ATTEMPTS ON THE SYNTHESIS OF THE PHEROMONE COMPONENT LINEATIN

BY

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C O N T E N T S

To my daughter

Rosaline Asimwe

and

my son

Delphine Mushani

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poorly achieved. Direct alkylation on the alkenal V with β-methallylmagnesium chloride followed by oxidative cleavage of 2,5,5-trimethylocta-1,7-diene-4-ol (VIII) and methylenation *via* a Wittig reaction gave an improved yield of the alkylated product, 4,4-dimethyl-5-(2-methyl-2-propenyl)oxacyclopentan-2-one (IX). This compound and its precursors showed a strong tendency to cyclize and it was therefore difficult to prepare a ketene precursor. Blocking the C_4-OH of compound VIII before oxidising the C-C double bonds was considered as one way of reducing this cyclization tendency. However, protection of the C_4-OH of VIII as a methyl ether followed by ozonolysis under reductive conditions (CH_2Cl_2/DMS) gave unexpectedly the cyclic product, 4,4-dimethyl-2-methoxy-5-(2-oxopropyl)oxalane (X) in which the methoxy group had migrated. Attempted halogenation of VIII resulted in (3*E*)-2,5,5-trimethyl-1,3,7-octatriene (XI). Selective oxidation of the C_4-OH of VIII to 2,5,5-trimethyl-1,7-octadiene-4-one (XII) was achieved with chromic acid in ether, but the strong tendency to isomerize to the α,β-unsaturated isomer before protection of the C_4 carbonyl group could be achieved precluded further manipulations on VIII.

In a different attempt to prepare the ketene precursor the alkenal V was oxidised to 2,2-dimethyl-4-pentenoic acid (XIII) which was converted into its methyl ester XIV. Upon ozonolysis under reductive conditions (CH_2Cl_2/DMS), XIV furnished 3,3-dimethyl-5-methoxyoxacyclopentan-2-one (XV) in which the methoxy group had migrated as well. A discussion of a mechanism of ozonolysis under reductive conditions in aprotic and protic media is presented to account for the intramolecular alkoxy

migration. These strategies and other related ones proved futile as routes to suitable precursors for the intramolecular ketene cyclization.

In one of the strategies aimed at the bicyclic oxaketone III, the anticipated Michael addition of the alkoxy anion of 3-methyl-3-buten-1-ol (XVI) on sec-butyl and tert-butyl 3-methyl-2-butenoates (XVII) to give the potential ketene precursor, furnished instead, the ester exchange product 3-methyl-3-butenyl 3-methyl-2-butenoate (XVIII). On the other hand, the reaction of the homoallylic alcohol XVI with NBS in the presence of acid catalyst gave 3-bromomethyl-3,7-dimethyl-4-oxa-7-octen-1-ol (XIX). Attempted debromination of XIX led to the formation of 2-methyl-2-(3-methyl-3-butenoxy)oxalane (XX). By protection of the bromoalcohol XIX as a trimethyl silyl ether and debromination with tributyltinhydride followed by Jones oxidation, 3,3,7-trimethyl-4-oxa-7-octenoic acid (XXI) was obtained in good overall yield. The corresponding acid chloride XXII was prepared by the reaction with oxalyl chloride in benzene and pyridine. The acid chloride was unstable and could not be purified without decomposition. Reaction of the crude acid chloride XXII with base did not give any bicyclic oxaketone III. Hence terminating our synthetic efforts of lineatin by an intramolecular ketene-ene cycloaddition approach.

The reaction of NBS with allyl and methallyl alcohols also gave the "dimerized" products, hence the reaction seems to be a general one. A mechanism for this reaction is discussed.

I

Chapter 1

INTRODUCTION

1.1 Pheromones and related compounds

It has long been known that animals communicate with each other. The communication becomes more important the more social the animal is. Even in microorganisms and plants communication seems important. For example, "biological communication" as broadly defined,[1] involves the release of one or more stimuli by an individual of a species to induce a reaction to the receiver and the benefit of such a reaction may be to the emitter, the receiver or both. The main ways of animal communication are chemical (olfactory or gustatory), mechanical (tactile or sonic) and radiotional (light perception or visual); among which chemical communication seems to be the most general, and it has been studied extensively in the last 20 years.

Whittaker and Feeney[2] proposed two broad classifications of chemical communication, viz. interspecific (or allelochemical) and intraspecific. The former was further categorized into:

(A) Allomones which have adaptive advantage for the emitting organism and include repellants, suppressants (eg. antibiotics), venoms and inductants (eg. those which cause galls and nodules).

(B) Kairomones have adaptive advantage for the receiving organism and include flower scents, inductants which stimulate adaptation (eg. the factor responsible for spine development in rotifers), attractants and phagostimulants that help predators find their pray and herbivores get their food plants.

(C) Depressants are waste products that inhibit or poison the receiving organism without resulting in any adaptive advantage for the emitter.

The intraspecific effects can also be subdivided:

(A) Autotoxins are waste products toxic for the emitter without any biological effect on other species.

(B) Adaption auto- inhibitors which are compounds that control the population of a species to its equilibrium level in the environment.

(C) Pheromones defined[3] as "substances that are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example a definite behaviour or a developmental process".

Law and Regnier[4] suggested the term "semiochemicals" for compounds that transmit messages between organisms, whether inter- or intraspecifically. This definition allows pheromones, allomones and kairomones to be placed under the same heading.

Two categories of pheromones have been defined by Wilson:[5] releasers, with instantaneous effect (eg. sex-, alarm-, aggregation-, trail- and territory-making pheromones), and primers, with a delayed effect (eg. the royal jelly of the queen bee and pheromones that cause some human females to synchronize their menstrual cycle[6]).

The knowledge of insect pheromones has progressed significantly in the past few years, partly due to their potential use for controlling insect pests, but also because the improvement in analytical methods and instrumentation made research on such minute amounts possible. Insect comprise approximately 80 % of all known animal species and some of the most serious pests known to man are caused or transmitted by this class of animals.

Sex and aggregation pheromones are the most important in insects. The sex pheromones are usually secreted by one of the sexes in order to attract the opposite sex for mating. On the other hand, aggregation pheromones attract both sexes to the source of emission. The trail pheromones are part of a system of scent whose function is the labelling of food or of trails leading to that food. Alarm pheromones are widespread among social insects and warn other members of the society about a prevailing danger.

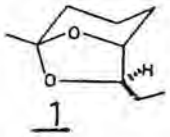
Pheromones are secreted by specialized glands of the emitter insects and detected by the antennae of the receiver. Since the isolation of the first insect pheromone, 10,12-hexadecadien-1-ol(bombykol) by Butenandt et al.[7] in 1959, improvement in isolation and analytical techniques have led to characterization of several other pheromones. The synthetic approach has been very important in pheromone studies as well. A number of isomers and analogs have been synthesized to clarify the pheromone structure-activity relationship. Final proof of the proposed structure including the geometry and relative and absolute stereochemistry have been achieved through synthesis. Finally, synthesis provides sufficient material for biological study such as field tests.

Structural, geometrical and optical isomerism all have been shown to affect the biological activity of pheromones. For example, the four possible geometrical isomers of bombykol, the pheromone of the silkworm moth (Bombyx mori) were synthesized[8-10] and compared for attractancy to the male silkworm moth. The biological activity as well as physical properties of (10E,12Z)-10,12-hexadecadien-1-ol was almost identical with those of the natural bombykol. The other three geometrical isomers possessed only moderate or weak biological activity.

Another example of stereochemical importance is provided by the pheromone of the oriental fruit moth (Grapholita molesta). The biological activity of the synthetic pheromone (Z)-8-dodecenyl acetate increased 25 times by addition of a small amount of the (E)-isomer.[11] In the case of gossyplure, the pheromone of pink bollworm moth (Pectinophora gossypiella), the pheromone consists of equal amounts of (7Z,11Z)-7,11-hexadecadienyl acetate and its (7Z,11E)-isomer.[12] Neither is biologically active alone. This suggests the existence of two different receptor sites on the pheromone receptor of the pink bollworm moth.

Structural isomerism is exemplified by two stereoisomers of 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane isolated from the frass of the western pine beetle (Dendroctonus brevicomins);[13] exo-brevicomin 1 (fig. 1.1) is biologically active and the endo-isomer 2 is not.

Figure 1.1



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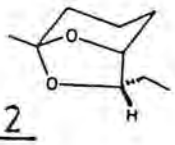

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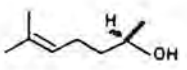
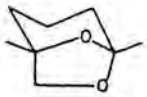


(R)-4



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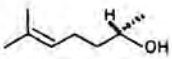


(S)-4

exo-Brevicomin 1 and frontalin 3 are chiral molecules. Both enantiomers of these pheromones have been synthesized[14-16] and tested biologically. In each case only one enantiomer possesses pheromonal activity.

An example to the contrary is provided by sulcatol 4, the aggregation pheromone produced by males of (Gnathotrichus sulcatus).[17] Both (+)-sulcatol [(S)-4] and (-)-isomer [(R)-4] have been synthesized,[18] and neither of these is biologically active. However, a racemic mixture of synthetic sulcatol was more active than the natural pheromone, which is a mixture of

65 % of (S)-4 and 35 % of (R)-4.[19] This behaviour is somewhat similar to that mentioned in the case of gossyplure and suggests the presence of enantiomer-specific active sites in the insect.

These few examples illustrate the importance of stereochemistry in the pheromone research. Reviews on pheromone synthesis have been published which focus on methodology,[20] selected pheromones (Lepidoptera, Coleoptera and Diptera),[21] achiral[22] and chiral[23] pheromones, respectively.

The potential use of insect pheromone in pest control is rapidly increasing. Sex pheromones have been used with success in trapping insects so as to minimize the use of pesticides. Aggregation pheromone affecting both sexes offer an additional advantage. The pheromone pest approach is very selective, since each pheromone in principle acts only on one insect species in contrast to pesticide. It is worth mentioning that there are other non-naturally occurring substances which exert a similar attraction effect as that of real pheromone. Djerassi et al.[24] suggested the term "biorational agent" for any chemical which is specific in its action. Pheromones, hormones, and their mimics and antagonists all fall within this definition.

Another new area of development has been the examination of plants for naturally occurring secondary metabolites that may have insect-repelling, insecticidal, antihormonal or anti-feeding characteristics on which novel ways to influence insect behaviour or development (or both) might be based. This has a great potential in the tropics as indicated by preliminary studies.[25] In general a carefully balanced combination of

insect hormones, pheromones or their mimics and pesticides may well be a reasonable proposition to solve pest management problems.

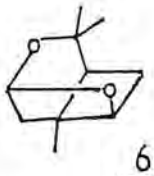
LINEATIN.

The damage caused to forests and timber throughout the northern hemisphere by ambrosia beetle pests, such as Trypodendron lineatum (Oliv.) is very extensive. Therefore, studies directed to their control are very important commercially.

About two decades ago, the aggregation pheromonal activity of T. lineatum was noted[26,27] and verified afterwards.[28] It has also been observed that ethanol and α-pinene are secondary attractants of this beetle.[29,30] The active main pheromone component of T. lineatum was isolated from frass produced by the female beetles by McConnel et al.[31] They proposed one of the two isomeric tricyclic acetals 5 or 6 (Fig. 1.2) from spectroscopic evidence and the trivial name, lineatin for the active component was suggested.

Figure 1.2.

5



6

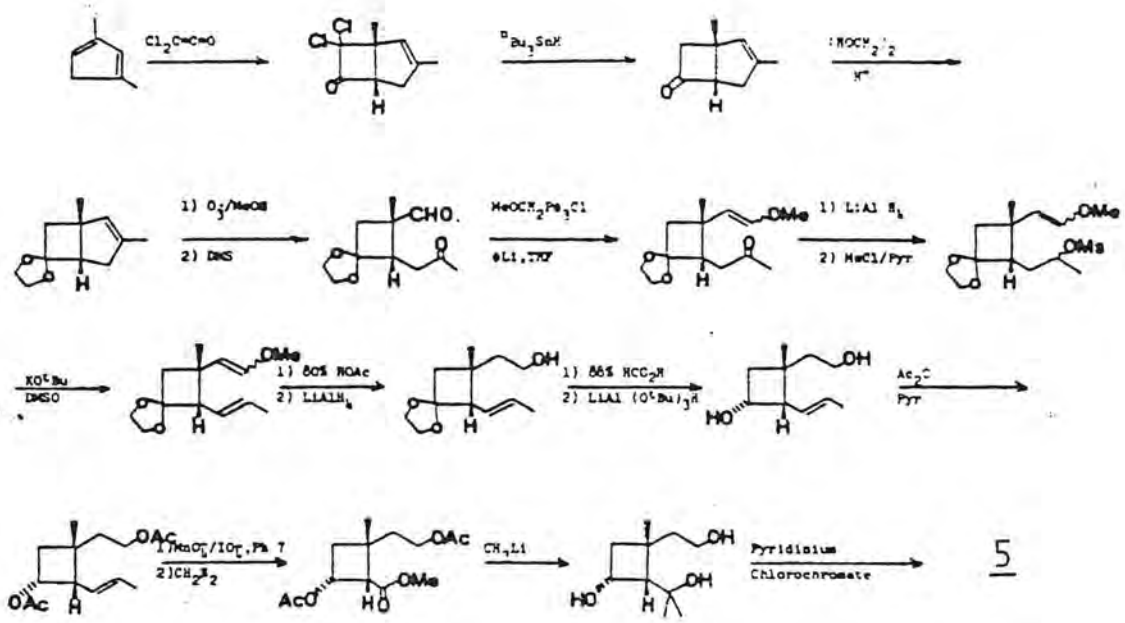
Structures 5 and 6 are also referred to as 4,6,6-lineatin and 4,5,6-lineatin or isolineatin, respectively.

Synthesis. The first synthesis of lineatin was published by Borden and co-workers[32] in 1979, and µg quantities were obtained from which the structures were confirmed as 5. Three synthetic strategies (schemes 1.1-1.3) were concluded. The key step in all attempts was the construction of the cyclobutane ring with the correct stereo- and regiochemistry. There is no detailed information about scheme 1.1, but it is mentioned that the yield of 5 was very low. Scheme 1.2, a seemingly attractive synthesis, the dihaloketene cycloaddition furnished only 5 % of the cycloadduct. The authors[32] also report that cycloaddition took place only when the ketene was generated by dehalogenation using zinc. An independent study of this reaction[33] led to isolation of a different cycloadduct 7 in 6 and 45 % yields using activated zinc by the methods of Brady[34] and Hassner,[35] respectively.

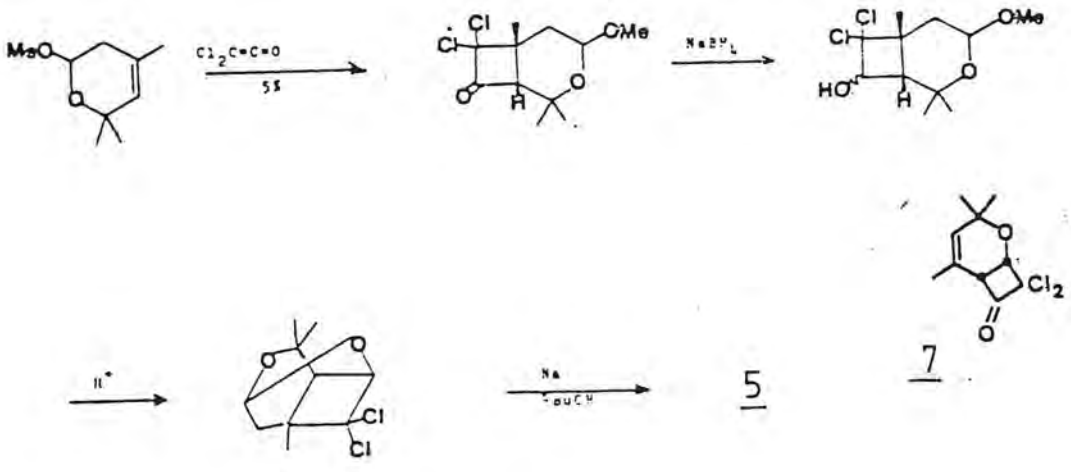
In the strategy shown in scheme 1.3, the cyclobutane ring was constructed photolytically to give a cycloadduct of correct regio- and stereochemistry in only 4 % yield, difficult to separate from the other isomers. The sequence was therefore carried out on the crude mixture and lineatin was isolated by prep. GC.

Details of scheme 1.4 are available in Handley's thesis.[36] The photo-cycloaddition gave good yields of the cycloadduct in a ratio of 2:1 exo and endo, and so was the sequence up to the ketoacetale 8. Subsequent reactions either led to poor yields

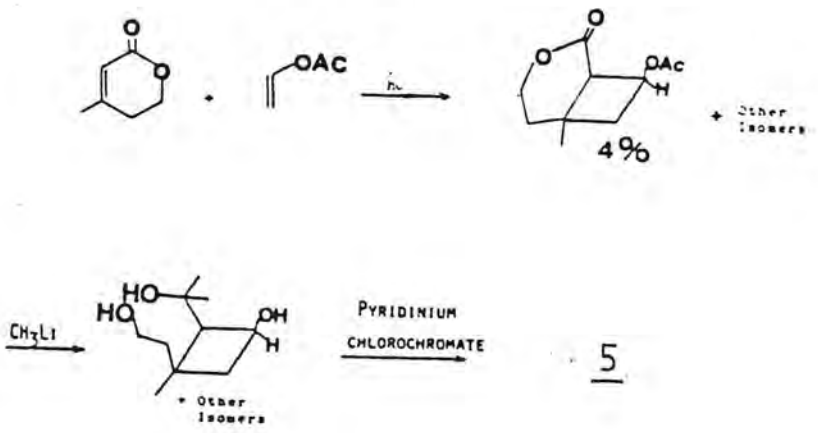
Scheme 1.1



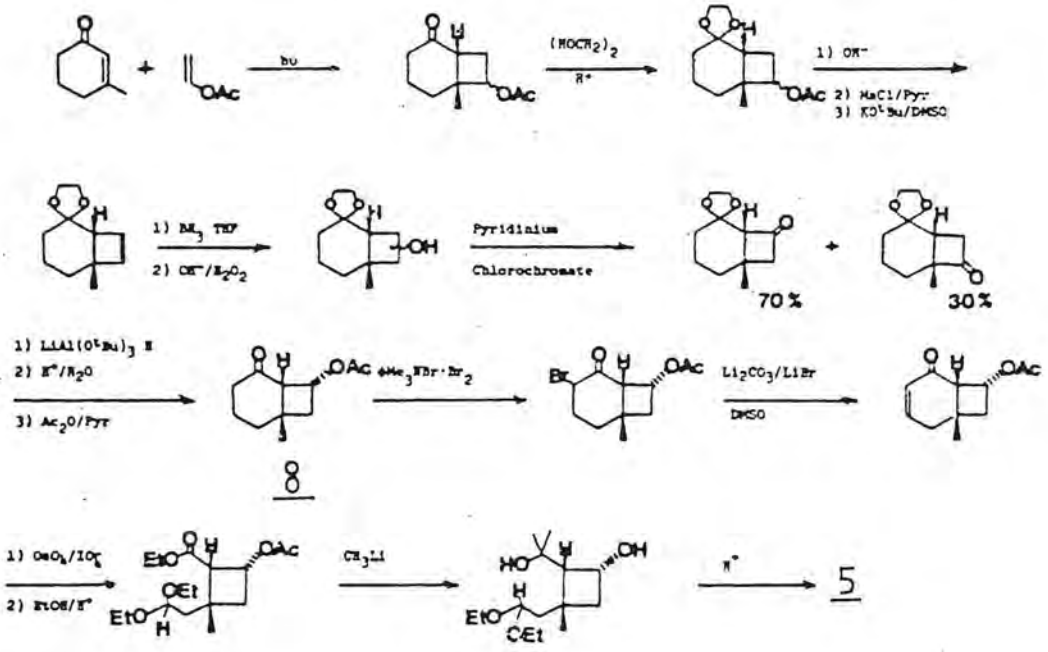
Scheme 1.2



Scheme 1.3



Scheme 1.4

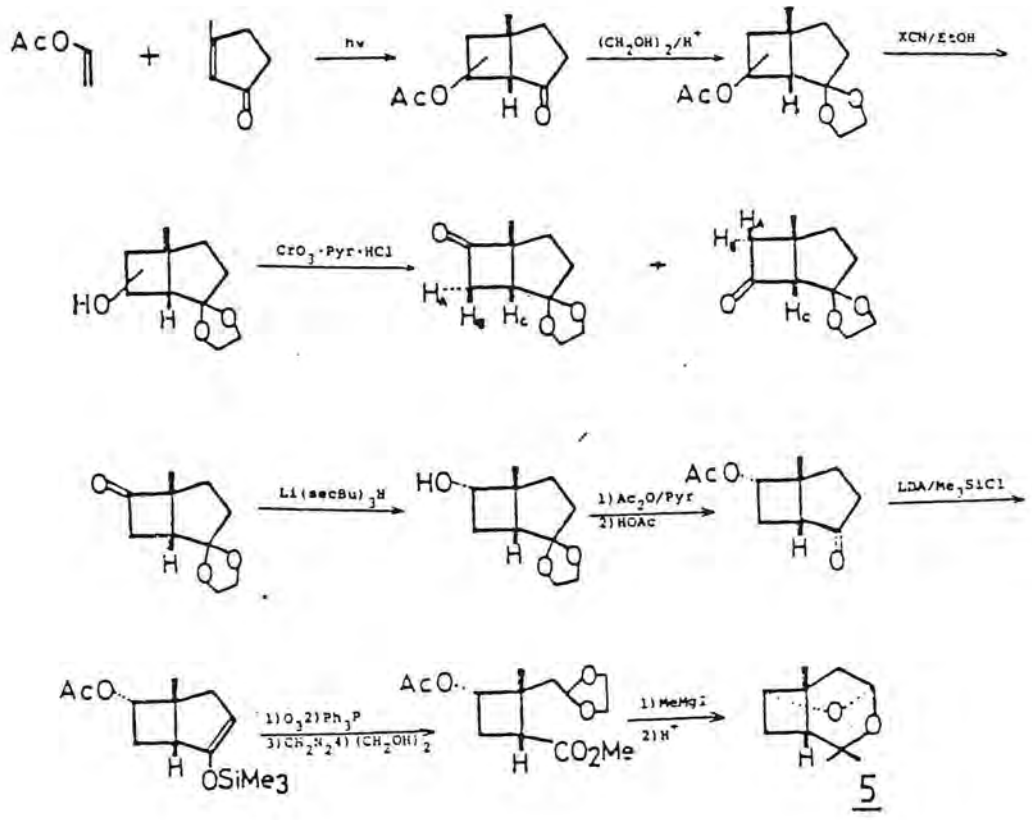


or were unsuccessful, making this approach impossible to give lineatin.

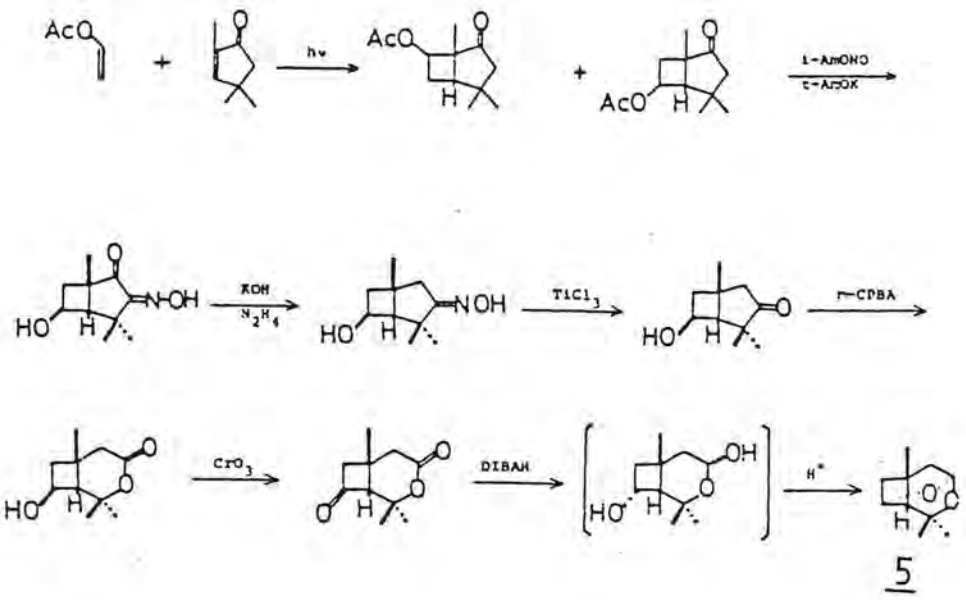
Subsequently, synthetic work to produce the compound by efficient and economic ways has been a target for a number of chemists.

Schemes 1.5 and 1.6 outline procedures of Mori et al.[37,38] The cyclobutane ring was formed photolytically from an olefin and cyclopentenones. In both cases a mixture of regioisomers was unavoidable, necessitating chromatographic separation at some stage of the synthesis. The overall yields were low. In the sequence shown in scheme 1.6 a resolution step was incorporated and both enantiomers of 5 were obtained. Unfortunately, the absolute configuration was wrongly assigned, but was later corrected[39,40] from another synthesis.

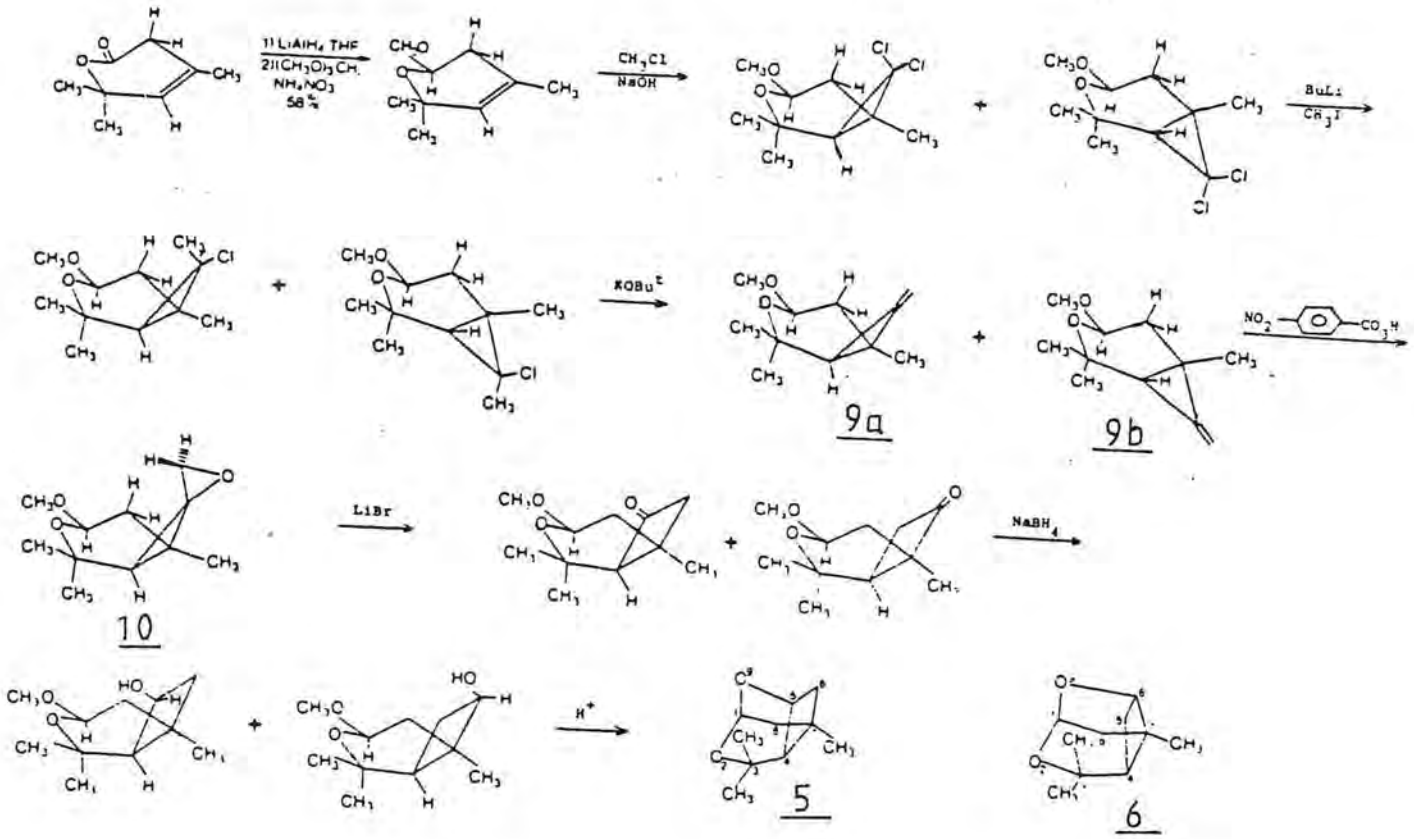
Scheme 1.5.



