STUDIES ON THE SYNTHESIS OF VITAMIN A AND RELATED COMPOUNDS

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

By

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COCHIN - 682 022

FEBRUARY 1989

CERTIFICATE

Certified that this thesis is based on the work done by Sri. Jose David, P. under my guidance in the Department of Applied Chemistry, Cochin University of Science and Technology and no part of this has been presented by him for any other degree.

Paul A. Vatakencherry

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Cochin - 682 022,
17th February 1989.

DECLARATION

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, 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.

Jose David, P.

Cochin - 682 022,
17th February 1989.

To

My Mom, Brothers and Sister

for their forbearance, love and encouragement.

ACKNOWLEDGEMENTS

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JOSE DAVID, P.

CONTENTS

ABSTRACT

In the present work different new approaches for the synthesis of Vitamin A are investigated. In these synthetic schemes, all the twenty carbon atoms of the target molecule are derived either fully from components isolated from common essential oils or partially from commercially available materials.

By retrosynthetic analysis, Vitamin A molecule can be disconnected into a cyclic and a linear unit. Different methods for the synthesis of the linear and the cyclic components are described.

The monoterpenes, geraniol and citral, major constituents of palmarosa and lemongrass oils, have the required basic carbon framework for consideration as starting materials for the synthesis of Vitamin A. The potential of these easily available naturally occurring compounds as promising starting materials for Vitamin A synthesis is demonstrated. Organoselenium and organosulfur mediated functional group transformations for the synthesis of the functionalised conjugated C_{10} linear components (ie., the dimethyloctatriene derivatives) are reported. The classical approaches as well as the attempted preparation of cyclic C_{10} and C_{13} units employed in the present study as intermediates for Vitamin A synthesis are described.

The utility of commercially available materials namely 2-acetylbutyrolactone and levulinic acid in the preparation of C_5 intermediates for Vitamin A synthesis is demonstrated. A simple

approach for the synthesis of methylheptenone - an important C_8 intermediate in the synthesis of terpenoids and perfumery chemicals and its allylic functionalisation is reported. A new synthesis of the C_8 intermediate in the BASF Vitamin A industrial process is also described.

The above intermediates are utilized for the synthesis of Vitamin A molecule through various olefin forming reactions. For building the C_{20} retinoid carbon skeleton, the approaches investigated are $C_{10} + C_8 + C_2$, $C_{13} + C_5 + C_2$, $C_{13} + C_7$ and $C_{10} + C_{10}$ modes of combination, employing sulfone-alkylation, Wittig reaction and sulfone-condensation methods in the coupling reactions. Using the first two combinations, approaches are developed for the synthesis of ß-C_{18} ketone - an important intermediate for the synthesis of Vitamin A. Since the conversion of ß-C_{18} ketone to Vitamin A is well established, these approaches constitute formal synthesis of Vitamin A. The $C_{13} + C_7$ sulfone-condensation approach using a linear C_7 unit derived from geranylacetate was not successful. In the $C_{10} + C_{10}$ approach, Vitamin A acetate synthesis was achieved through the Wittig reaction of ß-cyclogeranylbromide and the C_{10} functionalised triene - dimethyl octatriene aldehyde ester. The attempted conversion of 11, 12 dihydrovitamin A acetate, prepared by the condensation of ß-cyclocitral with terminal oxygenated geranylacetate, to Vitamin A acetate was unsuccessful.

Thus new approaches have been developed for Vitamin A

synthesis based on components derived exclusively from easily available natural sources and also using commercially available chemicals, employing recently developed olefin forming reactions.

CHAPTER I

INTRODUCTION

1.1 Introduction

Retinoids, the family of molecules comprising retinol, retinaldehyde, retinoic acid and their synthetic analogues are of paramount importance in the fields of nutrition and vision. The new surge of interest in these substances reflects their application both practical and theoretical to the study of many of the problems in biology and medicine. Vitamin A and related compounds (retinoids) have been implicated in a number of useful or necessary biological functions. Retinoids are seen as an essential factor in the process of vision and as fundamental mediators of cell differentiation and cell proliferation. Of late the potential effect of retinoids on the immune system has only increased the spectrum of its applications. The relevance of these findings suggest that they ultimately may play as important a role in clinical medicine as their relatives - the steroids.

1.2 Historical Background

The discovery of Vitamin A has been considered as the direct outcome of the fundamental studies on nutritional requirements. It has been suggested since ancient times that there might be a substance in the diet necessary for correcting abnormalities connected with the eye. The late 19th century and the early 20th century witnessed scientists describing the presence of a mysterious factor in the diet which was responsible for the maintenance of growth in animals[1].

In 1913 Mc Collum and Davis engaged in pioneering research reported a lipid soluble component present in certain foods capable of promoting growth[2]. In 1915 this group took the initial step in the long journey towards the subdivision of the growth promoting factors - later known as Vitamins, by postulating that this lipid soluble substance must be called 'Fat Soluble A' to distinguish it from the water soluble components[3]. The 'Fat Soluble A' was later named as Vitamin A by Drummond[4]. It was also shown that this factor not only maintained growth but also prevented night blindness. During the subsequent decades more information about the existence and property of this factor was obtained from the work of a number of investigators including Mc Collum and his associates[5].

Subsequently, the relationship between Vitamin A in animals and the provitamin carotene in plants was also clarified, particularly after Karrer and his associates determined the structure of ß-carotene in 1930[6] and of retinol in 1931[7]. Indeed, as will be seen ß-carotene was shown to be the main precursor of Vitamin A in animals. But the mechanism of the conversion of ß-carotene to retinaldehyde was explained only much later[8]. All provitamin A compounds are produced by plants or microorganisms. Animals possess enzymes occurring mainly in the intestinal mucosa which convert ingested provitamin to Vitamin A. So far this conversion has not been observed to occur in plants. Thus retinol is of animal origin, and is derived from ingested provitamins - carotenes, which in turn are not synthesised by animals.

Preformed Vitamin A is found almost exclusively in animals. This provitamin A concept was entirely new, and it proved to have great scientific and economic importance.

Shortly afterwards studies dealing with various aspects of physiology and metabolism of Vitamin A began. Particularly noteworthy was the achievement of Wald[9] who demonstrated in 1935 the link between Vitamin A and visual process and the identification by Morton[10] in 1944 the chromophore of the visual pigment as retinaldehyde. The importance of stereoisomerism of the pentaene chain was clearly recognised later through the establishment of the important role of 11-cis and all trans isomer in the visual process[11] and the successful identification and synthesis of various geometrical isomers of Vitamin A[12, 13]. These studies provided an insight into the mechanism of vision and the role of Vitamin A in vision, pathology and pathophysiology of Vitamin A deficiency. The role of isomers of Vitamin A in visual process and the mechanism of vision was excellently reviewed in monographs by Nakanishi[14] and others[15].

The synthetic challenges offered by Vitamin A molecule - having five double bonds, made it a choice target for chemists all over the world. The possibility of the molecule existing in sixteen geometrical isomers only enhanced the complexity. So research directed towards this aspect culminated in a total synthesis of Vitamin A molecule in 1948[16] and later many more approaches

followed. The rapid development of new synthetic techniques and separation methods have provided added impetus for the development of new methodologies for the synthesis of this pentaene derivative. The advent of new methodologies and advances in tracer chemistry now allow the synthesis of almost any desired isomer or any retinoid in radioactively labelled form.

Since 1967, major advances have occurred in understanding the pathology and pathophysiology of Vitamin A. There has been striking thrust in the development of new retinoids for application in the prevention of or treatment of diseases particularly in the areas of oncology and dermatology, and also in the study of toxicology of retinoids and their interactions with immune systems.

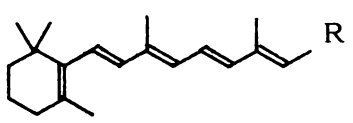
The domain of retinoid research thus have moved well beyond its classical routes in the study of nutrition and vision. The realization that retinoids are highly potent agents for control of cell differentiation and cell proliferation has created a great deal of excitement in the biomedical community. The ability of retinoids to arrest the progression of premalignant cells or to induce terminal differentiation of malignant cells has had a powerful influence in the field of cancer research. The retinoids have thus become valuable tools to study one of the most basic problems in biology - the control of cell differentiation. The clinical success of retinoids in treating both rare and common skin diseases that have previously been refractory to therapy has had a major impact on the practice of dermatology.

Very recently the evidence of the potential effect of retinoids on the immune system has thrown open a new area of research. The immuno stimulatory action of retinoids and their potential use as a tool to influence the immune system in clinical situations are now hot subjects of investigation.

It has been attempted to give a brief outline of the evolution of Vitamin A as an interesting molecule through years. The importance of Vitamin A as a target molecule for synthetic chemists and as a therapeutic agent is widely accepted now. The domain of Vitamin A research is still active with new findings - but since it is very vast many aspects still lie unexplored. Efforts by a multidisciplinary approach is necessary to understand the complexity and full potential of this versatile molecule.

1.3 Synthesis of Retinoids - Review

The three important naturally occuring retinoids are retinol (1) or Vitamin A, retinaldehyde or retinal (2) and retinoic acid (3), and these names always refer to the all trans compounds.



1, R-CH_2OH 1a, R-CH_2OAc

2, R-CHO 1b, R-CO_2Me

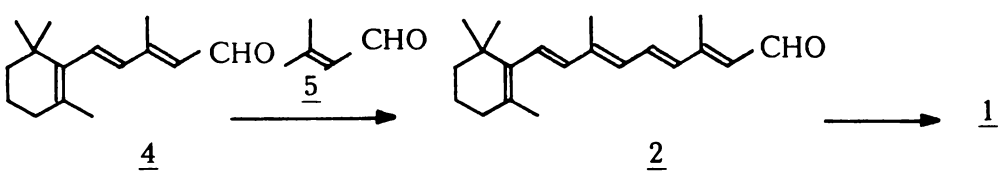
3, R-COOH 1c, R-CO_2Et

Vitamin A active substances are compounds other than carotenoids, that exhibit qualitatively the biological activities of retinol. The term retinoid is a general term that includes both the naturally occurring compounds with Vitamin A activity and synthetic analogues with or without biological activity of retinol. It was recommended that the term 'Vitamin A' should be used as the generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol[17].

The historical story of Vitamin A has been eloquently told by Karrer[18] in 1950 and by Moore[19] in 1957 in their excellent monographs which were the first to appear in this field. Another extensive review on Vitamin A appeared during this period was by Sebrell and Harris[20]. After that many more followed[21-24] and most notable was Isler's effort in bringing about an anthoritative treatise 'Carotenoids' in 1971[25] in which much of the synthetic chemistry of Vitamin A has been reviewed by Mayer and Isler. Many excellent reviews followed after this dealing mainly the synthetic aspects[26-28]. A summary of industrial processes for Vitamin A has also appeared[29, 30]. Very recently an excellent review on the photochemistry and syntheses of stereoisomers of Vitamin A has appeared[13]. Recently, the chemistry and biology of the entire domain of substances related to Vitamin A has been reviewed for the first time in a comprehensive manner by a two volume treatise[31].

The chemistry of retinoids is too exhaustive a field to cover and with this constraints in mind, a brief overview of the synthetic chemistry of retinoids is presented here with emphasis on novel approaches and recent advances in the field. No attempt is made to provide an exhaustive coverage of all methods developed in Vitamin A synthesis, since these are extensively reviewed many times elsewhere.

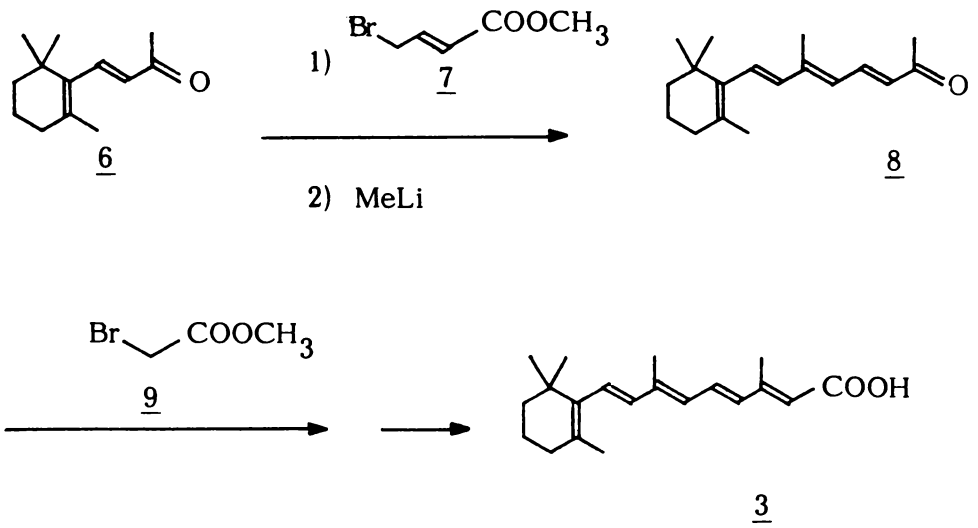
The first claim to have synthesised Vitamin A was made in 1936 by Fuson and Christ[16]. But no supporting evidence was available. Following this Kuhn and Morris[32] reported the synthesis of a retinoid by the Knoevinegal condensation of ß-C_{15} aldehyde 4 with dimethyl acrolein (5) (Scheme 1). This was an oily preparation, with very low



(Scheme 1)

biological activity. It is probably for this reason that over ten years passed before Kuhn's synthesis was generally recognised, when van Dorp and Arens[33] in 1948 confirmed this reaction sequence. Two more unconfirmed claims for the synthesis of retinoids followed[34]. These too did not get recognition due to the lack of supporting evidence. In 1946 van Dorp and Arens[35] reported a successful synthesis of all

trans retinoic acid starting from ß-ionone (6). Reformatsky reaction product of ß-ionone with C_4 bromoester 7 on treatment with methyllithium gave the ß-C_{18} ketone 8 which underwent Reformatsky reaction again with C_2 bromoester 9 followed by hydrolysis to give the Vitamin A acid (3) (Scheme 2). This is considered as the first synthesis of a retinoid.

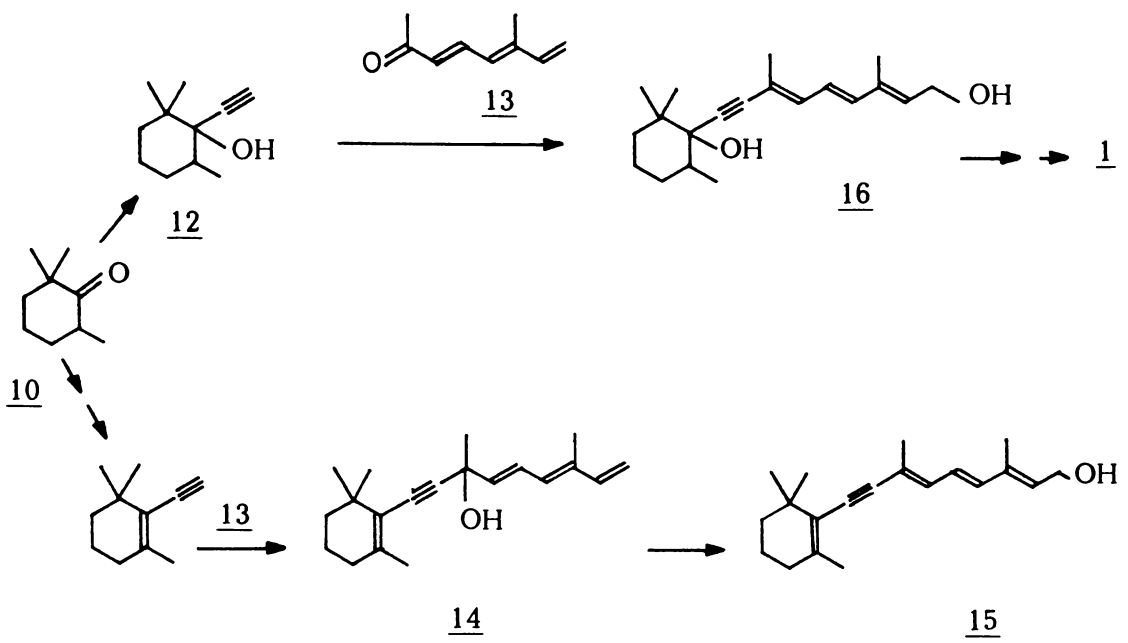


Scheme 2

Following this success, a number of approaches were developed for Vitamin A syntheses. Most of these synthetic scheme used C_{13} or C_{15} units as starting materials. Remaining carbon atoms are added in one step or in a stepwise manner to get the desired C_{20} skeleton. Thus ß-ionone (6) - a relatively inexpensive, readily available commercial chemical and to a lesser extent its

derivative - ß-C_{15} aldehyde 4 became the widely used building blocks. Now Vitamin A skeleton is being constructed in virtually every conceivable manner using different fragments. Hence the number of approaches now available are numerous.

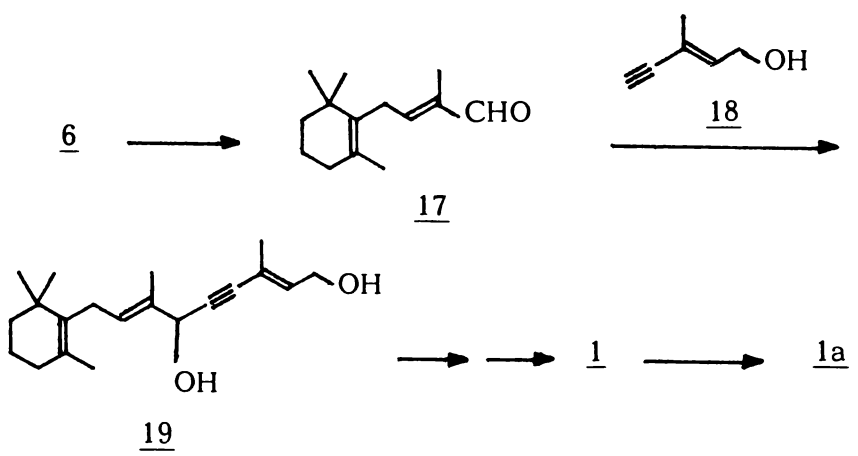
Eventhough ß-ionone still remains as the most common starting material for retinoid synthesis, way back in 1948 Heilbron suggested some alternative routes for the synthesis of Vitamin A avoiding ß-ionone[36]. Utilising one of these routes, Attenburrow[37] in 1952 prepared dehydrovitamin A (15) and modifying the process achieved a Vitamin A synthesis also, starting from 2, 2, 6-trimethyl cyclohexanone (10), obtained by the cyclohexanone methylation (Scheme 3). This is the first synthesis of a retinoid utilizing starting



Scheme 3

material other than ß-ionone. Many more syntheses of Vitamin A derivatives starting from ß-ionone have appeared since and are all well documented[38].

Isler in 1947 utilized an C_{14} + C_6 approach for Vitamin A acetate synthesis[39]. It was later developed into an industrial process at Hoffmann-La Roche. In Isler's synthesis, the C_{20} skeleton was built up from C_{14} aldehyde 17 and the C_6 acetylenic alcohol 18 by Grignard reaction. The resulting C_{20} diol 19 after partial hydrogenation, dehydration and acetylation afforded all E retinyl acetate. Using the cis or trans 18 all E, 11Z and 11Z 13Z isomers were prepared (Scheme 4). The C_{14} unit 17 was prepared from ß-ionone by the classic Darzen's glycidic ester reaction and the C_6 unit 18 is the allylic rearrangement product of the adduct of acetylene with methylvinylketone. This process constitutes the first industrial synthesis of Vitamin A.



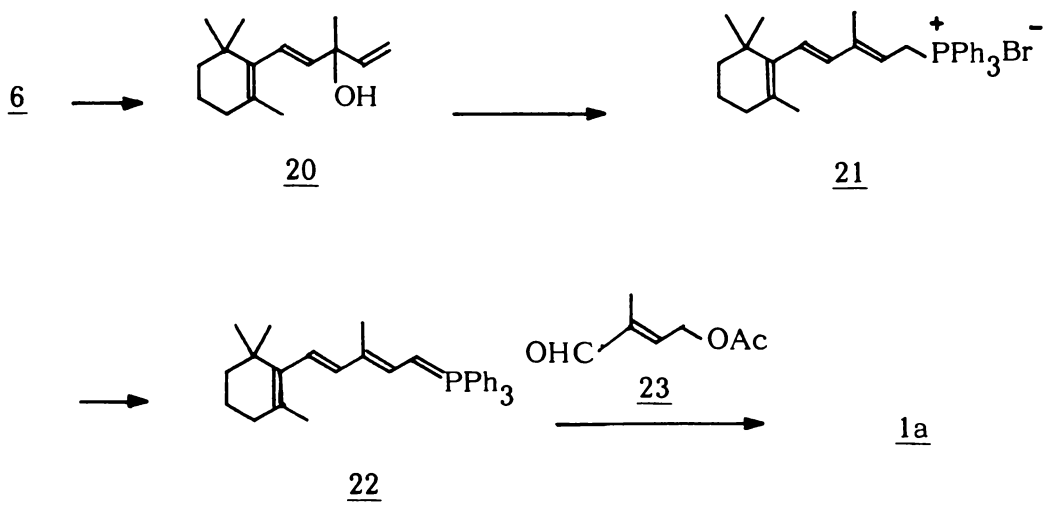
Scheme 4

In 1953, Wittig and Geissler[40] published the principles of Wittig reaction. This reaction has since became general chemical knowledge as the Wittig reaction or Wittig olefination, and it influenced the development of synthetic organic chemistry in the following years to an almost unparalleled degree. It initiated creative activity in laboratories throughout the world as the challenge was taken up to establish the preparative potential of the reaction, to study its mechanistic aspects and its stereochemistry.

Pommer of BASF laboratories investigated this reaction and employed this new olefin forming reaction for the syntheses of retinoids. Eventually, Pommer revolutionized polyene chemistry, providing it with a variety otherwise scarcely imaginable.

Pommer's investigative work in BASF laboratories culminated in a novel industrial process for Vitamin A[41]. In the BASF process ß-ionone is chain lengthened by two carbon atoms to get C_{15} vinyl ß-ionol (20) which on treatment with triphenylphosphine hydrochloride provided the phosphonium salt 21. The phosphorane 22 generated from 21 is condensed in a Wittig reaction with ß-formyl crotyl acetate (23) and subsequent isomerization provided Vitamin A acetate (Scheme 5).

Conventional Wittig olefin synthesis and Wittig reaction using modified reagents such as phosphoryl stabilised anions as well as Wittig-Horner-Wadsworth-Emmons modifications have raised polyene



Scheme 5

chemistry to the new frontiers of synthetic organic chemistry and substantially increased the spectrum of possible syntheses of retinoids and carotenoids.

This process of BASF and the one developed in Hoffmann-La Roche are the two most important industrial processes available today and probably satisfy a large part of the world demand for retinol.

The other industrial processes available for Vitamin syntheses are those developed by AEC, Sumitomo, Philips-Duphar, Glaxo and DPI owned by Eastman Kodak.

The process followed in the French firm AEC is the conversion of ß-ionone through ß-C_{15} aldehyde 4 and ß-C_{18} ketone 8 to Vitamin A aldehyde and acetate. The chain lengthening of ß-C_{18} ketone 8 by two carbon atoms was effected by Grignard reaction. Sumitomo process uses the condensation of C_{15} aldehyde 4 with ethyl senecioate (24) to get the Vitamin A acid ester[43]. Philips process too used the C_{15} aldehyde and converted it into Vitamin A aldehyde through C_{18} ketone[44]. The C_{18} ketone undergoes condensation with cyanoacetic acid (25) to give finally retinal.

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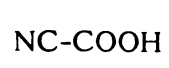

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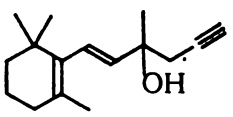
Manufacturing process developed by the DPI of Eastman Kodak and Glaxo Laboratories proceed through Grignard reaction of C_{16} propargyl ß-ionol (26) with ketobutanal acetal 27 to give Vitamin A aldehyde and acetate[45]. Glaxo was allowed to use this process in 1963 in India. Roche too is manufacturing Vitamin A in India.



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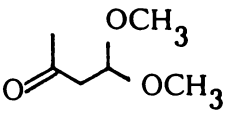

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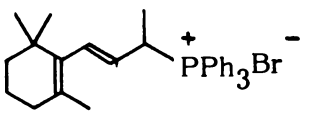
After the achievement of BASF using Wittig reaction, C_{13} + C_7 mode of coupling by Wittig reactions were tried successfully by many groups using C_{13} phosphonium salt 28 derived from ß-ionol and C_7 aldehydes 29[46, 47]. But the Wittig reaction of ß-ionone with C_7 phosphonium salt 30 was unsuccessful because of the low reactivity of ß-ionone. Moreover it is difficult to achieve a synthesis of tri- or tetrasubstituted olefins using conventional Wittig reagents[30]. This disadvantage can be circumvented by employing Wittig - Horner modification[48]. Thus using phosphonates like 31 improved yields on Vitamin A synthesis were achieved[46, 49].



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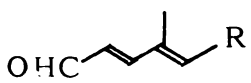
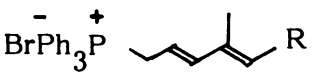


R - CH_2OH, CO_2Et, COOH

29



R - CH_2OH, CO_2Et, COOH

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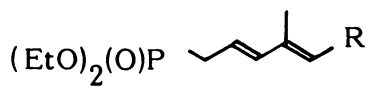

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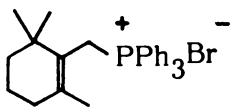
A patented process for Vitamin A acetate by the versatile C_{10} + C_{10} approach was reported from BASF laboratories using Wittig reaction[46, 50]. C_{10} phosphonium salt 32 was condensed with C_{10} triene aldehyde acid ester 33 to get all E Vitamin A acetate. Steric

reasons forced the newly formed double bond into the trans configuration.



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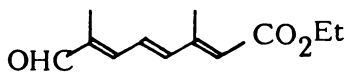

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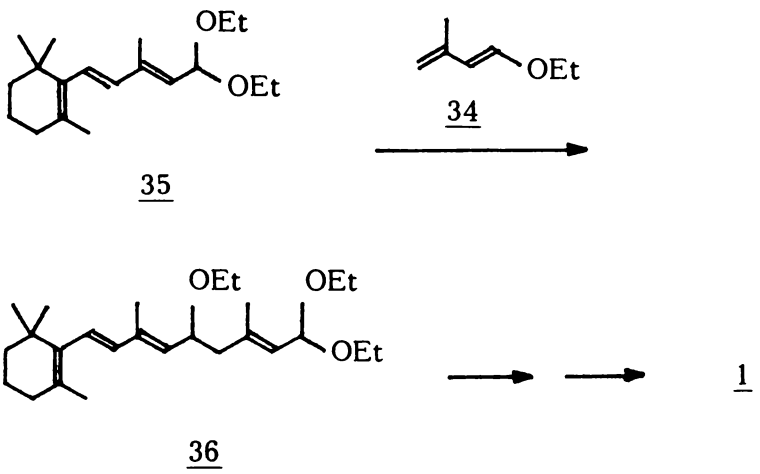
The C_{18} + C_2 method with the C_{18} ketone 8 via a Horner-Wadsworth-Emmons reaction remained unimportant as a preparative route owing to the low reactivity of C_{18} ketones towards phosphoryl anions.

During this period a Russian report on enol ether condensation for Vitamin A aldehyde synthesis has appeared[51, 52]. Using the enol ether 34 as the C_5 unit and condensing it with C_{15} acetal 35 in the presence of a Lewis acid, C_{20} ethoxy acetal 36 is formed. 36 on hydrolysis and alumina chromatography afforded Vitamin A aldehyde which was then reduced to Retinol (Scheme 6).

So thus far the reactions that were commonly used to construct the retinoid skeleton are Knoevinegal condensation, Reformatsky reaction, Wittig reaction, enol ether condensation and to a lesser extent aldol condensation. The advantages and disadvantages of these and their applicability in relation to technical retinoid syntheses has been excellently evaluated by Kienzle[30]. Few of these reactions namely Wittig type and acetylinic routes still retain their importance



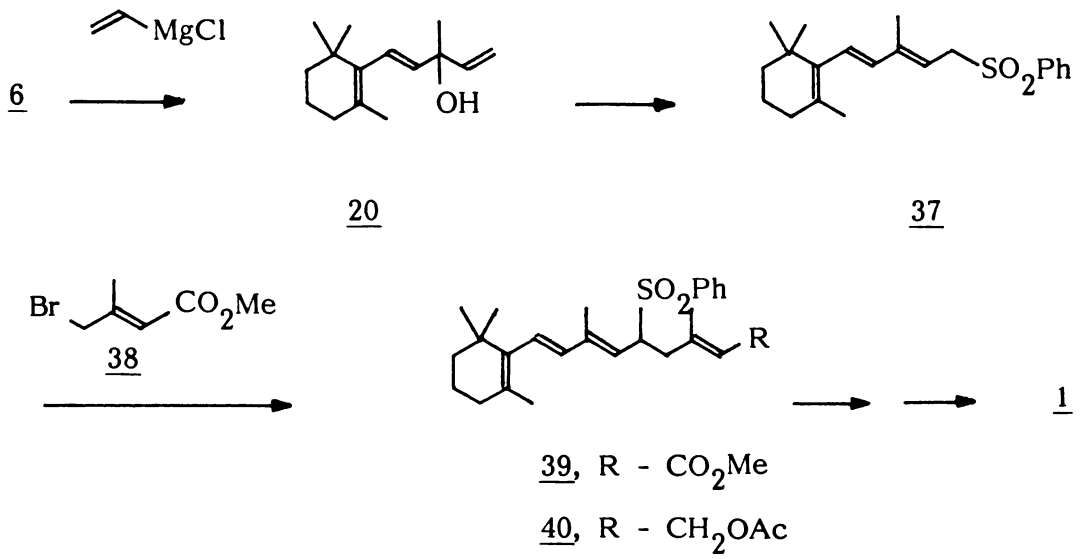
Scheme 6

as the principal methods for building up the carbon skeleton of retinoids[25]. Nevertheless a good deal of attention has been paid to new or improved methods of olefination.

The introduction of a novel technique for building up the C_{20} retinoid skeleton by Julia and Arnold[53] in 1973 saw the research on retinoid syntheses taking a new surge to break the barriers of classical organic synthetic methodologies. This reaction has been known for a while[54] but has been used only in the seventies for the synthesis of retinoids.

In Julia's synthesis the C_{15} sulfone 37 prepared from vinyl ß-ionol (20) and sodium phenyl sulfinate was alkylated with the

bromo acid ester 38 to give the C_{20} ester 39. Subsequent hydrolysis and elimination of phenyl sulfinic acid gave Vitamin A acid methyl ester (1b) which on reduction afforded a mixture of all E and 9Z Vitamin A (1) (Scheme 7).

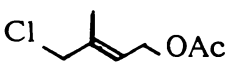


Scheme 7

Soon after Julia's success with the sulfone-alkylation approach, many groups have tried successfully the other strategic combinations of sulfones and allylic halides to construct the retinoid skeleton[55].

The Hoffmann-La Roche group headed by Manchand[56] developed a synthesis of Vitamin A in a similar C_{15} + C_5 route by alkylating C_{15} sulfone 37 with C_5 chloroacetate 41. Subsequent elimination

of sulfinic acid from the C_{20} sulfone 40 in homogeneous condition using large excess of sodium ethoxide in ethanol afforded Vitamin A in 88% yield with a fairly high trans content (73%). They also found that when a sulfinate substituted in the phenyl ring was used, the product obtained on sulfinic acid elimination was 4, 14 - retro retinyl acetate (42).



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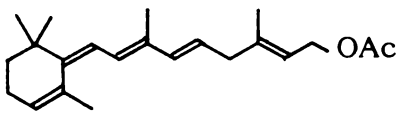

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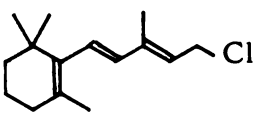
At the same time, Chabardes and co-workers at Rhone-Poulenc described a similar C_{15} + C_5 approach[57] independently starting from the same C_{15} sulfone 37 and chloroacetate 41. The important step in their synthesis is the elimination of sulfinic acid using potassium alkoxides as the base. It was shown that potassium alkoxides in heterogeneous medium are the best reagents to effect desulfonation and Vitamin A in 85% yield with 82% trans content was obtained.



