STUDIES ON THE SYNTHESIS OF PRELOG-DJERASSI LACTONE USING BAEYER-VILLIGER REACTION

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CERTIFICATE

Certified that this thesis is based on the work done by Mr. Sonny Sebastian 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.

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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 (Retd.), Department of Applied Chemistry, Cochin University of Science and Technology and has not been included in any other thesis submitted for the award of any degree.

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CONTENTS

ABSTRACT

Prelog-Djerassi lactone is a key degradation product of a number of macrolide antibiotics like Methymycin, Narbomycin, Erythromycin etc. The synthesis of this ten carbon molecule with four asymmetric centres has helped synthetic chemists to achieve the stereoselective synthesis of many macrolide antibiotics. Though it was isolated in 1956, its first stereoselective synthesis was achieved only in 1975. Thereafter a number of syntheses of the Prelog-Djerassi lactone in the recemic as well as in the optically active forms have been achieved. In the present work two new approaches have been developed for the synthesis of recemic Prelog-Djerassi-lactone.

In the first approach exo-dicyclopentadiene was converted to exo-dicyclopentadienol by selenium dioxide oxidation and was then oxidised to exo-dicyclopentadienone. A stereoselective conjugate addition of methyl group was carried out on exo-dicyclopentadienone using dimethyl copper lithium to obtain β-3-methyl tricyclo[5.2.1.$0^{2,6}$]-dec-8-en-5-one. This ketone was converted to β-2-methyl-4-ethylene dioxy bicyclo[3.3.$0^{1,5}$]octan-6,8 -dicarboxaldehyde

by ketalization of carbonyl group followed by oxidative cleavage of the double bond and the aldehyde groups present in the resulting compound were converted to methyl groups. Subsequent deketalization resulted in the formation of β-4-methyl α-6,8-dimethyl bicyclo[3.3.$0^{1,5}$]octan-2-one. The resulting bicyclic ketone was subjected to Baeyer-Villiger oxidation to afford a pair of lactones which were separated and treated with methyl lithium to get 2-(1-hydroxy α-3,5-dimethyl) cyclopentyl-2-oxo β-4-methyl-4-butane and 2-(1-acetyl -3,5-dimethyl) cyclopentyl-2-(β-2-methyl) ethanol. These two methyl ketones were independently subjected to Baeyer-Villiger oxidation and subsequent saponification followed by oxidation lead to a single product, namely 2-(1-oxo α-3,5-dimethyl) cyclopentyl-β-2-methyl-2-acetic acid. This keto acid on Baeyer-Villiger oxidation gave a mixture of products from which the Prelog-Djerassi lactone was isolated.

In the second method, dehydronorcamphor was alkylated using α-chlro methyl propanoate to get methyl-3-(2-oxo bicyclo[2.2.1] hept-5-en)2-propanoate. Protection of the carbonyl group of the alkylation product as ethylene ketal and subsequent oxidative cleavage of the double bond lead to a methyl ester with two aldehyde groups.

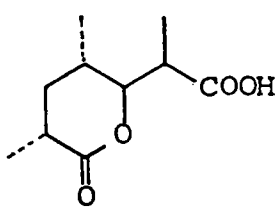
The aldehyde groups were converted to methyl groups and subsequent deketaliaation followed by esterification afforded methyl 2-(1-oxo-∝-3,5-dimethyl)cyclopentyl-2-propanoate. Baeyer-Villiger oxidation of this keto ester gave two lactones from which methyl ester of Prelog-Djerassi lactone was isolated.

CHAPTER I

INTRODUCTION

1.1 INTRODUCTION

Prelog-Djerassi lactone (1) occupies a prominent position in the Chemistry of macrolide antibiotics having served a key role both in their structure elucidation and synthesis. It was isolated independently by V.Prelog[1] and C.Djerassi[2] in 1956 as the degradation product of macrolide antibiotic Narbomycin and Methymycin respectively. This lactone is also an important intermediate for the synthesis of macrolide antibiotics by the application of new methods that allow the stereoselective elaboration of cyclic and acyclic carbon skeleta bearing a number of contiguous and/or alternating stereocentres.



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1.2 MACROLIDE ANTIBIOTICS

Antibiotics are chemical substances derived from microorganisms which have the capacity of inhibiting growth, and even destroying other microorganisms in dilute solution. Antibiotics have found extensive application in the treatment of infectious diseases of man, animals and to a smaller extent plants.

The term macrolide was originally applied to a group of basic antibiotics with a macrocyclic lactone ring in their chemical structure. Macrolides can be defined and distinguished from other groups of antibiotics by the unique feature of their chemical structure. They are poly-functional macrocyclic lactones and the majority of them contain at least one amino sugar moiety which is the cause of basicity of the molecule. Neutral macrolides containing only neutral sugar moiety are also known.

The chemistry of macrolide antibiotics originated with the isolation of Pikromycin by Brockmann and Henkel in 1950.[3] Soon afterwards streptomyces organisms yielded several other antibiotics which appeared to be chemically and antimicrobially related to Pikromycin. By the end of 1957 the elegent execution of classical chemical degradation of these antibiotics had led to the disclosure of the gross structure of Methymycin,[2] Erythromycin A[4] and B[5] and Carbomycin A[6-9] - demonstrating that each of them contains a lactone incorporated in a medium or large ring system. As the number of lactonic natural products has increased to well over one hundred, the word "macrolide" originally[6] restricted to the above antibiotics has gradually been used in a broader sense and in some cases overextended to cover even a macrocyclic lactam of plant origin.[10,11]

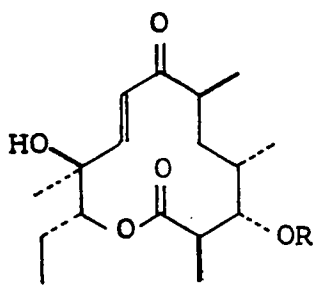
In the field of antibiotics the total synthesis of penicillins, cephalosporins and tetracyclins had already been completed by the end of the sixties. Thus the macrolides were the only remaining major family of antibiotics which presented an academic challenge to synthetic chemists. The macrolide antibiotics have also received due attention from the view points of both their biosynthesis and mode of antimicrobial activity.

1.2.1 Classification

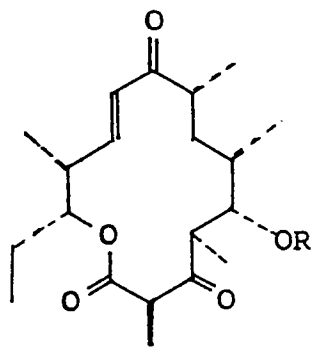
Because of the vast number of lactonic natural products commonly referred to as macrolides, a classification of these compounds into subgroups would now appear to be in order.

1.2.1.1 Polyoxomacrolides

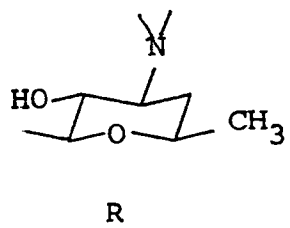
These are 12, 14 or 16 membered lactones. Other features are (1) an array of substituents uniquely and systematically attached to the ring system and (2) the linkage of one or more sugars, very often one of them being nitrogen containing, eg., Methymycin (12 membered) Narbomycin and Erythromycin (14 membered) and Tylosin[12] (16 membered).



Methymycin



Narbomycin



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1.2.1.2 Polyene macrolides[13]

In this class the lactone ring carries few alkyl substituents and accommodates a conjugated polyene containing upto as many as seven E double bonds. The size of the lactone enlarges to 38 members in some compounds. Most of them are antifungal and not antibacterial agents. eg. Amphotericin B.

1.2.1.3 Ionophoric macrolides

Macrolides of this group contains two or more lactone groups in a very large ring system. An antibiotic of this group has a hydrophilic hole capable of binding an alkali metal cation and thus of transporting ions in biological system. eg. Nonaction.[14,15]

1.2.1.4 Ansamycin[16,17]

More than 10 antibiotics possess a unique structure in which two nonadjacent positions of an

aromatic nucleus are connected by a long aliphatic bridge through an amide. Therefore this group does not belong to the macrolide in the correct sense but is included herein because of the close similarity of the aliphatic chain in structure and stereochemistry to that of the polyoxo-macrolides. Most of the Ansamycins are noted for their broad spectra of antibacterial activity and are also interesting as potential antitumor agents. eg. Rifamycin, Streptovaricin, Magtensin etc.

1.2.1.5 Other macrolides

Under this heading are listed several lactonic compounds of medium ring size which have not thus far grown into large families. Most of these lactones are of either mold or bacterial origin and exhibit varying biological activities. eg. Zearalenone,[18] Curvularin,[19] Pyrenophorin[20] etc.

1.2.2 Biosynthesis

Many reports[21,22] on the biosynthesis of macrolide antibiotics have appeared concomitant with the progress in analytical methods using labelled compounds (^{3}H, ^{14}C), ^{13}C NMR, blocked mutants, and inhibitory agents. Recently molecular microbiology has been applied

to the elucidation of macrolide pathways. The polyoxo-macrolide antibiotics, polyenes and the bridge system of Ansamycins are formed from simple metabolic intermediates like acetate, propionate, malonate, 2-methyl malonate, butyrate etc., much in the same manner as saturated long chain fatty acids are biosynthesised. Monomers with activated carboxyl group -(Thiol esters of Co-enzyme A or a Poly enzyme synthase) condense in rapid stepwise fashion with their carboxylated derivatives (malonate, 2-methyl malonate etc.) to yield a long chain polyoxo fatty acid which after a minimum of one biological reduction can form a lactone.

Grisebach in 1978[23] classified the biogenetic origin of macrolides into three groups:

1. Macrolides biosynthesised from propionate units
2. Macrolides derived from acetate and propionate units
3. Macrolides containing in addition to acetate and propionate units, butyrate or its biological equivalent.

Isotope labelled studies on growing culture of streptomyces Venezuleae using a mixture of CH_3-^{14}C methionine, 1-^{14}C and 2-^{14}C-propionic acid, 2-^{14}C-pyruvic

acid, 1-^{14}C formic acid, 1-^{14}C acetic acid and diethyl 2-^{14}C-malonate showed that 1-^{14}C-propionic acid and 2-^{14}C-propionic acid were incorporated exclusively in the aglycone of 12-membered macrolides. Most of CH_3-^{14}C-methionine was incorporated into the molecule of desosamine. Thus five propionic acid and one acetic acid units are used for the biosynthesis of methymycin (12-membered macrolide antibiotic) by the polyketide pathway.[24]

Degradation studies on the labelled macrolides showed that the lactone ring of erythromycin-A (14-membered macrolide antibiotic) is derived from seven propionate units. Friedmann et al. in 1964[25] proved that only one propionate unit was incorporated directly into the ring and other six propionate units were incorporated via methyl malonate.

According to Srinivasan and Srinivasan[26] the aglycone carbons of magnamycin-B (16 membered macrolide antibiotic) are derived from nine acetate, one propionate and one methionine units. ^{13}C NMR spectra suggested that Leucomycin-A3 is derived from five acetate, one propionate, one butyrate, one methionine and two unknown

carbon units. ^{13}C NMR spectra of Tylosin obtained from the culture showed that the aglycone of Tylosin was derived from two acetate, five propionate and one butyrate units.

The Lankacidin group[27] comprises 17-membered macrolide antibiotic. By the ^{14}C-labelled studies it was confirmed that the formation of a linear polyketide chain was initiated by glycine and was followed by the incorporation of eight acetic acid units with methionine responsible for the four branching methyl groups.

1.2.3 Antimicrobial Activity

Macrolide antibiotics are highly active against gram positive bacteria and mycoplasmas and hence are effective when administered orally against infectious diseases caused by these microorganisms.[28] Among numerous macrolide antibiotics discovered during the past 35 years erythromycin, oleandomycin, leucomycin, spiramycin, josamycin, midecamycin and tylomycin are therapeutically and economically important drugs and hence have been produced industrially.[29]

The mode of action of the macrolides was initially studied with erythromycin-A and a comparison has been made with a limited number of other macrolides.[30,31,32] There appears to be general agreement that all macrolide antibiotics affect protein synthesis in suceptible bacteria, mostly the gram-positive group. However, cellfree studies have shown that erythromycin inhibits protein synthesis in system from gram-negative bacteria. When the intra-cellular concentration of the antibiotic is high enough, intact cells of both groups are inhibited. The difference seems to be in their ability to accumulate the drug and there even seems to be some barrier to this process is highly sensitive gram-positive cells.[33]

Erythromycin-A inhibits the growth of bacteria and the mechanism of action involves a stoichiometric binding of high affinity of one molecule of the Erythromycin to a highly specific "site" on the 50s ribosomal submit. It appears that this occurs only at best, when the 50s unit is in the free state and that the Erythromycin/50s ribosomal adduct is able to form ribosomal assemblies (70s polysomes) which may function in

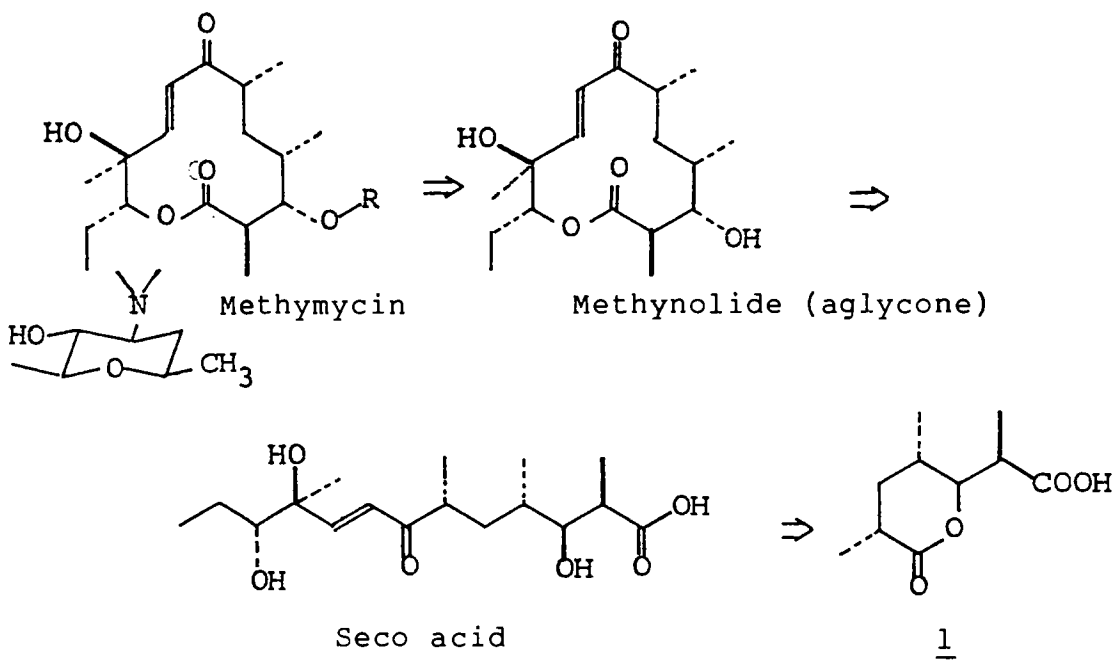
the synthesis of bacterial protein. On the average, however, these assemblies do not behave normally and overall cellular protein synthesis is disturbed.[31,33]

There is some controversy as to which part of the ribosome cycle is the primary target of the disturbance. Some macrolides appear to inhibit the action of Peptidyl synthetase, an enzyme activity which promotes the formation of a new amino acyl bond in the growing polypeptide chain. The study of Erythromycin action used radio active antibiotics of high specific activity and most comparison with other macrolides have depended on their ability to displace this Erythromycin from its binding site on the 50s ribosomal unit.[31,32]

In principle the macrolide antibiotics should be capable of inhibiting mammalian mitochondrial protein synthesis on this process is very similar to that in bacteria. Apparently Erythromycin (and presumably other useful macrolides) is unable to penetrate the mitochondrial membrane and for this reason it is not a cytotoxic agent.[31] This is in contrast to some other antibiotics with similar mode of action (chloramphenicol).

1.3 SYNTHESIS OF (±) PRELOG-DJERASSI LACTONE

The fascinating structural features of the macrolide antibiotics have, in the past, tempted synthetic organic chemists to explore feasible approaches to synthesise these compounds. Since the stereochemical relationships present in Prelog-Djerassi lactone are found in other macrolides and ionophore antibiotics, the strategies and tactics that have been developed for its assemblage may be extended to the stereoselective synthesis of those more complex natural products. Retrosynthetic analysis of a 12-membered macrolide antibiotic methymycin reveals the significance of the Prelog-Djerassi lactone as an attractive synthetic intermediate for the synthesis of macrolide antibiotics.

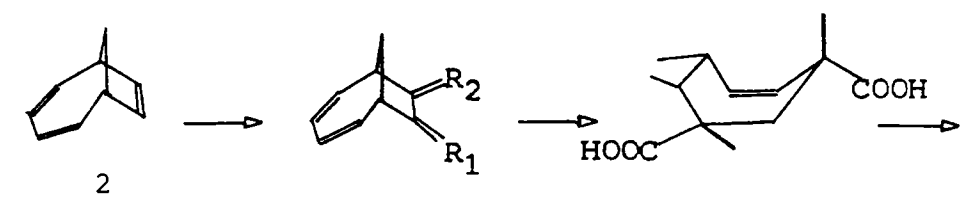


It is therefore not surprising that Prelog-Djerassi lactone has emerged as one of the standard benchmarks against which new methodology for effecting stereoselective carbon-carbon bond construction and functionalization of carbon frameworks is measured and at present nearly 40 successes in the venture have been reported. The majority of approaches to the synthesis entails the establishment of the chiral centres on acyclic precursors.

The first synthesis of Prelog-Djerassi lactone was reported by Bergelson and Batrakov in 1963[34] before the complete three dimensional structure was known.[35] Their route involved the reduction of a B-keto ester affording different diastereomeric products depending on the choice of reducing agent. They claimed that reduction with lithium aluminium hydride in ether at -65°C, with subsequent hydrolysis and purification, affords 28% yield of recemic Prelog-Djerassi lactone having m.p. 125-128°C. But the isomer isolated from this reaction was apparently incorrectly identified as the Prelog-Djerassi lactone by IR comparison with an authentic sample. Although all the C-2, C-3 stereomers were prepared, it is not possible to evaluate the stereo selectivity of these reduction from

the published information.[34] Later Yamaguchi et al.[36] repeated this synthesis and proved that the above one is a non-stereo selective synthesis.

Masamune et al.[37] carried out the first successful synthesis of Prelog-Djerassi lactone in 1975 (Scheme 1).