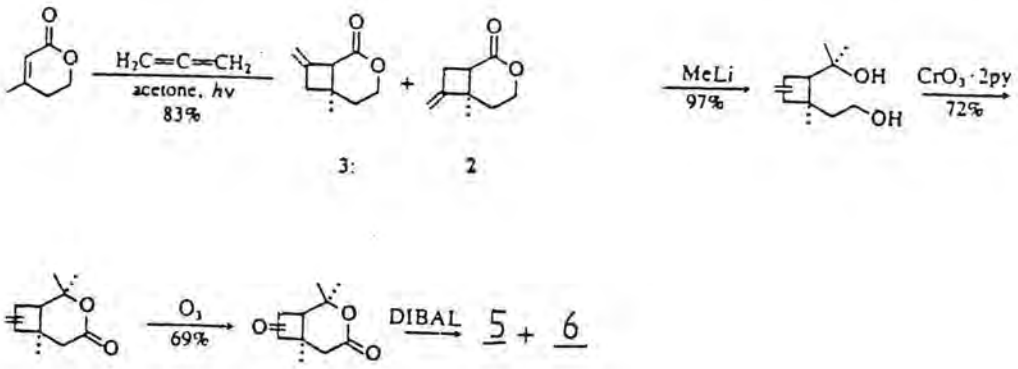
Scheme 1.6.



Scheme 1.7.



Scheme 1.8.



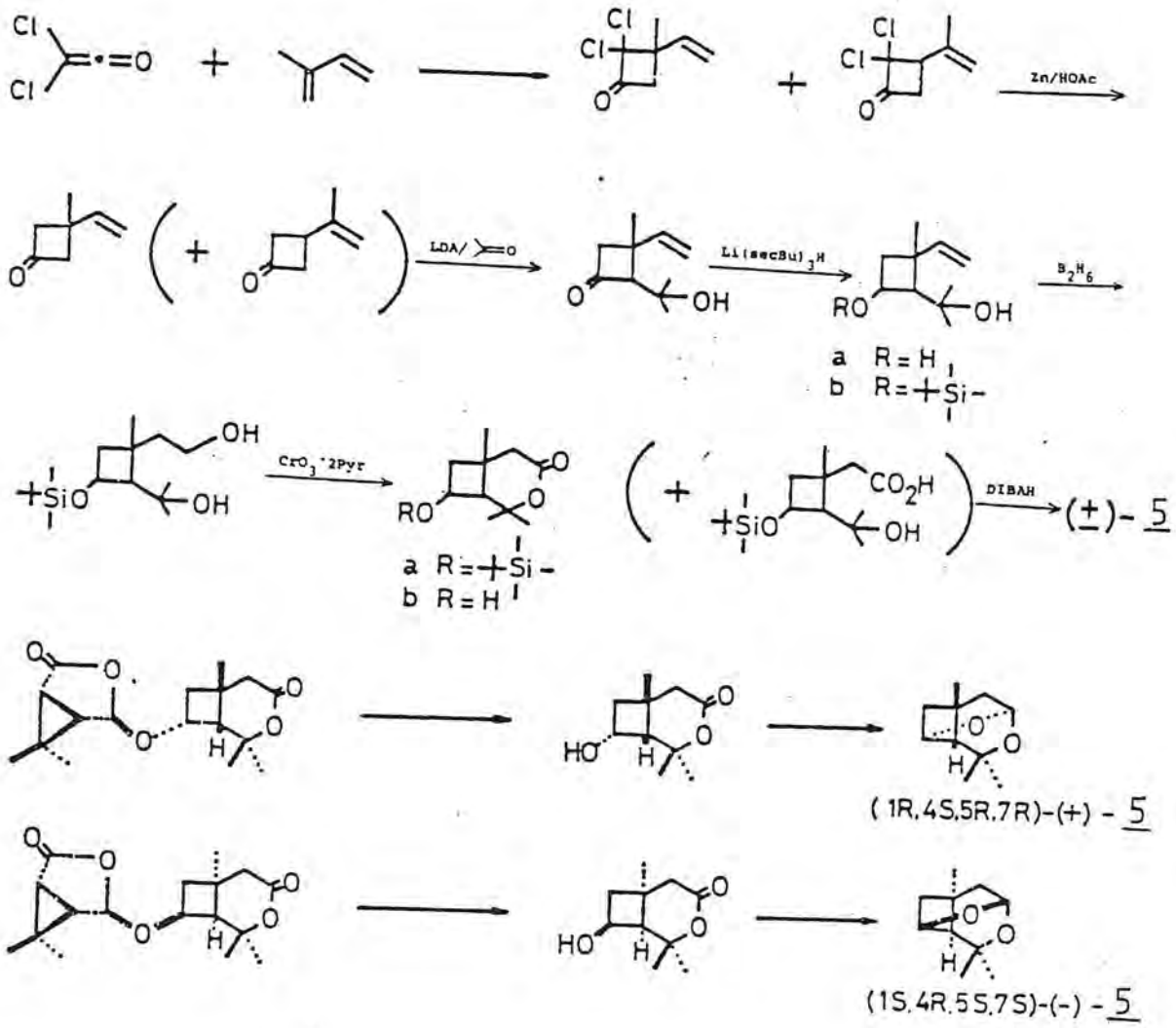
Slessor et al.[41] planned to avoid the regiochemical problem by constructing the cyclobutanone ring via the rearrangement of the oxaspiropentane 10 derived from methylene cyclopropanes 9 as outlined in scheme 1.7. The regioselectivity was achieved in a ratio of 4:1 and the ketones were manipulated to racemic lineatin and isolineatin, respectively; after chromatographic separation of the intermediate alcohols. A resolution step was incorporated as well, and the active form was proven to be (+)-5 of which they proposed the absolute configuration which was later confirmed.[39,40]

The synthesis by McKay et al.[42] partially depicted in scheme 1.8 utilized a photochemical cycloaddition of allene to α,β-unsaturated lactone. Two regioisomers were obtained in a ratio of 3:2. Despite several attempts, the regioselectivity could not be improved. The synthesis was carried through to 5 and 6 which were separated chromatographically. This synthesis achieved

6 % overall yield, the highest compared with syntheses mentioned so far (schemes 1.1-1.7) of $\leq$ 2 %.

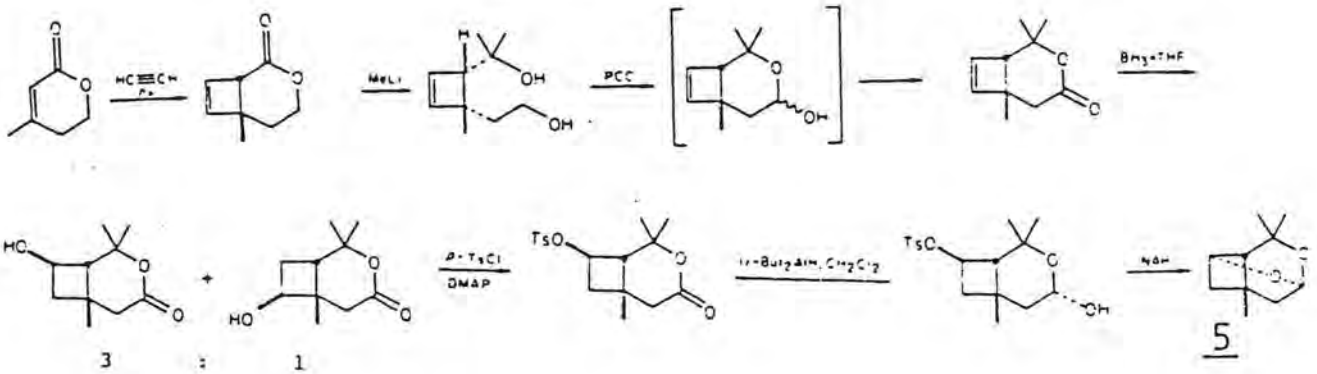
Scheme 1.9 outlines the synthesis developed by Mori et al.[39,40] involving a thermal dichloroketene cycloaddition to isoprene as a key step. By resolution of one of the intermediates the two enantiomers were obtained and the absolute configurations re-established in agreement to those suggested by others.[41]

Scheme 1.9.

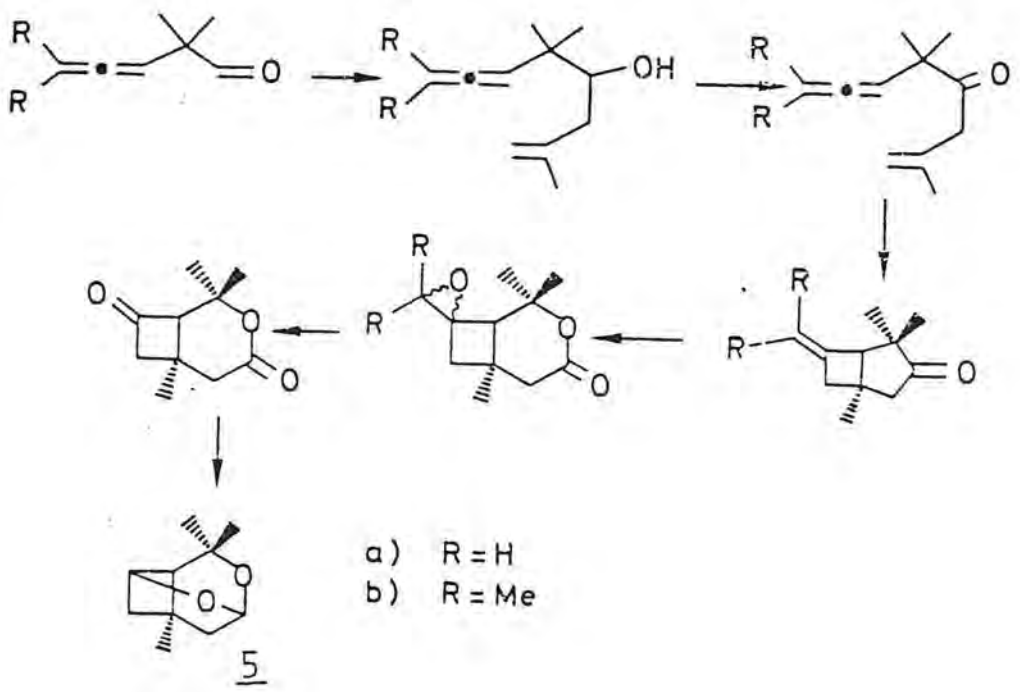


White et al.[43] have reported the synthesis of lineatin based on a photocycloaddition of acetylene to anhydromevalonolactone as outlined in scheme 1.10. Despite several attempts, a regiochemical challenge was experienced in the hydroboration step. Nevertheless, their eleven step synthesis in 8 % overall yield was quite outstanding until recently Skattebøl and Stenstrøm[44] achieved a regioselective synthesis by a thermal intramolecular allene-ene cyclization, depicted in scheme 1.11. This synthesis involved seven steps and racemic lineatin was obtained in 14 % overall yield.

Scheme 1.10



Scheme 1.11



For field application the racemic form of lineatin is satisfactory since no significant biological activity has been observed for the (-)-enantiomer.[45] Also since no activity is observed for isolineatin[46] a high regioselective synthesis may not be necessary for practical purposes. Current formulations blend the pheromone with either ethanol or a mixture of ethanol and α-pinene.[47,48]

1.2 Ketene Cycloadditions.

Generation of ketenes.

Ketenes are unstable reactive electrophilic species reacting with a variety of nucleophiles and many unsaturated systems. Their generation is, therefore, very much dependent on the nature of the substituents. For example, the most reactive dihaloketenes require mild conditions of generation while the less reactive dialkyl- or diarylketenes relatively high pyrolytic temperatures are usually employed. Only the chemistry of those ketenes which are frequently used in cycloaddition reactions shall be discussed.

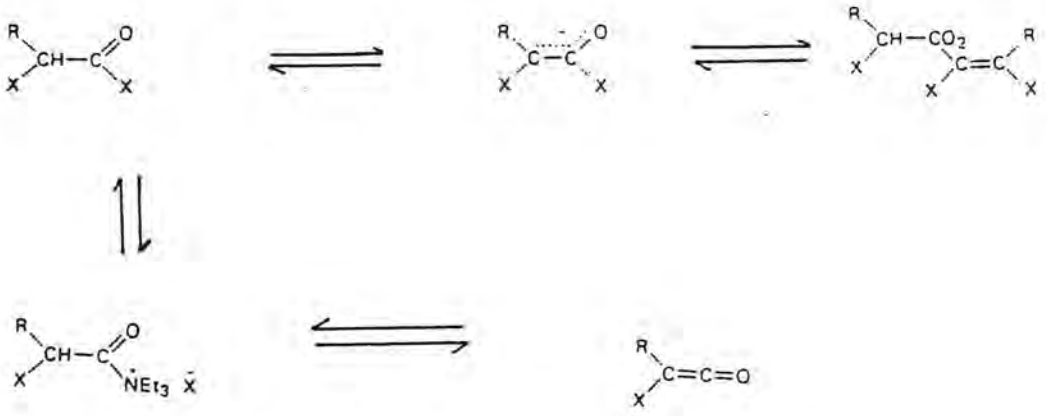
Alkyl ketenes: Are prepared by dehalogenation of 2-haloacylhalides, thermal decomposition of acid anhydrides,[49] thermal decomposition of ketene acylals[50] and dehydrohalogenation of acid halides. The last method of generation with base is the most commonly used for monoalkyl derivatives, but often suffer from byproduct resulting from other reactions catalysed by bases or Lewis acids.[51] However, intramolecular ketene-ene

cycloadditions have been achieved by this method of generation.[52,53] Dehalogenation of 2-bromoacyl halides with activated zinc suspended in THF is considered as a more satisfactory method.[54] The photochemical rearrangement of cyclic ketones, lactones and diazoketones is also a mild procedure for generating alkylketenes.[55-60] Thermal- and photo-induced Wolf-rearrangement of α-diazoketones have been used to generate ketene in intramolecular cycloadditions as well.[52,59,61-63] The photochemical rearrangement of cyclic ketones has also received significant attention with respect to intramolecular reactions of intermediate ketenes.[64,65]

Halogenated ketenes: These are quite reactive species generated in situ by dehalogenation or dehydrohalogenation. Because of their activity, they are the most widely studied in the cycloaddition reactions from both mechanistic and synthetic point of view.[51,66,67] Dehydrohalogenation of 2,2-dihaloacyl halides with a base are reported to give more reproducible results,[67] but the Lewis acid generated preclude use of electron rich olefins which readily polymerize.[51] Dehalogenation of 2,2,2-trihalo acyl halide with activated zinc has been widely used,[34] and a modified form[35] which incorporates $POCl_3$ has widened the scope to include olefins that tend to polymerize in the presence of Lewis acids. It is suggested that $POCl_3$ complexes with the zinc halide formed in the dehalogenation step.

Alkylhaloketenes: These are similarly prepared by dehydrohalogenation with a base from α-haloacylhalide.[68] The main competing reaction is the formation of α-halovinyl esters as outlined in scheme 1.12. This can be minimized if the acyl halide is slowly added to the amine.[69]

Scheme 1.12



Acylaldoketenes: Their importance stems from their participation in [2+2] intramolecular cyclizations. They are prepared by flash thermolysis of enolic form of β-ketoesters.[70] Thermolysis of 2-diazo-1,3-diketones also furnish the acylketenes as unstable intermediates.[71]

Vinylketenes: These conjugated ketenes have received considerable attention both mechanistically and synthetically. They are generated by a variety of methods, common ones being, dehydrohalogenation of α,β- and β,γ-unsaturated acylhalide,[72] by a Wolf-rearrangement of 5-acyl-3,3-dimethyl-3H-pyrazoles[73] and by photolytic cleavage of cyclohexa-2,4-dienone.[74] A recent example of the preparation of alkylidene cyclobutanones using these ketenes has been reported.[75]

Cycloadditions:

The [2+2] cycloaddition of ketenes to alkenes is a synthetically useful reaction to form a four-membered ring. Mechanistically the reaction is a [π^2s+π^2a] combination of a ketene and an olefin and is symmetry allowed according to the selection rules for pericyclic reactions.[76,77] Depending on the substrates involved, diradical, ionic and concerted mechanisms have been suggested.[78] The ionic mechanism is generally more appealing, since some of the observed high stereo- and regiospecificity, for example the reaction of dichloroketene and cyclopentadiene[67] is best explained in these terms.

The rates and regioselectivity can also be explained from the frontier orbital theory.[79] The reaction then being considered as the interaction of HOMO (ketenophile) and LUMO (ketene). Depending on the nature of the substituents the energies of these molecular orbitals may be raised or lowered; consequently explaining the relative reactivities. For example, electron withdrawing groups lower the energy of the LUMO of the ketene and the HOMO is raised in electron-rich olefins. A relatively fast reaction is therefore observed for this pair of reactants. Regiochemistry is then determined by preferential overlap between the atoms with large LUMO coefficient in the ketene and that with large HOMO coefficient in the ketenophile.

There are a large number of examples of [2+2] ketene cycloadditions reported in the literature occurring intermolecularly. On the other hand, only a few of the intramolecular type have been studied. These reactions are, however, synthetically

useful since whenever occur, high stereo- and regioselectivity is usually observed.

In table 1.1 we present most of the examples of intramolecular ketene-ene cycloadditions available in the literature.

The formation of cyclobutanones depicted under entries 1-3 are probably the first examples to demonstrate the intermediacy of ketene in acyclic structures. Ketene intermediacy was proposed in the "Homo-Favorskii" reaction, depicted in scheme 1.13,[80] but then rejected.[81]

Scheme 1.13.

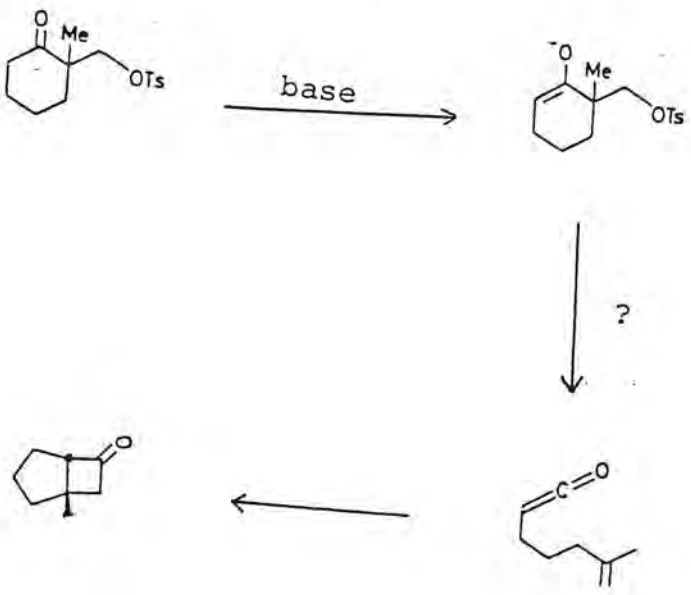


Table 1.1: Examples of Intramolecular Ketene Cyclizations.

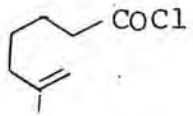
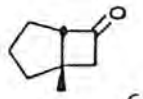
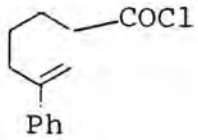
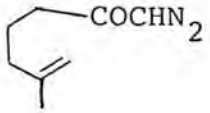
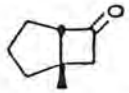
Entry	Substrate	Method of Ketene generation	Main Product(s)	References
1		Et_3N/CH_2Cl_2	 65 %	52
2		Et_3N/CH_2Cl_2	 58 %	52
3		hν/pentane	 low yield	52

Table 1.1, cont.

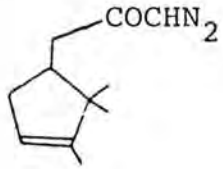
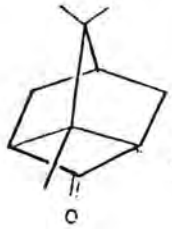
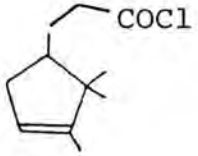
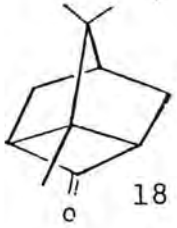
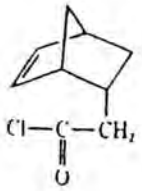
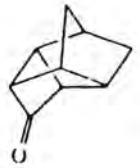
Entry	Substrate	Method of Ketene generation	Main Product(s)	References
4		hν/pentane	 76 %	63
5		Et_3N/PhH	 18 %	63
6		Et_3N/PhH	 61 %	53

Table 1.1, cont.

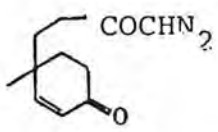
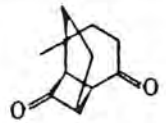
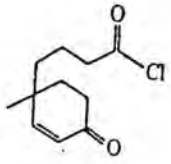
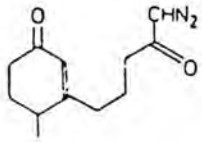
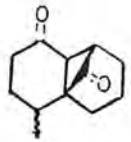
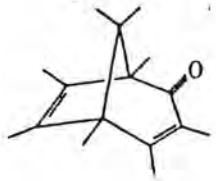
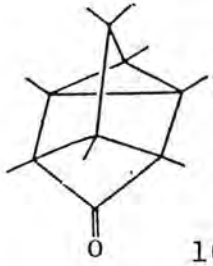
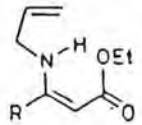
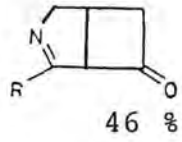
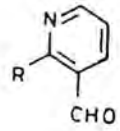
Entry	Substrate	Method of Ketene generation	Main Product(s)	References
7		hν/cyclohexane	 42 %	62
8		Et_3N	No reaction	62
9		hν/cyclohexane	 34 %	61

Table 1.1, cont.

Entry	Substrate	Method of Ketene generation	Main Product(s)	References
10		hν/pentane	 100 %	64
11		Flow pyrolysis 400 °C, 15 mm Hg	 46 % +  10 %	82

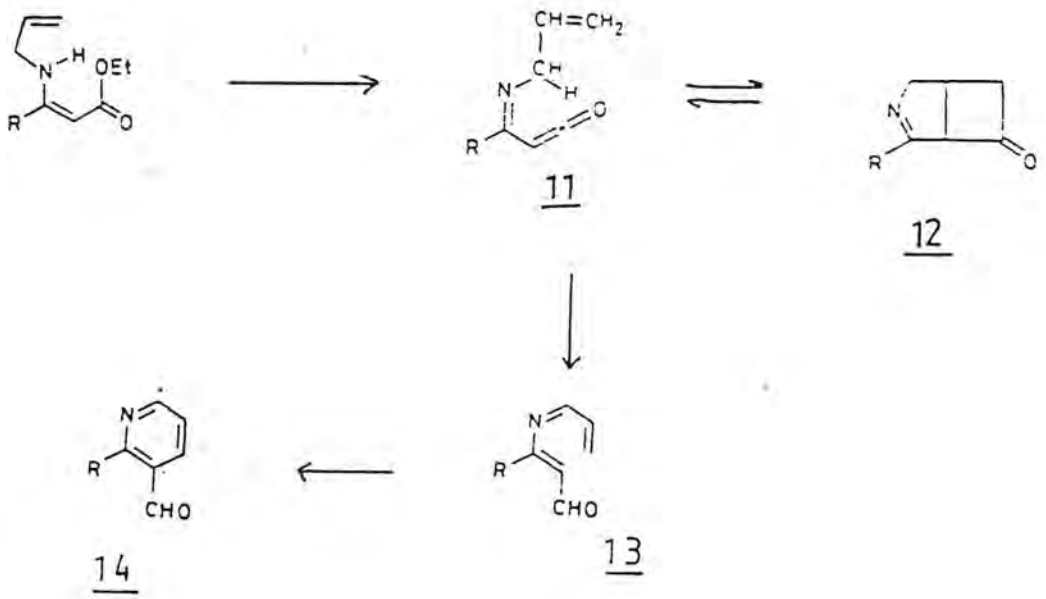
It is also observed that ketene generation by Wolf-rearrangement gave a low yield of the cyclobutanone product; presumably the α-ketocarbene enters other competitive reactions (entry 3). A contrast is provided by entry 4. A high yield of the cycloadduct was obtained by this generation mode. The difference probably arises due to the constrained structure in the latter case. The low yield obtained by the dehydrochlorination reaction (entry 5) is not easily explainable since in a similar example (entry 6) a high yield is reported. A change from 5- to 6-membered ring is not likely to bring about this dramatic difference. In entries 7-9, Becker and his coworkers[61,62] studied the intramolecular ketene addition on conjugated cycloalkenones. No reaction was observed when the ketene was generated by dehydrohalogenation (entry 8) as compared to entry 7.

The failure of the reaction was claimed to be due to the electron deficient C-C double bond of the enone.[62] The suggestion that intramolecular ketene-ene cycloadditions occur when the double bond is located in a 5-membered ring or in an acyclic structure and not in a 6-membered ring[62] is of doubtful validity. The result depicted in entry 6 is an example of the contrary. In entry 10, the photoisomerization *via* a ketene is synthetically useful. The product is readily isomerized thermally to the starting material.[64]

In entry 11, also outlined in scheme 1.14, the formation of a bicyclic heterocycle 12 and the pyridine derivative 14 are postulated to derive from the allylimino ketene 11. An intramolecular $[\pi^2 s+\pi^2 a]$ cycloaddition of 11 leads to 12 while a

1,5-hydrogen shift on 11 gives the hexatrienal 13 which gives 14 by electrocyclization.[82]

Scheme 1.14



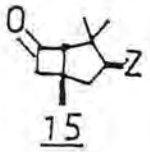
1.3 Objectives.

At the start of this work the only published syntheses of lineatin are those depicted in schemes 1.1-1.7. None of them seem convenient for a large scale preparation of the compound in an efficient and economical way. The general problems were the regio- and stereoselectivity in the construction of the cyclobutane ring.

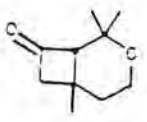
In all the strategies mentioned above and later ones (schemes 1.8-1.11) none involved an intramolecular ketene-ene cyclization as a way of constructing the cyclobutanone ring. We therefore envisaged to achieve an efficient synthesis of lineatin by this approach despite the relatively few examples of intramolecular ketene-ene cycloadditions available in literature.

From the retro-synthetic analysis of lineatin, the bicyclic compounds 15, 16, and 17 (Fig. 1.3) were the targets.

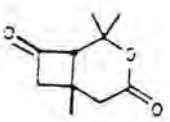
Figure 1.3.



15



16



17

2,2-Dimethyl-4-pentenal, easily prepared from cheap starting materials was conveniently chosen for the syntheses leading to 15. Manipulations on this alkenal are presented in chapter 2. 3-Methyl-3-buten-1-ol also easily prepared from inexpensive readily available chemicals was chosen for manipulatjons leading to 16 and/or 17 and the results are presented in chapter 3.

From the results presented in chapters 2 and 3 it is clear that the intramolecular ketene-ene approach is not likely to be an efficient synthesis of lineatin. In a number of approaches we abandoned reactions which either involved use of expensive reagents or several steps to achieve suitable intermediates.

