SYNTHESIS OF THE BOLL WEEVIL PHEROMONE AND SOME PHOTOCHEMICAL REACTIONS

a thesis presented by

PETER DUNCAN HOBBS

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Perkin Laboratory
Chemistry Department
Imperial College
London.

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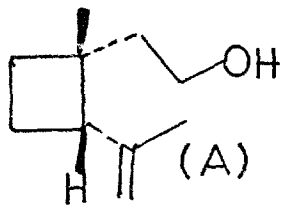
ABSTRACT

Pheromones are briefly defined and described in the introduction. Three reviews are presented. Part I outlines the isolation of the boll-weevil pheromone and previous approaches to the synthesis of the constituents. Part II describes the synthesis of the known naturally-occurring cyclobutanes and briefly presents the currently accepted biosynthetic schemes. Part III reviews the photochemical reactions of non-conjugated ketones in solution, with the emphasis on recent investigations of the structural factors affecting the nature of the products.

The discussion is divided into two parts. Part I describes the synthesis of (+)-grandisol (A), a component of the boll-weevil pheromone, from (-)-β-pinene, and discusses the photolysis of the cis- and trans-verbanones, (B) and (C) respectively. Part II summarises a brief investigation of the photolysis of 5-aryloxy-1-phenyl-1H-tetrazoles (D) in benzene, including the observation of a photo-Fries reaction of 2-phenoxybenzimidazole, (E).



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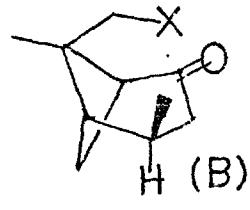

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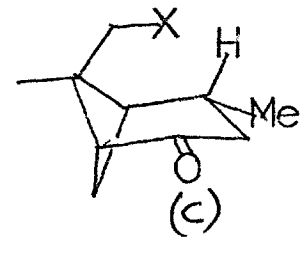

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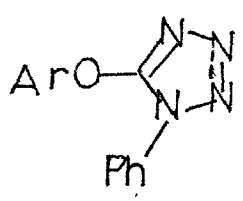

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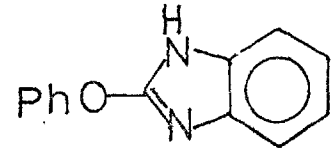

(E)

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I would like to express my sincere thanks to my supervisor, Dr. P.D. Magnus, for his guidance and encouragement.

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Peter D. Hobbs
Perkin Laboratory.

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CONTENTS

	page
Introduction	1
Review	
Part I. The boll-weevil pheromone	4
References to Part I	10
Part II. Naturally-occurring cyclobutanes	12
References to Part II	49
Part III. The photochemistry of non-conjugated ketones in solution	57
References to Part III	99
Discussion	
Part I. Synthesis of (+)-grandisol	107
Part II. Photolysis of 5-aryloxy--1-phenyl-1H-tetrazoles and photo-Fries rearrangement of 2-phenoxybenzimidazole	147
Experimental to Part I	151
Experimental to Part II	212
References to Parts I and II	219

INTRODUCTION

Two classes of insect attractants may be distinguished[1]. Host attractants may be defined as volatile constituents of plant or animal hosts which are utilised by insects in searching for food and oviposition sites. The oviposition attractant of a mature insect is generally the food attractant to the larvae. Host attractants are frequently the constituents of the characteristic odours of plants or vegetables, and a complex mixture of these constituents may be necessary to attract a particular species.

Pheromones[2] are substances which are secreted to the outside by an animal, especially an insect, and received by a second individual of the same species in which they release a specific reaction, for example a definite behaviour or developmental process. 'Releasers' elicit a more or less immediate behavioural response on reception. 'Primers' cause long-term physiological changes, and will not be further considered.

Very many pheromones are known but few have been characterised[3]. Isolation of sufficient attractant for structural determination generally requires chromatographic processing of extracts from 10^5 - 10^7 individuals.

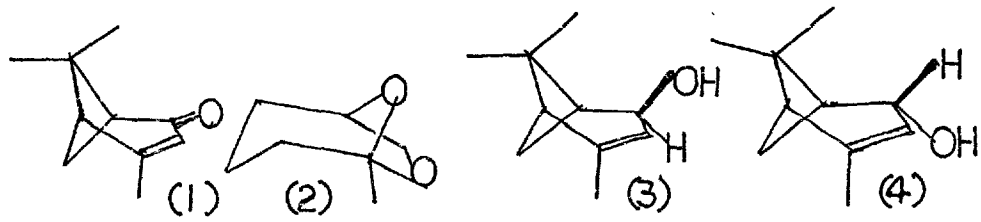
Most known pheromones are classified as sex attractants, population (aggregation) attractants, and trail-following or alarm pheromones.[4]

Sex attractants stimulate attraction over a distance. They may be vital for the survival of low-density populations of non-social insects. Communication distances of 100 metres are well established[5] by field studies. The lepidoptera (butterflies and moths) also employ short-range attractants in courting. Butenandt and Roeloffs have identified a number of these attractants, which are generally esters (particularly acetates) of unsaturated C_{12}-C_{14} aliphatic alcohols, although hydrocarbons, epoxides and alcohols also occur. As adults of these species often do not feed, lipid catabolism is the probable source of compounds of this type.

Population attractants are not always satisfactorily distinguished from sex attractants.[6] Generally, one sex is attracted by the volatile constituents of a host plant, the pioneer insects secrete pheromones (commonly a synergistic mixture) usually after feeding, which attract large numbers of both sexes, predominantly but not exclusively the opposite sex.

Combinations of pheromonal secretions and volatile terpenoids of host plants are common. Many species use the same compounds. Seasonal or geographic distributions may be sufficient to prevent cross-attraction, but synergists are also employed.[6] Population attractants are employed by beetles (Coleoptera) particularly the Scolytid genera, which are major forestry pests. Terpenoid constituents are normal in the attractants of Ips and Dendroctonus species.[4] D. brevicomis (Western pine beetle) females employ myrcin

from tree resin as a synergist although the pheromone, exo-brevicomin, is probably a product of lipid catabolism. D. frontalis males release verbenone (1), probably a metabolite of ingested α-pinene, as a male inhibitor to prevent cross-attraction, as both D. frontalis females and D. brevicomis males employ the same attractant, frontalin (2). Ips paraconfusus Lanier employs a mixture of terpene alcohols, including cis-verbenol (3), whereas Ips calligraphus employs a metabolite, trans-verbenol (4).



Sex attractant pheromones are currently of great interest as they may provide a highly specific method of controlling insect populations, particularly by the use of traps baited with pheromone. Most pheromones are virtually non-toxic to mammals, and are effective at extremely low concentrations in air.

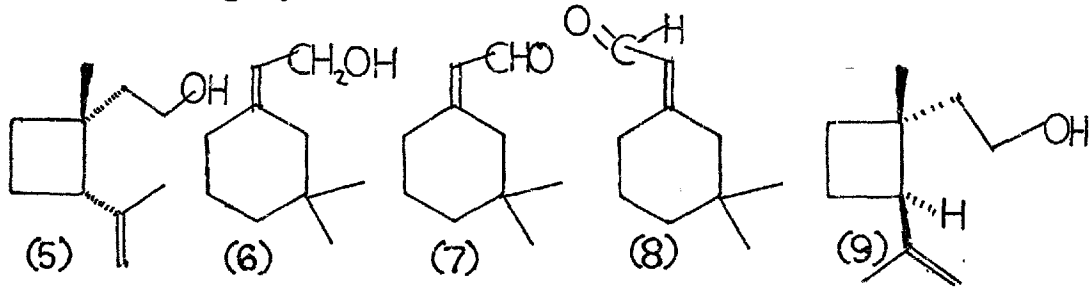
PART I: THE BOLL WEEVIL PHEROMONE

The boll weevil, Anthonomus grandis Boheman, is the principal insect pest of the north american cotton crop. Male weevils are attracted by the volatile terpenoid constituents of the cotton bud. After feeding, a pheromone is released which attracts female weevils for mating. The pheromone is generally classed as a sex attractant rather than an aggregation pheromone.

Gueldner, Thompson and co-workers succeeded in identifying many of the volatile constituents of the cotton bud[7] (Gossypium hirsutum L., var. Deltapine Smoothleaf). Over fifty components were present. The host attractant was apparently a complex mixture as many components elicited some positive response from male weevils.[8] A mixture of (+)-α-pinene (10ppb), (+)-limonene (3ppb), (-)β-caryophyllene (100ppb), (+)-β-bisabolol (100ppb) and caryophyllene oxide (from (-)-β-caryophyllene) proved to be rather more attractive than cotton buds, but male weevils were much more attractive to the female than the feeding stimulant mixture; as the intention was to develop a lure to attract weevils from the cotton crop to baited traps, an investigation of the sex attractant was undertaken.[9]

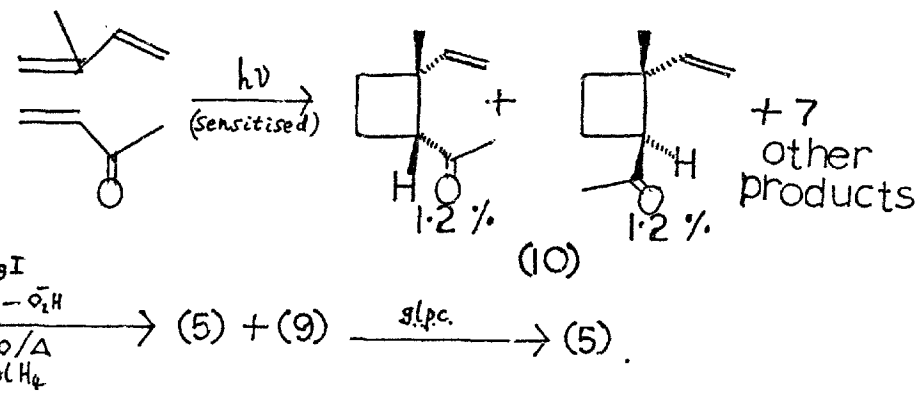
The pheromone was isolated[10] from extracts of 4.5 million weevils (of both sexes) and 54.7 kg of weevil faeces, normally a relatively concentrated source of pheromones, by steam distillation, extraction with dichloromethane, and successive column chromatography on silica and silver nitrate

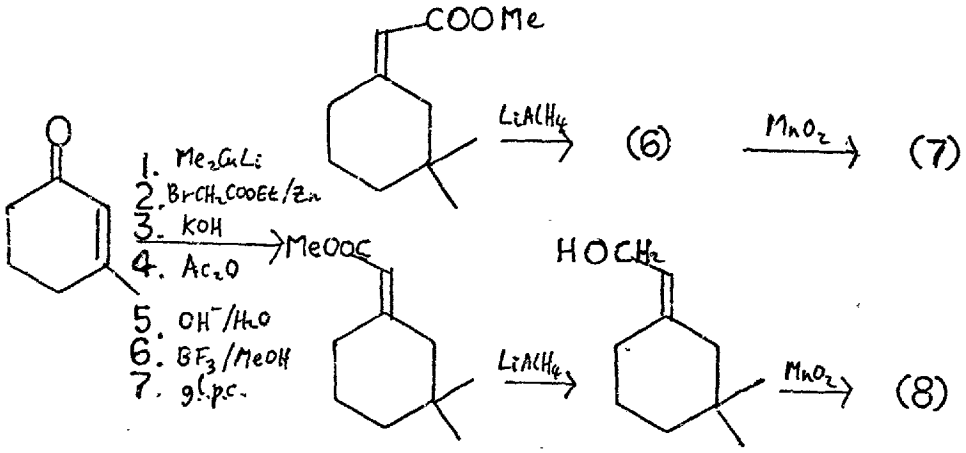
impregnated silica. Various combinations of fractions from the latter column were attractive to females, but individual fractions were not. Several synergistic components were therefore present. Separation was achieved by g.l.c. The relative concentrations of (5)-(8) were estimated as 0.76, 0.57, 0.06 and 0.06 ppm in faecal material, and at about one-tenth of these levels in weevils. Structures were assigned from spectroscopic data and by micro-ozonolysis. Synthesis of all four components (scheme 1) confirmed the assignments, and a mixture of the components in the correct ratios was highly attractive to female weevils.



The original synthesis[10] of (5) gave a low yield of cis and trans isomers. The cis isomer was spectrally identical with the natural compound. The trans compound (9) was found to be identical with a product, assigned the trans configuration, synthesised by Corey,[13] and also with the natural trans isomer from Artemisia fragrans.[14]

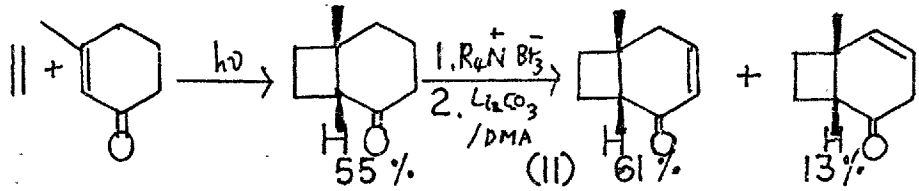
Scheme I

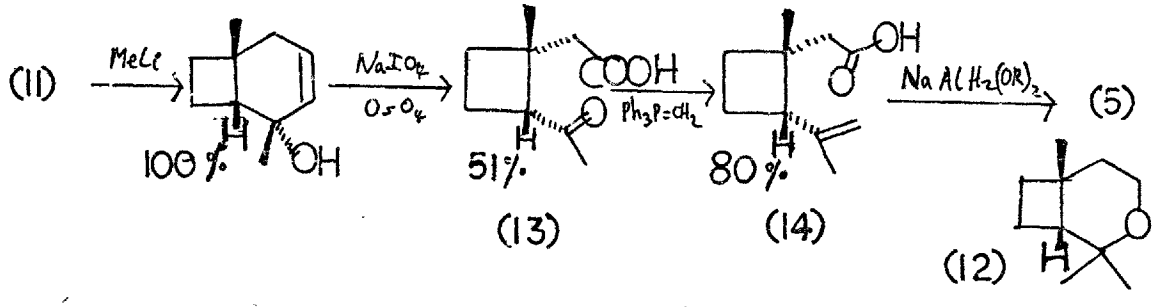




Two stereoselective syntheses of racemic grandisol (5) by (2 + 2) photocycloadditions were subsequently reported (schemes II and III).

Scheme II

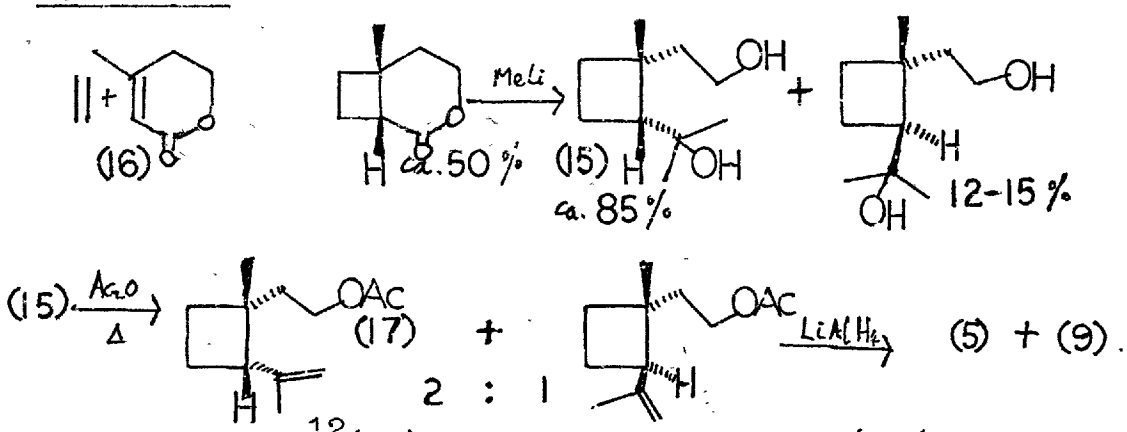




(13) and (14) contained 1% and 3% trans isomer, as determined by g.l.c. on the methyl esters.[11] The cis configuration of (13) was demonstrated by lactonisation of the hydroxy-acid obtained on reduction. Treatment of grandisol (5) with mercuric acetate followed by reduction yielded a cyclic ether (12) which confirmed the cis configuration

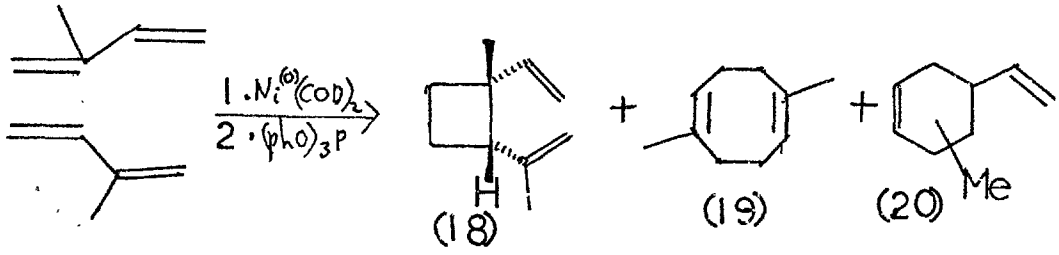
of the final product.

Scheme III



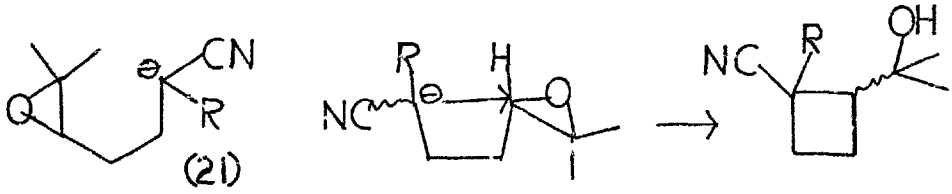
The lactone[12](16) was readily prepared (80% overall yield) by dehydration of mevalonolactone, obtained by Cornforth's method from 4-acetoxy-2-butanone. Alternative methods of elimination of water from the tertiary alcohol (15) (neutral and acidic alumina in refluxing toluene, pyridine-phosphorus oxychloride) gave largely the cyclic ether (12). Preliminary esterification of the primary alcohol followed by treatment with phosphorus oxychloride-pyridine, or dimethyl sulphoxide at 160°, gave 1:1 ratios of the cis and trans acetates (17). The desired isomer (15) was obtained by crystallisation of the cis-trans mixture from cyclohexane. A patent for this synthesis has been issued to Zoecon Corpn., Palo Alto, California.

A non-photochemical approach[15] yielded grandisol in two steps. A zero-valent nickel complex of 1,5-cyclo-octa-diene catalysed dimerisation of isoprene to give the cis diene (18) in 12-15% yield, based on consumed isoprene, together with (19) and (20).



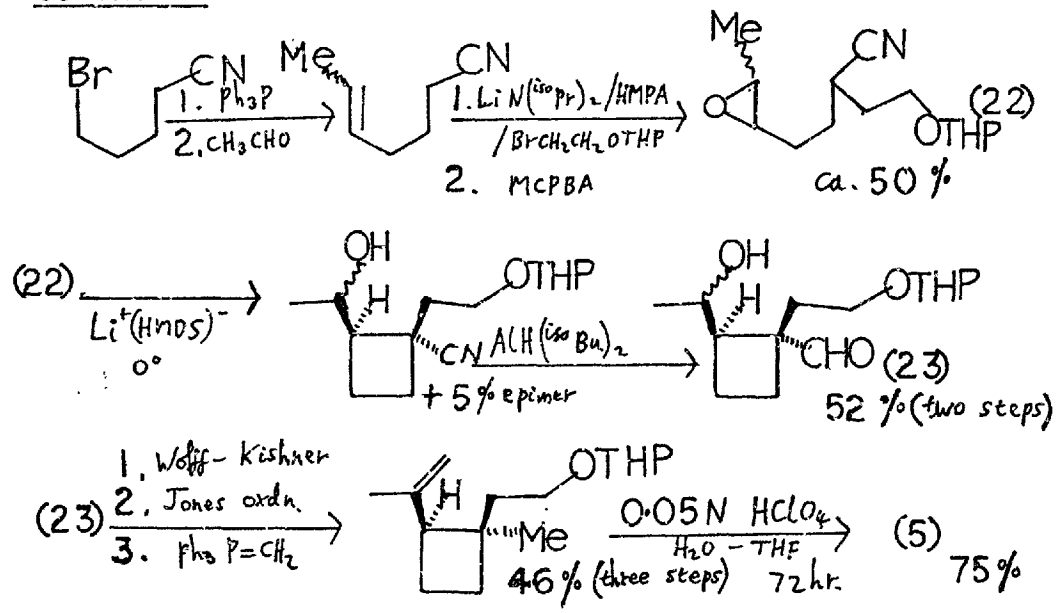
(18), uncontaminated by trans isomer, was isolated by fractional distillation at low temperature and reduced pressure as it underwent a Cope rearrangement to (19) above room temperature. Treatment of (18) with one equivalent of bis (3-methyl-2-butyl) borane followed by alkaline hydrogen peroxide gave predominantly grandisol, which was isolated in 52% yield by g.l.c.

Stork[16] has developed a general stereospecific synthesis of cyclobutanes, which has very recently been applied to the synthesis of grandisol (scheme IV). Cyclisation of a cyanoepoxide by treatment with base proceeds via colinear displacement. Thus (21) gives a cyclobutane and not a cyclopentane. The unsymmetrical substitution of the oxiran additionally favours this route, but is not critical.

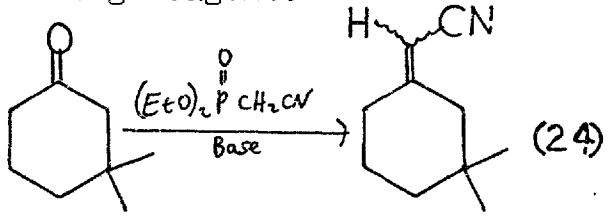


The reaction is virtually stereospecific. The metal salt of the allenic ion is presumably more bulky than an n-alkyl group.

Scheme IV



An alternative approach[17] to constituents (6)-(8) yielded only inseparable mixtures of cis and trans isomers of (24) by reaction of 3,3-dimethylcyclohexanone with a modified Wittig reagent.



The synthetic mixture of pheromone constituents ('Grandlure') is available commercially, but field trapping experiments have been only moderately successful. An unknown synergist, released by the male, may be involved.[9]

Only male weevils which have fed on cotton are very attractive to the females. The biosynthesis of the pheromone components from terpenoids in cotton will be discussed.

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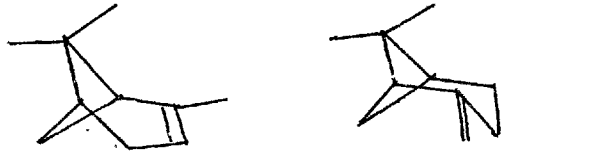
PART II: NATURALLY OCCURRING CYCLOBUTANES

Almost all known natural compounds possessing the cyclobutane function are mono- or sesqui-terpenoid. A few exceptions will be noted.

The biogenesis of cyclobutanes, and approaches to the synthesis of this moiety in naturally-occurring compounds, will be briefly reviewed. Total synthesis was an integral part of the determination of the structures and stereochemistry of several sesquiterpene members of this group. The more recently discovered compounds have mostly been subjected to X-ray crystallography and high resolution n.m.r. Structural evidence will be mentioned only for recently controversial examples.

(1) Monoterpenes. With a few exceptions, monoterpene cyclobutanes are pinane derivatives (25). Approximately twenty compounds of this structural type occur in either or both absolute configurations.[1] Compounds of antipodal configuration occasionally co-occur, particularly (+)-α- and (-)-β-pinene.

(25)



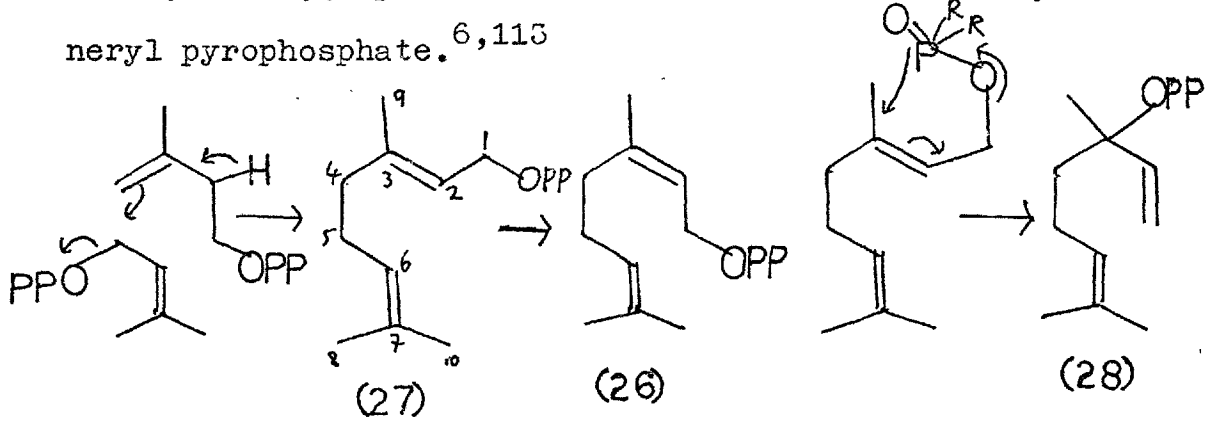
(+)-α-pinene (-)-β-pinene

Pinane derivatives are ubiquitous in plant essential oils; wood and leaf oils of the Coniferae are particularly important. Terpene alcohols are probably present as glycosides, esters and phosphate esters as well as uncombined. Phosphates are very readily hydrolysed by phosphatases

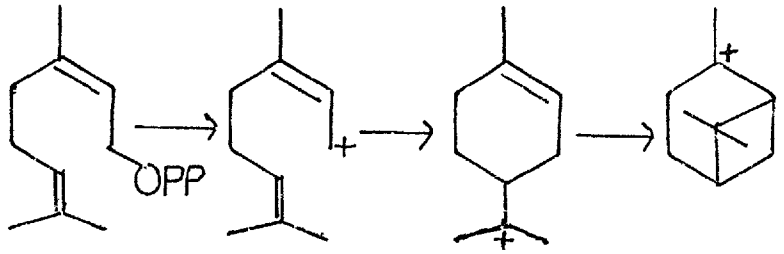
during extraction of plant material. Most terpenes have no obvious metabolic role. Inhibition of competing plants and bacteria is regarded as an accidental function. Biosynthesis of mono- and sesquiterpenes is generally rapid, and it has been suggested that they are by-products of an evolving network from which routes to essential plant hormones and carotenoids have been selected.

Animals do not generally accumulate monoterpenes. The pheromones and defensive substances of insects and arthropods are exceptions. In these cases, monoterpenes may be biosynthesised by the same routes as in plants[2] (acetate and mevalonate incorporation has been observed)[3] or alternatively may be degradation products of terpenes from ingested plant material. The minute quantities available make biosynthetic studies extremely difficult.

The biogenesis of isopentenyl pyrophosphate and dimethylallyl pyrophosphate from R(+)-mevalonic acid is well documented.[1] Neryl pyrophosphate (26) is generally accepted as the precursor of cyclic monoterpenes,[4] although geranyl pyrophosphate (27) is also a source of these compounds via conversion to a linalyl derivative (28).[5,6,7] However, even in species for which linalyl pyrophosphate cyclisation is important, α-pinene was found to be derived only from neryl pyrophosphate.[6,113]

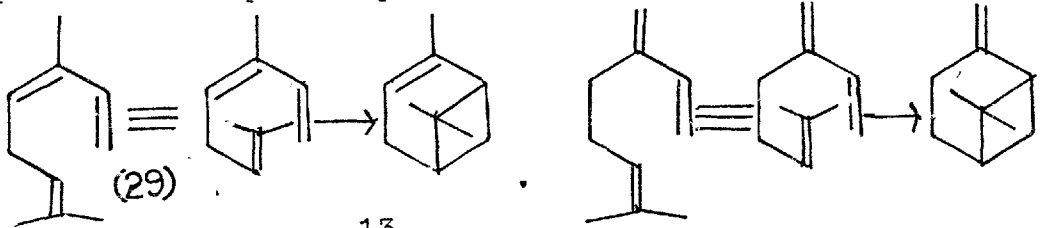


Ruzicka's biogenetic scheme for the monoterpenes is still largely accepted.[8,9] Cyclisation to the pinane skeleton is envisaged as a stepwise addition, the direction of internal addition being governed by Markownikov reaction:



The carbonium ion representation is a formalism; the true species involved may be alcohols, phosphate esters, glycosides, epoxides or sulphonium[10] salts. In vitro model cyclisations have been reported but the conditions involved probably bear little relation to the natural systems;[11] protein-bonded species may be involved. Different enzymes would explain the separate occurrence of enantiomeric pinenes. Epoxides and sulphonium salts are known to be involved in cyclisations of higher terpenes, and these processes are probably enzyme-controlled. Biogenetically-modelled cyclisations have apparently not yielded pinanes.

Alternatives to Ruzicka's scheme have little support in the case of pinanes. Radical-induced cyclisation of cis-ocimene or myrcene was proposed and has photochemical precedent,[12] but would require a protein-bound biradical to explain stereospecifity of the reaction:



(29)

Direct bicyclisation,[13] or direct condensation of iso-pentenyl and dimethylallyl pyrophosphates have been suggested

but with no supporting evidence.

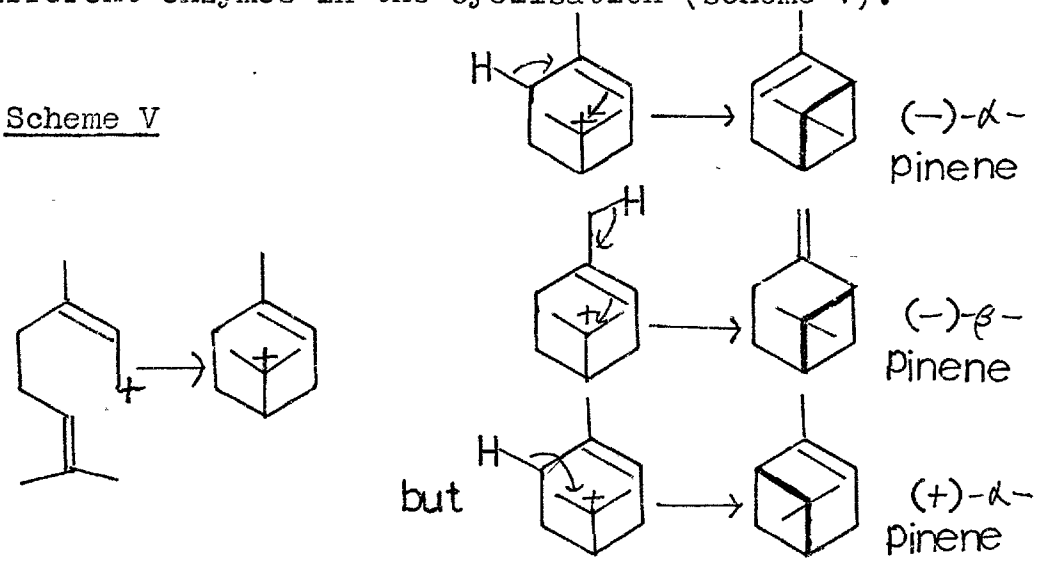
Tracer studies of monoterpene biosynthesis are extremely difficult. Incorporation of MVA or acetate is generally extremely low.[14] A number of possible explanations have been given by Banthorpe.[8] It is generally considered that MVA may not readily penetrate to the intracellular sites of monoterpenoid synthesis and that MVA itself may not be able to intervene as the free acid or lactone never occur in significant quantities. Cell-free systems are needed to test these hypotheses.

The labelling patterns of monoterpenes are frequently not those predicted from the accepted biosynthetic route. Dimethylallyl pyrophosphate derived C_5 units are sometimes almost unlabelled, which is explained by a 'metabolic pool' of this unit.[15] In contrast, monoterpenes produced in flower petals[16,15] were found to be normally labelled. An early tracer study of the biosynthesis of pinenes in Pinus nigra[17] indicated a labelling pattern in support of the 'biradical' mode of formation of α-pinene from cis-ocimene (29), but a more recent investigation[18] (on P. attenuata) proved an asymmetric pattern in support of the accepted mode of synthesis.

Non-tracer studies are based on inter-relationships in particular genera. A rigorous statistical approach has been developed by Zavarin[19] and applied to Pinus and Abies species. Compounds tend to occur in quantities which have a mathematical relationship to each other. Linkage of biosynthetic

pathways is probably responsible for these regularities. Zavarin used large numbers of species and individuals from different sources, and determined the probability of co-occurrence of certain compounds in the relations found. Rather different synthetic paths for (+)- and (-)-α-pinenes were proposed on the basis of a relation between occurrence of (-)-β- and (-)-α-pinenes, but not of (-)-β- and (+)-α- or (-)-α- and (+)-α- pinenes, which suggests involvement of different enzymes in the cyclisation (scheme V).

Scheme V



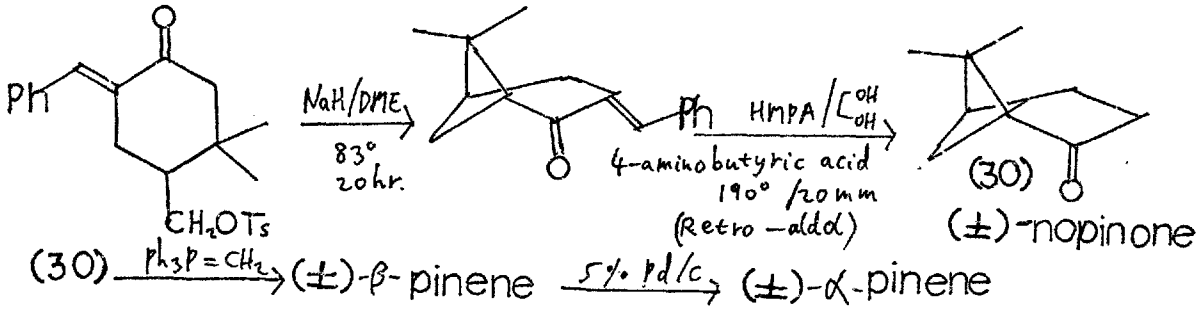
Modifying reactions, which give rise to the myrtenyl and verbenyl derivatives may be due to commonly occurring enzymes of low specificity, or may be non-enzymic. Specific enzymes are unlikely in view of the metabolic unimportance of the products. Photochemical processes in the chloroplasts may also be involved. Most modifying reactions are oxidations. 'Ene' reactions of oxygen with the olefin functions have been suggested.

The absolute configurations of the pinenes have been determined by oxidative degradation. (-)-β-pinene yielded (+)-2-methylsuccinic acid[20] of known configuration. Relative configurations of the other pinane derivatives have been

established by inter-conversions. The structures are very well established both by degradative and spectroscopic work, and recently by X-ray conformational studies employing heavy-atom derivatives, hence synthesis has not attracted attention. A number of non-photolytic routes to cyclobutanes are available.[21]

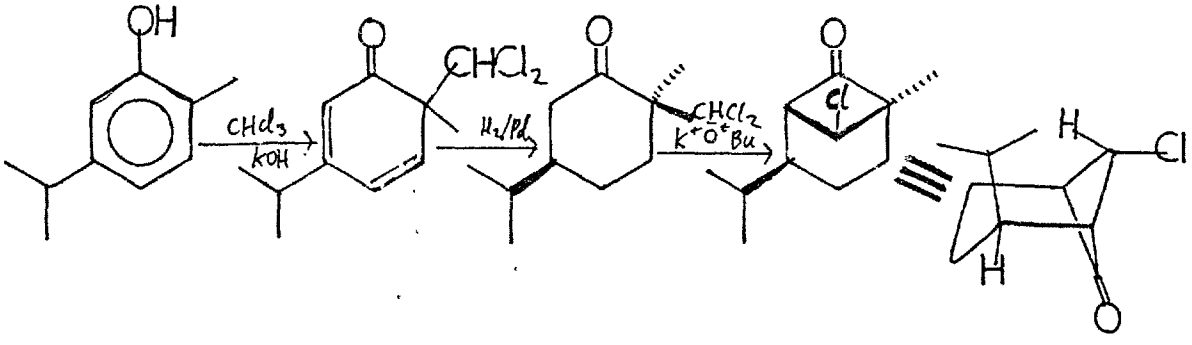
Fallis and Thomas[22] have synthesised (±)-α- and (±)-β-pinenes by straightforward nucleophilic displacement (scheme VI).

Scheme VI

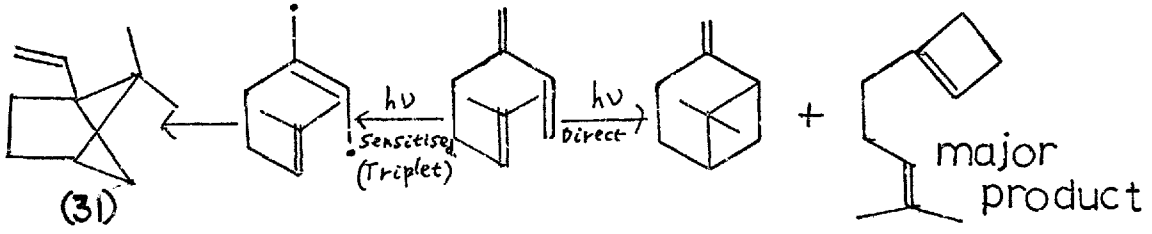


Wenkert has published a preliminary investigation[23] into the application of the 'abnormal' Reimer-Tiemann reaction products, the alkyldichloromethylcyclohexadienones, to the synthesis of the pinane skeleton. The product stereochemistry was proved by degradation. Copaene and the bergamotenes were the synthetic targets (scheme VII)

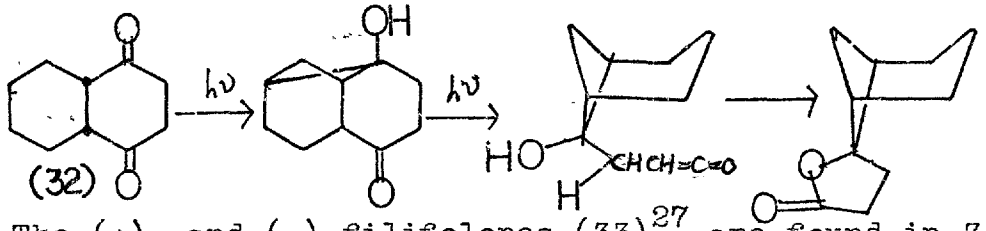
Scheme VII



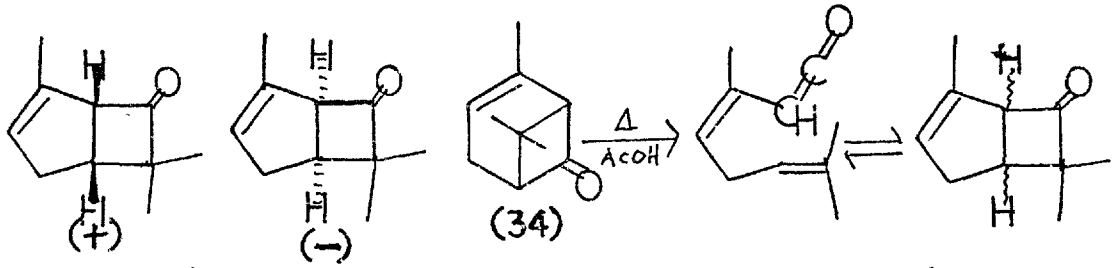
(±)-β-pinene is a minor photolysis product of myrcene[24] (scheme VIII):



The product of sensitised photolysis (31) has also been isolated from Mentha cardiaca.[25] No rotation was reported. Consequently it has not been determined if (31) is a true natural product or an artifact. Sensitised photolysis probably proceeds via an oriented complex of excited diene and ground state olefin, which yields, as is usual in biradical reactions, a five-membered ring.[26] Direct photolysis may be concerted or via a very short-lived singlet biradical. A similar approach to a photochemical synthesis of the bergamotenes was not successful. In contrast there are a number of photochemical routes to the bicyclo [2.1.1] hexanes. An interesting route to bicyclo [3.1.1] hexanes by successive type II and type I carbonyl photolyses of (32) is probably not of preparative significance.

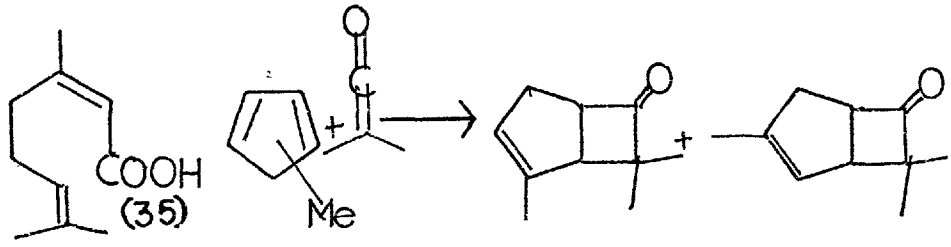


The (+)- and (-)-filifolones (33)[27] are found in Zieria smithii Andrews and Artemisia filifolia Torrey respectively. Racemic filifolone is produced by heating chrysanthenone (34)[28] in acetic acid. The keten (35) is probably the intermediate.

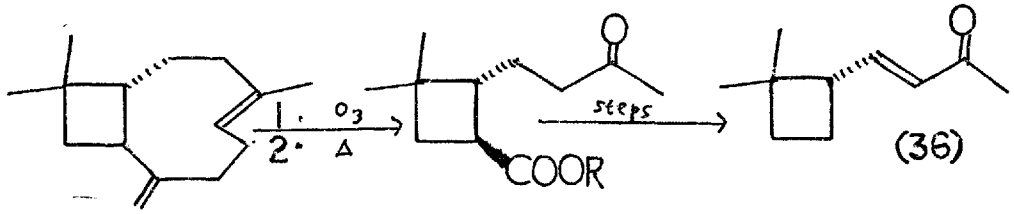


(33)

Racemic filifolone was similarly prepared from geranic acid (35).[28] An attempted synthesis by addition of dimethylketen to methylcyclopentadiene was not successful:[29]

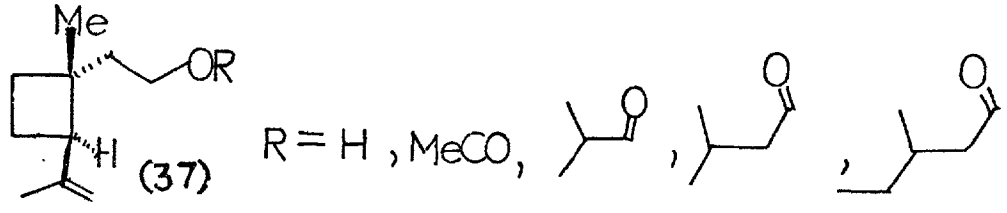


A reinvestigation of the oil of the fruit of Juniper communis L. yielded, as a very minor component, junionone (36).[30] Synthesis was easily achieved from the known ozonolysis product of caryophyllene.

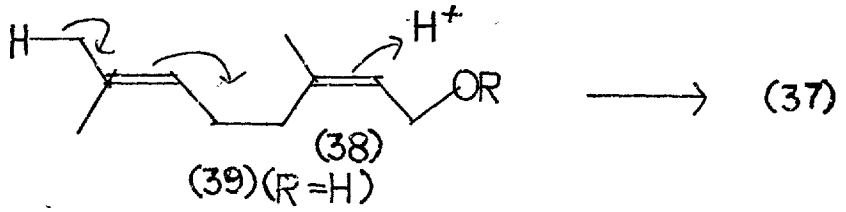


Insufficient material was isolated to obtain a rotation, and so the absolute configuration is unknown. Junionone is not a head-to-tail linked monoterpene, and consequently is a degradation product of a pinane derivative, and not the result of an unusual cyclisation.

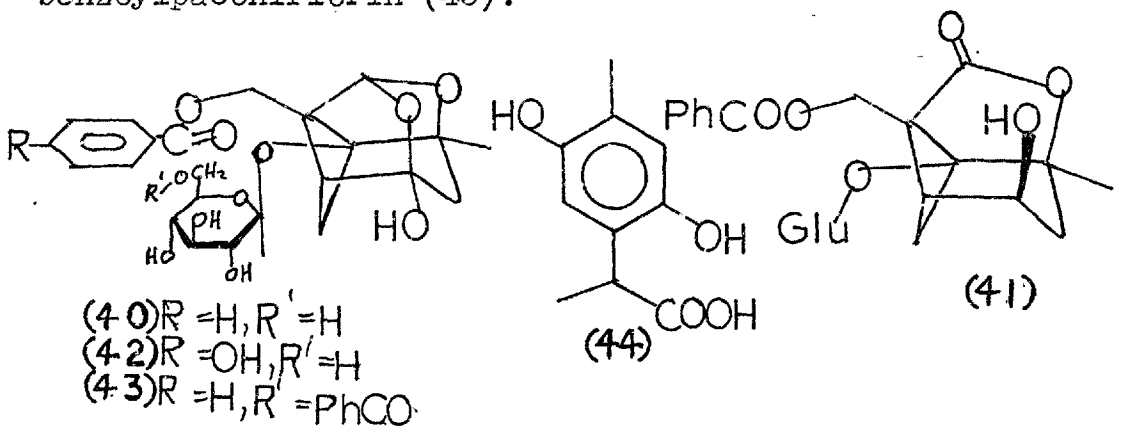
The trans isomer (9) of grandisol (5) has recently been isolated from Artemisia fragrans Willd. in which it occurs partly in the form of esters (37).[31]



This isomer has been synthesised in connection with the synthesis of grandisol. The reported n.m.r. data are identical. A proposed biosynthetic route (38) is supported by the co-occurrence in A. fragrans of nerol (39) and the same esters of nerol as of (37)



Chinese paeony root, Paeonia albiflora Pallas has yielded a group of remarkable pinane derivatives,[32] paeoniflorin (40), albiflorin (41), oxypaeoniflorin (42) and benzoylpaeoniflorin (43).

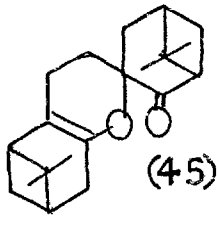


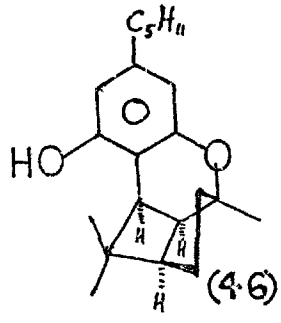
The structure of paeoniflorin was correctly deduced by degradative experiments, despite resistance to enzymatic hydrolysis of the glucoside; attempted acid hydrolysis gave (44). Confirmation was later obtained by X-ray determination of a bromo-derivative; the absolute configuration followed from the known configuration of D-glucose. Synthesis of this group of compounds would now serve little purpose. Probably the most interesting aspect is the nature of the non-specific enzyme presumably responsible for introducing oxygen functions at five carbon sites.

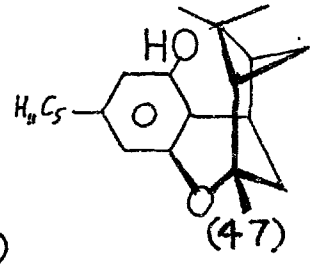
Aritasone[33] (45) was reported as a constituent of

Chenopodium ambrosioides. It is a dimer of l-pinocarvone, and is possibly an artifact.

Cannabicyclol (cannabipinol) (46), a minor constituent of hashish from Cannabis sativa L. was first isolated (1964) by Korte, who favoured structure and configuration (47)[34], but the structure remained controversial until X-ray determination on dibromocannabicyclol was performed (1970) by Crombie.[35]

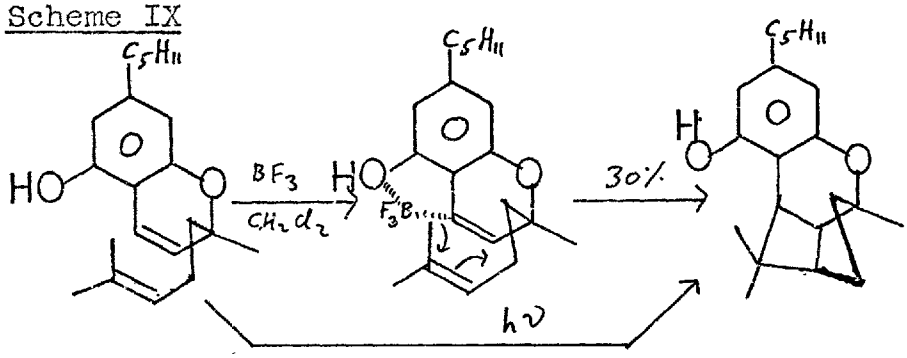






220 MHz n.m.r. also confirmed structure (46). The absolute configuration followed from degradation to menthane-carboxylic acid. Although a minor (1%) product[36] of the pyridine catalysed condensation of olivetol with citral, cannabicyclol is more readily obtained by acid-catalysed, or photolytic, cyclisation of cannabichromene[37] (scheme IX). A biogenetic scheme employed the same intermediates. However, the major products of the 'citrylidene' cyclisation which are found in C. sativa resemble the pyridine-catalysed and not acid-catalysed reactions. The major natural constituents are now believed to be derived from an electrocyclic reaction,[38] and cannabicyclol is not indicative of this path.

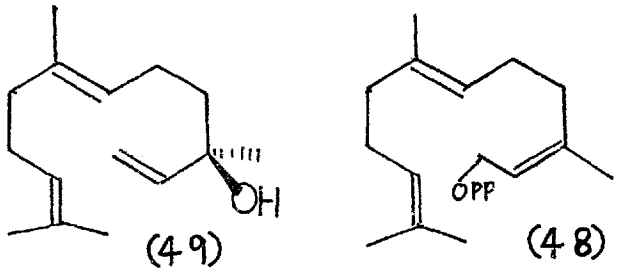
Scheme IX



(2) Sesquiterpenes. Reaction of geranyl or neryl pyrophosphate with an isopentenyl unit produces farnesyl pyrophosphate,[39,40] according to Ruzicka's scheme[41] the progenitor of nearly all the main sesquiterpene skeletons. The farnesyl unit (48) is usually assumed to have trans geometry of the central double bond, and a cis or trans terminal double bond. However, 2-cis, 6-cis, and 2-trans, 6-cis farnesyl units must be postulated to explain some product stereochemistries.

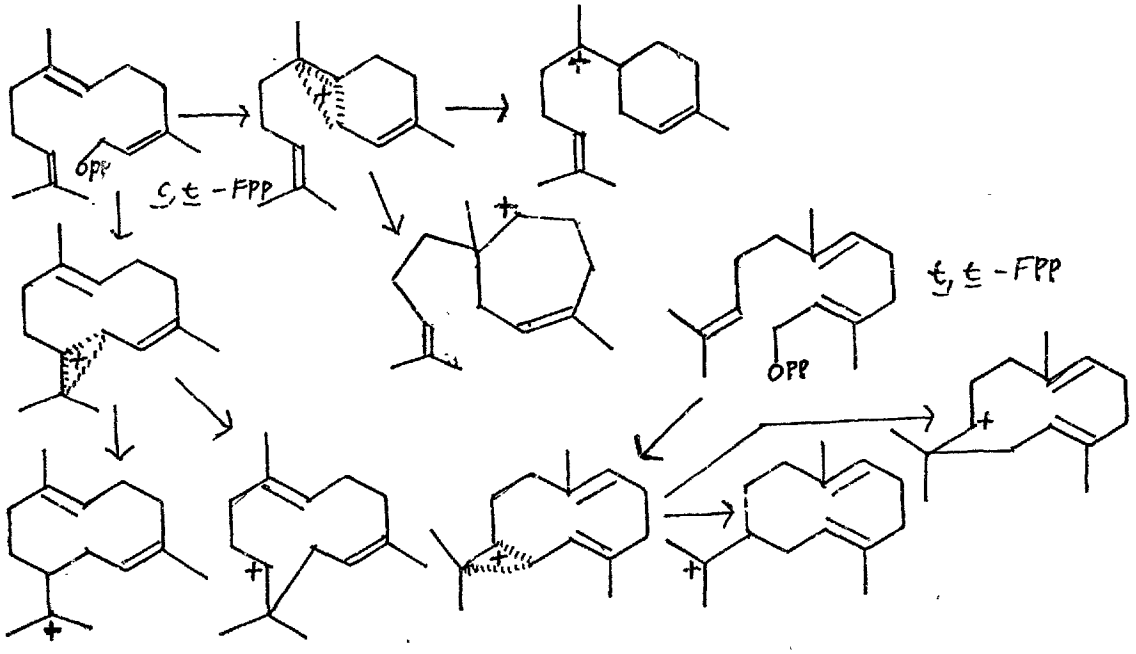
Recently direct proof[42] of 2-trans, 6-trans isomerisation has been obtained using all trans [1,1,5,5,9,9-$^3H_6$; 4,8,12-$^{14}C_3$] farnesyl pyrophosphate prepared enzymatically from [5,5-$^3H_2$; 2-^{14}C] mevalonate and cell-free systems. The ^3H - ^{14}C ratio showed loss of one ^3H atom on C_1 in the 2-cis isomer, which supports the proposed isomerisation via a redox scheme, possibly via the aldehyde. Enzymatic hydrolysis of farnesyl pyrophosphate produces nerolidol[43] (49) which occurs with farnesol. The initial cyclisations are represented in scheme X.

The cyclobutane functions are produced in subsequent Markownikov cyclisations.



(49) (48)

Scheme X



Few tracer studies have been reported as MVA incorporation is again poor in whole plants, but they have tended to confirm the accepted biogenetic scheme. Labelling patterns depend on the origin from trans, cis or cis, cis farnesyl pyrophosphate. Abnormal ring labelling patterns[39] are also encountered, and may be due to (a) condensation of a monoterpene skeleton with a C_5 unit, for example the dimethylallyl pyrophosphate 'pool'; (b) fission of a different sesquiterpene skeleton; or (c) cyclisation of a farnesyl double bond isomer. The labelling pattern does not always allow these possibilities to be distinguished.

For these reasons, biogenetic inter-relationships of the sesquiterpenes are best determined by stereochemical and absolute configurational correlations. Andersen[44] has

demonstrated the necessity of isolating all components of an essential oil before the biogenetic pathway can be reasonably discussed, and in a most important case (vetiver oil) of ensuring that components isolated by g.l.c. are not thermal artifacts.

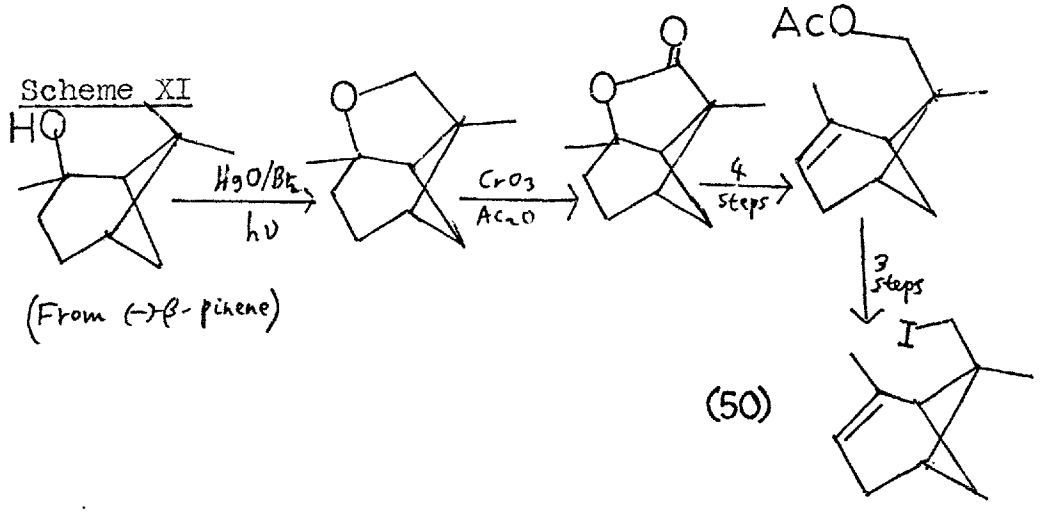
As for monoterpenes, it is unreasonable to expect enzymatic control of subsequent cyclisations of the monocyclic precursors. These 'chemical' processes are probably steric- and electronically controlled. Successful photochemical cyclisations have also been proposed as biogenetic possibilities.

Specific Classes

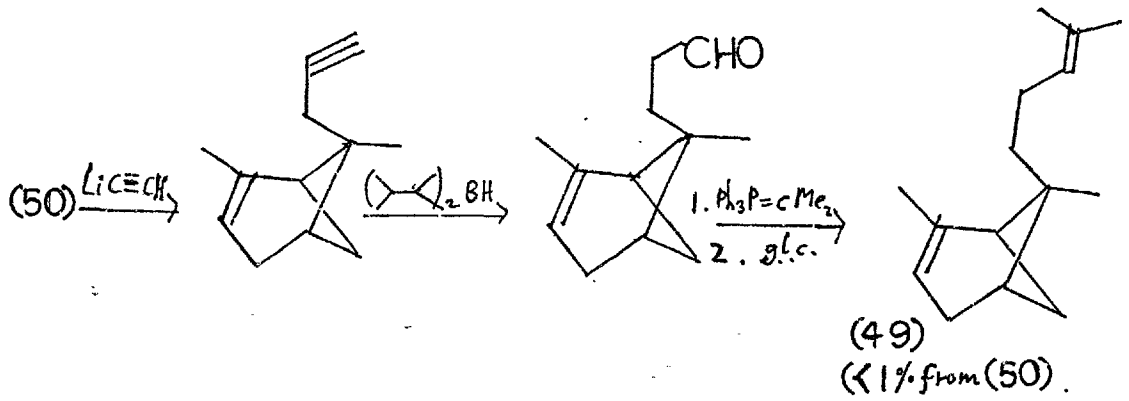
The bergamotenes

The structures of the bergamotenes have now been clarified by the combined synthetic work of Erman[45] and Corey.[46] Erman's (-)-α-cis-bergamotene was identical to the compound assigned that structure (49) from Commiphora erythraea var. glabrescens Engler and piper nigrum L[47] (scheme XI).