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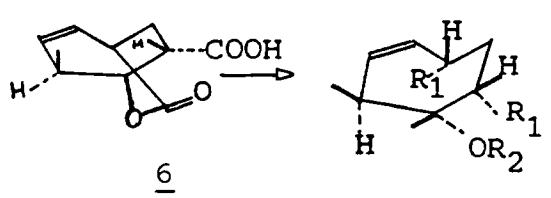
3 R_1 - OH, H; R_2 - H_2 5

4 R_1 - O; R_2 - CHOH



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7 R_1 - CH_2OH; R_2 - H

8 R_1 - CH_2OTS; R_2 - TMS

9 R_1 - CH_3; R_2 - TMS

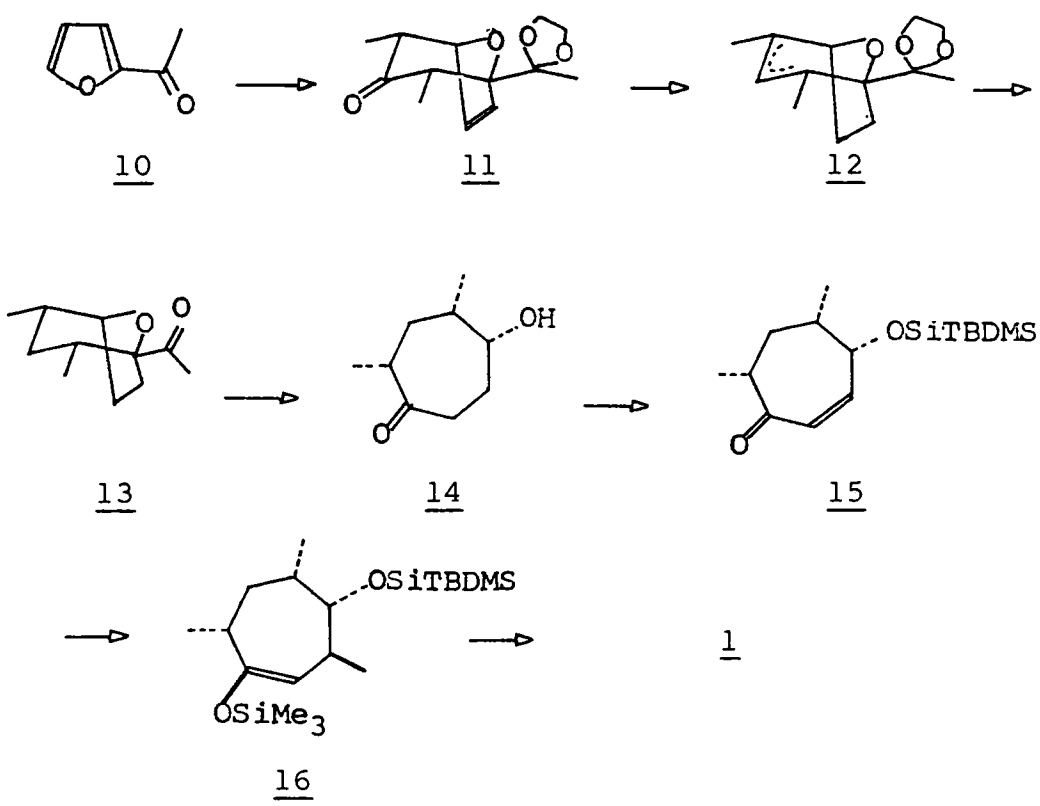
Scheme 1

Readily available bicyclo [4.2.1] nona-2,4,7 triene (2), obtained by means of pyrolysis of tricyclo [4.2.1] nona-3,7-diene,[38] was hydrated with bis-(3-methyl-2-butyl)borane and oxidative workup to provide the exo-hydroxy compound 3 in 75% yield.[39] It was then oxidised

to ketone 4 followed by formylation, sodium-m-periodate treatment and *m*-CPBA oxidation led to a 7:3 mixture of cis and trans epoxy dicarboxylic acids 5, which were further converted to lactonic ester 6 by treatment with CH_2N_2 and lithium dimethyl cuprate.[40] The 6 was then reduced with lithium aluminium hydride to triol 7. The two primary hydroxy groups were tosylated and the secondary one was trimethyl silylated to produce compound 8. Lithium dihydro cuprate,[41] a reagent developed for the present purpose, cleanly removed the tosyl group (without elimination of the homo allylic tosyl group) (without elimination of the homo allylic tosyl group) and the resulting cycloheptene derivative 9 was subjected to Lemieux-Rudloff oxidation[42] to lead directly to (±) Prelog-Djerassi lactone.

In another approach J.D.White et al.[43] synthesised (1) starting from 2-acetyl furan (10) (Scheme 2). The ethylene ketal of 10 was converted to an addition product 11 with 2,4 dibromopentan-3-one which was reduced to an alcohol followed by hydrogenation and treatment with methanesulphonyl chloride gave a mixture of two olefins 12. The 12 was deketalized and hydrogenated to a single saturated ketone 13 which was subjected to Baeyer-Villiger

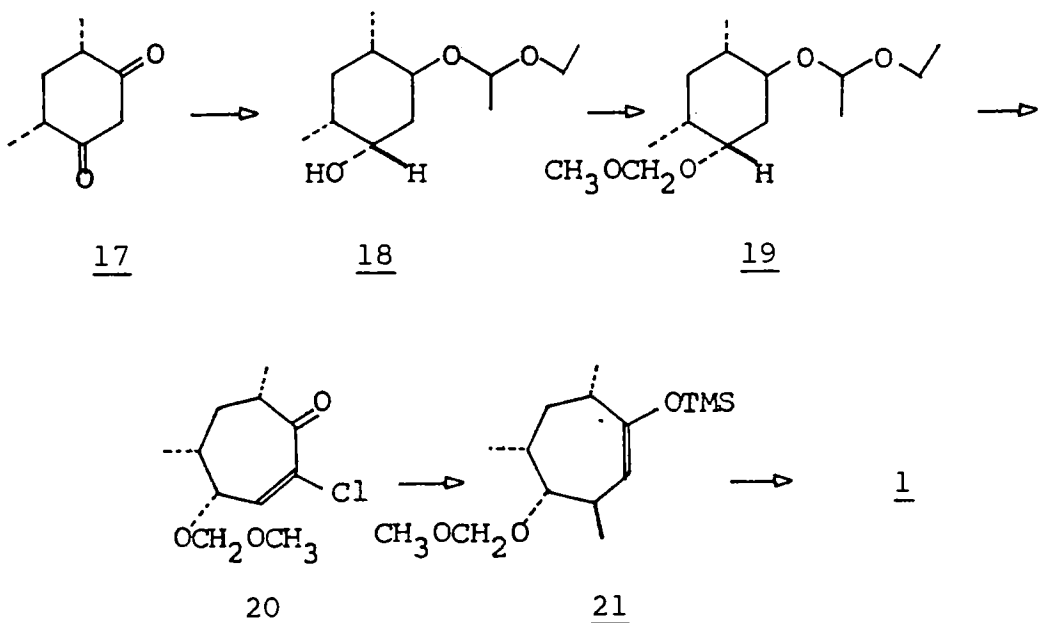
oxidation, saponification, mesylation followed by treatment with tetra n-butyl ammonium formate followed by saponification yielded 14. The hydroxyl function was protected and an enone function was introduced by deprotonation with lithium - 2,2,6,6 tetramethyl Piperidide followed by quenching with phenyl selenyl chloride and further oxidation gave 15. It was then treated with lithium dimethyl cuprate and the enolate was trapped with trimethyl silyl chloride to yield 16. The 16 was ozonized followed by reduction, deprotection and oxidation led to (±)1 in good yield.



10 11 12 13 14 15 16 1

Scheme 2

G.Stork et al.[44] have reported a stereo controlled and efficient synthesis of recemic 1 (Scheme 3). Cis-4,6-dimethyl cyclohexane 1,3-dione (17) was treated with treated with ethylvinyl ether followed by reduction with lithium selectride[45] gave the desired alcohol 18 which was then treated with chloromethyl ether in the presence of ethyldiisopropylamine afforded acetal 19. A methylene equivalent was introduced by treatment with dichlorocarbene followed by reaction with acetic acid and sodium acetate to get 20. It was then treated with lithiumdimethyl cuprate followed by reductive dehalogenation, treatment with acid and trimethylsilylchloride obtained 21 in very good yield. Ozonolysis followed by oxidation afforded (±1).

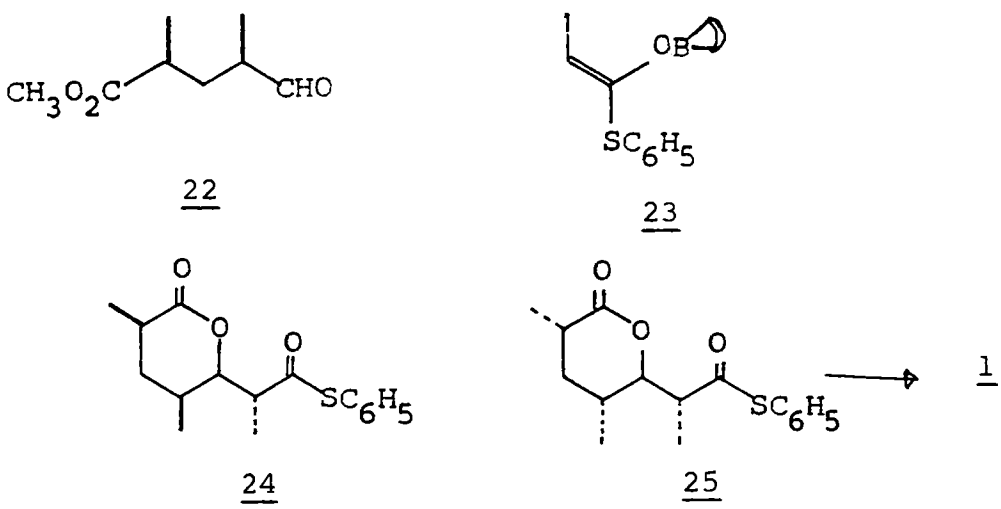


17 18 19

20 21 1

Scheme 3

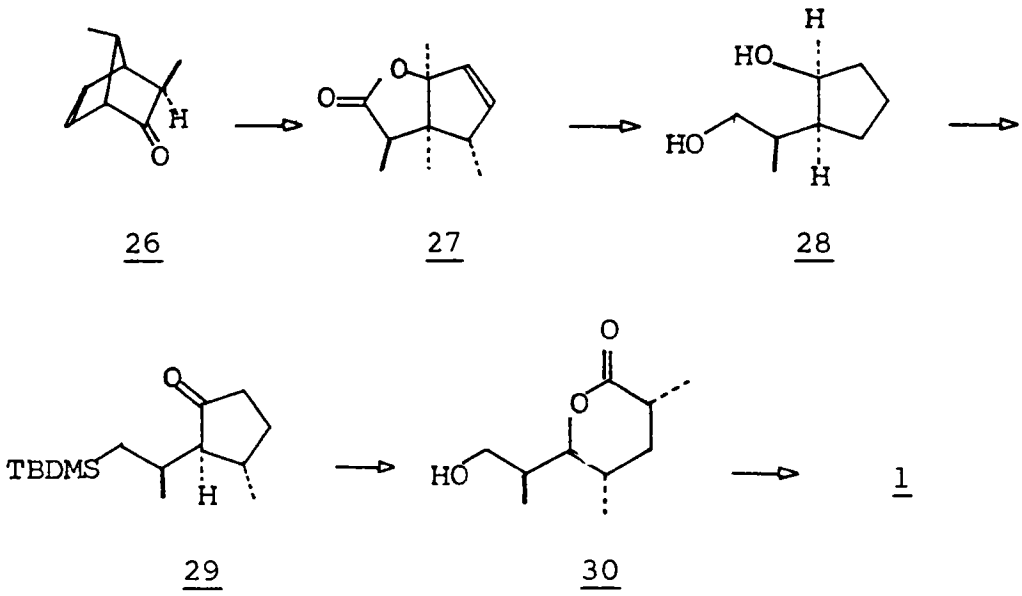
In 1979 Masammune[46] reported another method (Scheme 4) in which Meso-2,4-dimethyl glutaric acid anhydride underwent methanolysis afforded corresponding half methyl ester which was in turn converted to the aldehyde ester 22. Reaction of 22 with vinyloxyborane 23 followed by treatment with CF_3COOH in CH_2Cl_2 afforded two



Scheme 4

lactonic acid thiol esters 24 and 25 which were readily separated through SiO_2 column chromatography. The thiol ester 24 on hydrolysis with $Hg(CF_3CO_2)_2$ provided one isomer of Prelog-Djerassi lactone.

P.A.Grieco et al.[47] in 1979 recorded an efficient synthesis of Prelog-Djerassi lactone in both recemic and optically active forms (Scheme 5). Bicyclo [2.2.1] heptenone was methylated to get 26 which was subjected to Baeyer-Villiger oxidation afforded a lactone which smoothly rearranged to bicyclic lactone 27. Reduction of 27 followed by hydrogenation provided the crystalline diol 28. The primary hydroxyl group was protected as its tert. Butyldimethyl silyl ether and subsequent Collin's oxidation afforded cyclopentanone derivative 29. The ketone 29 was then subjected to Baeyer-Villiger oxidation followed by methylation gave 30. Desilylation followed by Jones oxidation afforded (±1) in very good yield.

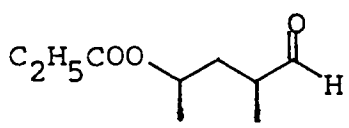


26 27 28

29 30

Scheme 5

A total synthesis of recemic Prelog-Djerassi lactone was introduced by Bartlett et al.[48] (Scheme 6). An aldehyde ester 31 readily prepared from Meso-2,4-dimethylglutaric anhydride was condensed with ethyl 2(triphenylphosphoranylidene) propionate followed by alkaline hydrolysis furnished a stereochemically pure erythro acid 32 in almost quantitative yield. Selective Fischer esterification on the non-conjugated side afforded 33 which was then reduced with diisobutyl aluminium hydride to get an aldehyde acid 34 which was then cyclized with mercuric acetate afforded a mixture of epimeric acetals 35. The demercuration was carried out with alkaline $NaBH_4$ and subsequent hydrolysis and oxidation afforded a recemic mixture of 1 in 95% yield.



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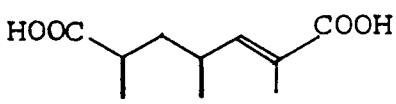

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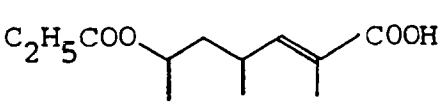

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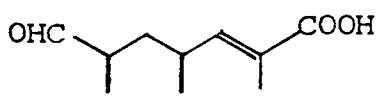

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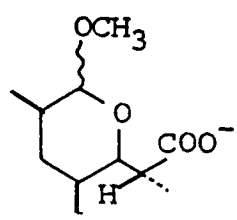

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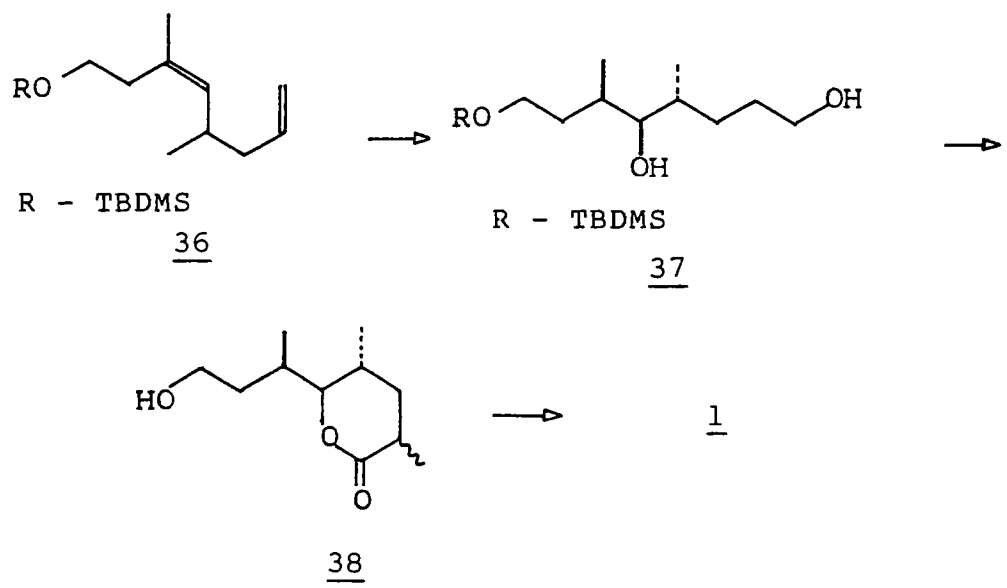
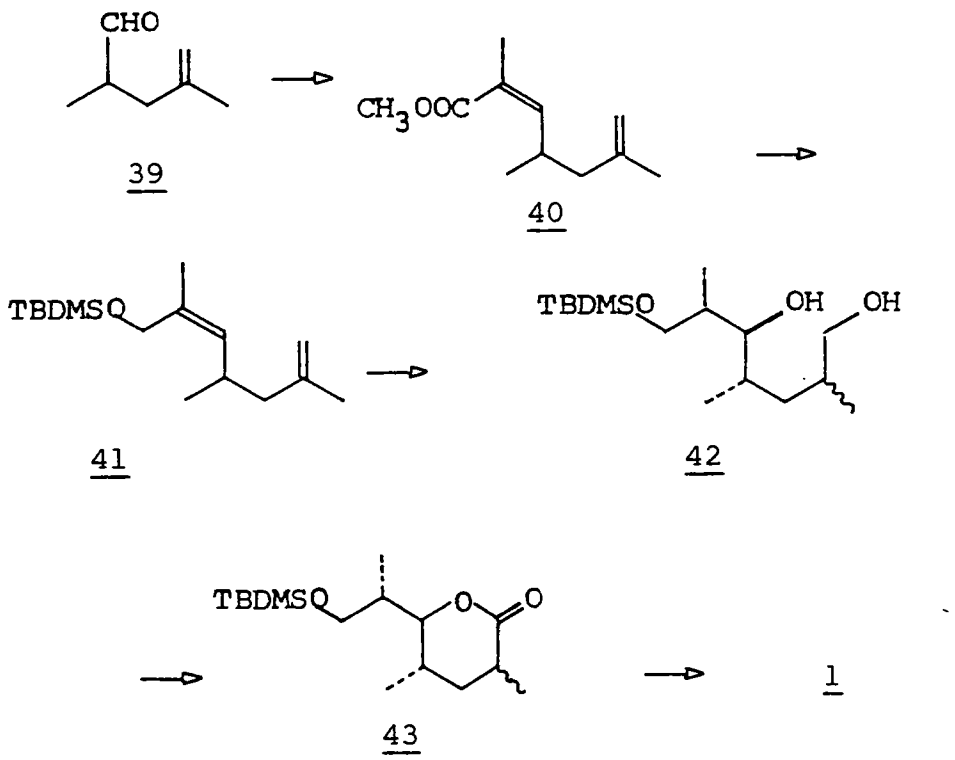
Scheme 6

D.J.Morgan et al.[49] in 1981 introduced a method for the synthesis of recemic (1) (Scheme 7). In this method substituted 1,5-diene was subjected to cyclic hydroboration and the major product 1,5-diol could be converted to the required lactone after a series of transformations. The silylether 36 upon hydroboration and oxidation afforded a mixture of diols from which the major product 37 was separated efficiently by flash chromatography. Oxidative cyclization, alkylation and silylether hydrolysis yielded the hydroxy lactone 38 which was then subjected to one carbon degradation followed by oxidation afforded (±1) identical in all respects with an authentic sample.



Scheme 7

W.C.Still et al.[50] published an intramolecularly directed hydroboration provides high asymmetric induction for the synthesis of Prelog-Djerassi lactone (Scheme 8).

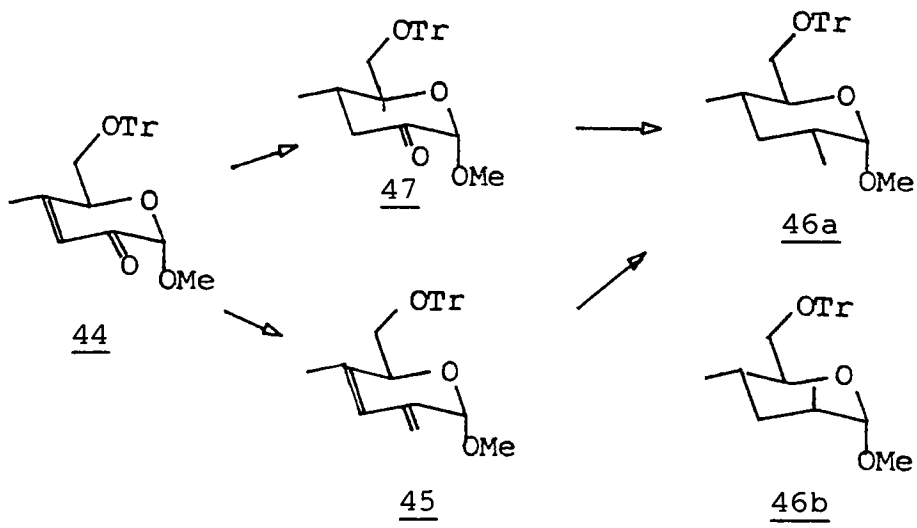


Scheme 8

The aldehyde 39 was subjected to kinetically controlled Horner-Emmons like olefination using the sodium salt of trimethylphophonopropionate to yield an unsaturated ester 40 and it was reduced with lithium aluminium hydride followed by protection of the hydroxyl group afforded 41.

