STUDIES ON THE SYNTHESIS OF IONONES, IRONES AND RELATED COMPOUNDS

THESIS SUBMITTED TO
THE COCHIN UNIVERSITY OF SCIENCE AND TECHNOLOGY
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
OF THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE FACULTY OF SCIENCE

By

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SEPTEMBER 1992

C E R T I F I C A T E

Certified that this thesis is based on the work done by ***Smt. V.S. Eswari*** *under my guidance in the Department of Applied Chemistry, Cochin University of Science and Technology and no part of this has been presented by her for any other degree.*

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Kochi - 682 022,
29th September 1992.

D E C L A R A T I O N

Certified that the work presented in this thesis is based on the original work done by me under the guidance of ***Dr. Paul A. Vatakencherry,*** *former Professor & Head, Department of Applied Chemistry, Cochin University of Science and Technology and has not been included in any other thesis submitted for the award of any degree.*

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Kochi - 682 022,
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C O N T E N T S

A B S T R A C T

A group of compounds known as ionones and irones possessing green violet odourare widely used in perfumery and flavour. The synthesis of these compounds produces great challenge to organic chemists. In the present work different new approaches for the synthesis of these compounds and conversion of ionones to irones are investigated.

In the disconnection approach for their synthesis ionones and irones are disconnected into cyclic and linear units. Different methods for the synthesis of these synthons are described by using citral – the main component of naturally availabale lemongrass oil and some easily available petrochemicals.

A number of methods are employed for the synthesis of C_{10} cyclic unit - β-cyclocitral in the present study starting from cyclohexanone by using Corey-Chaykovsky reaction, Wittig reaction and Glycidic ester synthesis etc. It was also synthesised from citral using a new route.

A simple approach for the synthesis of C_5 (1-Bromo Pent-2-en-4-one) and C_9 (2,3-dimethyl-hept-2-en-6-one)

intermediates from commercially available 2-acetyl butyrolactone and cyclopentanone is also described. The coversions of methyl heptenone to the C_9 intermediate through allylic functionalisation, followed by 1,4 adddition etc. or by reaction like epoxidation followed by epoxide opening etc. are also demonstrated.

The intermediate C_9 and C_5 units are utilised for the synthesis of C_{14} linear interemediate (Pseudoirone) by using various coupling reactions. The cyclisation of C_{13} (Pseudoionone) and C_{14} intermediates gave corresponsding α, β and γ - isomers of ionones and irones respectively.

The conversion of ionones to irones could be achieved only in the case of α-ionone since β and γ -isomers get rearranged in the intermediate steps.

A new method was developed for the synthesis of the isomeric C_{13} compound β -Damascone. This was achieved by using recently developed coupling reaction using cyclocitral and allyl bromide in the presence of Zn/DMF.

Thus new approaches have been developed for the synthesis of ionones, irones and β -Damascone, using citral and commercially available chemicals, employing recently developed reactions.

CHAPTER I

INTRODUCTION

INTRODUCTION

1.1. INTRODUCTION

Perfumes contain a wide range of compounds belonging to a variety of fragrance families. In particular, rose, jasmine and violet have long been appreciated and utilised in perfumery. Because of the impossibility of obtaining violet fragrance from the flower itself and because of the extremely high price of oil of violet, manufacture of compounds possessing odour related to the fragrance of this flower began. A group of compounds known as ionones and irones possessing green violet odours are used in perfumery and flavour. In nature α-and β-ionones occur in small quantities in the flavour components of most fruits and in the relatively large quantities in berry type fruits. Large amounts of ionones and irones are consumed annually by perfumery, soap and cosmetic industries.

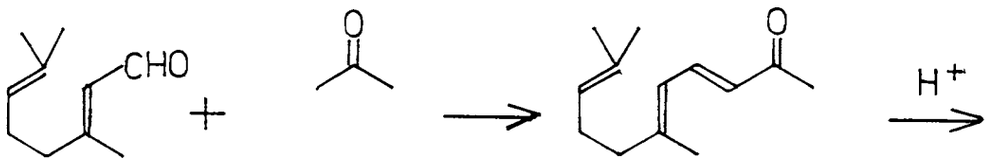
In general the incorporation of ionone in fragrance formulations imparts a pleasing sweetness which adds depth and warmth to the creation. In addition to this, the manufacture of synthetic Vitamin A has also created a strong demand for large quantities of β-ionone as intermediates. Apart from the use of violet perfumes, the ionones are valuable ingredients of artificial lily-of-the valley, tuberose, tea-rose, jasmine and of almost all fancy perfume compositions.

1.2 HISTORY and DISCOVERY

It is no wonder that, nearly a hundred years ago the organic chemist recognised the value of the violet fragrance in perfumery. A range of compounds known as ionones and irones were developed and used in large quantities. Certain acetylinic esters were also found to possess violet odour that could be used in compounding violet type fragrances.

The discovery of ionones constitutes one of the most fascinating chapters in the history of aroma chemicals. Around 1893, Tiemann investigated the compounds responsible for the fragrance of violet flowers. Oil from violet flowers was extremely expensive hence he decided to study the Orris flowers, which have somewhat similar fragrance with the assumption that the fragrance of both flowers must be due to the same chemical compound. Orris root oil contains a ketone usually to the extent of 70-80% which contributes to the characteristic aroma. Tiemann and Kruger[1] isolated this ketone and subjected it to elemental analysis and the formula found to be $C_{13}H_{20}O$. Later study proved that this was incorrect and the true formula was established to be $C_{14}H_{22}O$[2]. After the systematic study of this ketone, Tiemann and coworkers found out the structure and named it irone.

For the investigation of the exact structure of ionones Tiemann proceeded to examine by oxidative degradation experiments and finally proved it by synthesis. They reacted citral with acetone in the presence of $Ba(OH)_2$ by shaking it for several days. The unreacted citral was removed by steam distillation and the condensation product obtained was cylised by treatment with dil. H_2SO_4 in the presence of glycerol.



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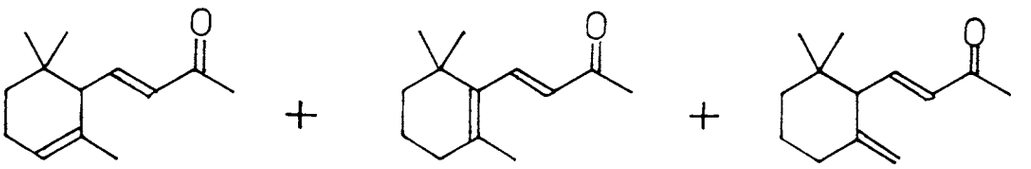
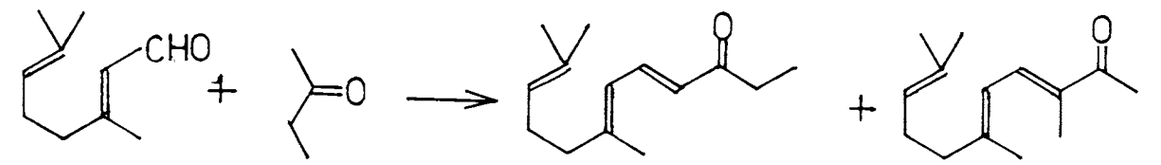


3 4 5

In nature ionones is found in raspberry, in the distillate from flowers of Boronia megatisma Nees and in few of the essencess. The odour of ionones obtained was reported to be similar to that of irone especially when highly diluted. Differences in odour and properties were attributed to isomerism resulting from the difference in the positions of double bond. Years after the discovery of ionones, it was realised that cyclisation of pseudoionone leads mainly to the formation of three isomers α, β and γ. Tiemann[3,4] investigated the separation techniques of three individual isomers by

preparing carbazones, bisulphite adduct etc. and later it was proved that these three isomers are separated by column chromatography[5].

Condensation of citral with ethyl methyl ketone and subsequent cyclisation giving methyl ionones. Six isomers are obtained as shown. The increase in the number of isomers from 3 to 6 results from the reaction of the aldehyde group of citral with either the methyl or methylene group of the ethylmethyl ketone.



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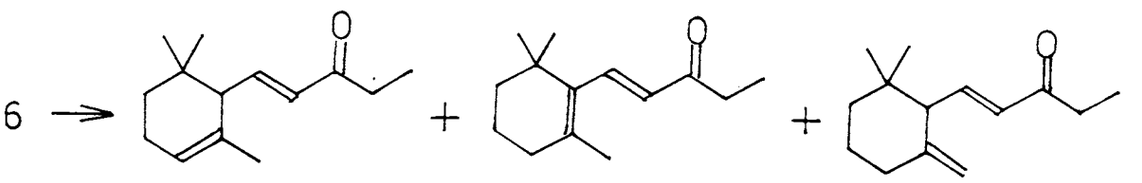

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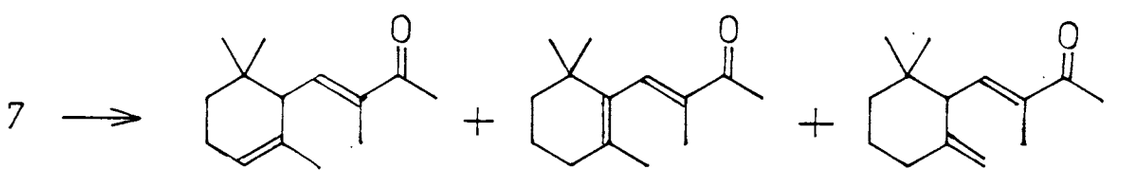
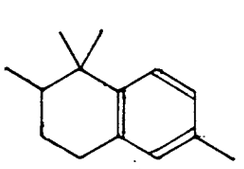


11 12 13

A study of the isomers of methyl ionones was made by Koster[6] who prepared α-cyclocitral and condensed it with methyl ethyl ketone in the presence of alkalies and also prepared methyl pseudoionone by condensing citral with ethyl methyl ketone and then cyclising it with acid.

Irone or 5-methyl ionone differs methyl ionone in that the methyl group is in the ring rater than in the side chain. Ruzicka[7] and his co-workers first showed that the hydrocarbon irene 14 is obtained on reduction of irone with red phosphorous and I_2. This is confirmed by synthesis. Further evidence from ozonolysis led Ruzicka to suggest a new structure 15 for irone, but a study of the degradation of tetrahydro irone led the same author to correct the structure for this compound, as 16. The same compound 16 proposed for tetrahydro irone was put forward by Naves et al in 1947[8], who compared this product with synthetic tetrahydro 5-methyl ionone.



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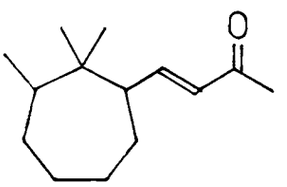

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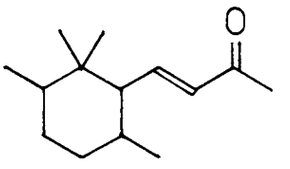

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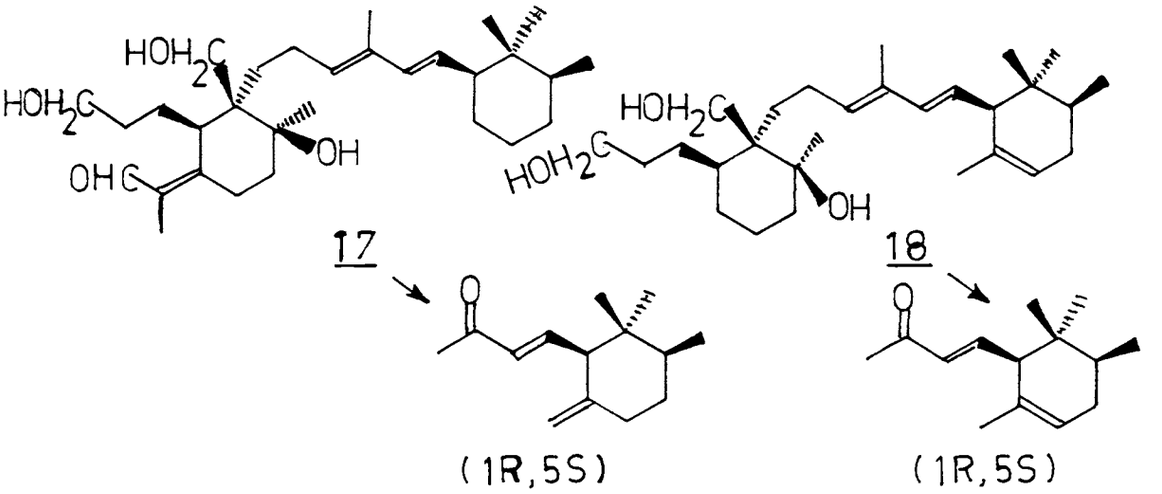
One of the two ethylinic bonds in irone is in conjugation with the carbonyl group[9]. According to the

position of the double bond in the ring it also existed in three isomers α , β and γ , like the ionones. It is a remarkable substance possessing a powerful and most pleasant violet odour, much superior to any of the methyl ionones[10].

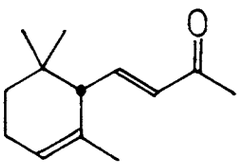
Natural irones are known to occur in enantiomeric forms in Iris oils of different origin. They are formed by oxidative degradation of the cycloiridals the C_{31} triterpenoids, found in rhizomes of various Iris species. The absolute configuation of iridals from different varieties were determined by ozonolysis of the triterpenoids and comparison of their degradation products with authentic samples of known configuration[11,12].



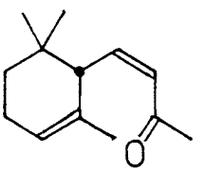
Stereochemistry

Ionone having one optically active carbon atom can exist d(+) and l (-) forms. In addition, having an exocyclic double bond, it can exist in cis and trans forms giving four α -ionones. β -ionone has no chirality so it can exist only in the cis and trans forms. γ -ionone, like α-ionone, has an

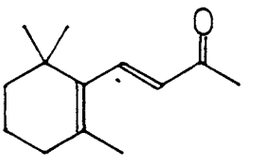
optically active carbon atom, it has a double bond in the side chain and can therefore exist in four forms. These make a total of 10 different isomers[13] as shown below.



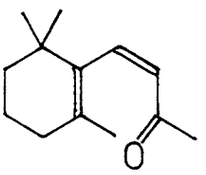
1. d-trans-α
2. l-trans-α



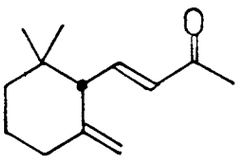
3. d-cis-α
4. l-cis-α



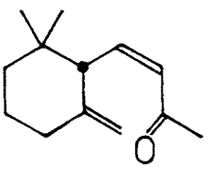
5. trans-β



6. cis-β

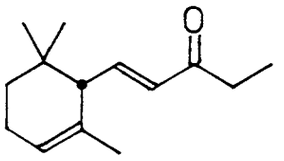


7. d-trans-γ
8. l-trans-γ

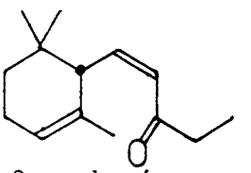


9. d-cis-γ
10. l-cis-γ

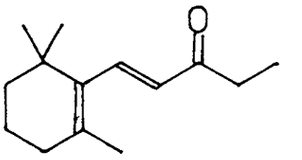
Condensation of methyl ethyl ketone and citral followed by cyclisation, leads to the formation of 20- different isomers of methyl ionone.



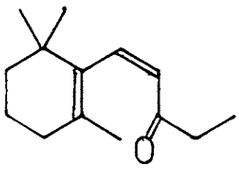
1. d-trans-α-n-methyl
2. l-trans-α-n-methyl



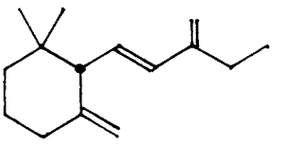
3. d-cis-α-n-methyl
4. l-cis-α n-methyl



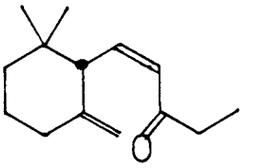
5. trans-β-n



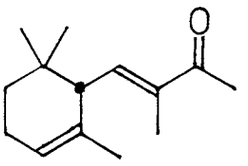
1. cis-β-n-methyl



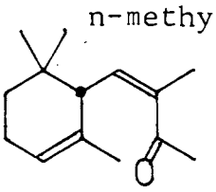
7. d-trans-γ-n-methyl
8. l-trans-γ-n-methyl



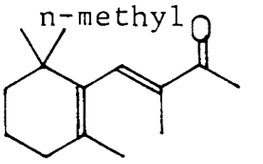
9. d-cis-n-methyl
10. l-cis-n-methyl



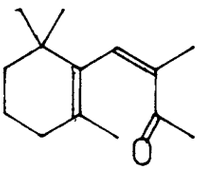
11. d-trans-α-isomer
12. l-trans-α-isomethyl



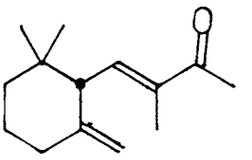
13. d-cis-α-isomer
14. l-cis-α-isomethyl



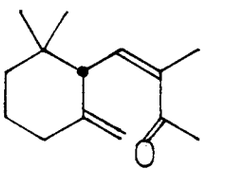
15. β-trans iso-methyl



16. β-cis-isomehtyl

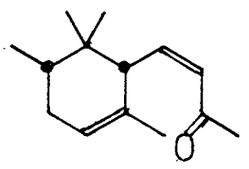


17. d-trans-γ-isomethyl
18. l-trans-γ-isomethyl



19. d-cis-γ-isomethyl
20. l-cis-γ-isomethyl

Because irone has two asymmetric c-atom in its α-and γ-isomers and one asymmetric c-atom in the β-isomer, it can theoretically exist in 20 isomers, α and γ having 16 and β having 4 optically active forms[14]. The ten geometrical isomers of irone can be represented as shown below.



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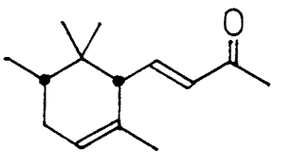

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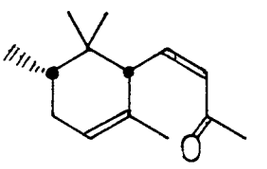

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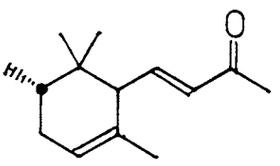

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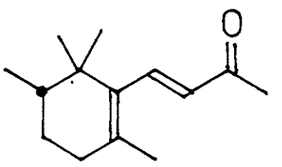

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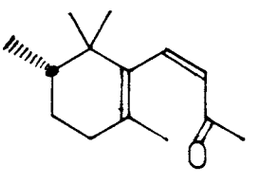

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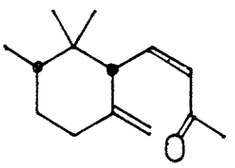

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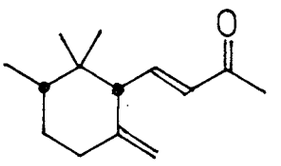

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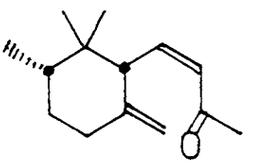

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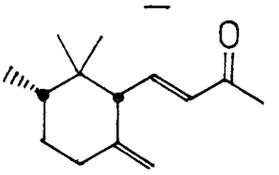


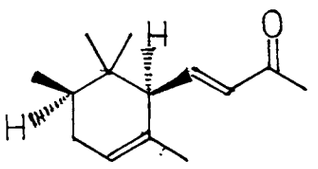
10

Their names are

1. α-irone, cis (1,5) - cis (1_1,1_2) α-irone
2. α-neoirone, cis (1,5) -trans (1_1, 1_2) α-irone
3. α-iso irone, trans (1,5) - cis (1_1, 1_2) α-irone
4. α-neo iso irone, trans (1,5)- trans (1_1, 1_2) α-irone
5. β-neo irone, trans (1_1, 1_2) β-irone
6. β-irone, cis (1_1,1_2)-β-irone
7. γ-irone, cis (1,5) cis (1_1, 1_2) γ-irone
8. γ-neo irone, cis (1,5)-trans (1_1, 1_2) γ-irone
9. γ-isoirone, trans (1,5)-cis (1_1, 1_2) γ-irone
10. γ-neo osoirone, trans, (1,5) - trans (1_1, 1_2) γ-irone

Literature indicates the presence of six isomers (1,2,3,4,6 and 8) in Orris root oil, some of which have been isolated in optically active form. It is claimed that natural Orris oil consists largely of α-irone and neo-iso-α-irone. The odours of neo-γ-irone and neo-α- irone are of lesser intensity, β-irone is reminiscent of β-ionone. Neo-iso α-irone is violet like while iso-α-irone is cedar woody.

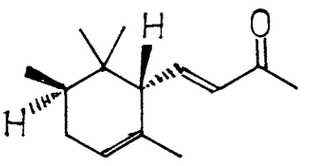
In 1971, approximately 80 years after the discovery of irones, Rautenstrach and Ohloff[15] established their absolute stereochemistry by a chemical correlation with (-) camphor, showing that all the isomers had the 5R-configuration.



(1S, 5R)(+) cis α-irone

+109°

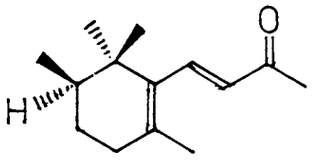
19



(-) (1R 5R) - trans-α-irone

-120°

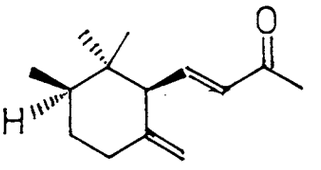
20



(+) 5R - β - irone

+59°

21



(+) (1S 5R) cis γ-irone

22

(+) cis- γ -irone 22 was converted into (+)-cis- α-irone 19, (-) trans α-irone 20 and (+) β-irone 21 which therefore also have the 5R-configuration. 1S-configuration of (+) cis α-irone 19 and (+) trans α-irone were determined by comparison of the C.D with that of R-α - ionones. The 1S-configuration of (+) cis-γ-irone was also established by chemical correlation with (+) cis-α -irone. From the CD spectra, it was proved that the preferred conformation of cis-α-irones and trans -

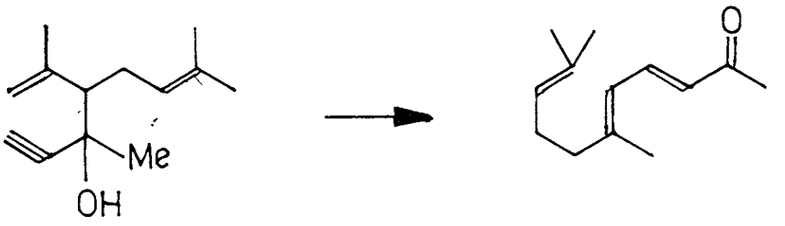
α-irones and α-ionones in solution are half chair with the side chain pseudoaxial[16]. Again PMR and ^{13}C NMR also proved that the H in the C(5) is axial and C(5)-CH_3 must be equatorial and the side chain pseudoaxial from a sample furnished by K.Mori[17], C. Rautenstrach [18] et al identified a trace amount of missing trans γ-irone by GCMS analysis.

1.4. Synthesis of ionones

Almost all synthesis of ionones involve two fundamental steps. 1, The preparation of pseudoionone and 2, its cyclisation to the ionones. A number of synthesis of pseudoionone with condensation of citral and acetone can be found in the literature[19,20].

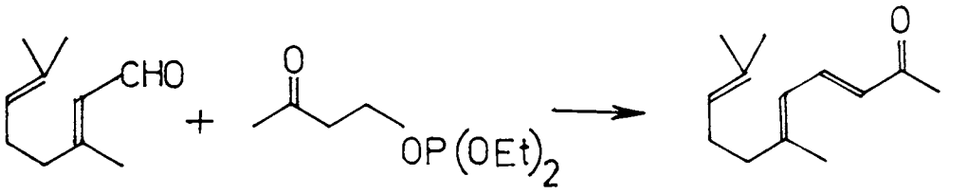
The classical method for the synthesis of pseudoionone is the condensation of citral with acetone. Some modifications of the first method is effected by changing the catalyst bases like sodium phenoxide, sodium ethoxide, glycerine[21] mediated reactions and finally by using basic alumina catalyst, 100% pure pseudoionones are reported[22]. Later total synthesis was also reported through linalool and dehydrolinalool as intermediates followed by Carroll and diketene addition reactions[23,24].

In some recently reported synthesis,Y.Fugita[25] et al brought about a halogen catalysed acetylinic oxy- cope rearrangement of enynols by using N-methyl 2-pyrolidone.



23 2

In 1981, Onishi and Takashi[26] adopted a solvent assisted oxy-cope rearrangement of the above starting material (23). By using Wittig -Horner reaction, V.Jean and R.Nantes[27] synthesized pseudoionone from citral.



1 24 2

Fugita et al[28] brought about an isomerisation of 2,5 dienones to 2,4 dienones by heating N-methyl pyrolidone and 2,5 dienones in the ratio 1:3 volume with Nickel acetyl acetone as catalyst.

Onishi and Takashi[26] prepared pseudoionone by the thermal rearrangement of a product obtained from mesityl oxide and prenyl chloride, in con. NaOH containing stearyl trimethyl ammonium chloride.

Cyclisation of Pseudoionone

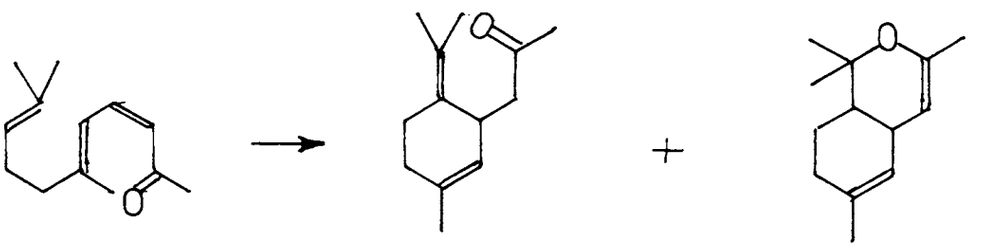
The second step in the synthesis of ionones involves the cyclisation of the pseudoionones. It has long been known that sulphuric acid favours the formation of β-ionone while phosphoric acd and other acids usually gives a preponderance of α-isomer[29]. The literature contains numerous references to the optimum conditions for screening the maximum yield of α or β -ionones[30]. The mechanism of cyclisation has been investigated[31] although more attention has been given to the practical aspects of the problem.

Using 100% H_2SO_4, the cyclisation of pseudoionones was studied over a range of temperatures[32]. At 60°C only α -ionones is formed, at -40°C either may predominate, depending upon the duration of the reaction. At higher temperatures proportion of β -isomer increases and at 10°C the product is almost all β -ionone. It should be noted that isomerisation of α -ionone to the β - form is merely the change from the unconjugated to the conjugated system. Obviously the latter is the more stable form.

