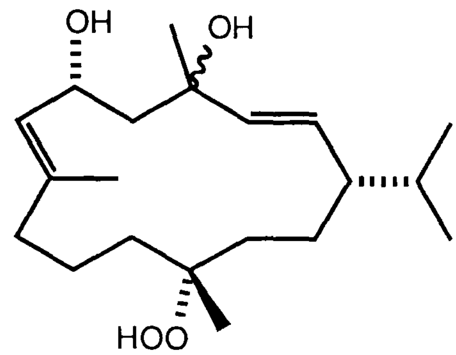


(13)

4S-Duvatrienediol



(14)



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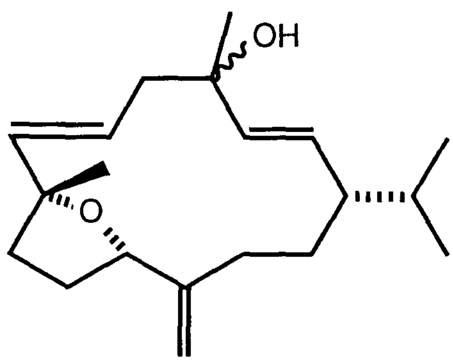

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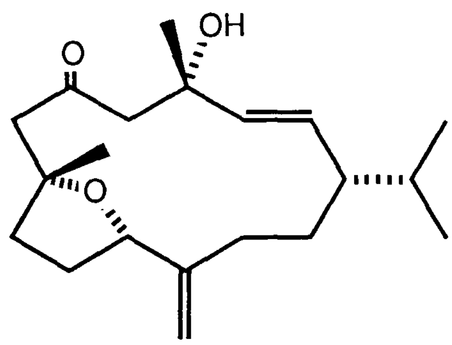
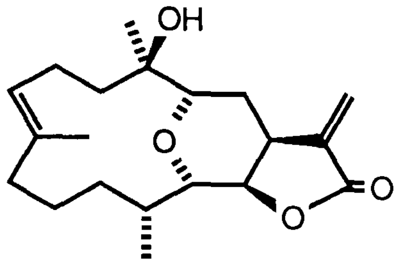


(17)

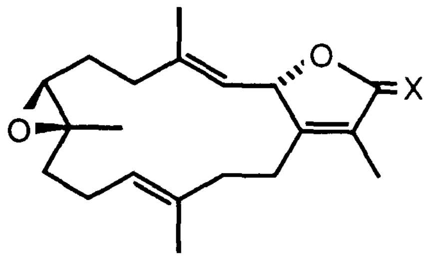
Some Tobacco Cembranoids

cembrene (1) which is also a minor tobacco constituent[20]. The duvatrienediols (12 and 13) are considered to be the key metabolites in the biogenesis of the majority of the forty or so known tobacco cembranoids which include the triol (14), the hydroperoxide (15), the epoxy bridged cembranoid (16) and the ketone (17)[17]. The cembranoids in tobacco readily undergo biodegradation during the post-harvest treatment of the leaf and so give rise to large numbers of odoriferous norcembranoids in tobacco products[21].

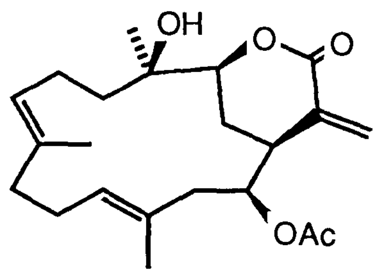
The vast majority of cembranoids have been isolated from marine sources, specifically from gorgonians and soft corals[22]. As early as 1960 a marine diterpene eunicin (18), possessing antibacterial properties, had been isolated from the gorgonian *Eunicea mammosa* and this was shown in 1968 to be a cembrane derivative[23]. Many cembranoids have repellent properties and so protect the soft corals and gorgonians against predators. Indeed cembranoids are often found in extremely high concentrations. Sarcophine (19), for instance, isolated from the soft coral *Sarcophytum glaucum* from the Red Sea, has been isolated as up to 3% of dry weight[24]. In the case of the gorgonian *Pseudoplexaura crassa*, simply squeezing the 'juice' from the fresh gorgonian produces crystals of the exceptionally toxic metabolite crassin acetate (20)[25]. It is possible that the gorgonians and soft corals owe their survival to the presence of these toxic compounds which may actually be biosynthesised by the symbiotic zooxanthellae (unicellular algae) also present[26]. These compounds have been shown to be a significant component in the gorgonians' chemical defence not



(18)
Eunicin

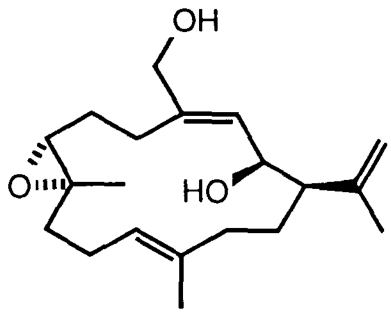


(19) X = O Sarcophine
(24) X = H_2 Deoxysarcophine



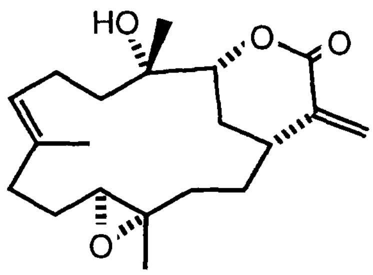
(20)

Crassin acetate

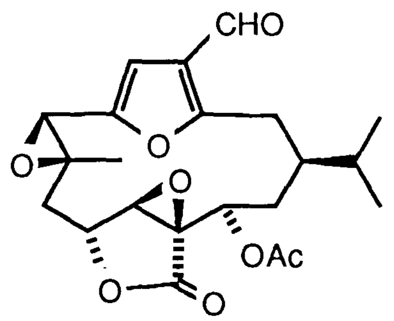


(21)

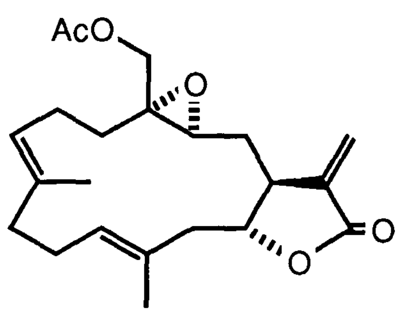
Asperdiol



(22)
Sinularin

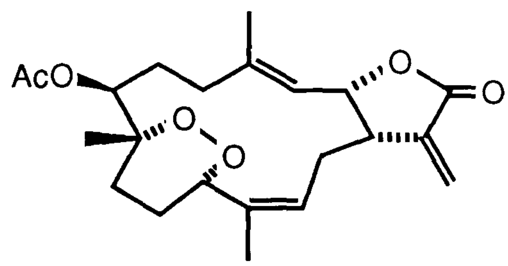


(23)
Lophotoxin



(25)

Lobolide



(26)

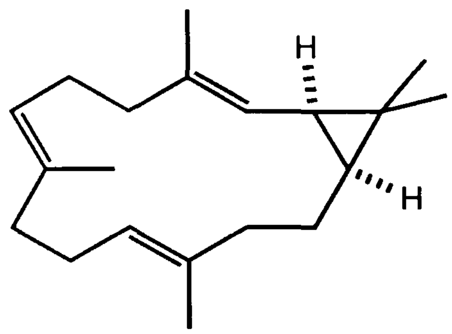
Denticulatolide

Some Marine Cembranoids

only against predation by large organisms, but also against potential encrustation and smothering by lower life forms such as juvenile forms of barnacle[27].

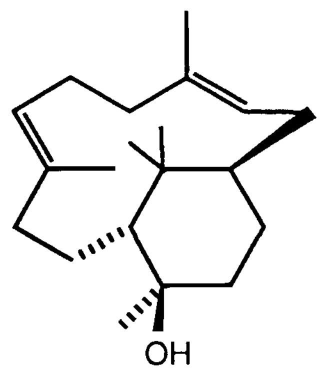
Many cembranoids have interesting pharmacological properties. Crassin acetate (20), as well as being a mild antibiotic, is a significant cytoxic and antineoplastic agent[27]. Other antineoplastic agents are asperdiol (21) found in the gorgonian Eunicea asperulu and Eunicea tourneforti[28], and sinularin (22) which has been isolated from the soft coral Sinularia flexibilis[29]. Lophotoxin (23) is a neuromuscular toxin isolated from four species of gorgonian of the genus Lophogorgia[30]. 16-Deoxysarcophine (24), isolated from Sarcophyton trocheliophorum[31], has been shown to possess calcium antagonist activity on the isolated rabbit aorta[31b] and also to be a potentiator of directly stimulated contraction of skeletal muscle in the isolated rat hemidiaphragm[32]. Many cembranoids show ichthyotoxic properties and two examples from soft corals are lobolide (25) from Lobophytum crassum[33] and the peroxide, denticulatolide (26) from Lobophytum denticulatum[34].

The cembranoids described so far give an impression of the diverse structures found in nature. In addition there are many closely related compounds. Amongst the diterpenes, casbene (27), an antifungal metabolite isolated from the castor bean, Ricinus communis[35], contains a cis-fused cyclopropane ring. Additional cyclohexane rings present in the diterpene verticillol (28) from the conifer Sciadopitys verticillata[36], and in the secotrinervitane (29) isolated from the frontal gland of soldier termites of Nasutitermes lujae[37].



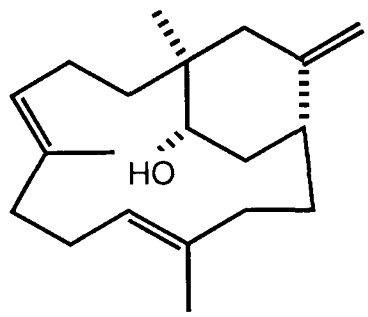
(27)

Casbene



(28)

Verticillol



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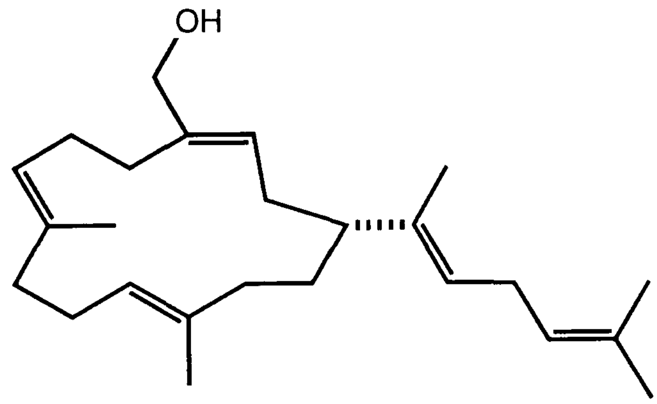
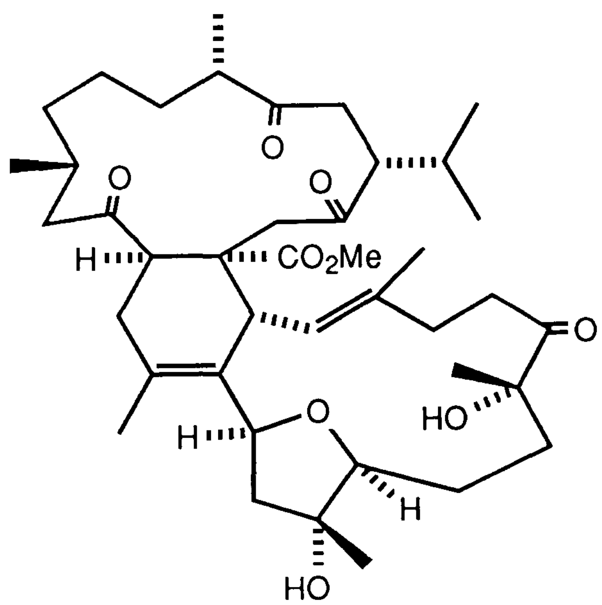


(30)

Ceriferol



(31)

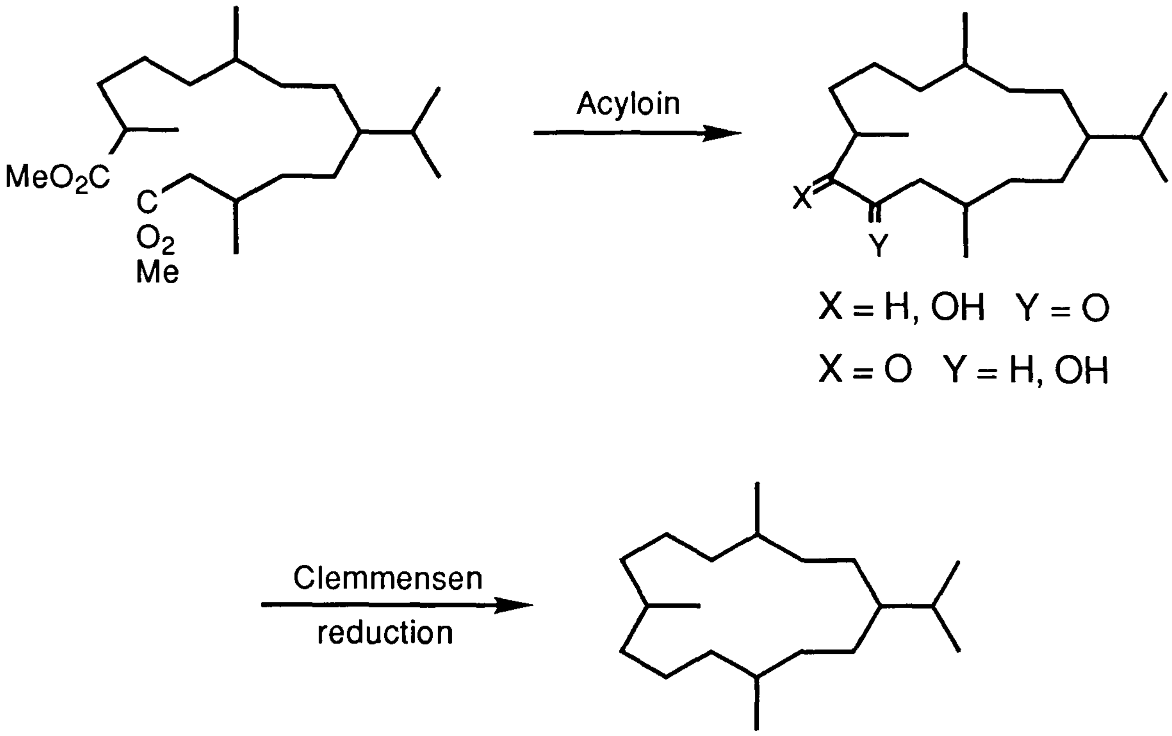
Methyl isosartortuoate

There are a number of larger terpenes containing a 14-membered ring. Ceriferol (30), a sesterpene isolated from the wax of the scale insect Ceroplastes ceriferus[38] is an example. A rare tetracyclic tetraterpenoid, methyl isosartortuoate (31) has recently been isolated from the soft coral, Cophyton tortuosum, found in the South China Sea[39]. This is presumably biosynthesised by a Diels-Alder type coupling of two different cembranoids.

(ii) A Summary of Cembranoid Syntheses

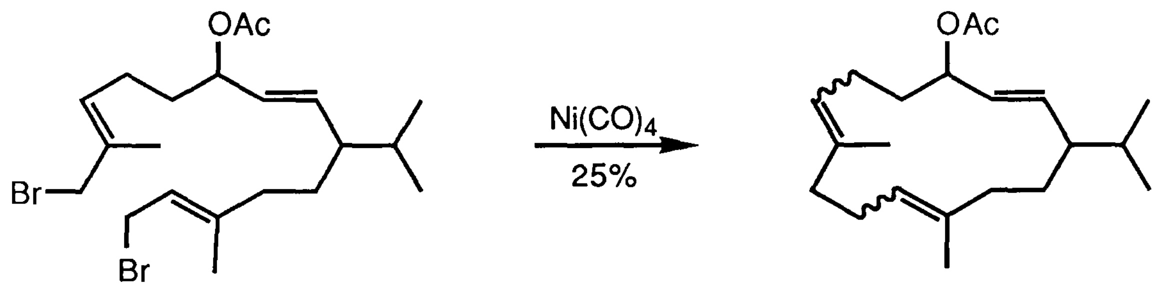
Despite the emergence of this plethora of cembranoid structures since 1962, it was not until 1974 that Dauben published the first total synthesis of a cembranoid -although the carbon skeleton of the parent saturated hydrocarbon, cembrane (32), had been prepared by means of an acyloin condensation reaction as early as 1966 (Scheme 2)[40]. The strongly reducing conditions of the acyloin condensation, however, prevented its use in the total synthesis of any naturally occurring cembranoids. Dauben's approach was to use a variant of the Wurtz coupling using nickel tetracarbonyl which Corey had previously used successfully in the synthesis of the 11-membered sesquiterpene humulene[41]. Having prepared the bis-allylic dibromide (33), Dauben was able to achieve the required cyclisation in a yield of 25% as a mixture of isomers at the two trisubstituted double bonds (Scheme 3). The cyclised product was then elaborated to give cembrene (1)[42].

Although much milder than the acyloin condensation, this route has various shortcomings. Firstly, the adjacent

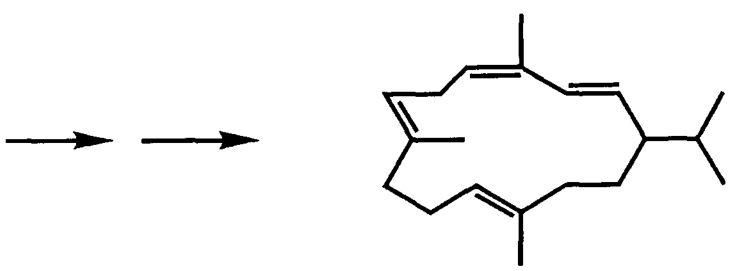


Scheme 2

(32)



(33)



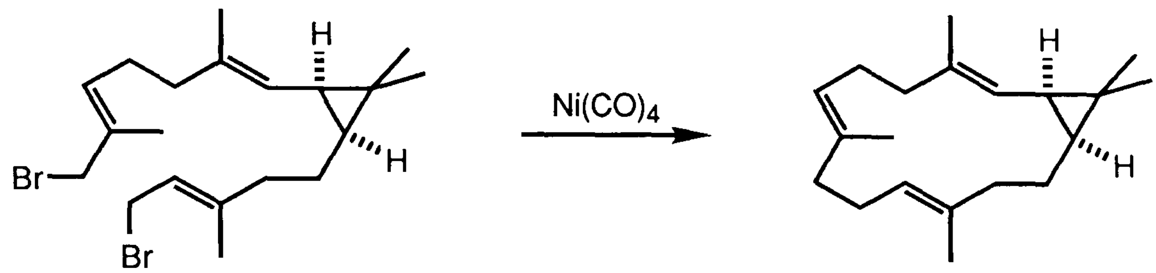
Scheme 3

(1)

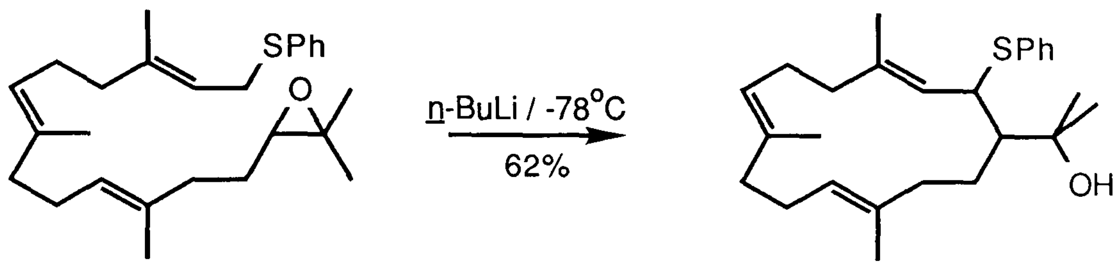
trisubstituted double bonds are observed to isomerise. Secondly, the reaction could not be carried out with the conjugated 1,3-diene unit ultimately required, as this showed reactivity with the nickel species. Thirdly, even the allylic acetate was not entirely inert to the reagent leading to some dimeric products. Despite these problems this route was later successfully used in a synthesis of casbene (27) (Scheme 4)[43].

A more biomimetic approach to cembranoids was chosen by Itô and Kodama in 1975, albeit with the reverse polarity to the biosynthetic process. Using a sulphide function as an anion stabilising group they achieved the cyclisation of the epoxide (34) to (35) in 62% yield[44]. Removal of the sulphide group in (35) then gave nephthenol (36), a natural cembanoid from the soft coral Nephthea brassica, which could be easily converted to neocembrene (3) (Scheme 5).

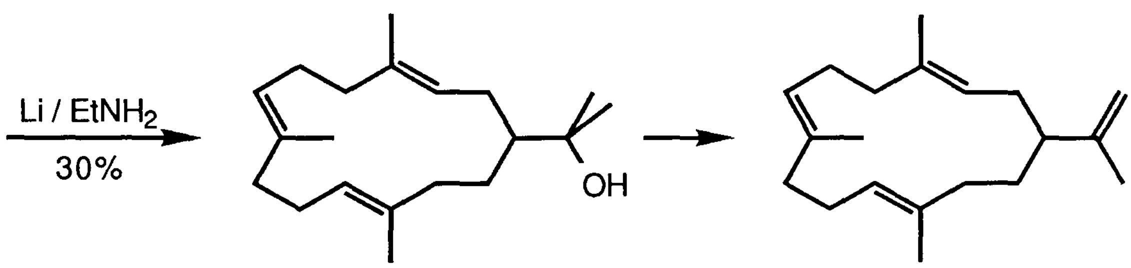
The main problems associated with this approach are, firstly, that both cyclisation and removal of the sulphur group are accompanied by isomerisation of the adjacent double bond to give a mixture of *E* and *Z* products and, secondly, the poor yield in the sulphide removal step (30%). The isomerisation accompanying this cyclisation was subsequently used to advantage by Itô and Kodama in a synthesis of the 2*Z*-isomer of neocembrene (38), a compound isolated from the frontal gland of soldier termites of Cubitermes umbraus[45]. More recently, in 1982, Itô has extended the scope of this reaction by elaborating the cyclised sulphide (35) to a cembranolide (37) isolated from the soft coral Sinularia mayi[46]. This was the first reported synthesis of a cembranolide.



Scheme 4 (27)



(34) (35)



(36) (3)

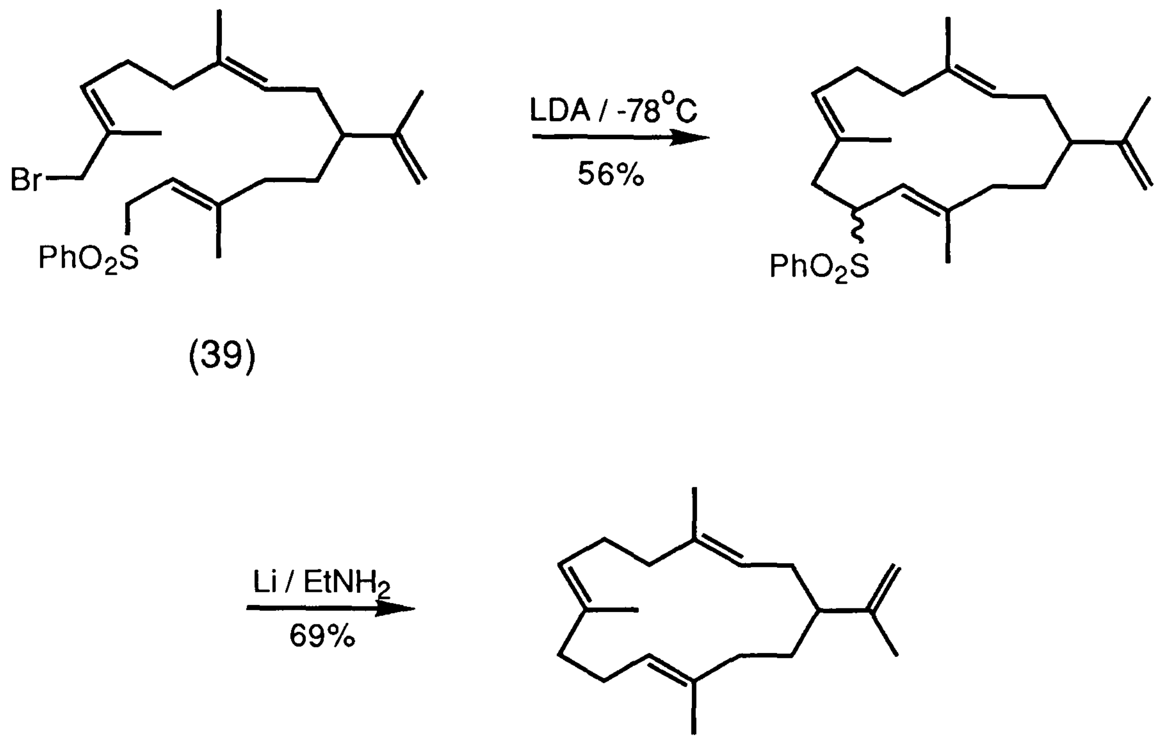
(37) (38)

Scheme 5

Since 1975, variations of this reaction have been used in a number of cembranoid syntheses. For example, Kato has cyclised the sulphone bromide (39) in a synthesis of neocembrene (3) (Scheme 6)[47]. Dauben[48] and Marshall[49] have also used this method to prepare the cembranoid carbon skeleton.

An even more closely biomimetic approach to cembranoid synthesis was published by Kato later in 1975. He had previously cyclised farnesoic acid chloride in the presence of tin tetrachloride and obtained only a cyclohexene derivative and no product containing a 10-membered ring[50]. He found, however, that geranylgeranoic acid chloride could be cleanly cyclised in 71% yield to give the cembranoid carbon skeleton. Kato then elaborated this product to give mukulol (41), a cembranoid isolated from Guggulu oil, which is a gum resin from the Indian tree Comiphora mukul, and cembrene (1) (Scheme 7)[51]. A vital requirement for cyclisation is the presence of a 2E double bond. The 2Z isomer of geranylgeranoic acid chloride gave only a 6-membered product on cyclisation[52].

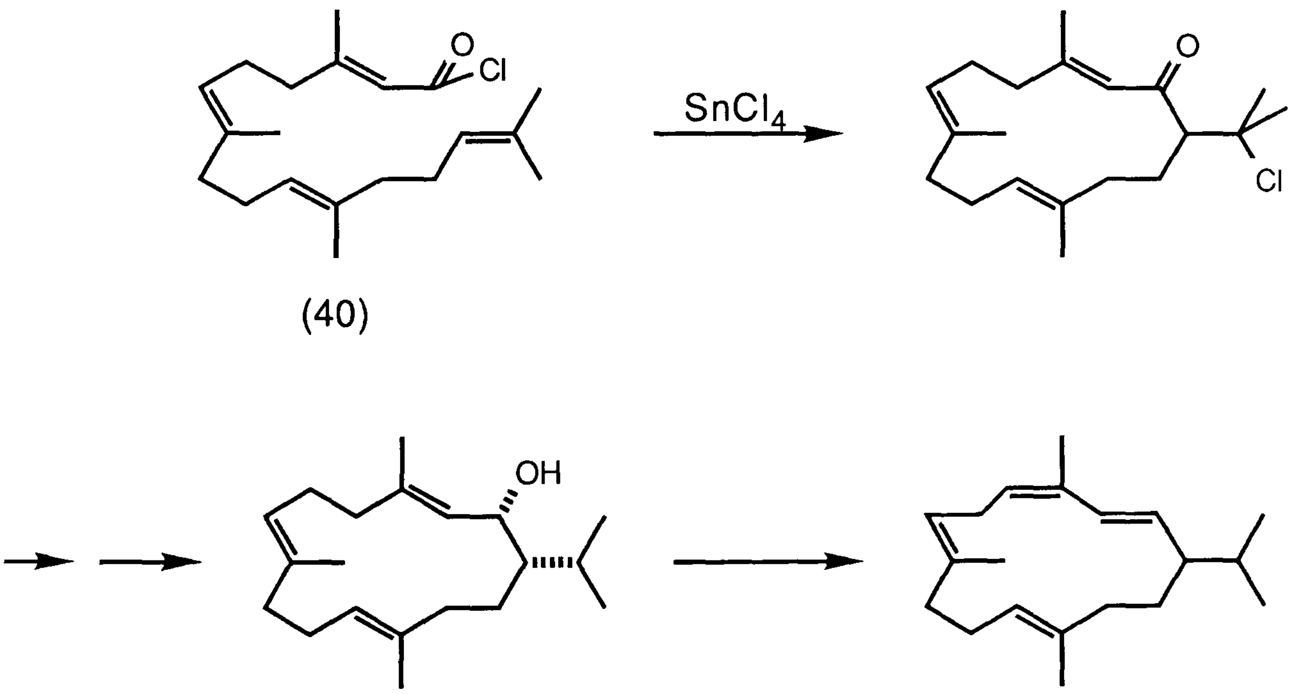
Kato has subsequently used this method in syntheses of neocembrene (3)[52,53], incensole (6)[54], incensole oxide (7)[55], thunbergol (5)[56], asperdiol (21)[57] and the cembranolide (37)[58]. A particularly interesting result is that cyclisation of geranylfarnesoic acid chloride (42) gave none of the 18-membered isomer but instead gave exclusively the 14-membered product (43) (Scheme 8). This suggests a strong thermodynamic and/or kinetic preference for this mode of cyclisation. This result has been used by Kato to synthesise ceriferol (30) and ceriferol-I (44)[52,59].



(39)

(3)

Scheme 6

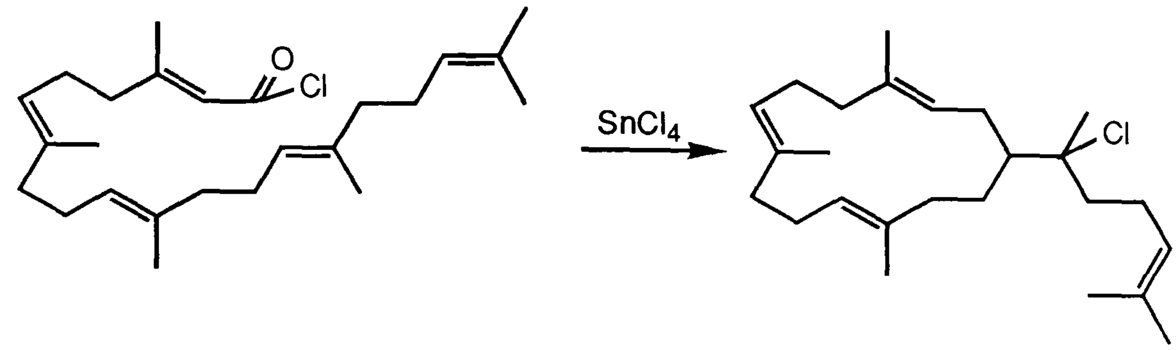


(40)

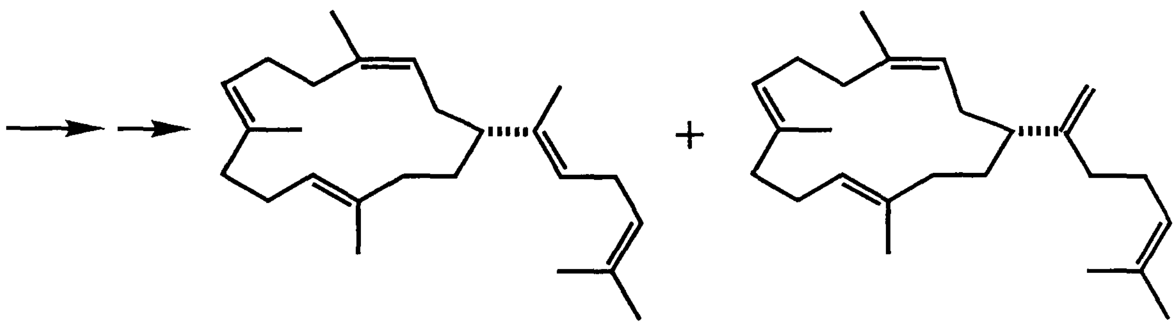
(41)

(1)

Scheme 7

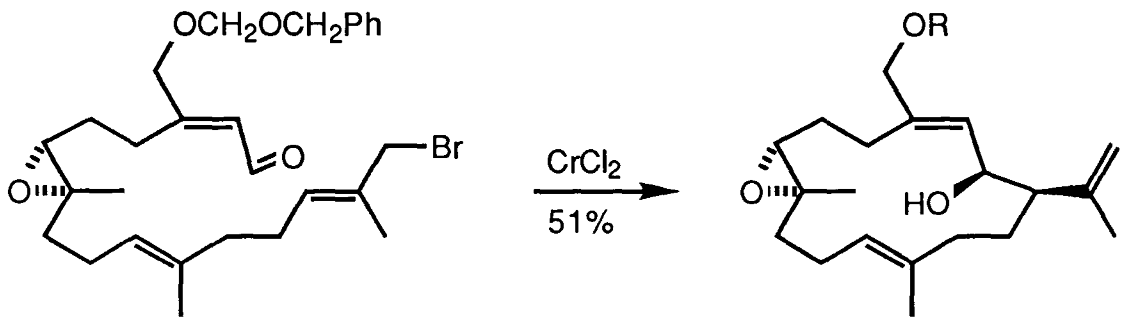


(42) (43)



(30) (44)

Scheme 8



R = CH$_2$OCH$_2$Ph

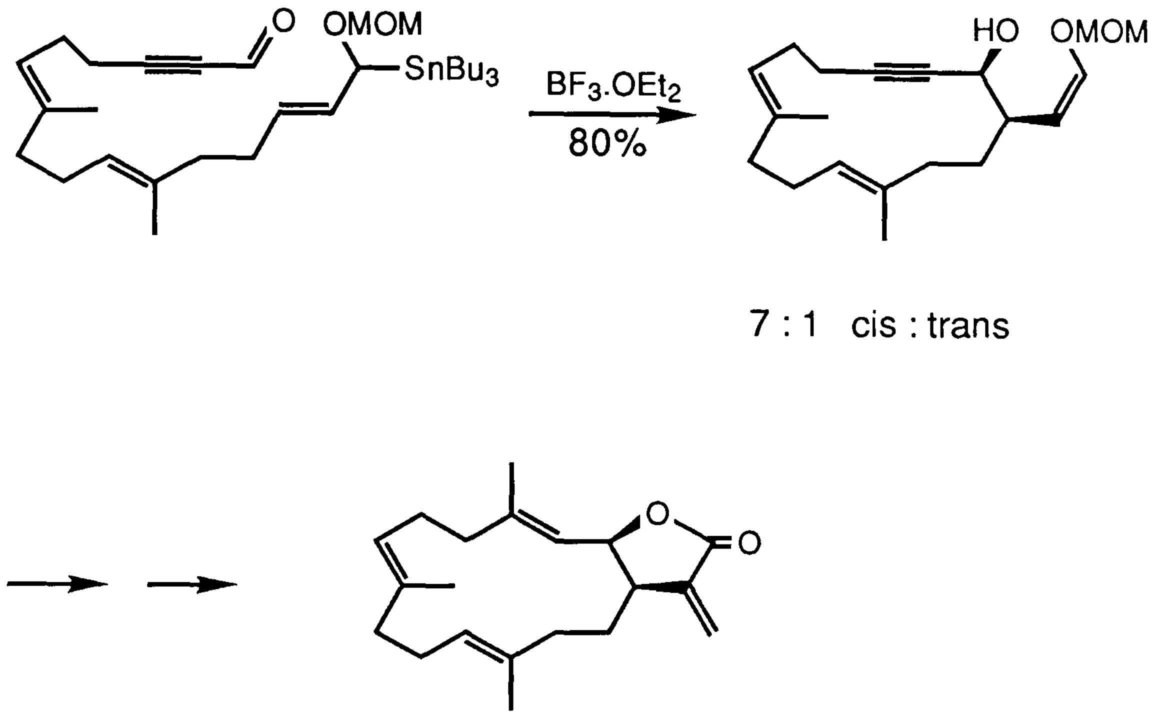
(21) R = H

Scheme 9

Apart from Dauben's original synthesis of cembrene using nickel tetracarbonyl, the use of organometallics in this area has been extremely limited. However, in 1983, Still published a synthesis of asperdiol (21) which used an allyl chromium species in the key cyclisation step (Scheme 9)[60]. This reaction, developed by Hiyama and Heathcock[61] had the advantage of being threo-selective and therefore gave the desired relative stereochemistry of the hydroxy and isopropenyl groups. Still observed that the cyclisation was directed by a conformational bias originating from the remote epoxide function giving predominantly the desired diastereoisomer. He also reported that other similar systems, such as allyl silanes and allyl stannanes, failed to cyclise. However, in 1987, Marshall succeeded in using an allyl stannane in a synthesis of the cembranolide (37) (Scheme 10)[62]. This cyclisation reaction, which went in 80% yield, gave a 7:1 ratio in favour of the desired cis-substituted product. Further, if the acyclic stannyl precursor was made chiral, a chiral product was obtained.

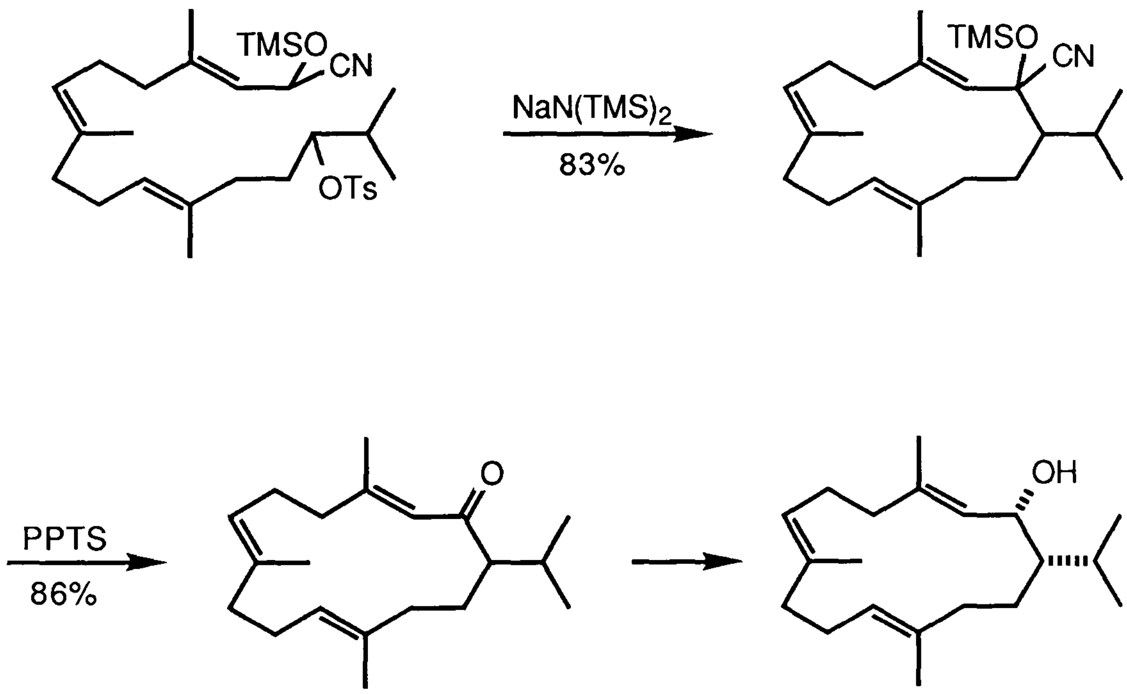
Sulphur is not the only anion stabilising group that has been used in macrocyclisations. In 1978 Kato published an approach to verticillol (28) using the anion stabilsing effect of a nitrile group. He observed the cyclisation of a chloro-nitrile in 15% yield[63]. This method has been used with higher yields in the cembranoid area by Takahashi, who has coupled the anion generated from a protected cyanohydrin to a secondary tosylate in a synthesis of mukulol (41) (Scheme 11)[64].

In 1986 a number of research groups published syntheses of



(37)

Scheme 10

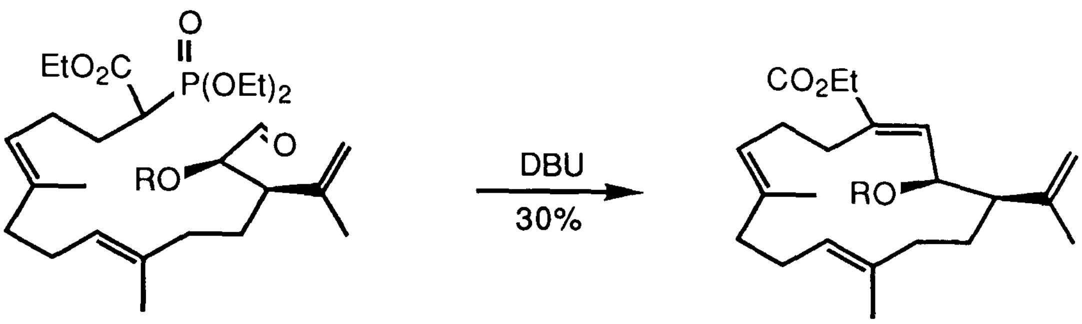


(41)

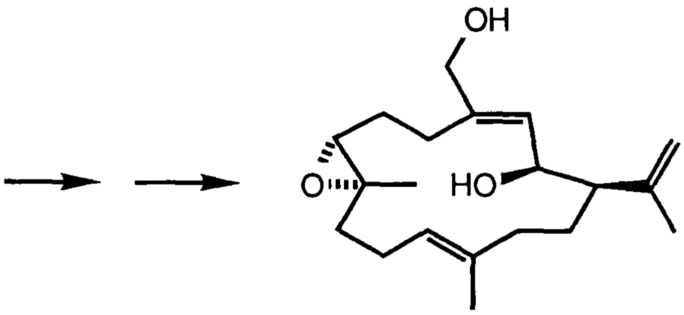
Scheme 11

cembranoids employing the use of an intramolecular Wadsworth-Emmons reaction to construct the 14-membered ring. This reaction had already been used extensively by Nicolaou in the synthesis of 16- and 18-membered rings[65] but had not previously been used to prepare the cembranoid carbon skeleton. Tius used the Wadsworth-Emmons reaction as the key cyclisation step in his synthesis of asperdiol (21) (Scheme 12). He obtained, however, only a 30% yield in the cyclisation step and observed a 2:1 mixture of _E_ and _Z_ isomers[66]. Kodama used a similar method in a synthesis of ceriferic acid (45), a 14-membered ring sesterpene isolated from the wax of the scale insect _Ceroplastes ceriferus_. He achieved a much improved yield of 76% but, unfortunately in this case, obtained a 2:1 ratio of isomers in favour of the undesired _Z_ isomer (Scheme 13)[67]. Later in 1986 Marshall published a synthesis of anisomelic acid (11) again using the Wadsworth-Emmons reaction (Scheme 14). He obtained a 40% yield for the cyclisation step and observed exclusively the desired _Z_ geometry[68]. The main drawback of this reaction is undoubtedly the lack of any predictable stereochemical control.

In the past few years there have been two novel approaches to cembranoid synthesis involving formation of the 14-membered ring _via_ a pericyclic reaction. In 1985 Wender published a chiral synthesis of 2_Z_-neocembrene (38) based on an oxy-Cope ring expansion reaction (Scheme 15)[69]. He was able to achieve a chiral synthesis by starting with the readily available _d_-carvone (46). This entirely novel approach to cembranoid synthesis has as its main drawback its limitation to the

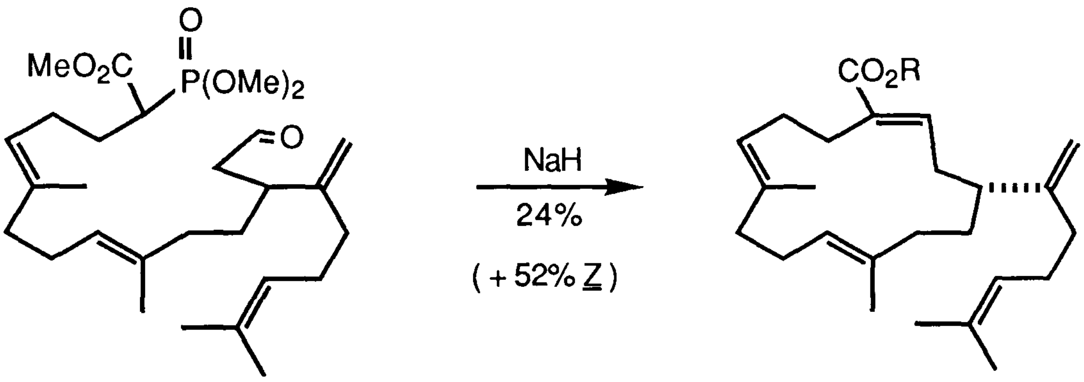


2 : 1 E : Z



(21)

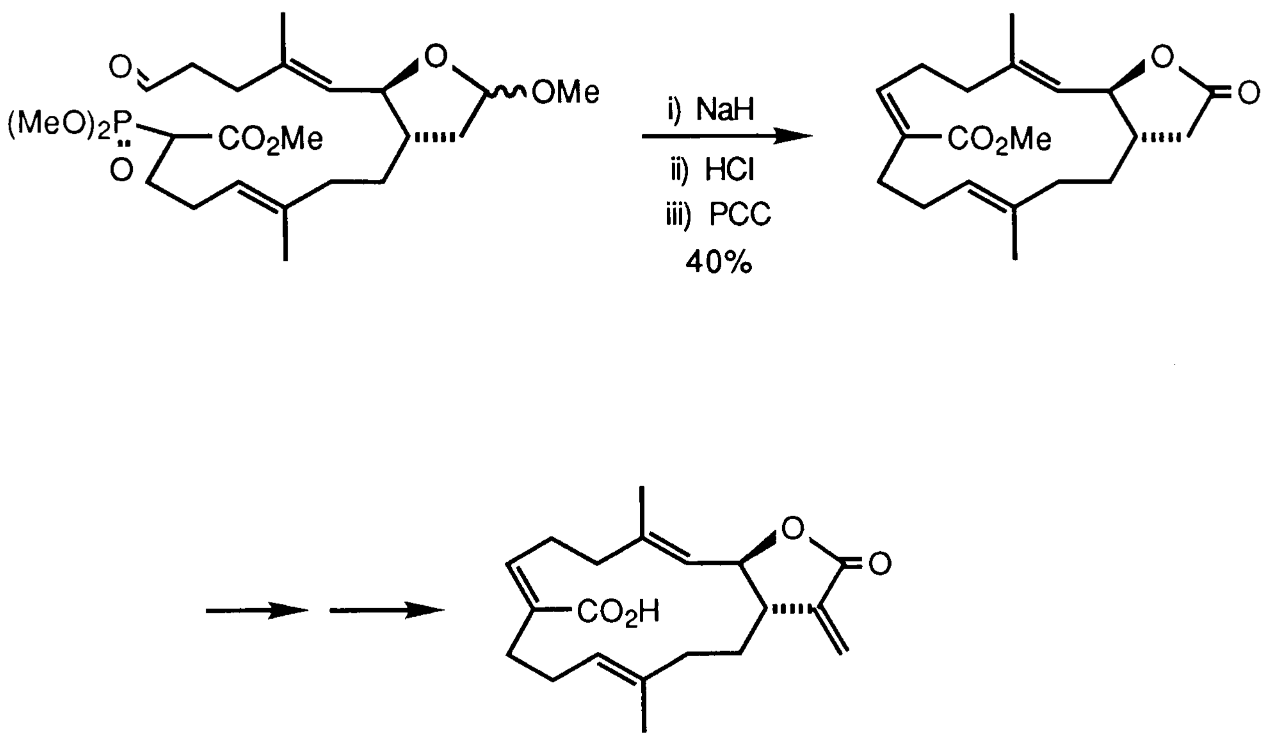
Scheme 12



R = Me

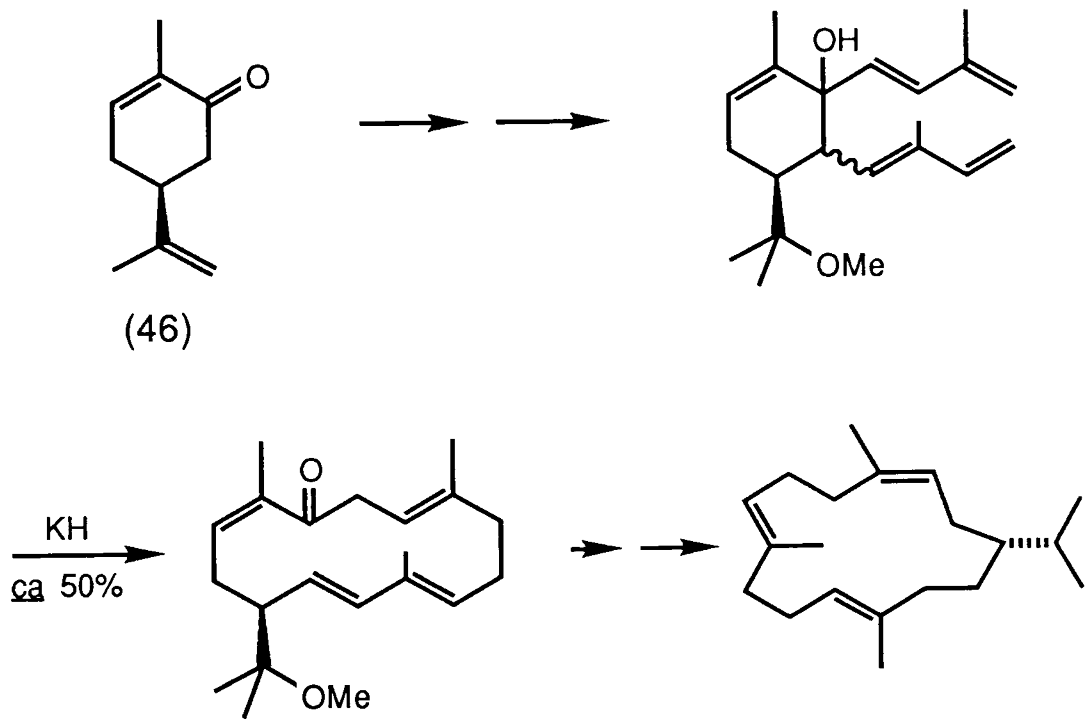
(45) R = H

Scheme 13



(11)

Scheme 14



(46)

(38)

Scheme 15

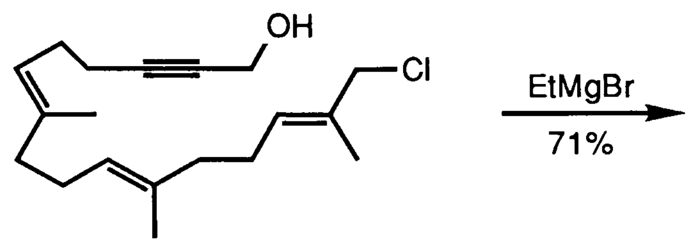
synthesis of 2*Z*-cembranoids.