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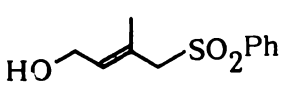
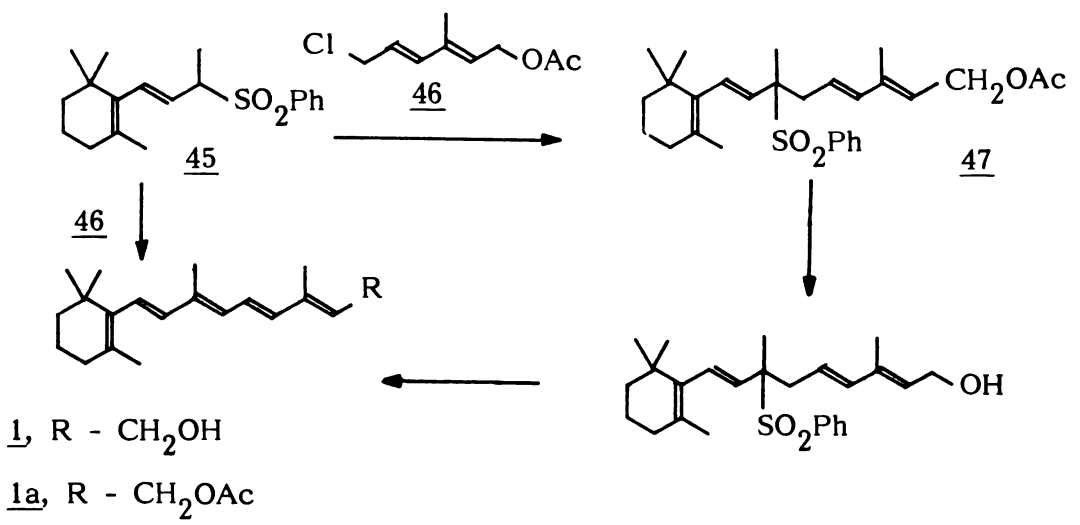


44

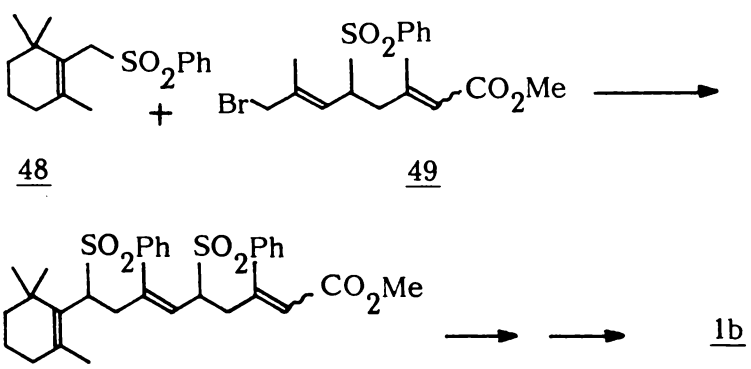
In a similar C_{15} + C_5 approach Olson[58] achieved a Vitamin A acetate synthesis in 75% yield using C_{15} halide 43 and C_5 hydroxy sulfone 44.

Starting from ß-ionyl phenyl sulfone (45) and an allylic chloride 46, Vitamin A synthesis has been achieved by Fischli and co-workers of Hoffman-La Roche employing a C_{13} + C_7 combination[59]. Alkylation of the sulfone 45 with the chloride 46 using potassium t-butoxide gave the C_{20} acetoxy sulfone 47 which on hydrolysis gave the alcohol sulfone, which on sulfinic acid elimination in the presence of sodium hydroxide in dimethylacetamide (DMA) gave a mixture of all E and 9Z retinol. Alternatively alkylation in the presence of sodium hydroxide in DMA gave the same isomeric mixture directly, which on acetylation, palladium catalyzed isomerization and crystallisation gave pure all E retinol in 50% overall yield (Scheme 8).



Scheme 8

An efficient synthesis of Vitamin A acid methyl ester was achieved using two non conjugated C_{10} units 48 and 49 in a versatile C_{10} + C_{10} sulfone-alkylation approach[60]. The obvious advantage of Uneyama's method is the elimination of the risk associated with using polyenes which are heat labile and photosensitive (Scheme 9). The final elimination step yielded Vitamin A acid ester in 94% yield with 83% all trans content.



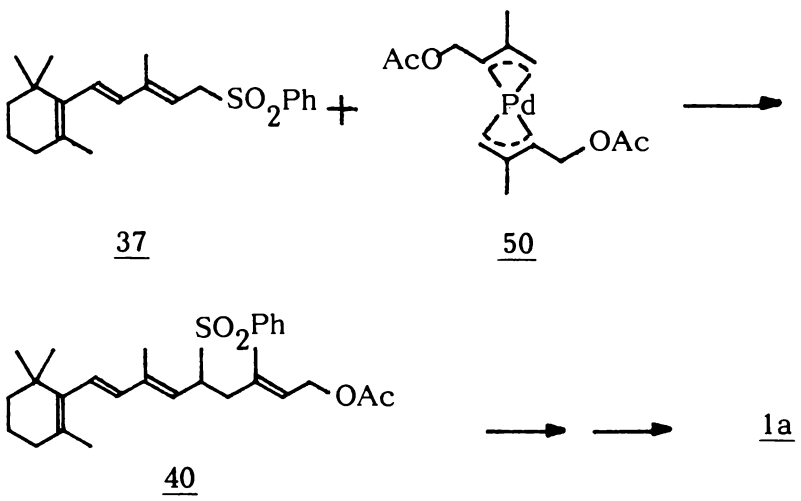
Scheme 9

A technical advantage of this sulfone-alkylation reaction as compared to the Wittig or Horner olefination is the direct recycling of the sulfinic acid without any chemical modification. In contrast the triphenylphosphine oxide formed in Wittig reaction has to be reduced again to triphenyl phosphine. But so far sulfone-alkylation has not

been commercially exploited. Probably the need to have activating substituents for the sulfone formation or the use of expensive bases in the alkylation as well as in the elimination steps are the obvious disadvantages. On the other hand the one advantage which will make sulfones very useful in the syntheses of special polyenes is that they are relatively chemically inert. So it is possible to carry out chemical transformations on the sulfone bearing molecule prior to olefination without destroying the sulfone group. However the range of application of sulfone-alkylation method in retinoid chemistry is still to be established, as has been done for the Wittig reaction in the past years.

The use of transition metal complexes in the synthesis of retinoids is exemplified by Manchand's effort in synthesising Vitamin A acetate via pi-allyl palladium complex[61]. These workers employed the alkylation of the sulfone with pi-allyl palladium complex of prenyl acetate 50 in a C_5 + C_{15} convergent approach. Thus the anion generated from the sulfone 37 with sodium hydride in dimethylsulfoxide is alkylated with the pi-allyl palladium complex 50 in the presence of triphenylphosphine to get the C_{20} sulfone 40 and the subsequent elimination of sulfinic acid using sodium ethoxide in boiling ethanol afforded Vitamin A in 81% yield with 67% all trans content. Acetylation and crystallization afforded all E Vitamin A acetate with 95% purity. (Scheme 10).

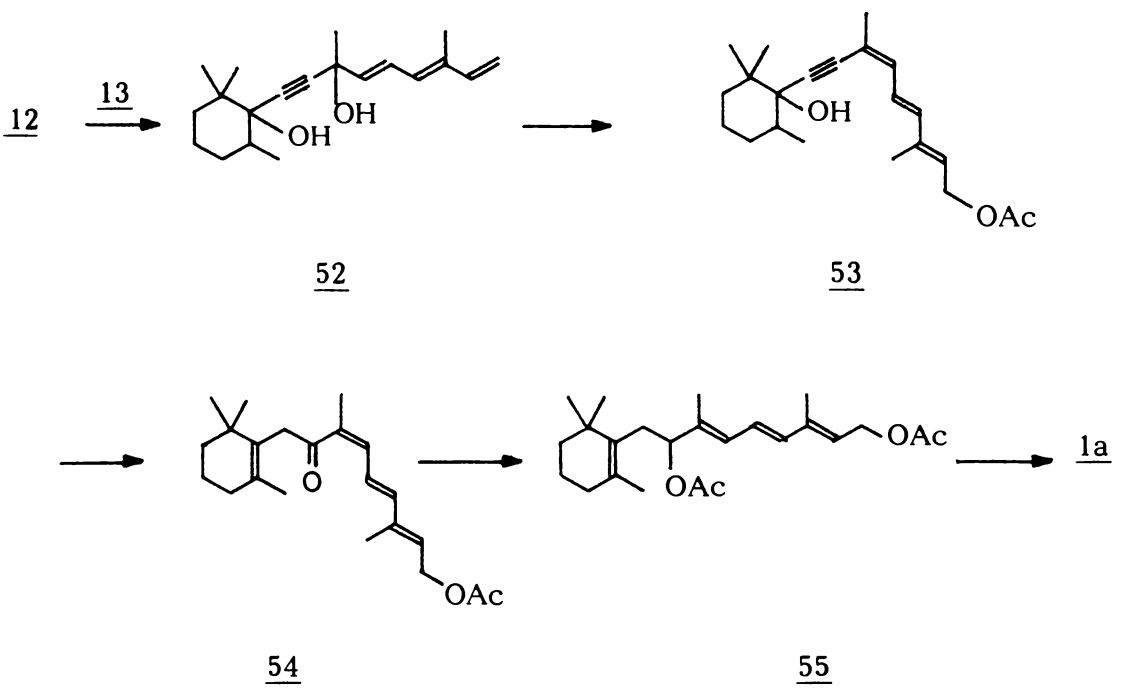
Even though many intermediates are now available for Vitamin A syntheses by way of ß-ionone and its derivatives, cyclohexanone



Scheme 10

and its trialkyl derivative - 2, 2, 6-trimethyl cyclohexanone (10) are still recognised as a convenient starting material[62]. After Attenburros's report[37] appeared no effort has been taken to utilize cyclohexanone as starting material until Olson[63] reported a stereospecific synthesis based on it. The methodology used is the alkyne addition to the carbonyl compound and the use of a novel vanadate rearrangement. Grignard addition of the acetylinic alcohol 12 prepared from cyclohexanone 10 and sodium acetylide (51) to the trienone 13 afforded the trienyl diol 52 in 97% yield, which on multiple allylic rearrangement and acetylation gave trienyl acetate 53. This underwent rearrangement

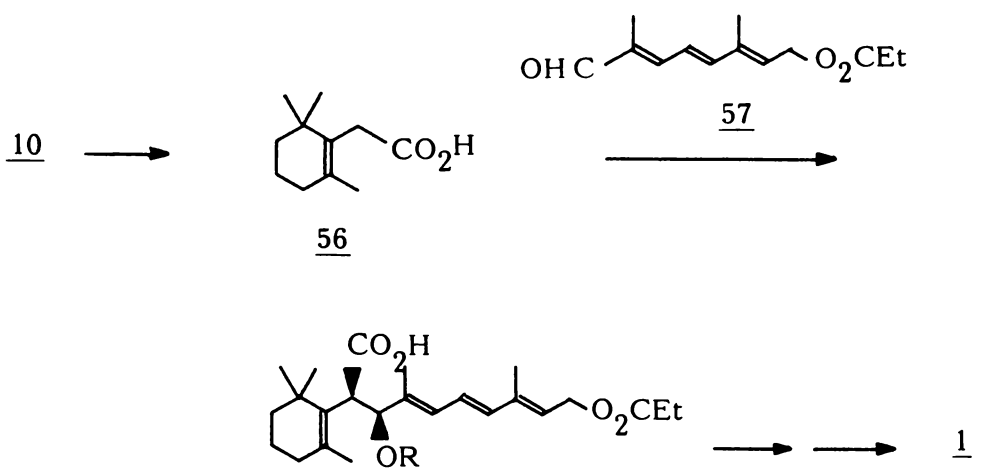
in the presence of tris-(tri-(3-nitrophenyl)-silyl) vanadate and triphenyl silanol to give an unsaturated ketone 54 which was then reduced, and acetylated to give the diacetate 55. On treatment with hydrobromic acid 55 gave Vitamin A in 44% yield (Scheme 11). Crystalization



Scheme 11

provided all E Vitamin A acetate in 99.8% purity. The key step in this sequence is the transformation of 53 to 54 in a new rearrangement catalysed by Vanadium(V). The other approaches to Vitamin A intermediates through cyclohexanone and its derivatives reported are by Derguini[64] and Colwell[65].

A novel C_{10} + C_{10} approach to retinoids employing palladium induced decarboxylative elimination is described by Trost[66], the starting material used again being trimethylcyclohexanone (10). The synthesis of Vitamin A ethyl ester utilizes the acid 56[67], which is prepared from 10 in 60% yield. The dianion of the acid added smoothly to the aldehyde ester 57[50, 68] to give an unstable hydroxy acid 58 as a single diastereomer, which was acetylated to get the acetoxy acid 59. This smoothly underwent decarboxylative elimination catalysed by tetrakis (triphenylphosphine)palladium(0) in the presence of triethylamine in tetrahydrofuran to give Vitamin A ester in 40% overall yield (Scheme 12).

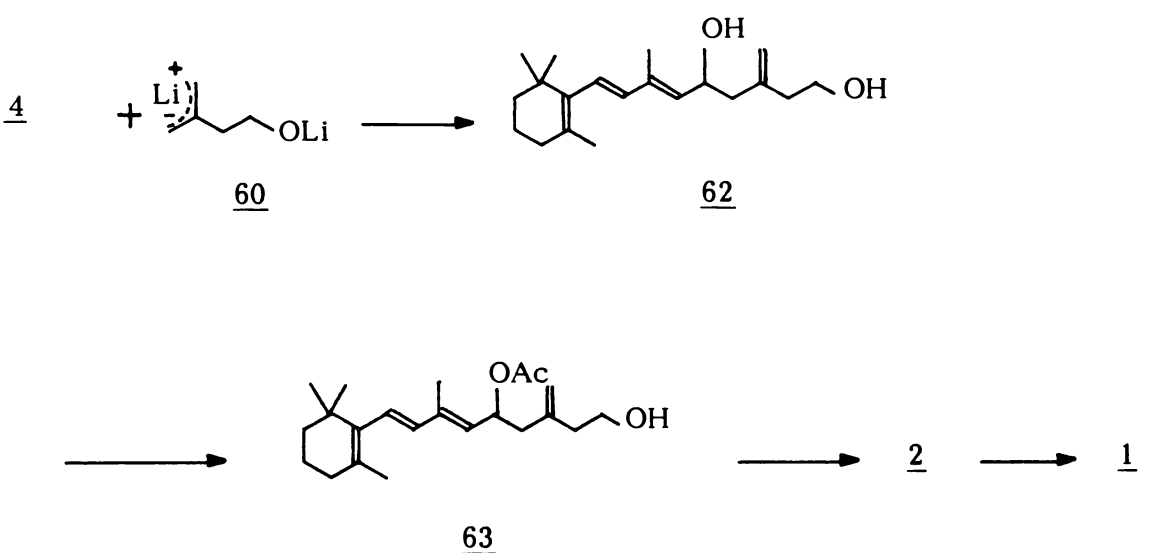


58, R - H

59, R - Ac

Scheme 12

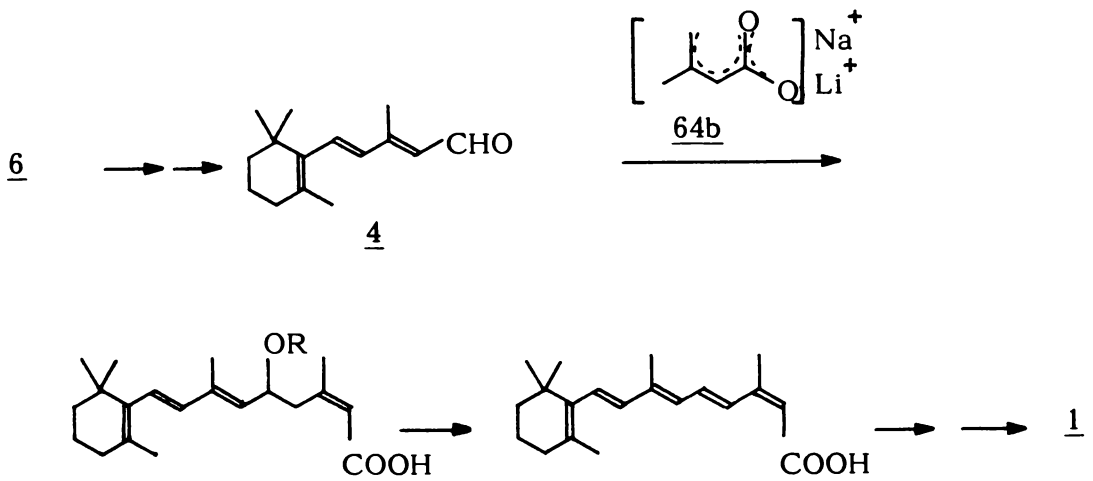
Cardillo in 1979 reported a procedure for the addition of a prenyl unit as a dianion 60 to the carbonyl compounds and achieved a C_{15} + C_5 synthesis of Vitamin A[28, 69]. The addition of the metallized lithium C_5 enolate 60 derived from 3-methyl-but-3-en-1-ol (61) and n-butyllithium-tetramethylethylenediamine complex to C_{15} aldehyde 4 afforded the diol 62 which was then acetylated and carefully saponified to get the alcohol acetate 63. This after oxidation and prolonged base treatment with potassium tertiary butoxide afforded all trans retinal and further reduction, all trans Vitamin A (Scheme 13).



60 62 63

Scheme 13

Similar utilization of these dianions as a masked prenyl unit was earlier reported by Cainelli[70] by using the dianion 64b derived from the sodium salt of 3-methyl-3-butenoic acid (64a) as the active prenyl unit. The dianion 64b reacted with the aldehyde 4 at -78° to give the cis hydroxy acid 65a in high yield. The hydroxy acid was acetylated to get the acetoxy acid 65b. This underwent base catalyzed elimination to give 13Z Vitamin A acid (65c). The conversion of 65c to all trans Vitamin A acid was accomplished by isomerization with iodine and retinol (1) was obtained by the reduction of the acid ester with lithium aluminium hydride (Scheme 14).



65a, R - H

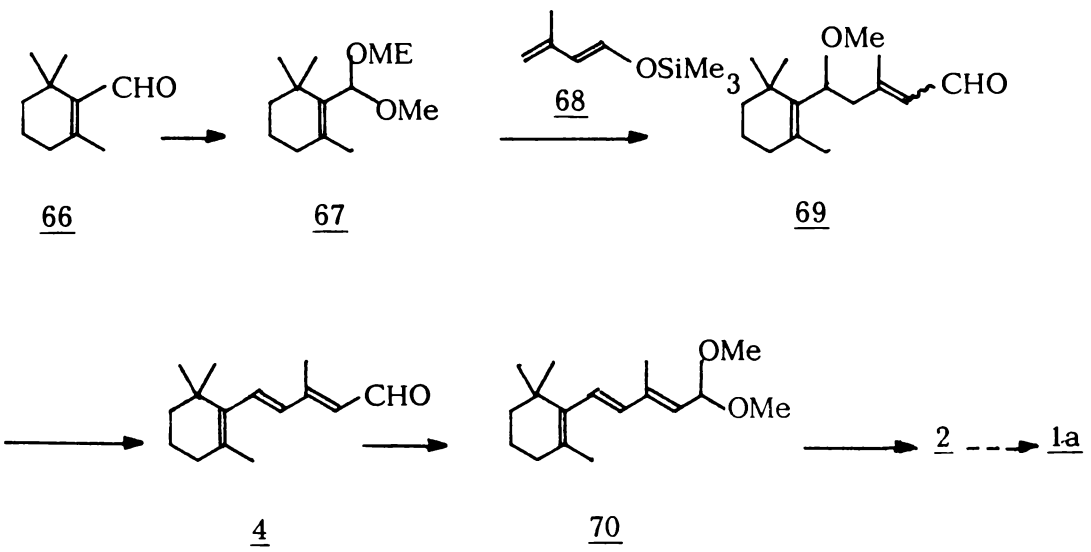
65b, R - Ac

65c

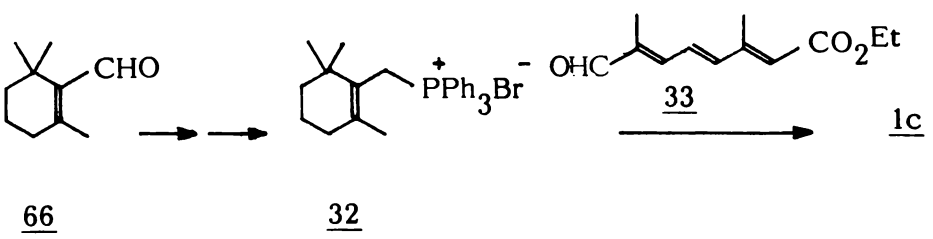
Scheme 14

Mukaiyama[71] has reported a C_{10} + C_5 + C_5 approach for Vitamin A starting from ß-cyclocitral (66)[72] closely following the C_{15} + C_5 approach earlier developed by the Russian workers[51, 52]. The main difference is that while Mukaiyama employed the successive addition of trimethyl silyl enol ether 68 as the C_5 units to the C_{10} acetal 67, the Russians added the C_5 ethyl enol ether 34 to C_{15} aldehyde acetal 35 to build the C_{20} skeleton. These two approaches demonstrated the utility of these enol ether synthons as the masked isoprene units. In Mukaiyama's approach titanium catalysed addition of 3-methyl-1-trimethylsiloxy-1, 3-butadiene (68) to ß-cyclocitral acetal (67) yielded the methoxy aldehyde 69 which on base treatment with 1, 8-diazabicyclo (5.4.0)undec-7-ene (DBU) and iodine catalysed isomerization yielded ß-C_{15} aldehyde 4. It was converted into the acetal 70 and the repetition of the reaction sequence afforded retinal which was then converted to Vitamin A acetate (Scheme 15).

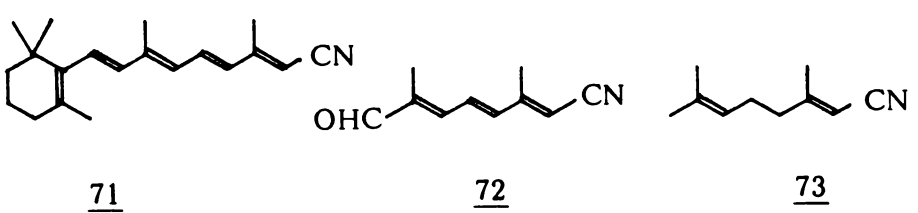
Bhat[73] in 1978 reported a C_{10} + C_{10} convergent approach for retinoic acid ethyl ester and retino nitrile 71 starting from ß-cyclocitral 66. The other C_{10} unit 33 was prepared by allylic oxidation of ethyl geranoate 73a followed by N-bromosuccinimide bromination-DBU catalyzed dehydrobromination. These two units were coupled by Wittig reaction (Scheme 16). Similarly Wittig reaction of the phosphonium salt 32 with 72 prepared from geranonitrile 73b by allylic oxidation and N-bromosuccinimide bromination-DBU catalyzed dehydrobromination, gave retinonitrile (71).



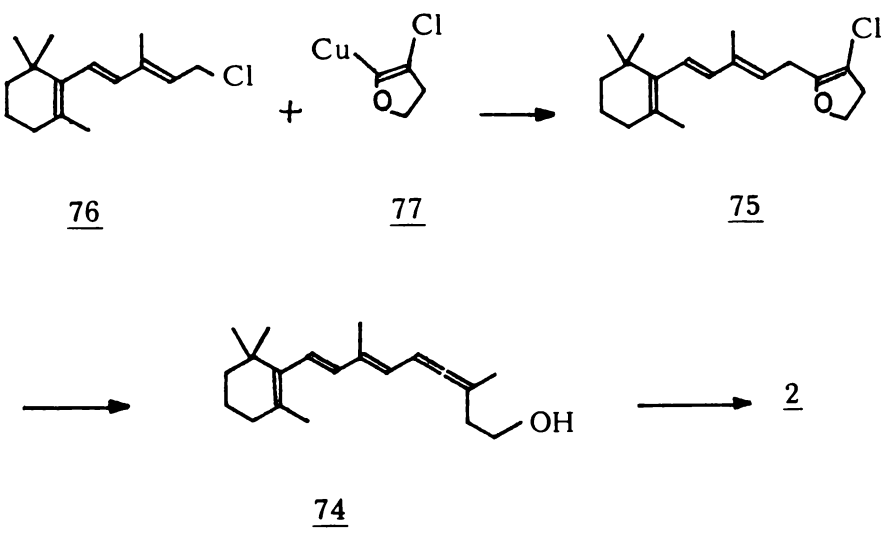
Scheme 15



Scheme 16



Ruzziconi has described an allene route to prepare all trans retinal[74]. This unorthodox entry into Vitamin A series was effected through the allene - 'isoretinol' 74 prepared by methylation of the chloro derivative 75 which has been obtained by the reaction of the C_{15} chloride 76 with the key reagent 3-chloro-4,5-dihydro-2-furyl copper (77). 74 on oxidation with N,N'-dicyclohexylcarbodiimide in dimethylsulfoxide afforded all E retinal together with 11Z 13Z, 11Z 13E and 11E 13Z isomers (Scheme 17).



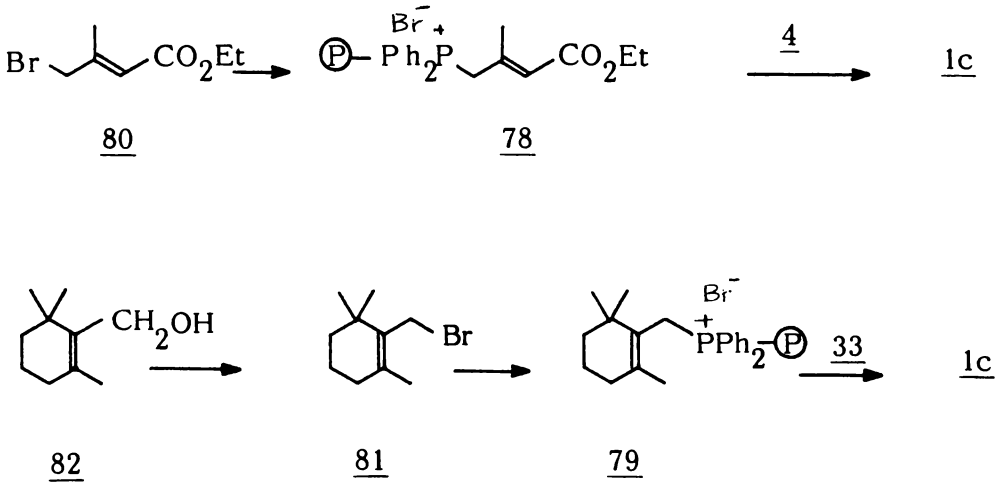
76 77 75

74

Scheme 17

An interesting development that has occured in the field of retinoid synthesis is the use of polymer supported Wittig reagents[75]. Thus using insoluble polystyryl Wittig reagents 78 and 79 prepared

by the reaction of diphenyl(polystyryl)phosphine with bromo ester 80 and cyclogeranyl bromide (81) obtained from cyclogeraniol (82) respectively, ethyl retinoate (1c) has been synthesized. Generation of the polymer bound phosphoranes with sodium ethoxide in ethanol in the presence of appropriate aldehydes 4 or 33 gave isomeric mixtures of ethyl retinoate in 55-70% yields (Scheme 18). The C_{15} + C_5 and C_{10} + C_{10} approaches are outlined in the following scheme.

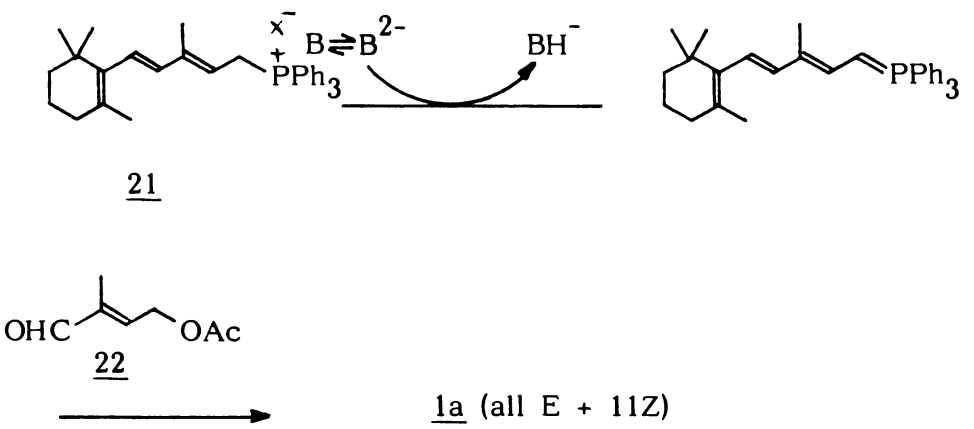


Scheme 18

The yields obtained by this method are as high as those reported from analogous soluble Wittig reagents. The advantage of this method is that, polymer supported Wittig reagents enable isolation

of isomeric mixtures of ethyl retinoate without need for chromatography, extraction or crystallization to remove the triphenylphosphine oxide byproduct. The insoluble polystyryl diphenylphosphine oxide can be removed from the retinoids by simple filteration.

Another new development in the retinoid syntheses is the use of electro-organic procedure for Wittig synthesis of retinyl acetate[76] from C_{15} Wittig salt 21 and the aldehyde 22 (Scheme 19). Electrogenerated base was prepared from the pro base ethyl-2-cyano-2-(fluoren-9-ylidine) acetate, with Li^+ as the cation of the electrolyte. Yields of upto 40% were obtained with 1:4 cis-trans ratio.



21

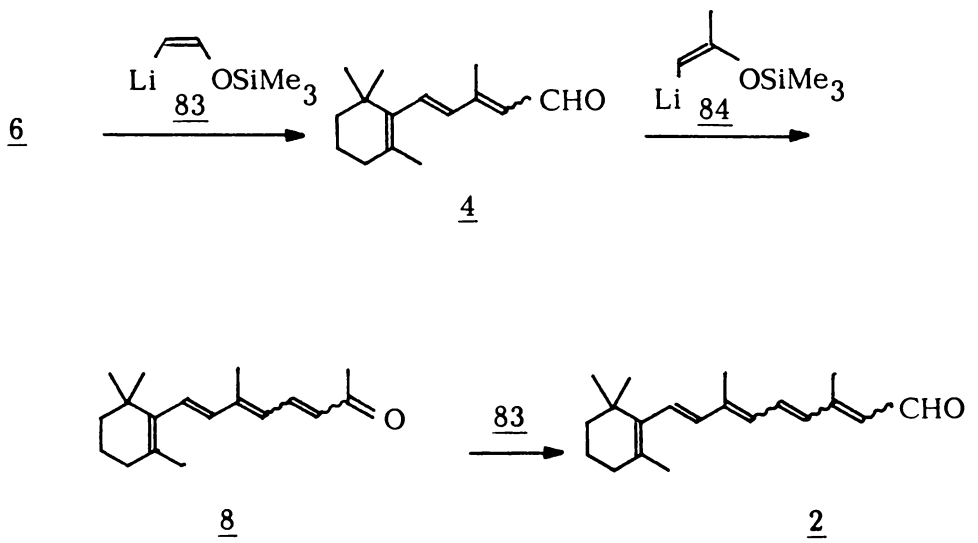
22

1a (all E + 11Z)

Scheme 19

Duhamel[77] very recently showed that 2-lithioethenyloxy (trimethyl) silane (83) and its methyl derivative 84 adds on to the

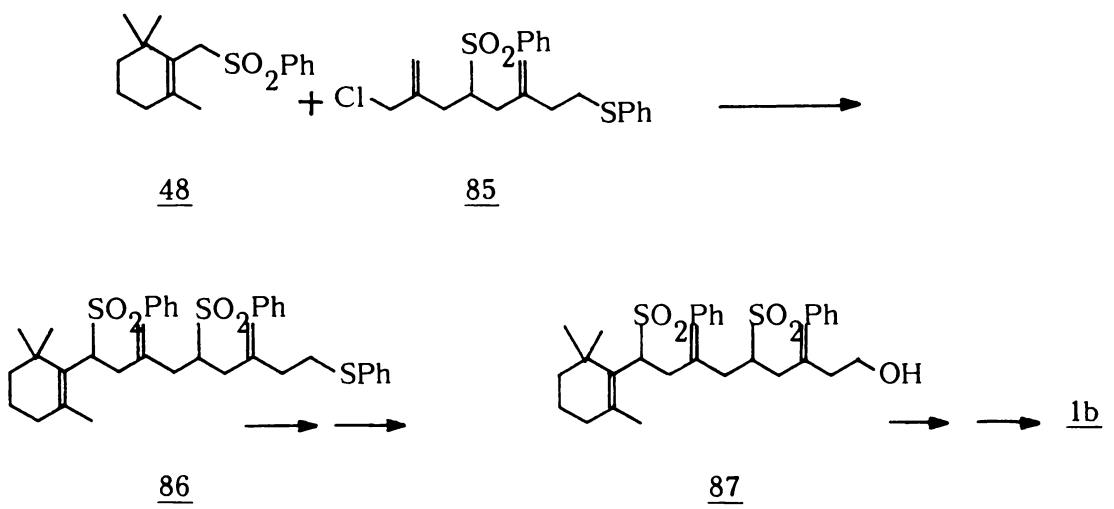
carbonyl compounds to effect two and three carbon additions. Thus ß-ionone was converted into the C_{15} aldehyde 4 by the reaction with the reagent 83 followed by hydrolysis. Repetition of the processes by using 84 to get the C_{18} ketone 8 and then again by 83 yielded retinals with 59% all trans content and the rest being 9Z 11E 13E, 9E 11E 13Z and 9Z 11E 13Z with an overall yield over 50% (Scheme 20). The advantage of this procedure is the simplicity of performance. The conditions used for the condensation and hydrolysis are very mild.