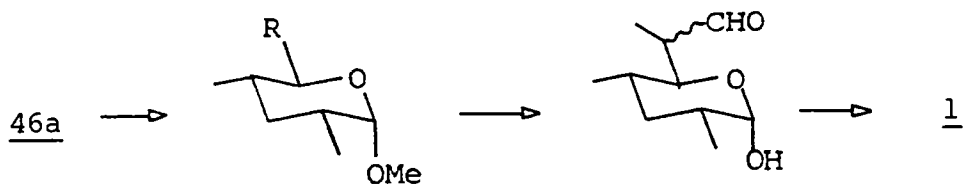
It was then treated with freshly prepared borane and the subsequent work up with alkaline H_2O_2 yielded a mixture of diols 42 and its isomer. Fetizon's reagent oxidation of 42 afforded the known lactone 43 from which the lactone (±1) was obtained in very good yield.

S.Jarosz et al.[51] developed a route to Prelog-Djerassi lactone from methyl-α,D-glucopyranoside in 1981 (Scheme 9). The enone 44 obtainable from methyl-α, D-glucopyranoside was converted into corresponding diene 45 which was hydrogenated to give predominantly the diequatorial dimethyl hexopyranoside 46a. Hydrogenation of 44 gave the equatorial C_4 methylketone 47 exclusively,



Scheme 9

which was further converted to 46a as the major product. The 46a was converted to alcohol 48a and further oxidised to aldehyde 48b. It was then converted to methylketone 48c and further to 49 by treatment with Ph_3 = CHOMe. Finally it was oxidised to a recemic mixture of Prelog-Djerassi lactone (Scheme 10).



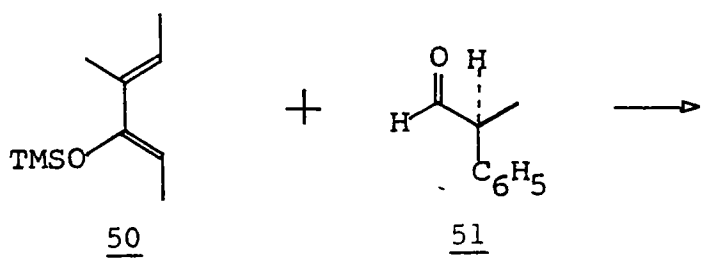
48a R - CH_2OH
48b R - CHO
48c R - $COCH_3$

49

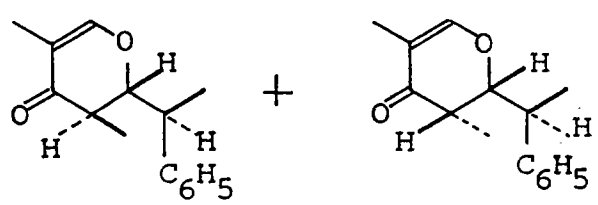
Scheme 10

Danishefsky et al[52] have described a Lewis acid catalysed cyclocondensation of 1,3-dioxygenated dienes with representative aldehydes for the preparation of (±1). The simplicity of modifying the configuration at C_4 and C_6 of the Prelog-Djerassi lactone is another feature of this approach. The readily available silyloxy diene 50 reacts with commercially available aldehyde 51 in CH_2Cl_2 at -78°C in the presence of $BF_3O(C_2H_5)_2$ followed by treatment with CF_3COOH in THF at room temperature afforded 4.3:1 mixture of 52 and its epimer 53 (Scheme 11). Reduction of 52 with

diisobutyl aluminium hydride followed by Ferrier rearrangement afforded the β-disposed anomer 54. The tendency of the Ferrier rearrangement[53] to produce an axial glycoside is undoubtedly responsible for the stereospecific formation of 54. Flanked as it is by two β-functions, the double bond in 54 suffers catalytic reduction from its α-face to afford 55. It was then subjected to ozonolysis followed by H_2O_2 oxidation yielded (±1) (Scheme 12).



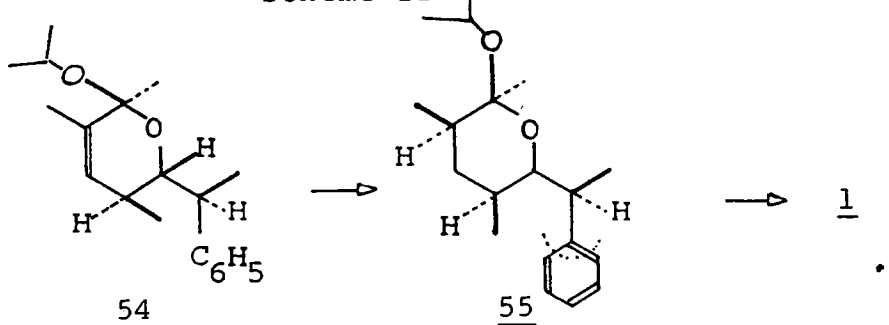
50 51



52 53

Scheme 11

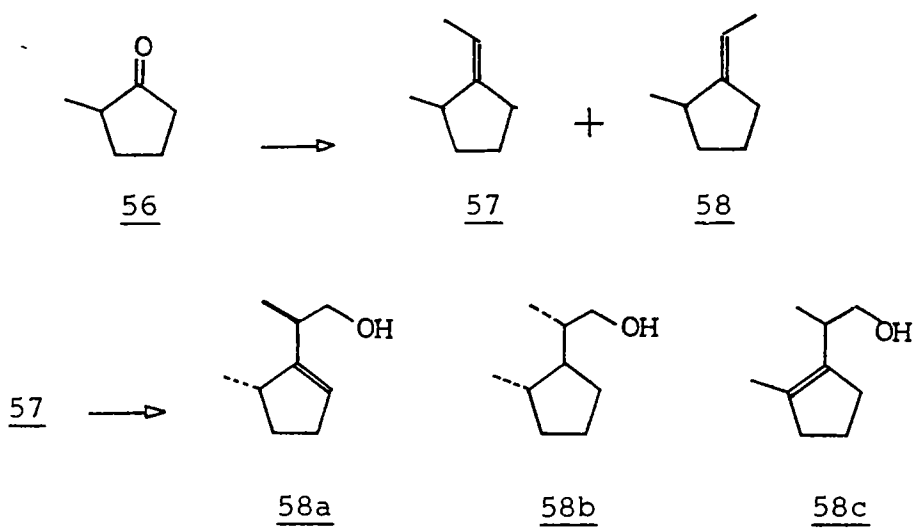
52



54 55

Scheme 12

In 1982, P.M.Wovkulich et al.[54] examined the regio and stereochemical outcome of the ene reaction of 1-ethylene 2-methyl cyclopentanes with formaldehyde and applied this in the synthesis of Prelog-Djerassi lactone. Exposure of 2-methyl cyclopentanone (56) to ethyledine triphenyl phosphorane led to 55:45 mixture of olefins 57 and 58 respectively. The Z-olefin 57 when treated with paraformaldehyde catalysed by BF_3-etherate underwent a smooth reaction to give a mixture of ene adducts 58a, 58b and 58c in a ratio of 86:10:4 respectively (Scheme 13).

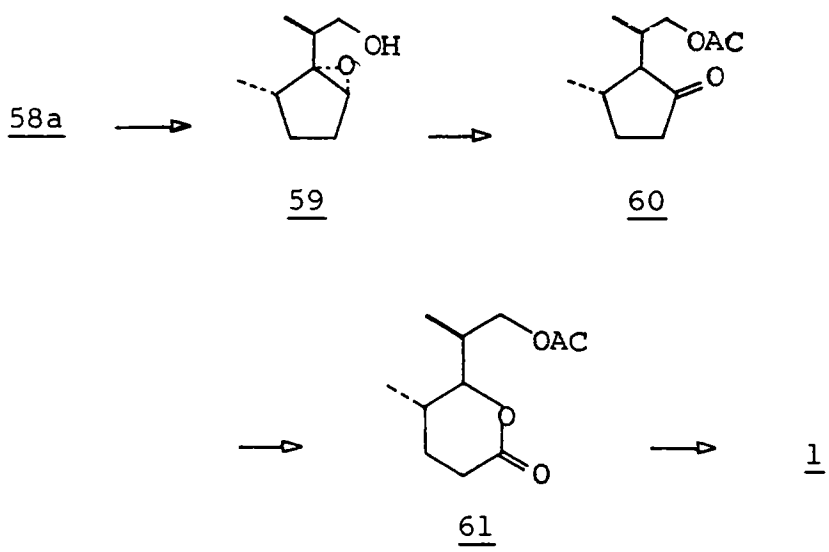


56 → 57 + 58

57 → 58a, 58b, 58c

Scheme 13

Epoxidation of 58a with ter.butylhydroperoxide-$Vo(acac)_2$ produced 59 which on acetylation followed by BF_3-etherate treatment yielded ketone 60. Hydrolysis followed by conversion to tert.butyl dimethylsilyl ether, Baeyer-Villiger oxidation and then removal of silyl group and again acetylation yielded 61. Further conversion to target molecule was achieved as in the usual manner (Scheme 14).

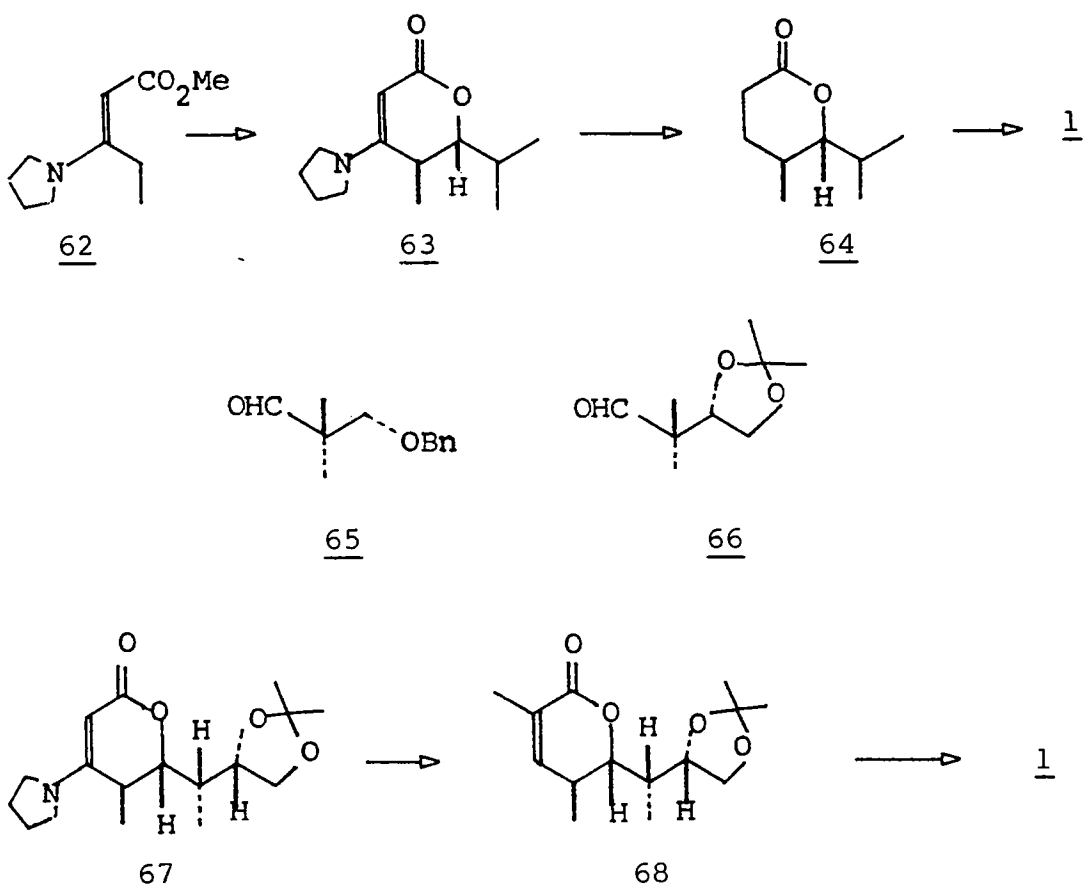


Scheme 14

Another method for the synthesis of (1) was put forward by R.H.Schlessinger et al.[55] Their plan stemmed from the notion that a threo-selective aldol lactonization

which also exhibited "Cram" behaviour could be used to prepare the three contiguous chiral centres at C_2,C_3 and C_4, the fourth centre being secured in a subsequent process (Scheme 15).

The enolate of a crotonate system 62 with isobutyraldehyde afforded a single lactonic product 63 in over 95% yield. It was converted into lactone 64 by standard means. The 'H NMR spectra of both 63 and 64



Scheme 15

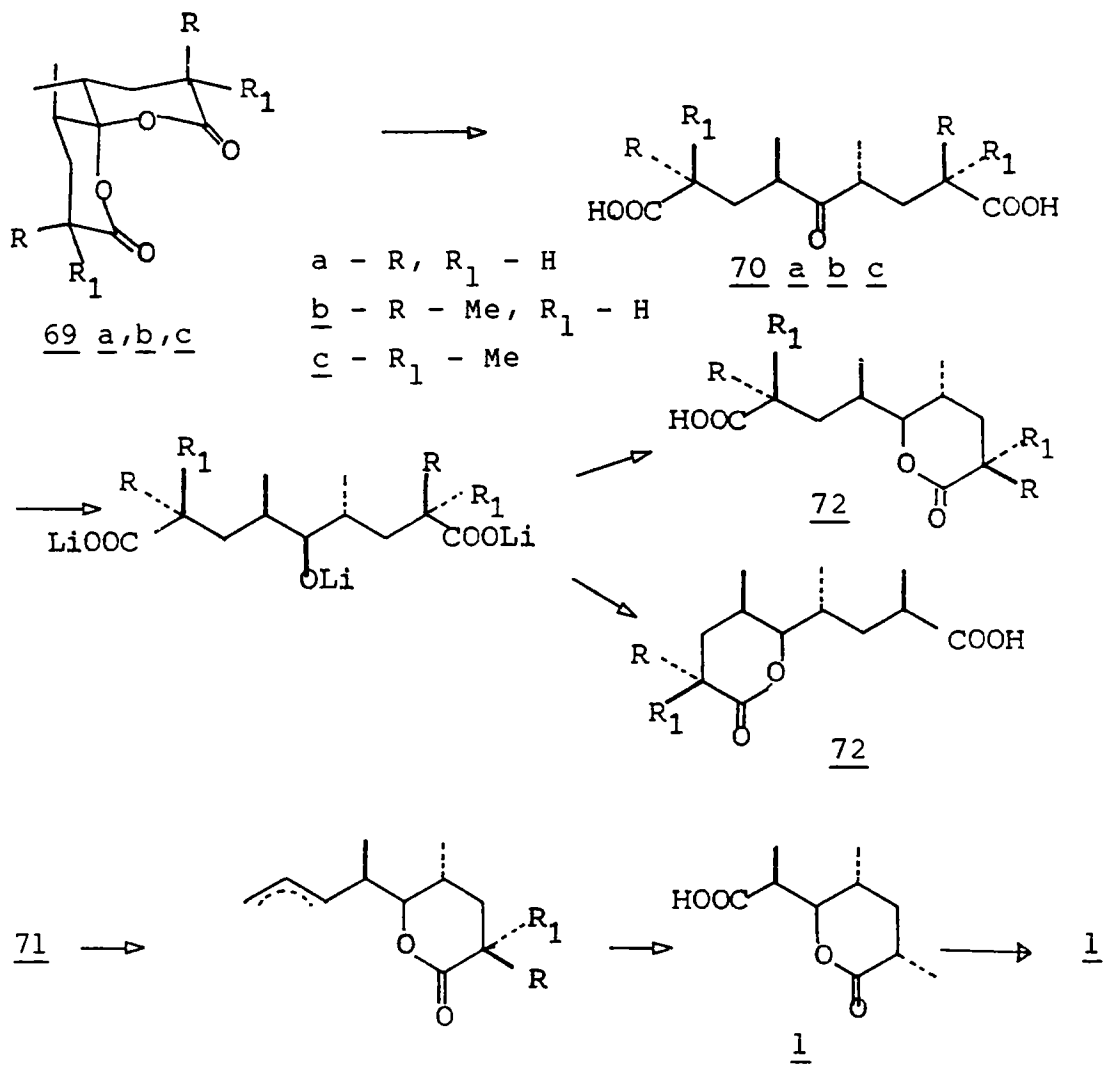
showed a trans relationship between the methyl and isopropyl groups indicating that the aldol lactonization had proceeded with greater than 95% threo selectivity.

The reaction was then modified by taking substituted aldehydes 65 and 66 instead of isobutyraldehyde.

The aldehyde 65 in combination with the enolate 62 gave a mixture of lactonic products in a ratio of 2.5:1 Cram to anti-Cram stereochemistry at the C_2-methyl group. However, the aldehyde 66 with 62 afforded a mixture of lactones in which the Cram product dominated to the extent of 9:1. The 67 was then reduced with Li/NH_3 followed by treatment with CH_3I, m-CPBA and trimethylamine afforded 68 in good yield. It was then reduced with diisobutyl aluminium hydride followed by hydrogenation and further work up led to the lactone (±1).

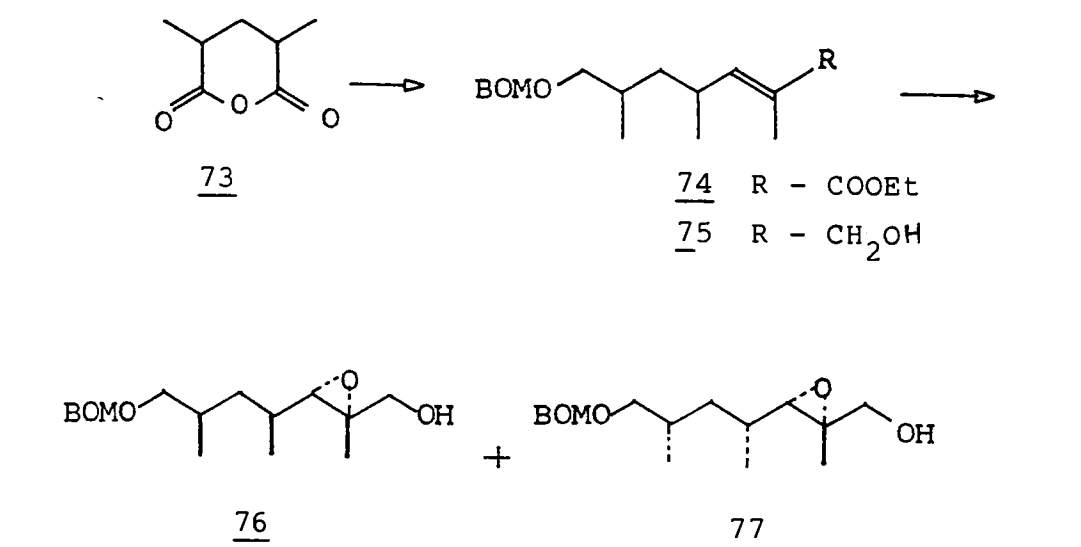
In 1984, T.R.Hoye et al.[56] utilized kinetic lactonization of 2,4,6,8 tetramethyl 5-hydroxy azelaic acid for the synthesis of Prelog-Djerassi lactone (Scheme 16).

The keto acid 70 obtained by the hydrolysis of 69, was converted to lithium salts followed by acid catalysed lactonization generated monolactone 71 and 72. Oxidative decarboxylation of 71c generated a mixture of olefins which were cleaved to provide a pair of acids from which the methyl ester of (±1) could be prepared.