In 1986 Marshall prepared the cembranoid carbon skeleton by means of a ring contraction reaction *via* a sigmatropic rearrangement (Scheme 16)[70]. Having formed the 17-membered propargyl allyl ether (47), a [2,3] Wittig rearrangement gave a 14-membered carbocycle. When carried out in hexane-THF a 4.5:1 mixture of *trans*:*cis* isomers was obtained, but use of THF-HMPA reversed the selectivity giving a 6:1 ratio of *cis*:*trans* isomers. The carbocycle could then be readily modified to give mukulol (41).

(iii) General Points

As has already been shown, the cembranoid diterpenes possess a wide range of structural diversity and many have interesting biological activities. Their synthesis is therefore of interest to the synthetic organic chemist. A number of syntheses of cembranoids have been published, but many have problems or limitations associated with them. Clearly the use of strongly basic or Lewis acidic conditions limits the functionality that can be present in the precursor before cyclisation. It was therefore felt that any new methodology that could be developed for the formation of macrocycles would be a significant contribution in this area.

The synthesis of macrocycles poses an additional problem over that of small rings -namely entropy. Whereas the collision rate for the ends of a C_5 or C_6 chain is very high, that of a longer C_{14} chain is considerably lower. The problem is compounded by transannular interactions and torsional strain



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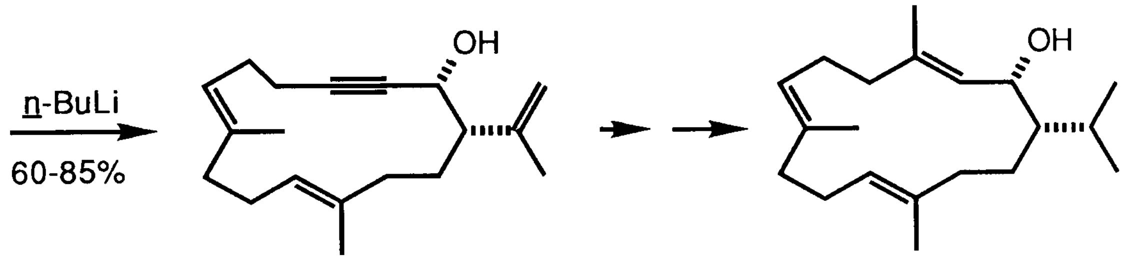
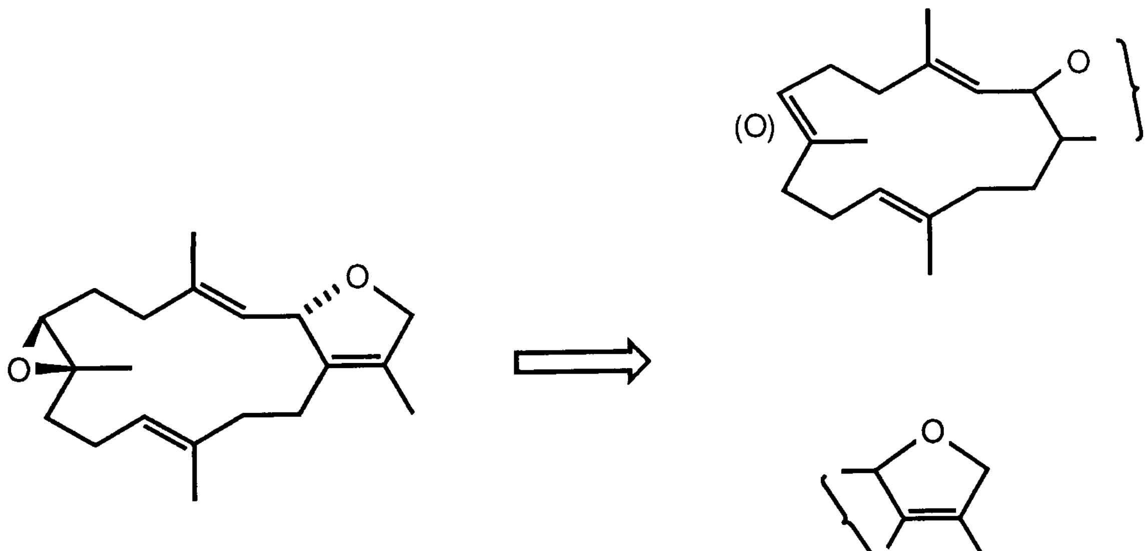


(41)

Scheme 16



(24)

Deoxysarcophine

Scheme 17

which may also hinder cyclisation. For these reasons a synthetic method that may work well for small rings may be unsuitable for large rings. Also, because of the entropic factor disfavouring macrocyclisations, it is all the more important to prevent intermolecular reactions. For this reason macrocyclisations are carried out at high dilutions, typically at about 5mM or less.

A structure of initial interest to us was that of deoxysarcophine (24) (Scheme 17). Deoxysarcophine exhibits biological activity as a calcium antagonist[31,32] and is therefore of interest to the pharmaceutical industry in the treatment of hypertension. Structurally it possesses, as well as the 14-membered carbocyclic ring and an epoxide function, a dihydrofuran ring. Such dihydrofuran rings occur rarely in nature and there is, as yet, no general procedure for their synthesis. Any synthesis of deoxysarcophine had to address two distinct problems. These were to find methodologies firstly for the preparation of the macrocycle and secondly for the synthesis of the dihydrofuran ring. An approach to the synthesis of the macrocycle which appealed to us was the use of carbon radical intermediates. Radical reactions can often be carried out under mild, neutral conditions and can tolerate the presence of a wide range of functionality. A radical synthesis of the cembranoid carbon skeleton would certainly provide a useful method complementing those already known.

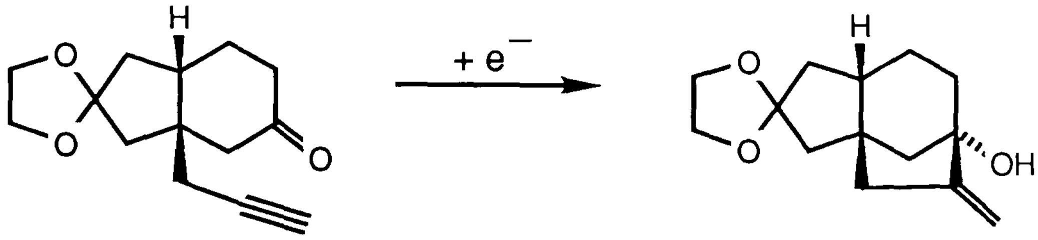
Our investigation was therefore in two parts. The larger part, on the feasibility of using radicals in the synthesis of macrocycles, is described in the following discussion. An approach to the synthesis of the dihydrofuran ring is then described in a short appendix.

DISCUSSION

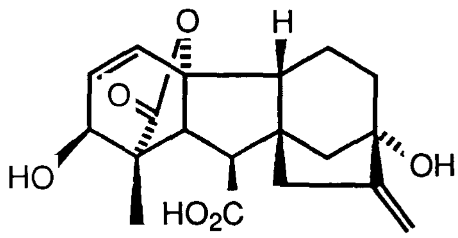
The construction of ring systems is of considerable importance in the total synthesis of natural products. There have been many studies of the use of radicals in this area[71], mostly of a mechanistic nature[72]. These studies have illustrated the huge potential for the application of radical cyclisation reactions in synthesis. The high degree of regio- and stereo-selectivity often observed in intramolecular radical processes is of particular significance[73]. Also their inherent 'umpulong' nature has revealed new routes to many synthetic targets. These features have led to a dramatic increase in the use of radical reactions and to the establishment of a large array of new methodologies for the formation of ring systems, generally under mild conditions. These have, however, been almost exclusively confined to the area of 5- and 6-membered rings.

One of the earliest examples of the synthetic use of radicals was in the total synthesis of gibberellin plant hormones (Scheme 18)[74]. Treatment of the keto-acetylene (48) with potassium in liquid ammonia was shown to promote reductive cyclisation to (49) thus forming the fused C/D ring portion of gibberellic acid (50) and simultaneously incorporating the tertiary allylic alcohol.

Radicals have also been generated by homolytic cleavage of carbon-heteroatom bonds, and many recent syntheses have used this methodology. For example, a synthesis of the sesquiterpene sativene (52) has been achieved via cyclisation of the bromide (51) (Scheme 19)[75]. Radicals can also be generated from the cleavage of carbon-metal bonds as in the use of mercuric hydride

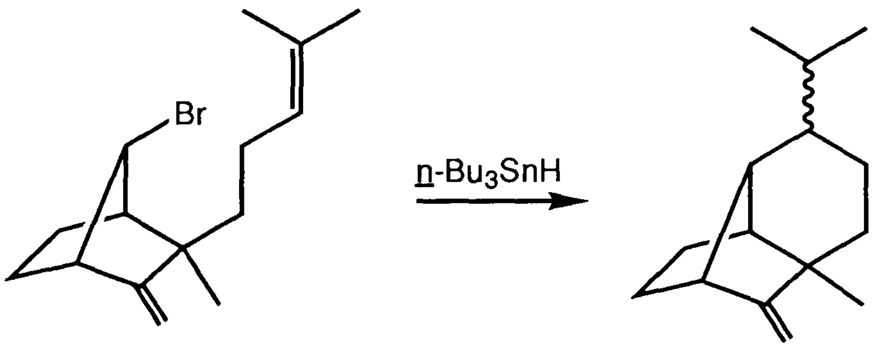


(48) (49)



(50)

Scheme 18



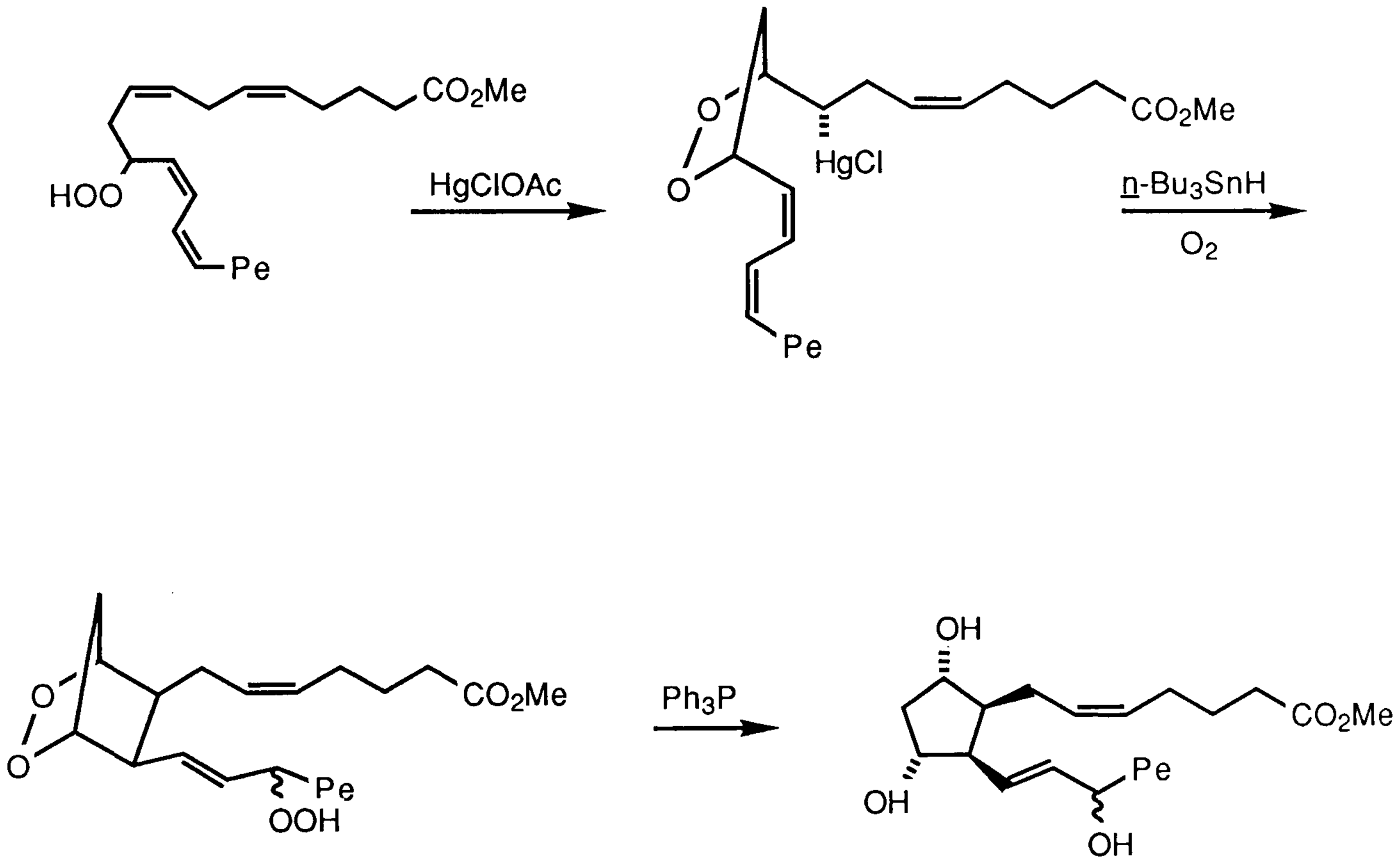
(51) (52)

Scheme 19

in a synthesis of prostoglandin (53) (Scheme 20)[76]. Other functionalities can also be used to generate radicals. For example, the bicycle (55) has been prepared from the selenide (54) (Scheme 21)[77] and the alkaloid (57) from the sulphide (56) (Scheme 22)[78]. Reactions can also be carried out by the generation of biradicals as in the case of the tricycle (59) which has been prepared from the diazene (58) (Scheme 23)[79]. Radical methodology readily lends itself to such tandem cyclisations. Another example is the synthesis of the related tricycle hirsutene (61) from the iodo-acetylene (60) (Scheme 24)[80].

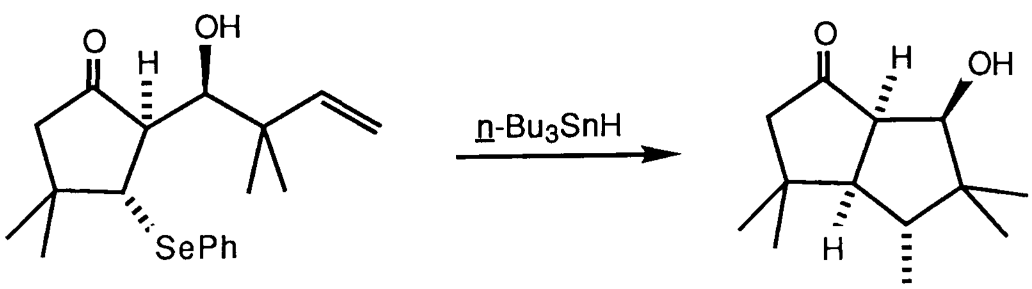
The use of radicals in synthesis has also been established in our own research group. For example, the synthesis of the sesquiterpene lactone, alliacolide (63), has been carried out by means of an intramolecular radical cyclisation of the iodo-lactone (62) (Scheme 25)[81]. Radicals have also been used to form the C ring of capnellenediol (64)[82] and the C ring of isoamijiol (65)[83]. Other work has demonstrated the use of allenes as radical traps[84] and, more recently, the use of cobalt(I) species[85]. Cobalt(I) can be used to generate a radical which will then add to a double bond. The product radical thus formed is then trapped by the cobalt species allowing further manipulation (Scheme 26).

In common with other research groups working in this area, interest had been confined to the synthesis of small rings. Indeed literature examples of the use of radicals in the synthesis of larger rings have been conspicuous by their absence. There are, however, two significant exceptions. The



(53)

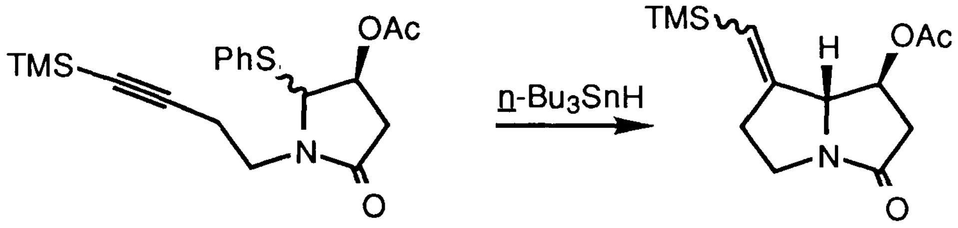
Scheme 20



(54)

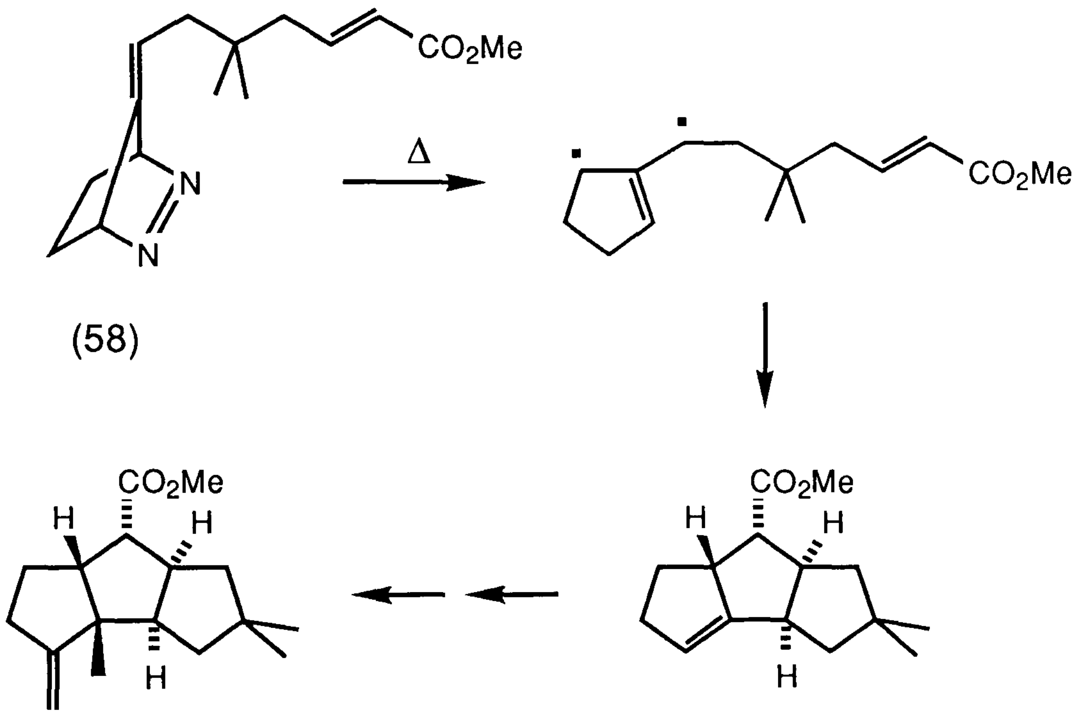
(55)

Scheme 21



(56) (57)

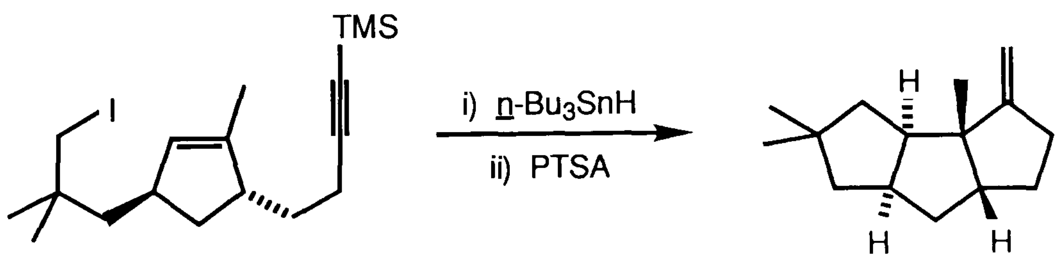
Scheme 22



(58)

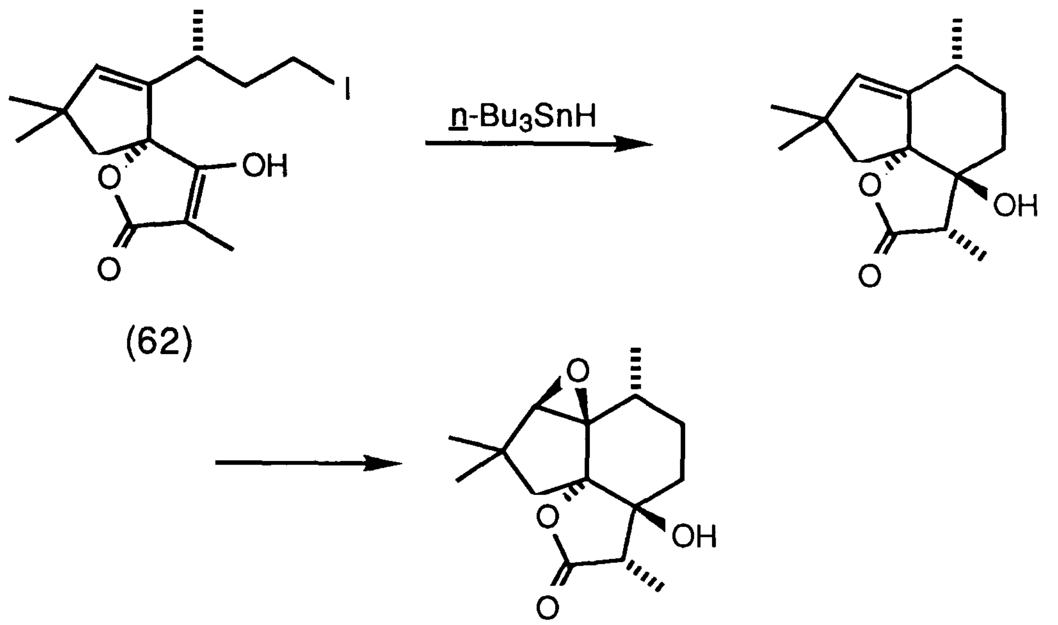
(59)

Scheme 23



(60) (61)

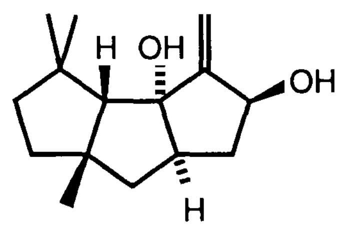
Scheme 24



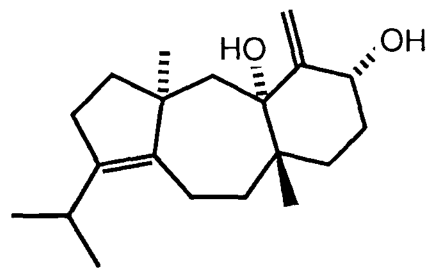
(62)

(63)

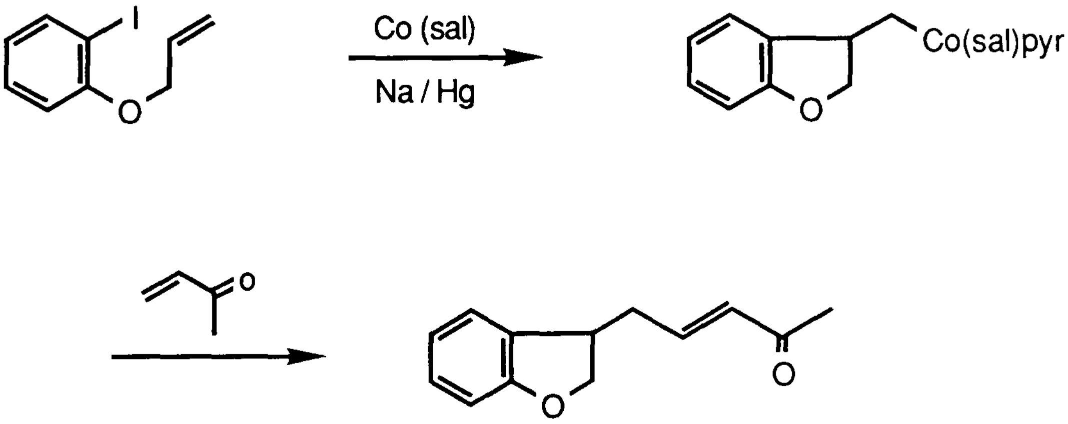
Scheme 25



(64)



(65)

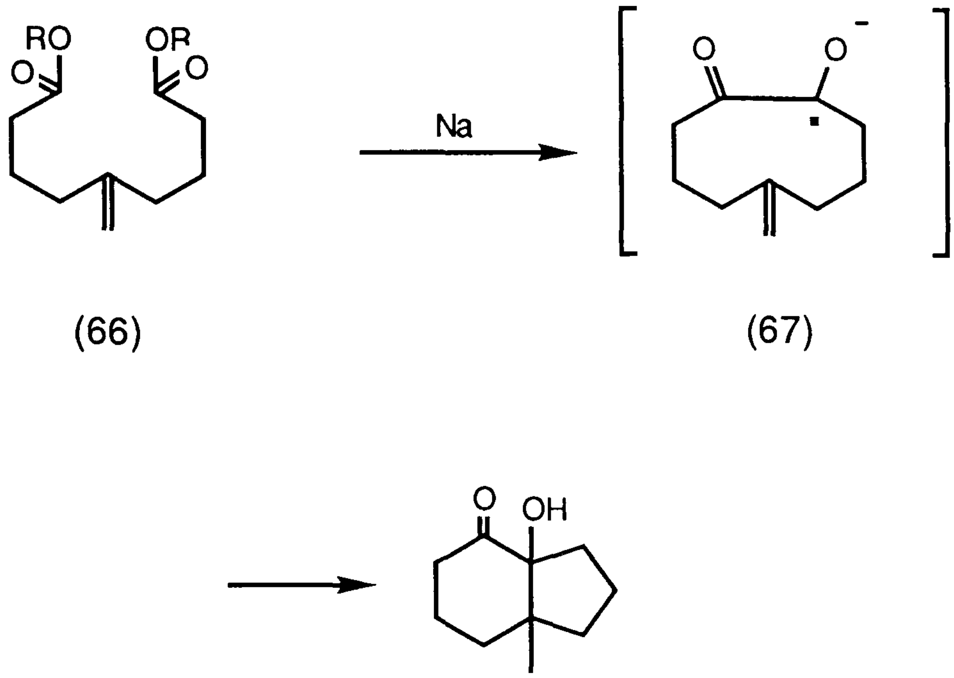


Scheme 26

acyloin condensation is considered to proceed *via* a ketyl radical[86]. This has been confirmed by the fact that the olefinic diester (66) (Scheme 27) undergoes a tandem cyclisation by intramolecular trapping of the intermediate alkoxy radical anion (67)[87]. It has also been suggested that the coupling of dicarbonyl compounds using low valent titanium to give cyclic olefins is radical in nature (Scheme 28)[88]. Both these methods have been very important synthetically for the preparation of medium and large rings[89]. However the conditions required are vigorous and strongly reducing, and this has imposed limitations on their use.

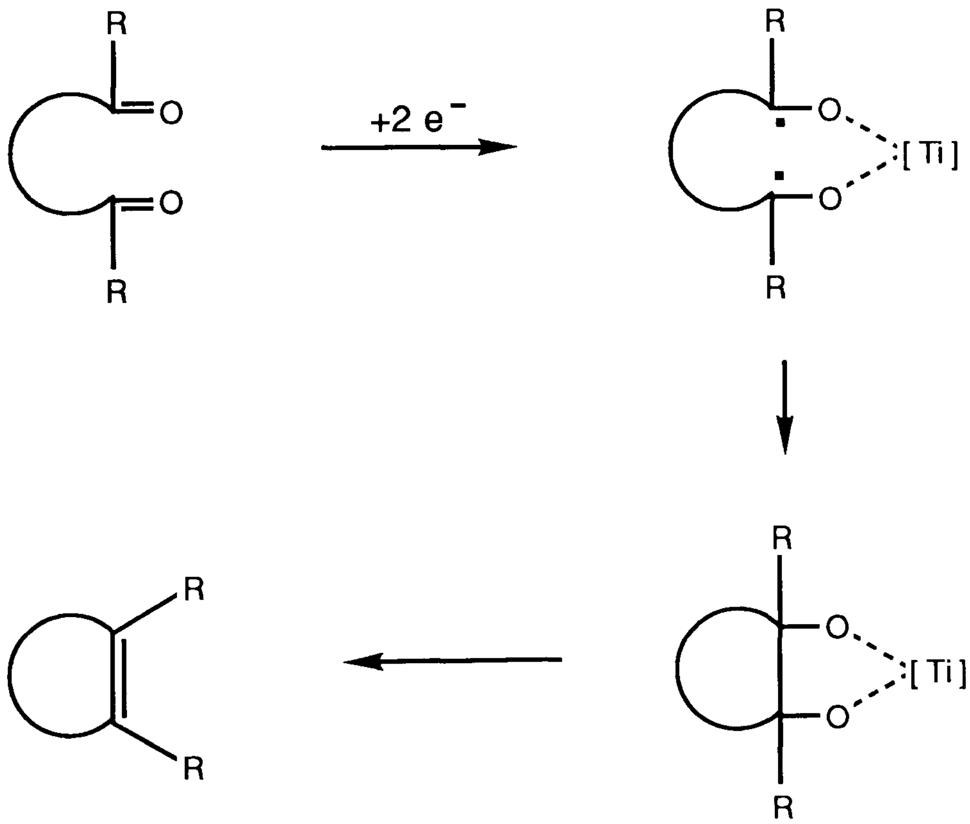
Although many methods for the generation of radicals under mild methods are now known, their use in the synthesis of medium or large rings is exceptional. 7-Membered rings can be prepared, however, when a fused β-lactam ring is present as the additional strain can lead to 7-*endo* cyclisation being favoured over 6-*exo* cyclisation (Scheme 29) depending on the nature of substituent R[90]. A rare example of medium ring synthesis using radicals is the cyclisation of the aromatic iodide (68) (Scheme 30)[91]. This method, which has been used to prepare 6-, 8- and 10-membered rings, can be considered to involve attack by a photolytically generated radical on an enolate anion.

In general, however, it has been found that radicals do not offer a synthetically useful route to the preparation of medium sized rings[92] and in 1985, when I began my studies, the same was thought to apply to the preparation of large rings. Despite this we felt that the use of radicals in the synthesis of large rings was of sufficient importance to merit a serious

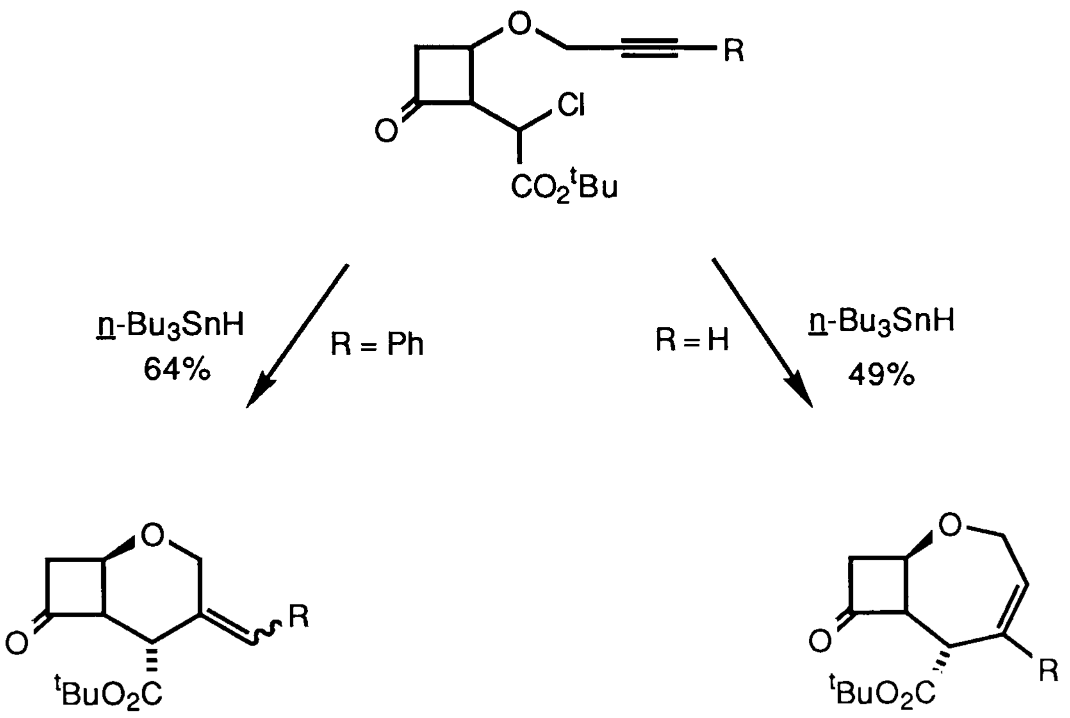


(66) (67)

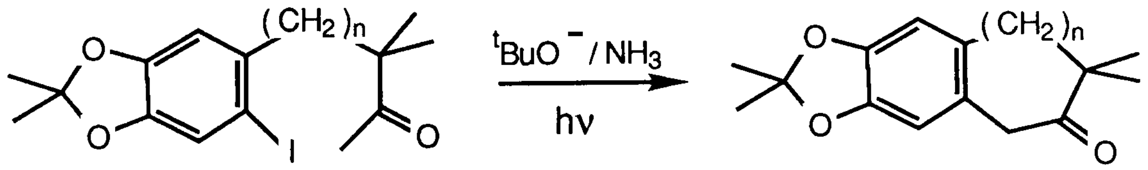
Scheme 27



Scheme 28



Scheme 29



(68)

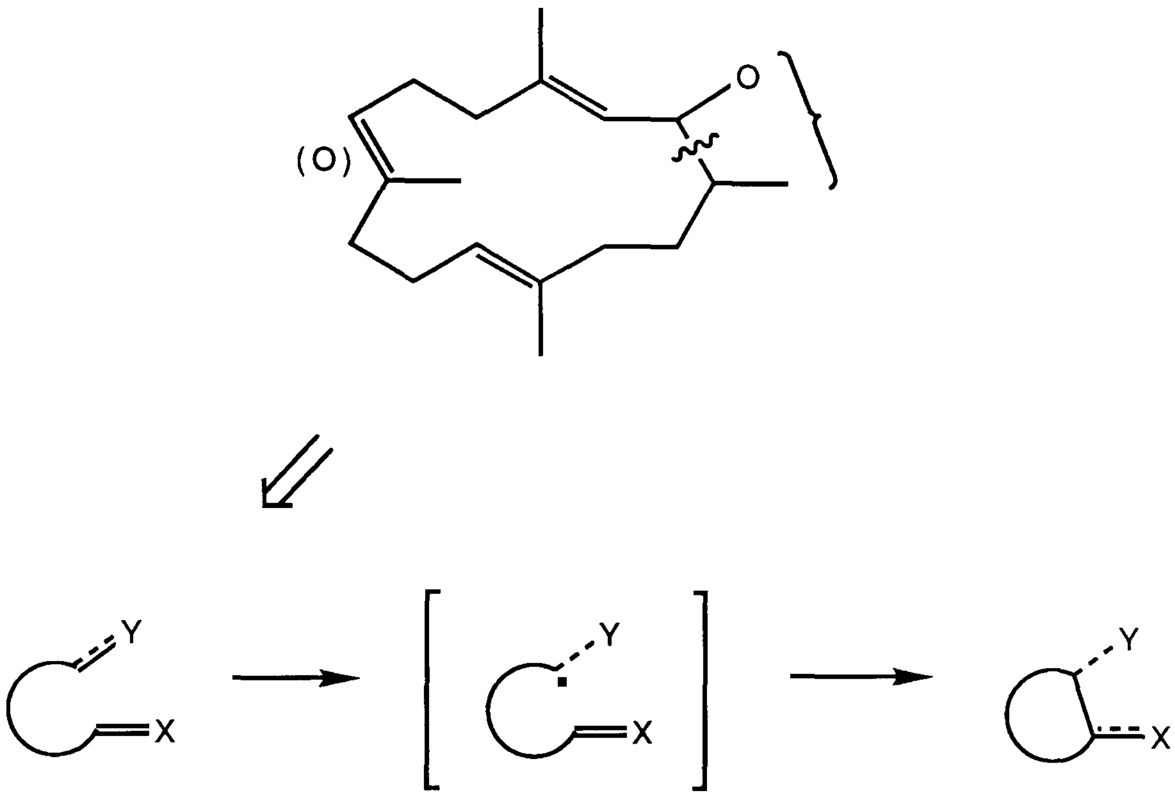
	Yield	Ring size
n = 1	99%	6
n = 3	73%	8
n = 5	35%	10

Scheme 30

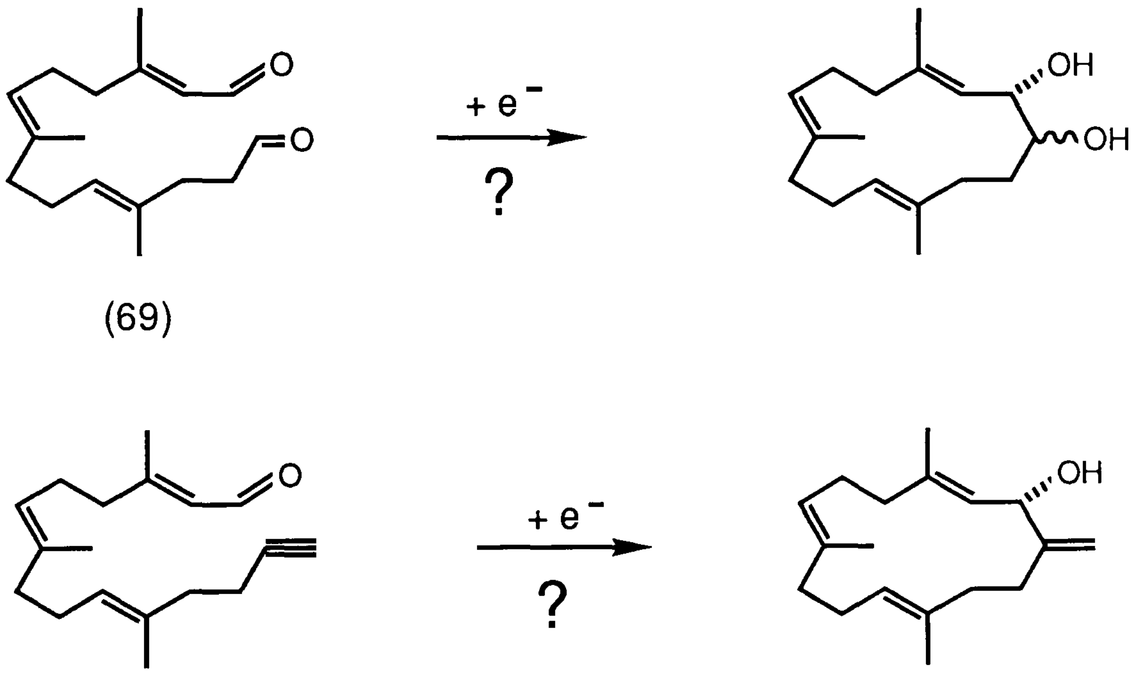
investigation. Thus we began to consider a radical cyclisation as the key step of a cembranoid synthesis.

In considering a radical macrocyclisation approach to deoxysarcophine (Scheme 31), functional groups were required from which a radical could be generated (Y) and by which a radical could be trapped (X). Radicals have been generated from and trapped by a wide range of functional groups[93]. An initial disconnection of deoxysarcophine (Scheme 31) suggested the use of a carbonyl group from which an alkoxide radical anion could be generated. This would have the advantage of leaving oxygen functionality at the required position after cyclisation. Of the possible radical traps an acetylene seemed preferable to an olefin on the grounds that, after cyclisation, this would leave functionality from which a dihydrofuran ring could be elaborated. An alternative approach considered was the use of a second carbonyl group which would also leave functionality, after cyclisation, that could be elaborated. Thus our initial approach focused on the possible cyclisation of the dialdehyde (69) and the acetylenic aldehyde (70) (Scheme 32).

Firstly, however, it seemed prudent to investigate some model systems. The first problem was to ascertain the suitability of generating an alkoxide anion radical from an α,β-unsaturated aldehyde. Much work has been carried out in the area of electropinacolisation and a variety of substrates have been investigated[94] including a number of highly conjugated aldehydes[95,96]. Two successful methods for the coupling of retinal (71) to give retinal pinacol (72), for example, were of particular interest as they specifically favoured 'head-to-head'



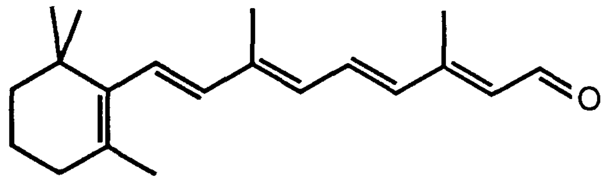
Scheme 31



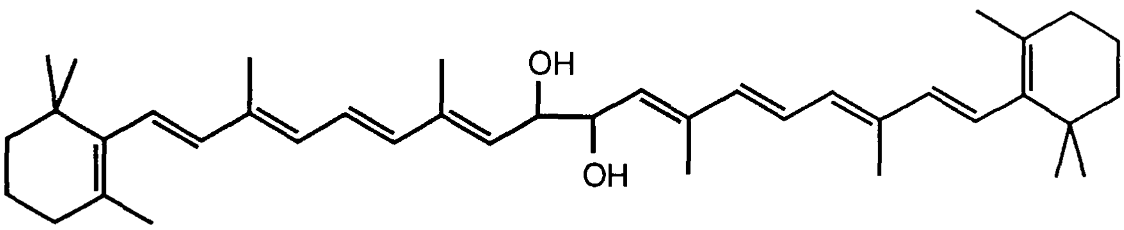
(69)

(70)

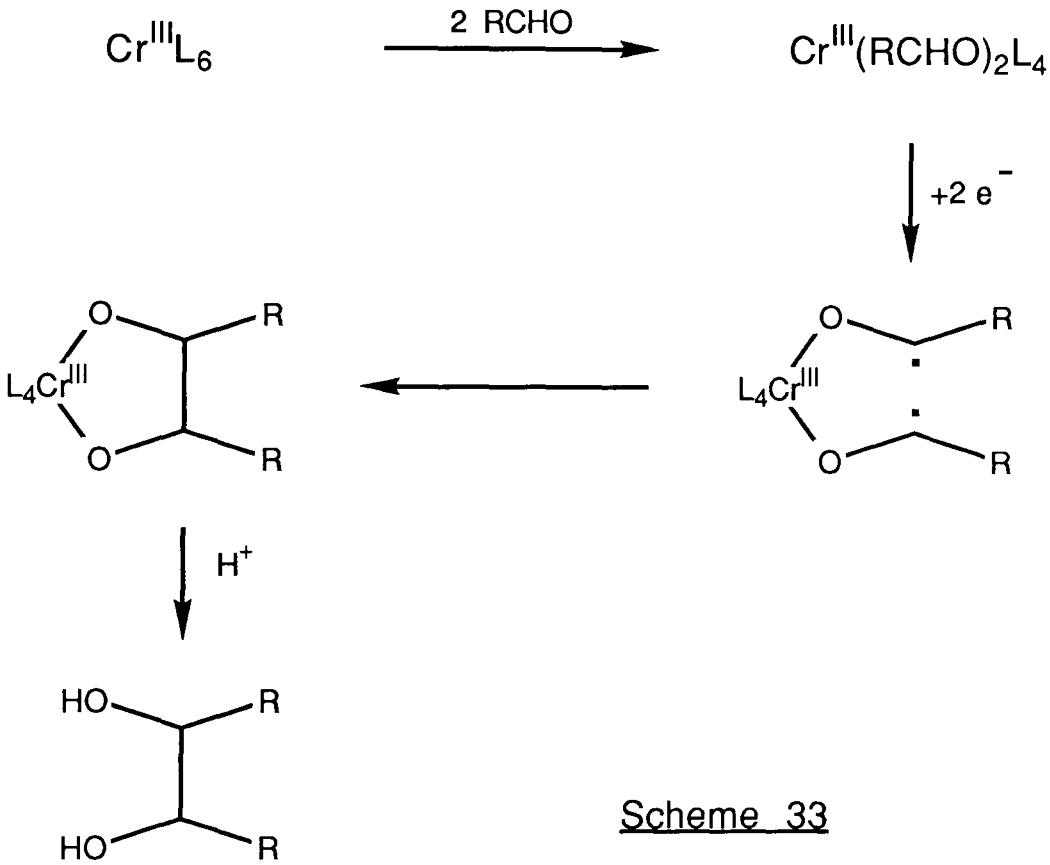
Scheme 32



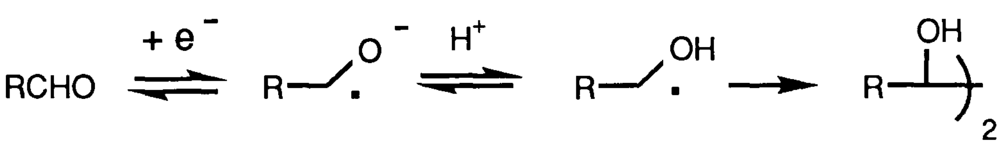
(71)



(72)



Scheme 33



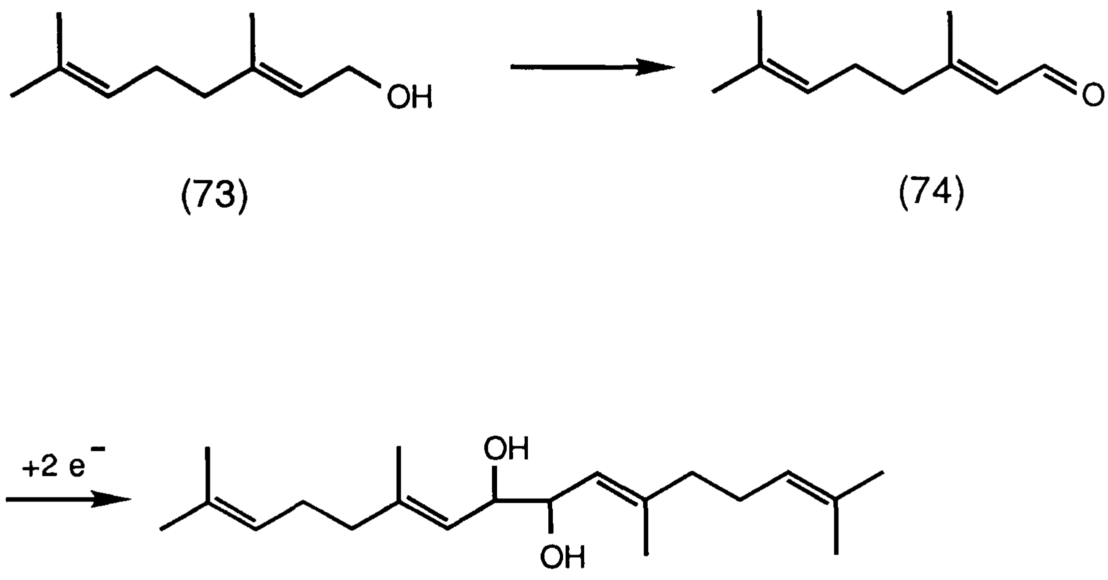
Scheme 34

coupling[97]. Firstly, chromium(III) has been used to assist coupling by first complexing to the aldehyde. This complex has a lower reduction potential than the uncoordinated aldehyde, so reduction to the alkoxide radical anion is assisted. Also the chromium ion can coordinate to two radicals so that dimerisation is favoured (Scheme 33)[95]. Secondly, diethyl malonate has been used as a weak proton source and been found to promote dimerisation (Scheme 34)[96]. Neither of these methods have previously been used to couple a simple α,β-unsaturated aldehyde.