Scheme XI

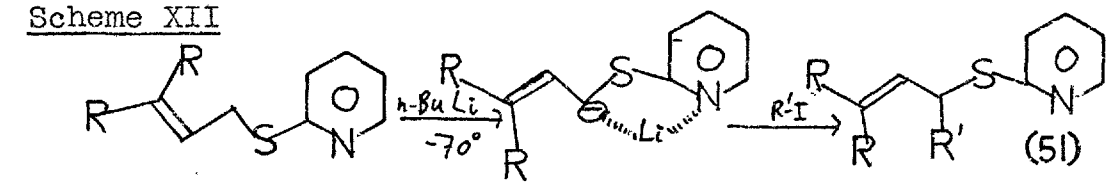


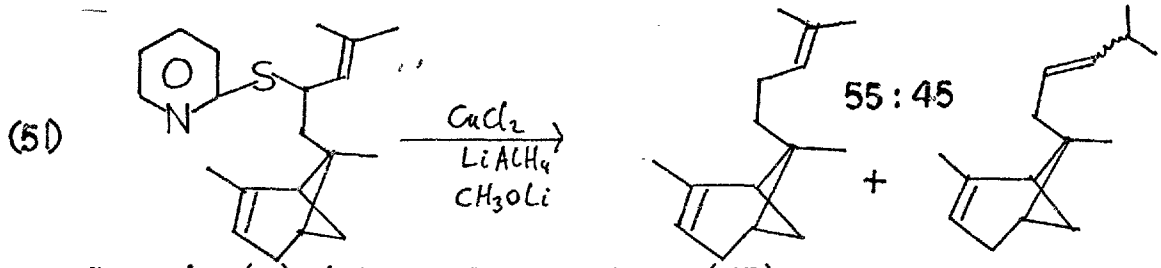
(50)



A variation of this synthesis has been reported.[48] The ingenious reagent for introducing the dimethylallyl group was designed to avoid olefin isomerisation in reaction of the allylic metal derivative with the alkyl iodide. A model compound (R = H) could be cleaved with copper (II) chloride and lithium aluminium hydride without any isomerisation, but the product (R = Me) using the dimethylallyl function could only be cleaved in the presence of base (lithium methoxide) with consequent isomerisation (scheme XII)

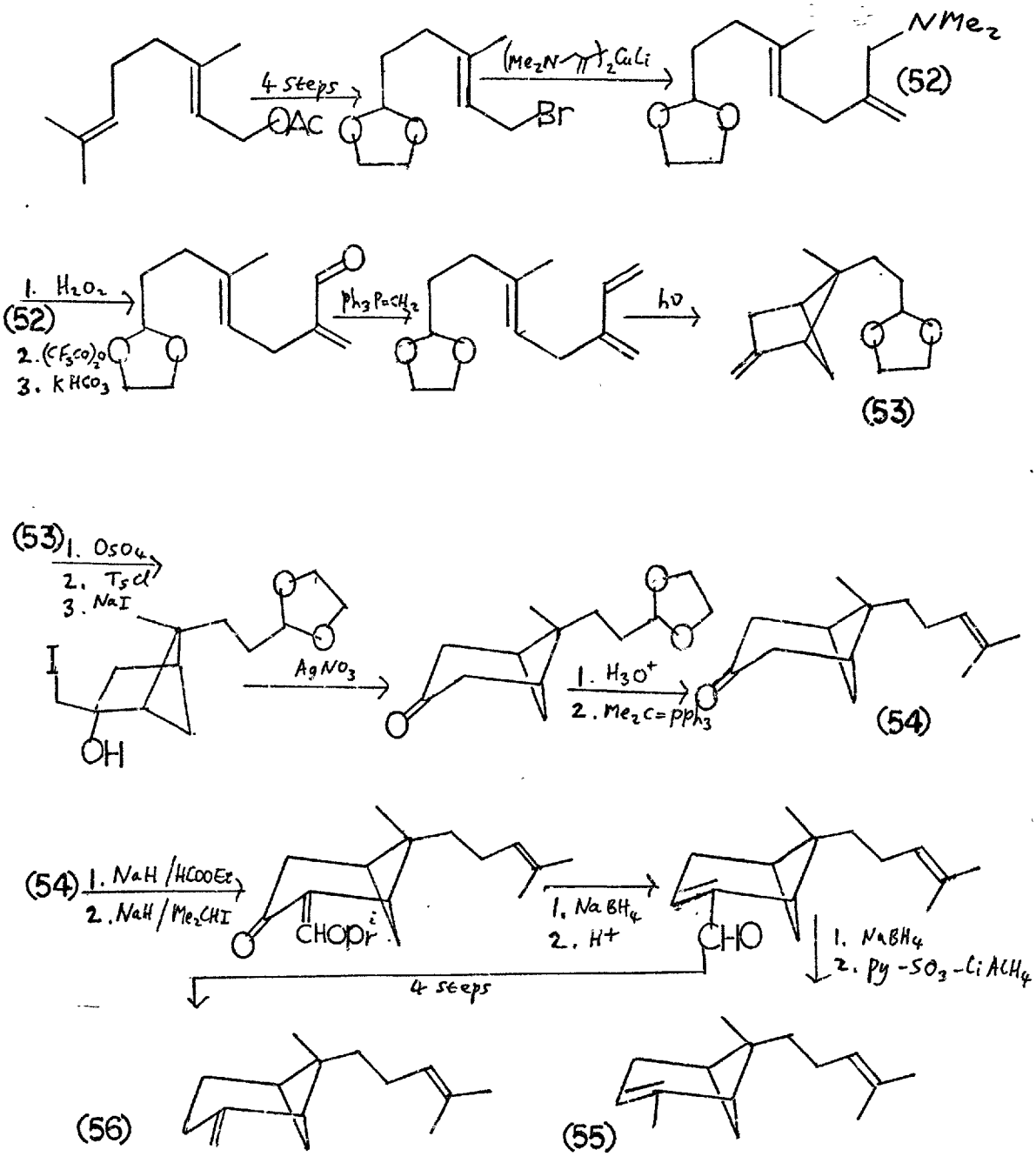
Scheme XII





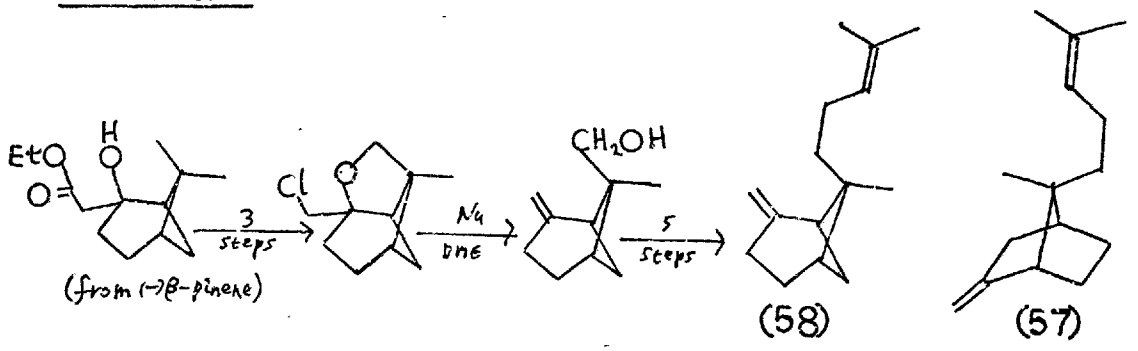
Corey's (±)-α-trans-bergamotene (55) was identical with the isomer assigned this structure from bergamot oil[49] and a number of other sources (scheme XIII). Corey also obtained (±)-β-trans-bergamotene (56), possibly a minor constituent of opoponax oil (C. erythraea).

Scheme XIII



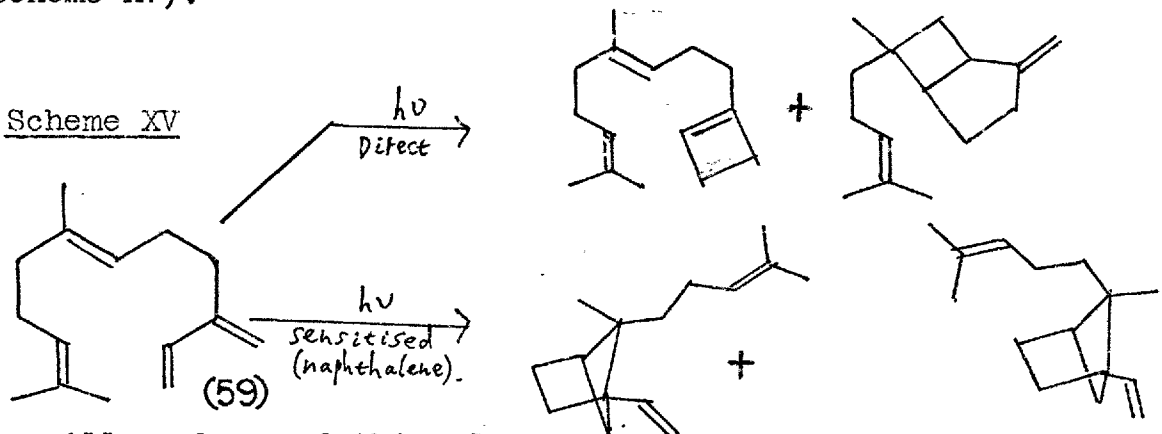
Neither Corey's β-trans isomer nor Erman's β-cis-bergamotene (scheme XIV) (58) was identical with Bhattacharyya's 'bergamotene'[50] from Indian valerian root oil, which was subsequently shown to be not a bergamotene but a γ,γ-dimethylallylfenchene[51](57) by comparison with a synthetic sample.

Scheme XIV

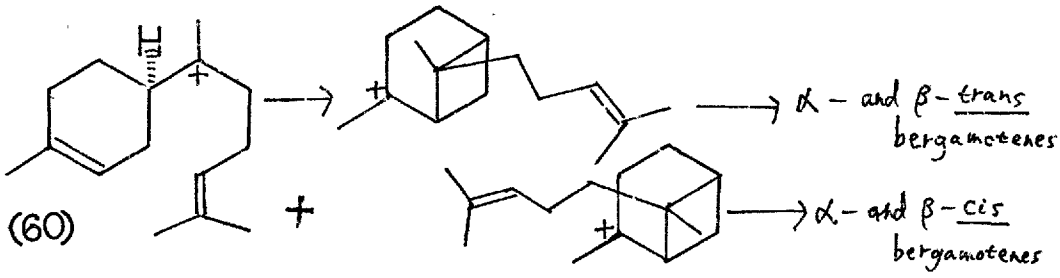


Photolysis[52] of trans-β-farnesene (59) did not yield the bergamotenes. Sensitised photolysis resulted in the five-membered ring products of excited diene-olefine reaction, and direct photolysis only in (2 + 2) cycloaddition (scheme XV).

Scheme XV

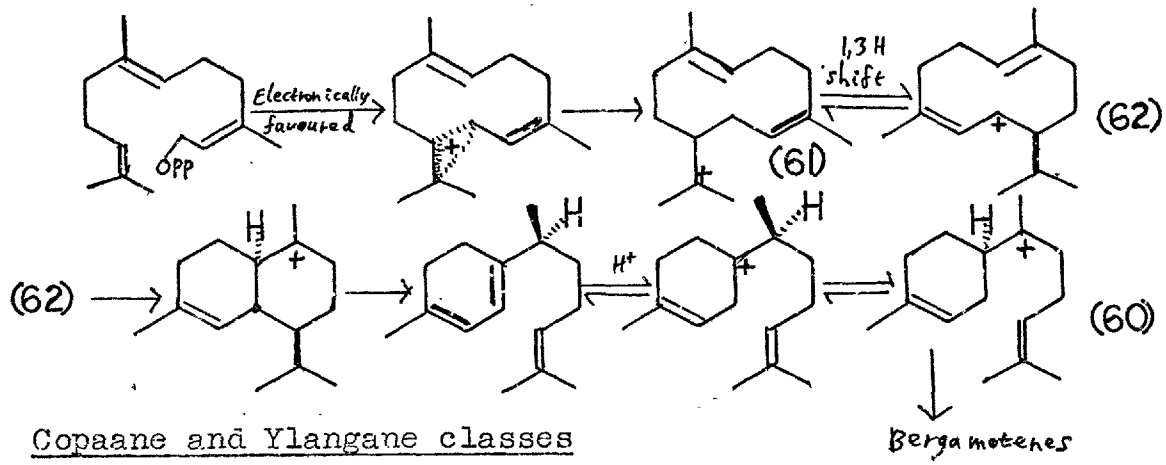


All members of this class are considered to arise from electronically favoured cyclisation of (60) (see scheme X).



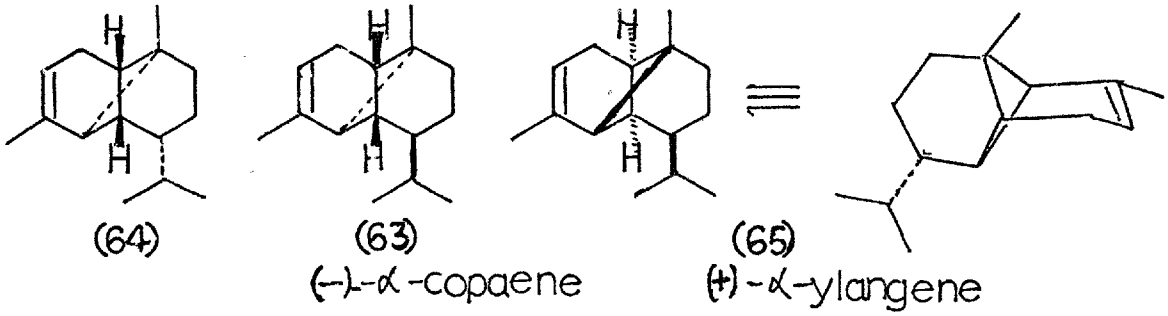
A simple rationalisation may explain biogenesis in some systems. A scheme for vetiver oil, due to Hirose,[53] (scheme XVI) is necessarily complex if the principal sesquiterpenes are derived from a single precursor (61) or an alternative precursor via (61).

Scheme XVI



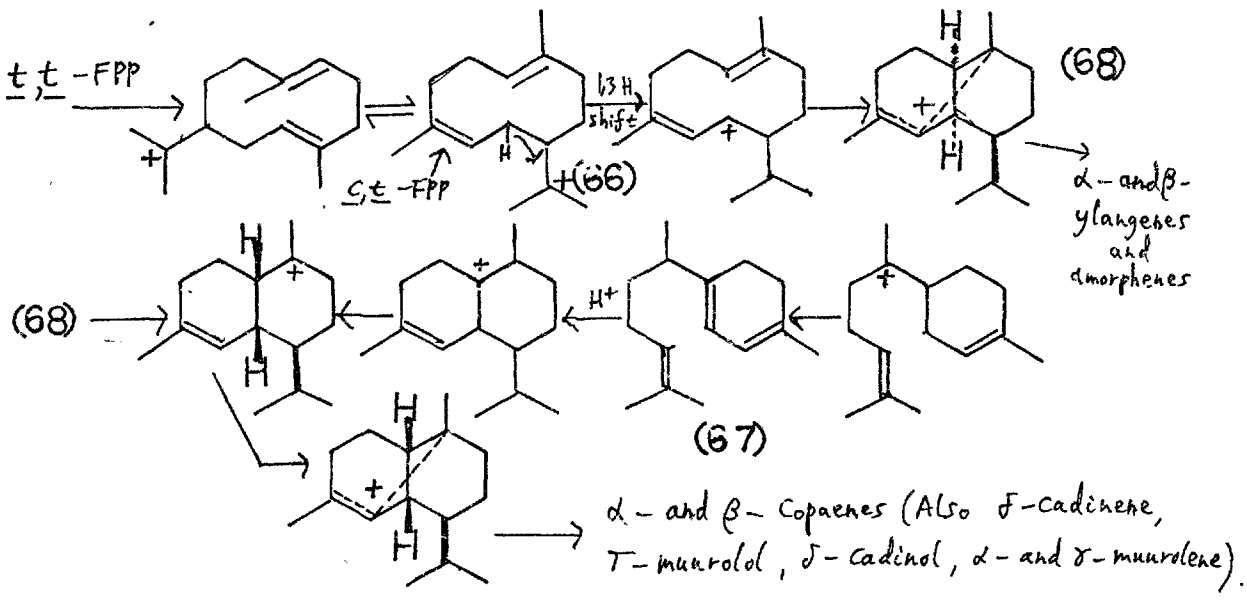
The known members of this group comprise (+)[54] and (-)[53]-α-ylangenes, (+)[55] and (-)-α-copaenes, β-copaene, and β-ylangene,[56] all from a wide variety of sources; (+)-copadiene[57] (Cyperus rotundus L.); mustakone (C. rotundus)[58] and brachylaenolones A and B (Brachylaena hutchinsii Hutch.).[59]

The key investigations of de Mayo[60] and S. Dev[58] yielded the structure and absolute stereochemistry of (-)-α-copaene,[63] which has been correlated with mustakone, and (±)-mustakone with copadiene. (-)-α-copaene was related by acid hydrolysis to (+)-δ-cadinene, (-)-α-muurolene, (-)-δ-cadinol and (-)-T-muurolol. (+)-α-ylangene was converted to known amorphenes, and on this evidence, (+)-α-ylangene was believed to have the configuration[61](64), since corrected to (65)[53]; an epimerisation had occurred in one of the amorphene degradation products.

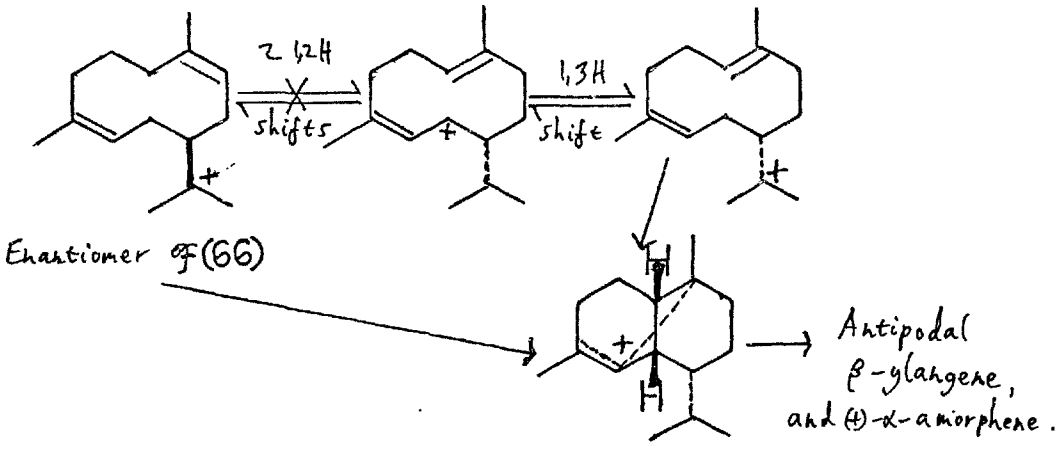


(+)-α-ylangene and (-)-α-copaene consistently co-occur and this observation was incorporated into Hirose's[53] biogenetic scheme, as corrected by Andersen[44] after the relative configurations had been determined. Hirose's scheme involving two 1,2 hydrogen shifts to explain the configuration (64) became redundant, although the isolation of antipodal β-ylangene by Westfelt must be explained by scheme XVIII. (66) (or equivalent) is generally accepted as the point of entry, although Hendrickson,[62] who considered cyclisation of farnesyl pyrophosphate (FPP) to (66) as unlikely on the grounds of strain and non-bonded interactions during cyclisation, favoured (67) (scheme XVII).

Scheme XVII

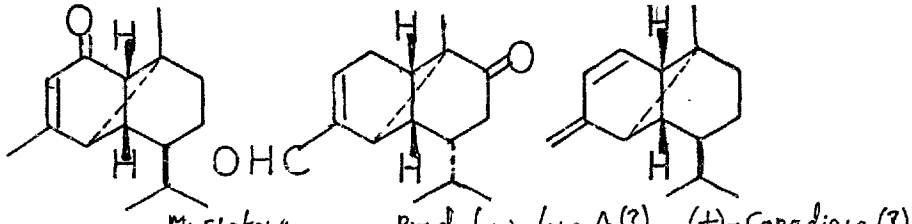


Scheme XVIII

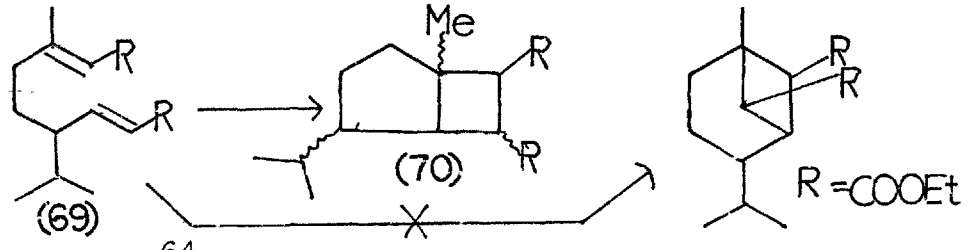


The antipodal sesquiterpenes do not occur with (-)-α-copaene. (-)-α-ylangene and (+)-α-copaene occur together in Brachylaena hutchinsii Hutch. and are therefore best explained as derived from an enantiomer of (66) (scheme XVIII).

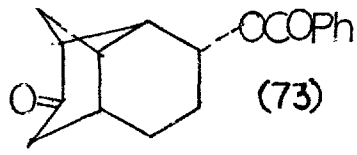
Mustakone and the brachylaenalones may be rationalised as products of modifying reactions (allylic oxidations).



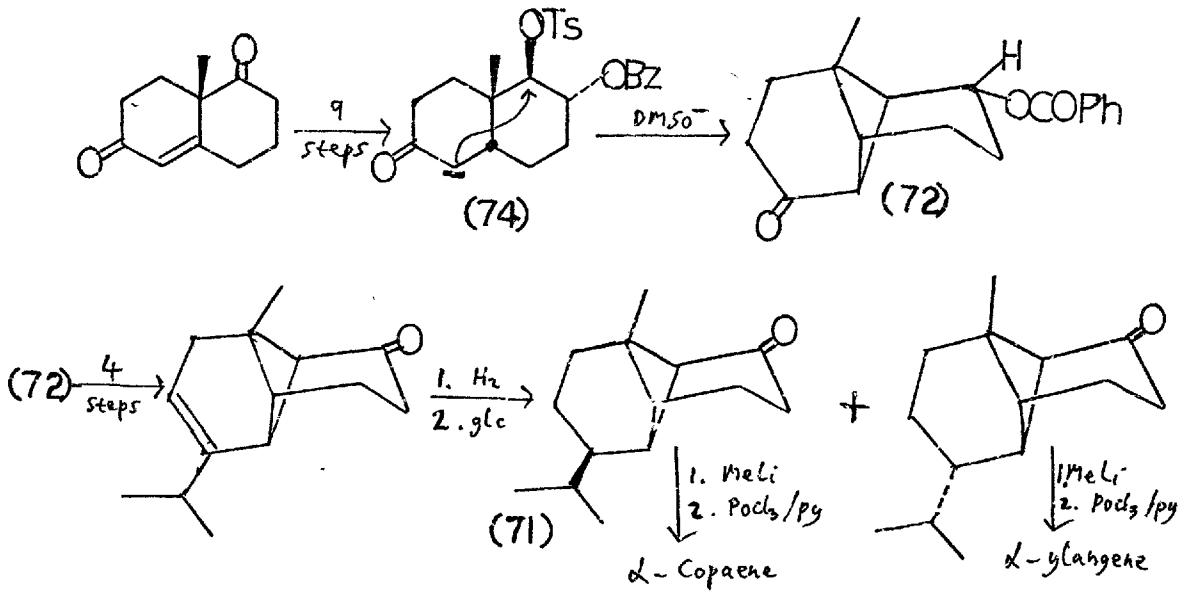
Only racemic copaenes and ylangenes have been synthesised. Brown photolysed the diene[63] (69) but obtained only (70) subsequently utilised in a synthesis of bourbonene. Direct and sensitised reaction gave the same product, probably via the triplet biradical.



Heathcock[64] synthesised racemic α- and β-copaenes and α- and β-ylangenes, using intramolecular nucleophilic displacement.(scheme XIX). No control of the configuration at C-7was employed; the ketones (71) were separated by g.l.c.



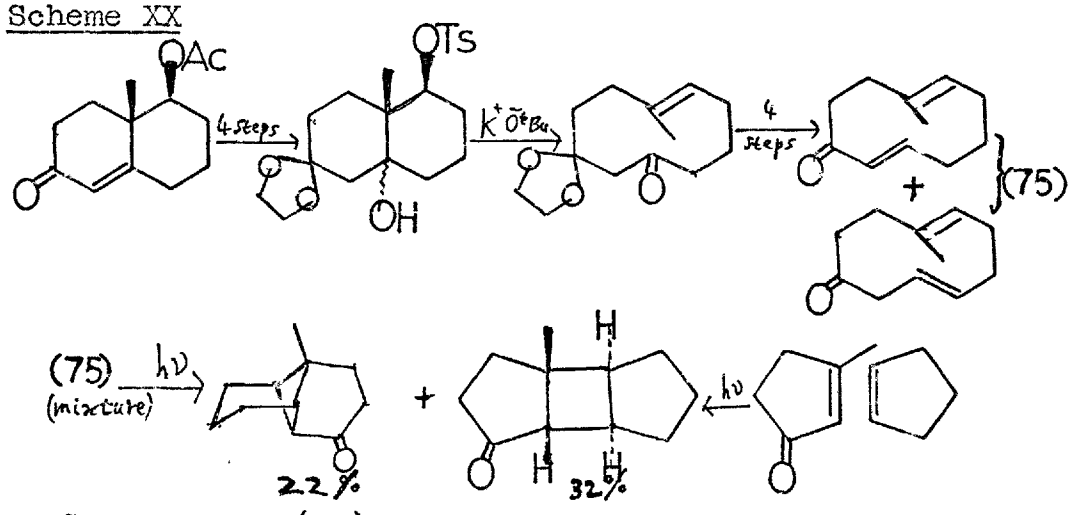
Scheme XIX



(74) did not yield any (73) on treatment with base; the line of departure of the p-toluenesulphonate leaving group is orthogonal to the π-orbital of the enolate in the transition state for this product.

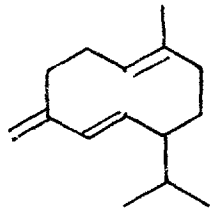
A later approach by Heathcock[65] again gave the bourbonane ring system in preference to a copaane (scheme XX).

Scheme XX



Germacrene D (76) gave bourbonene and very little copaene on direct photolysis. It has been suggested that copaene and bourbonene may arise from pigment-sensitised photocyclisation of a cyclodecatriene; concerted reaction

is not possible in nature owing to the wavelength required for the photolysis (p 36).

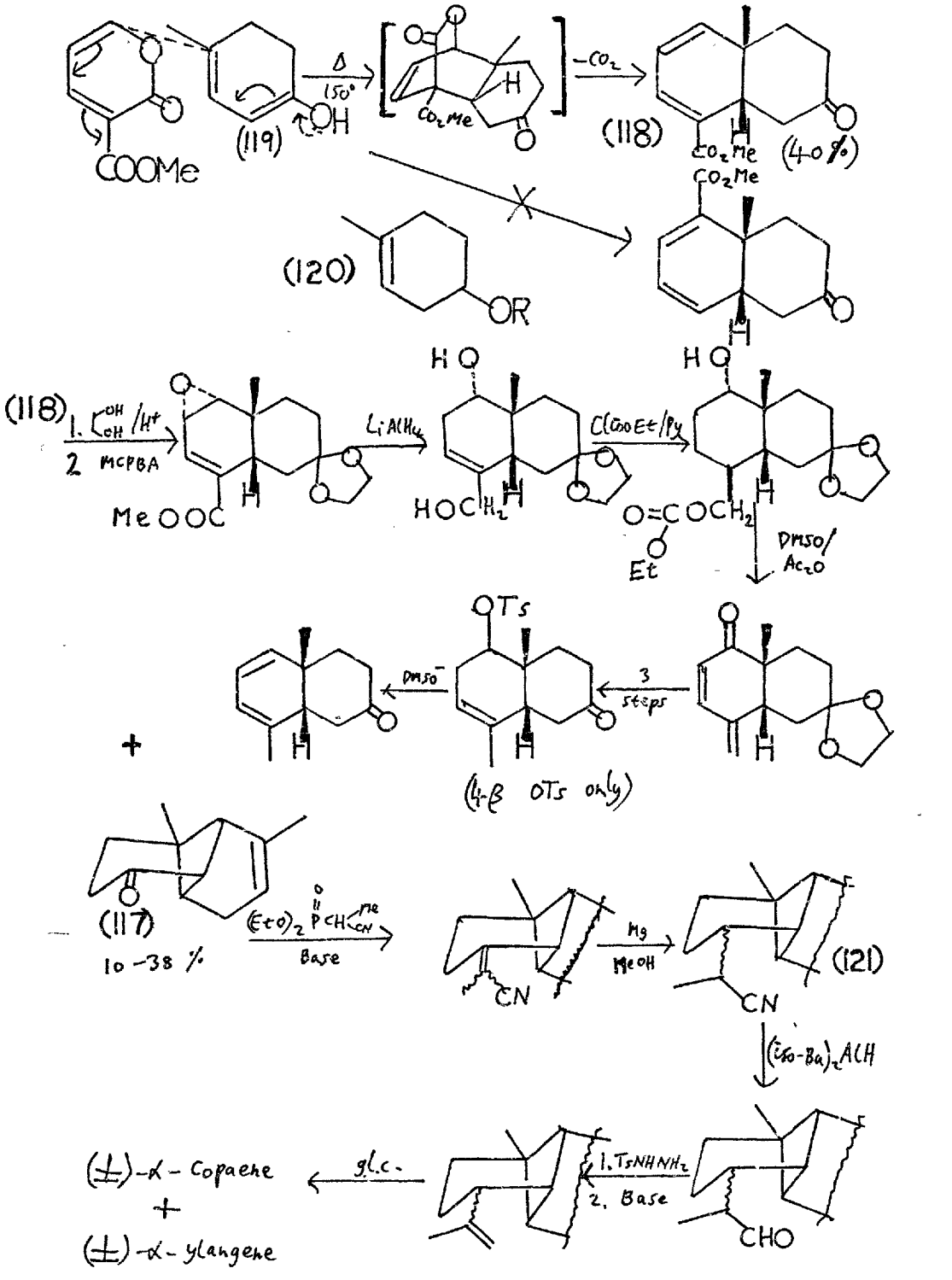


(76)

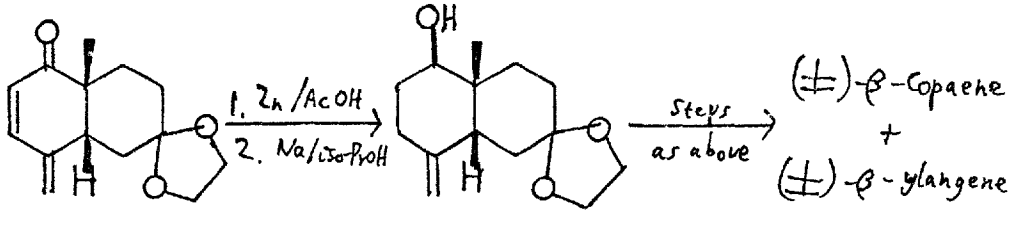
Corey's synthesis[66] (scheme XXX) of the racemic copaenes and ylangenes was marred by a poor yield for the intramolecular displacement step, employing sodium methylsulphinylmethide as base. Elimination occurred in preference even though the transition state required an axial leaving group, as opposed to the equatorial p-toluenesulphonate function for the displacement. Alternative bases gave no (117). (118) did not undergo intramolecular Michael reaction.

The epimerisation sequence for the hydroxyl at C-4 was found necessary as a β-epoxide function could not be introduced, directly or otherwise, in good yield. The observed stereoselectivity of the Diels-Alder reaction in the initial step was ascribed to participation of the enol (119) as the true dienophile, the electron-donating hydroxyl and accepting carbonyl functions controlling orientation in the transition state. In support of this hypothesis, (120) did not react with the α-pyrone under the same conditions. Corey separated α-copaene and α-ylangene on an ordinary 30 ft. Carbowax preparative g.l.c. column, whereas Heathcock found it necessary to use a 1,000 ft. x 0.03 in. capillary column.

Scheme XXX



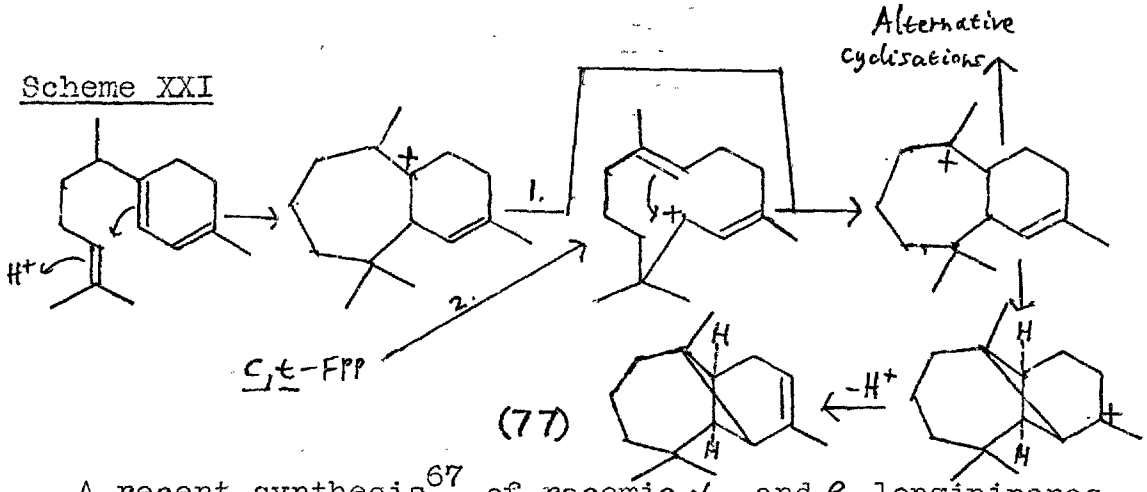
Similarly,



Longipinanes

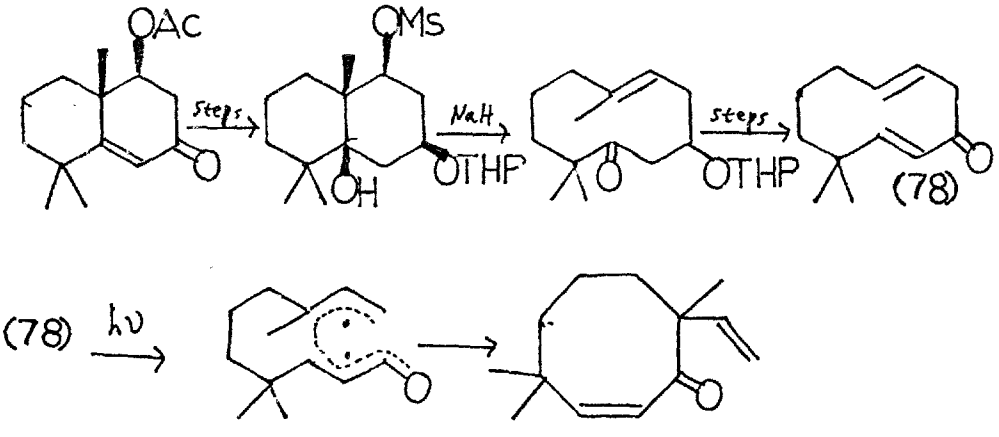
(+)-α-longipinene (77) is a constituent of Pinus silvestris L. The (-)α- and (-)β- isomers have recently been isolated from the liverwort, Scapania undulata.[67] A biosynthetic scheme incorporating the related structures of longiborneol, longifolene and longicyclene, is supported by preliminary tracer studies[68] employing 1 - ^{14}C acetate. Westfelt has proposed a scheme for the components of P. silvestris (scheme XXI).[69]

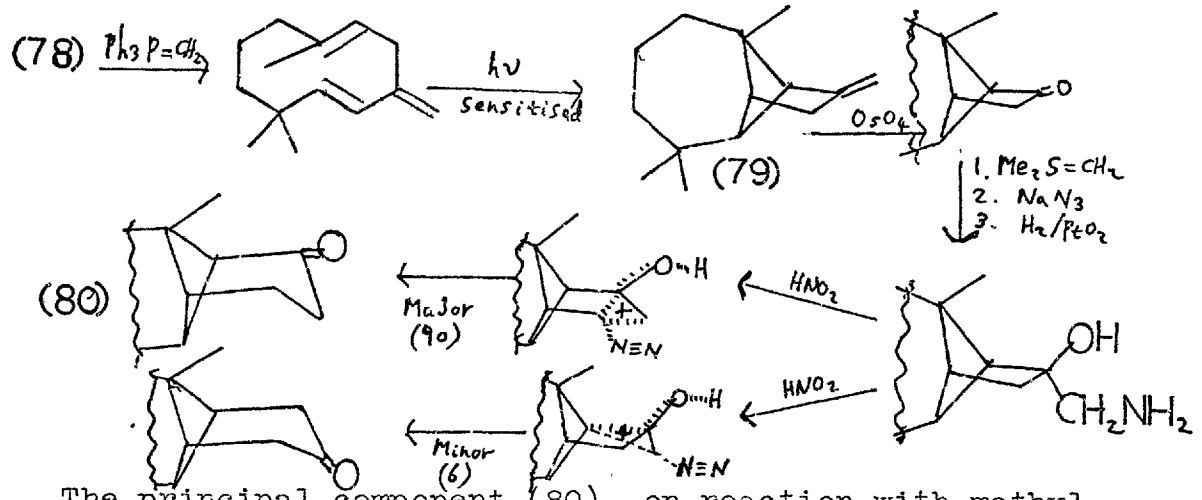
Scheme XXI



A recent synthesis[67] of racemic α- and β-longipinenes made use of the known tendency of cyclic dienes to produce five-membered rings on triplet (sensitised) photocyclisation, although this approach necessitated a subsequent ring expansion, successfully carried out as in scheme XXII.

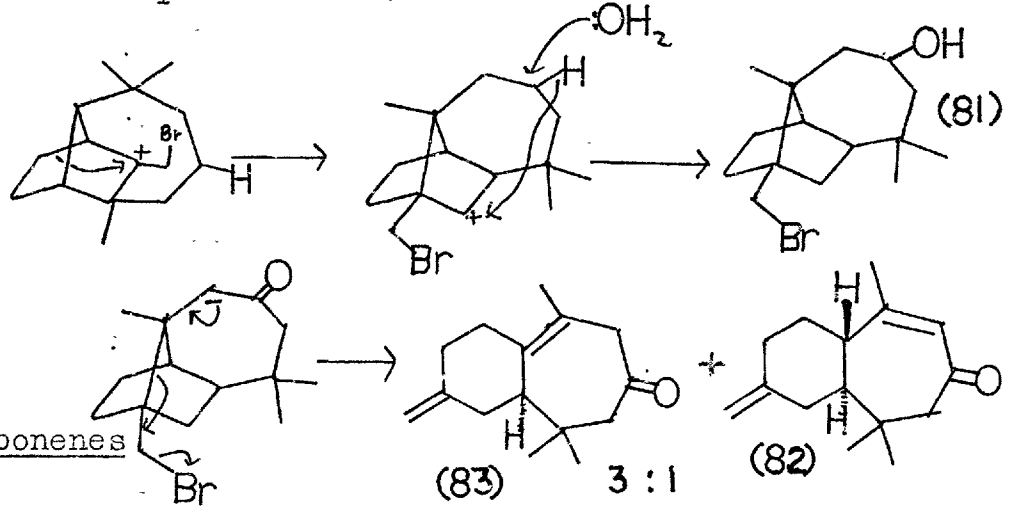
Scheme XXII





The principal component (80), on reaction with methyl lithium, then phosphorus oxychloride-pyridine, gave a mixture of (±)-α- and (±)-β- longipinenes, separated by g.l.c. or on silica impregnated with silver nitrate.

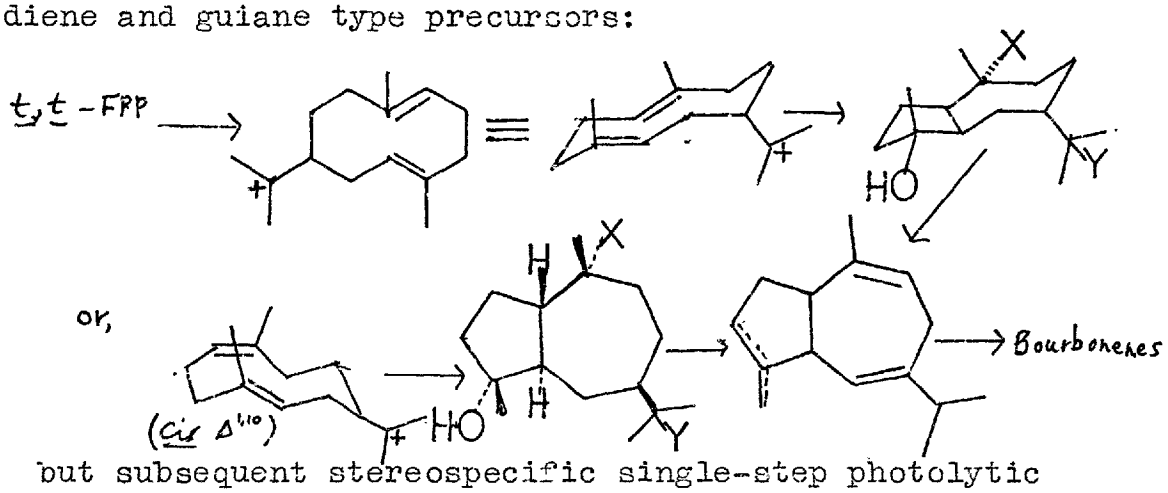
ω-bromolongifolene undergoes an unusual Wagner-Meerwein rearrangement, followed by a 1,5 hydrogen shift in trifluoroacetic acid. The product (81) (30%) after oxidation to the ketone and treatment with base gave the anticipated dienone mixture (80%), a potential precursor to α-longipinene.[70] The ring junction of (82) was assumed trans as it was a product of equilibration.



Bourbonenes

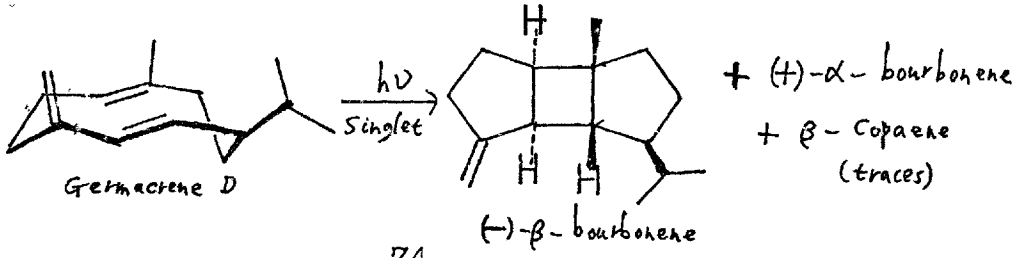
Geranium bourbon yields α- and β-bourbonenes and 11-norbourbon-1-one.[71] Mentha piperita is another source. As a comparatively recently isolated[72] class, structural

determination was quickly accomplished by n.m.r. and degradative work.[73] Absolute configurations were deduced from o.r.d. curves, and by degradation to S(+)-isopropylsuccinic acid. Synthetic bourbonenes have been resolved. Co-occurrence with the furopelargones suggested bicyclic diene and guiane type precursors:



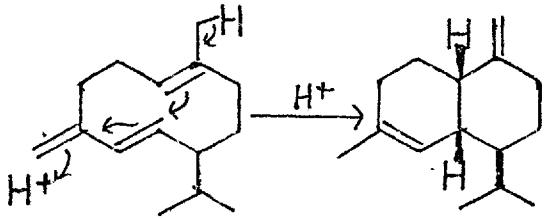
but subsequent stereospecific single-step photolytic syntheses suggest biosynthesis via the trienes. Singlet-state, probably concerted, reactions (scheme XXIII)[74] cannot be responsible in nature but non-concerted reactions may also be stereospecific for steric reasons.

Scheme XXIII

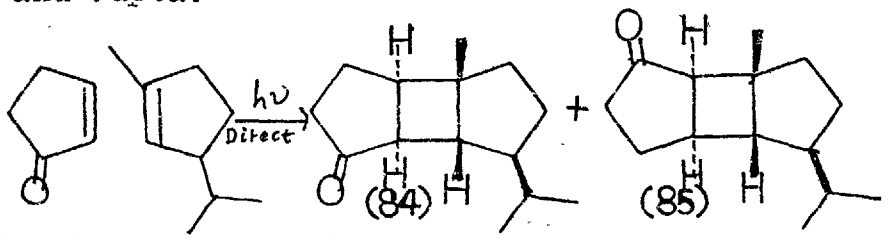


The occurrence[74] of germacrene D with the bourbonenes and with cadinenes in Pseudotsuga japonica, Pittosporum tobira, Kadsura japonica and Piper kadsura is particularly interesting. Germacrene D is not readily detected by g.l.c. due to rapid thermal decomposition. Treatment with silica gel, a mild acid catalyst, yielded (+)-γ-muurolene, (-)-α-amorphene, α-muurolene, (+)-δ-cadinene, and (+)-γ-

cadinene which may explain the occurrence, or at least the isolation, of these compounds from some sources.

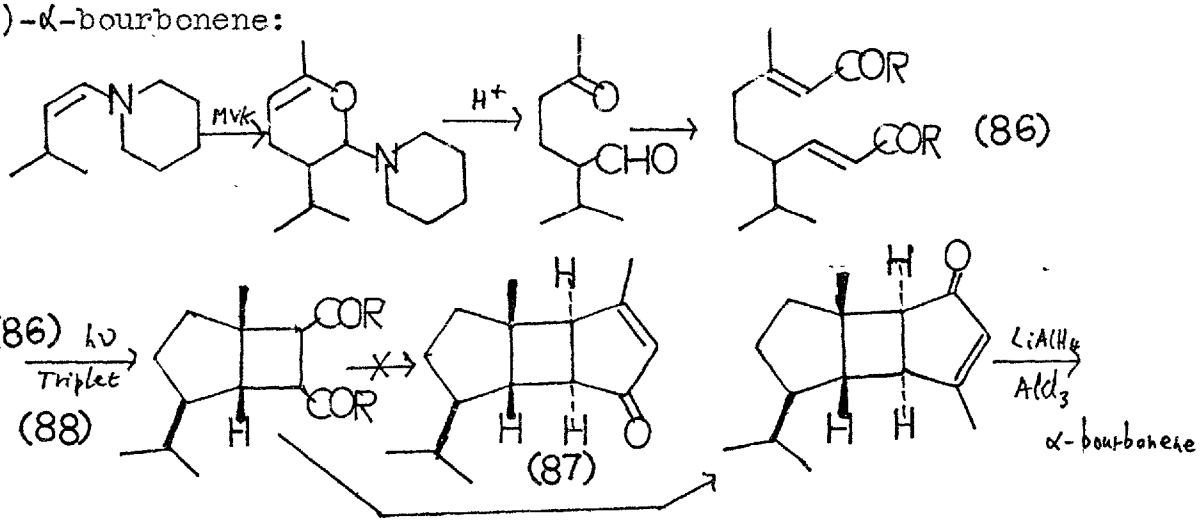


A number of other syntheses were quickly reported. Photolytic addition of an olefin to an enone was employed by White and Gupta.[76]



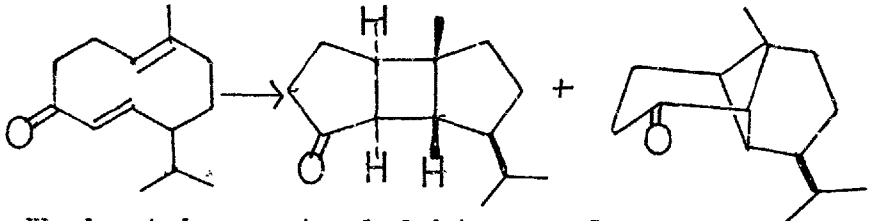
Cis, anti, cis ring junctions, and the exo isopropyl function, were expected from precedent, probably due to steric factors. Head-to-tail or head-to-head addition was found to be unselective, as expected. The isomers were easily separated by preferential formation of carbonyl derivatives by (84); moreover, direct treatment of a mixture of (84) and (85) with R(-)-2,3-butanediol gave only the derivatives of (84), which were separated by g.l.c. Hydrolysis yielded optically-active norbourbonanones, which were separately converted to α- and β-bourbonenes with the usual reagents.

Brown[63] reported a photocycloaddition which gave (±)-α-bourbonene:

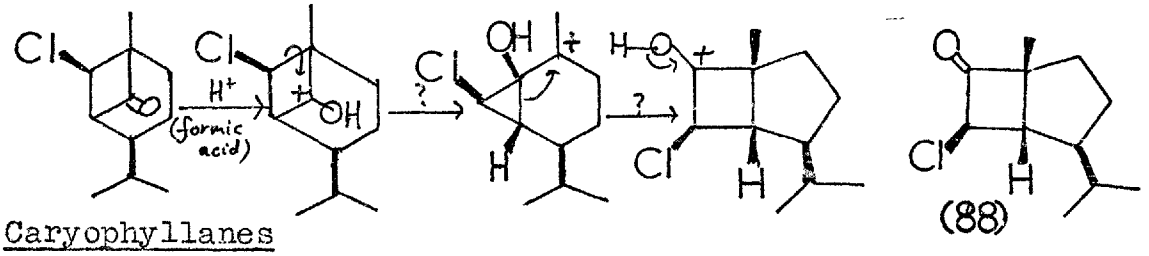


As in White's approach, triplet biradical cycloaddition produced only the five-carbon ring product. Aldol reaction of (88) gave no (87) owing to steric interactions of the quarternary methyl.

An intramolecular olefin - enone photoaddition also provides a stereospecific route to norbourbonene.[65]



Wenkert has extended his novel approach to cyclobutane monoterpenes to a bourbonene precursor[78](88):

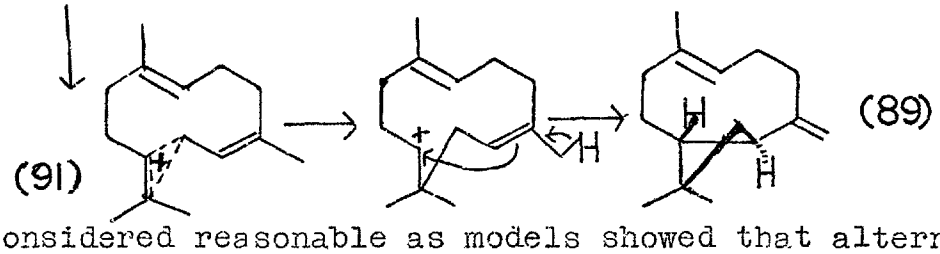


Caryophyllanes

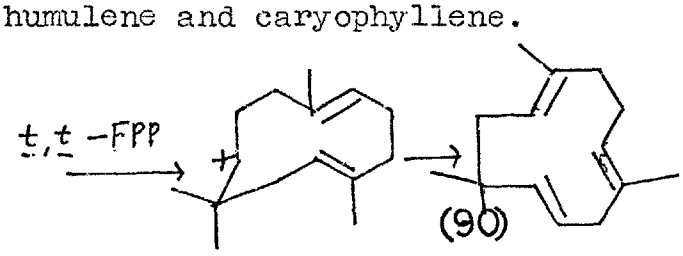
This class comprises (-)-β-caryophyllene (Zingiber zerumbet, Pimento dioica, Cinnamomum camphora Sieb., and many other sources), and (+)-β-caryophyllene (Libanotis transcaucasia); α-caryophyllenes have been reported; α- and β-betulenols[79,75](Betula alba L. (white birch)); isocaryophyllene, kobusone, and isokobusone[80] (Cyperus rotundus); tricyclohumuladiol (from hop oil); α-multijugenol[81] (Copaifera multijuga Hayne), caryophyllene epoxide (C. multijuga;[82] Artemisia scopania; and others) and caryophyllenols-I and -II. (Dipterocarpus pilosus).[83]

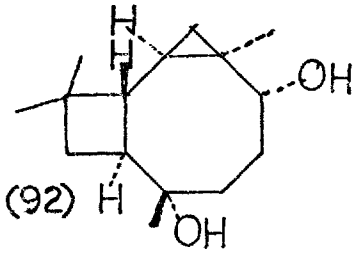
The original biogenetic scheme for caryophyllene (89)

2-cis, 6-trans - FPP



was considered reasonable as models showed that alternative cyclisations are sterically improbable.[84] Humulene and caryophyllene have been isolated together from many sources. Humulene has the all trans stereochemistry (90) and a postulated intermediate is the trans farnesyl cation. Prior to crystallographic determination of the geometry of humulene, the cis cation (91) was considered a possible common precursor to humulene and caryophyllene.



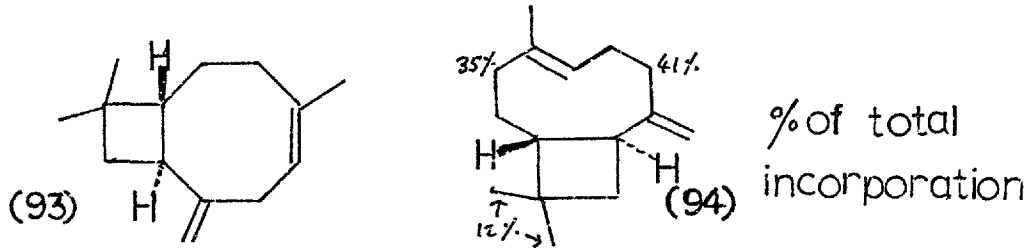


Caryophyllene was once considered to be an artifact of isolation procedures (during steam distillation of oil of clover) but this has been disproved by room-temperature extraction.[85]

Humulene has been considered as a precursor of caryophyllene. In vitro conversion has been carried out by two methods.[86,87] The intermediate of both routes, tricyclohumuladiol[88](92), was subsequently found in Japanese hop oil, but was racemic and therefore is not a precursor of (-) caryophyllene. Humulene 1,2 epoxide[89] may, however, be an intermediate in the biogenesis of tricyclohumuladiol.

Isocaryophyllene (93) may be an artifact of the isolation procedure as it is the more stable isomer.

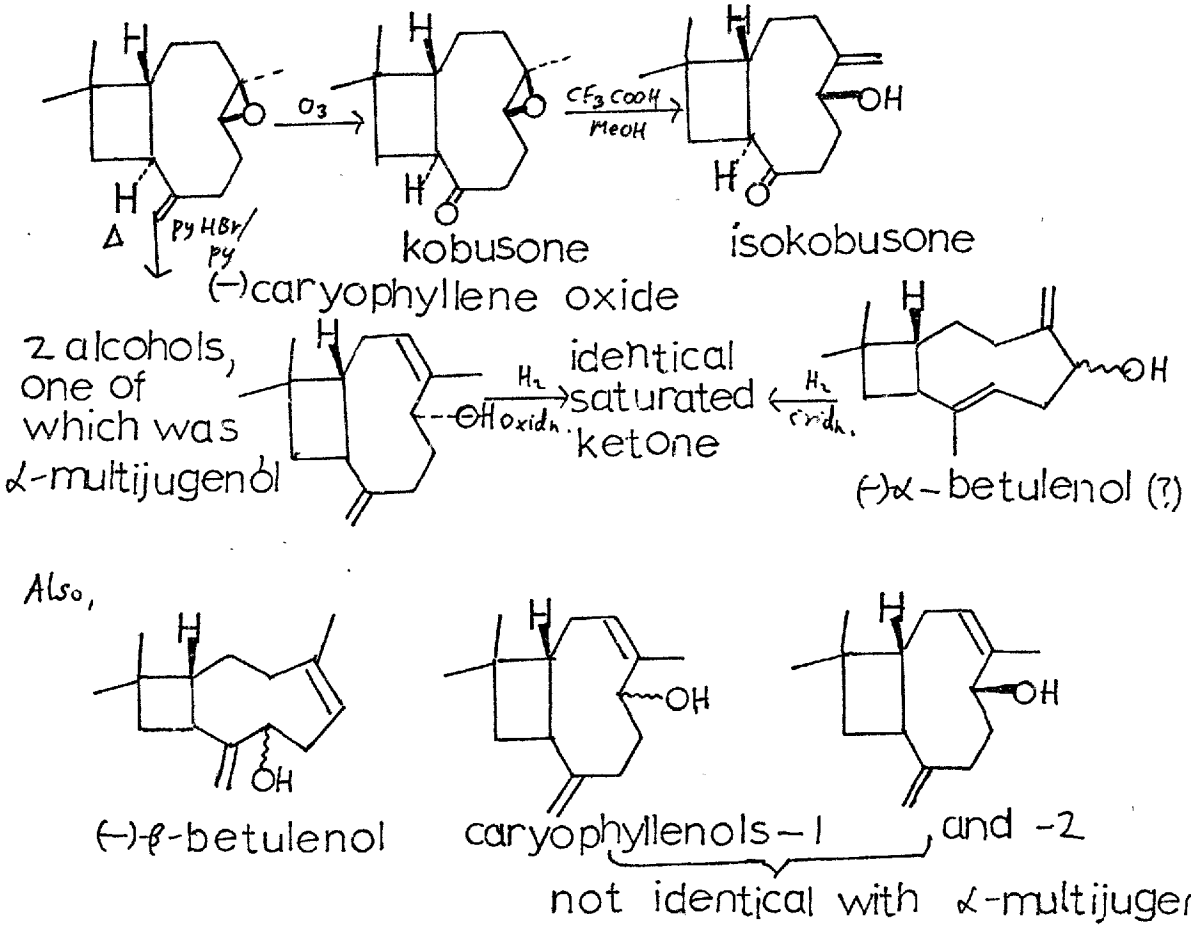
Alternatively, (93) may be biosynthesised from a cis- $\Delta^{6,7}$ farnesyl unit.



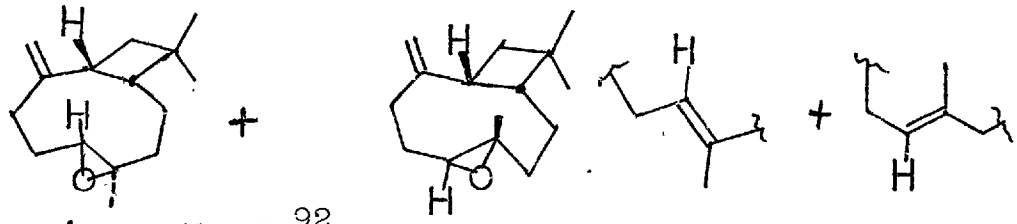
A tracer study of caryophyllene biosynthesis in Mentha piperita[77,90] from 2 - ^{14}C mevalonate showed comparatively little incorporation into the gem dimethyl group, (94), probably owing to the dimethylallyl unit 'pool' proposed to explain similar observations with monoterpenes.

Some confusion still exists over the structures of the kobusones, caryophyllenols, and multijugenol; all are related to caryophyllene oxide. The conversions of scheme XXIV have been reported.

Scheme XXIV

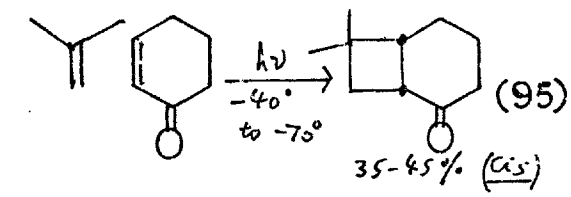


Srinivasan[91] has obtained evidence of distinct conformers of the epoxide by n.m.r. and partial separation, but could not determine whether the corresponding caryophyllene conformers were interconverting at room temperature. A barrier to rotation of the trans double bond in a nine-membered ring is well established in the case of trans cyclononene, which has been resolved, the optical half-life of the conformers being 4 minutes at 0°.

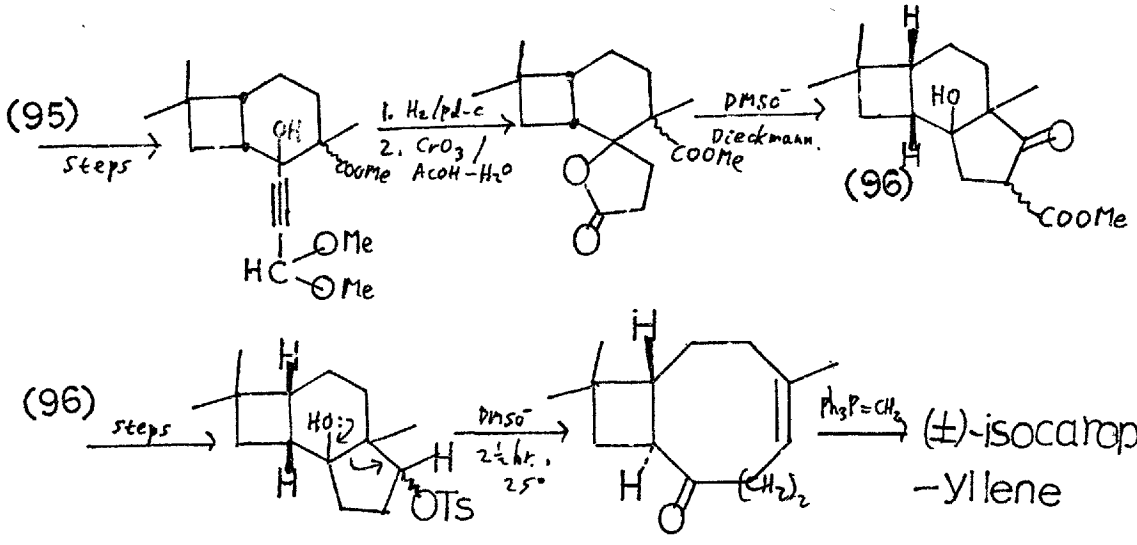


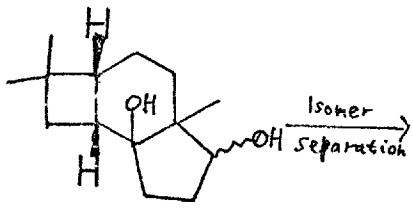
Corey's synthesis[92] was an early example of the olefin -enone photoaddition, which proceeds by addition to the olefin of the polarised triplet-excited enone, probably via an oriented complex.[93] Generally one isomer predominates. (scheme XXV)

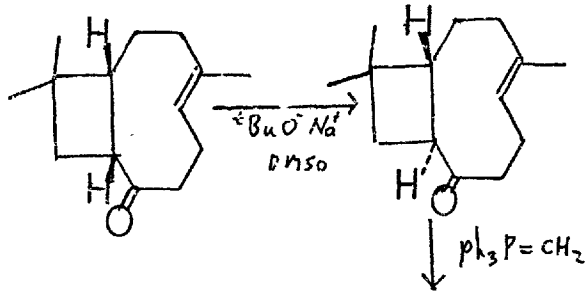
Scheme XXV



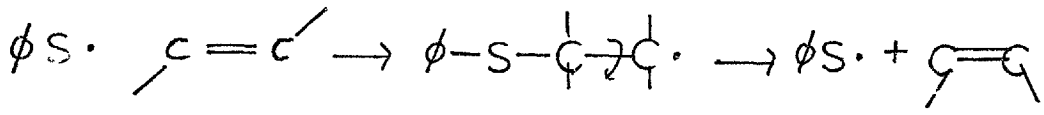
The cis and trans isomers were separable. In addition, the trans isomer was converted to cis (95) on heating or treatment with basic alumina.