Scheme 20

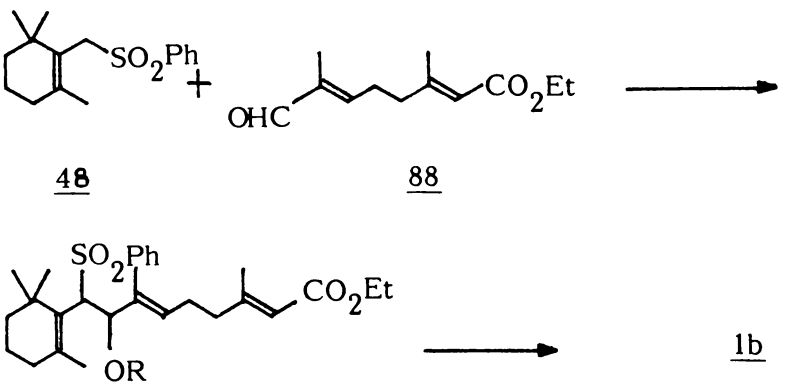
Mandai[78] have recently reported a novel synthesis of methyl retinoate by the sulfone-alkylation approach using the sulfone 48 and

the nonconjugated C_{10} chlorosulfone 85 and obtained methyl retinoate (1b) with 69% all E content, the rest being 13Z isomer (Scheme 21).



Scheme 21

Mandai again in 1984 synthesized Vitamin A acid methyl ester by introducing a novel double elimination sequence in the sulfone-condensation approach[79]. The addition of the aldehyde 88 to the C_{10} sulfone 48 afforded the C_{20} hydroxy sulfone 89, which was converted into its tetrahydropyranyl ether 90. This on base treatment underwent double elimination and following diazomethane methylation afforded all E methyl retinoate and its 13Z isomer in 1:1 ratio (Scheme 22).



48 88

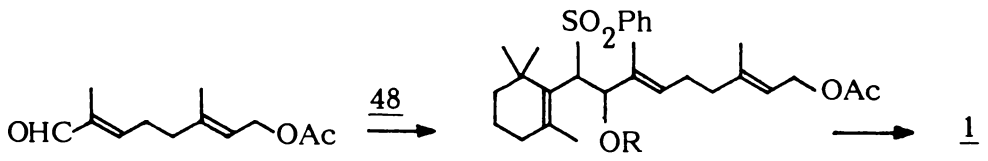
89, R-H

90, R-THP

1b

Scheme 22

Very recently in 1986 the same group headed by Otera[80] reported a very efficient C_{10} + C_{10} convergent route for the stereocontrolled synthesis of Vitamin A through the double elimination variation in sulfone-condensation approach. The addition of the aldehyde acetate 91 derived from geranyl acetate (92) to the C_{10} sulfone 48 afforded Vitamin A through the hydroxy sulfone 93a and its acetyl derivative 93b (Scheme 23). It was also showed that halosulfone 94 prepared by halogenation of 93a too underwent double elimination to afford all E Vitamin A in 95% purity. 13Z isomer of retinol too was synthesized similarly using the aldehyde ester 96 obtained from neryl acetate (95) by allylic oxidation using selenium dioxide.

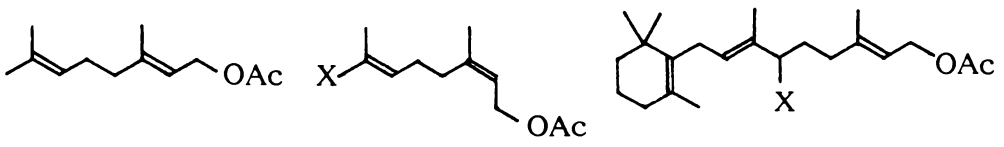


91

93a, R-H

93b, R-Ac

Scheme 23



92

95, X-CH_3

96, X-CHO

94, X-Cl, Br

There has been a report of the synthesis of 9Z, 13Z and all E isomers of retinal starting from ionones has also appeared[81]. Approaches that are developed recently have been well reviewed[13,82].

1.4 Stereo Isomers of Retinoids

Ever since the recognition of the importance of stereoisomerism in retinoids though the elegant work of Wald[11] and the elucidation of the role of 11-cis and all trans isomers in the visual process, identification and synthesis of all the sixteen isomers of the retinoid has become a challenge to synthetic chemists. In the recent years aided by the rapid development of analytical methods, especially NMR

and HPLC, which permit reliable and rapid structure assignments coupled with newer synthetic methods and knowledge of photochemistry, there has been a surge of interest in the synthesis of isomers and structurally modified analogues of retinoids.

The studies conducted in visual processes, structure-activity correlation studies and the interest in the role of various rhodopsin analogues also generated interest in the syntheses of various isomers and structurally modified derivatives of Vitamin A. These subjects have been thoroughly reviewed by Nakanishi[14].

As things stand now, all the sixteen isomers of Vitamin A have been synthesized and particularly noteworthy were the syntheses of isomers with 7-cis geometry which were once believed to be synthetically unattainable due to excessive steric crowding. Till 1986, no synthesis of two 7-cis isomers of retinal which are less stable has been reported.

The synthetic chemistry of geometric isomers of retinoids[13, 83], as well as the entire field of synthetic retinoids[84], has been reviewed. Other new analogues[85] and synthesis of isomers[81, 86] have since been reported.

So to conclude, this area still provide challenges to the chemists and there has been no lack of attempts to discover improved methodologies in terms of improved stereoselectivity and control for the synthesis of retinoids and its isomers.

CHAPTER II

STATEMENT OF THE PROBLEM

2.1 Introduction

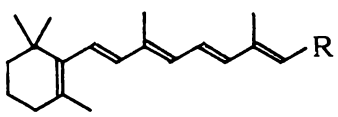
Vitamin A molecule by virtue of its complex nature is a challenge to synthetic chemists. While the academic field is still active because of the synthetic challenge offered by the molecule, on commercial front, its versatality as well as the competitive pressure has given rise to a great deal of research on more economical methods of production as evidenced by the patent literature indicating the work involved in industrial laboratories.

The synthesis of retinoids has been thoroughly studied for many years and the basic skeleton has been constructed in almost every conceivable manner. Virtually almost all combination of coupling of fragments have been tried to build the skeleton. But this area still provide challenges and there has been no lack of attempts to find improved methodologies over the existing ones or to find shorter reaction sequences for the controlled formation of the polyene chain.

An attempt for a commercially viable practical synthesis of Vitamin A is very much desirable because of the potential nature of the molecule. So devising a good Vitamin A synthesis flexible enough to provide analogues employing locally available easily accessible starting materials is of more than academic interest.

In the present work synthetic schemes are visualised employing readily available starting materials. In these schemes, the total carbon atoms are derived either fully from natural products or as fragments

from commercially available starting materials. Vitamin A (1) molecule can be considered as built from a cyclic and a linear unit. Different



1, R-CH_2OH

2, R-CHO

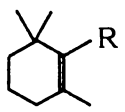
3, R-COOH

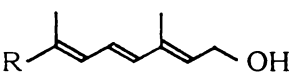
methods for the syntheses of the linear and cyclic components through appropriate functionalizations will be described. Different methods of terminal functionalizations of monoterpene molecules will be described. Approaches for the synthesis of different synthons through functional group modifications of easily accessible commercially available starting materials will be tried. Utilization of these intermediates in Vitamin A synthesis through various coupling reactions are attempted in the last part.

2.2 Synthesis of Linear C_{10} Unit

By way of disconnection approach Vitamin A molecule can be split into two C_{10} fragments - a cyclic and a linear. The cyclic component can be either ß-cyclocitral (4), ß-cyclogeraniol (5a) or its derivatives and now the effort is to synthesise the conjugated triene 6 or 7 so as to get the C_{10} linear component. The easily available

starting material for this purpose can be identified as either citral (8) or its reduced form geraniol (9). These monoterpenes are

1 



4, R-CHO

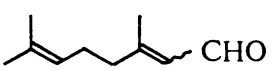
5a, R-CH_2OH

5b, R-CH_2Br

6, R-CHO

7a, R-CH_2OH

7b, R-CH_2Br



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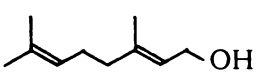


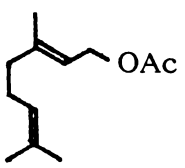
9

readily available materials and has the required basic carbon skeleton. While geraniol is the major constituent (~80%) of the oil of palmarosa (Cymbopogon martini), citral is present in oil of lemongrass (Cymbopogon flexuosus) to the extent of 80%.

Terminal allylic functionalization of these molecules are easy and introduction of a double bond in 4, 5 position and subsequent coupling with C_{10} cyclic moiety affords Vitamin A molecule. Such a synthesis of the terminal functionalised triene starting from a natural product has been tried only once before employing N-bromosuccinimide

bromination-dehydrobromination[1]. Though this is an important synthon for Vitamin A synthesis the previous syntheses of this triene were all total syntheses[2, 3]. So it is thought to devise mehtods for the syntheses of this terminal functionalised triene.

In this approach geranyl acetate (10), a derivative of geraniol (9) has been taken as the starting material. Organoselenium methodology has been tried in one approach. Epoxides are known to give allylic alcohols when reduced in presence of diphenyl diselenide followed by oxidative work up[4]. This methodology will be tried on geranyl acetate epoxide (11) to get the allylic alcohol 12. Further



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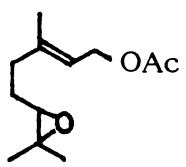

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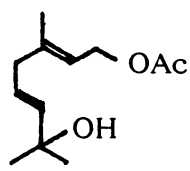

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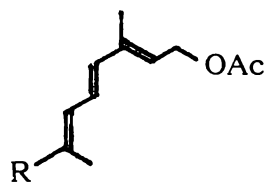


13, R-CH_3

14a, R-CHO

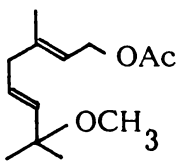
14b, R-CH_2OH

14c, R-CH_2Br

functional group manipulation is expected to give 13 and 14. The acetyl derivative of the intermediate 12 can also be obtained through the addition of benzene sulphenyl chloride to 10. Such organosulfur mediated transformation has also been reported[5]. It is hoped to get the required

target molecule through these transformations.

Conjugate diene synthesis employing iodine-copper(II)acetate in methanol[6] and iodine-periodate-aceticacid system[7] has been successfully carried out on steroidal molecule side chain. In an alternate approach this methodology will be extended to geranyl acetate with a view to effect the required transformation. The intermediates 15 and 16 formed in the above reactions can be transformed into the target molecule.



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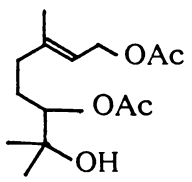

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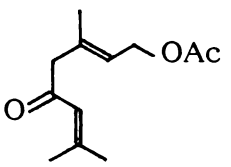


17

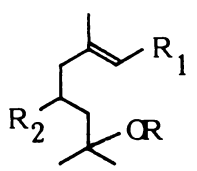
A variation of the allylic oxidation using tertiary butyl hydroperoxide - pyridinium dichromate system in 10 can give 17. Such a transformation has been reported in a similar system[8]. This also on further manipulation is expected to give the triene 13 and 14.

2.3 Synthesis of Cyclic C_{10} Unit

The C_{10} cylic component can be identified as ß-cyclocitral (4) or its derivatives. The available method of preparation of 4 is

through the acid catalyzed cyclization of citral schiff base[9] and through the ozonolysis-cleavage of ß-ionone[10].

Phenyl selenation of monoterpene alcohols or its acetates affords selenylated compounds like 18. These can be cyclised to get cyclic selenylated acetates or alcohols 19[11]. Analogous sulfur methodology can also afford similar intermediates. These cyclic intermediates on reductive work up can afford C_{10} cyclic compounds similar to 4, 5 or its derivatives.

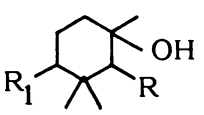


18

R-H, Me

R_1-CH_2OH, CH_2OAc

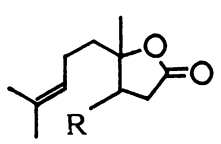
R_2-SPh, SePh



19

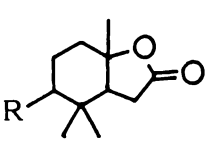
R-CH_2OH, CH_2OAc

R_1-SPh, SePh



20

R-SPh, SePh



21

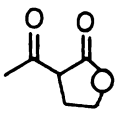
R-SPh, SePh

Homomonoterpenic acids when treated with organoselenium reagents undergo lactonisation to give 20 and later cyclization in the presence of acids to give ring fused bicyclic lactones 21[12]. These when extended to monoterpene acids are expected to give the ring fused lactones which could give the cyclic C_{10} components similar to 4 or 5 on further functional group manipulation.

ß-Ionone can be considered as a aldol condensation product of ß-cyclocitral with acetone. Hence it can undergo retro-aldol condensation at higher temperatures to give ß-cyclocitral and acetone. So under mildly basic conditions the retro-aldol condensation of ß-ionone can give ß-cyclocitral. If successful, this method could prove to be a viable alternative for the ozonolysis-cleavage method for the synthesis of ß-cyclocitral from ß-ionone[10]. ß-Ionone is prepared by the acid catalysed cyclization of pseudoionone, which in turn is the aldol condensation product of citral (8) and acetone.

2.4 Synthesis of C_5 Intermediates

The two commercially available starting materials considered for this synthesis are 2-acetylbutyrolactone (22) and levulinic acid (23). Suitable functional group modification and introduction of unsaturation in 23 can give 24. Similarly the lactone 22 can also be converted to 24. Suitable functionalization and preparation of corresponding derivatives like aldehydes and sulfones etc. can provide C_5 intermediates like 24 for various coupling reactions.



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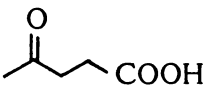
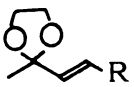


23



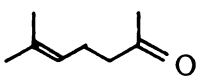
24a, R-CH_2OH

24b, R-CH_2Br

24c, R-CHO

2.5 Synthesis of C_8 Intermediates

The retro-aldol condensation product of citral (8) -methyl heptenone (25) can be identified as a suitable starting material with the necessary carbon framework.



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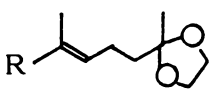


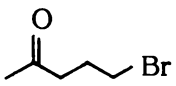
26, R-CHO

27, R-CH_2OH

Isopropylidene terminus functionalised ketal 26 or 27 can be used as synthons for Vitamin A synthesis. Methods of allylic functionalisation of 25 will be tried.

The potential of methyl heptenone (25) as an important industrial intermediate is well evidenced by its use in BASF process for Vitamin A synthesis[13] and in perfume industry[14]. So it was thought to devise a simple approach for the synthesis of methyl heptenone

starting from commercially available starting materials. Thus the phosphonium salt 29 prepared from the ketobromide 28 derived from 22 can condense with acetone to afford methyl heptenone (25). The fact that the starting material lactone 22, which in turn is produced



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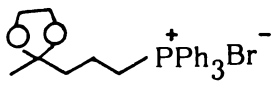


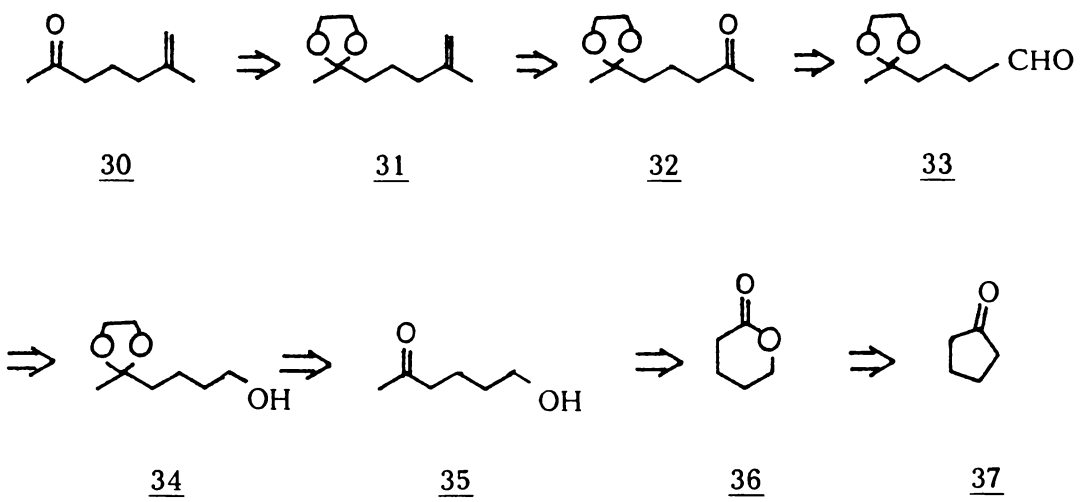
29

from ethylene oxide and ethyl acetoacetate, and acetone are industrial bulk chemicals and the reaction involved is the industrially exploited Wittig reaction makes this approach for methyl heptenone attractive. If successful this can have commercial significance.

A scheme for the synthesis of an industrial intermediate 30 in BASF process for Vitamin A synthesis[15] has been visualised. In the synthetic sequence, 32 forms the precursor for methyl heptenone (25). The retro synthetic analysis shows that cyclopentanone can be considered as a suitable starting material.

Thus cyclopentanone (37) on Baeyer-Villiger oxidation followed by methyl lithium treatment will give the methyl ketone 35. This can be converted to the ketal 32 through Grignard reaction of the aldehyde 33. Ketal 32 on methylene Wittig reaction and deprotection

will yield the intermediate 30. Epoxidation followed by ring opening of the ketal 31 could lead to allylic functionalised compounds 26 or 27 (Scheme 1).



30 31 32 33

34 35 36 37

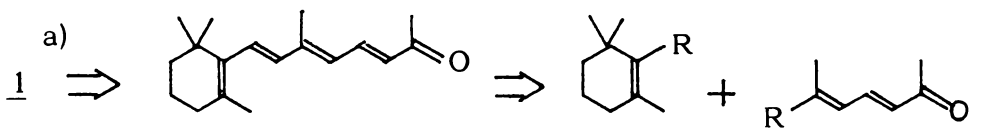
Scheme 1

2.6 Synthesis of Vitamin A

From the retrosynthetic analysis it can be seen that a number of disconnections are possible on Vitamin A molecule. Depending on which double bond in the molecule is disconnected, various fragments are possible. Many of these can be identified as derived from naturally occuring, easily available materials, its derivatives or the corresponding functionalised molecules. These fragments can be coupled in a variety of olefin forming reactions available to synthetic chemists now.

Of the many disconnections possible, only a few are considered here since others are beyond the scope of the present work (Scheme 2). These approaches can be conveniently classified as $C_{10} + C_8 + C_2$, $C_{13} + C_5 + C_2$, $C_{13} + C_7$ and $C_{10} + C_{10}$.

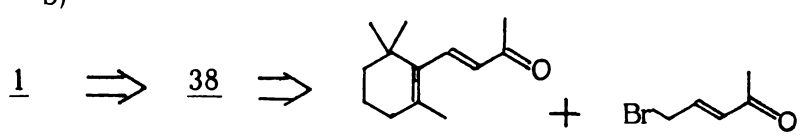
a)



1 ⇒ 38 ⇒ 4, R-CHO + 39, R-CH_2Br

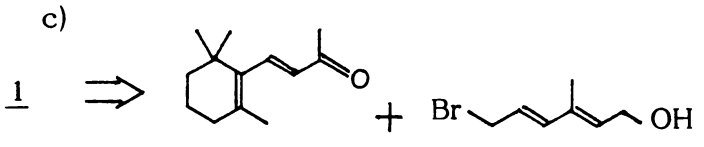
5, R-CH_2Br + 41, R-CHO

b)



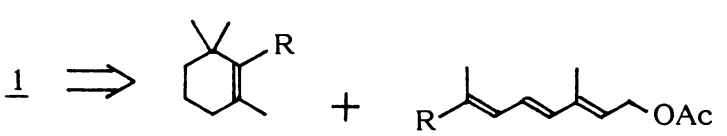
1 ⇒ 38 ⇒ 40 + 42

c)



1 ⇒ 40 + 43a

d)

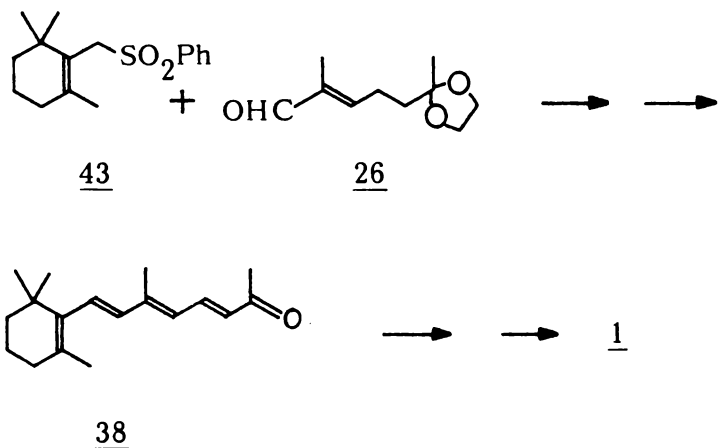


1 ⇒ 4 or 5c + 14a or 14c

Scheme 2

2.6.1 $C_{10} + C_8 + C_2$ Approach

According to this approach, Vitamin A skeleton can be built up from a C_{10} unit and a C_8 unit through the ß-C_{18} ketone. The synthetic plan according to this scheme involves the use of ß-cyclocitral or ß-cyclogeraniol derivatives as the C_{10} unit. This can be coupled with the properly functionalized C_8 unit to get the ß-C_{18} ketone. A two carbon homologation completes the sequence for the synthesis of Vitamin A (Scheme 3). Since the conversion of ß-C_{18} ketone to Vitamin A is known, this approach will constitute a formal synthesis of Vitamin A.



43 26

38 1

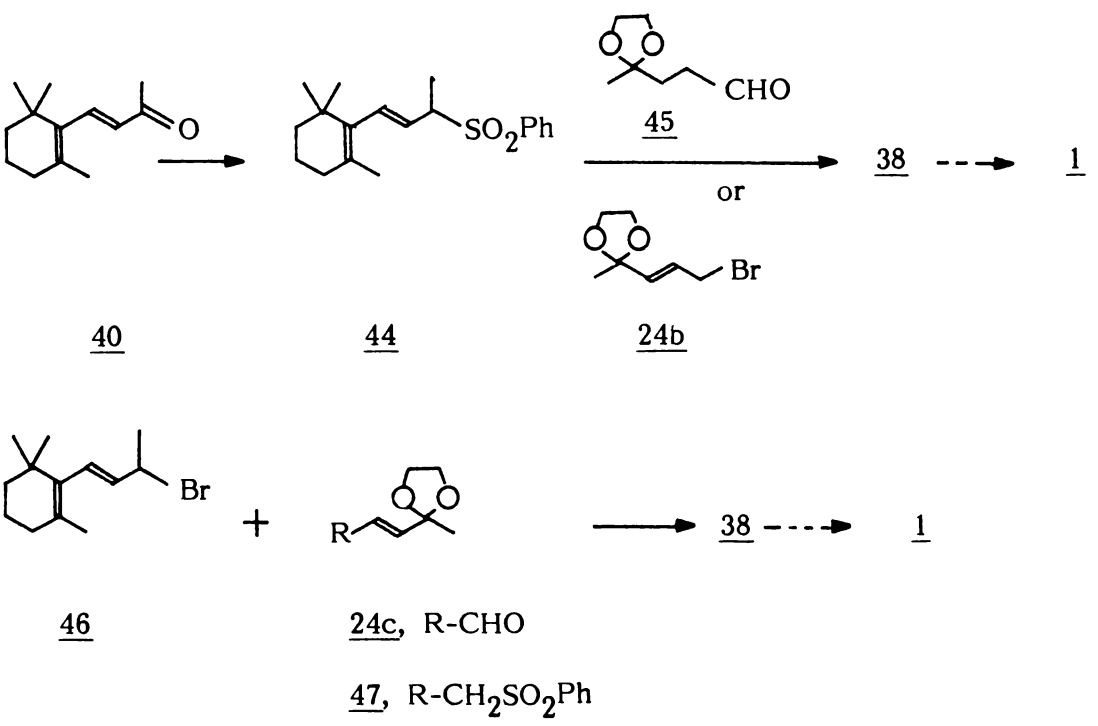
Scheme 3

Thus the condensation of the sulfone 43 with the aldedyde 26 and subsequent double elimination[16] of the intermediate hydroxy

sulfone will give the ß-C_{18} ketone which can be converted to Vitamin A.

2.6.2 C_{13} + C_5 + C_2 Approach

In another approach, Vitamin A skeleton can be built from a C_{13} unit and a C_5 unit and again through the C_{18} intermediate. The C_{13} fragment can be identified as ß-ionone (40) or its derivatives and when coupled with suitably functionalised C_5 unit through sulfone condensation, sulfone-alkylation or Wittig reaction, can give C_{18} ketone. Further two carbon homologation will give Vitamin A (Scheme 4).

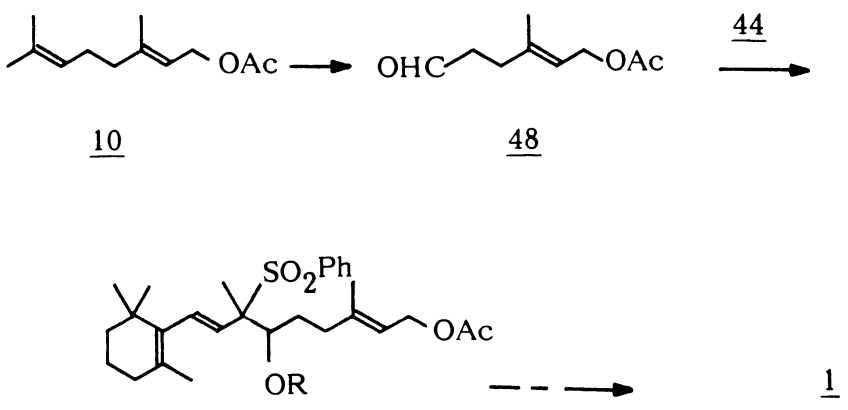


Scheme 4

Thus the alkylation of sulfone 44 with 24b or its condensation with the aldehyde 45 following double elimination[17] can give ß-C_{18} ketone. Alternatively alkylation of the sulfone 47 with 46 or Wittig condensation between 24c and 46 can also give ß-C_{18} ketone.

2.6.3 C_{13} + C_7 Approach

Yet another approach for Vitamin A molecule utilizes the combination of C_{13} and C_7 units. As in the previous scheme, the C_{13} unit remains the same - the sulfone 44 derived from ß-ionone. The C_7 unit used will be prepared from geranyl acetate by the cleavage of the isopropylidene double bond. This approach has been exploited earlier, using α , ß-unsaturated C_7 unit that has been totally



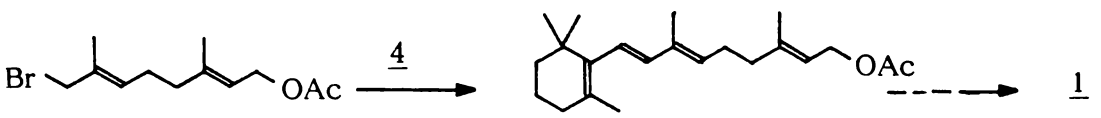
10 48 1

Scheme 5

synthesised[3, 18]. So in this approach the interest involved is in the preparation of C_7 unit 48 from a natural source and its utilization as such. Condensation of the sulfone 44 with 48 and subsequent double elimination is expected to give Vitamin A acetate (Scheme 5).

2.6.4 C_{10} + C_{10} Approach

A versatile approach for the C_{20} skeleton using two C_{10} units has already been reported[19]. Now the idea is to try other alternate approaches. 11, 12 dihydrovitamin A (50) could be prepared by coupling ß-cyclocitral (4) with allylic functionalised geranylacetate 49 by a Wittig olefination or by sulfone-alkylation (Scheme 6). Conversion

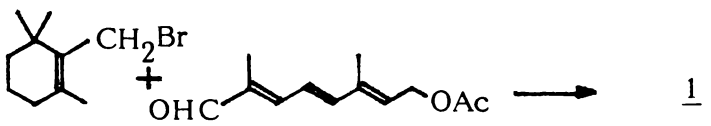


49 50

Scheme 6

of 50 to Vitamin A could be achieved if a good leaving group can be introduced at 11 or 12 position. Seleniumdioxide oxidation looks like a viable alternative. N-Bromosuccinimide bromination reaction cannot be tried here since in similar systems such a reaction is known to introduce a functionality in the ring at C-4, which is undersirable[20]. Approaches to effect this conversion, it is hoped, can turn successful.

Alternatively coupling of the C_{10} cyclic moiety 5b with the functionalised triene 14a in a Wittig reaction will give Vitamin A acetate directly (Scheme 7).



5b 14a

Scheme 7

CHAPTER III

RESULTS AND DISCUSSION

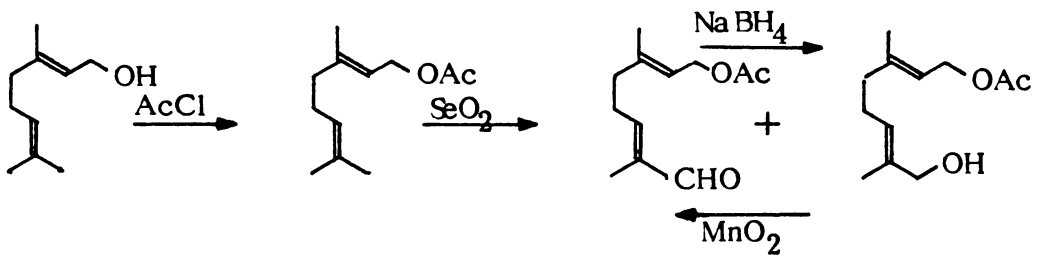
3.1 Allylic Oxidation of Monoterpenes

In the field of polyisoprenoid synthesis, one of the most versatile strategies has been the utilization of easily available natural or synthetic isoprenoids which contain inherently trisubstituted olefinic portions in the molecules as building blocks. Introduction of the framework of the isoprenoid building blocks into the target molecules requires at first highly site-, regio-, and stereoselective functionalisation of the former. Of the possible functionalization of acyclic isoprenoids, terminal and internal allylic oxidation of the isopropylidene terminus are potential methods for the synthesis of various types of compounds. The potential utility of these terminal functionalised olefins has gained importance from the view point of C-C bond formation with high geometric and positional control.

Thus terminal trans allylic functionalization can be carried out by oxidation using stoichiometric[1] or catalytic amounts[2] of selenium dioxide, through secondary allylic alcohols by photosensitised oxygenation[3] or epoxidation - ring opening[4] followed by allylic rearrangement, through allylic chlorides[5, 6] by treating with chlorinating agents[7] or by electrochemical methods[8] or through allyl-palladium complexes by direct metallation with palladium chloride[9] and through allylic sulfides through ene reaction of olefins with thiocetone derivatives or benzenesulfinylchloride (PhSOCl)[10]. Recently a report describing addition of benzenesulfinylchloride to isopropylidene terminus as a method of allylic functionalization has appeared[11].

3.1.1 Isopropylidene Terminus Oxygenation of Geranylacetate

Geraniol (1) isolated from oil of palmarosa by silica gel chromatography was acetylated using acetylchloride and pyridine at 0^{o} to afford geranylacetate (3) (Scheme 1). The method employing acetic anhydride and sodium acetate in refluxing temperature gave poor yields because of the drastic conditions used. When acetylation has carried out under phase transfer conditions using acetyl chloride and phase transfer catalysts like benzyltriethylammoniumchloride (BTEA) and tricaprylmethylammoniumchloride (Aliquat 336), the conversion could be achieved in lesser time in increased yields. Palmarosa oil which contains about 12% geranylacetate (by GLC) was acetylated and then chromatographed to separate geranylacetate.