A suitable model α,β-unsaturated aldehyde was E-citral (74). This was readily prepared from geraniol (73) by oxidation with manganese dioxide. Subsequent electroreduction at -1.0V in the presence of chromium trichloride gave the desired pinacol product (75) in 20% isolated yield (Scheme 35). Use of diethyl malonate as a proton source and an electrochemical reduction potential of -1.75V again gave the dimeric diol but in a reduced yield of 12%. These preliminary results confirmed that an α,β-unsaturated aldehyde would be a suitable function from which to generate an alkoxide anion radical and also offered hope that a cyclic diol might be formed via electropinacolisation of a suitable dicarbonyl precursor (69) (Scheme 32).

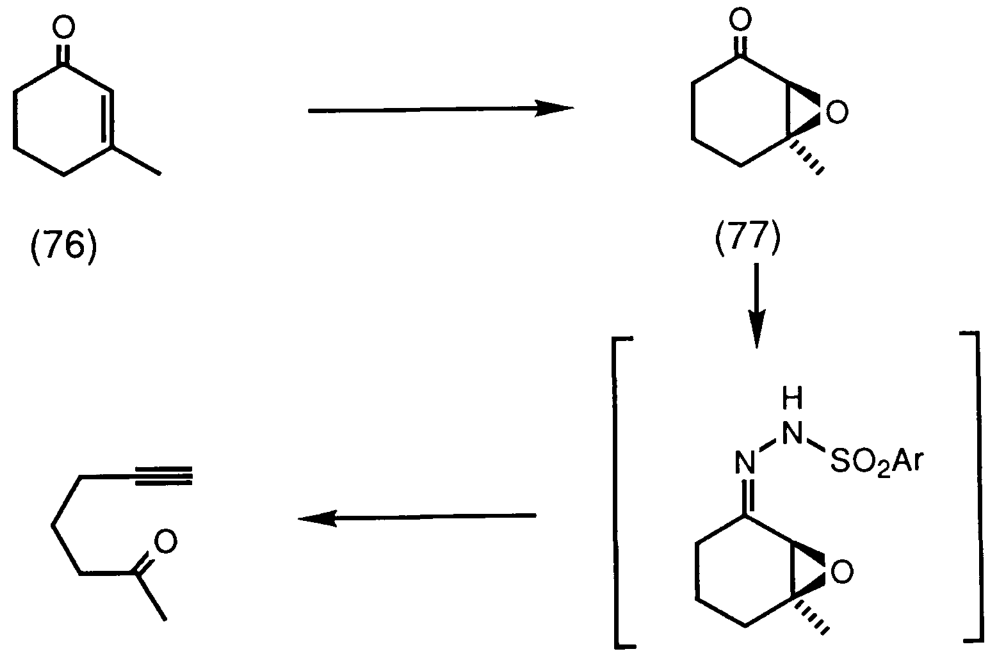
At this stage it seemed judicious to carry out a brief study on a model system to ascertain the limitations on ring size of a reductive cyclisation methodology[98]. The model system chosen was the series of acetylenic ketones (78, 83 and 84) which could be easily prepared.

The acetylenic ketone (78) was prepared as follows (Scheme



(73) (74) (75)

Scheme 35



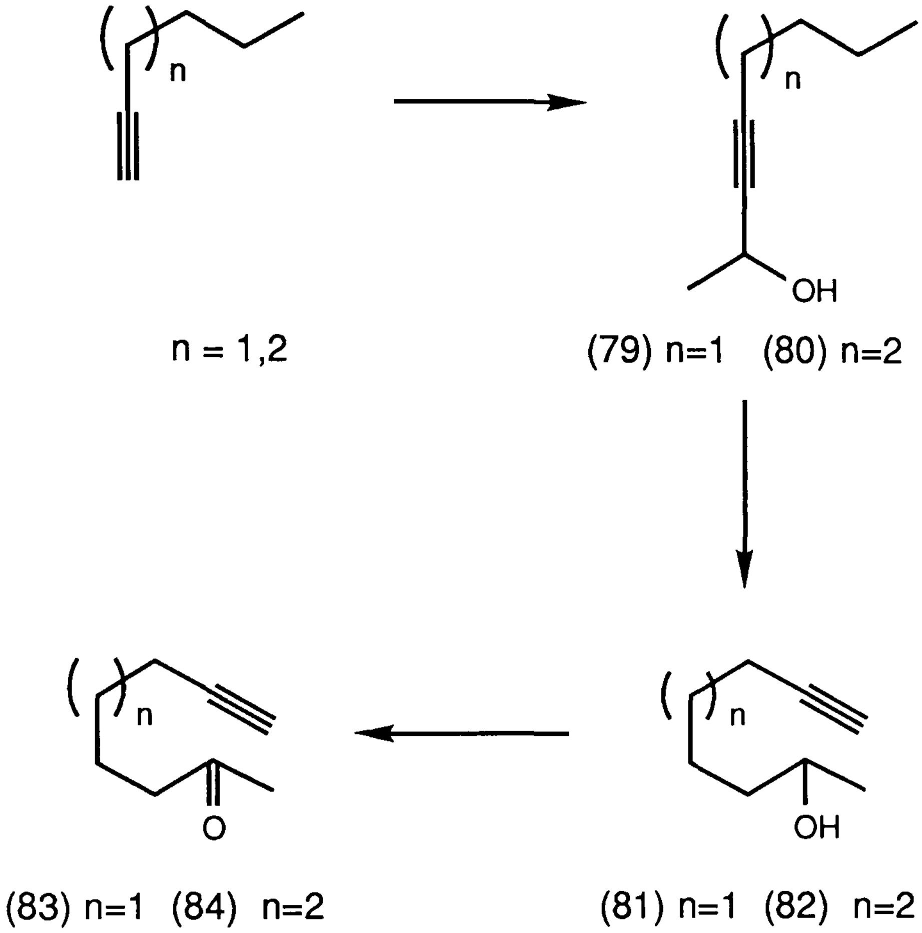
(76) (77) (78)

Scheme 36

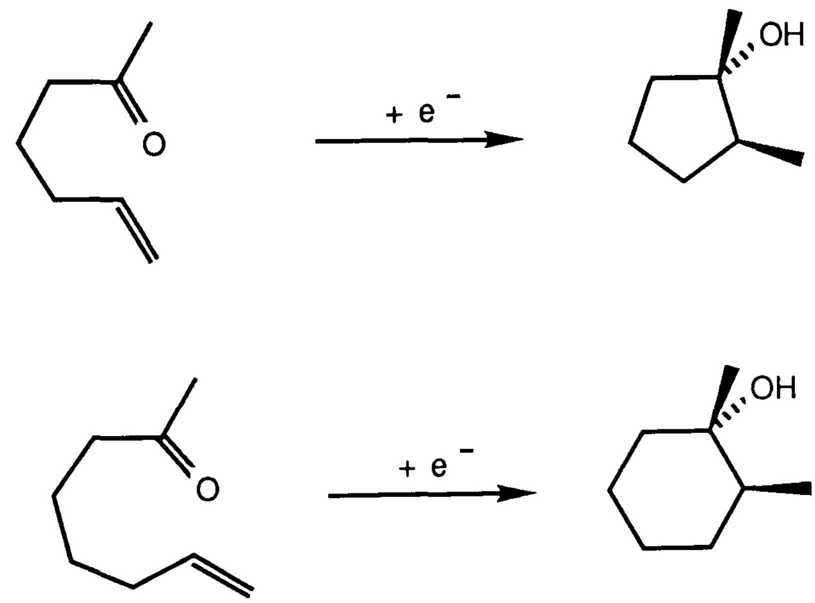
36)[99]. Treatment of 3-methylcyclohex-2-en-1-one (76) with a basic solution of hydrogen peroxide in methanol gave the epoxy ketone (77). The epoxy ketone was then subjected to an Eschenmoser fragmentation by initial treatment with p-toluenesulphonylhydrazine at -15°C followed by basic work up to give the desired acetylenic ketone (78).

The homologous acetylenic ketones (83 and 84) were prepared from hex-1-yne and hept-1-yne respectively (Scheme 37). Deprotonation of the acetylene with one equivalent of n-butyllithium at -15°C followed by addition of acetaldehyde first gave the acetylenic alcohol (79 and 80). Isomerisation to the terminal acetylene was then readily achieved by means of an 'acetylenic zipper' reaction using sodium hydride and 1,3-diaminopropane (NAPA) at 50°C for 15h[100]. Conversion to the required acetylenic ketone (83 and 84) was finally achieved by treatment with pyridinium chlorochromate.

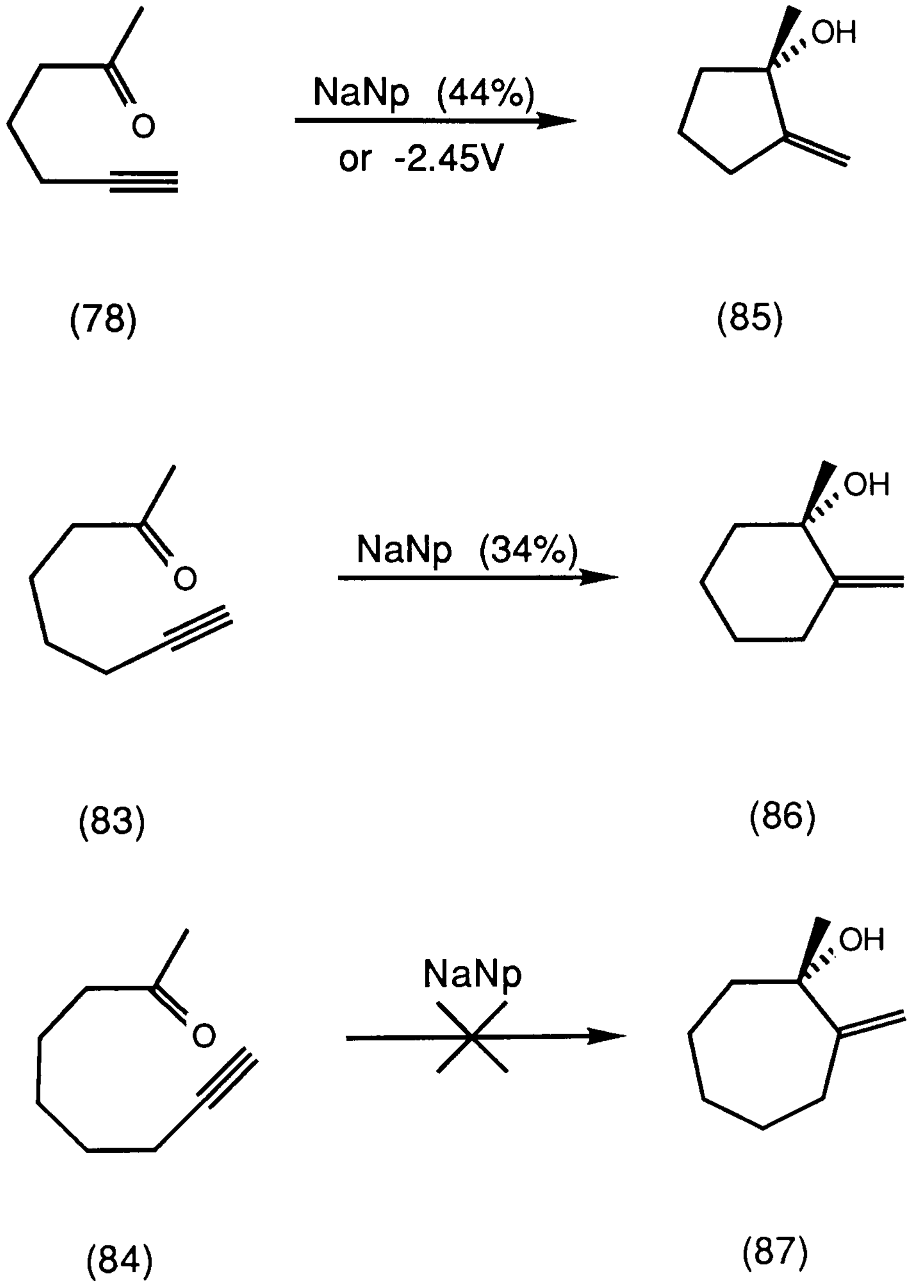
The reductive cyclisation of keto-acetylenes and keto-olefins has been much studied[98]. For our puposes mild conditions were considered preferable, so the methods of choice were electrochemistry or the use of sodium naphthalene radical anion rather than the more vigorous conditions of dissolving metal reductions. Electroreductions of the acetylenic ketone (78) at -2.45V using tetraethylammonium tosylate in dimethylformamide as electrolyte gave the desired cyclopentanol (85) in 11% isolated yield (Scheme 39). TLC analysis of the crude reaction mixture had suggested that this was infact the major product and it was therefore felt that the low yield reflected difficulty in isolation and loss due to volatility



Scheme 37



Scheme 38



Scheme 39

(82) (88)

rather than the existence of an alternative reaction pathway.

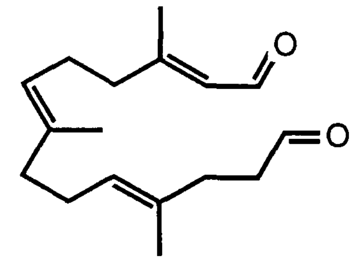
Treatment of the same acetylenic ketone (78) with a solution of sodium naphthalene radical anion in tetrahydrofuran proved more successful giving an isolated yield of 44% of the desired cyclopentanol (85). Treatment of the homologous acetylenic ketone (83) with sodium naphthalene radical anion likewise gave the desired cyclohexanol (86) though in a reduced 34% isolated yield. However treatment of the homologous acetylenic ketone (84) with sodium naphthalene radical anion failed to give any of the desired cycloheptynol (87), and only gave a complex mixture containing the acetylenic alcohol (82) and the naphthalene adduct (88) as identifiable products.

These results are in line with the observations of Shono who has studied the electrochemical reductive cyclisations of an analogous series of olefinic ketones (Scheme 38) and found that only 5- and 6-membered rings could be formed (in 66% and 50% yields respectively)[101].

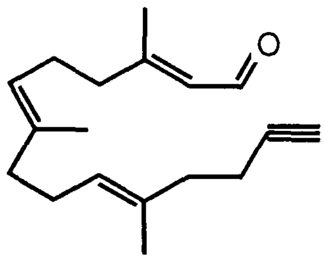
These results did not augur well for larger ring synthesis using reductive cyclisation methodology. However the acetylene carbonyl compound (70), which it had been planned to investigate, did differ in three important respects from the model system studied. Firstly, the precursor (70) is an aldehyde rather than a ketone; secondly, it is α,β-unsaturated (thus any radical generated will be allylic and so stabilised); and finally, the presence of additional double bonds in the carbon chain may provide a degree of rigidity thus favouring the approach of alkoxide radical anion and acetylene functions. Clearly it would have been possible at this stage to have launched into further model studies to investigate the effect of some or all of these features, but it was felt more appropriate at this point in time to move directly to studies on the precursors (69) and (70).

The synthesis of these precursors, however, would not be trivial, containing as they do three trisubstituted double bonds. Rather than assemble these molecules from smaller fragments it was decided to attempt to modify the structure of the natural diterpene geranylgeraniol (89) (Scheme 40). This diterpene is not commercially available but analytical work in our research group had shown geranylgeraniol to be a constituent of the oleoresin obtained from the dried seeds of the tropical shrub Bixa orellana[102]. These seeds are readily available commercially, being a source of the 'natural' food colouring annatto which has long been used to colour cheeses such as red Leicester and more recently is being used as a replacement for 'artificial' colourings in many other foodstuffs[103].

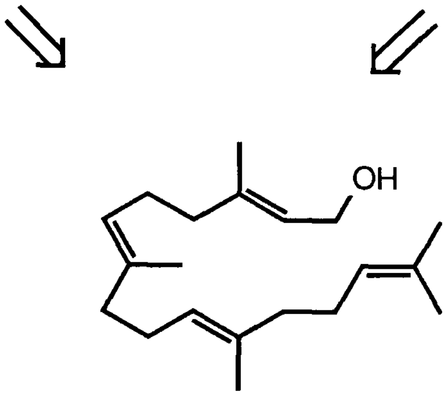
Extraction of the dried seeds in light petroleum ether followed by evaporation left a dark brown oleoresin. The lighter fractions could be readily separated by flash-distillation at reduced pressure to give a yellow-orange oleoresin. This was then purified by column chomatography on silica to give geranylgeraniol (89). The geranylgeraniol content of the seeds varied greatly from batch to batch (presumably due to differing origins and ages of dried seeds). Thus geranylgeraniol was observed to vary between 0.21% and 0.57% by weight of dried Bixa seeds, and between 12.5% and 37.5% by weight of oleoresin. Comparison of CMR spectra with



(69)

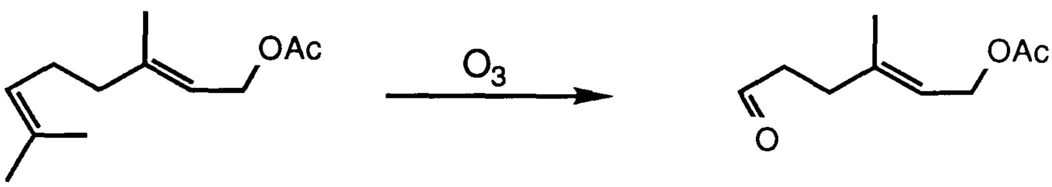


(70)

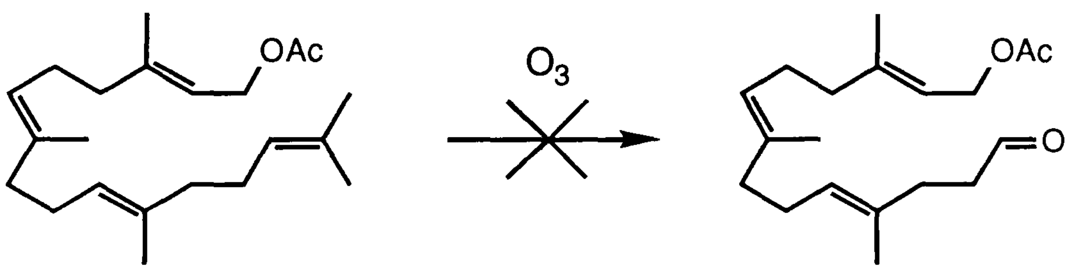


(89)

Scheme 40



(90) (91)



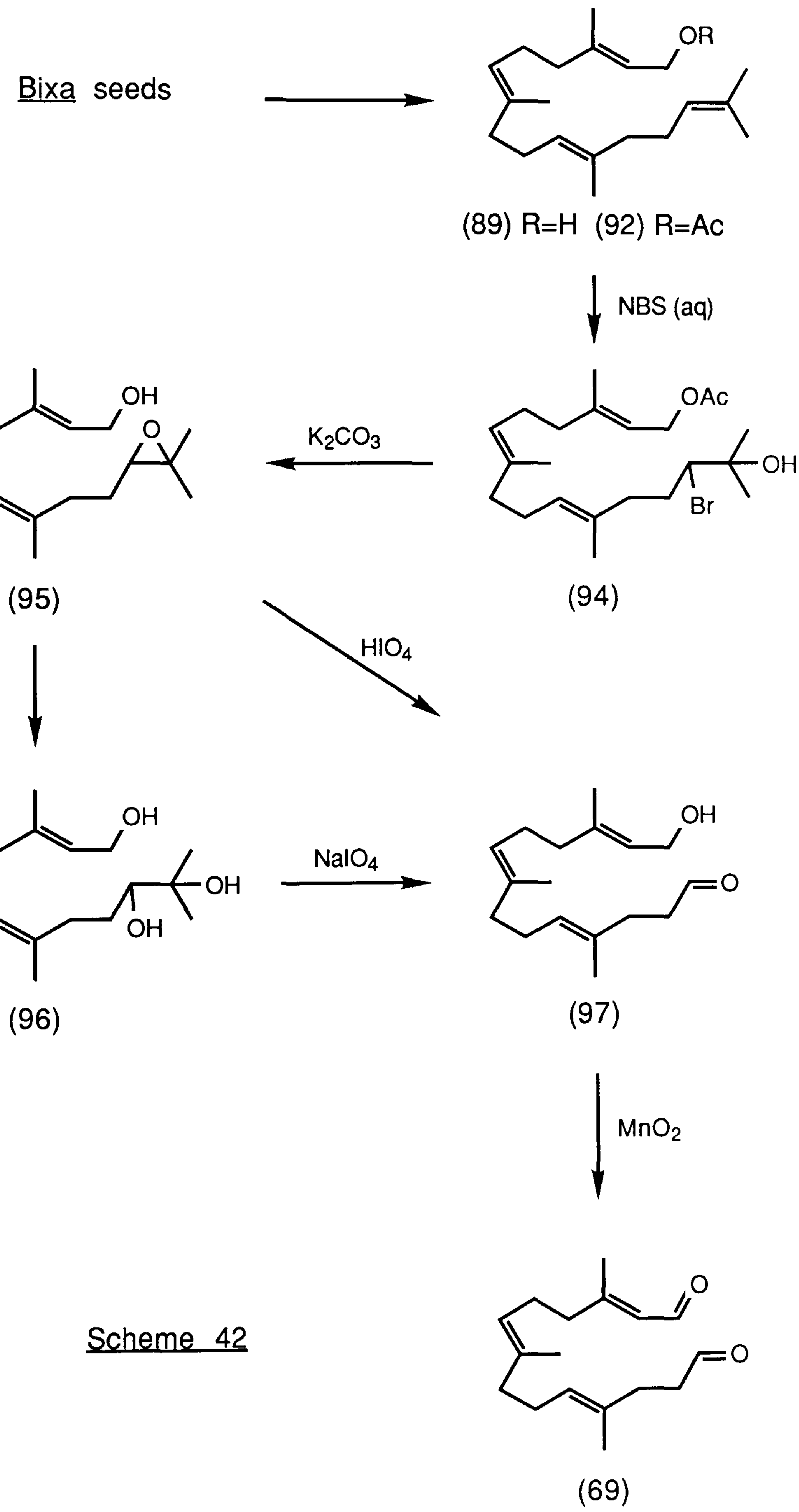
(92) (93)

Scheme 41

literature data[104] confirmed that the geranylgeraniol was indeed the required all-*E* isomer.

With a good stock of geranylgeraniol isolated, a method was then required for oxidative cleavage of the terminal double bond in order to generate the required dialdehyde precursor (69). Ozonolysis has been used successfully in the oxidative cleavage of the terminal double bond of the monoterpene derivative geranyl acetate (90) to give the aldehyde acetate (91) (Scheme 41)[105]. Although we found this result repeatable, it did not prove possible to extend this methodology to the diterpene system -only a complex mixture of products being obtained. This presumably reflects the outcome of statistical attack on the four double bonds.

A more promising approach was based on the route used by Van Tamelen to generate the terminal epoxide of geranylgeranyl acetate[106]. Geranylgeraniol (89) was therefore converted to the acetate (92) (Scheme 42) by treatment with acetic anhydride in pyridine. A dilute solution of the acetate (92) in tetrahydrofuran was then 'titrated' with water until the solution just became cloudy. Treatment with one equivalent of *N*-bromosuccinimide at 0°C gave, after purification, a 46% yield of the terminal bromohydrin (94). Base induced ring closure using potassium carbonate in methanol also led to deprotection of the acetate functionality giving the hydroxy terminal epoxide (95) in 95% yield. Initially cleavage of the epoxide was attempted as a two step process by first converting the epoxide to the diol (96) and then cleaving the diol with sodium periodate[107]. It proved more satisfactory however to carry out

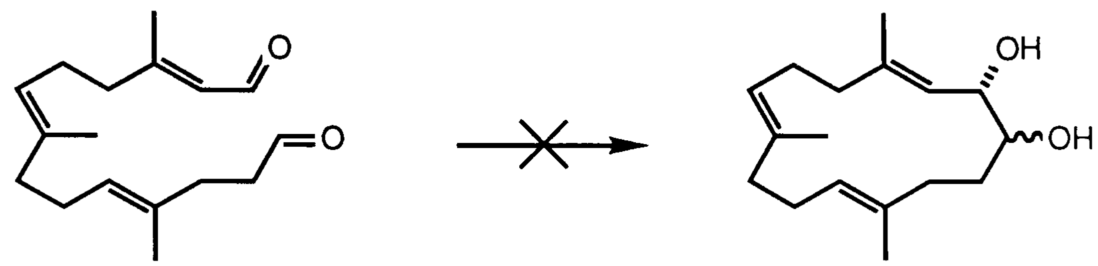

Bixa seeds
OR
(89) R=H (92) R=Ac
NBS (aq)
OAc
OH
Br
(94)
K_2CO_3
OH
O
(95)
HIO_4
OH
OH
OH
(96)
$NaIO_4$
OH
O
(97)
MnO_2
O
O
(69)

Scheme 42

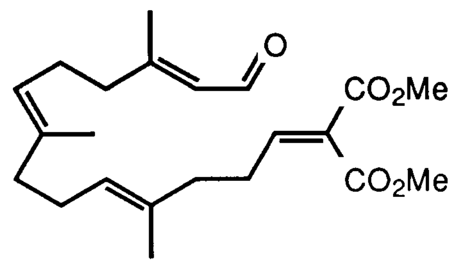
both steps at once by treatment of the epoxide (95) with periodic acid in tetrahydrofuran[108], which gave directly the hydroxy aldehyde (97) in 60% yield. Manganese dioxide oxidation then gave the required dialdehyde precursor (69).

With the dialdehyde precursor prepared, an investigation of the electropinacol cyclisation could be carried out. In order to favour intra- over intermolecular coupling it was important to maintain a high dilution of the dialdehyde during the reaction. Given the constraints on the size of electrochemical cells available, this was best achieved by slow addition using a syringe pump. In the light of our model studies the first attempt was made using chromium(III). However, slow addition of the dialdehyde (69) to an electrolyte solution of sodium perchlorate in dimethylformamide in the presence of chromium trichloride at a potential of -1.0V failed to give any of the desired product, only starting material being reclaimed. The likely problem in this case was reduction of the chromium species before significant dialdehyde had been added. Repetition of the electroreduction in the presence of dimethyl malonate instead of chromium(III), and application of a potential of -1.75V again failed to give the desired cyclised diol and instead gave, much to our surprise, the dimethyl malonate adduct (98) (Scheme 43). Attempts to carry out the cyclisation in the absence of either chromium(III) or dimethyl malonate also met with failure, giving only complex mixtures.

With this rather disappointing result, attention was turned to an acetylenic aldehyde precursor of the type (70). Recent work by Abidi[109] had suggested that methyl acetylenes could be

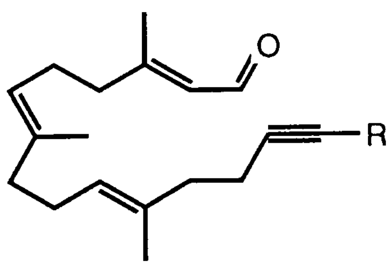


(69)

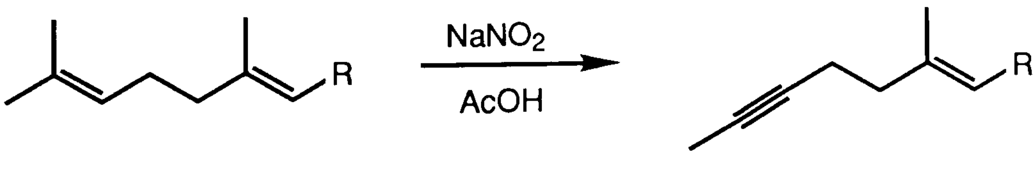


(98)

Scheme 43

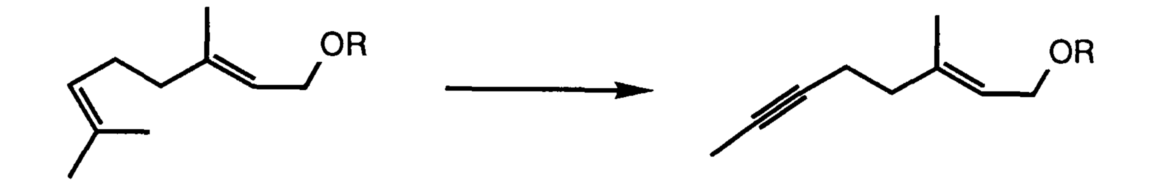


(70) R = H (99) R = Me

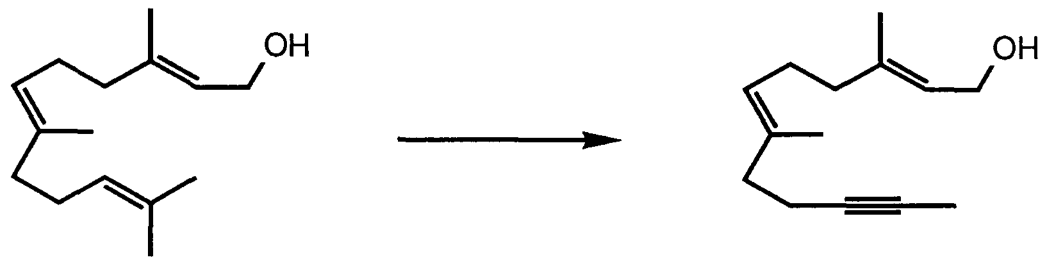


Scheme 44

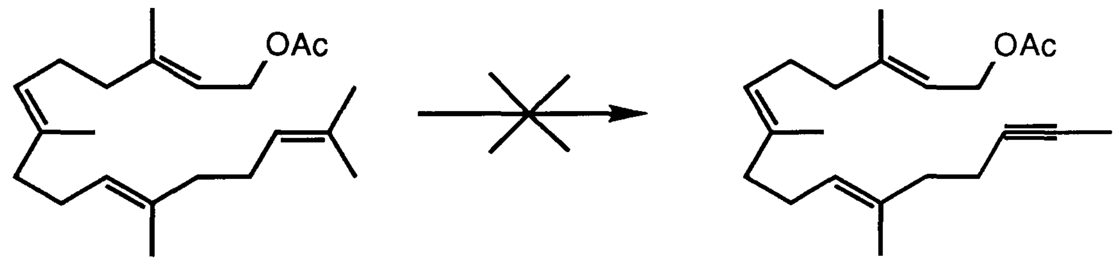
prepared directly from terpenes (Scheme 44). Of particular interest was that geraniol (73) was shown to react in 98% yield, and farnesol (102) in 30% yield to give the respective acetylenes (100, 103) (Scheme 45). Intrigued by the possibility of applying this reaction to prepare the acetylenic aldehyde (99) in only two steps from geranylgeraniol (89), we began a study of this reaction on a number of simple terpenes. However, our initial attempts to repeat Abidi's results proved only partially successful. Treatment of geraniol (73) with eleven equivalents of sodium nitrite in acetic acid at 0°C followed by heating at 60°C for 2h caused effervescence and the production of a brown gas and gave, after purification, the acetylenic alcohol (100) in only an 11% yield and as a mixture of *E* and *Z* isomers. The problem of geometric isomerisation could be avoided by initial protection of the alcohol as an acetate. Thus geranyl acetate (90), under the same conditions, gave the acetylenic acetate (101) in 10% yield. The presence of a triple bond was confirmed by CMR data (δ_c: 78.5, ⋮C; 76.1, ⋮C; 3.4, $\underline{C}H_3C$⋮ ppm) which also confirmed the geometric purity (δ_c: 140.7, :CMe; 119.5, :CH; 61.3, CH_2O ppm). Many attempts were made to improve the yields of these reactions but without success. Indeed Corey has subsequently repeated Abidi's work and also obtained substantially lower yields (*ca.* 33%) and these only after modification of Abidi's original procedure[110]. Corey has suggested a mechanism for this intriguing reaction (Scheme 46) involving stepwise addition of two nitro groups followed by oxidation and rearrangement with loss of carbon dioxide and nitric oxide to give the methyl acetylene (100). Support for



(73) R = H (90) R = Ac (100) R = H (101) R = Ac

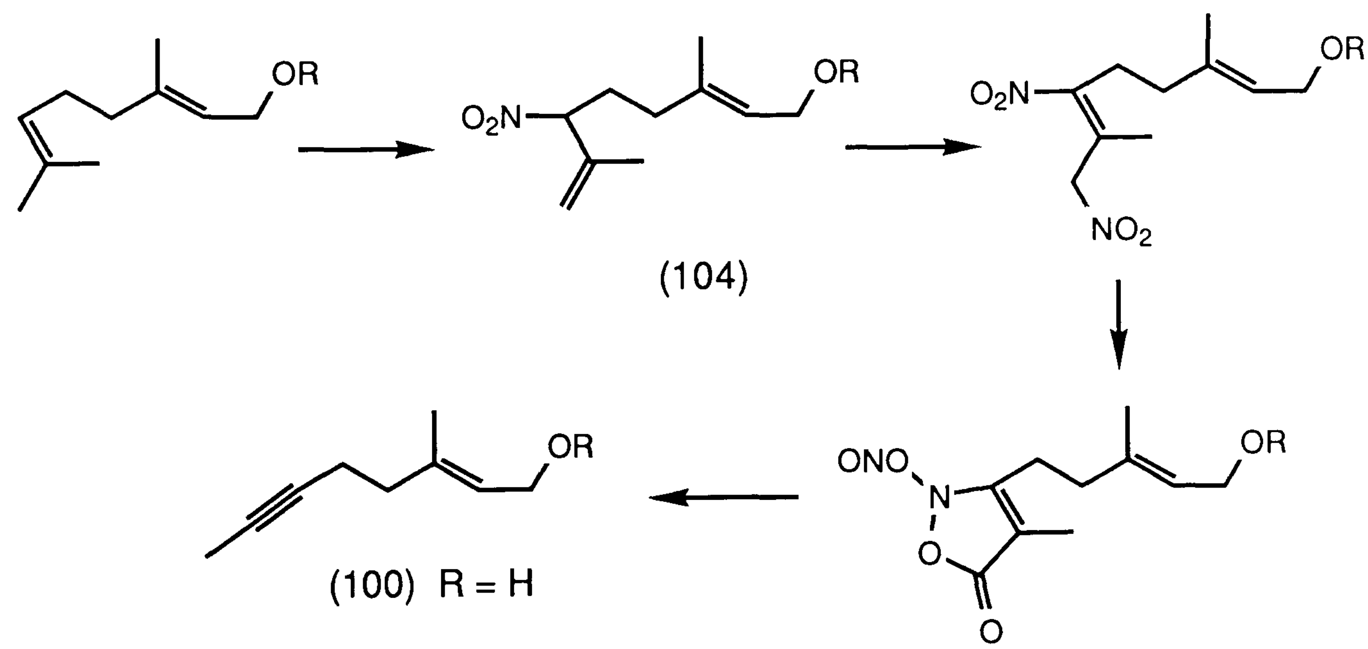


(102) (103)



(92)

Scheme 45



(104)

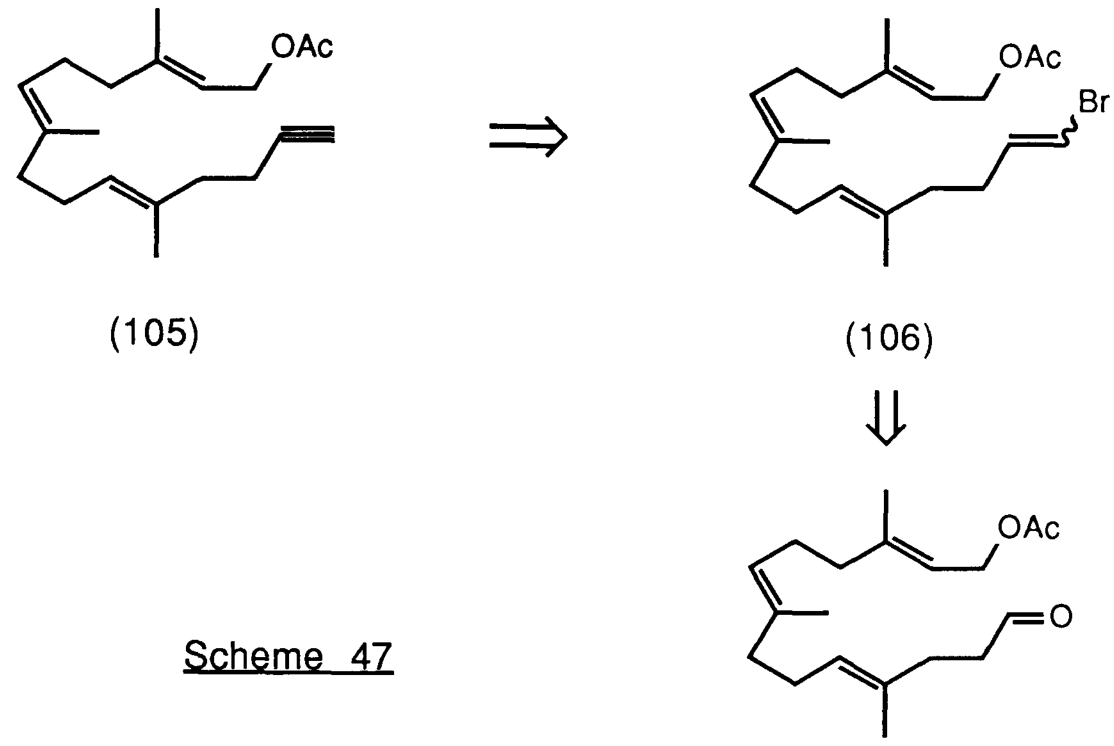
(100) R = H

Scheme 46

this mechanism is given by the isolation of the intermediate (104). Unfortunately our attempts to extend this method to either farnesol or geranylgeranyl acetate (92) proved completely unsuccessful.

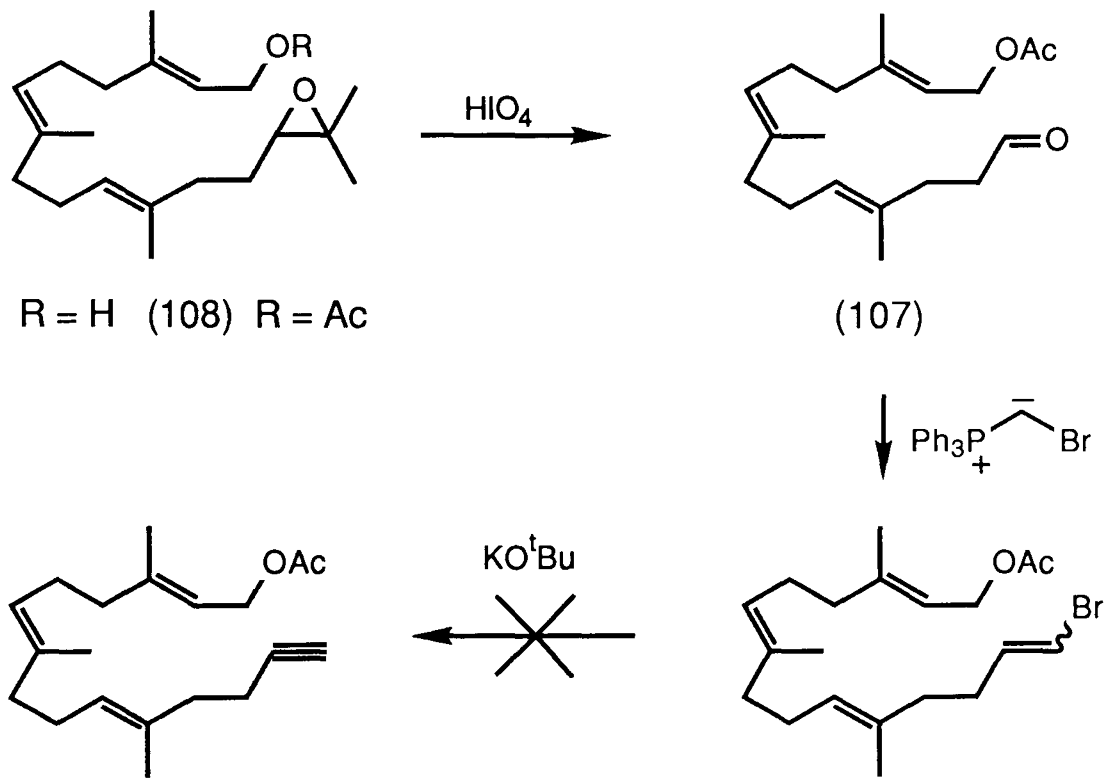
Our attention therefore turned to a more conventional approach based on the methodology already developed to prepare the dialdehyde (69). We planned to prepare the acetylene (105) from the vinyl bromide (106) which in turn could be prepared by a Wittig reaction on the aldehyde (107) (Scheme 47). It seemed sensible to first protect the hydroxy function before carrying out a Wittig reaction under strongly basic conditions. Hence the epoxy alcohol (95) (Scheme 48) was treated with acetic anhydride in pyridine to give the epoxy acetate (108). Cleavage of the epoxide ring using periodic acid in tetrahydrofuran as before then gave the aldehyde (107) in a yield of 84%. The required Wittig reagent was readily prepared from triphenylphosphine and dibromomethane by refluxing these compounds together in toluene for 24h (Scheme 49). The bromomethyltriphenylphosphonium bromide (110) thus formed was treated at -78°C with one equivalent of potassium t-butoxide in tetrahydrofuran to give a yellow solution of the ylid. Addition of the aldehyde (107) then gave the desired vinyl bromide (111) as a mixture of E and Z isomers in an isolated yield of 44%.