(96) steps →  isomer with methyl and sec.-OH cis. (97)

(97) 1. TsCl, 2. Base →  (±)-caryophyllene

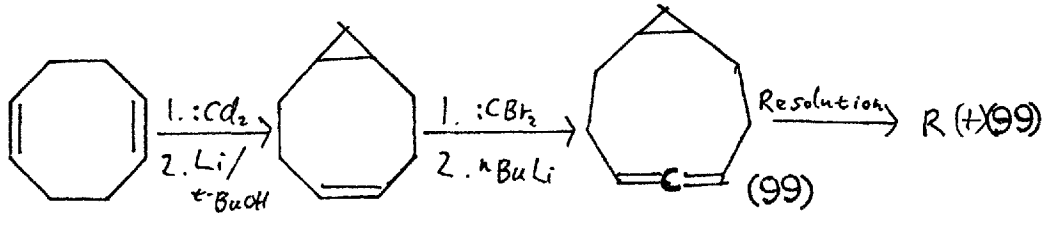
(-) caryophyllene is converted to (-) isocaryophyllene on photolysis in the presence of a trace of diphenyl disulphide to generate thiyl radicals.[94]

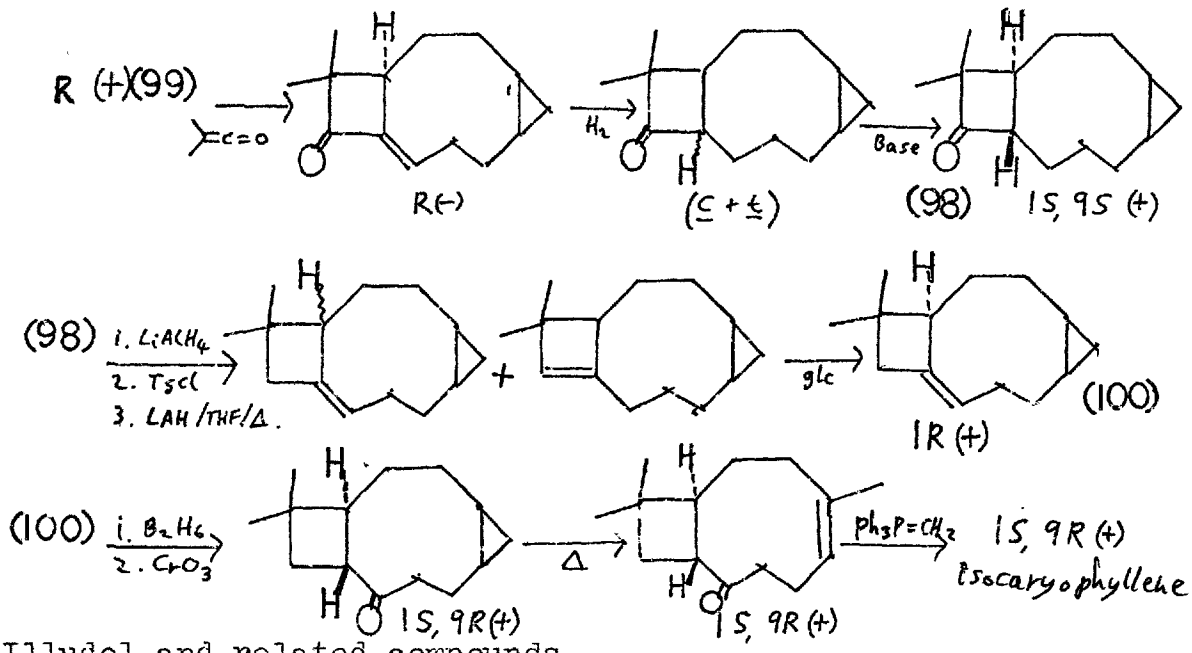


Sensitised photolysis also results in double bond isomerisation but oxetans are also produced by reaction with the ketone sensitiser.

(+)-isocaryophyllene has recently been synthesised[95] by resolution of an allene by hydroboration with diisopinocampheylborane, followed by treatment with keten. . . . The absolute configuration of (98) was determined from circular dichroism. (scheme XXVI)

Scheme XXVI



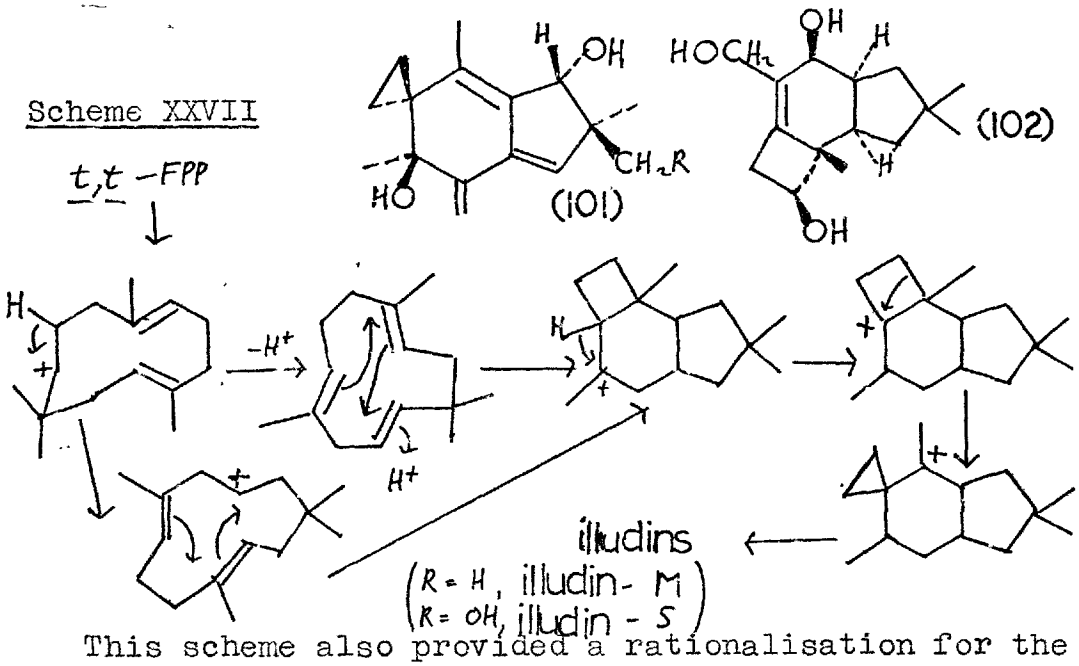


Illudol and related compounds

The fungal metabolites, illudins S and M (101) were isolated from Clitocybe illudens by McMorris and Anchel.[96] Illudin-S was found to be identical with a metabolite of Lampteromyces japonicus (Kawam) sing.[97]

X-ray structure determination gave the configuration shown. Both authors suggested the same biogenetic origin, via humulene or a humulene-type precursor (scheme XXVII).

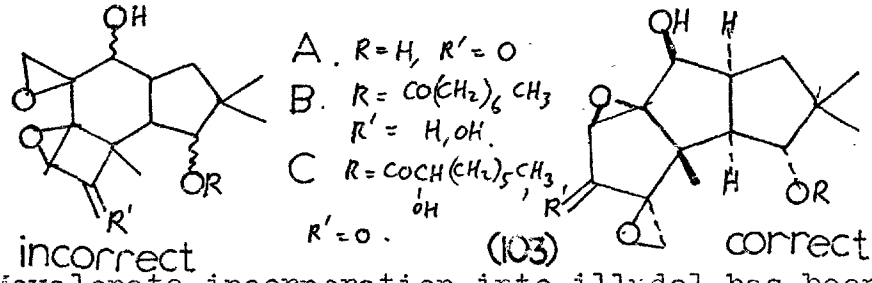
Scheme XXVII



This scheme also provided a rationalisation for the novel carbon skeletons of marasmic acid and hirsutic acid.

The subsequent isolation of illudol[98] from the same source[99] (C. illudens) was satisfactorily accounted for by the same scheme, and provided evidence for the postulated intermediates. The structure of illudol (102) was partly deduced by degradation.

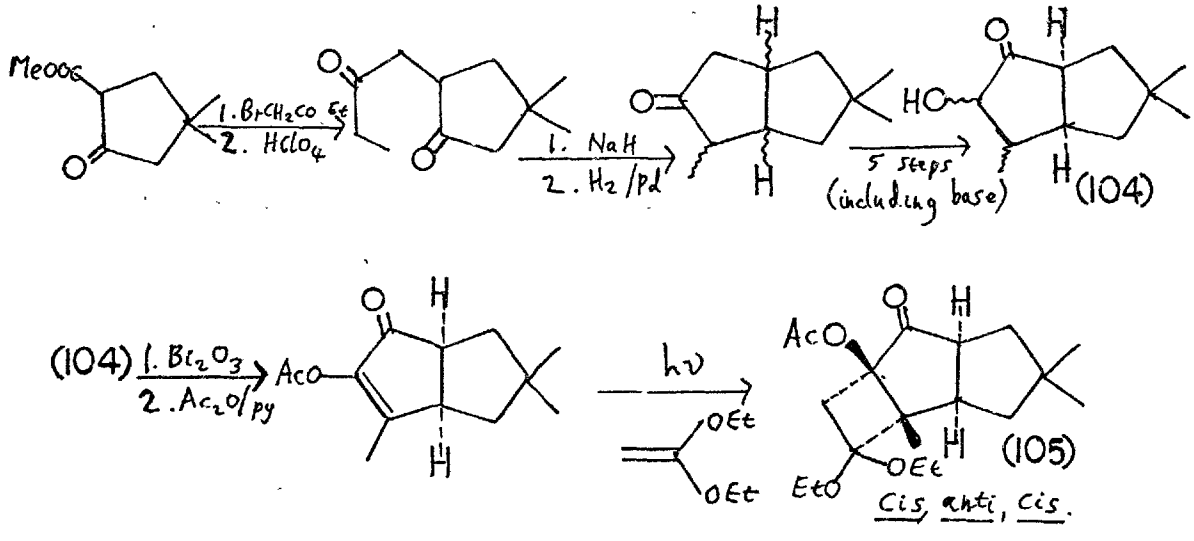
Coriolus consors yielded coriolins A, B and C, for which the same ring system as illudol was proposed.[100] These structures were subsequently revised (103).[101]



Mevalonate incorporation into illudol has been observed. In view of the secondary allylic alcohol function of illudol, zerumbone, rather than humulene, has been suggested as a precursor.

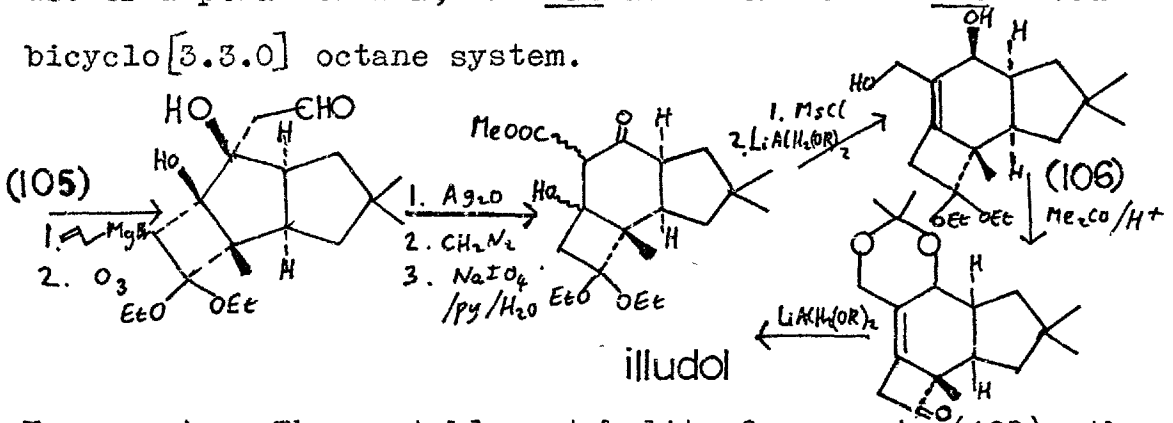
Illudol has been synthesised[102] (scheme XXVIII).

Scheme XXVIII

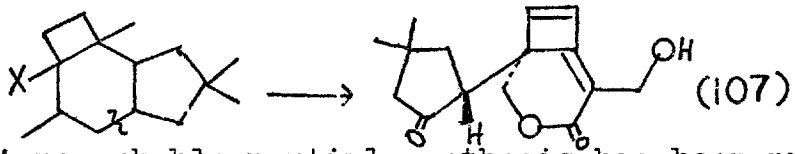


The orientation in the photoaddition was governed by the

use of a polar olefin, and exo addition to the cis-fused bicyclo[3.3.0] octane system.

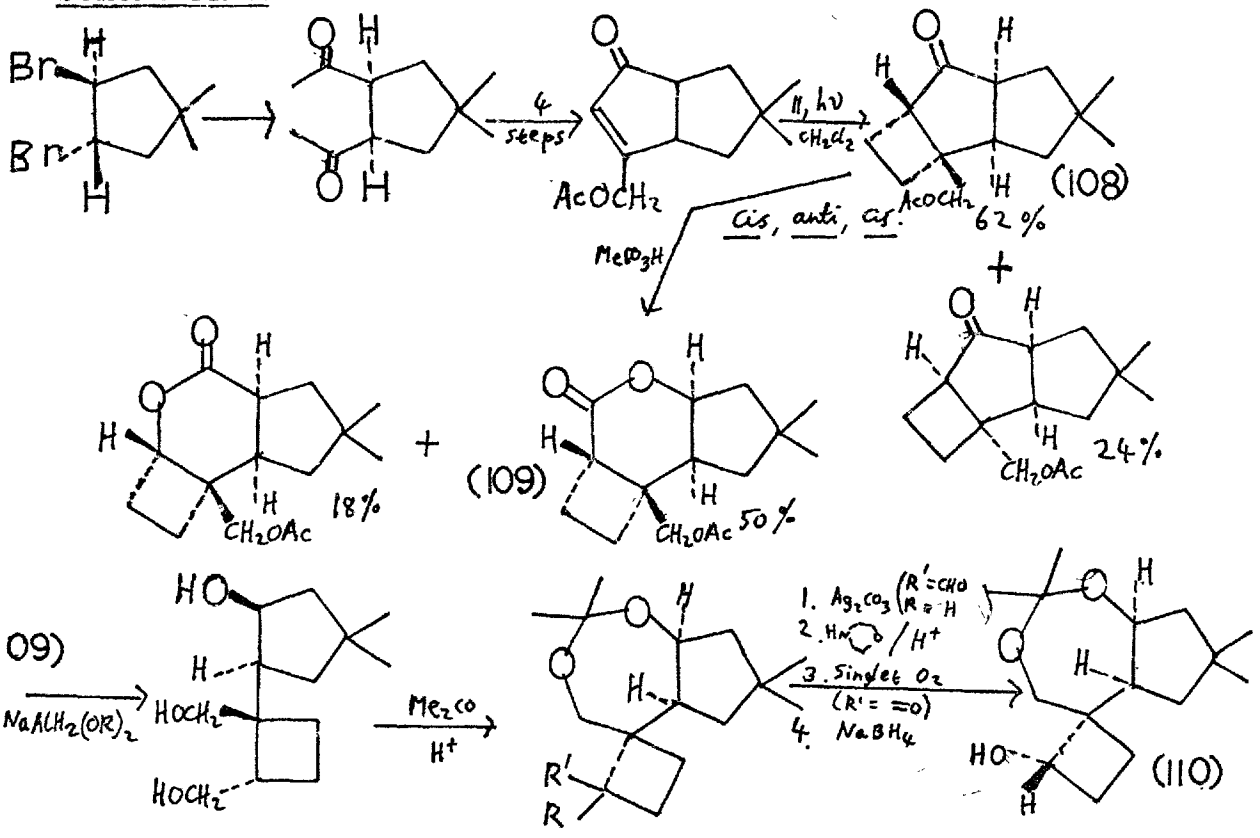


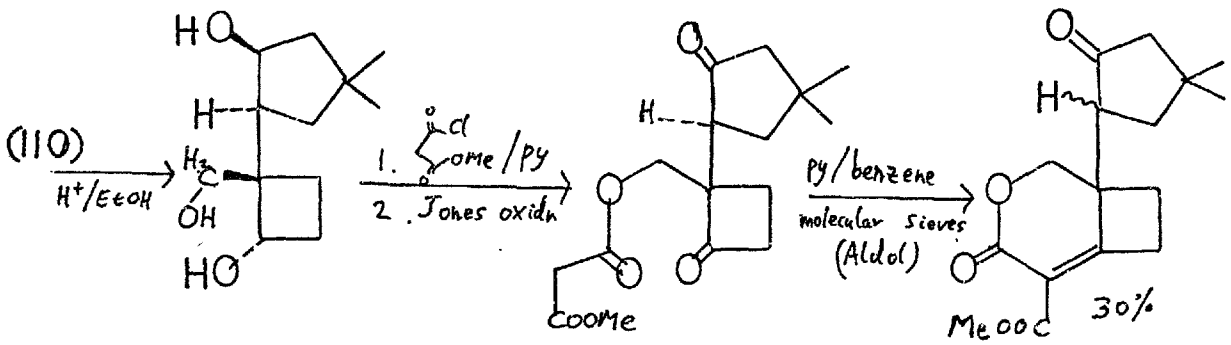
Fomannosin. The unstable metabolite fomannosin (107), the first known cyclobutene sesquiterpene, was obtained from the wood-rotting fungus Fomes annosus[103]. The structure was obtained by crystallography on a dibromobenzoylurethan of the more stable dihydrofomannosin.[104] (107) does not have a head to tail isoprenoid skeleton, and probably is derived from oxidative cleavage of the illudol skeleton:



A remarkable partial synthesis has been published[105] (scheme XXIX), unfortunately not completely stereospecific in the last recorded step.

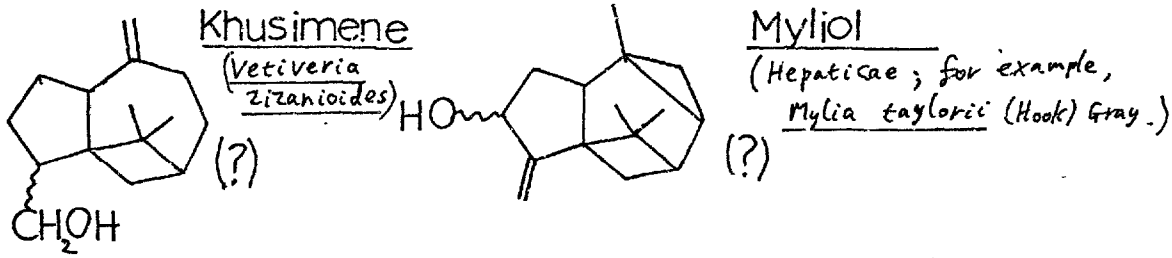
Scheme XXIX





Khusimene (Khusimol) and Myliol

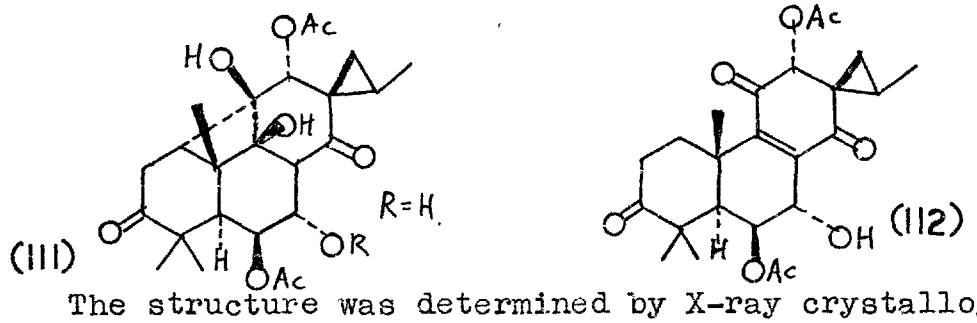
These compounds represent new carbon skeletons, but are as yet not satisfactorily characterised.



Both compounds are probably derived from guaiane precursors.

Diterpenes

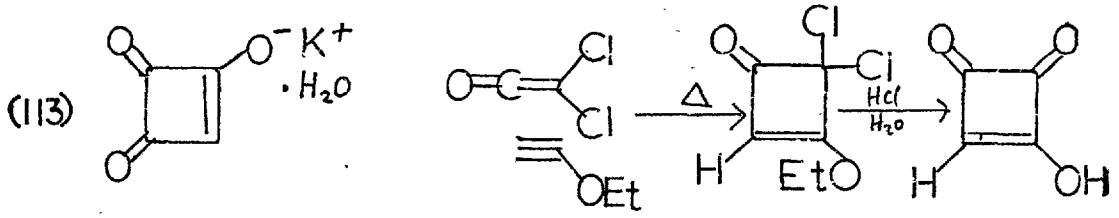
The recent isolation from Coleus barbathus (labiatae) of cyclobutatusin (111) provides the only known cyclobutane structure of the higher terpenoids.[108]



The structure was determined by X-ray crystallography (R = COC_6H_4Br). The biogenetic origin is uncertain. Cyclobutatusin, a minor component which occurs with barbatusin (112) may be a product of a biosynthetic sequence for quinonoid diterpenes, or alternatively may be a photolytic product of barbatusin, or a precursor.

Miscellaneous

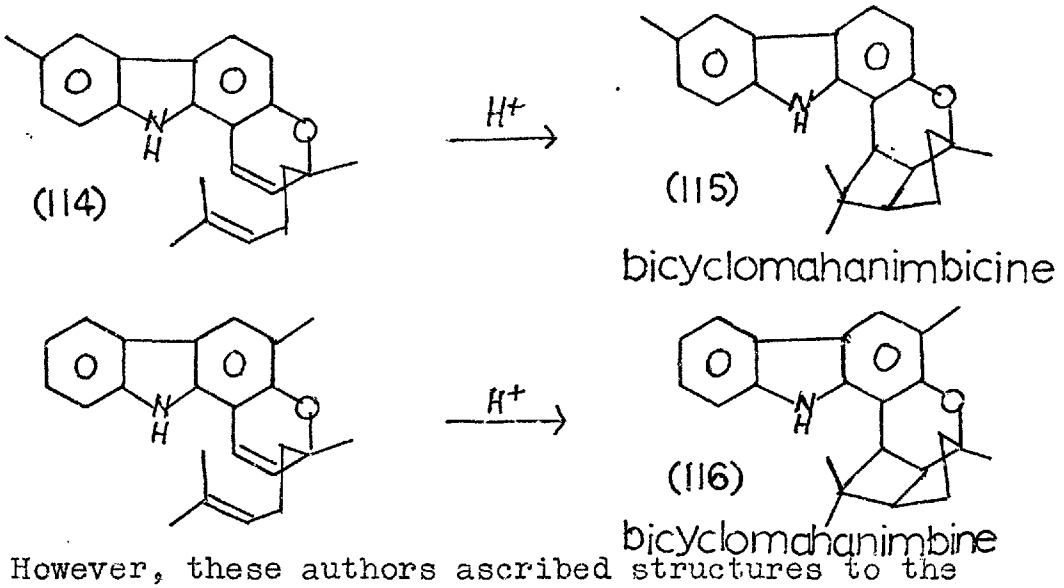
Moniliformin: A microbial toxin, moniliformin was isolated from Fusarium moniliforme,[109] from naturally-infected southern leaf blight-damaged corn seed. A different strain, Gibberella Fujikoroi, yielded the hydrated potassium salt of the same acid, whereas F. moniliforme provided the sodium salt. X-ray crystallography proved that moniliformin was a known compound (113), confirmed by an alternative synthesis:



The suggested biogenetic origin was microbial oxidation of myoinositol.

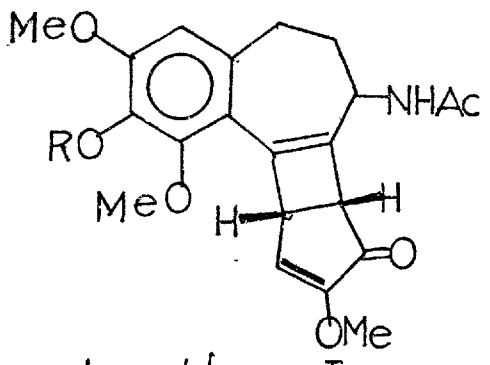
Bicyclomahanimbine and bicyclomahanimbicine: Murraya Koenigii Spreng contains a number of alkaloids derived from 2-hydroxy-6-methylcarbazole and 2-hydroxy-3-methylcarbazole. One member of each class was found closely related to cannabicyclol, along with precursors of analogous structures to the precursors of cannabicyclol.[110]

The structure of one of the precursors, mahanimbicine, (114) was proved by synthesis, employing a method related to Crombie's synthesis of cannabicyclol, and on acid treatment the precurscrs yielded bicyclomahanimbicine and bicyclomahanimbine, respectively.

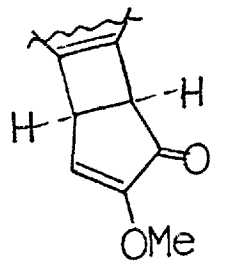


However, these authors ascribed structures to the cyclobutane products by analogy with the incorrect structures of cannabicyclol proposed by Korte, and a biogenetic scheme similar to that due to Kane for Korte's structure. Consequently Crombie suggested[35] the revised structures (115) and (116). As (115) and (116) are formed very readily on mild acid treatment of the dienes, they may be artifacts of isolation.

The lumicolchicines are a well-established class of cyclobutanoid alkaloids, often present as minor components with the corresponding tropolones in Colchicum species.[111] They may be synthesised by photolysis of the parent alkaloids. Alkaloid cyclobutanes will not be further considered.



Lumicolchicine-I



Lumicolchicine -II

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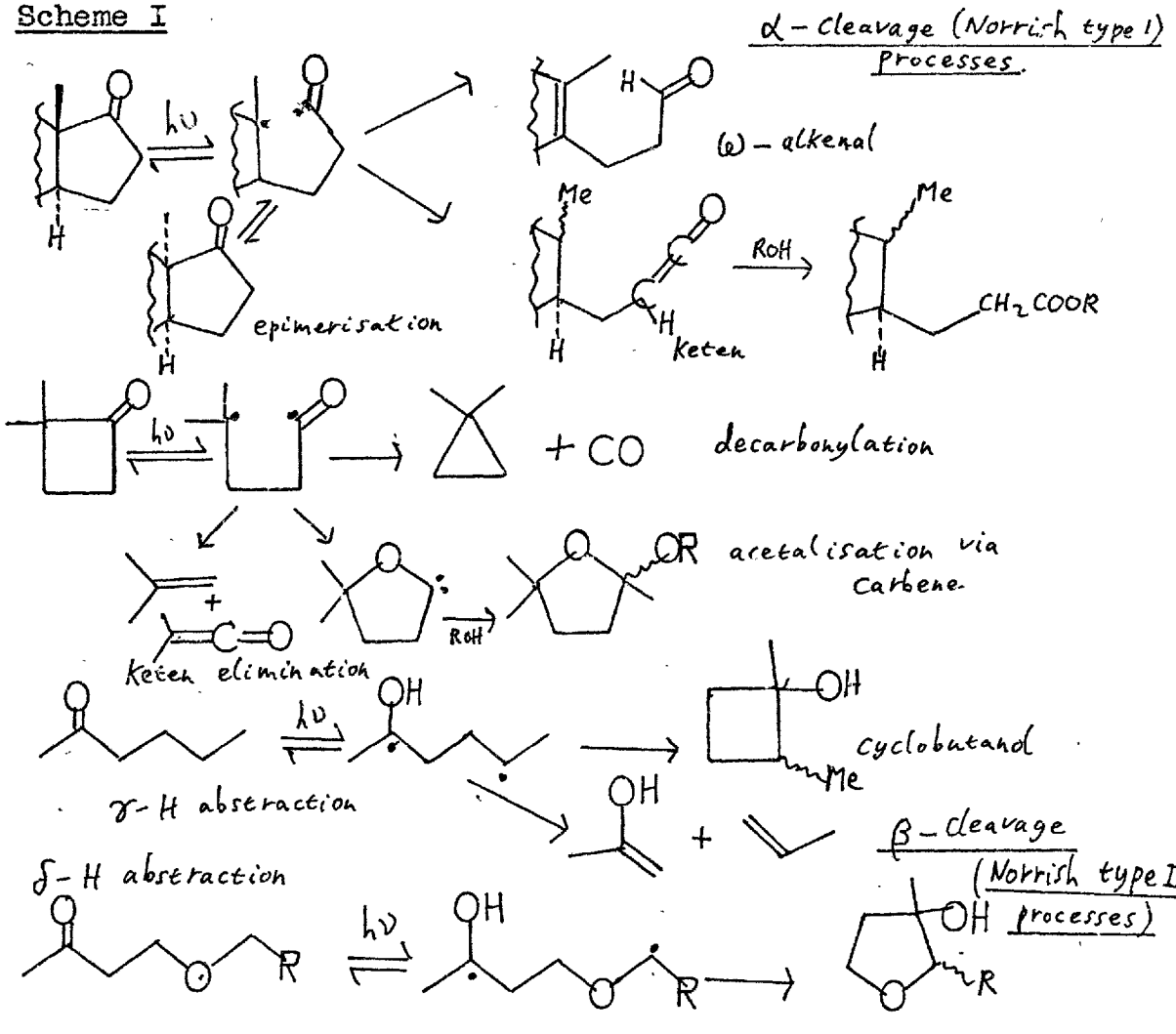
PART III: THE PHOTOCHEMISTRY OF NON-CONJUGATED KETONES IN SOLUTION

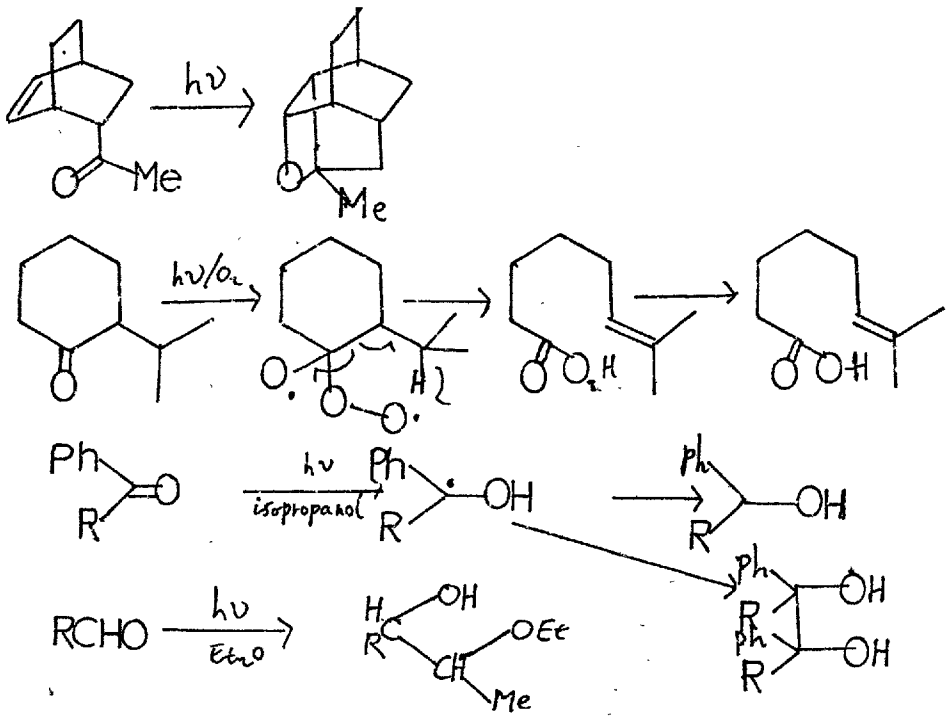
Despite the vast amount of work published in this field, the factors affecting product distribution are not well known. The following important classes will be considered: alkanones; cycloalkanones; unsubstituted phenyl alkyl ketones; certain nonconjugated unsaturated ketones; and ketones with certain oxygen containing functions. Aldehydes will be mentioned primarily as participants in secondary reactions.

The basic processes are very well established[1] (scheme I).

Scheme I



(Scheme I continued)



The singlet and triplet carbonyl nπ* states of non-conjugated ketones are the most readily accessible, the absorption maximum at ~280 nm corresponding to the n → π* transition. Electronic states of higher energy normally decay too rapidly to participate in chemical reactions. For alkyl phenyl ketones the nπ* and ππ* states are of very similar energy. The ππ* state may be of lower energy for substituted aryl ketones, whereas phenyl ketones undergo the n→π* transition except in polar solvents,[2] when the ππ* state is probably involved. The two states differ widely in electron distribution and consequently undergo quite different chemical reactions.

Evidence for reaction via the triplet state is normally obtained by sensitisation and/or quenching experiments, although it has been discovered that singlet state participation may also be affected by sensitisers and quenching reagents.[3]

Triplet reactions may also be quenched or sensitised by reaction products and so a change of mechanism with extent of reaction may be observed. Reactions from the singlet state may be detected by fluorescence and phosphorescence emission, and by reaction kinetics. Retention of configuration in singlet reactions is observed for both type II eliminations and oxetan formation, although these reactions are not considered to be concerted. Singlet biradical cyclisations are extremely fast, perhaps in the case of oxetan formation via oriented excited singlet complexes. Both type I and type II reactions proceed via simultaneous singlet and triplet paths. The relative importance will be indicated for each class of reaction.

Evidence for biradical intermediates is extensive. In the case of type I reactions of cycloalkanones, concerted reaction[4](proposed by Srinivasan) has been rejected on the evidence of investigations concerning (a) the isomer ratios of the alkenal products;[5,6] (b) the kinetics of ketone consumption and product formation;[7] (c) the effects of substitution on the quantum yields of alkenal formation;[8] (d) the effect of substitution on product ratios;[9] and (e) the labelling pattern in products formed from deuterated cyclohexanones.[10] Recently C.I.D.N.P. techniques have been used to demonstrate biradical intermediates and in many instances biradicals have been trapped, for example with furan.

The role of multiplicity of the electronic excited state is not clear in most reactions of the isolated

carbonyl function, except as one controlling factor of electronic and vibrational energy content of the species undergoing reaction. Although ground and excited state molecules are quite different chemical species, the electron distribution in $n\pi^*$ singlet and triplet states is similar. Both resemble the alkoxyl radical, $RO^{\cdot}$[11]

Additional factors which must be considered are the normal factors affecting ground state chemical reactions, namely, bond energies, steric interactions in the transition states, stereochemistry, conformational preferences, strain energies, solvents, and temperature. Activation energies for the fast competing paths are very low. Very small changes in the above factors may drastically change product ratios.

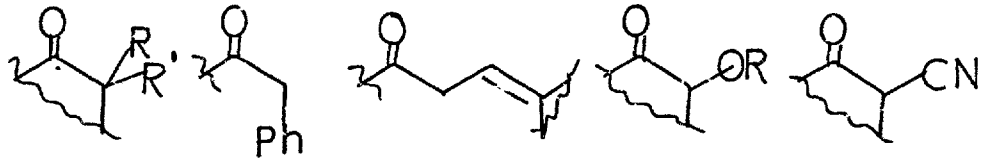
Difficulties are frequently encountered in the separation, or even detection, of isomeric products, which has led to incorrect[4] mechanistic proposals. Many reports refer only to a single product, sometimes in poor yield, and so it is difficult to assess the relative importance of reaction paths. Subsequent photochemical or thermal reactions of primary products must also be allowed for.

α-Cleavage (Norrish type I reactions)

a) Products alkenals, ketens and epimeric ketones.

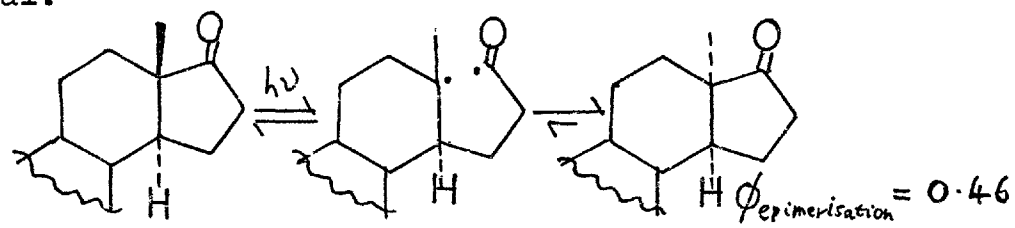
α-Cleavage reactions of cyclic ketones take place predominantly from the triplet state.[12] Acyclic ketone

reactions usually proceed via both the singlet and triplet states. Cleavage results from localisation of the electronic excitation energy of the carbonyl function in the weaker of the α bonds. Consequently this type of reaction is favoured by α-alkylation and by substituents which stabilise the resulting alkyl radical by orbital overlap(1):

(1) 

However, secondary or tertiary α-alkyl groups also favour γ-H abstraction from the side chain, and γ- or δ-H abstraction from an α-alkoxy function is frequently important.

The quantum efficiency of recombination of biradicals derived from cycloalkanones is often high, particularly for ketones with no α-substituents. Intermediacy of the biradical is supported by epimerisation of the starting material.[13]



The alternative hydrogen migrations which yield alkenals or ketens are both favoured by five- or six-membered transition states. The ideal transition state for an alkenal is less strained than that for a keten for unconstrained five- and six-membered cyclic ketones, and in the absence of other factors the alkenal is the major product. However, attainment of the ideal geometry of the transition state for hydrogen transfer to the acyl radical

is limited not only by ring size, but by ring substitution pattern. Alkyl substitution at positions other than α- to the carbonyl introduces rotational barriers to achievement of the transition state for hydrogen transfer which greatly decreases the quantum efficiency, ϕ_A, of this reaction path, both absolutely and relative to keten formation (Table I. ϕ_A = quantum efficiency for alkenal formation; ϕ_{SM} = quantum efficiency of disappearance of starting material)[8,14]

Table I

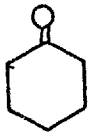
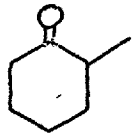
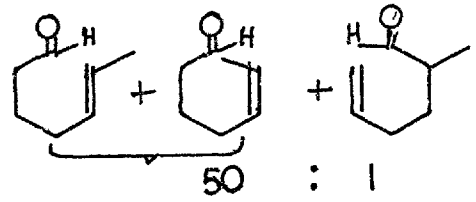
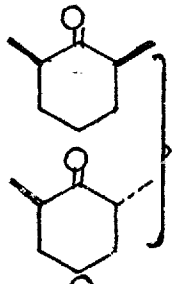
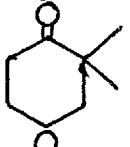
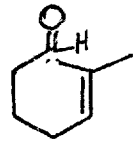
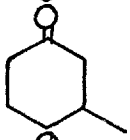
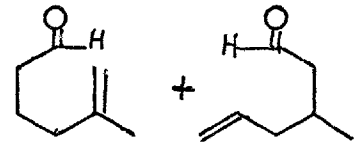
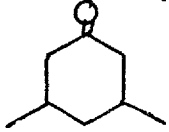
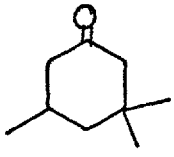
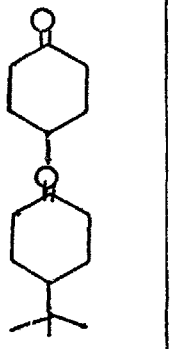
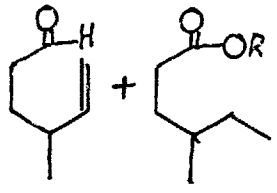
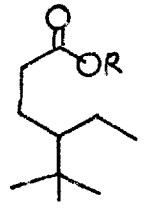
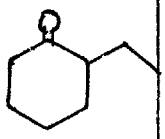
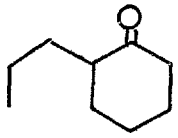
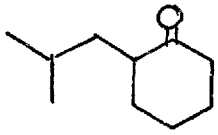
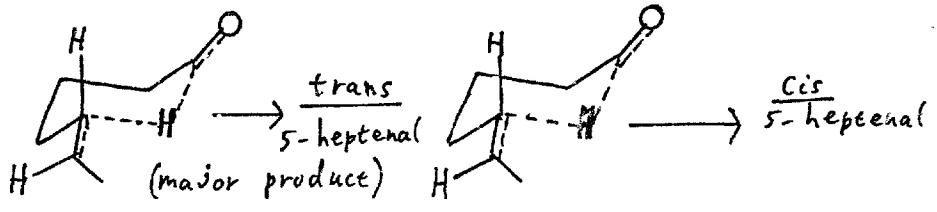
Compound	ϕ_A	ϕ_{SM}	Products (notes)
	0.09	0.20	
	0.42 (0.31)	0.50	 50 : 1
	0.40	0.55	Same isomer ratios[16] from cis and trans isomers.
	0.41	0.52	
	0.03[15]	0.08	 1 : 2
	0.005	0.03	
	0.002	0.02	

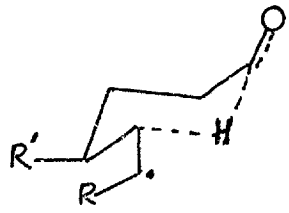
Table I (continued)

Compound	A	SM	Products (notes)
	0.07		 (keten trapped by ROH)
	zero		Reduction products +  (ditto)
	0.21		
	0.05		γ-H abstraction favoured
	0.03		ditto

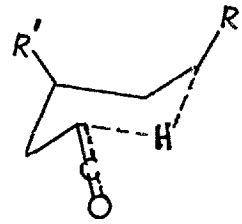
The preference for cleavage towards the substituted α-carbon atom of 2-methylcyclohexanone is considerable (table I).[5] Both cis and trans 5-heptenals were obtained. Conformational preference may explain the predominance of the trans isomer (2). The ratio is dependent on the wavelength of irradiation.[5]

(2) 

The low efficiency of the alkenal reaction for 4-alkyl cyclohexanones may be due to non-bonded interactions in the transition state for hydrogen transfer (3), which would not be involved in the keten transition state (4):



(3)

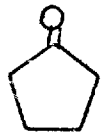
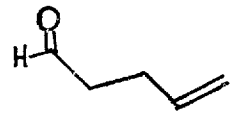
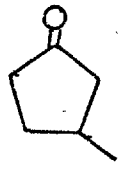
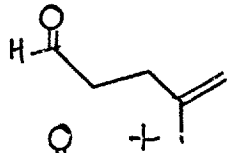
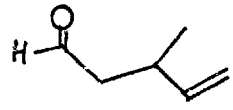
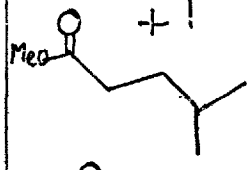
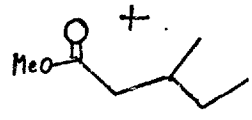
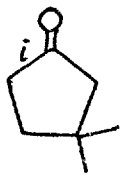
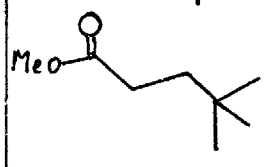
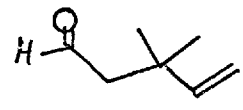
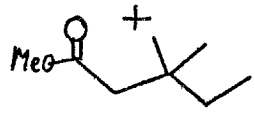
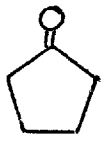
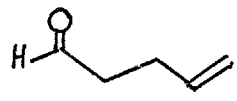
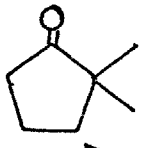
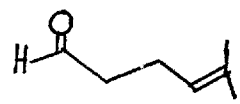
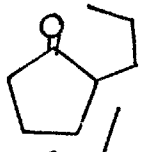
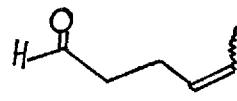
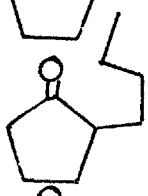
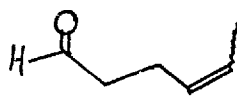
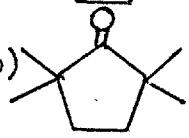
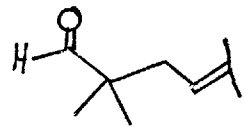


(4)

β-alkyl substituents not only reduce the rate of hydrogen transfer to the acyl radical, but the direction of α-cleavage is predominantly towards the least substituted carbon atom ,[10] presumably because hydrogen transfer from this direction is unaffected. Vibrational energy loss has also been suggested as a factor contributing to the β-alkyl effect.

Cyclopentanones give similar results (table II)[17] although the rate of α-cleavage is 10^1 - 10^2 greater.[14] Decrease of strain on ring fission has been proposed. Biradicals of higher vibrational energy would be anticipated, and in addition singlet state reaction is important for the fully substituted ketone (5).[18] The quantum efficiencies[14] of table II were obtained under different conditions and (a) and (b) are not directly comparable; (a) refers to photolysis in methanol, hence ketens were trapped as esters.

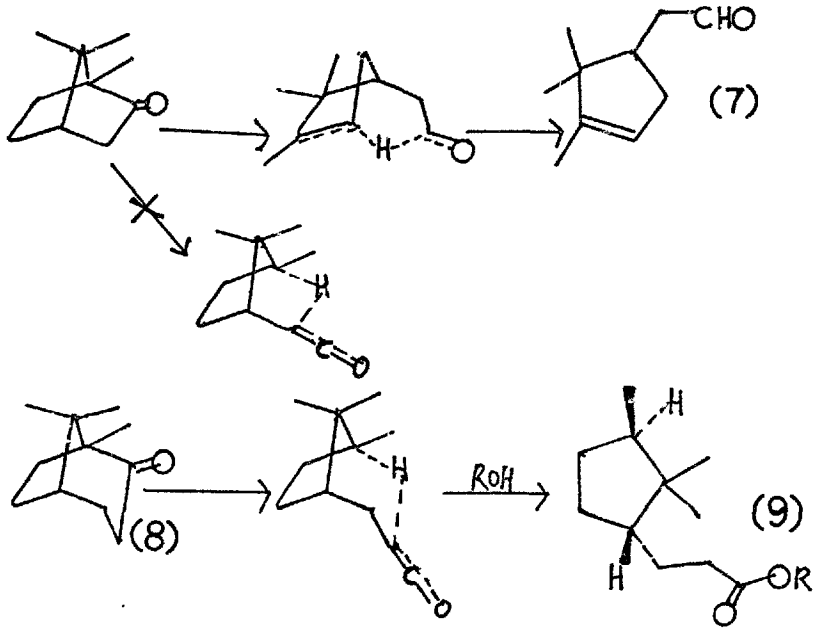
Table II

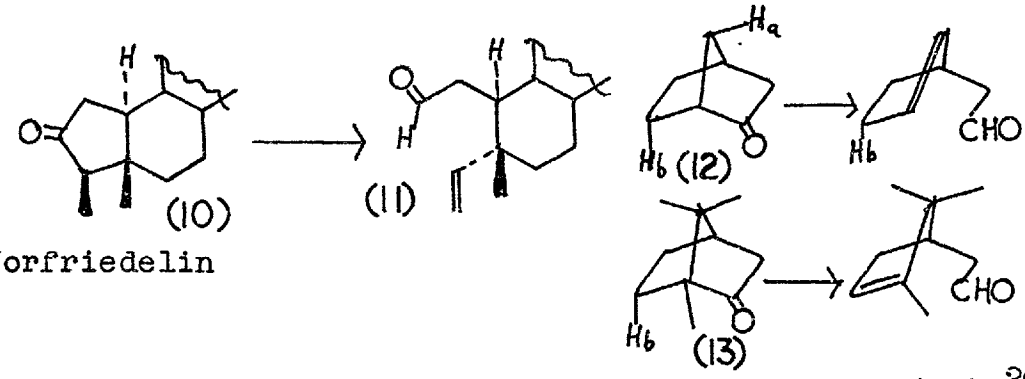
Compound	Products			
(a) 		ϕ =0.74		ϕ=0.03
(a) 		ϕ=0.08		ϕ=0.17
		ϕ=0.04		ϕ=0.07
(6)(a) 		ϕ=0.04		ϕ=0.14
				ϕ=0.27
(b) 		ϕ =0.11		
(b) 		ϕ=0.26		
(b) 		ϕ=0.38		
(b) 		ϕ=0.27		
(5)(b) 		ϕ=0.61		

3,3-Dimethylcyclopentanone (6) is particularly interesting as the transition state for hydrogen transfer yielding the keten after cleavage at bond (i) must actually be promoted by β-alkylation.

The aldehyde/keten ratio decreases with increasing temperature, which reflects the higher activation energy of the five-membered transition state leading to the keten.[19]

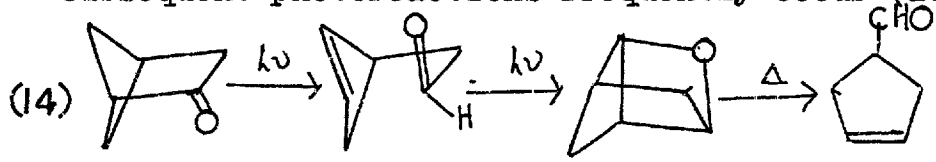
Constrained six-membered transition states favour alkenals. Camphor yields the alkenal[20](7), whereas homocamphor (8) produces the ester (9)[21] as the major product on photolysis in alcohol solvents, as the alkenal would require a seven-membered state. Norfriedelin (10), however, has been claimed to yield the aldehyde[22](11). (12) and (13) also yield alkenals; although highly substituted at the β-position, the β-alkyl functions are not free to rotate. The five-membered transition state with transfer of H_a is preferred for compound (12).



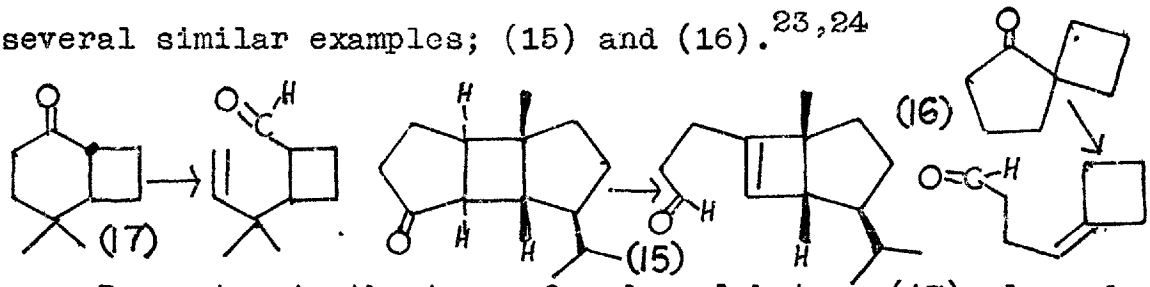


Norfriedelin

Subsequent photoreactions frequently occur (14):[20]

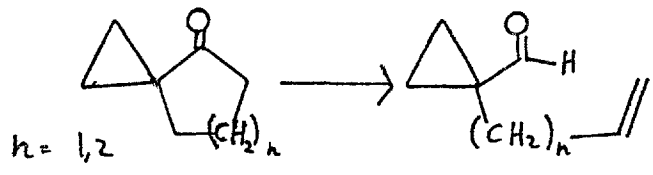


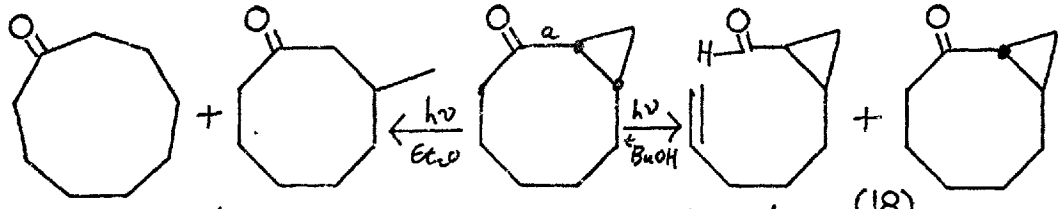
In this case, α-cleavage results in a strained cyclobutyl radical rather than a primary alkyl radical. There are several similar examples; (15) and (16).[23,24]



In contrast, the trans-fused cyclobutane (17) cleaved in the 'abnormal' direction.[25] The aldehyde was isolated as an oxetan in the presence of ethylene. The trans ring fusion was considered an important factor. Although the authors obtained the cis isomer by treatment with basic alumina, they did not report the photolysis of this product. 'Abnormal' ring cleavage will be further discussed.

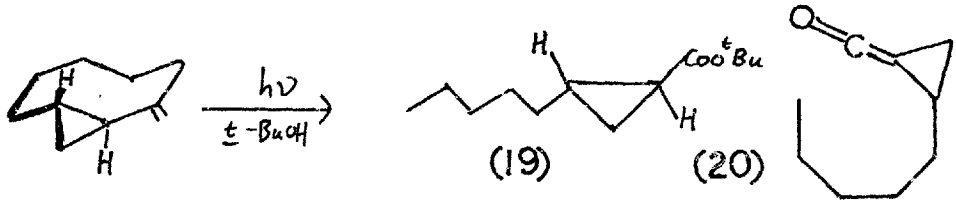
Ketones with an α-cyclopropyl function may react with involvement of the strained ring if p-orbital interaction with the excited carbonyl group is possible, but in the absence of this possibility the direction of α-cleavage is such as to avoid the cyclopropyl radical:[26]





(18)

Cleavage of bond (a) must result in rapid recombination, with some isomerisation to (18).[26] In complete contrast, the isolated trans isomer gave no ω-alkenal on photolysis in either t-butanol or ether. In t-butanol, only the keten-derived ester (19) was isolated, and in ether only polymer, probably also derived from the keten.



(19) (20)

Intermediacy of keten (20) and intramolecular hydrogen abstraction were proved by photolysis in t-C_4H_9OD, which gave no deuterium incorporation into (19). This provides one of the best examples recorded of a conformational effect on product distribution. Models suggest that maximised overlap of the excited carbonyl π-orbital with the internal cyclopropane bond p-orbitals is not possible in the case of the strained and relatively rigid trans isomer in the preferred conformation, and so the products of internal cyclopropane bond cleavage were not obtained. The keten was the observed product as the transition state for the alkenal would be the more strained. The preferred conformations of the more flexible cis isomer do allow good orbital overlap for cyclopropyl ring cleavage.

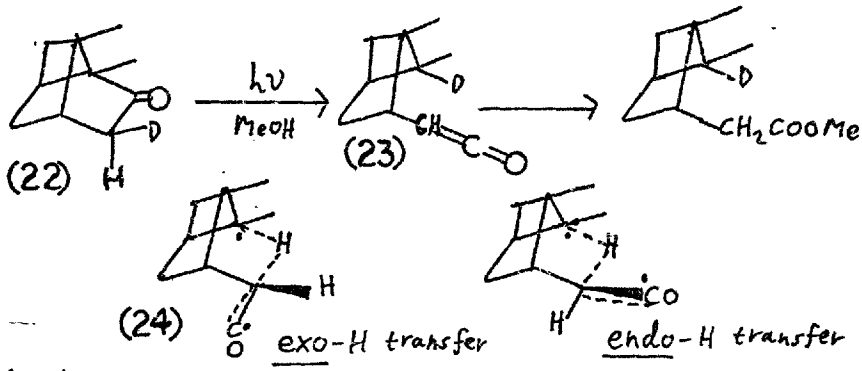
Cyclooctanone yields some type I products on photolysis. Medium and large ring ketones[27,15] without α-alkyl

substituents undergo γ-hydrogen abstraction and photoreduction.

Deuterium labelling experiments indicate little stereoselectivity for axial rather than equatorial hydrogen abstraction in the case of 3-methylcyclohexanone (21)[15] probably due to free rotation in the biradical intermediate of the alkenal product.

Carvone camphor (22) can only yield the keten (23).

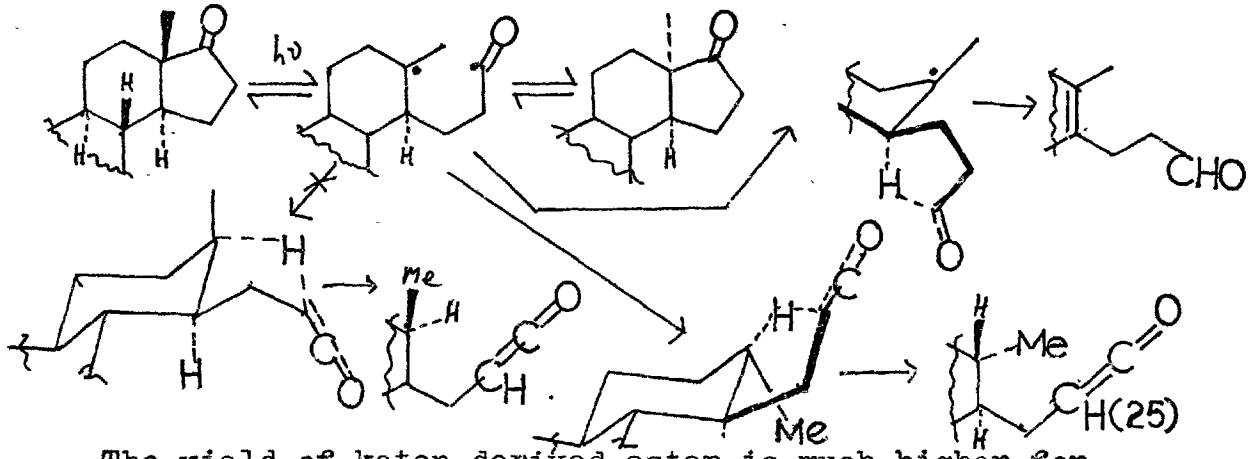
Greater than 90% exo-hydrogen transfer was found, despite the deuterium isotope effect of C-D bond breaking:[28]



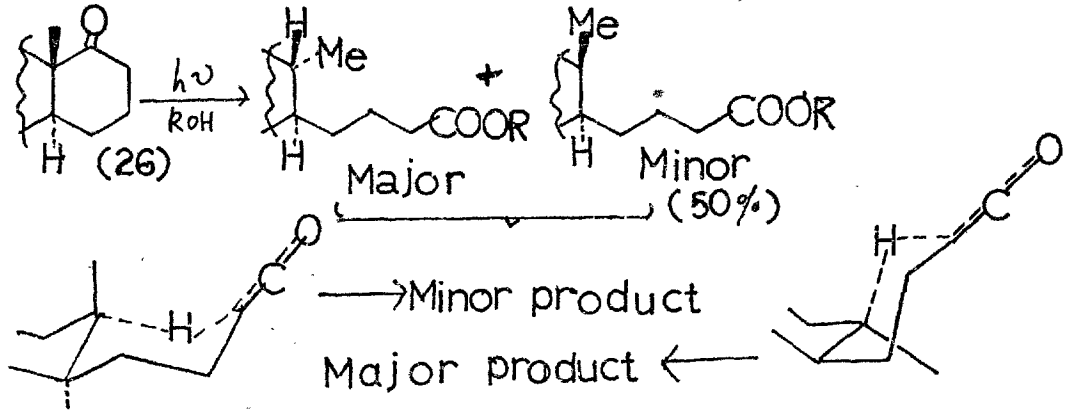
(24) is presumably favoured by reduced non-bonded interaction in the transition state. Alternatively, stereoselectivity could be a result of extremely fast hydrogen atom transfer after excitation of the carbonyl group, coupled with a tendency for the carbonyl to rotate away from the methyl groups, in the extreme a concerted reaction.

When photolysed in alcohols, 17-oxosteroids usually yield the epimeric ketones, the alkenal and the epimeric esters. If the terminus of the hydrogen shift yielding a keten becomes an unsymmetrical centre, its configuration

depends on the ring size.[21,29] In this case, one of the five-membered transition states is more strained than the alternative, and only (25) was obtained.[30]



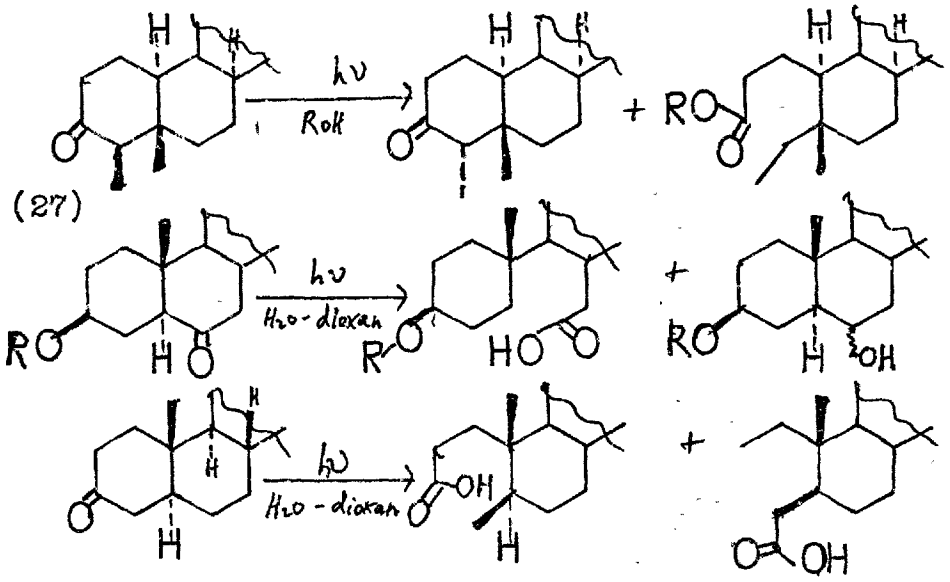
The yield of keten-derived ester is much higher for (26). Selectivity in hydrogen transfer is lower for cyclohexanones such as (26), as the difference in transition state strain is low:[29,30]



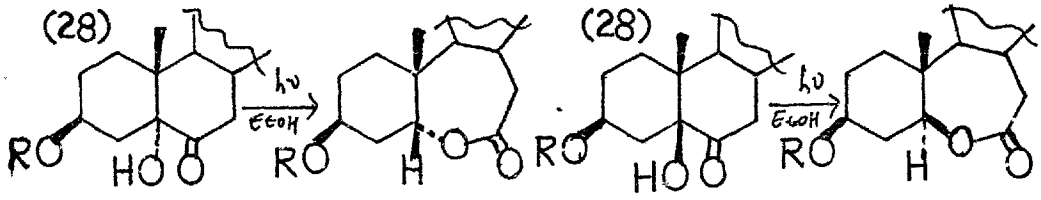
The intermediate ketens have been detected from the infra-red spectrum during low temperature photolysis in inert solvents.