1 3 4 5

Scheme 1

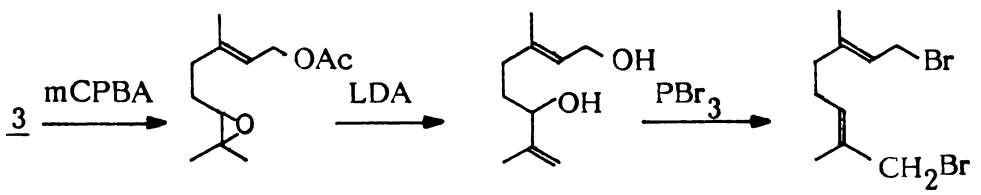
The terminal allylic oxidation of geranylacetate (3) was achieved using the much studied SeO_2 oxidation[12, 13] (Scheme 1). In SeO_2 oxidation trans aldehydes or alcohols are formed stereospecifically. While shorter reaction time and equimolar amount of reagent gave high alcohol content, longer reaction time and higher reagent ratio gave higher aldehyde content in the product mixture[12]. Since the

formation of organoselenium byproducts as well as the colloidal selenium, which make the work-up difficult, are the drawbacks of this reaction, methods have been devised to use catalytic amount of SeO_2 in combination with t-butylhydroperoxide to alleviate these problems[2]. Even with these disadvantages SeO_2 oxidation remains the most reliable and predictable reagent for insertion of oxygen into an allylic carbon-hydrogen bond, because of its positional selectivity.

The reaction product of SeO_2 oxidation of 3 which is a mixture of alcohol and aldehyde without purification was reduced with $NaBH_4$ in MeOH to get the alcohol 5. This step made the purification process easy to a limited extent. After purification the alcohol 5 was obtained in 59% yield. The alcohol was then oxidised by active MnO_2 in n-pentane[14] to afford the trans aldehyde 4. The singlet at δ 9.4 for one proton (carbonyl hydrogen) indicated that the aldehyde group is trans and since it is well known that the oxidation of allylic alcohols with active MnO_2 generally gives α , ß-unsaturated aldehydes without cis-trans isomerisation[14], it confirmed that the alcohol 5 is in trans configuration.

To prepare the alcohol 5, epoxide-ring opening followed by allylic rearrangement was tried. The m-chloroperbenzoicacid (mCPBA) oxidation[15] of geranylacetate (3) in CH_2Cl_2 at 0^o afforded the epoxide 6. The structure was confirmed by the shift of two gem dimethyl protons from δ 1.7 to δ 1.25 and δ 1.3 as well as by the appearance of a triplet for one proton at δ 2.7 ($-CH_2\underline{C}HO-$). When

the epoxide was opened by the action of pyrolidine in ether[16] as well as by the action of LDA in ether[17], it was found that the acetate group got hydrolysed to leave the free alcohol. Such a hydrolysis



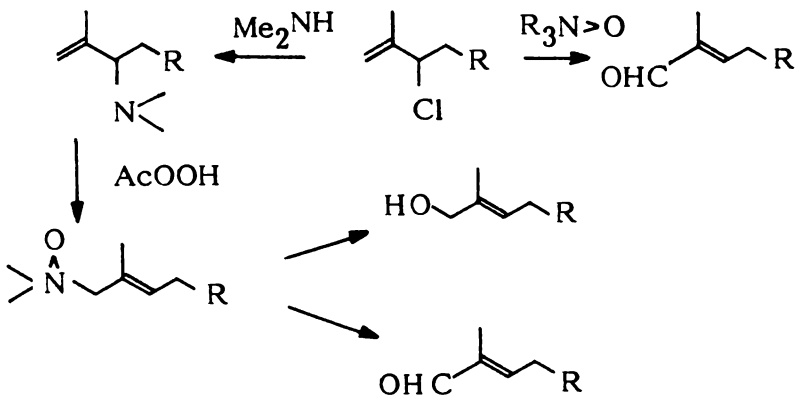
6 7 8

Scheme 2

with amines has been reported during the amination of acetoxy allyl chlorides with dimethylamine[5]. Thus the reaction gave the diol 7 confirmed by the presence of a doublet at δ 4.15 for the 1^{o} hydroxyl group (-$C\underline{H}_2$OH), a triplet at δ 4.0 for one hydrogen (-C$\underline{H}$(OH)-), and a doublet centered at δ 4.9 characteristic of the terminal methylene protons as well as by the absence of the sharp singlet at δ 2.0 for for 3 protons of acetyl group. IR also showed a absorption at 890 cm^{-1} (=CH_2). Even though 7 contained a 1^{o} as well as a 2^{o} hydroxyl groups, halogenation gave a rearranged primary dihalide[18]. Acetylation too gave a rearranged primary diacetate. Thus 7 on bromination with PBr_3 gave the dibromide 8 (Scheme 2). Such was the case, further manipulation became impossible.

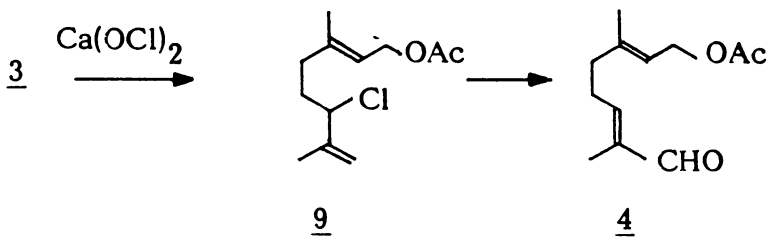
Allylic chlorides[19] can be converted to α , ß-unsaturated aldehydes. It has been reported that tertiary amine N-oxides effect

a smooth conversion of allylic chlorides into α ,ß-unsaturated aldehydes[6]. Similarly gem dimethyl olefin terminus of acyclic terpenes can be converted to terminal trans allylic alcohols or trans α , ß-unsaturated aldehydes through their allylic chlorides and allyl amine oxides[5] (Scheme 3).



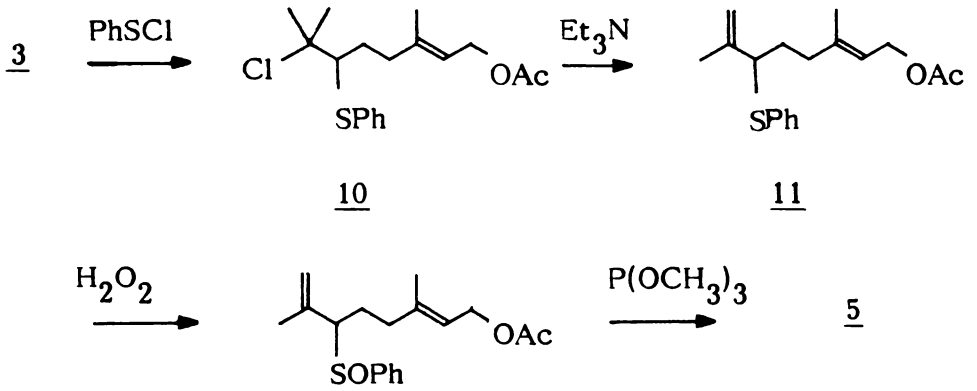
Scheme 3

Thus 3 was converted into its allylic chloride 9 in 70% yield by adding dry ice to a solution of 3 and $Ca(OCl)_2$ in CH_2Cl_2-H_2O. In ^1H NMR the presence of a doublet centered 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. The IR too showed a characteristic absorption at 890 cm^{-1} ($=CH_2$). This on treatment with triethylamine N-oxide and CuCl in dioxan at 50° afforded the aldehyde 4 in 60% yield. The appearance of carbonyl hydrogen at δ 9.4 confirmed the trans stereochemistry (Scheme 4).



Scheme 4

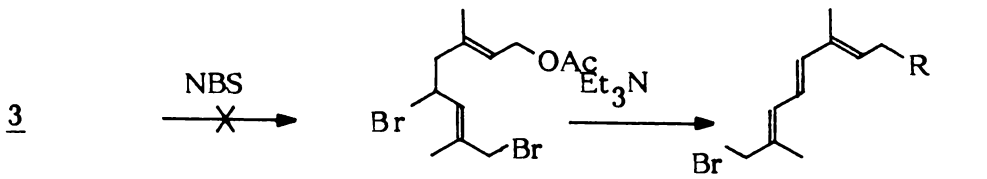
Masaki and co-workers have reported a novel method for the functionalization of the isopropylidene terminus of acyclic monoterpenes by way of benzenesulfenylchloride (PhSCl) addition[20]. Geranylacetate when treated with PhSCl in CH_2Cl_2 gave the adduct 10 instantaneously with the discharge of orange yellow colour. PhSCl[22] was prepared from diphenyldisulfide (PhSSPh) and sulfuryl chloride in the presence of pyridine in CH_2Cl_2 while PhSSPh was prepared from thiophenol and dimethylsulfoxide[23]. The adduct 20 without purification was warmed at 60° for 20 hrs. in DMF with excess of Et_3N to give terminal methallylic sulfide 11. The characteristic signal of -CH(SPh) at δ 3.45 as well as the broad singlets at δ 4.5 and 4.6 due to terminal methylene proton confirmed the structure 11. The allylic alcohol 5 was obtained from 11 by the method of Evans[24]. Oxidation of 11 with 30% H_2O_2 in acetic acid at 20° for 20 hrs. gave the sulfoxide 12 which underwent rearrangement when treated with trimethyl phosphite in MeOH at 20° for 48 hrs. to give 5 (Scheme 5). The spectral data were in agreement with that of the alcohol 5 earlier prepared.



Scheme 5

NBS in CCl_4 is known to brominate allylic positions[25]. If the dehydrobromination of the bromide results in the formulation of a conjugated triene or diene then such dehydrobromination is very much favoured[25]. NBS reaction of linalylacetate is reported to have brominated all the three allylic positions[26]. A report of the bromination and dehydrobromination of geranonitrile to get the bromide of the type 14 (R-CN) has appeared[27] (Scheme 6). Thus geranyl acetate was treated with NBS in CCl_4 at refluxing temperature to get the dibromide 13. Only about 50% conversion was observed. The reaction was then repeated using benzoyl peroxide as initiator as well as in the presence of $NaHCO_3$ and CaO[27]. No change in result has been observed. The attempt to purify the product at this by stage by column chromatography was unsuccessful. So the reaction mixture without purification was warmed with Et_3N in DMF for 18 hrs. to effect dehydrobromination to get the triene 14 (Scheme 6). This

too was unsuccessful since well characterised products could not be isolated.

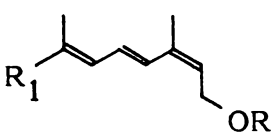


13 14, R-CH_2OAc

Scheme 6

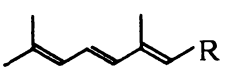
3.2 Synthesis of (E,E) Conjugated Triene Ester

Only a few naturally occurring monoterpenoid trienes are reported. Dehydroneryl isovalerate(I) has been isolated from the roots of Anthemis montana[28, 29]. The most oxidised dimethyloctane



I, R-isovalerate, R_1-CH_3

II, R-H, R_1-CH_2OH



III, R-CHO

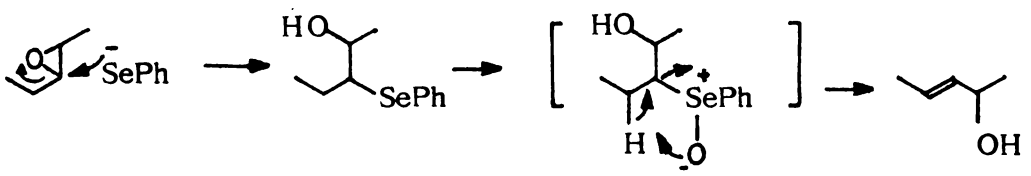
IV, R-COOH

V, R-COOR (R-geranyl)

monoterpenoid alcohol(II) in the form of various esters have also been isolated from Schkuria senecioides[30]. Similarly monoterpenoid triene

with all E configuration have also been isolated. Ambrosial(III) has been isolated from the essential oil of Ambrosia confertifolia[31], but its synthesis has been reported earlier[32]. Other all E trienes reported are dehydrogeranic acid(IV) - isolated from the essential oil of the wood of callitris glauca[33] and its geranyl ester isolated from callitropis araucarioides[34]. These two have been totally synthesised[29, 35].

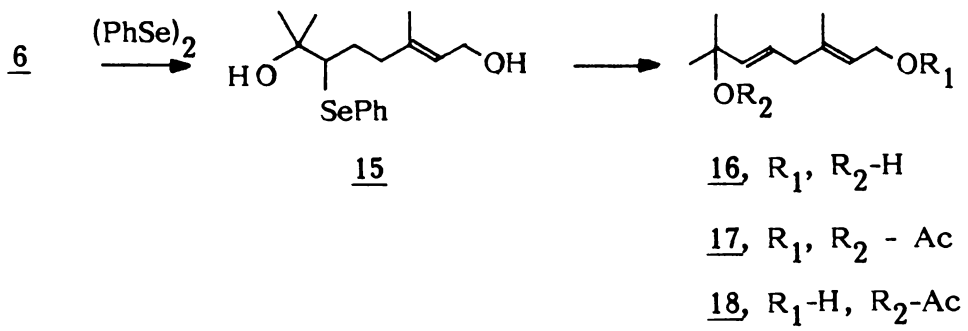
Since it was found to be difficult to introduce a double bond after the terminal functionalization, it was thought to functionalise the triene. Thus methods have developed to synthesise the triene ester 19. In one approach organoselenium methodology was tried. The selenium anion ($PhSe^-$) is an excellent nucleophile and easily opens epoxides to give hydroxy selenides. The hydroxy selenide is not isolated, but is oxidised with excess hydrogenperoxide to the unstable selenoxide which decomposes to give allylic alcohols[36] (Scheme 7).



Scheme 7

Geranylacetate epoxide 6 was treated with the phenyl selenyl anion generated in ethanol solution by the reduction of diphenyl diselenide (PhSeSePh) with $NaBH_4$ (Scheme 8). PhSeSePh was prepared

from phenylmagnesiumbromide and selenium metal powder according to the literature procedure and obtained as dark orange crystals[37]. The ß-hydroxy selenide 15 formed without isolation is oxidised[38] with

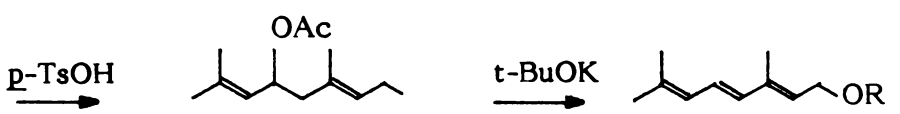


15

16, R_1, R_2-H

17, R_1, R_2 - Ac

18, R_1-H, R_2-Ac



20

21, R-H

19, R-Ac

Scheme 8

excess 30% H_2O_2 in THF and the unstable selenoxide formed decomposed to give the allylic alcohol 16. ^1H NMR showed the absence of acetate group in 16 (absence of the singlet at δ 2.05 for 3H). It is because of the hydrolysis due to acidity of the reaction medium due to the formation of benzene seleninic acid (PhSeOOH, pKa-4.7) in the oxidation step. The weakly acidic conidtion can be avoided by buffering the reaction mixture with pyridine[39] and that aspect was not investigated. The benzene seleninic acid is nonvolatile and is removed during

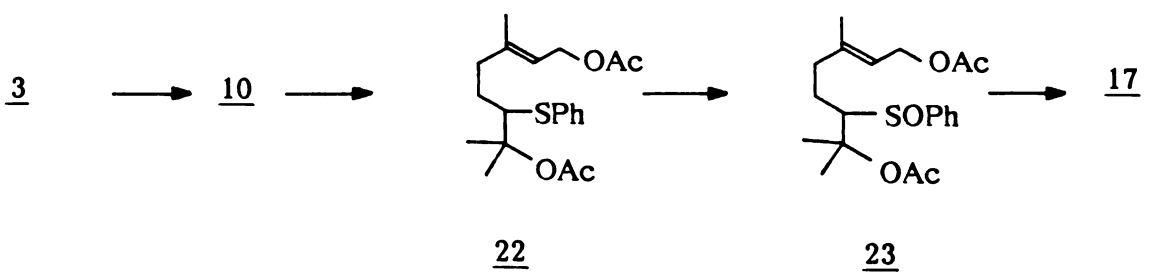
aqueous work-up and it can easily be reduced to PhSeSePh - which can be recovered in high yield[40]. A sharp singlet at δ 1.3 for six protons assignable to the gem dimethyl groups attached to carbon bearing OH group and a doublet at δ 4.1 due to -$C\underline{H}_2OH$ confirms the diol structure.

The diol 16 was then acetylated to get the diacetate 17. It is speculated that the presence of a 1^o acetoxy group during the base catalysed elimination step may cause a rearrangement to give the 'retro' compound, which is undesirable. As it turned out to be the elimination of 17 failed to give well characterised products. So the primary acetoxy group is selectively hydrolysed[41] using Na_2CO_3 in EtOH to give the monoacetate 18. The presence of a doublet at δ 4.1 for 2H due to -$C\underline{H}_2OH$ as well as the singlet at δ 2.05 for 3 protons (-$COCH_3$) confirmed the structure 18. Allylic rearrangement[42] of acetate 18 to 20 was achieved by treating 18 with a catalytic amount of p-toluene sulfonic acid in 1:1 AcOH-Et_2O at 0^o for 3 hrs. Appearance of a singlet at δ 1.7 for 6 H assignable to vinyl methyl groups ($(CH_3)_2C=$) and a three proton multiplet at δ 4.9-5.8 for two olefinic and -CH(OAc) protons agree with the structure 20.

The secondary acetate 20 when stirred with potassium t-butoxide in THF at 0^o for 30 min. underwent elimination[41] to give the alcohol, 21, which on acetylation with acetylchoride in 1:1 benzene-pyridine at 0^o afforded the triene acetate 19. The all E geometry

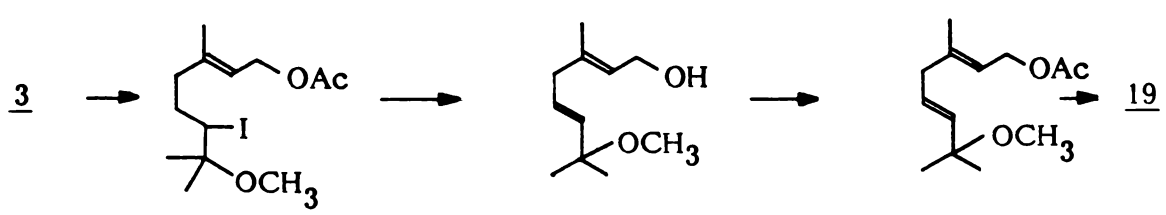
was confirmed by the absorption appeared at δ 6.1 and δ 6.4 assignable to the C_4-H and C_5-H, while for cis 4, 5 double bond, it will be at δ 5.6 and δ 6.5. The UV (λ_{max} 265nm) data too was in agreement with the conjugated triene structure.

The diacetate 17 was also prepared by the method of benzenesulfenylchloride addition[20, 21]. The adduct 10 on treatment with NaOAc in AcOH at 20° for 1 hr. gave the tertiary acetoxy sulfide 22. A singlet at δ 1.3 for 6 protons due to the two methyl groups attached to carbon bearing acetoxy group and a singlet at δ 2.05 for 3 protons ($COCH_3$) and a multiplet at δ 3.7-3.9 for one proton assignable to CH(SPh) system agrees with the structure 22. 22 was converted into the trans allylic acetate 17 though the sulfoxide 23 formed by the oxidation with 30% H_2O_2 in AcOH and by thermal elimination of sulfenic acid[43] from 23 in toluene under reflux in presence of $NaHCO_3$ (Scheme 9).



Scheme 9

The method[44] of introducing a double bond in steroidal side chain to get a diene system using $Cu(OAc)_2$-I_2 system has been extended to the monoterpene molecule - geranylacetate. In one approach to a solution of geranylacetate in CH_2Cl_2 containing Cu(II)acetate dissolved in MeOH was added iodine dissolved in CH_2Cl_2. One hour stirring followed by treatment with K_2CO_3 gave the methoxy iodide 24. 24 on treatment with potassium t-butoxide in THF underwent dehydroiodination to give the alcohol ether 25 which was then acetylated with 2:1 acetic anhydride-pyridine to give the acetoxy allylic ether 26. The presence of a multiplet from δ 4.9 - δ 5.4 for three olefinic hydrogens, a singlet at δ 3.2 for three hydrogens due to $-OCH_3$ group, a poorly resolved doublet at δ 1.25 for 6 H assignable to gem dimethyl group attached to carbon bearing methoxy group as well as the IR absorption at 2830 cm^{-1} for OCH_3 confirmed the structure 26. The allylic ether 26 in CH_2Cl_2- CH_3CN when treated with powdered sodium iodide and later with AcCl underwent elimination-rearrangement to give the triene ester 19 which had the comparable spectral data with 19 earlier prepared (Scheme 10).

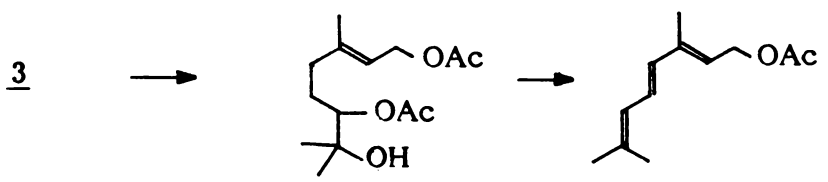


24 25 26

Scheme 10

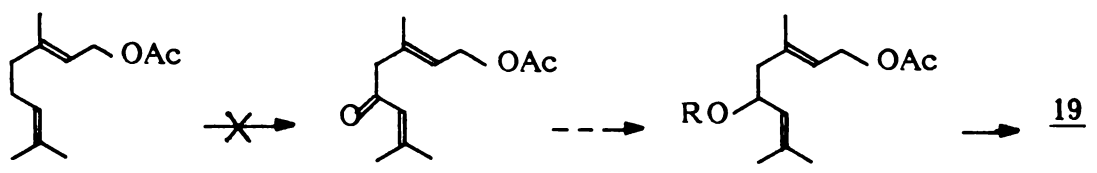
In another approach[45], which has been earlier applied for diene synthesis in steroidal side chain, geranyl acetate 3 was treated with I_2-KIO_3[46] in AcOH at 80° for 3 hrs. The work up yielded the hydroxy acetate 27. Its ^1H NMR spectrum - a singlet at δ 1.3 for 6H ($(CH_3)_2C$-O-) and a singlet at δ 2.05 for 6H (two OAc gr.) agree well with the structure 27. On stirring with p-TsOH in refluxing benzene, 27 afforded all E triene ester 19 whose spectral data agreed with the structure (Scheme 11).

t-Butylhydroperoxide-pyridiniumdichromate (TBHP-PDC) system has been used for allylic oxidation of citronellylacetate to get the α, ß-unsaturated ketone[47]. This method was extended to geranylacetate (Scheme 12). Thus geranylacetate in benzene was treated with pyridiniumdichromate (PDC)[48] and t-butyl hydroperoxide[49]



27 19

Scheme 11



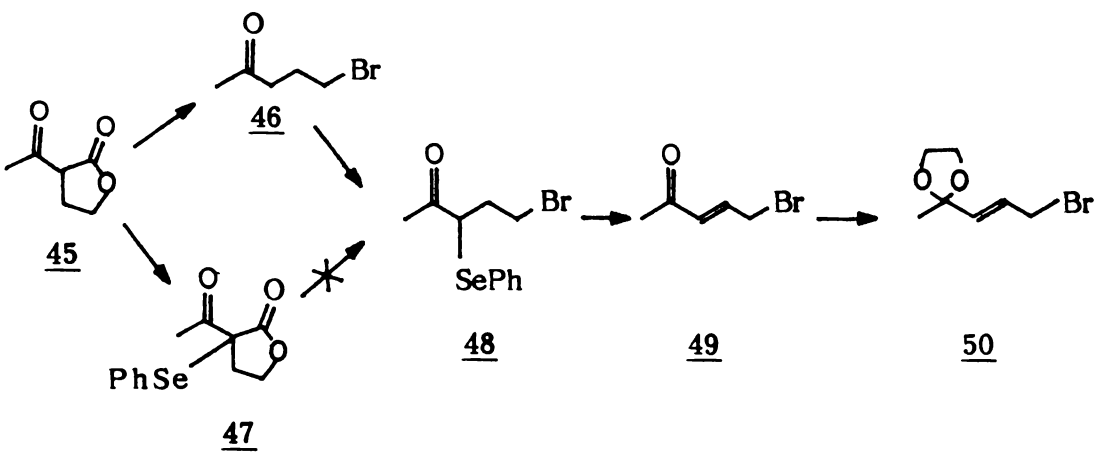
3 28 29, R-H
30, R-Ts

Scheme 12

at 10^{o}. The work up failed to yield any well characterised products. The expected α , ß-unsaturated ketone 28 is not formed. The ketone 28 if formed could have converted into the alcohol 29 and its tosylate 30 which on elimination would have given the expected triene 19. t-Butyl hydroperoxide prepared according to the procedure [49] was used as such. It is presumed that the hydroperoxide might not have been formed in the required strength. Repeated attempts of preparations of the hydroperoxide and its reaction proved unsuccessful.

3.3 Synthesis of C_5 Unit

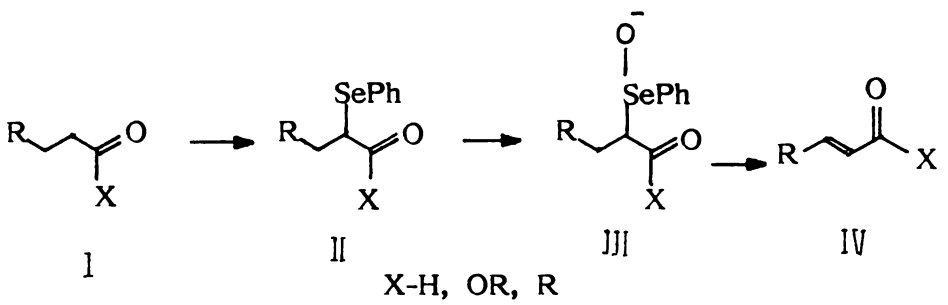
2-Acetyl butyrolactone (45), a commercially available chemical was opened up by treating with 48% aqueous HBr in phase transfer conditions to yield the keto bromide 46 in 85% yield[50] (Scheme 13). A singlet at δ 2.17 for 3H (CH_3CO-), a triplet at δ 3.5 for 2H and a multiplet in the region δ 2.2-2.8 for 4H confirms the structure 46.



Scheme 13

α ,ß-Unsaturation is to be introduced in 46 for it has to be converted into 50 through 49. There are a number of methods available for the conversion of carbonyl compounds to its α , ß-unsaturated analogues[51], the most important of which is α -bromination-dehydrobromination[51, 52].

For introducing α , ß-unsaturation in 46, organoselenium methodology has been tried because of its simplicity. The application of organoselenium reagents in the synthesis of α , ß-unsaturated carbonyl compounds has been reported[51, 53]. This method involves the oxidation of α -phenyl seleno carbonyl compound(II) derived from (I) to the corresponding selenoxide (III), which undergo clean syn elimination at room temp. to give the desired olefin (IV)[54] (Scheme 14).



Scheme 14

The α -phenyl seleno carbonyl compounds (II) are readily formed in a variety of ways[51, 53]. Use of the PhSeSePh/SeO_2 systems in CH_2Cl_2 for the α -selenylation of carbonyl compounds have reported[55]. A report on the synthesis of enones employing the addition of $PhSeCl_3$ has also appeared recently[56].

The keto bromide 46 was selenylated[55] by adding a solution of 46 in CH_2Cl_2 to a suspension of SeO_2 and PhSeSePh in CH_2Cl_2 containing a catalytic amount of con. H_2SO_4. The mixture was stirred at 0^o for 18 hrs. The work up yielded α -phenylselenylated keto bromide 48 in 70% yield. As a alternate method, the lactone itself was selenylated to get the selenylated lactone 47[55] using SeO_2/PhSeSePh system. But the subsequent ring opening using 48% aq. HBr yielded only the deselenylated opened up product 46 as evidenced by its ^{1}H NMR spectrum.

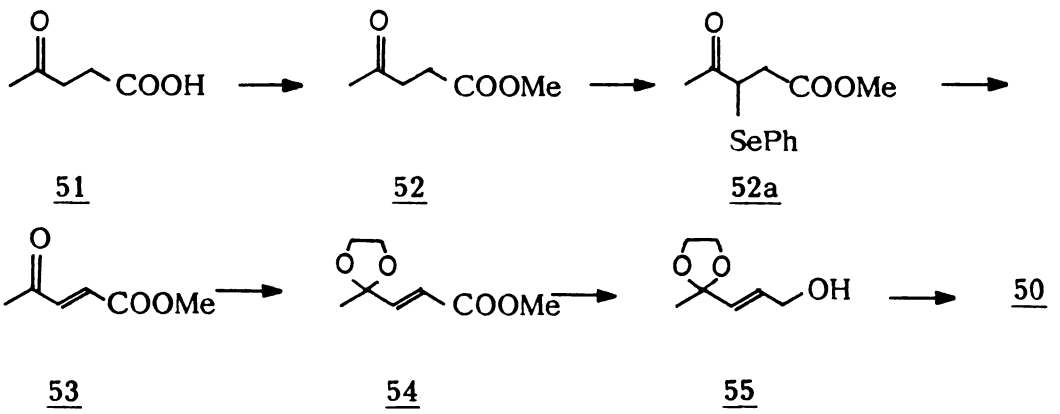
The selenylated ketone 48 was then oxidised with excess 30% H_2O_2 below 5^o and the subsequent selenoxide syn elimination[36,51] afforded the α ,ß-unsaturated keto bromide 49. A sharp singlet at δ 2.2 for 3H assignable to acetyl group and two doublets at δ 6.05 and δ 6.8 for each olefinic hydrogen confirmed the enone structure. The enone 49 was then protected as its ketal[57] by refluxing the ketone and ethylene glycol in thiophene free benzene containing catalytic amount of pyridinium p-toleuene sulfonate (PPTS). The ketal was obtained in 83% yield in 2 hrs. Use of PPTS as catalyst in ketal forming reactions has been reported recently[57]. High yields and shorter reaction times are the obvious advantages.

The ketal bromide 50 was also prepared starting from levulinic acid (51). The levulinic acid was converted into its ester 52 by the action of diazomethane in MeOH. Sharpless and co-workers have found that α -selenation of ketones with PhSeCl can be carried out in the presence of other functional groups such as alcohol, esters

and even certain double bonds[58]. Thus the ester 52 was selenylated at α -position of keto group by treating the ketoester 52 in EtOAc with PhSeCl generated *in situ* in CH_2Cl_2 by the addition of sulfuryl chloride to PhSeSePh in CH_2Cl_2 containing pyridine. The reddish orange solution was stirred until it had turned pale yellow. In this condition α -position of ester function is not selenylated. α -selenylation of esters are being done by the action of PhSeCl or PhSeBr in the presence of bases like LDA or though the displacement reaction of α -bromoester with $PhSe^-$ generated from PhSeSePh in EtOH[53].

The phenyl selenated ester 52a is oxidised with excess 30% H_2O_2 to afford the α ,ß-unsaturated ester 53. The keto group in 53 was then protected as ketal function to get the ketal 54. The appearance of a doublet at δ 5.2 and δ 6.9 assignable to α and ß-olefinic protons, a singlet at δ 3.4 for 3H due to ester methyl group as well as a sharp singlet at δ 3.9 for four protons ($-OCH_2CH_2O-$) confirms the structure 54. The ester 54 on LAH reduction gave the allylic alcohol 55 which on bromination gave the bromide 50 (Scheme 15), which showed identical spectral data with that of the ketal bromide 50 prepared earlier. To prevent the possibility of the α,ß-unsaturated double bond reaction, reverse addition of LAH was done (LAH was added portionwise to the reaction mixture).

The α -bromination of the acid 51 by way of Hell-Volhard-Zelinsky (HVZ) reaction[59] and dehydrobromination route to 53 was not tried, since it is speculated that the dehydrobromination step using bases will result in the formation of water soluble salts of the

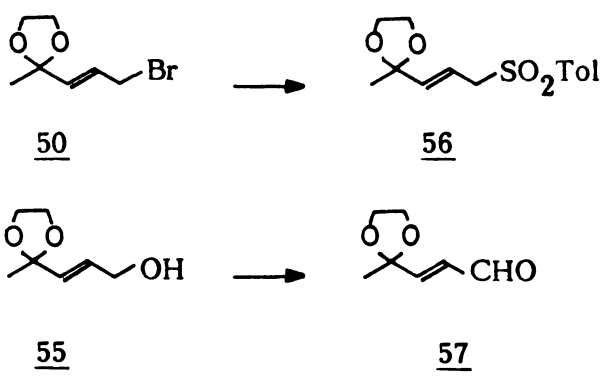


51 52 52a 53 54 55 50

Scheme 15

acid 51, whose recovery may pose problems and is undesirable.