Cyclisation of pseudoionone using a mixture of H_2SO_4 and acetic acid was studied by Naves and Ardizio[32]. It was found that the β -ionone proportion increased with a rise in percentage of H_2SO_4. It appears that the cyclisation product is not dependent on whether the starting material is cis, trans or a mixture of pseudoionones, since all gave the same product under

identical cyclisation procedures[31].

Cyclisation can be carried out using BF_3 at room temperature[33]. After a detailed study of problems of cyclisation, Náves and his co-workers[34] came to the conclusion that the cyclisation reagent determines the nature of the product. Thus sulphuric, phosphoric or formic acids gives β , and α -ionones. Lewis acids such as aluminium , ferric or $ZnCl_2$ give not only the above but also menthanic cyclisation products (25,26).



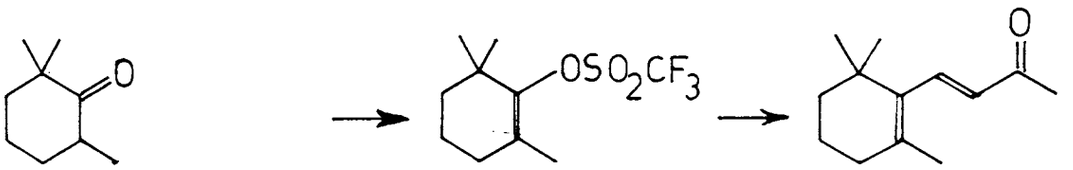
25 26

BF_3 gives mainly the three ionones. Stannic chloride and HCl do not give cyclisation products and titanic chloride gives a chlorinated product. Later it was found that p-toluene sulphonic acid also cyclises pseudoionones with greater amount of α -ionones within one hour at room temperature[35]. Then acidic alumina catalyses this reaction and the product formed is also found to be a mixture α -and β -ionones.

Ionones also have been obtained by condensation of cyclocitral with acetone or methyl ethyl ketone[36] since cyclocitral is prepared with some difficulty, however, this approach to ionone has seldom been investigated.

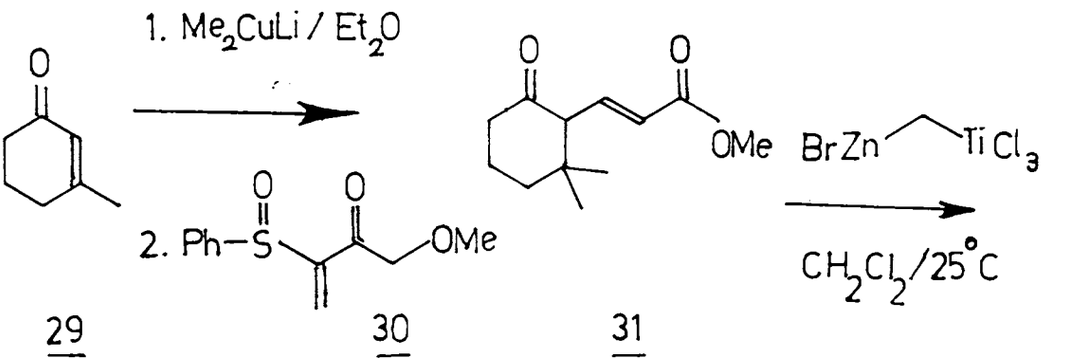
Commercial ionones consists mainly of α -and β -isomers. The methyl ionones contain varying proportions of four isomers.It has been demonstrated that these products have some quantities of γ -isomers[37]. It appears that the γ -isomers isomerize to the α - or β -form during the cyclisation reaction[38].

There is a report of synthesis of β -ionone without going through the pseudoionone intermediate route. 2,6,6 trimethyl cyclohexanone (27) was converted into its enol sulphonate (28) by treating 27 with N-phenyl trifluoromethane sulophonamide at 0° in THF. A palladium phosphine complex mediated condensation of 28 with methyl vinyl ketone in DMF at 75°C afforded β-ionone[39].



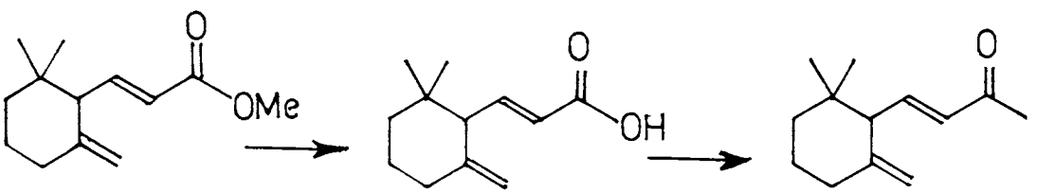
27 28 3

Another reported synthesis of α -ionone from 3-methyl cyclohex-2-enone (29) isshown below[40]. 29 on 1,4 addition with dimethyl copper lithium followed Michael addition with α -sulphenyl reagent. 30, gave 31 which on reaction with the complex reagent 32 gave ester 33.



29 30 31

Hydrolysis of 33 followed by treatment with MeLi gave γ -ionone.



33 34 5

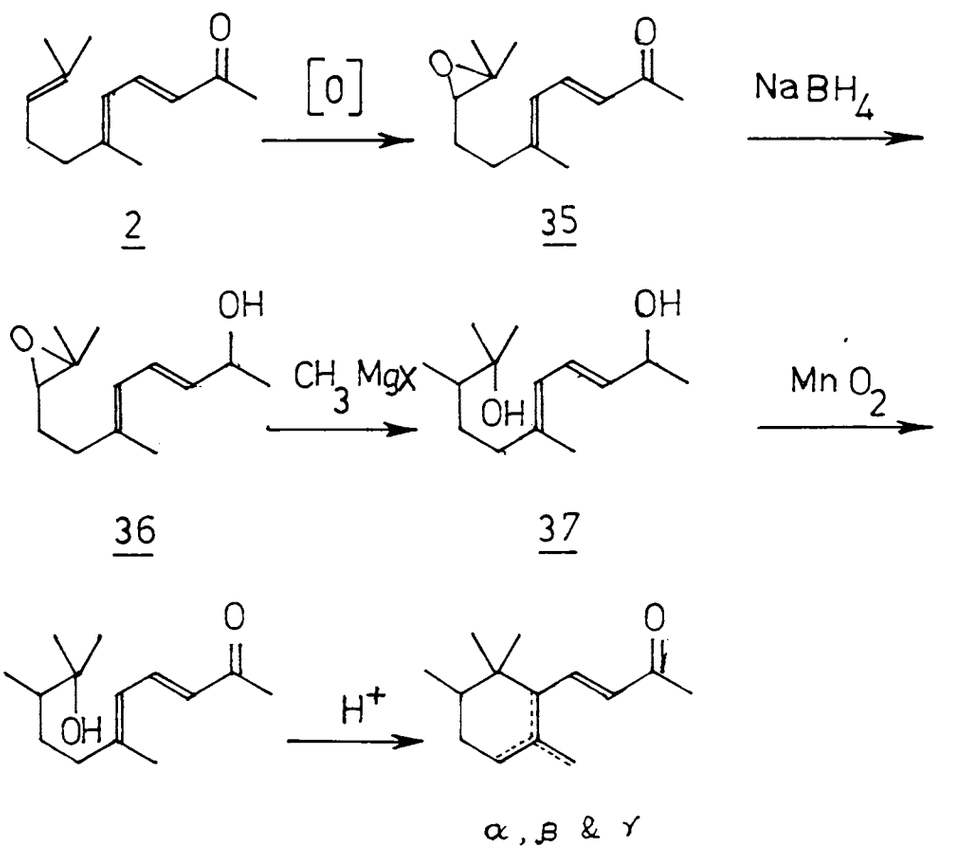
The above scheme was also used for synthesising cis and trans- γ-irone using 4-methyl derivative of 29.

1.6 Synthesis of irones

The chemistry of irones is in some respects similar to that of ionones and one can utilise the vast amount of information available on ionones when dealing with irones.

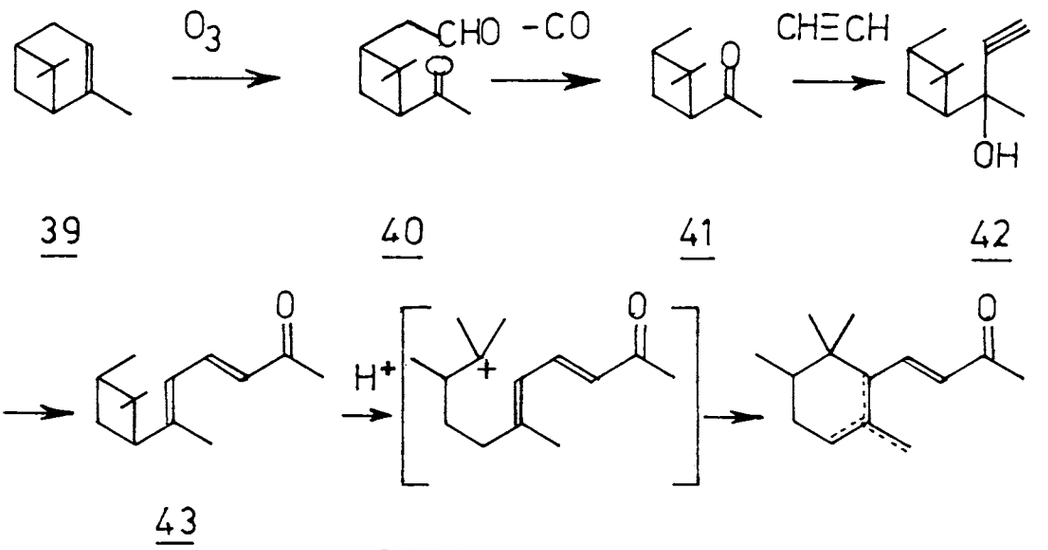
Several attempts to synthesis these compounds involved the acid catalysed cyclisation of 9-methyl pseudoionone; derived from 5,6 dimethyl-hept-5-en-2-one[41].

One of the methods of synthesis from pseudoironeis as shown in scheme -I[42]. Friedel-Craft type of methylation at the double bond of geraniol, citral and pseudoionone failed[43].



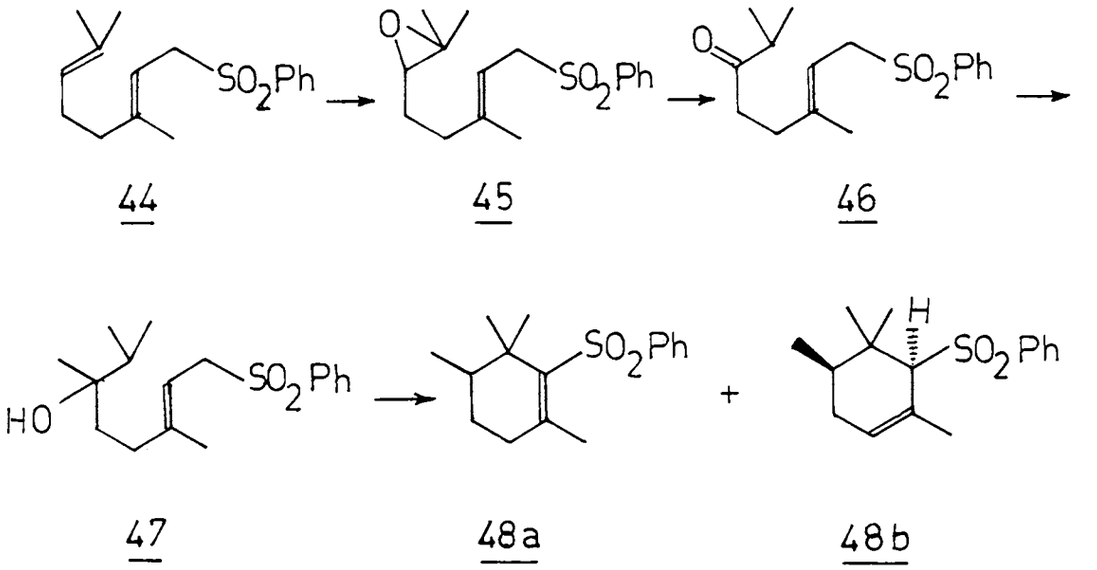
SCHEME I

Eschinazi[44] accomplished and elegant transformation, of α -pinene to 2-(2,2,3-trimethyl cyclobutyl)-hepta-2,4-dien-6-one(43), which was subjected to ring opening and simultaneous cyclisation resulting in the formation of a mixture of irones as showin in scheme - II.



SCHEME II

Introduction of a methyl group at the C-5 position of geraniol and its derivatives has also been examined. In 1980, S. Torri and et al[45] reported a stereoselective synthesis of irones of β, γ-cis and γ-trans isomers through cyclic sulphone intermediates (48a, 48b) which are prepared by the classical method as shown in scheme III. These sulphone intermediates were extended by C_3 unit by treatment with BuLi in THF at -50°C followed by propyleneoxide to give the corresponding alcohol (49). (49) on oxidation with PDC and introduction of double bond by reductive elimination of sulphonyl group with sodium methoxide in t-butanol gave the corresponding irone.



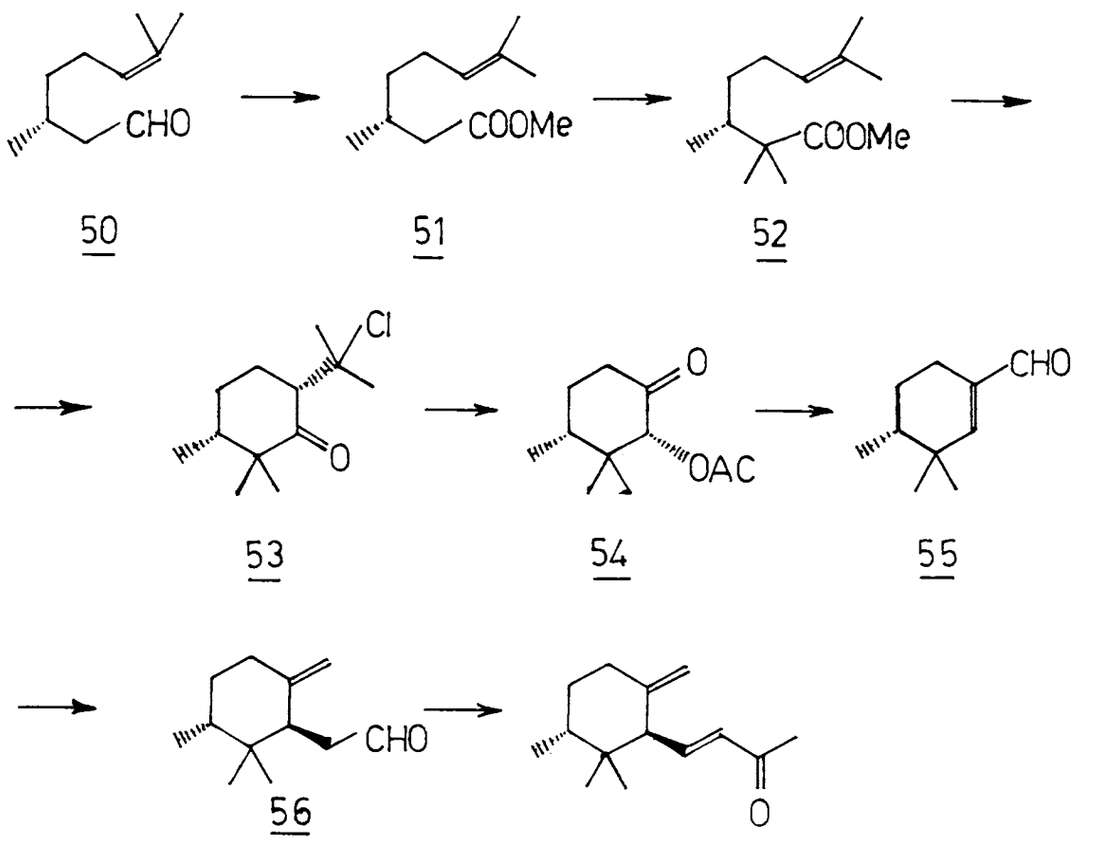
44 45 46

47 48a 48b

SCHEME III

Another new development in the synthesis of Natural enantiomers of irones from (+) citronellal was established by Yoshikoshi and et al[46]. (+) Methyl citronellate (51) obtained from(+) citronellal was methylated stepwise to give methyl 2,2,3,7-tetramethyl Oct-6-enoate(52). After hydrolysis of ester (52),resulting acid was converted into the corresponding acyl chloride, which was then cyclised by means of tin IV chloride to give 2,2,3-trimethyl 6(1-chloro-1-methyl-ethyl)-cyclohexanone(53). The cyclohexanone (53) was dehydrochlorinated, reduced, acetylated and then ozonised to give 2-acetoxy-3,3,4-trime -thyl cyclohexanone (54). The Wittig reaction of the lactone (54) with methoxy methylenetriphenyl phosphorane

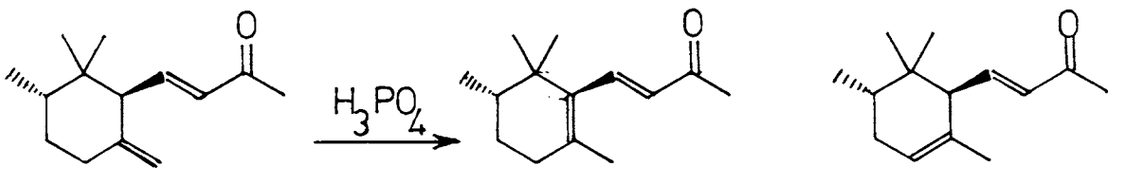
followed by hydrolysis and elimination of acetic acid provided 3,3,4-trimethyl cyclohexene-1-carbaldehyde (55). The vinyl ether of an allylic alcohol obtained by reduction of the aldehyde(55) was thermolysed to give the key intermediate 1-(2,2,3- trimethyl-6-methylene cyclohexyl) acetaldehyde (56) stereoselectively.



50 51 52 53 54 55 56

SCHEME IV

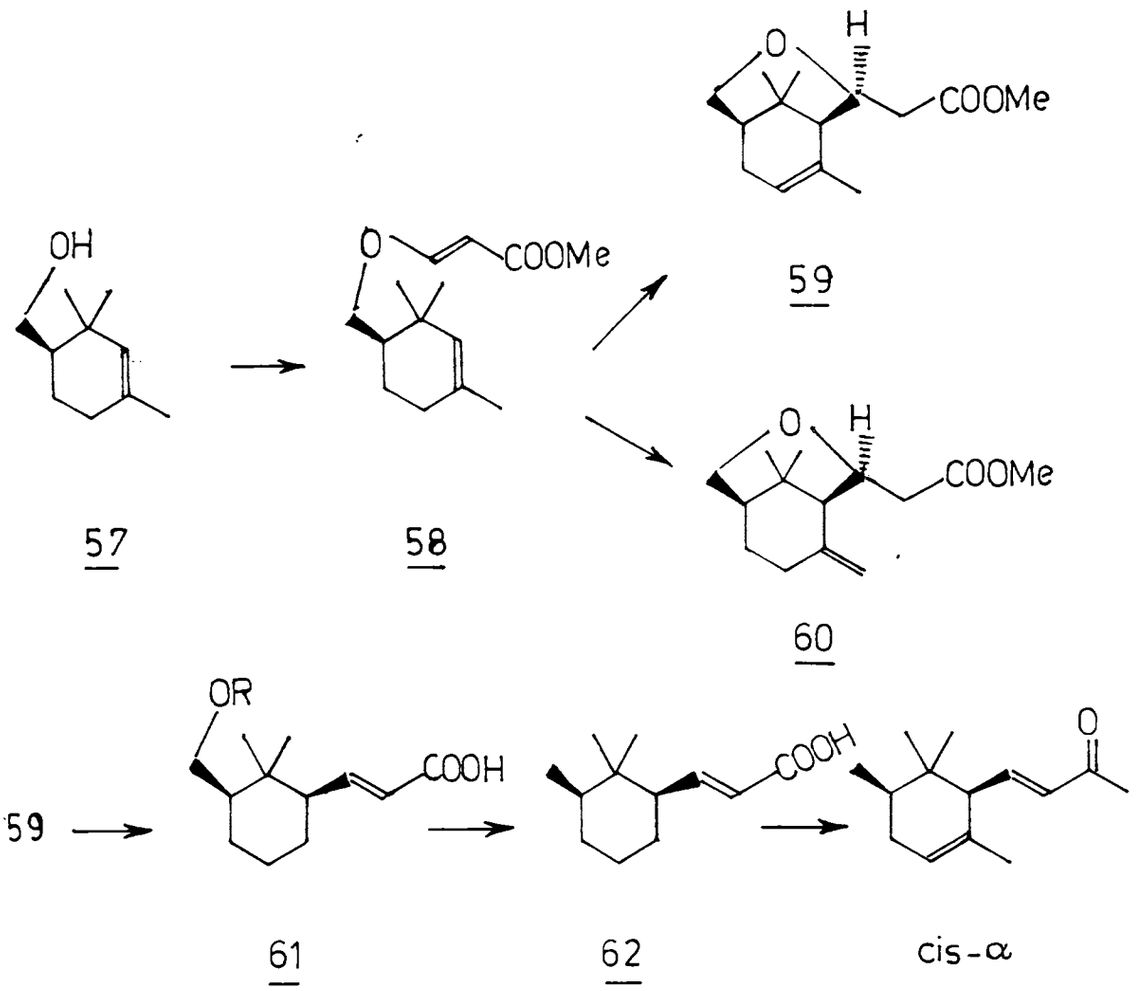
Elongation of the side-chain (56) afforded (+) trans-γ-irone as the major product. Treatment of this irone with phosphoric acid yielded(-) trans α-irone and trans β-irone in the ratio of 93:7.



(+) β (−) α (−)

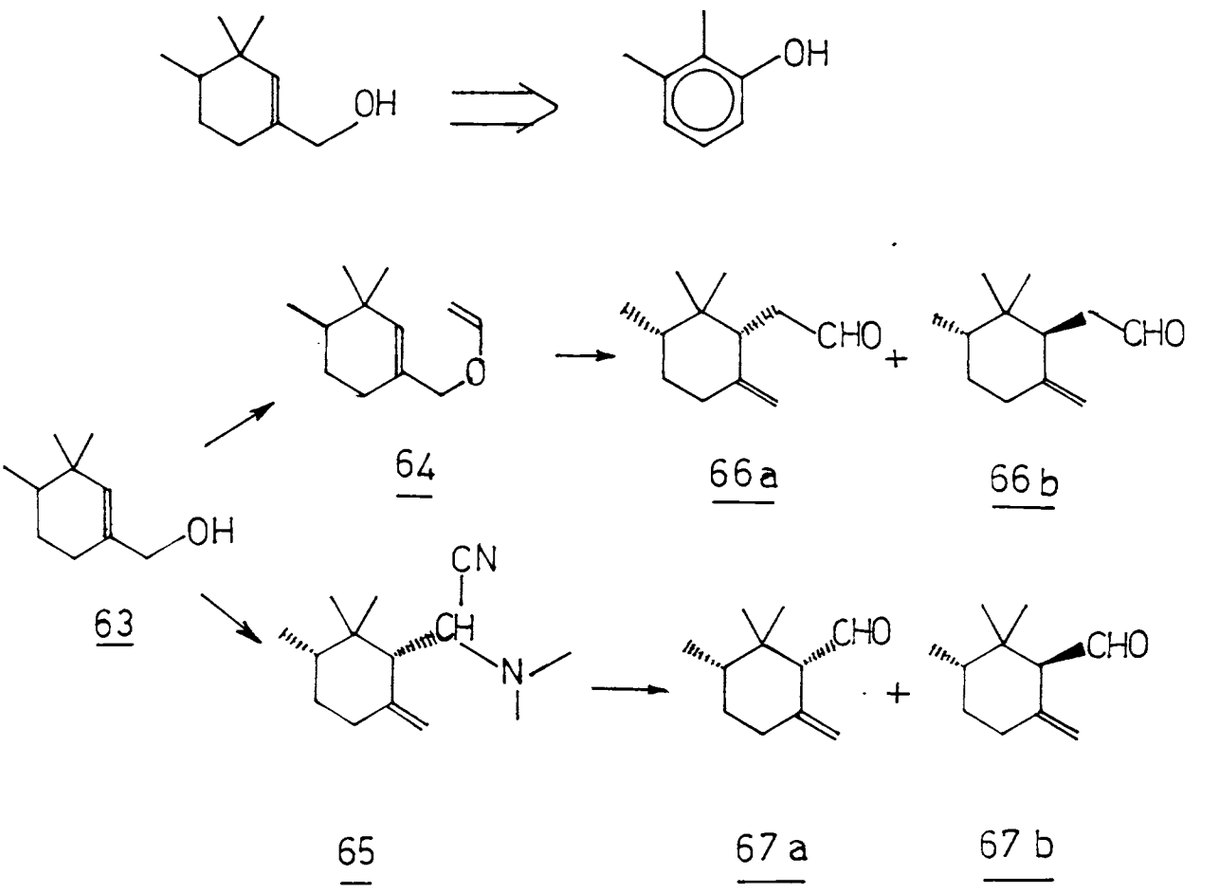
It is worthy to note that no cis α-irone was found in the isomerisation product of γ-irone. A similar observation was made by Rautenstruch and Ohloff[47], who observed no formation of trans γ-irone from cis-γ-irone on treatment with acid. These facts obviously demonstrated that the α-and β-irones were kinetic products of γ-irones, in the acid isomerisation . Isomerisation of trans-α-irone with base to cis α-and β-irones had been also reported.

Stereoselective synthesis of ± cis α-irone[48] and ± cis-γ-irone[49] were also reported by Nussbaumer and G. Frøster by using 2,2,4-trimethyl cyclohex-2-ene-1-yl methanol57.



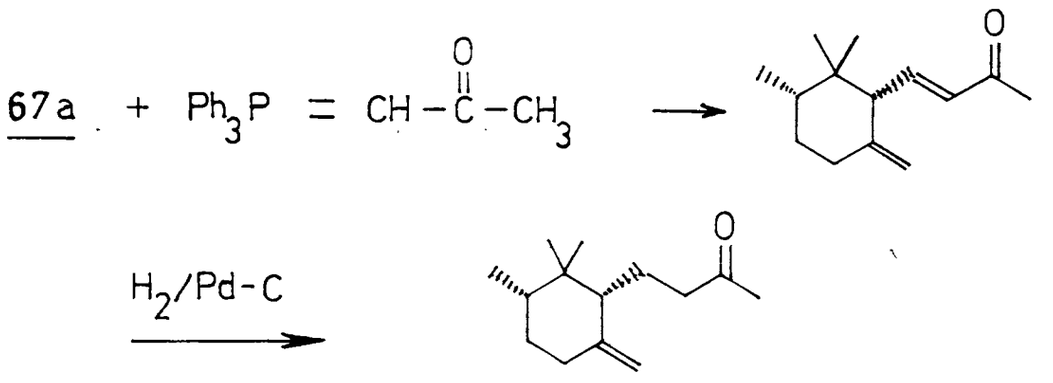
Addition of 57 to methyl propiolate in the presence of N-methyl morpholine afforded the β -alkoxy acrylate 58 which on exposure to catalytic amount of acid gave 59. But 58 on refluxing with toluene gave α—isomer of the cyclic ester60. The cleavage of tetrahydro pyran moiety and then reducing hydroxy methyl group via the corresponding mesylate, which was then treated with Zn/NaI in refluxing DME and finally with MeLi afforded (±) cis α-irone and (±) cis- γ -irone from 59 and 60.