3-[21,31,32] and 6-[21]oxosteroids (27) give the expected ketens and hence esters, but rarely in good yield. Products of decarbonylation and photoreduction are also obtained.[30] Steroids and triterpenoids with carbonyl functions in six-membered rings do not generally have hydrogen atoms suitably disposed to achieve the transition state for alkenal

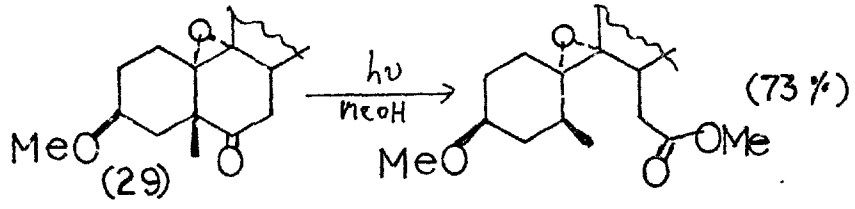
formation. If γ-hydrogen atoms are available, particularly from angular methyl groups, cyclobutanol formation (q.v.) is the characteristic reaction.[33,34,35]



Intramolecular trapping of a keten by a nucleophile can result in stereospecific reaction. (28) is a remarkable example as the radical centres usually allow attack by the rehybridised carbon atom on either side[32] of the molecule. Retention of configuration may be due to -OH-carbonyl hydrogen bonding:

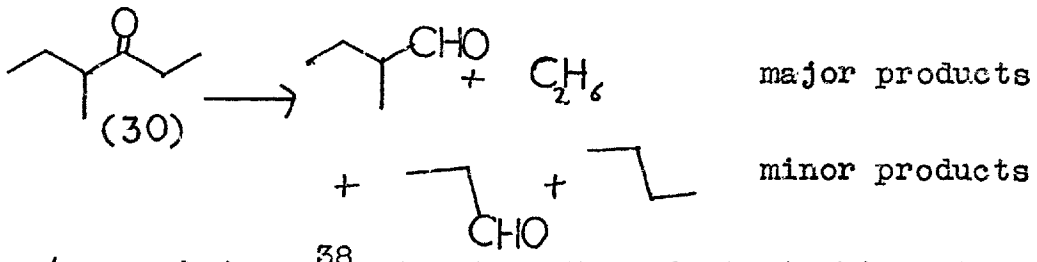


Retention of configuration was also observed for (29). Transfer of a deuterium label at C_7 to C_5 was demonstrated. The corresponding β-epoxyketone was photoinert.[36]

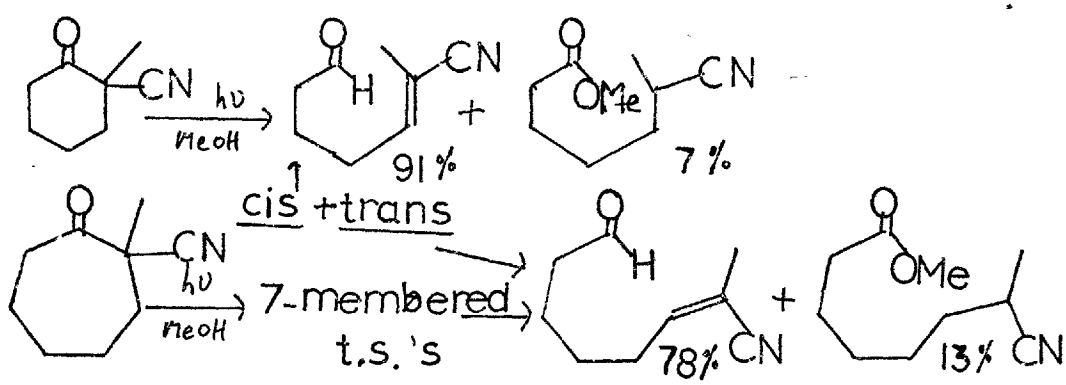


For acyclic ketones, predominance of type I or type II reactions depends on the substitution pattern. α-substituents aid α-cleavage, and γ-substituents favour γ-H

abstraction. Thus (30) underwent mainly type I fission, but surprisingly the cleavage was predominantly towards the unsubstituted carbon atoms. Solvent cage effects were proposed.[37]

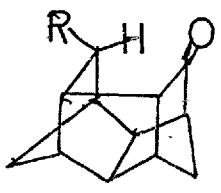


α-cyanoketones[38] give type I products in high yield by radical stabilisation. α-alkoxyketones, however, favour γ- or δ-H abstraction.



Type I reactions are completely suppressed if the geometry of the substrate does not allow efficient hydrogen transfer. Thus cyclobutanones give no alkenals or ketens, and (31) is inert.[39]

(31)



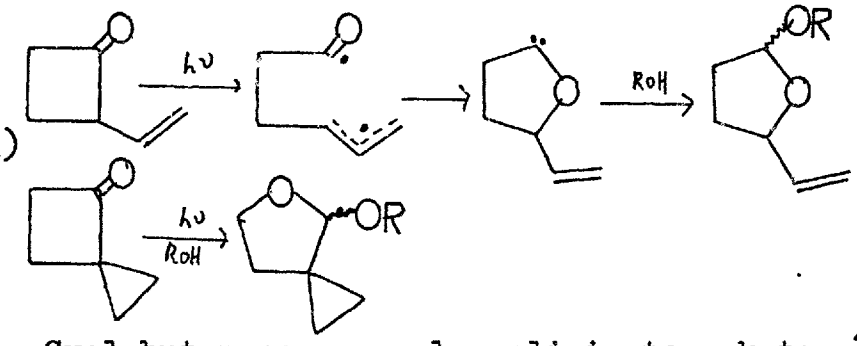
Solvents may reduce the importance of type I products by cage effects,[40,121] or by providing fast mechanisms for radiationless decay to the ground state. Alkenal products, and oxygen, may quench triplet state reaction, whereas certain solvents, in particular benzene, may act as sensitisers.

α-Cleavage: (b) Decarbonylation and oxacarbene formation.

Loss of carbon monoxide from the biradical followed by alkyl radical recombination or disproportionation is an important gas-phase reaction. In solution decarbonylation is very inefficient owing to rapid vibrational deactivation of the excited state except for a few classes of substrate. The principal classes are (i) ketones with two weak α bonds, or with α-substituents which can stabilise the radicals by p-orbital overlap:[6,41] di-tert.-alkyl ketones, benzyl ketones, and α,α'-dialkoxyketones, of which pyranoses are an important group; (ii) aromatic and tert.-alkyl aldehydes; (iii) cyclobutanones[42,43] and other small strained cyclic ketones,[18,118] for which type I and II reactions are sterically unfavourable. Decarbonylation occurs when skeletal restraints prevent isomerisation.

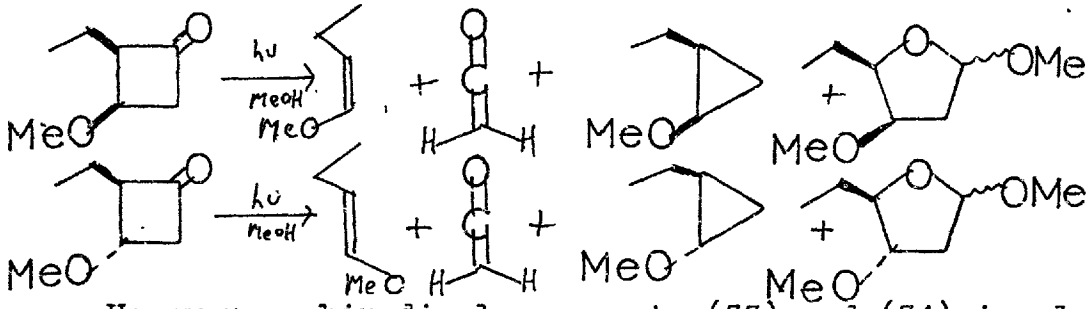
Oxacarbene-derived products commonly accompany decarbonylation and are most frequently encountered in cyclobutanone photolyses.[43] The intermediate is normally trapped as an acetal by reaction in an alcohol as solvent. Intramolecular trapping has also been observed.[43] (32) yields the acetal as the only significant product.

(32)

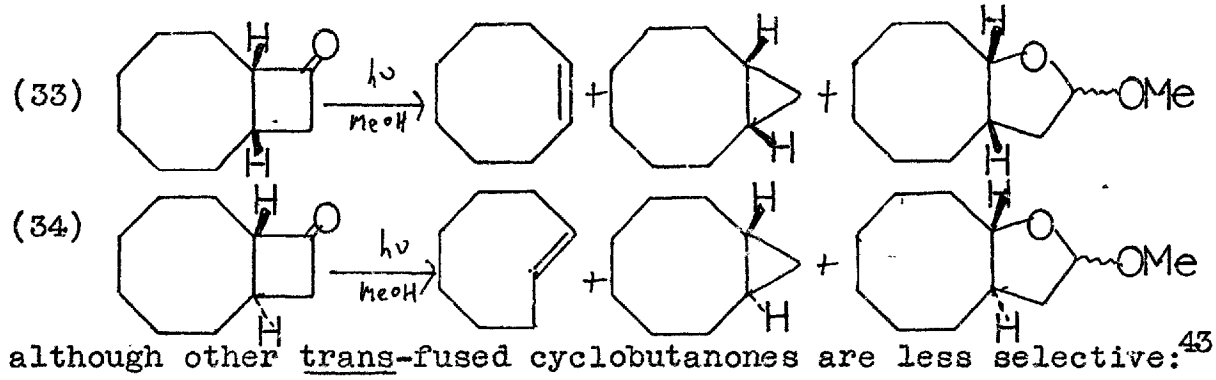


Cyclobutanones may also eliminate a keten.[44] A singlet biradical mechanism for both stereospecific elimination

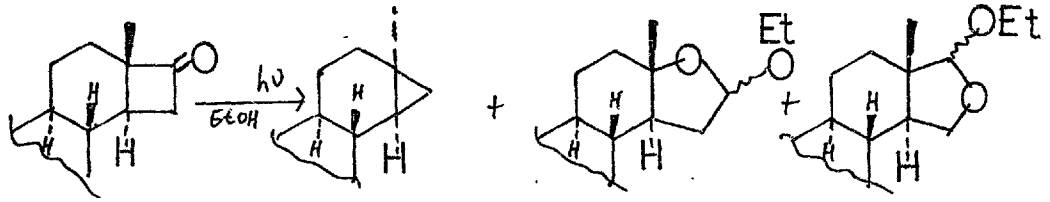
reactions is supported[45] by radical trapping, and in other instances by E.S.R. spectroscopy.



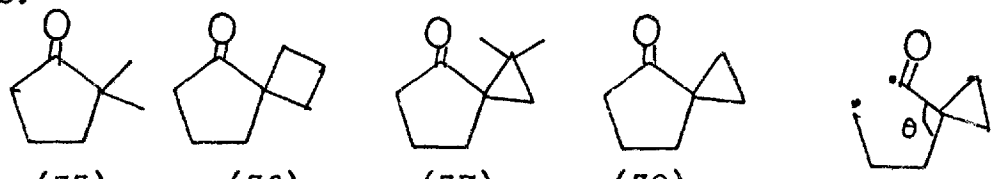
However, a biradical common to (33) and (34) is clearly not involved:[46]



although other trans-fused cyclobutanones are less selective:[43]



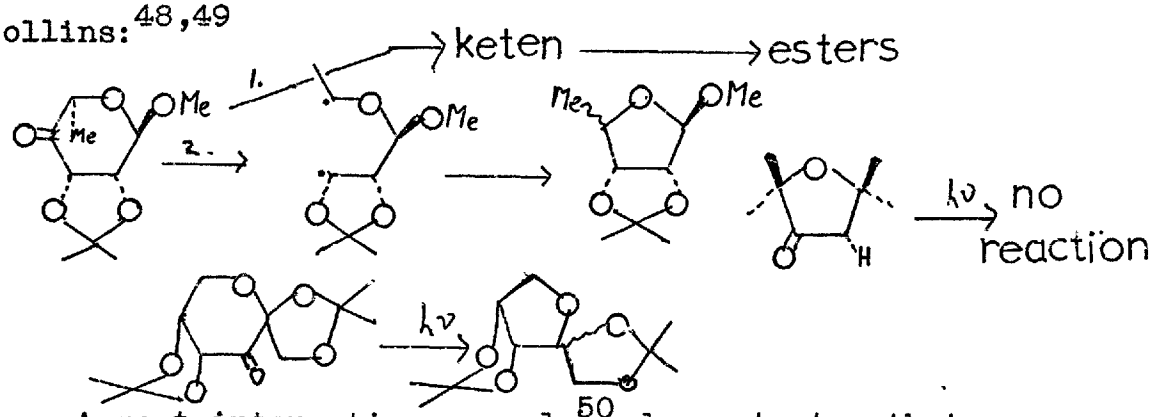
(35), (36) and (37) give no oxacarbene products, whereas (38) does:[23,47]



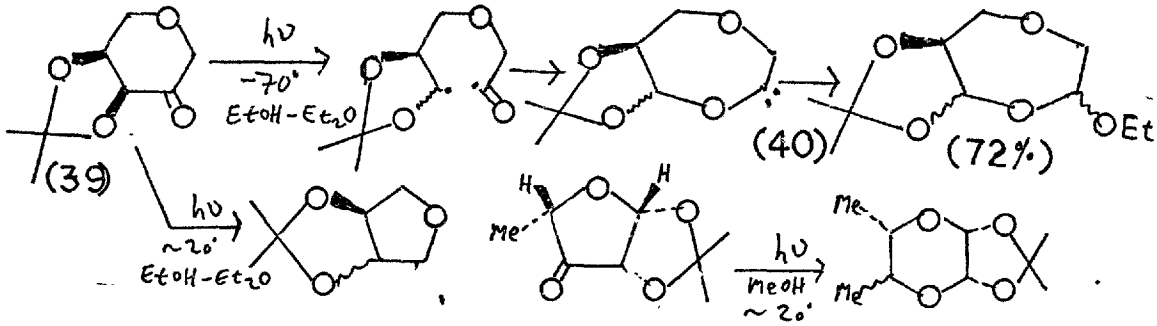
(35) (36) (37) (38)

(38) undergoes rapid type I alkenal formation, but ring expansion competes effectively[23] ($\phi_{alkenal}$ = 0.16, ϕ_{acetal} = 0.12). Resonance stabilisation and rehybridisation of the developing carbene by the cyclopropyl function in the intermediate biradical may be a factor. An alternative rationalisation assumed that the bond angle, θ, was critical for oxygen participation.

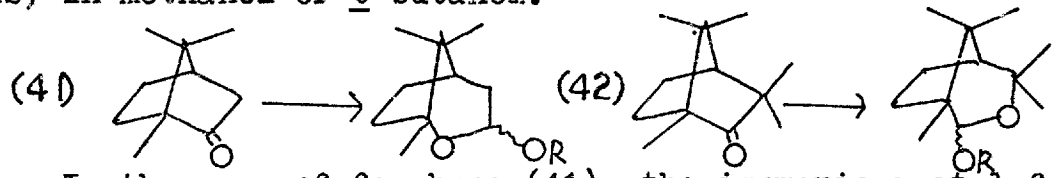
Non-stereospecific decarbonylation of a number of pyranoses, at room temperature, has been investigated by Collins:[48,49]



A most interesting example[50] demonstrates that oxacarbenes are favoured by radical stabilisation in the transition state, and also that the oxacarbene may be the product when the biradical possesses insufficient vibrational energy for decarbonylation. At room temperature (39) gave products of decarbonylation, but at -70°, (40) was obtained:



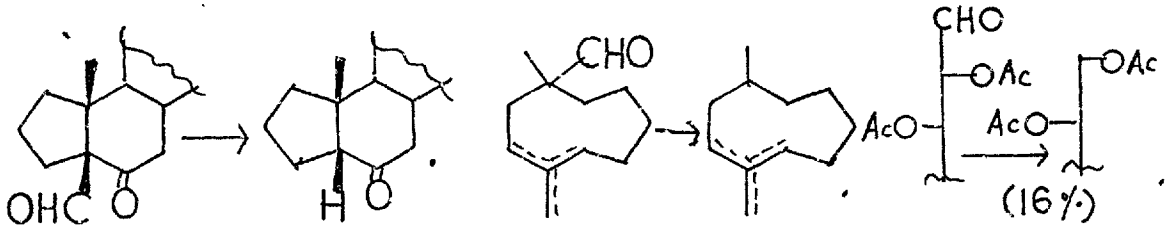
Acetals were minor products for photolysis of (41) and (42) in methanol or t-butanol.[51]



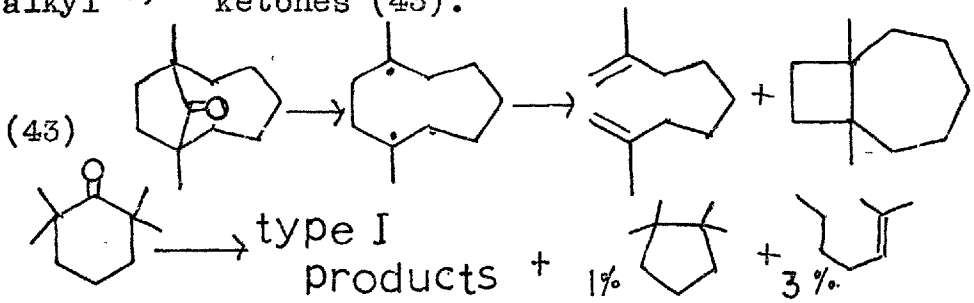
In the case of fenchone (41), the isomeric acetal from the alternative cleavage was not isolated.[52] The geometry of these rigid structures appears to be a factor as monocyclic five-and six-membered ketones do not yield oxacarbene products.

Tertiary aldehydes decarbonylate with retention of

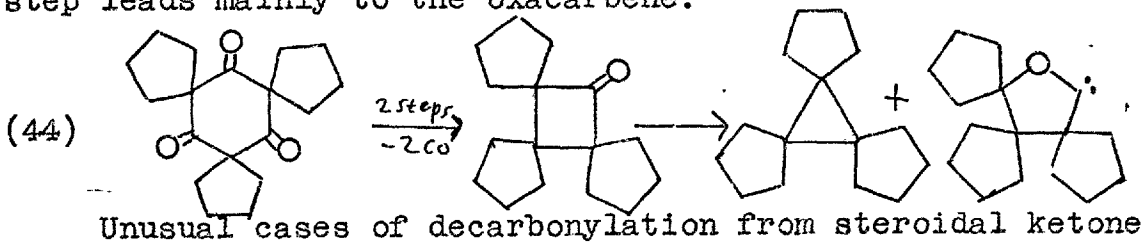
configuration via radical pairing from the singlet excited state.[53,119] Secondary aldehydes decarbonylate only very slowly, even with oxygen substituents on the α-carbon atoms,[54] via normal type I singlet and triplet reaction.



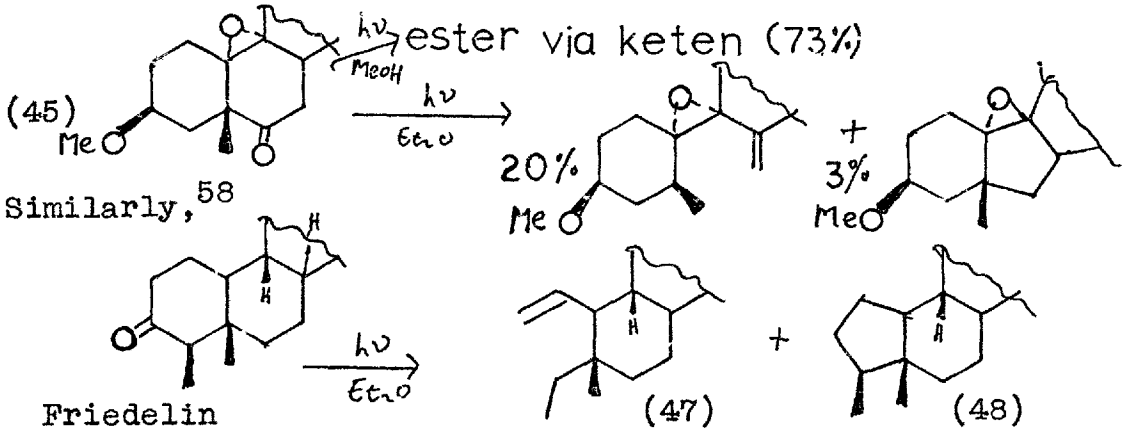
Aromatic aldehydes similarly lose carbon monoxide by a non-concerted mechanism,[55,75] as do benzyl[56] and di-tert.-alkyl[52,53] ketones (43).



Decarbonylation is efficient for (44), but the third step leads mainly to the oxacarbene:[57]



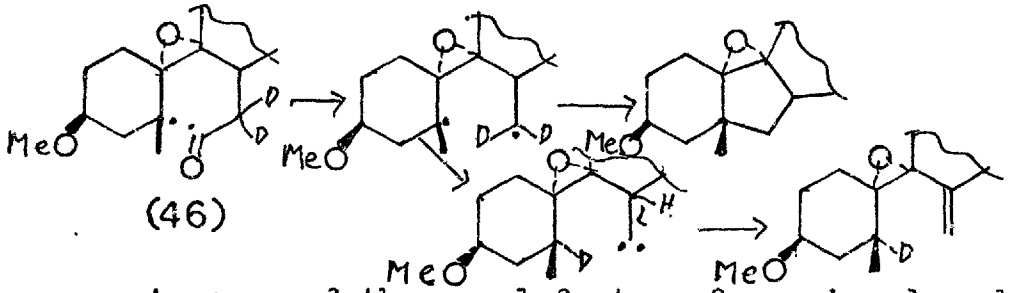
Unusual cases of decarbonylation from steroidal ketones in relatively high yield probably proceed via a carbene:[36]



Similarly,[58]

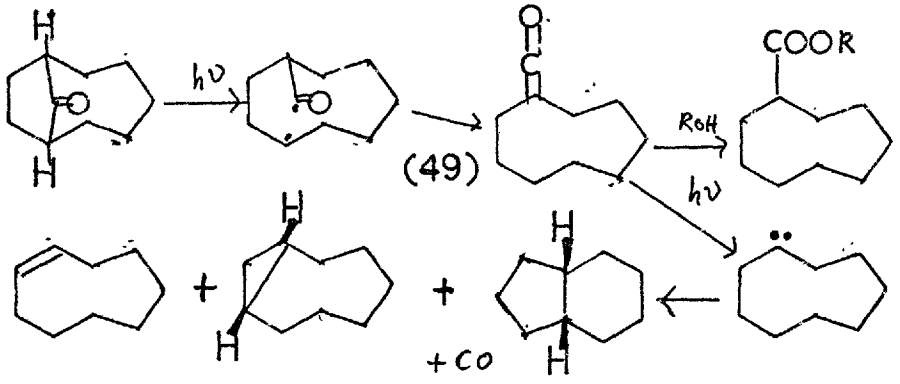
The proposed mechanism for (45) explained the transfer

of one deuterium label from C_7 to C_5, and also the retention of configuration if the two hydrogen shifts were synchronous, although the rigidity of (46) may introduce steric constraints to methyl epimerisation:



As none of the usual factors favouring decarbonylation are apparent, either (i) decarbonylation from the biradical following α-cleavage is generally a competitive process with hydrogen transfer leading to the keten, which is inefficient compared with type I alkenal formation reactions; this has not been recognised as the minor products in this class of reaction have rarely been investigated, even though yields of keten-derived products are frequently low; or (ii), the keten is an intermediate, which eliminates carbon monoxide giving rise to a carbene and hence the above products.

In the presence of an alcohol, (ii) would be much reduced. In either case, products analogous to (47) and (48) should be normal in reactions which yield ketens. The second rationalisation was proposed for the reaction:



for which the products are best accommodated by a carbene

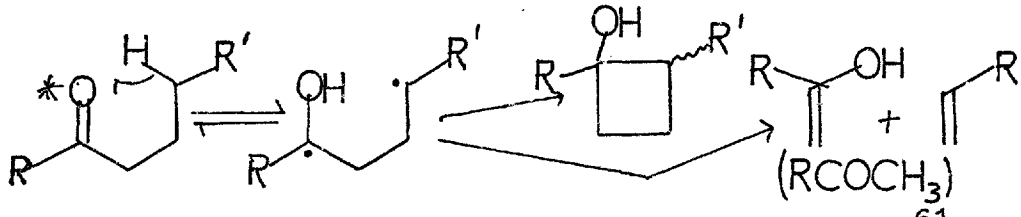
intermediate, rather than a biradical. This mechanism was confirmed by the preparation of keten (49) by a different route. Photolysis yielded the same products in the same ratio.

β-Cleavage.

Norrish type II reactions and cyclobutanol formation via γ-H abstraction; and related hydrogen abstractions.

For convenience, fragmentation and cyclobutanol formation following γ-hydrogen abstraction will be referred to as 'type II reactions.'

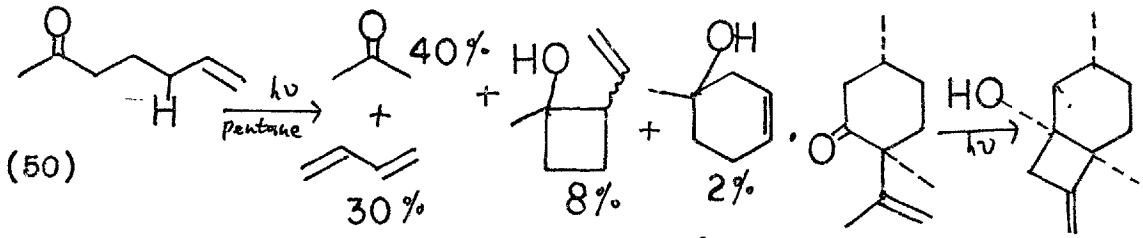
The excited carbonyl function may abstract a hydrogen atom, generally from the γ-carbon atom via a six-membered transition state. In the absence of other groups which may participate, the 1,4-biradical may undergo the reverse γ-H abstraction,[59] β-bond cleavage, or, if conformationally favourable, cyclisation to a cyclobutanol:[60]



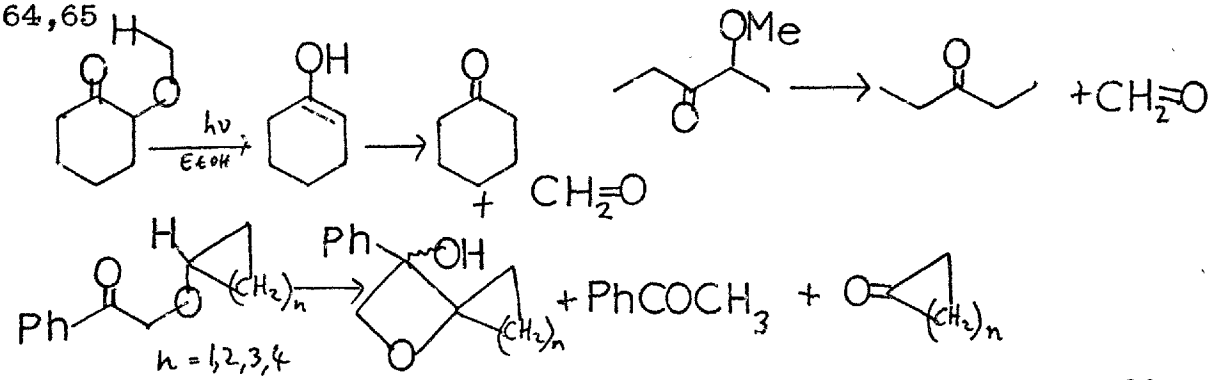
Triplet-state reaction is not stereospecific.[61] Singlet-state reaction competes with inter-system crossing and probably proceeds via a very short-lived biradical, yielding products with retention of configuration.[62] Concerted reaction has also been considered. Normally both states participate.

A weak γ C-H bond favours singlet reaction. The effect, if any, of substituents at other positions on the hydrogen abstraction step is controversial.[60] Fragmentation is, naturally, favoured by a weak β C-C bond.

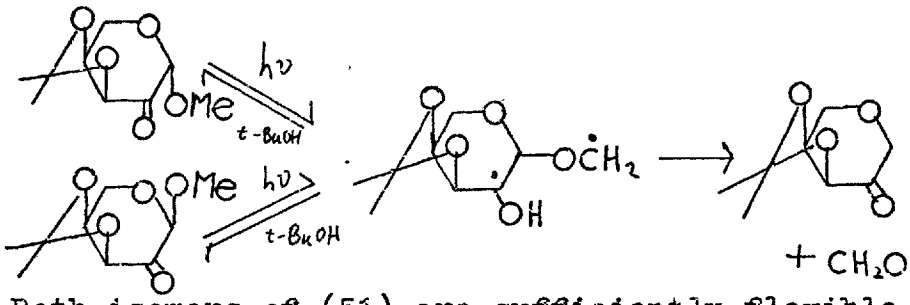
Alkyl phenyl ketones undergo very fast inter-system crossing to the triplet state, which is almost entirely responsible for subsequent reactions.[60] This function is commonly employed in investigations of type II reactions, as α-cleavage is almost completely suppressed. Type II reactions are also favoured by groups which can stabilise the γ-carbon radical by resonance. Thus short-chain ketones produce mainly ω-alkenals, whereas (50) yields type II products; the cyclobutanol and the ring-expanded alcohol are minor products for acyclic ketones for conformational reasons. The enol tautomers of the fragmentation products have been detected spectroscopically during photolysis.[63]



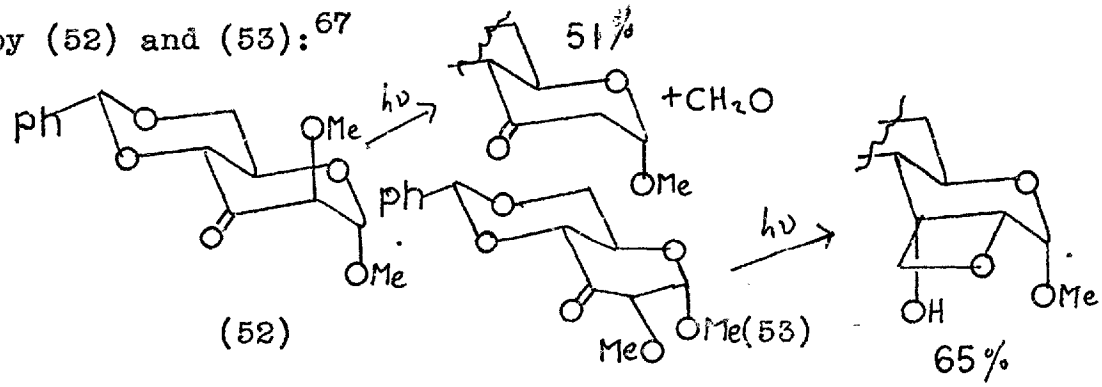
α-alkoxyketones, for which the β-atom is oxygen, are a major class of ketones for which γ-H abstraction is important;[64,65]



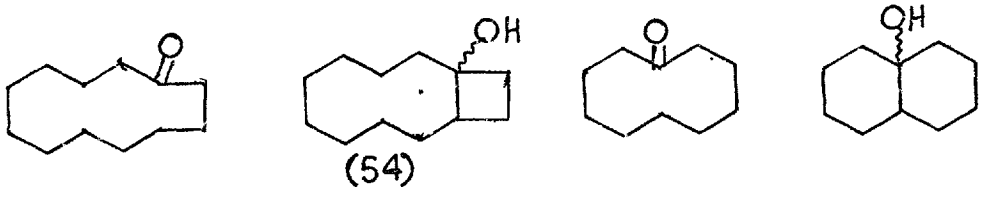
Similar examples have been provided by Collins' work.[66]

(51) 

Both isomers of (51) are sufficiently flexible to permit γ-H abstraction. The importance of a favourable conformation in the cyclobutanol reaction is demonstrated by (52) and (53):[67]



Conformational effects are also apparent for the medium- and large-ring cycloalkanones.[27] Type I reactions are inhibited partly by lack of α-substitution, and partly because of rapid γ-H abstraction from the singlet states. Cyclododecanone[68] yields 75% cyclobutanol (54), whereas cyclodecanone abstracts a transannular hydrogen atom:[69]



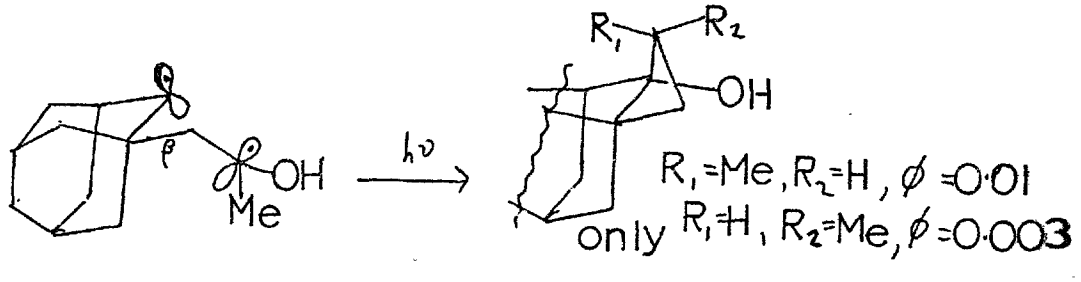
(54)

Increasing ring size greatly increases type II fragmentation, which suggests that this reaction is also limited by the ability of the ketone to adopt a correct transition-state conformation (table III).[27]

Table III

Cycloalkanone	Cyclobutanol products %	Reduction products %	Type II fragmentation products %
C_9	-	42	-
C_{10}	-	18	-
C_{11}	54	12	8
C_{12}	75	7	8
C_{13}	68	5	18
C_{14}	51	<1	30
C_{15}	28	<1	52
C_{16}	22	<1	58

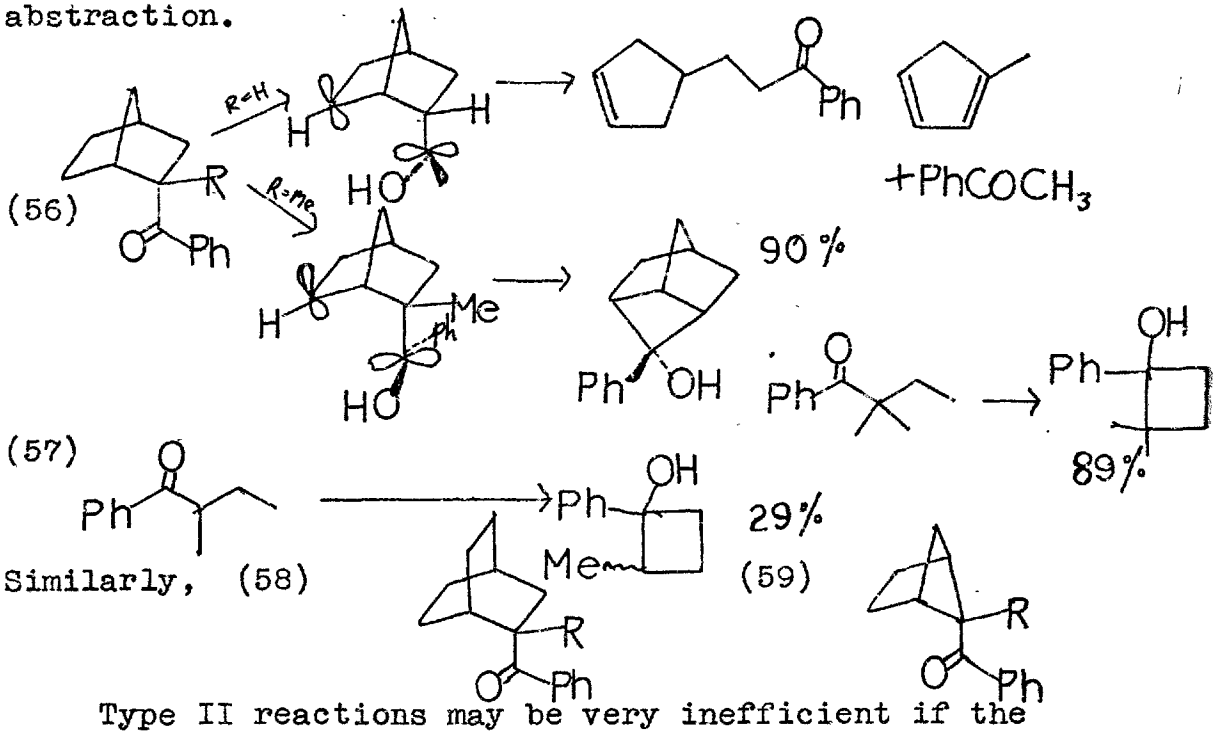
Conformational restrictions on type II reactions have been studied with phenyl ketones and methyl primary alkyl ketones to minimise type I products. Turro[70] has suggested that elimination will only occur efficiently when the β C–C bond and the radical centre 2p orbitals are parallel. For (55),[71] the β bond is held rigidly orthogonal to the radical centre, and so elimination is prevented, although the strain energy of a bridgehead double bond may also be a factor if elimination were virtually concerted. If fragmentation is prevented, the cyclobutanol may be obtained in very high yield, although the quantum yield is frequently low due to radiationless decay.



(55)

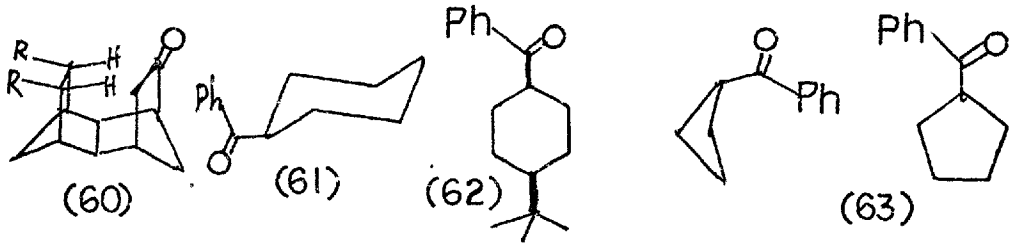
p-orbital overlap is readily prevented by non-bonded interactions in the transition state, even for acyclic ketones. Thus in all the following examples (56 - 59),[72] if R = Me, the cyclobutanols were obtained in high yield, and if R = H, elimination predominated. For (56), phenyl-methyl eclipsing prevented attainment of the transition state for elimination.[73]

The transition state geometry for hydrogen transfer is controversial.[122] M.O. calculations predict a planar transition state, but a non-planar state with minimal torsional strain is currently favoured. The rate of abstraction is definitely conformationally dependent; the greater the number of degrees of freedom the lower the efficiency of abstraction.



Type II reactions may be very inefficient if the

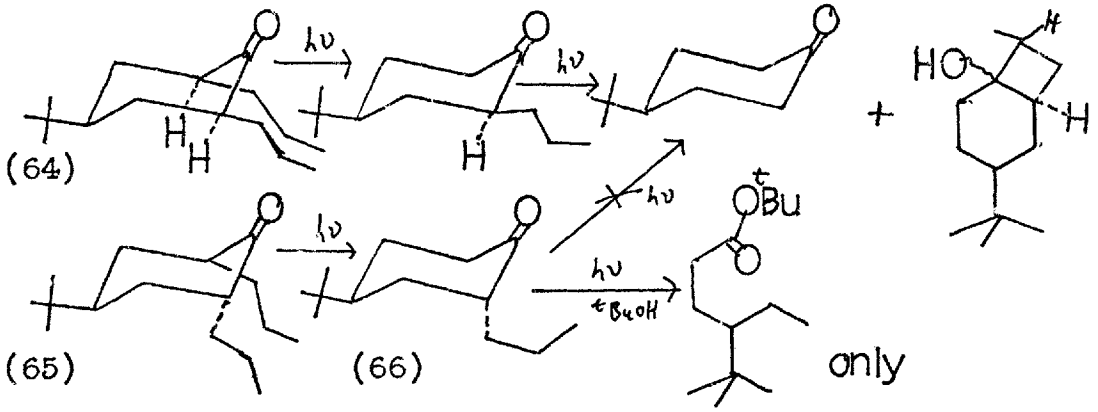
γ-hydrogen atom is inaccessible for configurational or conformational reasons. Thus (60),[39] (61) and (62)[74] do not readily permit γ-H abstraction.



(60) (61) (62) (63)

Cyclobutyl phenyl ketone slowly gives type II products, whereas (63) undergoes rapid and efficient β-cleavage.[74]

The steric requirement was demonstrated clearly by (64) and (65).[76] The cis and trans ketones were not interconverted during photolysis. Only equatorial cis n-propyl functions were eliminated, the stereoelectronic requirement being that the hydrogen transferred must be in the same plane as the carbonyl function. Elimination from the boat conformation should be possible for (66).but was apparently not involved. In all cases the cyclobutanols and ketens were competing products. Cyclobutanol formation was favoured over fragmentation from triplet-state (sensitised) reaction, probably due to the lower energy of this state.



(64) (65) (66) only

γ-H abstraction from the side chains of 2-alkycyclohexanones is greatly favoured by γ-carbon substitution, but for the series(table IV) conformations are again apparently

important.[77] Type I reactions accounted for the major alternative paths.

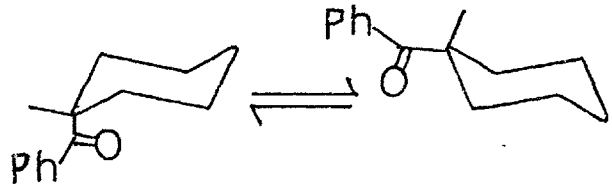
Table IV

R =	Et	n-Pr	iso-Pr	iso-Bu	t-Bu
% type II fragmentation	<1%	65%	14%	77%	49%
γ-H abstracted	CH_3	CH_2	CH_3	CH	CH_3

The quantum yields, however, actually decrease with change of the γ-H environment from $-CH_3$ to $-CHR_2$ in the case of alkyl phenyl ketones, possibly for steric reasons.

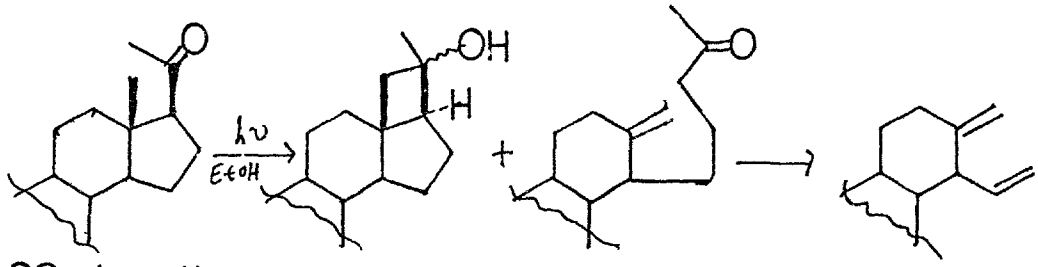
An attempt to correlate ground-state conformational populations (from ^{13}C N.M.R. investigations)[91] with the ratio of the rate constants for cyclisation and elimination for (67) was not promising.

(67)

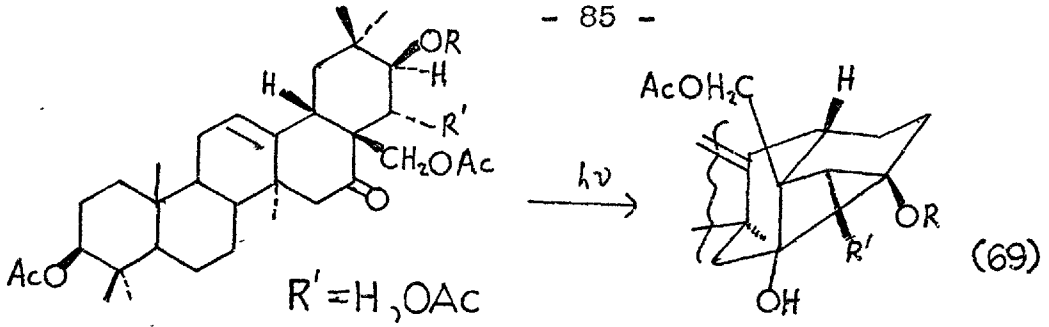


Triterpene and steroidal ketones frequently give good yields of cyclobutanols when the configuration is favourable, whereas type II fragmentation is unusual. (68) is an exception. (69) is favoured both by the cis ring fusion and the alkoxy function.[79]

(68)

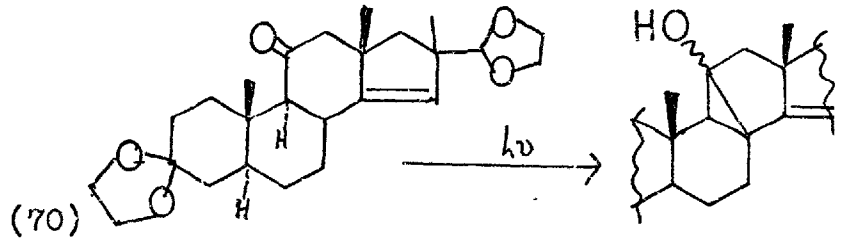


3,3-dimethoxypregnan-20-one



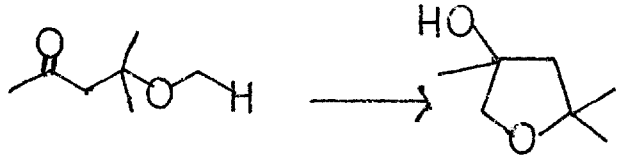
(69)

A case in which a five-membered transition state is preferred, due to radical stabilisation, rather than γ-hydrogen abstraction from the angular methyl group, is unique[80] except for examples where nitrogen lone-pair participation was possible.

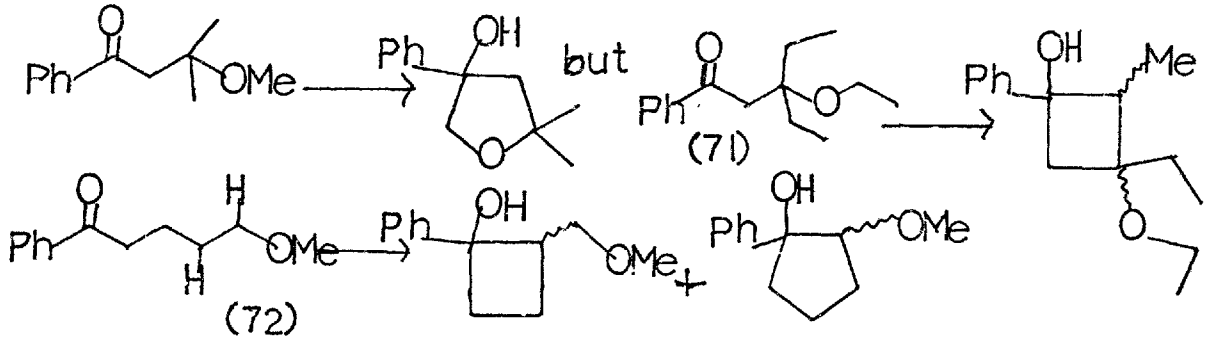


(70)

7-membered transition states are important if a δ C-H bond is much weaker than available γ C-H bonds, particularly for β-alkoxyketones, which generally yield furans:[81]

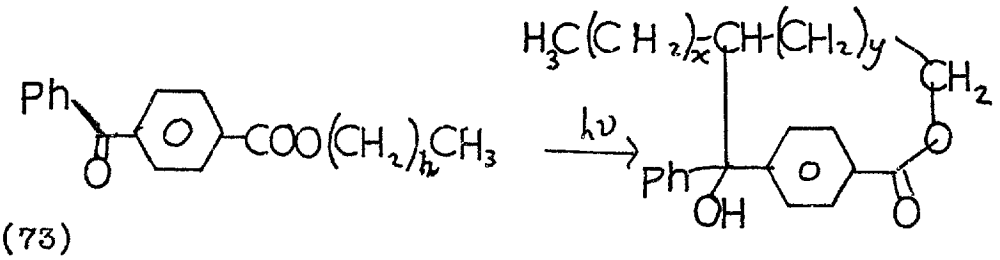


(71) however, preferentially abstracts a γ-hydrogen atom.[82] A δ-alkoxyketone may undergo δ-H abstraction[83] (72):



(72)

Hydrogen migration from remote carbon atoms in conformationally flexible molecules is familiar from Breslow's work, for example (73):[84]



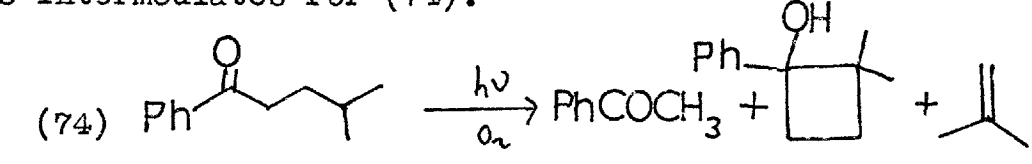
(73)

Type II elimination may be favoured when relief of steric crowding is a consequence, but it is difficult to demonstrate unequivocally when other factors must be taken into account.

Solvent effects on the elimination-cyclisation ratio are not well understood. Polar solvents disfavour cyclisation, possibly owing to hydrogen bonding in the biradical.[85] The quantum yields for both processes decrease in polar solvents for alkyl phenyl ketones, probably because of contribution by the $\pi\pi^*$ excited state. Reduction and pinacolisation is observed. Alcohol solvents stabilise $n\pi^*$ triplet excited states.[120]

Type II reactions are favoured over type I by lower temperatures, and high solvent viscosity,[40] as type I reactions require escape of radicals from a solvent cage.

Oxygen may participate, if present.[78] Oxygen is a triplet quenching agent, but also may increase type II product formation by reaction . Peroxides have been detected as intermediates for (74).



(74)

with an increase in yields.

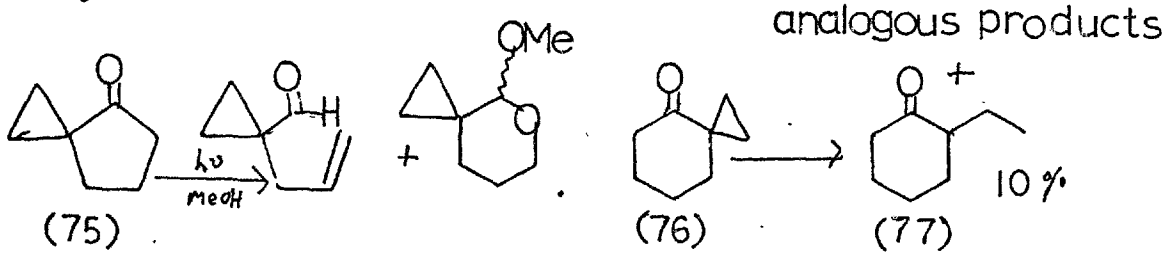
Finally, primary and secondary aliphatic aldehydes[9] undergo primarily type II reactions. The ratio of elimination to cyclisation products depends on the substitution pattern on the γ-carbon atoms, including the chain length of alkyl substituents.

Participation of cyclopropane and epoxide functions.

The absorption maximum for a cyclopropyl ketone $n-\pi^*$ transition is shifted to longer wavelength and increased in intensity, and therefore a mechanism for transfer of energy from the excited carbonyl to the $C_\alpha - C_\beta$ bond exists. α-cyclopropylketones may photolyse with participation of the strained ring by β-bond cleavage. If p-orbital overlap is poor, α-cleavage is generally predominant, but not so as to give the cyclopropyl radical.

(1) α-cleavage reactions

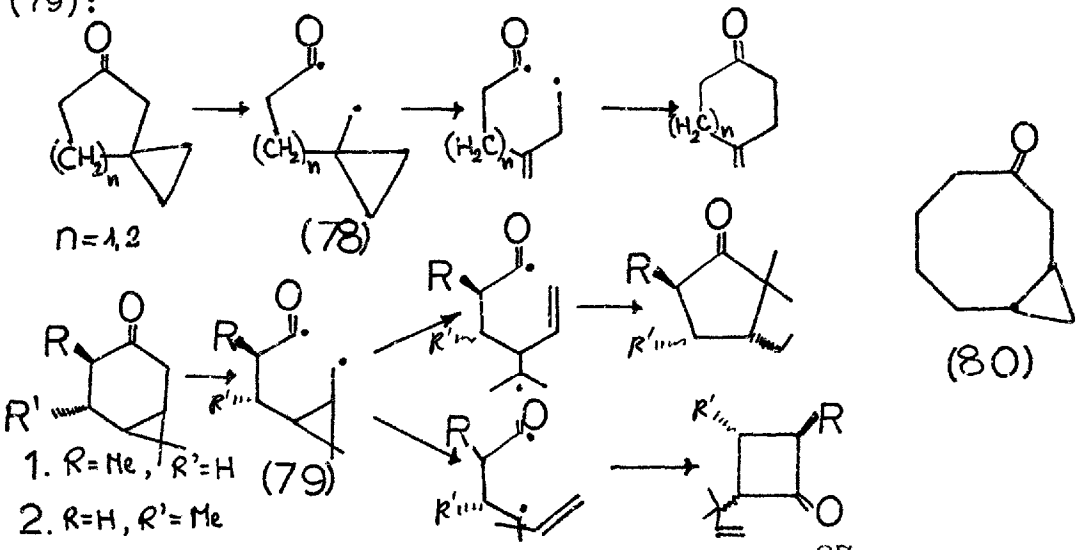
No involvement of the cyclopropane unit was observed for the spiroketone (75),[47] whereas (76) gave (77) as a minor product, presumably because of better orbital overlap of the cyclopropane C-C bond and the carbon atom of the carbonyl function.



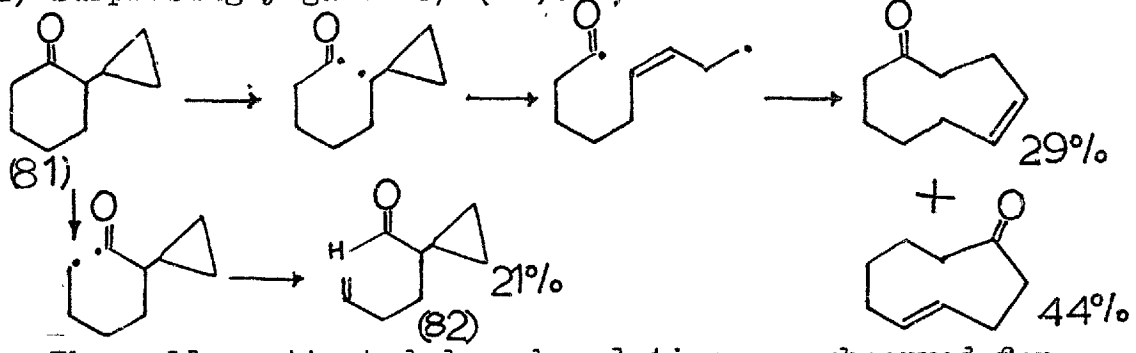
(75) (76) (77)

The preferred, but not exclusive, direction of bond fission of β-cyclopropyl ketones gives the stabilised

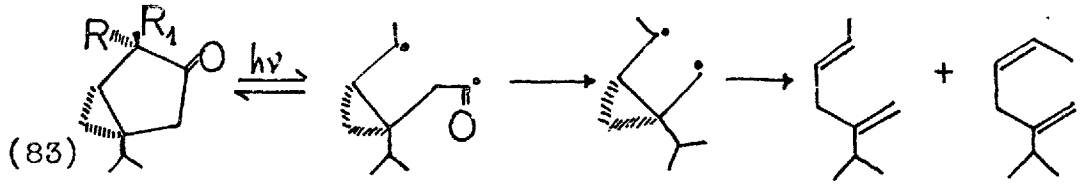
cyclopropylmethyl radical (78).[47] The same direction of α-cleavage is favoured if the other α-position is substituted (79):[86]



Analogous products were reported for (80).[87] Mixtures commonly result from cyclopropylmethyl radical intermediates. (81) surprisingly gave 21% (82).[88]



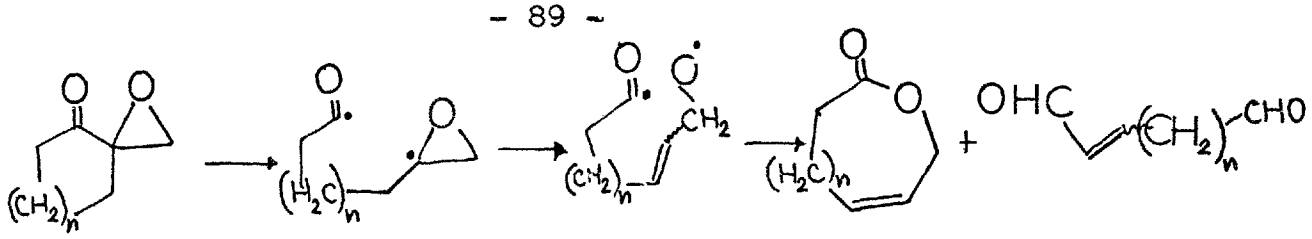
Thermally-activated decarbonylation was observed for thujone (83) at room temperature due to stabilisation of the transition state for elimination of carbon monoxide:[89]



1) R_1 = Me, R_2 = H

2) R_1 = H, R_2 = Me

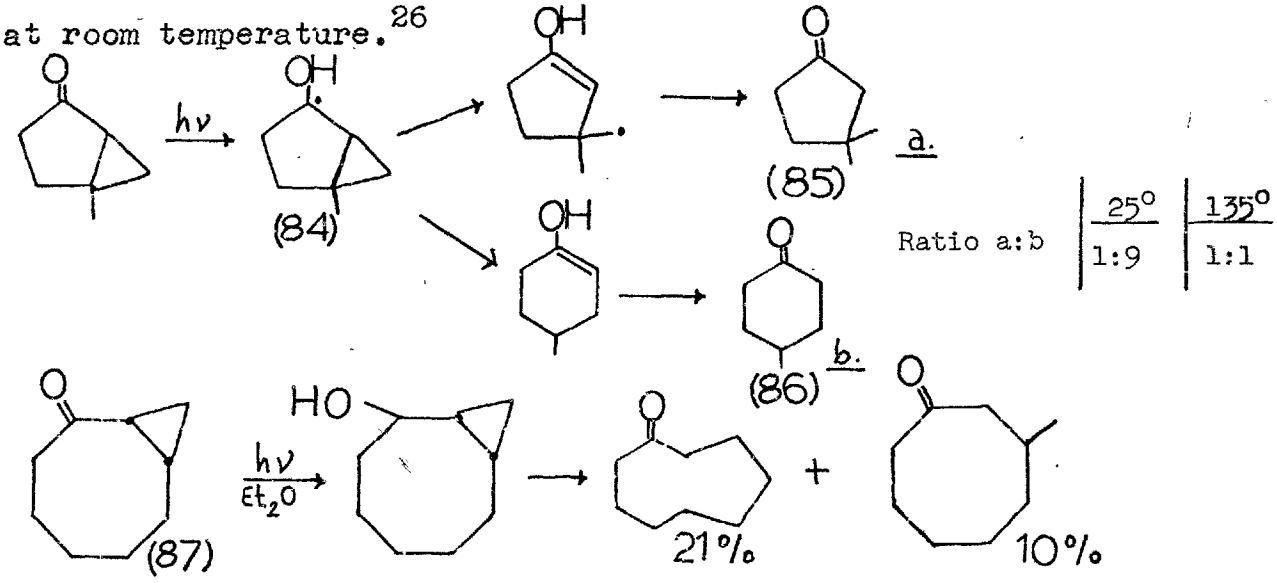
The oxiran function α to a carbonyl group behaves quite differently.[90] The direction of ring fission is towards the substituent:



whereas the oxiranylmethyl radical[91] rearranges predictably.