Scheme 16

M.Yamaguchi et al.[57] introduced another method starting from Meso-2,4-dimethyl glutaric anhydride. Compound 73 was reduced with lithium aluminium hydride followed by partial benzoxymethylation, swern oxidation and the resulting aldehyde was treated with 1-ethoxycarbonyl ethylidene triphenylphosphorane gave a mixture (E & Z) of unsaturated esters 74 (90%) and its isomer. The 74 was reduced to allylalcohol 75 which was then epoxidized under the presence of (+) diisopropyl-tartrate to give a mixture of diastereomeric epoxides 76



73

74 R - COOEt
75 R - CH_2OH

76 + 77

78 R_1 - $C_6H_5CH_2OCH_2$- , R_2 - H
79 R_1 - COOH, R_2 - CH_3CO-

80
R - CH_2OH

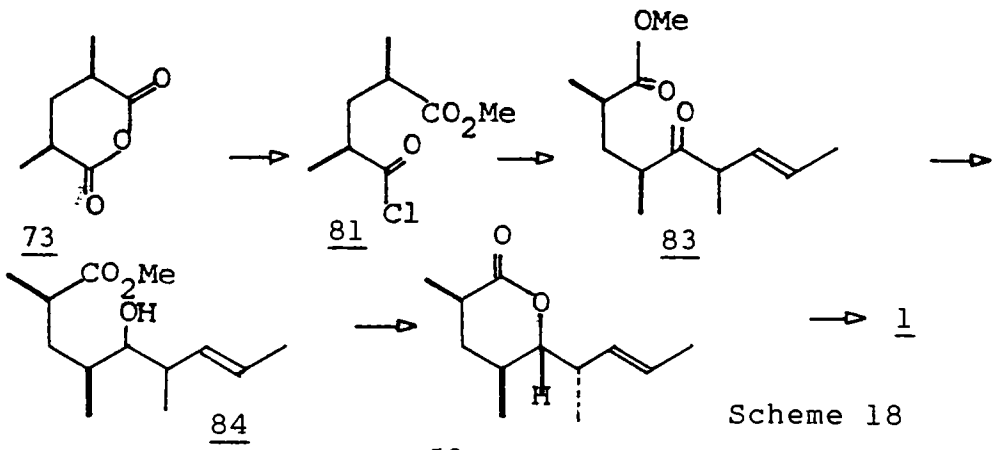
1

Scheme 17

and 77 (96%). Regio selective reduction of the epoxides was achieved by RED al, favouring the formation of 1,3 diol 78 and its diastereomer over the 1,2 diols with a ratio of >9:1 (Scheme 17).

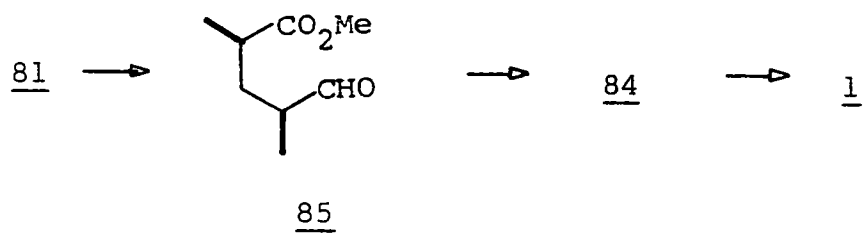
The diol mixture was acetylated followed by removal of benzyloxy methyl group and oxidation gave a carboxylic acid mixture 79, which was then saponified and acidified to get hydroxy lactone 80 which was further oxidised to the desired lactone mixture.

Another report in the same year by C.Santelli et al.[58] suggested that addition of trans-3-trimethylsilylpent-2-ene to derivatives of glutaric anhydride leads to precursors of the Prelog-Djerassi lactone and related δ-lactones. The meso 2,4-dimethyl-glutaric anhydride 73 was treated with $CH_3OH/SOCl_2$ to affort 81 (Scheme 18) which was treated with trans-3-trimethylsilylpent-2-ene (82) to get 83. The 83 was reduced to alcohol 84 followed by hydrolysis,lactonization to get 85 and further oxidation yielded the lactone (±1) . By another route the chloride 81 was converted to aldehyde 85 followed by treatment with 82 to get 84 which was converted to the lactone (±1) by hydrolysis, lactonization and oxidation (Scheme 19).

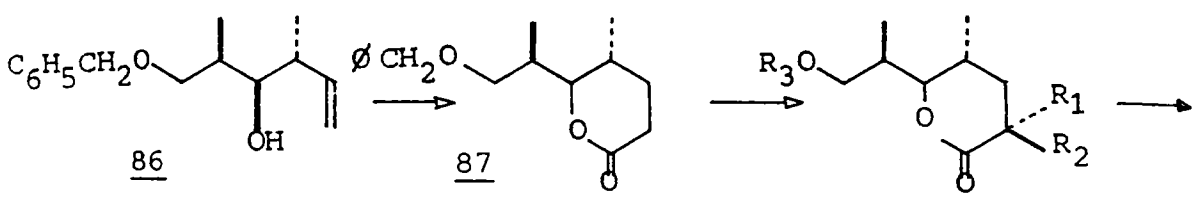


Scheme 18

P.G.Wuts et al.[59] introduced a method for the synthesis of Prelog-Djerassi lactone. A hydroformylation oxidation sequence was described for the efficient conversion of homoallylic alcohols to δ-lactone, catalysed by Rhodium acetate dimer (Scheme 20).



Scheme 19



88 R_1 - CH_3; R_2 - H; R_3 - $C_6H_5CH_2$

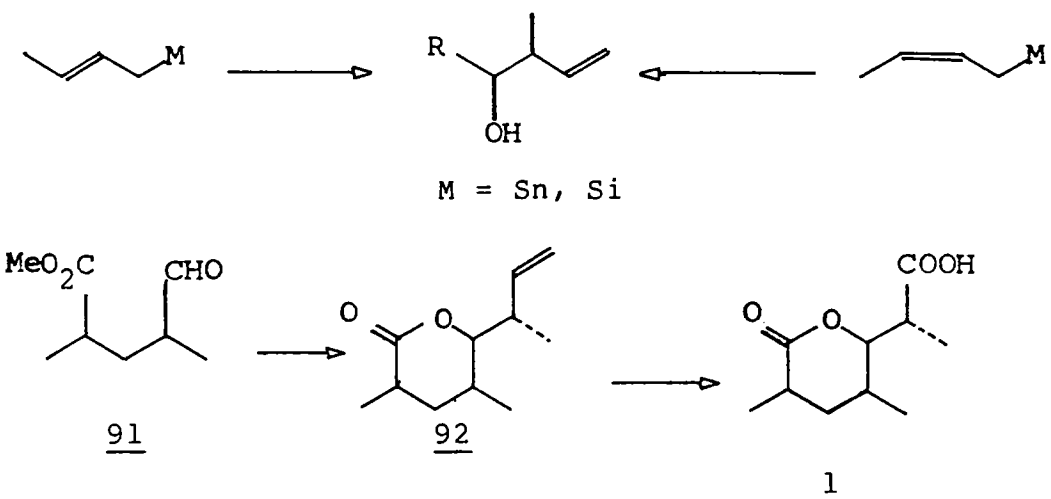
89 R_1 - H, R_2 - CH_3, R_3 - $C_6H_5CH_2$

90 R_1 - CH_3, R_2,R_3 = H

Schme 20

The alcohol 86 was subjected to hydroformylation and the resulting hemiacetate directly oxidized to lactone 87 which was then methylated to a mixture (1:1) of lactones 88 and 89. Isomerization and hydrogenolysis gave alcohol 90 which was further oxidized to lactone (±1).

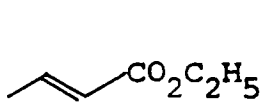
Yamamoto et al.[60] in 1984 developed a short synthesis of Prelog-Djerassi lactone via a Lewis acid mediated reaction of allylic stannanes with aldehydes. Allylation of aldehydes with allylic organometallic compounds has recently received wide attention as a basic synthetic method for control of a acylic stereochemistry (Scheme 21). The homoallylic alcohol is produced



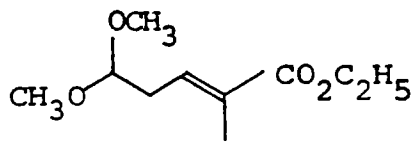
Scheme 21

predominantly regardless of the geometry of double bond. Allylic silanes also exhibit the same stereoselectivity in presence of Lewis acid. Although other Lewis acids such as $TiCl_4$, $SnCl_4$, BCl_3 were examined, the $BF_3O(C_2H_5)_2$ gave the best result both in diastereoselectivity and yield. The reaction of 91 with crotyltrialkyl stanne in presence of $BF_3O(C_2H_5)_2$ produced 92 in 92% yield. Ozonolysis of 92 followed by oxidation gave the lactone (±1) in 85% yield.

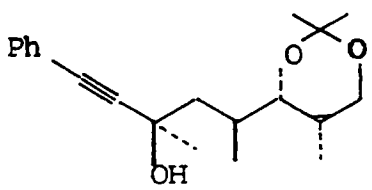
A stereo controlled synthesis of Prelog-Djerassi lactone was described by Ian Fleming et al.[61] in 1985. The stereo control was achieved from the high diastereoselectivity of electrophilic attack on a double bond adjacent to a chiral centre carrying a silyl group. Ethyl crotonate 93 was methylated using lithiumdienolate. It was again alkylated in the γ-position using silyl dienol ether to give the α-β-unsaturated ester 94 (Scheme 22). It was subjected to conjugate addition using silyl cuprate reagent followed by a series of functional group manipulations to give very nearly equal amounts of diastereomeric alcohols 95 and 96. They were separated and hydrolysed to triols 97 and 98. The 97 was acetylated and hydrogenated to get Cis-allylic acetate 99 while the



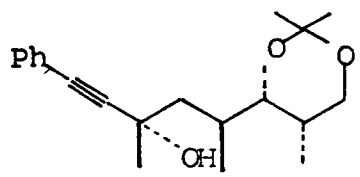
93



94



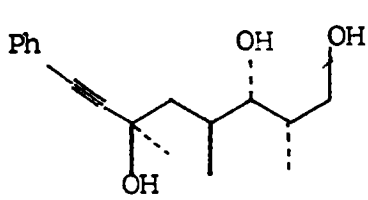
95



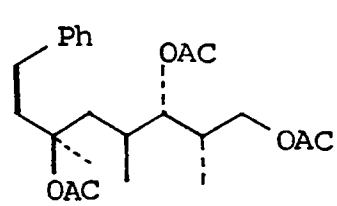
96

Scheme 22

98 was subjected to lithium aluminium hydride reduction followed by acetylation to get trans-acetate 100. The acetates 99 and 100 were treated with silylcuprate reagent to get stereochemically equivalent allylsilanes 101 and 102. The desilylation of both 101 and 102 led to 103 followed by simple functional group transformation (Scheme 23) gave recemic lactone (1) in very good yield.



97



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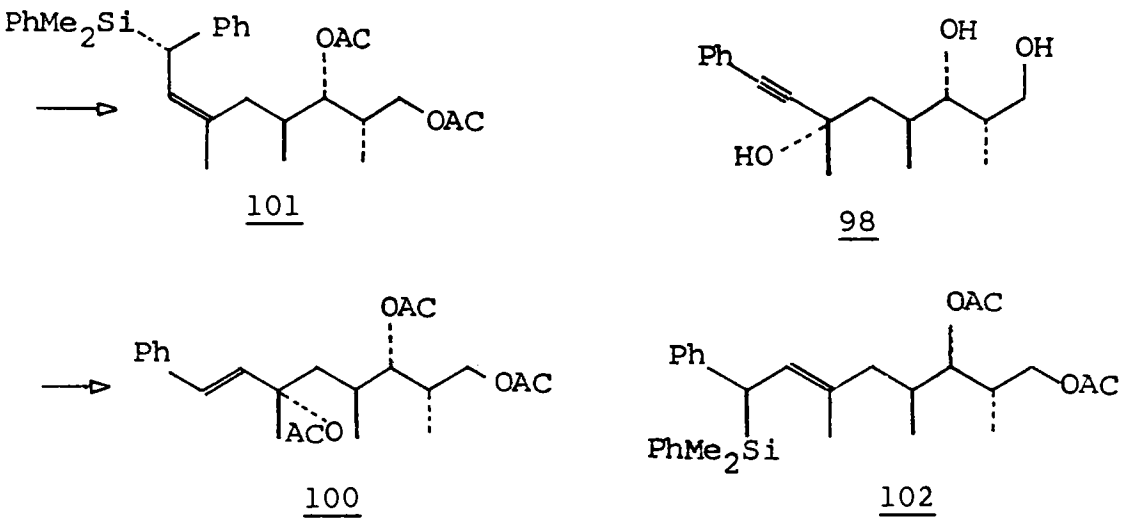
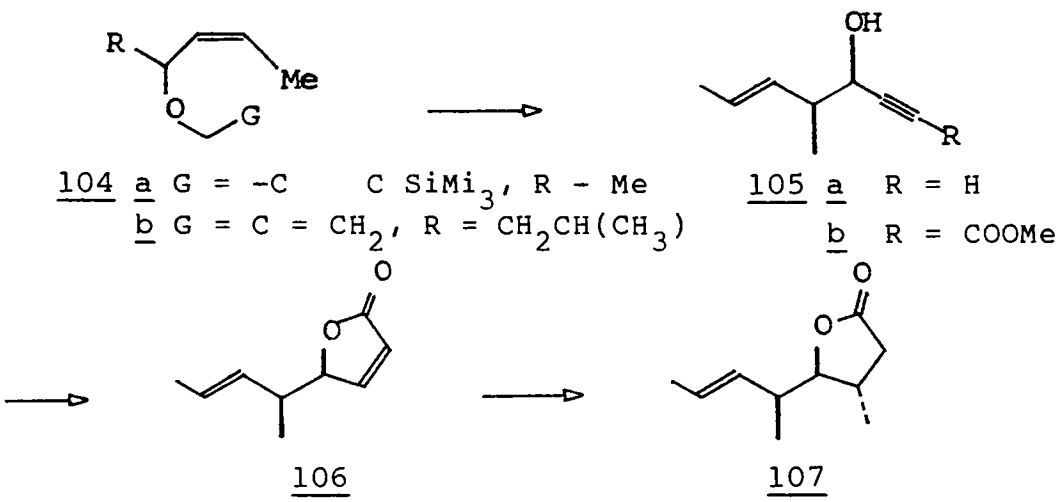
Scheme 23



Scheme 23

T.Nakai *et al.*[62] in 1985 introduced three 2,3-Wittig-based approaches for stereocontrol over three contiguous chiral centres within the context of the synthesis of Prelog-Djerassi lactone. In the first method the compound 104 was subjected to a series of reactions including 3,3-Wittig rearrangement, silylation, treatment with methyl chloroformate, hydrolysis followed by desilylation to get the acetylenic ester 105b. Selective hydrogenation yielded butenolide 106 which was subjected to Michael addition with lithium dimethylcuprate to afford δ-lactone 107 as a single isomer (Scheme 24).



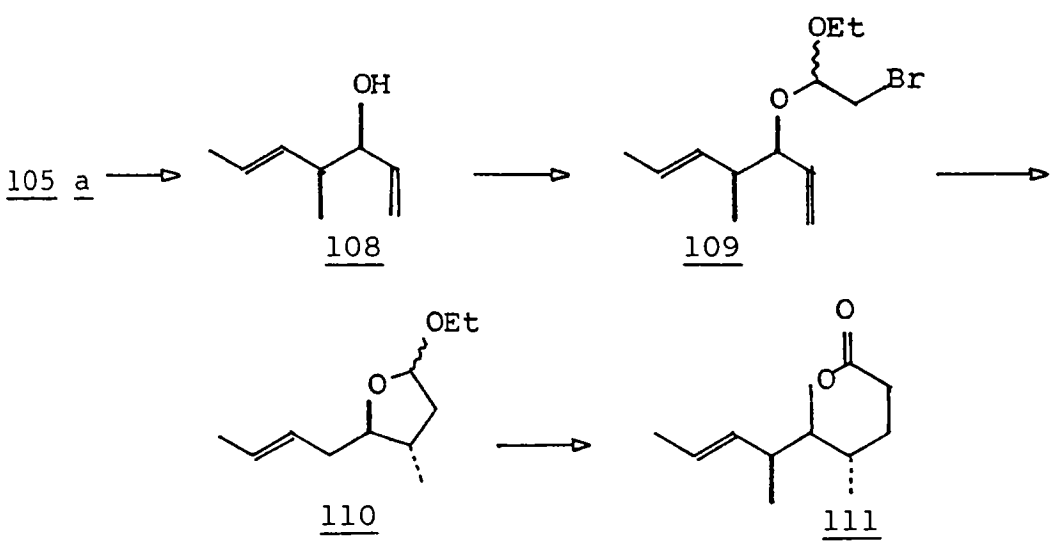
104 a G = -C C $SiMi_3$, R - Me
b G = C = CH_2, R = $CH_2CH(CH_3)$

105 a R = H
b R = COOMe

106 107

Scheme 24

In the second method the radical cyclization developed by Y.Ueno and G.Stork[63] employed as a stereo directing process (Scheme 25). The alcohol 105a

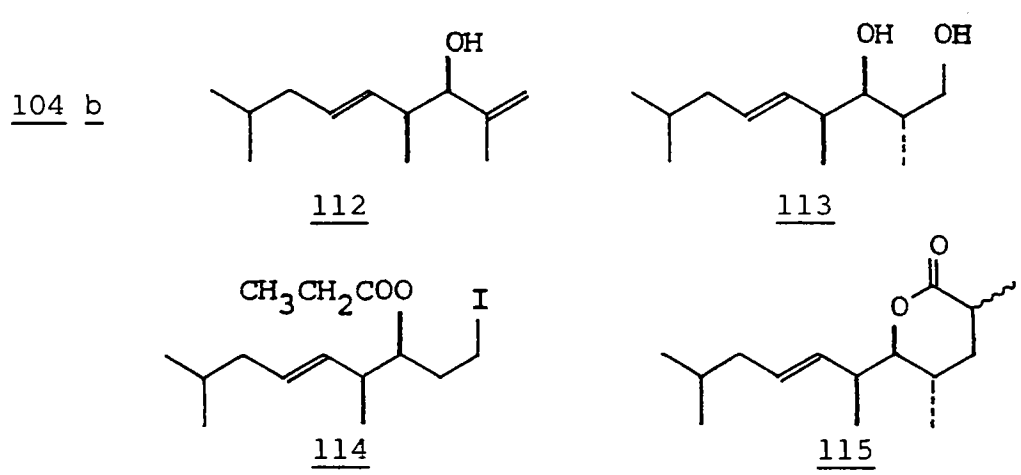


108 109 110 111

Scheme 25

was subjected to selective hydrogenation to 108 followed by convertion to the acetal intermediate 109 which was transformed to cyclized product 110 and finally oxidized to 107. The δ-lactone 107 obtained by above two methods could be converted by multistep process to the lactone 111 that undoubtedly serves as a potential precursor for Prelog-Djerassi lactone.

In the third method (Scheme 26) the 104b was rearranged to alcohol 112 which was then treated with 9-BBN followed by oxidation to the diol 113 as a single stereoisomer. Successive treatment of 113 with Tosylchloride and propionic anhydride gave a tosylate which was further treated with KI to afford 114. The

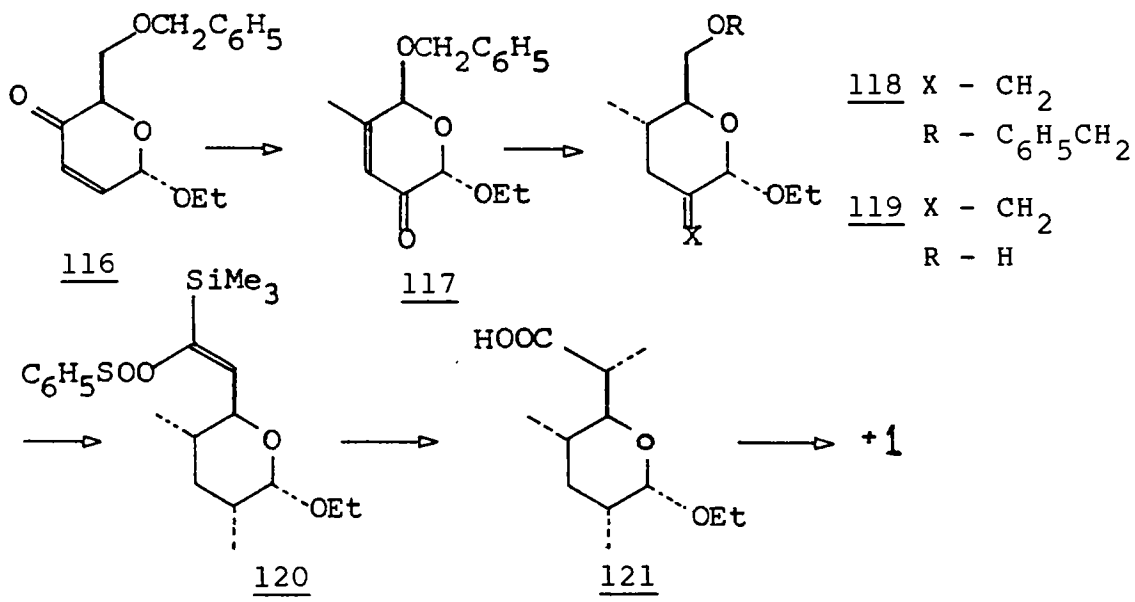


Scheme 26

iodide 114 was then reacted with lithium hexamethyl disilylamide followed by oxidative cleavage of the lactone 115 gave a mixture (57:43) of lactone (1) at its α-epimer.