The essentil oil of Irris rhizome is a very important perfume with its violet like scent and it is well known that its major fragrant constituent is cis- γ -irone. Cis dihydro γ -irone is another fragrant component found in oxidative degradation products of C_{31} triterpenoids in this Irris-rhisome[15b]. These compounds responsible for violet fragrance are synthesized via 3,3 Claisen or 2,3 sigmatropic rearrangement of 1-hydroxymethyl-3,3,4-trimethyl-1-cyclohexene derivative starting from 63[50].



Mesylation of 63 with MsCl in Et_3N, subsequent treatment with N,N-dimethyl aminoacetonitrile in presence of K_2CO_3 and the successive hydrolysis with aq. $AgNO_3$ afforded a mixture of 67 a and 67 b through 2,3 sigmatropic rearrangement, Stella[51] synthesised γ'-cyclocitral by employing 2,3 sigmatropic rearrangement, starting from 1-bromomethyl-3,3-dimethyl 1-cyclohexene and N,N dimethyl amino acetate 67a on Wittig reaction give cis γ'-irone which on reduction with H_2/Pd-C resulted in the formation of dihydro γ'-irone.

Claisen rearrangement was also examined under various conditions. The Claisen rearrangement of the ethyl vinyl ether of the allylic alcohol 63 in presence of pivalic acid was carried out at 5 hrs. resulting in the formation of the cis and trans aldehydes 66a and 66b. The aldehyde 66a on cyanohydration followed by dehydration and treatment of CH_3-Li gave ± cis-γ'-irone, which on again reduction gave the corresponding dihydro derivative.



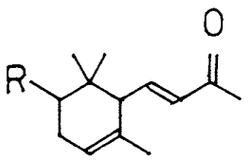
CHAPTER II

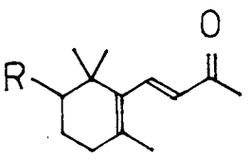
STATEMENT OF THE PROBLEM

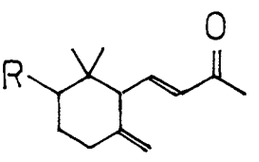
2.1. INTRODUCTION

The class of compounds known as ionones and methylionones, which possess green violet odour are widely used in perfume and flavour industries. A structurally similar higher homologue of ionones known as irones do possess these qualities and are widely used in perfume and flavour industries. The high demand of ionones and irones in perfumery, soap and cosmetic industries and the importance of β-ionone in Vitamin A manufacture provided an impetus for the development of new methods for the synthesis of these important classes of compounds. The structural similarity as well as the synthetic challenges involving stereochemistry had made irones an important target for synthetic chemists.

In this context, a new synthesis or an improvement over the existing methods for the synthesis of these compounds is of more than academic interests. The present work is the study of synthesis of ionones and irones using easily available starting materials by shortest route. Ionones and irones exist α , β and γ-isomers according to the double bond position. Irones are called 5-methyl ionones,isomeric with methyl ionones.



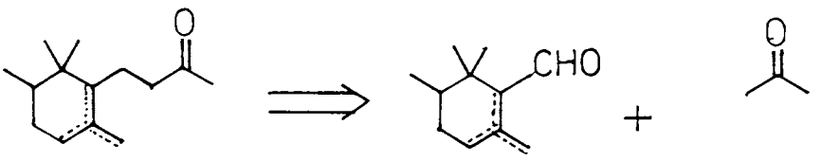




1 R= H, α-ionone 3 R= H, β-ionone 5 R= H, γ

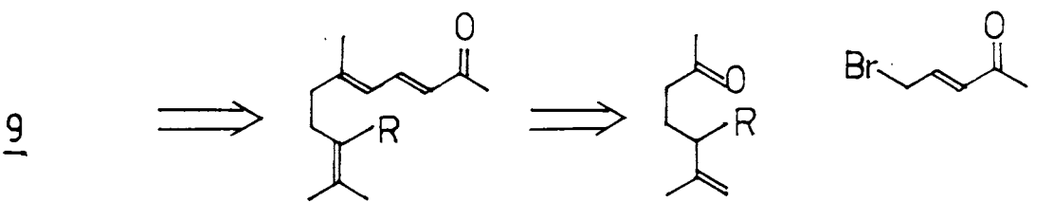
2 R= CH_3, α- irone 4 R= CH_3 β-irone 6 R= CH_3, γ

According to retrosynthetic approach ionones and irones are disconnected into cyclic and linear units. Different methods for the synthesis of these synthons will be described by using either natural products obtained from essential oils or commercially available chemicals like cyclohexanone, cyclopentanone, 2-accetyl butyrolactone etc.



9 10 R= H

11 R= CH_3



12 R= H 14 R= H 16

13 R= CH_3 15 R= CH_3

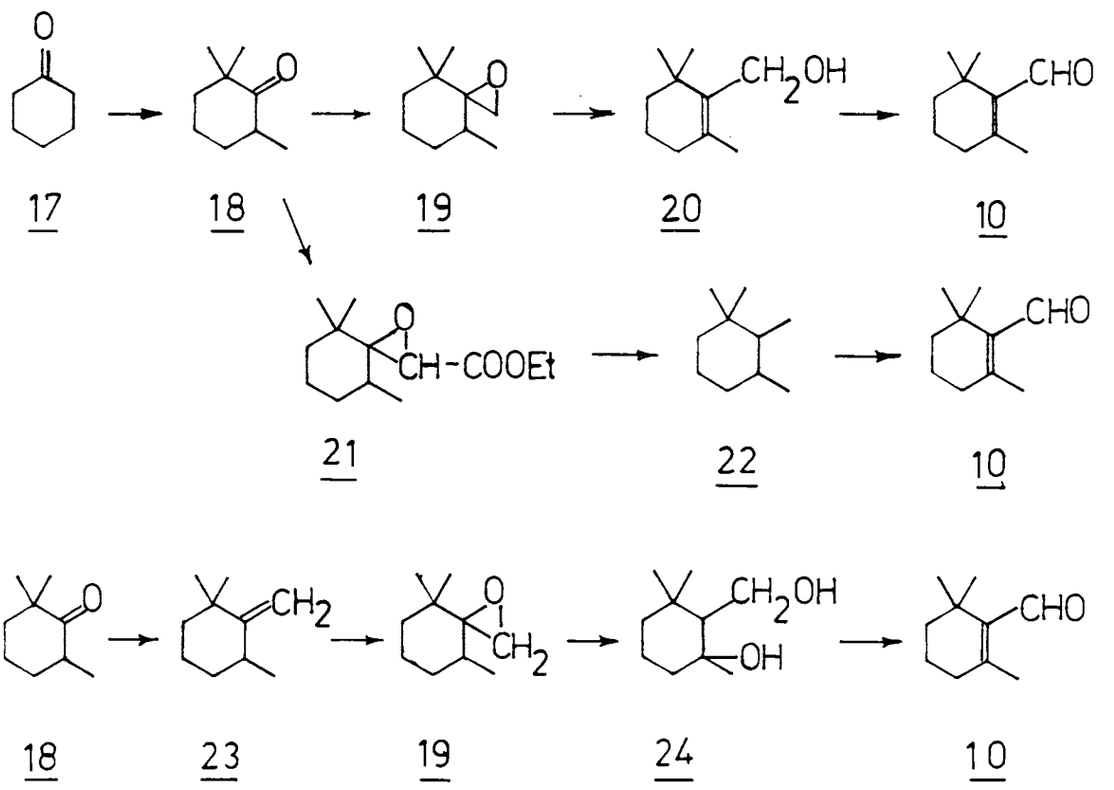
2.2. Synthesis of Cyclic C_{10} unit, β- Cyclocitral.

In cyclic C_{10} unit, three isomers α, β and γ exist according to the double bond position in the ring. β -isomer is important because of the importance of β -ionone in BASF synthesis[52] of Vit.A. manufacture. The available method of preparation of β -cyclocitral is the acid catalysed cyclisation of Schiff base of citral[53] and through the ozonolysis of cleavage of β -ionone[54].

Here synthesis of β -isomer can be obtained from alkylated cyclohexanone. Three methods can be adopted for this sythensis. Trimethyl cyclohexanone can be subjected to Corey-Chaykovsky reaction[55] followed by LDA treatment to get a cyclic alcohol called geraniol. Which on further oxidation should give β -cyclocitral.

In another approach, this trimethyl cyclohexanone can be converted into a glycidic ester with ethyl chloroacetate,[56] followed by hydrolysis can give a C_{10} aldehyde. Introduction of a double bond through α -bromination-dehydrobromination method should give the cyclocitral.

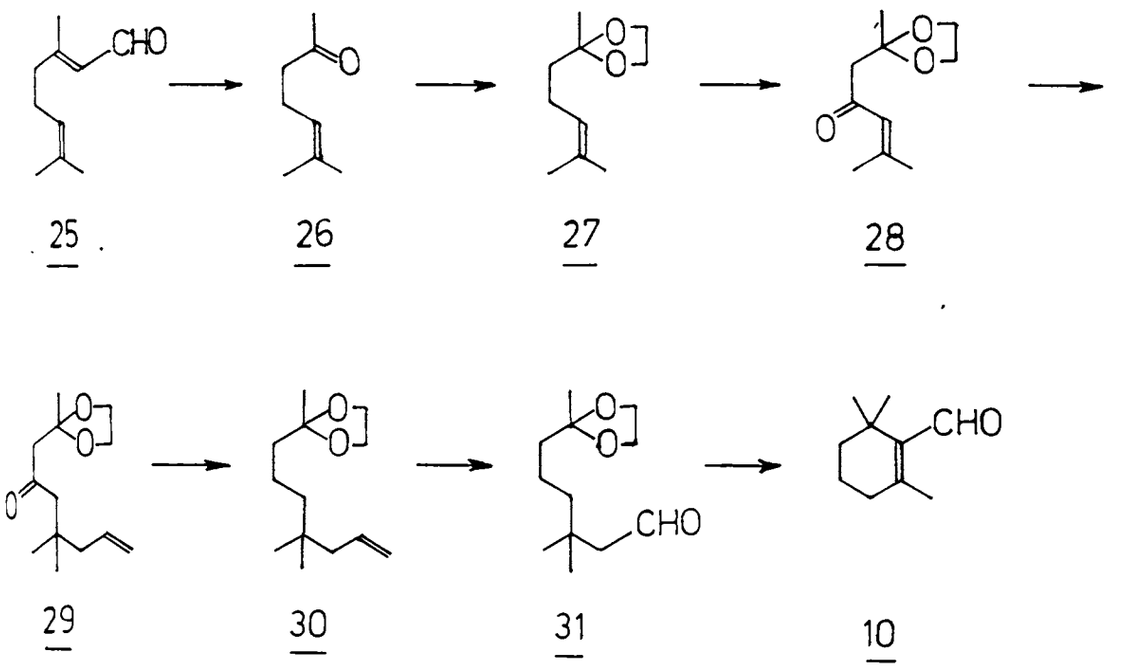
The epoxide (19) can also be prepared by using Wittig reaction followed by epoxidation epoxide opening with subsequent dehydration of the tertiary alcohol should give cyclogeraniol.



Synthesis of β-cyclocitral can also be tried with citral obtained from Lemongrass oil. Citral on retro aldol condensation give methyl heptenone, protection of the keto group, followed by allylic oxidation with PDC and t-butyl hydroperoxide[57] should give the α,β-unsaturated ketone 28. This on 1,4 addition with allyl bromide will yield the intermediate 29. Then reduction of the keto group of 29 followed by double bond cleavage, simultaneous deprotection and cyclisation will yield cyclocitral.

This C_{10} cyclic unit was an intermediate for the preparation of ionones and damascone, an isomeric compound

of ionone, which is a component of rose oil[58].

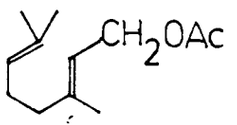


25 26 27 28

29 30 31 10

2.3 Synthesis of C_{11} cyclic unit.

In this approach geranyl acetate (32), a derivative of geraniol has been taken as the starting material. Epoxide of this geranyl acetate is known to give a cyclic diol on treatment with BF_3 etherate[59] which can be converted to 5-methyl derivative 8.



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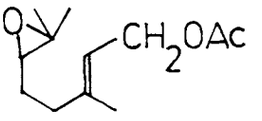

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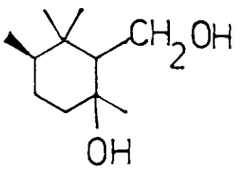

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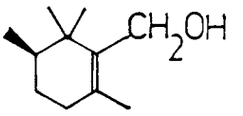
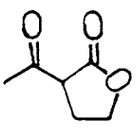


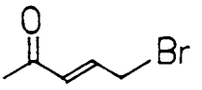
8

2.4 Synthesis of C_5 intermediate, 1-Bromo-pent-3-en-2-one.

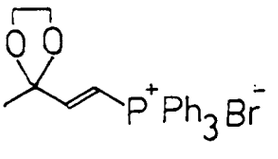
One of the commercially available starting material considered for this synthesis is 2-acetylbutyrolactone (35). Suitable functional group modifications and introduction of unsaturation can give 36. Then keto bromide 36 can be converted to a phosphonium salt 37.



35



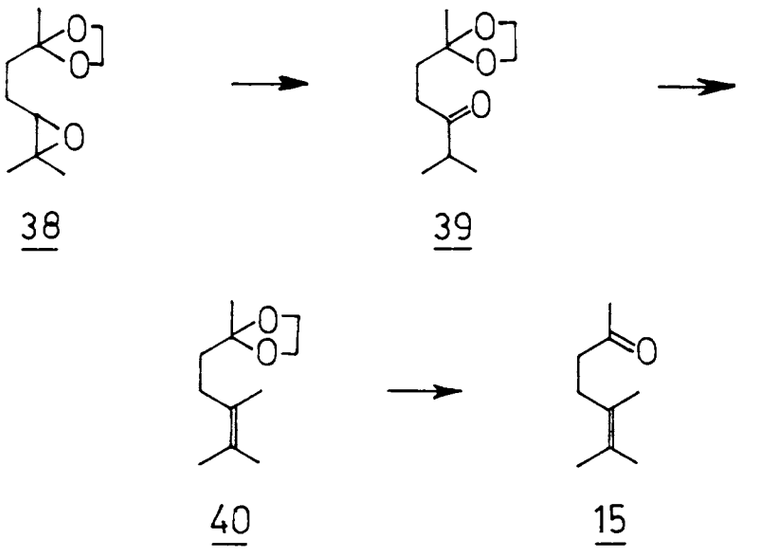
36



37

2.5 Synthesis of C_9 intermediate, 2-3- Dimethyl hept - 2-en-6-one.

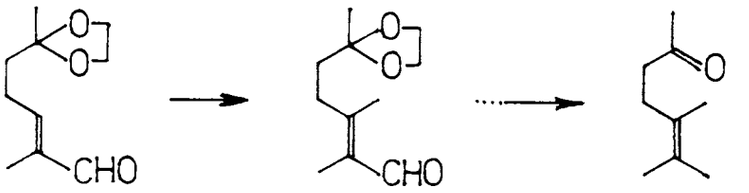
By using methyl heptenone obtained from citral is taken as the starting material. Epoxidation, protection of ketone andrearrangement of the epoxide in the BF_3 etherate can give a ketone (39), which can be converted to 5-methyl substituted methyl heptenone,ie. C_9 intermediate 15 through Grignard reaction.



38 39

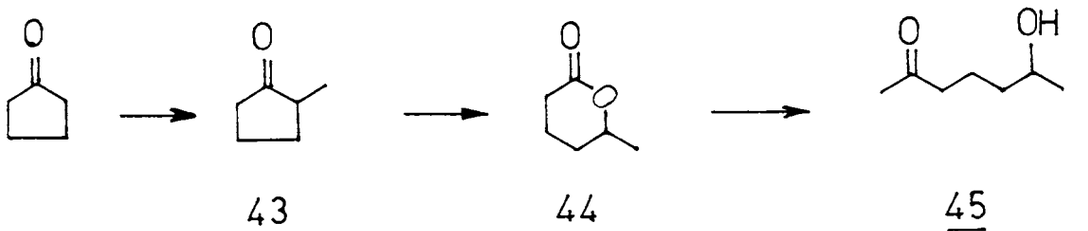
40 15

Allylic functionalisation of methyl heptenone followed by 1,4 addition, and introduction of unsaturation also give C_9 intermediate 15.

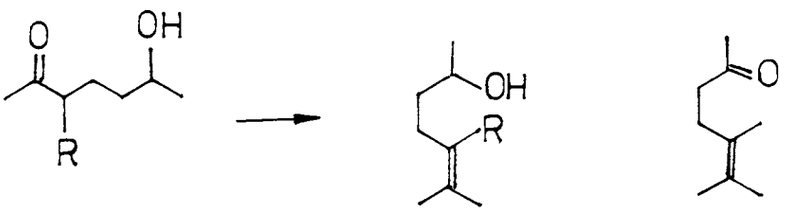


41 42 13

α-Phenyl selenylation of the carbonyl group and reductive elemination methodology[60] can also afford unsaturation. Mono-methyl cyclopentanone on Beayer-Villiger oxidation followed by methyl lithium treatment will give the keto alchohol (45), which on monoalkylation is converted to (47) through Grignard reaction followed by dehydration. This alchohol (47) on oxidation with PDC can give C_9 intermediate 15.



43 44 45



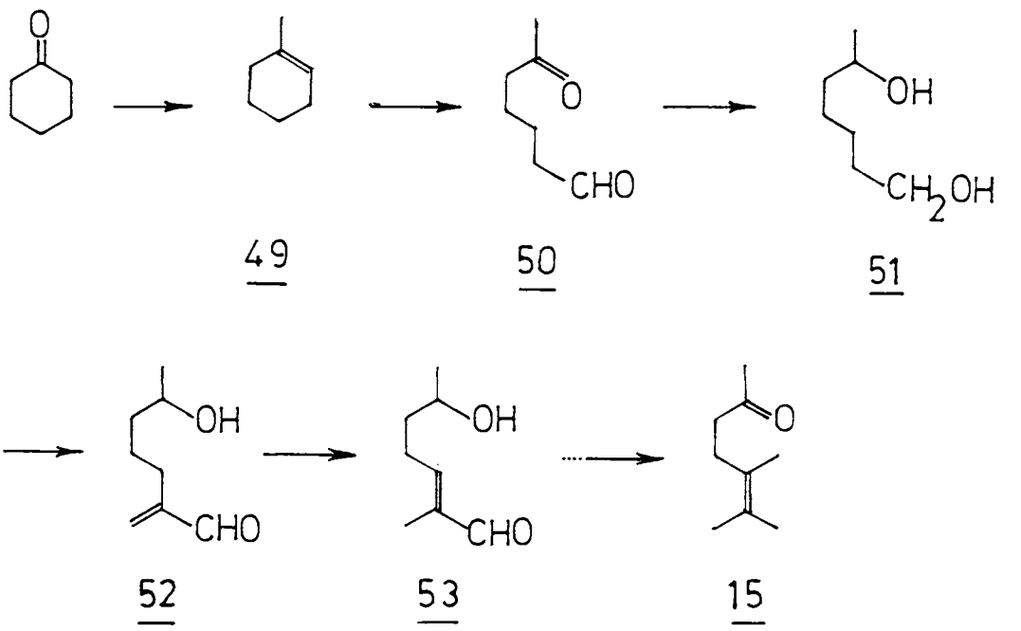
46. R=H
47 R=CH

48. R=CH_3
R=H

15

By eliminating the monoalkylation step from 45 to 46, these scheme will give the method of synthesis of C_8 ketone methyl heptenone.

This type of synthon has been prepared from cyclo hexanone. Cyclohexanone is converted to methyl cyclohexene, followed by cleavage at double bond position to gave the keto aldehyde 50. This keto aldehyde is reduced and converted to 52 by recently reported reaction with oxallyl chloride at -70°C in presence of trimethyl amine hydrochloride[61]. This can be easily converted to 53 by mild acid treatment.



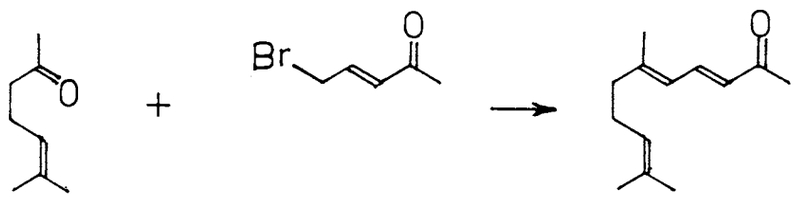
49 50 51

52 53 15

2.6 Synthesis of ψ -ionones and ψ-irones

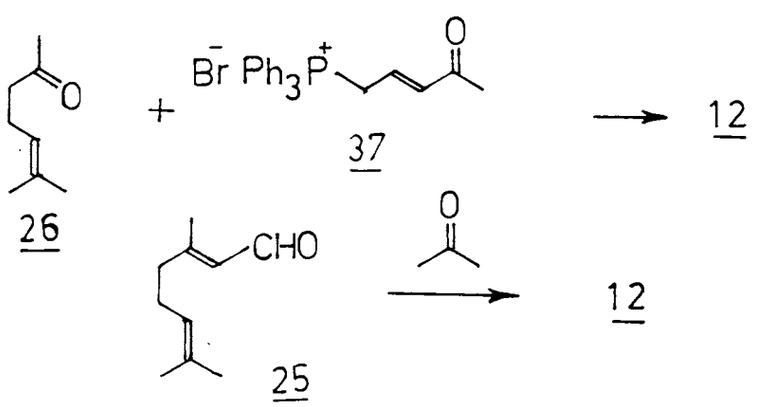
Numerous methods are available for the synthesis of ionone through pseudo-ionone cyclisation . So one of the methods is by using coupling reaction. C_8 and C_5 synthons are joined to C_{13} linear compound and then cyclised to give mixture of α , β and γ - isomers.

C_8 ketone 26 on coupling with C_5 allyl bromide 36 by using recently reported methodology using Zn/DMF.



26 36 12

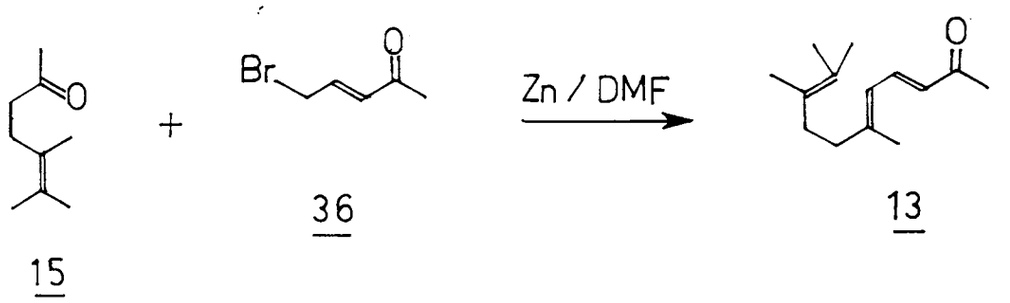
ψ-ionone can also be prepared by using Wittig reaction and by the classical method of condensation of citral with acetone.



26 37 25

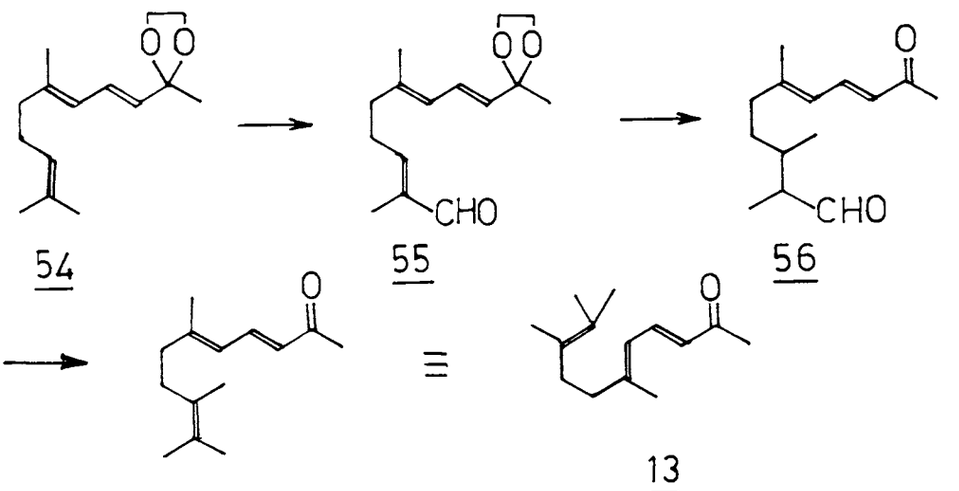
These above coupling methods are also applied with C_9.

Synthon C_9 + C_5 will produce C_{14} synthon and it is called pscudo-irone.



15 36 13

The pseudoionone, C_{13} compound is used as the starting material for synthesising C_{14} compound. Allylic functionalisation of ψ-ionone followed by 1,4 addition and subsequent phenyl selenilation and reductive elimination will produce C_{14} compound.

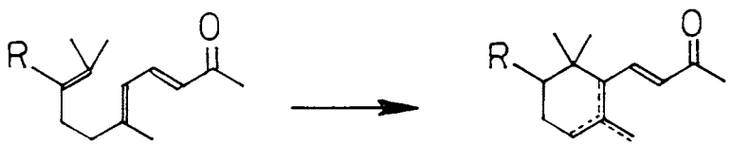


54 55 56 13

2.7 Synthesis of cyclic ionones and irones

C_{13} and C_{14} synthons, pseudoionone and pseudoirone

prepared by the above methods are cyclised to form α, β and γ-isomers of ionones and irones respectively.