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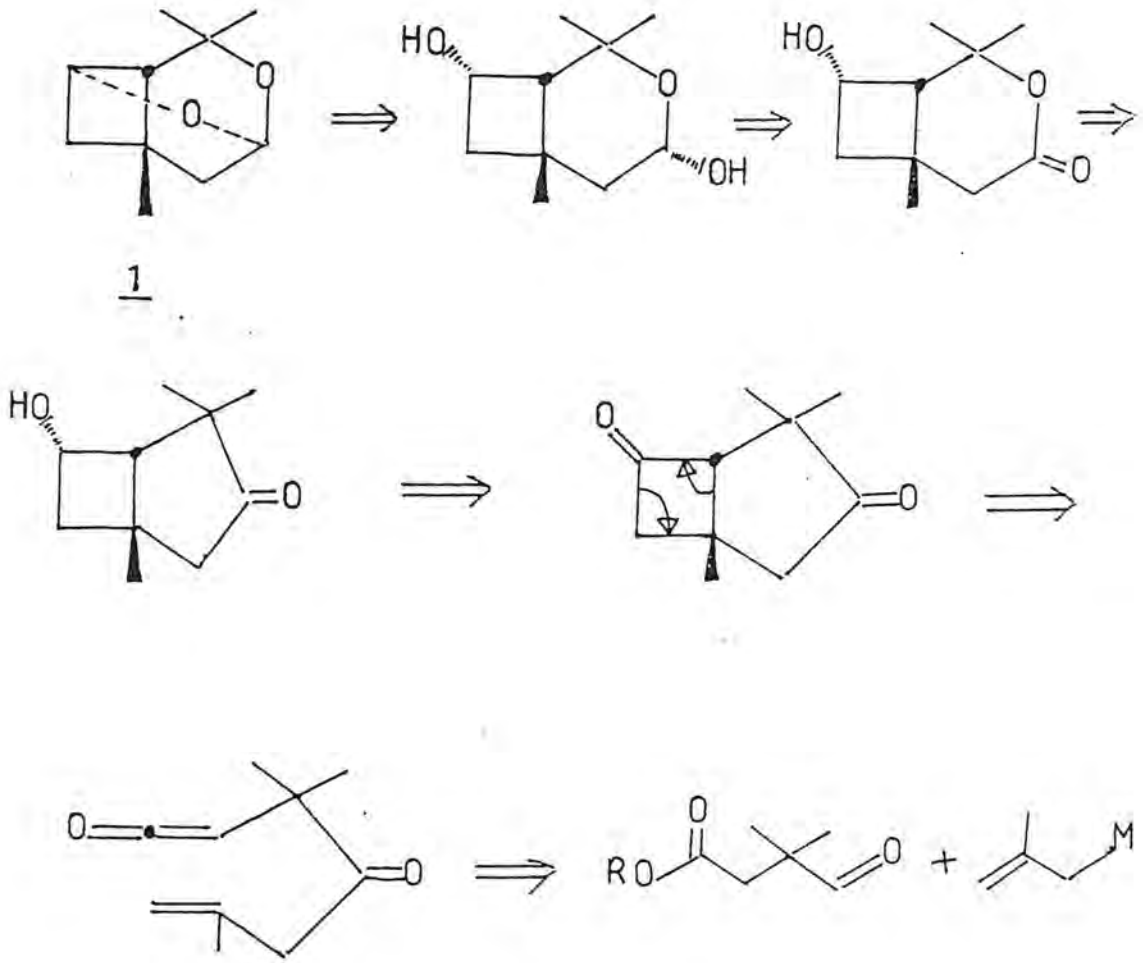
II

Chapter 2.

Attempted Synthesis of Lineatin from 2,2-dimethyl-4-pentenal and Analogues.

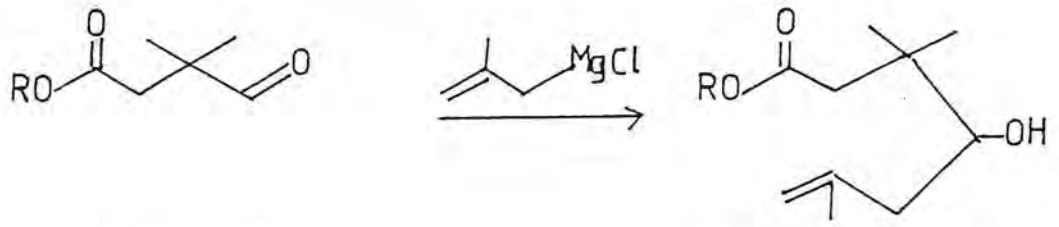
Our approach towards the synthesis of lineatin by an intramolecular ketene-ene cycloaddition was based on a retro-synthetic plan depicted in scheme 2.1. Accordingly we designed one synthetic strategy as shown in scheme 2.2.

Scheme 2.1.



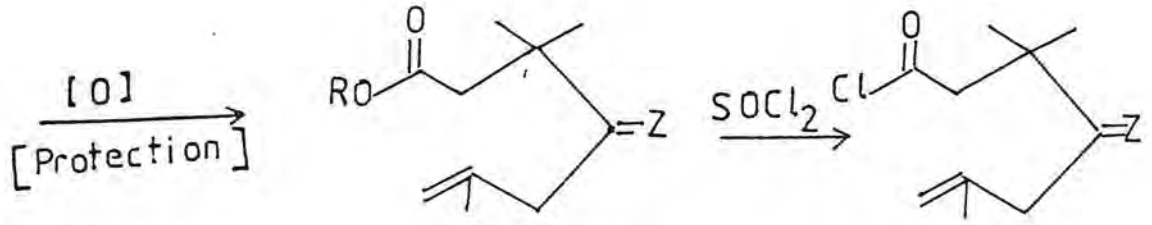
1

Scheme 2.2.



2, R = Alkyl

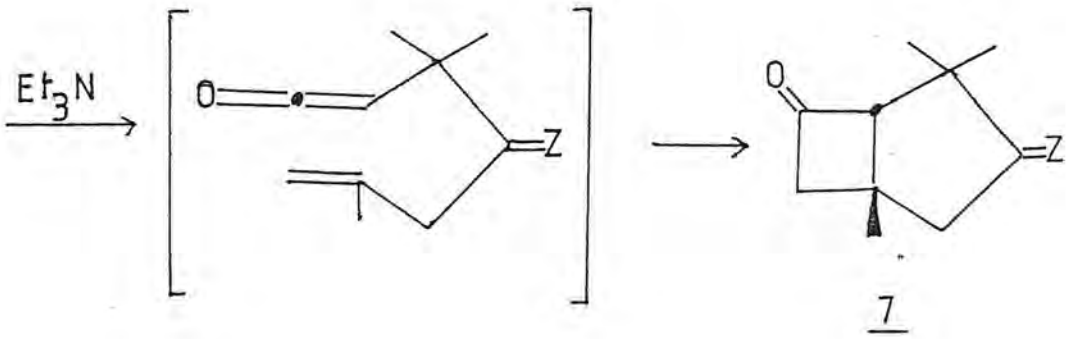
3, R = Alkyl



4, R = Alkyl

5, R = OH

6



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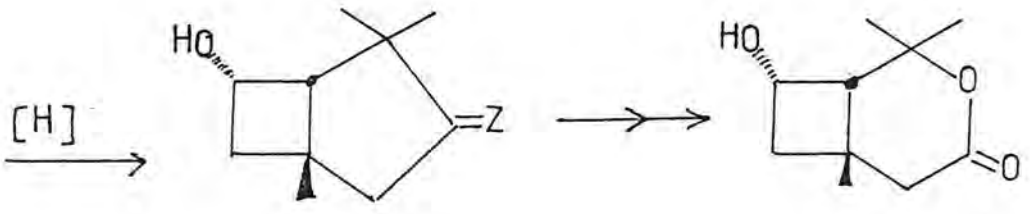

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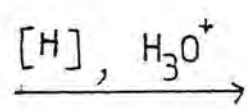


1

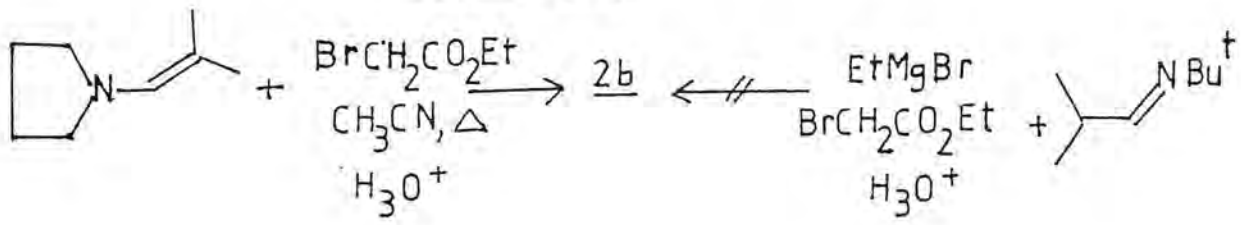
Selective reaction of the Grignard reagent at the aldehyde function of the oxoester 2 or the corresponding acid should lead to alkyl 3,3,6-trimethyl-4-hydroxy-6-heptanoate 3 or the parent acid. Oxidation of 3 with chromic acid followed by protection of the resulting carbonyl group should furnish the ester 4 which could be hydrolysed to the acid 5. Treatent of the acid chloride 6, derived from 5, with triethylamine should generate an intermediate ketene-ene, which could cyclize intramolecularly to the bicyclo[3.3.0] heptanone derivative 7. This is the key step of the synthesis. The transformation of 7 into lineatin ought to occur without problems. Similar transformations have already been carried out successfully.

Our first problem was to prepare the exoester 2 or the corresponding acid in an acceptable yield.

Ethyl 3,3-dimethyl-4-oxo-butanoate 2b (R=Et) has been prepared by alkylation of isobutyraldehyde pyrrolidine enamine with ethyl bromoacetate in refluxing acetonitrile in only 8% yield.[1]

We obtained 2b (R=Et) according to this procedure in 7% yield. Attempts to prepare it in a better yield by alkylation of isobutyl tert-butyl imine with ethyl bromoacetate in the presence of a Grignard salt[2,3] were unsuccessful (Scheme 2.3).

Scheme 2.3.

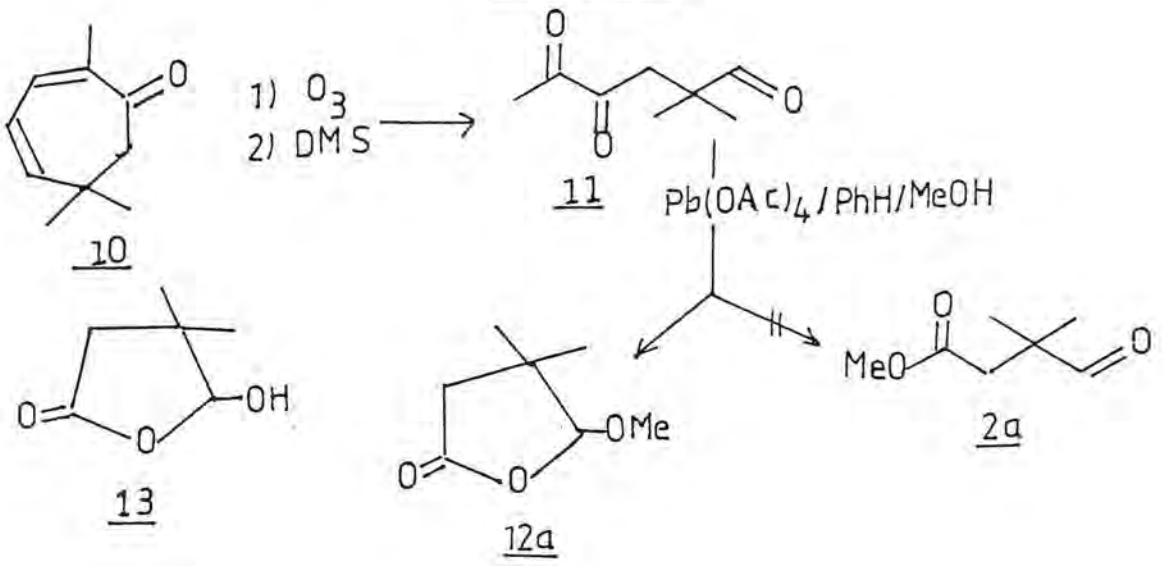


This was certainly not satisfactory, and we looked for better ways of making 2. Ozonolysis of 2,6,6-trimethyl-2,4-diene cycloheptanone 10 (eucarvone) under reductive conditions followed by lead tetraacetate cleavage of the resulting diketone 11 in benzene-methanol[4] was considered as a route to 2a (R=Me), (Scheme 2.4).

Eucarvone 10 was obtained from (-) carvone in 55% yield according to the literature.[5] Ozonolysis of 10 followed by reduction with dimethyl sulphide (DMS) gave 2,2-dimethyl-4,5-dioxohexanal (11) in 77% yield as an orange liquid. The ^{1}H NMR of 11 exhibited a singlet at 1.20 ppm due to the gem-dimethyl groups, and another singlet at 3.41 ppm for the terminal methyl group, adjacent to the carbonyl group. The methylene group gives rise to a resonance at 2.93 ppm and an aldehydic proton appears as a singlet at 9.45 ppm.

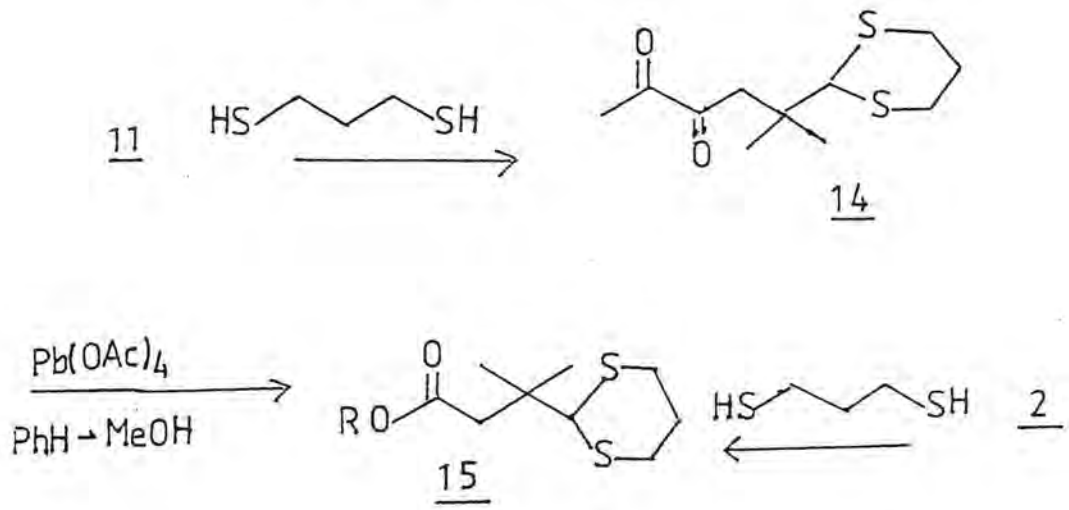
The lead tetraacetate cleavage furnished in 65% yield a product which was not 2a (R=Me), but an isomeric γ-lactone 12a probably formed from the hydroxy-γ-lactone 13 and methanol.

Scheme 2.4.



In order to avoid cyclization to 12a the aldehyde 11 was protected by reaction with 1,3-propanedithiol to compound 14 in 66% yield. The oxidative cleavage step was conducted by the same procedure as that used for the parent aldehyde 11. GC-MS revealed that the product consisted of 15a (R=Me) and unreacted starting material in a ratio of 1:3. (Scheme 2.5). We also prepared compound 15b (R=Et) from 2b in 59% yield. Although no attempt was made to optimize the preparation of 15 at this stage we believed that eucarvone was potentially a better starting material for the preparation of this compound than compounds 2.

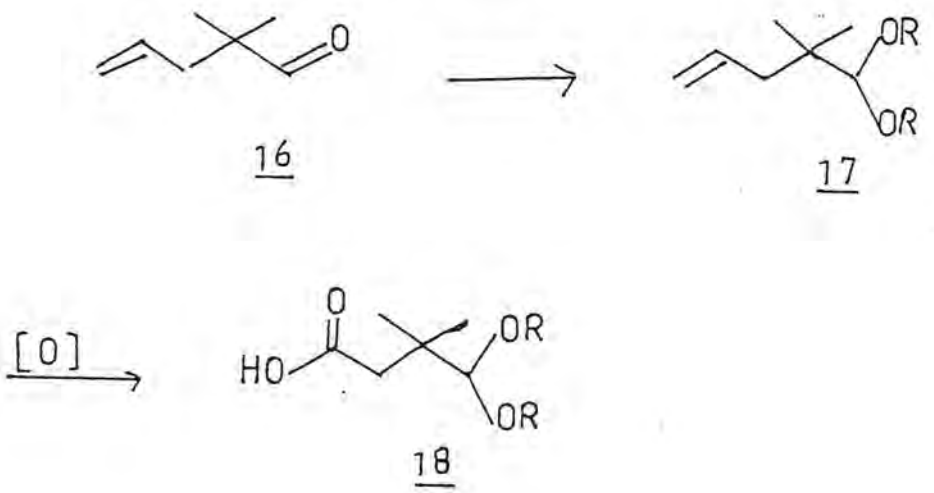
Scheme 2.5.



Another route to a protected derivative of 2 viz. the acid 18, started with the readily available aldehyde 16 as outlined in scheme 2.6. Three acetals 17 were prepared using a) methanol, b) ethanol and c) 1,2-ethanediol , and these were oxidized with potassium permanganate under phase transfer conditions.[6]

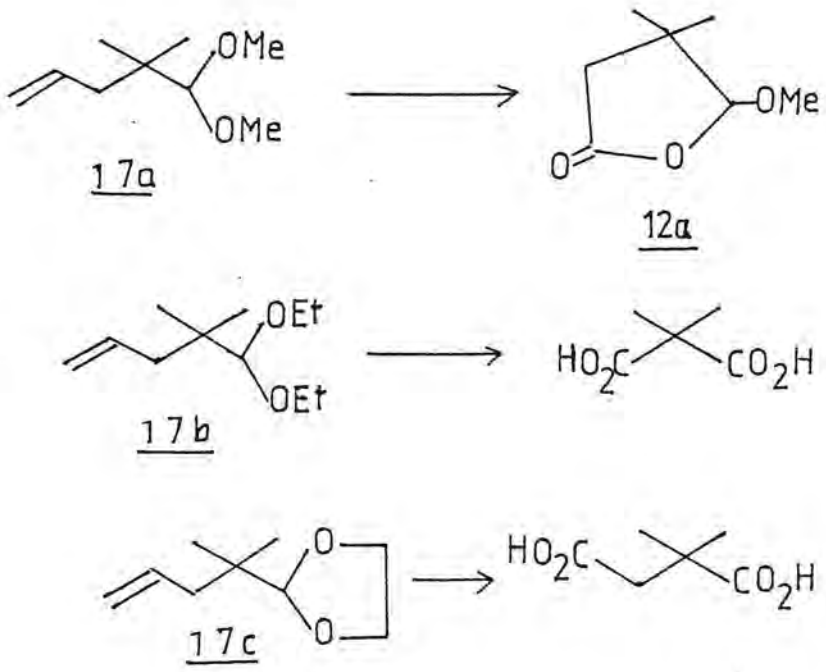
To our surprise, the reaction of the ethylene acetal 17c gave none of the expected acid 18c, but instead we isolated in 40% yield a solid product, m.p. 134-6°C which proved to be 2,2-dimetyl butanedioic acid by comparison of its spectroscopic data with those of an authentic sample. In addition 45% of the starting material was recovered. On the other hand, the dimethyl acetal 17a gave the γ-lactone 12a in yields varying from 45-70% along with two products which were not characterized. In the case of the diethyl acetal 17b the acetal function was oxidized with concomitant decarboxylation to 2,2-dimethyl propanedioic acid in about 50% yield together with about 30% of recovered starting material.

Scheme 2.6.



Hence, under the same conditions three similar acetals are oxidized to three different products. The only expected product was actually the lactone 12a which most probably derived from the corresponding acid, (scheme 2.7.).

Scheme 2.7.



A number of differently substituted acetals were prepared and oxidized under PTC in order to test the generality of this abnormal oxidation. Oxidations were then performed in benzene-water containing a 1:1 molar ratio of KMnO4-KOH and the pH of the aqueous medium was about 12 during the entire course of the reaction. The results are summarized in Table 2.1. Apparently under conditions of phase transfer permanganate oxidation of acetals to acids is a general reaction. Rates as well as yields seem to depend somewhat on the structure of the acetal.

Apparently overoxidation did not occur in either the cyclic or acyclic acetals of hexanal. Hexanoic acid was the only product isolated in yields ranging from 30-50% along with recovered starting material. It is also apparent that cyclic acetals are oxidized faster than the acyclic counterparts, and

of the latter the diethyl acetals react faster than the dimethyl analogoues. The mechanism of this oxidation and oxidative decarboxylation remain unclear to us.

Table 2:1. Oxidation of acetals: $R^1CH(OR)_2$ to carboxylic acids. [a]

Entry	R	R^1	[KMnO4]/[Acetal]	Time (h)	Temp. (°C) [b]	Yield (%) [c] Acid	Yield (%) [c] Acetal [d]
1.	Me	C_6H_5-	3.60	45	60-5	51	43
2.	Et	C_6H_5-	3.60	20	70	74	21
3.	$-CH_2-$	C_6H_5-	3.60	6 [e]	50-60	85	5
4.	Me	4-ClC_6H_4-	3.60	72	50	23	53
5.	Et	4-ClC_6H_4-	3.60	45	70	45	53
6.	$-CH_2-$	4-ClC_6H_4-	3.60	24	50-60	78	20
7.	Me	$CH_3(CH_2)_4$-	3.60	60	70	33	54
8.	Et	$CH_3(CH_2)_4$-	3.60	52	70	47	46
9.	$-(CH_2)-$	$CH_3(CH_2)_4$-	3.60	24	70	50	35
10.	Me	CH_2=CH-CH_2-C(Me)$_2$-	3.60	24	25	45-70 [f]	-

Table 2:1. cont.

Entry	R	R^1	[KMnO4]/[Acetal]	Time (h)	Temp. (^oC) [b]	Yield (%) [c] Acid	Acetal [d]
11.	Et	$CH_2=CH-CH_2-C(Me)_2-$	3.60	30	20	50 [g]	27
12.	$-(CH_2)-$	$CH_2=CH-CH_2-C(Me)_2-$	3.60	30	20	37 [h]	42

a) $KMnO_4$ ratio was 1.14, PhH/H_2O was 2.

b) Time refers to the decolorisation of benzene layer.

c) Isolated crude yields.

d) Isolated as 2,4-DNP hydrazones of the parent aldehydes.

e) After stirring at 25°C for 12 h.

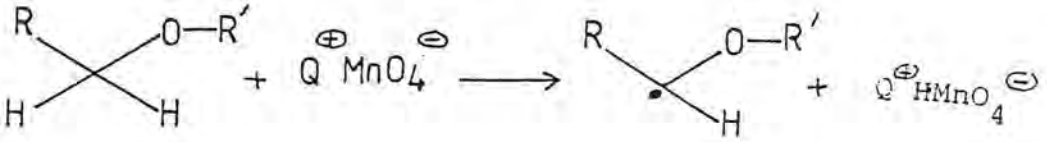
f) 4,4-Dimethyl-2-methoxyoxacyclopentan-2-one (12a).

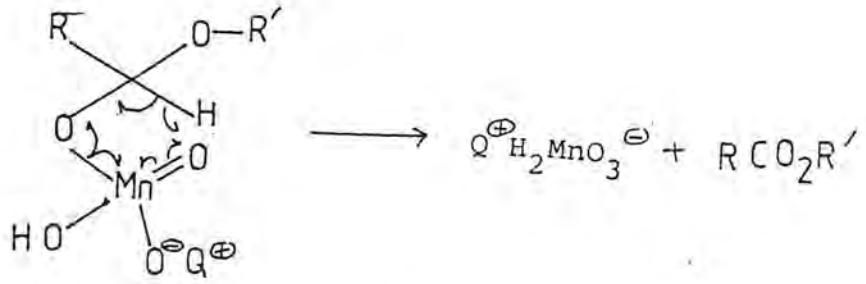
g) 2,2-dimethylpropanedioic acid.

h) 2,2-dimethyl-1,4-butanedioic acid.

Recently Lee[7] has reviewed the phase transfer assisted permanganate oxidations and the oxidation of aliphatic ethers to the corresponding esters in a non-polar solvent is discussed. The suggested mechánisms is depicted in scheme 2.8.

Scheme 2.8.



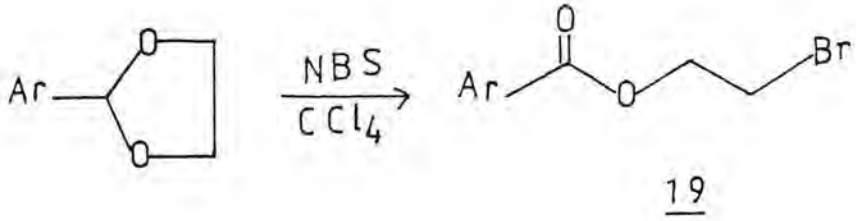


Moreover, Krapcho et al.[8] have pointed out the problem of over-oxidation of terminal olefins if the reaction is performed in an initially neutral or basic aqueous permanganate solution under heterogenous liquid-liquid conditions using quartenary ammonium salts as phase transfer agents.

Assuming the aldehyde is an intermediate further oxidation of the enol or enolate anion could explain the loss of a carbon atom in the final product, but this possibility has previously been rejected by other authors.[8]

The transformation of acetal group directly to the corresponding carboxylic acid is of synthetic interest. Pinnick et al.[9] solved the problem of converting dioxolanes into carboxylic acids under nonacidic conditions by refluxing the dioxalanes with NBS in carbon tetrachloride and subsequently treated the bromoethyl ester 19 with zinc and zinc chloride in THF or DMSO, (scheme 2.9). They obtained benzoic acid in 61% yield with a 30% recovery of the bromoethylester 19 (Ar=Ph). Although the yields were increased by using thiocarbonate ion[10] or cobalt(I)phthalocyamine[11] which are better reagents for cleavage of bromo-and chloroethyl esters to acids, our one step oxidation of acetals to acids with permanganate may prove more attractive. Our results also emphasize the limitation of potassium permanganate under phase transfer conditions as oxidizing agents when acetal groups are present in the molecule.

Scheme 2.9.



19

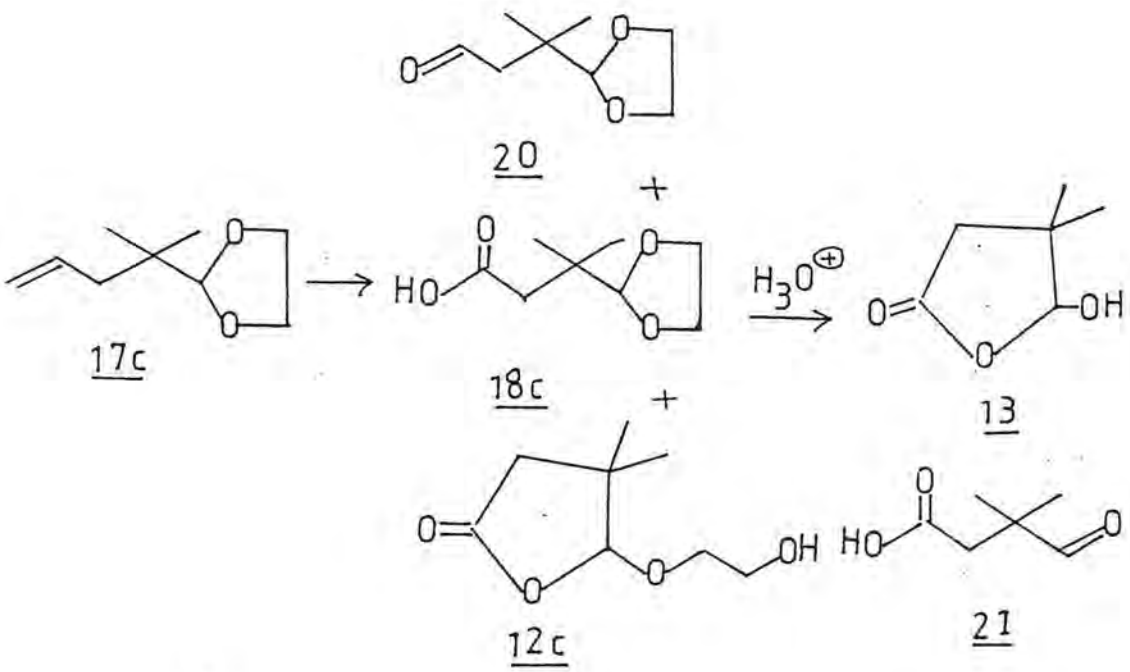
In our attempts to selectively oxidise the double bond of the protected aldehyde 17 we turned to the ruthenium trichloride-catalysed hypochlorite oxidation.[12] Sodium hypochlorite is expected to be unreactive towards the dioxalane group.[13] In our hands, the oxidation of 17c under these conditions[12] produced only mixtures of polymeric materials. Use of the solvent mixture H_2O-CCl_4-CH_3CN (3:2:2)[14] did not improve the result as also reported by others.[14]

The dioxalane group is expected to be unreactive towards sodium metaperiodate as well.[15] Oxidation of 17c with this reagent was initially performed on a 5 mmole scale according to the literature.[14] The reaction was performed at 25°C in a suspension of the metaperiodate. The product appeared to consist of mixtures of the aldehyde 20, the acid 18c and the γ-lactone 18c, (scheme 2.10) from the ^1H NMR and IR spectra of the crude product. Since it appeared possible to convert these compounds to a single product viz the oxoacid 21 or the cyclic form 13 we decided to scale up the reaction.

The reaction was then performed at 300 mmole and longer reaction period. GC analysis of the crude product revealed the presence of three main components in a ratio of 3:2:1. The major component was the starting material which was recovered in 59% yield as the parent aldehyde 16 after hydrolysis. The two other components were most probably the acid acetal 18c and derived γ-lactone 12c which on hydrolysis both afforded 13 in 15% combined yield. This compound decomposed to a significant extent on normal vacuum destillation, but was successfully distilled on a molecular still. It was characterized

on the basis of spectroscopic data. The hydroxyl absorption appears at 3360 cm^{-1} in the IR and a strong absorption at 1769 cm^{-1} is characteristic of a γ-lactone. The ^1H NMR spectrum displayed a singlet at 1.23 ppm due to the gem-dimethyl protons, the methylene group appears as a multiplet at 2.50 ppm while a downfield broad singlet at 5.47 ppm is assigned to the methine proton. The broad singlet at 5,00 ppm, exchangeable with D_2O is ascribed to the hydroxyl proton. The mass spectrum also showed the α-cleavage (M^+-H_2O) fragment at m/z 113, characteristic of γ-lactones.