The ketal bromide 50 was stirred at room temp. for 24 hrs. with sodium p-toluene sulfinate in DMF, to afford the sulfone 56 as a viscous liquid which could not be crystallised. The structure 56 was confirmed by its ^{1}H NMR data: a doublet at δ 3.8 for 2H due to the $C\underline{H}_2$ SO_2Tol group, two doublets at δ 7.3-7.9 for 4 aromatic protons, a singlet at δ 2.4 for 3 protons (Ph-$C\underline{H}_3$) and a multiplet at δ 5.7-6.1 for two olefinic protons. The aldehyde 57 was prepared

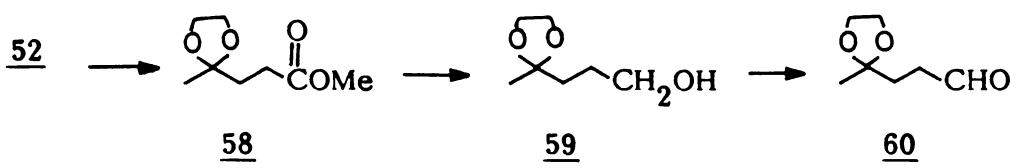


50 56 55 57

Scheme 16

in 79% yield by the active MnO_2 oxidation of the allylic alcohol 55 in n-pentane (Scheme 16). The α and ß-olefinic protons at δ 5.8 and δ 6.5 and singlet at δ 9.8 for one proton (CHO) confirms the structure 57.

The C_5 ketal aldehyde 60 was prepared from the levulinic acid ester 52. The keto ester 52 was converted into its ketal 58. LAH reduction of the ketal 58 afforded the alcohol 59, A triplet assignable to $-CH_2OH$ at δ 3.5 and a multiplet at δ 1.6-2.0 for $-CH_2CH_2-$ confirmed the alcohol structure 59. The alcohol 59 was then oxidised with pyridiniumchlorochromate (PCC)[60] in CH_2Cl_2 to give the aldehyde 60 (Scheme 17). Because of the presence of the



58 59 60

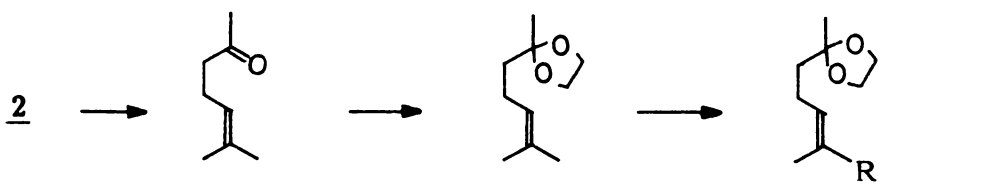
Scheme 17

acid labile ketal group in 59, the acidity of the reagent was controlled by buffering the reaction mixture with sodium acetate. The aldehyde showed a singlet at δ 1.3 for 3H for the methyl group, a sharp singlet at δ 3.95 for 4 protons ($-OCH_2CH_2O-$), multiplets at δ 2.1 and 2.9 for 4H ($-CH_2CH_2-$) as well a triplet at δ 9.8 (CHO).

3.4 Synthesis of C_8 Unit

3.4.1 Terminal Allylic Functionalisation of Methylheptenone Ketal 62

Citral (2) undergoes retro-aldol condensation in slightly alkaline conditions to give methylheptenone 61. When 2 is mixed with excess 1% Na_2CO_3 solution and is stirred under reflux, 61 is formed. The keto group in 61 was protected as its ketal. A sharp singlet at δ 3.9 for 4H confirmed the ketal structure and the values were in good agreement with the reported one[61]. (Scheme 18).



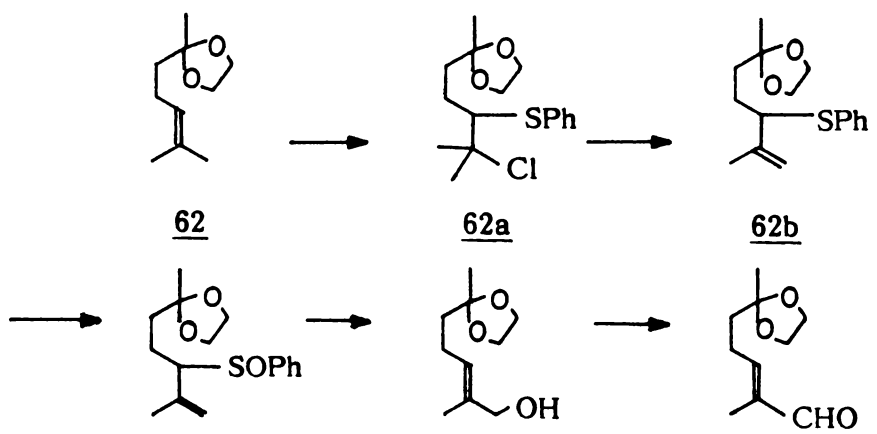
61 62 63a, R-CH_2OH
63b, R-CHO

Scheme 18

When allylic oxidation using SeO_2 in ethanol was attempted on 62 for 63a and 63b (Scheme 18), the results were not encouraging. The NMR data showed the absence of ketal function in the products, as evidenced by the disappearance of the singlet at δ 3.9 for 4 protons ($-OCH_2CH_2O-$). It is assumed that the acid labile ketal group might have got hydrolysed in the reaction medium. With the ketal group absent further synthetic manipulation became difficult. This could be explained on the basis of the strong acidity of the reaction medium due to the presence of seleneous acid (H_2SeO_3 pKa_1-2.62, pKa_2-8.32) which is a strong

acid. Similar observation has been recorded by Camps[62] who has studied the seleniumdioxide oxidation of compounds with acid labile groups. It is reported[62] that the SeO_2 oxidation product of citral acetal is p-cymene - formed by the ketal hydrolysis followed by the cyclization of the free aldehyde. In this context, only with speculation one must observe the report of Rapoport[12] about the successful SeO_2 oxidation of methyl heptenone ketal 62 to 63b. The attempt to buffer the reaction medium with pyridine to control the acidic nature was not successful[62].

The ene-type chlorination[19, 63] of the ketal 62 followed by its conversion to α , ß-unsaturated aldehyde was not tried to prepare 63b, since it involves the use of a acidic reagent, the hypochlorous acid (HOCl). So the method of benzenesulfenylchloride addition[20] was tried to synthesise 63b.



62 62a 62b

62c 63a 63b

Scheme 19

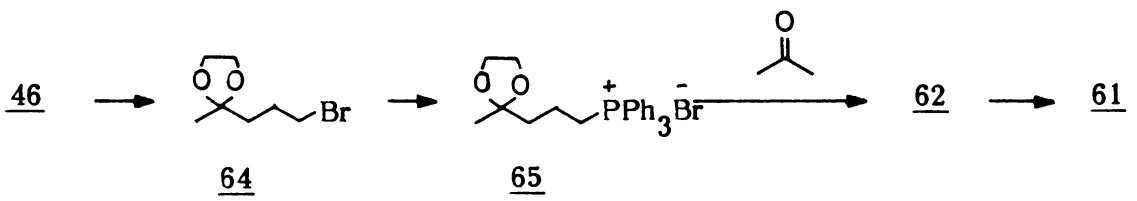
The addition of PhSCl to 62 in CH_2Cl_2 gave the adduct 62a which on treatment with Et_3N in DMF afforded the allylic sulfide 62b. Oxidation with 30% H_2O_2 in acetic acid gave 62c from 62b. 62c was then subjected to Evan's procedure (stirring with $P(OCH_3)_3$ in MeOH at 20^o for 48 hrs.) to yield 63a in an overall 51% yield. A singlet each for each methyl at δ 1.3 and δ 1.6 as well as the doublet at δ 3.9 for two hydrogen and four hydrogen assignable to CH_2-OH and $-OCH_2CH_2O-$ have confirmed the 63a structure. Active MnO_2 oxidation of 63a in n-pentane afforded 63b in an overall 45% yield (Scheme 19). A singlet each for three hydrogen at δ 1.35 and δ 1.7 assignable to two methyl groups, a sharp singlet at δ 3.9 for four hydrogen ($-OCH_2CH_2O-$) and a doublet due to the aldehyde proton at δ 9.4 confirmed the structure of 63b as trans aldehyde.

3.4.2 New Approach for Methylheptenone 61

A $C_5 + C_3$ approach was tried for the synthesis of 61. The ketobromide 46 obtained from the lactone 45 was converted into the ketal 64 by refluxing with ethylene glycol containing pyridinium p-toluene sulfonate in benzene. The ketal bromide 64 was then converted into its phosphonium salt 65 by refluxing with Ph_3P in benzene for 12 hrs. (Scheme 20).

The attempt to condense the phosphonium salt 65 with acetone using n-BuLi and LDA as bases was unsuccessful. The phosphorane could not be generated by the use of these bases. So

it was thought to utilize the base sodium methyl sulfinyl methide ($CH_3S(O)\bar{C}H_2\overset{+}{N}a$) earlier described by Corey and Chaykovsky[64]. The solution of sodium methyl sulfinyl carbanion in DMSO was prepared by the reaction of powdered sodium hydride with excess dry dimethylsulfoxide at 65-70°. The base is sufficiently strong for the conversion of phosphonium salts to ylides, thereby permitting a simple modification of Wittig reaction.

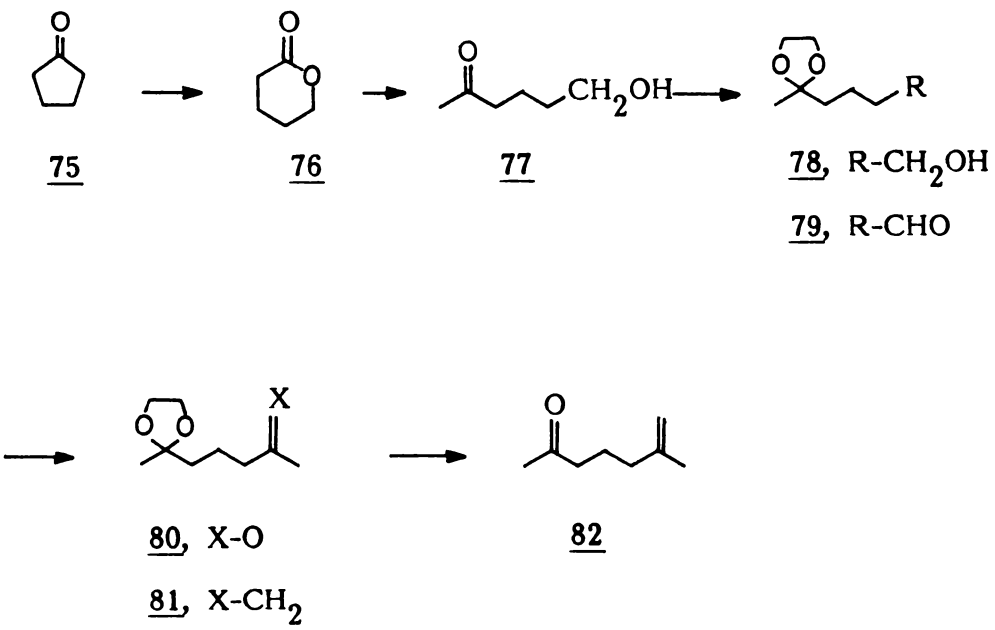


Scheme 20

When the phosphonium salt 65 was added to the solution of the base, the phosphorane was formed instantaneously indicated by the appearance of dark red colouration. To this solution of phosphorane was added acetone. Stirring continued for 40 hrs. The work up yielded the methylheptenone ketal 62 whose ^1H NMR data were in good agreement with that of the earlier described one. The deprotection of 62 was effected by refluxing the ketal in aqueous acetone containing p-TsOH to yield methylheptenone 61. This constitutes a simple new approach for methylheptenone - a vital intermediate for the synthesis of terpenoids and perfumery chemicals, from commercially available chemicals.

3.4.3 Synthesis of a C_8 Industrial Intermediate

In the BASF process[65] for Vitamin A, the ketone 82 forms an intermediate, which in the industrial process is produced from petrochemicals rather than from natural products[66], and later undergoes palladium catalysed isomerisation to give 61. So it was thought to devise a simple approach for the intermediate from a commercially available chemical. Thus cyclopentanone was converted into 82 by the following scheme (Scheme 21).



75 76 77 78, R-CH_2OH 79, R-CHO

80, X-O 81, X-CH_2 82

Scheme 21

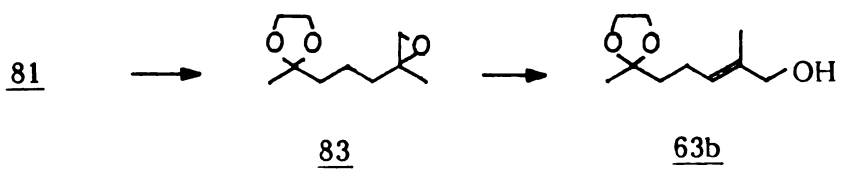
Cyclopentanone (75) on Baeyer-Villiger oxidation using Caro's acid[67] (amonnium persulfate and con. H_2SO_4 in ethanol)

gave the lactone 76 in 81% yield. Its ^{1}H NMR spectrum - multiplet for 4H at δ 1.5-1.9; multiplet for 2H at δ 2.1-2.5 and a triplet at δ 4.0-4.2 for 2H is well in order with the structure 76. The carbonyl absorption in IR at 1735 cm^{-1} indicated the six membered lactone structure. The lactone was ring opened by the action of MeLi to give the methyl ketone 77[68]. A singlet at δ 2.2 for 3H assignable to the CH_3CO- group as well as a doublet at δ 3.5 for 2H (-CH_2OH) confirmed the structure 77. After protecting the keto group as ketal, 77 was oxidised with PCC to the ketal aldehyde 79. Methyl Grignard of 79 followed by oxidation afforded the ketone 80, which is characterised by its ^{1}H NMR - a sharp singlet at δ 2.05 for 3H assignable to CH_3CO- group. Wittig reaction of 80 with methyl triphenyl phosphorane using n-BuLi as base followed by ketal deprotection by stirring with p-TsOH in aqueous acetone gave the ketone 82. A sharp singlet at δ 2.2 for 3H for the acetyl group as well as a doublet centered around δ 4.9 characteristic of terminal methylene group and a singlet at δ 1.7 for a vinyl methyl group confirmed the structure 82.

3.4.4 A Short Synthesis of Terminal Oxygenated Ketal

The intermediate 81 in the above conversion could be converted to the allylic alcohol 63b, which could not be prepared by the allylic oxidation using SeO_2 (Scheme 22). 81 was converted to its epoxide 83 in 91% yield by the action of mCPBA in methylene chloride. The NMR data were in good agreement with the structure

83. Two singlets at δ 1.3 and δ 1.4 for 3 hydrogen each are assignable to each methyl group attached carbon bearing oxygen atom. A singlet



83 63b

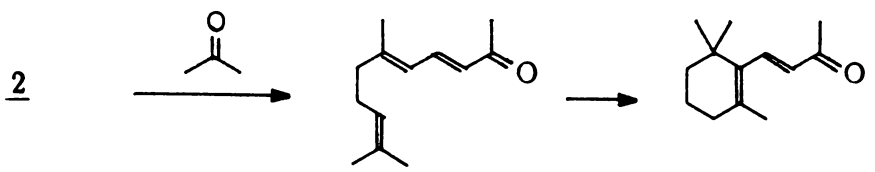
Scheme 22

at δ 2.55 for 2H accounts for the terminal epoxide (-CC$\underline{H}_2$OC-). The epoxide was ring opened by the action of LDA to afford the allylic alcohol 63b in good yield. Though GLC analysis showed a major component in 80% together with minor components, ^{1}H NMR gave a clear homogenous spectrum with characteristics well in agreement with the values of the earlier prepared alcohol 63b. No attempt has been made to isolate the reaction products in pure form by chromatography.

3.5 Synthesis of C_{13} Unit

Pseudoionone(43)[69], the aldol condensation product of citral(2)[70] and acetone is prepared by adding citral under stirring to a mixture of acetone and aqueous NaOH containing benzyltriethyl ammoniumchloride. The reaction was complete in 2 hrs. time. Recently a report of the alumina catalysed condensation of citral and acetone for the synthesis of pseudoionones has appeared[71]. Pseudoionone was cyclized to ß-ionone (44)[72] by treating with cold con. H_2SO_4.

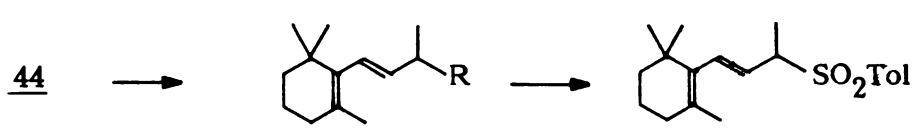
Electrogenerated acid-catalysed cyclization of pseudoionone to give ß-ionone in 57% yield has been reported[73] (Scheme 23).



43 44

Scheme 23

ß-ionone was reduced to ß-ionol (67) by $NaBH_4$ in MeOH, which was then converted into its bromide 68 by the action of PBr_3 in ether. ß-ionol was converted into ß-ionyl sulfone 69 by treating the alcohol 67 with sodium p-toluene sulfinate dihydrate in isopropanol-acetic acid solution at refluxing temperature for 16 hrs.[74] (Scheme 24). The ^1H NMR spectrum of 69 showed a singlet at



67, R-OH
68, R-Br

69

Scheme 24

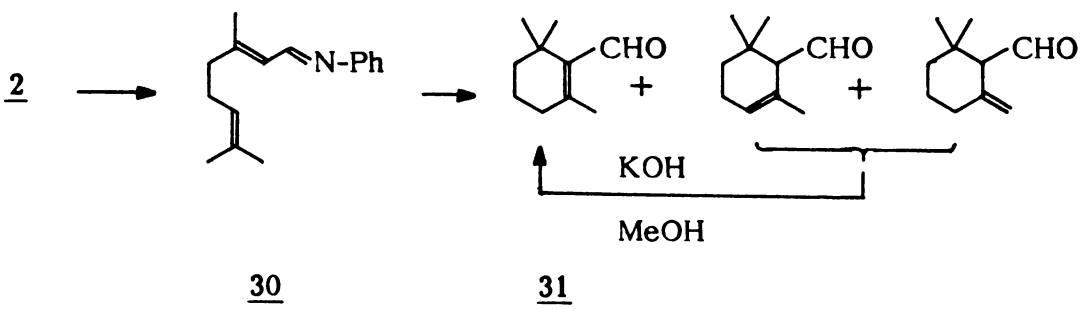
δ 1.4 for 3H due to CH_3 group attached to carbon bearing sulfur, a multiplet at δ 3.8 for one hydrogen assignable to $CHSO_2Tol$ and two doublets at δ 7.2-7.9 for four aromatic hydrogens and a singlet

for 3 hydrogens at δ 2.4 assignable to $ArC\underline{H}_3$, confirming the sulfone structure.

3.6 Synthesis of C_{10} Unit

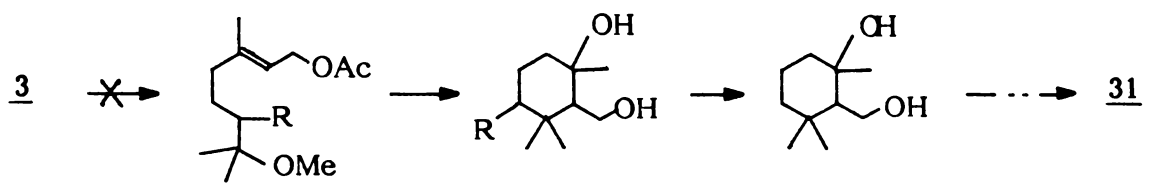
3.6.1 Synthesis of ß-Cyclocitral

Different approaches developed for the synthesis of ß-cyclocitral and its derivatives have been reviewed[75]. For preparing ß-cyclocitral, the classical approach is used[76]. Freshly distilled citral (2) was condensed with aniline to get the schiff base 30 which was then cyclised in presence of con. H_2SO_4 at 0^o. The reaction mixture was steam distilled to get a mixture of α, ß and γ -cyclocitrals. Isomerization of the reaction mixture with methanolic KOH followed by extraction and distillation gave pure ß-cyclocitral. Instead of steam distillation, when the reaction mixture was extracted with pet. ether in a liquid-liquid continuous extractor increased yield was obtained. (Scheme 25).



Scheme 25

Cyclization of selenium compounds derived from monoterpene alcohol and acetates by CF_3COOH has been reported[77]. Thus selenylation of geranylacetate has been tried using PhSeSePh in MeOH. The results were not encouraging and selenylated products could not be isolated (Scheme 26). Similar attempts using PhSCl addition to introduce -SPh group were also unsuccessful[17, 78]. The sulfur and selenium compounds if formed could have converted to ß-cyclocitral as in the scheme.

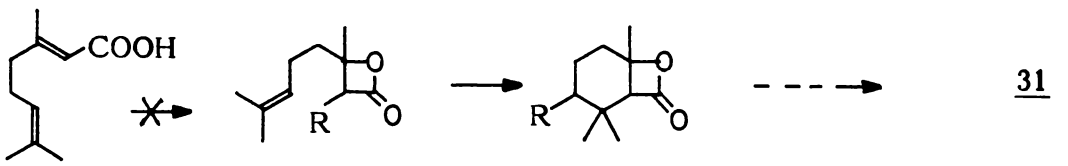


R - SPh, SePh

Scheme 26

Homomonoterpenoid acids have been converted to phenylseleno lactones by the reaction of PhSeCl[79]. Analogous reaction with terpenic acids with PhSeCl in AcOH-Et_2NH can give selenolactones. These lactones can be cyclized to ring fused lactones[80] as depicted in the scheme 27. These ring fused lactones could be converted to ß-cyclocitral. But when geranic acid was treated with PhSeSePh/$NaBH_4$ in AcOH/Et_2NH, no selenylated products were formed. Analogous sulfur methodology

using PhSCl too was unsuccessful.



31

R - SPh, SePh

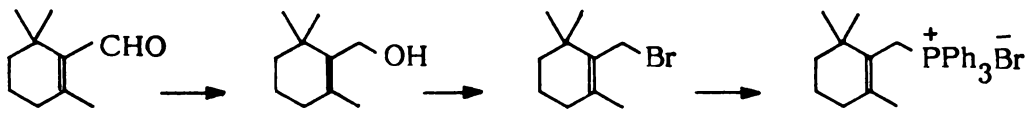
Scheme 27

Now the method of choice of synthesis of ß-cyclocitral is by the ozonolysis-cleavage of ß-ionone[81]. As an alternative to the ozonolysis method, the retroaldol condensation of ß-ionone was investigated. ß-ionone can be considered as the aldol condensation product of ß-cyclocitral and acetone. So it was thought that ß-ionone on retro aldol reaction would give ß-cyclocitral under basic conditions at higher temperatures. Thus ß-ionone was treated with 10% aq. K_2CO_3 solution containing a phase transfer catalyst and stirred under refluxing temperature. Aliquots were withdrawn at regular intervals and analysed by GLC. Only low conversions were observed (30-40% by GLC analysis). Extensive investigation was not carried out to get the optimum yield. If successful this could have become a viable alternative for the ozonolysis-cleavage approach for ß-cyclocitral. A method utilizing Corey-Chaykovsky reaction[82] has been reported for the synthesis of ß-cyclocitral[83].

3.6.2 Preparation of ß-Cyclogeranyl Derivatives

ß-Cyclocitral (31) was reduced to ß-cyclogeraniol (70)[84,85]

using $NaBH_4$ in anhydrous methanol. A singlet at δ 4.1 for two hydrogen assignable to $-C\underline{H}_2OH$ as well IR absorption at 3670 cm^{-1} confirmed the alcohol structure. Geraniol as such cannot be cyclised to get cyclogeraniol but its derivatives have been cyclized using different reagents[86]. The electrogenerated acid catalysed cyclization of geraniol gave not cyclogeraniol, but a mixture of limonene and terpenolene[73].



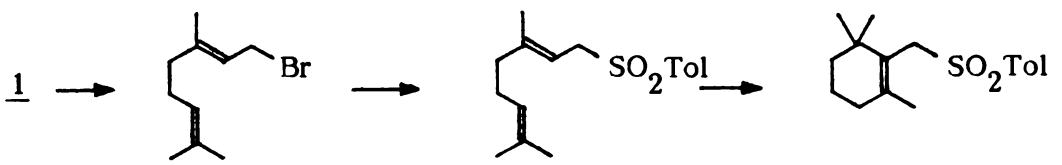
31 70 71 87

Scheme 28

The bromide 71 was prepared in 82% yield by treating 70 with 48% hydrobromic acid in n-pentane in a two phase system[87] at 0°. The product so obtained was essentially pure by spectroscopic analysis. Due to its unstability, it was immediately converted into the corresponding phosphonium salt 87 by stirring the bromide 71 and triphenylphosphine in dry benzene at room temp. for 30 hrs. (Scheme 28).

Treatment of geraniol (1) in anhydrous ether with PBr_3 at 0° afforded geranyl bromide (72)[88] in near quantitative yield. Treatment of 72 with sodium p-toluene sulfinate in anhydrous DMF at room temp. for 24 hrs. gave geranyl p-toluene sulfone (73) in 91% yield[89]. A doublet at δ 3.8 for two hydrogens assignable to

-C$\underline{H}_2SO_2$Tol, two doublets each for two aromatic protons at δ 7.2 and δ 7.8 as well as the singlet at δ 2.45 for PhC$\underline{H}_3$ confirmed the structure 73. The sulfone 73 was cyclized with con. H_2SO_4 in AcOH to afford a 1:4 mixture of α and ß-cyclogeranyl sulfones in good yield[90] (Scheme 29). The α and ß-isomers were not separated since



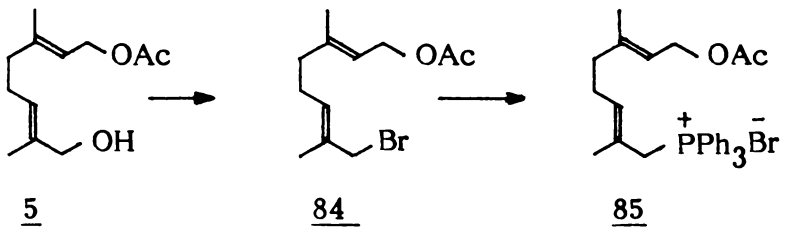
72 73 74

Scheme 29

in the conditions used for the sulfone-alkylation, on base treatment, the allylic sulfone in metallated exclusively. The synthesis of ionones from cyclogeranyl sulfones has been reported[90]. The structure 74 was confirmed by its ^{1}H NMR spectral data: a singlet at δ 1.05 for six protons assignable to two free CH_3 groups, a singlet for 3H at δ 1.7 due to the vinylic methyl, and a singlet for two hydrogens at δ 3.8 assignable to -C$\underline{H}_2SO_2$Tol.

3.6.3 Synthesis of Linear C_{10} Unit

The allylic alcohol 5 obtained by the allylic oxidation of geranyl acetate (3) was converted into its bromide 84 by the action of PBr_3 in ether at 0°. The bromide 84 was stirred with triphenyl phosphine in dry benzene for 24 hrs. at room temp. to give the

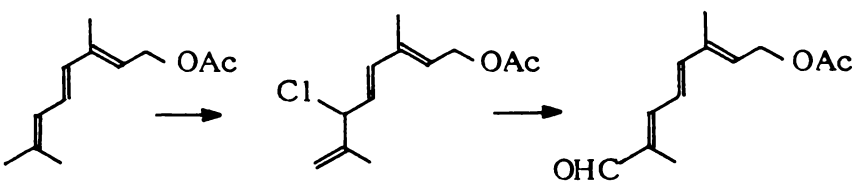


Scheme 30

phosphonium salt 85 (Scheme 30).

3.6.4 Synthesis of (E,E,E) Triene Aldehyde Ester

The terminal allylic functionalization of the triene ester 19 was carried out through its allylic chloride 88. Because of the complexity of the reaction, as well as the drastic conditions used, SeO_2 oxidation was not tried on the labile triene system. Eventhough the method of allylic oxygenation using PhSCl addition[20, 21] claims a terminal selectivity, it was not considered because of the comparatively lengthy synthetic manipulation involved. So it was thought to use the method of ene-chlorination[19, 63] followed by the conversion of allylic chloride to α , ß-unsaturated aldehydes[5, 6], for the terminal functionalization. This involves the reaction of HOCl with the isopropylidene terminus double bond to afford the allylic chlorides. The reaction of HOCl is regiospecific and it distinguishes well between isopropylidene terminus double bond and other double bonds as evidenced by the reaction on various olefins[63].



19 88 89

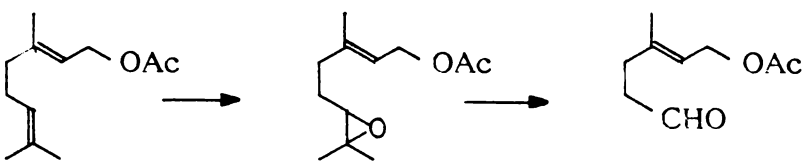
Scheme 31

Addition of dry ice to a mixture of calciumhypochlorite and 19 in methylene chloride-water, gave the allylic chloride 88. The crude allylic chloride 88 without purification was stirred with triethylamine N-oxide and CuCl in dioxan at 50°. The work up and purification by silica gel chromatography (100-200 mesh, 15% EtOAc in hexane) afforded 89 in 60% yield (Scheme 31). A singlet each at δ 1.6 and δ 1.7 for two methyl groups, a singlet at δ 2.05 for three protons due to CH_3CO- group, doublet at δ 4.6 assignable to -$C\underline{H}_2$-OAc, doublets at δ 6.1 and δ 6.4 for one olefinic proton each in 4, 5 double bond and the aldehyde proton peak at δ 9.4 confirms the all E stereochemistry of the triene 89 formed. The UV data (λ_{max}^{EtOH} 313nm) too is in order with the conjugated aldehyde structure.

3.7 Synthesis of C_7 Unit

In order to prepare the aldehyde ester 86 from geranyl acetate (3) selective cleavage of the isopropylidene double bond should be effected. In 3 such a selectively cannot be achieved. Selectivity

was created by epoxidising the the required double bond. Methods are available to cleave C-C bearing an epoxide. Epoxidation can be selectively done in the isopropylidene double bond with mCPBA or by the bromohydrin method. The disadvantage about the bromohydrin method is that in the epoxide formation step, base treatment hydrolyses the acetate group and a acetylation step became necessary for further manipulation.



3 6 86

Scheme 32

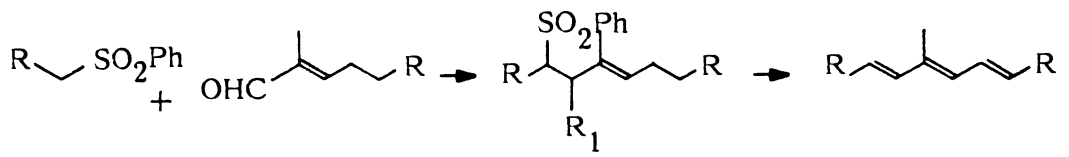
Thus the attempt to cleave the epoxide bearing C-C bond by converting the epoxide into the diol and subsequent cleaving of the diol by $NaIO_4$[91] was not successful. The preparation of diol from epoxide was attempted using $HClO_4$. The cleavage at the epoxide stage was then done using periodic acid in dioxan-water system[92]. The aqueous solubility of the product 86 posed a problem. The extraction was done by ether in a liquid-liquid continuous extractor to afford the aldehyde 86 in 54% yield (Scheme 32). The ^1H NMR spectrum showed the absence of gem dimethyl groups as well as the epoxide. A three hydrogen singlet at δ 1.65 for the vinylic CH_3, a three hydrogen

singlet at δ 2.1 (CH_3CO), doublet at δ 4.6 ($C\underline{H}_2OAc$) as well as a aldehyde proton peak at δ 9.85 and IR absorption at 1730 cm^{-1}(C=O) and 1740 cm^{-1} confirmed the aldehyde ester structure 86.

3.8 Synthesis of Vitamin A Derivatives

3.8.1 C_{10}+ C_8 + C_2 Approach

Mandai and coworkers have demonstrated a novel approach for the synthesis of polyenes by condensing sulfones (I) with α , ß-unsaturated aldehydes (II)[93]. The ß-hydroxy sulfones were converted to its acetyl or bromo derivatives and subsequent base treatment afforded the polyene (IV) (Scheme 33). This approach called double elimination has been utilized for the synthesis of methyl retinoate[93] retinol and retinyl acetate[94, 95].