1.4 ENANTIOSELECTIVE SYNTHESIS OF PRELOG-DJERASSI LACTONE

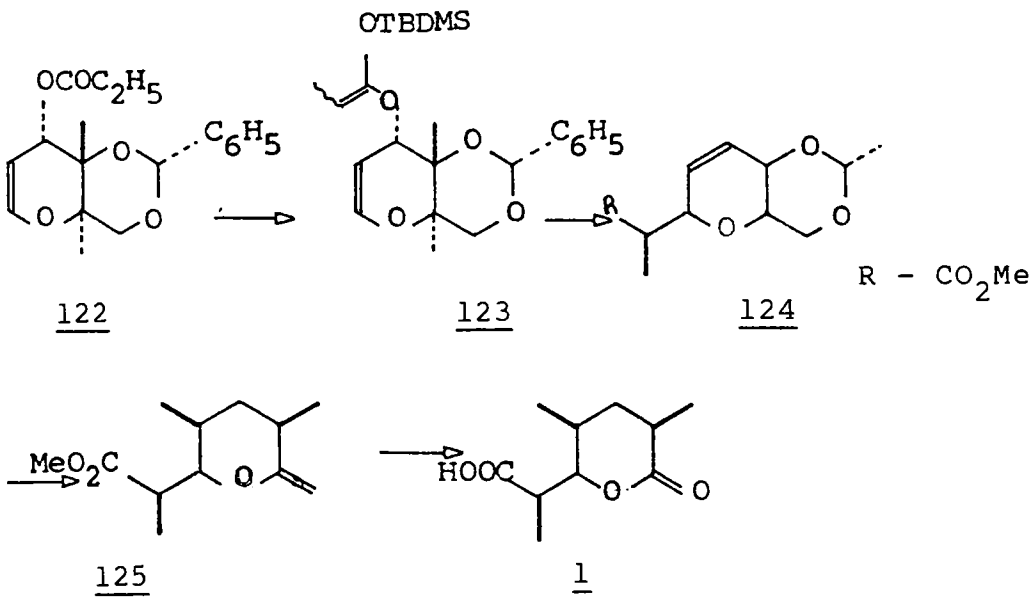
Isobe et al.[64] in 1981 reported an optically active Prelog-Djerassi lactone synthesis. The process involves heteroconjugate addition of Me_2CuLi onto an optically active Pyranosyl hetero olefin preparable from D-hexopyranose. Ethyl 6-o-benzyl-2,3-dideoxy-α-D-glycero hex-2-enopyranosid-4-ulose 116 was employed as the chiral starting material (Scheme 27). Addition of MeLi is



Scheme 27

followed by oxidation afforded enone 117 It was reduced with H_2/Pd/C followed by treatment with triphenyl phosphonium methylide afforded 118 which was again reduced with H_2/Pd/C to get alcohol 119. It was then converted to the hetero olefin 120 which was followed by a series of reaction including treatment with MeLi, Phenylselenyl chloride, 30% H_2O_2 to get carboxylic acid 121. Hydrolysis followed by oxidation with Br_2/DMF gave crystalline product ±1 in 98% yield.

An approach for the synthesis of optically active Prelog-Djerassi lactone has been developed by Ireland et al.[65] The propionate ester of glycal 122 was enolized with lithium hexamethyl disilazide afforded a mixture of enolates, which were trapped by tert-butyl dimethylsilyl

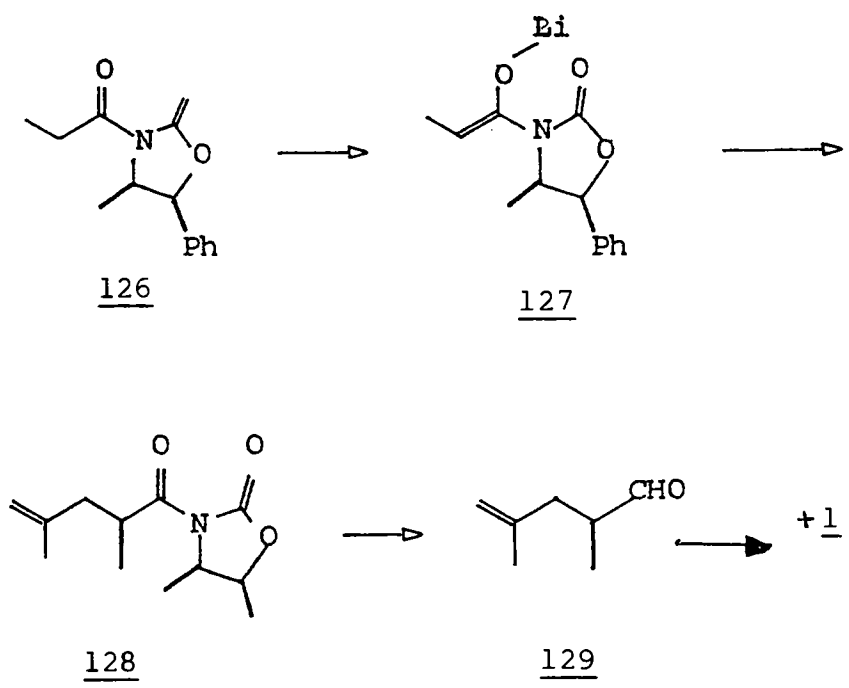


122 123 124 125 1

Scheme 28

chloride to get mixture of silylketene acetal 123. It was rearranged by heating and the product was converted to methyl ester 124 followed by a sequence of transformations gave 125 which was further subjected to ozonolysis and saponification yielded the target molecule +1 (Scheme 28).

In 1982, D.A.Evans et al.[66] developed a method for the synthesis of +1 (Scheme 29). Chiral propionamide 126 derived from (IS, 2R) norephedrine was transformed into lithium enolate 127 followed by treatment with methallyliodide to give a 97:3 ratio of diastereomeric alkylation products. The major diastereomer 128 was transformed into aldehyde 129 by the Parikh modification

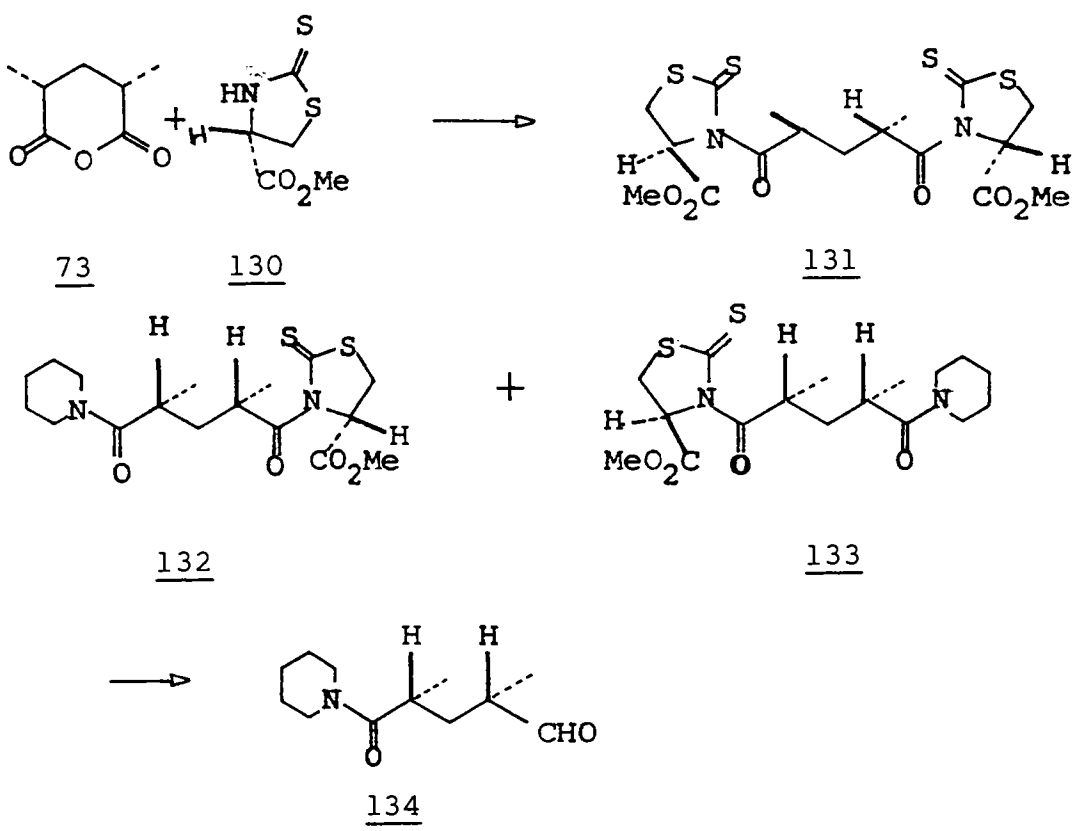


126 127 128 129

Scheme 29

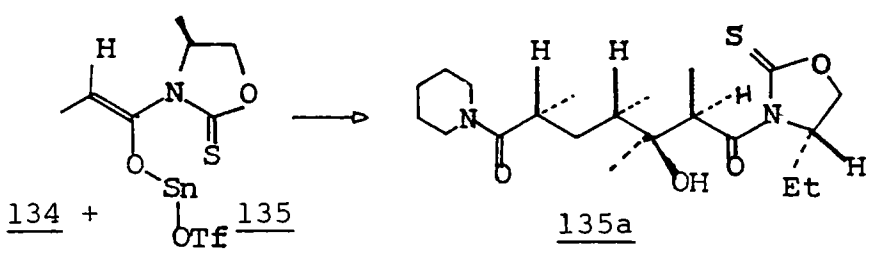
of Moffatt oxidation. Final methyl bearing asymmetric centre was introduced by hydroboration with thexyborane and further transformations including peroxide oxidation, acid hydrolysis and Ruthenium catalyst oxidation were carried out to get the lactone (+l).

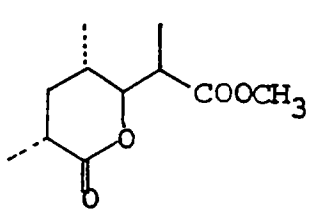
A facile chiral synthesis of (+) Prelog-Djerassi lactone using five membered heterocyclic chiral reagents has been reported by O.Chiai et al.[67] in 1985 (Scheme 30). Condensation between Meso-2,4-dimethyl glutaric acid anhydride 73 and 2 moles equivalents of 4(S) methoxy



Scheme 30

carbonyl-1,3-thiazolidine-2-thione 130 in presence of dicyclohexylcarbodiimide in Pyridine gave 131 Aminolysis with piperidine afforded a mixture (97.3:2.7) of diastereoisomers 132 and 133 The 132 was separated and subjected to reduction followed by oxidation with pyridinesulphurtrioxide complex yielded a mixture (91.7:8.3) of aldehydes 134 and its C_4 epimer. An aldol type condensation between 134 and Tin enolate 135 in presence of N-ethyl piperidine furnished 135a along with other minor diastereo isomers. Compound 135a was then converted to methyl ester of (+) Prelog-Djerassi lactone 136 by heating and esterfication (Scheme 31).

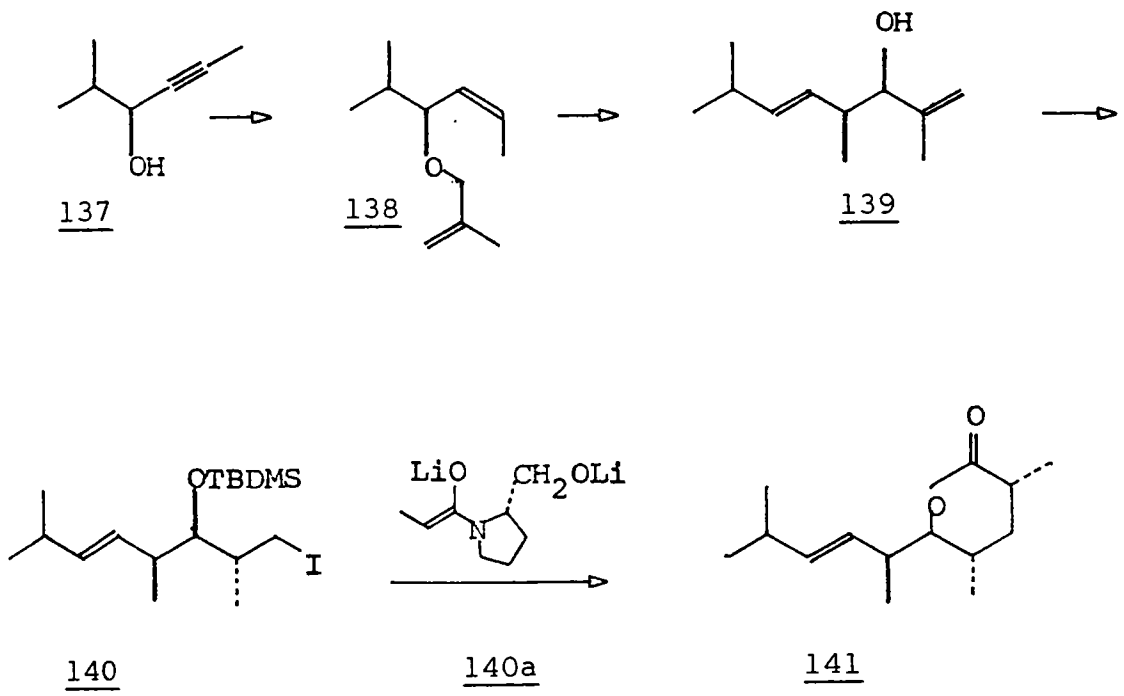




136

Scheme 31

M.Midland et al.[68] introduced a [2,3] sigmatropic Wittig rearrangement as a keystep for the synthesis of (+) Prelog-Djerassi lactone. This reaction was used to control the relative and absolute configuration of two of the four chiral centres of the lactone. The remaining centres were introduced by a stereoselective hydroboration and asymmetric alkylation (Scheme 32). The propargyl alcohol 137 obtained in 92% ee was reduced to allylic alcohol and converted to ether 138. It was then converted to 139 and the alcohol group was protected followed by the terminal olefin transformation into iodide 140. The chiral centre at C_6 was introduced by reaction of 140 with



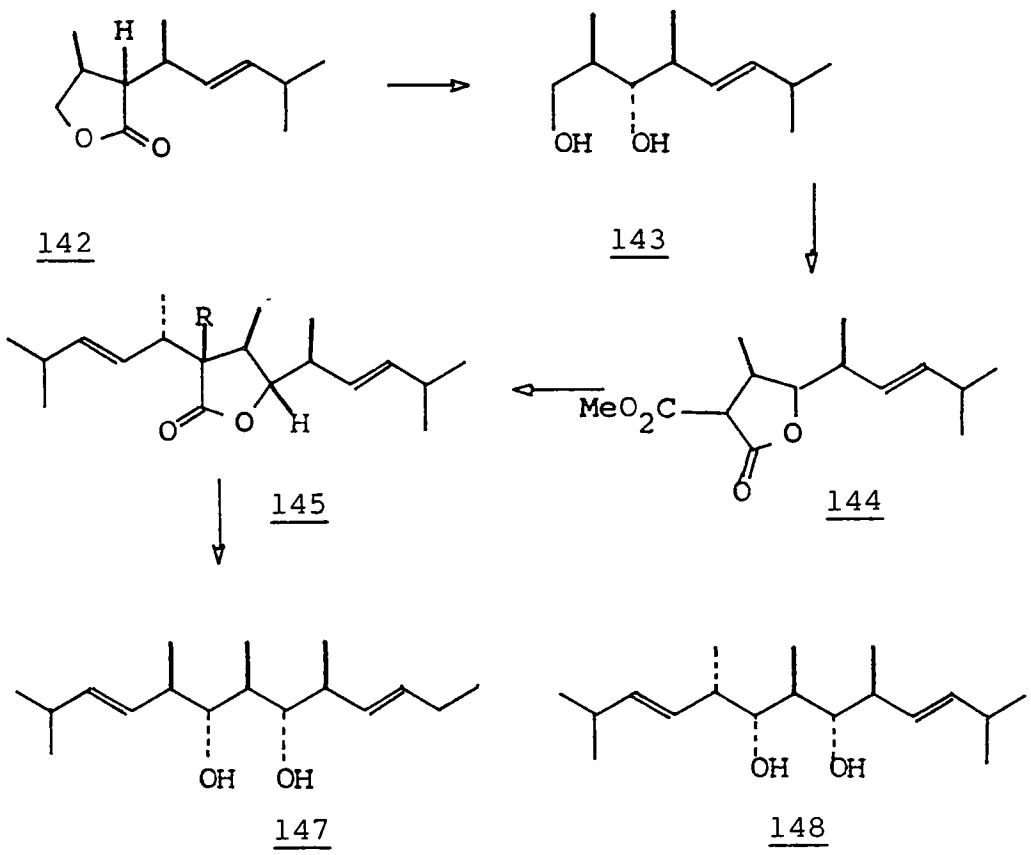
137 138 139

140 140a 141

Scheme 32

Evan's prolinol enolate 140a. Hydrolysis followed by lactonization afforded 141 which was subjected to ozonolysis and oxidation yielded pure (+1).

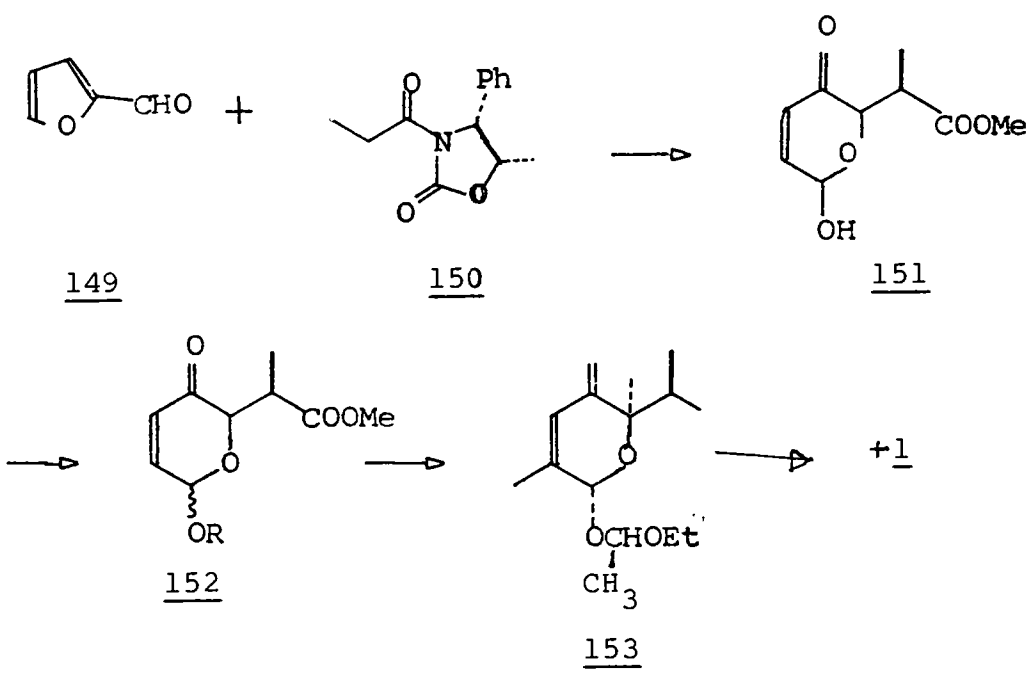
In 1986 F.E.Ziegler et al.[69] have reported an efficient method for the synthesis of optically active Prelog-Djerassi lactone (Scheme 33). Lactone 142 was converted to diol 143 which was subjected to a series of reactions to get a mixture of lactonic esters (13:1) 144.