Vinyl bromides and acetylenes have previously been prepared by this method[112] and the literature suggested that the use of a second equivalent of potassium t-butoxide in this last step would lead directly to the required acetylene (109). When this conversion was attempted, however, no reaction beyond initial



(105) (106) (107)

Scheme 47



(95) R = H (108) R = Ac (107) (111) (109)

Scheme 48

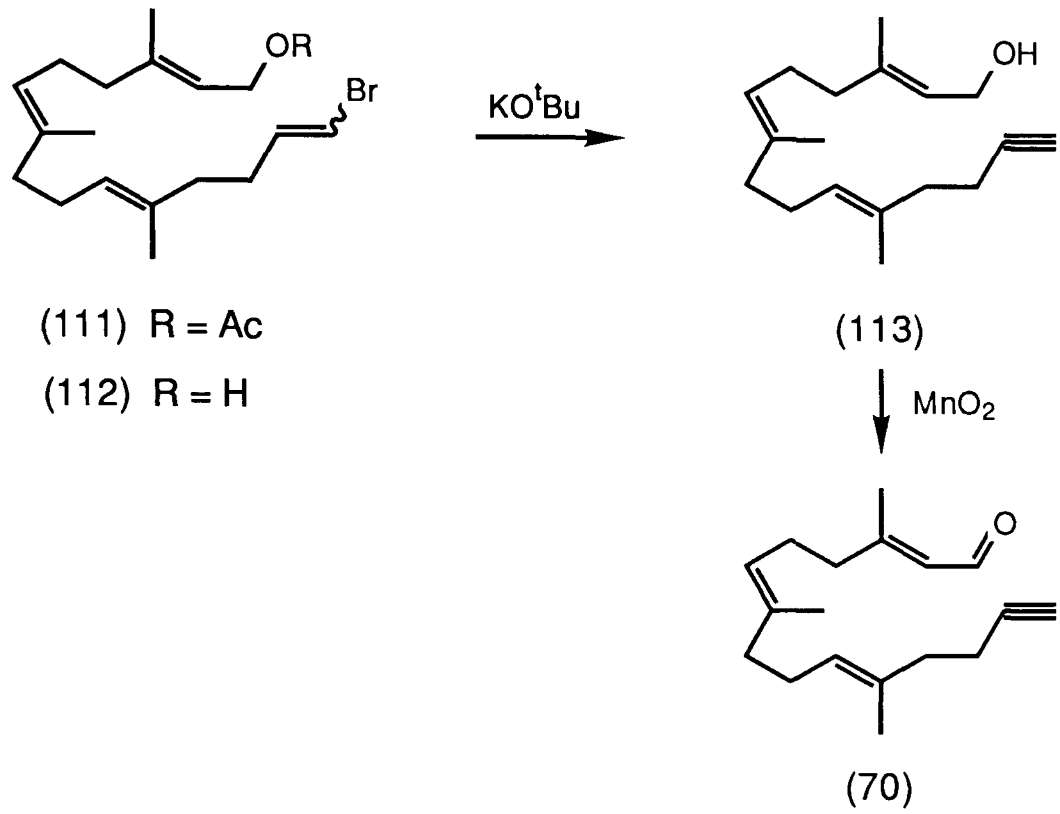
$$Ph_3P + CH_2Br_2 \longrightarrow [Ph_3PCH_2Br]^+Br^- \longrightarrow Ph_3\overset{+}{P}-\overset{-}{C}H-Br$$

(110)

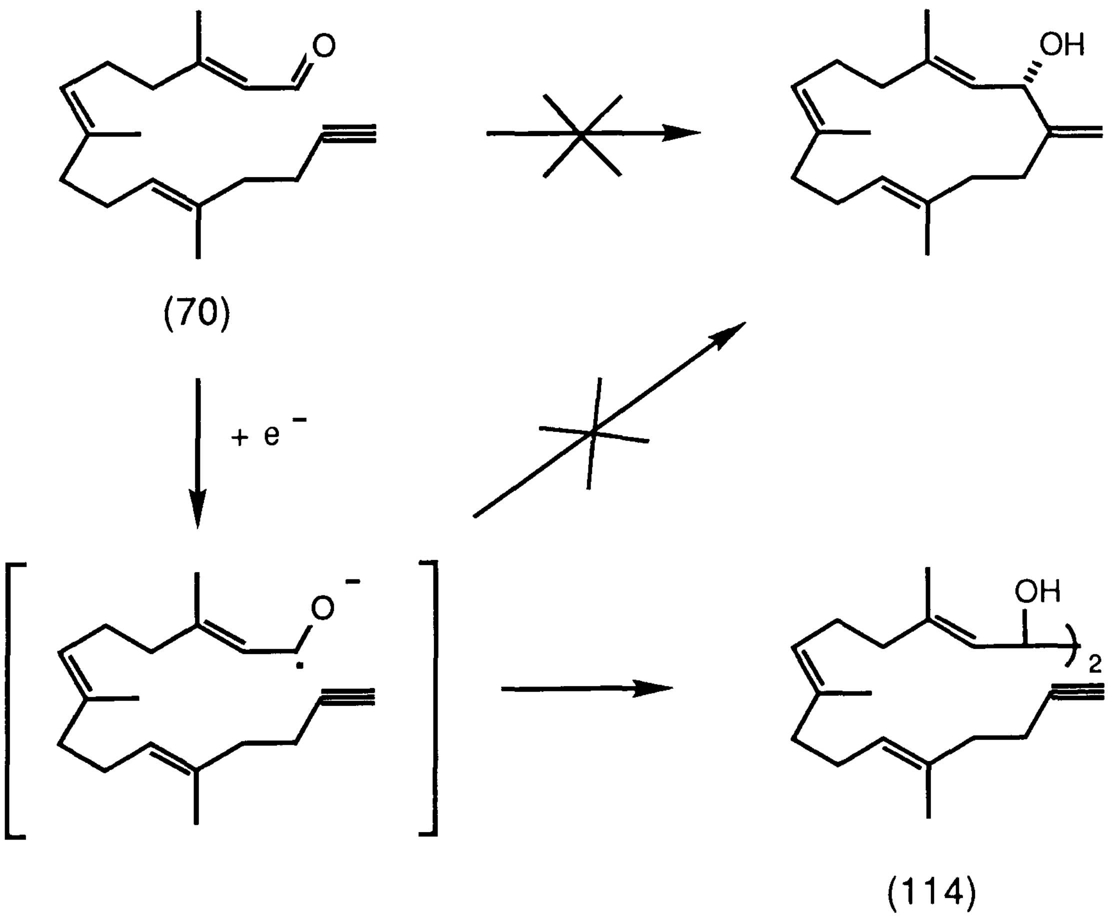
Scheme 49

formation of the vinyl bromide (111) was observed at -78°C and on warming to -25°C the bromide was observed to decompose to give a dark brown tar. This result was initially puzzling until a similar discolouration was observed to occur on treatment of ethyl acetate with potassium t-butoxide. It seemed probable, therefore, that the problem had been due to aldol type polymerisation of the acetate protecting group. This indeed seemed to be the case because deprotection of the acetate function of (111) (Scheme 50) using methanolic potassium carbonate to give the hydroxy vinyl bromide (112) and treatment with three equivalents of potassium t-butoxide at -25°C in tetrahydrofuran then smoothly gave the hydroxy acetylene (113) in 75% yield. Oxidation with manganese dioxide finally gave the required acetylenic aldehyde (70).

With the acetylenic aldehyde precursor (70) prepared, an attempt was made to carry out an electrochemical reductive cyclisation. Again a high dilution in the electrochemical cell was achieved by means of slow addition using a syringe pump. Thus the acetylenic aldehyde (70) was slowly added over 9h to an electrolyte solution of sodium perchlorate in dimethylformamide at a potential of -1.75V. However, after work up, TLC analysis showed a complex mixture of products and PMR analysis of this mixture showed the absence of any signals due to the required methylidene group. Careful analysis and purification of the crude reaction product did, however, identify the pinacol coupled dimer (114) (Scheme 51) in 11% isolated yield. A number of further attempts were made to achieve the desired cyclisation, but without success.



Scheme 50

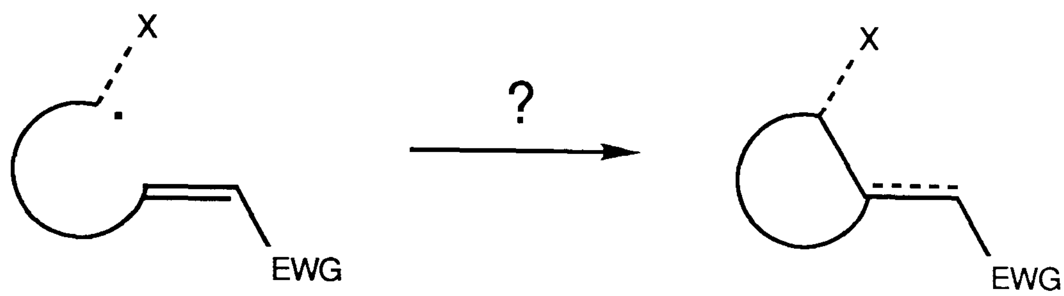


Scheme 51

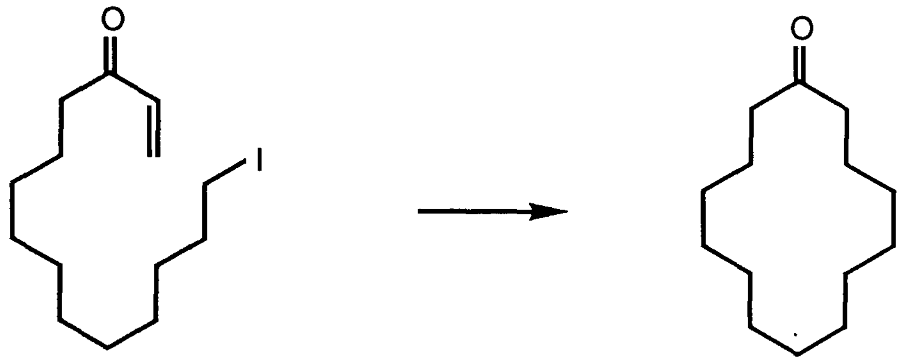
This result was of some interest as it suggested that the required alkoxide radical anion had been formed (Scheme 51) and had survived for long enough to react with another molecule, despite the high dilution, but had not been able to react intramolecularly with the acetylene functionality. We considered therefore that an isolated acetylene was not a sufficiently good radical trap in this system to allow cyclisation. As carbon radicals are nucleophilic in character it occurred to us that the acetylene could be activated by means of an electron withdrawing group (Scheme 52)[113]. This approach seemed further justified by a paper that appeared at this time in which it was reported that the iodo-enone (115) (Scheme 53) could be cyclised by means of a radical reaction to give cyclotetradecanone (116) in 63% yield[114].

With this in mind we set about re-designing a cembranoid precursor which would incorporate the required features. It was decided to use a carbonyl group as the activating group and so it seemed wise to use a different functionality from which to generate the radical. The halo-enal (117, 118) (Scheme 54) was chosen as a suitable precursor, containing an activated olefin as a radical trap and a halide function which, on treatment with tributyltin hydride and catalytic azodiisobutyronitrile, would generate a radical. It was hoped that this precursor could be prepared from geranylgeraniol (89) (Scheme 55) *via* allylic oxidation and simple functional group interconversions.

For the allylic oxidation of geranylgeranyl acetate, the use of selenium dioxide was first considered. This is a useful reagent for the allylic oxidation of olefins[115] and has been

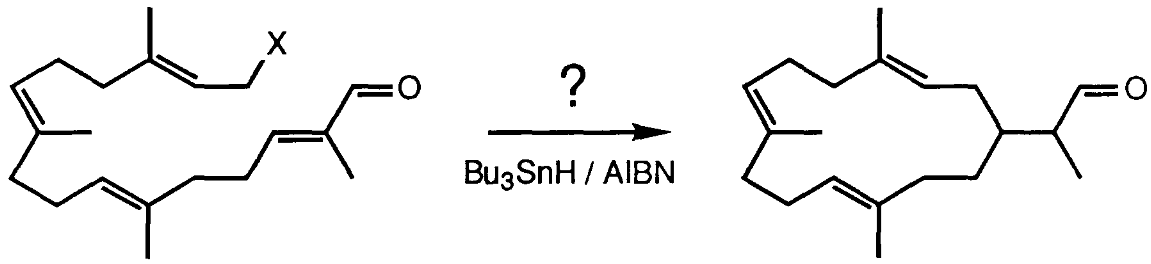


Scheme 52



(115) (116)

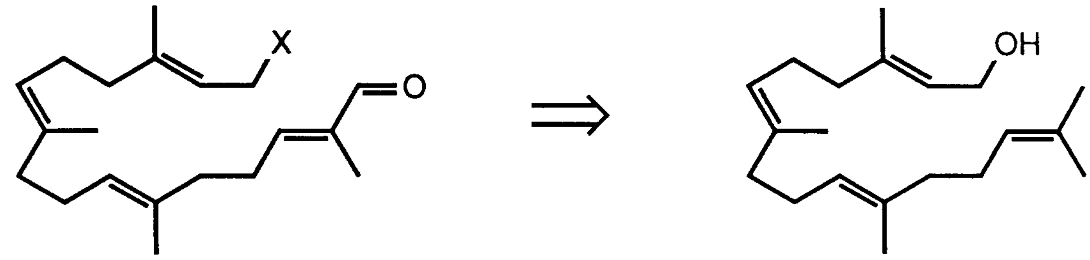
Scheme 53



(117) X = Br

(118) X = I

Scheme 54

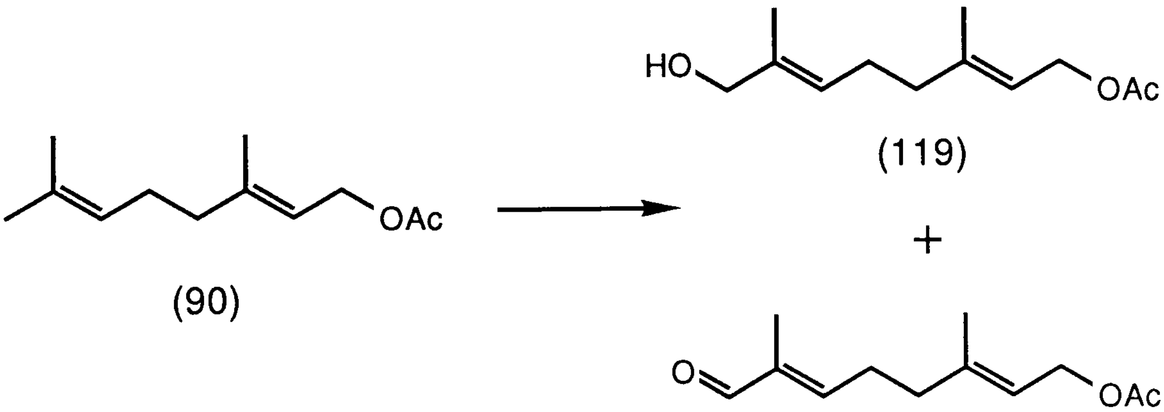


(117) X = Br

(118) X = I

(89)

Scheme 55



(90)

(119)

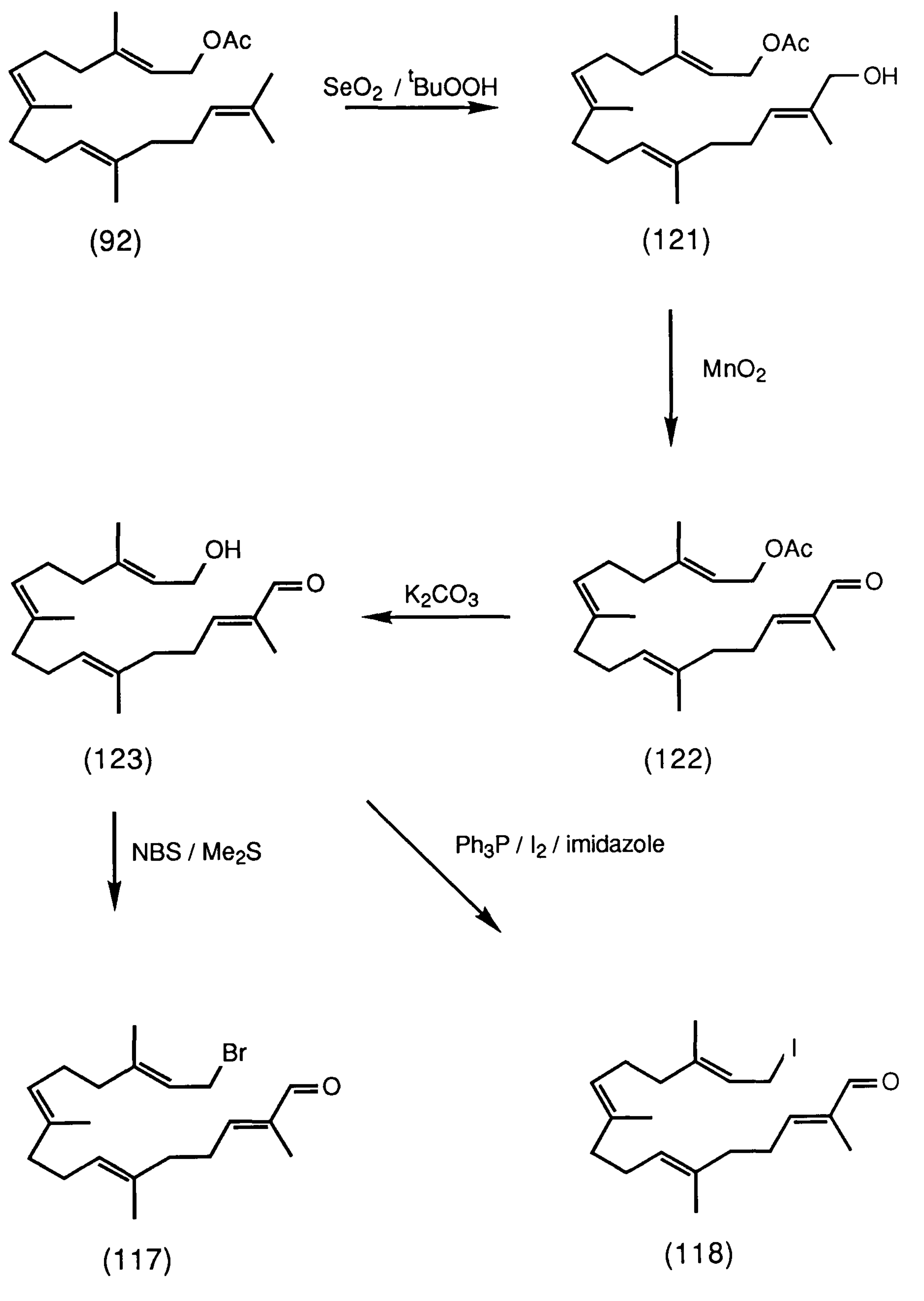
+

(120)

Scheme 56

used to convert geranyl acetate (90) to the alcohol (119) and the aldehyde (120) (Scheme 56)[116]. An initial attempt to convert geranylgeranyl acetate (92) (Scheme 57) directly to the enal (122) using selenium dioxide in refluxing ethanol[117] gave only selenium containing products. However use of catalytic selenium dioxide and excess t-butylhydroperoxide in dichloromethane[118] did give the desired allylic alcohol (121) in 11% isolated yield as the main product of oxidation together with the enal (122) which was isolated in 2% yield. The PMR spectrum of the allylic alcohol (121) showed a singlet at δ3.99 ppm confirming that one of the methyl groups had been oxidised. Irradiation at δ3.99 ppm gave an NOE of -6% at δ5.41 ppm thus confirming that it was the one trans-methyl group which had been oxidised. The allylic alcohol (121) was next converted to the enal (122) using manganese dioxide in dichloromethane. Deprotection using methanolic potassium carbonate then gave the hydroxy enal (123). This compound was used as the common precursor for the allylic bromide (117) and the allylic iodide (118). The bromide (117) was formed by treatment with dimethyl sulphide and N-bromosuccinimide in dichloromethane at 0°C[119]. The corresponding iodide (118) was formed by treatment with triphenylphosphine and imidazole in acetonitrile-diethyl ether at 0°C[120]. Both the bromide (117) and the iodide (118) were highly labile compounds and so were only prepared immediately before use.

With the halo-enals (117) and (118) prepared, an attempt could be made to carry out a radical macrocyclisation. It should be noted that the radical formed will be allylic (Scheme

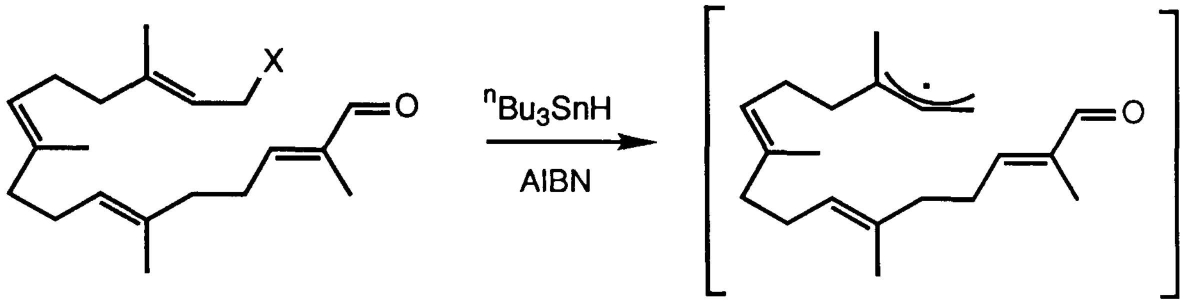

OAc
SeO_2 / ^tBuOOH
OAc
OH
(92)
(121)
MnO_2
OH
O
K_2CO_3
OAc
O
(123)
(122)
NBS / Me_2S
Ph_3P / I_2 / imidazole
Br
O
I
O
(117)
(118)

<u>Scheme 57</u>

58); thus coupling to the enal function might occur from either C_1 or C_3. It was hoped that coupling from C_1 would be favoured as 14-membered rings are generally more readily formed than 12-membered rings where transannular interactions and ring strain are greater factors. Another point of concern was the possibility of the formation of smaller 5- or 6-membered rings by attack at the unactivated double bonds. It was hoped that the activation would make sufficient difference to favour large ring formation over small ring formation.

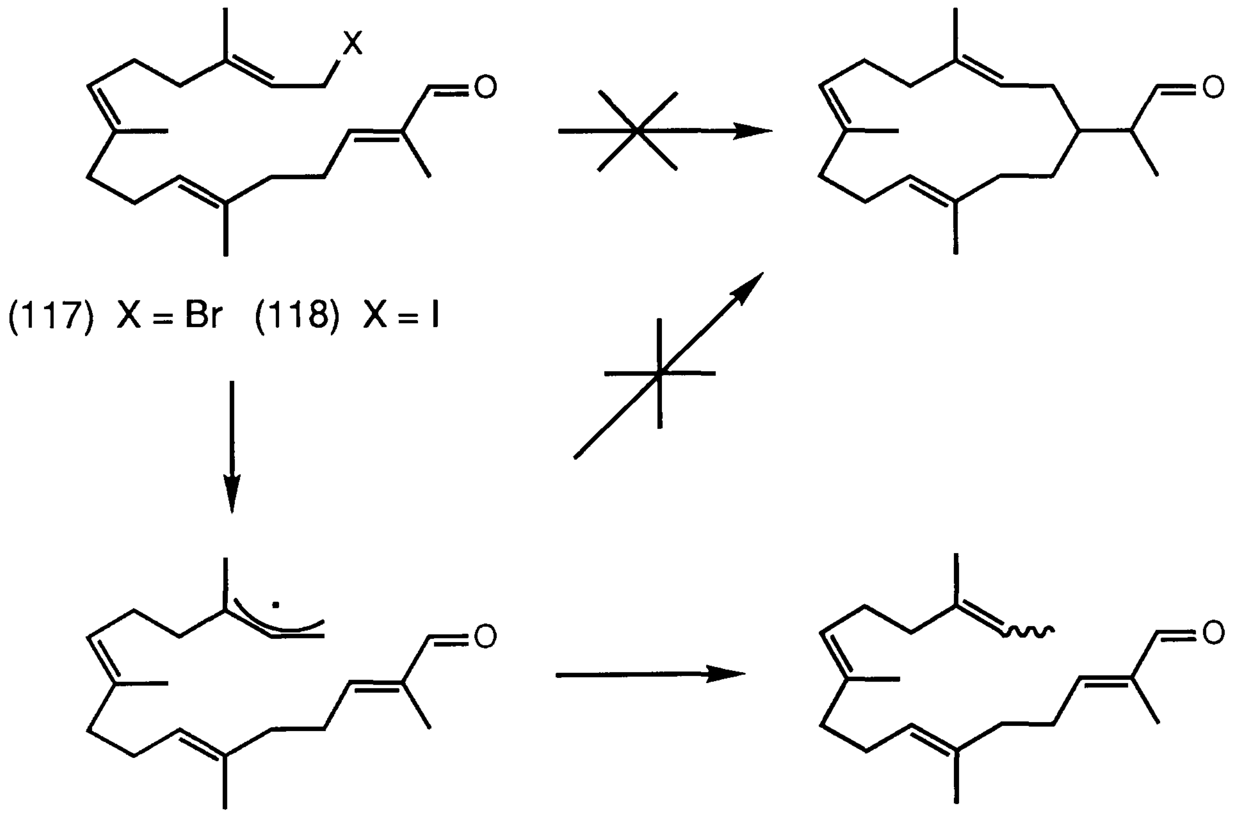
However, when the iodo-enal (118) (Scheme 58) was treated with one equivalent of tributyltin hydride and catalytic azodiisobutyronitrile in refluxing, dry, deaerated benzene at a concentration of 4.5mM, none of the desired cyclised product was obtained. PMR analysis of the crude product revealed no change in the singlet at δ 9.39 ppm showing the enal unit still to be intact. Separation of the reaction products showed the enal (124) to be a significant component (8%). Reaction of the bromo-enal (117) under identical conditions similarly showed the enal unit to be unchanged in the crude reaction product and gave the enal (124) as the only identified product (15%).

Before abandoning our whole approach, we wondered whether any alteration could be made to the system to favour macrocyclisation. It occurred to us that the effect of substitution at the β-position of the enal unit might be significant. It has been observed that intermolecular radical additions to acrylates are very much slower when there is substitution at the β-position. For example, addition of a cyclohexyl radical to an acrylate (Scheme 60) is slower by a



(117) X = Br
(118) X = I

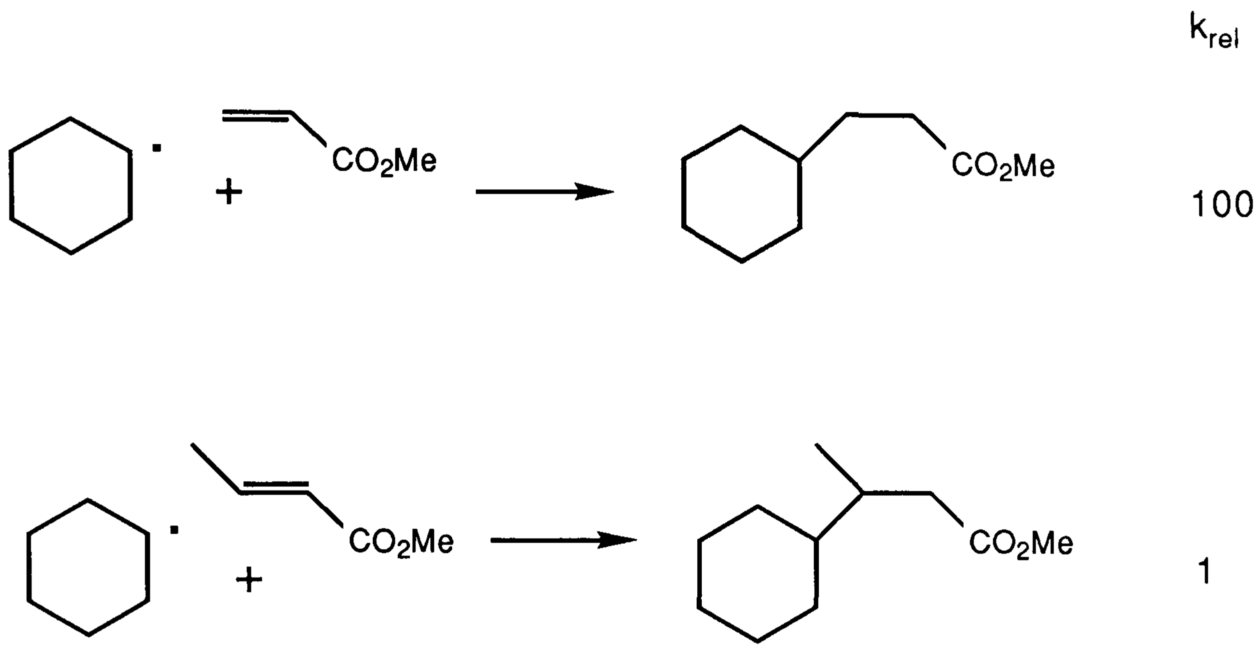
Scheme 58



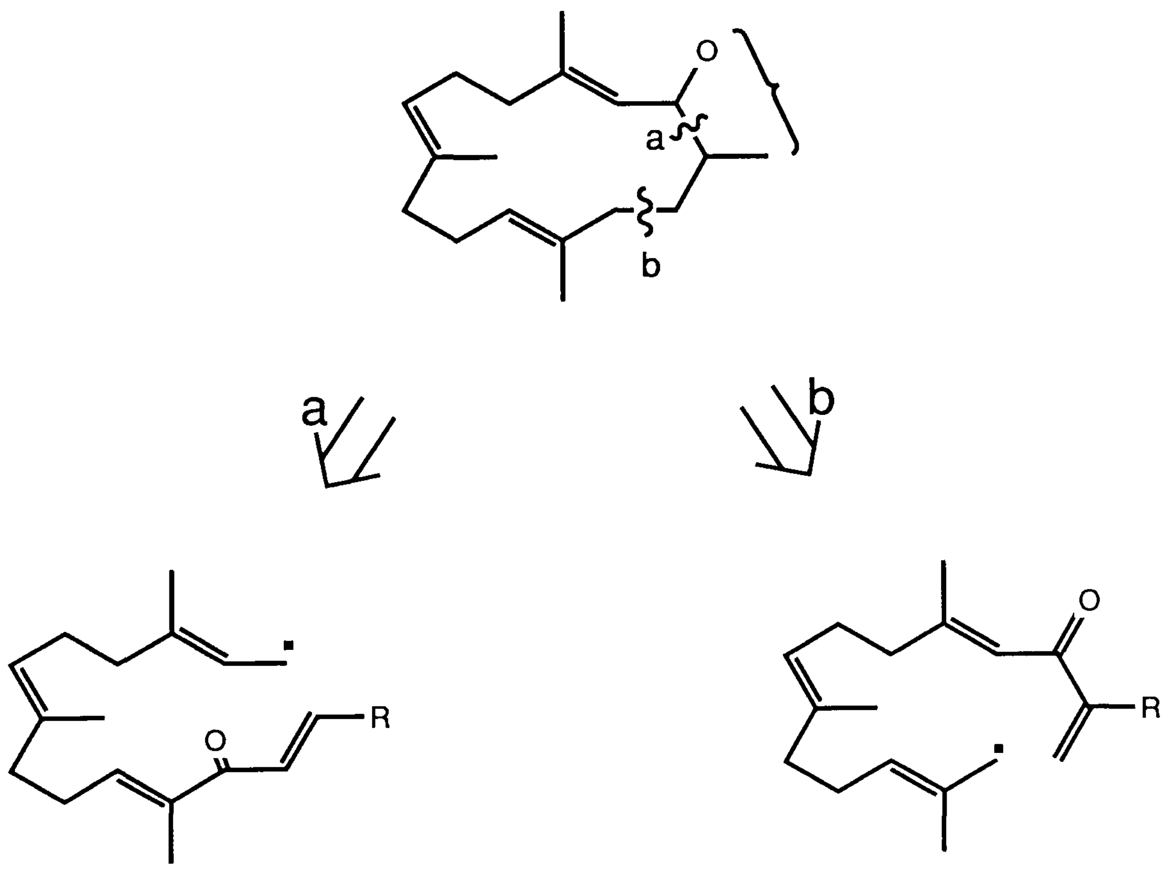
(117) X = Br (118) X = I

(124)

Scheme 59



Scheme 60



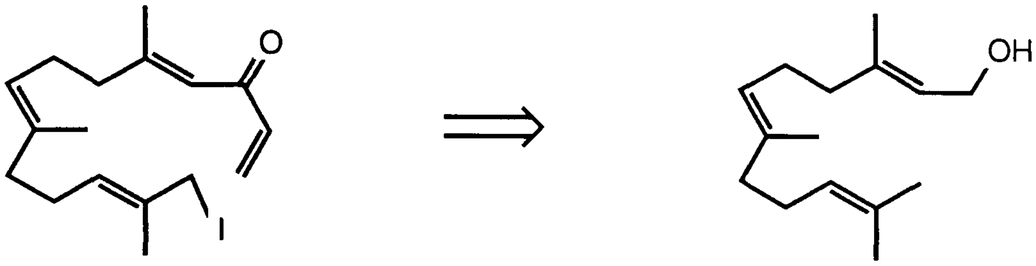
(125) R = H

(126) R = H , alkyl, etc.

Scheme 61

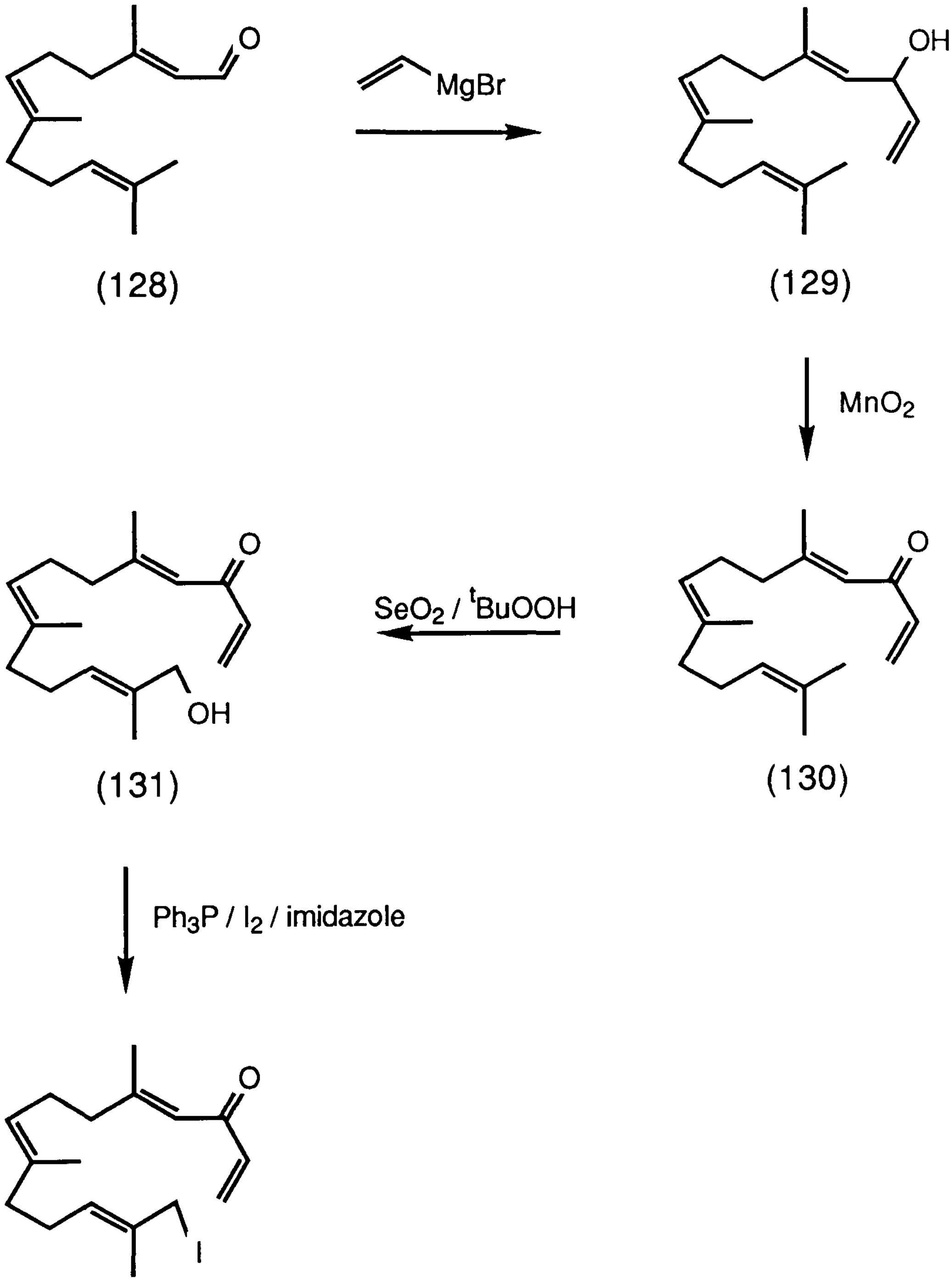
factor of 100 when there is substitution at the β-position[121]. We reasoned, therefore, that a disconnection of the cembranoid ring which would allow attack of a radical on an enone function with no substitution at the β-position might tip the balance in favour of macrocyclisation. With this in mind, additional possible disconnections of the cembranoid skeleton were now considered (Scheme 61). The first disconnection (a) corresponds to the same retrosynthetic bond cleavage as before. Dienone (125) would fulfil our criterion provided that R=H. The alternative disconnection (b) to dienone (126) also fulfils our criterion and has the advantage that the R group can now be varied, being α- rather than β- to the ketone. As the cembranoid carbon skeleton would require further elaboration at this position, this second approach seemed preferable, allowing greater flexibility in the nature of R. Again a halide was chosen as a suitable precursor for the required radical. Thus our target for synthesis became the iodo-dienone (127) (Scheme 62) which we planned to prepare from all E-farnesol (102).

All E-farnesol (102) (Scheme 63) was oxidised using manganese dioxide in dichloromethane to give all E-farnesal (128). Treatment with an excess of vinylmagnesium bromide in tetrahydrofuran-diethyl ether at 0°C then gave the bis-allylic alcohol (129) in 92% yield. Addition was observed to be exclusively 1,2- with no trace of the 1,4-addition product. Oxidation, again with manganese dioxide in dichloromethane, was somewhat slower, taking 16h to give the required dienone (130). Treatment with catalytic selenium dioxide and excess t-butylhydroperoxide in dichloromethane[118] then gave the



(127) (102)

Scheme 62



(128) (129) (130) (131) (127)

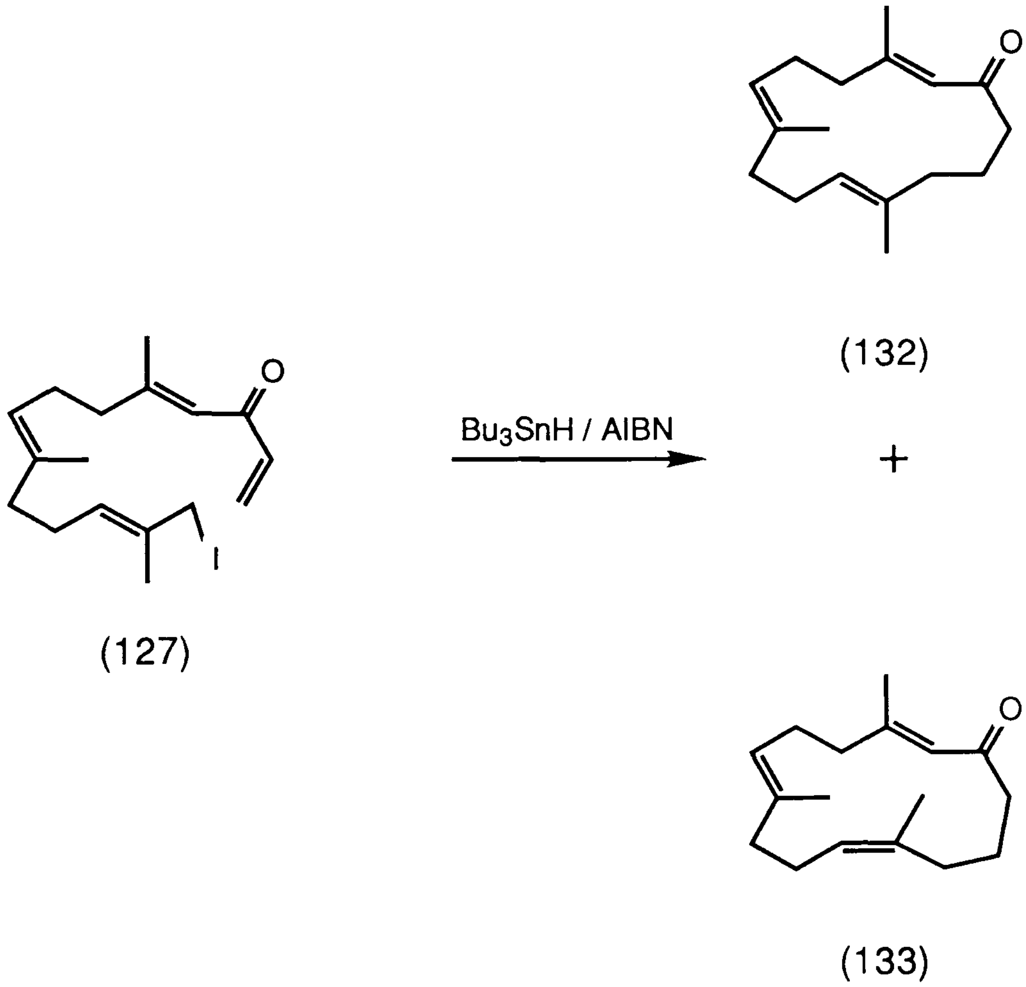
Scheme 63

required hydroxy dienone (131) in 28% yield. The PMR spectrum of the allylic alcohol (131) showed a singlet at δ3.98 ppm, irradiation of which gave an NOE of -10% at δ5.37 ppm. This confirmed that oxidation had occurred at the one trans methyl group. Initially methyltriphenoxyphosphonium iodide[122] was used to convert the hydroxy dienone (131) to the iodo-dienone (127), but this method proved unreliable. Use of triphenylphosphine and iodine in acetonitrile-diethyl ether in the presence of imidazole at 0°C[120], however, gave more consistent results, and the hydroxy dienone (131) was converted to the iodo-dienone (127) in 75% yield. The iodide (127) proved to be highly labile and so was only prepared immediately before use.

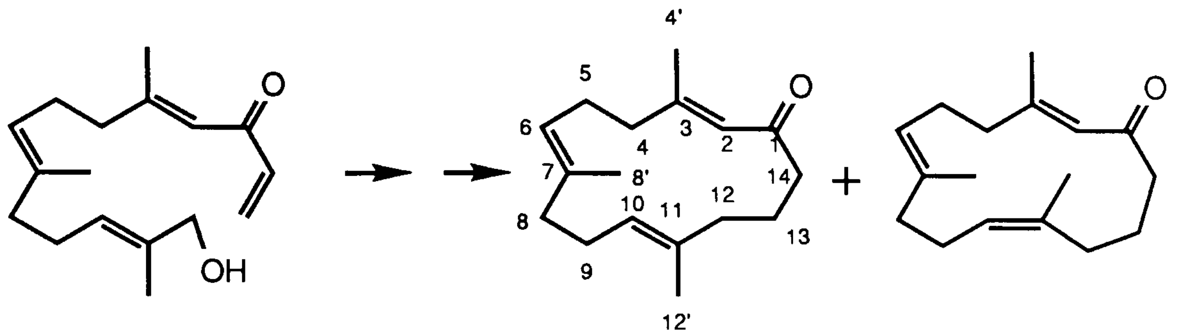
With the iodo-dienone (127) prepared, an attempt could be made to carry out a radical macrocyclisation. Again it should be noted that the radical formed will be allylic, allowing alternative modes of cyclisation, particularly as there is now also an additional internal enone unit present. Thus 14-, 12-, 10- and 8-membered ring closure might all be possible. However, in the light of our previous study, addition to the internal enone group seemed unlikely. It was nevertheless of some concern that, because the ketone was effectively sharing its electron withdrawing character between two olefin functions, activation might not be sufficient to favour macrocyclisation. Small ring formation to give 5- and 6-membered rings was also a potential problem.

However, convinced that this approach offered the most promise so far, the cyclisation was attempted. Thus the iodo-dienone (127) was treated with one equivalent of tributyltin hydride and catalytic azodiisobutyronitrile in refluxing, dry, deaerated benzene at a concentration of 4mM. On work up and subsequent analysis we were delighted to observe the desired cyclisation to have occurred, giving the cyclised enone as a mixture of the 10*E*-isomer (132) and the 10*Z*-isomer (133) (Scheme 64) in a ratio of 7:3 and in a combined isolated yield of 42-48%. The enones (132) and (133) could be readily separated from the other by-products by column chomatography, but could not be separated from each other. They could, however, be readily separated by preparative high pressure liquid chromatography.

The first clue that macrocyclisation had occurred was that the PMR spectrum showed loss of the ethenyl group in the starting material and also a shift in the positions of the non-conjugated vinyl signals from δ5.1-5.4 ppm to δ4.8-4.9 ppm (Table 1 and Fig. 1). This shift in the vinyl signals, which is presumably due to transannular interactions and/or ring strain, is typical of many cembranoids[123]. Interestingly the C_{10} proton of the 10*Z*-isomer (133) does not show this shift (Table 1 and Fig. 1), presumably because it is directed out of the ring instead of inwards. The structure of the 10*E*-isomer (132) was further confirmed by comparison of PMR and CMR data with literature data, the 10*E*-isomer (132) having been prepared by Kato by an alternative procedure[58]. Confirmation of the structure of the 10*Z*-isomer was achieved by comparison of CMR and PMR data with the 10*E*-isomer (Tables 1 and 2, and Figs. 1 and 2). The CMR spectrum (Table 2 and Fig. 2) revealed a shift in the positions of the signals due to the carbons associated



Scheme 64



(131) (132) (133)

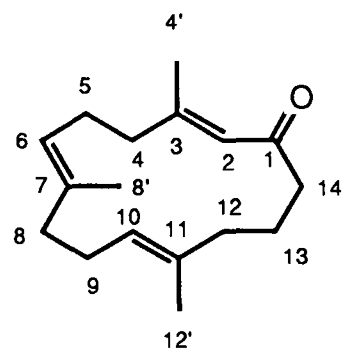
PMR CHEMICAL SHIFT DATA (ppm from TMS) FOR COMPOUNDS

(131), (132) AND (133)

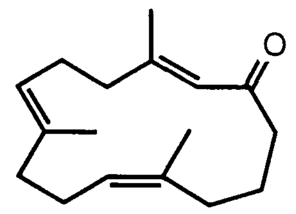
	(131)	(132)	(133)
2	6.28	5.93	5.98
4'	2.14	2.08	2.07
6	5.10	4.87	4.92
8'	1.68	1.59	1.59
10	5.37	4.79	5.96
12'	1.62	1.54	1.66
12	3.98	*	*
13	6.23, 5.76	*	*
14	6.42	*	*

* Part of a multiplet 2.4-1.8 ppm.