Scheme 2.10.



Sharpless[14] mentions problems such as very slow and/or incomplete reactions with metaperiodate- and hypochlorite-based catalytic oxidations. The failure of these reactions is attributed to inactivation of the ruthenium catalyst (normally present in amount of 1-5%). The use of acetonitrile as a cosolvent is reported to prevent this problem.[14] In our case the observed incomplete oxidation in the presence of acetonitrile

as a co-solvent is not easily explainable on these terms.

The metaperiodate-permanganate oxidation performed according to Lemiux-Rudloff[16] converts smoothly a variety of olefins to carboxylic acids, especially when conducted under slightly basis conditions,[17,18] but the method is inconvenient on a preparative scale because of the large amount of solvents to keep enough sodium periodate in solution. In this respect an improvement has been reported by Overberger et al.[19] who utilized acetone-water as solvents in the absence of a buffer to effect the reaction at high concentration. We adopted their procedure to oxidize the acetals 17a,b,c.

The dioxalane 17c gave a crude product in 68% yield which according to the IR spectrum consisted of a mixture of the γ-lactone 12c and the acid 18c. The mixture was hydrolysed with hydrochloric acid in dichloromethane-water to the γ-hydroxylactone 13 in 55% yield.

Under similar conditions the dimethyl acetal 17a furnished the γ-lactone 12a in 65% yield.

Starting with the diethyl acetal 17b the same procedure furnished the corresponding γ-lactone 12b in 67% yield.

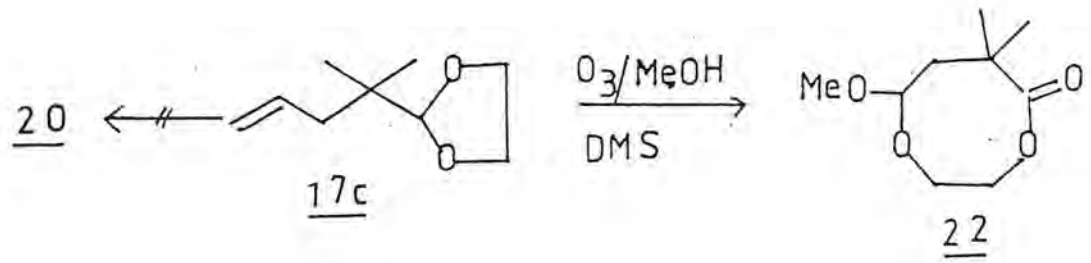
As expected the lactones 12a, 12b and 13 gave the same 2,4-dinitrophenylhydrazone derivative.

Finally we tried to oxidize selectively the dimethyl acetal 17a using ozone. The dimethyl acetal was chosen because this acetal

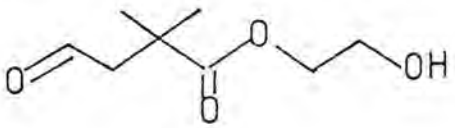
moiety reacts only very slowly with ozone.[20] Ozonolysis of 17c in methanol and subsequent oxidation of the ozonide with alkaline hydrogen peroxide according to the procedure of Freemery and Fields[21], but without removal of methanol, furnished the γ-lactone 12a in 56% yield.

At an early stage of our work we were unaware of the propensity for ozone to react with dioxalane ring. Hence, we treated the acetal 17c with ozone followed by reduction with DMS hoping to get the aldehyde 20. The reaction actually furnished the eight-membered cyclic lactone 22 in 80% yield, (scheme 2.11), possibly formed from the oxoester 23 and methanol. Dioxalanes are quantitatively converted to esters.[20] This will further be discussed later in the chapter.

Scheme 2.11.



22



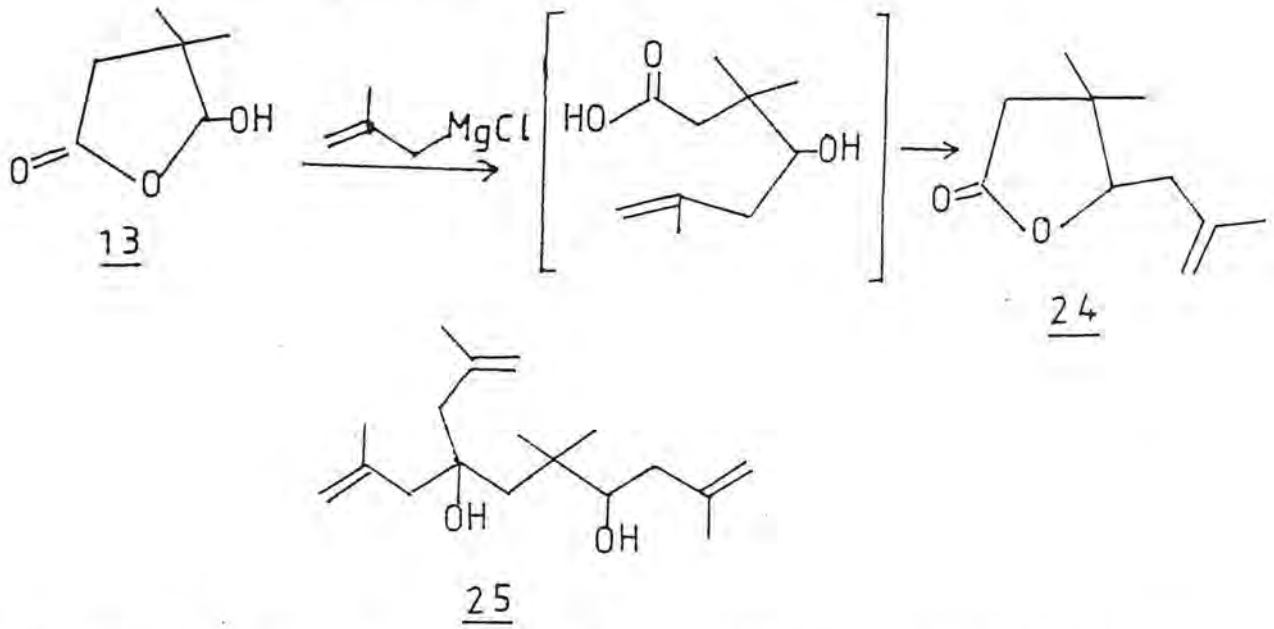
23

The compound could be purified by careful distillation, but some decomposition seemed unavoidable. It was also unstable on storage at room temperature. However, the structure was secured on the basis of spectroscopic evidence. A lactone absorption was observed at 1740 cm^{-1} in the IR. The ^{1}H NMR spectrum exhibited singlets at 1.00 and 1.67 ppm for the gem-dimethyl protons, a doublet of doublet at 1.80 ppm was due to the methylene protons coupled with the methine proton, which in turn resonated at 4.67 ppm as a doublet as well. The methoxy protons appeared as a singlet at 3.38 ppm and the methylene group adjacent to oxygen gave rise to a multiplet at 4.10 ppm. Except for the carbonyl carbon which was too weak to be observed, all other carbons gave rise to peaks at expected field in the ^{13}C NMR spectrum. The molecular ion was absent in the mass spectrum but a weak peak at 157 mass units indicates the $[M^{+}-OMe]$ fragmentation. Therefore we decided to conduct the methallylation on the hydroxylactone 13 rather than on the ester 2 as depicted in scheme 2.2.

Unfortunately the methallylation reaction did not proceed smoothly. At least five components appeared in varying proportions, according to TLC and GC analysis, when the reaction was carried out with three equivalents or less of the Grignard reagent at either $0^{o}C$ or $25^{o}C$. We were able to isolate by column chromatography the three major components of the product mixture obtained from a reaction conducted at $25^{o}C$ and three equivalent of the Grignard derivative. The product of interest viz. 4,4-dimethyl-5-(2-methylpropenyl)oxacyclopentan-2-one (24) was obtained in 25% yield as a liquid which was characterized from spectroscopic information. In the IR spectrum the γ-lactone

C=O and the C-C double bonds appear as bands of strong and medium intensity at 1778 and 1646 cm^{-1}, respectively. The ^{1}H NMR spectrum displayed singlets at 1.10 and 1.20 ppm due to the gem-dimethyl protons. The propenyl methyl protons appeared as a singlet at 1,80 ppm while the endocyclic methylene protons gave rise to a singlet at 2.35 ppm. A doublet, at 2.27 ppm is due to the exocyclic methylene protons and the methine proton appears as a triplet, at 4.37 ppm. The ^{13}C NMR spectrum fully confirms the assigned structure (scheme 2.12).

Scheme 1.12.



13 24

25

The major product was 2,9,6,6-tetramethyl-4-(2-methylpropenyl)-1,9-decadiene-4,7-diol,(25) which was isolated in 33% yield as a crystalline compound. This product probably results from further reaction of the Grignard reagent with the γ-lactone 24. The structural assignment of 25 was mainly based on the ^{13}C NMR spectrum. In the low field region two resonances of unequal intensity appear at 143.83 and 143.51 ppm which are assigned to the quartenary olefinic carbon atoms. The corre-

sponding terminal olefinic carbons are observed at 113.22 and 114.70 ppm, respectively. The quarternary carbinol carbon appears at 74.84 while the tertiary one gives rise to a signal at 74.90 ppm. The allylic carbons appear at 49.72, 49.46 and 49.30 ppm. Resonances at 38.72 and 40.04 ppm are due to the quarternary and secondary carbons, respectively. Five high field signals are due to the methyl groups.

The third component (20%) proved to be starting material.

The yield of the lactone 24 was not satisfactory for further manipulation, and we therefore turned to another strategy.

In this approach we planned to react the aldehyde 16 with methallymagnesium chloride to the alcohol which then should be oxidized. The strategy is outlined in scheme 2.13.

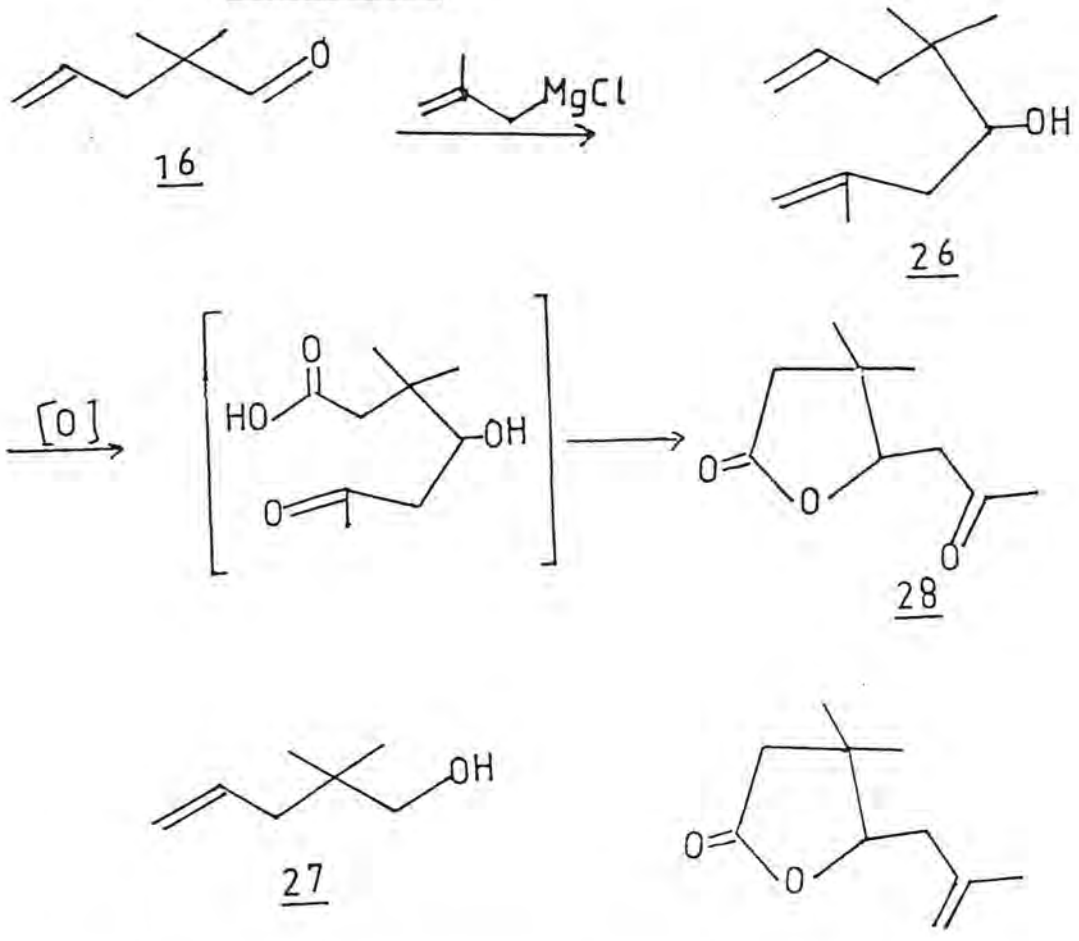
We first chose ozonolysis under oxidative conditions as a way of cleaving the double bonds of the dienol 26 to the ketoacid which we anticipated would cyclize spontaneously to the ketolactone 28.

2,5,5-Trimethylocta-1,7-diene-4-ol (26) was obtained in 80-85% yield from alkylation conducted in diethyl ether at 10-15°C. It was characterized from spectroscopic data. When the alkylation was conducted in THF at 40-50°C in the presence of unreacted magnesium, 2,2-dimethyl-4-pentenol (27)[22] was isolated in 10% yield. This compound was not observed when the reaction was repeated at the same temperature with a Grignard reagent free of metallic magnesium. A similar observation was made

when the reaction was carried out at 10-15°C with or without the presence of metallic magnesium. Thus the observed reduction is caused by the presence of active magnesium metal at a slightly elevated temperature.

Ozonolysis of 26 in methanol followed by oxidation of the ozonide with performic acid afforded the expected lactone 28 in 45-50% yield as a crystalline compound. The structure was established on the basis of spectroscopic data.

Scheme 2.13.

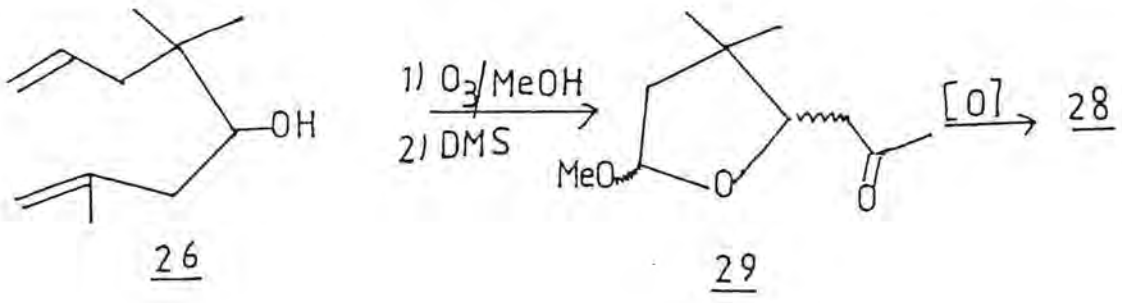


The reaction of 28 with an excess of methylenetriphenylphosphorane in diethyl ether afforded the olefinic γ-lactone 24 in 56% yield. In an attempt to improve the preparation of the lactone 28 the dienol 26 was ozonized in methanol followed by

by reduction of the ozonide with dimethyl sulfide. The product obtained in 80% yield was shown by GC to consist of two compounds in a 3:1 ratio. The close retention time suggested that the compounds were stereoisomers and this was confirmed by the fact that oxidation of the mixture with performic acid led to the lactone 28 as the sole product in 70% yield. Spectroscopic data revealed that the compounds were stereoisomers of 29. The IR spectrum displayed no hydroxyl absorption but bands due to carbonyl and ether functions were present. The ^{1}H NMR spectrum displayed singlets at 0,87 and 1.07 ppm due to the gem-dimethyl protons. Doublets at 1.70 and 1.83 ppm are assigned to the endocyclic methylene group while the exocyclic counterpart gives rise to doublets at 2.38 and 2.61 ppm. The acetyl and methoxy protons appear as singlets at 2.13 and 3.28 ppm, respectively. The methine proton gives rise to a doublet of doublet at 3.95 ppm, and the downfield multiplet at 4.83 ppm is assigned to the acetal proton.

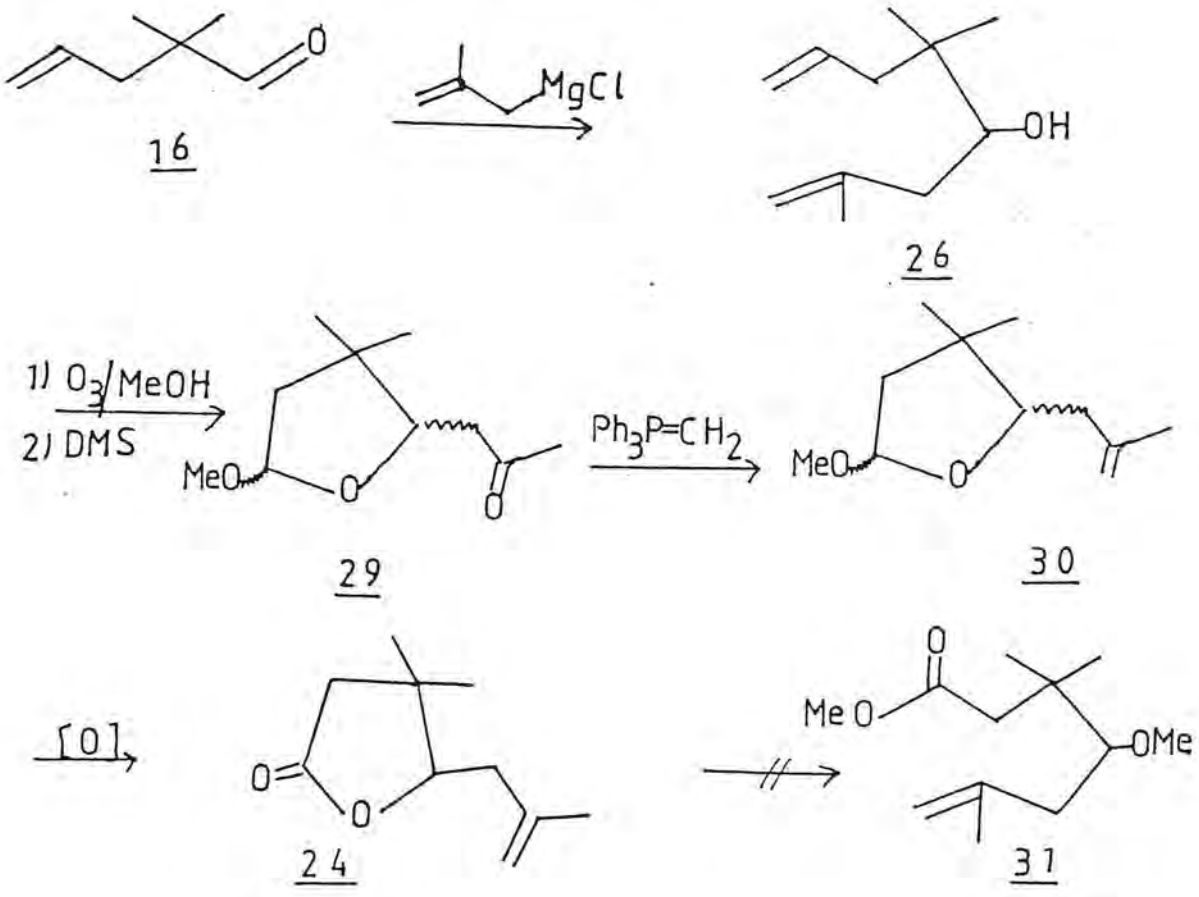
Clearly the methoxy group originates from the solvent methanol, but there are many ways this transfer could happen. The mechanism will be discussed later in this chapter. The reaction is depicted in scheme 2.14.

Scheme 2.14.



The formation of 29 in such a good yield was fortunate because its transformation to the lactone 24 seemed obvious without having to pass through the ketolactone 28. Hence, as expected, the stereoisomeric mixture of 29 underwent a Wittig reaction with methylenetriphenylphosphorane to give 30, which was oxidized with the Jones reagent to 24 in good yields. Starting from the aldehyde 16 we were now able to prepare the lactone 24 in 51% overall yield by the sequence of reactions outlined in scheme 2.15. However, all attempts to convert compound 24 into the methoxy ester 31, the precursor of compound 4 (scheme 2.2), was without reward, and again we had to turn our effort towards a new strategy.

Scheme 2.15.

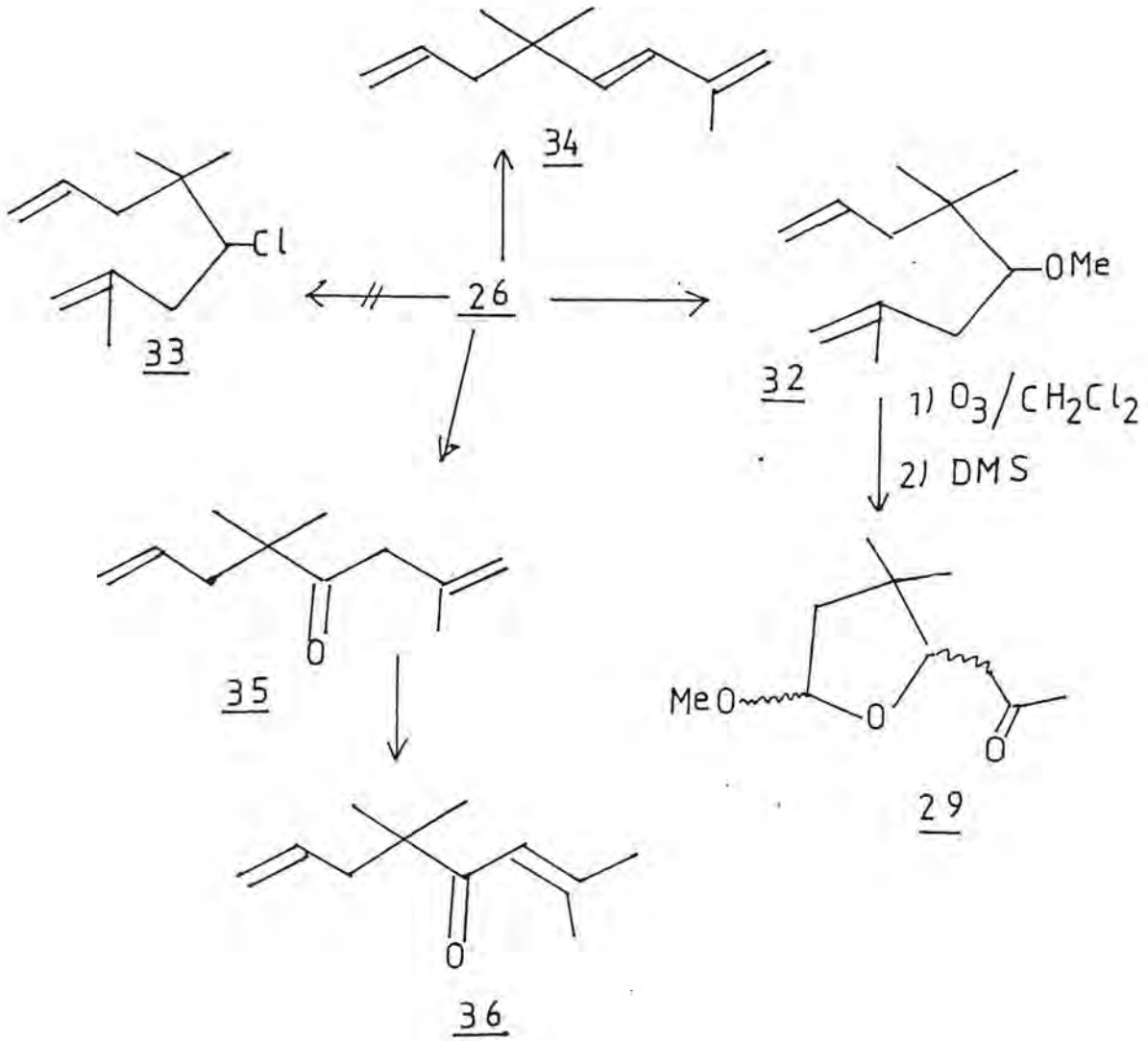


16 26 29 30 24 31

By protecting the hydroxyl group of 26 we hoped to reduce the possibility of cyclization which was clearly a problem in the routes attempted so far, (Scheme 2.16).

Ethers are known to resist ozonolysis at low temperature.[23] The ether 32 obtained in 80% yield from the corresponding alcohol was dissolved in dichloromethane and treated with ozone under reductive conditions. To our initial surprise the methoxy-tetrahydrofurane 29 as a 3:2 mixture of stereoisomers was obtained as a major product in 59% yield. Consequently this protection of the hydroxyl group was in vain.

Scheme 2.16



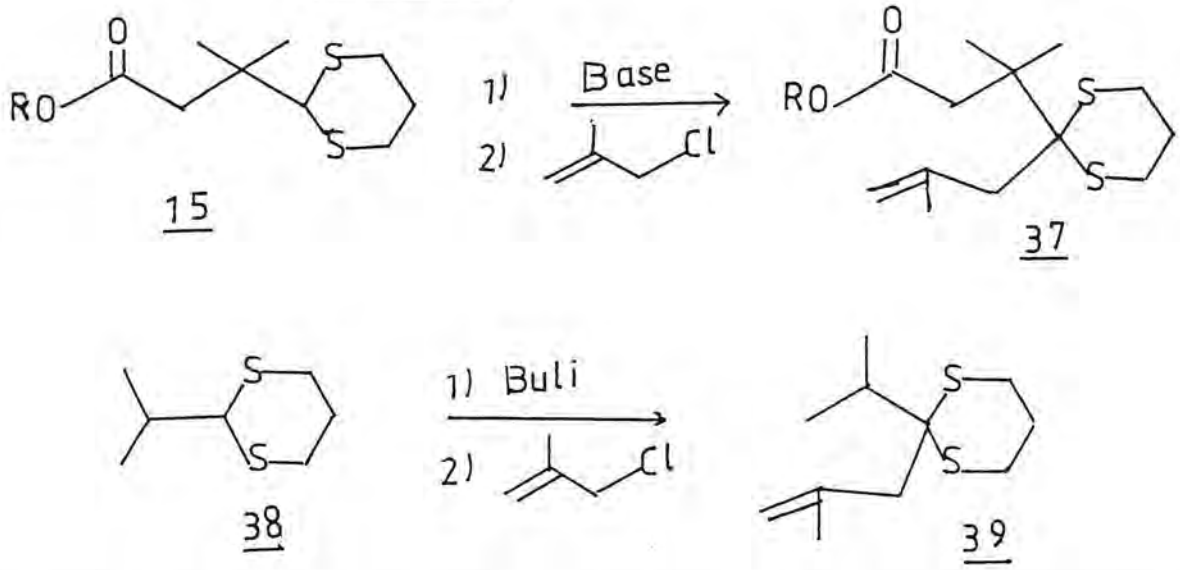
We also considered preparing the chloride 33 which would be another way of protecting the hydroxyl group. The treatment of the alcohol 26 in carbon tetrachloride with triphenylphosphine at room temperature resulted in none of the halide, but 3E-2,5,5-trimethyl,1,3,7-octatriene (34) was obtained in 47% yield. The stereochemical assignment was based on the large coupling (J 14 Hz) between the vicinal olefinic proton in the ^{1}H NMR spectrum. Elimination from secondary alcohols has been reported with these reagents, but in acetonitrile at elevated temperatures.[24]

We also considered protecting the oxygen function at C-4 as a carbonyl derivative prior to oxidation of the double bonds. Hence, the dienone 35 was obtained in 89% yield from the alco-(26) with chromic acid in ether. The reaction was very sluggish requiring 48 h at room temperature with an excess reagent.

Attempted preparation of the dimethyl acetal with trimethyl-orthoformate, catalysed by TsOH in the usual way, resulted in the formation of the conjugated ketone 36 and no acetal. Employing NH_4Cl as a catalyst no acetal formed, but isomerisation was not observed either. On the other hand, the dienone 35 dissolved in ether isomerized in the presence of Na_2CO_3 as well; after one week at room temperature a 1:1 mixture of isomers were present as indicated by GC. We also observed that a sample of the dienone 35 on standing at room temperature without any catalyst isomerized slowly (several months) to 36. The structures of 35 and 36 were assigned on the basis of spectroscopic data.

Another way of obtaining a protected oxygen function at C-4 would be the preparation of dithiane 37, and we contemplated making this compound as outlined in schemes 2.5 and 2.17.