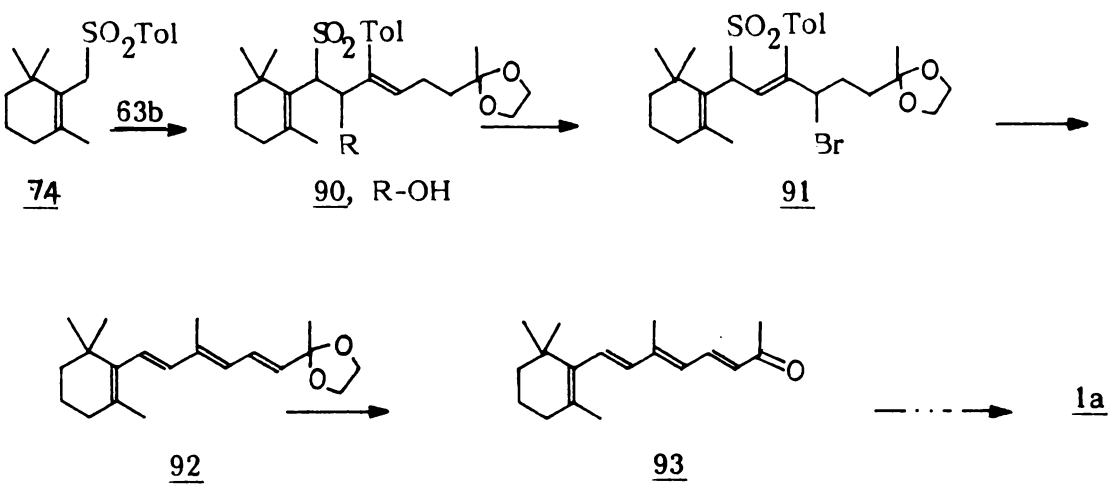


I II III, R_1-OAc,Br,OH IV

Scheme 33

In this scheme Vitamin A skeleton has been built in a C_{10} + C_8 + C_2 approach through the ß-C_{18} ketone. Thus for the synthesis of ß-C_{18} ketone 93[96-98], an important intermediate in the synthesis of Vitamin A, condensation of the sulfone 74 with the unsaturated aldehyde 63b was tried. The sulfone 74 was treated

with EtMgBr in toluene at 40-45°. After 3 hrs. stirring at this temperature, the mixture was cooled in a ice-salt mixture to -25 to -20°. To this solution was added the aldehyde 63b as a toluene solution. The mixture was stirred for 3 hrs. more. The reaction mixture was quenched at this temperature by adding ice cold water, to suppress the posibility of retro aldol condensation. Toluene from the reaction mixture was removed under reduced pressure, work up and purification by chromatography (20% ethylacetate in hexane) yielded the hydroxy sulfone 90, in 75% yield. The ^{1}H NMR spectral data - a five hydrogen multiplet at δ 3.8-3.95 assignable to -C<u>H</u>SO_2Tol and -OCH_2CH_2O- and a doublet for one hydrogen at δ 4.8 for -C<u>H</u>OH a four aromatic proton doublet at δ 7.4-7.8 and a 3 proton singlet due to C<u>H</u>$_3$Ph agreed well with the structure 90.



Scheme 34

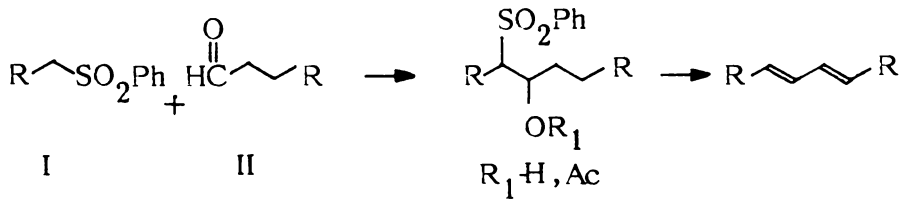
On bromination with PBr_3 in ether at 0^o, the hydroxy sulfone 90 gave the rearranged bromide 91. The attempts to effect double elimination in the hydroxy stage (90,R-OH) or at its acetate stage (90,R-OAc) using t-BuOK were unsuccessful. The bromide 91 underwent smooth elimination on treatment with MeOK in cyclohexane to afford the ketal 92 in 65% yield (Scheme 34). The attempt to effect elimination of the bromide 91 with t-BuOK was unsuccessful and a complex product mixture was obtained. The absence of absorption due to tolyl group, the appearance of five olefinic protons as multiplet in the region δ 5.5 to δ 6.7 and a sharp singlet for 3 protons at δ 3.9 due to $-OCH_2CH_2O-$ group as well as the IR data confirmed the ketal structure 92.

The deprotection of the ketal effected by gently refluxing the ketal 92 in aqueous acetone containing p-TsOH afforded the ß-C_{18} ketone in 35.9% overall yield from the sulfone 74. The spectral data were in good agreement with literature data[99,100]. ß-C_{18} ketone on two carbon homologation can be converted to Vitamin A derivatives. Since this conversion is known and the approaches available are well documented[99,100], this approach for ß-C_{18} ketone constitutes a formal synthesis of Vitamin A (100).

3.8.2 $C_{13} + C_5 + C_2$ Approach

This approach for Vitamin A also utilizes the C_{18} ketone intermediate. Sulfones (I) are known to condense with aldehydes (II) to give ß-hydroxysulfones which on acetylation and base catalysed

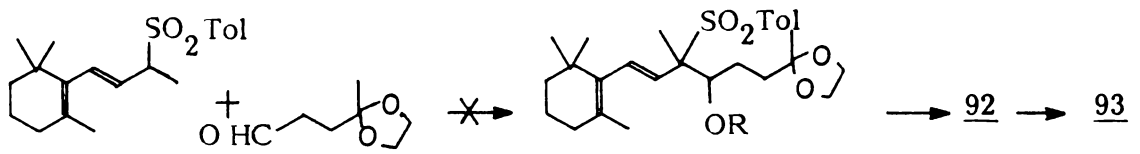
elimination gives trans dienes (Scheme 35)[102].



I II

Scheme 35

This variation of double elimination was applied in a C_{13} + C_5 scheme to synthesise ß-C_{18} ketone. To a THF solution of n-BuLi was added the sulfone 69 at -20° and to this solution was added the aldehyde 60 (Scheme 36). After 2 hrs. stirring, the reaction

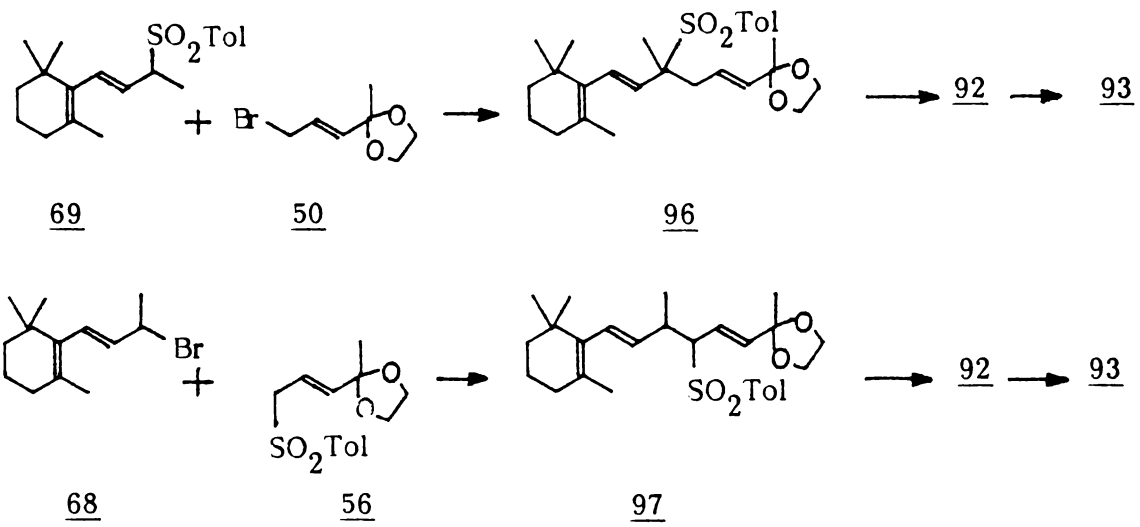


69 60 94, R-H
95, R-Ac

Scheme 36

work up failed to give any well characterized product. Use of base LDA in place of n-BuLi made no difference in the result. So in another approach, the sulfone-alkylation was tried. Thus the sulfone 69 was treated with NaH in anhydrous DMF to generate the anion[103] and to this red coloured solution was added a solution of the bromide 50. After stirring the mixture for 1.5 hrs. at 10°, the reaction mixture was worked upto get the sulfone 96 as a viscous liquid. The spectral characteristics were in accordance with the structure 96. The sulfone 96 underwent NaOEt catalyzed sulfinic acid elimination in EtOH at

refluxing temperature[103] to give the ketal 92, the structure of which is confirmed by the ^{1}H NMR data. Deketalization of 92 with p-TsOH afforded the ß-C_{18} ketone 93 in an overall yield of 47% (Scheme 37).

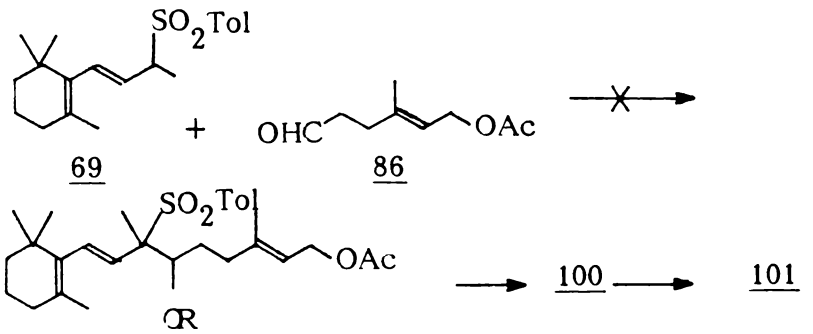


Scheme 37

Analogous reaction with the sulfone 56 and bromide 68 also gave ß-C_{18} ketone which had comparable spectral characteristics but in lesser overall yield of 40%. In this alkylation, the intermediate sulfone 97 has not been isolated, and elimination step was done directly using the crude sulfone.

3.8.3 C_{13} + C_7 Approach

The method of synthesising trans dienes[102] was utilized for the condensation sulfone 69 with the aldehyde 86. The aldehyde 86 was added to the solution of the sulfone 69 and n-BuLi in THF



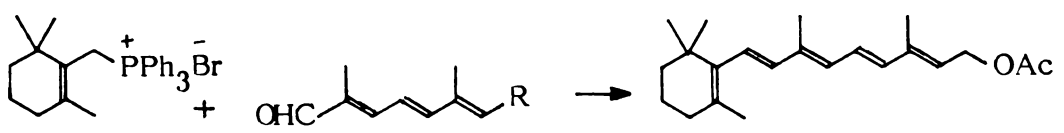
98, R-H ; 99, R-Ac

Scheme 38

at -20°. The reaction product after work up failed to give any well characterised product. Repetition of the condensation using the bases LDA and NaOEt too was unsuccessful. (Scheme 38).

3.8.4 C_{10} + C_{10} Approach

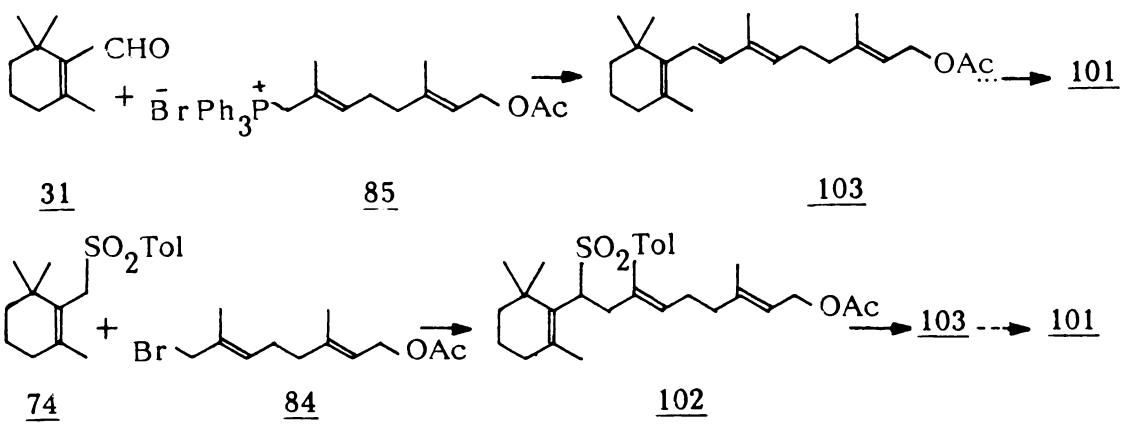
Wittig condensation of the phosphonium salt 87 with the C_{10} aldehyde ester (89, R-COOEt) is known[104]. Thus the condensation of the aldehyde 89 with the triphenyl phosphoniumbromide 87 using n-BuLi in ether afforded a light yellow viscous oil which showed the spectral properties of 101 (Scheme 39).



87 89, R-CH_2OAc 101

Scheme 39

11, 12 Dihydrovitamin A acetate (103) was synthesised from the aldehyde 31 and the phosphonium salt 85 using n-BuLi as the base in ether. Alkylation of the sulfone 74 by the bromide 84 using the base NaH also yielded 103 after the sulfinic acid elimination of 102 by NaOEt in refluxing ethanol (Scheme 40).



Scheme 40

The conversion of 103 to Vitamin A acetate was then tried. NBS bromination was not tried since such a reaction is known to introduce a functionality at C-4 in the ring in similar systems[105]. Since there is no isopropylidene terminus present in the molecule, it is thought that SeO_2 oxidation can oxygenate 11 or 12 position. The possibility of ring vinyl methyl group getting oxidised was not ruled out. Internal allylic oxidation in the presence of a isopropylidene terminus by SeO_2 has been reported[85]. The reaction was done with an apprehension considering the lability of the molecule. 103 was treated with SeO_2 in refluxing ethanol. As it turned out to be the product work up failed to give any indentifiable product.

CHAPTER IV

EXPERIMENTAL

4.1 General

The melting points were determined by capillary method and are uncorrected. The boiling and melting points are given in degree Celsius. 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 constants (J) in hertz (Hz), (s-singlet, d-doublet, t-triplet, bs-broad singlet, bd-broad doublet, dd-doublet of doublets, m-multiplet, Ar, ar-aromatic, H-hydrogen). Gas Chromatographic analysis were carried out on a Hewlett Packard 5730 Gas Chromatograph coupled with 3390 A Reporting Integrator either on a 12ft 1/4 in. 10% SE-30 on Chromosorb or on a 12ft 1/8 in. 5% Carbowax coloumns 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 as solvent unless otherwise specified. IR spectra were recorded as neat either on a Perkin Elmer 727B Infrared Spectrophotometer or on a Perkin Elmer 283 Grating Infrared Spectrophotometer.

The experiments involving organometallic reagents, air or moisture sensitive reagents were carried out in an inert atmosphere. Reactions involving polyenes were carried out in subdued light conditions. Column chromatography was done either using 60-120 or 100-200 mesh silica gel (Sisco or BDH) using n-hexane ($63\text{-}68^{o}$ fraction) as eluent. For monitoring the reactions Merck Silica Gel G (Art. 1/17631) containing

13% binder, coated plates were used. All solvents were distilled and dried according to the standard methods before use. After the extraction workup, organic layer was dried using anhydrous sodiumsulphate. Complete removal of the solvents were effected using a Buchi EL 130 Rotavapour.

4.2 (E)-3, 7-Dimethyl-octa-2, 6-dien-1-ol (1) (Geraniol)

Palmarosa oil containing 80% geraniol (by GLC) was chromatographed (Silica gel - 60-120 mesh, eluent - 19:1 hexane-ether, ratio of substance to adsorbent - 1:25) to isolate 1 in 95% recovery. bp 114-15^{o}/12mm.

UV : λ_{max} 193 nm (ε 18, 000)

IR : 3400, 1695, 1105, 1090, 1000 cm^{-1}

NMR : δ 1.6(s,3H), 1.65(s,6H), 2.1(m,4H), 4.1(d,2H), 5.1(t,1H), 5.4(t,1H).

4.3 (E)-Acetoxy-3,7-dimethyl-octa-2,6-diene (3) (Geranylacetate)

To a mixture of geraniol, 38.5g (0.25 mol) and pyridine, 19.75g (0.25 mol) in dichloromethane (250 mL) was added acetylchloride, 27.3g (0.35 mol) in dichloromethane (100mL) drop by drop over 30 min. under stirring at 0^{o}. Stirring continued for 1 hr. and allowed the bath to come to room temperature. The reaction mixture diluted with water (50 mL) and washed with saturated copper sulfate solution (3x50mL), sodium bicarbonate (2x50mL) and brine (2x50mL). The organic layer dried and solvent removed to get geranylacetate, 45g (91%). bp 98^{o}/15mm.

IR 1740, 1440, 1365, 1225 cm^{-1}

NMR : δ 1.6(s,3H), 1.7(s.6H), 1.9-2.05 (m, 4H), 2.05 (s,3H), 4.6(d,2H), 5.1(t, 1H), 5.4(t, 1H)

4.4 3,7-Dimethyl-octa-2,6-dien-1-al (2) (Citral)[70]

Lemongrass oil containing 79% citral (by GLC) was chromatographed (Silica gel - 60-120, ratio of substance to adsorbent-1:10, eluent - 19:1 hexane-isopropanol) to isolate 2 in 98% recovery. bp 92-93°/2.6mm.

UV λ_{max} 236 nm (ε 16,300)

IR 1665, 1625, 1603, 1398, 1190 cm^{-1}

NMR : 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).

4.5 (E,E)-8-Acetoxy-2,6-dimethyl-octa-2,6-dien-1-ol (5)

Seleniumdioxide, 15.54g (0.14 mol) dissolved in 95% ethanol (100mL) was added to a solution of geranylacetate (3), 27.44g (0.14 mol) in 95% ethanol (250mL) under reflux over a 30 min. period. The stirring was continued for 2 hrs. and the solution turned dark red with the precipitation of metallic selenium. Complete conversion has occurred in 2 hrs. (TLC). The reaction mixture was cooled, filtered and ethanol was removed under reduced pressure. The residue was dissolved in ether and extracted with ether (2x100mL), washed with water (3x50mL), sodium bicarbonate (3x50mL) and brine (2x50mL). The

organic layer dried and solvent removed to give 20.5g of crude product.

The crude mixture containing mainly alcohol and the rest aldehyde without purification was dissolved in anhydrous methanol (100mL). To this solution at 0^{o} was added sodium borohydride, 7.18g (0.19 mol) under stirring. After 1 hr. the conversion was complete. The excess sodium borohydride was decomposed by adding saturated ammonium chloride (150mL). The mixture was extracted with ether (2x150mL), washed with sodium bicarbonate (3x100mL) and water (2x100mL). The organic layer was dried, solvent removed and chromatographed (silica gel - 100-200 mesh, 1:3 ethylacetate-hexane)- to give 5, 17.5g (59%). bp 114-22^{o}/0.3mm.

IR : 3580, 3430, 1740, 1660, 1240 cm^{-1}

NMR : δ 1.7(d,each 3H), 2.05(s,3H), 2.1(m,4H), 4.0(s,2H), 4.6(d,2H), 5.1(t,1H), 5.45(t,1H).

4.6 (E)-Acetoxy-6,7-epoxy-3,7-dimethyl-oct-2-ene (6)

(a) m. CPBA method:

To a solution of geranylacetate, 7.84g (0.04 mol) in dichloromethane (100mL) at 0^{o} was added m-chloroperbenzoic acid, 7.74g (0.045 mol) dissolved in dichloro methane (60mL) under stirring. After stirring for 3 hrs. at room temperature, the contents were diluted with water (100mL). The organic layer separated, washed with saturated sodium carbonate solution (2x40mL), water (2x40mL) and dried. Solvent removal in vacuo and purification by chromatography afforded the epoxide 6, 7.6g (90%).

(b) Bromohydrin method:

To a mixture of dimethoxyethane (50mL) and water (30mL) containing N-bromosuccinimide, 7.12g (0.04 mol) was added geranylacetate, 7.84g (0.04 mol). The mixture was refluxed for 6 hrs. TLC showed complete conversion. The reaction product was then treated with excess potassium carbonate. The reaction mixture diluted with water (100mL) and extracted with ether (2x50mL). The ether layer washed with water (3x30mL) dried and solvent removed. The crude product was dissolved in 1:1 dry benzene-pyridine (100mL) and added acetyl chloride, 7.8gm (0.1 mol) under stirring at 0^{o}. Stirring continued for 2 hrs. The usual work up yielded the epoxy acetate 6, 6.02g (71%).

NMR : δ 1.25, 1.3(s, each 3H), 1.75(s,3H), 2.05(s,3H), 2.2(m,4H), 2.7(t,1H), 4.6(d,2H), 5.4(t,1H).

4.7 Epoxide ring opening of 6

Pyrolidine (0.5mL) was added to a solution of epoxide 6, 6.36g (0.03 mol) in ether (30mL) and the mixture was stirred under nitrogen at room temp. for 3 hrs. After washing with water (2x15mL) and brine (2x15mL) the ether layer was dried and solvent removed to get the alcohol 7, 4.5g (71%).

IR : 3400, 890 cm^{-1}

NMR : δ 1.7(s,3H), 1.75(s,3H), 1.8-2.3(m,4H), 4.0(m,1H), 4.15(d,2H), 4.9(s,2H), 5.4(m,1H).

4.8 Bromination of the alcohol 7 obtained from epoxide ring opening of 6

To a stirred mixture of alcohol 7, 2.24g (0.02 mol) and pyridine (0.1mL) in dry ether (50mL) was added phosphorous tribromide, 8.7g (0.032 mol) at 0^{o} over 1 hr. period. Stirring continued for 5 hr. at 0^{o}. The reaction mixture diluted with ice cold water (100mL), extracted with ether (2x50mL), washed with sodium bicarbonate (3x50mL), water (2x40mL) and brine (2x40mL). The ether layer dried and solvent removed in vacuo to get the bromide 8, 4.4g (80%).

NMR : δ 1.7(s,6H), 1.8-2.1(m,4H), 3.95(m,4H), 5.3-5.5(m,2H).

4.9 (E)-Acetoxy-6-chloro-3,7-dimethyl-octa-2,7-diene (9)

An excess amount of dry ice was added in portions to a mixture of geranylacetate, 9.8g (0.05 mol) and calcium hypochlorite (active chlorine 60%), 13.0g (0.055 mol) in dichloromethane (200mL) and water (50mL) below 0^{o} under stirring. The reaction mixture was stirred for 1 hr. below 5^{o} and then diluted with dichloromethane (100mL), washed with sodium bicarbonate (2x50mL) and water (2x50mL). The organic layer dried, solvent removed and purified to get the chloride 9, 8.0g (70%).

IR : 1740, 890 cm^{-1}

NMR : δ 1.7, 1.75(s, each 3H), 1.8-2.2(m,4H), 2.05(s,3H), 4.35(t,1H), 4.95(s,2H), 4.6(d,2H), 5.1(m,2H)

4.10 (E,E)-Acetoxy-3,7-dimethyl-8-oxo-octa-2,6-diene (4)

(a) From 9

A mixture of chloride 9, 6.5g (0.028 mol) in dioxan (15 mL), triethylamine N-oxide, 10.41g (0.088 mol) and copper(I)chloride, 0.276g (0.0028 mol) was stirred at 50° for 10 hrs. The reaction mixture was combined with 2.5% sulfuric acid (40 mL) and ethylacetate (40mL). The organic layer was washed with 2.5% sulfuric acid (2x20mL), sodium bicarbonate (4x20mL) and 10% sodium sulphite solution (2x30mL). The organic layer was dried and solvent removed in vacuo followed by chromatography on silica gel afforded the aldehyde 4, 4.4g (75%).

(b) From 5

Preparation of active manganese dioxide[14]:

A solution of manganese chloride tetrahydrate, 55g (0.279 mol) in water (500 mL) at 70° was gradually added during 10 min. under stirring to a solution of potassium permanganate, 40g (0.253 mol) in water (500mL) at 10°. The suspension was stirred for 2 hrs. and left at room temperature overnight. The precipitate formed was filtered, washed until neutral and dried at 120° for 18 hrs. to give active manganese dioxide as a brown amorphous powder, 45g.

To a solution of the alcohol 5, 5.3g (0.025 mol) in n-pentane (100mL) at 0° was added active manganese dioxide (50g). The mixture was stirred at 0° for 1 hr., filtered, solvent removed in vacuo to give the aldehyde 4, 4.2g (80%).

UV : λ_{max} 230nm

IR : 1740, 1690, 1235 cm^{-1}

NMR : δ 1.75(s,6H), 2.05(s,3H), 2.1-2.6(m,4H) 4.6(d,2H), 5.4(t,1H), 6.5(t,1H), 9.45(s,1H).

4.11 Preparation of diphenyl disulfide (PhSSPh)[23]

A mixture of thiophenol, 40.5g (0.361 mol) and dimethyl sulfoxide, 14.1g (0.181 mol) was stirred at room temperature for 24 hrs. The dimethyl sulfide formed as the byproduct was removed on a rotavapour and the oil which remained was cooled at $0^{o}C$ for 30 min. Crystals formed were filtered, washed with cold ethanol (20mL). Recrystallisation from hot ethanol gave crystals of diphenyl disulfide, 34.0g (95.7%). mp 60-61°.

4.12 Preparation of phenylsulfenyl chloride (PhSCl)[22]

To a solution of diphenyl disulfide, 22.6g (0.104 mol) in dry methylene chloride (65mL) containing pyridine (2mL) was added sulfuryl chloride, 14.0g (0.104 mol) drop by drop as a solution in dry methylene chloride (20mL) under stirring at room temp. The mixture was allowed to stir at room temp. for 2 hrs. Solvent removal gave a dark orange yellow oil. bp 55^{o}/5mm.

4.13 (E)-8-Acetoxy-2,6-dimethyl-3-phenylthio-octa-1,6-diene (11)

To a solution of geranyl acetate, 9.8g (0.05 mol) in dry methylenechloride (100mL) was added dropwise under nitrogen atmosphere a solution of phenyl sulfenyl chloride, 7.5g (0.05 mol) in dry methylene chloride (30mL) at -10^{o} over 10 min. The instantaneous discharge of yellow colour indicated the conversion. The mixture was allowed to stir for 15 min. more and concentrated under reduced pressure to give 16.5g (94%) of the crude adduct 10. It was then warmed with triethyl amine, 25.25g (0.25 mol) in dimethylformamide (100mL) at 60^{o} for 20 hrs. The mixture was cooled, diluted with water (150mL) extracted with ether (3x75mL) and washed with water (4x50mL). The organic layer dried, solvent removed and purified to get 11 as an oil, 10.64g (70%).

IR : 1730, 1635, 1580, 890 cm^{-1}

NMR : δ 1.7, 1.75(s, each 3H), 2.05(s,3H), 1.9-2.3(m,4H), 3.6(t,1H, J=7.0), 4.6 (d,2H,J=7.0), 4.75(bs,2H) 5.4(t,1H,J=7.0), 7.1-7.4(m,5ar.H).

4.14 (E)-8-Acetoxy-2,6-dimethyl-3-phenylsulfoxo-octa -1,6-diene (12)

To a solution of 11, 7.6g (0.0235 mol) in acetic acid (125mL) was added dropwise 30% hydrogenperoxide (2.5mL) at 20^{o} and the mixture was stirred at 20^{o} for 20 hrs. The mixture was diluted with water (200mL), extracted with dichloromethane (3x50mL) and washed successively with sodium bicarbonate (2x50mL), water (2x50mL) and

brine (2x50mL). The organic layer was dried, solvent removed to give crude 12 as an viscous brown oil, 6.5g (81%).

4.15 (E,E)-8-Acetoxy-2,6-dimethyl-octa-2,6-dien-1-ol (5) from 12

Crude 12 without purification was subjected to sulfenic acid elimination. A mixture of 12, 6.5g (0.02 mol) and trimethyl phosphite, 3.23g (0.04 mol) in methanol (150mL) was stirred at 20^{o} for 48 hrs. in nitrogen atmosphere. The mixture was diluted with water (200mL) extracted with ether (3x50mL), washed with sodium bicarbonate (3x50mL) and brine (2x40mL). The organic layer dried, solvent removed in vacuo followed by product isolation by chromatography gave the allylic alcohol 5, 3.8g (70%), which had comparable spectral characteristics with that of the alcohol 5 earlier prepared (4.5).

4.16 Attempted N-bromosuccinimide bromination of geranylacetate (3) to get (E,E)-5,8-dibromo-3,7-dimethyl-octa-2,6-diene (13)

Geranyl acetate, 3.92g (0.02 mol) in dry carbontetrachloride (25mL) and freshly crystallised (hot water) N-bromosuccinimide, 1.78g (0.01 mol) were refluxed on a water bath for 4 hrs. Only about 50% conversion was observed on TLC. The reaction mixture was cooled, filtered, washed with saturated sodium bicarbonate (2x20mL) dried and solvent removed to get a dark brown liquid, 4.0g, which could not be purified by silica gel chromatography.

4.17 Attempted elimination of 13 to get (E,E,E)-acetoxy-8-bromo-3,7-dimethyl-octa-2,4,6-triene (14)

The crude reaction product (4.4g) without purification was warmed with triethylamine (20mL) in dimethylformamide (100mL) at 60^{o} for 10 hrs. The reaction mixture cooled, diluted with water (150mL), extracted with ether (3x50mL) and washed with 2.5% sulfuric acid (2x30mL). The organic layer dried, and solvent removal followed purification by chromatography on neutral alumina gave a single component as a brown oil, 1.5g.

4.18 Preparation of diphenyl diselenide (PhSeSePh)[37]

To a solution of phenyl magnesium bromide, prepared from bromobenzene, 80.0g (0.51 mol) and magnesium turnings, 12.0g (0.49 g atom) in anhydrous ether (275mL) was added selenium powder, 35.0g (0.445 g atom) from a solid addition funnel with stirring under nitrogen 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, 1.5g (0.08 mol) was added dropwise to hydrolyse the excess Grignard reagent. The mixture was stirred and cooled in an ice bath and bromine, 37.15g (0.233 mol) was added at a rate such that ether does not reflux. A solution of ammonium chloride, 26.75g (0.5 mol) in water (70mL) was then added under stirring. The reaction mixture filtered and the precipitate washed with ether. The combined filtrates were evaporated and the residue was dissolved in hot hexane (250mL).

The hexane solution is filtered and allowed to crystallize at room temp. and then at 6^{o}. The yellow crystalline diphenyl diselenide formed is filtered, washed with n-pentane and dried in air, 45g (65%). mp 60-62^{o}.

4.19 (E,E)-7-Acetoxy-3,7-dimethyl-octa-2,5-dien-1-0l (18)

To a solution of diphenyl diselenide 3.5g (0.013 mol) in absolute ethyl alcohol (60mL) was added sodium borohydride, 0.874g (0.023 mol) in portions under nitrogen atmosphere at room temp. with stirring. Profuse evolution of hydrogen was observed. Stirring continued for 3 hrs. when the solution became light orange coloured. Then epoxide 6, 4.24g (0.02 mol) in ethanol (10mL) was added dropwise over 10 min. The colour turned yellow and the mixture was refluxed for 2 hrs. When TLC showed complete conversion, the reaction mixture was cooled and added tetrahydrofuran (30mL). 30% hydrogenperoxide, 21.4ml (0.234 mol) was then added dropwise with stirring over 30 min. below 0^{o} and stirring continued for 3 hrs. The solution turned colourless. The reaction mixture was diluted with water (100mL) and extracted with ether (2x50mL). Ether layer washed with sodiumcarbonate (4x50mL), dried, solvent removed and purified by silica gel chromatography to yield (E,E)-3,7-dimethyl-octa-2,5-dien-1,7-diol (16), 3.06g.

IR(CCl_4) : 3620, 3400 cm^{-1}

NMR : δ 1.3(s,6H), 1.6(s,3H), 2.8(bd,2H), 4.1(d,2H), 5.2(bd,1H), 5.4-5.7(bt,2H).

The alcohol 16, 3.06g was stirred with acetic anhydride (20mL) and pyridine (10mL) for 24 hrs. at room temp. The reaction mixture diluted with water (40mL), extracted with ether (2x50mL), washed with saturated copper sulfate solution (3x30mL), sodium bicarbonate (2x40mL), water (2x40mL) and brine (2x40mL). The ether layer dried, solvent removed and purified to get (E,E)-1,7-diacetoxy-3,7-dimethyl-octa-2,5-diene (17), 4.2g (83%).

IR 1740 cm^{-1}

NMR δ 1.45(s,6H), 1.7(s,3H), 2.05(d,6H), 2.75(bd,2H,J=6.0), 4.6(d,2H,J=7.0), 5.35(t,1H), 5.7(bt,2H).

Sodiumcarbonate (1.625g) was added to the diacetate 17, 3.8g (0.015 mol) in dry ethanol (50mL) and the mixture was refluxed for 8 hrs. under nitrogen. When TLC showed complete conversion, the reaction mixture was poured into ice water (100mL) and extracted with ether (2x50mL). The ether layer washed with water (2x40mL) and brine (2x40mL). After drying, solvent was removed and the residue was purified by silica gel chromatography to yield 18, 2.54g (80%).