Scheme 33

Diethylphosphonate of R-2 methylhex-4(E)-en-3-ol was prepared and reacted with sodium anion of lactoni esters 144 provided 2:1 mixture of alkylation products followed by decarboxylation to yield Cis (4%) and Trans (91%) 145 and 146 lactones. The major 146 was subjected to Criegee carbon extrusion process gave a mixture of diols 147 and 148 from which the 148 was subjected to ozonolysis, acetalization followed by the procedure of Deslongchamps[70] afforded the lactone (+1).

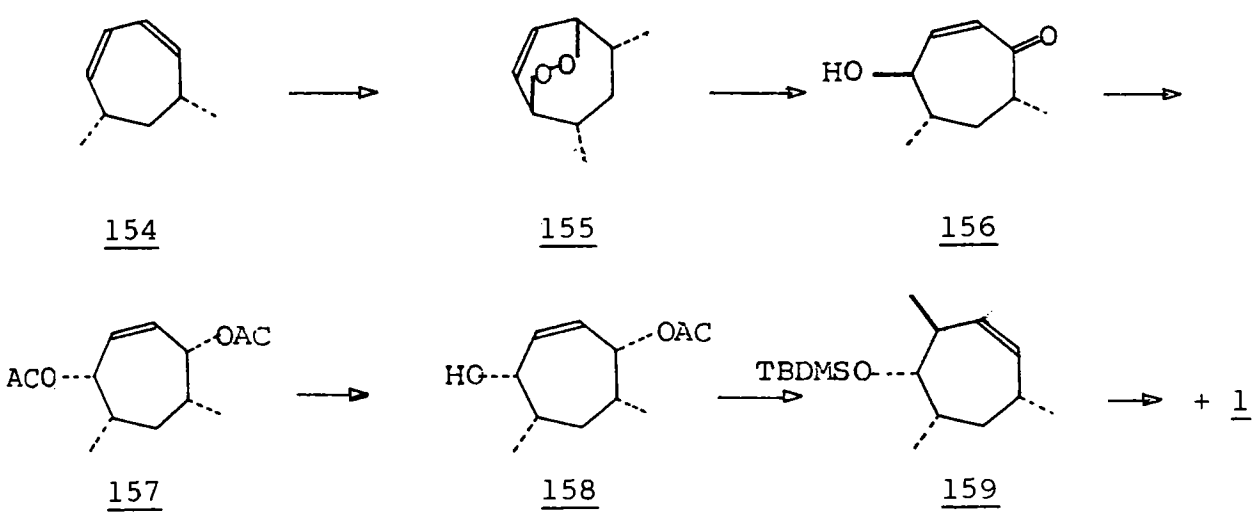
A stereoselective synthesis of (+) Prelog-Djerassi lactone from furanoid intermediates was introduced by S.F.Martin et al.[71] (Scheme 34).



Scheme 34

Furaldehyde (149) was condensed with boron enolate of chiral imide 150 followed by hydrolysis and treatment with Br_2 in CH_3OH afforded hydroxypyranone 151 as a mixture of α and β-anomers. It was then converted to α and β-ethoxy ethyl glycosides 152 by reaction with ethylvinyl ether. The 152a was subjected to lithium dimethyl cuprate reagent and the resulting enolate was trapped with trimethylsilyl-chloride followed by oxidation with Pd acetate gave 153. Wittig olefination of 153 followed by hydrogenation deprotection and oxidation afforded pure lactone (+1) in very good yield.

A.J.Pearson et al.[72] in 1989 have developed a method for the synthesis of optically active Prelog-Djerassi lactone (Scheme 35). Cis-5,7-dimethyl



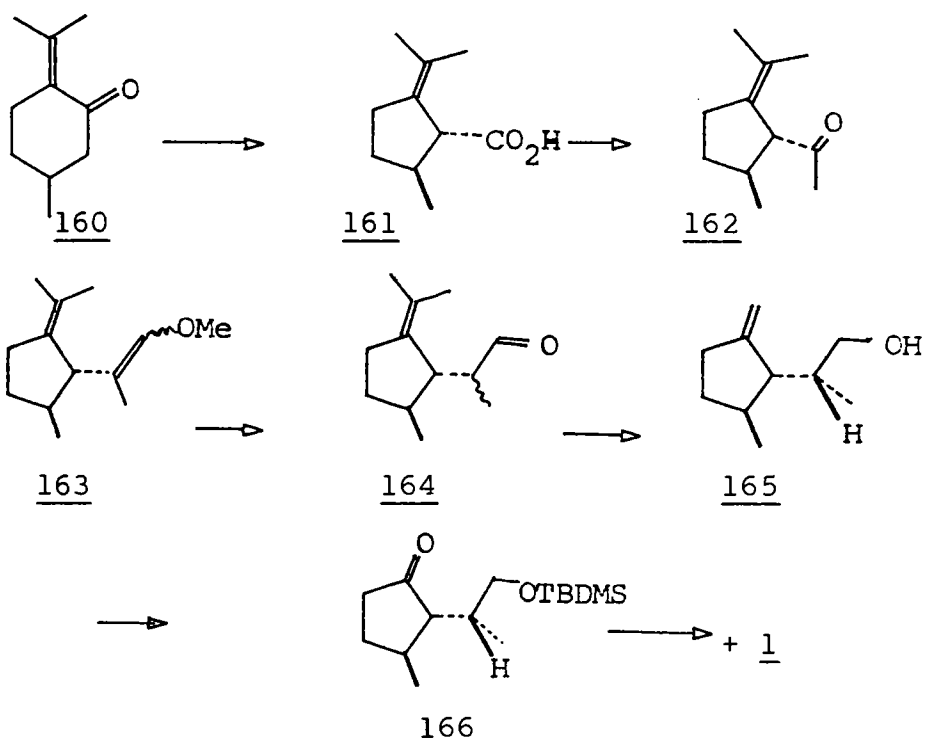
154 155 156

157 158 159

Scheme 35

cyclohepta-1,3-diene 154 was converted to 156 via an endoperoxide 155. It was then converted to diacetate 157 followed by lipase enzyme catalysed hydrolysis yielded hydroxyacetate 158 which was then converted to silyl ether 159. Oxidative cleavage followed by acid hydrolysis afforded (+) lactone in very good yield.

M.Santelli et al.[73] have reported a synthesis from (-) Trans-Pulegenic acid in 1989 (Scheme 36). (-) Pulegone (160) obtained from (S) (-) citronellal, was transformed into (-) trans Pulegenic acid 161 according to standard procedure. Addition of methyllithium afforded methylketone 162 followed by Wittig methoxymethylenation



160 161 162 163 164 165 166

Scheme 36

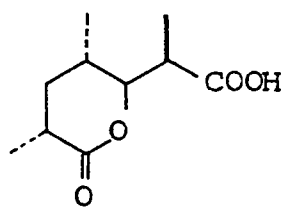
yielded 4:1 mixture of E/Z isomers of 163. Acid hydrolysis led to a mixture of aldehydes 164 followed by lithium aluminium hydride reduction afforded 165. Protection of hydroxyl group with t- butyl dimethyl-silyl ether and subsequent ozonolysis yielded 166 from which the Prelog-Djerassi lactone was obtained as optically pure by standard procedure.

CHAPTER II

STATEMENT OF THE PROBLEM

2.1 INTRODUCTION

Prelog-Djerassi lactone (1) has central place in the chemistry of macrolide antibiotics ever since its isolation by V.Prelog[1] and C.Djerassi[2] during degradation studies of Narbomycin and Methymycin respectively. Interest in the synthesis of this lactone was intensified after its structure and stereochemistry were illuminated and it was found to constitute the backbone of a number of biologically important macrolide antibiotics. A number of highly imaginative solutions to the problem of its synthesis have already appeared [3]. Different stereoisomers of the lactone were also synthesised [4-8].



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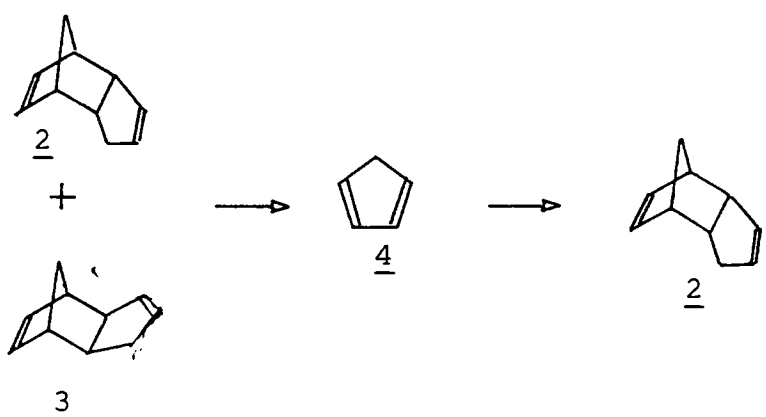
Present work deals with a study on the synthesis of Prelog-Djerassi lactone. An easily available tricyclic unsaturated hydrocarbon dicyclopentadiene was identified as a suitable starting material for the synthesis, considering the stereochemical control of the reactions this molecule

can offer. Also the exo-isomer of dicyclopentadiene (2) is having the desired stereochemistry so that the introduction of different substituents in the proposed scheme can be achieved easily.

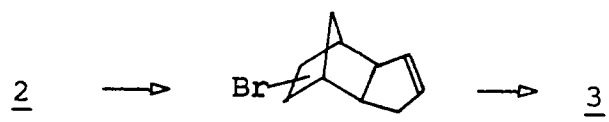
2.2 SYNTHESIS VIA exo-DICYCLOPENTADIENE

Commercially available dicyclopentadiene is a mixture of two isomers namely endo-dicyclopentadiene (2) and exo-dicyclopentadiene (3) in which major constituent is the endo-isomer. It was proposed to convert the mixture into pure endo-isomer by obtaining the monomer 4 and allowing it to dimerise at 0°C so that only the endo-isomer is formed[9] (Scheme 1).



Scheme 1

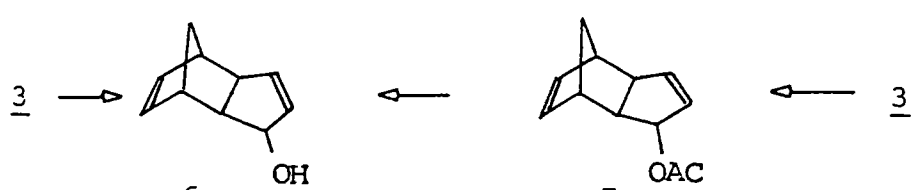
The pure endo-dicyclopentadiene thus obtained can be converted to the required exo-isomer by treating with hydrobromic acid followed by dehydrobromination[10] (Scheme 2).



5

Scheme 2

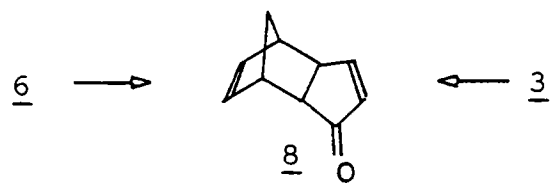
Allylic oxidation of exo-dicyclopentadiene (3) with selenium dioxide in dioxane can give the alcohol 6. The alcohol can also be obtained by hydrolysis of the acetate 7 obtained by the allylic oxidation of exo-dicyclopentadiene with selenium dioxide in acetic acid[11] (Scheme 3).



6 7

Scheme 3

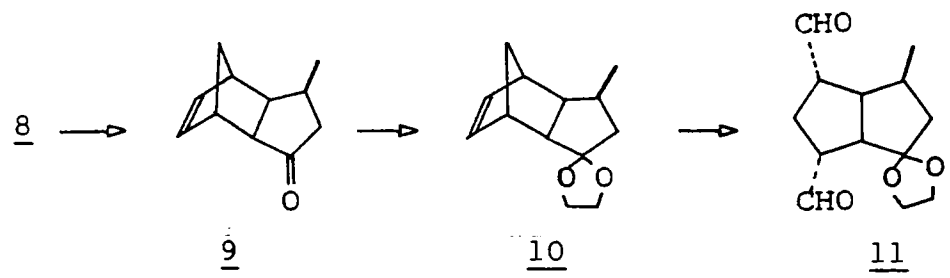
Different oxidation methods are available for the oxidation of secondary alcohol 6[12-15] to the ketone 8. Also the ketone 8 can be obtained directly from exo-dicyclopentadiene by treatment with pyridinium dichromate in presence of tertiary butyl hydroperoxide[16] (Scheme 4).



Scheme 4

The next step in the proposed scheme is introduction of a $-CH_3$ group at position-3 of the α-β unsaturated ketone 8. This can be achieved by methylation using cuprous ion catalysed methyl magnesium iodide or lithium dimethyl cuprate [17].

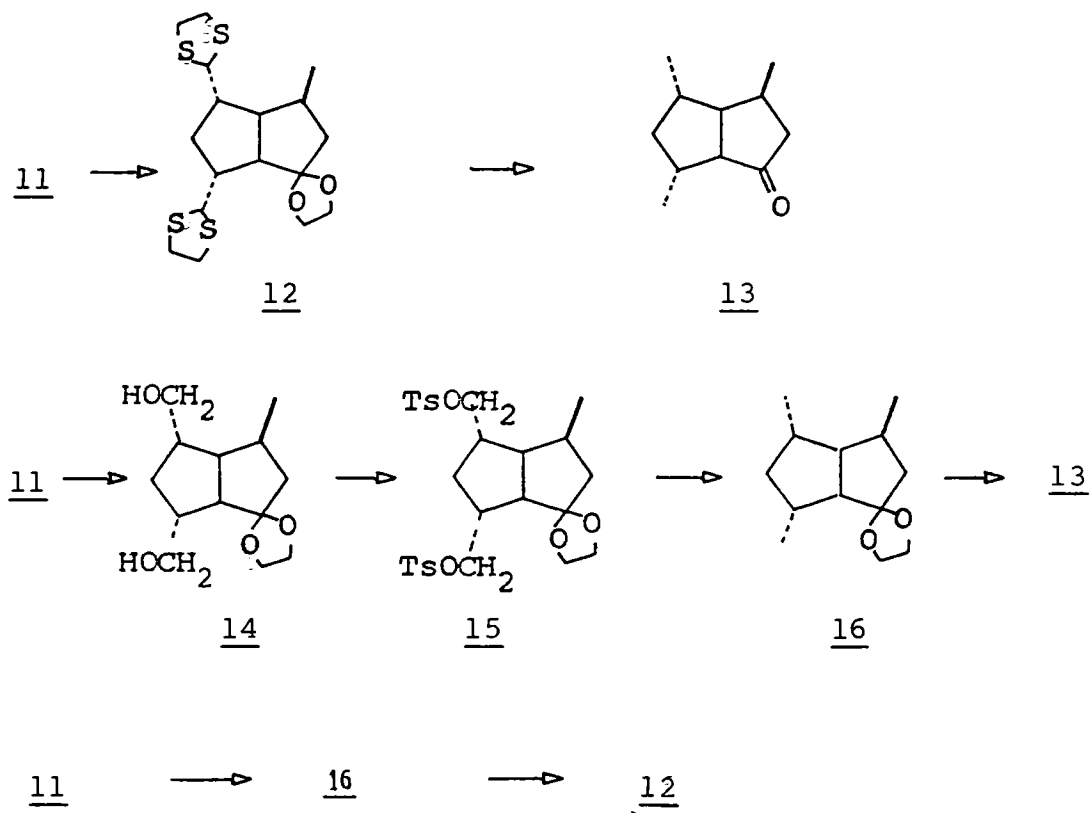
The carbonyl group of the ketone 8 has to be protected before conducting the oxidative cleavage of the double bond. Hence it was converted to the ketal 10 and subjected to oxidation with potassium permanganate or osmium tetroxide in presence of sodium meta periodate to get the dialdehyde 11 (Scheme 5).



9 10 11

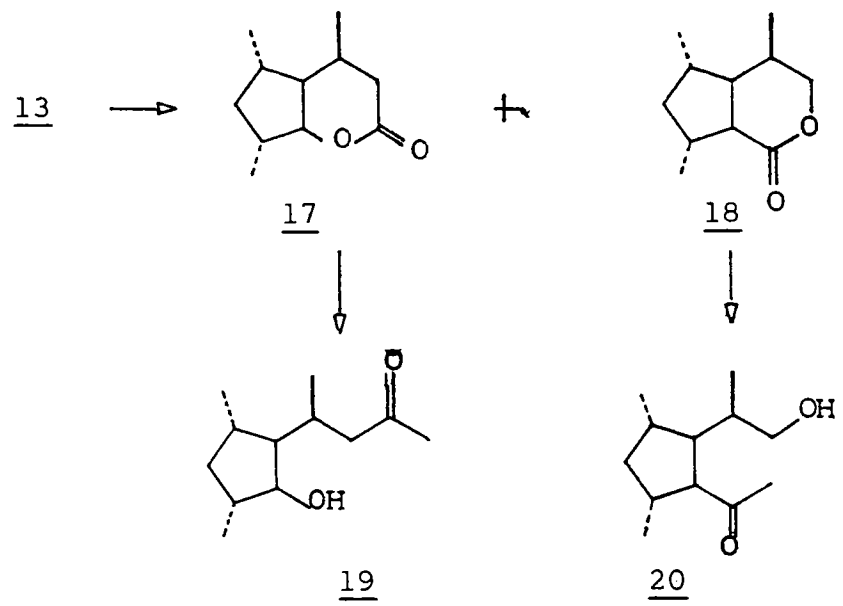
Scheme 5

It was necessary to reduce the two aldehyde groups of 11 to $-CH_3$ groups so that they become the $-CH_3$ groups at position-4 and -6 in the target molecule. Different methods are available for the conversion of aldehyde groups to $-CH_3$ groups[18-20] (Scheme 6). Conversion of the aldehyde to the corresponding thioketal 12 followed by reduction with Raney-Ni should give the required ketone 13. Also reduction of the aldehyde 11 to alcohol 14 followed by tosylation and reduction with lithium aluminium hydride is expected to give the ketone 13. Another method is the Huang-Minlon modification of Wolff-Kishner reduction by which the aldehyde 11 can be converted to the ketone 13.



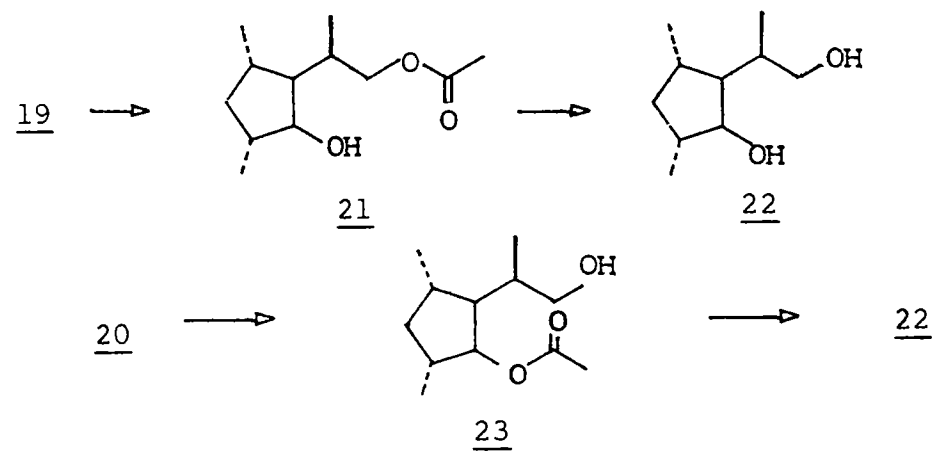
Scheme 6

The ketone 13, a key intermediate in the proposed scheme, can be converted to a lactone by Baeyer-Villiger oxidation (Scheme 7). However, depending upon the peracids and reaction conditions two products can be expected from 13. The lactones 17 and 18 thus obtained after the Baeyer-Villiger oxidation of 13 can be converted to the corresponding alcohols 19 and 20 by treating with CH_3Li.