(2) β-cleavage reactions

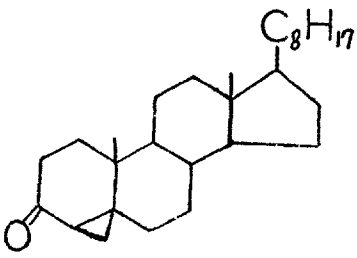
Investigations on the bicyclo[3.1.0]hexan-2-ones and bicyclo[4.1.0]heptan-2-ones have established biradical intermediates and revealed a steric effect of substituents in controlling preference for internal or external bond fission (table V).[92] Three reaction paths may be distinguished; (a) the excited carbonyl function abstracts hydrogen from the solvent, and the resulting cyclopropylmethyl radical (84) opens either by external or internal bond cleavage.[93] The ratio (85) to (86) was found to be temperature dependent. A higher temperature favoured internal bond cleavage, in contrast to (87) for which internal bond fission was favoured at room temperature.[26]



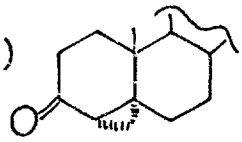
Ratio a:b	25°	135°
	1:9	1:1

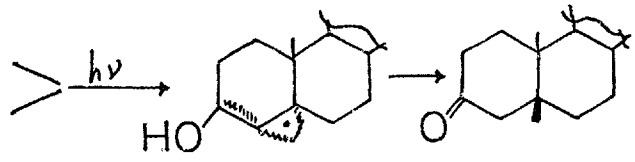
The intermediate may be regarded as a homoallylic radical, as (88) and (89) gave the same product.[94,95]

(88)

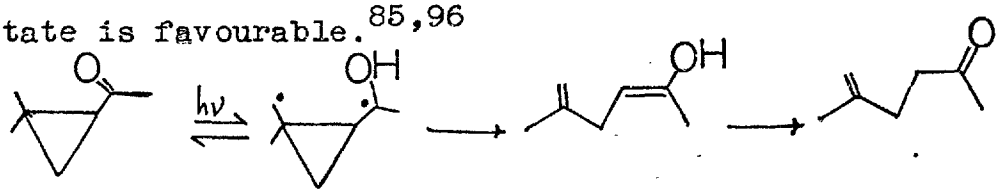


(89)

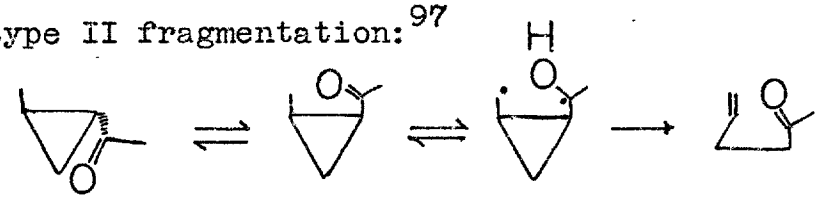




(b) Alkylation of the cyclopropane moiety favours β-cleavage via a normal type II reaction if the transition state is favourable.[85,96]

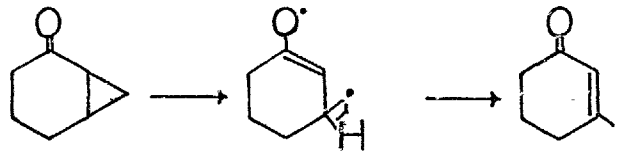


Reversible β-cleavage with epimerisation is a very efficient process of uncertain mechanism which may be accompanied by type II fragmentation:[97]



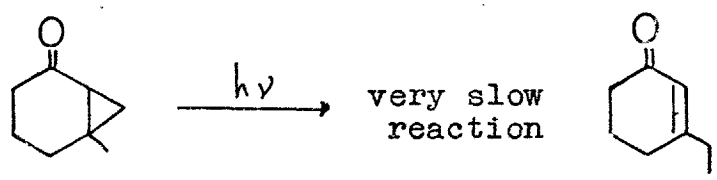
(c) Direct β C-C bond cleavage may be followed by 1,2 hydrogen or alkyl migration. The configuration of (90) favours external bond fission even though this does not produce the most stable biradical.[98]

(90)



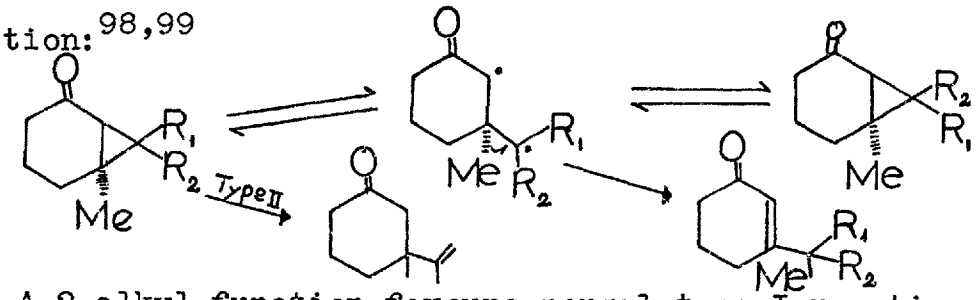
This type of fission is inhibited by a 6-alkyl function (91) probably for geometrical reasons:[98]

(91)

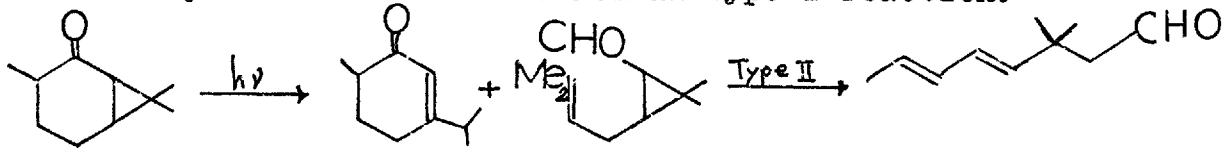


In contrast, a 7-alkyl group enhances β-bond cleavage and alkyl migration (92), concurrently with type II

reaction:[98,99]

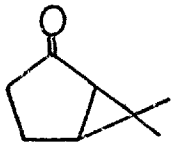
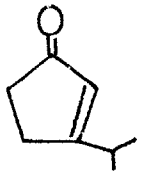
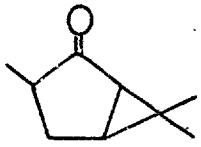
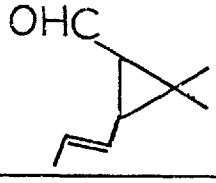
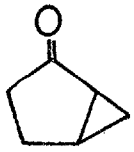
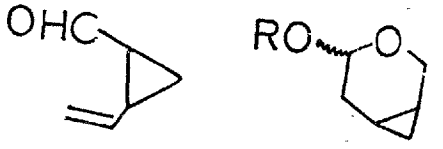
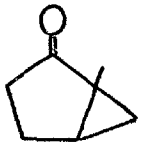
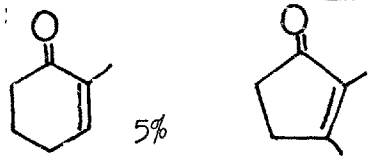
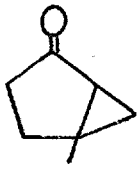
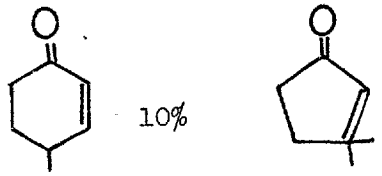
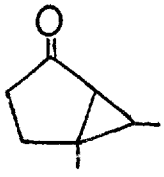
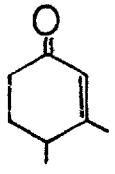
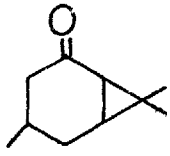
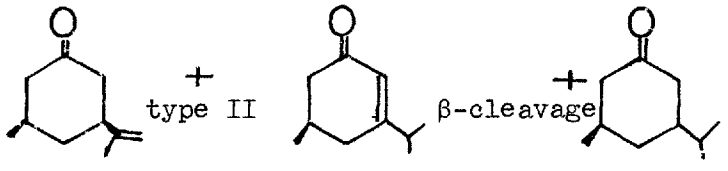
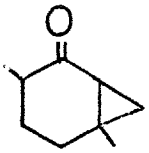
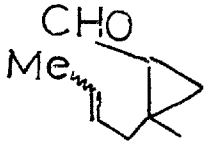
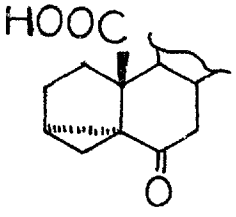
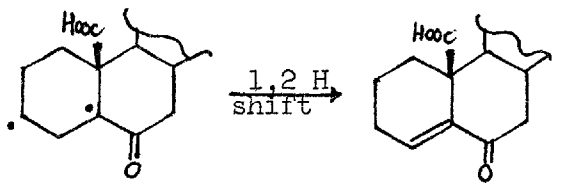
(92) 

A 2-alkyl function favours normal type I reaction:[98]

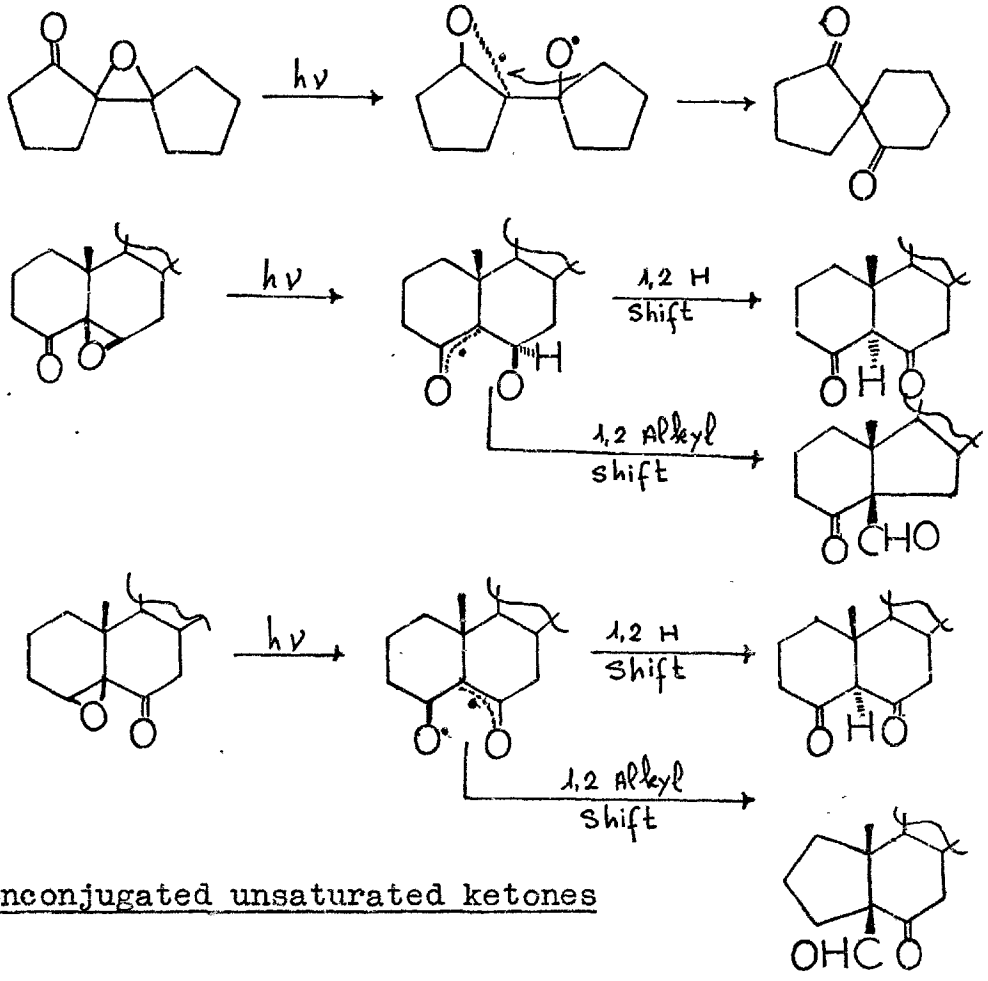


Additional examples are given below.[100,98,94,101]

Table V

Substrate	Products and reaction type
	 β-cleavage
	 type I
	 type I
	 5% β-cleavage
	 10% β-cleavage
	 72% Internal bond β-cleavage
	 + type II β-cleavage + reduction
	 type I
	 β-cleavage

Analogous β-cleavage of epoxides similarly gives 1,3-diketones via a 1,2 hydrogen or alkyl migration:[102,103]



Nonconjugated unsaturated ketones

(1) Intramolecular oxetan formation

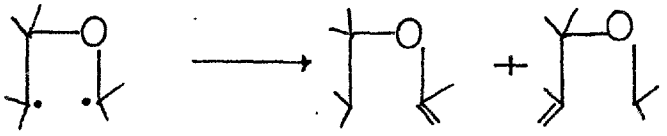
Intermolecular oxetan reactions have been much investigated employing vinyl ethers and conjugated unsaturated nitriles, which are not relevant to this review.[104]

The normal mode of reaction is by attack of the electron deficient oxygen atom of the triplet or singlet excited carbonyl function on the olefin.[104] Singlet reaction may be concerted or via a short-lived biradical and is stereoselective, but not stereospecific, whereas triplet reaction, generally the major path, proceeds via a definite

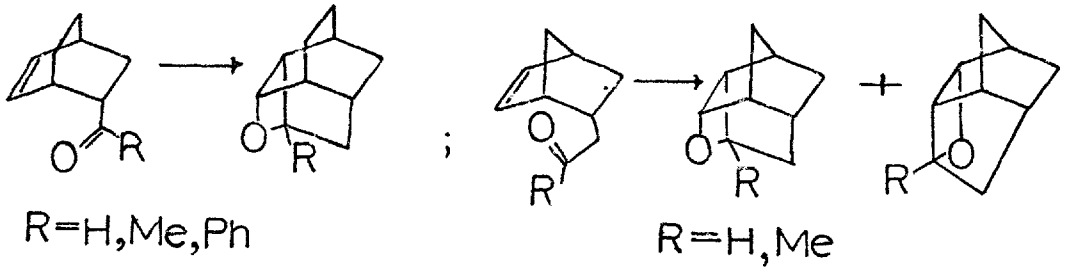
biradical intermediate with loss of configuration. The principal direction of addition is normally that which yields the most stable biradical intermediate, although mixtures are generally obtained. Simple olefins do not commonly give oxetans efficiently[105] as the high triplet energies of aliphatic ketones favour hydrogen abstraction reactions. Aryl alkyl ketones more readily yield oxetans.

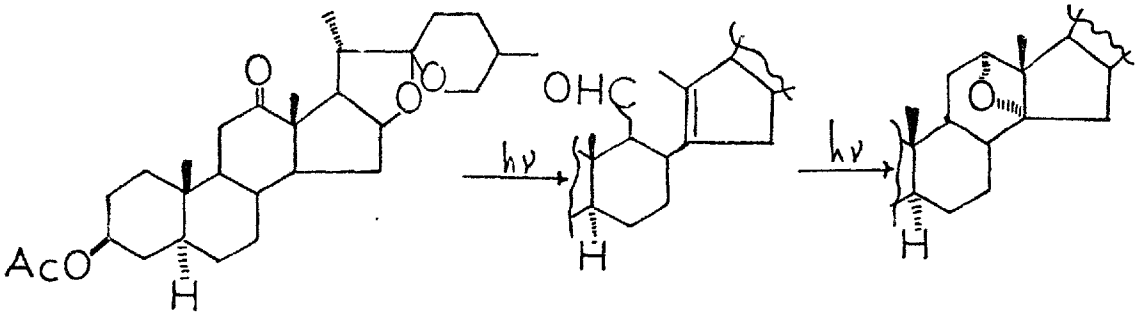
Product orientation can be influenced by factors other than radical stability.[104] If the formation of the intermediate is reversible, and closure to the biradical is influenced by steric repulsion, the reverse of the usual orientation may be observed. The reaction is also subject to the usual directive forces caused by steric interactions in the transition states.

Disproportionation of the biradical intermediate by 1,5 H transfer may intervene:[106]

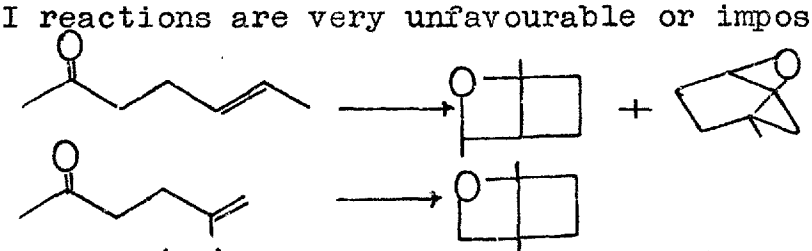


Intramolecular reactions may be important if favoured geometrically compared with γ-hydrogen abstraction:[107-9]

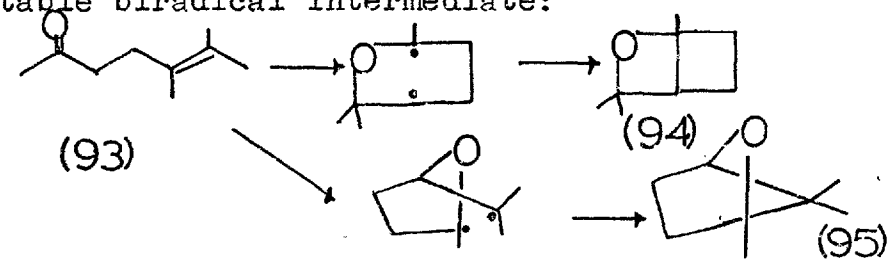




$\gamma\delta$-unsaturated acyclic ketones with no α-substituents are important oxetan precursors, as type I or II reactions are very unfavourable or impossible:[110]

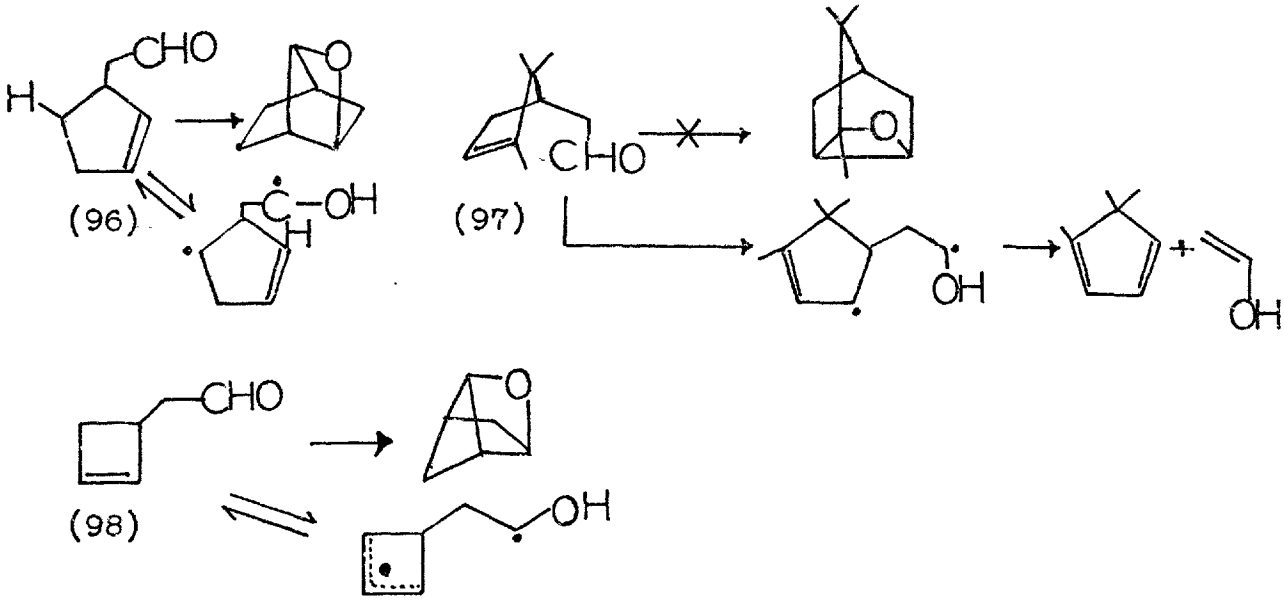


For (93), the major product was derived from the most stable biradical intermediate:[111]

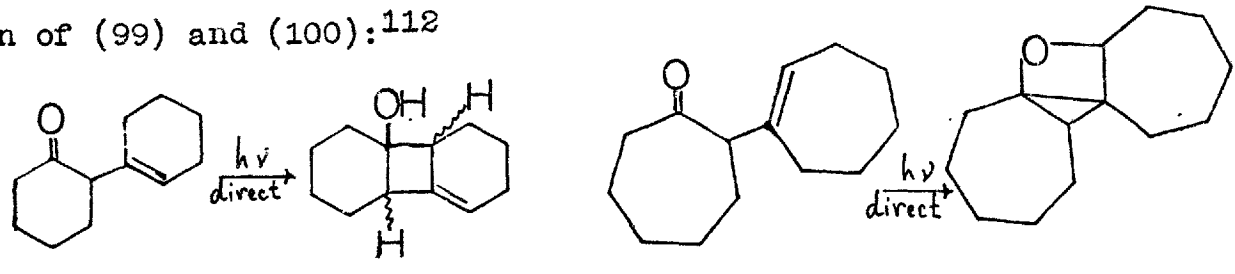


Ratio (94):(95)= 2 : 5

Cyclisation of (96)[20] is favourable, whereas (97) does not yield any oxetan, as the alternative route involves allylic γ-H abstraction. (98)[20] presumably reverts to the aldehyde rather than fragment to cyclobutadiene:



A conformational requirement is evident from a comparison of (99) and (100):[112]



(99) (100)

(2) $\beta\gamma$-unsaturated ketones

Many diverse reactions have been reported in the very extensive literature concerning photolysis of $\beta\gamma$-unsaturated ketones. The role of structural and stereochemical factors has recently been described as 'enigmatic.' The olefin-carbonyl geometry is critical, and therefore conformations may determine product distribution.

Intersystem crossing is rarely efficient, and the singlet and triplet states follow quite different reaction paths. Triplet reaction is therefore observed only on sensitisation. Cis-trans isomerisation of the double bond may occur from the triplet state. This efficient reversible process may entirely dissipate the excitation energy to the exclusion of other reactions; a 'free rotor' effect. Normal reaction is considered to be 1,3 acyl migration from the singlet state and 1,2 acyl migration on sensitisation.[113,114]

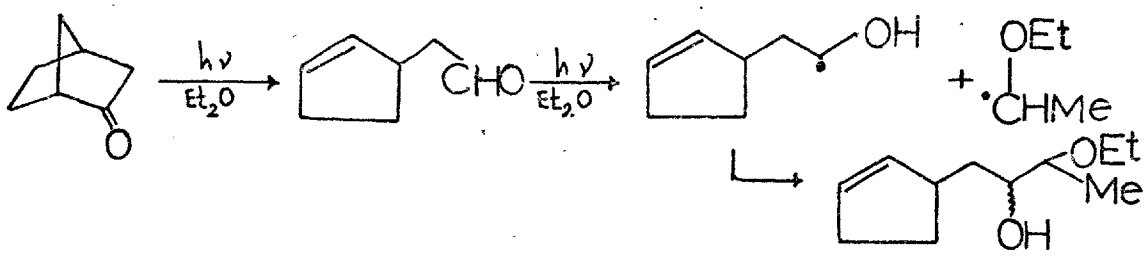
Leading references to this important class of carbonyl compounds are given by Hixson[115] and Hancock.[114] γ,δ-unsaturated ketones may also involve complex or unusual reaction mechanisms.[116]

Participation of solvents and oxygen

Reduction of the excited carbonyl function may take place if photolysis is carried out in a solvent with readily abstracted hydrogen. Isopropanol is only employed as a solvent when reduction is intended. Reduction is not fav-

oured by water, benzene, acetonitrile, acetic acid, or tertiary alcohols. In diethyl ether reduction is a major path if alternative reactions are inefficient. Aromatic ketones and α-diketones are particularly readily reduced. The more stable the ketyl radical, the greater the importance of reduction and pinacolisation. Pinacols are only commonly observed in these cases.[117]

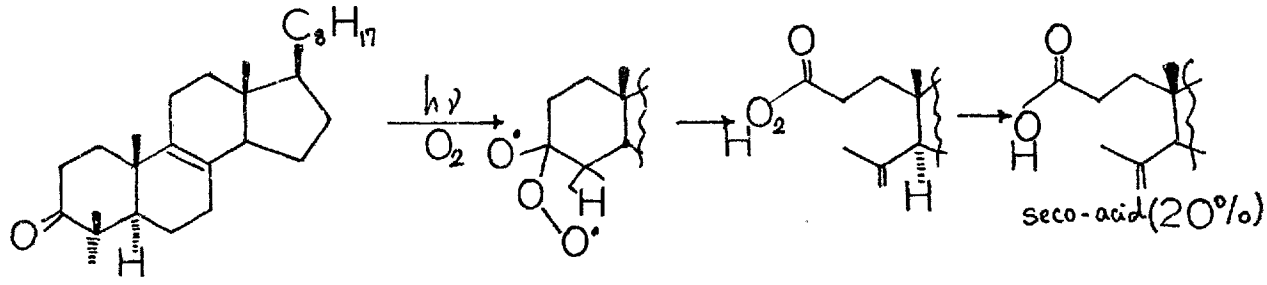
Ethers present an additional problem. The stabilised radical from hydrogen abstraction from an ether normally polymerises (the dimer is frequently isolated from photolyses in diethyl ether), but may react with the ketyl radical:[20]



The product is a mixture of diastereoisomers. Other ethers probably react in a similar manner.

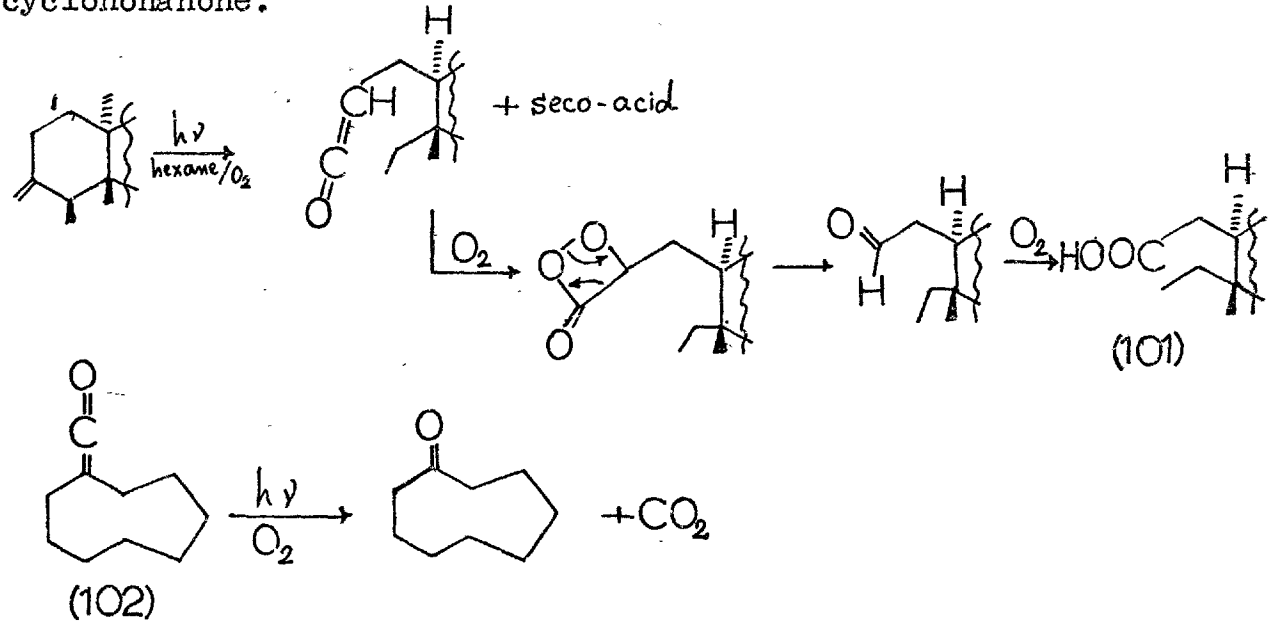
Methanol is commonly employed as solvent when alkenal products are expected, and frequently leads to the isolation of dimethyl acetals rather than aldehydes.[52] This result will be further discussed.

Intervention of oxygen is a preparatively important process. Direct reaction of molecular oxygen[6] with the excited carbonyl function is believed to be responsible for the isolation of carboxylic acids under anhydrous conditions:[16,29]



Most known examples are 3-oxosteroids or triterpenoids, with a 4,4-gem-dimethyl function.

Keten oxidation to an aldehyde explains the isolation of the carboxylic acid (101) which has an ethyl, not a vinyl substituent; a peroxide intermediate was detected.[58] The keten (102) on photolysis in a stream of oxygen yielded cyclononanone.[53]



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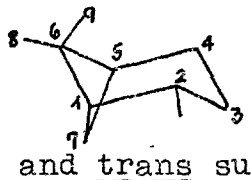
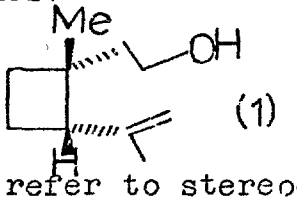
DISCUSSION: Part I

SYNTHESIS OF (+)-GRANDISOL

Throughout this discussion, the following nomenclature will be used regarding the pinanes:



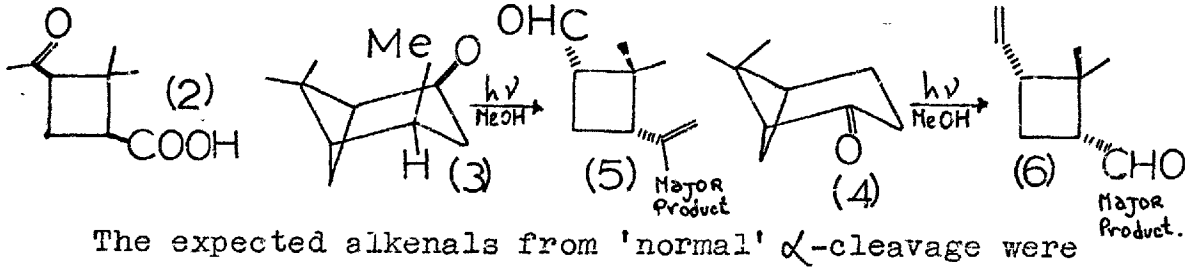


(1)

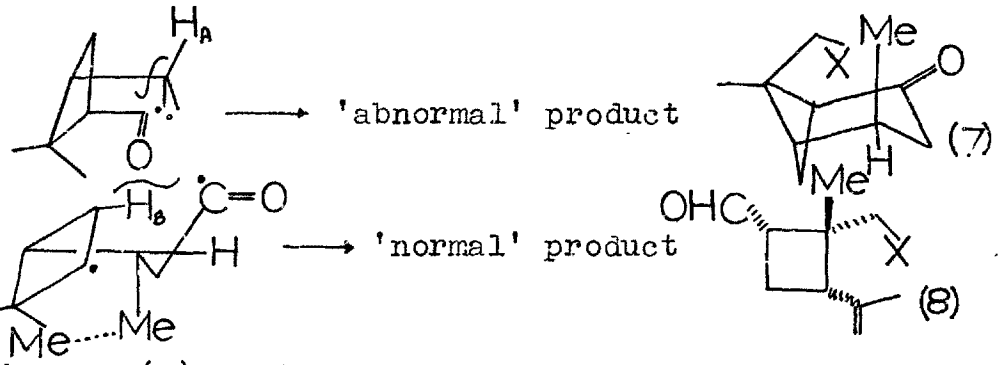
Cis and trans substituents will refer to stereochemistry with respect to the isopropylidene bridge. Cis substituents will also be referred to as β functions, the α-face being the least hindered. All structures are drawn in the correct absolute configurations.

The synthesis of the commercially significant compound grandisol (1) was undertaken for two reasons: (a) as an illustration of a synthesis and hence determination of absolute configuration of an optically-active terpene from a pinene, of known absolute configuration. This result may be a consideration in proposed biosynthetic routes to grandisol, and in addition demonstrates the synthetic utility of the pinenes, which until recently were little used as starting materials owing to the complexity of product mixtures from acid-catalysed rearrangements. Direct determination of the configuration of (1) by either X-ray anomalous dispersion of a derivative or by chemical degradation would be extremely difficult as an expensive and lengthy isolation procedure (p.4) gave only very small amounts of (1) - insufficient sample was obtained even for accurate measurement of the rotation, which would seem to rule out optical

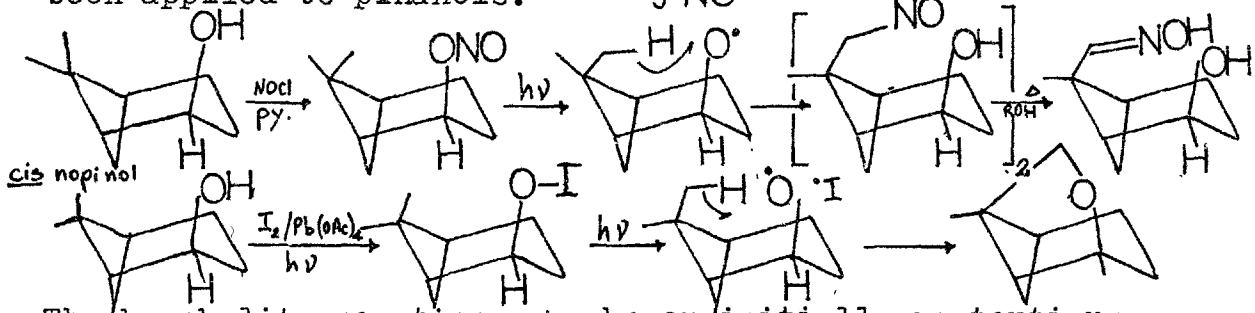
(o.r.d./c.d.) methods of determining the configuration. Resolution of synthetic grandisol (p.5-9), and converting one enantiomer to a pinane degradation product such as pinonic acid (2) would be at least as lengthy as the proposed synthesis. (b) In order to utilise the 'abnormal' photolytic α-cleavage reaction, namely C-C bond cleavage towards the least highly substituted carbon atom α to the excited carbonyl function of a ketone, in synthesis and from a very limited investigation of the scope of the reaction to draw some conclusions, if possible, as to the reason for the unusual photochemical behaviour of cis-verbanone (3)[2,3] and nopinone[4] (4).



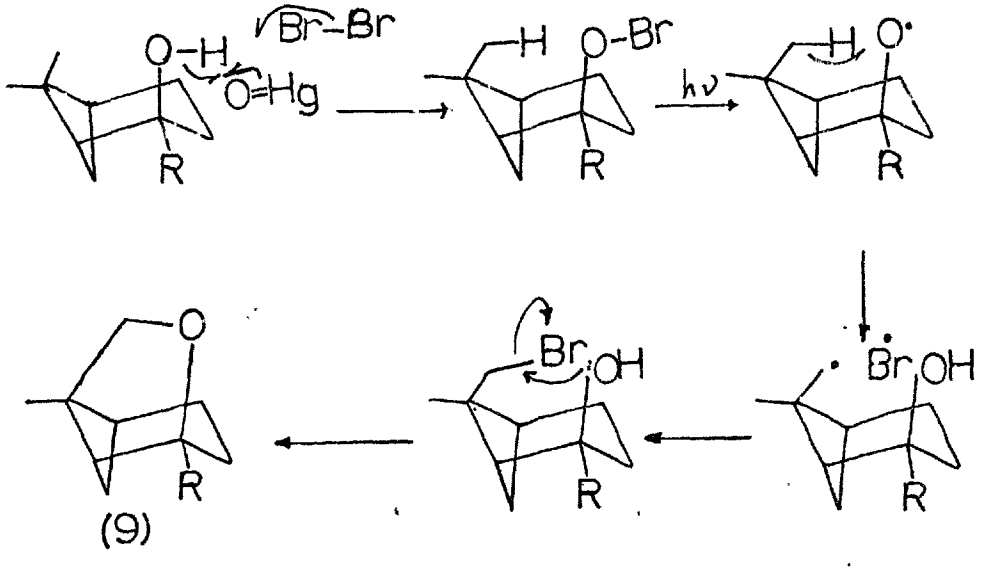
The expected alkenals from 'normal' α-cleavage were obtained only as minor products. Matsui[2] suggested that transfer of H_A to the carbon atoms of the excited carbonyl function was concurrent with, or even preceded, α-bond cleavage owing to excellent overlap of the carbonyl group and the sp^3 orbital of the β-hydrogen H_A in the preferred conformation. Shaffer[4] concurred with this view when investigating nopinone (4). Fallis[3] considered that for cis-verbanone (3) transfer of H_B following 'normal' α-cleavage towards the more highly substituted α-carbon atom was hindered by steric repulsion of the methyl groups and so the biradical intermediate of normal α-cleavage recombined efficiently, favouring the alternative α-cleavage. This argument does not apply to nopinone for which the extent of 'normal' reaction is, however, only a little greater.



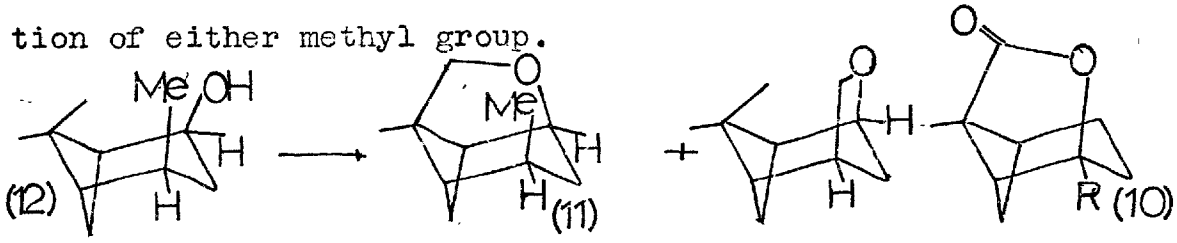
If a ketone (7) could be prepared, in which X represents a photoinert function by which the additional carbon atom of the hydroxyethyl group could be introduced, photolysis may yield (8). Decarbonylation of (8) would give a grandisol precursor. Moreover this route would be suitable for the introduction of other substituents to prepare compounds for screening purposes. Functionalisation of the C-9 methyl group may be achieved by means of nitrite ester photolysis[5] or hypohalite photolyses,[6,7] both of which have previously been applied to pinanols.[8,9,10]



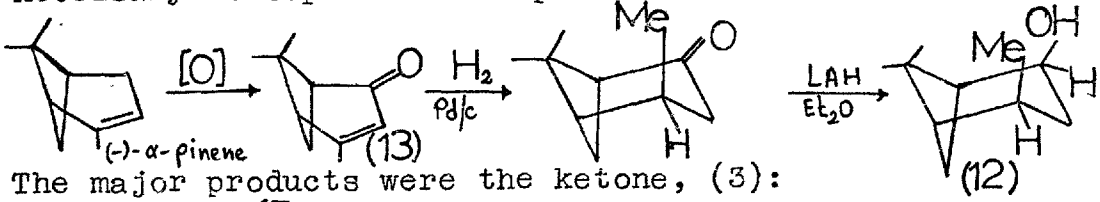
The hypohalite reaction was chosen initially as tertiary ethers (9) may be prepared in high yield[8,10] using bromine and mercuric oxide to generate the hypobromite.



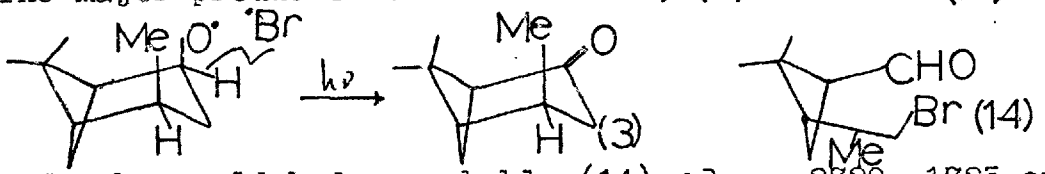
Unsymmetrically-substituted ethers such as (9) should undergo selective reactions under a variety of conditions to functionalise C-9 and retain the oxygen function on the cyclohexane ring. However, should the ether not prove a suitable starting material, oxidation to the lactone (10) would provide alternative approaches. The ideal ether (11) was considered inaccessible as the hypohalite reaction on neoisoverbanol (12) could yield two ethers via functionalisation of either methyl group.



As neoisoverbanol (2αH-pinan-4β-ol) was readily available from commercial verbenone (13)[22], a preliminary reaction was carried out employing bromine and yellow mercuric oxide in refluxing pentane under irradiation from a tungsten lamp. A combination of chromatography on silica and alumina was necessary to separate five products.



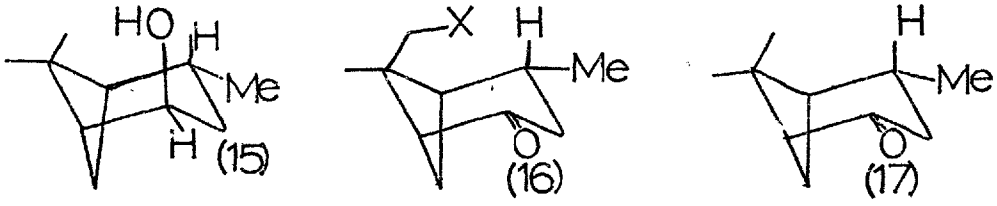
The major products were the ketone, (3):



and a bromoaldehyde, probably (14), ν_{max} 2720, 1725 cm^{-1}, m^+ 231+233, which readily oxidised in air to the corresponding acid. α-fragmentation products have previously been reported as minor products of the photolysis of pinanol hypohalites.[11] The total ether product, ν_{max} 1060, 1040 cm^{-1}, m^+ 152, was obtained in only ca 20% yield, and the reaction was not further proceeded with. A nitrite photo-

lysis was not attempted, although the C-9 methyl group may be significantly closer to the alkoxyl radical than the methyl on C-2.

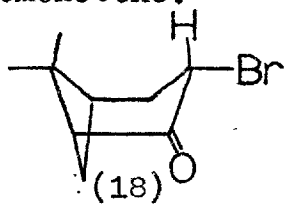
To avoid any possibility of reaction of this methyl function, neoverbanol (15) was considered as a substrate on the assumption that the corresponding functionalised ketone (16), with a methyl group trans to the isopropylidene bridge, would behave similarly to the cis compound when photolysed. There was no real precedent for this assumption; a comparison of cis and trans verbanones could provide information on the photoreaction mechanism.



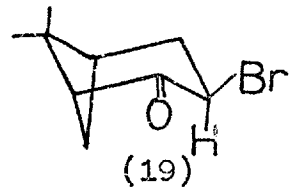
The early literature on the verbanols is highly confused as constant-melting mixtures of isomers were frequently obtained and considered to be pure compounds. Bose[12] established that neoverbanol (15) and trans-verbanone (17) were not known except as components of mixtures. Regan[13] isolated trans-verbanone from a mixture of cis and trans isomers by a very difficult g.l.c. separation, which could not be considered practicable as a preparative method. Neoverbanol was obtained by reduction of trans-verbanone. Consequently, a stereospecific synthesis was undertaken.

(+)-Nopinone was prepared by ozonolysis of (-)-β-pinene;[4] work-up with dimethyl sulphide was found most

convenient.[15] Treatment of (+)-nopinone with N-bromosuccinimide in carbon tetrachloride gave predominantly α-bromonopinone (18),[15,16] (the product of α-attack on the planar nopinone enol), m.p. 69-70°, which was isomerised by alumina to an equilibrium mixture of isomers, from which β-bromopinone (19), m.p. 112-13°, was crystallised. Repeated isomerisation of the mother liquor from crystallisation gave a higher total yield. Anhydrous cupric bromide and calcium carbonate in methanol[28] also reacted with nopinone to give the 3-bromoketone.



(18)



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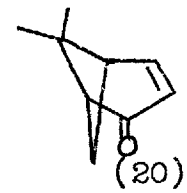


(20)

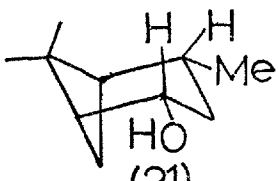
(19) was dehydrobrominated with lithium carbonate-lithium bromide in dimethyl sulphoxide at 140-145° for 72 hours, the only known satisfactory method for this reaction.[15] Elimination is particularly difficult since, assuming an ionic mechanism, the transition state requires an axial bromine atom and also because of hindrance by the gem-dimethyl function to approach of the base. The product, apoverbenone (20), was contaminated with <5 - 25% nopinone (4) from reduction of the bromoketone presumably by a radical mechanism. Very little reaction occurred at 130°, even after 120 hours, whereas at 150° the yield of apoverbenone was poor; much tar was produced, as well as nopinone. These observations suggest that dehydrobromination is also a radical reaction.

Apoverbenone could not readily be purified by distillation as the recorded boiling points of (20) and (4) under

reduced pressure were almost identical. Consequently, the mixture was used as such. Treatment of the enone with lithium dimethyl-cuprate in ether[17,18] gave trans-verbanone (17) by exclusive reaction on the α-face. No cis-verbanone (3), τ8.97, 8.82 (d,J7Hz), 8.64, was detected by n.m.r. The pure trans isomer, τ9.14 (3H,s), 8.65 (3H,s), 8.80 (3H,d, J9Hz) was obtained by preparative g.l.c. separation from nopinone, employing a 30 ft x 1 cm column of 15% E-30 on silanised Diatomite C at 155°. The oxime, a low melting solid, τ9.19 (3H,s), 8.72 (3H,s), 8.98 (3H,d,J7.5Hz) was also quite distinct from the known[12] cis-verbanone oxime, τ9.06 (3H,s), 8.71 (3H,s), 8.87 (3H,d,J7Hz) prepared for comparison. Racemic apoverbenone, from oxidation of apopinene via the symmetrical allyl radical, has also been converted to trans-verbanone by this method.[20]

Reduction of (+)-trans-verbanone with lithium aluminium hydride gave (-) neoverbanol from exclusive α-attack, as volatile white needles[19] (15) m.p 77-77.5° after crystallisation from petrol, $[\alpha]_D^{21.5}$ - 16.1° (c 3%, benzene) $[\alpha]_D^{21.5}$-8.2° (c 6%, $CHCl_3$), τ9.12 (3H,d,J7Hz), 8.95 (3H,s), 8.80 (3H,s). The alternative reduction product, (21), was not detected. Although the n.m.r. spectrum was in agreement with that recorded by Regan,[13] the melting point was not. Regan's product had m.p. 40.5°, but was prepared from (-)-α-pinene of low optical purity.

The configuration of the hydroxyl group was proved by subsequent conversion to the ether (22).



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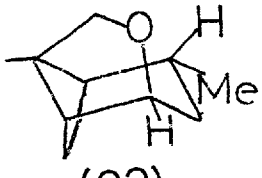
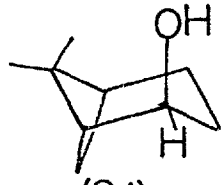


(22)

(23)



(24)

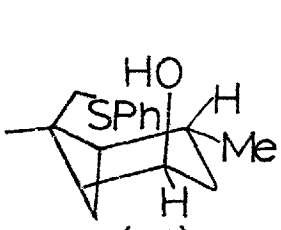
Use of iodine and mercuric oxide in carbon tetrachloride gave only the ketone (17). Bromine and mercuric oxide in pentane produced a mixture of (17) and the ether (21), ν_{max} 1050, 1030 cm^{-1}, separable on alumina. The CH_2O group of ethers of this type are characterised by a methylene AB quartet, in this case at τ6.40, which allows quantitative comparison of reaction products under varying conditions from the n.m.r. integrals. The optimum yield (70%) was difficult to attain (usually 50-60%) because it was necessary to use a small excess of neoverbanol over bromine; any hydrogen bromide generated in the reaction caused immediate polymerisation of the ether. (22) was particularly sensitive to acids, much more so than the tertiary ether (9) and could not be kept at room temperature even after isolation from slightly basic alumina. The known secondary ether[8] (23) was prepared from cis-nopinol(24) as a model in consistently high yield ($>$ 75%) by reaction in carbon tetrachloride, particularly when using a two-step procedure of forming the hypobromite at 0°, followed by irradiation at 0°, then at reflux, and this procedure may give improved results with neoverbanol.

Attempts to directly introduce a one-carbon function on the $-CH_2O-$methylene group were not successful. Dichloro-

carbene, generated from potassium t-butoxide and chloroform, did not insert into the ether. Any reaction in this case would have been unprecedented. Cyanogen chloride has been used to introduce the nitrile function on the α-carbon of an ether by photolysis, using excess liquid reagent as solvent.[21] The reagent is most difficult to handle, however, and the reaction is not very selective; primary and secondary functions, and even β-methylene groups, were substituted, and so only a low percentage conversion could be employed. A cursory examination of the action of cyanogen bromide on ether (22) on photolysis in pentane did not reveal any reaction under a veriety of conditions.

Monophenylthioborane,[24] $PhSBH_2$, may be prepared by reaction of diborane with thiophenol, or in situ by addition of boron trifluoride etherate to the product of reaction of sodium borohydride and thiophenol. When conducted in an ether solvent, monophenylthioborane reacts to give an ω-hydroxysulphide by selective reaction with the primary carbon-oxygen bond. However, the solubilities and reactivity of diborane and sodium borohydride make it necessary to use reactive ether solvents. Diborane is soluble in tetrahydrofurans but not in diglyme, but phenylthioborane reacts more rapidly with tetrahydrofuran than other ether solvents. Insufficient (22) was available for use as a solvent, consequently in situ reaction in diglyme was employed. As solvent was present in large excess over the ether, much of the borane reacted with diglyme, but the ether (22) yielded a single product (25), which after oxidation with m-chloroperbenzoic acid gave a hydroxysulphone, almost certainly

(26), m.p. 159-161°, ν_{max} 3600, 1305, 1290, 1150 cm^{-1}. Oxidation of (26) with chromium trioxide-pyridine in dichloromethane[25] gave a ketone (27) (and not an aldehyde), m.p. 148.5-151°, ν_{max} 1720 cm^{-1}.



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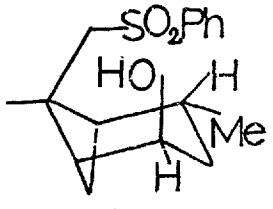

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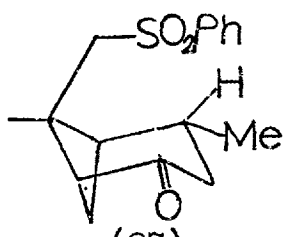
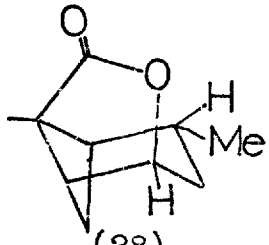


(27)



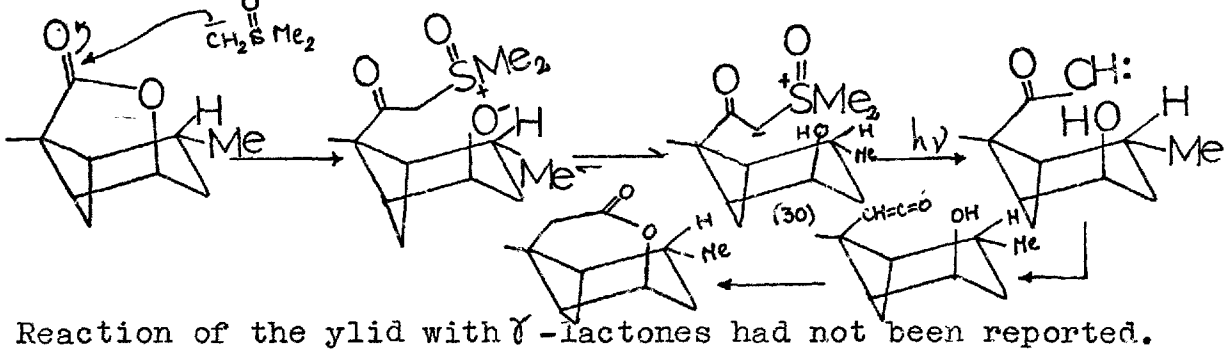
(28)

(27) is suitably functionalised for introduction of a one-carbon substituent. A micro-scale photolysis of (27) could not be followed by t.l.c. due to streaking.

The reactivity of the lactone (28) was then investigated. Oxidation of the ether (22) with excess chromium trioxide-acetic anhydride[27,8] at 100° yielded a mixture containing (28) (46%), m.p. 48-48.5°, ν_{max} 1770 cm^{-1}, $[\alpha]_D^{21}$ + 119.3° (c4%, $CHCl_3$) which was isolated from an alumina column. A more polar by-product (10-20%) was not obtained pure. Ether (22) was also oxidised with ruthenium tetroxide, using a small excess of potassium periodate and 5-10% molar of hydrated ruthenium dioxide, in a vigorously-stirred two-phase system, water-carbon tetrachloride.[29,30] Similar conditions have been employed for the oxidation of sec. alcohols, particularly carbohydrates, to ketones,[31,32] but the oxidation of ethers is very much slower. Using ca 7% molar RuO_2, reaction was complete within 38 hours. The crude ether, containing trans-verbanone and neoverbanol, could be used in this reaction as neoverbanol was oxidised to further trans-verbanone which could be separated on alumina and

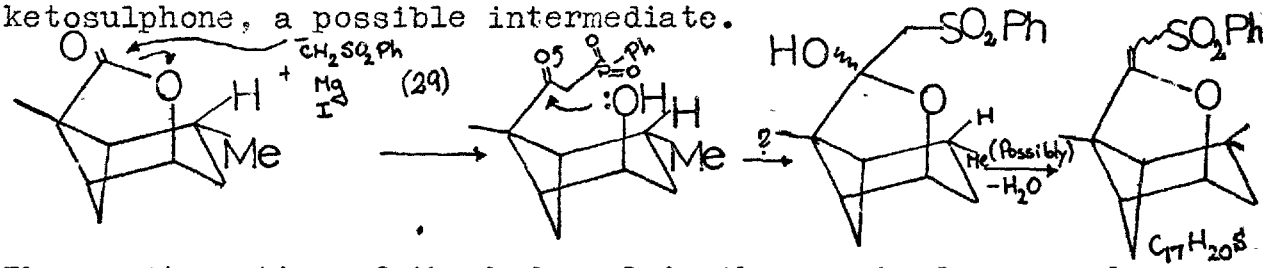
recovered. A more polar by-product was again obtained, presumably from oxidation at the alternative α-carbon atom; this product was not formed by continued exposure of pure (28) to ruthenium tetroxide. A ketone function, ν_{max} 1720 cm^{-1}, was apparent but the crude by-product did not give a derivative with the usual reagents, nor could it be obtained sufficiently pure to characterise. Only hydrated RuO_2, prepared by hydrolysis and atmospheric oxidation of the so-called trichloride, reacted with aqueous periodate; the commercial anhydrous product was inert.

It was anticipated that (28) would react with dimethyloxosulphonium methylide,[34] generated from sodium hydride and trimethyloxosulphonium chloride, to give the β-keto-oxosulphonium ylid (30) which could be irradiated in aqueous solution to excite the C-S charge-transfer band (λ_{max} 254 mμ) to yield the keten and hence the δ-lactone:



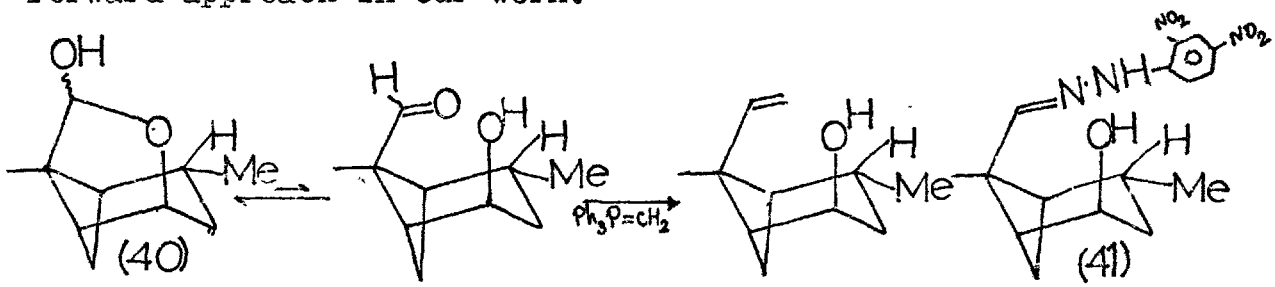
Reaction of the ylid with γ-lactones had not been reported. Aliphatic esters react only extremely slowly.[46] Even using a four-fold excess of the ylid and a long reaction time at reflux in tetrahydrofuran, most of the lactone was recovered unchanged, possibly owing to reversibility of the initial reaction. Photolysis of the crude reaction solution <u>in situ</u> gave only a trace of material with a molecular ion corresponding to the δ-lactone.

Lactone (28) reacted slowly with phenylsulphonylmethylmagnesium iodide[35,47] (29) or methylphenylsulphone-sodium hydride to give a compound with an intense olefin absorption ν_{max} 1620 cm^{-1}, and no hydroxyl, and not the expected β-ketosulphone, a possible intermediate.



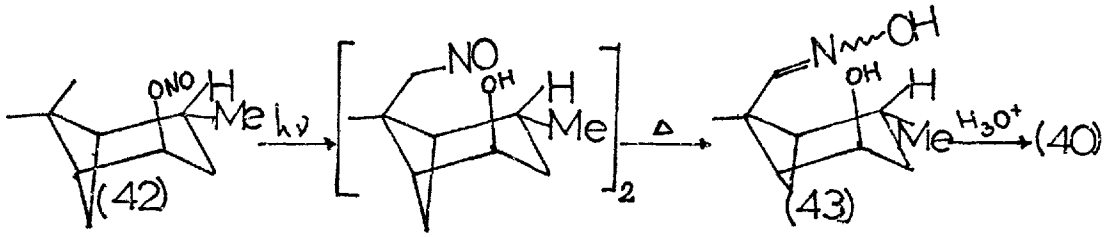
The configuration of the hydroxyl in the required compound favours the intermediate hemiketal. The product also had ether C-O maxima at 1090, 1030 cm^{-1}.

Corey's[48] prostaglandin syntheses made use of Wittig reactions on γ-lactols (hemiacetals), which offered a straightforward approach in our work.



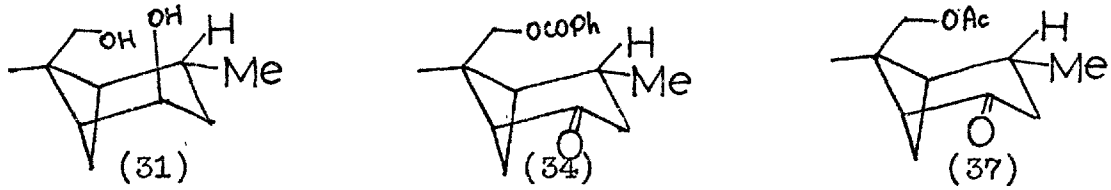
The hemiacetal (40) was prepared by reduction of lactone (28) with bis(3-methyl-2-butyl)borane[49] with oxidative work-up at controlled pH (8-9). The product existed almost entirely as the hemiacetal tautomer, ν_{max} 3350 cm^{-1}, as expected (to i.r. and n.m.r.) but gave a 2,4-dinitrophenylhydrazone (41). (40) was subsequently prepared more conveniently from neoverbanol nitrite ester (42), employing standard conditions of the Barton reaction.[5,8,9] The product gave a 2,4-dinitrophenylhydrazone identical with that of the alternative route. The intermediate oxime (43) was obtained pure from thermal rearrangement of precipitated

nitroso-dimer from photolysis of (41).

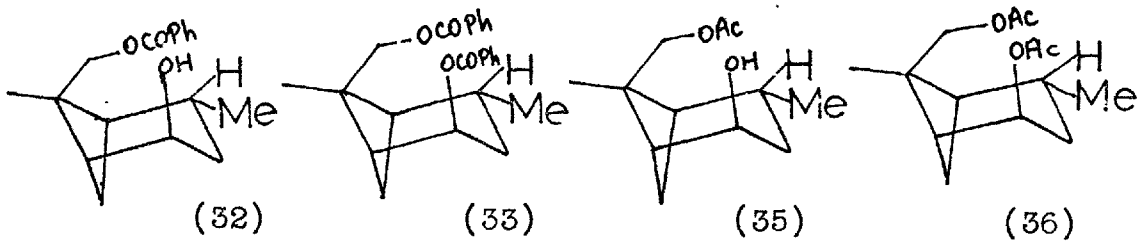


A preliminary reaction of the hemiacetal with triphenylmethylenephosphorane gave several olefinic products.

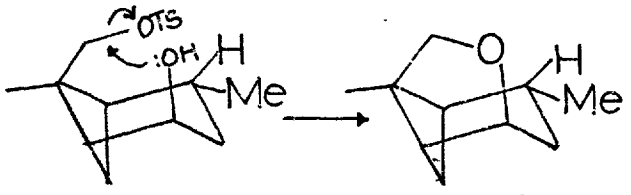
A comparison of the behaviour of cis and trans-verbanones and a 9-substituted trans-verbanone model on photolysis was required. The model compounds (34) and (37) were readily prepared. Reduction of the lactone (28) with lithium aluminium hydride gave a diol (31). The benzoate (34) was expected to photolyse rather slowly as the absorption band of the aromatic function coincides with the ketone $n\pi^*$ maximum, but (34) offered the advantage that products of subsequent reactions could be crystalline.



The diol was selectively esterified with benzoyl chloride or acetic anhydride in pyridine to give (32) and (35), (85% and 68% respectively). Very little of the dibenzoate (33) was obtained but acetylation was less specific; 22% of the diacetate (36) was isolated.



Oxidation of the secondary alcohols (32) and (35) with chromium-trioxide pyridine[25] gave the ketones quantitatively. In order to prepare the corresponding nitrile (38) neoverbanol was treated with p-toluenesulphonyl chloride in pyridine, but even when worked up at room temperature the leaving group was displaced intramolecularly to yield much of the ether (22), ν_{max} 1050, 1030 cm^{-1}, (2H,ABq,J9Hz).



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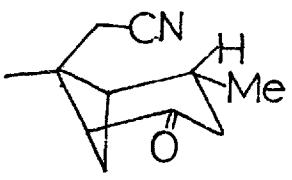
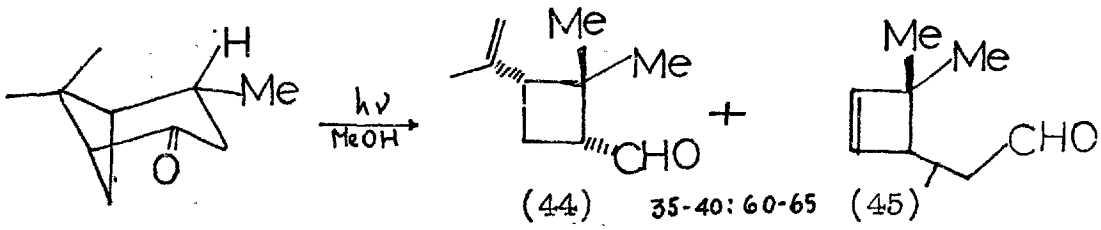


(38)

Photolysis of cis-verbanone was carried out in methanol containing sodium bicarbonate (Fallis' conditions[3]). The base prevents acid-catalysed acetalisation, and methanol prevents photoreaction of the aldehyde product by protection as a hemiacetal.[50] A yield of 65-70% of the aldehyde mixture (44) and (45) was obtained, in a ratio of 7-9:1, according to the ratio of olefin signal integrals in the n.m.r. spectrum, in agreement with Fallis, who reported a 7:1 ratio and characterised the minor product by thermal conrotatory ring-opening to the dienal. The olefin signals were quite distinct. (44) had two broad 1H singlets at τ (CCl_4) 5.35 and 5.18, whereas the cyclobutene protons appeared as a quartet at τ 3.99 (J3.5Hz).