Scheme 2.17.

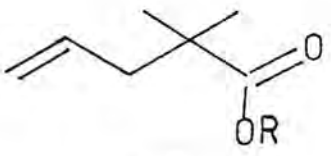


As a model substance we used the dithiane from isobutyraldehyde (38) which was alkylated with methallyl chloride to 39 in 75% yield. However, the alkylation of 39 was never carried out because we abandoned all routes starting with the ester 15 in favour of the approach described in chapter 3.

We also thought of generating the ketene from the appropriate diazoketone by the Wolf rearrangement, because the acid 40 and the esters 41 are readily available. As the first approach these compounds were ozonized in dichloromethane followed by DMS reduction in order to obtain the corresponding aldehyde 42. In the case of the acid the hydroxylactone 43 was obtained in 93% yield. It has previously been prepared by a lengthly procedure in 40%.[25a] Apparently the aldehyde spontaneously cyclized, and this was also the case when the methyl ester 41a was reacted in the same way; the methoxy-lactone 44 and the acid 45 were formed in 70 and 6% yields, respectively.

On the other hand the ethyl ester 41b furnished the aldehyde 42b in 39% yield admixed with the corresponding acid 45 (scheme 2.18). The structures were readily characterized from their spectroscopic properties and by comparison with those of authentic samples, as well.

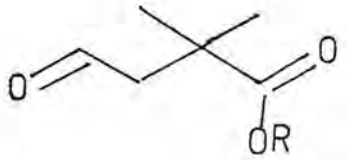
Scheme 2.18.



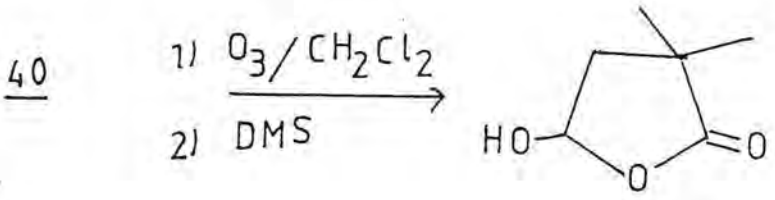
40, R = H

41a, R = Me

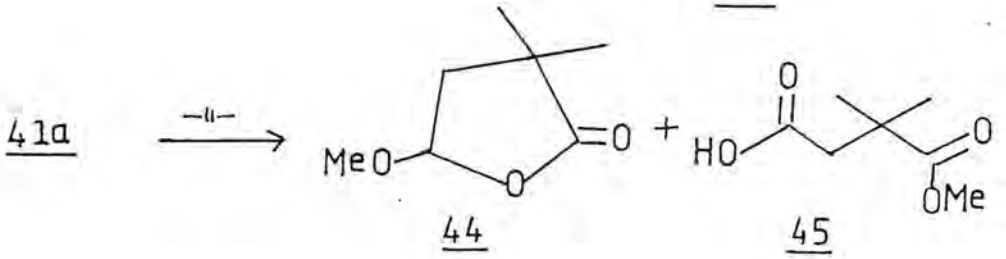
41b, R = Et



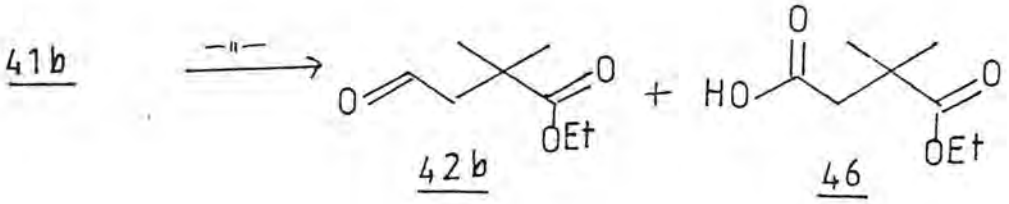
42



43



44 45



42b 46

At this point it seems opportune to review shortly the accepted mechanisms for ozonolysis and the reduction with dimethyl sulfide in order to see how our results fit in.

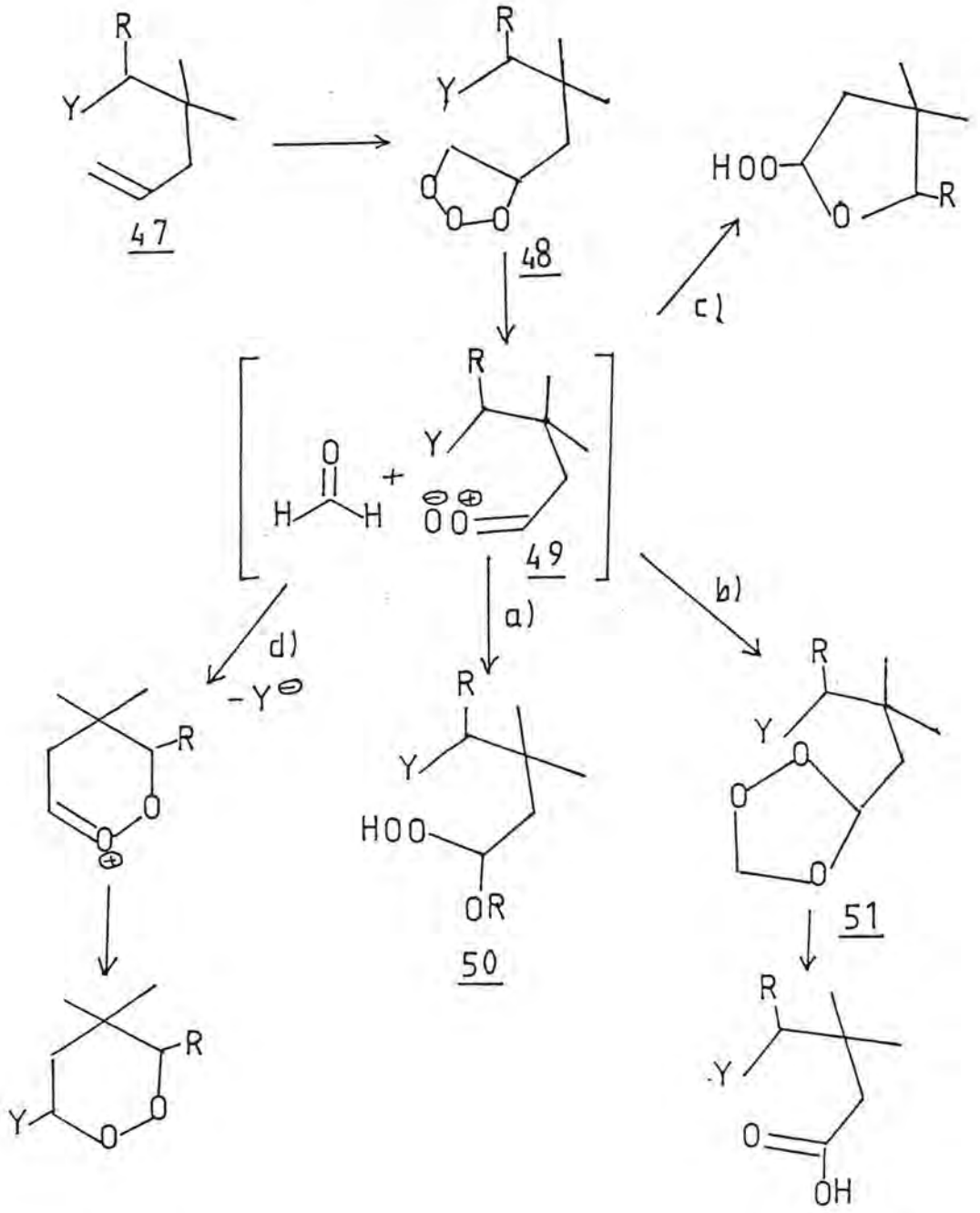
The ozonolysis of a C-C double bond proceeds to a primary ozonide 48 in either protic or aprotic media. It is also generally accepted that 48 fragments to a carbonyl oxide intermediate 49. However, the fate of 49 is strongly dependent on the solvent medium. With scheme 2.19 an attempt is made to summarize the various possibilities using as example the general structure 47 related to the compounds ozonized in the present work; the groups Y and R represent the oxygen functions studied such as alcohols, ethers, acetals, carboxylic acids and esters.

In a protic solvent like methanol addition to the carbonyl oxide 49 with formation of the hydroperoxide 50 is a characteristic reaction (path a). On the other hand in an aprotic medium like dichloromethane recombination of the carbonyl compound and the oxycarbonyl 49 is prone to occur with formation of the ozonide 51 (path b).[28,29] In addition intramolecular modes of reactions are available to 49 in both types of solvent media (paths c and d).[30-32, 33,34.]

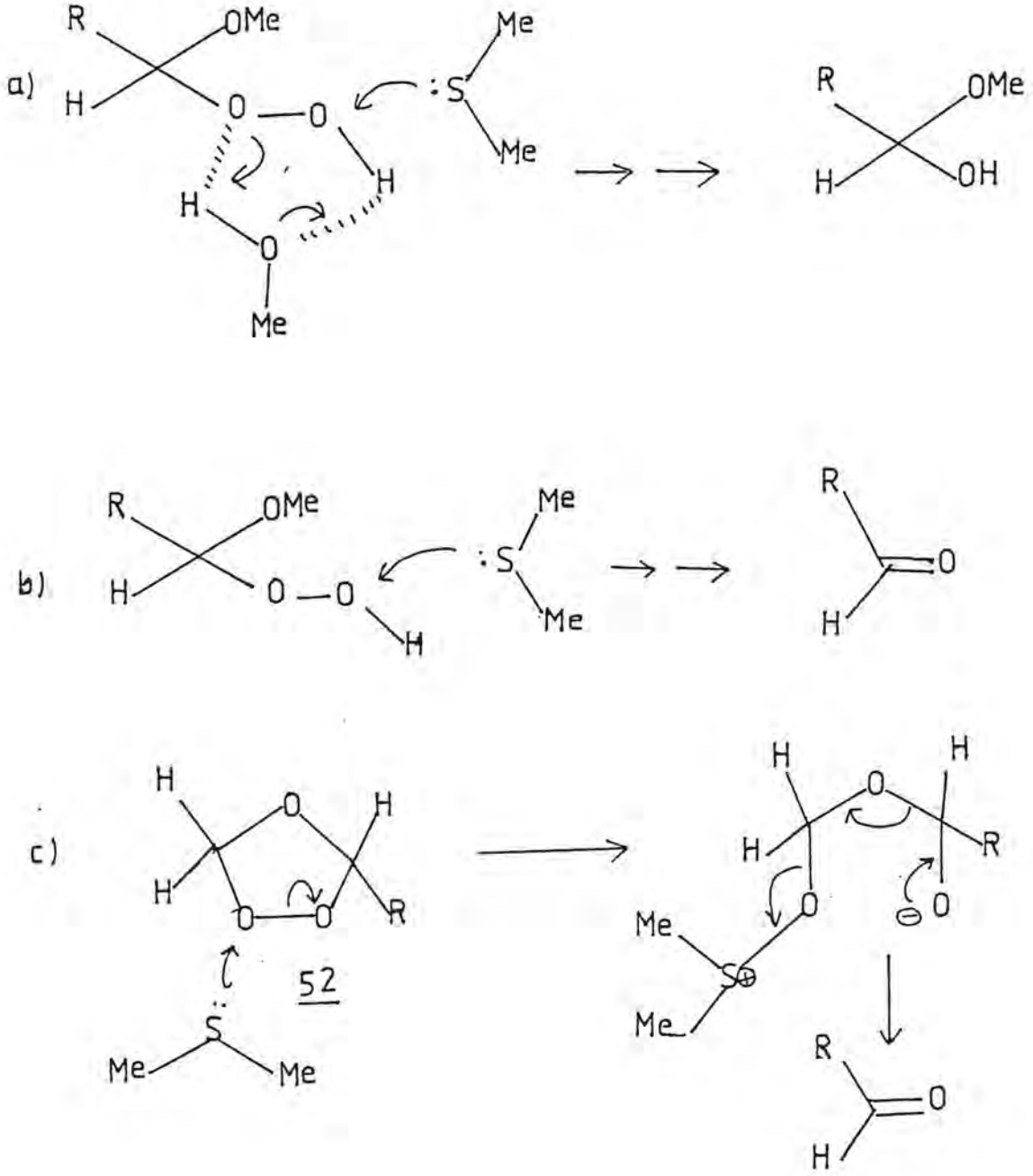
The reduction of the ozonide 51 and the hydroperoxide 50, respectively, lead to the observed product. Reduction with DMS or thiourea affords aldehydes or ketones by the mechanisms depicted in scheme 2.20. In the case of DMS the hydroperoxide is reduced by either path a) or b) while reduction with thio-

urea proceeds according to path a) only.[26] The reduction of the ozonide 52 occurs by nucleophilic attack on the peroxy oxygen as shown in path c).[27] This reaction is slow in dichloromethane and an excess of DMS is required in order to be competitive with disproportionation of the ozonide.[28]

Scheme 2.19.



Scheme 2.20.



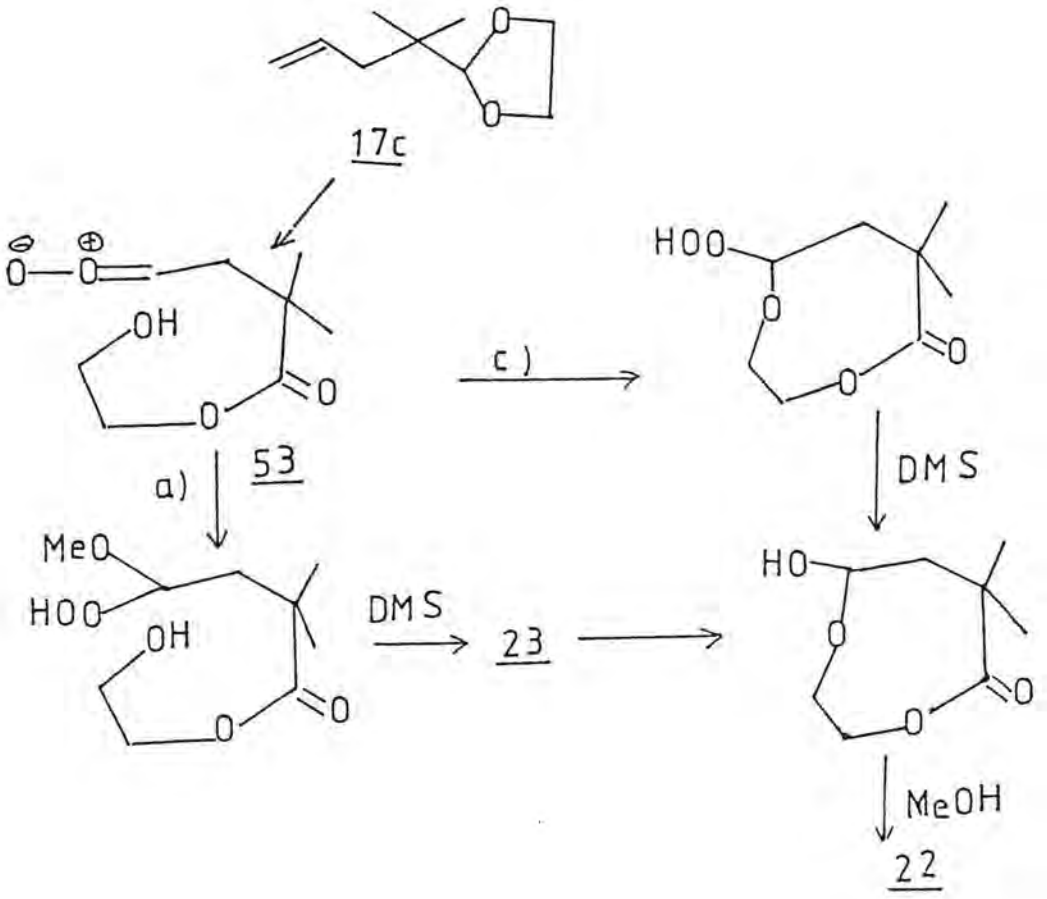
Results from the aprotic medium are explained by paths (b) and (d) of scheme 2.19. The acid 46 and aldehyde 42b obtained from the ethyl ester 41b (see scheme 2.18), are normal products by path b). The formation of lactone 44 and acid 45 from the methyl ester 41a is explained by paths b) and d). The difference in behaviour of the methyl and ethyl esters is not clear to us. Steric factors alone do not provide a satisfactory

explanation. The formation of compound 29 (scheme 2.16) is explained by the intramolecular path d) as well.

The quantitative conversion by ozonolysis of the acid 40 to the hydroxylactone 43 is not surprising since it is the only product expected from reactions of the intermediate oxycarbonyl anion 49, e.g. by paths b, c and d, followed by reduction.

The formation of the eight-membered ring lactone 22 (depicted in scheme 2.11) is particularly interesting. Dioxalanes are rapidly oxidized by ozone to esters[20] under the condition employed for osonizing the C-C double bonds. Since no kinetic data are available on the rate of ozonolysis of these functional groups the oxycarbonyl ester 53 may be postulated as an intermediate, (scheme 2.21),

Scheme 2.21.



which can either react by paths a) and/or c) as previously explained to give 22 as the final product.

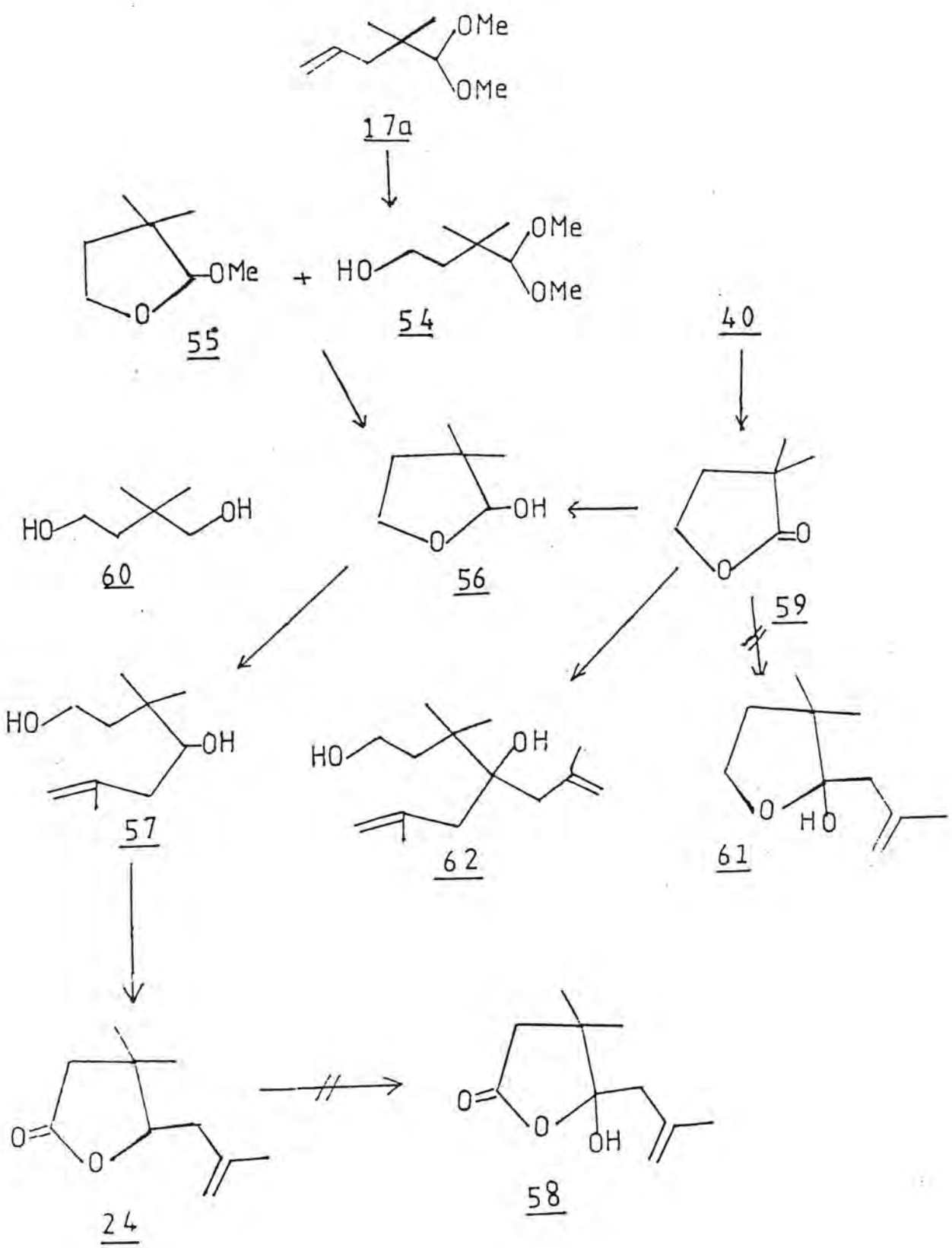
Finally attempts were made to prepare the hydroxylactone 58, a potential precursor for the ketene as outlined in scheme 2.22.

Ozonolysis of 17a followed by reduction with sodium borohydride gave approximately a 1:1 mixture of the alcohol 54 and the acetal 55. This mixture was hydrolysed to a single product 56 in 62% overall yield from 17a. Since no acid was involved during the reaction or the work-up the observed product 55 must result from a nucleophile displacement on the acetal carbon. The structures of 55 and 56 were established from spectroscopic evidence. On attempted isolation by preparative GC the alcohol 54 probably cyclized to 55 which was the only isolable component. However, 54 was characterized spectroscopically as the trimethyl silyl ether.

The compound 56 was also prepared in 86% overall yield from the acid 40 by ozonolysis and reduction with sodium borohydride to the lactone 59, which subsequently was further reduced with DIBAH. Reduction of the lactone 59 with LAH according to the literature[35] afforded the lactol 56 in only 20% yield, while the diol 60 was the major product, obtained in 75% yield.

The reaction of the lactol 56 with methallylmagnesium chloride gave in 87% yield the diol 57 which was oxidized with chromic acid to the previously prepared olefinic lactone 24 in 85% yield. The latter was not oxidized further to 58 even after

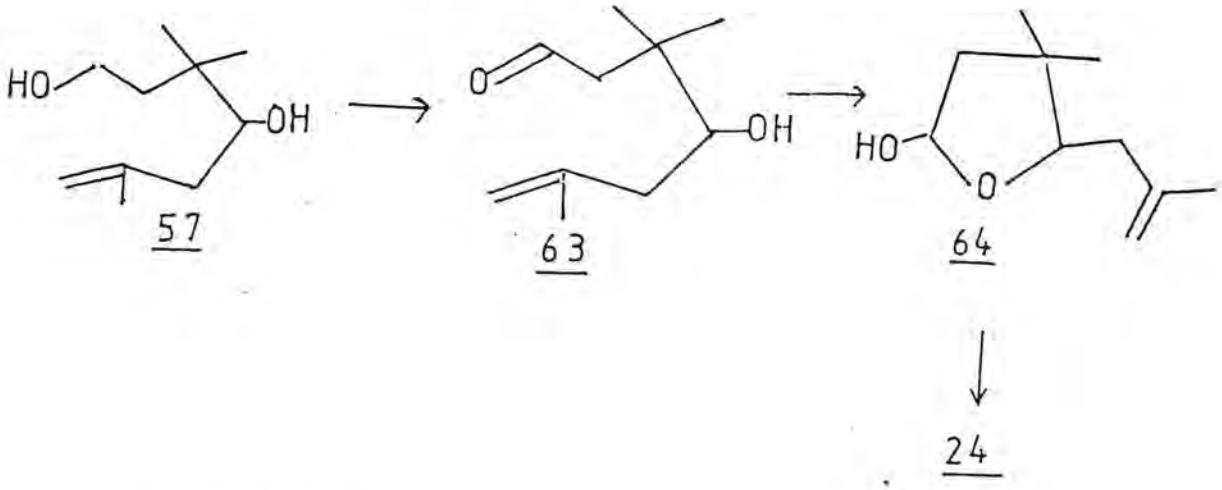
Scheme 2.22


OMe
OMe
17a
OMe
+ HO
OMe
55
54
40
HO
OH
60
OH
56
O
59
HO
OH
57
HO
OH
62
O
HO
61
O
O
24
O
O
OH
58

40 h with an excess of the oxidising agent.

Although we were unable to obtain 58, this route furnished the olefinic lactone 24 in 63% overall yield from the acid 40, which was an improvement over the previous synthesis (see scheme 2.15). The high yield of 24 is possibly a result of preferential oxidation of the less hindered primary alcohol of 57 to the intermediate hydroxyaldehyde 63 which as the lactol 64 is further oxidized to 24 (scheme 2.23). The secondary alcohol function of 57 is oxidized very slowly as we have experienced earlier.

Scheme 2.23.



Attempts to prepare the olefinic lactol 61 by reacting the lactone 59 with methallylmagnesium chloride[36] was not successful. With one equivalent of the Grignard derivative at -70°C and 10 minutes reaction time the product consisted of a mixture of 45% starting material, 20% of an unknown product and 34% of the diol 62. Extending the reaction time or carrying out the reaction at 0°C the diol 62 remained the sole isolable product. It was characterized from spectroscopic evidence. Similar results were obtained with methallyllithium in ether at -30°C.

Further attempts at obtaining compounds 58 and 61 by these routes seemed futile and we therefore had to look for quite different precursors for the intramolecular ketene-ene cycloaddition. This work is presented in the following chapter.

EXPERIMENTAL.

General Remarks.

Reagents: Unless otherwise stated all analytical grade reagents were used as commercially supplied. Pure and technical grades were distilled or recrystallized before use.

Gas Chromatography (GC); was carried out on either a VARIAN AEROGRAPH series 1400 or on a HEWLETT-PACKARD 5710E GAS CHROMATOGRAPHY using 3 or 10% SP 2100 and SP 2250 packed analytical columns of 2.4 m. Preparative GC was done on a VARIAN AEROGRAPH series 200 employing 20% SP 2100 or SP 2250 columns. Melting points were taken on a BüCHI melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a PELKIN ELMER 281B. Absorptions are indicated by (s) = string, (m) = medium, (w) = weak. ^{1}H NMR spectra unless otherwise stated were recorded on a VARIAN EM 360 A operating at 60 MHz with tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra unless otherwise stated, were recorded on a JEOL JNM-FX 60 FT-NMR instrument operating at 15.0 MHz, with TMS as internal standard. Mass spectra (MS) were obtained on a VG MICROMASS 7070F mainly by chemical ionization employing isobutane.

Ozonolysis:

Ozone generated from a BOC-MIC II OZONISER at a rate of 1.5-2.0 mmole per min. was bubbled through solutions of the respective substrates in methanol and/or dichloromethane at -78^{o}C until a blue colour persisted. Excess ozone was removed by flushing with dry nitrogen at -78^{o}C.

Isobutyraldehyde pyrrolidine enamine was prepared according to the lit.[1] in 77% yield, b.p. 43-5°C/12 mmHg,. (lit.[1] b.p. 43-44°C/12 mmHg).

Ethyl 3,3-dimethyl-4-oxobutanoate (2b) was prepared from the above enamine and ethylbromoacetate by the procedure of Opitz et al.[1] in 7% yield, b.p. 70-1°C/9 mmHg, (lit.[1] b.p. 72-74°C/10 mmHg). 2,4-DNP, mp 120-2°C (lit.[1] m.p. 123-4°C). ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 6H), 2.30 (t, J 7 Hz, 3H), 2.57 (s,2H), 4.17 (q, J 7 Hz, 2H), 9.60 (1, 1H).

Attempted preparation of 2b from isobutyl t-butyl imine and a magnesium salt.

The operation was conducted according to the lit.[3]

A solution of isobutyl t-butyl imine[3] (510 mg, 4 mmole) in dry THF (1 ml) was added via syringe to the vigorously stirred solution of ethylmagnesium bromide [prepared from ethyl bromide, (440 mg, 4 mmol) and magnesium (100 mg, 4.2 mmol) in THF] at 55°C under nitrogen. The mixture was refluxed for 30 minutes and cooled in an ice bath. A white precipitate formed. A solution of ethyl bromoacetate (670 mg, 4 mmole) in THF (1 ml) was added slowly, causing the precipitate to gradually dissolve and the reaction was mildly oxothermic. The resulting clear solution was heated under reflux for 24 h and the pH of of the water treated sample was approximately 8. The mixture was acidified (pH 1-2) with 10% aq. HCl solution, refluxed for 1 h and then cooled to room temperature. A saturated aq.NaCl solution was added, followed by extraction with ether. The ether extract was dried ($MgSO_4$) and after removal of solvent

under reduced pressure, 200 mg of a dark oil was obtained. The crude ^{1}H NMR indicated a very weak CHO signal.

The experiment was repeated at a 20 mmole scale, the product consisted of several components (GC).

2,6,6-Trimethyl-2,4-dienecycloheptanone (Eucarvone), (10).