Table 1



(132)



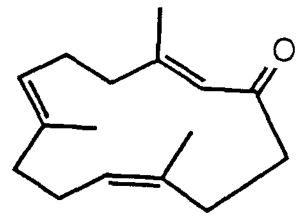
(133)

CMR CHEMICAL SHIFT DATA (ppm from TMS) FOR COMPOUNDS

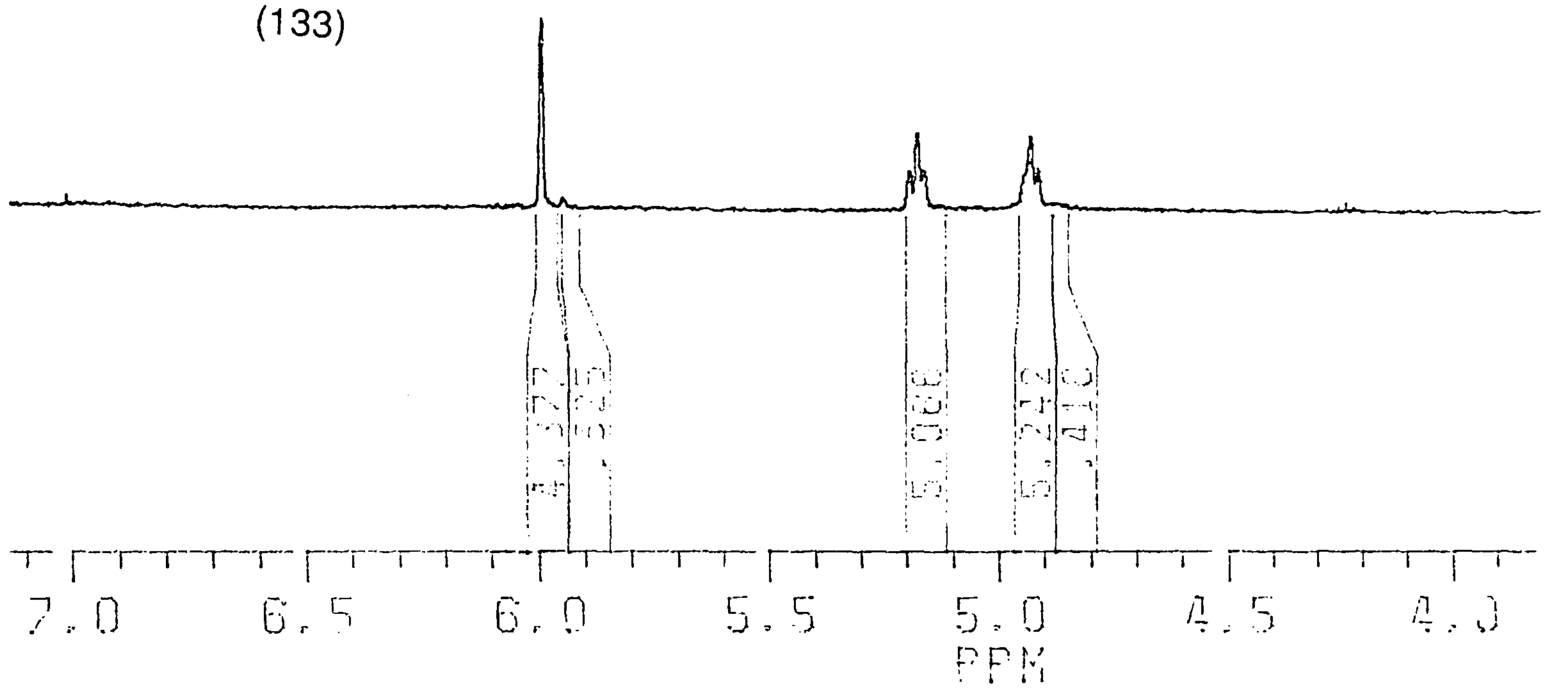
(132) AND (133)

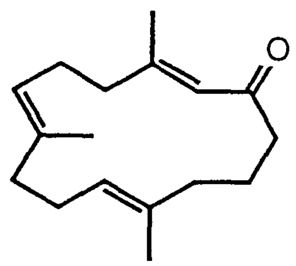
	(132)	(133)
C_1	202(s)	202(s)
C_2, C_6, C_{10}	125(d)	124(d)
	125(d)	125(d)
	126(d)	126(d)
C_3	156(s)	157(s)
$C_{4'}$	19(q)	19(q)
C_7	135(s)	135(s)
$C_{8'}$	15(q)	16(q)
C_{11}	133(s)	138(s)
$C_{12'}$	15(q)	23(q)

Table 2



(133)





(132)

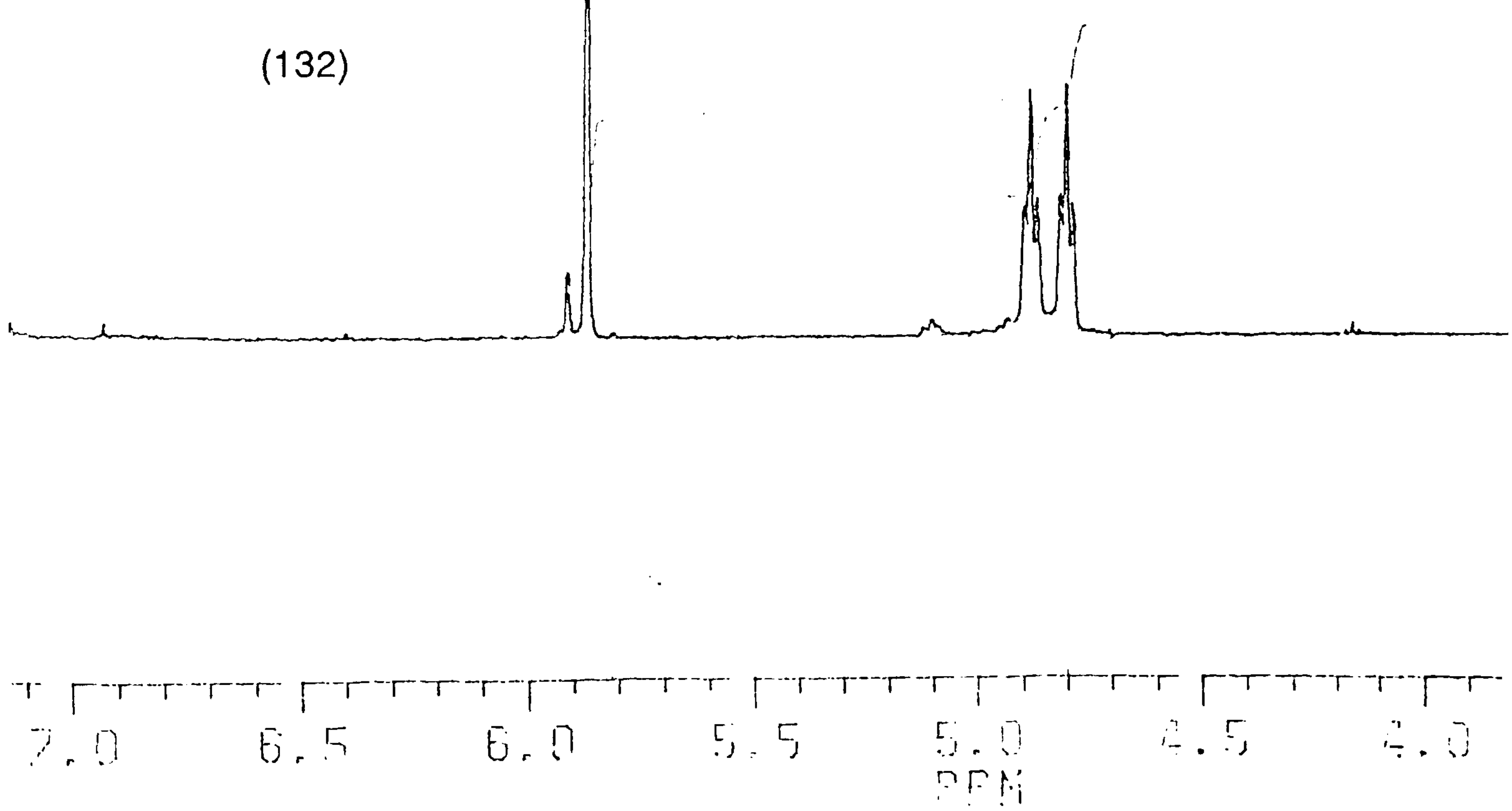


Fig. 1

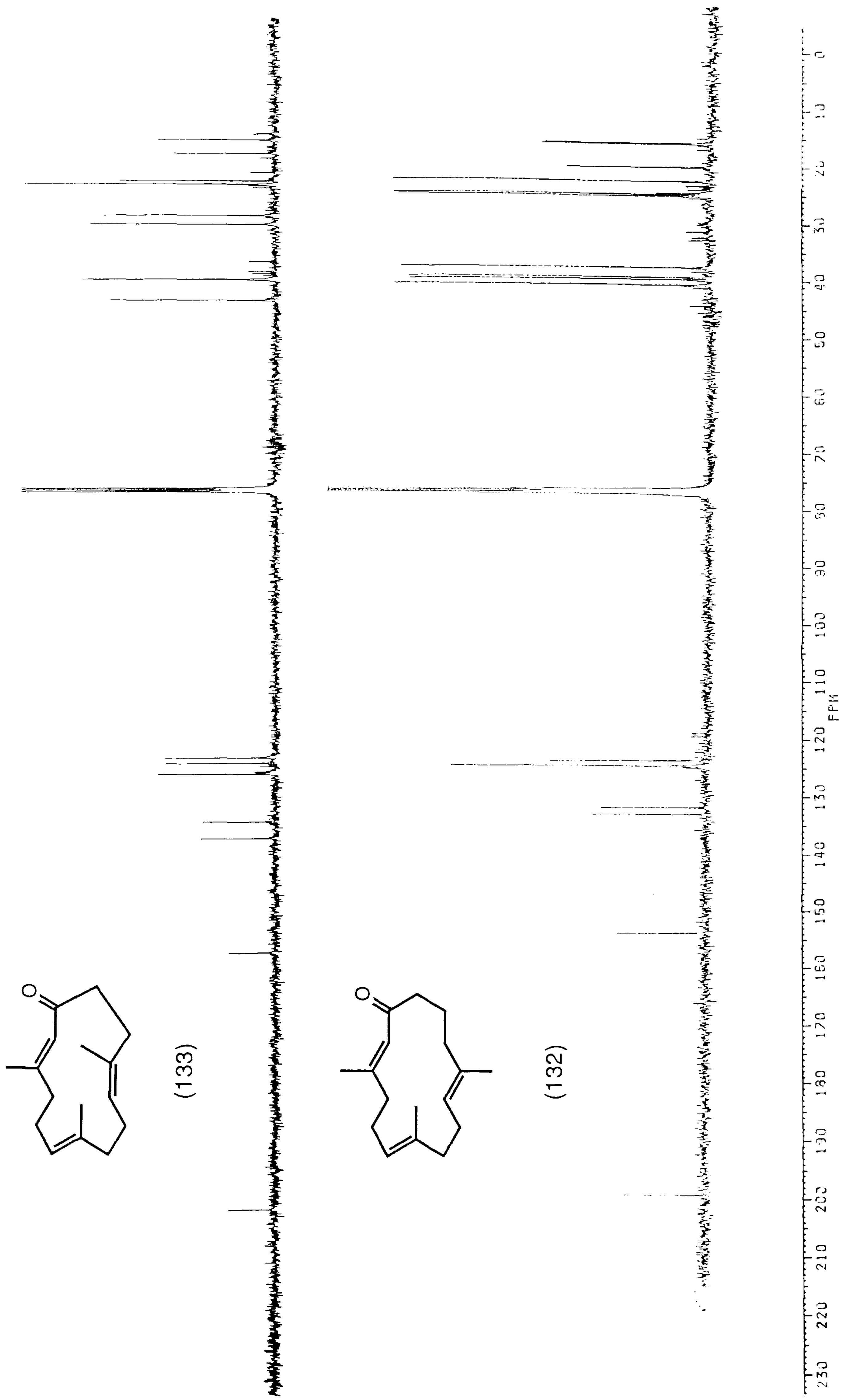

(133)
(132)
PPM
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

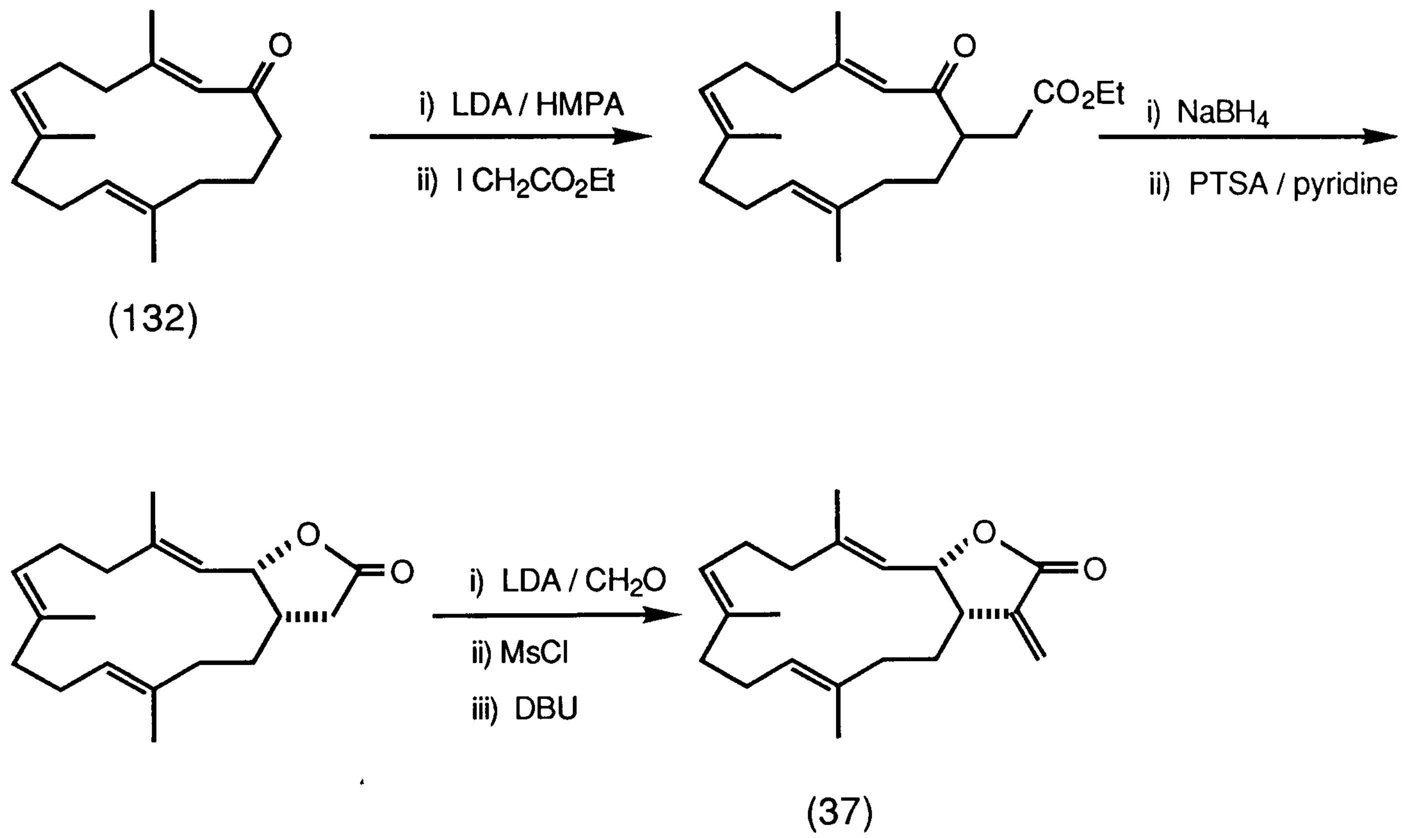
Fig. 2

with the 10*Z*-double bond. The shift in the signal due to C_{12}, was particularly large because of the γ effect.

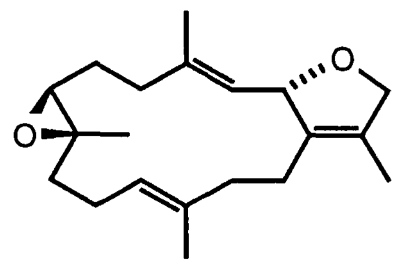
The 10*E*-enone (132) has been used by Kato in a synthesis of cembranolide (37) (Scheme 65)[58] which has been isolated from the soft coral *Sinularia mayi*[123]. Thus our synthesis of the cyclic enone (132) constitutes a formal synthesis of cembranolide (37).

Having developed a method for macrocyclisation using radical intermediates, we were keen to develop the method further. A question of some interest was whether fuctionality could be incorporated into the acyclic precursor before cyclisation. Our interest in deoxysarcophine (24) (Scheme 66) made us wonder whether an epoxide function would be stable under the cyclisation conditions. If it were, then a potential chiral synthesis of deoxysarcophine (24) could be envisaged using a chiral acyclic epoxide intermediate which could be prepared *via* Sharpless epoxidation methodology[124]. We decided, therefore, to investigate the cyclisation of the epoxy iodo-dienone (134) (Scheme 66). As we already had a route to hydroxy dienone (131), we chose to use it to prepare the epoxy iodo-dienone (134).

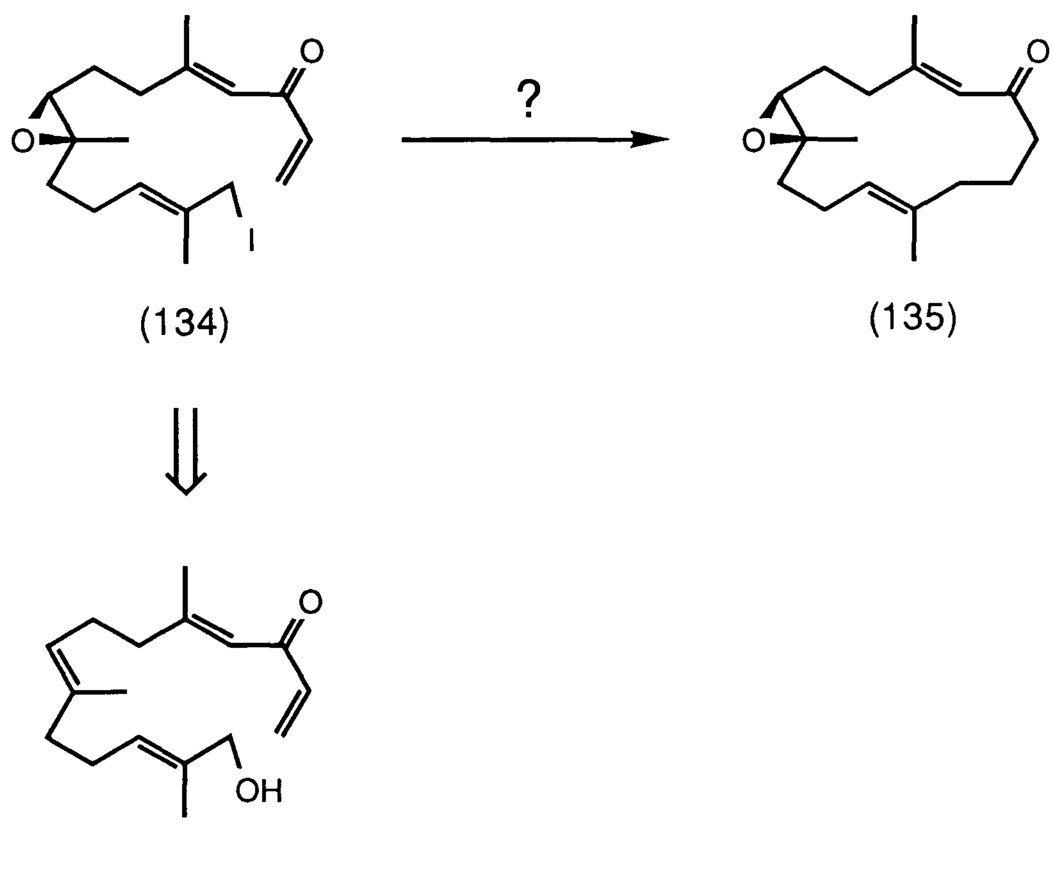
It seemed unlikely that direct epoxidation would lead to a significant degree of selectivity, although the use of *meta*-chloroperbenzoic acid should, on kinetic grounds, favour epoxidation of the most electron-rich double bond. However, using geraniol (73) (Scheme 67) as a model system revealed that treatment with one equivalent of *meta*-chloroperbenzoic acid in either dichloromethane or methanol at 0°C gave only a 4:3 mixture of the epoxides (136) and (137) in favour of the


O
i) LDA / HMPA
ii) I CH_2CO_2Et
O
CO_2Et
i) $NaBH_4$
ii) PTSA / pyridine
(132)
O
O
i) LDA / CH_2O
ii) MsCl
iii) DBU
O
O
(37)

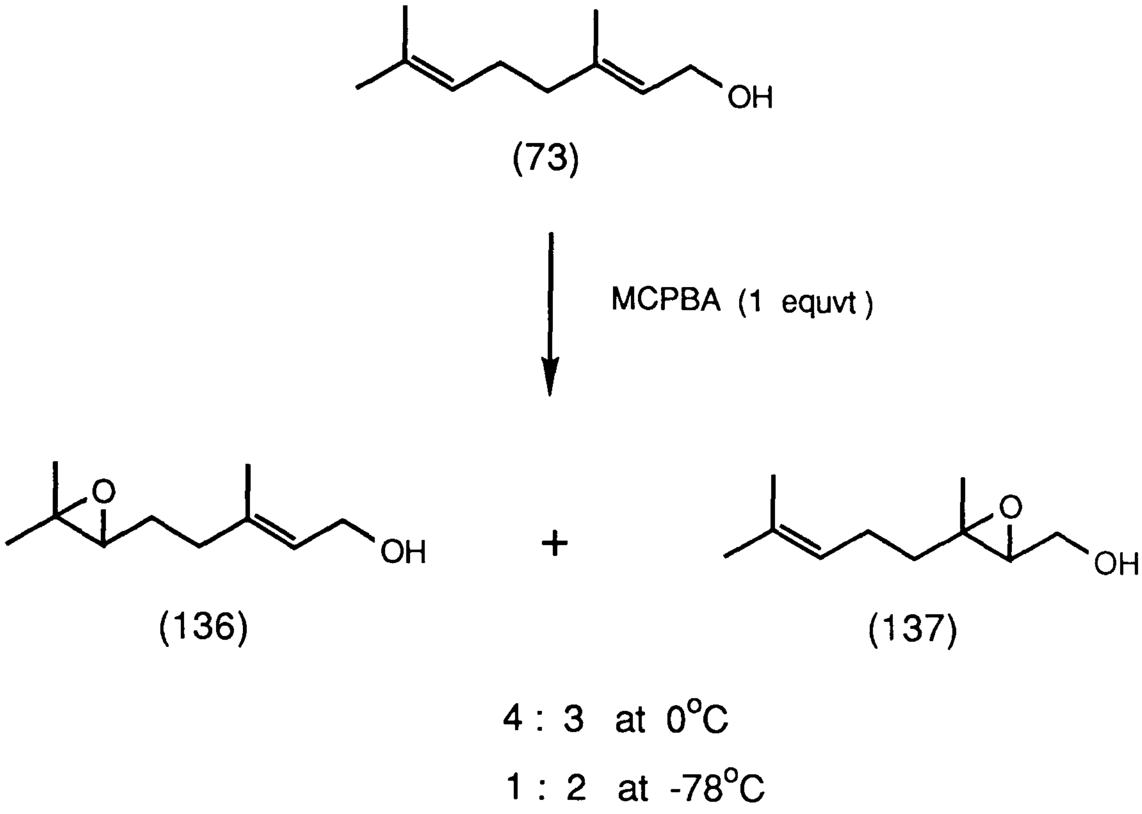
Scheme 65



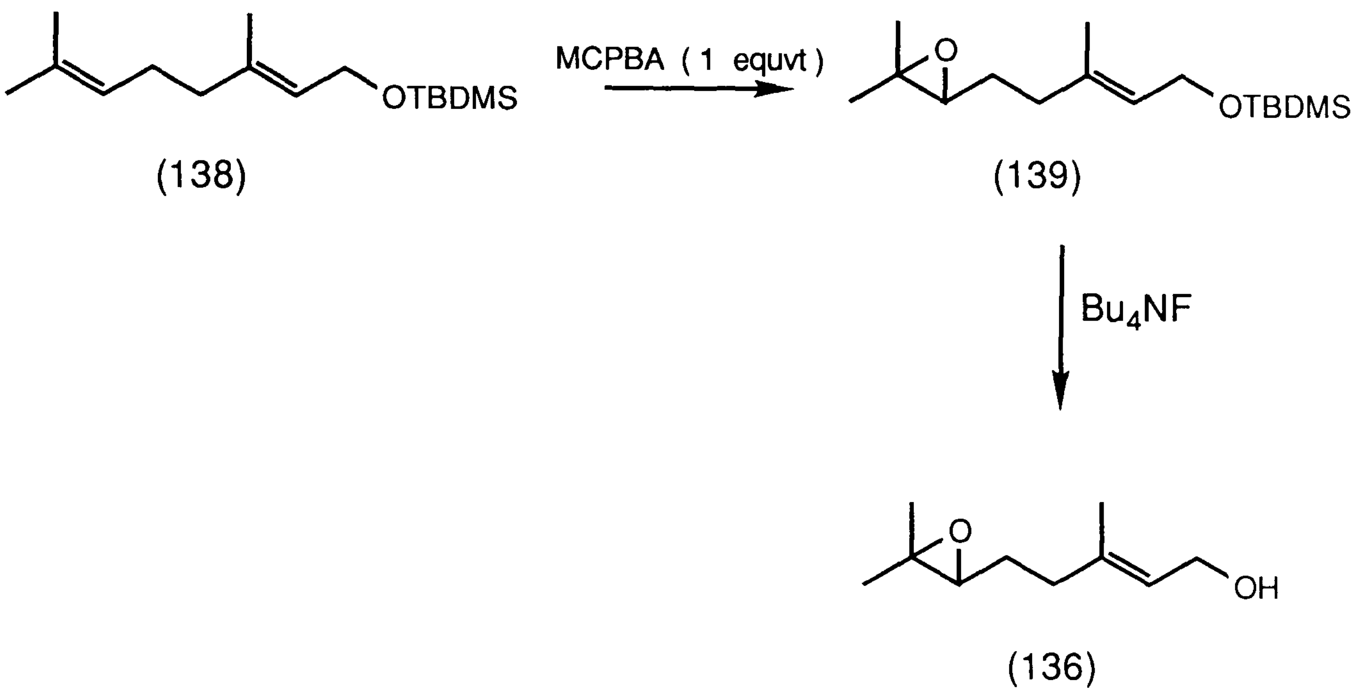
(24)



Scheme 66



<u>Scheme 67</u>



<u>Scheme 68</u>

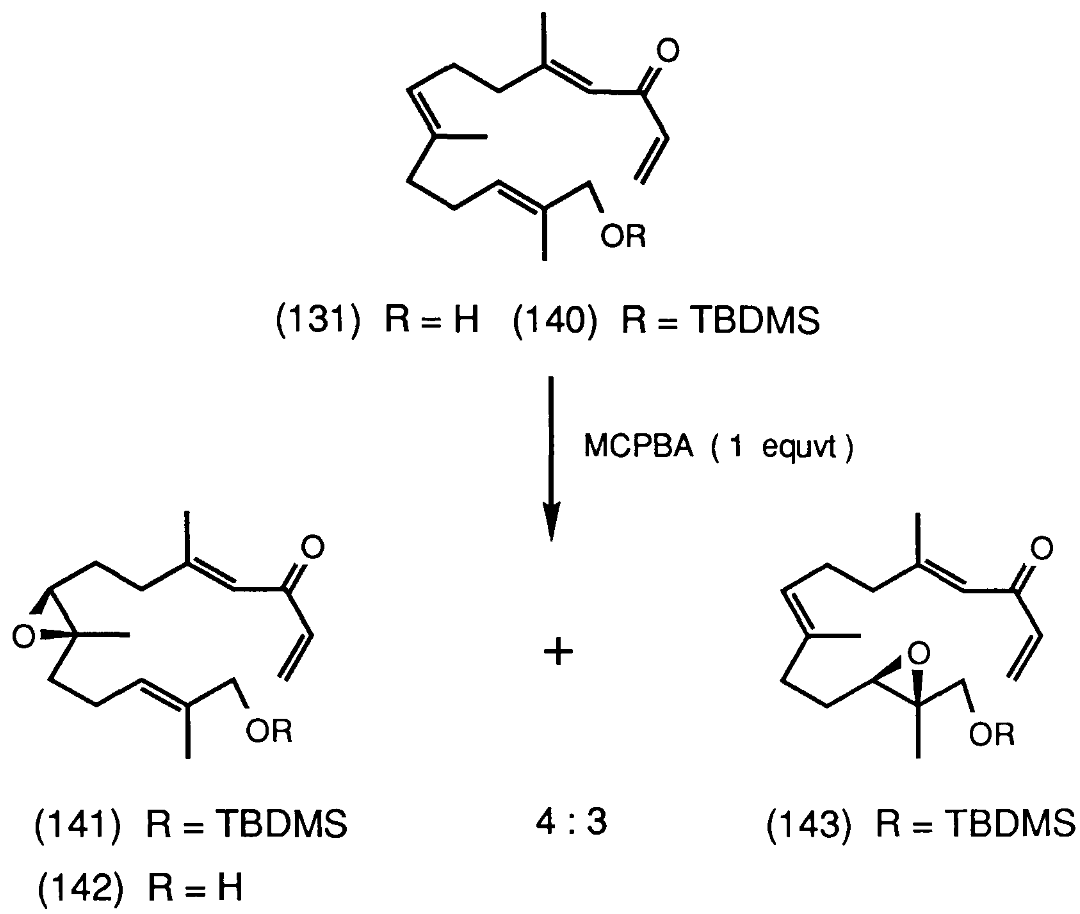
terminal epoxide (136). Carrying out the epoxidation at -78°C in an attempt to favour the kinetic product and improve this ratio infact gave a 2:1 mixture of the epoxides in favour of the 2,3-epoxide (137). Presumably the hydroxy group can deliver meta-chloroperbenzoic acid to the adjacent double bond, and this factor becomes increasingly important at lower temperatures.

It was decided, therefore, to protect the hydroxy group in an attempt to prevent this delivery. Also, we reasoned that use of a bulky protecting group would sterically hinder attack at the adjacent double bond. The t-butyldimethylsilyl protected derivative (138) (Scheme 68) was therefore prepared using 2 equivalents of t-butyldimethylsilyl chloride and 3.5 equivalents of imidazole in dimethylformamide[125]. Treatment of the silyl ether (138) with one equivalent of meta-chloroperbenzoic acid in dichloromethane at 0°C, we were pleased to observe, gave exclusively the terminal epoxide (139). Deprotection using a slight excess of tetrabutylammonium fluoride in tetrahyhrofuran then gave the epoxy alcohol (136).

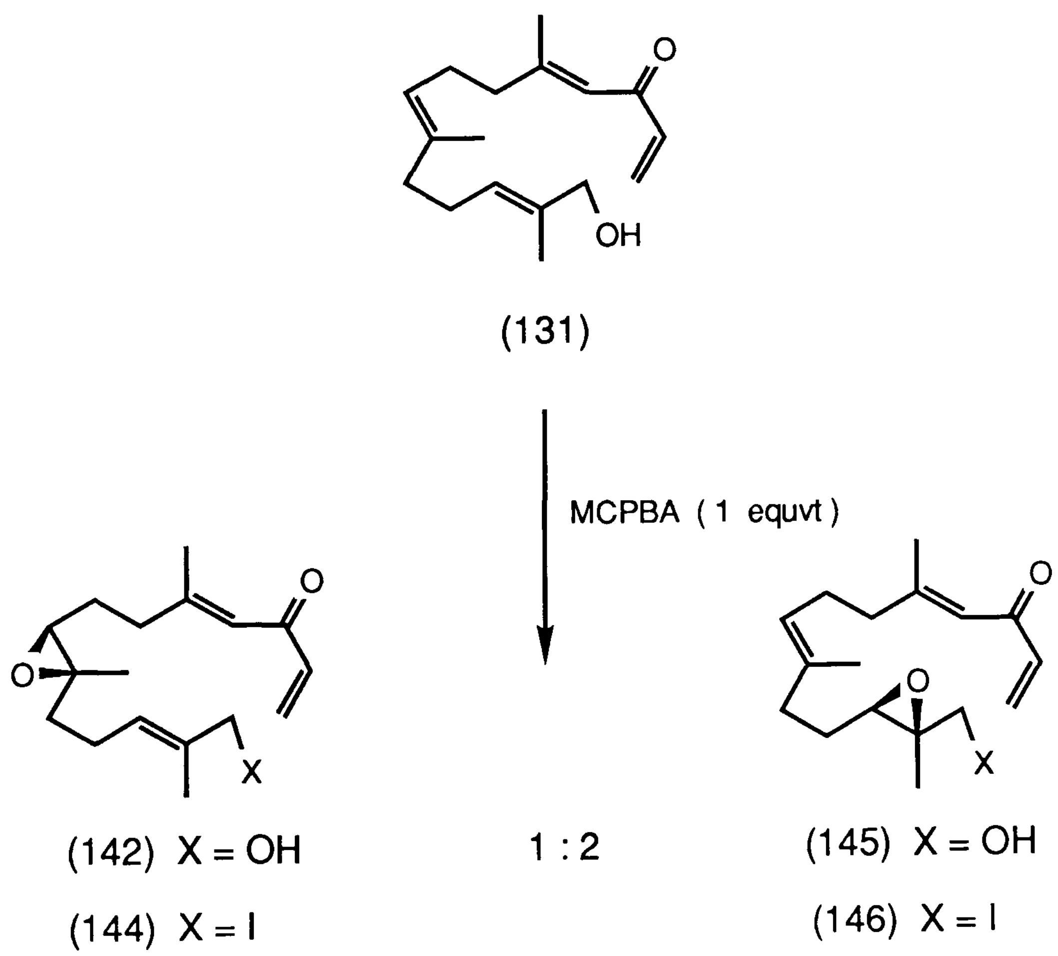
An attempt to carry out this procedure on the hydroxy dienone (131) immediately met with difficulty. Initial attempts to protect the hydroxy dienone (131) using t-butyldimethylsilyl chloride and imidazole led only to complete decomposition of starting material. This, almost certainly, reflects the instability of the dienone unit. Indeed, it had previously been observed that prolonged exposure to potassium hydroxide led to isomerisation of the 2E-double bond. It was subsequently found that treatment of the dienone (130) with imidazole alone led to decomposition at room temperature. Use of a slight excess of

4-(t-butyldimethylsilyloxy)-3-penten-2-one and catalytic para-toluenesulphonic acid in dimethylformamide[126] proved a more successful method, converting the hydroxy dienone (131) to the silyl ether (140) in 49% isolated yield (Scheme 69). Subsequent treatment with one equivalent of meta-chloroperbenzoic acid at 0°C did not, however, give the high selectivity hoped for, giving a 4:3 mixture of the epoxides (141) and (143). These could, however, be readily separated by column chromatography to give the t-butyldimethylsilyl protected epoxy dienone (141) in 31% isolated yield. Unfortunately, however, attempts to deprotect the silyl ether (141) to give the epoxy alcohol (142) using a slight excess of tetrabutylammonium fluoride in tetrahydrofuran completely failed giving only base line material by TLC analysis. The reasons for this have not been determined, but almost certainly again reflect the sensitivity of the dienone unit.

Frustrated in our attempts to prepare the epoxide in a selective manner, it was decided to carry out epoxidation using meta-chloroperbenzoic acid directly on the hydroxy dienone (131) (Scheme 70) and to separate the desired product from the isomeric mixture produced. Thus treatment of the hydroxy dienone (131) with one equivalent of meta-chloroperbenzoic acid in dichloromethane at 0°C gave a 1:2 mixture of epoxides (142) and (145). Unfortunately these proved extremely difficult to separate by chromatography; thus epoxides (145) and (142) were only isolated in yields of 26% and 9% respectively. The epoxy alcohol (142) was then converted to the epoxy iodide (144) using triphenylphosphine and iodine in acetonitrile-diethyl ether in



Scheme 69



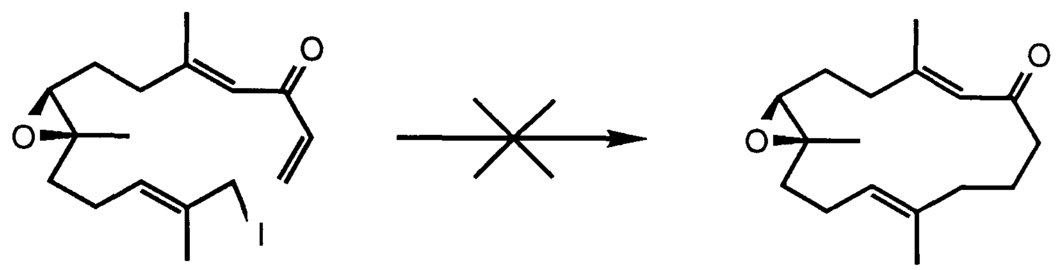
Scheme 70

the presence of imidazole at 0°C[127].

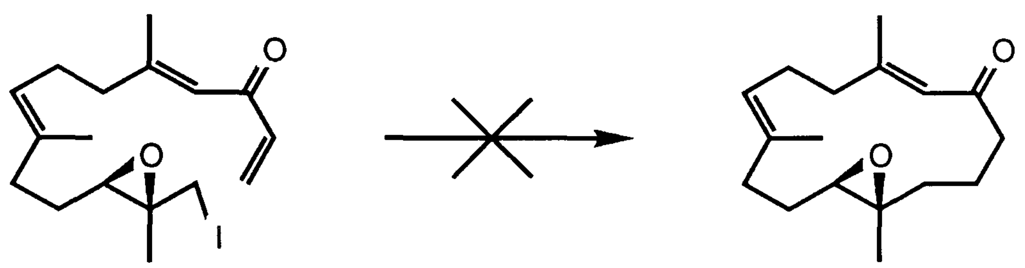
Having obtained the desired epoxy iodo-dienone (144), an attempt could be made to carry out a radical macrocyclisation. Thus the epoxy iodo-dienone (144) (Scheme 71) was treated with one equivalent of tributyltin hydride and catalytic azodiisobutyronitrile in refluxing, dry, deaerated benzene at a concentration of 3mM. However TLC analysis of the crude reaction product revealed mostly base-line material with only a small amount of material of higher R_f. PMR analysis also revealed that the epoxide function was no longer intact (loss of triplet at ca. δ3.0 ppm). A comparison was made by TLC analysis between the crude reaction product and a mixture of the epoxides (135) and (147) (Scheme 72) which could be readily prepared as a 1:1 mixture by treatment of the cyclic enone (132) with one equivalent of meta-chloroperbenzoic acid. This comparison confirmed that none of the desired product was present in the crude reaction product. An attempt to cyclise the epoxy iodo-dienone (146) proved equally unsuccessful[128].

The reason for the failure of these reactions is not entirely clear. It has been reported, however, that tin halides such as tributyltin iodide can react with epoxides to form iodo-tin salts(Scheme 73)[129]. As tributyltin iodide is produced as a biproduct in the generation of a radical from an iodide, this seems a plausible reason for the failure of this reaction. If this is indeed the problem then use of an alternative procedure to generate the required radical might prove more successful.

Rather than persuing this investigation further we chose

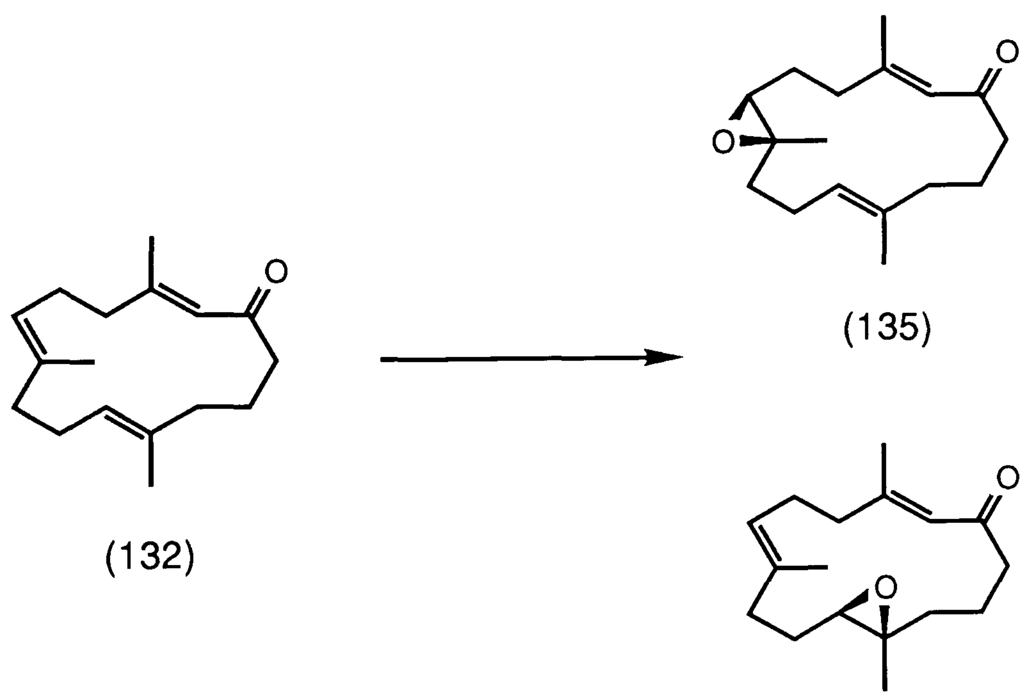


(144) (135)



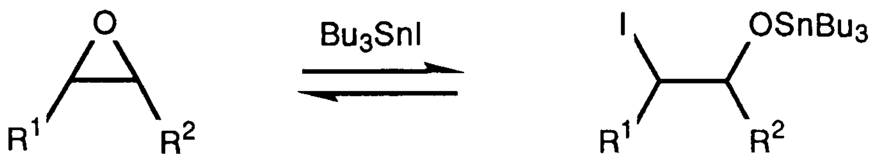
(146) (147)

Scheme 71

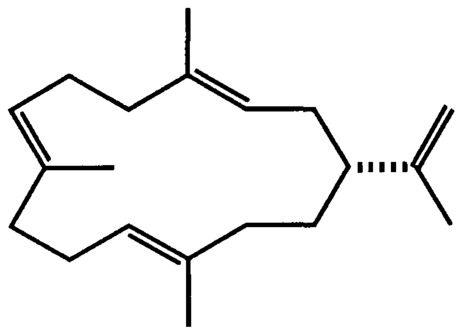


(132) (135) (147)

Scheme 72

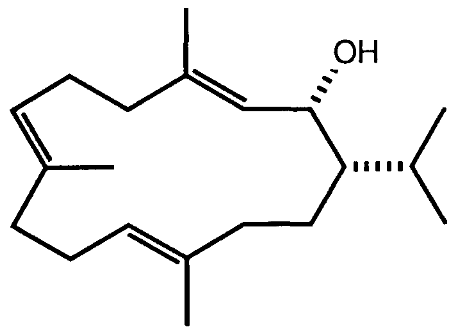


Scheme 73



(3)

Neocembrene



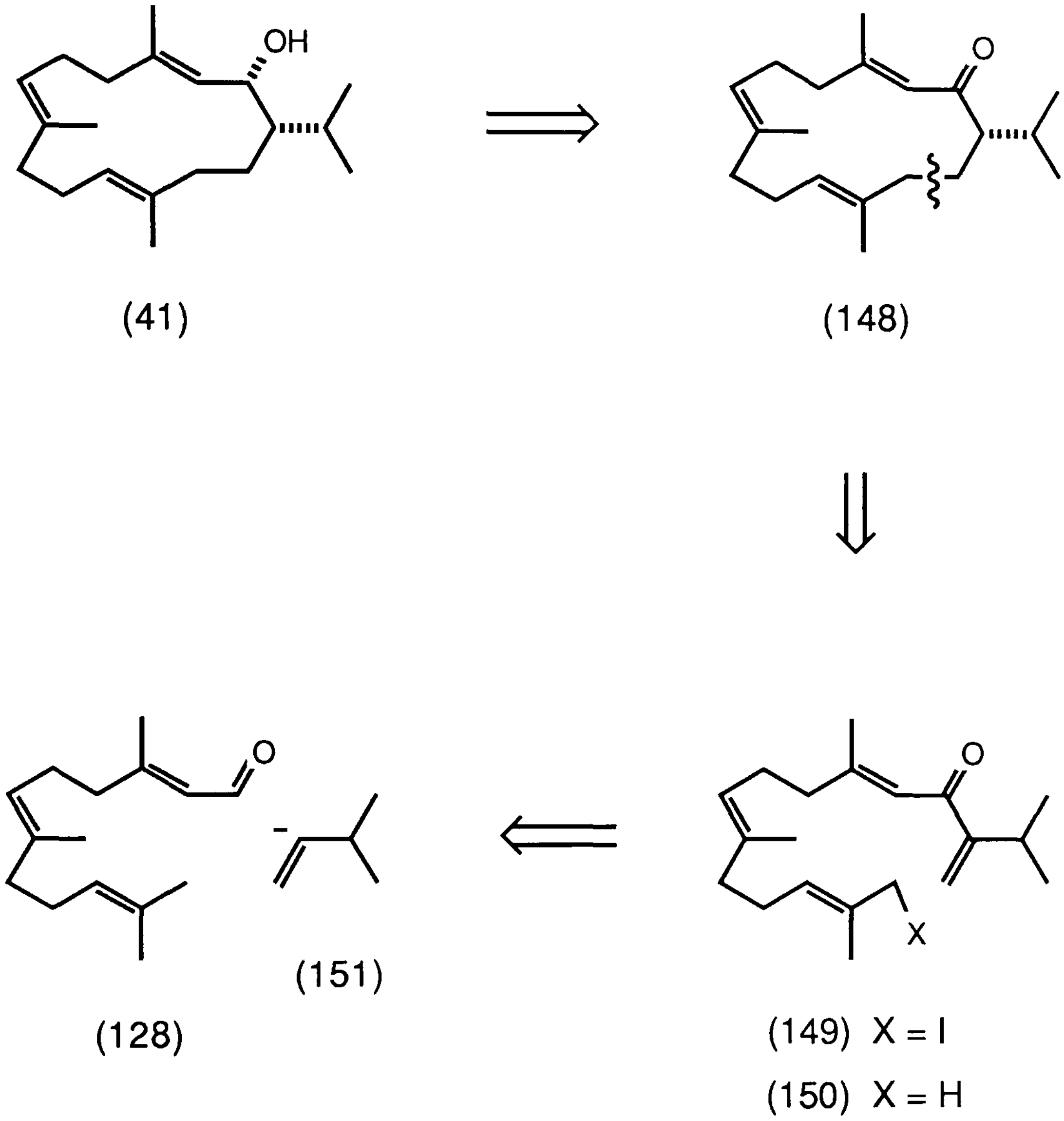
(41)

Mukulol

instead to attempt the synthesis of a second natural cembranoid using our new radical macrocyclisation methodology as the key step. The target that was chosen was the cembranoid mukulol (41). Mukulol was first isolated in 1972 from the gum resin from the Indian tree, Comiphora mukul[130]. This resin, known as Guggulu oil, is traided in India because the classical Ayurvedic[131] literature claims that it has useful medicinal properties, for example, in the treatment of rheumatoid arthritus, obesity and as a general therapeutic agent. Indeed recent pharmaceutical studies have shown that it does indeed have significant anti-inflammatory and anti-rheumatic and hypocholestremic/hypolipaemic activity[132]. Guggulu oil contains a complex mixture of compounds including steroids, aliphatic esters, carbohydrates and simple terpenes as well as containing two cembranoids, neocembrene (3) and mukulol (41).

A retrosynthetic analysis of mukulol (41) (Scheme 74) revealed the dienone (150) to be a suitable precursor. This, it was hoped, could be prepared from farnesal (128) by treatment with the vinyl anion (151).