Trans-verbanone, however, gave a complex but consistent mixture of volatile products (ca 14) when determined by g.l.c., whereas t.l.c. indicated two non-polar products, several minor compounds, and more polymeric material than obtained from the isomeric ketone. The most abundant

product had the same retention time as (44), but was only a small percentage of the total. Other major components coincided with the minor products of photolysis of the cis ketone. A silica column yielded the aldehyde fraction (53% total yield) which was clearly a mixture of (44) and (45) but in a ratio of 35-40:60-65:



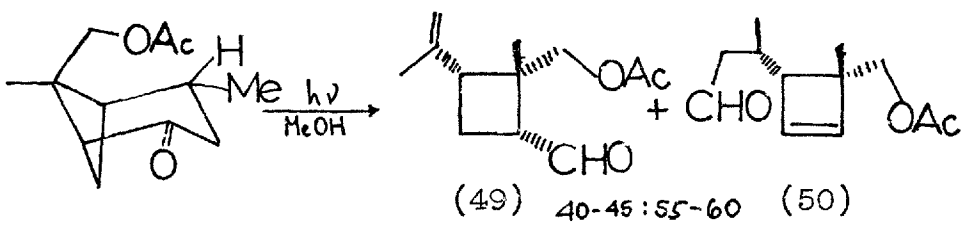
(44) 35-40:60-65 (45)

which explained the g.l.c. results; (45) decomposes readily on heating[3] and cannot be isolated from a g.l.c. column.

The photolysis conditions for trans-verbanone were varied to determine whether change of solvent, wavelength of irradiation, temperature or extent of reaction affected the yield of the required aldehyde (44) as determined by g.l.c. and n.m.r. No useful information was obtained. A number of solvents apparently participated in the photolytic reactions. Cyclohexane, which may reduce the biradical intermediate, gave mainly volatile products. Ethers (diethyl ether, glyme) gave predominantly less volatile compounds as anticipated.[50] Reaction in tetrahydrofuran appeared remarkably clean to g.l.c.; trans-verbanone gave only a compound corresponding to (44) and a less volatile product, which was formed in lower yield when photolysis was conducted at -22°, and involatile compounds, but work-up on a silica column gave only a poor total aldehyde yield and several major products probably derived from reaction with the solvent. Use of methanol in the absence of sodium bicarbonate gave a less

volatile compound. Petrol, acetonitrile, benzene and ethyl acetate produced rather more complex mixtures than reaction in methanol. Change of temperature, irradiation source, or time of reaction had no useful effect. Both (44) and (45) were base-sensitive. When the methanol solution containing sodium bicarbonate was warmed, and also when the crude product was chromatographed on alumina, a polar alcohol was obtained.

The model ketones were photolysed in methanol containing sodium bicarbonate. The benzoate (34) proved to be virtually inert. A very slow reaction gave polar material only. The acetate (37) gave a ca.64% yield of a mixture of two aldehydes, isolated, but not separable, on a silica column. The ratio of the integrals of the olefin signals, the acetate methyl singlets, the R_3CH_2O multiplets and the singlet due to the olefin on a double bond all indicated a mixture, ν_{max} (CCl_4) 3080, 2715, 1750, 1733, 1725, 1647, 1235, 1035, 900, 865 cm^{-1}, of (49) and (50) in a ratio of 40-45:55-60, very similar to the parent trans-verbanone.



(49) 40-45:55-60 (50)

An oily mixture of the semicarbazones of (49) and (50) could not be separated nor further characterised. A g.l.c. column suitable for the separation of (49) and the product of pyrolysis of (50) was not available.

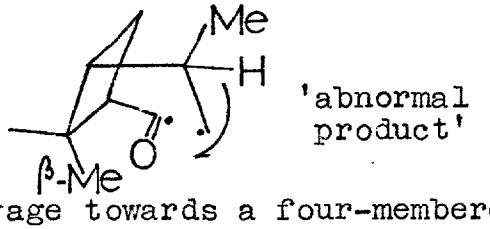
The 9-substituted cis-verbanone (74) (which will be further discussed) behaved exactly as the parent verbanone; photolysis gave a 60% total yield (isolated on a silica column) of (79) and a cyclobutene, probably (82), in a ratio of 8:1. The corresponding benzoate (78) was photoinert. Thus the reactions are consistent.

Matsui's mechanism (p. 108) involving concerted hydrogen transfer, or even transfer prior to C-C bond cleavage, on the α-face on excitation of the carbonyl function cannot apply to trans-verbanone, and concerted H atom transfer from the β-face is conformationally very unlikely. But 'abnormal' α-cleavage still occurs to a considerable extent with both trans-verbanone and the 9-acetoxyketone. The proximity of the H atom can at best be only a contributing factor. Hydrogen transfer from cis-verbanone is probably particularly rapid but not concerted with C-C bond cleavage. There is no accepted evidence for concerted alkenal formation in other systems.

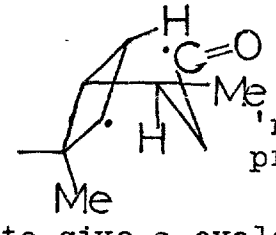
The boat-like conformation assumed for cis-verbanone in which the H atom is axial is supported by high-resolution n.m.r. analysis.[73] Shaffer assumed the same conformation in the excited state for nopinone in concurring with Matsui. The ground-state conformation for nopinone is generally agreed to be a flattened chair[74-76] but the reactive conformation in the excited state cannot be determined.

Fallis' argument (p. 108) applied to trans-verbanone suggests that neither 'normal' nor 'abnormal' reaction

should be severely hindered by steric interactions, and so 'normal' reaction should be more significant for trans than for cis-verbanone. This stereospecific effect of the 4-methyl group cannot be the entire explanation of 'abnormal' reaction as nopinone gives only 20% of the product of cleavage towards the more highly substituted carbon atom. However, both the verbanones and nopinone possess β-alkyl substituents on the isopropylidene bridge. The steric effect of these substituents alone, a β-alkyl effect (p. 64) well established for cyclohexanones, probably accounts for the unfavourable 'normal' α-cleavage of nopinone. Possibly the cyclobutyl radical is also destabilised by a fully-substituted α-carbon atom. It would be informative to investigate the photolysis of the bicyclo[3.1.1]heptan-2-ones, with and without 4-alkyl functions.



'abnormal product'



'normal product'

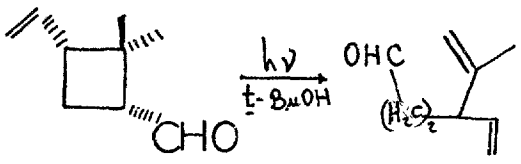
Cleavage towards a four-membered ring to give a cyclobutyl radical intermediate normally occurs in preference to the alternative α-bond fission to give a primary alkyl radical (p. 67). The energy of the cyclobutyl radical is therefore not prohibitive. However, the pinane system is unusual in that the six-membered ring is strained. Possibly the transition state to the cyclobutyl radical is less favourable (further distorted from the ideal sp^3 geometry) than for a monocyclic compound. That the 'abnormal' reaction is very efficient[4] compared with 3-alkylcyclohexanones (p. 63) is probably due to the strain released in cleavage of the six-membered ring which is believed to result in rapid

hydrogen abstraction (p. 64). In the absence of this factor, verbanones would be expected to photolyse slowly to give mainly the keten-derived esters, (p. 62). As the alkenal reactions are efficient[4] (ϕ(nopinone) 0.32, ϕ cis-verbanone 0.40) the six-membered transition states are not sufficiently hindered to favour the more strained six-membered transition states leading to the ketens. Esters were not isolated, but may account for the minor products observed.

Type II fragmentation would not be expected as the ring system is not sufficiently flexible to attain the required geometry of the transition state (p. 81). Cyclobutanol formation would require abstraction of hydrogen from either the 4-methyl group or from the cyclobutane both of which are very unfavourable.

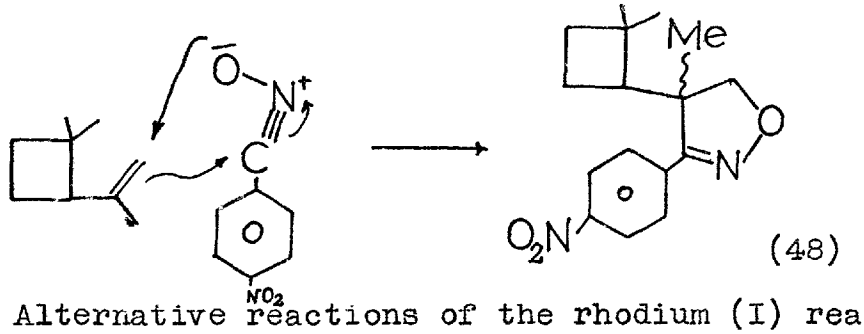
Subsequent photolytic decarbonylation of (44) to (47) was not observed. This was later confirmed by a g.l.c. comparison of authentic (47) with the volatile products of continued photolysis of cis-verbanone in methanol and in tetrahydrofuran. Decarbonylation could not be expected as (a) secondary aldehydes undergo α-cleavage only rather slowly, and (44) is an unfavourable case as a cyclobutyl radical intermediate is involved; and (b) a fast, efficient type II cleavage probably takes place as the methyl group cis to the aldehyde carbonyl allows efficient γ-hydrogen transfer. This process was observed by Shaffer[4] for the photolysis of nopinone in solvents other than methanol. The product of β-cleavage was characterised, but was found to polymerise rapidly during photolysis. Continued photolysis of (44) in

methanol containing sodium bicarbonate gave only polymer, presumably by the same route.



(47) $RhClCO(PPh_3)_2$ (46)

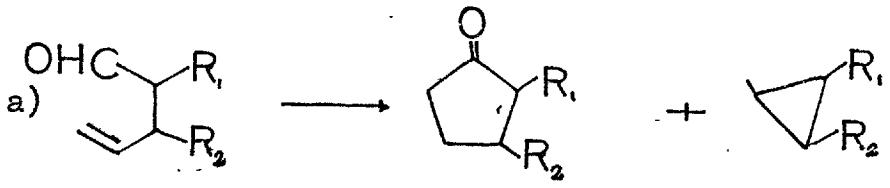
Radical-induced decarbonylations,[51] for example by photolysis in the presence of a thiol, or employing di-t-butyl peroxide and a thiol are not applicable to (44) as the RS· radicals would react with the olefin function. Consequently decarbonylation of the model aldehyde was carried out using tris(triphenylphosphine)chlororhodium (I).[52,71] The volatile hydrocarbon, ν_{max} 1645, 890 cm^{-1}, could not be obtained pure from a very small-scale reaction as a suitable g.l.c. preparative column was not available (47) was treated with p-nitrobenzonitrile oxide, generated *in situ*. The adduct (48) was obtained as a diastereoisomeric mixture m.p. 110-118°. N.m.r. showed two aromatic quartets almost superimposed and two singlets for the methyl function at C-4 of the isoxazoline ring. The isolated methylene group appeared as two singlets, at τ 6.98 and 6.80.



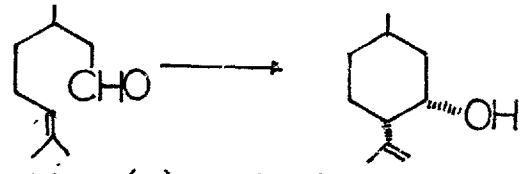
(48)

Alternative reactions of the rhodium (I) reagent with an ω-alkenal have been reported by Sakai and Oda:[52,53]

a)



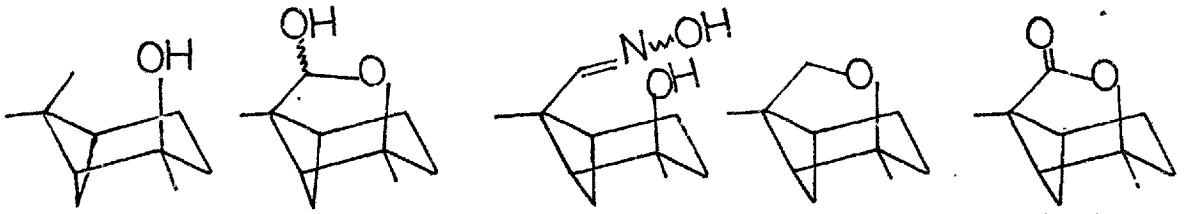
b)



Reaction (a) probably proceeds via the rhodium acyl complex intermediate of decarbonylation,[53] and (44) would be expected to give a verbanone. Examination of the decarbonylation products of (44) by t.l.c. and g.l.c. indicated no detectable verbanone. Polar compounds which could arise from a reaction similar to (b) were not investigated, but g.l.c. did demonstrate less volatile by-products. The rhodium carbonyl complex (46), ν_{max} 1990 cm^{-1}, cannot be converted back directly to the decarbonylation reagent.[52] (46) was found to react with pyridine on warming to give a decarbonylated complex as fine yellow needles, ν_{max} 1670, 1635, 1600, 1440, 1305, 1185, 1150, 1115, 1070, 990, 825, 775, 760, 730, 705 cm^{-1}, apparently distinct from the well-known dimeric complex $[RhCl(pph_3)_2]_2$ obtained by reaction of the decarbonylation reagent with pyridine. As the i.r. spectrum suggested a pyridine complex, the product was treated with hydrogen chloride in ethanol-dichloromethane containing triphenylphosphine, but tris(triphenylphosphine)chlororhodium (I) was not obtained. Moreover, the complex was not a decarbonylation reagent, and was not investigated further.

A new synthetic approach was required which would give a 9-substituted cis-verbanone. Pinan-2β-ol (51) was an attractive starting material[9,10,54] as it was readily

available optically pure by reaction of nopinone (4) with methyl magnesium bromide, and may be converted into the ether (54)[8,9,10] in excellent yield. Consequently the corresponding hemiacetal (52) obtained via nitrite ester photolysis should present no problem. As (54) is a tertiary ether, no oxidation at C-6 can occur in the preparation of the lactone (55). No g.l.c. separations would be required in the initial steps, and an esterification of a primary alcohol on C-9 of the pinanol would be completely selective in the presence of a C-2 tertiary hydroxyl function.

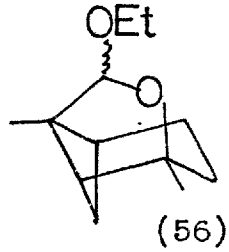


(51) (52) (53) (54) (55)

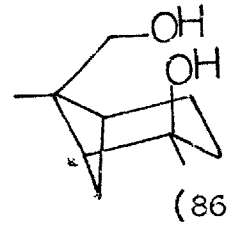
(52) was prepared with some variation of reaction conditions. The best yield (51% overall from (51)) was obtained as follows; photolysis of the crude nitrite ester of (51), containing some pyridine, in n-hexane at room temperature under anhydrous conditions to exhaustion gave precipitated nitroso-dimer and a solution containing further material. Heating the nitroso-compound in anhydrous isopropanol at reflux for two hours yielded virtually pure oxime (53) as a mixture of syn and anti isomers (to n.m.r.). (53) appeared on t.l.c. as two close-running spots. The cyclohexane solution on evaporation and pyrolysis in a similar manner gave a mixture containing some further oxime. Hydrolysis was best conducted separately from the pure compound. In each case, the oxime in ether was stirred with 2% concentrated hydrochloric acid in aqueous acetone (ca 10:1). The

pure oxime yielded pure hemiacetal, m.p. 58-60°, ν_{max} 3450 cm^{-1}. The crude sample was separated on alumina. The principal by-product (17%) proved to be the ether (54) a product of failure of the primary radical to trap nitric oxide in the solvent 'cage'. Possibly conducting the photolysis in a stream of nitric oxide would improve the overall yield. Hydrolysis by means of acid ion-exchange resin[56] in water-ether suspensions gave the hemiacetal in a clean reaction on a small scale, but considerable decomposition to an unsaturated aldehyde (not obtained pure) occurred on a preparative scale.

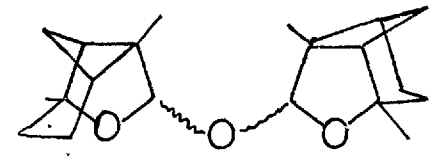
The lactol (52) was prepared in better overall yield (74% from (51)) via oxidation of ether (54) to the lactone with ruthenium tetroxide,[29-32] employing potassium periodate and 1-4% molar hydrated ruthenium dioxide in water-carbon tetrachloride. The lactone, m.p. 37-38°, has previously been reported (as a liquid) from oxidation of the ether with chromium trioxide-acetic anhydride[8,9] or with chromium trioxide-pyridine[55] (20 equiv.) in dichloromethane. The lactone was conveniently reduced to (52) in excellent yield with lithium triethoxyaluminium hydride[57] at -22°. Above this temperature excess reagent further reduced the hemiacetal to the diol[8] (86) m.p. 81-82° ν_{max} 3230 cm^{-1}. When hydrolysis of the reaction product was conducted at room temperature, the lactol (52) was largely converted into a separable mixture of two ethers, (56), a liquid, and (57), long needles, m.p. 115-115.5°, i.r. and n.m.r. identical with (52) except for the absence of hydroxyl.



(56)



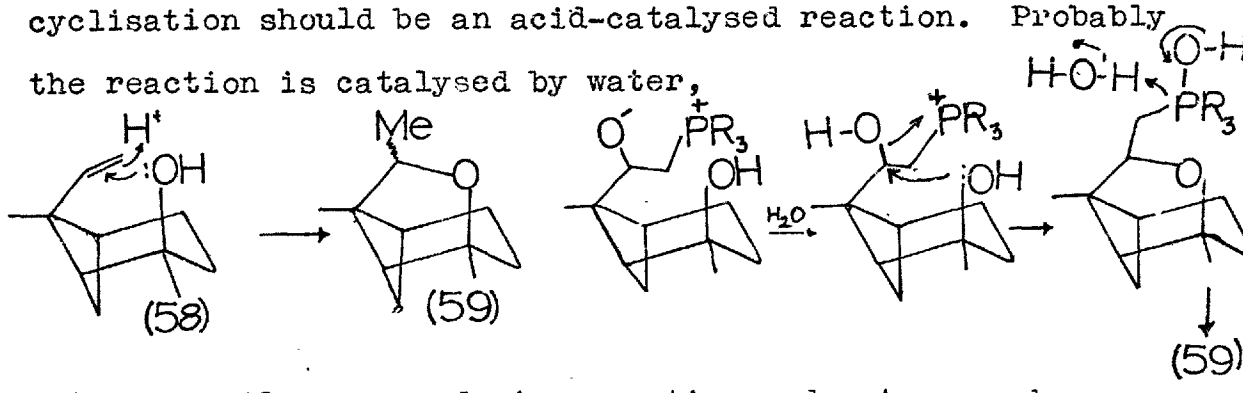
(86)



(57)

These products were not readily hydrolysed back to the hemiacetal. The subsequent acid-catalysed reaction could be avoided by careful hydrolysis at 0°, and complete removal of acid catalysts before warming the products. Heating the isolated hemiacetal or storage at room temperature resulted in some (57) by adventitious catalysis.

(52) reacted slowly with triphenylmethylenephosphorane as expected,[48] employing sodium methylsulphinylmethide[34] as base, to give the required olefin (58), m.p. 50.5-51.5°, which was isolated from an alumina column in 67% yield after 18 hours reaction (ca. 85% to completion). If allowed to proceed to completion, a considerable amount of the cyclised product (59) was invariably isolated. It was not established whether the hydroxyolefin subsequently cyclised to (59) during reaction. Although this appeared to be so from t.l.c., cyclisation should be an acid-catalysed reaction. Probably the reaction is catalysed by water,



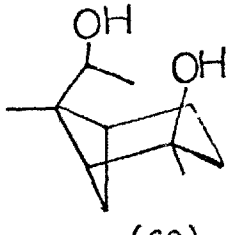
(58) (59) (59)

but apparently occurs during reaction and not on work-up; t.l.c. of the reaction mixture was a good indication of the isolated product composition. Unless atmospheric moisture

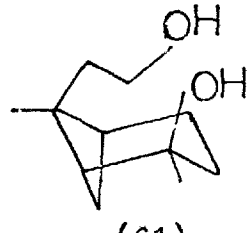
was carefully excluded, (59) was a major or even principal product.

(58) had ν_{max} 3300, 1630, 925 cm^{-1}. The olefin protons appeared as three separate multiplets. The R-CH = proton, deshielded by oxygen at 3.55, had two doublets, J = 10.5Hz and J = 18Hz, due to cis and trans vicinal coupling, respectively. The CH_2= C multiplet at τ4.75-5.15 could, consequently, be interpreted as two quartets, one due to cis vicinal coupling (J = 10.7Hz) and geminal coupling (J = 1.5Hz) and the other, trans vicinal coupling (J = 18Hz) and geminal coupling (J = 1.5Hz). The ether (59) showed only C-O absorption in the infrared spectrum, and the >CH-Me methine proton appeared as two overlapping quartets (J = 7Hz) at τ6.29 and 6.02, as expected. The methyl signal was also coupled. It is not clear whether the crystalline lactol (52) or the ethers (56) and (57) exist as mixtures of diastereoisomers as the methine singlets are comparatively broad, particularly for the lactol, although the lactol signal does have a shoulder.

Hydroboration[58] and oxidative work-up of olefin (58) gave a separable mixture (ca. 3:2) of the required primary alcohol (61), m.p. 110-111°, and the product of Markownikov-type addition, the secondary alcohol (60), m.p. 149-149.5°.



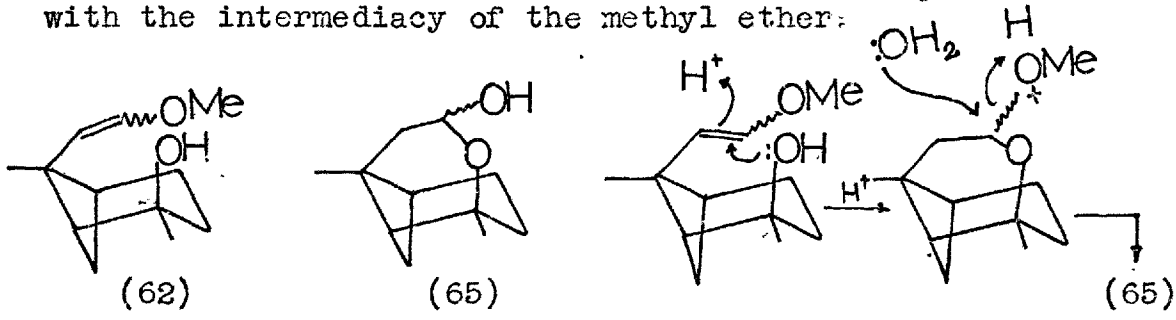
(60)



(61)

(60) showed a methyl doublet at 8.97 τ (J7Hz) and a methine quartet at 5.67 τ(J7Hz). The expected CH_2O triplet of (61) was obscured by a broad hydroxyl band and not satisfactorily resolved by addition of D_2O. Bis(3-methyl-2-butyl)borane reacted[58,37] with (58) to give a 95% yield of (61), identical in all respects.

An alternative method of preparation was considered. Methoxymethylenetriphenylphosphorane,[42,59,60] as a highly reactive ylid, was expected to react particularly rapidly with hemiacetal (52) to yield an enol ether (62) which should hydrolyse readily[61] to a δ-lactol (65), either directly or with the intermediacy of the methyl ether:

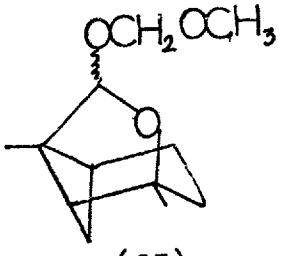


(62) (65) (65)

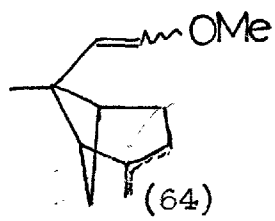
The δ-lactol should be reduced readily to the primary alcohol (61). The modified reagent is known to be unstable,[59,60] particularly with respect to the nucleophilicity of the base employed although the subsequent reactions have not been investigated in any detail. The hemiacetal (52) was found to have no reaction with the ylid when generated using n-butyl lithium[62] or phenyl lithium[62] as base, as the reagent decomposed much too rapidly. Potassium t-butoxide in t-butanol has been commonly employed.[63] Complete decomposition of the reagent (largely to tar and triphenylphosphine) was found to require at least 16 hours at 60°. At completion of reaction, two products were obtained. The more polar compound proved to be the required enol ether (62), ν_{max}

3550, 1660, 1110 cm^{-1}. N.m.r. conclusively demonstrated a mixture of cis and trans isomers in a 3:2 ratio; the methoxy function appeared as two singlets (τ6.46 and 6.41) and the cis isomer gave two one-proton doublets (J7Hz) at 5.18 and 4.26 ; the trans isomer similarly gave two one-proton doublets at 4.67 and 3.56 τ(J = 13Hz).

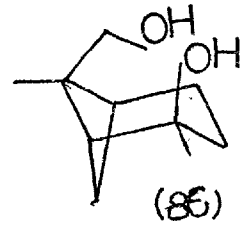
The non-polar component, ν_{max} 1160, 1110, 1020 cm^{-1}, was initially suspected to be the δ-lactol methyl ether, but n.m.r. showed a one-proton singlet at 5.13 τ and a two-proton AB quartet (J = 7Hz) at 5.37 τ, and not the expected pair of triplets due to the methine proton of the methyl ether of (65). Isolated (62) did not convert to the non-polar compound at all on prolonged reaction with the Wittig reagent. Moreover, the product hydrolysed very readily to the γ-lactol (52) and not a δ-lactol. The γ-lactol was confirmed by conversion to the ether (57) on heating with a trace of acid, and by reduction with lithium aluminium hydride to the diol (86), not (61). Consequently, this product must be (63).



(63)



(64)



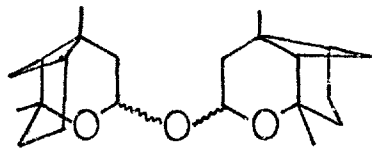
(86)

As expected for a methoxymethyl ether, (63) gave no molecular ion but showed fragments for loss of CH_3O (181), CH_2OCH_3 (166) and CH_3OCH_2O (151).

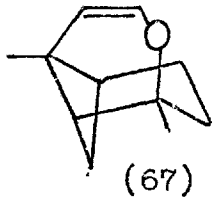
The Wittig reagent employed has previously been found to react with hydroxyl functions, but the products were not investigated.[61] It does not appear reasonable to propose reaction of the ylid and the hemiacetal to give (63). As a large excess of reagent, and commercial potassium t-butoxide were employed it is possible that sufficient water was present to hydrolyse some of the ylid to methoxymethanol followed by reaction with the hemiacetal. Deliberate addition of a little water increased the yield of the methoxymethyl ether. When sodium methylsulphinylmethide[34] was used as base, employing 4.6 equivalents of ylid at 60°, a slow reaction gave the required enol ether (62) as sole product, but only to 38% conversion.

Careful hydrolysis of (62), with cooling at 0°, using 1% concentrated hydrochloric acid in water (9)-acetone (1)/ether rapidly gave the δ-lactol (65) as an unstable oil, ν_{max} 3400 cm^{-1}, which was reduced immediately after isolation to the required diol (61), identical with previous samples, with lithium aluminium hydride at -20°. On warming or standing, (65) was converted into a separable mixture, the components probably being (a) the ether(66) ν_{max} 1070, 1005, 980, 930 cm^{-1}, n.m.r. identical to the δ-lactol except for the absence of hydroxyl, an oil which could not be crystallised probably due to a diastereoisomeric mixture. The $-CH\langle^{O}_{O}$ methine proton appeared as a quartet, J = 5Hz, although this may be the two superimposed triplets expected; and (b) the vinyl ether (67), ν_{max} 1640, 1250, 1070, 1050, 860, 785, 765 cm^{-1}. The olefinic protons appeared as expected as doublets (J = 6Hz) at 5.75 and 3.65 τ. Pure (66)

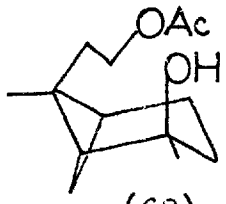
also decomposed at room temperature over a few days to (67) which was stable.



(66)

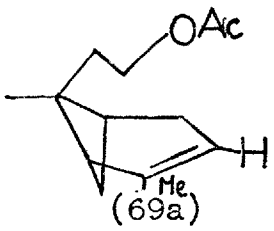


(67)

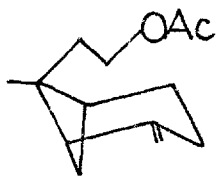


(68)

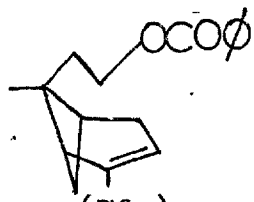
Diol (61) was readily converted to the monoacetate (68) (95%). Phosphorus oxychloride in pyridine[8,64,65] at 0° gave a 2:1 mixture (59%) of the α- and β-pinenes, (69a) and (69b) respectively, ν_{max} 1750, 1650, 1250 cm^{-1}.



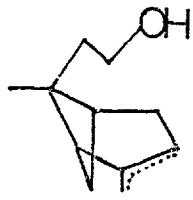
(69a)



(69b)



(76a)



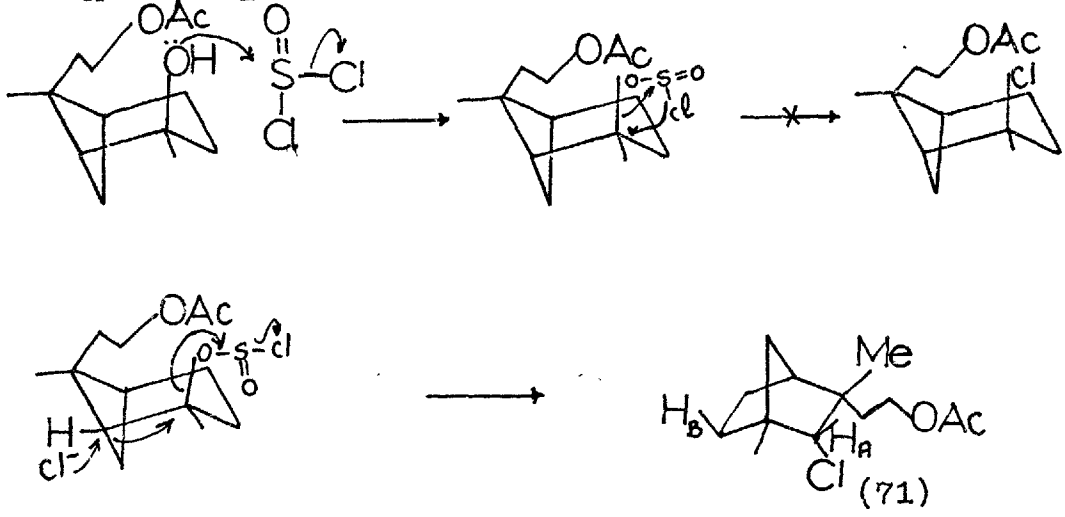
(70)

The methyl group on the double bond of (69a) appeared as a quartet (J = 2Hz) due to allylic coupling with the olefinic proton and homoallylic interaction with both protons of the adjacent methylene group, a characteristic pattern of the α-pinene system due to interaction of the rigid olefinic ring and the freely-rotating methyl group. The corresponding benzoate (76a) showed this pattern particularly clearly. The olefin signals were identified by comparison with α- and β-pinenes. The CH_2O functions appeared as the expected triplets at 5.98 and 6.02 τ (J = 8Hz).

As only one product was apparent to t.l.c., much of the tertiary alcohol must have been lost as a water-soluble phosphate ester. Alkaline hydrolysis of part of the aqueous

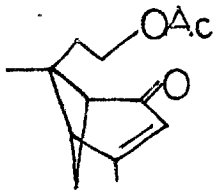
solution gave a mixture of (61) and an olefinic alcohol, probably (70). Reacetylation and treatment of the crude product with phosphorus oxychloride-pyridine gave some (13%) further (69). Yields of total olefinic products previously reported for this reaction on tertiary monoterpene alcohols have generally been in the range of 50-55%.[8,64]

Reaction of the acetate (68) with thionyl chloride in pyridine[65] at 0° yielded very little olefin. The principal product, an alkyl chloride, was not the anticipated 2β-chloropinane derivative but a norbornane, demonstrated by the one-proton doublet, J = 2Hz, as 6.40 τ, due to W-coupling of H_A with H_B (71), commonly observed in this system.[66]

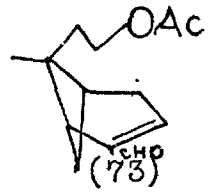


Allylic oxidation of the olefin to the enone (72) was expected to give only a moderate yield. The highest recorded yield for oxidation of α-pinene to verbenone (13) is 48%,[43] employing chromium trioxide-pyridine complex in dichloromethane. An attempt to use a procedure for oxidation with N-bromosuccinimide in aqueous tetrahydrofuran[67] containing calcium carbonate, while irradiated with a tungsten lamp, which has proved very successful in steroid and triterpenoid

reactions, gave many products. Small-scale oxidations of (69) with a large excess of chromium trioxide-pyridine complex gave 41-48% of the enone, either by reaction at room temperature (72 hours) or at reflux (16 hours), ν_{max} 1750, 1690, 1630 cm^{-1}; and ca.5% of an $\alpha\beta$-unsaturated aldehyde, ν_{max} 2720, 1750, 1690, 1635 cm^{-1} probably (73).

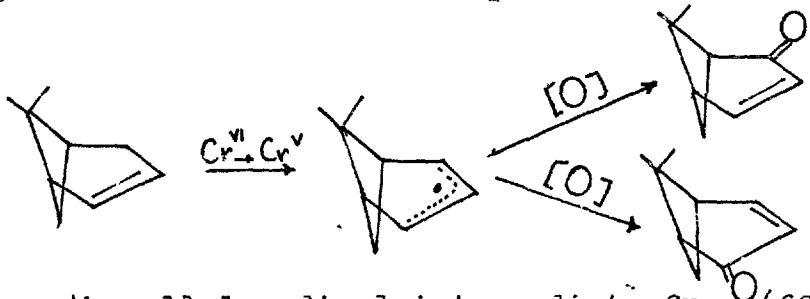


(72)



(73)

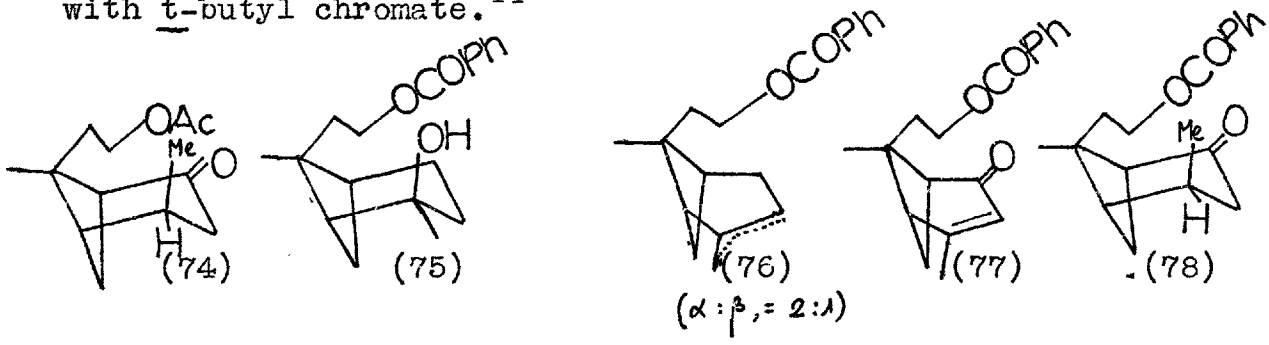
Both methylene groups of the acetoxy function of (72) appeared as triplets (J = 7Hz) and the olefinic proton at 3.19 τ as a quartet, presumably due to allylic coupling with the methyl group on the double bond, a doublet, J = 2Hz. The product had a reasonably large rotation ($[\alpha]_D^{21.5}$(corr.) - 161.2° ($CHCl_3$)) although not as large as verbenone. Apopinene gives apoverbenone[20] of very low optical purity by allylic oxidation but in this case the intermediate allyl radical is symmetrical and so oxidation at both allylic sites can give both enantiomers of apoverbenone:



whereas the allyl radical intermediate from (69) is not symmetrical. Under the reaction conditions, the β-pinene derivative (69b) may be converted to the more stable isomer (69a). The principal by-product of oxidation, a non-polar aromatic compound (ca.25%) with an aliphatic ketone function,

an alkoxyethyl group, but no acetate, was not further characterised. A large-scale reaction was less successful. Considerable over-oxidation to water-soluble products occurred. Dauben[43] has reported carboxylic acids as major products in some instances. Optimisation of the reaction conditions would require work-up and chromatography of each reaction as t.l.c. was not a good indication of the state of reaction.

(72) was readily hydrogenated to the required cis verbanone derivative, (74), ν_{max} 1750, 1720 cm^{-1}. A similar series of reactions on the diol monobenzoate (75) gave the ketone (78). None of these products could be crystallised. Allylic oxidation of (76) was also conducted with t-butyl chromate.[44]

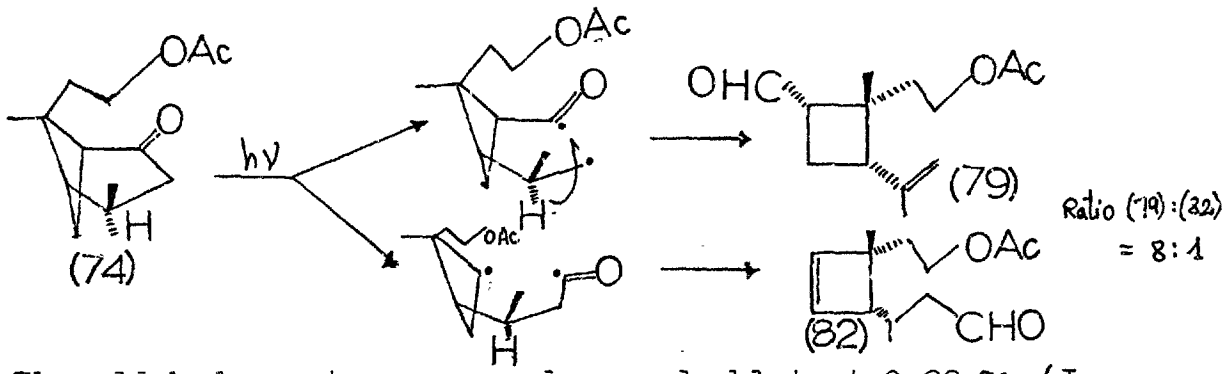


(74) (75) (76) (77) (78)

($\alpha:\beta$ = 2:1)

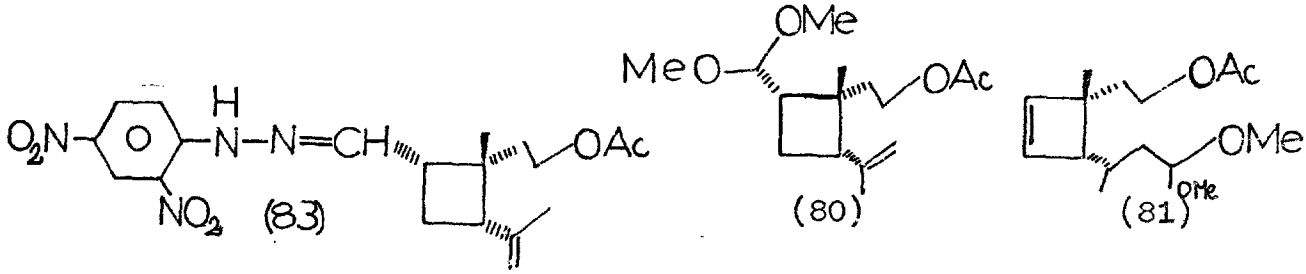
(78) proved to be photo-stable as previously demonstrated for the model benzoate (34). The acetate (34) on photolysis in methanol containing sodium bicarbonate gave as the major product (60%), isolated from a silica column, the required aldehyde (79), which was found to oxidise rapidly in air, ν_{max} (CCl_4) 3080, 2810, 2710, 1745, 1720, 1645, 1235, 1035, 970, 900 cm^{-1}, containing ca.10% of a cyclobutene (τ3.86, 2H q J=3Hz), presumed to be (82) but not isolable. The small coupling constant reflects the large C-C - C-H angle of a small unsaturated ring; 3Hz is typical for a

cyclobutene.



The aldehyde proton appeared as a doublet at 0.28 τ, (J = 2Hz) and CH_2= olefin protons as two broad singlets at 5.23 and 5.08 τ. The CH_2O protons of the acetoxyethyl group consistently gave a remarkably complex but symmetrical multiplet, ten signals apparent, (5.80-6.43 τ), integral 2H.

A 2,4-dinitrophenylhydrazone mixture was obtained from the aldehydes; the cyclobutene aldehyde also gave a derivative (τ 3.83). Crystallisation from ethanol gave the pure derivative (83) of the required aldehyde, m.p. 124-125°.

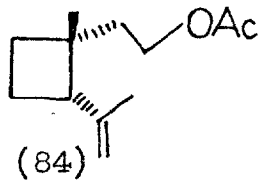


The derivative of the isomer was not separable on silica or alumina p.l.c. plates.

Photolysis in methanol in the absence of base initially yielded the aldehyde (to t.l.c.) which was rapidly converted to a less polar compound, the dimethyl acetal (80) containing some (81). After distillation, (80) had ν_{max} 1750, 1650, 1250, 1060, 970, 900 cm^{-1}. The methoxy groups appeared as

a six-proton singlet at 6.68 . A repeat reaction yielded no (80); on prolonged photolysis the aldehyde (79) polymerised, presumably with the intermediacy of the type II fragmentation product as observed for cis-verbanone.[3] No decarbonylation product was observed. Acetalisation of alkenal products in methanol by adventitious catalysis is a common problem observed by Meinwald.[50] If sodium bicarbonate is used to prevent this side-reaction, the solvent must be removed at room temperature and the product extracted into petrol as the aldehyde rapidly undergoes (presumably) aldol reaction on warming with aqueous or methanolic sodium bicarbonate.

Decarbonylation with tris(triphenylphosphine)chlororhodium (I) in dichloromethane gave a mixture (ca.75%) ν_{max} 1735, 1640, 1245, 1040, 895 cm^{-1} with grandisol acetate (84) the principal component; the major n.m.r. signals were in agreement with the recorded values.



(84)

$\tau(CCl_4)$ 8.80 (3H,s), 8.33 (3H,s), 8.05 (3H,s), 7.45 (1H,t, J8Hz), 6.01 (2H,t,J7.5Hz), 5.38 (1H,bs), 5.18 (1H,bs); a minor cyclobutene quartet appeared at 3.83 τ. Lit:[45] τ (CCl_4) 8.83 (3H,s), 8.36 (3H,s), 8.08 (3H,s), 7.47 (1H,q, J8Hz), 6.04 (2H,t,J7.5Hz), 5.43 (1H,bs), 5.24 (1H,bs). The CH_2O methylene group of the acetoxyethyl function gave the expected triplet. The multiplet of the corresponding protons of the aldehyde (79) must be due to a long range interaction

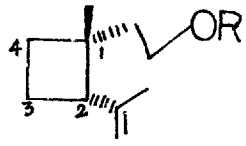
with the cis-aldehyde proton.

The acetate could not be purified further chromatographically, nor by distillation as it is thermally unstable. The dichloromethane solvent was purified by distillation from potassium carbonate, and a little potassium carbonate was also added to the reaction. Without this precaution some product of addition of hydrogen chloride to the isopropenyl group was obtained.

Reduction with lithium aluminium hydride yielded crude grandisol (85; R=H) which could not be purified directly; g.l.c. was not attempted. The crude product was converted into the p-nitrobenzoate (85; R = p-O_2N-ph-CO) which was recrystallised three times from hexane to constant melting point (m.p. 73-74°). The product, ν_{max} (CCl_4) 3050, 1730, 1640, 1605, 1520, 1350, 895 cm^{-1}, showed no cyclobutene protons in n.m.r. Again, the derivative of the by-product could not be isolated chromatographically from the supernatant solution of crystallisation.

Pure grandisol, (85; R=H)(to n.m.r.) was regenerated by alkaline hydrolysis, petrol extraction, and micro-distillation; ν_{max} (CCl_4) 3630, 3070, 1645, 890 cm^{-1}; Lit.[45] ν_{max} (CCl_4) 3630, 1642, 885 cm^{-1}. The n.m.r. spectrum on the undistilled compound showed a little petrol residue (methyl and methylene region) but was otherwise identical with a spectrum of synthetic (±) grandisol supplied by Dr. C.A. Henrick (Zoecon Corpn.); τ(CCl_4) 8.82 (3H,s), 8.33 (3H,s), 8.28 (2H,bs), 7.93 (OH,s, exchanged by D_2O and concentration

dependent), 7.48 (1H,t,J7.5Hz), 6.46 (2H,t,J7.5Hz), 5.40 (1H,bs) and 5.22 (1H,bs).



a) R=H

b) R= O_2N-⟨O⟩-CO

(85)

The distilled product had $[\alpha]_D^{21.5}$(corr.) + 15.9° (c.1%, n-hexane), $[\alpha]_D^{25}$(corr.) + 6.9° (c.3%, $CHCl_3$); $[\alpha]_D^{25}$(corr.) + 12.3° (c.3%, EtOH). After reconversion into the p-nitrobenzoate, further crystallisation (twice), hydrolysis and redistillation, the rotation was only slightly raised, to $[\alpha]_D^{21.5}$(corr.) + 18.4° (c.1%, n-hexane). Similar work-up of the mixture from the supernatant fluid of crystallisation of the p-nitrobenzoate gave very crude (ca.60%, to n.m.r.) pheromone, with a small negative rotation.

The known absolute configuration of (-)-β-pinene has been related to (+)-grandisol, which therefore has the (1R,2S) configuration shown (85).

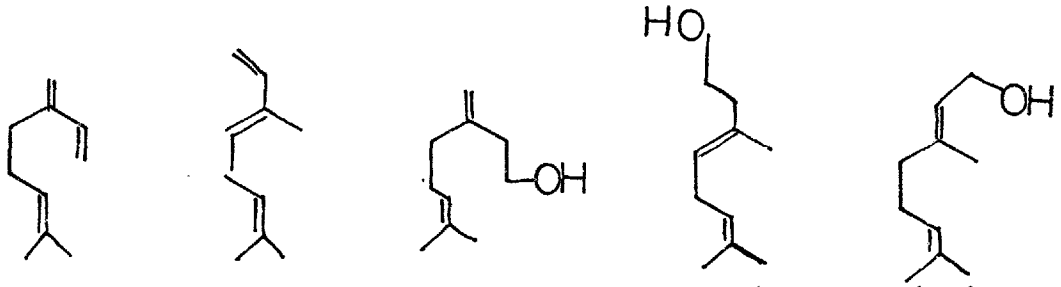
The natural pheromone constituent has been reported as having a rotation of +50°±10°,[69,70] an exceptionally high figure for a monoterpene alcohol.

Partial racemisation of our product during the photolytic reaction is conceivable, perhaps by a subsequent reversible β-bond cleavage, but very unlikely. The more stable trans isomer[70] should be obtained, but none was detected by n.m.r.

Although the configurations of the asymmetric centres of natural grandisol are the same as the corresponding centres of the principal optically-active monoterpene constituents of the cotton bud ((-)α-pinene, 8.9% of the total volatile oil; (-)-β-pinene, 1.0%; (-) limonene, 1.2%) (Review, part I), this correlation is almost certainly irrelevant, unlike the verbenol and verbenone pheromone constituents (p.3) of other species, which are oxidation products of natural α-pinene. To explain the co-occurrence of grandisol and the other constituents of the pheromone (p.5), which also possess a unique monoterpene carbon skeleton, an acyclic precursor must be invoked.

The trans isomer of grandisol (p.5) from Artemisia fragrans was rationalised as a cyclisation product of a nerol, or possibly geraniol, derivative (p.20) partly on the basis of the isolation from the same source of the same series of esters of (9), nerol, and geraniol.

Geraniol and nerol are only trace constituents of the volatile oil from the cotton bud, and it does not therefore seem reasonable to propose these alcohols, from cotton, as precursors to grandisol. Myrcene (87) and trans-β-ocimene (88) are the second and third most abundant monoterpene constituents (8.2% and 3.9% respectively) and both are reasonable biosynthetic sources of (5-8).

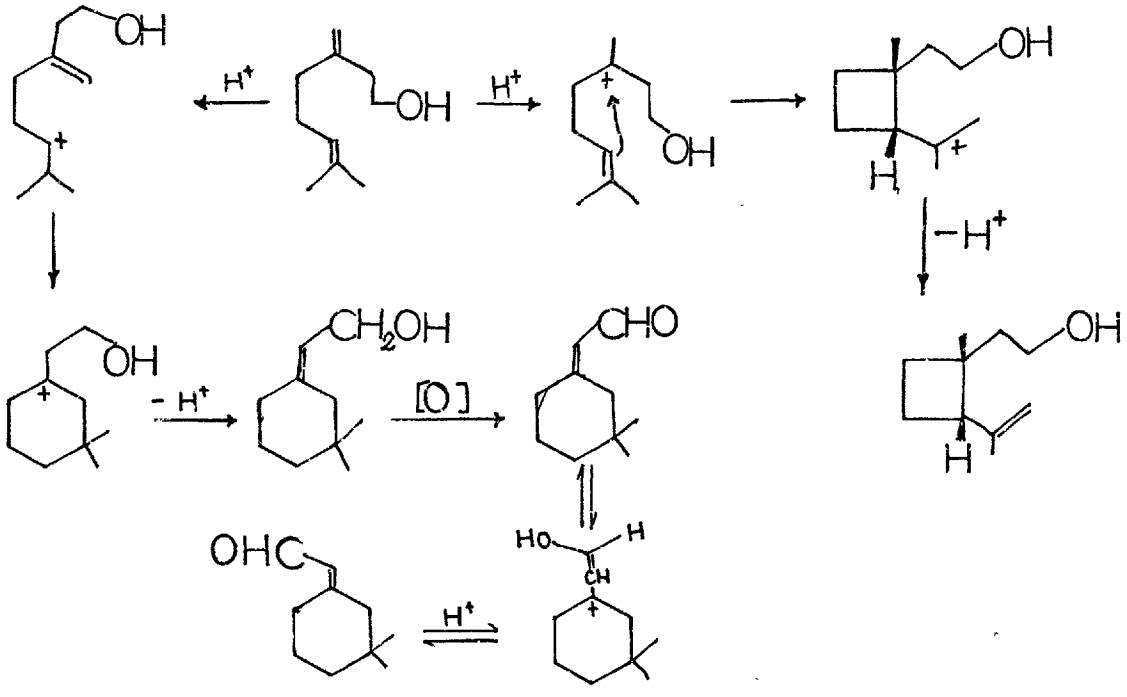


(87) (88) (89) (90) (91)

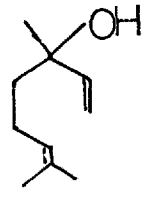
possibly via the alcohols or derivatives of the alcohols (89,90) although conceivably either myrcene or trans-β-ocimene could be converted to nerol (91) by A.grandis. (89) may be a minor constituent of the essential oil, as two unidentified acyclic monoterpene alcohols occur in reasonable amount (0.7% and 0.45%). Gueldner et al[72] speculatively proposed (89) as the precursor to all four pheromone constituents (scheme 1). Enzyme-controlled cyclisations may be invoked to account for the observed optical activity. Stork's cyclisations by colinear displacement on epoxides are not relevant to the cyclisation of (89-91) to grandisol. The unusual cyclisation is favoured by trisubstitution of the cyclobutane, which decreases the strain energy of the ring.

Whether A. grandis can synthesise the appropriate alcohol from (87) or (88), or must utilise the minor alcohol constituents of G. hirsutum is open to question. It may be possible to obtain some information by feeding the appropriate trienes and diene alcohols to the insects and determining the attractiveness of the males after feeding to the females; isolation of the pheromone would not be necessary.

Scheme 1



Linalool (92) would provide an optically-active substrate

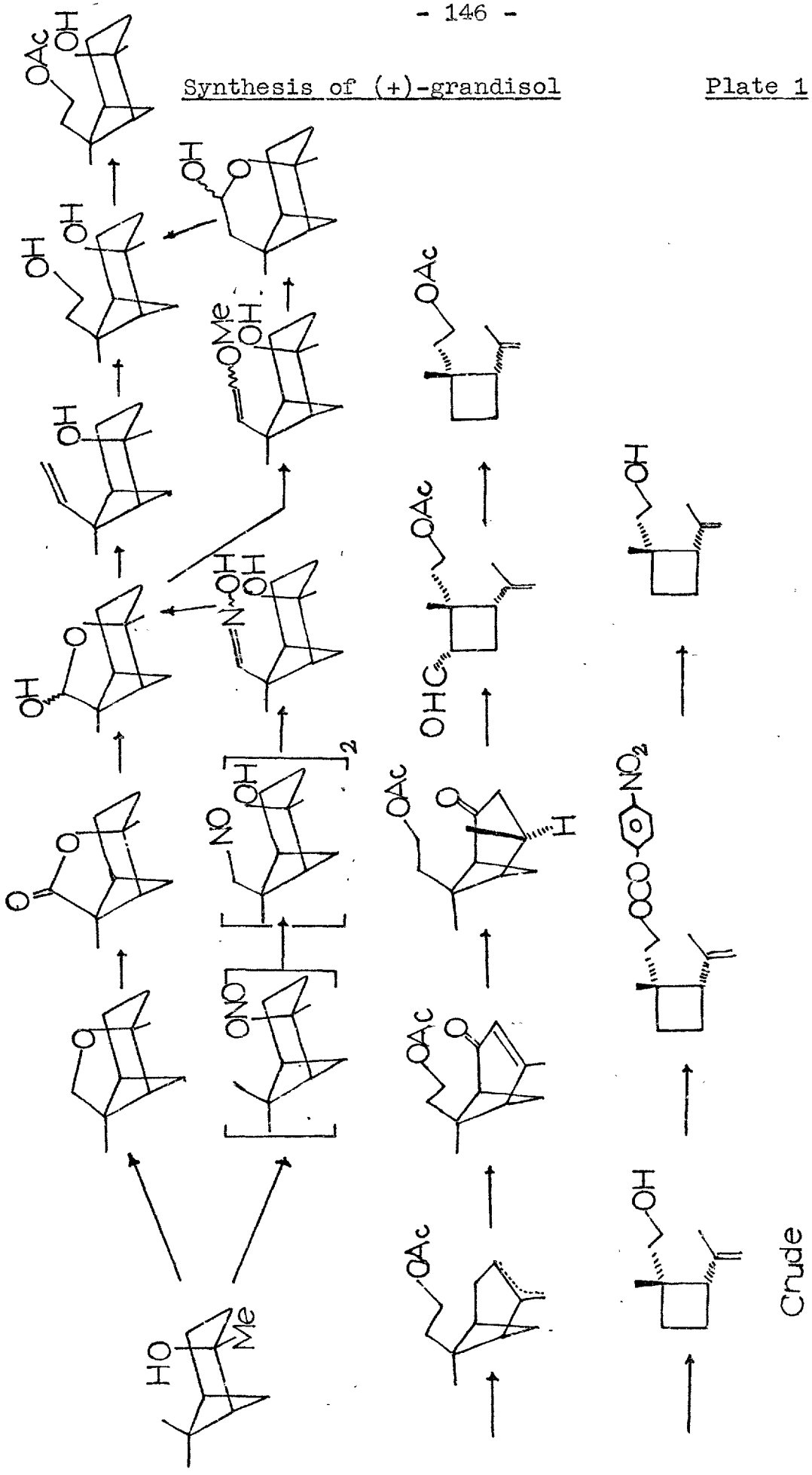


(92)

but the other pheromone constituents could not then be readily explained, assuming a common origin. Linalool is only a trace constituent of the essential oil.

To conclude, knowledge of the absolute configuration of grandisol does not provide any evidence regarding the biosynthesis of the pheromone components.

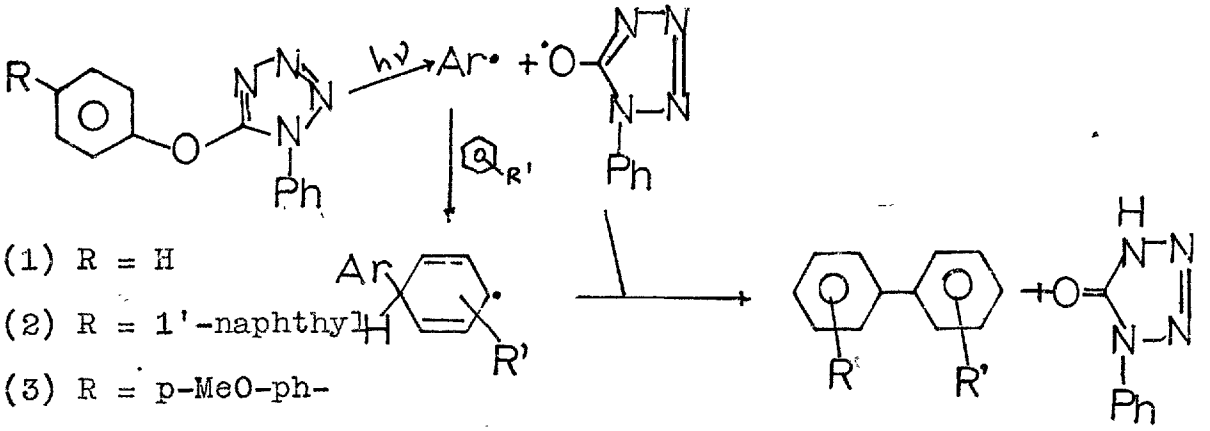
Synthesis of (+)-grandisol Plate 1



Part II

PHOTOLYSIS OF 5-ARYLOXY-1-PHENYL-1H-TETRAZOLES AND PHOTO-FRIES REARRANGEMENT OF 2-PHENOXYBENZIMIDAZOLE[7]

While investigating methods of preparation of certain unsymmetrical biphenyls required as starting materials for synthesis of Amaryllidaceae alkaloid models, the photoreaction (equ.1) was considered:

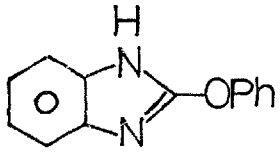


Equ. 1

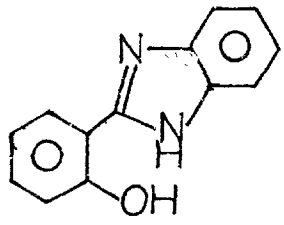
Hydrogenation of the tetrazoles[1] was reported to give the deoxygenated aromatic hydrocarbon. If the aryl-oxygen bond could also be cleaved photochemically the resulting aryl radicals could be trapped by aromatic solvents to produce biphenyls.

However, it had been reported[8] that photolysis of 5-phenoxy-1-phenyl-1H-tetrazole (1) in acetonitrile gave 2-phenoxybenzimidazole (5) in 25% yield. In view of the low yield of this product, the reaction was worth reinvestigation. Few photochemical reactions of tetrazoles have been reported.[6,9]

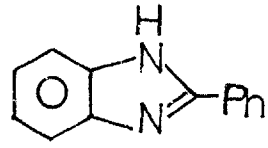
Photolysis of (1) in benzene gave a mixture from which the four principal components were isolated; 2-phenoxybenzimidazole (5) (36%, allowing for recovered starting material); 2-(O-hydroxyphenyl)benzimidazole (6) (22%); 2-phenylbenzimidazole (7) (25%); and biphenyl (10-15%, allowing for a little biphenyl produced on photolysis of pure benzene, under the same conditions, in a blank experiment).



(5)

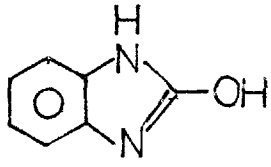


(6)

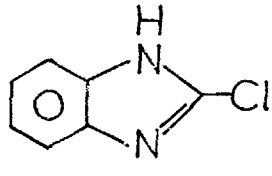


(7)

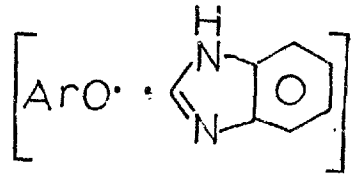
Irradiation of (1) in cyclohexane gave (5) and (6) but no biphenyl, nor (7). Oxygen did not affect the product distribution. Authentic samples of (5) and (7) were prepared by known methods.[2-5] (5) was prepared via 2-hydroxybenzimidazole (8) and 2-chlorobenzimidazole (9). (9), a vinyl chloride, did not react with phenol in acetone containing potassium carbonate and so was prepared by fusion with potassium phenoxide and copper powder. An authentic sample of (6)[14] was supplied by Dr. D. Goodgame of the department.



(8)



(9)



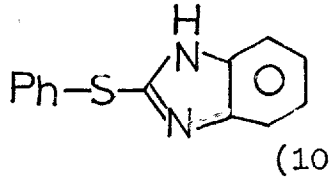
Equ. 2

Since (6) appeared to be a photo-Fries rearrangement[10] product of 2-phenoxybenzimidazole, (5) was photolysed in benzene; only two products, (6) and (7), besides biphenyl,

were obtained. The photo-Fries rearrangement had not previously been reported for a heterocyclic system. No products of para-type Fries rearrangements were isolated, but (7) requires escape of the benzimidazyl radical from the postulated solvent 'cage' (equ. 2) of one reasonable mechanism for the photo-Fries rearrangement. The isolation of (7) does not provide evidence of the mechanism of rearrangement of (5) to (6), however. Alternative radical[11,12] and concerted[13] paths have been proposed.