The compound was prepared according to the literature[5] from (-) carvone (50,0g, 0,335 mol). After destillation on a Fischer Spalt-rohr column at 88-92°C/ 10 mmHg pure 10 (27.50 g, 55%) was obtained. (lit.[5] b.p. 82°C/7 mmHg). ^{1}H NMR (CCl_4): δ1.03 (s, 6H), 1.85 (s, 3H), 2.53 (s, 2H), 5.43-6.43 (m, 3H).

2,2-Dimethyl-4,5-dioxohexanal (11).

Eucarvone (10) (7.50 g, 50 mmole) in dry methanol (100 ml) was ozonized at -78°C. After removal of excess ozone, dimethyl-sulfide (15 ml, 150 mmole) was added at -40°C and the mixture was allowed to warm to room temperature. After standing for 6-12 h, the reaction mixture was concentrated under reduced pressure and the residual orange oil was taken up in ether, washed successively with saturated aq. $NaHCO_3$ and NaCl, and then dried ($MgSO_4$). Removal of solvent under reduced pressure left a residue, 6.50 g, which was purified by destillation through a short column, to give 11 (6.05 g, 77%), b.p. 80-2°C/ 10 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 6H), 3.41 (s, 3H), 2.83 (s, 2H), 3.50 (s, 1H), 9.45 (s,1H). IR ($CDCl_3$): 1785 (s), 1728 (s) cm^{-1}. MS (CI): m/z 157 (M^++1).

4,4-Dimethyl-5-methoxyoxacyclopentan-2-one. (12a).

To a stirred solution of 11 (0.78 g, 5 mmole) in benzene/methanol (7:3, 20 ml) was added lead tetraacetate (2.90 g of 84% [37]) in small portions at room temperature under nitrogen. Each addition was made after the previous one had dissolved. After the addition was concluded the mixture was stirred for 3 h and three drops of ethanediol were added followed by water (10 ml). No precipitate formed. The clear solution was extracted with ether and washed successively with 5% aq. Na_2CO_3, saturated aq.NaCl and dried ($MgSO_4$). Solvent removal under reduced pressure and destillation gave 12a (0.45 g, 63%) b.p. 80-2°C/10 mmHg. IR (film): 1791 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.17 (s, 6H), 2.22 (m, 2H), 3.48 (s, 3H), 4.78 (s, 1H). MS (CI): m/z 145 (M^++1), 113 (M^+-OCH_3).

2-(1,1-Dimethyl,3,4-dioxopentyl)-1,3-dithiane (14) was prepared by the lit.[38] procedure from 11 (0.78 g, 5 mmole) and 1,3-propanedithiol (0.65 g, 6,2 mmole) in 66% yield, b.p. 100-8°C/0,02 mmHg. IR (film): 1700 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.17 (s, 6H), 2.00 (m, 2H), 2.25 (s, 3H), 2.83 (m, 6H), 4.25 (s, 1H). MS (CI): m/z 246 (M^+).

Lead tetraacetate oxidation of the dithiane, 14.

The oxidation was carried out on (100 mg, 0.40 mmole) as already described for the parent aldehyde 11. The crude product consisted of two compounds in a ratio 1:3 and were analysed by GC-MS. 2-(1,1-Dimethyl-2-methoxycarbonylethyl)-1,3-dithiane (15a) m/z 234 (M^+) was the minor component (30%). The major component was the starting material. No attempts were made to optimize the reaction conditions.

2-(1,1-Dimethyl-2-ethoxycarbonylethyl)-1,3-dithiane (15b) was obtained by a previously reported procedure[38] from 2b (0.87g, 5,50 mmole) and 1,3-propanedithiolin 59% yield, b.p. 90-2°C/ 0,011 mmHg. IR (film): 1730 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.13 (s, 6H), 1.37 (t, J 7 Hz, 3H), 2.00 (m, 2H), 2.42 (s, 2H), 2.87 (m, 4H), 4.08 (q, J 7 Hz, 2H), 4.38 (s, 1H). MS: m/z 250 (M^++2).

2,2-Dimethyl-4-pentenal (16). The compound was prepared in 89% yield according to the lit.[39] from allyl alcohol and isobutyraldehyde, b.p. 125-7°C/760 mmHg., (lit.[39] b.p. 124-6°C/ 760 mmHg).

2,2-Dimethyl-4-pentenal dimethyl acetal (17a), 2,2-Dimethyl-4-pentenal diethyl acetal (17b) and 2-(1,1-Dimethyl-3-butenyl)-1,3-dioxalane (17c) were prepared from 16 and methanol, ethanol and 1,2-ethanediol, respectively by standard procedures. Their physical properties are presented in table 2.2 together with the other acetals prepared.

Table 2.2: Physical properties of acetals $R^1CH(OR)_2$.

Entry	R	R^1	Yield (%)	Bp ^oC/mmHg [lit.]	^1H NMR δ $-\underline{CH}(OR)_2$	References
1.	Me	C_6H_5-	93	78/15 [74-8/10]	5.25	45
2.	Et	C_6H_5	83	36-7/0.015 [215.18/760]	5.40	43
3.	$-CH_2-$	C_6H_5-	75	42-4/0.02 [106-7/11]	5.65	41
4.	Me	4-ClC_6H_4-	95	37-40/0,02 [90/6]	5.30	46
5.	Et	4-ClC_6H_4-	96	50-52/0,015 [92-93/2]	5,50	44
6.	$-CH_2-$	4-ClC_6H_4-	90	50-52/0.015 [136-9/13]	5,61	41

Table 2.2. cont.

Entry	R	R^1	Yield (%)	Bp ^{o}C/mmHg [lit.]	^{1}H NMR δ -CH(OR)$_2$	References
7.	Me	$CH_3(CH_2)_4$-	84	79/40	4.25	47
8.	Et	$CH_3(CH_2)_4$-	85	94-5/30 [155-8/760]	4.35	45
9.	-CH_2-	$CH_3(CH_2)_4$-	65	90-2/38 [78-80/34]	4.70	42
10.		17a	87	55-7/19 [162-3.5/760]	3.70	22
11.		17b	86	60-5/19	3.87	-
12.		17c	92	58-60/10 [83/30]	4.43	40

Oxidations of acetals with alkaline potassium permanganate under PTC conditions.

General: Oxidations were carried out according to the reported procedures[6] for two phase oxidations of alkenes.

An average of three equivalents of $KMnO_4$ per mole of acetal was employed. The benzene layer was decolourized at a rate dependent on the acetal and in all cases the organic phase contained unreacted acetal. No attempt was made to establish the amount of $KMnO_4$ required for full conversion of the individual acetals. Work-up involved addition of a saturated aq. $NaHSO_3$ solution followed by a slow addition of 50% aq. hydrochloric acid, whereupon manganese dioxide dissolved (usually at pH 5-6). Separation of the phases at this pH facilitated the recovery of starting acetals. In some cases only an emulsion formed at this pH. Further acidification was necessary (pH∿1) to achieve separation. In these cases the unreacted acetals were recovered as the corresponding aldehydes from the neutral fractions in the form of 2,4-DNP derivatives.

The following description is representative:
To a magnetically stirred solution of $KMnO_4$ (1800 mg, 11.39 mmole) and KOH (56.1 mg, 10,00 mmole) in water (30 ml) was added benzene (15 ml) followed by tetrabutylammonium bromide (100 mg, 9,8 mol%). Freshly destilled benzaldehyde ethylene acetal (474.6 mg, 3.16 mmole) in benzene (1 ml) was added at once, and the mixture stirred at room temperature for 12 h under nitrogen. The benzene layer was still purple and GC analysis showed the presence of acetal. The mixture was then heated at 50-60^{o}C for 6 h upon which the benzene phase

became colourless, GC analysis indicated the acetal peak. The mixture was cooled to room temperature and treated with saturated aq. $NaHSO_3$. Slow addition of 50% aq. HCl gave a colourless solution at pH 5-6. After separation the aq. layer was acidified further to pH ∿ 1 and extracted with ether. The combined organic extracts were partitioned into basic and neutral fractions by treatment with 10% aq. Na_2CO_3. From the neutral fraction (23.7 mg, 5%) of the acetal was recovered, and benzoic acid (329.5 mg, 85%) was isolated from the basic fraction in the usual way. The m.p. and ^1H NMR were identical to those of an authentic sample.

Results of oxidations of other acetals are presented in table 2.1.

Oxidation of dioxalane 17c using $RuCl_3$-catalysed NaOCl.[12]

To a solution of 17c (3.12 g, 20 mmole) in dichloromethane (80 ml) was added approximately 10% aq. $NaHCO_3$ (80 ml) followed by 2% aq. $RuCl_3$ H_2O (0.5 ml). The mixture was cooled to 0^oC and titrated with 1.51 N NaOCl (80 ml) during 40 min., and stirred for 2 h at 0^oC, then 6 h. at room temperature, whereupon the dark green colour was discharged to yellow. The mixture was filtered through a Celite pad and the phases separated. The aq. phase was acidified with 10% aq. HCl and extracted with ether. The combined organic extracts were washed with cold water and brine, then dried ($MgSO_4$). Removal of solvent under reduced pressure left a residual oil, (2.90 g) which consisted of several components (GC, TLC).

Oxidation of 17c using ruthenium tetroxide catalysed metaperiodate.[14]

To a suspension of sodium metaperiodate (4.40 g, 20,5 mmole) in water (15 ml) was added tetrachloro methane (10 ml), acetonitrile (10 ml), 17c (0,7811 g, 5 mmole) followed by $RuCl_3 \cdot H_2O$ (25 mg, 2.4 mol%). The dark mixture was vigorously stirred at room temperature for 30 min. whereupon the reaction cleared to yellow for a few minutes and turned dark again. The solids were filtered on a Celite pad and washed with dichloromethane. The phases were separated and the organic phase washed with saturated aq.NaCl and dried ($MgSO_4$). Solvents were removed under reduced pressure to give a clear liquid (0,30 g). Crude IR (film): 3400-2600 (broad, CO_2H), 1780 (s), 1720 (s) and 1100 cm^{-1}. Crude ^1H NMR (CCl_4): δ 9.60 (t, J 2Hz, $CH_2C\underline{H}O$). These parameters suggested the product to consist of a mixture of 2-(1,1-dimethyl-2-carboxyethyl)-1,3-dioxalane (18c), 2-(1,1-dimethyl-3-oxopropyl)-1,3-dioxalane (20) and 4,4-dimethyl-5-(2-hyroxyethoxy)oxacyclopentan-2-one (12c). No problems were anticipated in converting the postulated compounds, 18c, 20 and 12c to the lactone 13. The reaction was thus repeated at 300 mmole of 17 for 2-21h. The product consisted of three main compounds in 48, 28, 18% on GC. After removal of solid products and solvents a dark oil (51.0 g) was obtained. This was dissolved in dichloromethane (100 ml), 50% aq. HCl (100 ml) was added and the reaction mixture stirred at room temperature overnight. The phases were separated and the organic layer was partitioned into basic and neutral fractions. From the neutral fraction, 19.76 g (59%) of 16 was recovered

after destillation. The residue (7.0 g) consisted of complex mixture (GC). Isolation of the acidic component from the basic fraction in the usual way afforded as a light yellow oil, 4,4-dimethyl-5-hydroxyoxacyclopentan-2-one (13), (6,0 g, 15%, or 37% yield after correction for unreacted material); b.p. 122-6°C/5 mmHg with extensive polymerization. Molecular destillation at 75°C/0,03 mmHg gave a analytically pure sample. IR (film): 3360 (s), and 1769 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1,23 (s, 6H), 2.50 (m, 2H), 5,00 (bs, 1H, D_2O exch.), 5. 47 (bs, 1H). MS: m/z 113 (M^+-H_2O).

Lemiux-Rudloff oxidations:

The procedure of Overberger and Kaye [19] was adopted.The dioxalane 17c (20.5 g, 0.128 mole) was added to a stirred and cooled (0°C) suspension of sodium metaperiodate (110,25, 0.461 mole) in water (450 ml) containing 380 ml of acetone. After stirring for 30-40 min. solutions of $KMnO_4$ (3.40 g, 0,0217 mole) in water (130 ml) and acetone (130 ml) were simultaneously added during 60-80 min. The resulting pink suspension was stirred at 0 ∿ 5°C overnight and the material was filtered and washed successively with acetone and ether. The filtrate was concentrated under reduced pressure, and extracted with ethyl acetate. Evaporation of the solvent under reduced pressure left a residue (15,10 g) which was hydrolysed with dichloromethane - aq. HCl as previously described. The acidic fraction of the usual work-up gave 13 (9.16 g, 55%) identical spectroscopically with the previously prepared sample.

The dimethyl acetal 17a was oxidised at 20 mmole scale to give 12a (1.87 g 65%), and was quantitatively hydrolysed to

13 using dichloromethane - aq. HCl in the usual way.

The diethyl acetal 17b was similarly oxidized at 20 mmole scale to afford 4,4-dimethyl-5-ethoxyoxacyclopentan-2-one (12b), (2.12g, 67%). The compound was similarly hydrolysed quantitatively to 13. An analytical sample of 12b was obtained by prep. GC. IR (film): 1786 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.17 (s, 6H), 1.21 (t, J 7 Hz, 3H), 2.20 (m, 2H), 3.63 (m, 2H), 4.81 (s,1 H). MS (CI): m/z 159 (M^++1), 113 (M^+-OEt).

Oxidative ozonolysis of acetal 17b. The acetal 17b (3.96 g, 25 mmole) in dry methanol was ozonised in the usual way. The procedure of Freemery and Fields[21] for the oxidation of ozonide with alkaline H_2O_2 was adopted with modification. Thus a solution of H_2O_2 (3,25 ml of 30%, 37.5 mmol) and NaOH (2.0 g, 50 mmole) in water (15 ml) was slowly added to the ozonide in methanol, keeping the temperature of the reaction mixture below 10°C. The resulting milky white mixture was stirred at room temperature overnight and refluxed until a clear solution was obtained (40 min). The reaction was cooled to room temperature, neutralized with dilute aq.HCl and extracted with ether. The ethereal layer was washed with saturated aq. $NaHSO_3$ and brine and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left a residual oil, (2.02 g, 56%), in all respects identical with an authentic sample of 12b.

The 2,4-DNP derivatives prepared in the usual way from 12a, 12b and 13 proved to be methyl 3,3-dimethyl-4-oxobutanoate 2,4-dinitrophenylhydrazine, m.p. 145-7°C (EtOH). ^1H NMR ($CDCl_3$): δ 1.33 (s, 6H), 2.57 (s, 2H), 3.67 (s, 3H), 7.48 (s, 1H),

7.73 (d, J 10 Hz, 1H), 8.17 (dd J 10, 2 Hz, 1H), 8.95 (d, J 2 Hz, 1H), 11.03 (bs, 1H). MS: m/z 324 (M^+).

3,3-Dimethyl-5-methoxy-1,6-dioxacyclooctan-2-one (22). A solution of the acetal 17c (3.12 g, 20 mmole) in methanol (100 ml) was ozonized, followed by reduction with DMS in the usual way. After removal of the solvent, a crude product, (3.0 g, 80%) was obtained which on destillation afforded 22 (2,04 g, 54%). b.p. 50-52°/0.015 mmHg. IR (film): 1740 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.00 (s, 3H), 1.67 (s, 3H), 1.80 (dd, J, 5, 10 Hz, 2H), 3.38 (s, 3H), 4.10 (m, 4H), 4.67 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 24.23, 24.50 ($2XCH_3$), 35.09 (CH_2), 41.39 (C), 55.75 (CH_3O), 64.84 , 65.49 ($-OCH_2CH_2O-$), 102.46 (CH). MS: m/z 157 (M^+-OCH_3).

Reaction of 4,4-dimethyl-5-hydroxyoxacyclopentan-2-one (13) with methallylmagnesium chloride. To a stirred solution of 13 (4.34 g, 0,0033 mole) in dry THF (30 ml) a 0.46 M solution of methallylmagnesium chloride in THF (220 ml, 0.10 mml) was slowly added at 25°C and the reaction mixture stirred for 12 h. TLC indicated the presence of three major components, one of which was the starting material. The mixture was cooled in an ice-bath and hydrolysed with dilute aq. HCl, extracted with ether, washed with cold water and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residue (5.67g) which was chromatographed on Silicagel. Elution with chloroform gave 2,9,6,6-tetramethyl-4-(2-methylpropenyl)-1,9-decadiene-4,7-diol (25) (2.98 g, 33%), m.p. 65-7°C (cyclohexane). IR ($CDCl_3$): 3406 (s) and 1648 (m) cm^{-1}. ^1H NMR (200 MHz,

$CDCl_3$): δ 0.96 (s, 3H), 1.09 (s, 3H), 1.42 (d, J 11.5 Hz, 1H), 1.80-1.90 (m, 1 OH), 2.17-2.28 (m, 5H), 2.55 (d, J, 11.5 Hz, 1H), 3.45 (broad s, 2H), 3.67 (d d, J 5, 10 Hz, 1H), 4.70-4.97 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 22.35, 24.88, 25.21, 26.18, 27.94 (5 X CH_3), 38.72 (C), 40.04 (CH_2), 49.30, 49.46, 49.72 (3 X CH_2), 74.84 (CH), 79,90 (C), 113.22, 114.70 (3 X CH_2=), 143.51, 143.83 (3 X -C=).

Further elution with chloroform gave 4,4-dimethyl-5-(2-methyl propenyl)oxacyclopentan-2-one (24), (1.40 g, 25%), b.p. 60-2°C/ 0.032 mmHg. An analytically pure sample was obtained by preparative GC. IR (film): 1778 (s), and 1646 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10, 1.20 (2s, 6H), 1,80 (s, 3H), 2.27 (d J 7 Hz, 2H), 2.35 (s, 2H), 4.37 (t, J 7 Hz, 1H), 4.83 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 21.25, 22.61, 25.01, (3 X CH_3), 37.23, 39.50, 44.71 (C, 2 X CH_2), 86.81 (CH), 113.25 (CH_2=), 141.44 (-C=), 175.95 (C=O). MS: m/z 168 (M^+), 113 ($M^+-C_4H_7$, base peak).
Finally, unreacted starting material (0.87g, 20%) was eluted.

2,5,5-Trimethylocta-1,7-diene-4-ol (26). Methallylmagnesium chloride was prepared in the usual way from β-methallylchloride (90.55 g, 1.0 mole) and magnesium (36.46 g, 1.50 mol) in dry ether (500 ml). 16 (63.0 g, 0.56 mole) was slowly added at 10°C and the reaction mixture stirred for 4 h. Aq. NH_4Cl, sufficient to hydrolyze the resulting magnesium complex was added and the ethereal phase decanted from the precipitated magnesium salts. The latter was washed with dry ether. Removal of solvent and other volatiles under reduced pressure left a residue which was distilled to give 26 (75.45 g, 80%) b.p.

78-89°C/10 mmHg. IR (film): 3478 (s) and 1637 (m) cm^{-1}. ^1H NMR (CCl_4): δ 0.87 (2s, 6H), 1.60 (2s, 1H, D_2O exch.), 3.33 (d d, J 5, 12.5 Hz, 1H), 4.80 (bs, 2H), 5.07 (s, 1H), 5.50-6.17 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 22.22, 22.74, 23.07 (3 X CH_3), 37.36, 40.28, 43.79 (C, 2 X CH_2), 74.46 (CH), 113.44 (CH_2=), 135.41 (-CH=), 143.66, (-C=). MS: m/z 168 (M^+).

A comparable yield, (84%) of the alcohol 26 was obtained using THF as solvent.

A byproduct 2,2-dimethyl-4-pentenal (27)[22] (10%) was obtained using THF as solvent and excess magnesium metal at 50°C.

4,4-Dimethyl-5-(2-oxopropyl)oxacyclopentan-2-one (28).
Method A: A solution of dienol 26 (56.17 g, 0,333 mole) in methanol (600 ml) was ozonized at -78°C. Excess ozone was flushed out with nitrogen and the mixture allowed to warm to 0°C followed by addition of 90% aq. HCO_2H (460 ml). Hydrogen peroxide (30%, 225 ml) was added during 40 min. keeping the temperature below 10°C. The clear solution was stirred at 20°C for an additional 30 min. The solution was concentrated under reduced pressure to approximately 500 ml, saturated with NaCl and extracted with ether. The ethereal layer was washed successively with saturated aq. $NaHSO_3$, water and brine and then dried ($MgSO_4$). The solvents and volatile products were evaporated at 60-80°C (bath temperature) and 0.015 mmHg leaving a dark oil which solidified on cooling. Recrystallization from pet.ether afforded 28 (27.17 g, 48%) m.p. 55-60°C. IR (KBr): 1762 (s), 1716 (s) cm^{-1}. ^1H NMR (CCl_3): δ 1,00, 1.16 (2s, 6H), 2.15 (s, 3H), 2.25 (2s, 2H), 2.55 (m, 2H),

4.46 (d d, J 5, 10 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.69, 24.81, 30.70 (3 X CH_3), 38.94 (C), 42.55 (CH_2), 44.02 (CH_2), 83.44 (CH), 175.55 (C=O lactone). MS: m/z 155 (M^+-CH_3), 128, (M^+-CH_2CO), 113 ($M^+-C_3H_7O$).

Method B: Ozonolysis of a methanolic solution of 24 (20.36 g, 0.121 mole) followed by reduction with DMS in the usual way gave a yellow liquid (20.0 g). This was dissolved in ether (30 ml) and H_2O_2 (30%, 16 ml) was added at room temperature followed by a slow addition of 90% HCO_2H (20 ml). After stirring for 2.5 h at room temperature the reaction was complete (GC). Water (40 ml) and ether (50 ml) were added and the phases were separated. The organic phase was washed with several portions of saturated aq. $FeSO_4$ or aq. $NaHSO_3$ until it was free from peroxide, followed by water and brine and then dried ($MgSO_4$). Evaporation of the solvents gave 28 (12.78 g, 70%), identical with the product obtained from method A.

Method C: The ozonolysis product (400 mg) obtained after reduction with DMS as described under method B, was dissolved in acetone (10 ml) and a stock solution of Jones reagent (2.0 ml) was added at 0°C. After stirring for 2 h the reaction was complete (GC). The acetone phase was pipetted out and treated with saturated aq. $NaHSO_3$ and filtered through a cotton plug. Removal of solvent under reduced pressure left 28 (395 mg, 100%) as a light yellow oil which solidified on standing.

4,4-Dimethyl-2-methyl-5-(2-oxopropyl)oxalane (29). A solution of 26 (17.24 g, 0.102 mole) in dry methanol (300 ml) was ozonized at -78°C in the usual way. After removal of excess

ozone, DMS (18,33 ml, 0,250 mole) was added at -78°C and allowed to warm to room temperature overnight. The residue obtained by evaporation under reduced pressure was dissolved in ether. The solution was washed successively with water, saturated aq. $NaHSO_3$, saturated aq. $NaHCO_3$, and brine and then dried ($MgSO_4$). Removal of solvents under reduced pressure and distillation of the residue gave 29 (15.20 g, 80%), b.p. 96-8°C/ 8 mmHg, as a 3:1 mixture of stereoisomers (GC). IR (film): 1710 (s), 1105 (s) cm^{-1}. ^1H NMR (CCl_4): δ 0.87 (2s, 6H), 1.70, 1.83 (2d, J 10 Hz, 2H), 2.13 (s, 3H), 2.38, 2.61 (2d, J, 10 Hz, 2H), 3.28 (s, 3H), 3.95 (dd J 5,10 Hz, 1H), 4.83 (m, 1H). The compound was quantitatively oxidized using Jones reagent to the ketolactone 28 as described in the preceding experiment.

Methylenation of the ketolactone 28. To a stirred suspension of methyl triphenylphosphonium bromide (dried over P_2O_5) (1.155 g, 3.60 mmole) in dry ether (90 ml) a solution of 1.80 M, n-Buli in hexane (1.65 ml, 2.97 mmole) was added dropwise via syringe at room temperature under nitrogen. The suspension dissolved to give a deep yellow solution and was stirred for a further 30 minutes before a solution of 28 (0,51 g, 3 mmole) in ether (30 ml) was slowly added. The deep yellow colour was discharged and the mixture was stirred for one additional hour. Water (10 ml) was added and the ether layer separated, washed with brine and dried ($MgSO_4$). Removal of ether under reduced pressure left a residue which was purified by column chromatography (silica gel, benzene) to give a crude product (0.36 g).

Distillation gave 24 (0.280 g, 56%) b.p. 58-60°C/0.028 mmHg, identical in all respects with a previously prepared sample.

Methylenation of the ketoacetal 29 and subsequent Jones oxidation. The Wittig reagent was prepared as in the preceeding experiment from triphenylphosphonium bromide (1.555 g, 3.60 mmole) and 1.80 M Buli (1.65 ml, 2.97 mmole) at room temperature under nitrogen. A solution of 29 (0,558, 3.0 mmole) in ether (30 ml) was slowly added and the reaction mixture was stirred for 1 h. Water (10 ml) was added and the organic phase was washed with water and dried ($MgSO_4$). Evaporation of the solvent left a residue which was chromatographed on a short column. Elution with hexane and evaporation gave crude 4,4-dimethyl-2-methoxy-5-(2-methylpropenyl)oxalane (30), (0.4146 g, 75%), which was used in the next step without further purification.

To a stirred and cooled (ice-bath) solution of the above crude 30 (0.4100 g, 2,23 mmole) in acetone (10 ml) a stock solution of Jones reagent (2 ml) was slowly added and the reaction mixture stirred for 2 h. Work-up in the usual way afforded 24 (0,3752 g, 100%), identical with a previously prepared sample.

4-Methoxy-2,5-trimethyl-1,7-octadiene (32). The compound was prepared according to the literature procedure,[48] from the dienol 26 (8.40 g, 0,050 mole) and methyl iodide (21.0 g, 0.148 mole) in 80% yield, b.p. 72-5°C/8 mmHg. IR (film): 1639 (m), 1191 (s) cm^{-1}. ^1H NMR (CCl_4): δ 0,93 (s, 6H), 1.83 (s, 3H), 2,13 (m, 4H), 3,00 (m, 1H), 3.38 (s, 3H), 4.67-6.30 (m, 5H). MS: m/z 151 (M^+-OMe).

(3E)-2,5,5-Trimethyl-1,3,7-octatriene (34). The procedure of Dowrie et al.[49] was adopted for this reaction. A mixture of dienol 26 (4.60 g, 27.4 mmole), tetrachloromethane (10 ml) and triphenyl phosphine (7.34 g, 28 mmole) was stirred at room temperature under nitrogen. The reaction was monitored by GC and after 76 h about 50% conversion was realized. The solids were filtered through a Celite pad and washed with dry hexane. The combined organic solutions were distilled through a Vigreux column at atmospheric pressure and the residue fractionated to give 34 (1.93 g, 47%) b.p. 44-46°C/10 mmHg. An analytically pure sample was obtained by preparative GC. IR (film): 3076 (m), 1639 (m), 1603 (c) cm^{-1}. ^1H NMR (CCl_4): δ 1.00 (s, 6H), 1.77 (s, 3H), 2.00 (d, J 8 Hz, 2H), 4,80 (s, 2H), 5,03 (s, 2H), 5,50 (m, 1H), 5,50 (d, J 14 Hz, 1H), 6,00 (d, J 14 Hz, 1H). MS: m/z 151 (M^+).

The second fraction, b.p. 73-5°C/10 mmHg was unreacted starting material (2.10 g, 46%).

2,5,5-Trimethyl-1,7-octadiene-4-one (35). To a stirred solution of 26 (25.5 g, 0.152 mole) in ether (250 ml) a solution of chromic acid (200 ml) prepared according to the lit.[50] was slowly added during 48 h. The ether phase was separated and washed successively with saturated aq. $NaHSO_3$, 10% aq. $NaHCO_3$ and brine and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was distilled to give 35 (22.5 g, 89%) b.p. 75-6°C/10 mmHg. IR (film): 1710 (s) and 1640 (m) cm^{-1}. ^1H NMR (CCl_4): δ 1.17 (s, 6H), 1.77 (s, 3H), 2.25 (d J 8 Hz 2H), 3.17 (s, 2H), 4.62-6.00 (m, 5H). MS (CI): m/z 167 (M^++1).

Attempted protection of C_4=O of 34.

a) With p-toluenesulphonic acid as catalyst. A mixture of the ketone 35 (10.0 g, 66 mmole), trimethylorthoformate (8.71 g, 82.5 mmole) dry methanol (20 ml) and TsOH (0,20 g, 1.8 mol %) was heated under reflux for 15 h. The reaction mixture was cooled to room temperature and solid K_2CO_3 was added to neutralize the acid used. The filtered solution was concentrated under reduced pressure and distilled to give 2,5,5-trimethyl-2,7-octadiene-4-one (36) (8.50 g, 85%), b.p. 80-2°C/7 mmHg. IR (CCl_4): 1690 (s) and 1627 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.07 (s, 6H), 1.90 (s, 3H), 2.10 (s, 3H), 2.23 (d, J 8Hz, 2H), 4.77-6.00 (m, 3H), 6,25 (s, 1H). MS: m/z 166 (M^+).

b) With ammonium chloride as catalyst. A stirred solution of 35 (0,83 g, 5 mmole) trimethylorthoformate (0,66 g, 6.25 mole) dry methanol (5 ml) and NH_4Cl (18 mg) was heated under reflux for 15-40 h. GC analysis revealed no product but the starting material.