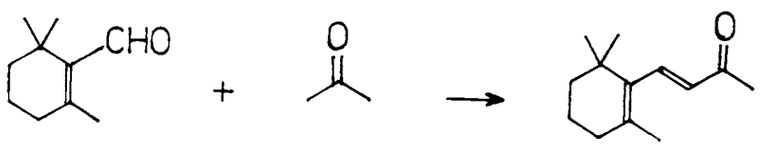
R = H
R = CH_3

R = H
R = CH_3

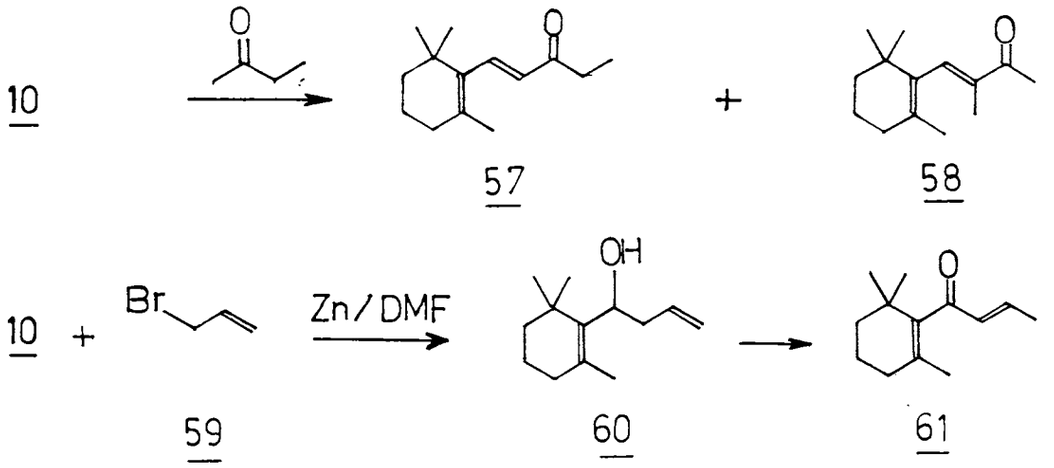
These mixtures of α , β and γ-isomers will be seperated by using column chromatography.

Cyclocitral prepared by the above methods is condensed with acetone in presence of base to give pure β-isomer of ionone. Methyl ionones are also formed on condensing with ethyl methyl ketone.

β-cyclocitral on coupling with allyl bromide with Zn/DMF and the resulting alcohol on Jone's oxidation or PDC oxidation will give an isomeric compound of β-ionone called β - Damascone (61).

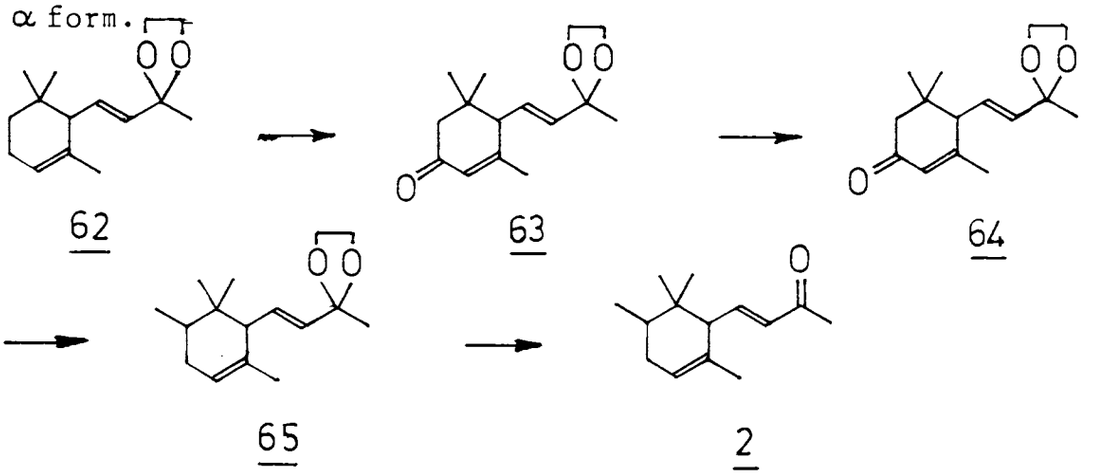


10 3



2.8 Conversion of ionone to irone

Cyclic α-ionone ketal on allylic oxidation using PDC and t-Butyl hydroperoxide followed by α-alkylation and reduction by Woulf-Kishner method and deprotection can give γ-irone. In the β-ionone there will be dienone ketone rearrangement and the γ-ionone isomerises to β and α form.



CHAPTER III

EXPERIMENTAL

3.1 GENERAL

Proton NMR spectra were recorded on a 60 MHz Hitachi R-600 FT Spectrometer with TMS as internal standard in $CDCl_3$ solution unless otherwise specified. Chemical shifts are expressed in δ values (ppm) and coupling constant (J) in Hertz (Hz), (S-Singlet, d-doublet, t-triplet, bs-broad singlet, bd-broad doublet, dd-doublet of doublets m-multiplet, Ar - Aromatic, H-Hydrogen). Gas chromatographic analysis was carried out on a Hewlett packard 5730 Gas chromatograph coupled with 3390 A reporting integrator either on a 12 ft. 1/4 in. 10% SE-30 on chromosorb or on a 12 ft. 1/8 in.5% carbowax columns employing a 40 mL/min and 30 mL/min. Flow rate of nitrogen respectively using FID detector. UV spectra were recorded on a Hitachi 200-20 UV-Vis spectrophotometer using ethanol or methanol as solvent unless otherwise specified. IR spectra were recorded on Perkin Elmer, model 727 B infrared spectrophotometer.

The experiments involving organometallic reagents, air or moisture sensitive reagents were carried out in an inert atmosphere. Column chromatography was done either using 60-120 or 100-200 mesh silicagel (Sisco or BDH) using

n-Hexne (63-68^{o} fraction) or petroleum ether (at 68^{o}) as eluent. For monitoring the reactions (Merck or BDH) silicagel G containing 13% binder coated plates were used. All solvents were distilled and dried according to the standard methods before use. After extraction work up, organic layer was dried using anhydrous sodium sulphate.

3.2 2,2,6-trimethyl cyclohexanone 2

Small pieces of potassium, 7.8 g (0.2 mole) was added to a stirred solution of t-butanol (150 mL) in N_2 atmosphere. Heated the mixture until the potassium was completely dissolved. Cyclohexanone, 196 g (0.2 mol) in dry dioxan (100 mL) was added slowly to the strried potassium t-butoxide. After 1 hr, added methyl iodide 56.8 g (0.4 mol) in dioxan (50 mL) was added with stirring. The mixture was stirred about three hour more. The reaction monitored by TLC. After the completion of the reaction, excess t-butanol was removed by vacuum distillation. Residue diluted with water (100 mL) extracted with ether (50 mL x 4), ether layer washed with water (40 mLx3) and with brine (40 mLx2), dried and solvent removed in vacuo. GLC shows three products, separated by column chromatography.

IR: 1720 cm^{-1}

^1H NMR : 1. δ 1 (S, 6H) 1.1 (d, 3H) 1·5 - 2 (m, 6H) 2.4 - 2.5 (m, 1H)

2. δ 1.1 (d, 6H) 1.5-2 (m, 6H) 2.4 - 2.6 (m, 2H)

3. δ 1 (d, 3H) 1·5 - 2 (m, 6H) 2.2 (q, 2H) 2.4 - 2.5 (m,1H)

3.3 Ethyl β , β - Penta methylene glycidate 3[2]

Ethyl chloro acetate

Refluxed a mixture of chloroacetic acid 95 g (1 mol) and absolute ethanol 60 g (1 mol) with catalytic amount of con. sulphuric acid 12 g for 6 hours. Reaction monitored by TLC, reaction mixture cooled, extracted with ether (50 mLx3), washed with water (40 mLx3), dried and concentrated. The crude mixtrue obtained was distilled to obtain pure ethyl chloroacetate 73 g (b.p. 142 - 145°C) yield 60%.

To a cooled stirred mixture of 2,2,6-trimethyl cyclohexanone 6.5 g (0.05 mol) and ethyl chloroacetate 6 g (0.05 mol) added a solution of potassium 2 g (0.05 mol) in 43 mL of dry t-butanol over a period of about 1.5 hrs. at 10-15°C. After the addition was complete, the mixture was stirred for an additional 1-1.5 hrs at 10°C. Solvent removed by vaccuum distillation, the residue extracted with ether (30 mLx3) combined extract washed with water

(30mLx2), then with saturated aqueous sodium chloride (30 mLx2) dried and concentrated to gave 9 g yield 80%.

IR : 1780 cm^{-1}

^1H NMR : δ 1.1 (S, 6H) 1.3 (d,3H) 1.5 (t,3H)
1.5 - 2 (m, 8H) 3.2 (S, 1H).

3.4 2,2,6-trimethyl cyclohexyl aldehyde 4

Added glycidic ester (3) 6.5 g (0.025 mol) to sodium ethoxide which is prepared by sodium 0.55 g (0.025 mol) in absolute alcohol 50 mL, with shaking. Cooled the flask externally to 15°C and added water (10mL) slowly. Strried for 1 hr and added dil. HCl to the mixture shaken well, extracted with ether (50mLx3), washed with water (20 mLx3) dried, concentrated in vacuo. The product purified by column chromatography (silicagel and petroleum ether - ethylacetate 95:5 as eluent) to yield 3.8 g (70%).

'H NMR : δ 0.9 (S, 6H) 1.1 (d, 3H) 1.5 - 2 (m, 6H)
9.5 (S, 1H)

3.5 1-bromo-2,2,6-trimethyl-cyclohexyl aldehyde 5

Added a cold solution of Bromine 0.7 g (4.4 m. mol) in glacial acetic acid (15 mL) slowly to a stirred

solution of 2,2,6-trimethyl cyclohexyl aldehyde (4) 3.25 g (2.25m. mol) at $0^{o}C$. The reaction mixture was stirred for 6-7 hrs. The reaction monitored by TLC. After the reaction was completed, mixture neutralised with Na_2CO_3, extracted with CH_2Cl_2 (20 mLx4), combined extract washed with water (20mLx3) dried and concentrated invacuo . The product obtained was found to be 4.5 g yield 60%.

3.6 2,6,6 -trimethyl cyclohexen-1-yl aldehyde 7 (cyclocitral

A slurry of K_2CO_3 1.05 g (8 m.mol) in dry methanol (10 mL) was added to a stirred solution of 1-bromo-2,2,6-trimethyl cyclohexyl-aldehyde (5) 0.25 g (8 m. mol) in dry methanol. The mixture was stirred for 6-7 hrs and diluted with 1N-HCl (75 mL). Extracted with ether (50 mLx3), washed with water (40 mLx 3), with NaCl (40 mLx3), concentrated in vacuo gave the product 0.15 g 90% yield.

UV : λmax 240 nm

IR : 1685, 1670 cm^{-1}

^1H NMR : δ 1.2 (S, 6H), 1.5 (S, 3H),
2.1 - 2.3 (m, 6H), 10.1 (S, 1H).

3.7 Preparation of diphenyl diselenide (Ph Se Se Ph)[44]

To a solution of phenyl magnesium bromide, prepared from bromobenzene, 80.0 g (0.51 mol) and magnesium turnings,

12.0 g (0.49 g atom) in anhydrous ether (275 mL) was added selenium powder, 35.0 g (0.445 g atom) from a solid addition funnel with stirring under N_2 atmosphere. The selenium was added over 30 min. at a rate sufficient to maintain a vigorous reflux. After the addition, the mixture was stirred under reflux for 30 min. more. To the reaction mixture water, 1.5 g (0.08 mol) was added dropwise to hydrolyse the excess Grignard reagent. The mixture was stirred and cooled in an ice bath and bromine, 37.15 g (0.233 mol) was added at a rate such that ether does not reflux. A solution of ammonium chloride, 26.75 g (0.5 mol) in water (70 mL) was then added under stirring. The reaction mixture filtered and the precipitate washed with ether. The combined fliterates were evaporated and the residue was dissolved in hot hexane (250 mL). The hexane (250 mL). The hexane solution is filtered and allowed to crystallise at room temperature and then at 6^{o}. The yellow crystalline diphenyl diselenide formed is filtered, washed with n-pentane and dried in air, 45 g (65%) m.p. 60-62^{o}.

3.8 **1-phenyl seleno 2,2,6-trimethyl cyclohexyl aldehyde 6**

2,2,6-trimethyl cyclohexyl aldehyde 3.85 g (0.025 mol) in dichloromethane (50 mL), added to a suspension of selenium dioxide 1.7 g (0.015 mol) in dichloromethane (25

mL) containing diphenyl diselenide, 9.4 g (.01 mol) and a catalytic amount of con.H_2SO_4, 0.590 g (0.006 mol). The mixture was stirred below 10^{o} for 18 hrs. The decolourised solution was diluted with ether (200 mL) filtered and washed with $NaHCO_3$ (3 x 50 ml). After drying, solvent removel under reduced pressure followed by product purification on silicgel gave 7, 5.4 g (70%).

^{1}H NMR : δ 1.2 (S,6H), 1.5 (S,3H), 2.1-2.3 (m,6H)
2.5 (m,1H), 7-8 (m,6H), 10.1 (S, 1H).

3.9 2,6,6-trimethyl cyclohexen-1yl aldehyde 7 cyclocitral from 6

α-phenyl seleno aldehyde 6 (0.02 mol) dissolved in tetrahydrofuran (30 mL) was stirred with excess 30% hydrogen peroxide 21.4 mL (0.234 mol) below 5^{o}. Hydrogen peroxide was added drop by drop and stirring continued for 1 hr. The decolourished solution is diluted with water (100 mL) and extracted with ether (3x 40 mL) ether layer washed with brine (2 x40 mL) dried and solvent removed to get 7 yield of 80%.

UV : λmax 240 nm

IR : 1685, 1670 cm^{-1}

^{1}H NMR : δ 1.2 (S, 6H), 1.5 (S, 3H), 2.1-2.3
(m, 6H), 10.1 (S, 1H)

3.10 2,6,6-trimethyl-1-methylene-cyclohexane 8

The ether solution of n-butyl lithium was prepared by adding n-butylbromide, 1.38 g (0.01 mol) in ether (3 mL) to lithium, 0.173 gm (0.025 mol) in ether (5 mL) at -20° and stirring the mixture for 30 min. To this solution of base was added methyl triphenyl phosphonium iodide 4.04 g (0.01 mol), (prepared by stirring triphenyl phosphine 2.62 g (0.01 mol) in benzene (2.2 mL) with methyl iodide, 2.13 g (0.015 mol) and removing the solvent). The mixture was allowed to stir for 30 min. To the phosphorane generated was added to the ketone 2, 1.24 g (0.01 mol) in ether (20 mL) under stirring. The mixture was stirred for 24 hrs. at room temperature. The reaction mixture poured into ice cold water (100 mL) and extracted with ether (3 x 30 mL), dried, solvent removed in vacuo and purification by neutral alumina chromatography gave 8, 1.1 g (80%).

^{1}H NMR : δ 0.9 (S, 6H), 1.2 (d, 3H) 1.5-2 (m, 6H)
2.5 (m, 1H), 6 (d, 2H)

11 (2,6,6-trimethyl-1-hydroxy-cyclohexyl) methanol

Olefine (8) 1.1 g (0.01 mole) in water (50 mL) was cooled to 5°, potassium permanganate 1.58 g (0.01 mol) in

100 ml water was added to Olefine at a rate of 25 c.c. per minutes with constant stirring. The temperature was kept at 5^{o}, soon after stirring is stopped the mixture sets to a gel; allowed to stand for two hrs. and the reaction mixture was heated for one hour on the steam bath. Filtered, the residue washed with water (50 mLx 3) combined filtrate extracted with ether using ether extractor. Combined the extracts dried and concentrated to get the diol 9 50% yield.

^{1}H NMR : δ 1(S, 6), 1.1 (S, 3H) , 1.3 - 1.5 (m,6H)
1.2 (m, 1H), 4.1 (S, 2H)

3.12 **2,6,6-trimethyl cyclohex-1-enyl methanol 10**

Thionyl chloride 8.3 g (0.1 mole) was slowly added to an ice cold mixture of the above diol 9, 17 g (0.1 mol) and pyridine (14 mL) in dry ether (50 mL) with stirring. After the addition was over, the reaction mixture allowed to stand for two days. It was decomposed by adding ice water (80 mL), extracted with ether (50 mLx3), combined extracts washed with dil. HCl (40 mL x 2), then with sodium bicarbonate (40 mL x 3) again washed with water (40 mLx3), dried and concentrated in vacuo to get 12.3 g (80%).

IR : 3670, 3650, 1650 cm^{-1}

^{1}HNMR : δ 1.05 (S, 6H), 1.3 - 1.7 (m,4H),
1.7 (S, 3H), 1.8 - 2.1 (m,2H),
4.1 (S, 2H)

.13 **2,6,6-trimethyl cyclohexyl methyl epoxide 11 from 8**

To a solution of olefine 8, 1.38 g (0.01 mole) in dichloromethane (25 mL) at 0°C was added m-chloroperbenzonic acid, 2.58 g (0.015 mol) dissolved in dichloromethane (20 mL) under stirring. After stirring for 3 hrs at room temperature, the contents were diluted with water (25 mL). Theorganic layer seperated washed with saturated sodium carbonate solution (20 mLx2), water (20 mLx2) and dried, solvent removal invacuo afforded the epoxide 11, 1 gm, 70%.

^{1}H NMR : δ 0.9 (S, 6H), 1.1 (d, 3H), 1.8-2.1
(m, 6H), 2.3 (m, 1H), 3.6 (S, 2H)

14 **2,6,6-Trimethyl-cyclohexyl methylene oxide 11 from 2**

To dimethoxy sulfonium methylide prepared from dry sodium hydride 0.316 g (0.0066 mol) (50% dispersion in

oil) and trimethyl sulphonium iodide 1.54 g (0.0066 mol) in dry dimethyl sulfoxide(4 mL) under nitrogen atmosphere was added the ketone 2, 0.5 g (0.0044 mol) in dry dimethyl sulfoxide (2 mL) dropwise and stirred for 18 hrs. at room temperature and then at 50° 1 hr. The mixture was cooled and added to cold water (10 mL) and extracted with ether (2x15 mL) ether layer washed with water (10 mLx2), dried and concentrated in vacuo gave epoxide 11.

2,6,6 Trimethyl cyclohex-1-enyl methanol 10 from 11

To lithium diispropylamide, prepared from lithium 0.144 g (0.008 mol, 50% dispersion in oi), n-butyl-bromide 0.60 g, (0.0025 mol) and diispropyllamine 0.252 g, (0.0025 mol) in anhydrous ether (10 mL) was added the epoxide 11 0.385 g (0.0025 mol) in dry ether (5 mL). After stirring at room temperature for 5 hrs., the solution was cooled and saturated ammonium chloride (5 mL) ws added . Ether layer separated, driedand concentrated and purified by column chromatography gave an alcohol 10, 11 g 68% yield.

3.16 Preparation of P.C.C.[12]

CrO_3 100 g (1 mole) is rapidly added with stirring to 6 N hydrochloric acid 184 mL (1.1 mole). After 5 minutes the homogeneous solution is cooled to 0^o and pyridine 79.1 g (1 mole) is carefully added over 10 minutes. Recooling to 0^o gives a yellow-orange solid which is collected on sintered glass filter and dried in vacuo for 1 hr. yield 180 g (84%).

.17 2,6,6-trimethyl-cyclohex-1-enyl-methanal (cyclocitral)

The alcohol 10 1.5 g (0.01 mol) in CH_2Cl_2 (10 mL) is added slowly to a suspension of P.C.C. 3.23 g (0.015 mol) in anhydrous methylene chloride (20 mL) with stirring. After 1.5 hr dry ether (50 mL) is added and the supernatant liquid is decanted, the insoluble residue washed with ether (20 mL x 3). The combined organic solution concentrated in vacuo , purified by column chromatography yielded 1.2 , 84%.

I R : 1685, 1670 cm^{-1}

UV : λ max 240 nm

^1H NMR : δ 1.2(S, 6H), 1.5 (S, 3H), 2.1-2.3 (m, 6H), 10.1 (S, 1H).

3.18 3,7- dimethyl-octa-2,6-dien-1-al(12) (citral)[40]

Lemon grass oil containing 79% citral by (GLC) was chrometographed (silicagel 60-120, ratio of substance to adsorbent - 1:10, eluent - 9:1 hexane-ethyl acetate) to isolate 12 in 98% recovery b.p. 92-93°/2.6 m.m.

UV : λ_{max} 236 nm

IR : 1665, 1603, 1398, 1190 cm^{-1}

^{1}HNMR : δ 1.65 (S, 6H), 2.15 (S, 3H), 1.9-2.1 (m, 4H), 5.0 (m 1H), 5.8 (d, 1H), 9.8 (d, 1H).

3.19 . 6-Methyl-5-hepten-2-one(13) (Methyl heptenone)

95% citral, 50 g (0.315 mol) was mixed with 1% sodium carbonate (750 mL) and the mixture was refluxed under stirring using short condenser for 6 hrs. The reaction mixture was cooled, aqueous layer separated and extracted with ether (150 mLx3). Organic layers combined, washed with water (4x75 mL), dried and solvent removed to get the crude methyl heptenone (13) purified by column chromatography using silicagel and hexane ethylacetate in the ratio 9:1 as eluent to yield 31.7 g 80% b.p. 58.5°/10 mm

IR : 1720 cm^{-1}

^1H NMR : δ 1.65 (d, 6H), 2.1 (S, 3H), 2.15-2.7 (m, 4H), 5.1 (t, 1H).

3.20 6,6-Ethylene dioxy-2-methyl-hept-2 ene (14)

A mixture of ketone 13, 18.9 g (0.15 mol) and ethylene glycol, 19-8 g (0.33 mol) in thiophene free benzene (250 mL) was refluxed under stirring in a Dean-Stark set up for 6 hrs. The reaction mixture diluted with water (100 mL), benzene removed under reduced pressure and the residue extracted with ether (100 mLx2). The ether layer washed with water (40 mLx2), Sodium bicarbanate (2x40 mL), dried, solvent removed and purified by silicagel chrometography to get the ketal 14, 22 g, 85% b.p. $58^{o}/1.5$ mm.

^1H NMR : δ 1.35(S, 3H), 1.65 (d, 6H), 1.9-2.4 (m, 4H), 3.95 (S, 4H), 5.15 (t,1H)

.21 6,6-Ehylene dioxy-2-methylhept-2-en-4-one (15)

Preparation of pyridiniumdichromate : To a cooled solution of chromium trioxide, 100 g (1 mole) in water (100

mL) was added dropwise pyridine 80.6 ml (1 mole).Diluted with acetone (400 mL) and cooled to -20°. After three hrs. orange crystals are separated,filtered, washed with cold acetone and dried in vacuo . 257 g 68% m.p. 144 - 146°.

Methyl heptenone ketal (14) 17.4 g (0.1 mol) was added to PDC 75 g (0.2 mol) in benzene (150 mL) then added t-butylhydroperoxide 18 g (0.2 mol) drop by drop to a stirred reaction mixture at below 20°. After 8 hrs, added excess ether, and decanted. The solid residue washed with ether (50 mLx4). Combined ether layer concentrated, purified by column chromatography, to gave 15 11.2 g 60%.

I.R. : 1670 cm^{-1}

^1H NMR : δ 1.1 (S, 3H), 1.7 (S, 6H), 2.1 (S, 2H)
2.5 (S, 1H), 4.1 (S, 4H)

3.22 6,6-Ethylenedioxy 2-allyl-2-methyl heptan-4-one 17

Allyl magnesium bromide (0.01 mol) was prepared by slowly adding allyl bromide 1.21 g (0.01 mol) to magnesium 0.24 g (0.01 mol) in dry ether (50 mL) containing small amount iodine. After the addition,

stirring continued for one more hour. Then added catalytic amount of cuprous iodide 800 mg with stirring. Then added α,β-unsaturated ketone 15, 1.8 g (0.01 mol) slowly with stirring at 10°C. Stirring continued for 1 hr. Reaction monitored by TLC. After the completion of the reaction, reaction mixture was pouredinto ice cold solution of saturated ammonium chloride (100 mL) containing few amounts of ammonia (10 mL) with vigorous shaking. Extracted with ether (50 mLx3), washed with ammonium hydroxide (20 mLx3), then with water (20 mLx2) dried and concentrated to give the 1,4 addition product 17, 1.5 g 70% yield.

23 **4,4-dimethyl 8,8- ethylenedioxy-non-1-ene 18**

Preparation of thioketal[19] : A mixture of ketone 17, 1.88 g (0.01 mole) and ethanedithiol (2.3 mL) was treated with BF_3 etherate 4 mL, swirled and let stand for 45 minutes. The homogeneous mixture was diluted with water (20 mL), extracted with ether (3 x 20 mL) washed with NaOH solution (3x50 mL) and then with water (3 x 50 mL) dried and concentrated to get 1.95 g yield 76%.

Preparation of Raney Nickel[20]

To 19 g of NaOH in 75 mL water at 10°C added Ni-Al alloy 15 g in small portions, with stirring, at such a rate

that the temperature does not rise above 25°C. When all the alloy has been introduced, stop the stirrer, removed the beaker from the ice bath and allowed to attain room temperature. When the evolution of H_2 becomes slow, heat the reaction mixture on a water bath, until the evolution again becomes slow (about 8-12 hours), added distilled water to restore the original volume, stirred the mixture, allowed to settle and decant the supernatent liquid. Transferred the Nickel to stoppered flask and added a solution of 2.5 g of NaOH in 25 mL water, shake thoroughly allow to settle and decant the alkali solution. Wash the Nickel thoroughly with distilled water decantation until the washings are neutral to litmums. About 25-40 times washings are required. Repeated washing process three times with 100 mL of rectified spirit (95% ethanol) and three times with absolute ethanol. Store the catalyst in stoppered bottles which are completely filled with absolute alcohol. Raney Ni contained in suspension weighs about 7.5 g.

Desulfurisation

A mixture of thioketal 1.5 g (0.005 mol) and Ra-Ni two teaspon (6 g) in absolute methanol (150 mL) was refluxed

under stirring for 24 hrs. The Ni was filtered, washed with hot methanol (25 mLx3) concentrated to yield 75% reduced product 18.

24 **7,7-Ethylene dioxy-3,3-dimethyl octanal 19**

Under stirring and protection from light, Osmium tetroxide 0.1 g was added to a solution of alkene 18, 2.12 g (0.01 mol) in dioxan (25 mL), the mixture stirred for 15 minutes, then admixed with, in drops, a solution of sodium periodate 4.5 g (0.021 mol) in water (35 mL) over 1 hr stirred overnight, filtered the residue, washed the residue with ether, the combined filtrate and washings evaporated *in vacuo*. The residue extracted with methylene chloride (50 mLx3), the organic extract washed with brine, dried and concentrated to gave 19, 1.5 g 65% of yield.

IR : 1685, 1670 cm^{-1}

^1H NMR : δ 0.9(S, 6H), 1.1 (S, 3H), 1.5-2(m, 6H)
2.1 (d, 2H), 10.1 (S, 1H)

25 **3,3-demethyl 7-oxo-octanal-20**

The solution of the ketal 19, 0.22 g (0.001 mol) and p-toluene sulphoic acid (10 mg) in 6:1 aqueous acetone (20

mL) was gently refluxed for 2 hrs. The mixture was cooled, acetone removed under reduced pressure and the residue extracted with ether (20 mLx3) washed with water (20 mLx3), dried and concentrated.