Scheme 7

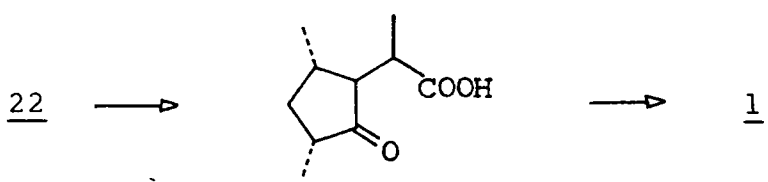
The products 19 and 20 can be converted to the alcohol 22 by Baeyer-Villiger oxidation followed by hydrolysis of the ester obtained (Scheme 8). In short the



Scheme 8

ketone 13 can be converted to 22 irrespective of the structure of the lactone obtained from it by Baeyer-Villiger oxidation.

The alcohol 22 can be oxidised to a keto acid 24. The final step in the proposed scheme (Scheme 9) is conversion of the 24 to the target molecule 1 by Baeyer-Villiger oxidation.

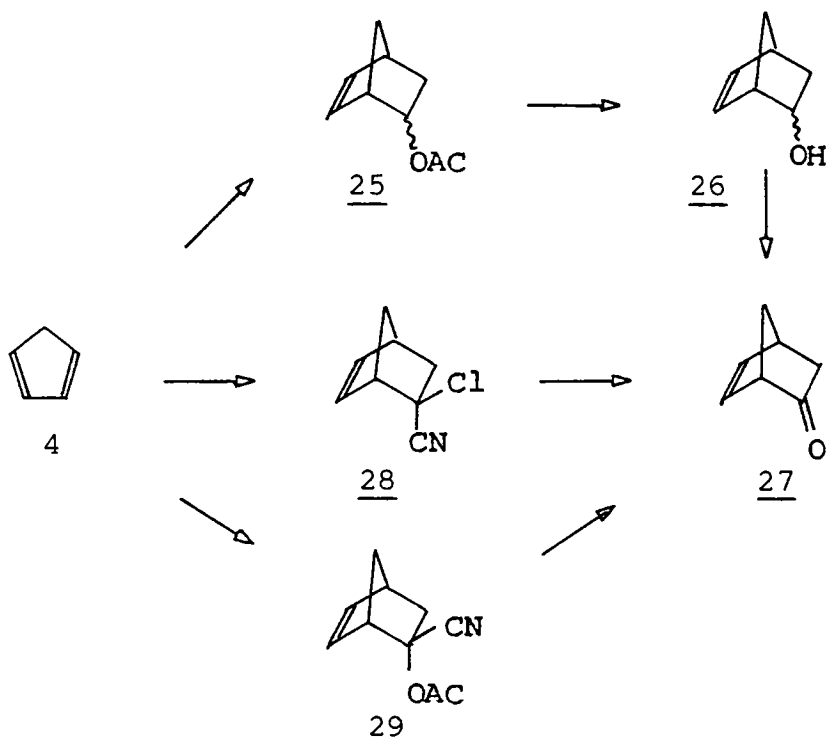


24

Scheme 9

2.3 SYNTHESIS VIA DEHYDRONORCAMPHOR

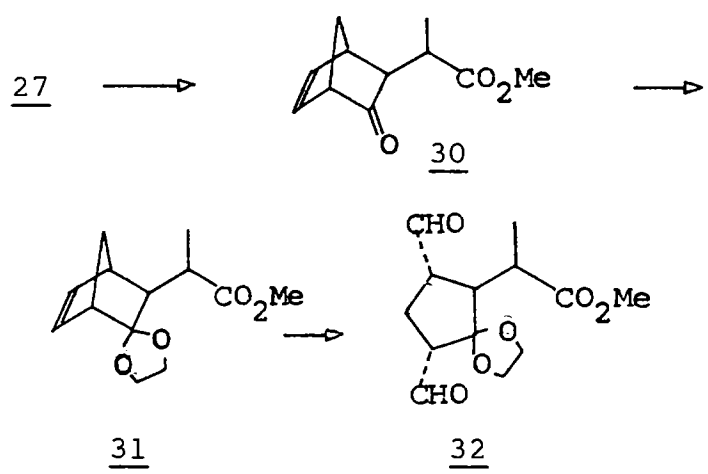
Dehydronorcamphor (27) is an important intermediate for the synthesis of natural products like prostaglandin [21]. In the present work it was proposed to devise a new synthetic route for the synthesis of Prelog-Djerassi lactone using dehydronorcamphor. Different methods are available for the synthesis of dehydronorcamphor (Scheme 10).



Scheme 10

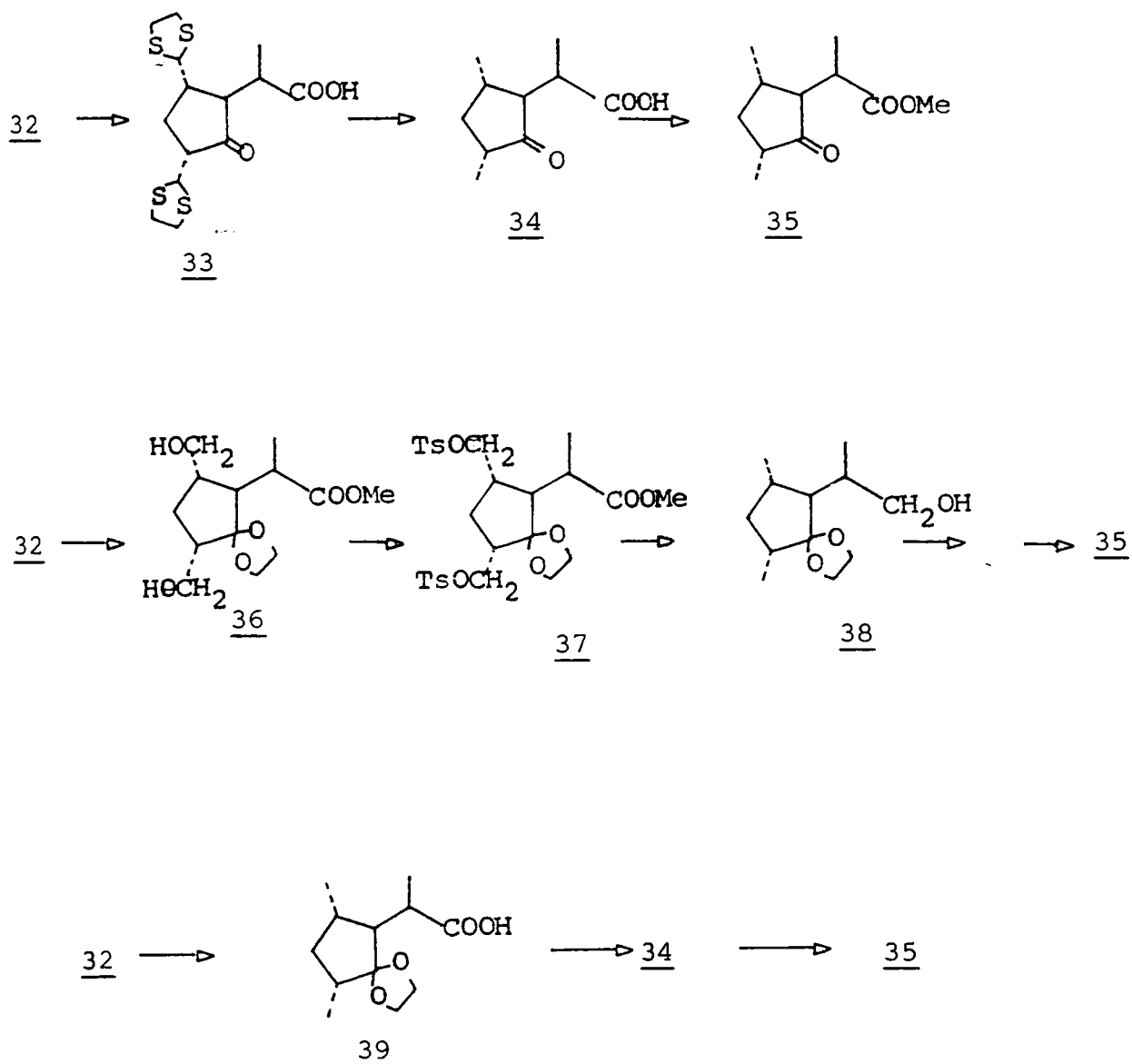
Diels-Alder reaction of cyclopentadiene (4) with vinyl acetate followed by hydrolysis of the acetate 25 and oxidation of the resulting alcohol should give the ketone 22. Diels-Alder reaction of cyclopentadiene with ∝-chloro-acrylonitrile[23] and ∝-acetoxy acrylonitrile[24] are also expected to get compounds 28 and 29 respectively which can be further converted to the ketone 27 by treatment with aqueous potassium hydroxide.

Alkylation of the ketone 27 with methyl ester of ∝-chloropropanoic acid can lead to the ketone 30 which can be converted to the dialdehyde ester 32 (Scheme 11). The carbonyl group of 30 was protected as ketal 31 and subjected to oxidative cleavage of the double bond using potassium permanganate or osmium tetroxide in presence of sodium metaperiodate.



Scheme 11

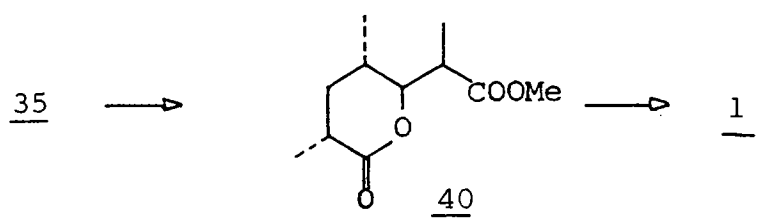
Conversion of aldehyde groups in 32 to $-CH_3$ groups can be achieved by different methods (Scheme 12). Conversion of 32 to keto acid 34 via thioketal 33 followed by esterification is expected to give the keto ester 35. By another method the keto ester 35 can also be prepared



Scheme 12

from 32 by a series of chemical reactions via the thiol 36, the tosylate 37, the ketal 38 and the keto acid 34. In another route for the synthesis of 35, the 32 can be subjected to modified Wollf-Kishner reduction of the -CHO groups followed by esterification.

The keto ester 35 is another key intermediate in the synthesis of Prelog-Djerassi lactone since it can be converted to the lactone 40 by Baeyer-Villiger oxidation (Scheme 13). Since the stereochemistry of methyl group at position-2 has not been fixed, the ester 40 can lead to the target molecule, as a mixture of epimers at position-2. There have been reports of enzyme catalysed hydrolysis[25] of recemic ∝-substituted carboxylic esters. The chance of



Scheme 39

hydrolysis of these esters is decided by the stereochemistry of the substituent at α-position. It is reported that in the case of methyl substituted esters, the ester with methyl group having β-configuration will be hydrolysed and the other isomer will remain unhydrolysed. Hence it is possible to hydrolyse the methyl ester 40 to get the target molecule by enzymic hydrolysis.

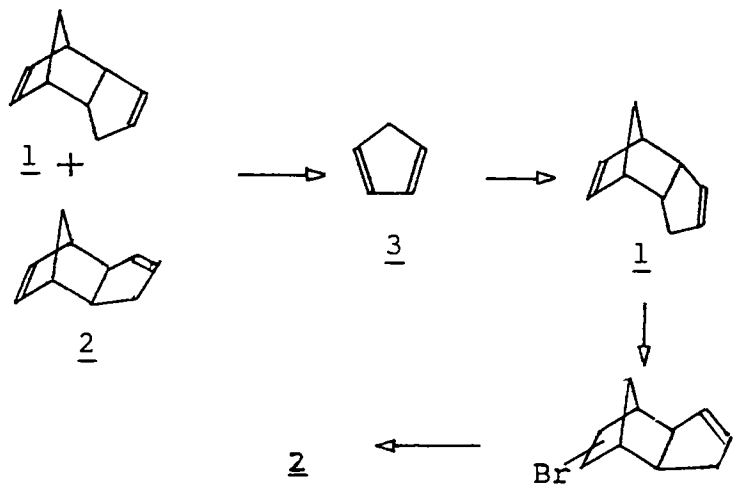
CHAPTER III

RESULTS AND DISCUSSION

3.1 Synthesis of exo-Dicyclopentadienol (5)

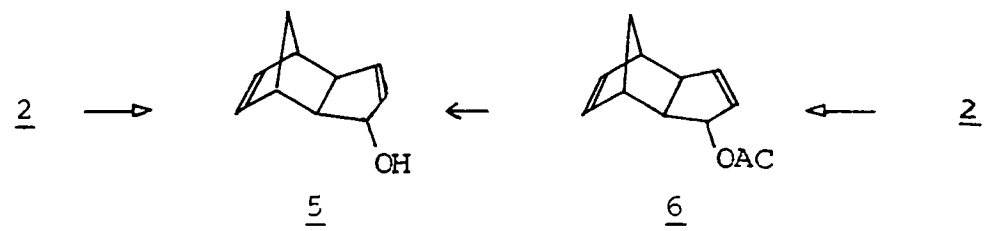
exo-Dicyclopentadienol (5) was prepared from exo-dicyclopentadiene (2). Commercially available dicyclopentadiene is a mixture of both endo-dicyclopentadiene and exo-dicyclopentadiene in which endo-isomer is the major one. Here the exo-isomer was selected as the starting material because it is having the right stereo chemistry by which the introduction of different substituents in the proposed scheme can be achieved easily. It was decided first to convert the mixture of dicyclopentadiene into completely endo-isomer (Scheme 1). This was carried out by cracking[1] the mixture of endo- and exo-dicyclopentadiene to its monomer-cyclopentadiene and allowing the monomer to dimerise slowly at 0°C into the endo-isomer[2]. The endo-isomer was finally purified by distillation under reduced pressure (59°C, 17 Torr).

The endo-isomer thus obtained was converted to exo-isomer by a chemical method[3]. A solution of 48% hydrobromic acid was treated with the endo-isomer and HBr adduct formed was subjected to dehydrobromination with alcoholic KOH to get the exo-isomer in 80% yield. Further purification of exo-isomer was done by distillation under reduced pressure (63°C, 11 Torr).



Scheme 1

...e exo-dicyclopentadiene (2) was refluxed with ...ium dioxide in a mixture of dioxane and water for 3 ... ...eme 2). The alcohol 5 was isolated from the aqueous solution by extraction with ether. Evaporation of ether followed by fractional distillation (106°C, 7 Torr) gave the alcohol 5 in 51% yeld [4]. The alcohol 5 was also obtained by the hydrolysis of the acetate 6 formed by the seleniumdioxide oxidation of exo-dicyclopentadiene in acetic acid. By this method alcohol 5 was obtained in 70% yield [4]. Formation of the acetate 6 was confirmed by IR absorption at 3050 C^{-1} (=CH-), 1735 (-$\overset{O}{\overset{\|}{C}}$-O-), 1100 cm^{-1} (-C-O). ^1H NMR spectrum showed 3H singlet at δ 3.4 ($-OCH_3$)



5 6

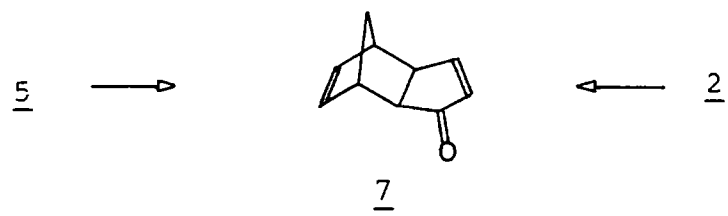
Scheme 2

and multiplet of olefinic hydrogen at δ5.9 and δ6.3. The alcohol 5 showed characteristic absorption for -OH group at 3450 and 1050 cm^{-1} in the IR spectrum.

3.2 Tricyclo[5.2.1.$0^{2,6}$]deca-3,8 dien-5-one (Dicyclopentadienone) (7)

Oxidation of secondary alcohols by hexavalent chromium derivatives is the most commonly employed method to prepare ketones. Usually Jones reagent[5] is used for this purpose. Although oxidation with aqueous chromic acid has long been a standard method, many modified procedures have been developed to employ the isolation process, to achieve certain selectivity and to improve the yield as well as purity of the products [6]. Oxidation of secondary alcohol proceed very simply and cleanly in a two phase system involving ether and chromic acid [7]. Adopting this

procedure a solution of dicyclopentadienol (5) in ether was treated with freshly prepared 8N chromic acid at 0°C. After usual work up the ketone 7 was obtained in 82% yield (Scheme 3). The ketone 7 was further purified by distillation under reduced pressure (82-87°C, 4 Torr).



Scheme 3

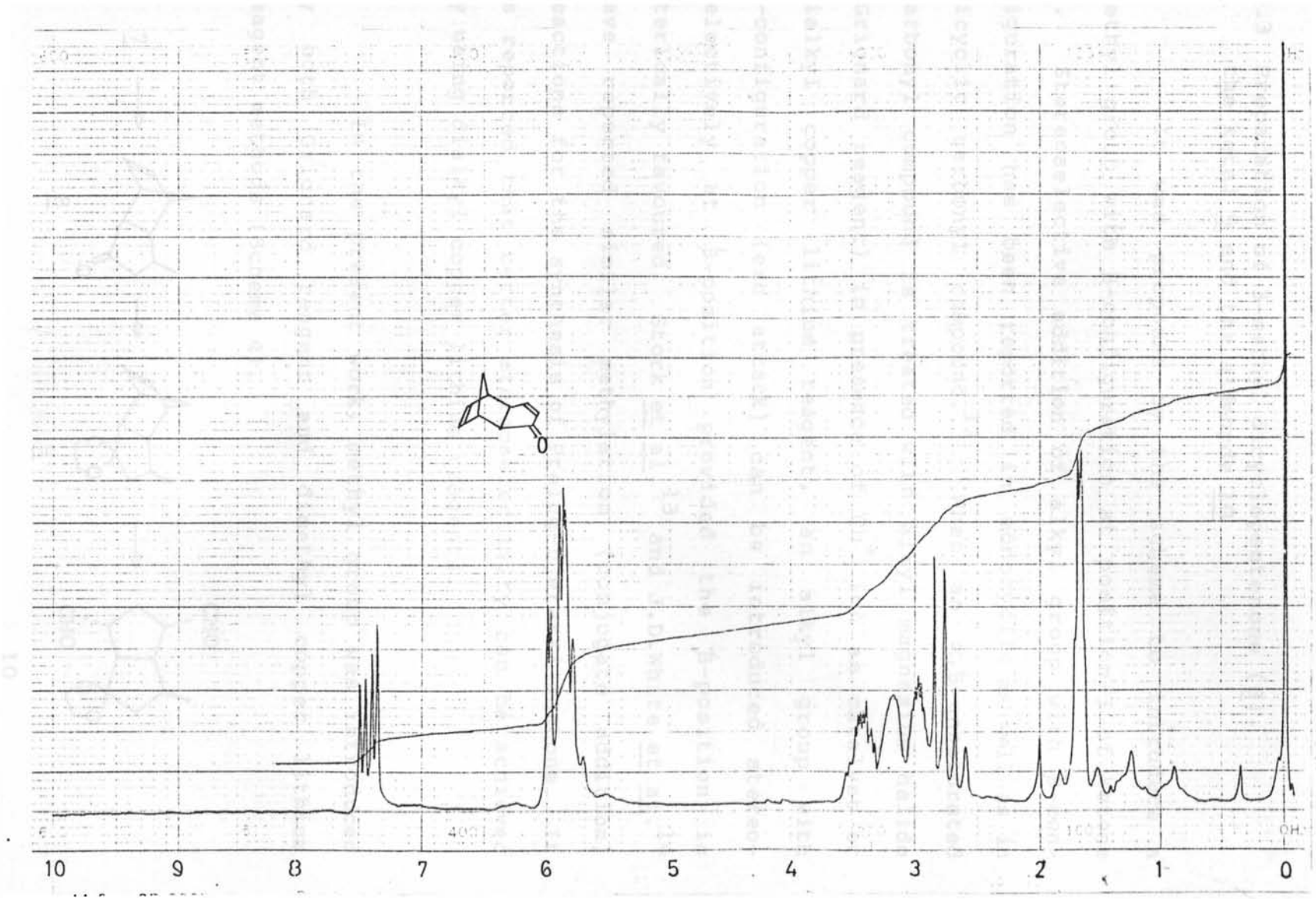
Oxidation of dicyclopentadienol (5) was also carried out using a versatile oxidant-pyridinium chloro chromate (PCC) [8]. It shows a high capability to convert primary alcohols to aldehydes and secondary alcohols to ketones. Oxidation is carried out in nonaqueous solvents like CH_2Cl_2. Hence isolation of product is easy compared to the chromic acid oxidation in aqueous conditions. PCC was prepared by adding pyridine to a solution of CrO_3 in 6N HCl with stirring at 0°C. Orange-yellow crystals formed was filtered and dried to get the reagent in 80% yied [8].