Preparation of the iodo-dienone (149) was carried out as follows (Scheme 75). Bromination of 3-methylbutene in dichloromethane at 0°C gave the dibromide (153) in 85% yield[133]. Attempts to carry out a selective elimination to favour the desired vinyl bromide (154) using sodium 2,6-dimethyl-phenoxide[133] proved unselective and low yielding. Treatment with ethanolic potassium hydroxide[134] proved higher yielding, giving a 51% yield of a 1:1 mixture of the isomeric vinyl bromides (154) and (155). Careful distillation using a 50cm



(41)

(148)

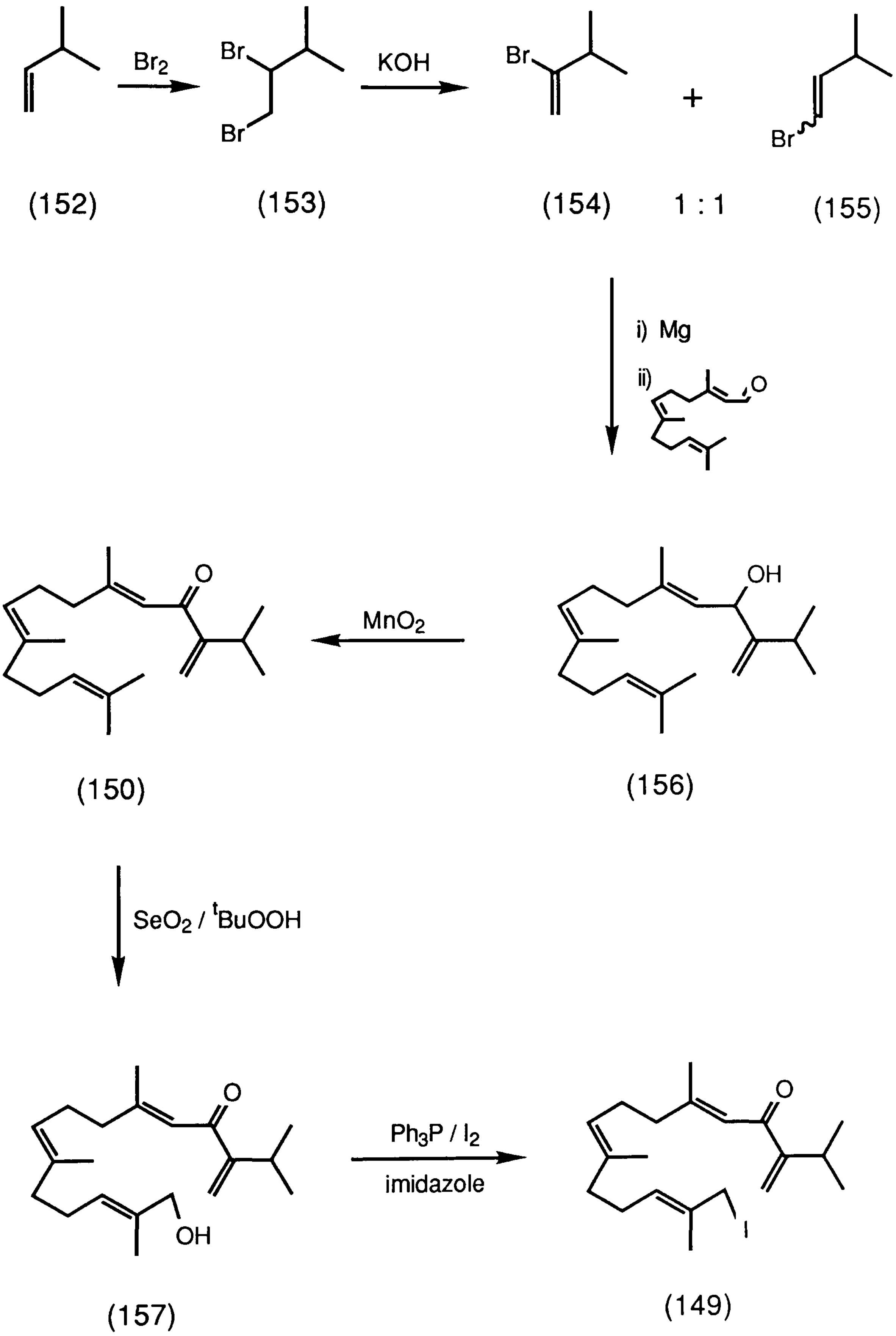
(128)

(151)

(149) X = I

(150) X = H

Scheme 74

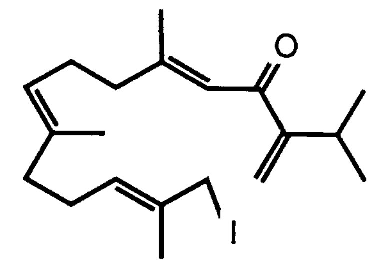


Br2
KOH
+
(152)
(153)
(154)
1 : 1
(155)
i) Mg
ii)
MnO2
(150)
(156)
SeO2 / tBuOOH
Ph3P / I2
imidazole
(157)
(149)

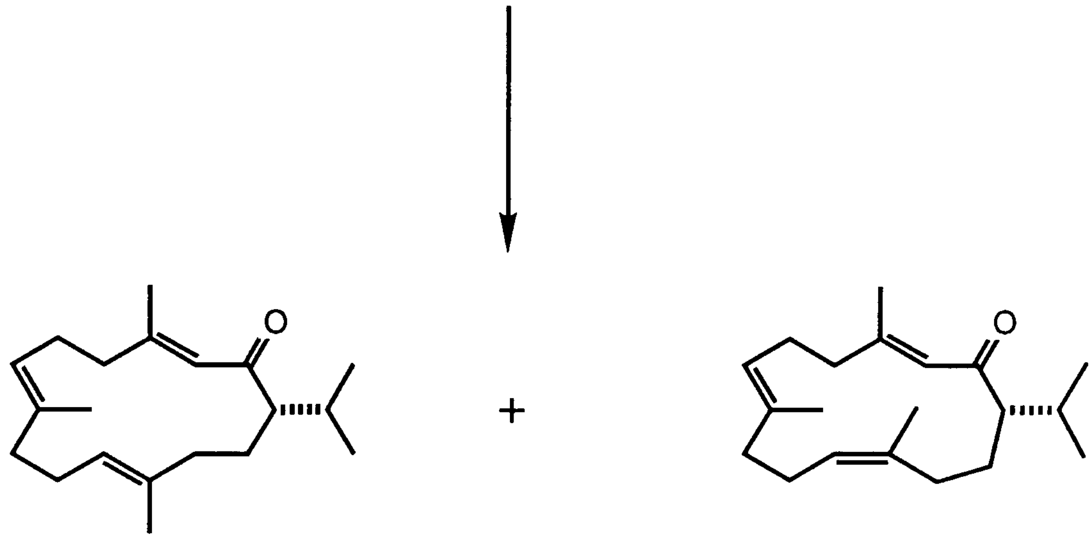
Scheme 75

Vigreaux column gave an improved ratio of 2:1 in favour of the required vinyl bromide (154). Addition of this isomeric mixture to magnesium turnings in tetrahydrofuran at 0°C generated the respective Grignard reagents. Subsequent addition of all E-farnesal (128) gave the bis-allylic alcohol (156) in 54% isolated yield (based on vinyl bromide (154)), and oxidation with manganese dioxide in dichloromethane then gave, after 17h, the required dienone (150) in 95% yield. Treatment with catalytic selenium dioxide and excess t-butylhydroperoxide in dichloromethane[118] finally gave the required hydroxy dienone (157) in 19% yield. The PMR spectrum of the allylic alcohol (157) showed a singlet at δ3.99 ppm, irradiation of which gave an NOE of -6% at δ5.38 ppm. This confirmed that oxidation had occurred at the one trans-methyl group. Use of triphenylphosphine and iodine in acetonitrile-diethyl ether in the presence of imidazole at 0°C[120] then gave the required iodo-dienone (149) in 74% yield. The iodide (149) proved to be highly labile, and so was only prepared immediately before use.

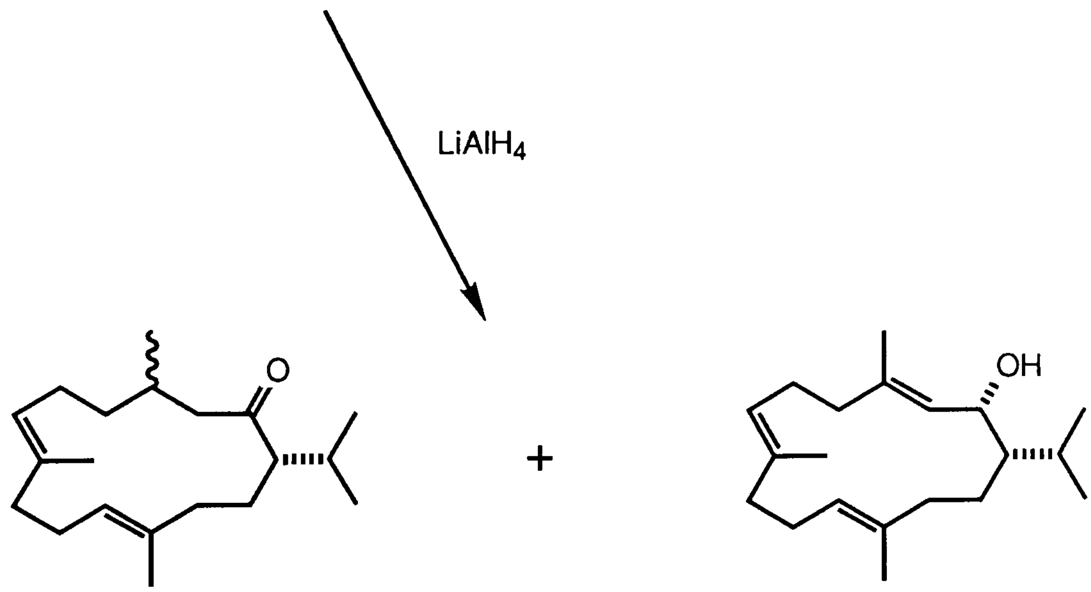
With the iodo-dienone (149) prepared we were ready to attempt our new radical methodology to prepare the macrocycle. Thus the iodo-dienone (149) was treated with one equivalent of tributyltin hydride and catalytic azodiisobutyronitrile in dry, deaerated, refluxing benzene at a concentration of 3mM. We were again delighted to observe that cyclisation had occurred, giving the cyclised enone as a mixture of the 10E-isomer (148) and the 10Z-isomer (158) (Scheme 76) in a ratio of 4:1 and in a combined isolated yield of 35%. The cyclic enones (148) and (158) were readily separated by preparative high pressure liquid



(149)



(148) 4 : 1 (158)



(159) (41)

<u>Scheme 76</u>

chromatography. PMR and CMR data closely matched that for the cyclic enones (132) and (133) prepared previously. Again, the 10*Z*-isomer showed a large shift in the CMR spectrum for C_{12}, (from δ15 ppm to δ23 ppm) due to the γ effect. Cyclic enone (148) had previously been prepared by a different route by Kato in a total synthesis of mukulol[51] (41) and comparison of spectral data confirmed its structure.

The final reduction step had previously been carried out by Kato using lithium aluminium hydride -but only in poor yield. We therefore tried a number of alternative procedures. Sodium borohydride in methanol or ethanol failed to react at all and addition of cerium trichloride[135] was to no advantage. Ultimately we were forced to resort to the literature method. Thus the cyclic enone (148) was treated with an excess of lithium aluminium hydride in diethyl ether at 0°C to give, after work up and purification, the cyclic ketone (159) in 33% yield, and *dl*-mukulol (41) in 22% yield. Spectral data for *dl*-mukulol were in excellent agreement with the literature[51].

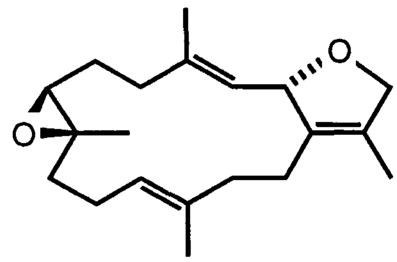
In conclusion, our studies of radical macrocyclisation have covered a number of systems. It has been found that an alkene/alkyne precursor requires additional activation compared with the small ring case. Not only this but the substitution of the alkene is of critical importance, any degree of substitution at the β-position apparently preventing cyclisation. Nevertheless, provided these conditions are fulfilled, radical macrocyclisation is possible and indeed offers a convenient method for the preparation of large rings. This has been illustrated by the formal synthesis of a cembranolide (37) and the total synthesis of dl-mukulol (41), both involving a radical macrocyclisation as the key step.

APPENDIX

Dihydrofuran rings of the type contained in deoxysarcophine (24) occur only rarely in nature. This is almost certainly because of the ease with which they can be oxidised to furanones (for example deoxysarcophine, on exposure to air and light, is readily autoxidised to sarcophine (19)[136]) or to furans. Some examples which are known have alkyl substituents such that oxidation is prevented, for example the carotenoids rubichrome (160)[137] and citroxanthin (161)[138]. Thus deoxysarcophine (24) is particularly unusual in this respect. Two rare examples of non-cembranoidal dihydrofurans without such substitution, (162) and (163), have recently been isolated from Davana oil, the Indian essential oil from *Artemisia pallens*[139]. These dihydrofurans are responsible for the exotic aroma of the oil.

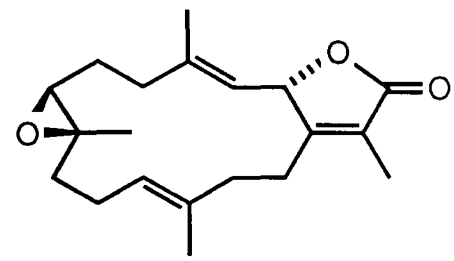
Among the marine cembranoids isolated from soft corals, a number of related compounds contain a dihydrofuran ring. The simplest is sarcophytonin-A (164) isolated from *Sarcophyton glaucum*[140]. As well as deoxysarcophine (24), two other epoxides, the 10,11-epoxide isosarcophytoxide (165) and the *bis*-epoxide (166), have been isolated from an unknown species of the genus *Sarcophyton*[141]. A more complex example is sarcoglaucol (167), a potent icthyotoxin isolated from *Sarcophyton glaucum*[142].

With a number of natural products containing the dihydrofuran ring, a general procedure for its synthesis is certainly of some interest. An approach which appealed to us was the use of a low valent titanium induced coupling of a 1,5-dicarbonyl compound to form the double bond (Scheme 77). Extensive studies have been made of the use of low valent



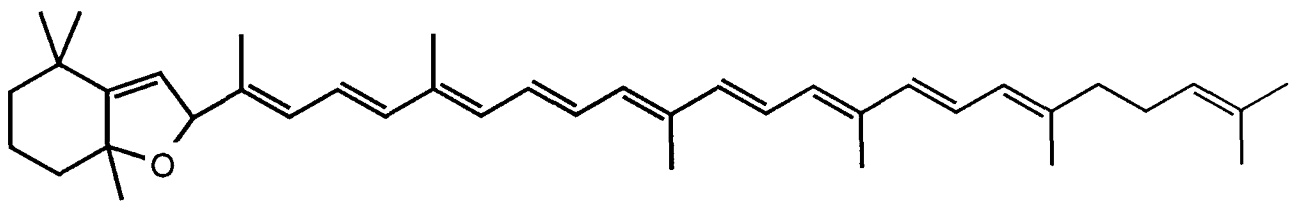
(24)

Deoxysarcophine



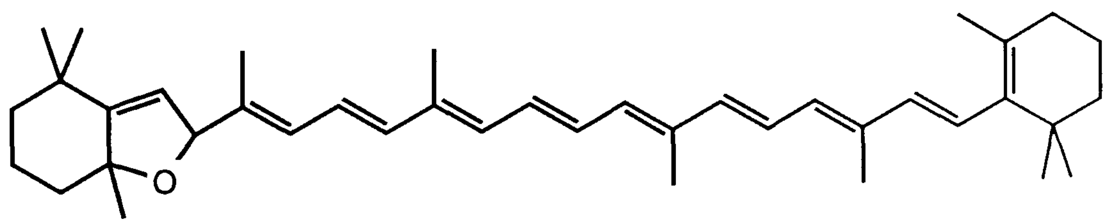
(19)

Sarcophine



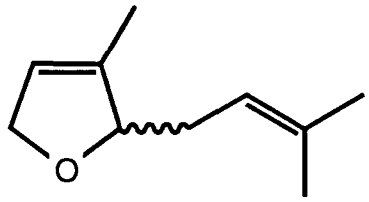
(160)

Rubichrome

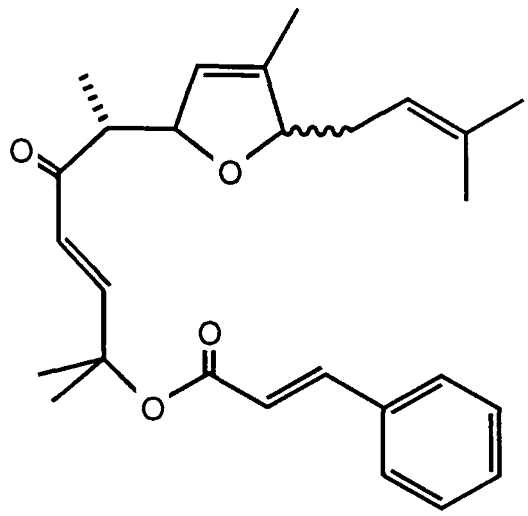


(161)

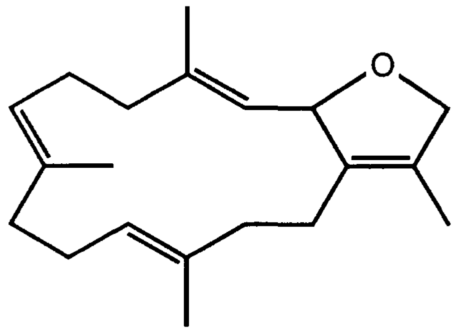
Citroxanthin



(162)

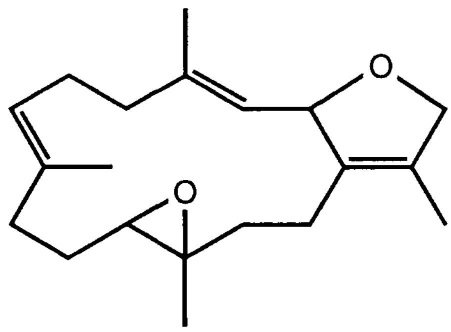


(163)



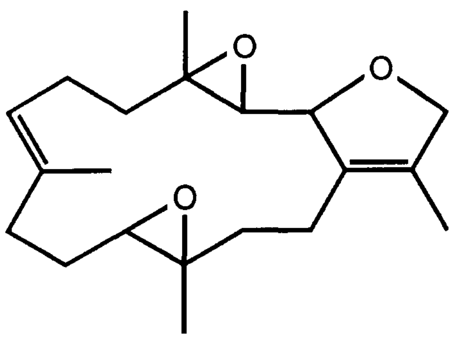
(164)

Sarcophytonin-A

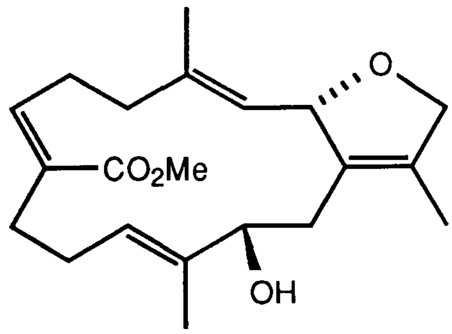


(165)

Isosarcophytoxide

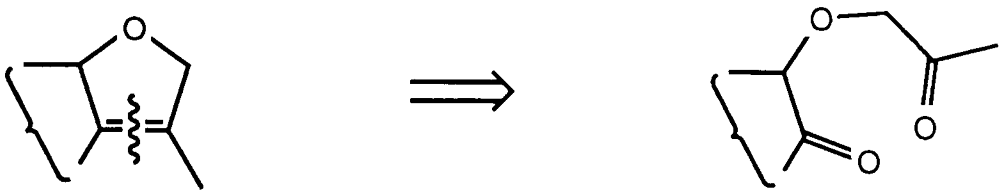


(166)

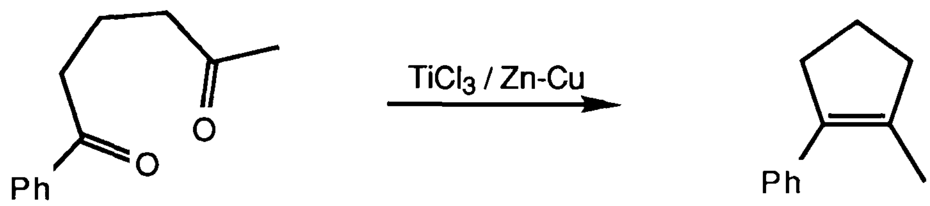


(167)

Sarcoglaucol

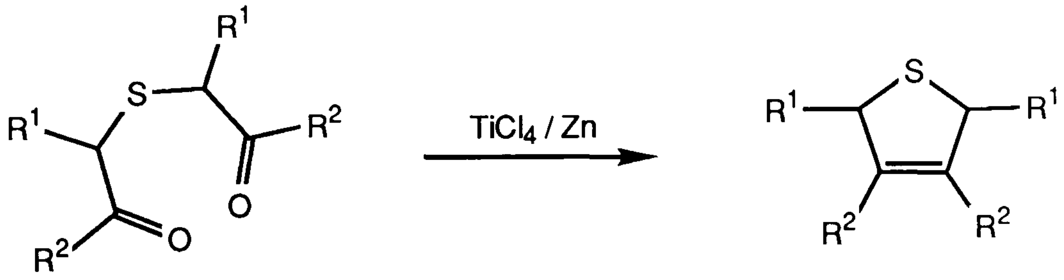


Scheme 77

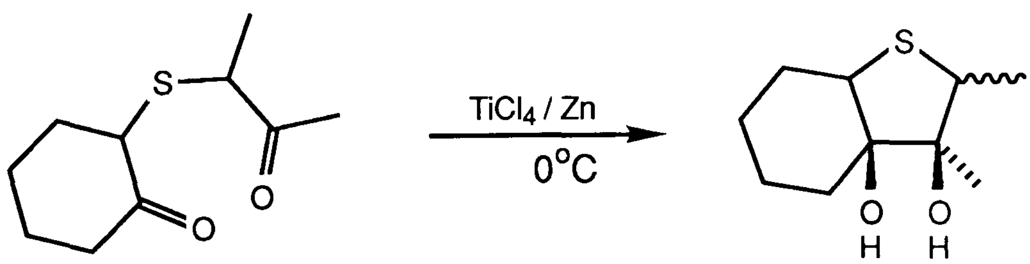


(168)

Scheme 78



Scheme 79

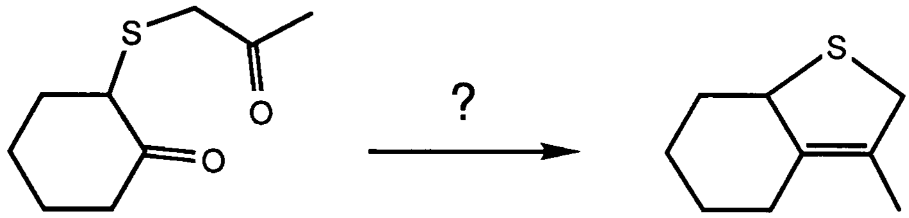


(169) (170)

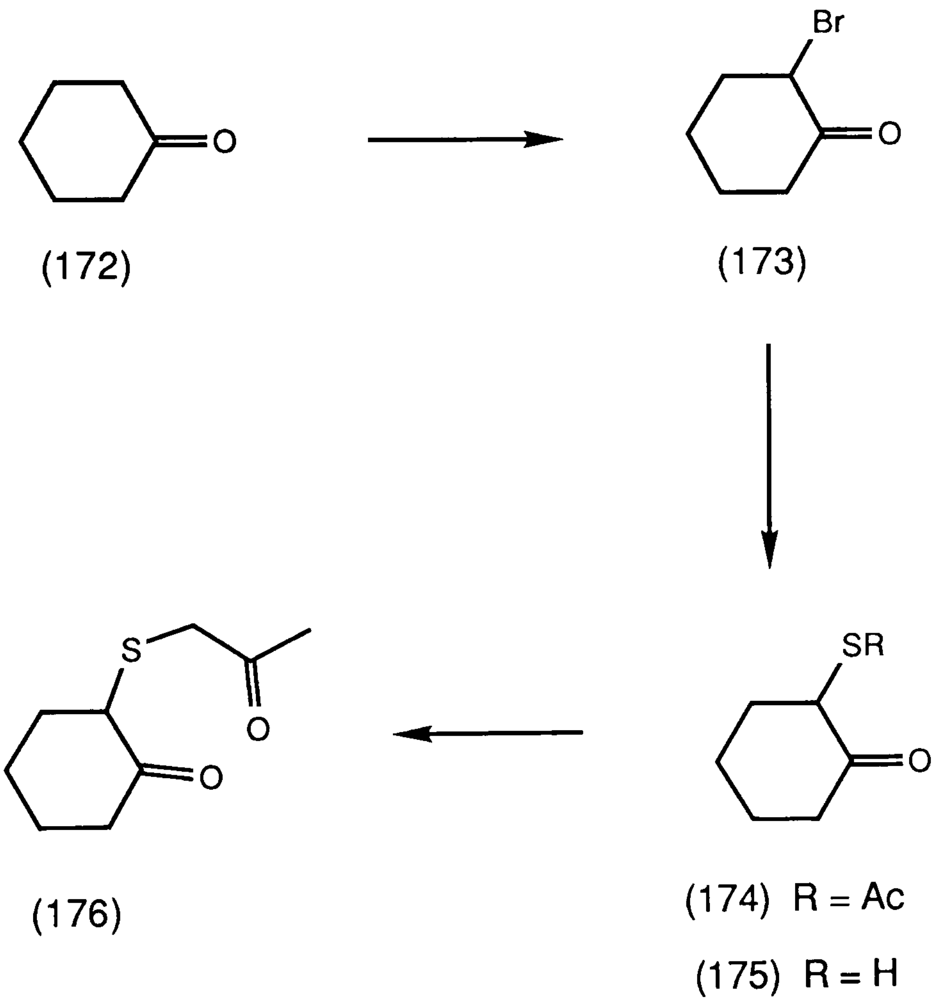
Scheme 80

titanium in synthesis[89], and McMurry has shown that this is a suitable method for the preparation of the cyclopentene (168) (Scheme 78). Also Nakayama has subsequently used a similar procedure in the preparation of dihydrothiophenes (Scheme 79)[143]. However, the above examples all possess an aromatic substituent (R_2=Ar). Such a substituent would have a large stabilising effect on the transition state which is almost certainly radical in character[88]. Thus one key question is whether the aromatic substituent is a critical feature for the reaction to occur. It should be noted that many of McMurry's other examples, forming larger rings, do not possess aromatic substituents and that Nakayama has reported the cyclisation of diketone (169) (Scheme 80)[144], using milder conditions, to give the cyclised diol (170). It was decided therefore to carry out an initial study on an analogous sulphur containing system (Scheme 81).

Thus the diketone (176) was prepared as follows (Scheme 82). Initial formation of the thiol (175) was achieved <u>via</u> bromo-ketone (173). Cyclohexanone (172) was treated with one equivalent of bromine in water at 0°C to give bromocyclohexanone (173) in 44% yield[145]. Treatment of this with one equivalent of the sodium salt of thiol acetic acid in tetrahydrofuran gave the thioester (174) in 64% yield. Saponification of the thioester using a two phase system of aqueous sodium hydroxide and diethyl ether gave, after acidic work up, the thiol (175) in approximately quantitative yield[146]. Addition of the 2-oxopropyl group was then achieved by reaction of the thiol (175) with chloroacetone in tetrahydrofuran at 0°C in the



Scheme 81

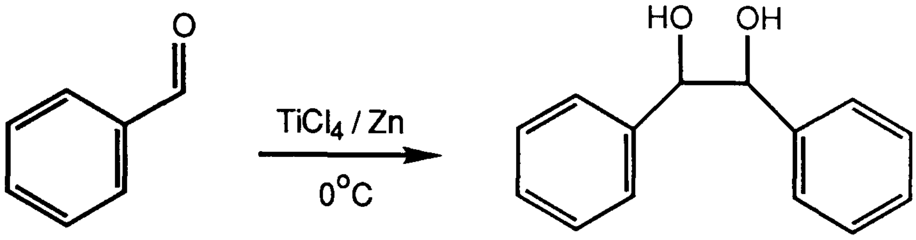


Scheme 82

presence of triethylamine to give the diketone (176) in 53% yield[146].

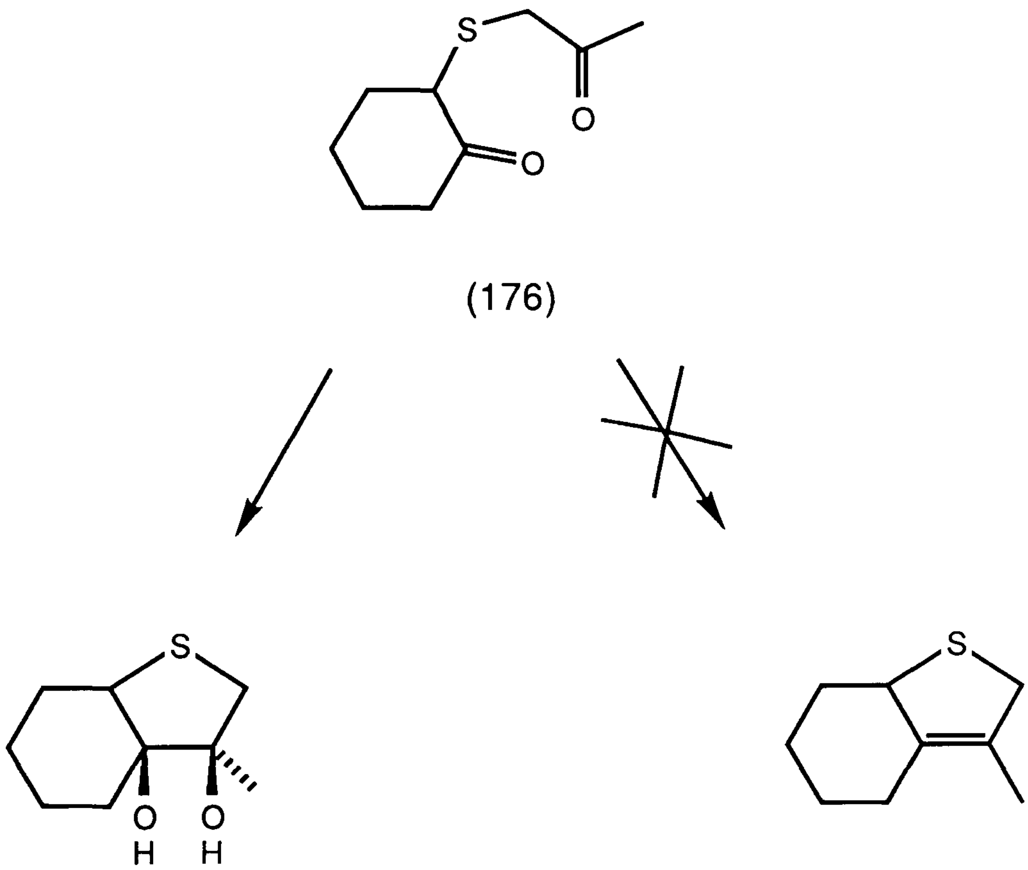
With the diketone (176) in hand, attempts could be made to carry out a cyclisation using low valent titanium. Given Nakayama's success in cyclising the related diketone (169) under mild conditions to give the cyclic diol (170), we initially attempted a similar coupling under the same conditions on diketone (176). First, however, we wished to ensure that the correct reaction conditions could be generated. Thus a model coupling of benzaldehyde was carried out (Scheme 83). Treatment of a solution of benzaldehyde in tetrahydrofuran at 0°C with an excess of titanium tetrachloride and zinc gave the expected diol (177) as a mixture of diastereoisomers in an excellent 98% yield[147]. Moving to the diketone (176), reaction under the same conditions did give the cyclic diol (178) (Scheme 84), though only in a yield of 8% (compare Nakayama's yield of 50% for Scheme 80[144]). Unfortunately, attempts to carry out the reaction at elevated temperatures in order to favour formation of the dihydrothiophene (179) failed entirely.

Despite these rather disappointing initial results, it was decided to extend the investigation to the analogous oxygen containing system. The diketone (184) was prepared by an alternative procedure to that used to prepare the sulphur analogue. Thus slow addition of cyclohexene oxide (180) (Scheme 85) to a large excess of 2-methylprop-2-en-1-ol (181) in dichloromethane in the presence of catalytic boron trifluoride etherate[148] gave the alcohol (182). This was readily oxidised to the ketone (183) using pyridinium chlorochromate in



(177)

Scheme 83

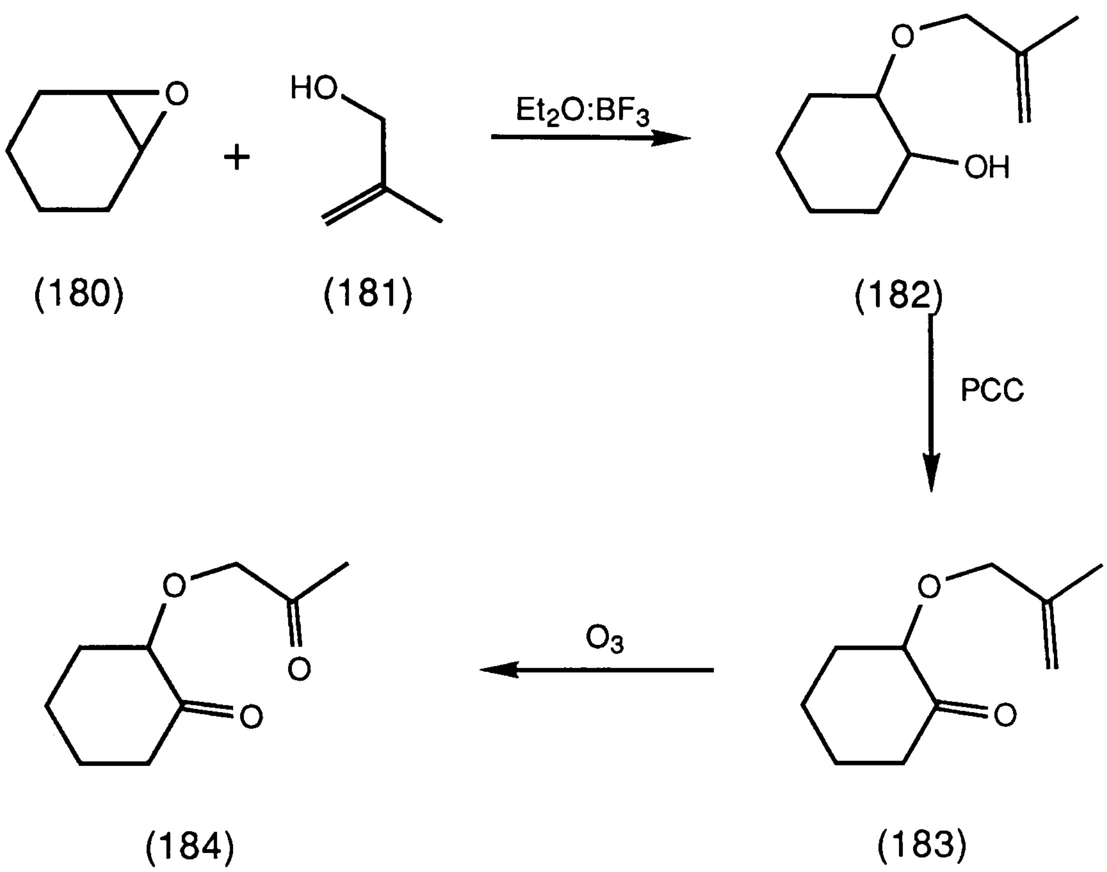


(176)

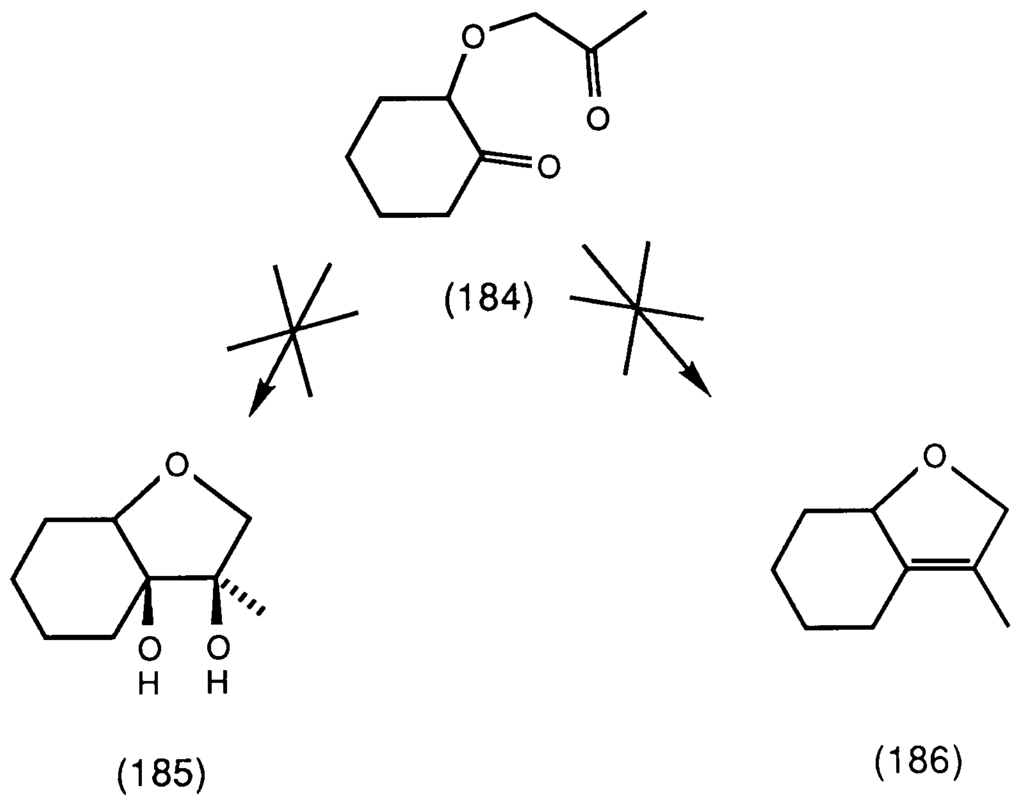
(178)

(179)

Scheme 84



Scheme 85



Scheme 86

dichloromethane. Cleavage of the olefin using ozone in dichloromethane at -78°C, followed by the addition of dimethyl sulphide then gave the required diketone (184) in 72% yield.

With the diketone (184) in hand, attempts could be made to carry out a cyclisation using low valent titanium. Unfortunately, under no conditions (titanium tetrachloride-zinc/0°C, titanium tetrachloride-zinc/66°C or titanium trichloride-lithium aluminium hydride/66°C) was cyclisation observed to occur to give either the diol (185) or dihydrofuran (186) (Scheme 86).

The reason for the failure of these reactions is not entirely clear. It may be that without aromatic substitution there is insufficient driving force for formation of the olefin, thus permitting alternative side reactions. Also, without blocking the α-positions, various aldol reactions may occur giving rise to the complex mixtures observed. Another important point in the dihydrofuran case is the affinity of titanium for oxygen (illustrated by the conversion of diols and epoxides to olefins[149]) which might lead to attack of the ether linkage.

In conclusion, it has been shown that the use of low valent titanium would not appear to be a suitable method for the general preparation of dihydrofurans and dihydrothiophenes.

EXPERIMENTAL SECTION

GENERAL DETAILS

Melting points were determined using a Kofler hot-stage instrument and are uncorrected and Kugelrohr bulb-to-bulb distillations were performed on a Büchi GKR-50 rotating bulb apparatus.

Infra-red spectra were recorded on a Pye-Unicam SP3-100 spectrometer. Spectra were recorded as thin liquid films on sodium chloride discs or as solutions in the stated solvent. Ultraviolet absorption spectra were obtained on a Philips PV 8720 UV/Visible scanning spectrophotometer as dilute solutions in the stated solvent (ϵ follows λ_{max} in parentheses).

Proton magnetic resonance spectra were recorded at 90MHz unless otherwise stated and were recorded as either continuous wave spectra at 90MHz on a Perkin Elmer R32 instrument or as pulsed fourier transform spectra on a Bruker WP80SY PFT, a Jeol FX90Q PFT, a Bruker WM250 PFT, or a Bruker AM400 PFT spectrometer at 80MHz, 90MHz, 250MHz and 400MHz respectively. Carbon-13 nuclear magnetic resonance spectra were also recorded on these instruments at 20.15MHz, 22.5MHz, 62.9MHz and 100.6MHz respectively as stated. All NMR measurements were obtained for dilute solutions in deuteriochloroform containing tetramethylsilane (TMS) or chloroform as an internal standard and chemical shifts (δ) are reported in ppm from TMS. Line separations (*J*) are given in hertz and multiplicities are designated as follows: no designation -singlet, d -doublet, t -triplet, q -quartet, m -multiplet, br -broad. For CMR, designations were determined by distortionless enhancement by polarisation transfer (DEPTA) pulse sequences in conjunction with broad-band decoupled CMR.

Mass spectra were recorded on an AEI MS902 or on a VG 7070E instrument using either electron impact or chemical ionisation (C.I.) techniques. Microanalyses were performed using a Perkin Elmer 240B elemental analyser. Microanalyses have been obtained on key intermediates where possible. Many of the oils, however, although pure by TLC, CMR and accurate mass spectroscopy, failed to give microanalytical data within the required limits.

All organic solutions were dried over magnesium sulphate or sodium sulphate and solvents were removed under reduced pressure on a Büchi rotary evaporator. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F254 aluminium backed plates which were visualised with UV light (254nm) or alternatively with basic potassium permanganate, acidic alcoholic 2,4-dinitrophenylhydrazine, dilute aqueous sulphuric acid or acidic alcoholic vanillin spray reagents. Silica refers to silica gel 60.

Gas-liquid chromatography (GLC) was performed on a Pye-Unicam GCD chromatograph with flame-ionisation detection using a nitrogen flow rate of 40ml/min.

High pressure liquid chromatography (HPLC) was performed on a Waters Associates Liquid Chromatograph equipped with a 30cm column (internal diameter 7.8mm) packed with μPorasil.

An LG-2-LI Corona generator (Grace, Davison Chemical Instruments) was used for ozone production from oxygen.

Electrochemical Reductive Cyclisations: General Procedure-

The electrolysis apparatus used was a standard H-cell in which the diaphragm was a Nafion cation-exchange membrane. Two H-cells were used which differed only in size. The smaller H-cell (used for attempted small ring cyclisations and intermolecular couplings) had cathodic and anodic chambers of 12ml and 5ml respectively. The larger H-cell (used for attempted macrocyclisations) had cathodic and anodic chambers of 100ml and 50ml respectively. The cells were equipped with a mercury pool cathode (of 2.2cm or 3.5cm diameter), a platinum anode, and a reference electrode comprising a silver wire immersed in a DMF solution of tetrabutylammonium iodide (10mg/ml). The electrolyte (30ml or 150ml) was placed in the cathodic and anodic chambers and the ketone or aldehyde was then added to the catholyte. The electrolysis was then carried out at the appropriate cathodic potential. The mercury pool cathode and catholyte were stirred with a magnetic bar under a nitrogen or argon atmosphere during the electrolysis, and the control reduction potential was maintained with a Hi-tek Instruments DT 2101 potentiostat. When TLC analysis showed no further change in composition and/or the observed current had fallen to *ca.* zero, the catholyte was poured into water and extracted with diethyl ether. Evaporation of the dried extracts gave the crude product which was purified by column chromatography on silica.

E-Citral (74).-A solution of geraniol (500mg) in dichloromethane (2ml) was added in a single portion to a stirred suspension of manganese dioxide (5.0g) in dichloromethane (50ml). The mixture was stirred at room temperature for three hours and then filtered under suction. Evaporation of the filtrate left the enal (470mg, 95%) as a pale yellow oil, b.p. 108-110°C/13mmHg (lit[150]; b.p. 93-95°C/5mmHg); λ_{max}(EtOH) 238 (11,000) nm; ν_{max}(film) 2780, 1680, 1635, 1610 cm^{-1}; δ_H 10.02(d, J8, HC:O), 5.92(d, J8, :CH.C:O), 5.11(br, :CH), 2.4-2.15(m, $2xCH_2$), 2.20(CH_3.C:C.C:O), 1.71(CH_3), 1.63(CH_3) ppm; (Found: m/z 152; $C_{10}H_{16}O$ requires M 152).

2,6,11,15-Tetramethylhexadeca-2,6,10,14-tetraene-8,9-diol (75): Method A.-Electroreduction of the aldehyde (74) was carried out following the general procedure using a solution of sodium perchlorate (2.57g) in dry DMF (140ml) as electrolyte. In addition, chromium trichloride hexahydrate (370mg) was added to the catholyte to give a bright green solution.

A solution of the aldehyde (74) (200mg) in dry DMF (1ml) was added in a single portion and a cathodic potential of -1.0V was then maintained for 6.5h by which time the current had fallen to zero and TLC analysis showed consumption of the aldehyde. The catholyte was poured into water (50ml) and extracted with hexane (4x100ml). The combined extracts were then washed with water (4x50ml) and brine (50ml). Evaporation of the dried extracts left a colourless oil. The oil was purified by column chromatography on silica using hexane-diethyl ether (5:1) as eluant to give firstly unreacted aldehyde (60mg) and then the diol (75) (40mg, 20%) as a colourless oil; $\nu_{max}(CHCl_3)$ 3400(br), 1670, 1605, 1105 cm^{-1}; δ_H 5.10(br m, 4x:CH), 4.25(br m, 2xC<u>H</u>OH), 2.2-1.9(m, $4xCH_2$), 1.69($4xCH_3$), 1.60($2xCH_3$) ppm; (Found: m/z 306.2546; $C_{20}H_{34}O_2$ requires <u>M</u> 306.2559).

<u>Method B</u>.-Electroreduction of the aldehyde (74) was carried out following the general procedure using a solution of anhydrous tetrabutylammonium perchlorate (4.80g) in dry DMF (140ml) as electrolyte. In addition, diethyl malonate (500mg) was added to the catholyte solution.

A solution of the aldehyde (74) (100mg) in dry DMF (1ml) was added in a single portion and a cathodic potential of -1.75V was then maintained for 0.5h by which time TLC analysis showed consumption of the aldehyde. The catholyte was poured into water (50ml) and extracted with hexane (4x100ml). The combined extracts were then washed with brine (4x50ml). Evaporation of the dried extracts left an oily residue (290mg). The residue was purified by column chromatography on silica using hexane-diethyl ether (4:1, 2:1, 1:1) as eluant to give firstly diethyl malonate and then the diol (75) (12mg, 12%) as a colourless oil having identical physical and spectral data to those obtained previously.

6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (77).-A solution of sodium hydroxide (6M, 3.6ml) was added dropwise over ca. 20min to a stirred solution of 3-methylcyclohex-2-en-1-one (3.86g) and hydrogen peroxide (30% in water, 12.4ml) in methanol (90ml). During the addition the temperature of the solution was maintained below 30°C. The solution was then stirred at room temperature for 2h, then diluted with water (80ml) and then extracted with diethyl ether (5x40ml). The combined extracts were washed with water (15ml) and then with brine (15ml). Evaporation of the dried extracts left an oily residue (5.11g), distillation of which gave the epoxy ketone (1.54g, 35%) as a colourless oil, b.p. 82°C/13mmHg (lit[151]; b.p. 71-73°C/9mmHg); ν_{max}(film) 1705 cm^{-1}; δ_H 3.05(CH), 2.7-1.6(m, $3xCH_2$), 1.45(CH_3) ppm; (Found: m/z 126; $C_7H_{10}O_2$ requires M 126).

Hept-6-yn-2-one (78).-p-Toluenesulphonylhydrazide (2.31g) was added in a single portion to a stirred solution of the epoxide (77) (1.55g) in glacial acetic acid (16ml) and dichloromethane (16ml) at -15°C. The resulting yellow solution was stirred at -15°C for 1h, then at 0°C for 1h and finally at room temperature for 2h before it was cautiously poured into a saturated solution of sodium carbonate (60ml). Sodium carbonate was added to the mixture until effervescence stopped (ca. 22g). The mixture was diluted with water (10ml) and then extracted with dichloromethane (3x70ml). The combined extracts were washed with saturated sodium carbonate solution (40ml). Evaporation of the dried extracts left an orange solution (1.94g), distillation of which gave the keto-acetylene (410mg, 30%) as a colourless oil, b.p. 54-56°C/7mmHg (lit[152]; b.p. 63°C/11mmHg); ν_{max}(film) 3300, 2120, 1710 cm^{-1}; δ_H 2.52(t, *J*7.5, $CH_2C{:}O$), 2.3-1.6(m, 2xCH_2), 2.10(CH_3), 1.91(t, *J*2.5, ⋮CH) ppm.

Oct-3-yn-2-ol (79).-Hex-1-yne (5.0g) was added to a stirred solution of *n*-butyllithium (1.28M in hexane, 48ml) in dry THF (15ml) and dry diethyl ether (30ml) at -15°C. Acetaldehyde (2.68g) was added to the yellow solution formed and the solution allowed to warm to room temperature over 3.5h to give a deep red solution. The reaction was quenched by the addition of ice-water (50ml) and then extracted with diethyl ether (2x50ml). The combined extracts were washed with water (2x50ml) and then with saturated ammonium chloride solution (2x40ml). Evaporation of the dried extracts left an oily residue (11.48g), distillation of which gave the hydroxy acetylene (4.18g, 54%) as a colourless oil, b.p. 100°C/25mmHg; δ_H 4.51(m, C*H*OH), 2.90(br, OH), 2.19(m, CH_2C⋮), 1.8-1.3(m, 2xCH_2), 1.40(d, *J*6.5, $C\underline{H}_3CHOH$), 0.91(t, *J*7, $CH_2C\underline{H}_3$) ppm; (Found: m/z(C.I.) 111.0825; $C_8H_{14}O$ requires *M*-CH_3 111.0810).