2-Isopropyl-1,3-dithiane (38), was prepared from isobutyraldehyde and 1,3-propanedithiol as already described in 81% yield, b.p. 94-8°C/9 mmHg. (lit.[51] b.p. 96°C/10 mmHg). ^1H NMR (CCl_4): δ 1.05 (d, J 8 Hz 6H), 1.93 (m, 6H), 2.83 (m, 4H), 4,00 (d, J 5 Hz, 1H). MS: m/z 164 (M^++2).

2-Isopropyl-2-(2-methylpropenyl)-1,3-dithiane (39). The preparation was an adaption of literature procedure.[38,52] A solution of dithiane 38 (0,81 g, 5 mmole) in THF (20 ml) was cooled to -40°C and a 1.80 M solution of Buli in hexane (6.70 ml, 12 mmole) was added via syringe and stirred for 5 h. This

was followed by a dropwise addition of methallyl chloride (1.35 g, 15 mmole) in THF (5ml) under nitrogen. The mixture was stirred at -20°C for 10 h, GC indicated quantitative conversion. The reaction was quenched with water. After the usual work-up and evaporation of the volatiles, crude 39 (0.80 g, 75%) was obtained. An analytical sample was obtained by preparative GC. IR (film): 1639 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (d, J 8.8 Hz, 6H), 1.97 (m, 5H), 2.33-3.13 (m, 6H), 4.93 (broad s, 2H). MS: m/z 216 (M^++2).

2,2-Dimethyl-4-pentenoic acid (40) was obtained in 96% yield by oxidation of 16 using silver(I)oxide according to the lit.[53] b.p. 90-2°C/10 mmHg (lit.[22] b.p. 92-3°C/8.5 mmHg).

Methyl 2,2-dimethyl-4-pentenoate (41a) was obtained in 83% yield by esterifying the acid 40 according to the procedure of Kadaba[54] b.p. 58-60°C/27 mmHg. IR (film): 1733 (s) and 1639 (m) cm^{-1}. ^1H NMR (CCl_4): δ 1.17 (s, 6H), 2.27 (d, J 8 Hz, 2H), 3.67 (s, 3H), 4.78-6,27 (m, 3H).

Ethyl 2,2-dimethyl-4-pentenoate (41b) was prepared in 70% yield from the acid 40 by the procedure used for 41a b.p. 62-4°C/ 2 mmHg (lit.[55] b.p. 78°C/39 mmHg).

Ozonolysis and reduction with DMS in CH_2Cl_2.

General: 5-10% solution of substrates in dry dichloromethane were ozonized at -78°C and excess ozone removed in the usual way. DMS was added at -78°C in slight excess and stirred for 1 h, allowed to warm to room temperature and left to stand over-

night at room temperature. Excess DMS and CH_2Cl_2 were removed at 25-30°C through a short column by a nitrogen pressure assisted evaporation into a $KMnO_4$ (aq) trap kept at or below 0°C. The residues were diluted with ether, washed with saturated aq. $NaHCO_3$, NaCl and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residues analysed. Acidic products were obtained from the bicarbonate phase in the usual way.

The ether 32 (1.82 g, 10 mmole) gave from the neutral fraction a crude product (1.10 g, 59%), consisting of one major product as a mixture of isomers in 3:2 ratio (GC). An analytical sample obtained by preparative GC was identical in all respects with the ketoacetal 29 previously prepared.

The acid 40 (12.82 g, 0.10 mole) gave after acidification of the bicarbonate phase, continuous extraction with ether and evaporating the latter to dryness a solid product (12.15 g, 93%), identified as 3,3-dimethyl-5-hydroxyoxacyclopentan-2-one (43), m.p. 57-9°C (pet.ether/$CHCl_3$, 8:2) (lit.[25b] b.p. 100°C/0,3 mmHg, m.p. 60°C), also supported by spectroscopic data.

The methyl ester 41a (16,0 g, 0,113 mole) gave after distillation 3,3-dimethyl-5-methoxyoxacyclopentan-2-one (44) (11.40 g, 70%), b.p. 67-70°C/8 mmHg, (lit.[25b], b.p.115°C/50 mmHg). IR (CCl_4): 1799 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.20, 1.28 (2s,6H), 2.07 (m, 2H), 3.47 (s, 3H), 5.22 (d d, J 6,5, 7.5 Hz, 1H). Ms (CI): m/z 145 (M^++1).

From the acidic fraction 3-methyl-3-methoxycarbonylbutanoic acid (45) (1.0 g, 6%) was obtained. An analytical sample was obtained by preparative GC. IR (CCl_4): 3500-2500 (broad), 1714 (s) cm^{-1}. ^1H NMR (CCl_4): 1.20 (s, 6H), 2.52 (s, 2H), 3.60 (s, 3H), 9.43 (broad s, 1H). MS (CI): m/z 161 (M^++1).

The ethyl ester 41b (7.86 g, 50 mmole) gave from the neutral fraction ethyl 2,2-dimethyl-4-oxobutanoate (42b) (3.67 g, 39%), b.p. 78-80°C/10 mmHg. IR (film): 1726 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30 (s, 6H), 1.30 (t, J 7Hz, 3H) 2.67 (d, J 2 Hz), 4.20 (q, J 7Hz, 2H), 9.77 (t, J 2 Hz, 1H). MS (CI): m/z 159 (M^++1). The acidic fraction gave after destillation 3-methyl-3-ethoxycarbonylbutanoic acid (46) (4.03 g, 51%), b.p. 70-72°C/0.025 mmHg. IR (film): 3200-2500 (broad), 1733 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.30 (s, 6H), 1.30 (t, J 7 Hz, 3H), 2.60 (s, 2H), 4.17 (q, J 7 Hz, 2H), 11.47 (s, 1H).

Ozonolysis and reduction with $NaBH_4$.[56] A solution of the acetal 17a (15.82 g, 0.10 mole) in 100 ml of $MeOH/CH_2Cl_2$ (4:1 v/v) was ozonized at -78°C in the usual way. The reaction mixture was warmed to -30°C and slowly added to a stirred solution of NaOH (5.92 g, 0.148 mole) and $NaBH_4$ (7.94 g, 0.21 mole) in 50% aq. MeOH (100 ml) while keeping the temperature below -10°C. The mixture was then stirred overnight and excess solvent was removed through a vigreux column at 30 mmHg. The concentrate was saturated with solid NaCl, extracted with ether, and dried ($MgSO_4$). Removal of the solvent at 20 mmHg left a residue, (12,70 g) which according to GC analysis consisted of two compounds in 45% and 55%. The crude IR of the mixture exhibited a hydroxyl absorption band. Upon preparative GC only the com-

pound corresponding to the less predominant peak was isolated and characterized as 3,3-dimethyl-2-methoxyoxalane (55). IR (film): 1098 (s) and 1050 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.00 (2s, 6H), 1.65 (m, 2H), 2.20 (s, 3H), 2.80 (m, 2H), 3.22 (s, 1H). MS (CI): m/z 131 (M^++1).

The second component reacted with chlorotrimethylsilane and was identified as trimethylsilyl ether of 3,3-dimethyl-4,4-dimethoxybutanol (54). ^{1}H NMR (CCl_4): δ 0,06 (s, 9H), 0.86 (2, 6H), 1.45 (t, J 8.5 Hz, 2H), 3.43 (s, 6H), 3.58 (t, J 8.5 Hz, 2H), 3.78 (s, 1H).

The acid 40 (31.50, 0.246 mole) was similarly ozonized and reduced. After removal of alcoholic solvents, the concentrated aq. solution was washed with ether, acidified with 6M HCl at 0 ∿ 5°C and continuously extracted with ether. After drying ($MgSO_4$), removal of solvent under reduced pressure and distillation of the residue, 3,3-dimethyloxacyclopentan-2-one (59) (25.4 g, 90%) was obtained, b.p. 76-8°C/10 mmHg (lit.[25a] b.p. 116°C/60 mmHg).

3,3-Dimethyl-2-hydroxyoxalane (56).

Method A. The crude product mixture of 54 and 55 (10.0 g) obtained from 17a by $O_3/NaBH_4$ was vigorously stirred overnight in dichloromethane (25 ml) and 50% aq. HCl (25 ml). The phases were separated and the organic phase dried ($MgSO_4$). Removal of solvent and destillation gave 56 (7.17 g, 62% from 17a), b.p. 78-80°C/15 mmHg. IR (film): 3399 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.03 (2 s, 6H), 1.73 (m, 2H), 3.95 (m, 2H), 4.42

(s, 1H D_2O exch.), 4.85 (s, 1H).

Method B. The lactone 59 was reduced with DIBAH according to lit. procedures.[57,58] Thus to a solution of 59 (11.62, 0.10 mole) in dry ether (200 ml), a 1.0 M solution of DIBAH in hexane (120 ml, 0.12 mol) was added dropwise at -70°C under nitrogen. After addition was completed the mixture was stirred for an additional 20 min. and the reaction was quenched by slow addition of saturated aq. NH_4Cl solution (ca. 100 ml) at -70°C. The reaction mixture was then allowed to warm to -10°C and 20% aq. HCl was slowly added, keeping the temperature below 0°C, until a clear two phase mixture was obtained. The phases were separated and the aq. layer continuously extracted with ether. The ethereal extract was dried ($MgSO_4$) and solvent was removed through a vigreux column at atmospheric pressure. The residue was distilled to furnish 56 (11.03 g, 95%), b.p. 77-80°C/15 mmHg - identical in all respects with a previously prepared sample.

Reduction of 59 (5 mmole) with LAH in THF at -50°C according to lit.[35] gave the lactol 56 (20%) and 2,2-dimethyl-1,4-butanediol (60) in 75% yield according to GC analysis of the crude product. On the larger scale (80 mmole) the diol was the exclusive product, isolated in 95% yield, b.p. 70-76°C/0.02 mmHg. IR (film): 3340 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0,87 (s, 6H), 1.57 (t, J 7Hz, 2H), 3.33 (s, 2H), 3.70 (t, J 7 Hz, 2H), 4.27 (broad s, 2H, D_2O exch.).

2,5,5-Trimethyl-1-hepten-4,7-diol (57). To an ice-cooled

stirred solution of (6,20 g, 53.4 mmole) in dry THF (30 ml) was added dropwise during 1 h a 0,54 M solution of methallylmagnesium chloride in THF (205 ml, 111 mmole) under nitrogen. The mixture was stirred at 0°C for 20 min. and quenched with a saturated aq. NH_4Cl solution. The phases were separated and the aq. layer was extracted with ether after saturation with NaCl. The combined organic extract was dried ($MgSO_4$). Evaporation of the solvent and destillation of the residue furnished 57 (7.94 g, 87%), b.p. 85-90°C/0,034 mmHg. IR ($CDCl_3$): 3411 (s) and 1643 (n) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00 (2s, 6H), 1.67 (m, 2H), 1.83 (2, 3H), 2.23 (m, 2H), 3.03 (broad s, 2H, D_2O exch.), 3.47 (dd, J 6.3, 11.3 Hz, 1H), 3.75 (t, J, 7.5 Hz, 2H), 4.90 (broad s, 2H). ^{13}C NMR ($CDCl_3$): δ 22.29,, 24.04, 25.01, (3 X CH_3), 36.97, 40.15, 42.30, (C, 2 X CH_2), 58,80 (CH_2), 74.91 (CH), 113,48 (CH_2=), 143.59 (-$\dot{C}$=). MS: m/z 155 (M^+-H_2O).

Oxidation of 2,5,5-trimethyl-1-hepten-4,7-diol (57) with Jones reagent. A solution of 57 (5.0 g, 28 mmole) in acetone (30 ml) was cooled in an ice-bath and a stock solution of Jones reagent (20 ml) was added. After stirring for 1-2 h the reaction was complete (GC). After the usual work-up and distillation the olefinic lactone 24 (4.15 g, 85%) was obtained, in all respects identical with an authentic sample.

Alkylation of 3,3-dimethyloxacyclopentan-2-one (59).
(a) With methallylmagnesium chloride.[36] A solution of 59 (250 mg, 2.19 mmole) in THF (5 ml) was cooled to -70°C and a 0.765 M solution of methallylmagnesium chloride in THF, (2.80 ml, 2.19 mmole) was added under nitrogen. After 10 min. a sample was examined by GC and was found to consist of 45%

starting material, 20% of an unknown product and 34% of the diol. After 40 minutes the mixture consisted of 61% diol, 29% starting material and an unknown product 7% on GC.

The experiment was repeated with 1.6 equivalents of the Grignard reagent at 0°C, 1h, 2,5,5-trimethyl-4,(2-methylpropenyl)-1-hepten-4,7-diol (62) was obtained (80%). b.p. 100-2°C/0,02 mmHg. IR (film): 3346 (s), 3070 (m), and 1638 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.01 (s, 6H), 1.71 (t, J 7Hz, 3H), 1.80 (s,6H), 2.38 (2s, 4H), 3.68 (t, J 7Hz, 2H), 4.83 (broad s, 4H). ^{13}C NMR ($CDCl_3$): δ 22.78, 25.21 (4 X CH_3), 41.74, 42.36 (2 X CH_2), 44.05 (2 X CH_2), 59.32 (C), 77.97 (>COH), 115.59 (2 X CH_2=), 144.42 (2X-C=). MS (CI): m/z 171 ($M^+-C_4H_7$).

(b) With methallyllithium. To a solution of methallyltriphenylphosphine[59] (1.17 g, 3 mmole) in ether (10 ml) was slowly added a 2.0 M solution of phenyllithium (1.0 ml, 2 mmole) at room temperature and under nitrogen. The mixture was stirred for 40 min. and allowed to settle. The clear solution was removed via syringe and added slowly to a stirred solution of lactone 59 (250 mg, 2.19 mmole) in ether (5 ml) at -30°C. After 40 min. GC analysis showed a mixture consisting of a diol 55% and 43% of the starting material. The operation was abandoned.

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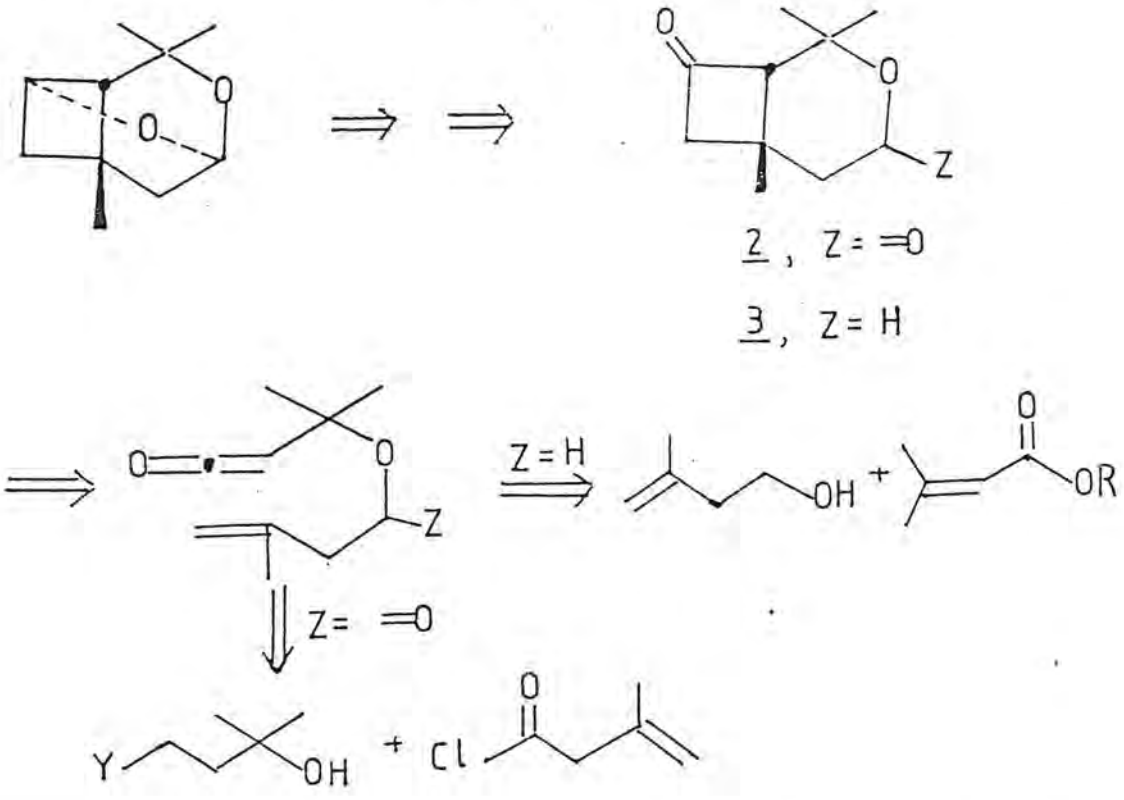
III

Chapter 3.

Attempted synthesis of Lineatin from 3-methyl-3-butenol and Analogues.

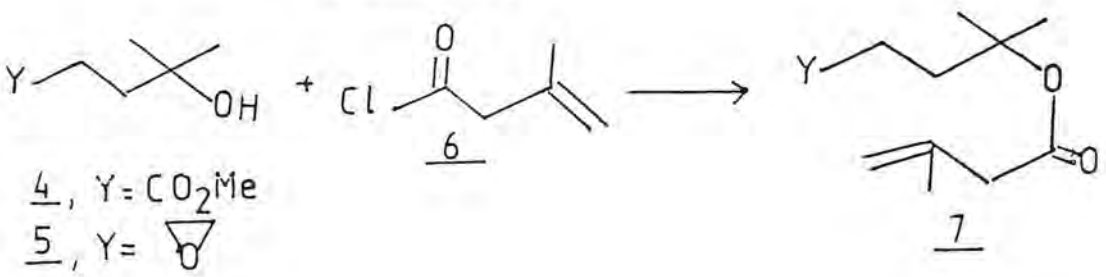
In this chapter we present synthetic studies which are based on the retro-synthetic approach depicted in scheme 3.1. The target compounds being the ketolactone 2 or the oxaketone 3. An intramolecular ketene-ene cycloaddition is the key step in this approach (compare chapter 2, scheme 2.1).

Scheme 3.1.



We first attempted a synthesis of 2 as shown in scheme 3.2.

Scheme 3.2.

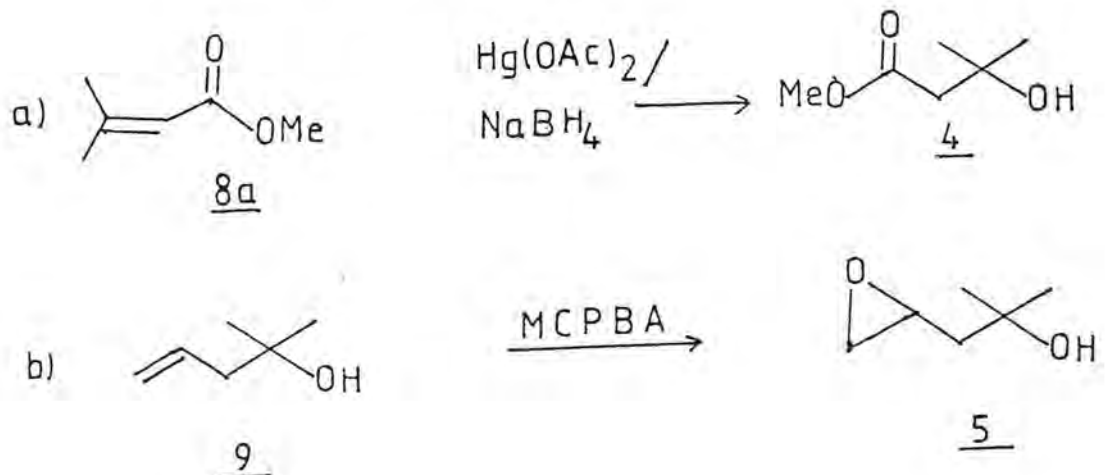


Condensation of 6 and either 4 or 5 was expected to give 7 which could be manipulated to the ketolactone 2, the precursor of lineatin.

Compound 6 is readily prepared[1], and we tried to obtain 4 using methyl 3-methyl-2-butenoate (8a)[2] as starting material (scheme 3.3.).

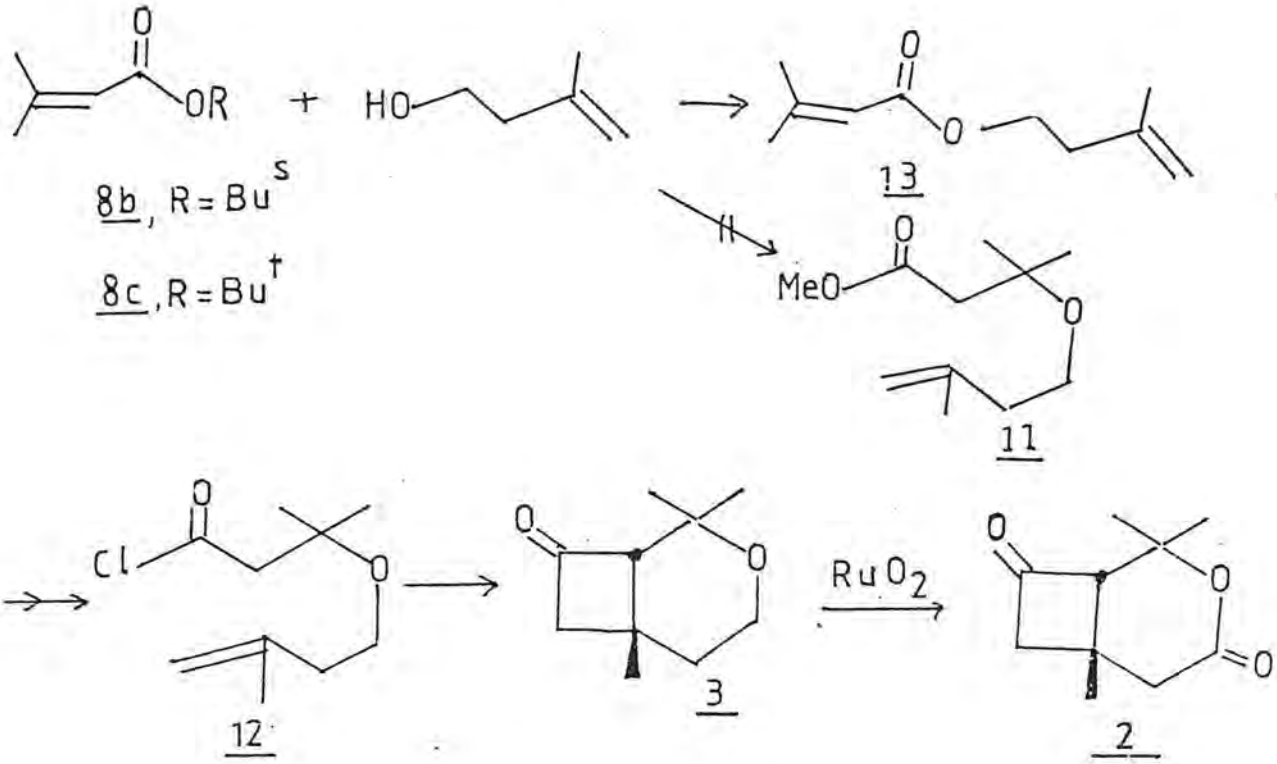
Brown and co-workers have reported the Markovnikov hydration of C-C double bonds in good yields by oxymercuration followed by reduction. However, when 8a was subjected to this mild treatment the product consisted of only 20% of 4 according to GC, whilst 80% was unreacted starting material. Attempts to improve the conversion by varying the reaction time and conditions were unsuccessful. In another approach (scheme 3.3) we aimed at the epoxyalcohol 5. This was obtained in 72% yield by epoxidation of the alkenol 9, prepared in 68% yield from allyl magnesium chloride and acetone. However, attempted condensation of 6 and 5 in the presence of a base such as triethylamine, pyridine or N,N-dimethylaniline, led to a mixture consisting of at least four uncharacterized compounds according to GC.

Scheme 3.3.



We then aimed at making the oxaketone 3, which we anticipated would be easily oxidised to 2 by the sequence outlined in scheme 3.4.

Scheme 3.4.

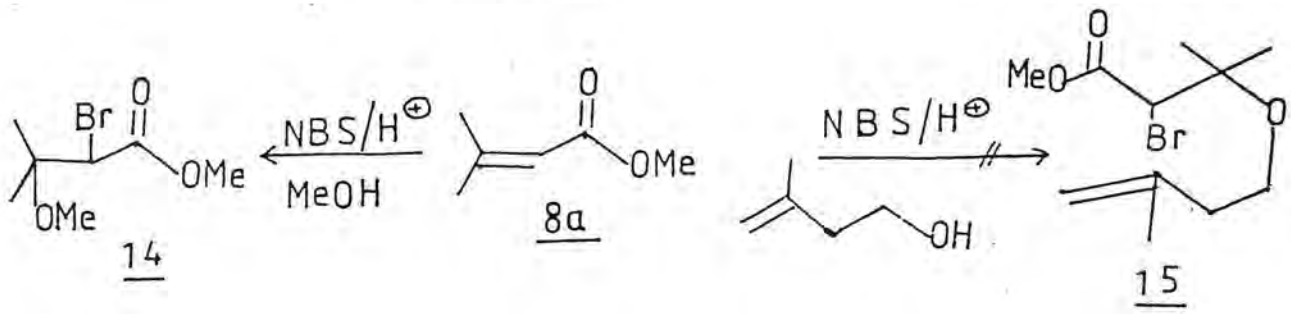


The esters 8b-c were obtained in good yields by standard procedures. Attempted Michael addition on these esters with the alkoxy anion of 10, generated with NaH in THF, gave the ester exchange product 13 in 65-70% yields, and none of 11. The structure of 14 was established on the basis of spectroscopic information.

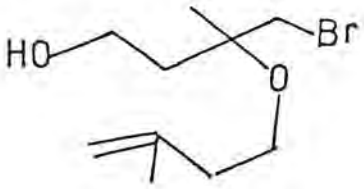
Recently, Heasley et al.[4] have reported the transformation of α,β-unsaturated carbonyl compounds with N-bromosuccinamide (NBS) in methanol to the corresponding α-bromo-β-methoxy derivatives in good yields. Using this procedure we converted the ester 8a to the α-bromo-β-methoxy ester 14 in 83% yield. The success

of this model reaction, led us to attempt the preparation of compound 15 from 8a by the same method by replacing methanol with the homoallylic alcohol 10 as outlined in scheme 3.5. Fortuitously, the bulk of the ester 8a was recovered unchanged and the product was proved to be the bromoalcohol 16 from spectroscopic evidence.

Scheme 3.5.