IR : 3400, 1740 cm^{-1}

NMR δ 1.3(s,6H), 1.7(s,3H), 2.05(s,3H), 2.75(bd,2H,J=7.0), 4.1(d,2H,J=7.0), 5.3-5.4(t,2H), 5.7(t,1H).

4.20 (E)-5-Acetoxy-3,7-dimethyl-2,6-dien-1-ol (20)

The internal allylic acetate 18, 1.7g (0.008 mol) was stirred in 1:1 ether-acetic acid (80mL) with p-toluene sulfonic acid, 0.304g (0.0016 mol) dissolved in water (5mL) for 6 hrs. at $0^{o}C$.

The reaction mixture diluted with water (100mL), extracted with ether (2x50mL), ether layer washed with sodiumbicarbonate (2x40mL), water (2x40mL) and brine (2x40mL). The ether layer dried, solvent removed and product isolation by chromatography yielded secondary allylic acetate 20, 1.37g (81%).

IR 3400, 1740 cm^{-1}

NMR : δ 1.7(d,3H,6H), 2.05(s,3H), 2.8(bd,2H,J=6.0), 4.1(d,2H,J=7.0), 4.95-5.8(m,3H).

4.21 (E,E)-1,7-Diacetoxy-3,7-dimethyl-6-phenylthio-oct-2-ene (22)

The phenyl sulfenyl adduct 10, 17.5g (0.05 mol) was stirred with sodiumacetate, 9.9g (0.15 mol) in acetic acid (150mL) at 20^{o} for 2 hrs. The reaction mixture was diluted with water (200mL) extracted with ether (2x60mL) ether layer washed successively with sodium bicarbonate (3x50mL), water (2x40mL), and finally with brine (2x40mL). The organic layer dried, solvent removed and purification gave the acetoxy sulphide 22 as an oil, 16.1g (90%).

IR : 1740 cm^{-1}

NMR : δ 1.4(s,6H), 1.7(s,3H), 2.05(s,6H), 3.7-3.9(d,1H), 4.6(d,2H,J=7.0), 5.3(t,1H), 7.2-7.6(m,5ar.H)

4.22 (E,E)-1,7-Diacetoxy-3,7-dimethyl-octa-2,5-diene (17) from 22

The ß-acetoxy sulfide 22, 7.28g (0.02 mol) was stirred with 30% hydrogenperoxide (30mL) in acetic acid (100mL) at 20^{o} for 20 hrs. The reaction mixture diluted with water (150mL) and extracted

with ether (3x50mL). The ether layer washed successively with water (6x50mL), sodiumbicarbonate (3x50mL) and brine (1x50mL). The organic layer was dried and solvent removed to get 6.84g (90%) crude acetoxy sulfoxide 23 as a dark coloured oil. This without purification was heated in toluene (210mL) with sodiumcarbonate (7g) under reflux for 1.5h. The reaction mixture was cooled, water added (50mL) and toluene was removed in vacuo. The mixture was then extracted with ether (2x40mL), washed with water (2x50mL), brine (2x50mL), dried , solvent removed and purified to get the tertiary allylic acetate 17, 3.81g (75%), which showed comparable spectral data with 17 earlier prepared (4.19).

4.23 (E)-Acetoxy-6-iodo-7-methoxy-3,7-dimethyl-oct-2-ene (24).

To geranylacetate, 4.88g (0.025 mol) dissolved in dichloromethane (180mL) was added copper(II)acetate monohydrate, 3.3g (0.0165 mol) dissolved in methanol (300mL) under vigorous stirring at room temperature. The reaction mixture was protected from light by an aluminium foil and iodine, 6.02g (0.0237 mol) dissolved in dichloromethane (120mL) was added with stirring. After 1.5 hrs. of stirring, the dark solution filtered and the filtrate was stirred with potassiumcarbonate (22.5g). After 30 min. the discoloured green solution was filtered and distilled to dryness. The residue was dissolved in dichloromethane (375mL) and washed with water (3x250mL). The organic layer was dried and solvent removed to get the crude methoxy iodide 24.

4.24 (E,E)-Acetoxy-7-methoxy-3,7-dimethyl-octa-2,4-diene (26)

The crude methoxy iodide 24 obtained from the last step without purification was dissolved in tetrahydrofuran (300mL). Potassium t-butoxide, 11.93g (0.106 mol) (prepared from potassium 4.15g (0.106 mol) and excess dry t-butyl alcohol (150mL), excess t-butyl alcohol was removed in vacuo to get a solid) was added and the mixture was refluxed for 2.5 hrs. with stirring under nitrogen. The reaction mixture was cooled and ammonium chloride (6g) was added to destroy the excess base. The solution was filtered and evaporated to dryness. The residue was dissolved in dichloromethane (300 mL) and washed with water (3x250mL). The organic layer was dried and solvent removed to get the crude alcohol 25, 3.6g (85%). The alcohol 25 was stirred with 2:1 acetic anhydride-pyridine (25mL) at room temp. for 24 hrs. The reaction mixture was diluted with water (50mL), extracted with ether (2x50mL), washed with sodiumbicarbonate (3x40mL) and water (2x40mL). The organic layer dried and solvent removed to get the crude allylic ether. This was purified by chromatography on silica gel to get 26, 3.83g (65%).

IR 2830, 1740 cm^{-1}

NMR : δ 1.25(d, each 3H), 1.7(s,3H), 2.05(s,3H), 3.2(s,3H), 4.6(d,2H, J=7.0), 4.9(d,1H), 5.0-5.4(m,2H)

4.25 (E)-1,6-Diacetoxy-6-hydroxy-3,7-dimethyl-oct-2-ene (27)

To a solution of geranylacetate, 1.96g (0.01 mol) in acetic acid (30mL) was added potassiumiodate, 2.14g (0.01 mol) and iodine,

2.54g (0.01 mol). The resulting mixture was well stirred and heated at 80^{o} for 3 hrs. The reaction mixture diluted with water (50mL) and extracted with ether (2x50mL). The ether layer washed with sodiumbicarbonate (3x40mL) and then with water (2x40mL). The ether layer dried and solvent removed to get the hydroxy acetate, 27, 1,71g (63%).

IR : 3620, 1745 cm^{-1}

NMR : δ 1.3(s,6H), 1.7(s,3H), 2.05(s,6H), 2.8(m,2H), 3.9(t,1H), 4.6(d,2H), 5.4(t,1H).

4.26 (E)-Acetoxy-3,7-dimethyl-octa-2,6-dien-5-one (28)

Preparation of pyridium dichromate:[48] To a cooled solution of chromium trioxide, 10.0g (0.1 mol) in water (10mL) was added dropwise pyridine, 7.9g (0.1 mol) at room temperature. The reaction mixture diluted with acetone (40mL) and cooled to -20^{o}. The bright orange crystals formed were filtered, washed with cold acetone and dried, 12.4g (66%). mp 144-146^{o}.

Preparation of t.butyl hydroperoxide:[49] To a solution t-butanol, 7.4g (0.1 mol) in ether (50mL) containing sulfuric acid (2.5mL) was added 30% hydrogenperoxide, 12.5mL (0.11 mol) drop by drop under stirring at -20^{o}C. The reaction mixture diluted with water (40mL) extracted with ether and ether layer dried to get a ether solution of t-butyl hydroperoxide.

To the solution of t-butyl hydroperoxide prepared above,

containing pyridinium dichromate, 3.76g (0.01 mol) and benzene (50mL) was added geranylacetate, 1.96g (0.01 mol) under stirring at 0-5^{o}. After 11 hrs. of stirring organic phase washed with 10% KOH and brine, and extracted with ether (60mL) to get a brown liquid, which could not be characterised by analysis.

4.27 (E,E)-Acetoxy-3,7-dimethyl-octa-2,4,6-triene (19)

(a) From 20

To a solution of 20, 1.06g (0.005 mol) in tetrahydrofuran (10mL) under nitrogen was added at 0^{o} potassium t-butoxide, 0.56g (0.005 mol). The mixture was stirred for 30 min. It was then diluted with water (50mL), added ammonium chloride and extracted with ether (3x30mL), washed with water (2x40mL), dried and solvent removed to get the alcohol 21. The crude 21 was dissolved in 1:1 dry benzene-pyridine (20mL) and acetylchloride, 0.95g (0.012) mol) in dry benzene (10mL) was added at 0^{o} with stirring. After 3 hrs. the mixture was diluted with water (50mL), extracted with ether (3x30mL), ether layer washed with saturated coppersulfate solution (2x30mL), water (2x30mL) and then with brine (2x30mL). The ether layer was dried and solvent removal in vacuo gave the acetate 19, 0.73g (75%).

b) From 26

To a solution of the ether 26, 1.2g (0.0053 mol) in acetonitrile (25mL) and dichloromethane (25mL) was added powdered sodiumiodide, 0.78g (0.0052 mol) and the mixture was stirred at room

temp. under nitrogen. To this solution was added, acetylchloride, 0.410g (0.0052 mol) dropwise. After 10 min., water (50mL) was added and the mixture was extracted with ether (3x40mL). Ether layer washed with water (2x40mL), brine (2x40mL), dried and solvent removed to get an yellow oil, 0.62g (60%).

(d) From 27

To a solution of 27, 1.6g (0.006 mol) in benzene (50mL) was added p-toluene sulfonic acid, 1.9g (0.01 mol). The mixture was refluxed for 2 hrs. The reaction mixture was cooled, water (10mL) added and benzene removed in vacuo. The residue extracted with ether (2x30mL), ether layer washed with water (2x30mL), dried, solvent removed and purified to get a light yellow oil, 0.87g (75%).

UV : λ_{max} 265nm

IR : 1740, 1670 cm^{-1}

NMR : δ 1.6(s,3H), 1.7(s,6H), 2.05(s,3H), 4.6(d,2H,J=7.0), 5.2-5.4(m,2H), 6.1(d,1H), 6.4(d,1H).

4.28 2,6,6-Trimethyl-cyclohex-1-ene-1-carboxaldehyde (31) (ß-Cyclocitral)[76]

A solution of freshly prepared citral, 15.2g (0.1 mol) in ether (15mL) was mixed with a solution of aniline, 9.3g (0.1 mol) in ether (10mL) in small portions. The mixture was allowed to stand for 30 min. at room temp. The ether layer was separated and this solution of schiff base was used directly for cyclization. To well stirred cooled con. sulfuric acid (100mL) was added the solution of

citraldineaniline dropwise under stirring at -15 to -20° over 30 min. Stirring continued for 45 min. at -15° and the reaction mixture was poured into crushed ice and steam distilled. The hydrolysis took place fast and cyclocitral distilled over together with ether and water. The distillate is then saturated with sodium chloride, extracted with ether (3x60mL) and solvent removed to get crude cyclocitral. The crude mixture of cyclocitrals was then stirred with 8.5% methanolic potassium hydroxide (60mL) under N_2 at 0°. Extraction with ether (3x50mL) gave ß-cyclocitral, 9.1g (60%). bp 83-89°/8mm.

UV : λ_{max} 240nm

IR : 1685, 1670 cm^{-1}

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

Instead of steam distillation, when the reaction mixture was extracted with petroleum ether by liquid-liquid continuous extraction, increased yield of ß-cyclocitral was obtained.

4.29 (E,E)-6,10-Dimethyl-undeca-3,5,9-triene (43) (Pseudoionone)

To a solution of sodium hydroxide, 6g (0.15 mol) in water (120 mL) and acetone, 58g (73mL, 1.0 mol) containing benzyl triethyl ammonium chloride, 2.28g (0.01 mol) was added with vigorous stirring citral, 30.4g (0.2 mol) drop by drop over 30 min. at room temp. Stirring continued for 2 hrs. more. Excess acetone was removed by distillation. The residue extracted with ether (4x125mL) washed repeatedly with water till neutral and then with brine (2x75mL). The organic layer dried, solvent removed and purified by silica gel

chromatography to yield pseudoionone 43, 35.7g (93%). bp 101-10°/2mm.

UV : λ_{max} 291 (ε 15,550)

IR 1675 cm^{-1}

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)

4.30 4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (44) (ß-ionone)

Con. sulfuric acid, 58.8g (31.6mL, 0.6 mol) was added dropwise under stirring to ethyl acetate (25.5mL) below 5°. To this cooled solution was added pseudoionone, 29.95g (0.15 mol) drop by drop with stirring over 30 min. During the addition temperature was maintained at 0-5°. Stirring was continued for 1 hr. more. Ethylacetate (100mL) was added to the reaction mixture and organic layer separated. It was then washed repeatedly with water until the solution is not acidic and then with sodiumbicarbonate and finally with brine. The ethylacetate layer dried and solvent removed. The crude product was then purified by silica gel chromatography to give ß-ionone, 24.0g (80%). bp 92-96°/2mm.

UV : λ_{max} 296nm (ε 9700), 218nm (ε 7190)

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

NMR : δ 1.1(s,6H), 1.8(s,3H), 2.0-2.25(m,6H), 2.3(s,3H), 6.25(d,1H), 7.4(d,1H).

4.31 Retro-aldol condensation of ß-ionone (44) - Attempted preparation of ß-cyclocitral (31)

ß-ionone, 1.92g (0.01 mol) was mixed with benzyl triethyl ammonium chloride, 0.228g (0.001 mol) and 10% potassiumcarbonate solution (75mL). The mixture was refluxed under stirring with a short condenser for 6 hrs. During this period, aliquots were withdrawn and analysed by GLC to determine the extent of conversion.

4.32 5-Bromo-2-pentanone (46)[50]

A solution of 2-acetyl butyrolactone (45), 30.0g (0.234 mol) in chloroform (300mL), benzyl triethyl ammonium chloride, 5.2g (0.0234 mol) and 48% aqueous hydrobromic acid (300mL) were stirred under nitrogen for 18 hrs. at room temp. The conversion was almost complete by this time. After the reaction, the aqueous layer was separated and extracted with chloroform. The combined chloroform layer was washed with water (3x125mL), dried and solvent removed in vacuo to get the ketobromide, 46, 32.8g (85%).

IR 1715 cm^{-1}

NMR : δ 2.17(s,3H), 2.2-2.8(m,4H), 3.5(t,2H).

4.33 2-(3-Bromopropyl)-2-methyl-1,3-dioxolane (64)

Ethylene glycol, 26.4g (0.44 mol), benzene (200mL) and pyridinium p-toluene sulfonate, 6.25g (0.025 mol), (prepared by adding excess pyridine to a solution of p-toluene sulfonic acid, 4.75g

(0.025 mol) in ether and repeatedly washing with ether to remove excess pyridine and finally removing traces of ether to get the solid salt), were refluxed for 4 hrs. in a Dean-Stark set up to remove the water. To this solution, ketobromide 46, 33.0g (0.2 mol) was added and refluxing continued for 2 hrs. After the reaction, the mixture was diluted with water (100mL) and benzene removed under reduced pressure. The residue extracted with ether, (3x50mL), washed with water (2x40mL), sodium bicarbonate (2x40mL) and finally with brine (2x30mL). The ether layer was dried and solvent removed in vacuo followed by product purification yielded the ketal 64, 37.2g (89%). bp 103-105°/20mm.

IR : 2985, 1445, 1380, 1120, 1060 cm^{-1}

NMR : δ 1.3(s,3H), 1.7-2.3(m,4H), 3.5(t,2H,J=6.5), 3.95(s,4H)

4.34 2-Acetyl-2-phenylseleno-butyrolactone (47)

To a suspension of seleniumdioxide, 1.7g (0.015 mol) in dichloromethane (25mL) containing diphenyl diselenide, 9.36g (0.010 mol) and a catalytic amount of con. sulfuric acid, 0.294g (0.003 mol) was added 2-acetyl butyrolactone, 3.2g (0.025 mol) in dichloromethane (25mL) at 10° under stirring. The mixture was stirred at 10° for 10 hr. until the colour changed from yellow to reddish brown, with precipitation of selenium. The reaction mixture poured into ether (150mL) and ether layer was washed with sodiumbicarbonate (2x50mL). The organic layer dried, solvent removed and purification by silica gel chromatography yielded 47, 5.58g (79%).

NMR : δ 2.6(s,3H), 2.8(m,2H), 4.1(m,2H), 7.2-7.7(m,5 ar.H)

4.35 5-Bromo-3-phenylseleno-pentan-2-one (48)

Ketobromide 46, 8.25g (0.05 mol) in dichloromethane (50mL), added to a suspension of selenium dioxide, 3.4g (0.03 mol) in dichloromethane (50mL) containing diphenyl diselenide, 18.72g (0.02 mol) and a catalytic amount of con. sulfuric acid, 0.590g (0.006 mol). The mixture was stirred below 10^{o} for 18 hrs. The decolourised solution was diluted with ether (200mL) filtered and washed with sodiumbicarbonate (3x50mL). After drying, solvent removal under reduced pressure followed by product purification on silica gel gave 48 as anyellow oil, 10.85g (70%).

IR : 1715 cm^{-1}

NMR : δ 1.6-2.9(m,2H), 2.2(s,3H), 3.5(m,3H), 7.3-7.8(m,5ar.H).

4.36 (E)-5-Bromo-3-penten-2-one (49)

Phenyl seleno ketobromide 48, 6.2g (0.02 mol) dissolved in tetrahydrofuran (30mL) was stirred with excess 30% hydrogenperoxide 21.4mL (0.234 mol) below 5^{o}. Hydrogenperoxide was added drop by drop and stirring continued for 1 hr. The decolourised solution is diluted with water (100mL) and extracted with ether (3x40mL). Ether layer washed with brine (2x40mL), dried and solvent removed to get 49, 2.9g (90%).

IR : 1675 cm^{-1}

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

4.37 Methyl-4-oxo-pentanoate (52)

Heated a mixture of acetyl methyl urea, 49.0g (prepared by adding aqueous sodium hydroxide (40g in 160mL of water) with stirring to a solution of acetamide (59g) in bromine (28mL), heating the resulting yellow solution on a steam bath until effervesence sets in. Cooled in an ice bath for 1-2 hrs. and filtered the crystals of acetyl methyl urea) and con. hydrochloric acid (50mL) with hand stirring until it is apparent that no more solid is dissolving. Continued the heating for 3-4 min. Diluted with water (50mL). Cooled the solution below 10^{o} and added slowly below the surface of the liquid a cooled aqueous solution of sodium nitrite (38g in 55mL water). Filtered the nitrosomethyl urea formed at the pump and washed with cold water (10mL).

To a solution of the levulinic acid, 20.88g (0.18 mol) in dry methanol (250mL) was added a solution of diazomethane ~8.5g (0.2 mol) in ether, (generated by adding 34g of nitrosomethyl urea to a mixture of ether (350mL) and 50% potassiumhydroxide solution (99mL) and distilling the mixture to get a ether solution of diazomethane) under stirring at 10^{o} over 30 min. Profuse gas evolution was observed. The appearance of yellow colour indicated the completeness of the reaction. Solvent removal under reduced pressure gave the ester 52, 22.9g (98%).

IR : 1735, 1715 cm^{-1}

NMR : δ 2.2(s,3H), 2.5-2.8(bs,4H), 3.65(s,3H)

4.38 (E)-Methyl-4-oxo-pent-2-enoate (53)

A solution of phenylselenylchloride[53] in methylenechloride (75mL) is generated in situ by the addition of sulfurylchloride, 1.34g (0.01 mol) dissolved in methylene chloride (25mL) to a solution of diphenyl diselenide, 3.12g (0.01 mol) in methylene chloride (50mL) containing pyridine (0.2mL) at room temperature and stirring the reaction mixture for 30 min. To this solution was added the ketoester 52, 1.3g (0.01 mol) at 0^{o}. The mixture was stirred at this temperature for 2 hrs. Methylenechloride removed under reduced pressure and added tetrahydrofuran (50mL). To this solution was added 30% hydrogen peroxide (10mL) at 0^{o} and stirring continued for 30 min. The decolourised solution is diluted with water (100mL) and extracted with ether (3x40mL), washed with water (3x30mL) and dried. Solvent removal afforded the enone 53, 1.0g (77%).

IR : 1720, 1675 cm^{-1}

NMR : δ 2.1(s,3H), 3.65(s,3H), 6.9-7.3(m,2H)

4.39 (E)-Methyl-4,4-ethylenedioxy-pent-2-enoate (54)

Ethylene glycol, 2.64g (0.044 mol), the ester 53, 2.56g (0.02 mol) and pyridinium p-toluene sulfonate, 0.625g (0.0025 mol) in thiophene free benzene (20mL) were refluxed under N_2 in a Dean-Stark set up for 2 hr. After cooling, the reaction mixture diluted with water (10mL) and benzene removed under reduced pressure. Residue extracted with ether (3x20mL), washed with water (2x20mL), dried and solvent

removed to get the ketal 54, 3.2g (95%).

UV : λ_{max} 210nm

IR : 1725, 1060 cm^{-1}

NMR : δ 1.3(s,3H), 3.65(s,3H), 3.9(s,3H), 5.25(d,1H), 6.95(d,1H)

4.40 (E)-4,4-Ethylenedioxy-2-penten-1-ol (55)

To a solution of the ester 54, 3.44g (0.02 mol) in dry ether (50mL) was added lithiumaluminiumhydride, 0.76g (0.02 mol) portion wise under stirring. When the reaction was over, excess of the reagent was destroyed by adding aqueous ether drop by drop. Diluted the mixture with water (50mL). The reaction mixture was then extracted with ether (2x40mL), washed with water (2x40mL), brine (2x40mL), dried and solvent removed to get 55, 1.84g (64%).

IR : 3400, 1060 cm^{-1}

NMR : δ 1.3(s,3H), 3.95(s,3H), 4.15(d,2H), 5.7(d,1H), 6.1(d,1H)

4.41 (E)-5-Bromo-2,2-ethylenedioxy-pent-3-ene (50)

(a) From 49

Ketobromide 49, 4.9g (0.03 mol), ethylene glycol 3.96g (0.066 mol) and pyridinium p-toluene sulfonate, 0.95g (0.0038 mol) in thiophene free benzene (50mL) were stirred under reflux for 2 hrs. in a Dean-Stark set up. When the reaction was complete, the mixture was cooled, water (100mL) added and benzene removed under reduced pressure. The residue extracted with ether (2x50mL), washed with

water (4x40mL) and dried. Solvent removal under reduced pressure yielded the ketal 50, 5.15g (83%).

(b) From 55

To a stirred mixture of the alcohol 55, 5.76g (0.04 mol) and pyridine (0.2mL) in dry ether (100mL) was added drop by drop phosphoroustribromide, 16.26g (0.06 mol) in dry ether (40mL) at 0-5^{o} under stirring over 1 hr. period. Stirring continued at this temp. for a further period of 5 hrs. The reaction mixture was poured into ice water (200mL), extracted with ether (3x50mL), washed with water (2x50mL), sodiumbicarbonate (3x50mL) and finally with brine (2x50mL). The ether solution was dried and concentrated in vacuo to give the bromide 50, 7.7g (93%). bp 60-65^{o}/0.2 mm.

IR (CCl_4) : 3010, 2900, 1375, 970 cm^{-1}

NMR : δ 1.4(s,3H), 3.9(s,4H), 3.95(d,2H), 5.65(dd,1H,J=15.0), 6.1(t,1H).

4.42 (E)-4,4-Ethylenedioxy-1-p-toluenesulfonyl-pent-2-ene (56)

The ketal bromide 50, 8.28g (0.04 mol) was stirred with sodium p-toluene sulfinate dihydrate, 10.7g (0.05 mol) in dimethylformamide (25mL) for 24 hrs. at room temp. The reaction mixture diluted with water (50mL), extracted with ether (2x60mL) and washed with water (2x50mL). The ether solution was dried and concentrated in vacuo to get the sulfone 56, 9.5g (84%).

IR : 1150, 1060 cm^{-1}

NMR : δ 1.25(s,3H), 2.4(s,Ar-CH_3), 3.7-3.8(d,2H), 3.95(s,3H), 5.7-6.1(m,2H), 7.3-7.9(2d,each 2 ar.H)

4.43 (E)-4,4-Ethylenedioxy-2-penten-1-al (57)

To a suspension of active manganesedioxide (75g) in n-pentane (200mL) was added alcohol 55, 4.32g (0.03 mol) in dichloromethane (20mL) in a single lot under stirring at room temp. The mixture was filtered and solvent removed under reduced pressure to give the aldehyde 57, 3.36g (79%).

UV : λ_{max} 220nm

IR : 1685, 1060 cm^{-1}

NMR : δ 1.3(s,3H), 3.95(s,3H), 5.8(d,1H), 9.8(s,1H).

4.44 Methyl-4,4-ethylenedioxy-pentanoate (58)

Ethylene glycol, 13.2g (0.22 mol), the ketone 52, 13.0g (0.1 mol) in thiophene free benzene (200mL) were refluxed under N_2 in a Dean-Stark set up for 2 hrs. After cooling, the reaction mixture diluted with water (50mL) and benzene removed under reduced pressure. Residue extracted with ether (3x75mL), washed with water (3x60mL) dried and solvent removed to get the ketal 58, 16.0g (92%).

IR : 1735, 1065 cm^{-1}

NMR : δ 1.3(s,3H), 2.4-2.9(bs,4H), 3.65(s,3H), 3.9(s,3H)

4.45 4,4-Ethylenedioxy-pentan-1-ol (59)

To a suspension of lithium aluminium hydride, 1.71g (0.045 mol) in ether (50mL) was added the ester 58, 6.96g (0.04 mol) under stirring at refluxing temperature. Stirring and heating continued for 2 hrs. The excess reagent destroyed by the addition of aqueous

ether. Extracted with ether (2x50mL), washed with water (2x50mL), dried and solvent removed to get the alcohol 59, 4.8g (83%).

IR : 3410, 1070 cm^{-1}

NMR : δ 1.3(s,3H), 1.6-2.0(m,4H), 3.5(t,2H), 3.9(s,4H)

4.46 4,4-Ethylenedioxy-pentan-1-al (60)

To a suspension of pyridinium chlorochromate, 9.67g (0.045 mol) in dichloromethane (60mL) containing sodiumacetate, 0.74g (0.009 mol) was added the alcohol 59, 4.38g (0.03 mol) dissolved in dichloromethane (30mL) rapidly under stirring at room temperature. The solution became homogenic for a while and a viscous black deposit started to appear. Stirring continued for 2 hrs. The reaction mixture was diluted with ether (100mL), solvent decanted, residue washed twice with ether (2x50mL) and the combined ether layer filtered through a pad of silica gel to get the aldehyde 60, 3.37g (78%).

IR : 1725, 1070 cm^{-1}

NMR : δ 1.3(s,3H), 1.9-2.2(m,4H), 2.8-3.0(t,2H), 3.95(s,4H), 9.8(s,1H)

4.47 6-Methyl-5-hepten-2-one (61) (Methylheptenone)

95% citral, 50g (0.315 mol) was mixed with benzyltriethyl ammoniumchloride, 7.15g (0.0315 mol) and 1% sodiumcarbonate (750mL) 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 (3x150mL). Organic layers combined, washed

with water (4x75mL), dried and solvent removed to get the crude methylheptenone (61) contaminated with starting material. It was then purified by silicagel chromatography to yield pure 61, 25.8g (65%). bp 58.5^{o}/10mm.

IR : 1720 cm^{-1}

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

4.48 6,6-Ethylenedioxy-2-methyl-hept-2-ene (62)

A mixture of ketone 61, 18.9g (0.15 mol), pyridinium p-toluene sulfonate, 4.75g (0.019 mol) and ethylene glycol, 19.8g (0.33 mol) in thiophene free benzene (250mL) was refluxed under stirring in a Dean-Stark set up for 2 hrs. The reaction mixture diluted with water (100mL), benzene removed under reduced pressure and the residue extracted with ether (2x100mL). The ether layer washed with water (2x40mL), sodiumbicarbonate (2x40mL), dried, solvent removed and purified by silica gel chromatography to get the ketal 62, 22.6g (89%). bp 58^{o}/1.5mm.

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

4.49 (E)-6,6-Ethylenedioxy-2-methyl-2-hepten-1-al (63b)

To a solution of methylheptenone ketal 62, 8.5g (0.05 mol) in dry methylene chloride (100mL) was added dropwise under N_2 a solution of phenyl sulfenyl chloride, 7.2g (0.05 mol) in dichloromethane (30mL) below -5^{o}. The mixture was stirred for 1 hr. and concentrated

in vacuo to give the crude adduct 62a. It was then warmed with triethylamine, 25.25g (0.25 mol) in dimethylformamide (200mL) at 60^{o} for 20 hrs. The work up gave the allylic sulphide 62b. To a solution of the allylic sulfide in acetic acid (150mL) was added 30% hydrogen peroxide (5mL) drop by drop at 20^{o} and the mixture was stirred at 20^{o} for 20 hrs. The work up provided the crude sulfoxide 62c which was then treated with trimethylphosphite, 12.4g (0.1 mol) in methanol (200mL) and the mixture was stirred at 20^{o} for 48 hrs. under N_2. Dilution with water followed by extraction work up yielded (E)-6,6-ethylenedioxy-2-methyl-2-hepten-1-ol (63a), 3.9g (51%).

IR : :3580, 3460, 1065 cm^{-1}

NMR (CCl_4) : δ (1.2(s,3H), 1.6(s,3H), 2.1-2.7(m,4H), 3.9(s,6H), 5.3(bt,1H,J=7.0)

The alcohol 63a, 1.86g (0.01 mol) was stirred with active manganesedioxide (25g) in n-pentane (50mL). Filteration of the reaction mixture and concentration gave the ketal aldehyde 63b in 45% overall yield. bp 102^{o}/1mm.

UV : λ_{max} 230nm

IR : 1685, 1060 cm^{-1}

NMR (CCl_4) : δ 1.35(s,3H), 1.7(s,3H), 2.1-2.6(m,4H), 3.9(s,4H), 6.7(t,1H), 9.4(s,1H)

4.50 4,4-Ethylenedioxy-pentyltriphenylphosphoniumbromide (65)

To a solution of the triphenylphosphine, 22.0g (0.084 mol) in benzene (18.3mL) was added the ketal bromide 64, 17.5g (0.084 mol)

in one lot. The mixture was stirred under reflux for 12 hrs. The crystalline solid separated was filtered, washed with cold benzene and dried to get the phosphonium salt 65, 35.6g (90%).

4.51 6,6-Ethylenedioxy-2-methyl-hept-2-ene (62)

The base, sodiummethylsulfinylmethide was generated by adding dimethylsulfoxide (2mL) drop by drop to sodiumhydride (50% oil dispersion), 0.240g (0.120g of NaH, 0.005 mol, made free from mineral oil by repeated washing with dry petroleum ether (40-60^{o}) and removing traces of the wash liquid by flushing with N_2) under N_2 and stirring the mixture at 70-75^{o} until evolution of hydrogen ceases (45 min.). The temperature was never allowed to go above 75^{o}. To this cloudy, pale yellow grey solution of base cooled in ice bath was added the phosphonium bromide 65, 2.35g (0.005 mol) in one lot. The dark red solution was stirred for 30 min., brought to room temperature and added acetone, 0.58g (0.01 mol). Stirring was continued for 40 hrs. at room temp. The reaction mixture was extracted with 40-60^{o} petroleum ether (2x30mL) and washed with dimethylsulfoxide (2x20mL), water (2x20mL) and brine (2x20mL). The organic layer was dried, solvent removed in vacuo and purification by chromatography yielded the ketal 62, 0.50g (69%).

The ketal was then stirred with p-toluene sulfonic acid (0.05g) in 6:1 aqueous acetone (50mL). The work up yielded 6-methyl-hept-5-ene-2-one (61). The spectral properties of the ketal 62 and ketone 61 were identical with those of earlier reported (4.47 and 4.48).

4.52 4-(2,2,6-Trimethyl-1-cyclohexen-1-yl)-but-3-ene-2-ol (67) (ß-Ionol)

To a solution of ß-ionone, 8.06g (0.042 mol) in anhydrous methanol (50mL) was added sodiumborohydride, 3.2g (0.084 mol) in small portions over 1 hr. at $10^{o}C$ under stirring. It was continued for 1 hr. The reaction was monitored by TLC. When the conversion is complete, the excess borohydride was decomposed by aqueous ammonium chloride, and the usual work up gave the alcohol 67, 6.1g (86%).

IR : 3620, 1670 cm^{-1}

NMR : δ 1.0(s,6H), 1.3(d,3H), 1.65(s,3H), 1.8-2.1(m,6H), 4.4(m,1H), 5.6(t,1H), 6.0-6.2(d,1H)

4.53 2-Bromo-4-(2,2,6-trimethyl-1-cyclohexen-1-yl)-but-3-ene (68) (ß-Ionylbromide)

To a stirred solution of the alcohol 67, 15.52g (0.08 mol) and pyridine (0.4mL) in dry ether (200mL) was added dropwise phosphoroustribromide 32.52g (0.12 mol) in dry ether (80mL) at $0-5^{o}$ over 1 hr. period under stirring. Stirring continued at this temperature for 5 hrs. The reaction mixture was then poured into ice water (400mL), extracted with ether (3x75mL) and the work up yielded the bromide 68, 18.3g (89%).