26 **2-Hydroxy-2,6,6-trimethyl cyclohexyl methanol 21**

The keto aldehyde 20 (0.001 mol) was gently treated with diethylamine (20 mL) in methanol (50 mL) with stirring for 4 hrs. Reaction monitoring by TLC. After the completion, neutralised with dil. HC1 (50 mL), extracted with ether (30 mLx3) washed with water (30 mLx2), dried and concentrated. Purified by column chromatography in silicagel column and Hexane ethylacetate inthe ratio 9:1 as eluent.

IR : 1670, 1685, 3450 cm^{-1} (broad)

^1H NMR : δ 0.9 (S,6H), 1 (S, 3H), 1.3-1.8 (m,6H)
2.3 (S, 1H)

The tertiary alcohol obtained in the above experiment on dehydration with thionyl chloride and pyridine gave cyclocitral 7.

.27 5-Bromo-2-pentanone (22)

A solution of 2-acetyl butyrolactone, 30.0 g (0.234 mol) in chloroform (300mL), benzyl triethylammonium chloride, 5.2 g (0.0234 mol) and 48% aqueous hydrogen bromide (300 mL) were stirred under N_2 for 18 hrs at room temperature. After the reaction, the aqueous layer was separated and extracted with chloroform. The combined chloroform layer was washed with water (100 mLx3) dried and solvent removed in vacuo to get ketobromide 22, 32.8 g (85%).

IR : 1715 cm^{-1}

^{1}HNMR : δ 2.17 (S, 3H), 2.2-2.8(m, 4H), 3.5(t, 2H)

28 5-Bromo-3-phenyl seleno-pentan-2-one (23)[6]

Ketobromide 22, 8.25 g (0.05 mol) in dichloromethane (50 mL), added to a suspension of selenium dioxide 3.4 g (0.03 mol) in dichloromethane (50 mL) containing diphenyl diselenide, 18.72 g (0.02 mol) and a catalytic amount of con. sulphuric acid, 0.590 g (0.006 mol). The mixture was stirred below 10° for 18 hrs. The decolourised solution was diluted with ether (200 mL) filtered and washed with sodium bicarbonate (50 mLx3). After drying, solvent removal under reduced pressure followed by product purification by column chromatography gave 23 as a yellow oil, 10.85 g (70%).

IR : 1715 cm^{-1}

^1H NMR : 1.6 - 2.1 (m, 2H), 2.2 (S, 3H) 3.5 (m, 3H)
7.3 - 7.8 (m, 5 Ar H).

.29 **(E)-5-Bromo-3-penten-2-one (24).**

Phenyl selenoketobromide 23, 6.2 g (0.02 mol) dissolved in tetrahydrofuran (30 mL) was stirred with excess 30% hydrogen peroxide 21.4 mL (0.234 mol) below 5^o. Hydrogen peroxide was added drop by drop and stirring continued for 1 hr. The decolourised solution is diluted with water (100 mL) and extracted with ether (40 mLx3). Ether layer washed with brine (40 mLx2), dried and solvent removed to get 24, 2.9 g (90% yield).

IR : 1675 cm^{-1}

^1H NMR : δ 2.2 (S, 3H), 3.9 (d, 2H), 6.05(d, 1H),
6.8 (d, 1H)

(E)-5-Bromo-2,2-ethylenedioxy-pent-3-ene (25)

Ketobromide 24, 4.9 g (0.03 mol), ethylene glycol 3.96 gm (0.066 mol) and pyridinium p-toluene sulphonate 0.95 g (0.0038 mol) in thiophene free benzene (50 mL) were stirred under reflux for 2 hrs. in Dean-Stark set up. When the

reaction was complete, the mixture was cooled, water (100 mL) was added and benzene removed under reduced pressure. The residue extracted with ether (50 mLx2) washed with water (40 mLx4) and dried and concentrated in vacuo yielded the ketal 5.15 gm (83%).

.31 **5-Bromo-2,2-ethylenedioxy-pent-3-enyl triphenyl phosphonium Bromide (26).**

Added the ketal bromide 25, 2.07 gm (0.01 mol) in benzene (20 mL) to a stirred solution of triphenyl phosphine 2.62 g (0.01 mole) in benzene (10 mL). Stirred the mixture ten hour more after the addition. Solvent removed in vacuo to get corresponding phosphonium bromide 26.

2 **2-methyl-2,3-epoxy-heptan-6-one 27**

Added slowly 40% solution of peracetic acid 16.4 g (0.15 mole) to a stirred solution of methylheptenone 12. 6 g (0.1 mole) in methylene chloride (100 mL). Stirring continued for four hour. Reaction mixture neutralised by adding sodium bicarbonate (100 mL) organic layer separated, extracted with CH_2Cl_2 Combined extracts washed with water (40 mlx4) then with brine (40 mlx2),dried and concentrated in vacuo purified by column chromatography on

silicagel and hexane ethyl acetate 9:1 ratio as eluent to get epoxy ketone 7.1 g (50%).

IR : 1670 cm^{-1}

^1H NMR : δ 1.25 (3H, S), 1.3 (S, 3H), 2.1 (S, 3H), 1.5-2 (m, 4H), 2.7 (t, 1H).

33 **6,6-Ethylene dioxy-2-methyl-2,3-epoxy heptane 28**

Reflux the epoxy ketone 27, 7 g (0.05 mol) and ethylene glycol 6.2 g (0.1 mole) and pyridinium paratoluene sulphonate 0.95 g (0.0038 mol) in thiophene free benzene with stirring for about 3 hrs. Cooled the reaction mixture, added water (100 mL) and benzene removed under reduced pressure. The residue extracted with ether (50 mLx3) washed with water (40 mLx4) dried and concentrated in vacuo yielded the ketal 7.4 g (80%).

6,6-Ethylenedioxy-2-methyl-heptan-3-one 29

To a benzene solution (50 mL) of epoxide 25, 5.5 g (0.03 mol) was added BF_3 etherate (0.06 mol) at room temperature. The mixture was stirred at 100° under N_2 for 1 hour. After cooling in ice water the mixture was quenched at saturated $NaHCO_3$, and the organic substance extracted with ether (50 mLx3). The extracts were washed with brine (40 mLx2), dried and concentrated in vacuo to get the ketone 29,3.3 g 60 % yield.

IR : δ 1720 cm^{-1}

^1H NMR : 0.9(d, each 3H), 1.1 (S, 3H), 1.3-2.1 (m,4H), 2.3 (m, 1H).

3.35 6,6-Ethlenedioxy-2,3-dimethyl hepta-2-ene 30

The above ketone 26 ,3.3 g (0.018 mol) in dry ether (10 mL) was slowly added to methyl magnesium iodide (prepared by adding methyl iodide (0.018 mol) in dry ether to a stirred ether solution containing Mg 1 g (0.018 mol) and catalytic amount of I_2, stirring continued for 1 hr) with stirring below 20°C. Reaction monitored by TLC. After the completion of the reaction hydrolysed by adding 10% dil. Sulphuric acid (50 mL), extracted with ether (50 mlx3), washed with $NaHCO_3$ (40 mLx3), then with water (40 mLx3), dried and concentrated to get the tertiary alcohol with 80% yield.

The tertiary alcohol dehydrated by using thionyl chloride and pyridine to get 6,6-ethylenedioxy-2,3-dimethyl-hept-2-ene 30.

^1H NMR : δ 1.35 (S, 3H), 1.6 (S, 6H), 1.7 (S, 3H) 1.9-2.4 (m, 4H), 4.1 (S, 4H).

3.36 2,3-Dimethyl -hept-2-en-6-one 31

To a solution of the ketal 30 (0.01 mol) in aqueous acetone (6:1, 25 mL), p-toluene-sulphonic acid (10 mg) was added and the mixture was refluxed on a water bath. After 6 hrs the mixture was cooled, 1% aqueous sodium bicarbonate solution was added and the solvent was removed under reduced pressure. The residue was dissolved in ether (50 mL), washed with water (20 mLx2), dried and concentrated in vacuo to give the ketone 31 (81%).

IR : 1720 cm^{-1}

^1H NMR : δ 1.6 (d, each 3H), 1.7 (S, 3H), 2.1 (S, 3H)

1.7-2.1 (m, 4H).

3.37 3-Chloro 6,6-ethylene dioxy 2-methyl-heptene 32[28] from 14

An excess amount of dry ice was added in portions to a mixture of methyl heptenone ketal 14,8 g (0.05 mol) and calcium hypochlorite (active chlorine 60%), 13.0 g (0.055 mol) in dichloromethane (200 mL) and water (50 mL) below 0^o under stirring. The reaction mixture was stirred for 1 hr. below 5^o and then diluted with dichloromethane (100 mL), washed with sodium bicarbonate (50 mLx2) and water (50 mLx2). The organic layer dried, solvent removed to get the compound 32, 7.1 g (70%).

^{1}H NMR : δ 1 (S, 3H), 1.5 (S, 3H), 1.5-21 (m, 4H), 4.35 (t, 1H), 4.95 (d, 2H), 4.1 (S, 1H), 2.1 (S,3H).

3.38 **6,6-Ethylenedioxy-hept-2-enal 33**

A mixture of chloride 32, 6 g (0.028 mol) in dioxan (15 mL), triethylamine N-oxide 10.41 g (0.088 mol) in Copper (1) chloride, 0.276 g (0.0028 mol) was stirred at 50^o for 10 hrs. The reaction mixture was combined with 2.5% sulphuric acid (40 mL) and ethylacetate (40 mL). The organic layer was washed with 2.5% sulphuric acid (20 mlx2), sodium bicarbonate (40 mLx2) and 10% sodium sulphite solution (30 mLx2). The organic layer dried and solvent removed in vacuo followed by chromatography on neutral alumina afforded the aldehyde 33 only 40% yield.

^{1}H NMR : δ 1 (S, 3H), 1.5 (S,3H), 1.5-2 (M, 4H) 5.15 (t, 1H), 9.1 (S, 1H).

3.39 **6,6-Ethylenedithio-2-methyl-hept-2-ene 34**

To a cold solution of methyl heptenone 12.6 g (0.01 mole) in $CHCl_3$ (50 mL) added ethylene dithiol 9.4 g (0.1 mole) and then added Borontrifluoride etherate (10 drops) with cooling and stirring. After 5 minutes cooling bath removed and stirring continued for 2 hrs. Added KOH

solution (50 mL) to the reaction mixture, extracted with chloroform (50 mLx3), combined extracts washed with potassium hydroxide (20 mLx3), then with water (20 mLx3) dried, concentrated and purified by column chromatography to get 34 16 g, yield 80%.

3.40 **3-chloro-6,6-ethylene dithio-2-methyl-heptene 35**

An excess amount of dry ice was added to a mixture of the above methyl heptenone thioketal 34, 20 g (0.1 mol) and calcium hypochlorite 26 g (0.15 mol) in dichloromethane (250 mL) and water (75 mL) below 0^{o} under stirring. The reaction mixture was stirred for 1 hr. below 5^{o} and then diluted with dichloromethane (100 mL), washed with sodium carbonate (50 mLx2) and water (50 mLx2), dried solvent removed to get the chloride 35, 17.2 g (65%).

^{1}H NMR : δ 1.1 (S, 3H), 1.5 (S, 3H), 1.5-2 (m,4H), 4.35 (t,1H), 4.95 (d,2H), 4.15 (S, 4H).

3.41 **6,6-Ethylenedithio-2-methyl-hept-2-enal 36**

A mixture of chloride 35, 13 g (0.05 mol), in dioxan (30 mL), triethylamine N-oxide (0.1 mole) and copper (I)

chloride, 0.5 g (0.004 mole) was stirred at 50° for 1 hr. The reaction mixture was mixed with 2.5% sulphuric acid (40 mL) and ethylacetate (40 mL). The organic layer washed with 2.5% sulphuric acid (20 mLx2), sodium bicarbonate (40 mLx2) and 10% sodium sulphite solution (30 mLx2). The organic layer dried and solvent removed *in vacuo* followed by chromatography on neutral alumina to get the aldehyde 36.

IR : 1670, 1685 cm^{-1}

^1H NMR : δ 1(S, 3H) 1.7 (S, 3H) 1.7-2.1 (m,4H)
5.15 (t, 1H)9.4 (S, 1H)

3.42 6,6-ethylenedithio-2,3-dimethylheptanal 37

Methyl magnesium iodide, 4.15 g (0.025 mol) was prepared by adding methyl iodide, 3.5 g (0.025 mol) to Mg 0.6 g (0.025 mol) in dry ether (50 mL) containing small amount of iodine. After the addition, stirring continued for 1 hr. Then added catalytic amount of cuprous iodide 1 g with stirring . Then added the ketone 35,6.12 g (0.025 mol) slowly with stirring at below 10°C. After the completion of the reaction, reaction mixture was poured into ice cold mixture of ammonium chloride (100 mL) containing few amounts of ammonia (10 mL) with vigorous shaking extracted with ether (50 mLx3) and washed with ammonium hydroxide (20 mLx3), then with water (20 mLx2), dried and concentrated to

give the 1,4 addition product 37, 4.8 g yield 80%.

3.43 **2,3-Dimethyl-6: 6- thylenedithio-hept-2-enal 38**

A solution of Br_2 (0.35 g, 2.2 m.mol) in glacial acetic acid (10 mL) was added to a stirred, cooled solution of the aldehyde 37, 0.5 g (2m mol) in glacial acetic acid. The mixture was stirred about 6 hrs. Reaction mixture neutralised with Na_2CO_3 solution (20 mL), extracted with CH_2Cl_2 (20 mLx4) washed with water (20 mLx3) dried and concentrated to get α-bromo derivative.

A slurry of K_2CO_3 (1.05 g, 8 m.mol) in dry methanol (10 mL) was added to the stirred solution of above bromide in dry methanol (10 mL). Stirred the reaction mixture about 7 hrs. Then neutralised with 1N HCl (30 mL), extracted with ether (20 mLx4) combined extracts washed with water (20 mLx3), dried and concentrated to get 38, 1.4 g 70% yield.

^1H NMR : δ 0.9 (S, 3H) 1.3 (d, each 3H) 1.5-2 (m,4H)
4.2 (S, 4H) 9.4 (S, 1H)

3.44 **2,3 Dimethyl 6.6-ethylene dithio-hept-2-ene 39**[31]

Hydrazine hydrate 4.33 g , (0.0866 mol) was added to amixture of the aldehyde 38 1 g, (0.005 mol), powered

potassium hydroxide 3.76 g (0.06 mol)and ethyle glycol (10 mL). The mixture was refluxed for 4 hrs. After adding water (12 mL) to the cold solution, the mixture was extracted with pentane (25 mLx4) and combined organic layer was washed with water until the washings became neutral. It was then washed with brine (10 mLx2), dried and concentrated to gave 39 0.6 g 82%.

^{1}H NMR : δ 0.9 (S, 3H) 1.3 (d, each 3H) 1.4 (S, 3H) 1.5-2 (m, 4H)

3.45 **2,3-Dimethyl-hept -2-en-6-one 31**

To the thio ketal 39, 0.22 g (0.001 mol) added excess BF_3 etherate (10 mL) in $CHCl_3$ with stirring at 0^o C. After the addition, reaction mixture was stirred at room temperature for 5 hrs. Added water (20 mL) to the reaction mixture extracted with $CHCl_3$ (20 mLx3) washed with water (20 mLx3) dried and concentrated to get 31 a C_9 synthon.

IR : 1720 cm^{-1}

^{1}H NMR: δ 1.6 (d, each 3H), 1.7 (S, 3H), 2.1 (S, 3H), 1.7-2.1 (m, 4H)

3.46 Methyl Cyclopentanone 40

Small pieces of potassium, 7.8 g (0.2 mol) was added to a stirred solution of t-butanol (150 mL) in N_2-atmosphere. Heated the mixture until the postassium was completely dissolved. cyclopentanone 16.8 g (0.2 mol) in dry dioxan (100 mL) was added slowly to a stirred potassium t-butoxide. After 1 hr; added methyl iodide 10 mL (0.2 mol) in dioxan (50 mL) was added with stirring. The mixture was stirred about three hour more. The reaction monitored by TLC. After completion, excess t-butanol was removed by vacuum distillation. Residue diluted with water (100 mL) extracted with ether (50 mLx4) Ether layer washed with water (40 mLx3) and with brine (40 mLx2) dried and solvent removed in vacuo, purified by column chromatography in silicagel to get 15 g, 70% yield.

IR : 1720 cm^{-1}

^1H NMR : δ 1(d, 3H), 1.5-2.3 (m, 6H) 2.5 (m, 1H)

3.47 Methyl- δ - Valerolactone 41

To a cooled mixture of con. sulphuric acid 90 mL and water (30 mL) was added ammonium persulphate 52.5 g (0.23 mole) in portions keeping the temperature at 10-12°. Ethanol (150 mL) was then added, maintaining the temperature below 12°. To this cooled mixture added a

solution of 2-methyl cyclopentanone 14.7 g (0.15 mol).in ethanol 50 mL drop by drop over 1 hr under stirring. The progress of the reaction monitored by TLC. After complete conversion, the mixture was allowed to come to room temperature, diluted with water (250 mL) and extracted repeatedly with ether layer (75 mLx4). The ether layer washed with sodium bicarbonate (75 mLx4) and then with water (50 mLx2). Solvent removal after drying yielded the lactone 41, 13.5 g 81% yield.

IR : 1735 cm^{-1}

^1H NMR: δ 1.5 (d, 3H) 1.7-1.9 (m, 4H) 2.1-2.5 (m, 2H) 4.5-5 (t, 1H)

3.48 **6-Oxo heptan-2-ol 42**

To a solution of lactone 41, 11.4 g (0.1 mol) in ether (100 mL) was added an ether solution of methyllithium prepared from lithium, 3.1 g (0.454 mol) and methyliodide, 27.5 g (0.194 mol) in anhydrous ether (100 mL) under stirring at-25°. Stirring continued for 30 minutes more and water (100 mL) added. The reaction mixture allowed to come to room temperature. The organic phase separated and washed with brine (3x30 mL). Ether layer dried, solvent removed and purified to get the keto alcohol 42, 6.8 g (60%).

IR : 3410, 1715cm^{-1}

^{1}H NMR : δ 1.1 (d, 3H) 1.7-2.3 (m, 4H) 2.2 (S, 3H)
2.7 (t, 2H) 4.1 (m, 1H)

3.49 6-Oxo-5-methylheptan-2-ol 43

The keto alcohol 42 , 6.8 g (0.05 mol) in dioxan was slowly added to a solution of potassium t-butoxide (0.05 mol). Which is prepared by dissolving potassium 2 g (0.05 mol) in t-butanol with stirring at room temperature. Then added methyl iodide 7 g (0.05 mol) to the reaction mixture. Stirring contuined for 2 hrs. Reaction monitored by TLC, Added to water (100 mL) to the reaction mixture. Ether layer separated, extracted with ether (50 mLx3) washed with water (50 mLx2) dried and concentrated to get 43 with 80% yield.

IR : 3410, 1715 cm^{-1}

^{1}H NMR : δ 1.1 (d, 3H), 1.5 (t, 3H), 1.7-2.3 (m, 2H),
2.2 (S, 3H), 2.9 (m, 1H) 4.1 (m, 1H).

3.50 2,3-Dimethyl hepta-2, 6-diol 44

The keto alcohol 43 7 g (0.05 mol) was added to methyl magnesium iodide, which was prepared by adding

methyl iodide 7 g(0.05 mol) to magnesium 1.7 g, (0.05 mol) in dry ether, with constant stirring at 20°C. After the addition, reaction mixture was stirred 2 hrs. more. Hydrolysed by adding 10% dil. H_2SO_4 to the reaction mixture, extracted with ether (10 mLx4) washed with sodium bicarbonate, (50 mLx3) then with water (50 mLx3) dried and concentrated in vacuo, to yield 7 g (90%).

2,3-dimethyl hept-2-en-6-ol 45

Pyridine 14 mL dissolved in dry ether (50mL) was added to the tertiary alcohol 44, 7 g (0.05 mol) with stirring at 0°C thionyl chloride 10 mL was added dropwise with constant stirring. After the addtion was over, the reaction mixture was allowed to stand for two days. It was then decomposed by adding crushed ice, extracted with ether (50 mLx4) combined extractes washed with dil. HCl (50 mLx4) then with sodium bicarbonate (50 mLx3) and with water (50 mLx2) dried and concentrated to get the dehydrated product 45, 5 g yield 80%.

^{1}H NMR : 1.5 (d, 3H) 1.8-2.1 (m, 4H) 1.7 (S, 9H)
4.1 (m,1H)

2,3-Dimethyl hept-2-en-6-one 31

To the alcohol 5 g (0.05 mol) dissolved in methylene chloride (75 mL) was added pyridinium chlorochromate (PCC)

21.5 g (0.01 mol) with stirring. Stirring contuinued for 2 hrs. The organic layer decanted, residue washed with dichloromethane (40mLx2). The combined organic layer washed with water (40mLx2) dried and solvent removed to get the ketone 31 4.5 g 90% yield.

.53 **Methyl Cyclohexene 46**

Cyclohexanone 9.8g (0.1mol) was slowly added to methyl magnesium iodide, which was prepared by adding methyl iodide 14.2 g (0.1 mole) to magnesium 2.4 g (0.1 mole) in dry ether with constant stirring at 20°C. After the addition reaction mixture was stirred 2 hrs. Hydrolised by adding 10% dil. H_2SO_4 to the reaction mixture, extracted with ether (100mLx4) washed with sodium bicarbonate (50 mLx3) then with water (50 mLx2) dried and concentrated to yield 90% of the product methyl cyclohexanol 10.2 g.

Pyridine 14mL dissolved in dry ether was added to the above tertiary alcohol 5.5. g (0.05 mol) with stirring at 0°C. Thionyl chloride 10 mL was added dropwise with constant stirring. After the addition was over, the reaction mixture was allowed to stand for two days. It eas then decomposed by adding ice water, extracted with ether (100 mLx4). Combined extracts washed with dil. HCL (50 mLx3), then withsodium bicarbonate (50 mLx3) and with water (50 mLx2), dried and

concentrated to get methyl cyclohexene 46, 4.5 g 80% yield.

B.P. : $110^{o}C$

^{1}H NMR : δ 1.7 (S, 3H) 1.75-2 (m, 8H)

5.7(d of d J=10 Hz and J^{1}3Hz for 1H)

.54 1-Methyl Cyclohexan-1,2,-diol 47

Methyl cyclohexene 46, 9.6 g (0.1 mol) in water (150 mL) contained in 1 litre R.B. flask was cooled to $5^{o}C$. Potassium permanganate 15.9 g (0.1 mole) in water (300 mL) was added to it at a rate of 25 mL per minutes with constant stirring . The temperature was kept constant at $5^{o}C$. Soon after stirring was stopped the mixture sets to a gel. It was then allowed to stand for two hours and the reaction mixture was heated for one hr. on the steam bath. It was then filtered through Buckner funnel. The residue manganese dioxide was washed thoroughly with water. The filtrate was cooled and extrated with ether using liquid-liquid extractor. Combined extracts dried and concentrted to yield 50% of the diol, 6.5 g.

.55 6-Keto heptaldehyde 48

Preparation of Lead tetra acetate $Pb(OAc)_4$

A mixture of acetic acid (12 mL) and acetic anhydride 8

mL in a three necked flask was heated to 55° with constnt stirring. Added red lead (Pb_3O_4) 14 g in portions. A fresh addition is made only after the colour due to proceding portion has largely disappeared and the temperature was kept between 55 and 80°C. At the end of the reaction, reaction mixture cooled, crystals filtered and washed with acetic acid. The crude product dissolved in hot acetic acid and decolourised by charcoal or Norrit, filtered and cooled. Colourless crystals filtered and used in oxidation.

To a solution of diol 47, 6.5 g (0.05 mol) in benzene (80 mL) added lead tetraacetate (0.08 mol) in about 25 minutes with stirring, temperature does not exceed 30°C . Stirring continued for 1 hour. The reaction mixture filtered, precipitate washed with benzene. Filtrate concentrated by distillation under reduced pressure to get 6-keto heptaldehyde 48, 70% yield.

3.56 Hepta-1,6-diol 49 (reduction of 48 with $NaBH_4$/Alumina)[45,46]

To a suspension of sodium borohydride 20 g and alumina 40 g in 200 mL ether, a solution of 6 g (0.05 mol) of 48 in 100 mL ether was added. After being stirred at room tempeture for 1 hr., the solution was filtered residue washed with ether (50 mLx3). The combined filtrate dried and concentrated to yield 5 g, 80%.

IR : 3430, 2995 cm^{-1}

^1H NMR : 1.3 (d, 3H) 1.7-2 (m, 8H)
3.98 (m, 2H) 4.32 (m, 1H)

3.57 6-Hydroxy-2-methylene-heptaldehyde 50[24]

To a stirred solution of oxallyl chloride 1.02 mL (12 m. moL) in methylene chloride (30 mL) was added dimethyl sulphoxide 1.2 mL (24 m.mol) dropwise at -70°C, and after 15 minutes alcohol 49 0.5 g (4m.mol) followed by triethylamine 6.2 mL (44 m.mol) are added at the same temperature. After having stirred at room temperature for 15 min., methylene-N,N-dimethyl ammonium chloride 752 mg (8 m.mol)was

added to the mixture and the stirring was continued for 15 hrs; at the same temperature. The mixture was taken up into methylenechloride (30 mL) washed with sodium bicarbonate (30 mLx3), and then with brine (30 mLx3), dried and concentrated to gave the aldehyde 0.45 g 90 % yield.

IR : 1720, 1650, 3430 cm^{-1}

^1H NMR : δ 1.2(d,3H) 1.7 - 2 (m,6H) 4.38 (m, 1H) 6.6 (S,1H) 5.9 (S, 1H) 10.1 (S,1H)

58 **6-Hydroxy-2-methyl hept-2-enal51**

The methylene heptadehyde 50, 0.45 g was added to stirred solution of 10% paratoluene sulphonic acid (20 mL) in ethyl acetate. The reaction mixture stirred 2 hrs.more, neutralised with sodium bicarbonate extrated with ethylacetate, washed with water (30 mLx3) then with brine (30 mLx3), dried and concentrated to gave 51 with 80% yield.

^1H NMR : δ 1.2(d, 3H) 1.8-1.9 (m, 4H) 1.7 (S,3H), 5.1 (t,1H) 4.3 (m,1H) 9.8 (S,1H)

59 **(E,E) 6,10-Dimethyl undeca-3,5,9-trien-2-one (Pseudoionone) 52**

To a solution of sodium hydroxide, 6 g (0.15 mol) in water (120 mL) and acetone, 58 g (73 mL, 1.0 mol) containing

benzyl triethyl ammonium chloride 2.28 g (0.01 mol) was added with vigorous shaking citral (13), 30.4 g (0.2 mol) drop by drop over 30 min. at room temperature. Stirring continued for 2 hrs. more. Excess acetone was removed by distillation. The residue extracted with ether (125 mLx4) washed repeatedly with water till neatral and then with brine (75 mLx2). The organic layer dried, solvent removed and purified by silicagel chromatography to yield pseudoionone 52, 35.7 g (93%) b.p. 101-110°/2 mm

UV	λ max 291 nm
IR	1675 cm^{-1}
^1H NMR	δ 1.65 (d,6H), 1.9 (S, 3H), 2.1 (m, 4H), 2.25 (S,3H), 5.1 (t, 1H), 5.9 (d, 1H), 6.2 (d,1H), 7.4 (m, 1H).