Photolyses of compounds (3) and (4) in benzene gave p-methoxybiphenyl (11%) and 2-phenylbenzimidazole (21%), and p-terphenyl (8%) and 2-phenylbenzimidazole, respectively, as well as other products which were not examined further. In each case, one major product was highly fluorescent under u.v. light, as is compound (6). (2) gave 2-phenylbenzimidazole (17%), and 1-phenylnaphthalene, identified from the u.v. spectrum only and not obtained pure.

2-phenylmercaptobenzimidazole (10) yielded 2-phenylbenzimidazole and a complex mixture of sulphides and disulphides. and so it was not practicable to detect a possible photo-Fries type reaction on this system.



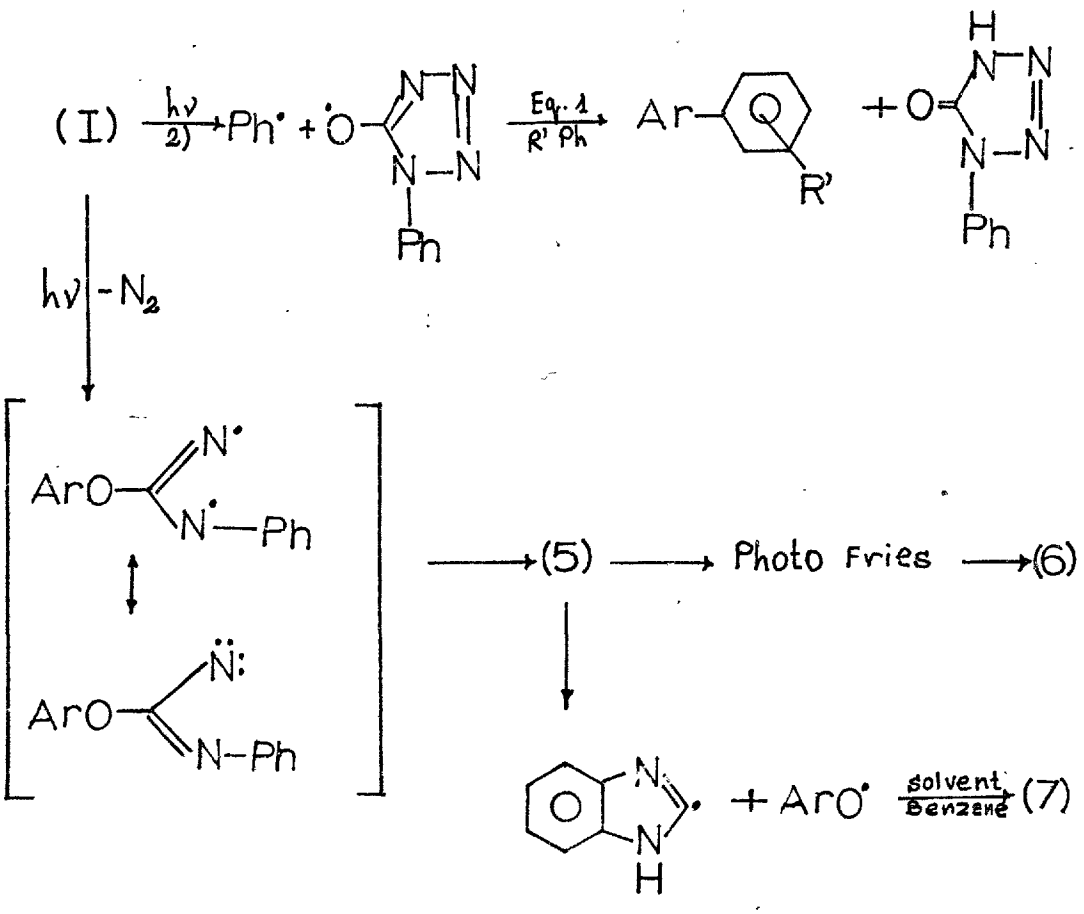
(10)

The processes involved in the photochemistry of 5-aryloxy-1-phenyl-1H-tetrazoles may be summarised (scheme 1) as competing extrusion of nitrogen and aryl-oxygen bond cleavage, the minor path. Products derived from the phenoxy

radicals from homolytic cleavage of 2-aryloxybenzimidazoles were not isolated. Several minor products were detected but could not be obtained sufficiently pure for characterisation.

Since the biphenyls were formed in similar yields, it would appear that aryl-oxygen cleavage is limited by the nitrogen extrusion reaction irrespective of the substituents on the aryloxy function, although use of a filtered high-pressure u.v. source, giving longer wavelength irradiation, was not attempted.

Scheme 1



EXPERIMENTAL

Part I

The following data apply unless otherwise stated.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded for Nujol mulls or liquid thin films on Pye Unicam SP 200, SP 1000 and Perkin-Elmer 157 instruments, except, where stated, for high-resolution spectra which were recorded for solutions in carbon tetrachloride with a Perkin-Elmer 257 instrument. Ultraviolet spectra were measured on a Pye Unicam SP 800 spectrophotometer, and n.m.r. spectra were recorded with Varian A-60 or T-60 instruments for solutions in [^{2}H]chloroform, unless stated otherwise, with tetramethylsilane as internal standard. Mass spectra were taken with an A.E.I. MS-9 high resolution instrument, and optical rotations measured as solutions in given solvents on a Perkin-Elmer 141 polarimeter. Analytical and preparative g.l.c. was performed by a Perkin Elmer F11 and a Pye 105 instrument respectively.

Solvents were dried by standard techniques. Light petroleum refers to the fraction of b.p. 40-60°. Alumina (G3) refers to Brockmann Grade III neutral alumina. Silica t.l.c. plates were prepared using Merck G_F 254 silica.

(-)-β-pinene from two sources was employed as a starting material. A sample of 98% optical purity was supplied by Fritzsche, Dodge and Olcott Inc., New York, and material of

90% optical purity by Ralph N. Emanuel, Wembley. Rotations of compounds prepared from the latter sample have been corrected to 100% optical purity, and are recorded thus: $[\alpha]_D^t$(corr.).

Unless stated, photolyses were performed using a Hanovia 500W water-cooled medium-pressure lamp.

The following abbreviations are employed for n.m.r. data: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; bs = broad singlet.

(+)-6,6-Dimethylnorpinan-2-one ((+)-nopinone) (4)

Ozonolysis[14,15] of (-)-pin-2(10)-ene in dry methanol at room temperature, and reaction of the products with dimethyl sulphide gave (+)-nopinone(4), purified by distillation through a short Vigreux column; b.p. 70-73° at 7mm Hg. ν_{max} 1710 cm^{-1}; τ9.15 (3H,s) and 8.66 (3H,s). $[\alpha]_D^{23}$ + 39.1°(c4%, MeOH) (lit.[15] $[\alpha]_D^{22}$ + 39.9 ± 0.3°, (c4% MeOH)).

3β-Bromo-6,6-dimethylnorpinan-2-one (3β-bromonopinone)[15] (19)

A solution of (+)-nopinone (75g, 0.51 mole), N-bromosuccinimide (120g, 0.65 mole, recrystallised from water) and dibenzoyl peroxide (4g) in dry carbon tetrachloride (750 ml) was gently refluxed, with mechanical stirring, for 3 hours on an oil bath. A 3l flask was employed to minimise possible loss from sudden foaming which occurred at completion of

reaction. Precipitated succinimide was filtered from the cold solution. Evaporation gave a yellow oil, consisting mainly of 3α-bromonopinone.[15] The crude product was adsorbed on alumina (G3, 1 kg) in ether, and eluted with ether after standing 70 hours. The eluate was concentrated to a small volume; 3β-bromonopinone, m.p. 112-113° (from petrol) (lit.[15] m.p. 112-113°) crystallised as colourless needles. The residual oil was readsorbed on alumina (G3, 400g) in ether, and the equilibration, elution, and crystallisation repeated three times. The total yield of (19) was 76.3g, 67%. (lit.[15] 59%) ν_{max} 1725 cm^{-1}; τ 9.12 (3H,s), 8.60 (3H,s) and 5.15 (1H, ABq, J 8 Hz).

3α-Bromo-6,6-dimethylnorpinan-2-one (3α-bromonopinone)[15]

(18)

(+) Nopinone was reacted with N-bromosuccinimide as given (above). The crude 3α-bromonopinone from evaporation of the carbon tetrachloride was purified by column chromatography on acid (HNO_3)-washed alumina, eluted petrol-ether. Yield of white needles (18), 57%, m.p. 69-70° (lit.[14] m.p. 69.5-70°). ν_{max} 1725 cm^{-1}. τ 9.14 (3H,s), 8.58 (3H,s), 5.53 (1H, ABq, J 3.5 Hz).

A sample was dissolved in ether and equilibrated on alumina (G3) for 72 hours. Elution with ether and crystallisation of the product from petrol yielded 3β-bromonopinone (19), m.p. 112-112.5°.

(+)-6,6-Dimethylnorpinan-3en-2-one (Apoverbenone)[15](20)

A suspension of anhydrous lithium carbonate (130g, 1.67 mole) in dry dimethyl sulphoxide (650 ml) containing 3β-bromonopinone (19) (75.0g, 0.345 mole) and anhydrous lithium bromide (130g, 1.50 mole) was stirred under argon on an oil bath at 140-145° for 72 hours. After cooling the dark brown semisolid mixture was extracted with water (3l) filtered, the precipitated lithium carbonate washed with ether, and the filtrate extracted with ether (4 x 1l). The ethereal solution was washed twice with water (1l), dried ($MgSO_4$) and evaporated to yield a black oil, which was washed through a wide alumina column (G3) in benzene to remove tar. The yellow-brown oil was distilled to give apoverbenone (20), 31.6g, b.p. 68-9° at 5 mm Hg, containing 17% nopinone (4) according to n.m.r and g.l.c. Yield, allowing for purity, 56%. The crude colourless product partly crystallised, m.p. 17-18° (lit.[15] m.p. 17-19°). Subsequent reactions under the same conditions gave apoverbenone of from 75%to greater than 95% purity. The crude products were used to prepare (+)-trans-verbanone. At a reaction temperature of 130°, very little dehydrobromination had occurred after 120 hours, and at 150° the yield was much reduced by decomposition to tar.

A relatively pure sample had ν_{max} 1675, 925, 740 cm^{-1}, τ8.97 (3H,s) 8.48 (3H,s) 7.88 (1H,d, J 8 Hz), 4.08 (1H,d, J 9 Hz), 2.48 (1H, ABq, J 5.5 Hz); peaks due to nopinone at τ9.15(s) and 8.66(s). $[\alpha]_D^{22}$ + 295.6° (c3%, $CHCl_3$);(lit.[15] $[\alpha]_D^{25}$+ 319° (c2.4, $CHCl_3$))

(+)-Trans-verbanone (2βH-pinan-4-one) (17)

Methyl lithium solution (0.87 mole; 350 ml 2.5 molar) was added via a serum cap to a stirred suspension of cuprous iodide (76g, 0.4 mole as [Cu I] dried under vacuum at 70°) in dry ether (1.5l), under argon at 0°, over 45 minutes. After 2 hours at 0° most of the cuprous iodide had dissolved. A solution of apoverbenone (26.5g, 75% pure ≡ 0.15 mole)(20) in dry ether (500 ml) was added over 30 minutes, and stirring continued for 2 hours at 0°, and 20 hours at room temperature. The reaction product was poured cautiously into saturated ammonium chloride solution, the ether layer separated, washed with 0.880 ammonia solution to remove copper complexes, then with water, and dried over sodium sulphate. After removal of solvent, the yellow oil was distilled, b.p. 68-71° at 5 mm Hg, to yield a colourless liquid, a mixture of trans-verbanone (75%) and unreacted (+) nopinone (25%), by g.l.c. (column: 20: 80 silicone grease on chromosorb P.60-80 mesh, at 120°; t_R trans-verbanone 5.7 minutes, t_R nopinone 4.5 minutes) Yield, allowing for purity, 88%. τ 9.14(3H,s), 8.80 (3H,d.J 9 Hz), 8.65 (3H,s); the nopinone methyl signals at τ9.15, 8.66 were superimposed. Subsequent reactions employed apoverbenone of 83% and of >95% purity. The product obtained from the latter sample was almost pure and used as such for the preparation of neoverbanol. A small-scale preparation (on 1.45g apoverbenone) was complete after 1 hour at 0°, by t.l.c. and i.r.

Trans-verbanone of 98% purity (to g.l.c.) was obtained from an 83% sample by preparative g.l.c., employing a 30ft.

x 1cm column of 15% E-30 on silanised diatomite C (60-72 mesh) at 155°, and manual injection. Recovery, 75%; t_R nopinone 33 minutes, t_R trans-verbanone 45 minutes. ν_{max} 1713 cm^{-1}; $\eta_D^{22.5}$ 1.4665; n.m.r. principal signals as for crude sample. $[\alpha]_D^{21}$ + 22.4° (c10%, benzene). m/e 152 (m^+), 137 ($m^+ - CH_3$), 134 ($m^+ - H_2O$), 119-20, 109, 105-6, 95, 91, 83, 71, 57, 55.

Trans-verbanone oxime

Pure trans-verbanone (500mg, 3.3mmole) and hydroxylamine hydrochloride (600mg, 8.6 mmole) in dry pyridine (4 ml) were heated to 110° for 16 hours. The pyridine was largely distilled off, the residue diluted with water and extracted with ether (10 ml). The organic layer was washed twice with water, dried (Na_2SO_4) and evaporated. The residual oil was very soluble in cold petrol and could not be crystallised satisfactorily. The crude material was purified by short-path distillation at 80°/2 mm Hg. The distillate slowly crystallised to yield white needles of the oxime, melting at around 18°. A sample was redistilled for analysis: ν_{max} 3300, 1670, 970 cm^{-1}; τ 9.19 (3H,s), 8.98 (3H,d,J7.5Hz), 8.72 (3H,s), $[\alpha]_D^{21}$ + 32.0° (c4%, $CHCl_3$). M/e 167 (m^+), 152 ($m^+ - CH_3$), 150 ($m^+ - OH$), 149 ($m^+ - H_2O$), 125-6, 108-10, 91, 83, 81, 69, 67, 57, 55. (Found: C, 71.81%; H, 10.25%; N, 8.37%. Calculated for $C_{10}H_{17}NO$, C, 71.71%; H, 10.02%; N, 8.23%).

(-) Neoverbanol (2βH-pinan-4β-ol) (15)

(+)-Trans-verbanone (5.00g, 0.033 mole, >95% pure) in

dry ether (100 ml) was reduced with excess lithium aluminium hydride at reflux for 1 hour. Work-up in the usual way with ammonium chloride solution, and washing the ether extract with water gave crude neoverbanol (5.0g). Crystallisation from a little petrol (b.p. 30-40°) at 0° gave the pure product (15) as long, fine white needles, m.p. 77-77.5° (90%). Repeated crystallisation did not affect the melting point. An analytical sample was prepared by sublimation with no change in melting point. Neoverbanol is volatile at atmospheric pressure. Crude neoverbanol, from reduction of 83% trans-verbanone, containing cis-nopinol (24) had m.p. 72-74° after one crystallisation and was not obtained pure after a second crystallisation. The pure compound had ν_{max} 3250 cm^{-1}, τ9.10 (3H, d J 6.5 Hz), 8.93 (3H,s), 8.77 (3H,s), 5.80 (OH; 1H, m). $[\alpha]_D^{21.5}$ -16.1° (c3%, benzene); -16.2 (c7%, benzene); -8.24° (c6%, $CHCl_3$). m/e 154 (m^+), 139 (m^+-CH_3), 136 (m^+-H_2O), 121, 110-2, 107, 92-8, 85, 83, 69, 58, 55. (Found: C, 77.87%; H, 11.76%. $C_{10}H_{18}O$ requires C 78.10%; H 11.81%).

4α,9-Dimethyl-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (22)

(-) Neoverbanol (6.0g, 39 mmole) and yellow mercuric oxide (13.0g, 51 mmole; dried 13 hours at 70°) were stirred in pentane (70 ml; free of olefins) at reflux under argon. A solution of dry bromine (6.0g, 38 mmole) in pentane (40 ml) was added at such a rate (over 30 minutes) as to maintain gentle reflux when the heat source to the oil bath was removed, while the reaction was irradiated with a 750 W. tungsten lamp from 40cm. The solution of bromine in pentane

was protected from light during the addition. The suspension was refluxed for a further hour, cooled, and filtered. The pentane solution was washed with saturated aqueous sodium bicarbonate, saturated sodium chloride solution, aqueous pyridine (to remove any alkyl bromides), and again with sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina (G3) carefully eluted with light petroleum to separate the ether (22), a colourless liquid (50-70%), from olefins and trans-verbanone. Distillation (b.p. 62° at ca 5 mm Hg) yielded pure product, ν_{max} 1050, 1030, 935 cm^{-1}; τ 8.72 (3H,s), 9.13 (3H, d, J 6Hz), 6.40 (2H, ABq, J 9Hz), 5.47 (1H, m). $[\alpha]_D^{21.5}$ + 62.7 (c4%, $CHCl_3$). m/e 152 (m^+), 134 (m^+-H_2O), 123, 119-20, 109, 105, 94-6, 91, 84, 83, 81, 79, 71. (Found: C, 78.62%; H, 10.40%; $C_{10}H_{16}O$ requires C, 78.89%; H, 10.59%).

4α,9-Dimethyl-7-oxatricyclo[4.3.0.$0^{3,9}$]nonan-8-one (28)

a) Oxidation with $CrO_2(OAc)_2$

The ether (22) (1.3g, 8.6 mmole) in acetic anhydride (12 ml) was treated with a solution of chromium trioxide (1.60g, 16 mmole) in acetic acid (37 ml) and water (4 ml) at 100-110° for 4 hours. Ethanol (4 ml) was added to the cooled solution. The mixture was poured on to ice and extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. The crude oil, which consisted of the lactone (28), unreacted ether and three minor products, was chromatographed on alumina (G3) eluted petrol 98-ethyl acetate 2.

The lactone (0.65g, 46%) crystallised from petrol (b.p. 30-40°) as large white needles, m.p. 48-48.5°, ν_{max} 1770, 1225, 1075, 970 cm^{-1}; τ 9.07 (3H, d, J 6Hz), 8.62 (3H,s), 5.05 (1H, m). $[\alpha]_D^{21}$ + 119.3 (c4%, $CHCl_3$); m/e 166 (m^+), 151 ($m^+ - CH_3$), 137-8 (m^+-CO), 121-5 (m^+-CHnCO and m^+-CO), 109-11, 107, 93-8. (Found: C, 72.26%; H, 8.49%. Calculated for $C_{10}H_{14}O_2$, C 72.06%, H 8.43%).

b) Oxidation with RuO_4

Neoverbanol (15) was converted to a mixture of the ether (22) and trans-verbanone (17) by reaction with mercuric oxide and bromine. The crude reaction product, which contained ca. 6g of the ether (to n.m.r.) was added to a vigorously stirred two phase system consisting of sodium metaperiodate (30 g, excess) in water (300 ml), and carbon tetrachloride (250 ml) to which hydrated ruthenium dioxide (400 mg) had been added. After 38 hours stirring at room temperature the black suspension of regenerated RuO_2 remained in solution as yellow RuO_4 and oxidation of the ether was complete. The carbon tetrachloride layer was separated, washed with water, and dried over sodium sulphate. Ethanol (5 ml) was added to reduce RuO_4 to RuO_2(hydrated) which was recovered by filtration through Celite. After evaporation of solvent, the lactone (5.4g) was isolated by chromatography on alumina (G1), eluted petrol-ethyl acetate. Trans-verbanone was also recovered; unreacted neoverbanol in the crude ether was also oxidised to trans-verbanone. The lactone was contaminated with ca 10% of a more polar by-product which was not readily separated by chromatography or distillation. Crystallisation

from petrol at 0° afforded pure (28), identical with the product of method (a). The by-product could not be obtained pure for characterisation.

c) The pure lactone (28) (0.50g) in carbon tetrachloride (5 ml) was added to a well-stirred two-phase mixture of sodium metaperiodate (5g) in water (200 ml) carbon tetrachloride (150 ml) containing hydrated ruthenium dioxide (100 mg). After 260 hours at room temperature, the lactone was recovered unchanged. The crude product from the supernatant fluid of crystallisation of the lactone from petrol, which contained the oxidation by-product, was treated with (a) 2,4-dinitrophenylhydrazine reagent as a solution in phosphoric acid-ethanol, and (b) semicarbazide solution in aqueous ethanol. Neither reagent gave a derivative, although i.r. showed a carbonyl peak at 1720 cm^{-1}.

2βH-Pinan-4β,9-diol (31)

The lactone (336 mg, 2.0 mmole) in dry ether (10 ml) was reduced at reflux for 30 minutes with excess lithium aluminium hydride. Ethyl acetate was added dropwise to destroy excess reducing agent and the product worked up with saturated ammonium chloride solution. The diol (31) (300 mg, 87%) m.p. 82.5-83.5° (from ether-petroleum ether) crystallised as fine white needles, ν_{max} 3300, 1030, 1020, 1005 cm^{-1}; τ 9.11 (3H, d, J 6 Hz), 8.65 (3H,s), 5.67 (m), 6.05 (1H, m), 6.95 (bs). $[\alpha]_D^{21.5}$ - 41.0° (c4.9%, $CHCl_3$). m/e 170 (m^+), 152 (m^+-H_2O), 137, 134, 121, 109, 94. (Found: C, 70.71%; H, 10.48%. Calculated for $C_{10}H_{18}O_2$, C, 70.55%;

H, 10.66%).

2βH-9-Benzoyloxypinan-4β-ol (32)

To a stirred solution of the diol (31) (270 mg, 1.59 mmole) in dry pyridine (1 ml) and dry ether (2 ml) at 0° was added redistilled benzoyl chloride (250 mg, 1.77 mmole, 1.12 equiv.) in ether (1 ml). Pyridine hydrochloride separated within a few minutes. After stirring overnight at room temperature the solution was poured into water, diluted with ether, and the ether layer washed successively with water, 0.5N hydrochloric acid, sodium bicarbonate solution, and water, dried (Na_2SO_4) and evaporated. Chromatography on alumina (G3) eluted light petroleum-ethyl acetate (increasing polarity) yielded dense crystals of the monobenzoate (32) (371 mg, 85%) m.p. 106.5-107.5° (from ether-petroleum ether); ν_{max} 3500, 1705, 1605, 1585, 1290, 1265, 1125, 1030, 960, 730 cm^{-1}; τ9.08 (3H, d, J 6Hz), 8.59 (3H,s), 5.49 (3H,m), 2.49 + 1.97 (5H, m); m/e 274 (m^+), 256 ($m^+ - H_2O$), 238, 231, 218, 205-6, 201-2, 193, 183, 152 (m- ph COOH), 137, 134, 122; $[\alpha]_D^{21.5}$ + 8.5° (c1.9%, $CHCl_3$). (Found: C, 74.49%; H, 8.04%. Calculated for $C_{17}H_{22}O_3$, C 74.42%; H 8.08%).

The column also yielded traces of unreacted diol (m.p. 81-2°) and of the dibenzoate (35 mg, 8%) (33), ν_{max} ($CHCl_3$) 1710, 1600, 1585, 1280, 910 cm^{-1}; τ9.07 (3H, d, J 6Hz), 8.65 (3H,s), 5.52 (2H,9, J 5Hz), 4.48 (1H, m), 1.9-2.85 10H, m).

9-Benzoyloxy-trans-verbanone (2βH-9-benzoyloxypinan-4-one) (34)

A solution of chromium trioxide (1g) in dry pyridine (5 ml) was diluted with dry dichloromethane (10 ml; free of olefins). The diol monobenzoate (371 mg, 1.35 mmole) (32) in dichloromethane (3 ml) was added at room temperature. A black precipitate separated almost immediately. Ethanol (1 ml) was added after 5 hours to destroy excess reagent, and the red solution decanted. The residue was washed twice with dichloromethane, and the combined solution and washings evaporated. Elution of the residue through a short alumina column (G5) in petrol-ethyl acetate yielded the virtually pure ketone (34) (356 mg, 97%) as a pale yellow oil which was short-path distilled (b.p. ca 100° at 2 x 10^{-4} mm Hg) to give a colourless product; ν_{max} 1725, 1610, 1585, 1275, 725 cm^{-1}; τ 8.93 (3H d J 6Hz), 8.50 (3H,s), 5.90 (2H, d, J 2Hz), 1.90-2.58 (5H, m). $[\alpha]_D^{24}$ -0.6° (c2%, $CHCl_3$). m/e 272 (m^+), 202, 167 (m^+-phCO), 150-1 (m^+-phCOOH), 135, 122, 105, 77. (Found: C, 75.05%; H, 7.50%. Calculated for $C_{17}H_{20}O_3$, C, 74.97%; H, 7.40%).

2βH-9-Acetoxypinan-4β-ol (35)

Redistilled acetic anhydride (480 mg, 4.7 mmole) in dry ether (2 ml) was introduced to a stirred solution of the diol (31) (400 mg, 2.35 mmole) in pyridine (1.5 ml) and ether (5 ml) at room temperature. Reaction was followed by t.l.c. When little diol remained (ca 8 hours) water (3 ml) was added, and stirring continued overnight. The mixture

was poured into water, extracted with ether, the ether layer washed successively with water, saturated sodium bicarbonate solution, and water, dried (Na_2SO_4) and evaporated. Residual pyridine was pumped off at room temperature into a cold trap. An alumina (G1) column, eluted successively with petrol 97-ethyl acetate 3; petrol 90-ethyl acetate 10; and petrol 75-ethyl acetate 25, yielded the pure monoacetate (35) (340 mg, 68%), a colourless oil, b.p. 70° at 3 x 10^{-4} mm Hg, ν_{max} 3500, 1740, 1725, 1250, 1030, 1020 cm^{-1}; ν_{max} (CCl_4) 3550, 1735, 1240 cm^{-1}. τ 9.12 (3H, d, J6Hz), 8.75 (3H,s), 7.97 (3H,s), 5.77 (2H, Abq, J6Hz) (superimposed with 1H,m). m/e 212 (m^+), 170 (m^+-CH_2CO), 152 (m^+-CH_3COOH), 149, 137, 134, 119-23. $[\alpha]_D^{22.5}$ -9.0° (c3%, $CHCl_3$). (Found: C, 67.71%; H, 9.29%. Calculated for $C_{12}H_{20}O_3$, C 67.89%; H 9.50%).

The diacetate (36) (22%), a colourless oil, was also obtained. ν_{max} ($CHCl_3$) 1730, 1265, 915 cm^{-1}; τ 9.11 (3H,d, J7Hz), 8.75 (3H,s), 8.03 (3H,s), 7.97 (3H,s), 5.88 (2H,s), 4.78 (1H,m).

9-Acetoxy-trans-verbanone (2βH-9-acetoxypinan-4-one)(37)

Oxidation of the diol monoacetate (35) (200 mg) was carried out with excess chromium trioxide in pyridine-dichloromethane exactly as for the monobenzoate (34). Yield, 192 mg, 94%. Microdistillation yielded a colourless oil, b.p. ca 65° at 3 x 10^{-4} mm Hg; ν_{max} (CCl_4) 1745, 1720, 1245 cm^{-1}; τ 8.95 (3H,d), 8.63 (3H,s) 7.99 (3H,s), 6.18 (2H,s). $[\alpha]_D^{24}$ + 5.5° (c3%, $CHCl_3$). (Found: C, 68.26%; H, 8.36%. $C_{12}H_{18}O_3$ requires C, 68.55%; H, 8.63%).

Attempted photolytic reaction of ether (22) with cyanogen bromide

The ether (22) (400 mg) in pentane (20 ml) containing a large excess (3g) of cyanogen bromide was photolysed under argon in a quartz vessel, employing medium and low pressure u.v. lamps, for up to 9 hours. Only unreacted starting material could be recovered.

2βH-9-phenylsulphonylpinan-4β-ol (26)

To sodium borohydride (645 mg, 17 mmole) and redistilled thiophenol (2.82 g, 25.6 mmole) in dry diglyme (8 ml) at 0° was added redistilled boron trifluoride etherate (1.42g, 10 mmole).[24] After 10 minutes at 0°, the ether (22) (ca 200 mg, 1.3 mmole) in diglyme (3 ml) was added all at once. After stirring overnight at room temperature, the solution was poured into 1N sodium hydroxide solution and extracted with ether. The organic layer was washed three times with water, dried (Na_2SO_4) and evaporated. T.l.c. indicated a number of compounds including unreacted (22) and products derived from reaction of phenylthioborane with solvent. The total product was chromatographed on alumina (G3) eluted petrol-ethyl acetate. Unreacted ether (22) (ca 90 mg) was recovered. The product (25) was detected as the only polar compound containing sulphur (as determined by palladium chloride development of a t.l.c. plate). Yield of crude (25), 95 mg; ν_{max} 3450, 1590, 1440, 1030, 745, 700 cm^{-1}.

The crude sulphide (25) was stirred with excess meta-

chloroperbenzoic acid in ether for 1 hour at room temperature. The ether solution was extracted repeatedly with saturated sodium bicarbonate solution, washed with water, dried (Na_2SO_4) and evaporated. Crystallisation of the white plates from ethyl acetate afforded the sulphone, (26) (83 mg, 21%) m.p. 159-161°; ν_{max} 3600, 1305, 1290, 1150, 1045, 755, 695 cm^{-1}; τ 8.91 (3H,d,J6Hz), 8.67 (3H,s), 7.45 (1H,m), 6.53 (2H, bs), 2.00-2.40 (5H,m). m/e 295 (m^++ H), 277 (m^+-H_2O), 249-50, 235, 217,(m^+-ph), 200, 182, 153, (m^+ - $phSO_2$). (Found: C, 65.07%; H, 7.45%; S, 11.05%. Calculated for $C_{16}H_{22}SO_3$, C, 65.27% H, 7.53%; S, 10.89%).

2βH-9-phenylsulphonylpinan-4-one (27)

The sulphone alcohol (30 mg) was treated with excess chromium trioxide in pyridine-dichloromethane for 4 hours at room temperature, and worked up in the usual manner. The crude product was washed through a short alumina column (1 x 4 cm) in benzene. The ketone (27) (quantitative yield) m.p. 148.5-151° (from ethyl acetate) crystallised as white needles; ν_{max} ($CHCl_3$) 1720, 1605, 1590, 1290, 1150, 1090, 1080 cm^{-1}. m/e 292 (m^+), 263, 235, 195, 182, 150-2 (m^+-$phSO_2$), 141-3. (Found: C, 65.38%; H, 6.93%. Calculated for $C_{16}H_{20}SO_3$, C. 65.72%; H, 6.89%).

Reaction of 2βH-pinan-4β,9-diol with p-toluenesulphonyl chloride

The diol (31) (255 mg, 1.5 mmole) was treated with p-toluene sulphonyl chloride (286 mg, 1.5 mmole) in pyridine

(1 ml)-dry ether (3 ml) at 0° for 3 hours, poured into water, extracted with ether, washed with water, dried (Na_2SO_4) and evaporated at room temperature to give an oil containing a white solid. I.r. (ν_{max} 1050, 1030 cm^{-1}) and n.m.r. spectra (τ6.40, ABq, J9Hz) indicated much of the ether (22) as well as a p-toluenesulphonate.

Trimethyloxosulphonium chloride (39)[33,34]

Dimethyl sulphoxide and methyl iodide were reacted to yield trimethyloxosulphonium iodide.[33] Chlorination of this product in water at 50-60° gave thechloride[34] as white needles, m.p. 223-4° (from ethanol) after drying at 70° under vacuum, (lit[34] m.p. 220-2°), in 71% yield. Chlorination was terminated when no further iodine precipitated, as soon as the colour of the aqueous solution changed from red (due to free iodine) to yellow (due to ICl). Excessive chlorination was found to produce a yellow product contaminated with an unstable interhalogen salt.

Attempted reaction of 4α,9-dimethyl-7-oxatricyclo [4.3.0.$0^{3,9}$]nonan-8-one (28) with dimethyloxosulphonium methylide

Sodium hydride (150 mg, 80% NaH in paraffin oil = 5 mmole) and trimethyloxosulphonium chloride (645 mg, 5 mmole) in dry tetrahydrofuran (10 ml) was refluxed and stirred under argon for 3 hours. A white solid separated and hydrogen was evolved. The pure lactone (28) (166 mg, 1 mmole) in dry tetrahydrofuran was added via a serum cap. After refluxing

under argon for 68 hours, t.l.c. indicated starting material and a very polar product. The reaction mixture was poured into water, extracted with ether, dried (Na_2SO_4) and evaporated. The residue was dissolved in acetonitrile and extracted with petrol to remove paraffin oil. Evaporation yielded an oil, which according to t.l.c., n.m.r., i.r. and mass spectra was almost pure lactone starting material. The aqueous solution was evaporated. A white solid (largely sodium chloride) remained. Extraction with ether gave only a trace of oil.

A similar reaction was carried out, but the aqueous solution from pouring the reaction mixture into water was photolysed (medium pressure lamp), and then extracted with ether. Only starting material was obtained.

Reaction of the lactone (28) with methyl phenyl sulphone

a) Sodium hydride as base

Methyl phenyl sulphone was prepared by m-chloroperbenzoic acid oxidation of thioanisole[35] and purified by sublimation.

The sulphone (312 mg, 2 mmole) in dry dimethyl sulphoxide (2 ml) (twice distilled from calcium hydride at 30 mm Hg) was treated with sodium hydride (80% in paraffin, 60 mg, 2 mmole) and heated to 65° for 30 minutes under argon. Hydrogen was evolved. Tetrahydrofuran (1 ml) (twice distilled from lithium aluminium hydride) was added via a serum cap, followed

by the lactone (190 mg, 1.15 mmole) in tetrahydrofuran (0.5 ml). A solid separated almost immediately. After 3 hours at 65°, the mixture was poured into dilute acetic acid (0.5 N) and extracted with dichloromethane. Crystallisation of the crude extract from petrol-ethyl acetate yielded a mixture (359 mg) of methyl phenyl sulphone and an olefinic compound, ν_{max} 1620 cm^{-1}. The supernatant fluid contained only unreacted lactone (ν_{max} 1770 cm^{-1}) and methyl phenyl sulphone as determined by i.r. and t.l.c. Both compounds were isolated by p.l.c. on silica and were identical with starting materials (to n.m.r.).

The crystalline mixture was sublimed at 80°/ 1 mm Hg to yield pure methyl phenyl sulphone, ν_{max} 1585, 1285, 1150, 970, 795, 755, 695 cm^{-1}, and a non-volatile residue (41 mg), ν_{max} 1620, 1580, 1300, 1135, 1090, 970, 875, 850, 815, 760, 725, 710, 690 cm^{-1}, m.p. 190-191.5° (from ethyl acetate); No hydroxyl was apparent; m/e 304 (m^+, $C_{17}H_{20}SO_3$), 248, 236, 184 ($phSO_2CH_2CHO$), 163 (m^+-$phSO_2$), 125, 123. (Found: C, 67.23%; H, 6.61%; S, 10.38%. Calculated for $C_{17}H_{20}SO_3$, C, 67.07%; H, 6.62%; S, 10.50%). The product was apparently derived from loss of water from the anticipated β-keto-sulphone, and was not further characterised.

b) Use of phenylsulphonylmethylmagnesium iodide (29)

A solution of methyl magnesium iodide, prepared from magnesium (24 mg, 1 mmole) and methyl iodide (142 mg, 1 mmole) in dry ether (2 ml) was treated with methyl phenyl sulphone (156 mg, 1 mmole) in dry benzene (5 ml) and refluxed for 2

hours under argon. A solution of the lactone (166 mg, 1 mmole) in ether (2 ml) was introduced and refluxing continued 1 hour. After leaving overnight at room temperature, the solution was worked up with ammonium chloride solution, extracted with ether, the ether layer washed with saturated sodium chloride solution, dried (Na_2SO_4) and evaporated. The crude material was crystallised from petrol-ethyl acetate and worked up as in method (a). Unreacted lactone and sulphone were recovered as well as a product, m.p. 190-191°, identical with that obtained by method (a); (94 mg, 31%). No compounds with hydroxyl or enol functions (i.r.) were isolated.

4α,9-Dimethyl-8-hydroxy-7-oxatricyclo [4.3.0.$0^{3,9}$] nonane (40) by reduction of the lactone (28) with bis(3-methyl-2-butyl)borane

Diborane solution[36] (39 ml, 1.21 molar in [BH_3], 0.047 mole [BH_3]) was added over 1 hour via a serum cap to 2-methyl-2-butene (7.2g, 0.103 mole) in dry tetrahydrofuran (10 ml) at -10° while stirring under nitrogen (static). The solution of bis (3-methyl-2-butyl) borane ('disiamylborane')[37] was allowed to stand at 0° to -5°, 16 hours. The lactone (28) (166 mg, 1 mmole) in dry tetrahydrofuran (2 ml) was added to this solution (3 ml) at 0°, via a serum cap. After standing 3 hours at room temperature, the solution was hydrolysed with water (5 ml) and treated dropwise with excess 30% hydrogen peroxide while keeping the pH at 8-9 with sodium hydroxide solution (3N), also added dropwise, at 0°. After standing at room temperature 15 hours, the suspension was

extracted with ether, the ether solution washed with water, dried (Na_2SO_4) and evaporated. The residual oil was pumped off at room temperature to remove 3-methyl-2-butanol, to yield the hemiacetal (40), ν_{max} 3350, 1080, 1050, 1020, 1000 cm^{-1}, as an unstable oil which polymerised on standing at room temperature. The crude hemiacetal was treated with a solution of 2,4-dinitrophenylhydrazine in 85% phosphoric acid-ethanol. The orange 2,4-dinitrophenylhydrazone (41) had m.p. 185-7° (from ethyl acetate), ν_{max} 3320, 3250, 3100, 1620, 1585, 1500, 1340 cm^{-1}; m/e 348 (m^+), 313, 249, 183, 167, 151, 133. (Found: C, 55.22%, H, 5.69%; N, 16.04%. Calculated for $C_{16}H_{20}N_4O_5$, C, 55.15%; H, 5.79%; N, 16.09%). A semicarbazide derivative could not be obtained. Attempted preparation of the hemiacetal under the same conditions except that work-up was carried out at pH 10-12 gave only a highly insoluble viscous polymer.

Attempted reduction of lactone (28) with sodium borohydride

The lactone (28) (80 mg, 0.5 mmole) and sodium borohydride (30 mg) in tetrahydrofuran (3 ml) were stirred at 0° for 120 hours, poured into water, and the products extracted with ether. After washing with water, drying (Na_2SO_4) and evaporating, the residue consisted of two immiscible oils, ν_{max} (CCl_4) 3380, 1770, 1710 cm^{-1}. Chromatography on alumina (G3) yielded unreacted lactone, and the diol (31), m.p. 81-3° (from ether-petroleum ether). 2,4-dinitrophenylhydrazine reagent gave only a low-melting derivative which was not an alcohol (to i.r.). The reaction was repeated in

water-tetrahydrofuran at room temperature. No hemiacetal (40) was isolated. Very slow reduction of the lactone by lithium tri-t-butoxyaluminium hydride[38] gave similar results.

4α,9-Dimethyl-8-hydroxy-7-oxatricyclo[4.3.0.$0^{3,9}$] nonane (40) from neoverbanol (15)

Nitrosyl chloride (2.2g, 0.032 mole, 1.5 equiv), condensed in a flask at -20°(CCl_4/CO_2 bath) was allowed to evaporate into a stirred solution of neoverbanol (3.3g, 21.5 mmole) in dry pyridine (40 ml) at 0°, and stirring continued 1 hour at 0°. After allowing to reach room temperature over a further 1 hour, the dark solution and precipitate (pyridine hydrochloride) was poured into water, extracted three times with ether, the extract washed with water (twice), dried (Na_2SO_4), filtered, and evaporated on a water bath kept at ca 30° (above this temperature brown fumes were evolved) to give the crude nitrite ester (42), 3.9g, ν_{max} 1640 cm^{-1}. The crude product was dissolved in cyclohexane (100 ml) and photolysed under argon at room temperature using a water-cooled pyrex glass jacketed medium-pressure u.v. lamp (500 W). After 11 hours, approximately 1.6g crude nitroso-compound (a semisolid mass) had precipitated on to the walls of the apparatus and the water jacket; the cyclohexane was also evaporated to yield an oil.

Each product was dissolved in warm isopropanol (50 ml each) and refluxed 24 hours; t.l.c. indicated reaction probably complete after 2 hours, however. The product from the cyclohexane-soluble photolysis products contained

30-40% oxime (43) but was a complex mixture and was not worked up. After evaporation of the solvent, the oxime (43) from the precipitated nitrosodimer was distilled, b.p. 48° at 1.5 mm, to give a colourless oil (1.33g), ν_{max} 3350, 1630, 1105, 1085, 1055, 1025, 1005 cm^{-1}; m/e 183 (m^+), 166-8 (m^+ -OH, H_2O), 151 (m^+-NOH), 139, 135-7, 121-3. (Found: C, 65.32%; H, 9.22%; N, 7.65%. $C_{10}H_{17}NO_2$ requires C, 65.54%; H, 9.35%; N,7.65%). The oxime (1.25g, 6.8 mmole) was dissolved in acetone (56 ml) and hydrochloric acid (1.5 ml) in water (14 ml) added (equivalent to 17 mmole 2% concentrated hydrochloric acid in 80% acetone-water). The homogeneous solution was allowed to stand overnight at room temperature, poured into water (200 ml), extracted with ether (3 x 80 ml), dried (Na_2SO_4) and evaporated, to give the hemiacetal (40), 1.04g 90%, ν_{max} 3350, 1080, 1050 cm^{-1}.

A 2,4-dinitrophenylhydrazone was prepared as before; m.p. 186-186.5° (from ethyl acetate) identical with the previous sample (41).

Cis-verbanone[13] (2αH-pinan-4-one) (3)

Cis-verbanone was prepared by catalytic (10% Pd/c) hydrogenation of verbenone (13) in ethanol.[13,22] Reaction was complete in 1 hour at room temperature. The crude product was purified by chromatography on alumina (G3) eluted petrol-ethyl acetate. Distillation (b.p. 70° at 6.5 mm Hg) yielded (3) (75%), pure to g.l.c., ν_{max} 1710 cm^{-1}. τ 8.97 (3H,s), 8.64 (3H,s), 8.82 (3H,d,J7Hz). The product was not optically pure: $[\alpha]_D^{20}$ + 15.2° (c 3.3%, benzene) (lit[12]: + 68.8°)

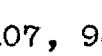
Cis-verbanone oxime was prepared by the method given for trans-verbanone oxime (q.v.). The crude product was purified by sublimation at 80°/1 mm Hg to yield 85%, m.p. 60-62.5° (not optically pure), ν_{max} 3250, 1665 cm^{-1}, τ9.06 (3H,s), 8.71 (3H,s), 8.87 (3H,d,J7Hz), m/e 167 (m^+), 152,(m^+-CH_3), 150 (m^+-OH), 125-6, 108-10, 91, 83, (Found: C, 71.98%; H, 10.06%; N, 8.15%. $C_{10}H_{17}NO$ requires C, 71.81%; H, 10.25%; N, 8.37%).

Neoisoverbanol[13] (2αH-pinan-4β-ol) (12)

Reduction of cis-verbanone with lithium aluminium hydride in ether yielded neoisoverbanol (12) (90%), m.p. 67-68.5° (from petroleum ether) of low optical purity. (Lit.[13] m.p. 69.5° not optically pure); τ8.80 (3H,s), 8.75 (3H,s), 8.94 (3H,d,J7Hz), 6.25 (1H,m).

Reaction of neoisoverbanol (12) with bromine and mercuric oxide

A solution of bromine (3.0g, 19 mmole) in pentane (25 ml; protected from light) was added over 25 minutes to a stirred suspension of dry yellow mercuric oxide (6.2g, 29 mmole) in refluxing pentane (25 ml) containing neoisoverbanol (3.0g, 19 mmole) under a stream of argon, while irradiated with a tungsten lamp (500 W, ca 40 cm from the flask). Reaction was continued for two hours at reflux, cooled, filtered, and washed successively with aqueous pyridine, four times with water, dried (Na_2SO_4) and evaporated. The product consisted of five compounds which were separated

by successive chromatography on an alumina column (G1) eluted petrol 99.9-ethyl acetate 0.1, and silica p.l.c. plates (60 x 20 cm x 1 mm), eluted petrol-ethyl acetate. The major products were cis-verbanone (3), ν_{max} 1710 cm^{-1}, (n.m.r., i.r., identical with an authentic sample) and a bromoaldehyde, probably (14), ν_{max} 2720, 2730 cm^{-1}, m/e 231 + 233 (m^+), 181, 176 + 178, 151, 136 + 137 (m^+- ), 121 107, 93-97, which oxidised in air to a carboxylic acid, m/e 248 + 250 (m^+). The expected ethers (11) were minor products (ca 20%); ν_{max} 1060, 1040, 875, 855 cm^{-1}; m/e 152 (m^+), 137 (m^+-CH_3), 121, 107-11, 97, 81-3, and these products were not further characterised.

Cis-1-formyl-2,2-dimethyl-3-isopropenylcyclobutane(44)[2,3]

Preparative photolysis of cis-verbanone in methanol.

a) The ketone (3) (5.5g, 36 mmole) in dry methanol (12) containing sodium bicarbonate (1.0g) was photolysed with a 500W immersion water-cooled medium-pressure quartz jacketed u.v. lamp, under argon at room temperature. Little ketone remained after 6 hours. Methanol was removed at room temperature by pumping off into a cold trap until a small volume (ca 20 ml) remained. The residue was diluted with water, and extracted twice with petrol, the petrol solution washed with water, dried (Na_2SO_4) and evaporated. The crude aldehyde was purified by distillation, b.p. 66° at 17 mm Hg, to give a pale yellow liquid (3.5g, 64%), ν_{max} 2750, 1725, 1645, 895 cm^{-1}, largely (44) (>75%) but containing four minor products, as determined by g.l.c. (column; 2m, 20:80

silicone grease on chromosorb p(60-80 mesh) at 120°).
$\tau(CDCl_3)$ 8.33 (3H,s), 8.61 (3H,s), 9.10 (3H,s), 5.31 (1H,bs), 5.13 (1H,bs). 0.19 (1H,d,J2Hz).

b) When the methanol-sodium bicarbonate solution was concentrated on a rotary evaporator, no aldehyde was isolated. Only an alcohol, ν_{max} 3400 cm^{-1}, was obtained.

c) Distillation of the crude aldehyde was rendered difficult by persistent foaming. Attempted isolation of the aldehyde on alumina (G3) gave only an alcohol by decomposition; ν_{max} 3400, 1645, 890 cm^{-1}.

d) The aldehyde (44) (66%) was isolated from the crude photolysis product by chromatography on a silica column, eluted petrol 99-ethyl acetate 1. The product, which contained 10% of the isomer (45) had ν_{max} (CCl_4) 3080, 2810, 2710, 1725, 1650, 895 cm^{-1}, τ (CCl_4) 9.13 (3H,s), 8.63 (3H,s), 8.37 (3H,s), 5.35 (1H,bs), 5.18 (1H,bs), 0.39 (1H,d,J2Hz) and 3.97 (10% of 2H,q).

Photolysis of cis-verbanone in tetrahydrofuran

The ketone (3) (410 mg) in pure tetrahydrofuran (40 ml) was photolysed under the usual conditions for 4.5 hours. G.l.c. indicated only two products, the aldehyde (44) and one other, besides a polar compound. T.l.c. showed a number of products including much polymer. A silica column eluted petrol-ethyl acetate (increasing polarity) gave four aldehydes (by i.r.) and several polar compounds, which were

not further characterised. Trans-verbanone gave a similar mixture.

Photolysis of trans-verbanone in methanol

Trans-verbanone (350 mg) (17) in methanol (35 ml) containing sodium bicarbonate (35 mg) was photolysed and worked up under the same conditions as cis-verbanone (above). More polymer and several minor products were present which were not formed from cis-verbanone. The aldehyde fraction (53%) was obtained from a silica column, eluted petrol 99-ethyl acetate 1, to yield a mixture of (44) and (45) in a ratio of 35-40:60-65 (to n.m.r.); υ_{max} (CCl_4) 3075, 3030, 2805, 2710, 1735, 1725, 1645, 915, 890 cm^{-1}. τ (CCl_4) 9.12 (m; including superimposed 3H,s and 3H,d), 8.88 (6H,s; integral 0.65 of 6H), 8.68 (3H,s; integral 0.4 of 3H), 8.38 (3H,s; integral 0.4 of 3H), 7.85 (m), 5.37 (1H,bs) + 5.20 (1H,bs; total integral 0.35 of 2H), 3.99 (2H,q,J3.5Hz; integral 0.65 of 2H), 0.38 (1H,m).

Tris(triphenylphosphine)chlororhodium (I)[39]

The reagent was prepared (theoretical yield) by reaction of hydrated rhodium trichloride with triphenylphosphine in ethanol; υ_{max} 1440, 1085, 745, 695 cm^{-1}.

P-nitrophenylhydroxamic Chloride[40]

A solution of p-nitrobenzaldoxime (1.5g) in ethyl acetate (10 ml) was treated with chlorine at 0° for 2 hours.

After evaporation and crystallisation from chloroform, pale yellow needles (1.1g, 61%), m.p. 123-125° (lit[40]; 126°) were obtained.

Decarbonylation of cis-1-formyl-2,2-dimethyl-3-isopropenylcyclobutane

The crude distilled aldehyde (600 mg, containing ca 3 mmole (44)) and tris(triphenylphosphine)chlororhodium (2.77g, 3 mmole) were reacted in dichloromethane (free of hydrogen chloride; twice distilled from potassium carbonate before use) (15 ml) at reflux for 16 hours. Yellow chlorocarbonyl-bis(triphenylphosphine) rhodium (I), (46), ν_{max} 1990 cm^{-1}, separated. T.l.c. indicated one non-polar product. No compound corresponding to cis-verbanone was observed. The solution was filtered, the precipitate washed with dichloromethane (10 ml), and the solvent distilled off on an oil bath at 70-80°. Ethanol (4 ml) was added to the residue to precipitate remaining rhodium complexes, the filtrate poured into water, and extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4) and the dichloromethane distilled off. Both dichloromethane distillates were subjected to g.l.c., which indicated very little loss of the volatile hydrocarbon product. Distillation of the residue yielded a colourless volatile liquid consisting of the decarbonylation product, 2,2-dimethylisopropenylcyclobutane (47), contaminated with some of the aldehyde, triphenylphosphine, and minor products including impurities in the starting material (to g.l.c.); ν_{max} 1720 (aldehyde), 1645, 890, 775 + 745 + 700 cm^{-1} (triphenylphosphine); m/e 152

(aldehyde), 123 ((47), m^+-H), 109 (m^+-CH_3), 95-97, 81-3. Purification of the olefin required a suitable (preferably squalane) preparative g.l.c. column, which was not available, and so (47) was characterised as a nitrile oxide adduct, (48).

To a solution of the crude olefin (47) (74 mg) and triethylamine (120 mg, excess) in dichloromethane (2 ml) was added p-nitrophenylhydroxamic chloride (108 mg, 0.54 mmole) in dichloromethane (4 ml). The solution immediately became yellow as the nitrile oxide was generated. After 1 hour at room temperature, eight products were apparent under u.v. on a silica t.l.c. plate, but only one developed on heating with sulphuric acid and therefore contained an aliphatic carbon function. The dichloromethane solution was concentrated, applied to a p.l.c. plate (silica, 60 x 20cm x 1mm), and eluted with petrol-ethyl acetate. The band corresponding to the compound which developed with sulphuric acid was extracted and the crude compound crystallised from benzene-light petroleum as very pale yellow plates, m.p. 110-118° after drying at 70° under vacuum; ν_{max} 1610 + 1605, 1575, 1520, 1320, 1285 + 1275, 950, 860, 755, 695 cm^{-1}; τ 8.88 (3H,s), 8.83 (3H,s), 8.68 (3H,2s not resolved), 6.98 (1H,s), 6.80 (1H,s), 1.90 (4H, two superimposed quartets, J9Hz); m/e 288 (m^+), 271 (m^+-CH_3), 245, 232 (m^+-[illegible]), 231, 217 (m^+-[illegible]), 205 (m^+-[illegible]), 163 (m^+-[illegible]), 109, 83, in good agreement with the structure (48), 3-p-nitrophenyl-4-methyl-4-(2',2'-dimethyl)cyclobutyl-2-isoxazoline; (Found: C, 66.78%; H, 7.28%; N, 9.59%; $C_{16}H_{20}N_2O_3$ requires C, 66.65%; H, 6.99%; N, 9.72%).

Photolysis of 9-acetoxy-trans-verbanone (37) in methanol

The ketone (37) (100 mg, 0.48 mmole) in dry methanol (15 ml) containing sodium bicarbonate (ca 20 mg) was photolysed 6 hours under nitrogen in a water-cooled tube of 'Vycor' glass using an external medium-pressure lamp. Methanol was pumped off at room temperature into a cold trap, the residue diluted with water (5 ml), and extracted with pentane (2 x 10 ml). The hydrocarbon solution was dried (Na_2SO_4) and evaporated, and the residue chromatographed on a silica column (1 x 12cm), eluted petrol-ethyl acetate. The aldehyde fraction (64 mg, 64%) proved to be a mixture of (49) and (50) in a ratio of 40-45:55-60; the mixture had ν_{max} (CCl_4) 3080, 2715, 1750, 1733, 1725, 1647, 1235, 1035, 900, 865 cm^{-1}; τ (CCl_4) 9.13 (m), 8.78 (3H,s) + 8.75 (3H,s), 8.62 (s) (may be part of a doublet obscured by peak at 8.75), 8.30 (3H,bs; intergral 0.45 of 3H), 8.08 (3H,s; integral 0.4 of 3H), 8.02 (3H,s; integral 0.6 of 3H), 7.77 (m), 7.40 (m), 6.12 (2H,m; integral 0.45 of 2H), 5.90 (2H,d,J3Hz; integral 0.55 of 2H), 5.25 (1H,bs) + 5.12 (1H,bs; total integral 0.5 of 2H), 3.93 (2H,m; integral 0.5 of 2H), 0.33 (1H,m).

Methoxymethyltriphenylphosphonium chloride[41,42]

Chloromethyl methyl ether, prepared from formaldehyde, methanol and hydrogen chloride,[41] was reacted with triphenylphosphine in benzene. Crystallisation of the product from chloroform-ethyl acetate gave a solvate, which on heating at 125° under vacuum 48 hours yielded the unsolvated phosphonium salt (87%), m.p. 198-99°, as a white powder.

Pinan-2β-ol[9,10] (51)

Reaction of (+) nopinone (4) with excess (1.3 equiv.) methyl magnesium bromide in ether yielded pinan-2β-ol (93%) contaminated with 7-8% unreacted ketone. Recrystallisation from light petroleum at 0° gave a poor recovery of purer alcohol, ν_{max} 3380, 1125, 1105, 955, 940, 910 cm^{-1}. Sublimation did not eliminate the contaminant. The crude product was used without purification in subsequent reactions; τ 8.88 (3H,s), 8.77 + 8.75 (6H,2s); signals due to nopinone at τ 9.16 (s), 8.67 (s). A sample sublimed at atmospheric pressure had m.p. 57.5-59°. (lit.[10] m.p. 57-59°).

6,9-Dimethyl-8-hydroxy-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (52) from pinan-2 -ol (51)

a) Initial approach employing standard conditions[5,8] of the Barton reaction.

The tertiary alcohol (51) was converted into the nitrite ester, ν_{max} 1625 cm^{-1}, which was photolysed in cyclohexane to give the corresponding nitrosodimer exactly as for the isomeric pinanol, neoverbanol (p 171).

The crude nitrosodimer and the residual oil from evaporation of cyclohexane were both refluxed in isopropanol 24 hours. The nitrosodimer yielded two close-running non-polar products, inseparable on an alumina column, apparently the syn and anti isomers of the oxime (53). The residual oil yielded some further oxime, much of the ether (54) (to t.l.c)

and a number of more polar products. The crude mixture was partly separated on alumina (G3), but the recovery of oxime was poor, suggesting hydrolysis on alumina. The pure oxime (8.05g, 52%) was micro-distilled; b.p. ca 50° at 1mm Hg. (Found: C, 65.32%; H, 9.22%; N, 7.65%. $C_{10}H_{17}NO_2$ requires C, 65.54%; H, 9.35%; N, 7.65%).

The oxime (4.0g) was hydrolysed exactly as for the isomer (43) (p 172) with 2% concentrated hydrochloric acid in 80% acetone-water. Continuous extraction of the product was not attempted. (52) had ν_{max} 3450, 1090, 1010, 990 cm^{-1}; $\tau(CDCl_3)$ 8.75 (3H,s), 8.65 (3H,s), 4.87 (1H,s); $\tau(CCl_4)$ 8.79 (3H,s, fine splitting J1Hz), 8.70 (3H,s), 5.90 (1H,bs, OH), 4.95 (1H,s). m/e 168 (m^+), 151 (m^+-OH), 135, 125, 122 (m^+-CHOH), 113. b.p. ca 40° at 1 mm Hg; $[\alpha]_D^{22.5}$(corr.) + 59.4° (c 4%, $CHCl_3$). (Found: C, 71.20%; H, 9.54%. Calculated for $C_{10}H_{16}O_2$, C, 71.40%; H, 9.59%). The product was characterised as an oil, but subsequently crystallised. No 2,4-dinitrophenylhydrazone or semicarbazone could be obtained.

b) Preparative conditions

Liquid nitrosyl chloride (16.0g, 0.24 mole) was allowed to distil into a stirred solution of the crude tertiary alcohol (20g, 0.12 mole) in dry pyridine (250 ml) at 0° over 1.5 hours. After a further 1 hour at 0°, the solution was allowed to reach room temperature over 2 hours, poured into water, dried (Na_2SO_4) and concentrated to ca. 200 ml. The ether solution was again washed with water (400 ml), dried, and evaporated. A little pyridine (ν_{max} 1585, 1440 cm^{-1})

remained in the crude nitrite ester, ν_{max} 1625 cm^{-1}. The ester was photolysed 17 hours at room temperature under nitrogen in n-hexane (700 ml) using a glass-jacketed medium-pressure lamp. The semisolid precipitate of the nitrosodimer was dissolved in warm isopropanol and added to the product of evaporation of the hexane. The isopropanol solution (200 ml) was refluxed 2 hours, and evaporated. Some oxime was lost by evaporation with the solvent (t.l.c.).

The residue, containing oxime (53) and apparently some hemiacetal isopropyl ether, in ether (300 ml) was stirred vigorously overnight with acetone (50 ml)-2% concentrated hydrochloric acid in water (650 ml; containing 13 ml hydrochloric acid). The aqueous layer was separated, diluted with water (500 ml), and extracted with ether (300 ml), and the combined ether layers washed successively with saturated sodium bicarbonate and saturated sodium chloride solutions, dried (Na_2SO_4), and evaporated. Chromatography on alumina (G3) eluted petrol-ethyl acetate of increasing polarity yielded the ether (54), 3.1g, (17% from pinan-2β-ol;) ν_{max} 1050, 1030 cm^{-1}, identical with an authentic sample (n.m.r.); nopinone, an impurity in the pinan-2β-ol, 0.8g, ν_{max} 1710 cm^{-1}; and the hemiacetal (52), 10.3g, 51% overall from pinan-2β-ol, m.p. 58-60° (from petrol) identical with the product of method (a).

c) Attempted hydrolysis of the oxime (53) employing cation exchange resin

1. Small scale. The pure oxime (1.0g) in acetone (5.5 ml)-water (1.5 ml) containing 'Amberlite' IR-120H cation exchange resin in the acid form (1.9 mequiv ml^{-1} s.g. 0.79, 0.2g ≃ 0.1 equiv) was stirred for 18 hours at room temperature. After filtration, dilution with water and ether extraction the pure hemiacetal (52), ν_{max} 3450, 1090. 1020, 995 cm^{-1}, was obtained.

2. Large scale. The crude oxime from heating the total photolysis product of the nitrite ester with isopropanol, (20g), was stirred 18 hours in water (25 ml)-acetone (60 ml) containing IR-120H resin (5g). The reaction was worked up as for (1) above, and chromatographed on alumina (G3). The hemiacetal (40% from pinan-2β-ol) was separated from a mixture containing an unsaturated aldehyde (not obtained pure), ν_{max} 2750, 1730, 1720, 1650, 1640, 1260 cm^{-1}.

6,9-Dimethyl-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (54)[8-10]

Two methods of preparation were employed. Reaction of pinan-2β-ol (51) with bromine and yellow mercuric oxide in pentane at reflux[8] while irradiated with a tungsten lamp gave 75% of undistilled (54) after purification by chromatography on alumina (G3); ν_{max} 1050, 865 cm^{-1}. τ 8.73 (6H,2s), 8.55 (1H,d,J9Hz), 6.42 (2H,ABq,J9Hz), $[\alpha]_D^{24.5}$ + 22.1° (c 6%, $CHCl_3$). A higher yield (90%, undistilled) was obtained by

the two-step procedure of reaction of the alcohol with bromine and mercuric oxide at 0° in carbon tetrachloride, filtering, and irradiating (tungsten lamp) the hypobromite solution. The crude product was washed through a short alumina column (G3) to remove polar material, but no further purification was necessary.