4.54 (1-Methyl-3-(2,2,6-trimethyl-1-cyclohexen-1-yl)-allyl)-p-toluene sulfone (69) (ß-Ionyl sulfone)

To a solution of ß-ionol, 6.98g (0.036 mol) in isopropanol

(7mL) and acetic acid (10mL) was added sodium p-toluene sulfinate dihydrate, 9.67g (0.045 mol). The well mixed mixture was kept at room temperature for 15 min. and then refluxed on an oil bath for 16 hrs. The reaction mixture was cooled, diluted with water (70mL) and extracted with ether (2x60mL). The ether layer was washed with sodiumbicarbonate (3x40mL), water (2x40mL) and finally with brine (2x30mL). The ether layer dried and solvent removal in vacuo gave the sulfone 69 as a viscous liquid which failed to crystallise even on repeated attempts, 9.95g (83%).

NMR : δ 0.9(s,6H), 1.4(d,3H), 1.6(s,3H), 1.8-2.1(m,6H), 2.4(s,Ar-CH_3), 3.8(m,1H), 5.4(m,1H), 6.0(d,1H), 7.2-7.9(2d,each 2 ar.H)

4.55 1-(2,6,6-Trimethyl-1-cyclohexenyl)methanol (70) (ß-Cyclogeraniol)

To a solution of ß-cyclocitral, 15.2g (0.1 mol) in dry methanol (100mL) was added powdered sodiumborohydride, 5.7g (0.15 mol) in portions over 30 min. under stirring at 0-5°. Reaction was monitored by TLC. When the conversion was complete, the excess of the reagent was quenched by adding aqueous ammonium chloride solution (50mL). The usual work up afforded the alcohol 70, 13.4g (87%). bp 55-57°/0.2mm.

IR : 3670, 3500, 1650 cm^{-1}

NMR : 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).

4.56 1-Bromomethyl-2,6,6-trimethyl-1-cyclohexene (71) (ß-Cyclogeranyl bromide)[85]

A cooled solution of 48% hydrobromic acid (500mL) was

added to the alcohol 70, 12.2g (0.07 mol) with cooling in ice bath and stirring under nitrogen. The mixture was stirred for 10 min. and n-penta ne (300mL) was added. Stirring continued for 3 hrs. at 0^{o}. The reaction mixture poured into ice cold water (500mL) and aqueous layer extracted with n-pentane (2x100mL). The combined extracts were washed with sodiumbicarbonate (2x100mL) and brine (2x100mL), dried and concentrated in vacuo to give 71, 14.0g (82%) as a pale yellow oil.

IR 1645 cm^{-1}

NMR : δ 1.1(s,6H), 1.3-1.7(m,4H), 1.7(s,3H), 2.0(m,2H), 4.0(s,2H).

4.57 (E)-1-Bromo-3,7-dimethyl-octa-2,6-diene (72) (Geranylbromide)

Geranylbromide was prepared from geraniol 15.4g (0.1 mol) dissolved in dry ether (150mL) containing pyridine (0.6mL) and phosphoroustribromide, 40.65g (0.15 mol), 18.88g (87%).

4.58 (E)-3,7-Dimethyl-1-p-toluenesulfonyl-octa-2,6-diene (73) (Geranyl sulfone)[89]

To a solution of the bromide 72, 11.93g (0.055 mol) in dimethylformamide (35mL) was added sodium p-toluene sulfinate dihydrate, 13.7g (0.064 mol) and the mixture was stirred at room temp. for 24 hrs. The work up and crystallisation from pentane-ethylacetate mixture yielded the sulfone 73 as white flakes, 14.6g (91%). mp 44^{o}.

NMR : δ 1.4(s,3H), 1.6(s,3H), 1.7(s,3H), 2.0(d,4H), 2.45(s,Ar-CH_3), 3.8(d,2H), 4.9-5.4(m,2H), 7.4-7.8(2d, each 2 ar.H).

4.59 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-1-p-toluenesulfonylmethane (74) (ß-Cyclogeranylsulfone)[90]

To a solution of the sulfone 73, 14.6g (0.05 mol) in glacial acetic acid (150mL) was added con. sulfuric acid, 156.8g (87mL, 1.6 mol) drop by drop over 15 min. at 10-12° under stirring. Stirring continued for 15 min. more. The reaction mixture was diluted with ice cold water (300mL) and extracted with ether (3x100mL). The ether layer was washed well with water (3x60mL) and then with sodium bicarbonate (4x50mL). The ether layer was dried and solvent removed to get a viscous liquid which was purified by chromatography to yield the sulfone 74, 12.7g (87%).

NMR : δ 1.05(s,6H), 1.4-2.1(m,6H), 1.7(s,3H), 2.45(s,Ar-CH_3), 3.8(s,2H), 7.4-7.8(2d,each 2 ar.H)

4.60 δ -Valerolactone (76)

To a cooled mixture of con. sulfuric acid (177.5mL) and water (60mL) was added ammoniumpersulfate, 105.5g (0.46 mol) in portions keeping the temperature at 10-12°. Ethanol (250mL) was then added maintaining the temperature below 12°. To this cooled mixture added a solution of cyclopentanone, 20.25g (0.24 mol) in ethanol (50mL) drop by drop over 1 hr. under stirring. The progress of the reaction was monitored by TLC. When TLC showed complete conversion, the mixture was allowed to come to room temp., diluted with water (500mL) and extracted repeatedly with ether (4x75mL). The ether layer washed with sodiumbicarbonate (4x75mL) and then with water

(2x50mL). Solvent removal after drying yielded the lactone 75, 19.5g (81%). bp 58-60^{o}/0.5mm.

IR : 1735 cm^{-1}

NMR : δ 1.5-1.9(m,4H), 2.1-2.5(m,2H), 4.0-4.2(t,2H)

4.61 5-Oxo-hexan-1-ol (77)

To a solution of δ -valerolactone, 10.0g (0.1 mol) in ether (100mL) was added a ether solution of methyllithium prepared from lithium, 3.1g (0.454 mol) and methyliodide, 27.5g (0.194 mol) in anhydrous ether (100mL) under stirring at -25^{o}. (To the lithium metal in ether (50mL) was added a solution of methyliodide in ether (50mL) drop by drop, such a way that the ether keeps boiling. After the addition the reaction mixture was diluted with ether (100mL) and the filtered solution was used directly). Stirring continued for 30 min. more, and water (100mL) added. The reaction mixture allowed to come to room temperature, the organic phase separated and washed with brine (3x30mL). Ether layer dried, solvent removed and purified to get the keto alcohol 77, 6.96g (60%).

IR : 3410, 1715 cm^{-1}

NMR : δ 1.7-2.3(m,4H), 2,2(s,3H), 2.7(t,2H), 3.5(t,2H)

4.62 5,5-Ethylenedioxy-hexan-1-ol (78)

The ketone 77, 5.8g (0.05 mol) together with ethylene glycol, 6.6g (0.11 mol) and pyridinium p-toluene sulfonate, 1.58g (0.0063 mol)

in thiophene free benzene (150mL) was refluxed under stirring for 2 hrs. in a Dean-Stark set up. The reaction mixture was cooled and the wok up yielded the ketal 78, 7.44g (93%).

IR : 3415, 1060 cm^{-1}

NMR : δ 1.3(s,3H), 1.7-2.5(m,6H), 3.5(t,2H), 3.9(s,4H)

4.63 5,5-Ethylenedioxy-hexan-1-al (79)

To the ketal 78, 6.4g (0.04 mol) dissolved in methylenechloride (150mL) was added sodium acetate, 0.99g (0.012 mol). To this well stirred mixture added pyridinium chlorochromate, 21.5g (0.1 mol). Stirring continued for 2 hrs. The organic layer decanted, residue washed with dichloromethane (2x40mL). The combined organic layer washed with water (2x60mL), dried and solvent removed to get the aldehyde 79, 6.0g (95%).

IR : 1725, 1060 cm^{-1}

NMR : δ 1.3(s,3H), 1.9-2.2(m,4H), 2.8-3.0(t,2H), 3.9(s,4H), 9.8(s,1H)

4.64 6,6-Ethylenedioxy-heptan-2-one (80)

To a ether solution of methylmagnesiumiodide (prepared from magnesium turnings, 0.73g (0.03g atom) and methyliodide, 4.97g (0.035 mol) was added the aldehyde 79, 4.74g (0.03 mol) in ether (30mL) drop by drop over 30 min. The mixture was refluxed for 2 hrs. The reaction mixture poured into ice water (100mL) stirred with aqueous ammonium chloride solution (100mL) until homogenous. The reaction mixture was then extracted with ether (3x50mL), washed with water

(2x50mL) and brine (2x30mL). Organic layer after drying and solvent removal afforded the secondary alochol which was then dissolved in dichloromethane containing sodium acetate, 0.74g (0.009 mol) and pyridinium chlorochromate, 16.28g (0.075 mol) was added. The reaction mixture was stirred at room temp. for 2 hrs. The work up gave the ketone 80, 3.35g (65%). bp 114-16°/10mm.

IR : 1725, 1250, 1070, 950 cm^{-1}

NMR : δ 1.3(s,3H), 1.5-2.0(m,4H), 2.05(s,3H), 2.35(t,2H), 3.9(s,4H)

4.65 6,6-Ethylenedioxy-2-methyl-hept-1-ene (81)

The ether solution of n-butyllithium was prepared by adding n-butylbromide, 1.38g (0.01 mol) in ether (3mL) to lithium shavings, 0.173g (0.025 mol) in ether (5mL) at -20° and stirring the mixture for 30 min. To this solution of base was added methyltriphenyl phosphonium iodide, 4.04g (0.01 mol), (prepared by stirring triphenyl phosphine, 2.62g (0.01 mol) in benzene (2.2mL) with methyliodide, 2.13g (0.015 mol) and removing the solvent). The mixture was allowed to stir for 30 min. To the phosphorane generated was added the ketone 80, 1.72g (0.01 mol) in ether (20mL) under stirring. The mixture was stirred for 24 hrs. at room temp. The reaction mixture poured into ice cold water (100mL) and extracted with ether (3x30mL), dried, solvent removed in vacuo and purification by neutral alumina chromatography gave 81, 1.36g (80%). bp 82-84°/10mm.

IR : 2780, 1660, 1070, 890 cm^{-1}

NMR (CCl_4) : δ 1.23(s,3H), 1.7(s,3H), 1.3-2.2(m,6H), 3.9(s,4H), 4.7(s,2H)

4.66 6-Methyl-hept-6-ene-2-one (82)

The ketal 81, 1.36g (0.008 mol) and p-toluene sulfonic acid (0.1g) in 6:1 aqueous acetone (60mL) were refluxed for 6 hrs. Acetone removed in vacuo, and the work up afforded the ketone, 82, 0.91g, (90%).

IR 1715, 890 cm^{-1}

NMR : δ 2.2(s,3H), 1.7(s,3H), 1.8-2.2(m,4H), 2.7-2.9(t,2H), 4.9(s,2H)

4.67 1,2-Epoxy-6,6-ethylenedioxy-heptane (83)

To a solution of 81, 1.7g (0.01 mol) in methylene chloride (40mL) was added m.chloroperbenzoic acid, 2.06g (0.012 mol) dissolved in methylene chloride (40mL) drop by drop over 1 hr. under stirring at 0^{o}. Stirring continued for 3 hrs. more. The reaction mixture diluted with water (50mL) and the work up gave the epoxide 83, 1.7g (91%).

NMR : δ 1.3(s,3H), 1.4(s,3H), 2.55(s,2H), 3.9(s,4H), 1.7-2.5(m,6H).

To a solution of lithiumdisopropylamide in ether prepared from diisopropylamine, 1.01g (0.01 mol) and n-butyl lithium (prepared from lithium shavings, 0.19g (0.027 mol) and n-butyl bromide, 1.37g (0.01 mol) in ether) was added the epoxide 83, 1.86g (0.01 mol) dissolved in ether (50mL) and stirred the reaction mixture for 5 hrs. at room temp. The reaction mixture saturated with ammonium chloride, and extracted with ether (3x40mL), washed with water (2x30mL) and dried. Solvent removal and purification gave the alcohol 63a which had comparable spectral characteristics with that of 63a prepared earlier (4.49).

4.68 (E,E)-Acetoxy-8-bromo-3,7-dimethyl-octa-2,6-diene (84)

A solution of phosphorustribromide, 20.3g (0.075 mol) in ether (50mL) was added drop by drop to the solution of the alcohol 5, 10.6g (0.05 mol) in ether (100mL) at 0-5^{o} over 1 hr. under stirring. After 5 hrs. of stirring, the reaction mixture was poured into ice water (200mL), the extraction work up yielded the bromide 84, 11.8g (86%). bp 95-100^{o}/1mm.

IR : 1740, 1235, 1210 cm^{-1}

NMR : δ 1.74(s,6H), 1.98(s,3H), 2.15(s,4H), 3.94(s,2H), 4.55(d,2H), 5.37(m,1H), 5.6(m,1H)

4.69 (E,E)-8-Acetoxy-2,6-dimethyl-octa-2,6-dienyltriphenylphosphonium bromide (85)

The bromide 84, 11.0g (0.04 mol) was added in one lot to a solution of triphenylphosphine, 10.48g (0.04 mol) in benzene (9mL) and the resulting mixture was stirred at room temp. from 24 hrs. The solid separated was filtered washed with cold benzene and with a small amount of cold ether and dried to get the phosphonium salt, 85, 19.1g (89%).

4.70 (E)-Acetoxy-3-methyl-6-oxo-hex-2-ene (86)

To a solution of the epoxide 6, 10.6g (0.05 mol) in a mixture of dioxan (50mL) and water (20mL) was added periodic acid, 15.96g (0.07 mol). The resulting mixture was stirred at room temp. for

6 hrs. When TLC showed complete conversion, the reaction mixture was diluted with water and extracted with ether, in a liquid-liquid continous extractor. The ether layer was dried, solvent removed and purified by silica gel chromatography to get 86, 4.6g (54%).

IR : 1740, 1725 cm^{-1}

NMR : δ 1.65(s,3H), 2.1(s,3H), 2.0-2.3(t,2H), 2.8-3.1(m,2H), 4.6(d,2H), 5.4(t,1H), 9.75(s,1H).

4.71 1-(2,6,6-Trimethyl-1-cyclohexenyl)methyltriphenylphosphonium bromide (87)

The bromide 71, 10.85g (0.05 mol) was added to the solution of triphenyl phosphine, 13.1g (0.05 mol) in dry benzene (11mL) and the mixture was stirred at room temperature for 30 hrs. The solid separated was filtered, washed with little cold ether and dried to get the phosphonium salt 87, 21.5g (90%).

4.71 (E,E,E)-Acetoxy-3,7-dimethyl-8-oxo-octa-2,4,6-triene (89)

An excess amount of dry ice was added in portions to a mixture of 19, 0.97g (0.005 mol) and calcium hypochlorite (active chlorine 60%), 1.3g (0.0055 mol) in dichloromethane (20mL) and water (5mL) below 0^{o} under stirring. The reaction mixture was stirred for 1 hr. below 5^{o} and extraction work up gave the crude (E,E)-acetoxy-6-chloro-3,7-dimethyl-octa-2,4,7-triene (88)

The crude chloride 88 was stirred with triethylamine

N-oxide, 1.77g (0.015 mol) and copper(I)chloride, 0.05g (0.005 mol) in dioxan (5mL) at 50^{o} for 10 hrs. The reaction mixture was combined with 2.5% sulfuric acid (10mL) and ethylacetate (10mL). The reaction mixture diluted with water (20mL). The organic layer separated, washed with 2.5% sulfuric acid, saturated sodiumbicarbonate (3x10mL) and 10% sodium sulfite solution (2x10mL). The organic layer dried and solvent removed to get the aldehyde, 89, 0.63g (60%).

UV : λ_{max} 313nm (ε 40,000) ; IR : 1670, 1740 cm^{-1}

NMR : δ 1.6(s,3H), 1.7(s,3H), 2.05(s,3H), 4.6(d,2H), 5.4(t,1H), 6.1(d,1H), 6.4(d,1H), 6.8(t,1H), 9.4(s,1H)

4.73 (E)-2,2-Ethylenedioxy-7-hydroxy-6-methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-8-(p-toluenesulfonyl)-oct-5-ene (90)

To a solution of 74, 5.85g (0.02 mol) in toluene (50mL) was added a ether solution of ethyl magnesium bromide, 1.75g (0.013 mol) (prepared from ethylbromide, 1.526g (0.014 mol) and magnesium turnings, 0.316g (0.013 mol) in anhydrous ether; ethyl bromide was prepared by adding con. sulfuric acid (12.0g) in portions with shaking to 48% hydrobromic acid (41.5g). The mixture was cooled and added 95% ethanol, 10.0g (0.206 mol) and then con. sulfuric acid, 20.0g. The mixture was distilled and worked up to get 20.5g (91%) of ethylbromide) at 20^{o}. The mixture was stirred at 40-45^{o} for 3hrs. Then the reaction mixture was cooled to 25^{o} and the aldehyde 63, 1.84g (0.01 mol) in toluene (10mL) was added dropwise with stirring under nitrogen. The mixture was stirred at this temperature

for 3 hrs. more. The reaction mixture was then quenched with water (150mL) and toluene removed under reduced pressure. The residue was extracted with ether, (3x30mL), washed with water (2x40mL) brine (2x40mL) and dried. Solvent removal and purification gave the hydroxy sulfone 90.

IR : 3625, 1660, 1150, 1060 cm^{-1}

NMR : δ 1.05(s,6H), 1.35(s,3H), 1.7-1.75(d,each 3H), 1.8-2.1(m,6H), 2.1-2.6(m,4H), 2.45(s,Ar-CH_3), 3.8-3.95(m,5H), 4.8(d,1H), 5.3(t,1H), 7.4-7.8(dd,each 2 ar.H)

4.74 (E)-5-Bromo-2,2-ethylenedioxy-6-methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-8-p-toluenesulfonyl)-oct-6-ene (91)

To a dichloromethane solution (20mL) of 90, 1.78g (0.005 mol) and pyridine, 0.12g (0.0015 mol) was added phosphorus tribromide, 1.63g (0.0006 mol) at 0^{o}. The mixture was stirred at this temperature for 2 hrs. and poured into ice cold water (40mL), extracted with ether (3x30mL). Ether layer washed with sodium bicarbonate (2x30mL), brine (2x30mL), and with water (2x30mL). The organic layer was then dried, solvent removed and purified to get 91, 1.7g (82%).

IR : 1670, 1150, 1060 cm^{-1}

NMR : δ 1.05(s,6H), 1.35(s,3H), 1.7(s,3H), 1.8(s,3H), 1.9-2.8(m,10H), 2.45(s,Ar-CH_3), 3.9(s,4H), 4.2-4.6(m,2H), 5.9(d,1H), 7.4-7.8(dd,each 2 ar.H)

4.75 (E,E)-2,2-Ethylenedioxy-6-methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-5-(p-toluenesulfonyl)-octa-3,7-diene (96)

To a cooled (-7^{o}), stirred slurry of sodium hydride, 0.528g (50% oil dispersion, 0.264g NaH (0.011 mol) washed free of oil by light petroleum ether) in anhydrous dimethyl formamide (15mL) was added a solution of the sulfone 69, 3.32g (0.01 mol) in dimethylformamide (15mL) at such a rate that the internal temperature was maintained at -5^{o} to 7^{o}. The resulting red solution was stirred at this temperature for 15 min. and to this solution was added the bromide 50, 2.07g (0.01 mol) dissolved in dimethylformamide (15mL) drop by drop over 30 min. The mixture was stirred at 10^{o} for 1.5 hr. and then poured into ice cold water (25mL) and extracted with ether (3x25mL). The ether layer was washed with water (2x25mL). The ether layer was washed with water (2x25mL) and brine (2x25mL). After drying solvent was removed and purified to get the sulfone 96, 3.2g (70%).

IR : 1670, 1150, 1060 cm^{-1}

NMR : δ 0.95(s,6H), 1.4(s,3H), 1.5(s,3H), 1.7(s,3H), 1.2-2.1(m,8H), 2.45(s,3H), 3.9(s,4H), 5.3-6.1(m,3H), 6.7(m,1H), 7.4-7.8(dd,each 2 ar.H).

Similarly alkylation of the sulfone 56, 2.82g (0.01 mol) with the bromide 68, 2.57g (0.01 mol) gave the crude sulfone 97 which was used directly in the desulfonation step.

4.76 (E,E,E)-2,2-Ethylenedioxy-6-methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-octa-3,5,7-triene (92)

(a) From 91

To a solution of 91, 0.84g (0.002 mol) in cyclohexane (30mL) was added potassium methoxide, 1.4g (0.02 mol) (from potassium, 0.8g (0.02 mol) and excess anhydrous methanol) as a methanol solution (20mL) and the mixture was stirred at 40^{o} for 3 hrs. Ammonium chloride solution (20mL) was then added and the mixture was extracted with ether (2x20mL) and washed with ammonium chloride solution (2x20mL). The organic layer was dried and solvent removed to get the crude ketal 92, 0.38g (65%).

(b) From 96

To a stirred solution of sodium ethoxide, 3.4g (0.05 mol) in ethanol (40mL) was added the sulfone 96, 2.29g (0.005 mol). The mixture was refluxed for 18 hrs. The reaction mixture was cooled, ethanol removed in vacuo and the residue extracted with ether (2x50mL). The ether layer washed with water (2x30mL) and brine (2x30mL). Solvent removal after drying afforded the crude ketal which was purified to get the ketal 92, 0.94 g (73%).

Similarly the crude sulfone 97 obtained from the sulfone 56 and bromide 68 was desulfonated in the same way to yield the ketal 92 in 70% yield.

UV : λ_{max} 290nm.

IR (CCl_4) : 2960, 1450, 1370, 1040, 970 cm^{-1}

NMR : δ 1.9(s,6H), 1.5(s.3H), 1,65(s,3H), 1.9(s,3H), 1.2-2.1(m,6H), 3.90(s,4H), 5.6(d,1H), 6.0(d,1H), 6.0-6.1(m,3H), 6.7(d,1H).

4.77 (E,E,E)-6-Methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-oxo-octa-3,5,7-triene (93) (ß-C_{18} Ketone)

The solution of the ketal 92, 0.29g (0.001 mol) and p-toluene sulfonic acid (10mg) in 6:1 aqueous acetone (20mL) was gently refluxed for 2 hrs. The mixture was cooled, acetone removed under reduced pressure and the work up afforded the ß-C_{18} ketone, 0.22g (90%).

UV : λ_{max} 350nm (ε 28,400)

IR (CCl_4) : 1660, 1570, 1265, 1145, 970 cm^{-1}

NMR (CCl_4) : δ 1.1(s,6H), 1.5-1.55(m,4H), 1.7(s,3H), 2.0-2.1(m,5H), 2.2(s,3H), 5.9-6.2(m,4H,J=15.0), 7.4(m,1H).

4.78 (E,E)-1-Acetoxy-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-9-(p-toluenesulfonyl)-nona-2,6-diene (102)

To a cooled (-7°), stirred slurry of sodiumhydride, 0.528g (50% oil dispersion, 0.264g NaH, (0.011 mol), washed free of oil with pet. ether) in anhydrous dimethylformamide (15mL) was added a solution of the sulfone, 74, 2.92g (0.01 mol) in dimehtylformamide (15mL) at such a rate that the internal temperature was maintained at -5° to -7°. The resulting red solution was stirred at this temperature for 15 min. and to this solution was added the bromide 84, 2.75g (0.01 mol) dissolved in dimethylformamide (15mL), drop by drop over 30 min. The mixture was stirred at 10° for 1.5 hrs. and then poured

into ice cold 4% sulfuric acid (25mL) and extracted with ether (4x20mL). The ether layer was washed with sodium bicarbonate (2x25mL), water (2x25mL) and brine (2x25mL). After drying solvent was removed in vacuo to yield a viscous liquid which failed to crystallise even after repeated attempts, 3.35g (69%). The sulfone 102 was used as such in the next step.

4.79 (E,E,E)-1-Acetoxy-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)-nona-2,6,8-triene (103) (11,12 Dihydrovitamin A acetate)

(a) From 31 and 85

To a solution of n-butyl lithium in ether (prepared by adding n-butyl bromide, 1.35g (0.01 mol) in ether (10mL) to lithium shavings, 0.173g (0.025 mol) suspended in anhydrous ether (10mL) and stirring the reaction mixture for 1 hr. at -20^{o}) was added the phosphonium salt, 85, 5.91g (0.01 mol) suspended in ether (20mL). The scarlet red phosphorane was formed instantaneously. Stirring was continued for 15 min. The colour was then faded into a rose colour. To this phosphorane solution, was added ß-cyclocitral (31), 1.67g (0.11 mol) as solution in ether (16mL), drop by drop. Stirring continued for 5 hrs. at room temperature. When TLC showed disappearance of starting material, cold water (50mL) was added to the reaction mixture and extracted with ether (2x50mL). The ether layer washed with brine (2x30mL), water (2x30mL) and dried. Solvent removal and purification afforded 103 as a dark yellow viscous oil, 2.45g (74%).

(b) From 102

To a stirred solution of freshly prepared sodium ethoxide, 3.4g (0.05 mol), (prepared from sodium, 1.15g (0.05 mol) and ethanol, 25mL) was added the sulfone 102, 2.43g (0.005 mol). The mixture was refluxed for 18 hrs. The reaction mixture was cooled, ethanol was removed under reduced pressure and the residue dissolved in ether (50mL). The ether layer was washed with water (2x20mL) and brine (2x20mL). Solvent removal afforded the corresponding alcohol. The crude alcohol was then mixed with 2:1 acetic anhydride-pyridine (20mL) and stirred for 24 hrs. at room temperature. The reaction mixture was diluted with water (50mL) and extracted with ether (3x30mL). The ether layer washed with sodium bicarbonate (2x30mL), brine (2x30mL) and water (2x30mL). Drying, solvent removal and purification gave a dark yellow viscous oil, 1.0g, (60%).

UV : λ_{max} 272nm

NMR : δ 1.0(s,6H), 1.65(s,3H), 1.85(s,3H), 1.95(s,3H), 1.8-2.5(m,10H), 2.05(s,3H), 4.7(d,2H,J=7.0), 5.5(t,1H,J=7.0), 6.0-6.15(m,3H,J=7.0)

4.80 (All E)-1-Acetoxy-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)-nona-2,4,6,8-tetraene (101) (Retinyl acetate, Vitamin A acetate)

To a solution of n-butyl lithium in ether (10mL) prepared from n-butyl bromide, 0.69g (0.005 mol) and lithium shavings, 0.087g (0.0125 mol) was added the phosphonium salt 87, 2.4g (0.005 mol) suspended in ether (15mL) at -10^{o}. The red coloured phosphorane was formed instantaneously. The reaction mixture was allowed to

stir for further 15 min. To this phosphorane solution was added a solution of the aldehyde 89, 0.85g (0.005 mol) in ether (10mL). The reaction mixture was stirred for 6 hrs. and then poured into ice cold water (50mL) and extracted with ether (2x40mL). Ether layer washed with water (2x30mL), brine (2x30mL) and dried. Solvent removal gave 101 as a light yellow viscous oil, 1.16g (71%).

UV : λ_{max} 325nm (ε 48,500)

NMR : δ 1.0(s,6H), 1.65(s,3H), 1.85(s,3H), 1.95(s,3H), 2.0(s,3H), 4.75(d,2H, J=7.0), 5.55(t,1H,J=7.0), 6.0(d,1H,J=7.0), 6.1(s,2H), 6.25(d,1H,J=7.0), 6.6(dd,1H,J=12.0).

CONCLUSION

Vitamin A (Retinol) because of its wide biological applications especially in the fields of vision and cancer therapy, has gained importance in the scientific and clinical world, as a versatile molecule. Attempts have been made in this work to find new synthetic routes to Vitamin A, based on easily available natural products. The potential of a few commercially available chemicals for the synthesis of Vitamin A, is also demonstrated.

In the introduction which is not exhaustive, an attempt has been made to reflect the contemporary interest and excitement in retinoid research. The evolution of Vitamin A as an important and interesting molecule through the years is also briefly outlined.

Over these years, the synthesis of Vitamin A has been achieved in a number of ways. Almost all conceivable combinations have been used to build the C_{20} retinoid skeleton. But, the development of new methods of olefin formation, discovery of new and efficient reagents as well as realization of improved yields in various steps in the known syntheses of retinoids reported in recent literature makes it meaningful to try to develop more efficient routes for the synthesis of retinoids.

In this work, different approaches for the synthesis of Vitamin A are investigated, based on geraniol and citral - the two important monoterpenes which are the major constituents of palmarosa and lemongrass oils respectively. By retrosynthetic analysis,

Vitamin A molecule can be disconnected into a cyclic and a linear unit. Different cyclic and linear units have been synthesised, to be used as intermediates in different synthetic schemes.

The C_{10} and C_{13} cyclic units namely ß-cyclocitral and ß-ionone employed in the study are derived from citral. Acid catalyzed cyclization of Schiff bases of citral gave ß-cyclocitral, while cyclization of pseudoionone, the aldol condensation product of citral and acetone, gave ß-ionone, as the major products under specific conditions. Different derivatives of ß-cyclocitral and ß-ionone like the corresponding alcohol, bromide, sulfone etc. have been used in the synthetic schemes investigated.

The C_{10} linear conjugated unit has been synthesized from geranylacetate. Organoselenium and organosulfur mediated internal allylic oxidation of geranylacetate and its further manipulation gave the all E triene ester. This has been terminally functionalised through ene-chlorination. Conjugated diene synthesis effected in the side chain of steroid molecules has been successfully extended to geranylacetate to synthesize the required conjugated triene. The attempted internal allylic oxidation of geranylacetate using PDC-TBHP was unsuccessful.

Synthesis of ß-cyclocitral through cyclisation using organoselenium and organosulfur reagents were unsuccessful, while the attempt through the retroaldol condensation of ß-ionone was only partially successful. The utility of 2-acetylbutyrolactone and levulinic acid as convenient sources of C_5 units in the synthesis of Retinol has been demonstrated. A new $C_5 + C_3$ approach has been developed

for the synthesis of methylheptenone, a key intermediate in the synthesis of monoterpenoids, Vitamin A and perfumery chemicals. A synthesis of the C_8 intermediate used in the BASF industrial process for Vitamin A, and its conversion to allylic functionalised methyl heptenone has been achieved.

In the synthetic schemes outlined below the products formed were a mixture of stereoisomers. In the coupling reactions it is asssumed that all E isomers are formed as the major products along with small amounts of other isomers. No attempt has been made to isolate and characterise all the minor isomers. To restrict the problem to a reasonable scope, only all E compounds were considered. Considering the lability of the polyenes to light and heat, no attempt has been made to completely purify the products.

The different modes of combination used in the present study for the synthesis of Vitamin A are $C_{10} + C_8 + C_2$, $C_{13} + C_5 + C_2$, $C_{13} + C_7$ and $C_{10} + C_{10}$. Olefin forming reactions like Wittig reaction, sulfone-alkylation and sulfone-condensation have been used to build the C_{20} retinoid skeleton.

Using the $C_{10} + C_8 + C_2$ and $C_{13} + C_5 + C_2$ approaches, Vitamin A synthesis has been achieved though the well known ß-C_{18} ketone intermediate. Thus ß-C_{18} ketone was synthesized using these two approaches. While sulfone-condensation has been employed in $C_{10} + C_8$ approach, it was not successful in the case of $C_{13} + C_5$ approach. Hence sulfone-alkylation approach has been employed to

get the target molecule. The reverse combination was also successful in this case. Since the conversion of ß-C_{18} ketone to Vitamin A is well established, these approaches constitute formal syntheses of Vitamin A.

Using a linear C_7 unit derived from geranylacetate, Vitamin A synthesis has been tried by a C_{13} + C_7 approach. This attempt was not successful.

Finaly, the C_{10} + C_{10} approach has been successfully employed to build the C_{20} skeleton using the cyclic and the linear conjugated C_{10} units, derived from citral and geraniol respectively. Thus through the Wittig condensation, a synthesis of Vitamin A acetate has been achieved in which all the twenty carbon atoms of the target molecule were derived from easily available natural sources. Similarly 11, 12 dihydrovitamin A acetate has been synthesised, however its attempted conversion to Vitamin A proved to be unsuccessful.

The work reported here consists of attempts made to contribute a little more to the everwidening horizon of synthetic retinoid chemistry. The topic of retinoid chemistry has been under investigation for about seven decades and yet remain synthetically challenging and biologicaly important. The progress made in the retinoid research in the past decades has been indeed great, and it is anticipated that major advances concerning the chemistry, biology and potential clinical uses of retinoids, will continue to be made in the years to come.

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