14 8a 15



16

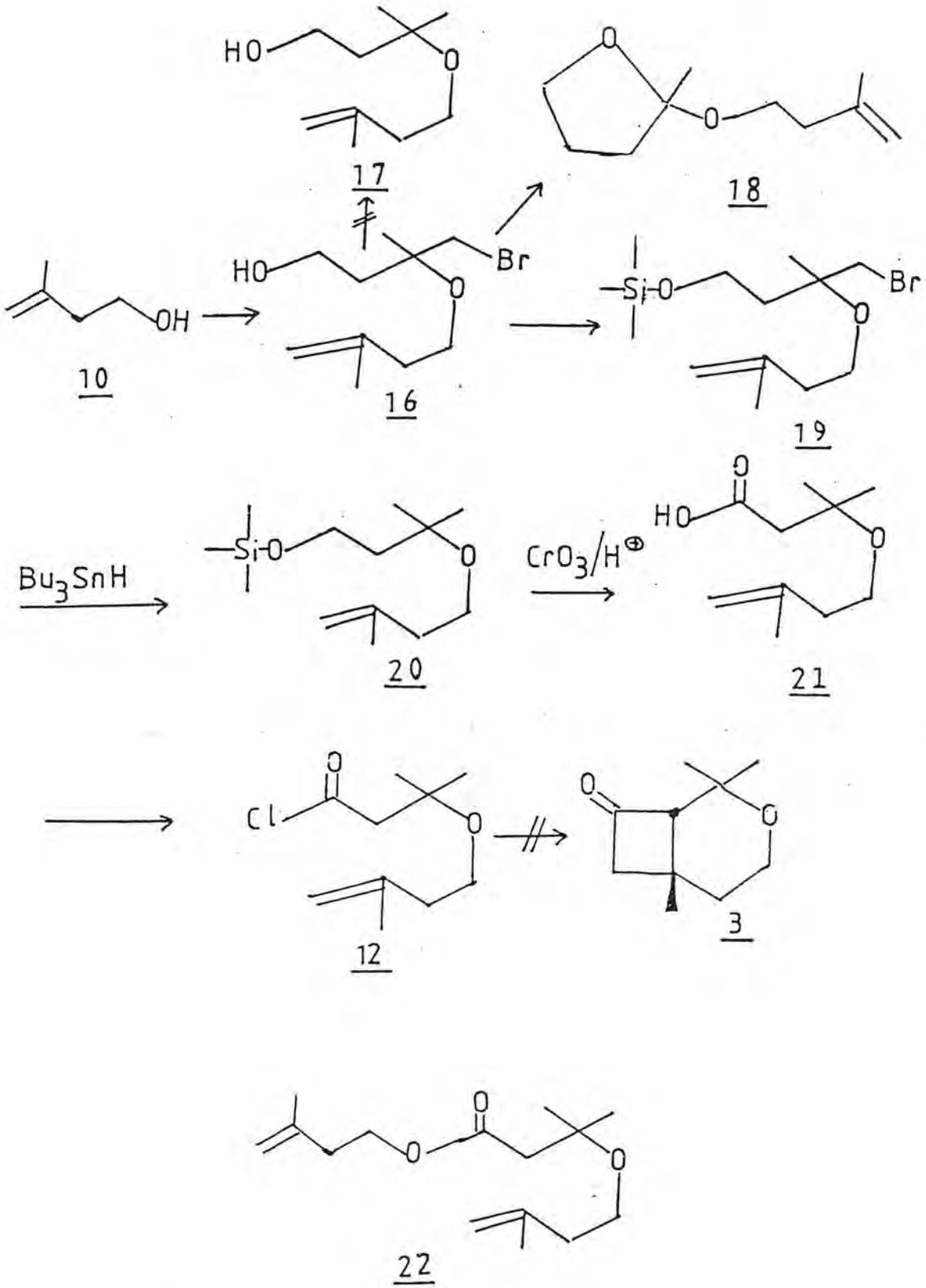
The ^{1}H NMR spectrum of 16 exhibits singlets at 1.40 and 1.77 ppm for the methyl groups. The methylene group adjacent to the quartenary carbon gives rise to a triplet at 1.93 ppm and the triplet observed at 2.30 ppm is due to the allylic counterpart. A singlet at 2.90 ppm exchangeable with D_2O is assigned to the hydroxylic proton while another singlet at 3.48 ppm is due to the bromomethyl group. The methylene protons adjacent to the hydroxyl and ether functions give rise to triplets at 3.80 and 3.57 ppm, respectively. A broad singlet resonating at

4.80 ppm is assigned to the olefinic protons. The structure is further supported by the strong hydroxyl absorption at 3412 cm^{-1} in the IR in addition to the appearance of the molecular ion in the mass spectrum.

The formation of 16 was nevertheless encouraging since its transformation to the desired acid chloride 12 seemed quite possible. We therefore concentrated on optimizing the yield of 16. High yields were obtained using 8-10 equivalents of the alcohol 10 in the presence of 2-4 mol% of conc. H_2SO_4 as catalyst at -10-5°C under nitrogen and with exclusion of light. Addition of the alcohol to NBS followed by the acid catalyst or adding NBS in small portions to the alcohol containing the acid catalyst at the same temperature did not affect the yields when the reactions were carried out at high dilution. At low dilution (5-6 equivalents) the former mode of addition was accompanied with increased side products while the latter procedure furnished a clean reaction. Certainly this was still not satisfactory since a large excess of the alcohol 10 was employed. Comparable results were obtained, however, employing pentane as solvent with 2-3 equivalents of 10.

The bromoalcohol 16 decomposed on attempted destilllation. The crude product was, however, sufficiently pure for the next step, the reduction of the bromide to the alcohol 17 (scheme 3.6). Because of the ether linkage we avoided reduction methods conducted in acidic medium, such as zinc in acetic acid. In our hands,all attempted reductions using Li/Bu^tOH in THF,[5] $LiEt_3BH$,[6] $Na(CN)BH_3$ in HMPA[7] and Bu_3SnH[8] led to the cyclic acetal 18 in 73-88% yields and none of 17. It was therefore necessary

Scheme 3.6.


HO
17
18
10
OH
HO
Br
16
Si-O
Br
19
Bu3SnH
Si-O
CrO3/H⊕
HO
20
21
Cl
12
3
22

to protect the hydroxyl group. This was carried out on crude 16 with chlorotrimethyl silane in excess of triethylamine, furnishing the silyl ether 19 in 69% overall yield from 10. The reduction of 19 proceeded without difficulty with tributyltin hydride[8] to 20 in 84% yield. It was possible to convert compound 20 directly to the acid 21 in 87% yield by the careful addition of Jones reagent at -20°C and allowing the temperature of the reaction mixture to rise to 25°C. The acid 21 was distilled on a molecular still and the structure assigned from its spectroscopic properties. Contrary to our expectation the preparation of the acid chloride 12 from 21 was not easily achieved. With thionyl chloride in either pentane, dichloromethane or benzene in the presence of pyridiene at $\leq$ 0°C, the reaction resulted only in tarry products.

The reaction of triphenylphosphine and carbon tetrachloride with the acid 21 according to the literature[9] was too slow at room temperature. When heated to 50-60°C, the reaction took place, but the product seemed to contain a mixture of the acid chloride 12, the esters 13 and 22 as indicated by the ^{1}H NMR spectrum of the crude product. Employing an excess of oxalyl chloride in a mixture of pyridine and benzene[10] we were able to obtain crude 12 in 80% yield exhibiting satisfactory ^{1}H NMR and IR spectra. Attempted destillation of 12 led to decomposition products from which the esters 13 and 22 were obtained by preparative GC, and identified spectroscopically. Consequently we decided to carry out the ketene generating step on crude 12.

A dilute solution of triethylamine (1.2 equivalent relative to 12) in benzene was heated to reflux. A dilute solution of 12

in benzene was then added slowly as described in the literature.[11,12] (The reaction was also carried out in separate runs using dichloromethane or pentane as solvents). These reactions resulted in either mixtures of products dominated by the esters 13 and 22, according to GC analysis, or polymeric material.

With disappointment we terminated our efforts to synthesize lineatin by this seemingly attractive approach. The dehydrochlorination of 12 with base is the simplest way of generating the corresponding ketene; however, this method suffers from disadvantage that the base can cause the generated ketene to dimerize, trimerize or polymerize.[13,14] The reported successful thermal intramolecular ketene-ene cycloadditions[11,12] by base induced dehydrochlorination of the carbon analogues of 12, suggest that our failure is connected with the presence of the ether oxygen.

The Wolf-rearrangement of the ketocarbene derived from 12 could be another alternative to generate the ketene. However, the competitive cyclopropanation and the unpredictable influence of the ether oxygen rend this approach less attractive. Generating the ketene by way of dehalogenation of the 2-haloacyl halide derived from 12 using activated zinc[14-16] is worthy of consideration, but its preparation may be problematic. It is also quite possible that the zinc halide formed in the reaction may as a Lewis acid promote cleavage of the ether bond.

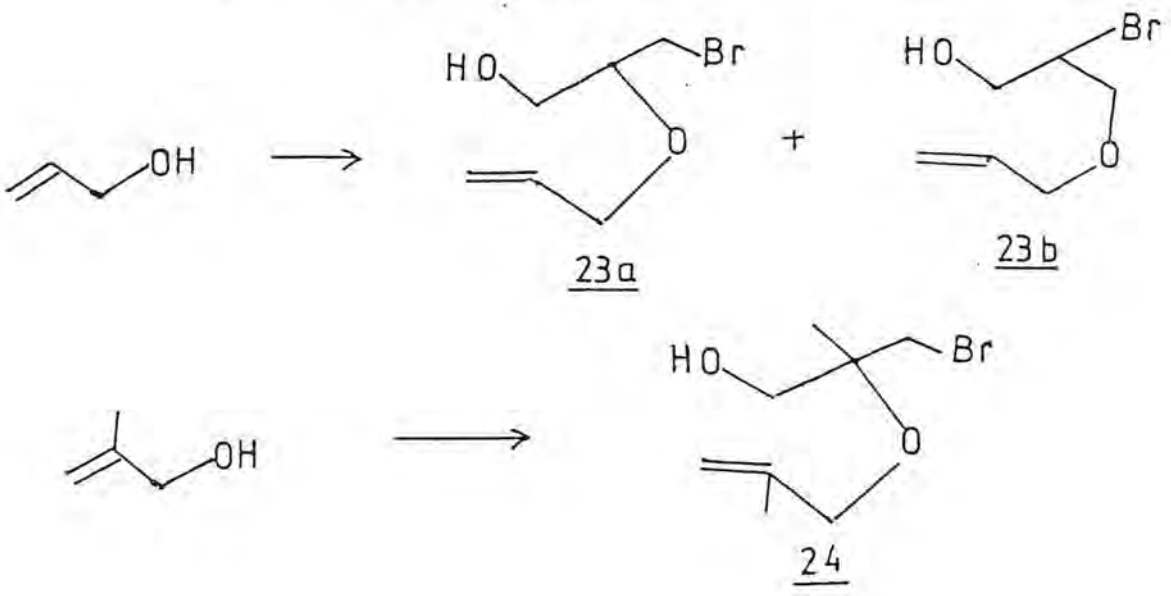
The dimerisation of the homoallylic alcohol 10 to 16 in NBS was particularly interesting, as was the subsequent conversion to the olefinic ether 18, both of which occured in good yields.

Compound 18 could be of synthetic value through transformation of the C-C double bond.

To test the generality of this unusual dimerization we reacted allyl and methallyl alcohols in the same way (scheme 3.7). The allyl alcohol reacted at a rate comparable to that of 10 to give the expected regioisomers 23a and 23b in a ratio of 3:2 in 95% yield. Methallyl alcohol also dimerized to give 24 in 90% yield.

However, the reaction was quite violent when the alcohol was added to NBS at -10~0°C, even in the absence of the catalyst, giving a mixture of uncharacterized products. The careful addition of NBS to the alcohol at the same temperature resulted in a clean controllable reaction.

Scheme 3.7.



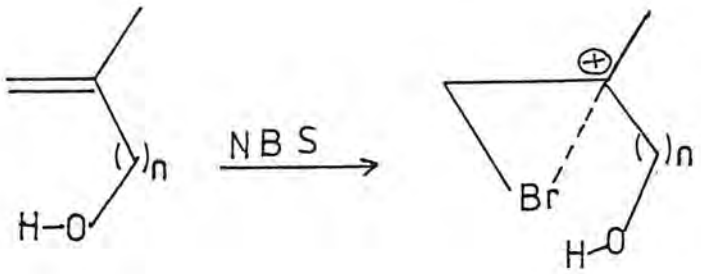
Hence, the NBS-mediated dimerization of alkenols seems to be a general reaction and a possible application of this reaction is being investigated.

We attempted to react the ester 8a and the alcohol 10 with N-chlorosuccinamide (NCS) under acidic catalysis, but no significant reaction occured either under similar conditions to those used with NBS or at room temperature.

There is ample evidence in the literature[17-20] that NBS under the reaction conditions used in the present work reacts with double bonds forming bromomium ions. This electrophilic addition is rate determining and the rate depends on the availability of the π-electrons. In the case of bromonium ions derived from unsymmetrically substituted double bonds the bromine atom will be less bonded to that carbon of the three-membered ring that can stabilize a positive charge e.g. by electron donating substituents. A nucleophile, like an alcohol, will attack preferentially the electron deficient carbon of such a bromonium ion.

According to this mechanism the α-bromoester 14 whould be formed preferentially from 8a as observed. It is also expected that from a mixture of the ester 8a and 10, the latter reacts exclusively with NBS forming compound 16 selectively. The same conclusion applies to the reactions of NBS with the allylic alcohols both with regard to regiochemistry and reactions rates, (scheme 3.8). The seemingly faster rate observed for methallyl alcohol compared with that of 10 is possibly due to an additional anchimeric assistance by the allylic hydroxyl group.

Scheme 3.8.



10: R=Me, n=2

Allyl alcohol: R=H, n=1

Methallyl alcohol: R=Me, n=1

25

$CH_2=C(R)(CH_2)_nOH$

16, 23, 24.

EXPERIMENTAL:

The general methods mentioned in chapter two apply to this chapter as well.

3-Methyl-3-butenoyl chloride (6)[1] was prepared in 88% yield from 3-methyl-3-butenoic acid [21] (prepared by carbonylation of methallylmagnesium chloride in 38% yield), and thionyl chloride.

Methyl 3-methyl-2-butenoate (8a)[2] was obtained in 83% yield by esterification of the 3-methyl-2-butenoic acid[21] (prepared by acid catalysed isomerisation of 3-methyl-3-butenoic acid[21]) according to the lit.[22]

sec.Butyl 3-methyl-2-butenoate (8b) was prepared in 70% yield by esterification of the parent acid according to the lit.[23], b.p. 78-80°C/20 mmHg (lit.[24] b.p. 68-70°C/13 mmHg).

tert-Butyl 3-methyl-2-butenoate (8c) was obtained in 60% yield b.p. 74°C/20mmHg (lit.[25] b.p. 68-74°C/23 mmHg) by esterification of the parent acid via the acid chloride in the usual way.

Methyl 3-hydroxy-3-methylbutanoate (4). The procedure of Brown and Georghegen[3] was adopted for this preparation. To a solution of mercuric acetate (3.19 g, 10 mmole) in water (10 ml) and THF (10 ml), 6a (1.14 g, 10 mmole) was added. The resulting yellow solution became colourless on stirring at room temperature for 10 min. Stirring was continued for further 30 min. and a solution of (3.0M) NaOH (10 ml) was added, followed by addition of a

solution of (0.5 M) $NaBH_4$ in (3.0M) NaOH (10 ml). The mercury formed was allowed to settle and the liquid phases were decanted, and separated. The aq. phase was saturated with NaCl, extracted with ether and the combined extracts were dried ($MgSO_4$). The solvents were removed at atmospheric pressure to leave a residue (1.0 g) consisting of two compounds, 80 and 20% respectively on GC, which were isolated by prep. GC. The minor component was 4: IR(film): 3443(s), and 1733(s) cm^{-1}. ^1H NMR (CCl_4): δ 1.35 (s, 6H), 2.80 (s, 2H), 3.60 (s, 3H), 3.80 (s, 1H, D_2O exch.).

The major component was starting material.

3-Methyl-4-penten-2-ol (9) was obtained in 68% yield from allylmagnesium chloride and acetone in dry ether in the usual way, b.p. 48-50°C/33 mmHg (lit.[26] b.p. 46-46.5°C/30 mmHg).

2-Methyl-4,5-oxidopentan-2-ol (9). To a stirred solution of 9 (10,0 g, 0.10 mole) in dichloromethane (200 ml), cooled in an ice-bath, m-chloroperbenzoic acid (10 mmole) was added in small portions. The reaction mixture was stirred at 10-15°C for 24 h and filtered. The precipitate was washed with dichloromethane and the combined filtrates were successively washed with saturated solutions of aq. $NaHSO_3$, $NaHCO_3$, NaCl and then dried (K_2CO_3). The solvent was removed under reduced pressure and destillation of the residue furnished 5 (8.40 g, 72%), b.p. 72-5°C/10 mmHg. IR (film): 3410(s), 1378(s), 1135(s) and 869(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (s, 6H), 1.70 (m, 2H), 2.30-3.27 (m, 4H).

3-Methyl-3-butenol (10) was prepared on a 0,1 mol scale in 80% yield by LAH reduction of 3-methyl-3-butenoic acid according to the literature.[27] Reduction of 3-methyl-3-butenoyl chloride

(6) (0.01 mole) using LAH or inverse $LAH/AlCl_3$ according to the procedure of Nyström[28] gave 10 in comparable yields of 78% and 75% respectively. For a large preparation of 10 (40-100 g) a slightly modified lit.[31] procedure of formylation of methallylmagnesium chloride was adopted. Methallylmagnesium chloride was prepared in the usual way from magnesium (46.0 g) and methallyl chloride (138 g, 1.50 mole) in ether (2.5 l). Paraformaldehyde (40 g, 1.33 mole, dried over P_2O_5) was added in small portions with vigorous stirring at 10°C and stirred for an additional 10-12 h at the same temperature. A sufficient amount of saturated aq. NH_4Cl was added to hydrolyse the magnesium complex and the organic phase was decanted. The magnesium salts were washed with several portions of dry ether. The organic decant was combined and the solvent removed via a Vigreux column at atmospheric pressure. The residue consisting mainly the alcohol and 2,5-dimethyl-1,5-hexadiene were fractionated on a Spalt-rohr colums to give 10 (40.0 g, 46%), b.p. 70-72°C/83 mmHg, 132-133°C/760 mmHg, (lit.[29], b.p. 130°C/760 mmHg).

3-Methyl-3-butenyl 3-methyl-2-butenoate (13)

To a stirred suspension of NaH (10 mmole) in dry THF (10 ml) a solution of 10 (0.86 g, 10 mmole) in THF (5 ml) was slowly added at room temperature under nitrogen. The reaction mixture was stirred under reflux for approximately 2 h followed by addition of 8b (1.56 g, 10 mmole). The reaction was further refluxed for 3 h until the reaction was complete (GC). After cooling to room temperature water (1 ml) was added followed by a saturated aq. NaCl solution and the layers were separated. The organic layer was washed successively with 2% aq. H_2SO_4, water and then dried ($MgSO_4$). The solvent was removed under reduced pressure and destillation gave 13 (1.18 g, 70%), b.p. 66-7°C/9 mmHg. IR (film):

1718 (s), 1652 (s) and 1145 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.77 (s, 3H), 1.88 (s, 3H), 2.13 (s, 3H), 2.30 (t, J 7 Hz, 2H), 4.15 (t, J 7 Hz, 2H), 4.73 (broad s, 2H), 5.58 (s, 1H). MS (CI): m/z 169 (M^++1).

The ester 8c (5.8 mmole) reacted similarly to give crude 14 (0.63 g, 65%). A prep. GC sample was identical in all respect with the sample prepared above.

Methyl 2-bromo-3-methoxy-3-methylbutanoate (14) was prepared by the procedure of Heasley et al.[2] in 83% yield from the ester 8a (4.30 mmole). An analytical sample was obtained by preparative GC. IR (film): 1748 (s) and 1145 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.43 (s, 6H), 3.38 (s, 3H), 3.80 (s, 3H), 4.37 (s, 1H). MS (CI): m/z 224/226 (M^+).

3-Bromomethyl-3,7-dimethyl-4-oxa-7-octen-1-ol (16). Freshly recrystallized N-Bromosuccinamide (10.56 g, 60 mmole) dried over P_2O_5, was introduced into a reaction flask, wrapped with aluminium foil and kept under nitrogen. The flask was cooled in an ice-salt-water bath and 10 (45.0 g, 552 mmole) was added slowly while the temperature was kept below 0°C. After stirring for further 10 min. conc. H_2SO_4 (0.10 ml) was added dropwise and the reaction was monitored by KI-starch test. The reaction was complete after stirring at 0∿5°C for 4 h. A sufficient amount of solid K_2CO_3 was added to neutralize the acid used and excess 10 was recovered at 40°C/0,03 mmHg. The residue was triturated with ether and filtered. The filtrate was concentrated under reduced pressure leaving 17 (13.55 g, 90%) as an oil, which could be destilled at 80-2°C/0,028 mmHg only with substantial decomposition. The

crude product was, however, sufficiently pure for spectroscopic characterization. IR(film): 3412 (s), 1647 (m), and 1087 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.40 (s, 3H), 1.77 (s, 3H), 1.93 (t, J 6Hz, 2H), 2.30 (t, J 6Hz, 2H), 2.90 (s, 1H, D_2O exch.), 3.48 (s, 2H), 3.57 (t, J 6Hz, 2H), 3.80 (t, J 6Hz, 2H), 4.80 (broad s, 2H). MS (CI): m/z 250/252 (M^+).

3-Methyl-3-(3-methyl-3-butenoxy)oxalane (18). a) To a solution of 16 (502 mg, 2 mmole) in THF (2 ml) containing Bu^tOH (300 mg, 4 mmole) freshly cut lithium metal (40 mg, 6 mmole) was added at once under nitrogen. The reaction mixture was heated under reflux causing the metal to dissolve and gas evolution to occur. The reaction was complete after 30 min. (GC). The reaction mixture was cooled to room temperature and quenched by addition of a few drops of water, followed by brine (2 ml). The layers were separated and the organic layer filtered through a cotton-plug and dried ($MgSO_4$). The solvents were evaporated under reduced pressure to give crude 18 (300 mg, 88%). An analytical sample was obtained by preparative GC. IR (film): 3074 (m), 1646 (m), 1148 (s) and 1068 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (s, 3H), 1.70 (m, 4H), 1.90-2.43 (m, 3H), 3.33-3.63 (m, 3H), 3.73-4.01 (m, 3H), 4.77 (broad s, 2H). MS: m/z 170 (M^+).

b)
To a stirred and cooled (ice) solution of 16 (502 mg, 2 mmole) in freshly destilled THF (2 ml) a 1.0M solution of lithium triethylborohydride in hexane (5 ml, 5 mmole) was slowly added under nitrogen. The reaction was stirred at 25°C and was monitored by GC. After stirring for 12 h it was complete. The reaction mixture was diluted with water (1 ml) and the phases separated. Evaporation of solvents left crude 18 (280 mg, 82%),

identical with product obtained above.

c). Reduction of 16 (502mg, 10 mmole) with $Na(CN)BH_3$ (10 mmole) in HMPA (5 ml) gave after stirring at 60°C for 4 h and usual work-up gave 18 (250 mg, 73%), identical with an authentic sample.

a) A solution of 16 (502 mg, 2 mmole) in cyclohexane (2 ml) was added slowly to a refluxing solution of Bu_3SnH (0.58 g, 2.5 mmole) in cyclohexane (5 ml) containing catalytic amount of α,α'-azo-isobutyronitrile. After 20 min. the reaction was complete (GC). Few drops of chloroform were added and the solvents removed under reduced pressure. The residue was carefully dropped on a molecular still at 40°C/0.02 mmHg to give 18 (204 mg, 60%), identical with a previously prepared sample.

3-Bromomethyl-3,7-dimethyl-4-oxa-7-octen-1-ol trimethyl silyl ether (19). A sample of crude 16 (46.0 g, 0.184 mol) was dissolved in dry THF (100 ml) and triethylamine (70 ml) was added and the mixture cooled to 0°C. Chlorotrimethyl silane (24.0 g, 0.22 mol) was slowly added at 0°C and the resulting suspension stirred at 25°C for 4 h. The reaction mixture was diluted with dry ether and the ammonium salt was filtered and washed with several portions of dry ether. The combined filtrates were concentrated under reduced pressure and destillation gave 19 (45.7 g, 77%), b.p. 70-2°C/0.025 mmHg. IR(film): 3072 (m), 1649 (m), 1129 (s) and 1089 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (s, 3H), 1.82 (s, 3H), 1.95 (t, J 7Hz, 2H), 2.30 (t, J 7Hz, 2H), 3.50 (s, 2H), 3.50 (t, J 7 Hz, 2H), 3.77 (t, J 7 Hz, 2H), 4.80 (broad s, 2H). MS: m/z 236/238 ($M^+-C_5H_9O$).

3,3,7-Trimethyl-4-oxa-7-octen-1-ol trimethyl silyl ether (20). Reduction of 16 (20.0 g, 61.92 mmole) with Bu_3SnH (28.0 g, 96,23 mmole) at 70°C, according to the procedure already described[8] furnished 20 (12.70 g, 84%), b.p. 40-42°C/0,025 mmHg. IR (film): 3074 (m), 1649 (m), 1167 (s) and 1083 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.07 (s, 6H), 1.63 (s, 3H), 1.63 (t, J 7Hz, 2H), 2.10 (t, J 7 Hz, 2H), 3.30 (t, J 7 Hz, 2H), 3.57 (t, J 7 Hz, 2H), 4.62 (s, 2H). MS: m/z 159 ($M^+-C_5H_9O$, base peak).

3,3,7-Trimethyl-4-oxa-7-octenoic acid (21). A solution of 20 (30.0 g, 0.10 mol) in acetone (300 ml) was cooled to -20°C. Jones reagent (75 ml) was slowly added, causing the temperature of the reaction mixture to rise gradually to 25°C. The reaction mixture was stirred for a further 2 h, when GC showed the presence of one product. After usual work-up 21 (13.0 g, 87%) was obtained by distillation on a molecular still at 78°C/0.02 mmHg. IR (film): 3400-2500 (broad), 1714 (s) and 1647 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.33 (s, 6H), 1.77 (s, 3H), 2.30 (t, J 7 Hz, 2H), 2.57 (s, 2H), 3.60 (t, J 7Hz, 2H), 4,80 (s, 2H), 10.70 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.29 (CH_3), 24.88 (CH_3), 38.27 (CH_2), 46.59 (CH_2), 60.10 (CH_2), 74.27 (C), 112.34 (CH_2=), 142.16 (-C=), 173.48 (CO_2H). MS: m/z 169 (M^+-OH).

3,3,7-Trimethyl-4-oxo-octenoyl chloride (12). To a stirred solution of 22 (1.0 g, 5.40 mmole) in benzene (30 ml) and pyridine (3.25 ml) kept at 0°C under nitrogen, oxalyl chloride (2.30 ml, 26.88 mmole) was added dropwise causing a white precipitate to form with gas evolution. The reaction mixture was allowed to warm to room temperature and heated to 50°C. The reaction

was monitored by ^{1}H NMR by observing the change of the chemical shift of the methylene protons adjacent to the carbonyl group, which appear at lower field for the product (δ 3.10) than for the starting material (δ 2.57). The reaction was complete after 5 h. The reaction mixture was cooled to room temperature and filtered. The solid was washed with several portions of dry ether. The solvents were removed under reduced pressure to leave crude 12 (0.88 g, 80%) as dark coloured liquid. IR ($CDCl_3$): 1798 (s), 1744 (m) and 1648 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.77 (s, 3H), 2.20 (t, J 7 Hz, 2H), 3.10 (s, 2H), 3.47 (s, 2H), 4.70 (s, 2H). Attempted destillation on a molecular still at 56°C/0.02 mmHg led to decomposition. According to GC analysis the destillate consisted of mainly five components. The two major ones, present in 22 and 46% respectively, were isolated by prep. GC. The former was proven to be identical with an authentic sample of 13 and the latter was characterized as 3-methyl-3-butenyl 3,3,7-trimethyl-4-oxa-7-octenoate (22). IR(film): 3075 (m), 1738 (s), and 1648 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 6H), 1.77 (s, 6H), 2.23 (m, 4H), 2.50 (s, 2H), 3.50 (t, J 7 Hz, 2H), 4.22 (t, J 7 Hz, 2H), 4.77 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 22.48, 23.00, 25.86 (4 X CH_3), 36.71, 38.59, 45.41, 60.55, 62.57 (5 X CH_2), 73.74 (C), 111.7, 112.21 (2 X CH_2=), 141.71, 143.33 (2 X -$\dot{C}$=), 171.01 (C=O). MS: m/z 255 (M^+).

2-Bromomethyl-3-oxa-5-hexen-ol (23a) and 2-bromo-4-oxa-6-hepten-1-ol (23b). NBS (3.8 g, 21.5 mmole) was introduced into a dry reaction flask as previously described, and allyl alcohol (14.52 g, 250 mmole) was added at 0°C, followed by addition of conc. H_2SO_4 (2 µl). The reaction mixture was stirred at

0-5°C for 4 h, solid K_2CO_3 was added and excess allyl alcohol recovered at 50°C/0.07 mmHg. The residue was diluted with ether and filtered. Evaporation of the solvent under reduced pressure left 3.98 g (95%) of 23a and 23b in a ratio of 3:2 as determined by GC. An analytical sample was obtained by preparative GC. IR (film): 2408 (s), 1645 (m) and 1073 (s) cm^{-1}. ^1H NMR (CCl_4): δ 2.45 (s, 2H), 3.33-4.30 (complex abs. 14H), 5.00-6.14 (complex abs., 6H). MS: m/z 194/196 (M^+).

2-Bromomethyl-2,5-dimethyl-3-oxa-5-hexen-1-ol (24). β-Methallyl alcohol (18.05 g, 250 mmol) was cooled in an ice-salt bath and NBS (3.80 g, 21.5 mmol) was added in small portions. The reaction mixture was stirred at 0°C for 2 h and excess methallyl alcohol was removed and the product isolated in the usual way to give 24 (4.32 g, 90%) which was molecularly destilled at 64°C/0.05 mmHg. IR (film): 3412 (s), 1654 (m) and 1047 (s) cm^{-1}. ^1H NMR (CCl_4): δ 1.25 (s, 3H), 1.70 (s, 3H), 2.63 (s, 1H, D_2O exch.), 3.43 (s, 2H), 3.53 (s, 2H), 3.83 (s, 2H), 4.87 (m, 2H). MS (CI): m/z: 223(225 (M^++1).

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