(E,E) 6,10 - Dimethyl undeca-3,5,9-trien-2-one (Pseudoinone) (Basic Alumina method) [40]

Pure citral 5 g (0.033 mol) was dissolved in acetone (200 mL) poured into basic alumina (100 g) with stirring under reflux at 60°C. Stirring continued for 4 hrs. Reaction monitored by TLC. After the completion of the reaction, reaction mixture was filtered, alumina washed with acetone

Filtrate concentrated to get a pale yellow oil b.p. 106-110°/2mm with 97% yield (6.28 g).

61 2,2-Ethylenedioxy 6,10-Dimethyl 6-hydroxy undeca-3,9-diene 53

To a stirred solution of methyl heptenone 14 12.6 g (0.1mol) and the ketal bromide (C_5 unit) 17.5 g (0.1 mol) in DMF (50 mL), zinc powder 9 g (0.1mol) was added in small portions at room temerature. An exothermic reaction started within 10 minutes and it ceased in 30 minutes. Then the reaction mixture was poured into saturated ammonium chloride (100 mL) extracted with ether (50 mLx3) and the combined organic layer was dried and concentrated to get tertiary alcohol 53 with 95% yield.

IR : 1610, 3325 (bd) cm^{-1}

^1H NMR : δ 1.5 (d, 6H) 1.7 (d, 6H) 2,1(m, 6H)
4.1 (5,4H) 5.1 (t, 1H) 5.9 (m, 1H)
6.2 (d, 1H)

The tertiary alcohol was dehydrated using thionyl chloride and pyridine as in the previous experiment to get the pseudoionone ketal 54.

62 2,2-Ethylenedioxy 6,10-dimethyl undeca-3,5,9- triene (Pseudoionone ketal) (Wittig method) 54

To a solution of n-butyllithium in ether (10 mL)

prepared from n-butylbromide, 0.69 g (0.005 mol) and lithium shavings, 0.087 g (0.0125 mol) was added the phosphonium salt 26, 25 g(0.005 mol) suspended in ether (15 mL) at -10°C. The red coloured phosphorane was formed instantaneously. The reaction mixture was allowed to stir for a further 15 min. To this solution added a solution of the methylheptenone 14 0.6 gm (0.005 mol) in ether (10 mL) . The reaction mixture was stirred for 6hrs. and then poured into ice cold water (50 mL) and extracted with ether (40 mLx2). Ether layer washed with water (30 mlx2) and brine (30 mLx2and dried. Solvent removal gave 54, 8.25 g 71% yield.

(E,E)-6,10-Dimethyl undeca-3,5,9-trien-2-one (Pseudoionone) 52 from 54 .

The solution of the ketal 54 0.2680 g(0.001 mol) and p-toluene sulphonic acid (10 mg)in 6:1 acetone (20 mL) was gently refluxed for 2 hrs. The mixture was cooled acetone removed under reduced pressure and the work up afforded the ketone 52, 0.24 gm 90% yield.

4-(2,6,6-trimethyl 2-cyclohexen-1-y1) 3-butene-2-one (α-ionone)[42]

Pure pseudoionone 1 g dissolved in ethyl-acetate (40 mL) was added to acidic alumina (20 g) soaked in a 10% solution of

a paratoluene sulphonic acid in ethyl acetate (40 mL) with stirring. Stirring continued for 1 hour. Reaction mixture filtered and washed with ethylacetate, filtrate washed with water (20 mLx3) then with brine (20 mlx3), dried and concentrated to give 0.95 g (95%) . G.C. and T.L.C. shows three components, purified by column chromatography on silicagel (Sisco-mesh size 100-200 activated for 1 hour at 100^{o}C) using hexane and ethyl acetate as eluents in the ratio 9:1.

α = 54.44%, β =8.35% γ = 36.9%

65 **4-(2,6,6-Trimethyl-1-cyclohexen -1-yl) 3-buten-2-one (β-ionone)**

Pseudoionone 3 g (0.015 mol) prepared in the above methods, was added to a stirred mixture of con. sulphuric acid 5.88 g (0.06 mol) and ethyl acetate (15 mL) at-5^{o}C within 1.5 hrs. Stirring continued for 1 hr. Reaction mixture was decomposed by pouring into a mixture of crushed ice and ethyl acetate (50 mL). The organic layer separated, aqueous layer was extracted with ethyl acetate (50 mLx4). Combined extracts washed with water (40 mLx3), 1% sodium carbonate till alkaline, then with brine (30mLx3), dried and concentrated to get 2.4 g 85% yield.

B.P. : 92-96°/2 mm

UV : λ max 296 nm (ε 9700)

218 nm (ε 7190)

It was then purified by column chromatography on silicagel (Sisco 100-200) using hexane and ethyl acetate as eluents in the ratio 95:5.

UV : λ max 297.5 nm, 218 nm (ε 7190)

^{1}H NMR : δ 1.07 (S, 6H)

1.78 (S, 3H) 2-2.1 (m, 6H) 2.31 (S, 3H)

6.11 (d, 1H), 7.28 (d, 1H)

IR : 2850, 1720, 1610, 1360, 1260, 975 cm^{-1}

.66 **Methyl Pseudoionones (iso- and n-)**

Pure citral 2.5 g (0.015 mol) was dissolved in ethyl methyl ketone (150 mL) poured into basic alumina (50 g) with stirring under reflux. Stirring continued for 2 hours. Reaction monitored by TLC. After the completion of the reaction, reaction mixture was filtered, alunina washed well with acetone filtered filtrate concentrated to get pale yellow oil. TLC & GLC analysis shows three isomers. These are separated by column chromatography using silicagel column, hexane ethylacetate in the ratio 98:2 as eluent.

^{1}H NMR : δ 1.3 (t, 3H) 1.65 (d, 6H) 1.9 (S, 3H)
2.1 (m, 4H) 2.25 (m, 2H) 5.1 (t, 1H)
5.9 (d, 1H) 6.2 (d, 1H) 7.4 (m, 1H)

2 and 3 : δ 1.65 (d, 6H) 1.7 (S, 3H) 1.9 (S, 3H)
2.1 (m, 4H) 2.3 (S, 3H) 5.1 (t, 1H)
5.9 (d, 1H) 6.2 (d, 1H)

3.67 Cyclisation of methyl Pseudoionone (Acidic Alumina Method)

Pure methyl pseudoionone 1 g was dissolved in ethylacetate (40 mL) was added to acidic alumina (20 g) soaked in a 10% solution of para toluene sulphonic acid in ethylacetate (40 mL) with stirring. Stirring continued for 1 hr. Reaction mixture filtered and washed with ethylacetate, filtrate washed with water (20 mLx3) then with brine (20 mLx3) dried and concentrated to give 0.8 g with 95% yield. GLC shows three components separated by column chromatography on silicagel column and hexane ethyl acetate in the ratio 9:1 eluent.

68 Cyclic C_{10} + C_3 Unit

Cyclocitral (0.01 mol) was dissolved in ethyl methyl ketone (100 mL) poured into basic alumina with continuous stirring under reflux. Stirring continued for 4 hrs. Reaction mixture filtered, Alumina washed well with ethyl methyl

ketone, concentrated to get 75% conversion mixture of n- and iso-methylionones separated by column chromatography.

UV : λ_{max} 297 nm

3.69 **2,2-Ethylenedioxy-6-hydroxy-6,9,10-trimethyl-undeca-3,9-diene 64 (C_9 + C_5)**

To a stirred solution of 2,3-dimethylhept-2-en-6-one 31, 7 g (0.05 mol) and the ketal bromide 25, 10 g (0.05 mol) in DMF (50 mL), zinc powder (0.06 mol) was added in small portions at room temperature. An exothermic reaction started within 10 minutes and ceased in 30 min. The reaction mixture was poured into saturated amonium chloride (100 mL) extracted with ether (50 mLx3) and the combined organic layer was dried and concentrated to a tertiary alcohol, 64, 12 g , 98% yield.

^{1}H NMR : δ 1.5 (d, 6H) 1.7 (S, 6H) 1.75 (d, 3H)
2.1 (m, 6H) 4.1 (S, 4H) 5.25 (t, 1H)
6.2 (d, 1H)

3.70 **6,9,10-Trimethyl undeca-3,5,9,trien-2-one 65 (Pseudoirone)**

The alcohol 64, 2.68 g (0.01 mol) in dry pyridine (10 mL) was treated with a cold solution of thionyl chloride

2.17 g (0.018 moL) and kept at 0^{o} for 17 hrs. Ether (40 mL) was added to the mixture and it was then treated with cold dil. HCL (25 mL). The mixture was then extracted with ether (3x50 mL), ether layer washed with sodium bicarbonate (15 mLx3), water (50 mLx3) and dried. The residue was mixed with p-toluene sulphonic acid (2 g) in dry benzene (25 mL) and refluxed for 10 hrs. The mixture was diluted with water (20 mL) and solvent was removed in vacuo. The residue was extracted with ether (50 mLx3), washed with water (30 mLx20) dried and concentrated in vacuo to get pseudoirone 65, 1.5 g 70% yield.

IR : 1675, 1620 cm^{-1}

^{1}H NMR: δ 1.65 (d, 6H) 1.8 (S, 3H) 1.9 (S,3H)
2.1 (m,4H) 2.3 (S,3H) 5.9 (d,1H)
6.2 (d,1H) 7.4 (m,1H)

Pseudoirone (Wittig Method)

Sodium hydride (0.816 g, 0.017 mol, 50% dispersion) was washed with dry ether (5 mLx3) under nitrogen atmosphere. Anhydrous dimethyl sulfoxide (3 mL) was added and the mixture was stirred at 70^{o} for 30 min. under nitrogen. The solution was cooled to room temperature and triphenylphophonium bromide (0.016 mol) dissolved in hot dimethyl sulfoxide (3 mL) was added . The mixture was warmed at 80^{o} for 30 min. and the C_9 ketone 31, 0.14 g (0.016 mol)

dissolved in dimethylsulphoxide (5 mL) was added. After heating at 80°C for 6 hrs. The mixture was cooled to room temperature and quenched with cold water (10 mL). The mixture was extracted with ether (30 mLx3), washed with water until the washings are neutral to litmus and dried. Solvent was removed under reduced pressure to get ketal, which on hydrolysis with p-toluene sulphonic acid lead to 65.

4-(2,5,6,6-Tetramethyl-1-cyclohexen-1-yl) 3-buten-2-one (β-irone)

Pseudoirone prepared in the above methods, 4.12 g (0.02 mol) was added to a stirred mixture of con. H_2SO_4 6 mL (0.01 mol) and ethylacetate (15 mL) at -5°C within 1.5 hr. Stirring continued for 1 hr. Reaction mixture was decomposed by poured into a mixture of crushed ice and ethyl acetate (50 mL). The organic layer separated, aqueous layer extracted with ethylacetate (50 mLx4) combined extracts washed with water (40 mLx3), with 1% sodium bicarbonate till alkaline, then with brine (30 mLx3) dried and concentrated to get 3.2 g 80% yield. GLC analysis showed that it contain three isomers in the ratio 58:32:10. These three are separated using column chromatography

UV : λ_{max} 298 nm

IR : 1690, 1630 cm^{-1}

^{1}HNMR : δ 0.9 (d, 3H) 1.07 (S, 6H) 1.7 (S, 3H)

1.9 (m, 4H) 2 (t, 1H) 2.2 (S, 3H)

6.11 (d, 1H), 7.28 (d, 1H)

3.73 **4-(2,5,6,6-Tetramethyl-2-cyclohexen-1-yl) 3-buten-2-one (α -irone) 66**

Pure pseudoirone 1 g was dissolved in ethylacetate (40 mL) was added to acidic alumina (20 g) soaked in a 10% solution of paratoluenesulphonic acid in ethylacetate (40 mL) with stirring. Stirring continued for 1 hour. Reaction mixture filtered and washed with ethylacetate, filtrate washed with water (20 mLx3) then with brine (20 mLx3) dried and concentrated to give mixture of irones which are separated by column chromatography to get pure α -irone 66 with 70% yield.

UV : λ max 229 nm

IR : Same as β -irone

^{1}H NMR : δ 0.9 (d, 3H) 1.07 (S, 6H) 1.7 (S, 3H)
2.2 (S, 3H) 1. 9 (m, 2H) 2 (t, 1H)
4.5 (S, 1H) 4.65 (S, 1H), 5.3 (t, 1H)
6.8 (d, 1H) 7.4 (d, 1H)

3.74 **4-(2,6,6 - Trimethyl 2-cyclohexen-1-yl) -2,2-ethylene dioxy 3-butene 69**

A mixture of α -ionone (54), 28.7 g (0.15 mol) and

ethylene glycol 19.8 g (0.33 mol) in thiophene free benzene (250 mL) was refluxed under stirring with catalytic amount of pyridinium para toluene sulphonate for 5 hrs. The reaction mixture diluted with water (100 mL), benzene removed under reduced pressure and the residue extracted with ether (100 mLx2). The ether layer washed with (40 mLx2), sodium bicarbonate (40 mLx2), dried, solvent removed and purified by silicagel chromatrography to get the ketal 14, 21 g 70% yield.

^{1}H NMR : δ 1.07 (S, 6H) 1.5 (S, 3H) 1.78 (S, 3H) 3.9 (S, 4H) 2-2.1 (m, 4H) 5.8 (t,1H) 6.11 (d, 1H) 7.28 (d, 1H)

4- (2,6,6-Trimethyl-3-oxo-2-cyclohexen-1-yl)-2,2-ethylene dioxy 3-butene 70.

α-ionone ketal 20 g (0.1 mol) was added to PDC 75 g (0.2 mol) in benzene (150 mL). Then added t-butyl hydroperoxide 18 g (0.2 mol) drop by drop to a stirred mixture below 20°C. After 6 hrs. added exess ether and decanted. The solid residue washed with ether (50 mLx4). Combined ether layer concentrated, purified by column chromatography to gave 15, 12 g, 60%.

IR : 1710 cm^{-1}

^{1}HNMR : δ 1 (S, 6H) 1.5 (S, 3H) 1.7 (S, 3H) 2.1 (S, 2H) 3.9 (S, 4H) 6.11 (d, 1H) 7.1 (S, 1H) 6.9 (d, 1H)

4-(2,5,6,6-Tetramethyl-3-oxo-2-cyclohexen-1-yl) -2,2-ethylene dioxy-3-butene 71

To sodium hydride 0.23 g (0.01 mol) washed with anhydrous ether (20 mLx3) was added anhydrous dimethoxy ethane 30 mL followed by the above ketone 70, 12 g (0.05 mol) in dry dimethoxy ethane with stirring under nitrogen atmosphere. Stirring continued for 2 hrs. To the mixture added freshly distilled methyl iodide 7 g (0.05 mol) at $0^{o}C$. After stirring 2 hrs., the mixture was poured into a slurry of ice and saturated ammonium chloride solution, extracted with ether (50 mLx4), ether layer washed with water (20mLx3) dried and concentrated *in vacuo* afforded the ketone 71, 5.4 g 60% yield.

4-(2,5,6,6-Tetramethyl-2-cyclohexen-1-yl)-2,2-ethylene dioxy-3-butene 72

A mixture of ketone 71, 2.16 g (0.01 mol) and ethane dithiol (2.3mL) was treated with BF_3: etherate (4 mL), swirled and let stand for 45 minutes. The homogeneous mixture was diluted with water (20 mL), extracted with ether (20 mLx3) washed with sodium hydroxide solution (50 mLx3) and then with water (50 mLx3) dried and concentrated to get thioketal.

A mixture of thioketal of 71 and Raney - Nickel two spoon (6 g) in absolute methanol (150 mL) was refluxed under stirring for 24 hours. The nickel was filtered, washed with hot methanol (25 mLx3) concentrated, to yield 75% reduced product 72.

^{1}H NMR : δ 0.9 (S, 1H) 1.07 (5, 6H) 1.5 (S, 3H) 1.7 (S, 3H) 1.9 (d, 2H) 3.9 (S, 4H) 5.9 (t, 1H) 6.2 (d, 1H) 7.1 (d, 1H)

4-(2,5,6,6-Tetramethyl-2-cyclohexen-1-yl)-3-buten-2-one (α -irone) 66.

The α -irone ketal (72), (0.001 mol) and para toluene sulphonic acid (10 mg) in 6:1 aqueous acetone (20 mL) was gently refluxed for 2 hrs. This mixture was cooled, acetone removed under reduced pressure and the residue extracted with ether (20 mLx3),washed with water (20 mLx3), dried and concentrated to get α -irone (66).

^{1}H NMR : δ 0.9 (S, 3H) 1.07 (S, 3H) 1.7 (S, 3H) 1.8-1.9 (m, 4H) 2.1 (S, 3H) 5.9 (t, 1H) 6.11 (d, 1H) 7.28 (d, 1H)

4-(2,6,6-Trimethyl 1-cyclohexen-1-yl)-1-buten -4-ol (73)

To a stirred solution of cyclocitral 30 g (0.2 mol) and allyl bromide (26.2 g, 0.2 mol) in DMF (50 mL), zinc powder (19.5 g , 0.3 mol) was added in small portions at room

temperature. An exothermic reaction started within 10 minutes and it ceased in 30 minutes. Then the reaction mixture was poured into a saturated ammonium chloride (100 mL) extracted with ether (50 mLx3) and the combined organic layer was dried (Na_2SO_4) and concentrated to give 36.8 g of homoallyl alcohol, yield 95%.

^1H NMR : δ 1.38 (S, 3H) 1.7 (S, 3H) 1.8 (S, 3H) 1.9-2.1 (m, 6H) 2.58 (m, 2H) 4.2 (t, 1H) 5.8 (d, 2H) 5.38 (S, 1H) 5.88 (d, 1H)

IR : 3450 (b), 3080, 2920, 1640, 1660, 1050,910 cm^{-1}

80 **4-(2,6,6-Trimethyl-1-1-cyclohexen-1-yl) 1-buten -4-one (75)**

PDC 16.5 g (0.05 mol) was added to a solution of the alcohol (1.94 g, 0.01 mol) in DMF (50 mL) at 25°C and the mixture was stirred for an additional 3 hrs. Water (100 mL) was added, extracted with ether (25 mLx3). The combined extracts washed with water, dried (Na_2SO_4) concentrated *in vacuo* and purifed by column chromatography using silicagel ethylacetate and hexane (3:97) as eluent to give 5.5 g of ketone yield 64%.

^1H NMR : δ 1.8 (S, 3H) 1.38 (S, 3H) 2.5 (t, 2H) 5 (S, 1H) 5.3 (d, 1H) 5.8 (d, 1H)

IR : 2920, 1710, 1640, 1660 cm^{-1}

3.81 **4-(2,6,6-Trimethyl-cyclohexen-1-yl)-2-buten -4-one (β -Damascone) 74.**

To a solution of ketone (1.9 g, 0.01 mol) in acetone (40 mL) was added to HCL (3.6 g , 0.01 mol) dropwise during the period of half an hour. The reaction was followed by TLC and was completed within one hour. Reaction mixture was neutralised by sodium bicarbonate, extracted with ether (50 mLx3). Combined organic layer washed with water (30 mLx2) dried, concentrated in vacuo. Purified column chromatography, gave 70% of the compound.

^{1}H NMR : δ 1.38 (S, 3H) 1.48 (S, 3H) 1.7 (S, 6H) 1.7 - 2.1 (m, 6H) 6.5 (d, 1H) 6.8 (m, 1H)

IR : 2920, 1710, 1625, 1450, 1390 cm^{-1}

3.82 **4-(2,6,6-Trimethyl-cyclohexen-1-yl) 2-buten-4-one (β -Damascone)**

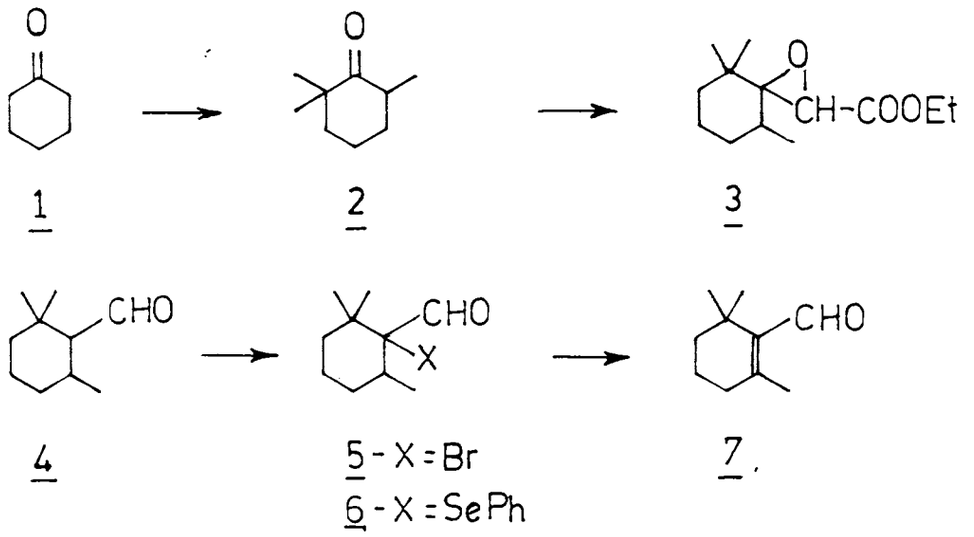
Jones reagent was added dropwise to the alcohol 73 (1.9 g , 0.01 mol) in acetone (50 mL) untill red colour persists. Reaction followed by TLC and was completed within 30 minutes. Water was added (50 mL) to the reaction mixture, acetone distilled off extracted with ether (50 mLx3). Combined extracts washed with sodium bicarbonate (50 mLx3) and with water (50 mLx2), dried and purified to get 8.4 g yield 70%.

CHAPTER IV

RESULTS AND DISCUSSION

4.1 Synthesis of C_{10} Cyclic Unit (Cyclocitral)

Different approaches developed for the synthesis of β-cyclo citral and its derivatives have been reviewed[1]. Here three methods have been tried for the synthesis of β -cyclocitral from cyclohexanone. Cyclo hexanone on alkylation with potassium tertiary butoxide gave mono, di and tri alkylated ketones, these are separated by using column chromatography. 2,2,6-Trimethyl cyclohexanone was converted to a glycidic ester[2] 3 by using ethyl chloroacetate and potassium t-butoxide as base. (A sharp IR peak at 1780 cm^{-1} shows an ester group and NMR peak at δ 1.1, δ 1.2 and δ 1.5 shows four methyl groups and the one singlet at δ 3.2 shows a single hydrogen at the O-CH-COOEt). The epoxy ester (3) was converted to 2,2,6-trimethyl cyclohexyl aldehyde (4) on treatment with sodium ethoxide followed by dil.HCl. (A singlet at δ 9.5 assignable for hydrogen of the aldehyde group and one doublet at δ 1.1 for one methyl group and a singlet at δ 0.9 for other two methyl groups in the ^1H NMR spectrumconfirmed the structure 4) (Scheme - I).



1 2 3

4 5 - X = Br 7

6 - X = SePh

SCHEME - I

The aldehyde 4 was converted to β -cyclocitral by introducing an α , β - unsaturation. There are a number of methods available for the conversion of carbonyl compounds to its α,β-unsaturated analogues[3-7], the most important of which is α -bromination dehydrobromination[4]. Organoselenium methodology has also been tried becauseof its simplicity. The application of organo selenium reagents for the synthesis of α,β-unsaturated carbonyl compounds has been reported[5]. This method involves the oxidation of α-phenyl seleno carbonyl compound 6 (derived from carbonyl compound with $PhSeSePh/SeO_2$ in CH_2Cl_2[6]) to the corresponding selenoxide, which undergo clean syn elemination at room temperature to give the α, β - unsaturated carbonyl compound[7]. The aldehyde 4 was selenylated by adding a solution of 4 in CH_2Cl_2 to a suspension of SeO_2 and

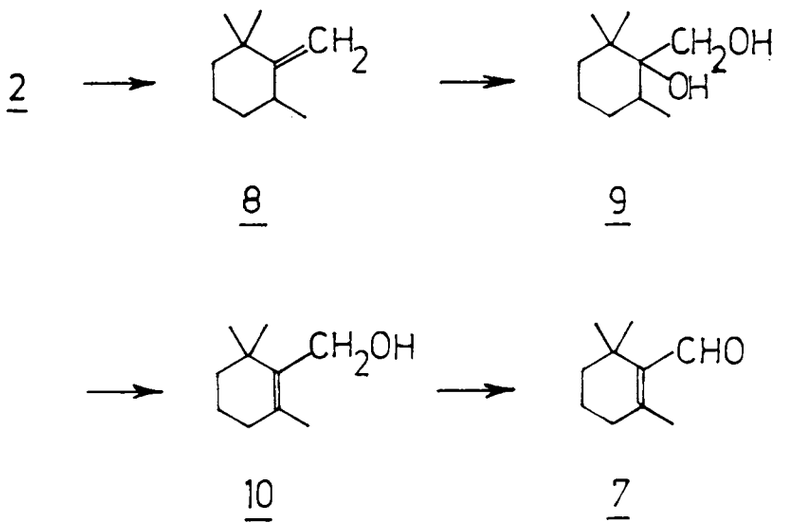
PhSeSePh in CH_2Cl_2 containing catalytic amount of H_2SO_4[6]. The mixture was stirred below 10° for 18 hrs. The work up yielded the α-phenyl selenylated aldehyde with 70% yield. (A multiplet at δ 7 - 8 for 5-hydrogen of the phenyl group and a singlet at δ 9.8 for single hydrogen of the aldehyde group in its ^1H NMR confirm the structure 6).

The α-phenyl selenylated ketone 6 was then oxidised with excess 30% H_2O_2 below 5°[7] and the subsequent selenoxide syn elimination afforded the α,β-unsaturated aldehyde-β-cyclocitral (7). (A sharp singlet for one hydrogen at δ 9.8 and a singlet for 6H at δ 1.2 and singlet for three hydrogen at δ 1.5 in its ^1H NMR spectrum confirmed the structure. Also UV λ max 240 nm for α, β unsaturated aldehyde and IR at 1685 cm^{-1} and 1670 cm^{-1} proved the aldehyde structure).

Second method of preparation of cyclocitral was tried by using the Wittig reaction. Wittig condensation of the phosphonium salt with the carbonyl compounds was reported[8]. Condensation of 2,2,6-trimethyl cyclohexanone with methyl triphenyl phosphonium iodide in presenceof n-butyl lithium afforded the olefine 8. (A singlet at δ 0.9 for six hydrogen and a doublet at δ 1.2 for 3H assigned for three methyl,

groups and a doublet at δ 6.6 for 2H shows the methylene hydrogens in the ^1H NMR spectrum confirmed the structure of 2,2,6-trimethyl 1-methylene cyclohexane 8) (Scheme -II).