Oct-7-yn-2-ol (81).-Dry 1,3-diaminopropane (150ml) was added cautiously to sodium hydride (10.02g) at room temperature. The mixture was heated to 70°C and stirred at 70°C for 1h during which time hydrogen gas was evolved. The mixture was cooled to 50°C and then the alcohol (79) (4.18g) was added dropwise over *ca*. 5min to form a deep red solution. The mixture was stirred at 50°C for a further 15h before it was allowed to cool to room temperature. The mixture was quenched with ice-water (100ml) and then extracted with diethyl ether (3x100ml). The combined extracts were washed successively with water (2x100ml), dilute hydrochloric acid (5%, 100ml) and brine (100ml). Evaporation of the dried extracts left the hydroxy acetylene (4.02g, 96%) as a colourless oil; ν_{max}(film) 3360(br), 3310, 2120, 1120 cm^{-1}; δ_H 3.84(m, C<u>H</u>OH), 2.22(m, $CH_2C\vdots$), 1.97(t, <u>J</u>2.5, $\vdots$CH), 1.7-1.35(3xCH_2), 1.21(d, <u>J</u>7, CH_3) ppm; (Found: m/z(C.I.) 109; $C_8H_{14}O$ requires <u>M</u>-OH 109).

<u>Oct</u>-7-<u>yn</u>-2-<u>one</u> (83).-The alcohol (81) (4.18g) was added in a single portion to a stirred mixture of pyridinium chlorochromate (18.2g) and celite (8.0g) in dry dichloromethane (200ml) at room temperature and the dark brown slurry formed was then stirred for 3h at room temperature. Evaporation left a powdery residue which was purified by chromatography on a short pad of Florisil using diethyl ether as eluant to give the keto-acetylene (3.84g, 93%) as a colourless oil, b.p. 85-90°C(oven)/16mmHg (lit[153]; 80°C/17mmHg); ν_{max}(film) 3290, 2120, 1710 cm^{-1}; δ_H 2.49(t, <u>J</u>7, CH_2C:O), 2.23(dt, <u>J</u>2.5 and 7, $CH_2C\vdots$), 2.17(CH_3), 1.98(t, <u>J</u>2.5, $\vdots$CH), 1.9-1.4(m, 2xCH_2) ppm; δ_C(20MHz) 208.1, 84.0, 68.6(d), 43.1(t), 29.7(q), 28.0(t), 22.9(t), 18.3(t) ppm; (Found: m/z(C.I.) 125.0969; $C_8H_{12}O$ requires <u>M</u>+H 125.0966).

<u>Non</u>-3-<u>yn</u>-2-<u>ol</u> (80).-Hept-1-yne (5.0g) was added to a stirred solution of <u>n</u>-butyllithium (1.6M in hexane, 32.5ml) in dry THF (15ml) and dry diethyl ether (30ml) at -15°C. Acetaldehyde (2.30g) was added to the cloudy white solution formed and the solution allowed to warm to room temperature over 3.5h to give a

deep orange solution. The reaction was quenched by the addition of ice-water (50ml) and then extracted with diethyl ether (2x50ml). The combined extracts were washed with water (2x50ml) and then with brine (50ml). Evaporation of the dried extracts left an oily residue (7.30g), distillation of which gave the hydroxy acetylene (5.19g, 71%) as a colourless oil, b.p. 90°C/8mmHg; δ_H 4.56(q, J6.5, CHOH), 3.26(br, OH), 2.45-2.1(m, CH_2C⋮), 1.7-1.1(m, $3xCH_2$), 1.44(d, J6.5, CH_3CHOH), 0.92(t, J7, CH_2CH_3) ppm; (Found: m/z(C.I.) 123.1180; $C_9H_{16}O$ requires M-OH 123.1174).

Non-8-yn-2-ol (82).-Dry 1,3-diaminopropane (150ml) was added cautiously to sodium hydride (10.80g) at room temperature. The mixture was heated to 70°C and stirred at 70°C for 1h during which time hydrogen gas was evolved. The mixture was cooled to 50°C and then the alcohol (80) (5.00g) was added dropwise over ca. 5min to form a deep red solution. The mixture was stirred at 50°C for a further 15h before it was allowed to cool to room temperature. The mixture was quenched with ice-water (150ml) and then extracted with diethyl ether (3x100ml). The combined extracts were washed successively with water (2x100ml), dilute hydrochloric acid (5%, 100ml) and brine (100ml). Evaporation of the dried extracts left the hydroxy acetylene (4.93g, 98%) as a colourless oil; $\nu_{max}(CHCl_3)$ 3460(br), 3320, 2120, cm^{-1}; δ_H 3.82(q, J6.5, CHOH), 2.54(br, OH), 2.35-2.1(m, CH_2C⋮), 1.98(t, J2.5, ⋮CH), 1.7-1.3(m, $4xCH_2$), 1.19(d, J6.5, CH_3) ppm; (Found: m/z(C.I.) 125.0982; $C_9H_{16}O$ requires M-CH_3 125.0966).

Non-8-yn-2-one (84).-The alcohol (82) (4.93g) was added in a single portion to a stirred mixture of pyridinium chlorochromate (18.0g) and celite (18.0g) in dry dichloromethane (200ml) at room temperature and the dark brown slurry formed was then stirred for 4h at room temperature. Evaporation left a powdery residue which was purified by chromatography on a short pad of Florisil using diethyl ether as eluant to give the keto-acetylene (4.36g, 90%) as a colourless oil, b.p. 110-115°C(oven)/16mmHg; ν_{max}(film) 3310, 2120, 1710 cm^{-1}; δ_H 2.37(t, J6.5, $CH_2C{:}O$), 2.10(m, $CH_2C\vdots$), 2.05(CH_3), 1.88(t, J2.5, $\vdots CH$), 1.7-1.3(m, 3xCH_2) ppm; δ_C(20MHz) 208.4, 84.1, 68.2(d), 43.3(t), 29.6(q), 28.1(2xt), 23.1(t), 18.1(t) ppm; (Found: m/z(C.I.) 139.1142; $C_9H_{14}O$ requires M+H 139.1123).

Reductive Cyclisations Initiated with Sodium Naphthalene Radical Anion: General Procedure.-Freshly cut sodium (580mg) was added in small pieces to a stirred solution of dry recrystallised naphthalene (2.0g) in dry THF (30ml) under nitrogen and the resulting dark green solution was then stirred at room temperature for 3h. This routinely gave a *ca.* 0.5M solution of the reagent.

The solution of sodium naphthalenide was added dropwise under nitrogen to a well stirred solution of the acetylene ketone in dry THF at room temperature until a faint green end-point was reached. The colouration discharged itself in about 1min. The mixture was poured into dilute hydrochloric acid (5%, 25ml), then diluted with water (100ml) and extracted with diethyl ether (3x25ml). The combined ether extracts were washed successively with dilute hydrochloric acid (5%, 25ml), water (4x25ml) and brine (25ml). Evaporation of the dried extracts left the crude product which was purified by column chromatography on silica.

1-Methyl-2-methylenecyclopentan-1-ol (85): Method A.- Electroreduction of the ketone (78) was carried out following the general procedure using a solution of tetraethylammonium tosylate (3.40g) in dry DMF (17ml) as electrolyte.

A solution of the ketone (78) (180mg) in dry DMF (1ml) was added in a single portion and a cathodic potential of -2.45V was then maintained for 19h by which time TLC analysis showed consumption of the ketone. The catholyte was poured into brine (30ml) and extracted with diethyl ether (3x20ml). The combined extracts were washed with water (20ml) and then with brine (20ml). Evaporation of the dried extracts left an oily residue (170mg). The residue was purified by column chromatography on silica using hexane-diethyl ether (2:1) as eluant to give the alcohol (20mg, 11%) as a colourless oil; $\nu_{max}(CHCl_3)$ 3430(br), 1655, 910 cm^{-1}; δ_H 5.09(m, :C$\underline{H}$H), 4.93(m, :CH$\underline{H}$), 3.74(br, OH), 2.45(m, CH_2C:), 1.8-1.6(m, $2xCH_2$), 1.37(CH_3) ppm.

Method B.-Treatment of a solution of the ketone (78) (60mg) in dry THF (20ml) with a solution of sodium naphthalene radical anion (ca. 0.5M in THF, 2ml), by the general procedure, followed by column chromatography on silica using pentane then dichloromethane as eluants gave the alcohol (26.6mg, 44%) as a colourless oil having identical physical and spectral data to those obtained previously.

1-*Methyl*-2-*methylenecyclohexanol* (86).-Treatment of a solution of the acetylene ketone (83) (500mg) in dry THF (30ml) with a solution of sodium naphthalene radical anion (*ca*. 0.5M in THF, 10ml), by the general procedure, followed by column chromatography on silica using pentane then dichloromethane as eluants gave the alcohol (170mg, 34%) as a colourless oil; ν_{max}(film) 3400(br), 1640, 895 cm^{-1}; δ_H 4.92(m, :C*H*H), 4.73(m, :CH*H*), 2.2(m, CH_2C:), 1.8-1.4(m, 3xCH_2), 1.36(CH_3) ppm; (Found: m/z 125.0970; $C_8H_{14}O$ requires *M*-H 125.0966).

Attempted Reductive Cyclisation of non-8-yn-2-one (84).-Treatment of a solution of the acetylene ketone (84) (500mg) in dry THF (40ml) with a solution of sodium naphthalene radical anion (0.5M in THF, 9.5ml), by the general procedure, followed by column chromatography on silica using pentane-diethyl ether (1:0, 1:1, 1:2) as eluant gave firstly the acetylene alcohol (82) (34mg, 7%) as a colourless oil having identical physical and spectral data to those obtained previously, and secondly the *naphthalene adduct* (88) (70mg, 7%) as a colourless oil; ν_{max}(film) 3320(br), 3300, 2130, 1110, 765 cm^{-1}; δ_H 7.18(C_6H_4), 6.18(m, 2x:CH), 3.52(m, CH_2C: and CH), 2.81(br, OH), 2.22(m, $CH_2C\vdots$), 1.95(t, *J*2.5, $\vdots$CH), 1.51(m, 4xCH_2), 1.33(CH_3) ppm; (Found: m/z 250.1733; $C_{19}H_{24}O$ requires *M*-H_2O 250.1722).

Geranyl ethanoate (90).-Acetic anhydride (6.7g) was added in a single portion to a stirred solution of geraniol (10.27g) in pyridine (6.3g). The solution was stirred at room temperature for 18h, then quenched with water (100ml) and extracted with diethyl ether (3x20ml). The combined extracts were washed successively with dilute hydrochloric acid (5%, 30ml), water (2x30ml) and brine (30ml). Evaporation of the dried extracts left a pale yellow residue, distillation of which gave the acetate (12.00g, 92%) as a colourless oil, b.p. 122-123°C/20mmHg (lit[154]; b.p. 130-132°C/22mmHg); ν_{max}(film) 1735, 1665, 1235 cm^{-1}; δ_H 5.42(t, J7, :C<u>H</u>CH_2O), 5.16(br m, :CH), 4.65(d, J7, CH_2O), 2.25-1.9(m, 2xCH_2), 2.08(CH_3C:O), 1.74(2xCH_3), 1.64(CH_3) ppm.

6-Acetoxy-4-methylhex-4(E)-enal (91).-Pyridine (0.6g) was added to a stirred solution of the acetate (90) (1.5g) in dichloromethane (20ml) at -78°C. Ozone was bubbled through the solution until GLC analysis (5% Carbowax 20M, 150°C) showed complete consumption of starting material. Dimethyl sulphide (3.5ml) was added and the solution was then allowed to warm to room temperature over 1h. Evaporation left a dark brown oil which was dissolved in diethyl ether (20ml) and then washed successively with dilute hydrochloric acid (5%, 4x20ml), sodium hydroxide solution (2M, 3x5ml) and brine (5ml). Evaporation of the dried extracts left an oily residue (410mg). The residue was purified by column chromatography on silica using petroleum ether-diethyl ether (2:1) as eluant to give the aldehyde (160mg, 12%) as a colourless oil; δ_H 9.77(t, J1.3, HC:O), 5.37(t, J7.0,

:CH), 4.58(d, *J*7.0, CH_2O), 2.7-2.1(m, $2xCH_2$), 2.05(CH_3C:O), 1.73(CH_3) ppm; R_t(150°C, 5% Carbowax 20M), 4.4min.

E,E,E-Geranylgeraniol (89).-Commercially available seeds of *Bixa orellana* (800g) were added to petroleum ether (1.5l) and stirred vigorously for 18h at room temperature. The opaque orange coloured liquid was then decanted off and filtered to give a clear orange solution. Petroleum ether (800ml) was then added to the seeds and stirred vigorously for a further 4h before the orange coloured liquid was again decanted off and filtered. The combined filtrates were evaporated to leave a dark brown oleoresin (23.7g) which was then flash distilled (b.p. 140-185°C/2.5-3mmHg) to give an orange-brown oil (7.50g). The oil was purified by column chromatography on Silica gel G using first petroleum ether to remove two less polar extracts then petroleum ether-diethyl ether (1:1) to give geranylgeraniol (1.30g, 5% by weight of oleoresin) as a pale yellow oil, b.p. 170-175°C/4.5mmHg (lit[104]; b.p.(oven) 135-140°C/0.1mmHg); ν_{max}(film) 3330(br), 1660, 1005 cm^{-1}; δ_H 5.48(br t, *J*7, :C*H*CH_2O), 5.17(br m, $3xCH_3$), 4.18(d, *J*7, CH_2O), 2.18-1.94(m, $6xCH_2$), 1.71($2xCH_3$), 1.64($3xCH_3$) ppm; δ_C(22.5MHz) 138.9, 135.1, 134.7, 130.8, 124.4(d), 124.2(d), 123.9(d), 123.7(d), 59.0(t), 39.6(3xt), 26.7(t), 26.6(t), 26.3(t), 25.5(q), 17.5(q), 16.1(q), 15.8(2xq) ppm; (Found: m/z 290.2612; $C_{20}H_{34}O$ requires *M* 290.2610).

E,E,E-Geranylgeranyl ethanoate (92).-Acetic anhydride (20ml) was added in a single portion to a stirred solution of the alcohol (89) (10.00g) in pyridine (80ml). The solution was stirred at room temperature for 18h then quenched with water (300ml) and then extracted with hexane (3x100ml). The combined extracts were washed successively with dilute hydrochloric acid (5%, 3x100ml), water (2x100ml) and brine (100ml). Evaporation of the dried extracts left the acetate (11.08g, 97%) as a pale yellow oil, b.p. 170-175°C(oven)/2.8mmHg; ν_{max}(film) 1730, 1665, 1010 cm^{-1}; δ_H 5.40(br t, J7, :CHCH$_2$O), 5.16(br m, 3x:CH), 4.62(d, J7, CH$_2$O), 2.26-1.97(m, 6xCH$_2$), 2.08(CH$_3$C:O), 1.75(CH$_3$), 1.73(CH$_3$), 1.65(3xCH$_3$) ppm; (Found: m/z 272.2513; $C_{22}H_{36}O_2$ requires M-$C_2H_4O_2$ 272.2504).

14-Bromo-15-hydroxy-3,7,11,15-tetramethylhexadeca-2(E),6(E),10(E)-trienyl ethanoate (94).-Water (ca. 1.6l) was added dropwise to a stirred solution of the acetate (92) (11.00g) in THF (2l) until a slight cloudiness persisted. The solution was then cooled to 5°C and NBS (6.30g) added in a single portion. The solution was stirred under nitrogen for 1h and the temperature maintained at 0-5°C. The solution was then divided into three equal portions and each was diluted with water (800ml), extracted with hexane (3x300ml) and the hexane extracts washed with water (300ml). Evaporation of the dried combined extracts left an oily residue (15.54g). The residue was purified by column chromatography on silica (deactivated with 10% water) using hexane-diethyl ether (20:1, 10:1, 5:1) as eluant to give the bromohydrin (7.45g, 52%) as a pale yellow oil; ν_{max}(film) 3460(br), 1740, 1720, 1665 cm^{-1}; δ_H 5.35(br t, J7.0, :CHCH$_2$O), 5.19(br m, 2x:CH), 4.58(d, J7.0, CH$_2$O), 3.98(dd, J10.1 and 3.0, CHBr), 2.46-1.85(m, 6xCH$_2$), 2.05(CH$_3$C:O), 1.70(CH$_3$), 1.60(2xCH$_3$), 1.34((CH$_3$)$_2$COH) ppm; (Found: m/z 368.1716 and 370.1689; $C_{22}H_{37}BrO_3$ requires M-$C_2H_4O_2$ 368.1715 and 370.1694).

14,15-Epoxy-3,7,11,15-tetramethylhexadeca-2(E),6(E),10(E)-trien-1-ol (95).-Potassium carbonate (20.0g) was added in a single portion to a stirred solution of the bromohydrin (94) (7.40g) in methanol (500ml) and stirred at room temperature for 24h. The mixture was then diluted with water (500ml) and extracted with hexane (4x200ml). The combined hexane extracts were washed with water (200ml) and then with brine (200ml). Evaporation of the dried extracts left the epoxy alcohol (4.84g, 92%) as a pale yellow oil; ν_{max}(film) 3400(br), 1665, 1010 cm^{-1}; δ_H 5.42(br t, J6.8, :CHCH$_2$O), 5.16(br m, 2x:CH), 4.14(d, J6.8, CH$_2$O), 2.70(t, J6.1, HCO(epoxy)), 2.4-1.9(m, 6xCH$_2$), 1.67(CH$_3$), 1.61(2xCH$_3$), 1.30(CH$_3$(Me)CO), 1.26(Me(CH$_3$)CO) ppm; (Found: m/z(C.I.) 307; $C_{20}H_{34}O_2$ requires M+H 307).

14-Hydroxy-4,8,12-trimethyltetradeca-4(E),8(E),12(E)-trienal (97).-Periodic acid dihydrate (500mg) was added in a single portion to a vigorously stirred solution of the epoxy alcohol (95) (650mg) in THF (8ml) and diethyl ether (2ml) at 0°C. The solution was allowed to warm to room temperature over 1h before it was diluted with water (30ml) and extracted with diethyl ether (3x20ml). The combined ether extracts were washed successively with saturated sodium bicarbonate solution (20ml), water (20ml) and brine (2x20ml). Evaporation of the dried extracts left the hydroxy aldehyde (550mg, 98%) as a pale yellow oil which was comparatively pure. A small sample was purified by chromatography on silica; ν_{max}(film) 3400(br), 2720, 1720, 1665 cm^{-1}; δ_H 9.73(t, J1.8, HC:O), 5.41(t, J6.9, :C*H*CH_2O), 4.13(d, J6.9, 2x:CH), 2.6-1.8(m, 6xCH_2), 1.67(CH_3), 1.60(2xCH_3) ppm; δ_C(22.5MHZ) 202.5(d), 139.2, 135.0, 133.0, 125.5(d), 124.2(d), 123.8(d), 59.3(t), 42.2(t), 39.5(2xt), 31.9(t), 26.6(t), 26.4(t), 16.3(q), 16.1(q), 16.0(q) ppm; (Found: m/z 246.1988; C, 77.07; H, 10.95%; $C_{17}H_{28}O_2$ requires M 246.1984; C, 77.22; H, 10.67%).

3,7,11-Trimethyltetradeca-2(E),6(E),10(E)-triene-1,14-dial (69).-A solution of the hydroxy aldehyde (97) (410mg) in chloroform (2ml) was added in a single portion to a stirred suspension of manganese dioxide (4.0g) in chloroform (40ml). The mixture was stirred at room temperature for 3h and then filtered under suction. Evaporation of the filtrate left a yellow residue. The residue was purified by column chromatography on silica using hexane-diethyl ether (3:2) as eluant to give the dialdehyde (160mg, 37%) as a pale yellow oil; λ_{max}(EtOH) 238(25,500) nm; ν_{max}(film) 2730, 1730, 1675, 1635, 1615 cm^{-1}; δ_H 10.11(d, J8, :CH.*H*C:O), 9.86(t, J1.8, CH_2.*H*C:O), 5.97(d, J8, :C*H*.HC:O), 2.65-1.95(m, 6xCH_2), 2.20(CH_3.C:C.C:O), 1.64(2xCH_3) ppm; δ_C(22.5MHz) 202.3(d), 191.0(d), 163.4, 136.2, 133.1, 127.5(d), 125.2(d), 122.8(d), 42.1(d), 40.6(d), 39.4(d), 31.9(d), 26.5(d), 25.7(d), 17.6(q), 16.0(2xq) ppm; (Found: m/z

244.1817; $C_{17}H_{26}O_2$ requires $\underline{M}$-H_2O 244.1827).

Attempted Electrochemical Cyclisation of 3,7,11-Trimethyltetradeca-2(E),6(E),10(E)-triene-1,14-dial (69):

Method A.-Electroreduction of the dialdehyde was carried out following the general procedure using a solution of anhydrous sodium perchlorate (2.40g) in dry DMF (130ml) as electrolyte. In addition, chromium trichloride hexahydrate (150mg) was added to the catholyte to form a bright green solution.

A solution of the dialdehyde (69) (150mg) in dry DMF (5ml) was added dropwise by syringe-pump over 18h to the catholyte solution whilst maintaining a cathodic potential of -1.0V. This potential was maintained for a further 4h after the addition by which time the current had fallen to zero and the catholyte had become a grey suspension in a pale green solution. The catholyte was poured into water (60ml) and extracted with diethyl ether (6x50ml). The combined extracts were then washed with water (4x50ml) and brine (50ml). Evaporation of the dried extracts left an oily residue (100mg) which was shown by TLC analysis and PMR to be almost entirely unreacted starting material with no trace of the desired cyclic diol.

Method B.-Electroreduction of the dialdehyde was carried out following the general procedure using a solution of anhydrous sodium perchlorate (370mg) in dry DMF (30ml) as electrolyte. In addition, dimethyl malonate (230mg) was added to the catholyte solution.

A solution of the dialdehyde (69) (90mg) in dry DMF (5ml) was added dropwise by syringe-pump over 8h to the catholyte solution whilst maintaining a cathodic potential of -1.75V. This potential was maintained for a further 2h after the addition by which time the current had fallen to almost zero. The catholyte was poured into water (30ml) and extracted with diethyl ether (3x20ml). The combined extracts were then washed with water (2x20ml) and brine (20ml). Evaporation of the dried extracts left a yellow oil (230mg). The oil was purified by column chromatography on silica using diethyl ether-hexane (1:5, 1:2) as eluant to give firstly unreacted starting material (40mg), secondly dimethyl malonate (120mg) and finally dimethyl 4, 8, 12-trimethyl-12-oxotetradeca-4(*E*),8(*E*),12(*E*)-trienylidene-malonate (98) (11.0mg, 9%) as a colourless oil; λ_{max}(EtOH) 237 (9,500) nm; ν_{max}($CHCl_3$) 1745, 1725, 1670, 1635, 1610 cm^{-1}; δ_H 10.00(d, *J*7.7, HC:O), 7.27(m, HC:C.CO_2Me), 5.88(d, *J*7.7, :CH.C:O), 5.08(br, 2x:CH), 3.73(2xOCH_3), 2.4-1.9(6xCH_2), 2.18 (CH_3.C:C.C:O), 1.60(2xCH_3) ppm; (Found: m/z 376.2256; $C_{22}H_{32}O_5$ requires *M* 376.2250).

Method C.-Electroreduction of the dialdehyde was carried out following the general procedure using a solution of tetrabutylammonium perchlorate (22.2g) in dry DMF (130ml) as electrolyte.

A solution of the dialdehyde (69) (87mg) in dry DMF (5ml) was added dropwise by syringe-pump over 36h to the catholyte solution whilst maintaining a cathodic potential of -2.4V. This potential was maintained for a further 4h after the addition by which time the current had fallen to zero. The catholyte was poured into water (60ml) and extracted with diethyl ether (6x50ml). The combined extracts were then washed with water (4x50ml) and brine (2x50ml). Evaporation of the dried extracts left a tar-like residue (50mg) which was shown by TLC analysis to be a complex mixture of products and shown by PMR to contain no trace of the desired cyclic diol.

3-Methyloct-2-en-6-ynol (100).-Sodium nitrite (13.0g) was added in four portions over 1h to a vigorously stirred solution of geraniol (1.01g) in glacial acetic acid (20ml) and water (13ml) at -5°C. The solution was allowed to warm to room temperature and then stirred for 1.75h. The solution was heated to 60°C to give a pale orange solution and then stirred at 60°C for 2h. The reaction was quenched with water (60ml) and then extracted with dichloromethane (3x10ml). The combined extracts were washed with saturated sodium bicarbonate solution (20ml) and then with brine (20ml). Evaporation of the dried extracts left an oily residue (700mg). The residue was purified by column chromatography on silica using petroleum ether-diethyl ether (1:1) as eluant to give the acetylene (100mg, 11%) as a mixture of *E* and *Z* isomers and as a colourless oil; $\nu_{max}(CHCl_3)$ 3400(br), 1605, 1095 cm^{-1}; δ_H 5.7-5.4(m, :CH), 4.20(d, *J*7, CH_2O major isomer), 4.17(d, *J*7, CH_2O minor isomer), 2.25-2.0(m, $2xCH_2$), 1.79(CH_3), 1.71(CH_3) ppm; (Found: m/z 138.1036; $C_9H_{14}O$ requires *M* 138.1045).

3-Methyloct-2(E)-en-6-ynyl ethanoate (101).-Sodium nitrite (13.0g) was added in four portions over 1h to a vigorously stirred solution of the acetate (90) (1.37g) in glacial acetic acid (20ml) and water (20ml) at 0°C. The solution was allowed to warm to room temperature and then stirred for 1.5h. The solution was heated to 60°C to give a pale orange solution and then stirred at 60°C for 16h. The cooled reaction mixture was quenched with water (60ml) and then extracted with petroleum ether (4x25ml). The combined extracts were washed with saturated sodium bicarbonate solution (25ml) and then with brine (25ml). Evaporation of the dried extracts left an oily residue (580mg). The residue was purified by column chromatography on silica using petroleum ether-diethyl ether (10:1) as eluant to give the acetylene (130mg, 10%) as a colourless oil; ν_{max}(film) 1735, 1665, 1235 cm^{-1}; δ_H 5.47(t, J7, :CH), 4.53(d, J7, CH_2O), 2.27(br s, $2xCH_2$), 2.08(CH_3C:O), 1.81(CH_3), 1.76(CH_3) ppm; δ_C(20MHz) 170.9, 140.7, 119.5(d), 78.5, 76.1, 61.3(t), 38.9(t), 21.0(t), 17.7(q), 16.3(q), 3.4(q) ppm; (Found: m/z 120.0943; $C_{11}H_{16}O_2$ requires M-$C_2H_4O_2$ 120.0939).

14,15-Epoxy-3,7,11,15-tetramethylhexadeca-2(E),6(E),10(E)-trienyl ethanoate (108).-Acetic anhydride (10ml) was added in a single portion to a stirred solution of the alcohol (95) (2.40g) in pyridine (30ml). The solution was stirred at room temperature for 20h, then quenched with water (150ml) and extracted with hexane (3x100ml). The combined extracts were washed successively with dilute hydrochloric acid (5%, 4x50ml), water (2x50ml) and brine (50ml). Evaporation of the dried extracts left the epoxy-acetate (2.39g, 88%) as a pale yellow oil; ν_{max}(film) 1735, 1665, 1025 cm^{-1}; δ_H 5.34(t, _J_7.2, :C_H_CH_2O), 5.12(br m, 2x:CH), 4.58(d, _J_7.2, CH_2O), 2.69(t, _J_6.0, HCO(epoxy)), 2.2-1.9(m, $6xCH_2$), 2.04(CH_3.C:O), 1.70(CH_3), 1.60($2xCH_3$), 1.29(Me(CH_3)CO), 1.25(CH_3(Me)CO) ppm; (Found: m/z 288.2440; $C_{22}H_{36}O_3$ requires _M_-$C_2H_4O_2$ 288.2453).

14-Acetoxy-4,8,12-trimethyltetradeca-4(_E_),8(_E_),12(_E_)-trienal (107).-Periodic acid dihydrate (880mg) was added in a single portion to a vigorously stirred solution of the epoxy-acetate (108) (1.25g) in THF (15ml) and diethyl ether (2ml) at 0°C. The solution was allowed to warm to room temperature over 1h before it was diluted with water (30ml) and extracted with diethyl ether (3x20ml). The combined extracts were washed successively with saturated sodium bicarbonate solution (20ml), water (2x20ml) and brine (20ml). Evaporation of the dried extracts left the acetoxy-aldehyde (1.03g, 94%) as a pale yellow oil which was comparatively pure. A small sample was purified by column chromatography on silica to give a colourless oil; ν_{max}(film) 2720, 1740, 1665, cm^{-1}; δ_H 9.72(t, _J_1.7, HC:O), 5.34(br t, _J_7.3, :CH.CH_2O), 5.10(br m, 2x:CH), 4.56(d, _J_7.3, CH_2O), 2.6-1.9(m, $6xCH_2$), 2.02(CH_3.C:O), 1.69(CH_3), 1.59($2xCH_3$) ppm; δ_C(22.5MHz) 201.6(d), 170.4, 141.6, 134.8, 132.8, 125.1(d), 123.7(d), 118.4(d), 61.0(t), 41.9(t), 39.2(2xt), 31.6(t), 26.3(t), 26.0(t), 20.6(q), 16.2(q), 15.8(2xq) ppm; (Found: m/z 246.1983; $C_{19}H_{30}O_3$ requires _M_-$C_2H_4O_2$ 246.1984).

Bromomethyltriphenylphosphonium bromide (110).-Dibromomethane (89.2g) was added to a solution of triphenylphosphine (60g) in dry toluene (500ml) and the solution heated to reflux for 24h. The solution was then cooled to 0°C and a first crop of off-white crystals was collected by filtration. The filtrate was heated to reflux for a further 24h before again cooling to 0°C and collecting a second crop of off-white crystals by filtration. The combined crystals (63.69g) were purified by recrystallisation from methanol-ethyl acetate to give the phosphonium salt (31.16g, 31%) as large white hexagonal crystals, m.p. 225-228°C (lit[111]; m.p. 232-235°C); $\nu_{max}(CHCl_3)$ 1590, 1440 cm^{-1}; δ_H 8.0-7.6(m, $3xC_6H_5$), 5.83(d, J5.7, CH_2) ppm.

15-Bromo-3,7,11,15-tetramethylpentadeca-2(E),6(E),10(E),14-tetraenyl ethanoate (111).-Potassium t-butoxide (600mg) was added in a single portion to a stirred solution of the phosphonium salt (110) (1.28g) in dry THF (50ml) at -78°C under nitrogen and the solution stirred at -78°C for 1h. The acetoxy aldehyde (107) (820mg) was then added dropwise over 5min to the resulting bright yellow solution and the solution stirred at -78°C for a further 1.5h after which time TLC analysis showed complete consumption of the aldehyde. The reaction mixture was then quenched by the dropwise addition of water (20ml) and the solution allowed to warm to room temperature. The product was then extracted with diethyl ether (3x50ml). The combined extracts were washed with water (2x50ml) and then with brine (2x50ml). Evaporation of the dried extracts left a yellow residue (1.21g). The residue was purified by column chromatography on silica using hexane-diethyl ether (20:1) as eluant to give the vinyl bromide (14*E*, 14*Z* mixture, 330mg, 32%) as a pale yellow oil; ν_{max}($CHCl_3$) 1730, 1670, 1620, 1605 cm^{-1}; δ_H 6.25-6.0(m, :CHBr, HC:CHBr), 5.37(br t, *J*7, :C*H*CH_2O), 5.15(br m, 2x:CH), 4.60(d, *J*7, CH_2O), 2.4-2.0(m, 6xCH_2), 2.05(CH_3.C:O), 1.73(CH_3), 1.63(2xCH_3) ppm; δ_C(22.5MHz) 170.9, 142.1, 135.3, 134.5(d), 133.8, 125.2(d), 123.9(d), 118.5(d), 107.7(d), 61.3(t), 39.6(2xt), 37.9(t), 28.3(t), 26.7(t), 26.3(t), 21.0(q), 16.5(q), 16.0(q), 15.9(q) ppm; (Found: m/z 324.1248 and 322.1274; $C_{20}H_{31}BrO_2$ requires *M*-$C_2H_4O_2$ 324.1276 and 322.1296).

15-Bromo-3,7,11,15-tetramethylpentadeca-2(*E*),6(*E*),10(*E*),14-tetraen-1-ol (112).-Potassium carbonate (200mg) was added in a single portion to a stirred solution of the acetoxy vinyl bromide (111) (160mg) in methanol (10ml) and stirred at room temperature for 18h. The mixture was then diluted with water (20ml) and extracted with hexane (4x50ml). The combined hexane extracts were then washed with water (20ml) and then with brine (20ml). Evaporation of the dried extracts left the hydroxy vinyl bromide (14*E*, 14*Z* mixture, 120mg, 85%) as a pale yellow oil; ν_{max}($CHCl_3$) 3450(br), 1665, 1620, 1605 cm^{-1}; δ_H 6.15-5.8(m, :CHBr, HC:CHBr), 5.34(t, *J*7, :C*H*CH_2O), 5.05(br m, :CH), 4.07(d, *J*7, CH_2O), 2.4-1.95(m, 6xCH_2), 1.61(d, *J*0.7, CH_3), 1.53(2xCH_3) ppm; δ_C(22.5MHz) 139.6, 135.2, 134.6(d), 133.9, 125.2(d), 124.0(d), 123.6(d), 107.7(d), 59.4(t), 39.6(2xt), 37.9(t), 28.3(t), 26.7(t), 26.4(t), 16.3(q), 16.0(q), 15.9(q) ppm; (Found: m/z 324.1283 and 322.1288; $C_{18}H_{29}BrO$ requires *M*-H_2O 324.1276 and 322.1296).

3,7,11,15-Tetramethylpentadeca-2(E),6(E),10(E)-trien-14-yn-1-ol (113).-A solution of the hydroxy vinyl bromide (112) (70mg) in dry THF (1ml) was added rapidly to a stirred solution of potassium t-butoxide (70mg) in dry THF (15ml) at -23°C under nitrogen and the solution stirred at -23°C for 20min. The reaction mixture was then quenched by the dropwise addition of dilute hydrochloric acid (5%, 10ml) and the solution allowed to warm to room temperature. The product was then extracted with hexane (4x20ml). The combined extracts were washed with water (20ml) and then with brine (20ml). Evaporation of the dried extracts left a yellow residue. The residue was purified by column chromatography using hexane-diethyl ether (5:1, 2:1) as eluant to give the hydroxy acetylene (40mg, 75%) as a pale yellow oil; $\nu_{max}(CHCl_3)$ 3430(br), 3310, 2120, 1670 cm^{-1}; δ_H 5.33(t, J7.0, :CHCH$_2$O), 5.03(br m, 2x:CH), 4.06(d, J7.0, CH$_2$O), 2.2-1.8(m, 6xCH$_2$, ⋮CH), 1.60(CH$_3$), 1.53(2xCH$_3$) ppm; δ_C(22.5MHz) 139.6, 135.2, 133.2, 125.6(d), 124.0(d), 123.5(d), 84.4, 68.4(d), 59.4(t), 39.6(2xt), 38.5(t), 26.7(t), 26.4(t), 17.7(t), 16.3(q), 16.0(q), 15.8(q) ppm; (Found: m/z 242.205; $C_{18}H_{28}O$ requires M-H$_2$O 242.2035).

3,7,11,15-Tetramethylpentadeca-2(E),6(E),10(E)-trien-14-ynal (70).-A solution of the hydroxy acetylene (113) (90mg) in chloroform (1ml) was added in a single portion to a stirred suspension of manganese dioxide (900mg) in chloroform (10ml). The mixture was stirred at room temperature for 4h and then filtered under suction. Evaporation of the filtrate left the aldehyde (73.6mg, 82%) as a colouless oil; λ_{max}(EtOH) 238(7,200) nm; ν_{max}($CHCl_3$) 3320, 2790, 2130, 1665, 1635, 1610 cm^{-1}; δ_H(400MHz) 10.00(d, J8.1, HC:O), 5.89(dd, J8.1 and J1.1, :CH.C:O), 5.16(t, J6.8, :CH), 5.09(m, :CH), 2.3-1.9(m, 6xCH_2), 2.17(d, J1.1, CH_3.C:C.C:O), 1.94(t, J2.5, ⋮CH), 1.61(2xCH_3) ppm; δ_C(101MHz) 197.3(d), 163.8, 136.5, 133.4, 127.5(d), 125.4(d), 122.7(d), 84.4, 68.4(d), 40.7(t), 39.6(t), 38.5(t), 26.6(t), 25.8(t), 17.7(t), 17.7(q), 16.1(q), 15.9(q) ppm; (Found: m/z 258.1958; $C_{18}H_{26}O$ requires M 258.1984).

Attempted Electrochemical Cyclisation of 3,7,11,15-Tetramethylpentadeca-2(E),6(E),10(E)-trien-14-ynal (70).-Electroreduction of the aldehyde was carried out following the general procedure using a solution of anhydrous sodium perchlorate (18.40g) in dry DMF (150ml) as electrolyte.

A solution of the aldehyde (70) (51mg) in dry DMF (5ml) was added dropwise by syringe-pump over 9h to the catholyte solution whilst maintaining a cathodic potential of -1.75V. This potential was maintained for a further 1h after the addition by which time the current had fallen to zero. The catholyte was poured into water (60ml) and extracted with diethyl ether (6x50ml). The combined extracts were then washed with water (4x50ml) and brine (2x50ml). Evaporation of the dried extracts then left a yellow residue (35.1mg) which was shown by TLC analysis to be a complex mixture of products. The residue was purified by column chromatography on silica using hexane-diethyl ether (1:1) as eluant to give the diol dimer (114) (5.4mg, 11%) as a colourless oil; δ_H 5.18(m, 4x:CH), 4.4-4.1(m, CHOH), 2.3-1.9(m, $12xCH_2$, 2xC:H), 1.71($2xCH_3$), 1.60($4xCH_3$) ppm; (Found: m/z 500.4014; $C_{36}H_{54}O_2$ requires M-H_2O 500.4018).

16-Acetoxy-2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14(E)-tetraen-1-ol (121).-The acetate (92) (10.75g) was added dropwise over 10min to a stirred mixture of selenium dioxide (250mg), salicylic acid (500mg) and t-butylhydroperoxide (70% in water, 17ml, extracted into dichloromethane and dried over magnesium sulphate) in dichloromethane (17ml) at 0°C. The stirred mixture was allowed to warm to room temperature and then stirred for 60h before it was concentrated to leave a yellow residue which was immediately taken up in diethyl ether (50ml). The solution was then washed with sodium hydroxide solution (10%, 2x25ml) and then with brine (2x25ml). Evaporation of the dried extracts left a yellow residue (8.15g). The residue was purified by column chromatography on silica using hexane-diethyl ether (5:1, 4:1, 3:1, 5:2) as eluant to give the aldehyde (122) (220mg, 2%) as a colourless oil having identical physical and spectral data to that obtained subsequently, and then the hydroxy acetate (1.21g, 11%) as a colourless oil; ν_{max}($CHCl_3$) 3400(br), 1725, 1675, 1605 cm^{-1}; δ_H(400MHz) 5.41(tq, J6.9 and 1.4, :CH.CH_2OAc), 5.34(tq, J7.1 and 1.2, HC:C.CH_2OH), 5.11(m, 2x:CH), 4.59(d, J7.1, CH_2OAc), 3.99(CH_2OH), 2.2-1.95(m, $6xCH_2$), 2.05(CH_3C:O), 1.71(CH_3), 1.67(CH_3), 1.60($2xCH_3$) ppm; irradiation at δ3.99 ppm gave an NOE of -6% at δ5.41 ppm; δ_C(101MHz) 171.1, 142.3, 135.5, 134.9, 134.8, 126.1(d), 124.6(d), 123.8(d), 118.5(d), 69.0(t), 61.5(t), 39.8(t), 39.7(t), 39.5(t), 26.7(t), 26.4(t), 21.1(q), 16.6(q), 16.1(2xq), 13.9(q) ppm; (Found: m/z 288.2435; $C_{22}H_{36}O_3$

requires $\underline{M}-C_2H_4O_2$ 288.2453).

16-Acetoxy-2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14(E)-tetraenal (122).-A solution of the alcohol (121) (1.21g) in dichloromethane (3ml) was added in a single portion to a stirred suspension of manganese dioxide (12.0g) in chloroform (100ml). The mixture was stirred at room temperature for 18h and then filtered under suction. Evaporation of the filtrate left the enal (1.09g, 91%) as a colourless oil; λ_{max}(EtOH) 224 (26,800) nm; ν_{max}(film) 2720, 1750, 1690, 1640, cm^{-1}; δ_H 9.37(HC:O), 6.46(br t, $\underline{J}$7, HC:C.C:O), 5.34(br t, $\underline{J}$7.2, :C$\underline{H}$CH$_2$OAc), 5.12(br m, 2x:CH), 4.57(d, $\underline{J}$7.2, CH$_2$O), 2.55-1.85(m, 6xCH$_2$), 2.53(CH$_3$C:O), 1.73(CH$_3$), 1.71(CH$_3$), 1.59(2xCH$_3$) ppm; (Found m/z 286.2298; $C_{22}H_{34}O_3$ requires $\underline{M}-C_2H_4O_2$ 286.2297).

16-Hydroxy-2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14(E)-tetraenal (123).-Potassium carbonate (60mg) was added in a single portion to a stirred solution of the acetoxy enal (122) (70mg) in methanol (25ml) and the mixture was then stirred at room temperature for 18h. The mixture was diluted with water (10ml) and then extracted with hexane (3x15ml). The combined hexane extracts were washed with water (10ml) and then with brine (10ml). Evaporation of the dried extracts left the hydroxy enal (43.4mg, 82%) as a colourless oil; λ_{max}(EtOH) 224 (16,600) nm; ν_{max}(CHCl$_3$) 2730, 3460(br), 1675, 1640 cm^{-1}; δ_H 9.37(HC:O), 6.47(t, $\underline{J}$7.0, HC:C.C:O), 5.41(t, $\underline{J}$6.9, :C$\underline{H}$CH$_2$O), 5.15(m, 2x:CH), 4.15(d, $\underline{J}$6.9, CH$_2$O), 2.55-1.9(m, 6xCH$_2$), 1.75(CH$_3$), 1.68(CH$_3$), 1.61(2xCH$_3$) ppm; δ_C(22.5MHz) 195.1(d), 154.2(d), 139.7, 139.2, 135.2, 133.4, 125.7(d), 124.1(d), 123.6(d), 59.4(t), 39.6(2xt), 38.0(t), 27.5(t), 26.7(t), 26.4(t), 16.3(q), 15.9(2xq), 9.2(q) ppm; (Found: m/z 287.2331; $C_{20}H_{32}O_2$ requires M-OH 287.2375).

16-Bromo-2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14(E)-tetraenal (117).-Dimethyl sulphide (0.13ml) was added in a single portion to a stirred solution of NBS (400mg) in dry dichloromethane (5ml) at 0°C under nitrogen to give an opaque yellow solution. The solution was cooled to -18°C and then a solution of the hydroxy enal (123) (450mg) in dry dichloromethane (1ml) was added dropwise over 3min. The solution was stirred at 0°C for 18h before it was diluted with ice-water (5ml) and then extracted with hexane (3x20ml). Evaporation of the dried extracts left the bromo-enal (200mg, 37%) as a highly labile yellow oil; $\nu_{max}(CHCl_3)$ 2720, 1675, 1640, 1600 cm^{-1}; δ_H 9.38(HC:O), 6.47(t, J6.9, HC:C.C:O), 5.54(t, J8.4, :CHCH$_2$Br), 5.15(m, 2x:CH), 4.02(d, J8.4, CH$_2$Br), 2.65-1.8(m, 6xCH$_2$), 1.74(2xCH$_3$), 1.64(2xCH$_3$) ppm; (Found: m/z 286.2293; $C_{20}H_{31}BrO$ requires M-HBr 286.2296), which was used immediately without further purification.

16-Iodo-2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14(E)-tetraenal (118).-Triphenylphosphine (300mg) and a solution of imidazole (87mg) in acetonitrile (1ml) was added to a stirred solution of the hydroxy enal (123) (150mg) in dry diethyl ether (1.5ml). The solution was stirred under nitrogen at 0°C for 10min and then iodine (350mg) was added in portions over 2min.

The solution was stirred at 0°C for 30min and then was diluted with pentane (15ml). The extracts were washed successively with saturated sodium thiosulphate solution (5ml), saturated cupric sulphate solution (5ml) and water (5ml). Evaporation of the dried extracts left the iodo-enal (100mg, 47%) as a highly labile yellow oil; δ_H 9.39(HC:O), 6.48(t, *J*7, :C.C:O), 5.15(m, 3x:CH), 3.48(d, *J*9.9, CH_2I), 2.6-1.8(m, $6xCH_2$), 1.64(br, $4xCH_3$) ppm, which was contaminated with a small amount of triphenylphosphine oxide and was used immediately without further purification.

Attempted Radical Cyclisation of 16-Bromo-2,6,10,14-tetramethylhexadeca-2(*E*),6(*E*),10(*E*),14(*E*)-tetraenal (117).- Tributyltin hydride (70μl) and AIBN (5mg) were added to a solution of the bromo-enal (54mg) in dry, deaerated benzene (15ml) under nitrogen. The solution was heated to reflux and held at reflux for 3h. The solution was allowed to cool to room temperature before it was concentrated to leave a colourless residue (345mg). The residue was purified by column chromatography on silica using hexane-diethyl ether (50:1, 20:1, 10:1) as eluant to give 2,6,10,14-tetramethylhexadeca-2(*E*),6(*E*),10(*E*),14-tetraenal (124) (6.4mg, 15.1%) as a colourless oil; λ_{max}(EtOH) 228 (10,700) nm; ν_{max}($CHCl_3$) 2730, 1675, 1640, 1600 cm^{-1}; δ_H(400MHz) 9.38(HC:O), 6.47(t, *J*7.2, HC:C.C:O), 5.16(m, 3x:CH), 2.5-1.9(m, $6xCH_2$), 1.75-1.55(m, $5xCH_3$) ppm; (Found: m/z 288.2449; $C_{20}H_{32}O$ requires *M* 288.2453).

Attempted Radical Cyclisation of 16-iodo-2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14(E)-tetraenal (118).- Tributyltin hydride (60μl) and AIBN (5mg) were added to a solution of the iodo-enal (92mg) in dry, deaerated benzene (50ml) under nitrogen. The solution was heated to reflux and held at this temperature for 3h. The solution was allowed to cool to room temperature before it was concentrated to leave a colourless residue. The residue was purified by column chromatography on silica using hexane-diethyl ether (50:1, 20:1, 10:1) as eluant to give 2,6,10,14-tetramethylhexadeca-2(E),6(E),10(E),14-tetraenal (124) (5.0mg, 8%) as a colourless oil having identical physical and spectral data to that obtained previously.