6,9-Dimethyl-8-oxo-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (55)

Hydrated ruthenium dioxide was prepared by addition of sodium hydroxide (1.0g) in water (10 ml) to a solution of hydrated ruthenium trichloride (1.5g, 41% Ru) in water (10ml), followed by passage of oxygen for 1 hour. The black dioxide was allowed to settle, filtered on celite, and dried in the air.

A two-phase system of water (2 l), potassium periodate (220g, 1 mole), carbon tetrachloride (750 ml), ruthenium dioxide (ca 600 mg, 1% molar) and the tertiary ether (54) (from 66.7g, 0.43 mole, of pinan-2β-ol) was stirred vigorously at room temperature to completion of reaction (8 days). The organic layer was separated, washed with water and ethanol (5 ml) added to precipitate regenerated RuO_2. Sodium sulphate was added to dry the suspension, which was filtered through celite, concentrated to 150 ml, and passed through a short (10 cm) column of alumina (eluted carbon tetrachloride) to remove suspended reagent. All the RuO_2 residues were retained - stirring with aqueous potassium periodate - carbon tetrachloride regenerated RuO_4 almost quantitatively. The solution of crude lactone was evaporated, and the residue

distilled through a short column. After a low-boiling fore-run, the lactone (55) distilled at 87-96° at 2 mm Hg. Yield, 58.0g, 76% overall from pinan-2β-ol, containing a little non-polar material (to t.l.c.). The distillate, coloured due to a trace of a ruthenium compound, crystallised completely at room temperature; m.p. 37-38° (from petrol, b.p. 30-40°). A redistilled sample also had m.p. 37-38°; ν_{max} 1765, 1090, 1050, 940 cm^{-1}; τ 8.63 (3H,s), 8.53 (3H,s); m/e 166 (m^+), 124 (m^+-CO_2), 123, 111, 107-8, 95-6. $[\alpha]_D^{22.5}$(corr.) + 49.7° (c 3%, $CHCl_3$). (Found: C, 72.23%; H, 8.29%. Calculated for $C_{10}H_{14}O_2$, C, 72.26%; H, 8.49%). A reaction on ¼ of the above scale, employing 4% molar hydrated RuO_2 was complete after 48 hours.

6,9-Dimethyl-8-hydroxy-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (52) by reduction of 6,9-dimethyl-8-oxo-7-oxatricyclo-[4.3.0.$0^{3,9}$]nonane (55)

A saturated solution of lithium aluminium hydride in dry ether was prepared by refluxing 3 hours, cooling, and allowing to stand 1 hour. The solution was carefully decanted into a calibrated flask. Two 2ml samples of this solution were carefully hydrolysed by addition to ether, to which ethyl acetate, water, and 2N hydrochloric acid were added successively. The aluminium content of the resulting solutions was determined gravimetrically by precipitation of the 8-hydroxyquinoline complex. Three different solutions of $LiAlH_4$ in ether were determined as 1.35, 1.41, and 1.45 molar. Subsequently, a saturated solution was assumed to be 1.4 molar.

Ethanol (3 equiv.) was added over 1.5 hours to a vigorously stirred solution of $LiAlH_4$ in ether. A gelatinous precipitate ($LiAl(OEt)_4$) separated. A solution of the lactone (55) (10g, 60 mmole) in dry ether (100 ml) at -22° (CO_2-CCl_4 bath) was reduced by addition of the lithium triethoxyaluminium hydride solution, by means of a wide tube and pipette filter, until reaction was complete (to t.l.c.). Excess reagent did not further reduce the hemiacetal product at this temperature. The product was added slowly to a stirred solution of ammonium chloride kept at 0°, the mixture filtered from insoluble $LiAl(OEt)_4$, and the ether layer separated. The aqueous solution was extracted with ether, and the combined ethereal solutions washed three times with water, dried (Na_2SO_4) and evaporated. The crystalline hemiacetal (52), 9.8g, 97%, m.p. 58-60° (from petrol) was identical with the product of the alternative method of preparation (p 181).

Hydrolysis of the reaction product at room temperature resulted in a mixture of the hemiacetal and two non-polar compounds. Chromatography of the mixture on alumina (G3) separated (a) 6,9-dimethyl-8-ethoxy-7-oxatricyclo[4.3.0.$0^{5,9}$] nonane, (56), a colourless liquid, b.p. ca 50° at 3 x 10^{-4} mm Hg, ν_{max} 1110, 1065, 1020 cm^{-1}, τ 8.77 (3H,s), 8.65 (3H,s), (3H,t partly obscured by the methyl singlets), 6.40 (2H,m), 5.22 (1H,s); m/e 196 (m^+), 181 (m^+-CH_3), 167 (m^+-Et), 151 (m^+-OEt), 141, 133, 125, 122-3 (m^+-$\overset{OEt}{H}\!\!>\!\!=O$), 107, 93-6. (Found: C, 73.07%; H, 10.74%. Calculated for $C_{12}H_{20}O_2$, C, 73.43%; H, 10.27%); and (b) the hemiacetal ether (57), long needles, m.p. 115-115.5° (from petrol), ν_{max} 1110,

1100, 1065, 1010, 990 cm^{-1}; $\tau(CDCl_3)$8.80 (6H,s), 8.70 (6H,s), 4.92 (2H,s). m/e (no m^+), 167, 151, (167 + 151 = m^+), 133 (151-H_2O), 123 (151-CO), 109, 107, 93-95. $[\alpha]_D^{22.5}$(corr.) + 221.2° (c 2%, $CHCl_3$). $\tau(CCl_4)$ 8.83 (6H,s), 8.73 (6H,s) 5.10 (2H,s). (Found: C, 75.22%; H, 9.32%. $C_{20}H_{30}O_3$ requires C, 75.43%; H, 9.50%).

9-Methylenepinan-2β-ol (58)

Methyltriphenylphosphonium iodide was heated at 125° for 40 hours under reduced pressure before use. Dry dimethyl sulphoxide (375 ml) and sodium hydride (12.7g, 80%, 0.425 mole) were stirred under nitrogen 2 hours at 57-59°. A clear, almost colourless solution was produced under these conditions. After cooling to room temperature over 30 minutes, methyltriphenylphosphonium iodide (189g, 0.47 mole) was rapidly added via a powder funnel with minimal exposure to atmospheric moisture, and the yellow solution stirred 1 hour at room temperature. The hemiacetal (52) (23.5g, 0.141 mole) in dimethyl sulphoxide (45 ml) was introduced via a serum cap and reaction continued 18 hours at 65-66° under nitrogen. The cold product was poured into ice water (2 kg), extracted with petrol (3 x 500 ml), the petrol extract washed with water, dried (Na_2SO_4) and evaporated. Triphenylphosphine oxide separated. The product was extracted with a little cold petrol (0°), concentrated by evaporation, and cooled to 0°. Further triphenylphosphine oxide, ν_{max} 1445, 1200, 1125, 760, 730, 705 cm^{-1}, and some triphenylphosphine (m.p. 79-81°), ν_{max} 1440, 1100, 1035, 770, 755, 710 cm^{-1}, crystallised. The petrol solution was applied to an alumina column (G3)

eluted with petrol to remove triphenylphosphine, and then petrol 99.5-ethyl acetate 0.5, and petrol 99-ethyl acetate 1, to yield two compounds; (a) 6,8,9-trimethyl-7-oxatricyclo [4.3.0.$0^{3,9}$]nonane (59), a colourless liquid, 2.5g, 11%, b.p. ca 50° at 5mm Hg, ν_{max} 1145, 1090, 985, 955, 905 cm^{-1}, τ 8.83 (3H,s), 8.73 (3H,s), 9.03-8.77 (3H,m), 6.29 (1H,q, J7Hz) + 6.02 (1H,q,J7Hz) (total integral 1H); m/e 166.1351 (m^+); (calculated for $C_{11}H_{18}O$, 166.1358). $[\alpha]_D^{24.5}$(corr.) + 34.1° (c 7.5%, $CHCl_3$); (b) 9-methylenepinan-2β-ol (58), (13.55g, 58% (67% allowing for 2.9g recovered hemiacetal)); long white needles, m.p. 50.5-51.5° (from petrol). The olefin sublimed readily at 50° and 7 mm Hg without change of melting point; ν_{max} 3330, 1630, 1125, 1005, 925, 915 cm^{-1}. τ 8.75 (3H,s), 8.63 (3H,s), 7.93 (OH,s), 4.78-5.15 (2H,m) 3.55 (1H,2d,J18Hz and 10.5Hz). m/e 166 (m^+), 151 (m^+-CH_3), 148 (m^+-H_2O), 137, 133, 123, 119, 111; $[\alpha]_D^{24.5}$(corr.) -23.5° (c 3.5%, $CHCl_3$). (Found: C,79.18%; H, 10.68%. Calculated for $C_{11}H_{18}O$, C, 79.46%; H, 10.91%).

Hydroboration of 9-methylenepinan-2β-ol (58)

A solution of diborane in tetrahydrofuran (1.28 N in $[BH_3]$) was prepared by Brown's method[36]. To 9-methylenepinan-2β-ol (166 mg, 1 mmole) in dry tetrahydrofuran (3 ml) was added diborane solution (1.6 ml, 2 m equiv.$[BH_3]$) at 0° via a serum cap. After 30 minutes at 0°, excess reagent was hydrolysed by water (5 ml) and the borane worked up oxidatively with 3 N aqueous sodium hydroxide solution (3 ml, 9 mmole) and 30% hydrogen peroxide solution (1 ml), introduced dropwise at 30-40°, to give two polar products after stirring

for 1 hour. The solution was extracted with ether, washed twice with water, dried (Na_2SO_4) and evaporated. An alumina column (G3) eluted petrol 90-ethyl acetate 10 separated the crystalline mixture to give (a) the less polar compound, 9-methyl-pinan-2β,9-diol (60), 72 mg, 39%, as fine needles, m.p. 149-149.5° (from ether-petroleum ether), ν_{max} 3330, 1135, 930 cm^{-1}; τ 8.97 (3H,d, J7Hz), 8.77 (3H,s), 8.67 (3H,s), 5.67 (1H,q,J7Hz), 2.9 (OH,bs). $[\alpha]_D^{25}$(corr.) -29.6° (c 1%, $CHCl_3$). (Found: C, 71.69%; H, 10.77%. $C_{11}H_{20}O_2$ requires C,71.69%;, H, 10.94%); and (b) 9-hydroxymethylpinan-2β-ol(61) 103 mg, 56%, dense crystals m.p. 110-111° (from ether-petroleum ether), unchanged by sublimation. ν_{max} 3270, 1135, 1080, 965, 935 cm^{-1}; τ 8.71 (6H, 2s superimposed), 6-6.38 (2H+OH, m+bs). $[\alpha]_D^{24.5}$(corr.)-28.5° (c 2%, $CHCl_3$). (Found: C, 71.81%; H, 10.89%. Calculated for $C_{11}H_{20}O_2$, C, 71.69%; H, 10.94%).

Reaction of 9-methylenepinan-2β-ol (58) with bis(3-methyl-2-butyl)borane

A solution of disiamylborane[37] was prepared by introduction of diborane solution in tetrahydrofuran (310 ml, 1.46 N in $[BH_3]$; 0.45 equiv $[BH_3]$) to 2-methyl-but-2-ene (70.5 g, 105 ml, 1.00 mole, 2.2 equiv) in dry tetrahydrofuran (50 ml) at -22°, over 1 hour via a serum cap, followed by stirring at 0° 6 hours.

The dialkylborane solution (285 ml, ca 0.28 mol, 2.5 equiv) was introduced to a solution of the olefin (58) (18.3g, 0.110 mol) in tetrahydrofuran (30 ml) at 0° over 1 hour,

employing a syringe. Stirring at 0° was continued for 18 hours. The reaction mixture was poured into water (300 ml) with stirring, and sodium hydroxide solution (335 ml, 3 N, 1 mole) added carefully, followed by 30% hydrogen peroxide (100 ml, 1 mole) during 30 minutes at 30-35°. After 3 hours stirring at room temperature, dilution with water (400 ml), and extraction with ether (3 x 500 ml), (a tetrahydrofuran layer separated before ether extraction) the organic layer was washed with water, dried over sodium sulphate, and evaporated. Much 3-methyl-butan-2-ol was removed on the rotary evaporator, the remaining by-product by pumping off 18 hours at 5 mm Hg into a cold trap. The crystalline residue was washed with a little warm petrol, the petrol cooled to 0° to precipitate some dissolved diol, and filtered. The residual diol (61), 19.2g, 95%, spectrally identical with the more polar product of hydroboration of the olefin (58), was virtually pure and recrystallisation was not necessary.

9-Methoxymethylenepinan-2β-ol (62)

a) Potassium t-butoxide as base

A stirred suspension of methoxymethyltriphenylphosphonium chloride[42] (46.3g, 0.135 mole) in dry t-butanol (300 ml) under argon was treated with dry potassium t-butoxide (13.44g 0.120 mole) to give a deep red solution of the ylid. After 30 minutes at 50°, a solution of the hemiacetal (52) (5.04g, 30 mmole) in t-butanol (40 ml) was introduced with a syringe, and reaction allowed to proceed 40 hours at 60-65°. No

hemiacetal remained (to t.l.c.). A wide coil condenser was necessary to minimise the risk of blockage by solid t-butanol which sublimed into the condenser. The cold solution was poured into water (1.5l) extracted three times with ether, the organic layer washed twice with water (equal volume), dried (Na_2SO_4) and evaporated. The residue, a brown oil, was treated with petrol and cooled to 0°. The petrol solution was decanted from precipitated triphenylphosphine oxide and a tar (from thermal decomposition of excess ylid), concentrated by evaporation, and cooled. Triphenylphosphine, m.p. 79-80°, separated. Chromatography on alumina (G3) of the supernatant fluid gave (a) triphenylphosphine, eluted with petrol; (b) a non-polar liquid, 6,9-dimethyl-8-methoxymethoxy-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane, (63), eluted with petrol 98-ethyl acetate 2, 2.9g, 47%, b.p. ca 60° at 0.5 mm Hg, ν_{max} 1160, 1110, 1020, cm^{-1}, τ (CCl_4) 8.73 (3H,s), 8.65 (3H,s), 6.62 (3H,s), 5.37 (2H,q,J7Hz), 5.13 (1H,s). m/e 181 (m^+-OCH_3), 166 ($m^+-CH_2OCH_3$), 151 ($m^+-OCH_2OCH_3$); and (c) a colourless oil, 9-methoxymethylenepinan-2β-ol (62), eluted petrol 95-ethyl acetate 5, 2.1g, 36%, b.p. ca 50° at 3 x 10^{-4}mm, ν_{max} 3550, 1660, 1110 cm^{-1}; τ 8.75 (3H,s), 8.57 (3H,s), 6.46 (3H,s) + 6.41 (3H,s) (total integral 3H), 5.18 (1H,d,J7Hz) + 4.26 (1H,d,J7Hz), 4.67 (H,d,J13Hz) + 3.56 (1H,d,J13Hz) (total integral 2H, cis:trans ratio 3:2); m/e 196.1466. (Calculated for $C_{12}H_{20}O_2$, 196.1463). $[\alpha]_D^{24}$(corr.) + 10.9° (c 5%, CCl_4). A small scale reaction, employing the hemiacetal (52) 336 mg, 2 mmol, under the same conditions yielded in addition a non-polar compound, ν_{max} 1685, 1645, 1160, 1110 cm^{-1}, possibly (64) but this result was not reproducible and the product was not further

characterised.

b) Sodium methylsulphinylmethide[34] as base

Dry dimethyl sulphoxide (5 ml) containing sodium hydride (165 ml, 80% in oil, 5.5 mmole, 4.6 equiv) was stirred under argon at 55° for 4 hours, cooled to room temperature over 30 minutes, and methoxymethyltriphenylphosphonium chloride (2.05g, 6.0 mmole) added rapidly, with minimal exposure to atmospheric moisture. The deep red solution was stirred at room temperature 1 hour, and a solution of the hemiacetal (52) (200 mg, 1.2 mmole) in dry dimethyl sulphoxide (1 ml) introduced using a syringe. After 48 hours reaction at 60° under argon the reaction was worked up as for method (a) to yield the enol ether (62), 89 mg, 38%, spectrally identical with product (c) of method (a); and recovered hemiacetal, 104 mg, 52%. None of the methoxymethyl ether (63) was detected when the reaction was conducted under strictly anhydrous conditions.

Reaction of 9-methoxymethylenepinan-2β-ol(62) with excess triphenylmethoxymethylenephosphorane

The enol ether (62) (400 mg, 2 mmole) in t-butanol (2g) was introduced to a solution of the ylid prepared from potassium t-butoxide (900 mg, 8 mmole) and the phosphonium salt (3.08g, 9 mmole) in t-butanol (18 ml), and stirred 42 hours at 65° under argon. The usual work-up gave only unchanged enol ether.

Hydrolysis of the hemiacetal methoxymethyl ether (63)

a) The ether (63) (500 mg) in diethyl ether (5 ml) was stirred with water (7 ml)-acetone (1 ml) containing concentrated hydrochloric acid (0.2 ml) until hydrolysis was complete. The aqueous layer was extracted with ether, and the combined ether layers washed successively with saturated aqueous sodium bicarbonate and sodium chloride solutions, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on alumina (G3) eluted initially with petrol 99-ethyl acetate 1, and then with petrol 50-ethyl acetate 50, to yield the hemiacetal (52), 74%, spectrally identical with an authentic sample. Hydrolysis employing homogeneous solutions in aqueous acetone or dioxan resulted in a poor yield of hemiacetal. When the crude hydrolysed product in ether was evaporated, omitting the washing with sodium bicarbonate solution, the major product, isolated from an alumina column eluted petrol 99-ethyl acetate 1, proved to be the hemiacetal ether (57), m.p. 112-115°, spectrally identical with an authentic sample.

b) Reduction of the hydrolysis product

Reduction of the hemiacetal obtained by hydrolysis of the methoxymethyl ether (63) employing either lithium aluminium hydride in ether at room temperature or sodium borchydride (large excess) in aqueous tetrahydrofuran at room temperature for 20 hours in both cases gave a diol, m.p. 81-82° (from ether-light petroleum), white needles, ν_{max} 3230, 1130, 1045, 1030, 1015, 930 cm^{-1}; τ 8.96

(1H,d,J9Hz), 8.70 (3H,s), 8.72 (3H,s), 6.37 (2H,q,J11Hz), 7.20 (OH,bs), identical with the product of reduction of authentic hemiacetal (52) by lithium aluminium hydride under the same conditions, and with a literature preparation.[8] (lit.[8] m.p. 82°).

1,5-Dimethyl-3-hydroxy-2-oxatricyclo[4.4.0.$0^{5,8}$]decane (65)

The enol ether (62) (200 mg, 1 mmole) in ether (5 ml) was stirred at 0° with water (9 ml) containing concentrated hydrochloric acid (0.1 ml)-acetone (1 ml) for 30 minutes. Work up exactly as for hydrolysis of the methoxymethyl ether (above) gave the δ-lactol, (65), 137 mg, 74%, as a colourless oil which decomposed rapidly at room temperature; ν_{max} 3400, 1145, 1125, 1105, 1070, 955 cm^{-1}, $\tau(CCl_4)$ 8.83 (3H,s), 8.75 (3H,s), 5.15 (OH,bs), 4.71 (1H,m). m/e 182.1309 (Calculated for $C_{11}H_{18}O_2$, 182.1307), b.p. ca 60° at 5 x 10^{-4} mm.

Reduction of the δ-lactol (65) to 9-hydroxymethylpinan-2β-ol

The δ-lactol (65)(50 mg) was reduced with excess lithium aluminium hydride in ether (2 ml) at room temperature immediately after purification. Work-up in the usual manner with ammonium chloride solution gave a quantitative yield of white needles, m.p. 110-111° (from ether-light petroleum) identical with the product (61) of hydroboration of olefin (58) with disiamylborane; ν_{max} 3250, 1135, 1080, 965, 935 cm^{-1}. τ 8.77 (6H,2s), 8.15 (s), 5.88-6.42 (2H + 20H, m)

Hydrolysis of 9-methoxymethylenepinan-2β-ol at room temperature

a) The enol ether (250 mg, 1.3 mmole) in acetone (12 ml)-water (9 ml containing 1.5% of concentrated hydrochloric acid) was stirred at room temperature for 10 minutes. The dark solution contained three products and some insoluble polymeric material. Sodium bicarbonate solution was added to neutralise the acid, the acetone partly removed by pumping off at room temperature into a cold trap, the aqueous suspension poured into water and extracted with ether (3 x 15 ml). The ethereal layer was washed with saturated sodium chloride solution, dried (Na_2SO_4), evaporated, and rapidly chromatographed on alumina (G3) to yield (a) a volatile vinyl ether, 1,5-dimethyl-2-oxatricyclo[4.4.0.$0^{5,8}$]dec-3-ene (67), ν_{max} 1640, 1250, 1070, 1050, 860, 785, 765 cm^{-1}, $\tau(CCl_4)$ 8.85 (3H,s), 8.76 (3H,d,J1Hz), 8.23 (s), 5.75 (1H,d, J6Hz), 3.65 (1H,d,J6Hz); (b) the hemiacetal ether (66), an oil which could not be crystallised, ν_{max} 1070, 1005, 980, 930 cm^{-1}, $\tau(CDCl_3)$ 8.83 (6H,s), 8.77 (6H,s), 8.17 (s), 4.60 (2H,q,J5Hz); and (c) the δ-lactol (65) identical with an authentic sample.

b) The pure δ-lactol (65) decomposed at room temperature over 5 days to a mixture of (66) and (67). The products were separated on an alumina column and compared with authentic samples.

c) The pure hemiacetal ether (66) decomposed slowly at room temperature to (67) (by n.m.r.).

Attempted reaction of the enol ether (62) with phosphorus oxychloride in pyridine

9-methoxymethylenepinan-2β-ol (62) (100 mg, 0.5 mmole) in pyridine (1 ml) at 0° was treated with phosphorus oxychloride (300 mg, 2 mmole) and stirred at room temperature 16 hours. T.l.c. indicated four non-polar major products.

9-Acetoxymethylpinan-2β-ol (68)

To the diol (61) (19,2g, 0.104 mole) in pyridine (80 ml) was added acetic anhydride (16.0g, 0.157 mole) in pyridine (15 ml) at 0° .

After stirring 3 hours at room temperature, the solution was poured into water (60 ml), stirred 1 hour to hydrolyse excess acetic anhydride, extracted with ether (3 x 200 ml), the organic layer washed twice with water, dried, evaporated, and pumped off 5 hours at 2 mm Hg to remove pyridine. Yield of colourless oil, 22.45g, 95%, virtually pure to t.l.c. and n.m.r., b.p. ca 80° at 10^{-3} mm; ν_{max} (liquid film) 3500, 1750 + 1730, 1250, 1055, 1040, 925 cm^{-1}; τ 8.77 (3H,s), 8.73 (3H,s), 7.97 (3H,s), 5.87 (2H,t,J8Hz; each signal showed additional splitting, J3Hz); m/e 226.1577 (Calculated for $C_{13}H_{22}O_3$, 226.1569). (Found: C, 68.76%; H, 9.58%. $C_{13}H_{22}O_3$ requires C, 68.99%; H, 9.80%).

Reaction of 9-acetoxymethylpinan-2β-ol with phosphorus oxychloride in pyridine

Dropwise addition of phosphorus oxychloride (25.65, 0.165 mole) to a stirred solution of the diol monoacetate (68) (24.5g, 0.108 mole) in dry pyridine (100 ml) at 0° followed by stirring 17 hours at 0° gave only one product to t.l.c. except for a polar compound on the origin of the t.l.c. plate. The brown solution was carefully poured into ice-water, extracted with petrol (40-60°) three times, the petrol layer washed three times with water, dried (Na_2SO_4), evaporated, and the residual pyridine pumped off into a cold trap, to give an almost pure mixture of the 9-acetoxymethyl-α- and -β-pinenes (2:1, by n.m.r.), 13.3g, 59%. A sample was micro-distilled; b.p. ca 60° at 3 x 10^{-4} mm; ν_{max} 1750, 1650, 1250, 1065, 1045 cm^{-1}; τ 8.75 (3H,s) + 8.72 (3H,s) (total integral 3H), 8.30 (3H,q,J2Hz) (actual integral 0.65 of 3H), 7.97 (3H,s), 60.2 (2H,t,J8Hz) + 5.98 (2H,t,J8Hz) (total integral 2H), 5.37 (2H,m) (integral ca 0.35 of 2H), 4.75 (1H,m) (integral 0.7 of 1H): $[\alpha]_D^{23}$(corr.) -29.1° (c 3%, $CHCl_3$); m/e 208.1454 (Calculated for $C_{13}H_{20}O_2$, 208.1463). (Found: C, 74.87%; H, 9.98%. Calculated for $C_{13}H_{20}O_2$, C, 74.96%; H, 9.68%).

Continuous extraction of the aqueous layer yielded very little additional material. The aqueous layer was made alkaline with excess solid sodium hydroxide and heated on a steam bath for 1 hour. An organic layer rapidly separated above the aqueous solution, and was separated, the aqueous layer extracted with ether. The separated organic layer was

treated with just sufficient 2N hydrochloric acid, with shaking, to react with all the pyridine present, and this mixture extracted three times with the previous ether extracts; the ether layer was washed with water (twice), dried, and evaporated to give a dark oil (ca 8g). T.l.c. and i.r. (ν_{max} 3450, 1650, 1225, 1155, 1080, 1045, 1010 cm^{-1}) suggested a mixture of recovered diol (61) and the 9-hydroxymethylpinenes (70) (ca 1:3). A sample (1g) of the crude mixture was treated with pyridine (3 ml) and acetic anhydride (1g) overnight at room temperature, and the crude esters isolated in the usual manner. The total crude product was reacted with phosphorus oxychloride (1g) in pyridine (4 ml) at 0° and worked-up as above. Yield of (69) after purification on alumina (G3), 371 mg, an additional 13%.

1,3-Dimethyl-2α-chloro-3α(2'-acetoxyethyl)norbornane (71)

A stirred solution of the diol monoacetate (68) (452 mg, 2 mmole) in pyridine (1.5g) at 0° was treated with thionyl chloride (310 mg, 2.6 mmole). After 60 hours at 0°, the orange-brown solution was poured on to ice-water, extracted three times with petrol, the petrol solution washed with water (three times), dried over sodium sulphate, and evaporated. The brown oil (291 mg) contained ⟨20% of the olefin mixture (69) (to t.l.c.), along with a new non-polar product and polymer. Chromatography on alumina (G3) gave a colourless oil (71), 185 mg, 38%, ν_{max} 1745, 1240 cm^{-1}; τ 8.95 (3H,s), 8.91 (3H,s), 7.99 (3H,s), 6.40 (1H,d,J2Hz), 5.91 (2H,t,J7.5Hz); m/e 244.1240 (calculated for $C_{13}H_{21}O_2Cl$,

244.1230).

9-Acetoxymethylpin-2-en-4-one (72)

a) Small-scale reaction

Dichloromethane was purified from olefins by shaking successively three times with concentrated sulphuric acid (10% volume of the solvent), water, saturated sodium bicarbonate solution, and water, drying over potassium carbonate, and distillation. Unpurified dichloromethane gave a considerable black precipitate with chromium trioxide in pyridine. The orange-red complex of chromium trioxide and pyridine was prepared[43] by direct reaction in excess pyridine at 0°. The precipitate was filtered, washed with petrol, and stored under vacuum over potassium hydroxide.

A mechanically-stirred solution of the complex (45g, 32 equiv; 0.174 mole) in dichloromethane (300 ml) was treated with the mixture of 9-acetoxymethylpinenes (69), (1.2g, 5.3 mmole) and the solution refluxed 26 hours. The supernatant orange solution was decanted from a black semi-solid precipitate of chromium complexes, the precipitate washed twice with dichloromethane, and the total organic solution extracted successively with water, sodium bicarbonate solution, and water, dried (Na_2SO_4), evaporated, and pyridine pumped off into a cold trap. Chromatography on an alumina column (G3) gave a little recovered olefine (69) (112 mg), and another minor olefinic product, an α,β - unsaturated aldehyde, probably (73), (51 mg, 4%), ν_{max}

2720, 1750, 1690, 1835, 1250, 1064, 1045 cm^{-1}; the <u>enone</u> (72), the most polar product, as a colourless oil (520 mg, 41%; 45% allowing for recovered starting material), ν_{max} 1750, 1690, 1630, 1250, 1065, 1045 cm^{-1}; τ8.45 (3H,s), 7.93 (3H,d,J2Hz), 7.96 (3H,s), 8.20 (2H,t,J7Hz), 5.97 (2H, t,J7Hz), 3.19 (1H,q). m/e 222.1251 (calculated for $C_{13}H_{18}O_3$, 222.1256). $[\alpha]_D^{23}$(corr.) -162.1° (c 2%, $CHCl_3$) A sample was micro-distilled for analysis, b.p. ca 80° at 3×10^{-4}mm. (Found: C, 69.97%; H, 8.00%. $C_{13}H_{18}O_3$ requires C, 70.24%; H, 8.16%).

Two significant non-polar by-products were isolated. The minor component (106 mg), ν_{max} 1745, 1605 + 1585, 1250 cm^{-1}, was not characterised. A major product (286 mg), a colourless oil, ν_{max} 3100, 1720, 1605, 1585, 1290, 1130, 1080, 765, 675 cm^{-1}, τ8.70 (bs), 5.70 (2H,t,J6Hz), 2.58-2.22 (2H, symmetrical multiplet), m/e 278.1512 (calculated for $C_{16}H_{22}O_4$, 278.1518), 223 (base peak, $C_{13}H_{19}O_3$), b.p. ca 120° at 10^{-3}mm Hg, may be a mixture. (Found: C, 69.69%; H, 8.88%. $C_{13}H_{20}O_3$ requires C, 69.61%; H, 8.99%).

b) <u>Large-scale reaction</u>

Reaction of the chromium complex (232g, 0.90 mole, 30 equiv.) in dichloromethane (2.3l) with the olefin (69), (6.24g, 30 mmole) at reflux (oil bath) for 18 hours gave, after working-up as above, the enone (72) (1.34g, 20%), spectrally identical with an authentic sample; the $\alpha\beta$-unsaturated aldehyde (450 mg, 7%); and the aromatic ketone by-product, (1.40g). Probably much of the enone was over-

oxidised to an acid,[43] lost in the aqueous pyridine solution.

2αH-9-acetoxymethylpinan-4-one (74)

The enone (72) (3.0g) in ethanol (100 ml) containing 20% pd/c (300 mg) was hydrogenated until uptake was complete at room temperature and atmospheric pressure (1.5 hours). The solution was filtered through celite, the filter aid washed with ethanol, the ethanol solution evaporated and residual solvent pumped off at room temperature into a cold trap. The product (74) (2.7g, 90%) did not need any further purification; ν_{max} 1750, 1720, 1250, 1060 cm^{-1}. τ 8.77 (3H,d,J6Hz), 8.58 (3H,s), 7.92 (3H,s) 5.90 (2H,t, J7Hz); m/e 224.1418 (calculated for $C_{13}H_{20}O_3$, 224.1412). $[\alpha]_D^{24.5}$(corr.) -34.5° (c 1%, $CHCl_3$) Micro-distilled, b.p. ca 75° at 3 x 10^{-3} mm. (Found: C, 69.44%; H, 8.87%. $C_{13}H_{20}O_3$ requires C, 69.61%; H, 8.99%).

9-Benzoyloxymethylpinan-2β-ol (75)

Redistilled benzoyl chloride (1.1g, 7.8 mmole) was introduced to a solution of the diol (61) (1.0g, 5.2 mmole) in dry pyridine (8 ml) at 0°. After 3 hours at 0°, the solution containing precipitated pyridine hydrochloride was poured into water, stirred at room temperature 2 hours and extracted with ether. The ether layer was washed three times with water, dried (Na_2SO_4), evaporated, and pyridine removed under 5 mm Hg pressure. The viscous monobenzoate (75), 1.54g 98%, needed no purification but could not be crystallised. ν_{max} 3450, 1710, 1600, 1585, 1325, 1290,

1130, 1080, 1040, 970, 930, 725 cm^{-1}; τ 8.75 (3H,s), 8.72 (3H,s), 5.62 (2H,t,J7Hz), (each signal further split, J = 2Hz), 2.73-1.83 (5H,m). m/e (no m^+), 270 (m^+-H_2O). $[\alpha]_D^{25}$(corr.) + 9.1° (c 1%, $CHCl_3$). Micro-distilled for analysis, b.p. ca 100° at 3 x 10^{-3}mm. (Found: C, 74.81%; H, 8.34%; $C_{18}H_{20}O_3$ requires C, 74.97%; H, 8.39%).

Reaction of 9-benzoyloxymethylpinan-2β-ol with phosphorus oxychloride in pyridine

The diol monobenzoate (75) (362 mg, 1.26 mmole) and phosphorus oxychloride (585 mg, 3.8 mmole) in pyridine (2.5g) were allowed to react 18 hours at 0°, and worked up exactly as for the acetate (69). The olefin (a 2:1 mixture of the α- and β-pinene derivatives), 154 mg, 45%, a colourless oil, ν_{max} 1715, 1650, 1600, 1585, 1280, 725 cm^{-1}; τ 8.63 (3H,s), 8.26 (3H,q,J2Hz), 5.73 (2H,t,J7.5Hz) (each signal showed fine splitting, J2Hz), 4.74 (1H,m), 5.30 (2H,m), 2.77-1.87 (5H,m). m/e 270.1624 (calculated for $C_{18}H_{22}O_2$, 270.1620). B.p. ca 85° at 10^{-3} mm. (Found: C, 79.84%; H, 8.24%. $C_{18}H_{22}O_2$ requires C, 79.96%; H, 8.20%).

9-Benzoyloxymethylpin-2-en-4-one (77)

a) A solution of the olefin (76) (191 mg, 0.7 mmole) in dichloromethane (60 ml) was treated with chromium trioxide-pyridine complex[43] (4.5g, 17.5 mmole, 25 equiv.) and shaken at room temperature for 44 hours. The combined solution and dichloromethane extracts of the tar residue were washed three times with water, dried (Na_2SO_4) and evaporated, and

the product isolated by elution (petrol-ethyl acetate) from an alumina column (1 x 10cm). Yield of very pale yellow oil (77), 65 mg, 32%; ν_{max} 1730, 1690, 1285, 730 cm^{-1}; τ 8.37 (3H,s), 7.95 (3H,d,J2Hz), 5.75 (2H,t,J7Hz), 4.20 (1H,q,J2Hz), 2.63-1.87 (5H,m); m^+ 284.1416 (calculated for $C_{18}H_{20}O_3$, 284.1412). Micro-distilled for analysis, b.p. ca 110° at 3 x 10^{-3} mm Hg. (Found: C, 76.10%; H, 7.28%. Calculated for $C_{18}H_{20}O_3$, C, 76.03%; H, 7.09%). An α,β-unsaturated aldehyde was isolated as a minor product; ν_{max} 3100, 2750, 1730, 1690, 1285, 1120, 1080, 730 cm^{-1}. Recovered starting material (ca 35 mg, 18%) and non-polar aromatic products, ν_{max} 3100, 1735, 1725, 1610, 1590, 1320, 1285, 1185, 1120, 1080, 1040, 730 cm^{-1}, were also obtained.

A 2,4-dinitrophenylhydrazone was prepared in phosphoric acid (85%)-ethanol in the usual manner. The red gum (79) was purified on an alumina preparative t.l.c. plate and extracted with acetonitrile. The product crystallised only on standing 7-10 days, m.p. 121-2°, and could not be satisfactorily recrystallised. N.m.r. suggested a mixture of <u>syn</u> and <u>anti</u> isomers in a 1:2 or 2:1 ratio. ν_{max} 3270, 2820, 1705, 1610, 1580, 1515, 1335 cm^{-1}; τ 8.37 (3H,s) (major) + 8.32 (3H,s)(minor)(total integral 3H), 7.97 (3H,d,J2Hz)(minor) + 7.90 (3H,s)(major)(total integral 3H), 5.73 (2H,t,J7Hz) (major) + 5.77 (2H,t,J7Hz)(minor)(total integral 2H), 3.68 (1H,m)(major) + 3.90 (1H,m)(minor)(total integral 1H), 2.80-1½67 (8H,m). m/e 464 (m^+).

b) A solution of <u>t</u>-butyl chromate was prepared[44] by addition of chromium trioxide (1.6g) to dry <u>t</u>-butanol (4 ml) with

cooling (10°) over 3-4 minutes, followed by dry carbon tetrachloride (14 ml) and sodium sulphate (2g). After 10 minutes, the filtered red solution was concentrated to half volume at room temperature by pumping off into a cold trap. The t-butyl chromate solution (1 ml) was introduced at room temperature to a solution of the olefin (76) (50 mg) in carbon tetrachloride (2 ml) containing acetic acid (300 mg) and acetic anhydride (150 mg). After 48 hours at room temperature, carbon tetrachloride (5 ml) was added and the product was stirred with excess aqueous oxalic acid 3 hours, separated, the organic layer washed successively with water, sodium bicarbonate solution, and water, dried, and evaporated. T.l.c. indicated a product distribution very similar to that of method (a). Purification on alumina preparative t.l.c. plates yielded the enone (77), ν_{max} 1730, 1690, 1285, 1115, 725 cm^{-1}.

2αH-9-benzoyloxymethylpinan-4-one (78)

The α,β -unsaturated ketone (77) was hydrogenated exactly as for the acetate (72) to a single, less polar, product, (78), ν_{max} 3100, 1720, 1605, 1585, 1285, 1120, 725 cm^{-1}; τ 8.79 (3H,d,J7Hz), 8.55 (3H,s), 5.70 (2H,t,J7Hz), 2.63-1.80 (5H,m). m^+ 286.1569 (calculated for $C_{18}H_{22}O_3$, 286.1570). Micro-distilled, b.p. ca 120° at 2 x 10^{-4} mm, to yield a colourless, viscous oil. (Found: C, 75.42%; H, 7.76%. $C_{18}H_{22}O_3$ requires C, 75.50%; H, 7.74%).

Photolysis of 2α-H-9-benzoyloxymethylpinan-4-one (78) in methanol

A solution of the ketone (78) (30 mg) in methanol (4 ml) containing sodium bicarbonate (few mg) in a tube of 'Vycor' glass immersed in water, was photolysed under nitrogen at room temperature using an external medium-pressure u.v. lamp. After 2.5 hours t.l.c. indicated that the ketone was photoinert; only a little polar material was produced. The usual work-up gave starting material only (to i.r., n.m.r.). A sample of cis-verbanone (3) was photolysed under identical conditions. Reaction was complete, giving one, less polar, product in less than 1 hour.

Photolysis of 2α-H-9-acetoxymethylpinan-4-one (74) in methanol in the absence of sodium bicarbonate

a) A solution of the ketone (74, 150 mg) in methanol (15 ml) was photolysed in a 'Vycor' glass tube under nitrogen, under the usual conditions. After 3 hours, the starting material was almost absent and the less polar aldehyde (79) was the major product. After 9 hours photolysis, most of the aldehyde was converted into a new, less polar, product, and polar material. This subsequent reaction was complete after 22 hours. Methanol was pumped off at room temperature into a cold trap and the residue chromatographed on a short alumina (G3) column, eluted petrol-ethyl acetate, to remove polar products. Evaporation of solvent yielded a colourless liquid, 46 mg, 37%, cis-2-(2'-acetoxy)ethyl-cis-3-isopropenyl-2-methylcyclobutanecarbaldehyde dimethyl acetal (80) contain-

ing ca 10% of a cyclobutene isomer, probably (81). ν_{max} 1750, 1650, 1250, 1060, 970, 900 cm^{-1}; τ 8.77 (3H,s), 8.30 (3H,s), 7.97 (3H,s), 6.68 (6H,s), 6.10-5.57 (3H,m), 5.32 (1H,bs), 5.15 (1H,bs); 3.87 (2H,m; integral ca 10% of 2H); m/e 270 (m^+), 238-9 (m^+-MeO, MeOH), 223 (m^+-MeOMe), 205, 178-9, 170-1, 162-4, 151, 149. m^+ 270.1840 (calculated for $C_{15}H_{26}O_4$, 270.1831). B.p. ca 65° at 3 x 10^{-3} mm. (Found: C, 66.49%; H, 9.63%. $C_{15}H_{26}O_4$ requires C, 66.64%; H, 9.69%).

b) A repeat photolysis exactly as in (a) gave polar material and very little (80). A similar reaction in the presence of Amberlite IR-120H acid ion-exchange resin gave (80) as sole product, spectrally identical with the previous sample.

c) The ketone (74) (50 mg) in dry redistilled tetrahydrofuran (5 ml) was photolysed under the same conditions as in (a). A slow reaction gave much polar material and several nonpolar products.

Cis-2-(2'-acetoxy)ethyl-cis-3-isopropenyl-2-methylcyclobutanecarbaldehyde (79)

The ketone (74) (250 mg, 1.1 mmole) in dry methanol (25 ml) containing sodium bicarbonate (25 mg) in a 'Vycor' glass tube was photolysed under nitrogen employing the usual conditions until reaction was 80-90% complete (to t.l.c.). Methanol was pumped off into a cold-trap, the residue treated with water and extracted twice with petrol. The petrol solution was extracted with water, dried (Na_2SO_4) and

evaporated at ca 30°. Separation on a silica column, eluted petrol 98-ethyl acetate 2 gave the aldehyde (79) containing ca 10% of a cyclobutene isomer, probably (82), which was not separable although just apparent on t.l.c. as a slightly less polar compound. Yield, 128 mg, 60%, allowing for recovered starting material (39 mg). (A more polar product, 42 mg, was also isolated). The aldehyde had ν_{max} 3080, 2700, 1735, 1705, 1645, 1245, 1040, 910 cm^{-1}. ν_{max} (CCl_4) 3080, 2810, 2710, 1745, 1720, 1645, 1235, 1035, 970, 900 cm^{-1}. τ (CCl_4) 8.58 (3H,s), 8.30 (3H,s), 8.07 (3H,s)(minor signals at τ8.78, 8.40 and 8.13), 7.47 (1H,t,J7Hz), 6.12 (2H,m), 5.23 (1H,bs), 5.08 (1H,bs), 0.28 (1H,d,J2Hz); 3.86 (2H,q,J3Hz); integral 10-15% of 2H). B.p. ca 65° at 3 x 10^{-4} mm. (Found: C, 69.43%; H, 8.84%. $C_{13}H_{20}O_3$ requires C, 69.61%; H, 8.99%). The product oxidised appreciably on standing several hours in air.

A 2,4-dinitrophenylhydrazone was prepared by reaction of the crude aldehyde (79) in phosphoric acid (85%)-ethanol. The crude derivative was purified on an alumina p.l.c. plate (20 x 60cm x 1mm) to yield (83) as yellow non-polar crystals, m.p. 124-5° (from ethanol, crystallised three times to remove the derivative of the cyclobutene isomer), ν_{max} 3280, 1720, 1625, 1590, 1520, 1350, 1310, 1275, 1140, 905 + 900 cm^{-1}; τ 8.70 (3H,s), 8.28 (3H,s), 8.02 (3H,s), 7.20 (1H,bt,J9Hz), 6.03 (2H,m), 5.25 (1H,bs), 5.08 (1H,bs), 2.40-1.60 (3H,m), 0.90 (1H,d,J3Hz). (The cyclobutene olefin signals of a sample before recrystallisation appeared at τ 3.83 (2H,m, integral 10-15% of 2H)). m^+ 404.1705 (calculated for $C_{19}H_{24}N_4O_6$, 404.1696). (Found: C, 56.63%; H, 6.01%;

N, 13.72%. Calculated for $C_{19}H_{24}N_4O_6$, C, 56.43%; H, 5.98%; N, 13.85%).

Grandisol acetate (1-methyl-cis-1-(2'-acetoxy)ethyl-2-isopropenylcyclobutane (84)

The ketone (74) (430 mg) (1.9 mmole) was photolysed in methanol (40 ml) containing sodium bicarbonate (40 mg) to ca 80% of completion (to t.l.c.) and worked up in the usual manner. Immediately after isolation, the crude aldehyde (79) in dichloromethane (6 ml, purified by refluxing 1 hour over potassium carbonate)containing tris(triphenylphosphine) chlororhodium (I), (1.78g, 1.0 equiv based on (74)) and potassium carbonate (100 mg) was refluxed under nitrogen (static) for 10 hours while protected from light. Dichloromethane was distilled off on an oil bath, and the residue extracted repeatedly with petrol (40-60°), filtered, and concentrated by evaporation. An alumina column (G3) yielded triphenylphosphine (i.r. identical with an authentic sample) when eluted with petrol, followed by the impure pheromone acetate (149 mg, 52% over two steps, allowing for recovered ketone (74), 103 mg). The product, a volatile, colourless liquid, had ν_{max} (liquid film) 1735, 1640, 1245, 1040, 895 cm^{-1}; τ (CCl_4) 8.80 (3H,s), 8.33 (3H,s), 8.05 (3H,s), (minor signals at τ9.17, 9.05, 8.75 and 8.43), 7.45 (1H,t, J8Hz), 6.01 (2H,t,J7.5Hz), 5.38 (1H,bs), 5.18 (1H,bs); and 3.83 (2H,q, integral 10-15% of 2H). τ ($CDCl_3$) 8.82 (3H,s), 8.33 (3H,s), 7.97 (3H,s), 7.53 (1H,t,J7Hz), 5.90 (2H,t, J7.5Hz), 5.32 (1H,bs), 5.15 (1H,bs); and 3.83 (2H,q, integral 10-15% of 2H).

Reduction of crude grandisol acetate (84)

Crude (84) was reduced with excess lithium aluminium hydride in ether at -20°, the excess reagent destroyed with ethyl acetate, and the product worked up with 3 N sodium hydroxide solution. The ether layer was washed with water, dried over sodium sulphate and evaporated. The crude oil could not be purified chromatographically. (1), ν_{max} 3380, 3080, 1645, 1055, 1020, 900 cm^{-1}. $\tau(CCl_4)$ 8.82 (3H,s), 8.33 (3H,s); (minor signals at τ 9.17, 9.07), 7.56 (CH,s), 7.48 (2H,t,J7.5Hz), 6.46 (3H,t,J7.5Hz), 5.40 (1H,bs), 5.22 (1H,bs), 3.90 (2H,q, integral 10-15% of 2H).

Grandisol p-nitrobenzoate (85)

Crude pheromone (1) (239 mg) was heated 30 minutes at 70-80° in pyridine (3 ml) with p-nitrobenzoyl chloride (415 mg, 1.5 equiv), treated with water to hydrolyse excess reagent, cooled, and poured into water. The aqueous solution was extracted with ether, washed with water, dried (Na_2SO_4) and evaporated. The crude ester (85) was isolated from a silica p.l.c. plate (20 x 60cm x 1mm). Attempted purification of the product by multiple elution of 0.5 mm silica p.l.c. plates was not successful, although qualitative separation on thin plates was apparent. Crude (85), 200 mg, m.p. 66-71°, was crystallised three times from petrol to yield very pale yellow plates, m.p. 73-74°, ν_{max} (CCl_4) 3050, 1730, 1640, 1605, 1520, 1350, 1275, 1120, 1105, 895 cm^{-1}; $\tau(CCl_4)$ 8.75 (3H,s), 8.32 (3H,s), 7.42 (1H,t,J8Hz), 5.68 (2H,t,J7.5Hz), 5.35 (1H,s), 5.17 (1H,s), 1.77 (4H,s).

m/e 303(m^+), 150-151 (P-O_2N-ϕ-CO), 137 (m^+- P-O_2N-ϕCOO), 121, 107-9. 104, 93, 68. m^+ 303.1475 (calculated for $C_{17}H_{21}NO_4$, 303.1470) (Found: C, 67.29%; H, 6.97%;. N, 4.68%. $C_{17}H_{21}NO_4$ requires C, 67.31%; H, 6.98%; N, 4.62%)

(+)Grandisol (+)(1R,2S)-1-methyl-1-(2'-hydroxy)ethyl-2-isopropenylcyclobutane (1)

Recrystallised grandisol p-nitrobenzoate (200 mg) was treated with potassium hydroxide (600 mg) in methanol (2.5 ml)-water (2.5 ml) 30 minutes at 100°, then cooled. Solid CO_2 was carefully added to neutralise the base, the solution poured into water, and extracted three times with petrol. P-nitrobenzoic acid was completely insoluble in petrol. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The pheromone, (1), a colourless oil, pure except for a hydrocarbon residue from the solvent, had υ_{max} (CCl_4) 3630, 3070, 1645, 1240, 1075, 1045, 990, 890, 690 cm^{-1}. (lit.[45] 3630, 1642, 885 cm^{-1}) τ(CCl_4) 8.82 (3H,s), 8.33 (3H,s), 7.93 (OH,s, concentration dependent and exchange by D_2O), 7.48 (1H,t,J7.5Hz), 6.46 (2H,t, J7.5Hz), 5.40 (1H,bs), 5.22 (1H,bs). (lit.[45] 8.82 (3H,s), 8.33 (3H,s), 8.12 (OH,s, concentration dependent), 7.43 (1H, t,J8Hz), 6.44 (2H,t,J7.5Hz), 5.40 (1H,bs), 5.20 (1H,bs). Micro-distillation at 50-60° at 1 mm Hg gave 60 mg colourless liquid, $[\alpha]_D^{21.5}$(corr.) + 15.9° (c 1%, n-hexane); $[\alpha]_D^{25}$(corr.) + 6.9° (c 3%, $CHCl_3$); $[\alpha]_D^{25}$(corr.) + 12.3° (c 3%, EtOH). The mother liquor from the first crystallisation of the p-nitrobenzoate was concentrated and applied to a silica p.l.c. plate; multiple elution in petrol-ethyl acetate did not

separate the cyclobutene derivative. The crude p-nitrobenzoate was hydrolysed exactly as for the pheromone derivative and the oil micro-distilled; $[\alpha]_D^{21.5}$(corr.) -7.0° (c 2%, n-hexane)

The purified pheromone (30 mg) was converted back to the p-nitrobenzoate exactly as given, the derivative crystallised twice from petrol, with no change in melting point, and hydrolysed and distilled as before. The very pure sample had $[\alpha]_D^{21.5}$(corr.) + 18.4° (c 1%, n-hexane).

Part II

5-phenoxy-1-phenyl-1H-tetrazole[1] (1)

5-Chloro-1-phenyl-1H-tetrazole (2.72g, 15 mmole), phenol (1.56g, 16.5 mmole), lithium iodide (0.225g, 1.5 mmole) and anhydrous potassium carbonate (4.14g, 20 mmole) were refluxed in dry acetone (30 ml) 17 hours. The product had the same Rf as the starting material on a silica t.l.c. plate. The suspension was filtered, evaporated, the residue dissolved in dichloromethane, washed with 5% sodium hydroxide solution, then water, dried (Na_2SO_4) and evaporated; m.p. 128.5-129.5° (from ethanol), large white rhombic crystals, 3.04g, 84% (lit.[1] m.p. 124.5-126.5), ν_{max} 1600, 1540, 1505 + 1495, 1180, 765, 735, 690 cm^{-1}; λ_{max}^{EtOH} 229 (ε 12,190); m/e 238 (m^+), 209-10 (m^+-CO), 181-2 (m^+-$2N_2$), 117, 93.

5-(1'-Naphthyloxy)-1-phenyl-1H-tetrazole[1] (2)

Substitution of 1-naphthol (2.30g, 16.5 mmole) for phenol in the preparation of (1) gave crude (2) as a violet solid. The product was crystallised from ethanol containing charcoal. Yield of white needles, m.p. 107-8° (from ethanol) 3.05g, 71%. ν_{max} 1600, 1550, 1505, 1225, 1160, 1130, 1105, 1073, 1037, 1018, 780, 765, 675 cm^{-1}; λ_{max}^{EtOH} 279 (ε 10,400), 270 (ε 9,600), 224 (ε 56,900), 289 (sh, ε 7,300) nm.

5-(p-methoxyphenoxy)-1-phenyl-1H-tetrazole[1] (3)

Substitution of p-methoxyphenol (2.04g, 16.5 mmole) for phenol in the preparation of (1) gave (3), 3.77g, 94%,

m.p. 87-87.5° (from ethanol); ν_{max} 1610, 1595, 1545, 1500, 1250, 1190, 1175, 835, 760 cm^{-1}; λ_{max}^{EtOH} 227 (ϵ 25,400), 280-3 (sh), 270.8 (sh) nm.

5-(biphenyl-4'-yloxy)-1-phenyl-1H-tetrazole[1] (4)

Reaction as for preparation of (1) but employing 4-hydroxybiphenyl (2.80g, 16.5 mmole) gave (4), 4.62g, 98%, m.p. 154-5° (from ethanol) as large white needles; ν_{max} 1595, 1545, 1500, 840, 760, 695, 690 cm^{-1}, λ_{max}^{EtOH} 250 (ϵ 26,800) nm.

Photolysis of 5-phenoxy-1-phenyl-1H-tetrazole in benzene

All photolyses of tetrazoles employed a 500W water-cooled medium pressure immersion lamp, with quartz jacket, unless otherwise stated.

The tetrazole (1) (400 mg) in redistilled pure benzene (11) was photolysed under argon 46 hours. A little yellow powder separated and the solution fluoresced bright blue. The solution was evaporated and the residue applied to silica p.l.c. plates (2, 20 x 60cm x 1mm) and eluted benzene 85-ethyl acetate 15. Six bands were apparent under u.v. light. Each product was further purified on silica p.l.c. plates, where necessary. The products isolated, allowing for recovered starting material (186 mg) were (a) biphenyl (20%), λ_{max}^{EtOH} 247.5, ν_{max} 725, 695 cm^{-1}, m.p. 68-70° (from ethanol), m/e 154 (m^+), 77 (m^+-ph), in accord with the

literature values. (b) 2-phenoxybenzimidazole (5)(36%)white needles, m.p.229-30° (from benzene-ethyl acetate) λ_{max}^{EtOH} 281, 274.5, 237(sh)nm, (ϵ 7810, 8280, 8650 respectively), ν_{max} 2700, 2600, 1660, 1635, 1600, 1535, 1500, 1260, 1190, 1160, 1010, 770, 740, 730 cm^{-1}, m/e 210(m^+), 181 (m^+-N_2H), 133 (m^+-ph), 106 (m^+-phCO). (c) 2-(O-hydroxyphenyl)benzimidazole (6)(22%), m.p. 242-4° (from benzene), white needles with a strong blue fluorescence under u.v. light. λ_{max}^{EtOH} 331.5, 317.5, 292, 286, 273.5, 263(sh), 248, 240, 234nm (ϵ 19,400, 20,900, 13,600, 11,100, 8,600, 6,300, 6,900, 11,100, 11,500) ν_{max} 3300, 1640, 1600, 1500, 1325, 1280, 1260, 845, 805, 770, 755, 745 cm^{-1}; identical with an authentic sample supplied by Dr. D. Goodgame of this department; and (d) 2-phenylbenzimidazole (7)(25%), m.p. 291-3°, white needles, λ_{max}^{EtOH} 317, 303.5, 296.5, 241.5nm (ϵ 13,100, 23,100, 20,900, 11,800) ν_{max} 2800, 1415, 750, 745 cm^{-1}; all samples were identical with authentic samples.

A blank photolysis of pure benzene (1 l) under the same conditions gave a little biphenyl (< 10 mg) and hence the yield of biphenyl must be corrected to 10-15%.

Several minor products, including an isomer of (1) and a product from reaction with solvent without loss of nitrogen (m^+ 314) were detected but not obtained pure.

2-Phenylbenzimidazole[2] (7)

Fusion of O-phenylenediamine and benzamide at 200-210° yielded a dark mass containing (7). A pure sample was obtained by chromatography on silica, eluted benzene 90-ethyl acetate 10; m.p. 288-291° (from ethyl acetate)(lit.[2] m.p.

291-293°), identical with the product of photolysis of (1) in benzene.

2-Hydroxybenzimidazole[3] (8)

Fusion of O-phenylenediamine and urea at 180° until no further ammonia was evolved gave very crude (8). The product was twice purified by extraction into 4 N sodium hydroxide solution, and precipitation with hydrochloric acid, to yield fawn plates, m.p. 311-12° (from ethanol), 35.6g, 93%; ν_{max} 3150, 2750, 1740, 1275, 1200, 1030, 740, 730, 705 cm^{-1}; λ_{max}^{EtOH} 282, 286 (sh), 227 mm.

2-Chlorobenzimidazole[1,4] (9)

2-Hydroxybenzimidazole was treated with dry hydrogen chloride in phosphorus oxychloride at reflux. The product was extracted from the residue after removal of phosphorus oxychloride with cold 4 N hydrochloric acid, and precipitated with 0.880 ammonia solution; m.p. 211-15° (decomp.), remelting at >325° (from acetone 95-water 5 with addition of charcoal), white needles, ν_{max} 3100, 2750, 2670, 1445, 1275, 1240, 1015, 990, 740 cm^{-1}. λ_{max}^{EtOH} 280.5, 274, 268(sh), 242 nm. Lit.[1,4] m.p. 212-15° (decomp).

2-Phenoxybenzimidazole[5] (5)

Potassium phenoxide and 2-chlorobenzimidazole were heated with copper bronze powder at 175° for 5 hours. The crude compound was purified by chromatography on alumina (G3). A poor yield of white needles, m.p. 227-9° (from acetone) was obtained, identical with a product of photolysis of (1) in benzene.

Photolysis of 5-phenoxy-1-phenyl-1H-tetrazole (1) in benzene under oxygen

a) The tetrazole (1) (400 mg) in pure benzene (1 l) was photolysed under the same conditions as above but under a stream of oxygen. A bright yellow solution and precipitate were obtained. The usual work-up gave the same products in similar amounts as for reaction under argon, except for a minor bright yellow polar compound, λ_{max}^{EtOH} 393, 376 nm, which could not be separated completely from 2-phenylbenzimidazole. The yield of biphenyl was not increased.

b) A similar reaction employing a quartz-jacketed low-pressure u.v. lamp gave the same products in similar amounts as in (a): biphenyl, 10-15%; 2-phenoxybenzimidazole, 35%; 2-(O-hydroxy)phenylbenzimidazole, 30%; 2-phenylbenzimidazole, 19%.

Photolysis of tetrazole (1) in cyclohexane

The tetrazole (400 mg) in pure cyclohexane (1 l) was photolysed under argon for 48 hours using a medium-pressure lamp. Work-up as before gave 2-phenoxybenzimidazole (23%) and 2-(O-hydroxyphenyl)benzimidazole (18%). No biphenyl nor 2-phenylbenzimidazole was isolated. Two other major products were not obtained pure.

Photolysis of 2-phenoxybenzimidazole (5) in benzene

2-Phenoxybenzimidazole (30 mg) was photolysed in benzene (1 l) for 22 hours under the usual conditions. A silica preparative t.l.c. plate yielded 2-(O-hydroxyphenyl) benzimidazole (ca 50%) 2-phenylbenzimidazole (ca 25%) and recovered starting material.

Photolysis of 5-(p-methoxyphenoxy)-1-phenyl-1H-tetrazole (3) in benzene

The tetrazole (400 mg) in benzene (1 l) was photolysed under argon 48 hours under the usual conditions. Work-up gave 4-methoxybiphenyl (11%) m.p. 87-89° (from ethanol), λ_{max}^{EtOH} 261; m/e 184 (m^+), 169, 141, 115; ν_{max} 1610, 1520, 1495, 1260, 1045, 840, 765, 695 cm^{-1}; and 2-phenylbenzimidazole (21%), both identical with authentic samples. The two other principal products were not investigated.

Photolysis of 5-(biphenyl-4'-yloxy)-1-phenyl-1H-tetrazole (4) in benzene

Photolysis of (4) (400 mg) in benzene (1 l) under the usual conditions gave p-terphenyl (8%) m.p. 210-212.5° (from ethanol). λ_{max}^{EtOH} 278 nm; ν_{max} 1225, 845, 770, 755 cm^{-1}; and 2-phenylbenzimidazole (7), both identical with authentic samples; other products were discarded.

Photolysis of 5-(1'-naphthyloxy)-1-phenyl-1H-tetrazole in benzene

An identical procedure employing (2) gave 1-phenylnaphthalene, (m^+ 204) although not obtained completely pure, and 2-phenylbenzimidazole (17%).

2-Phenylmercaptobenzimidazole[5] (10)

2-Chlorobenzimidazole (3.05g, 20 mmole), thiophenol (2.42g, 22 mmole), hydrated lithium iodide (0.50g, 3.3 mmole) and anhydrous potassium carbonate (4.14g, 30 mmole) were refluxed in dry acetone 96 hours and filtered. The filtrate was evaporated, dissolved in dichloromethane, washed with water, dried over sodium sulphate and evaporated. Yield of long white needles, 3.55g , (78%) m.p. 203-204.5 (from acetone 95-water 5). (lit.[6] m.p. 198-9°) λ_{max}^{EtOH} 292, 285.5, 242 nm. m/e 226 (m^+), 225, 167, 150 (m^+-ph), 122 (ph5CH=), 113, 90, 77. ν_{max} 2750, 1515, 1420, 1355, 1275, 1245, 760, 755 cm^{-1}.

Photolysis of 2-phenylmercaptobenzimidazole (10) in benzene

Photolysis of (10) (400 mg) in benzene (1 l) gave much (55%) unreacted starting material, a yellow insoluble solid and a yellow solution containing thiophenol (odour), from which was obtained 2-phenylbenzimidazole (7) (22%) and a complex mixture of yellow non-polar sulphides and/or disulphides. The photo-fries product (11) was not detected.

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