The olefine 8 was converted to cyclogeraniol through diol 9. Many methods are available for the conversion of olefine (8) to the diol[9] (9). Aqueous $KMnO_4$ oxidation of the olefine was tried by adding aqueous $KMnO_4$ to the olefine in water at 5°C. The reaction mixture filtered and extracted with ether in a liquid-liquid continuous extractor to yield about 50% diol[10].



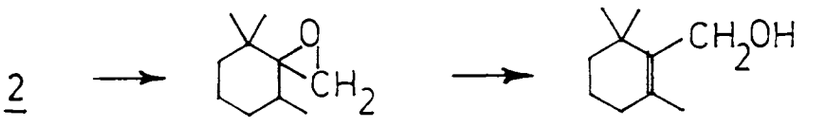
SCHEME -II

The diol obtained from 8 contains one tertiary alcoholic group. This tertiary alcohol was dehydrated by using thionylchloride and pyridine[11] to gave the α,β - unsaturated alcohol, β -cyclogeraniol. (The broad IR peacks at 3670 cm^{-1} and 3650 cm^{-1} indicate the alcoholic group and at 1650 cm^{-1} confirm the unsaturation. ^1H NMR spectrum also confirmed the structure of alcohol as β-cyclogeraniol (10).

β-Cyclogeraniol on oxidation with P.C.C. or P.D.C. gave corresponding aldehyde β-cyclocitral without any allylic rearrangement.

A method utilising Corey-Chaykovsky reaction[13] has also been tried from cyclohexanone for the synthesis of β -cyclocitral. By using Corey's base dimethoxy sulfonium methylide the ketones are converted to a methylene oxide 11. This epoxide was directly converted to alcohol by using lithium diisopropylamide. Here,for synthesis of β-cyclocitral 2,2,6-trimethyl cyclohexanone on treatment with Corey's base prepared from trimethyl sulphonium iodide and dry sodium hydride gave 2,2,6-trimethyl-cyclohexyl methylene oxide 11. (A singlet

at δ 4.1 for two hydrogen indicate $-CH_2O-$ group and singlet for 6H at δ 0.9 and a doublet at δ 1.2 for 3H indicate the three methyl groups and δ 1.5 - 2.1 multiplet for 6H in the ^1H NMR spectrum indicated structure 11 for the epoxide.



11 10

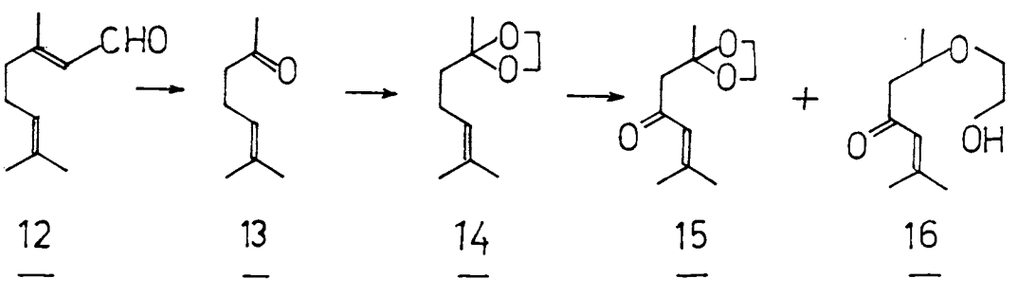
SCHEME - III

This epoxide 11 is also prepared from the olefine 8 on epoxidation with peracid. This epoxide on treatment with LDA gave the α,β-unsaturated alcohol- β -cyclogeraniol (10) which on P.C.C.[12] oxidation gave corresponding aldehyde β-cyclocitral (7). Of these three methods, involve only two steps in Corey-Chaykovsky method.

Citral obtained from Lemongrass oil was also used as the starting material for the synthesis of cyclocitral. Citral (12) on retroaldol condensation in slightly alkaline conditions is known to give methyl heptenone (13)[14]. When citral is mixed with excess of 1% Sodium carbonate solution

and is stirred under reflux; methyl heptenone is formed. The keto group in 13 was protected as its ketal by refluxing the ketone with ethylene glycol in dry benzene using Dean-Stark apparatus[15]. (A sharp singlet at δ 3.95 for 4H confirmed the $-O-CH_2-CH_2-O-$ linkage and the disappearance of the singlet at δ 2.1 for 3H of $-COCH_3$ group in methyl heptenone observed in the ^1H NMR spectrum confirmed the ketal structure).

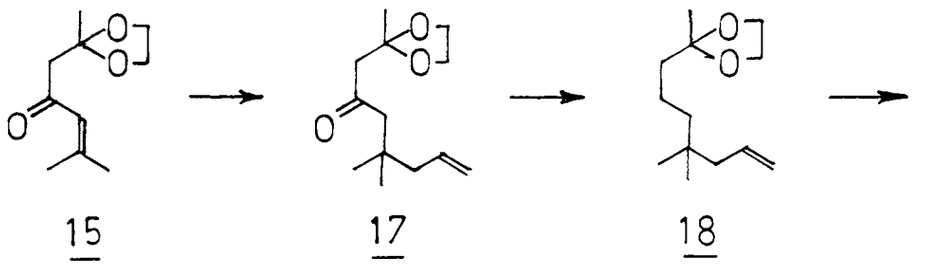
Tertiary butyl hydroperoxide and pyridinium dichromate (TBHP-PDC) system has been used for allylic oxidation of citronellylacetate to get the α,β-unsaturated ketone without affecting the terminal methyl group[16]. This method of allylic oxidation was applied to methyl heptenone ketal 14. Methyl heptenone ketal 14 in benzene on treatment with PDC[17] and t-butylhydroperoxide at 10°, gave the ketone 15 with only about 60% yield, because some of the ketal is converted to hemi ketal.



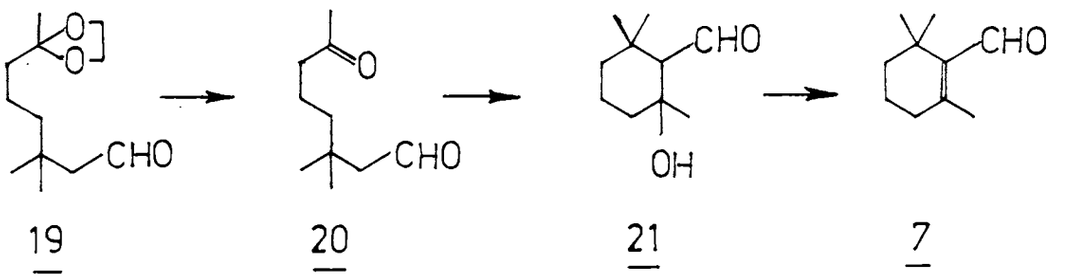
12 13 14 15 16

(The structure of 15 was assigned by the IR peak at 1700 cm^{-1} and NMR singlet at δ 2.3 for 2H proved $-CO-CH_2-$ group. In compound 16 the sharp singlet at δ 4.11 changed into a doublet shows $-O-CH_2-CH_2-OH$).

For alkylation at β-position of the α,β-unsaturated ketone 15, the reported[18] cuprous halide catalysed Grignard reaction was used[18]. α,β-unsaturated ketone 15 on 1,4 addition with allylmagnesium bromide, prepared from allyl bromide and magnesium and cuprous iodide as catalyst gave an olefine 17 in 80% yield.



15 17 18



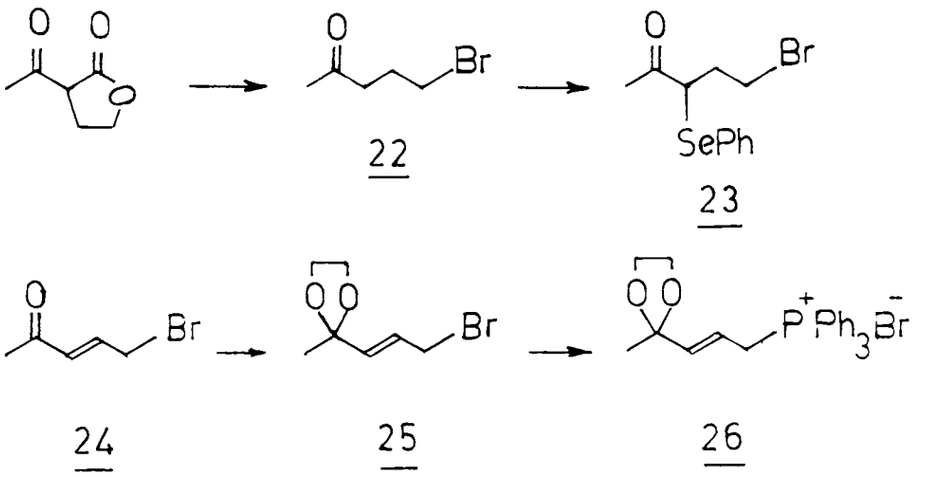
19 20 21 7

For reduction of the carbonyl group to a methylene group, the thioketal and Raney-Nickel reductive elimination[19] was adopted because of mild condition and simplicity of the reaction, under this condition the functional group is not affected. So 17 on treatment with ethanedithiol with catalytic amount of BF_3 etherate gave thioketal[19b]. Thioketal on refluxing with Raney-Nickel in absolute methanol gave the reduced product in about 95% yield. The preparation of Raney Nickel[20] from Ni-Al alloy was time consuming , nevertheless mild condition and easy work up of this reaction with thioketal made this the method of choice.

The aldehyde 19 deketalised by refluxing with p-toluene sulphonic acid, followed by base treatment gave the cyclised tertiary alcohol-21. In the cyclisation step two other components were also obtained which could not be identified. The tertiary alcohol 21 on dehydration with thionyl chloride and pyridine gave the β-cyclocitral(7) about 30% yield. No attempt have been made to find the exact yield of this reaction.

4.2 Synthesis of C_5 Unit, 1-Bromo Pent-2-en-4-one (24)

2-Acetyl butyrolactone a commercially available chemical was opened up by treating with 48% aqueous hydrobromic acid in phase transfer conditions to yield the keto bromide 22 in 85% yield[21] (Scheme VI). (A singlet at 2.17 for 3H (CH_3-CO-), a triplet at δ 3.5 for 2H and a multiplet in the region δ 2.2-2.8 for 4 H in the ^1H NMR spectrum confirms the structure 22).



SCHEME VI

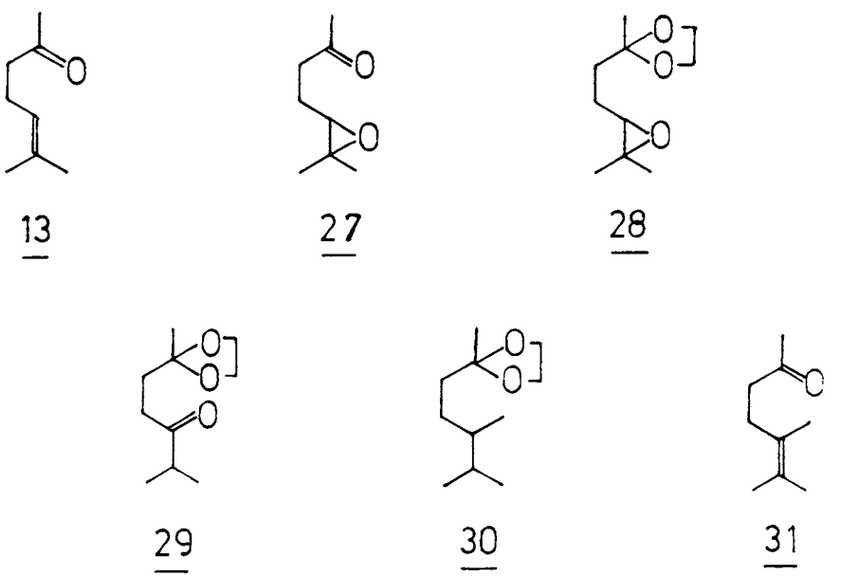
Introduction of α,β-unsaturation was done by phenyl selenylation using PhSeSePh/SeO_2 in methylene chloride followed by oxidation with 30% hydrogen peroxide as in the synthesis of β-cyclocitral, afforded the α,β-unsaturated

keto bromide 24. (A sharp singlet in the ^1H NMR spectrum at 2.2 for 3H assignable to acetyl group and two doublets at 6.05 and δ 6.8 for each olefinic hydrogen confirmed the enone structure).The enone 24 was then protected as its ketal[22] by refluxing the ketone and ethylene glycol in thiophene free benzene containing catalytic amount of pyridinium paratoluene sulphonate (PPTS). The ketal was obtained in 83% yield in 2 hrs. Use of PPTS as catalyst in ketal forming reactions has been reported[22]. High yields and shorter reaction times are the obvious advantages. The ketal bromide 25 was converted to corresponding triphenyl phosphonium bromide 26 by adding 25 with triphenyl phosphene and keeping for 12 hours. This triphenyl phosphonium bromide was used for Wittig coupling reaction[23]. But 25 also has been directly used in recently reported zinc mediated coupling reactions[24].

4.3 Synthesis of C_9 Unit, 2,3-dimethyl-hept-2-en-6-one(31)

To prepare the C_9 unit 31, epoxide ring opening followed by Grignard reaction was tried starting from methyl heptenone. Methyl heptenone 13 on epoxidation with peracetic acid[25], prepared by mixing acetic acid and 30% hydrogen peroxide in the ratio 3:1 gave an epoxide 27 in 50% yield.

(The structure was confirmed by the appearance in the ^1H NMR spectrum of a triplet for one proton at δ 2.7 ($-CH_2-CH-O-$) and theshift of two gem-dimethyl protons from δ 1.7 to 1.25 and δ 1.3). The epoxide 27 was ketalised by refluxing withethyleneglycol in thiophene free benzene and catalytic amount of PPTS. For converting an epoxide to a ketone many methods are available. Here, the epoxide was treated with BF_3 etherate[26] and then heated at 100° for 1 hour cooled and after work up gave the ketone 29 (See Scheme VII).



13 27 28

29 30 31

SCHEME - VII

An IR peak at 1720 cm^{-1} confirmed the presence of keto group in 29.

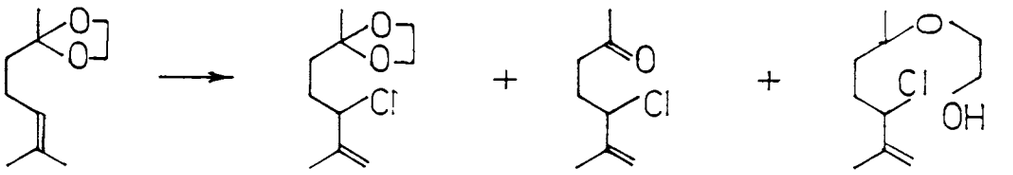
6,6-Ethylenedioxy-2-methyl-heptan-3-one 29 on Grignard reaction with methyl magnesium iodide in dry ether, followed by dehydration of the tertiary alcohol gave an olefine 30 which on deketalisation gave the C_9 synthon, 2,3-dimethyl-hept-2-en-6-one (31).(A sharp IR peak at 1720 cm^{-1} and in the ^1H NMR spectrum the additional singlet for 3H at δ 1.7 and the disappearance of a triplet for 1H at 5.1 in methyl heptenone also confirm the structure of the important synthon 2,3-dimethyl-hept-2-en-6-one 31). On coupling this C_9& C_5units theC_{14} linear unit pseudo-irone for irone synthesis was obtained.

The synthesis of C_9 unit was also achieved by terminal allylic functionalisation of the isopropylidene derivative of the small terpene molecules like citral or methyl-heptenone. Regio and Stereo selective C-C bond formation was possible through allylic functionalisation[27].

Allylic chlorides[28] can be converted to α,β -unsaturated aldehydes. It has been reported that tertiary amine N-oxides convert allylic chlorides into α,β -unsaturated aldehydes[29]. Many methods are available for the preparation of N-oxides from tertiary amines[30].

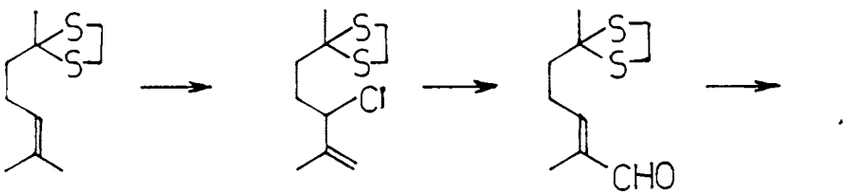
The methyl heptenone ketal 14 converted into its allylic chlorides 32 in 70% yield by adding dry ice to a solution of 14 and calcium hypochlorite in CH_2Cl_2/H_2O. (In ^1H NMR the presence of a doublet centred around δ 4.95 assignable to the terminal methylene protons and a triplet for one hydrogen at δ 4.35 (-CH(Cl)) confirmed the structure . But one drawback of this reaction was that it hydrolyses the protective group of the ketal by the production of HOCl *in situ*.

If we give more reaction time, more and more ketal group was removed (See scheme VIII). So the keto group of methyl heptenone was protected as thioketal with ethane dithiol with catalytic amount of BF_3 etherate. Then the ketal 34 was converted to ene- chloride. This allyl chloride 35 on treatment with triethylamine N-oxide and cuprous chloride in dioxan at 50°C afforded the aldehyde 36 in 60% yield. (The appearance of aldehyde hydrogen at δ 9.4 in the ^1H NMR spectrum confirm the structure of aldehyde). (See Scheme IX).

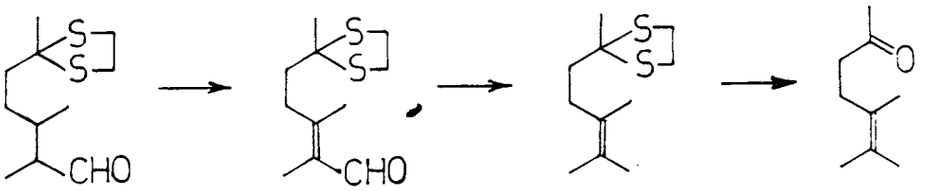


14 32

SCHEME - VIII



34 35 36



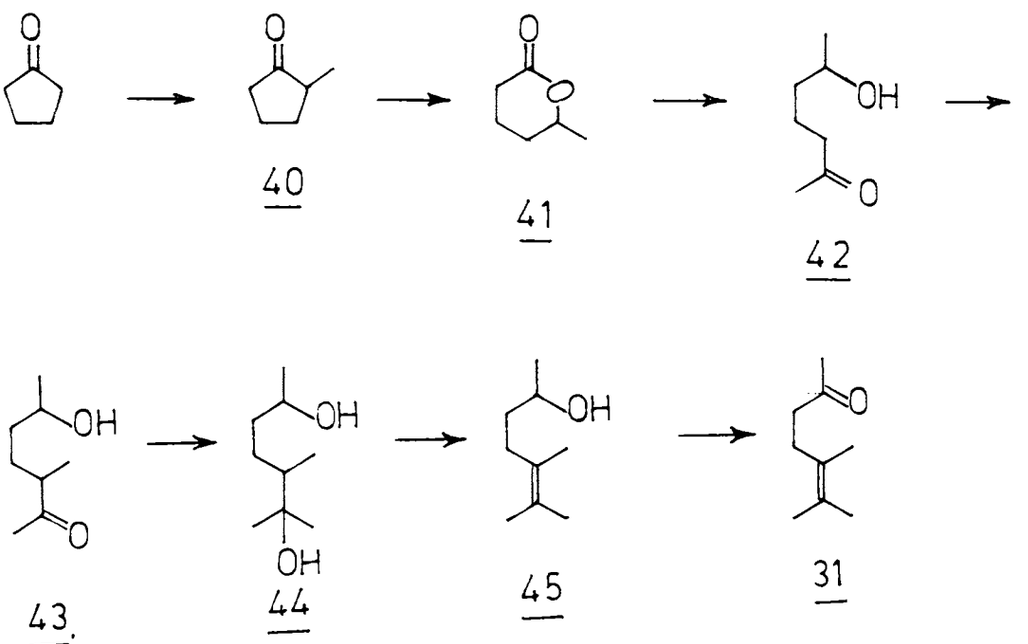
37 38 39 31

SHEME - IX

The α,β unsaturated aldehyde 36 on 1,4 addition with methyl magnesium iodide with catalytic amount of Cuprous iodide gave a methyl substituted aldehyde[18] which on α-bromination followed by dehydrobromination produced an α,β unsaturation to give 38 . Conversion of 38 to 31 was accomplished by the Huang-Minlon modification of Wolff

Kishner[31] reduction followed by deketalisation with excess BF_3 etherate[32]. Reaction of 38 with hydrazine hydrate and potassium hydroxide in ethylene glycol afforded 39 in 82.6% yield. (^1H NMR. peaks due to four methyl groups at δ 0.9 (s, 3H) 1.3 (d, each 3H) 1.4(S,3H) confirms the structure 39). Thio ketal 39 on treatment with excess BF_3 etherate gave the deketalised ketone C_9 unit 2,3-dimethyl hept -2-en-6-one (31).

Cyclopentanone was also converted to the C_9 synthon 31 by the following scheme (See Scheme X).



SCHEME-X

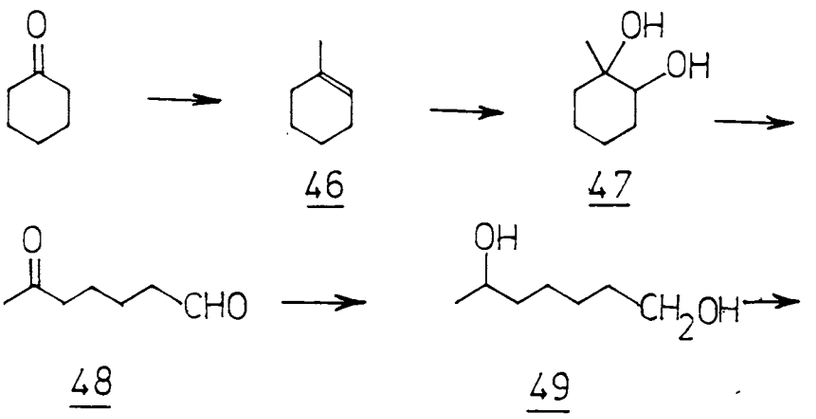
Cyclopentanone on alkylation gave mono alkyl-derivative 40, which on Baeyer-Villiger oxidation using Caro's acid[33] (ammonium persulfate and con.H_2SO_4 in ethanol) gave the lactone 41 in 81% yield. (A doublet at δ 1.5 for 3H multiplet for 4H at δ 1.7 - 1.9, multiplet at δ 2.1-2.5 for 2H and a triplet at δ 4.5 - 5 for 1H in the ^{1}H NMR spectrum is well in order with the structure 41. The carbonyl absorption in IR at 1735 cm^{-1} indicated the six membered lactone structure). The lactone ring was opened by the action of methyl lithium to give the methyl ketone 42[34]. (A singlet in the ^{1}H NMR spectrum at δ 2.2 for 3H assignable to the CH_3CO- group as well as a multiplet at 4.1 for 1H (-CH-OH) confirmed the structure (42). Then 42 on mono alkylation with methyl iodide followed by methyl Grignard gave a tertiary alcohol 44 which is easily dehydrated with pyridine and thionyl chloride to give 45. (In the ^{1} H NMR spectrum, singlet at δ1.7 shows the three methyl groups and at δ 1.3 one methyl and a multiplet at δ 4.1 the -CH-OH confirming the structure 45). The secondary alcohol on P.C.C. oxidation gave the keton C_9 synthon (31). (A sharp singlet in the ^{1} H NMR spectrum at δ 2.2 for 3 H confirmed the oxidation).

Cyclohexanone can also be converted to the C_9 unit by a series of reactions. Cyclohexanone on reaction with methyl Grignard followed by dehydration gave methyl cyclohexene with about 80% yield. (^{1}H NMR peaks at δ 1.7 singlet for 3H, and a multiplet at δ 1.9 - 2.1 for 8H and a doublet of doublet at δ 5.7 for 1H confirmed the structure for methyl cyclohexene (46)).

Methyl cyclohexene was cleaved at its double bond to gave 43 which was achieved through the diol - 47 obtained by the aqueous potassium permanganate oxidation[10]. Since sodium periodate-osmium tetroxide oxidation is not useful in this case because of the water solubility of the ketoaldehyde. (47 was reacted with lead tetraacetate[35] to gave a diketone 48). The keto aldehyde was reduced with sodium borohydride to the diol 49. (IR peaks at 3560 cm^{-1} shows the hydroxyl groups and in the ^{1}H NMR spectrum one triplet at δ 4.1 for two hydrogen for $-CH_2OH$ and a multiplet at δ 5.25 for one hydrogen -CH-OH confirmed the structure of 49).

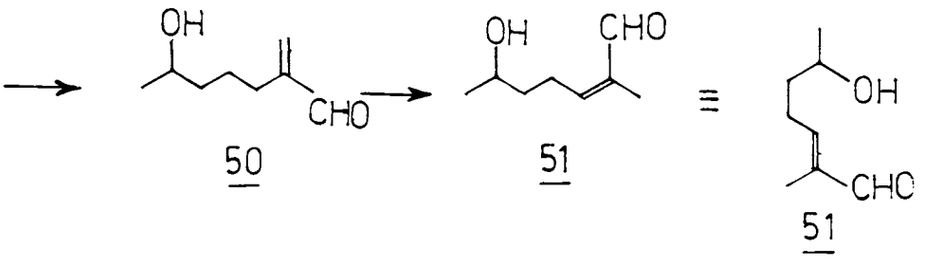
Conversion of primary alcohols to α -methylene aldehydes[24] by using oxallylchloride, triethylamine and

methylene -N,N- dimethyl ammonium chloride was recently reported[24]. The preparation of α -methylene aldehydes have already been reported earlier by J.L. Grass in 1978 [36], which involves a conversion of a carbonyl compound to α-methylene substituted compound, with N - methyl anilium trifluoroacetate (TAMA) . The alcohol 49, was treated with a mixture of oxallyl chloride in methylene chloride and dimethyl sulphoxide at -70°C. After 15 minutes added triethylamine at same temp. The reaction mixture was allowed to attain room temp; then stirred again for 15 minutes. Then added α -methylene dimethyl ammonium chloride[37]. Stirring continued for 15 hours. After the work up gave 93% α -methylene substituted aldehyde 50, in which the secondary alcohol was unaffected. (IR and ^{1}H NMR details confirmed the structure 50. IR peaks at 1662, 1610 and 3540 cm^{-1} shows the ketone, methylene and hydroxyl group respectively. ^{1}H NMR spectrum also confirmed the structure 50 for the product).