3,7,11-Trimethyldodeca-2(E),6(E),10-trienal (128).-A solution of E,E-farnesol (10.00g) in dichloromethane(20ml) was added in a single portion to a stirred suspension of manganese dioxide (40.0g) in dichloromethane (400ml). The mixture was stirred at room temperature for 16h and then filtered under suction. Evaporation of the filtrate left the enal (9.12g, 95%) as a pale yellow oil, b.p.(oven) 190-194°C/11mmHg (lit[155]; b.p. 98-118°C/0.5mmHg); λ_{max}(EtOH) 238(11,000) nm; ν_{max}(film) 2770, 1685, 1635, 1615 cm^{-1}; δ_H(250MHz) 9.99(d, J8, CHO), 5.89(d, J8, :CH.CHO), 5.08(br m, 2x:CH), 2.3-1.9(m, $4xCH_2$, CH_3), 1.64(CH_3), 1.58($2xCH_3$) ppm; δ_C(22.5MHz) 189.7(d), 162.1, 135.7, 130.5, 126.9(d), 123.8(d), 122.2(d), 40.0(t), 39.2(t), 26.2(t), 25.3(t), 25.0(q), 17.0(q), 16.8(q), 15.4(q) ppm.

5,9,13-Trimethyltetradeca-1,4(E),8(E),12-tetraen-3-ol (129).-A solution of the enal (128) (9.10g) in dry ether (15ml) was added dropwise over 15min to a stirred solution of vinylmagnesium bromide (0.1M) in THF (100ml), under nitrogen at 0°C. The solution was stirred at 0°C for 20min and then quenched by the addition of saturated ammonium chloride solution (30ml). The mixture was diluted further with brine (500ml) and then extracted with diethyl ether (4x150ml). The combined extracts were washed with water (200ml) and then with brine (150ml). Evaporation of the dried extracts left the alcohol (9.45g, 92%) as a pale yellow oil which was comparatively pure. A small sample was purified by chromatography on silica to give a colourless oil; ν_{max}(film) 3330(br), 1665, 1005, 905 cm^{-1}; δ_H(250MHz) 5.90(ddd, J18, 10 and 8, H_2C:CH), 5.23(d, J18, :CHH), 5.25-5.0(m, 3x:CH), 5.12(d, J10, :CHH), 4.87(br dd, J8 and 8, CHOH), 2.15-1.9(m, $4xCH_2$), 1.70(CH_3), 1.67(CH_3), 1.58(CH_3), 1.45(br, OH) ppm; δ_C(20MHz) 140.2(d), 138.9, 135.4, 131.3, 126.0(d), 124.4(d), 123.8(d), 113.9(t), 69.9(d), 39.7(t), 39.6(t), 26.8(t), 26.3(t), 25.7(q), 17.7(q), 16.7(q), 16.0(q) ppm; (Found: m/z 248.2110; C, 81.8; H, 11.4%; $C_{17}H_{28}O$ requires M 248.2140; C, 82.2; H, 11.4%).

5,9,13-Trimethyltetradeca-1-4(E),8(E),12-tetraen-3-one (130).-A solution of the alcohol (129) (9.20g) in dichloromethane (20ml) was added in a single portion to a stirred suspension of manganese dioxide (92.0g) in dichloromethane (500ml). The mixture was stirred at room temperature for 16h and then filtered under suction. Evaporation of the filtrate left the dienone (7.03g, 77%) as a pale yellow oil, b.p.(oven) 178-180°C/7mmHg; λ_{max}(EtOH) 250(5,500) nm; ν_{max}(film) 1680, 1670, 1630, 1610, 980 cm^{-1}; δ_H(250MHz) 6.52(dd, J18 and 11, H_2C:CH.C:O), 6.35(:CH.C:O), 6.29(dd, J18 and 2, :CHH), 5.83(dd, J11 and 2, :CHH), 5.18(br, 2x:CH), 2.35-2.0(m, $4xCH_2$, CH_3.C:C.C:O), 1.78(CH_3), 1.70($2xCH_3$) ppm; (Found: m/z 246.1988; $C_{17}H_{26}O$ requires M 246.1984) which was used without further purification.

14-Hydroxy-5,9,13-trimethyltetradeca-1,4(E),8(E),12(E)-tetraen-4-one (131).-A solution of the dienone (130) (6.80g) in dichloromethane (10ml) was added in a single portion to a stirred mixture of selenium dioxide (1.50g) and t-butylhydroperoxide (80% solution in di-t-butylperoxide, 6.0ml) in dichloromethane (90ml) at 0°C. The stirred mixture was allowed to warm to room temperature over 2h before it was concentrated to leave a yellow residue which was immediately taken up in diethyl ether (50ml). The solution was washed with sodium hydroxide solution (10%, 2x50ml) and then with brine (50ml). Evaporation of the dried extracts left a yellow residue. The residue was purified by column chromatography on silica using pentane-diethyl ether (2:1, 3:2, 1:1) as eluant to give the hydroxy dienone (2.03g, 28%) as a pale yellow oil; λ_{max}(EtOH) 264(9,800) nm; ν_{max}(film) 3420(br), 1660, 1628, 1604, 990 cm^{-1}; δ_H(250MHz) 6.42(dd, J15 and 10, H_2C:CH.C:O), 6.28(:CH.C:O), 6.23(dd, J15 and 2, :CHH), 5.75(dd, J10 and 2, :CHH), 5.37(t, J5, :CH), 5.10(br, :CH), 3.98(CH_2OH), 2.3-1.9(m, $4xCH_2$), 2.14(d, J1, CH_3.C:C.C:O), 1.68(CH_3), 1.62(CH_3) ppm;

irradiation at δ3.98ppm gave an NOE of -10% at δ5.37ppm; δ_C(22.5MHz) 190.6, 160.1, 138.4, 135.9, 134.9, 126.9(t), 125.7(d), 123.2(d), 121.7(d), 68.9(t), 41.3(t), 39.3(t), 26.2(t), 26.1(t), 19.7(q), 16.0(q), 13.7(q) ppm; (Found: m/z(C.I.) 263; C, 77.4; H, 9.9%; $C_{17}H_{26}O_2$ requires M+H 263; C, 77.8; H, 10.0%).

14-Iodo-5,9,13-trimethyltetradeca-1,4(E),8(E),12(E)-trien-4-one (127).-Triphenylphosphine (200mg) and a solution of imidazole (60mg) in acetonitrile (0.5ml) was added to a stirred solution of the hydroxy dienone (131) (100mg) in dry diethyl ether (1ml). The resulting pink solution was stirred under nitrogen at 0°C for 10min and then iodine (240mg) was added in 12x20mg portions. The solution was stirred at 0°C for 30min and then was diluted with pentane (15ml). The extracts were washed successively with saturated sodium thiosulphate solution (5ml), saturated cupric sulphate solution (5ml) and water (5ml). Evaporation of the dried extracts left the iodo-dienone (106mg, 75%) as a highly labile pale yellow oil; ν_{max}(film) 1655, 1620, 1598, 990 cm^{-1}; δ_H 6.8-6.1(m, 3x:CH), 5.9-5.6(m, 2x:CH), 4.9-4.65(br, :CH), 3.99(CH_2I), 2.35-2.0(m, 4xCH_2, CH_3), 1.80(CH_3), 1.64(CH_3) ppm; (Found: m/z 245; $C_{17}H_{25}IO$ requires M-I 245), which was used immediately without further purification.

3,7,11-Trimethylcyclotetradeca-2(*E*),6(*E*),10(*E*)-trien-1-one (133) and 3,7,11-Trimethylcyclotetradeca- 2(*E*),6(*E*),10(*Z*)-trien-1-one (132).-Tributyltin hydride (0.54ml) and AIBN (50mg) were added to a solution of the iodo dienone (127) (720mg) in dry, deaerated benzene (650ml) under nitrogen. The solution was heated to reflux and held at reflux for 3h. The solution was then allowed to cool to room temperature before it was concentrated to give a colourless residue (2.0g). The residue was purified by column chromatography on silica using diethyl ether-hexane (1:30, 1:20) as eluant to give a mixture of the two isomers (133) and (132) (230mg, 48%) inseparable by column chromatography. Separation was achieved by HPLC eluting with diethyl ether-hexane (1:40) which gave the major isomer (72%), the all *E* cyclic ketone (133) as a colourless oil; $_{max}$(EtOH) 240(10,800) nm; $_{max}$($CHCl_3$) 1680, 1610 cm^{-1}; $_H$(400MHz) 5.93(:CH.C:O), 4.87(br m, :CH), 4.79(br m, :CH), 2.30-1.78(m, $7xCH_2$), 2.08(d, *J*0.8, CH_3.C:C.C:O), 1.59(CH_3), 1.54(d, *J*0.7, CH_3) ppm; $_C$(101MHz) 202.4, 155.8, 134.6, 133.4, 125.9(2xd), 125.0(d), 40.4(t), 39.5(t), 39.1(t), 37.3(t), 24.5(t), 24.2(t), 21.9(t), 19.3(q), 15.1(q), 15.0(q) ppm; (Found: m/z 246.1974; $C_{17}H_{26}O$ requires *M* 246.1984), and the minor isomer (28%) the 2(*E*),6(*E*),10(*Z*) cyclic ketone (132) as a colourless oil; λ_{max}(EtOH) 241(9,400) nm; ν_{max}($CHCl_3$) 1675, 1615 cm^{-1}; δ_H(400MHz) 5.98(:CH.C:O), 5.16(t, *J*6.5, :CH(*Z*)), 4.92(br m, :CH(*E*)), 2.40-1.90(m, $7xCH_2$), 2.07(d, *J*1.2, CH_3.C:C.C:O), 1.66(d, *J*1.2, CH_3), 1.59(d, *J*1.1, CH_3) ppm; $_C$(101MHz) 201.8, 157.4, 137.5, 134.6, 126.4(d), 124.5(d), 123.6(d), 44.2(t), 40.6(2xt), 31.0(t), 29.5(t), 24.0(2xt), 23.4(q), 18.6(q), 16.2(q) ppm; (Found: m/z 246.1975; $C_{17}H_{26}O$ requires M 246.1984).

6,7-Epoxy-3,7-dimethyloct-2(E)-en-1-ol (136) and 2,3-epoxy-3,7-dimethyl-6-en-1-ol (137).-MCPBA (85%, 660mg) was added portionwise over 10min to a stirred solution of geraniol (500mg) in dichloromethane (10ml) at 0°C and the resulting mixture was then stirred at 0°C for a further 30min. Calcium hydroxide (5.0g) was added and the mixture was then filtered. Evaporation of the filtrate left a colourless oil which was purified by column chromatography on silica using hexane-diethyl ether (2:1) as eluant to give firstly the 2,3-epoxide (137) (130mg, 24%), as a colourless oil; δ_H 5.16(br t, J7, :CH), 3.78(m, CH_2O), 3.01(t, J6, CHO(epoxy)), 2.41(br, OH), 2.3-1.5(m, $2xCH_2$), 1.72(CH_3.C:), 1.65(CH_3.C:), 1.45(CH_3.CO) ppm, and then the 6,7-epoxide (136) (150mg, 27%) as a colourless oil; ν_{max}($CHCl_3$) 3420(br), 1665 cm^{-1}; δ_H 5.54(t, J7, :CH), 4.20(d, J7, CH_2O), 2.76(t, J6, CHO(epoxy)), 2.5-1.7(m, $2xCH_2$), 1.73(CH_3.C:), 1.34(CH_3.CO), 1.29(CH_3.CO) ppm; (Found: m/z 152.1201; $C_{10}H_{18}O_2$ requires M-H_2O 152.1201).

1-(t-Butyldimethylsilyloxy)-3,7-dimethylocta-2,6-diene (138).-Geraniol (1.00g) was added in a single portion to a stirred solution of t-butyldimethylsilyl chloride (2.0g) and imidazole (1.54g) in dry DMF (10ml) at room temperature under nitrogen. The solution was stirred for 18h before it was quenched with saturated sodium bicarbonate solution (10ml) and the resulting mixture was then extracted with diethyl ether (2x10ml). The combined extracts were washed with saturated sodium bicarbonate

(3x10ml). Evaporation of the dried extracts left a crude residue (2.2g) which was purified by column chromatography on silica eluting with hexane then hexane-diethyl ether (100:1) to give the silyl ether (1.65g, 95%) as a colourless oil; ν_{max}(film) 1670, 1070 cm^{-1}; δ_H 5.30(br t, J7, :C<u>H</u>CH_2O), 5.08(br, :CH), 4.16(d, J7, CH_2O), 2.00(m, 2xCH_2), 1.65(CH_3), 1.58(2xCH_3), 1.38($(CH_3)_3C$), 0.03(2xCH_3Si) ppm; (Found: m/z 268.2202; $C_{16}H_{32}OSi$ requires M 268.2222).

1-(t-Butyldimethylsilyloxy)-6,7-epoxy-3,7-dimethyloct-2(E)-ene (139).-MCPBA (55%, 590mg) was added portionwise over 1h to a stirred solution of the silyl ether (138) (380mg) in dichloromethane (20ml) at 0°C and the resulting mixture was then stirred at 0°C for a further 20min. Calcium hydroxide (3.0g) was added and the mixture filtered. Evaporation of the filtrate left a colourless oil (500mg). The oil was purified by column chromatography on silica using hexane-diethyl ether (10:1) as eluant to give the epoxide (170mg, 43%) as a colourless oil; ν_{max}(film) 1675, 1070 cm^{-1}; δ_H 5.34(t, J7, :CH), 4.16(d, J7, CH_2O), 2.66(t, J6, CHO(epoxy)), 2.25-1.5(m, 2xCH_2), 1.59(CH_3C:), 1.24(CH_3CO), 1.19(CH_3CO), 0.83($(CH_3)_3C$), -0.01(2xCH_3Si) ppm; (Found: m/z 227.1472; $C_{16}H_{32}O_2Si$ requires M-C_4H_9 227.1467).

6,7-Epoxy-3,7-dimethyloct-2(E)-en-1-ol (136) from 1-(t-butyldimethylsilyloxy)-6,7-epoxy-3,7-dimethyloct-2(E)-ene (139).-A solution of tetrabutylammonium fluoride in THF (1.1M, 1.65ml) was added in a single portion to a stirred solution of the epoxide (139) (430mg) in dry THF (5ml) at room temperature under nitrogen. The solution was stirred for 1h before it was diluted with water (5ml) and extracted with diethyl ether (2x5ml). The combined extracts were washed with water (3x5ml) and then with brine (5ml). Evaporation of the dried extracts left an oily residue (350mg). The residue was purified by column chromatography on silica to give the epoxy-alcohol (130mg, 51%) as a colourless oil with physical and spectral data identical to those obtained previously.

14-(t-Butyldimethylsilyloxy)-5,9,13-trimethyltetradeca-1,4(E),8(E),12(E)-tetraen-3-one (140).-
4-(t-Butyldimethylsilyloxy)-3-penten-2-one (230mg) was added in a single portion to a stirred solution of the hydroxy dienone (131) (100mg) and PTSA (5mg) in dry DMF (2ml) at room temperature under nitrogen. The solution was stirred for 16h before it was quenched with water (2ml) and diluted with pentane (3ml). The aqueous phase was further extracted with pentane (5x3ml). Evaporation of the dried combined extracts left an oily residue (420mg). The residue was purified by column chromatography on silica using hexane-diethyl ether (10:1) as eluant to give the silyl ether (70mg, 49%) as a colourless oil; λ_{max}(EtOH) 264 (6,800) nm; ν_{max}(film) 1680, 1670, 1630, 1605, 1110 cm^{-1}; δ_H 6.4-6.1(m, 2xCH.C:O, :CHH), 5.74(dd, J9.2 and 2.8, :CHH), 5.39(br, HC:C.CH_2O), 5.14(br, :CH), 4.03(CH_2O), 2.3-1.95(m, 4xCH_2), 2.20(CH_3.C:C.C:O), 1.64(2xCH_3), 0.96((CH_3)$_3$C), 0.08(2xCH_3Si) ppm; δ_C(22.5MHz) 190.4, 159.8, 138.5(d), 136.0, 134.5, 126.7(t), 124.2(d), 123.1(d), 121.7(d), 68.6(t), 41.4(t), 39.4(t), 26.2(2xt), 26.0(3xq), 19.7(q), 18.4,

16.0(q), 13.4(q), -5.2(2xq) ppm; (Found: m/z 319.2087; $C_{23}H_{40}O_2Si$ requires M-C_4H_9 319.2093).

14-(t-Butyldimethylsilyloxy)-8,9-epoxy-5,9,13-trimethyltetradeca-1,4(E),12(E)-tetraen-3-one (141).-MCPBA (85%, 620mg) was added portionwise over 15min to a stirred solution of the dienone (140) (1.08g) in dichloromethane (50ml) at 0°C and the resulting mixture was then stirred at 0°C for a further 30min. Calcium hydroxide (6g) was added and the mixture was filtered. Evaporation of the filtrate left an oily residue (1.07g). The residue was purified by column chromatography on silica using hexane-diethyl ether (10:1, 5:1) as eluant to give the epoxy-silyl ether (330mg, 32%) as a colourless oil; λ_{max}(EtOH) 259 (13,750) nm; ν_{max}($CHCl_3$) 1670, 1660, 1625, 1605 cm^{-1}; δ_H 6.4-6.1(m, 2x:CH.C:O, :CHH), 5.75(dd, J9.2 and 2.8, :CHH), 5.37(br, :CH), 4.01(CH_2O), 2.74(t, J6.1, HCO(epoxy)), 2.3-1.7(m, 4xCH_2), 2.19(d, J1.3, CH_3.C:C.C:O), 1.61(CH_3C:), 1.28(CH_3CO), 0.91((CH_3)$_3$C), 0.06(2xCH_3Si) ppm; δ_C(22.5MHz) 190.6, 158.9, 138.5(d), 135.3, 127.3(t), 123.6(d), 122.1(d), 68.6(t), 62.9(d), 61.1, 38.7(t), 38.3(t), 27.3(t), 26.2(3xq), 23.5(t), 19.8(q), 17.5, 16.9(q), 13.6(q), -5.1(2xq) ppm; (Found: m/z 335.2041; $C_{23}H_{40}O_3Si$ requires M-C_4H_9 335.2042).

12,13-Epoxy-14-hydroxy-5,9,13-trimethyltetradeca-1,4(E),8(E)-trien-3-one (145) and 8,9-epoxy-14-hydroxy-5,9,13-trimethyltetradeca-1,4(E),12(E)-trien-3-one (142).-MCPBA (85%, 340mg) was added portionwise over 10min to a stirred solution of the dienone (131) (400mg) in dichloromethane (25ml) at 0°C and the resulting mixture was then stirred at 0°C for a further 30min. Calcium hydroxide (2.0g) was added and the mixture was filtered. Evaporation of the filtrate left an oily residue (340mg). The residue was purified by column chromatography on silica using hexane-diethyl ether (1:1, 2:3) as eluant to give firstly the 12,13-epoxy-dienone (110mg, 26%) as a colourless oil; λ_{max}(EtOH) 263 (21,000) nm; ν_{max}(film) 3430(br), 1670, 1655, 1620, 1595 cm^{-1}; δ_H(400MHz) 6.41(dd, *J*17.5 and 10.5, *H*C:CH_2), 6.26(:CH.C:O), 6.21(d, *J*17.5, :C*H*H), 5.75(dd, *J*10.5 and 2, :CCH*H*), 5.16(br, :CH), 3.67(dd, *J*12.2 and 4.2, C*H*HOH), 3.56(dd, *J*12.2 and 8.5, CH*H*OH), 3.02(t, *J*6.2, CHO(epoxy)), 2.2-1.6(m, 4xCH_2), 2.17(CH_3.C:C.C:O), 1.75(m, OH), 1.64(:C.CH_3), 1.28(CH_3CO) ppm; δ_C(101MHz) 190.7, 160.1, 138.3(d), 135.1, 127.2(t), 123.7(d), 121.7(d), 65.4(t), 60.8, 59.7(d), 41.3(t), 36.3(t), 26.8(t), 26.0(t), 19.7(q), 16.0(q), 14.3(q) ppm, and secondly the 8,9-epoxy-dienone (40mg, 9%) as a colourless oil; λ_{max}(EtOH) 261 (8,500) nm; ν_{max}(film) 3450(br), 1675, 1665, 1630, 1600 cm^{-1}; $_H$(400MHz) 6.42(dd, *J*17.5 and 10.5, *H*C:CH_2), 6.32(q, *J*1.2, :CHC:O), 6.23(dd, *J*17.5 and 1.3, :C*H*H), 5.77(dd, *J*10.5 and 1.3, :CH*H*), 5.38(tq, *J*7.1 and 1.3, :CH), 4.00(CH_2O), 2.73(dd, *J*5.6 and 6.8, CHO(epoxy)), 2.4-1.4(m, 4xCH_2), 2.19(d, *J*1.2, CH_3C:C.C:O), 1.67(CH_3C:), 1.41(br, OH), 1.28(CH_3CO) ppm; δ_C(101MHz) 190.6, 158.9, 138.2(d), 135.3, 127.4(t), 124.9(d), 121.9(d), 68.7(t), 62.6(d), 60.9, 38.3(t), 38.1(t), 26.9(t), 23.3(t), 19.6(q), 16.6(q), 13.7(q) ppm; (Found: m/z(C.I.) 279; $C_{17}H_{26}O_3$ requires *M*+H 279).

12,13-*Epoxy*-14-*iodo*-5,9,13-*trimethyltetradeca*-1,4(*E*),8(*E*)-*trien*-3-*one* (146).-Triphenylphosphine (93mg) and a solution of imidazole (24mg) in acetonitrile (1ml) was added to a solution of the hydroxy dienone (145) (90mg) in dry diethyl ether (2ml) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10min and then iodine (90mg) was added in *ca.* ten portions over 5min. The solution was stirred at 0°C for 20min and was then diluted with pentane (10ml). The extracts were washed successively with saturated sodium thiosulphate solution (5ml), saturated cupric sulphate solution (5ml) and water (5ml). Evaporation of the dried extracts left the *iodo-dienone* (80mg, 64%) as a highly labile yellow oil; δ_H 6.45-6.05(m, 2xO:C.CH:, :C*H*H), 5.72(dd, *J*10 and 2, :CH*H*), 5.17(br, :CH), 3.23(d, *J*10, C*H*HI), 3.06(d, *J*10, CH*H*I), 2.84(t, *J*6, CHO(epoxy)), 2.3-1.55(m, 4xCH_2), 2.16(CH_3.C:C.C:O), 1.63(:C.CH_3), 1.43(CH_3CO) ppm; (Found: m/z 261; $C_{17}H_{25}IO_2$ requires *M*-I 261), which was used immediately without further purification.

8,9-*Epoxy*-14-*iodo*-5,9,13-*trimethyltetradeca*-1,4(*E*),12(*E*)-*trien*-3-*one* (144).-Triphenylphosphine (41mg) and a solution of imidazole (11mg) in acetonitrile (0.5ml) was added to a solution of the hydroxy dienone (142) (40mg) in dry diethyl ether (1ml) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10min and then iodine (60mg) was added in *ca.* six portions over 5min. The solution was stirred at 0°C for 30min and was then diluted with pentane (2ml). The extracts were washed successively with saturated sodium thiosulphate solution (2ml), saturated cupric sulphate solution (2ml) and water (2ml).

Evaporation of the dried extracts left the iodo-dienone (40mg, 72%) as a highly labile yellow oil; δ_H 6.7-6.15(m, 2xO:C.CH:, :CHH), 5.83(dd, J10 and 2, :CH), 5.73(br m, :CH), 3.98(CH_2I), 2.76(t, J7, CHO(epoxy)), 2.4-1.2(m, 4xCH_2), 2.23(CH_3.C:C.C:O), 1.82(CH_3C:), 1.29(CH_3CO) ppm; (Found: m/z 261; $C_{17}H_{25}IO_2$ requires M-I 261), which was used immediately without further purification.

1,2-Dibromo-3-methylbutane (153).-A solution of bromine (228g) in dichloromethane (100ml) was added over 45min to a stirred solution of 3-methylbut-1-ene (100g) in dichloromethane (500ml) at 0°C. The solution was stirred at 0°C for 1h and then poured into ice-water (500ml). The organic layer was washed with saturated sodium sulphite solution (500ml) and then with brine (500ml). Evaporation of the dried ($CaCl_2$) extracts left a pale yellow liquid, distillation of which gave the dibromide (234.8g, 72%) as a colourless liquid, b.p. 55-57°C/7mmHg (lit[133]: b.p. 75-79°C/22mmHg); ν_{max}(film) 2970, 770 cm^{-1}; δ_H 4.4-4.15(m, CHBr), 4.1-3.4(m, CH_2Br), 2.45-2.05(br m, $CHMe_2$), 1.08(d, J7, CH_3), 0.95(d, J7, CH_3) ppm.

2-Bromo-3-methylbut-1-ene (154).-A solution of potassium hydroxide (12.22g) in ethanol (200ml) was added dropwise over 20min to the dibromide (153) (50.0g) which was stirred vigorously at room temperature. After stirring for an additional 20min, the mixture was distilled (b.p. 76-80°C) and the distillate was then diluted with brine (150ml) and extracted with pentane (4x40ml). Evaporation of the dried extracts left a residue (16.59g) consisting of a 1:1 mixture of vinyl bromides (154) and (155), careful distillation of which, using a 50cm Vigreaux column, gave an improved ratio of 2:1 in favour of the required vinyl bromide (154) (6.74g, 21%) as a colourless oil, b.p. 98-101°C (lit[134]; b.p. 100-101°C); ν_{max}(film) 1630, 890, 720 cm^{-1}; δ_H 6.70(:C<u>H</u>H), 6.45(:CH<u>H</u>), 2.72-2.24(m, $CHMe_2$), 1.18(d, <u>J</u>7, $2xCH_3$) ppm, which was used without further purification.

<u>2,6,10,14-Tetramethyl</u>-3-<u>methylenetetradeca</u>-5(<u>E</u>),9(<u>E</u>),13-<u>trien</u>-4-<u>ol</u> (156).-A solution of the vinyl bromides (154) and (155) (2:1 mixture) (4.88g) in dry THF (25ml) was added dropwise over 15min to dry magnesium turnings (880mg) in dry THF (25ml) with stirring at room temperature under nitrogen. When the magnesium turnings had all been consumed, the solution was cooled to 0°C and the aldehyde (128) (6.57g) in dry THF (10ml) was then added dropwise over 10min. The solution was stirred at room temperature for 16h, then quenched by the addition of saturated ammonium chloride solution (20ml) and then extracted with diethyl ether (3x50ml). The combined extracts were washed with water (2x50ml) and then with brine (50ml). Evaporation of the dried extracts left a yellow residue (8.03g). The residue was purified by column chromatography on silica using hexane-diethyl ether (5:1) as eluant to give the <u>alcohol</u> (3.11g, 54% based on vinyl bromide (154)) as a colourless oil, ν_{max}(film) 3350(br), 1660, 1640, 910 cm^{-1}; δ_H 5.25-4.75(m, 2x:CHR, C<u>H</u>OH), 5.12(:C<u>H</u>H), 4.88(:CH<u>H</u>), 2.2-1.8(m, $4xCH_2$, $CHMe_2$), 1.73(d, <u>J</u>1.3, CH_3), 1.68(CH_3), 1.60($2xCH_3$), 1.07(d, <u>J</u>6.8, CH_3), 1.05(d, <u>J</u>6.8, CH_3)

ppm; δ_C(22.5MHz) 158.0, 138.0, 135.0, 130.7, 127.3(d), 124.3(d), 123.7(d), 106.0(t), 70.4(d), 39.6(2xt), 29.9(d), 26.7(t), 26.2(t), 25.4(q), 22.9(q), 22.4(q), 17.4(q), 16.4(q), 15.8(q) ppm; (Found: m/z 290.2615; C, 82.99; H, 11.85%; $C_{20}H_{34}O$ requires M 290.2610; C, 82.70; H, 11.80%).

2,6,10,14-Tetramethyl-3-methylenetetradeca-5(E),9(E),13-trien-4-one (150).-A solution of the alcohol (156) (180mg) in dichloromethane (1ml) was added in a single portion to stirred suspension of manganese dioxide (2.0g) in dichloromethane (25ml). The mixture was stirred at room temperature for 17h and then filtered under suction. Evaporation of the filtrate left the dienone (170mg, 95%) as a pale yellow oil, b.p. 224-226°C/12mmHg; λ_{max}(EtOH) 243(7,800), 258(8,350) nm; ν_{max}(film) 1660, 1605, 930 cm^{-1}; δ_H 6.39(:CH.C:O), 5.83(:CHH), 5.57(:CHH), 5.12(br, 2x:CH), 3.16-2.76(m, $CHMe_2$), 2.2-2.0(m, $4xCH_2$, CH_3.C:C.C:O), 1.67(CH_3), 1.60($2xCH_3$), 1.04(dt, J6.8, 1.6, $CH(CH_3)_2$) ppm; δ_C(22.5MHz) 193.8, 157.2, 156.7, 135.8, 131.0, 124.2(d), 123.0(d), 121.4(d), 118.9(t), 41.0(t), 39.6(t), 28.0(d), 26.7(t), 26.0(t), 25.5(q), 21.7(2xq), 19.2(q), 17.5(q), 15.9(q) ppm; (Found: m/z 288.2457; C, 83.45; H, 11.17%; $C_{20}H_{32}O$ requires M 288.2453; C, 83.27; H, 11.18%).

15-Hydroxy-2,6,10,14-tetramethyl-3-methylenetetradeca-5(E),9(E),13(E)-trien-4-one (157).-A solution of the dienone (150) (100mg) in dichloromethane (1ml) was added in a single portion to a stirred mixture of selenium dioxide (18mg) and t-butylhydroperoxide (90% solution in di-t-butylperoxide, 0.1ml) in dichloromethane (4ml) at 0°C. The stirred mixture was allowed to warm to room temperature over 2h before it was concentrated to leave a yellow residue which was immediately taken up in diethyl ether (5ml). The solution was washed with sodium hydroxide solution (10%, 2x5ml) and then with brine (5ml). Evaporation of the dried extracts left a yellow residue (40mg). The residue was purified by column chromatography on silica using hexane-diethyl ether (2:1) as eluant to give the hydroxy dienone (20.1mg, 19%) as a pale yellow oil; λ_{max}(EtOH) 237(8,800), 258(10,500) nm; ν_{max}(film) 3400(br), 1665, 1615, 930 cm^{-1}; δ_H(250MHz) 6.37(d, J1, :CH.C:O), 5.84(:CHH), 5.59(:CHH), 5.38(t, J1.3, HC:CMe.CH_2OH), 5.12(br, :CH), 3.99(CH_2OH), 2.95(septet, J6, $CHMe_2$), 2.3-2.0(m, $4xCH_2$), 2.08(d, J1, CH_3.C:C.C:O), 1.66(CH_3), 1.62(CH_3), 1.04(d, J6, $CH(CH_3)_2$) ppm; irradiation at δ3.99ppm gave an NOE of -6% at δ5.38ppm; δ_C(22.5MHz) 194.1, 157.1, 156.8, 135.6, 134.9, 125.2(d), 123.1(d), 121.5(d), 119.2(t), 68.4(t), 40.9(t), 39.2(t), 28.0(d), 26.1(t), 25.9(t), 21.7(2xq), 19.2(q), 15.9(q), 13.4(q) ppm; (Found: m/z(C.I.) 305; C, 79.08; H, 11.00%; $C_{20}H_{32}O_2$ requires M+H 305; C, 78.90; H, 10.59%).

15-Iodo-2,6,10,14-tetramethyl-3-methylenetetradeca-5(E),9(E),13(E)-trien-4-one (149).-Triphenylphosphine (260mg) and a solution of imidazole (67mg) in acetonitrile (1ml) was added to a stirred solution of the hydroxy dienone (157) (150mg) in dry diethyl ether (1.5ml) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10min and then iodine (250mg) was added in ten portions over 5min. The solution was stirred at 0°C for 30min and then was diluted with pentane (10ml). The extracts were washed successively with saturated sodium thiosulphate solution (5ml), saturated cupric sulphate solution (5ml) and water (5ml). Evaporation of the dried extracts left the iodo dienone (150mg, 74%) as a highly labile pale yellow oil; ν_{max}(film) 1655, 1605 cm^{-1}; δ_H 6.38(:CH.C:O), 5.85(:CHH), 5.65(br, HC:CMe.CH_2I), 5.58(:CHH), 5.12(br, :CH), 3.93(CH_2I), 3.15-2.75(m, $CHMe_2$), 2.3-1.95(m, 4xCH_2), 2.08(d, J1.5, CH_3.C:C.C:O), 1.60(CH_3), 1.54(CH_3), 1.04(d, J6.4, $CHMe_2$) ppm; (Found: m/z 414; $C_{20}H_{31}IO$ requires M 414), which was used immediately without further purification.

14-Isopropyl-3,7,11-trimethylcyclotetradeca-2(E),6(E),10(E)-trien-1-one (148) and 14-Isopropyl-3,7,11-trimethylcyclotetradeca-2(E),6(E),10(Z)-trien-1-one (158).- Tributyltin hydride (0.1ml) and AIBN (6mg) were added to a solution of the iodo-dienone (149) (150mg) in dry, deaerated benzene (125ml) under nitrogen. The solution was heated to reflux and held at reflux for 3h. The solution was then allowed to cool to room temperature before it was concentrated to give a colourless residue. The residue was purified by column chomatography on silica using diethyl ether-hexane (1:50) as eluant to give a mixture of the two isomers (148) and (158) (50mg, 35%) inseparable by column chomatography. Separation was achieved by HPLC eluting with diethyl ether-hexane (1:100) which gave the major isomer (79%), the all E cyclic ketone (148) as a colourless oil; λ_{max}(EtOH) 241(6,200) nm; ν_{max}($CHCl_3$) 1675, 1610 cm^{-1}; δ_H(400MHz) 5.89(:CH.C:O), 4.94(br m, :CH), 4.83(br m,

:CH), 2.36-1.65(m, $6xCH_2$, 2xCH), 2.11(CH_3.C:C.C:O), 1.60(CH_3), 1.52(CH_3), 0.89(d, J6.8, CH(CH_3)Me), 0.87(d, J6.8, CHMe(CH_3)), ppm; δ_C(101MHz) 205.5, 155.8, 134.5, 133.7, 126.5(d), 125.9(d), 125.2(d), 56.7(d), 39.5(t), 38.9(t), 37.2(t), 31.2(d), 26.0(t), 24.4(t), 24.0(t), 21.2(q), 20.3(q), 19.5(q), 15.3(q), 14.6(q) ppm; (Found: m/z 288.2449; $C_{20}H_{32}O$ requires M 288.2453), and the minor isomer (21%) the 2(E),6(E),10(Z) cyclic ketone (158) as a colourless oil; λ_{max}(EtOH) 236(5,500) nm; ν_{max}($CHCl_3$) 1670, 1610 cm^{-1}; δ_H(400MHz) 5.97(:CH.C:O), 5.15(t, J7, :CH(Z)), 4.90(br m, :CH(E)), 2.30-1.70(m, $6xCH_2$, 2xCH), 2.11(d, J1.0, CH_3.C:C.C:O), 1.66(d, J0.7, CH_3), 1.60(CH_3), 0.93(d, J6.7, CH(CH_3)Me), 0.87(d, J6.6, CHMe(CH_3)) ppm; δ_C(101MHz) 204.0, 157.8, 137.5, 134.8, 126.1(d), 123.9(d), 123.4(d), 60.8(d), 40.8(t), 40.4(t), 29.7(t), 29.5(t), 29.4(d), 27.7(t), 24.0(t), 23.1(q), 21.5(q), 20.1(q), 18.9(q), 16.4(q) ppm; (Found: m/z 288.2442; $C_{20}H_{32}O$ requires M 288.2453).

dl-Mukulol (41).-Lithium aluminium hydride (1.0mg) was added in a single portion to a stirred solution of the cyclic ketone (148) (4.5mg) in dry diethyl ether (1ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 30min then quenched by the addition of water (0.5ml) and then extracted with diethyl ether (2x2ml). Evaporation of the dried organic extracts left a colourless residue (3.0mg). The residue was purified by column chromatography on silica using pentane-diethyl ether (5:1) as eluant to give first the deconjugated ketone (159) (1.5mg, 33%) as a colourless oil; δ_H(400MHz) 5.02(m, :CH), 4.91(m, :CH), 2.3-1.65($7xCH_2$, 3xCH), 1.50($2xCH_3$), 0.95-0.75(m, $3xCH_3$) ppm;

(Found: m/z 290.2607; $C_{20}H_{34}O$ requires M 290.2610) and then dl-mukulol (1.0mg, 22%) as a colourless oil; δ_H(400MHz) 5.33(d, J8.8, :CH.CHOH), 5.04(t, J6.1, :CH), 4.92(t, J6.5, :CH), 4.60(d, J8.8, CHOH), 2.3-1.7(m, $6xCH_2$, 2xCH), 1.60(d, J4.3, CH_3), 1.57($2xCH_3$), 1.00(d, J6.8, $CHMe(CH_3)$), 0.96(d, J6.8, $CH(CH_3)Me$) ppm; (Found m/z 290.2588; $C_{20}H_{34}O$ requires M 290.2610).

2-Bromocyclohexan-1-one (173).-Bromine (16.0g) was added dropwise over 1h to a stirred solution of cyclohexanone (10.0g) in water (30ml) at 0°C. The resulting orange solution was allowed to warm to room temperature over 1.5h before it was extracted with diethyl ether (2x10ml). The combined extracts were washed with water (10ml) and then with brine (10ml). Evaporation of the dried extracts left an oily residue (13.69g), distillation of which gave the bromo-ketone (7.96g, 44%) as a pale yellow liquid, b.p. 60-65°C/0.3mmHg (lit[145]; 83°C/6mmHg); δ_H 4.54(t, J5.5, CHBr), 3.2-2.75(m, CH_2C:O), 2.4-1.7(m, $3xCH_2$) ppm.

2-(1'-Oxoethylthio)-cyclohexanone (174).-The bromo-ketone (173) (7.50g) was added in a single portion to a stirred solution of thiolacetic acid (2.8ml) and anhydrous sodium carbonate (4.19g) in dry THF (55ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 21h before it was filtered through a short pad of celite. Evaporation of the extracts left the thioacetate (4.36g, 64%) as a labile pale yellow solid; λ_{max}(EtOH) 230 (3,400) nm; $\nu_{max}(CHCl_3)$ 1720, 1695 cm^{-1}; δ_H 4.23(m, CHS), 2.7-1.6(m, $4xCH_2$), 2.35(CH_3)ppm, which was used without further purification.

2-Mercaptocyclohexan-1-one (175).-Sodium hydroxide solution (10%, 60ml) was added over 10min to a vigorously stirred solution of the thioacetate (174) (4.00g) in diethyl ether (60ml) at room temperature. The mixture was stirred vigorously for a further 20min during which time the aqueous phase became bright yellow in colour. The aqueous phase was acidified to pH7 with dilute sulphuric acid (10%, ca. 40ml), to give a colourless solution which was then extracted with dichloromethane (3x30ml). Evaporation of the dried extracts left the thioketone (2.99g, 98%) as white crystals, m.p. 153-4°C (lit[156]; 151-2°C); $\nu_{max}(CHCl_3)$ 1710 cm^{-1}; δ_H 4.14(br, SH), 3.65(m, C<u>H</u>SH), 2.5-1.5(m, $4xCH_2$) ppm; (Found: m/z 130.0462; $C_6H_{10}OS$ requires M 130.0452).

2-(2'-Oxopropylthio)-cyclohexanone (176).-Triethylamine (1.85g) was added in a single portion to a stirred solution of the thio ketone (175) (2.38g) in dry THF (50ml) at 0°C under nitrogen and the solution was then stirred for 30min. Chloroacetone (1.70g) was added dropwise to the resulting pale yellow solution to give a dark grey mixture which was allowed to warm to room temperature over 2h. The mixture was then filtered through a short pad of silica. Evaporation of the dried extracts left the diketone (1.80g, 53%) as a pale yellow oil; ν_{max}(film) 1715 cm^{-1}; δ_H 3.41(m, C<u>H</u>SCH$_2$), 3.34(CH$_2$S), 2.5-1.5(m, $4xCH_2$), 2.26(CH$_3$) ppm; (Found: m/z 186.0647; $C_9H_{14}O_2S$ requires M 186.0715).

Low Valent Titanium Induced Couplings: General Procedure:

Method A.-Titanium tetrachloride (1.53g, 8.0mmol) was added dropwise over ca. 2min to a stirred solution of the diketone (2.7mmol) in dry THF (30ml) at -78°C under nitrogen to give a dark brown solution. Zinc dust (1.05g, 25mmol) was added with vigorous stirring, and the mixture was then allowed to warm to either 0°C or room temperature over 3h during which time the solution became dark grey to black in colour. The reaction was quenched with potassium carbonate solution (10%, 40ml), and the mixture was then extracted with diethyl ether (2x50ml). The combined ether extracts were washed with brine (20ml). Evaporation of the dried extracts left a crude residue which was purified by column chromatography on silica.

Method B.-An identical procedure to method A was carried out with the exception that, after addition of zinc dust, the mixture was refluxed for 5h, then cooled to room temperature before quenching.

Method C.-A solution of the diketone (0.6mmol) in dry THF (16ml) was added dropwise over 1h to a vigorously stirred and refluxing mixture of titanium trichloride (2.0g) and lithium aluminium hydride (0.25g) in dry THF (40ml). The reflux was continued with vigorous stirring for a further 16h before cooling to 0°C. The reaction was quenched with undried diethyl ether (10ml) and then cautiously with water (4ml). The mixture was filtered through a short pad of Florisil which was subsequently flushed with diethyl ether (20ml). The organic layer was washed with water (2x40ml) and then with brine (20ml). Evaporation of the dried extracts left a crude residue which was purified by column chromatography on silica.

1,2-Diphenylethane-1,2-diol (177).-Benzaldehyde (320mg) was treated with titanium tetrachloride (860mg) and zinc dust (590mg) in dry THF (30ml) according to the general procedure (method A) at 0°C for 2h to give the diol (320mg, 98%) as a mixture of diastereoisomers and as a white crystalline solid, m.p. 95-96°C (lit[157]; 122-3°C for racemate); $\nu_{max}(CHCl_3)$ 3430(br), 1605, 1585, 1490 cm^{-1}; δ_H 7.35-6.9(m, $2xC_6H_5$), 4.79(CHOH minor isomer), 4.65(CHOH major isomer), 2.95(br, 2xOH) ppm; (Found: m/z 196.0876; $C_{14}H_{14}O_2$ requires M-H_2O 196.0888).

Hexahydro-2,3-dimethylbenzo(b)thiophene-3,3a-diol (178).-Diketone (176) (500mg) was treated with titanium tetrachloride and zinc dust according to the general procedure (method A) at room temperature for 3h to give an oily residue (300mg). The residue was purified by column chromatography on silica eluting with hexane-diethyl ether (10:1, 2:1, 1:1, 1:2) to give the diol (40mg, 8%) as a colourless oil; ν_{max}(film) 3430, 1125 cm^{-1}; δ_H 3.60(m, CHS), 2.94(d, J12, CHHS), 2.77(d, J12, CHHS), 2.39(br, OH), 2.34(br, OH), 1.9-1.3(m, $4xCH_2$), 1.24(CH_3) ppm; (Found: m/z 188.0857; $C_9H_{16}O_2S$ requires M 188.0871).

Attempted Dihydrothiophene Preparation Using Low Valent Titanium.-Diketone (176) (500mg) was treated with titanium tetrachloride and zinc dust according to the general procedure (method B) to give an oily residue (450mg) which was shown by subsequent analysis to be a complex mixture of products not containing the desired dihydrothiophene (179).

2-(2'-Methylprop-2'-enyloxy)-cyclohexan-1-ol (182).-A solution of cyclohexene oxide (4.85g) in dry dichloromethane (30ml) was added dropwise over 3h to a stirred solution of 2-methylprop-2-en-1-ol (42ml) in dry dichloromethane (100ml) containing boron trifluoride etherate (0.5ml), at room temperature under nitrogen. The solution was stirred for a further 30min and then triethylamine (5ml) was added. The solution was stirred for 30min and then washed successively with dilute hydrochloric acid (5%, 50ml) and saturated sodium bicarbonate solution (50ml). The solvent and excess 2-methylprop-2-en-1-ol were removed by distillation at 24°C/0.5mmHg to leave the alcohol (8.31g, 98%) as a colourless oil; ν_{max}(film) 3430(br), 1655, 1070, 915 cm^{-1}; δ_H 4.98(br, :C$\underline{H}$H), 4.87(br, :CH$\underline{H}$), 4.07(d, $\underline{J}$12.6, C$\underline{H}$HO), 3.85(d, $\underline{J}$12.6, CH$\underline{H}$O), 3.43(br m, C$\underline{H}$OH), 3.09(br m, CHOR), 2.67(br, OH), 2.1-1.0(m, 4xCH_2), 1.75(CH_3) ppm; (Found: m/z 170.1307; $C_{10}H_{18}O_2$ requires $\underline{M}$ 170.1307).

2-(2'-Methylprop-2'-enyloxy)-cyclohexan-1-one (183).-The alcohol (182) (8.20g) was added in a single portion to a stirred mixture of pyridinium chlorochromate (35.0g) and celite (35g) in dry dichloromethane (250ml) at room temperature. The dark brown slurry formed was then stirred for 5h at room temperature. Evaporation left a powdery residue which was purified by column chromatography on a short pad of Florisil using diethyl ether as eluant to give the ketone (5.94g, 73%) as a pale yellow oil, b.p.(oven) 105-110°C/18mmHg; ν_{max}(film) 1725, 1655, 1080, 915 cm^{-1}; δ_H 5.05(br, :CHH), 4.98(br, :CHH), 4.18(d, J11, CHHO), 4.1-3.75(m, CHO), 3.88(d, J11, CHHO), 2.6-1.1(m, $4xCH_2$), 1.79(CH_3) ppm; (Found: m/z 168.1158; $C_{10}H_{16}O_2$ requires M 168.1150).

2-(2'-Oxopropyloxy)-cyclohexan-1-one (184).-Pyridine (0.5g) was added to a stirred solution of the olefin (183) (1.00g) in dichloromethane (30ml) at -78°C. Ozone was bubbled through the solution until it became bright blue in colour. Oxygen was then bubbled through the solution until the colour faded. Dimethyl sulphide (0.5ml) was added and the solution was then allowed to warm to room temperature over 1h before it was washed successively with dilute hydrochloric acid (5%, 2x30ml), water (2x30ml) and saturated sodium bicarbonate solution (2x30ml). Evaporation of the dried extracts left the diketone (730mg, 72%) as a white crystalline solid, m.p. 47-48°C; ν_{max}($CHCl_3$) 1720, 1115 cm^{-1}; δ_H 4.33(d, J17, CHHO), 4.1-3.8(m, CHO), 4.03(d, J17, CHHO), 2.5-1.5($4xCH_2$), 2.17(CH_3) ppm; δ_C(20MHz) 209.4, 206.7, 83.0(d), 75.2(t), 40.7(t), 34.4(t), 27.4(t), 26.3(q), 23.4(t) ppm; (Found: m/z 170.0949; $C_9H_{14}O_3$ requires M 170.0943).

Attempted Low Valent Titanium Induced Cyclisation of 2-(2'-oxopropyloxy)-cyclohexan-1-one (184).-Attempts to cyclise the diketone (184) using methods A, B and C all failed, giving complex mixtures showing no trace of the desired cyclisation products.

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ABBREVIATIONS

Ac	Acetyl
AIBN	Azodiisobutyronitrile
CMR	Carbon-13 nuclear magnetic resonance
DMF	Dimethylformamide
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
MCPBA	*meta*-Chloroperbenzoic acid
NaNp	Sodium naphthalenide
NBS	*N*-bromosuccinimide
NOE	Nuclear Overhauser effect
PCC	Pyridinium chlorochromate
PMR	Proton magnetic resonance
PTSA	*para*-toluenesulphonic acid
TBDMS	*t*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSO	Trimethylsilyloxy