46 47

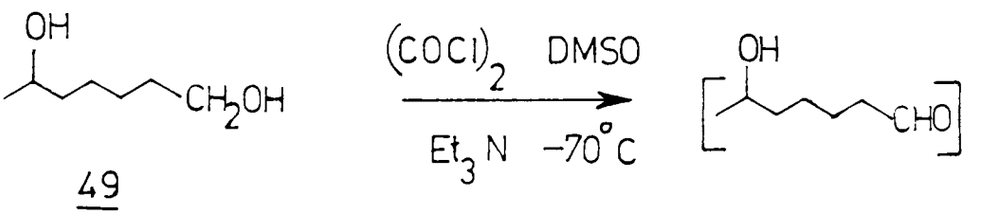
48 49



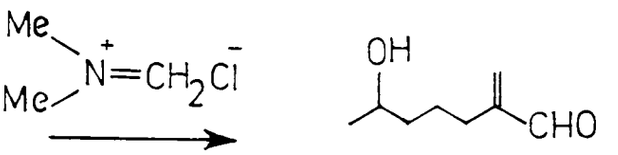
50 51 51

SCHEME XI

50 on treatment with acid was rearranged to 51 the allylically functionalised C_8 synthon. So this synthon 51 was also converted to the C_9 unit 31. 51 is an important synthon for the synthesis of perfumery materials, like methyl heptenone, ionones, irones and methyl ionones.



49



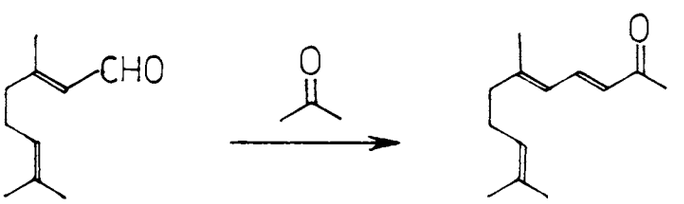
50

SCHEME XII

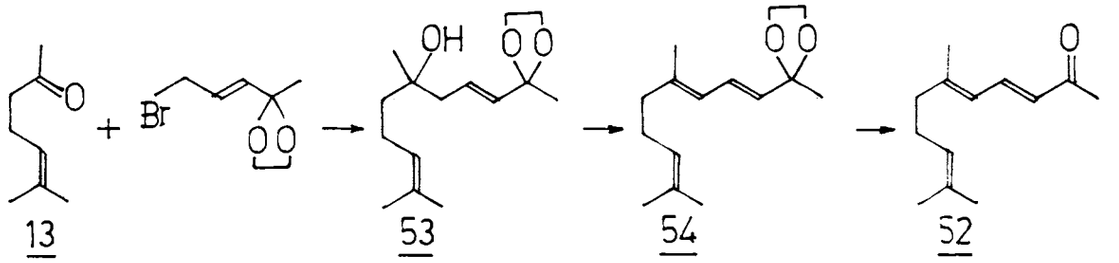
Synthesis of linear C_{13} Unit (Pseudoionone)

Pseudoionone 52 the aldol condensation product of citral and acetone is prepared by adding citral under stirring to a mixture of acetone and aqueous sodium hydroxide[38] containing benzyltriethyl ammonium chloride[39]. The reaction was complete in 2 hrs. But side products are formed in this method and so column chromatographic separation was needed for purification.

Recently, a report of the basic alumina catalysed condensation of citral[40] and acetone for the synthesis of pseudoionone has appeared . In this method citral was added to a stirred mixture of acetone and basic alumina at refluxing temperature 60°C. Reaction was completed within 4 hrs. The reaction mixture was only filtered and filtrate concentrated to get pure pseudoionone in 97% yield.



12 52



13 53 54 52

SCHEME XIII

Zinc catalysed condensation of ketones with allylic bromides are recently reported with 100% conversion within half an hour[24]. This reaction was applied for the preparation of pseudoionone. Ketones on reaction with allylic halides with Zn/DMF, an exothermic reaction takes place within 10 minutes. Reaction was completed within half an hour. After work up gave the tertiary alcohol.

Zinc powder was added in portions to a mixture of methyl heptenone (13) in DMF and the ketal bromide 25 (a C_5 synthon) with stirring. Stirring was continued for half an hour more. An exothermic reaction took place to give a tertiary alcohol 53. (A broad IR peak at 3425 cm^{-1} indicate the hydroxyl groups and the ^1H NMR spectrum - δ 1.5 doublet for 6H and δ 1.7 doublet for 6H indicate the 4-methyl groups and a triplet at δ 5.1, a multiplet at δ 5.9 and a doublet at δ 6.2 indicate the three olefinic hydrogen confirm the structure of 53).

Tertiary alcohol on dehydration with thionylchloride and pyridine followed by deketalisation using p-toluene sulphonic acid gave pseudoionone (52).

(IR peak at 1675 cm^{-1} shows the $COCH_3$ and ^1H NMR spectrum singlet at δ 2.2 shows $COCH_3$ and peak corresponds to other three methyl groups and four olefinic hydrogens confirmed the structure of pseudoionone 52).

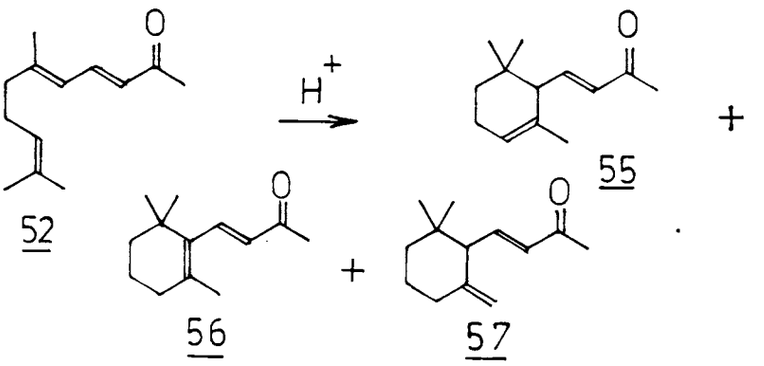
Another method for $C_8 + C_5$ approach was also tried by Wittig reaction with methyl heptenone and a C_5-triphenyl phosphonium bromide 26 with n-BuLi as base. The product formed 54 on deketalisation gave pseudoionone 52.

Synthesis of Ionones

The pseudoionone prepared by the above methods was cyclised with acids or under acidic conditions gave α, β and γ -isomers of ionones. Cyclisation with con. H_2SO_4[41] gave more β-isomer and recently reported cyclisation with acidic alumina soaked with p-toluene sulphonic acid[42] gave more of γ-isomer. In these methods the α, β and γ-isomers are separated by column chromatography.

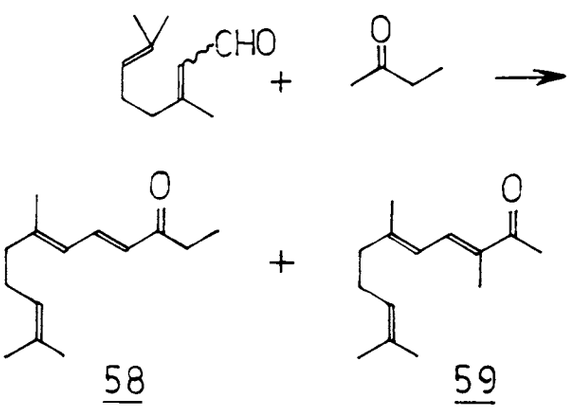
For getting exclusively β-isomer, β-cyclocitral was used. β-cyclocitral obtained by the previous method was condensed with acetone gave exclusively β-ionone[47]. Here we chose the condensation method using basic alumina at

refluxing temperature. This method gave exclusively pure β -ionone in about 75% yield.



SCHEME XIV

Methyl ionones, the next higher homologue of ionones were also synthesised by these methods. Citral was condensed with ethyl methyl ketone to get methyl pseudoionones. The reaction however is more complex than the synthesis of pseudoionones.



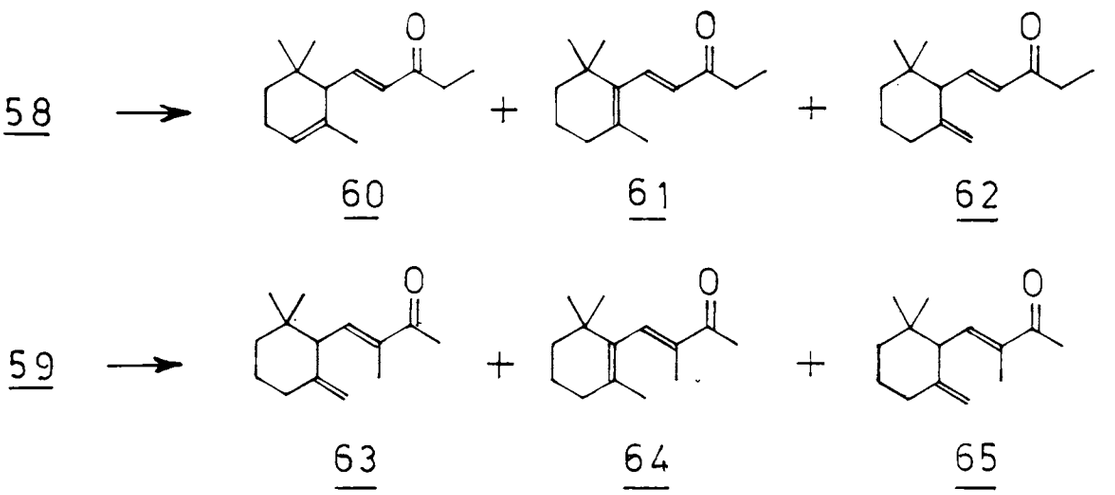
SCHEME XV

The reaction of the aldehyde group of citral with either methyl or methylene group of ethyl methyl ketone gives n- and iso-methyl pseudoionones 58 and 59 respectively, each of which being capable of occurring as cis-trans isomers. The ratio of major isomers in the mixture depends on the condensation catalyst and the reaction conditions. Under common alkaline conditions n-isomers are formed preferentially. In presence of basic alumina catalyst TLC and GLC analysis shows three components.

Separation of these components by column chromatography was tried, on a silicagel (using a mixture of hexane and ethylacetate in the ratio 95:5 as the eluent) and the three components are separated quantitatively. ^{1}H NMR spectroscopic data provides that one component is normal other two are iso-isomers.

Acidic alumina soaked with p-toluene sulphonic acid was tried for the cyclisation of methyl pseudoionones. 95% conversion of methyl pseudoionones to methyl ionones occured after 1 hr. at room temperature TLC and GLC analysis showed the mixture of three isomers in the ratio

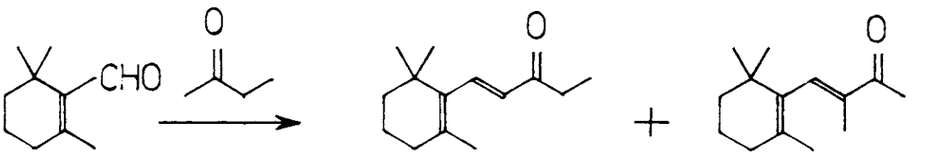
of 45:42:13. These three isomers was separated by column chromatography on a silicagel column (using hexane ethylacetate mixture in the ratio 9:1 as eluent).Spectral data showed that α and γ - isomers are formed in major amounts and β -methylionone formed only in relatively low amounts. Since α -methyl ionone is more valuable than the β -isomer in perfumery, this method of cyclisation can have commercial applications.



SCHEME XVI

β -cyclocitral condensed with ethyl methyl ketone in presence of basic alumina gave two products. These were separated and spectral data showed that one is normal and other is the iso-isomer. It is found that iso-isomer is in

greater amounts than the n-isomer.



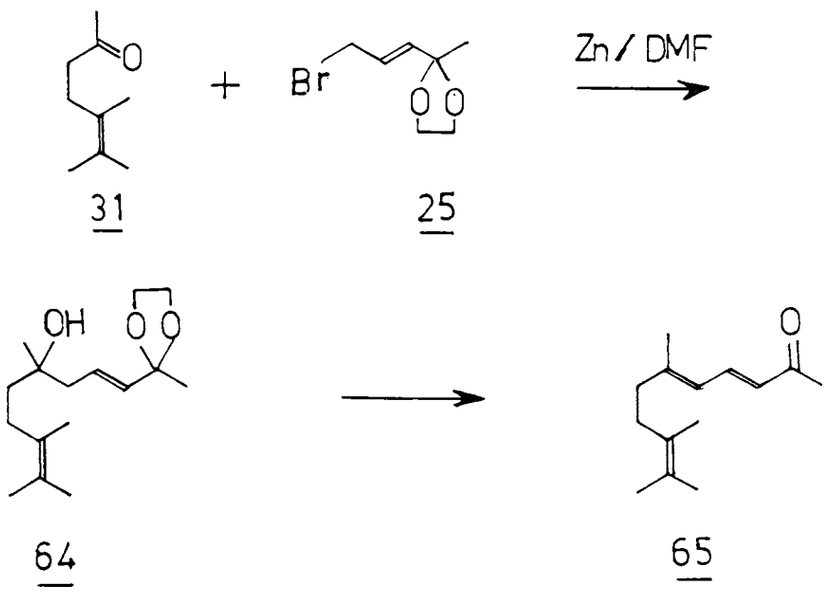
7 61 64

SCHEME XVII

Because of the mild base-basic alumina, thermodynamically controlled, more stable enolate ion formed, condensed with the aldehyde to give product corresponding to that enolate ion. This is found to be iso-isomer. If it is done in the presence of strong base like sodium hydroxide, kinetically controlled enolate ion results and so normal isomer will be the major condensation product.

Synthesis of C_{14} -Linear Unit (C_9 + C_5-approach)

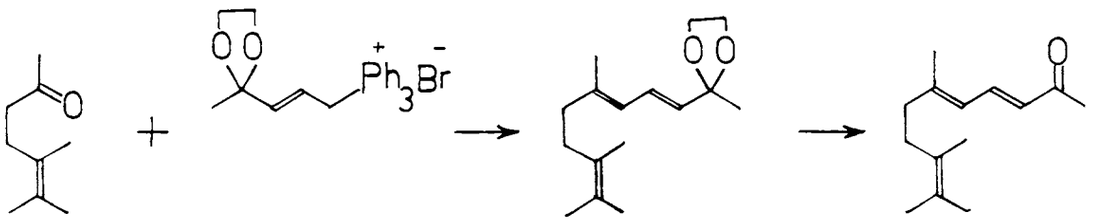
The C_9 unit[31] synthesised earlier on coupling with the C_5 allylic bromide 25 using Zn/DMF gave 100% conversion to a tertiary alcohol 64 within half an hour. (^{1}H NMR peaks at δ 1.5 for 6H doublet, a singlet at 1.7 for 6H and a doublet at 1.75 shows the 5-methyl groups, $(-C-CH_3)$ and $(=C<^{CH_3}_{CH_3})$. A triplet at δ 5.21 for 1H and a doublet at 6.2 for 1H shows the two olefinic hydrogens and a multiplet at 2.1 and a singlet at 4.1 for 4H confirmed the structure of tertiary alcohol 64). The tertiary alcohol on dehydration with thionyl chloride and pyridine, followed by deketalisation gave the C_{14} ketone, pseudoirone (65) as shown in scheme XVIII.



31 25 64 65

SCHEME XVIII

Pseudoirone (65) was also synthesised by C_9 + C_5 approach through Wittig reaction. C_5 - unit 25 was converted to triphenyl phosphonium salt, which in presence of base was converted to Wittig reagent. This Wittig reagent on coupling with C_9 - ketone 31 gave a C_{14} unit, which on deketalisation gave pseudoirone (65). Coupling reaction with Zn/DMF is an easier method and gave greater yield than that obtained using Wittig reaction.



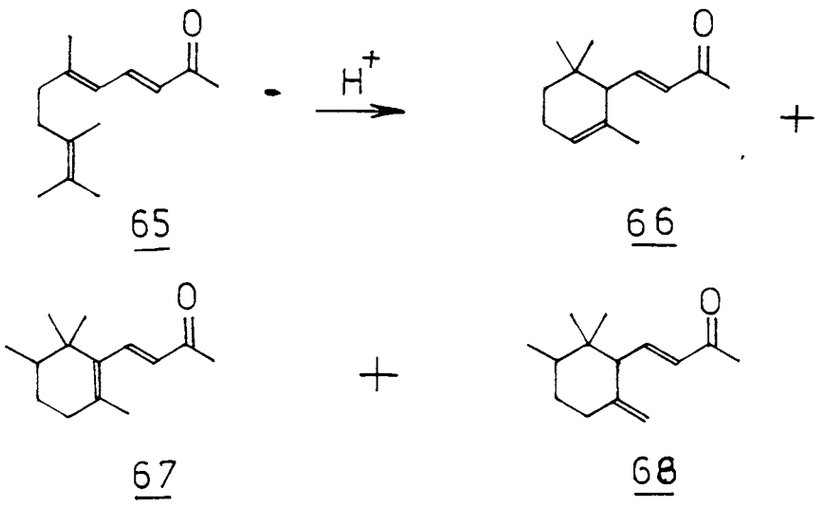
31 26 65

Cyclised C_{14} Unit (Irones)

Many types of cyclisation reagents are available[43]. The linear C_{14} unit when cyclised with con. H_2SO_4 gave three isomers of irone(α, β and γ isomer), the β -isomer predominating. The three isomers are separated by using column chromatography using silicagel and hexane-ethylacetate in the ratio 9:1 as eluent. The spectral value of individual compounds showed them to be

α,β and γ isomers of irone.

The cyclisation using p-toluenesulphonic acid was also tried. In this method also, as in the case of the ionones α -isomer is the major product (about 70%). No attempt have made to seperate the stereo isomers of these irones.

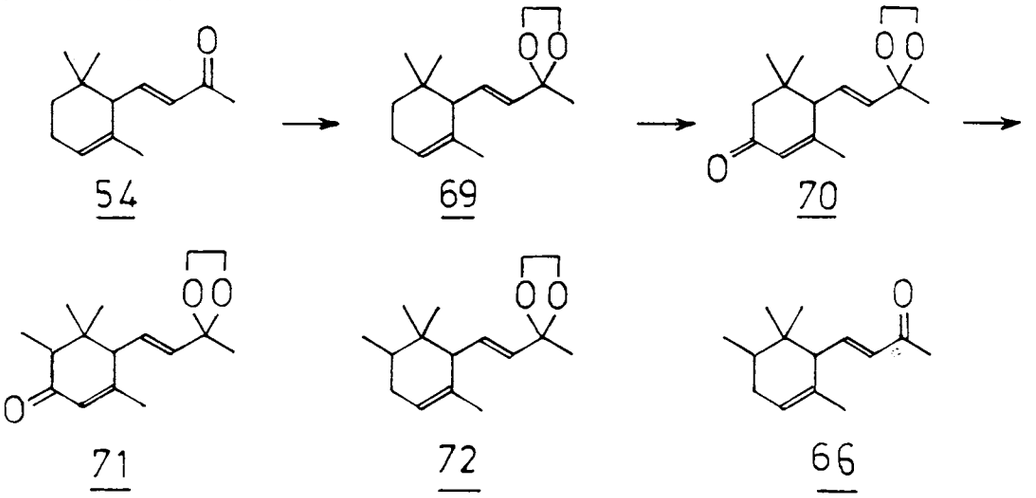


SCHEME XIX

Conversion of α -ionone to α -irone

α-ionone (54) was converted to its ketal by refluxing in dry benzene with ethylene glycol with catalytic amount of pyridinium paratoluene sulphonate (PPTS). This ketal on allylic oxidation in ring using t-butyl hydroperoxide and PDC gave the ketone 70. But the production of chromic acid in reaction changed some of the ketal into hemiketal or deketalised. These are separated.

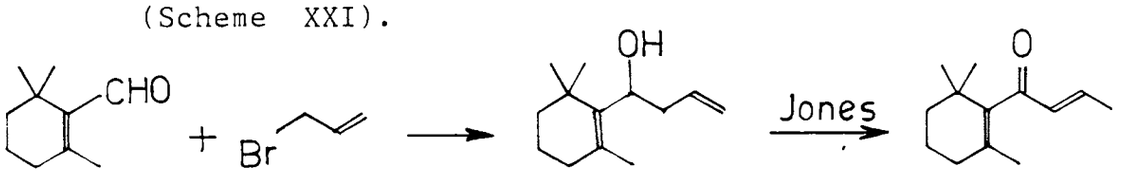
By adjusting the reaction time, the product containing the ketal groups was obtained in about 60% yield. This allylically oxidised ketal on monomethylation with methyl iodide and sodium hydride as base in DME gave the methylated product 71. Then the ketone in the ring was removed by converting it to thioketal with ethane dithiol using catalytic amounts of BF_3 etherate followed by reaction with Reney - Nickel . This ketal -72 on deketalisation by refluxing with p-toluene sulphonic acid yield α-irone (66). Five steps are involved in this conversion. But β and γ -ionones cannot be converted by this method to corresponding irones because of the dienone ketone rearrangement of β -ionone and the γ-ionone was easily isomerised to α and β -isomers under the acidic conditions used. So only α -ionone was converted to α -irone by the above series of reaction (Scheme XX).



SCHEME XX

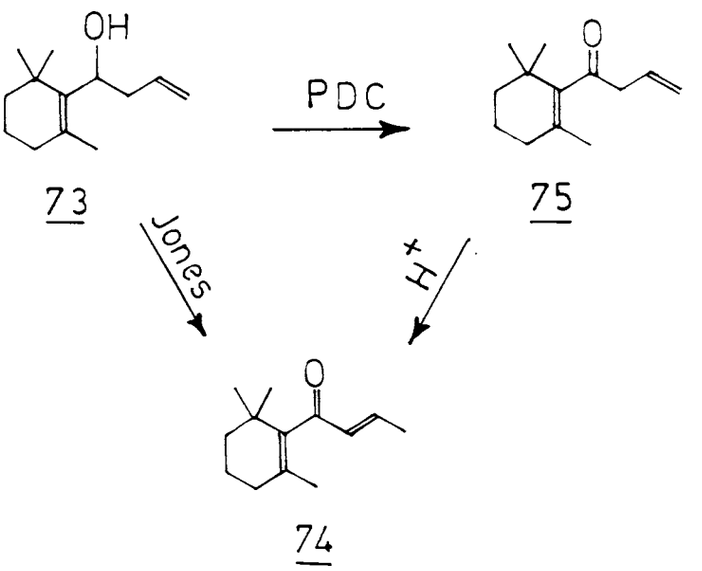
4.9 Synthesis of β-Damascone (C_{10} + C_3 approach)

β-Cyclocitral 7 on coupling with the C_3 unit allyl bromide using Zn/DMF, followed by oxidation get an isomeric compound of ionone called β- Damascone[48-50] (Scheme XXI).



7 73 74

SCHEME XXI



73 75 74

SCHEME XXII

Zinc powder was slowly added to a mixture of cyclocitral and allylbromide in DMF, to give the secondary alcohol 73 in 100% yield. This alcohol is also obtained by Grignard reaction. Allyl bromide with megnesium gave allylmagnesium bromide, which on reaction with cyclocitral gave the secondary alcohol 73 in 70% yield (IR peaks at 3450 (b)1640, 1660 cm^{-1} confirmed the alcohol and methylene groups. ^1H NMR spectrum at δ 4.3 (doublet of doublet for 1H) shows -CH-OH and singlet at 5.8 for 1H and doublet at 5.38 for 2H shows the CH_2-CH = CH_2 groups. Therefore spectral data confirms the structure of 73).

The secondary alcohol 73 on PDC oxidation gave a ketone 75 which on treatment with acid gave a rearanged ketone 74. Alternatively 73 on Jone's oxidation gave directly the rearranged ketone 74. (IR peaks at 1710, 1625cm^{-1} shows the ketone and an olefine, ^1H NMR spectrum a singlet at δ 1 for 6H and at δ 1.48 singlet for 3H and a dcublet at 1.5 for 3H and at δ 6.8 multiplet for 1H and doublet at δ 6.58 for 1H and a multiplet at δ 1.7 - 2.18 for 6H confirmed the structure of Damascone 74.

CHAPTER V

CONCLUSION

CONCLUSION

The compounds ionones and irones are responsible for the violet fragrance in the oil of violet and orris root oil respectively. Non availability and high price of these oils and high demand of these compounds in perfumery and cosmetic industries make it meaningful to develop more efficient routes for the synthesis of ionones and iornes .

In the introduction, an attempt has been made to give a brief account of the synthetic routes developed already over these years. In this work, new synthesis or improvement over existing methods has been made using easily available natural products and commercially available chemicals.

Different approaches for the synthesis of cyclocitral, ionones, irones and a structural isomer of β-ionone called Damascone - an important constituent of rose oil , are investigated in the present study. Ionone and irone molecules can be disconnected into different cyclic and linear units, which have been synthesised as intermediates using different synthetic schemes.

Synthesis of β-cyclocitral, a very useful C_{10} synthon was achieved from cyclohexanone by using reactions like Wittig reaction, Glycidic ester condensation, Corey -

Chaykovsky reaction and C_{13} linear units - pseudoionone, synthesised from citral obtained from Lemongrass oil, by base catalysed condensation with acetone. Methyl heptenone obtained from citral and the C_5 unit -1-Bromo Pent-2-en-4-one condense in the presence of Zn|DMF and give pseudoionone. On acid catalysed cyclisation of pseudoionone, α , β and γ-isomers of ionones are obtained. Condensation of β -cyclocitral with acetone gives only the β -ionone. Methyl ionones are also synthesised by these ablove methods.

Synthesis of the C_9 linear units - 2,3-dimethyl-hept-2-en-6-one was achieved from methylheptenone. Two routes were adopted for this synthesis. One is by allylic oxidation followed by 1,4 addition, followed by introduction of double bond achieved by using organoselenium reagents. The second method is epoxidation followed by BF_3 treatment followed by Grignard reaction and dehydration to give the C_9 intermediate - 2,3-dimethyl-hept-2-en-6-one. Another approach for the synthesis of C_9 linear unit from cyclopentanone was successfully carried out. Cyclohexanone was also converted to allylic functionalised C_8 synthon - 2 - methyl - 6 - hydroxy hept - 2 - enal. This intermediate can be converted to suitable C_8 or C_9 synthons.

For obtaining C_{14} linear unit - pseudoirone, the combination of $C_9 + C_5$, olefine forming reaction like Wittig and condensation using Zn/DMF have been used. The C_{14} unit - pseudoirone on cyclisation with acid catalysts gave α, β and γ-isomers. The products formed in these synthetic schemes were a mixture of stereo-isomers. In the coupling reaction it is assumed that all trans isomers which are thermodinamically more stable are formed as the major products.

In the conversion of ionones to irones only α -ionone could be converted to α -irone. Internal allylic oxidation of α-ionone ketal was successfully achieved by using PDC and tertiary butyl hydroperoxide. On mono-alkylation and reduction this gave α-irone.

β-cyclocitral on coupling with allylbromide using Zn/DMF gave a homoallyl alcohol. This alcohol, on Jone's oxidation, gave rearranged ketone Damascone.

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