The oxidation of 5 was carried out by adding the reagent slowly to a solution of the alcohol 5 in CH_2Cl_2

with stirring and keeping the reaction temperature below 20°C. The product formed was purified by column chromatography to get ketone 7 in 85% yield.

Oppenauer oxidation was also tried for the oxidation of alcohol 5. By this method the alcohol was treated with a mixture of p-benzoquinone and aluminium t-butoxide in dry benzene. After six hours of reaction the ketone 7 was isolated in 75% yield.[9]

A number of methods are available for allylic and benzylic oxidations using Cr(VI) complexes. Recently a method has been introduced to convert dicyclopentadiene directly to the ketone 7 [10]. In this method a combination of t-butyl hydroperoxide and pyridinium dichromate[11] has been used to oxidise exo-dicyclopentadiene (2) to the ketone 7. But the yield of 7 obtained was only 61%. IR spectrum showed absorption bands at 3040, 1720 and 1620 cm^{-1} which are characteristic of the structure of 7. Structure 7 was further confirmed by ^1H NMR spectrum which had signals for olefinic protons at δ 5.9 as multiplet (-CH=CH-) and 7.4 as multiplet (-CH=CH-C(=O)-).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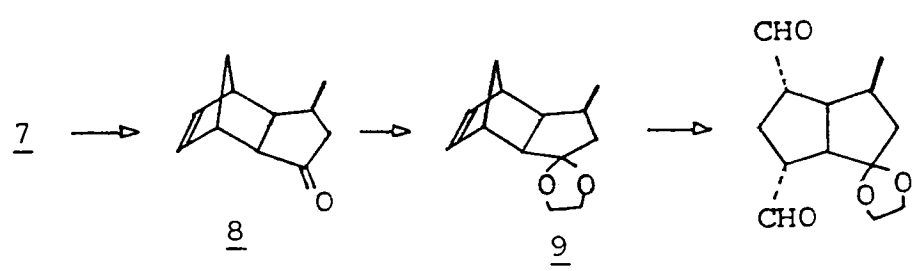
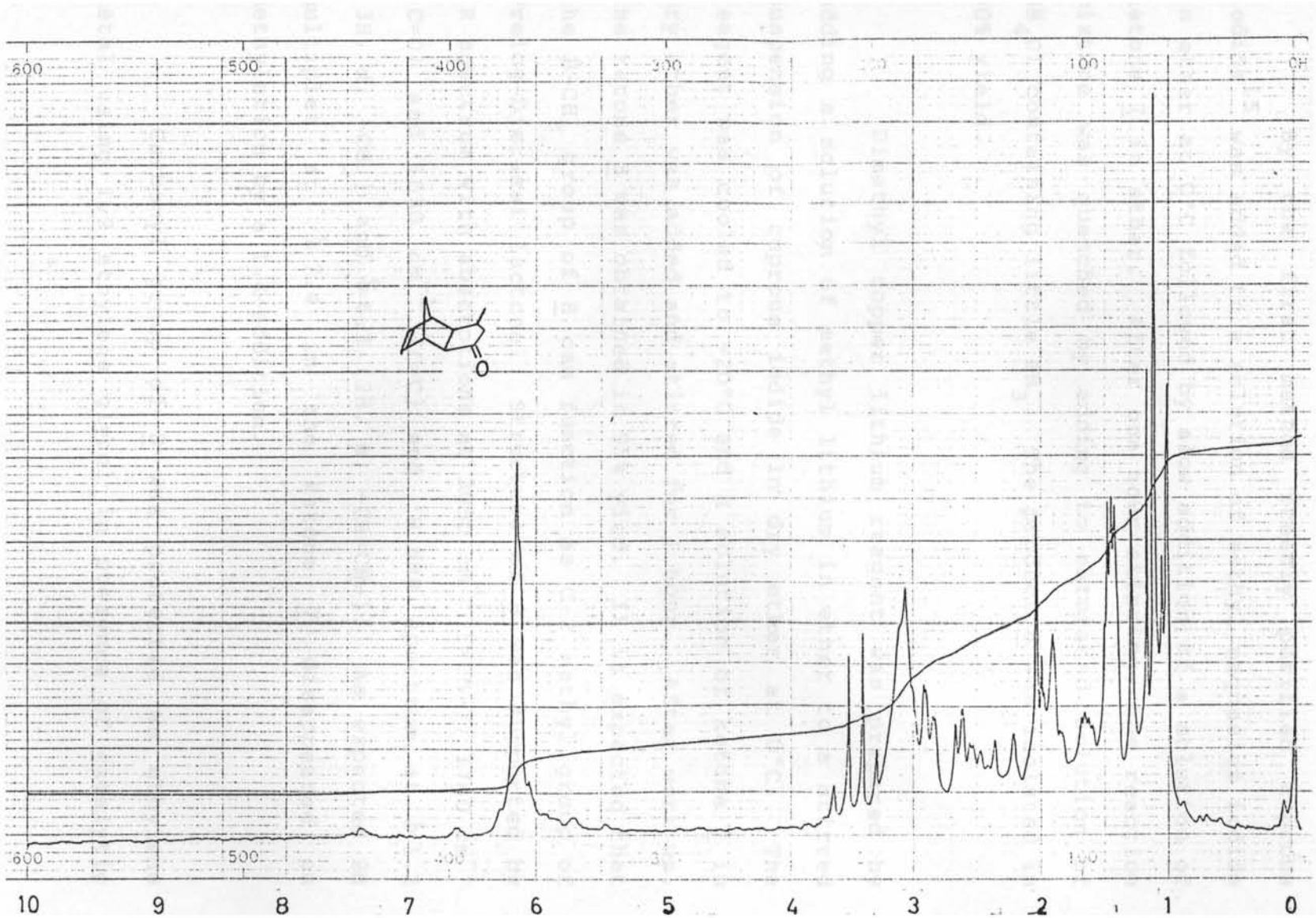
3.3 Preparation of 3-methyl dicyclopentenone (8), the ketal 9 and the aldehyde 10

It was proposed by the scheme to introduce a methyl group with β-configuration at position-3 of ketone 7. Stereoselective addition of alkyl group with β-configuration has been reported in monocyclic as well as in bicyclic carbonyl compound.[12] When an α,β-unsaturated carbonyl compound is treated with alkyl magnesium halide (Grignard reagent) in presence of Cu^+ ion as catalyst or dialkyl copper lithium reagent, an alkyl group with β-configuration (exo attack) can be introduced stereoselectively at β-position provided the β-position is sterically favoured. Stork et al.[13] and J.D.White et al.[14] have reported similar methylation (conjugate addition) reactions for the synthesis of Prelog-Djerassi lactone. It is reported that better stereoselectivity can be achieved by using dialkyl copper lithium reagents.

In the present work, methyl group was introduced by both Grignard reagent and dimethyl copper lithium reagent methods (Scheme 4).



Scheme 4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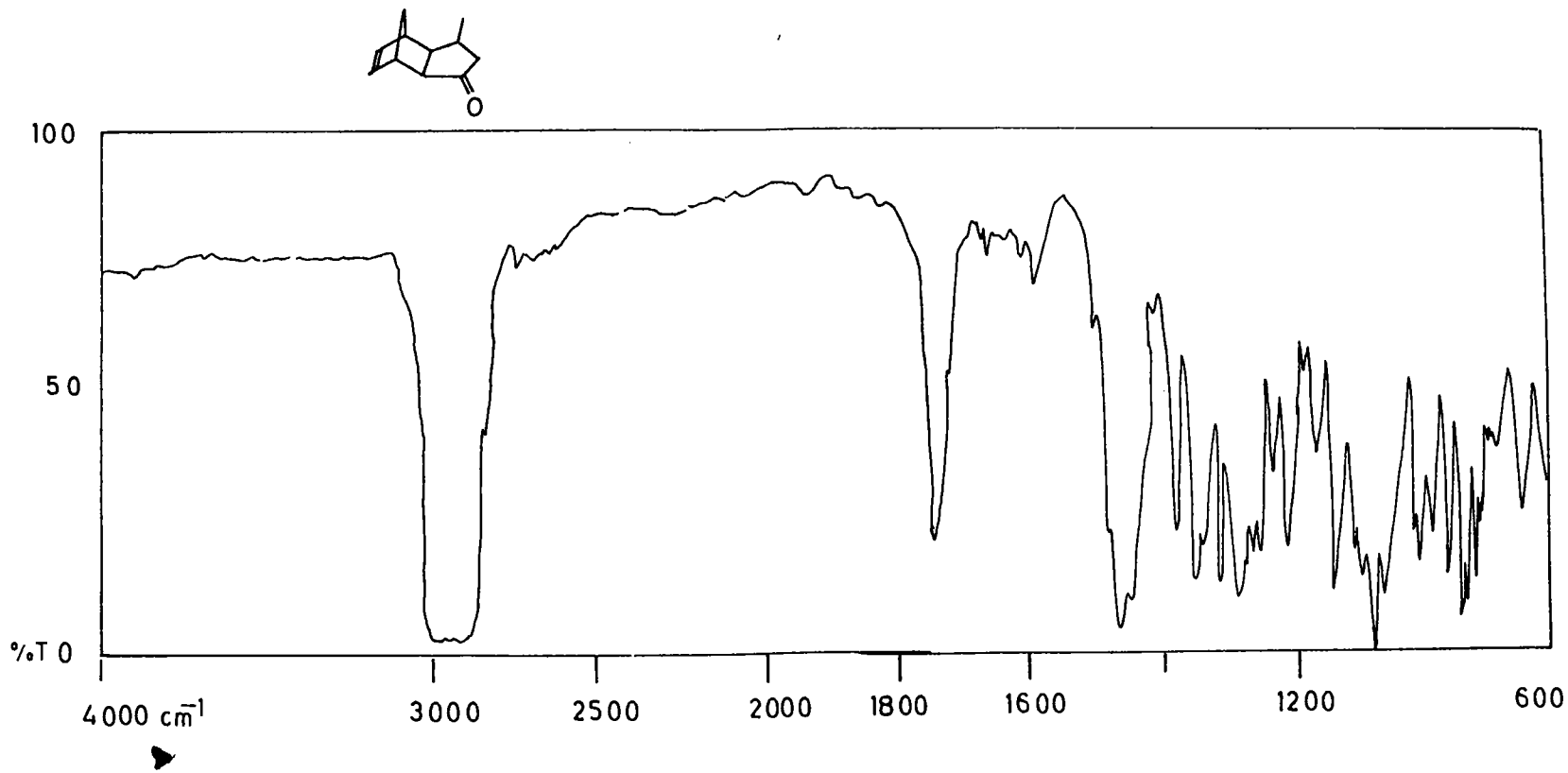
By the first method freshly purified cuprous iodide[15] was added to a solution of methyl magnesium iodide in ether at 0°C followed by slow addition of a solution of ketone 7 in ether. After one hour stirring, the reaction mixture was quenched by adding to saturated solution of NH_4Cl containing little NH_3. The product 8 was isolated in 90% yield.

Dimethyl copper lithium reagent was prepared by adding a solution of methyl lithium in ether to a stirred suspension of cuprous iodide in dry ether at 0°C. The reagent was cooled to -20°C and a solution of ketone 7 in dry ether was added and stirred for 1 hour. After work up, the ketone 8 was obtained in 95% yied. It is expected that the β-CH_3 group of 8 can function as C-2 methyl group of Prelog-Djerassi lactone. Structure of 8 was supported by IR spectrum with absorptions at 3050 cm^{-1} (=CH-), 1740 cm^{-1} (C=O) and 1630 cm^{-1} (C=C) and 'H NMR spectrum at δ 1.2 (3H, d, $-CH_3$) and δ 6.3 (2H, m, -CH=CH-). As expected 2H multiplet at δ 7.4 in the ketone 7 disappeared on methylation by a 1,4-addition.

Carbonyl group of 8 was protected as ethylene ketal using 1,2 ethylene glycol in presence of catalytic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%T 0
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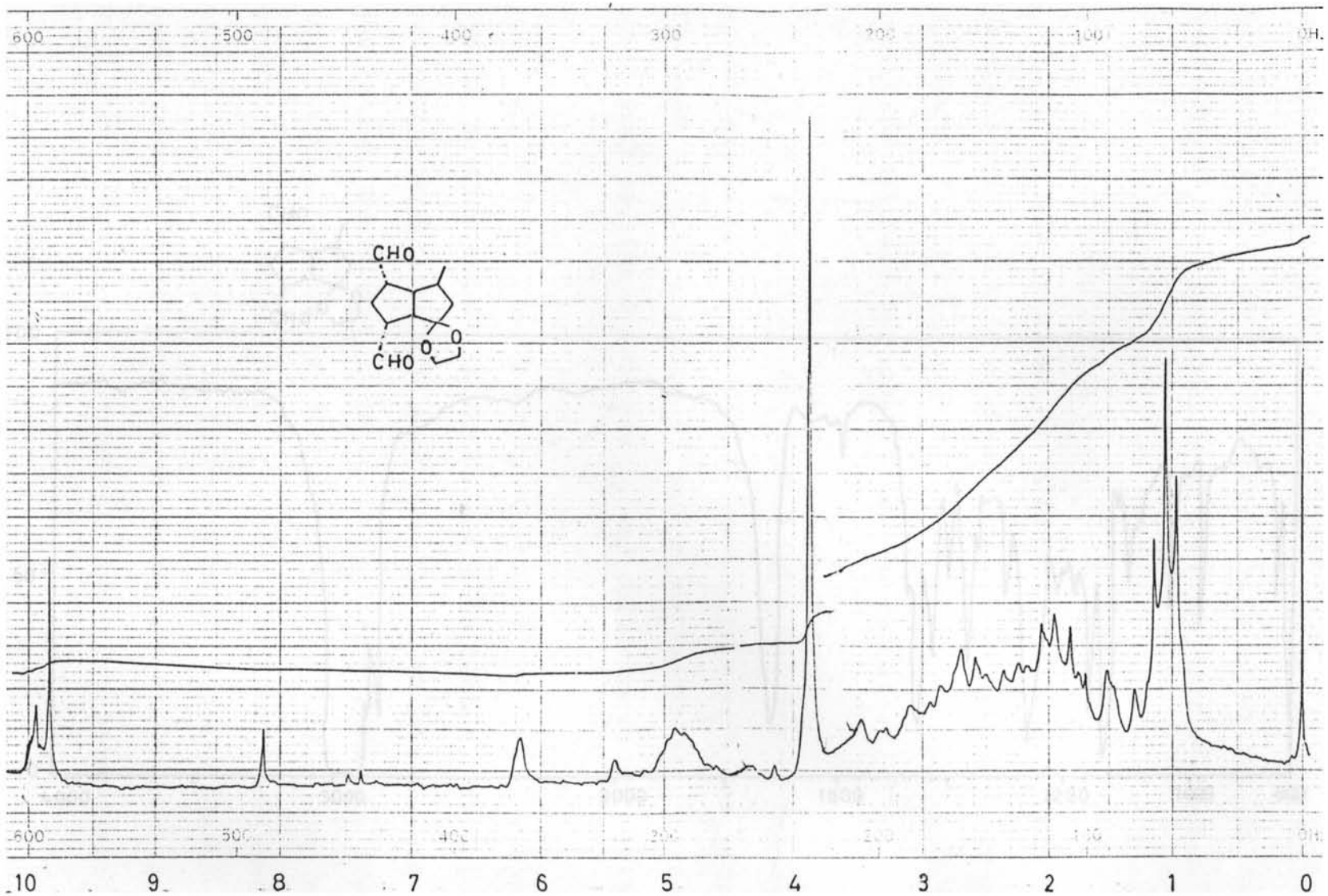
2000
1800
1600
1200
600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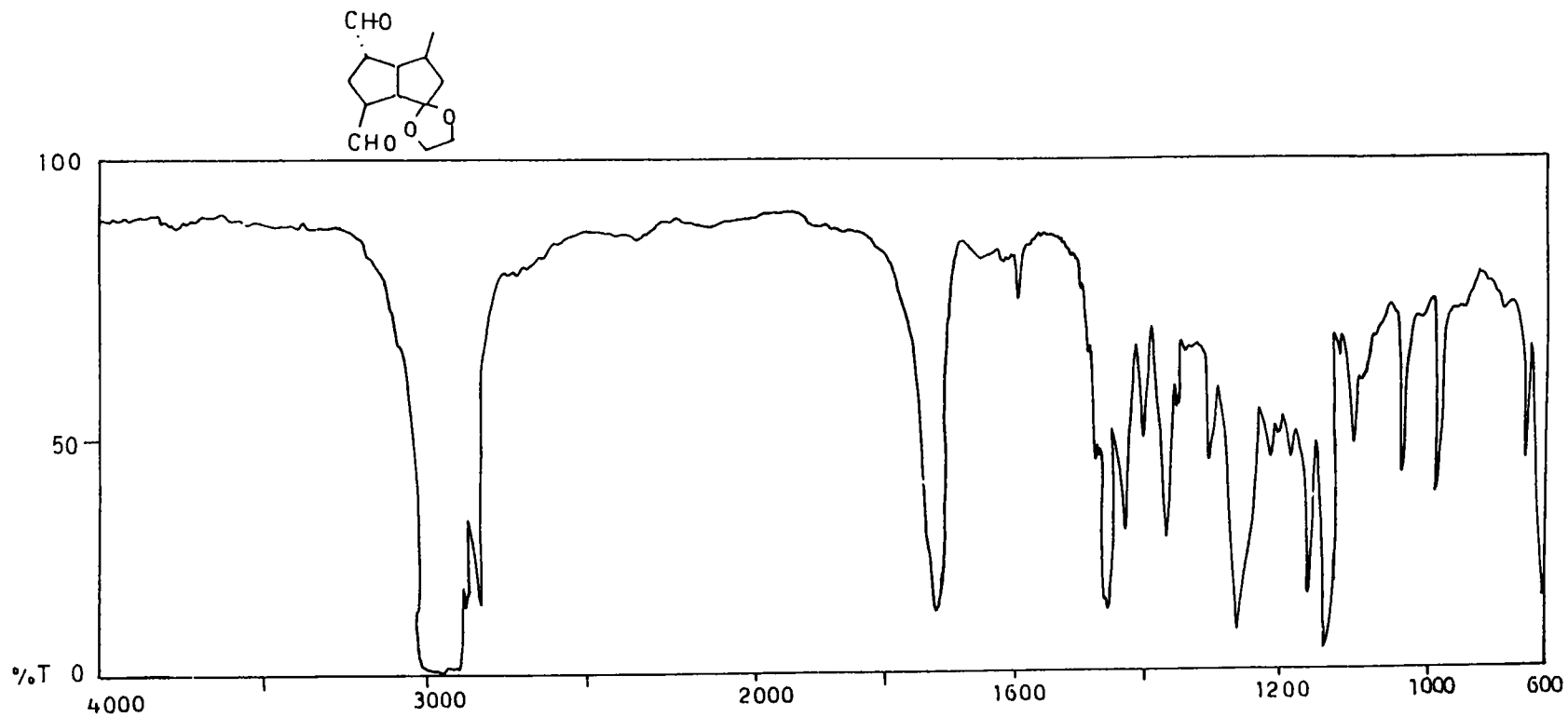
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amount of p-toluenesulphonic acid. Formation of ketal 9 was confirmed by the 'H NMR signal at δ 3.8 as singlet for 4H ($-OCH_2-CH_2-O-$) and absence of IR absorption at 1740 cm^{-1} (C=O).

It was required to cleave the double bond of 9 resulting in the formation of two aldehyde groups (Scheme 4). A combination of OsO_4 and sodium-meta periodate was used for the double bond oxidation.

To a solution of ketal 9 in a mixture of dioxane and water, catalytic amount of osmium tetroxide was added followed by slow addition of sodium metaperiodate. After usual work up, the dialdehyde 10 was obtained in 80% yield.

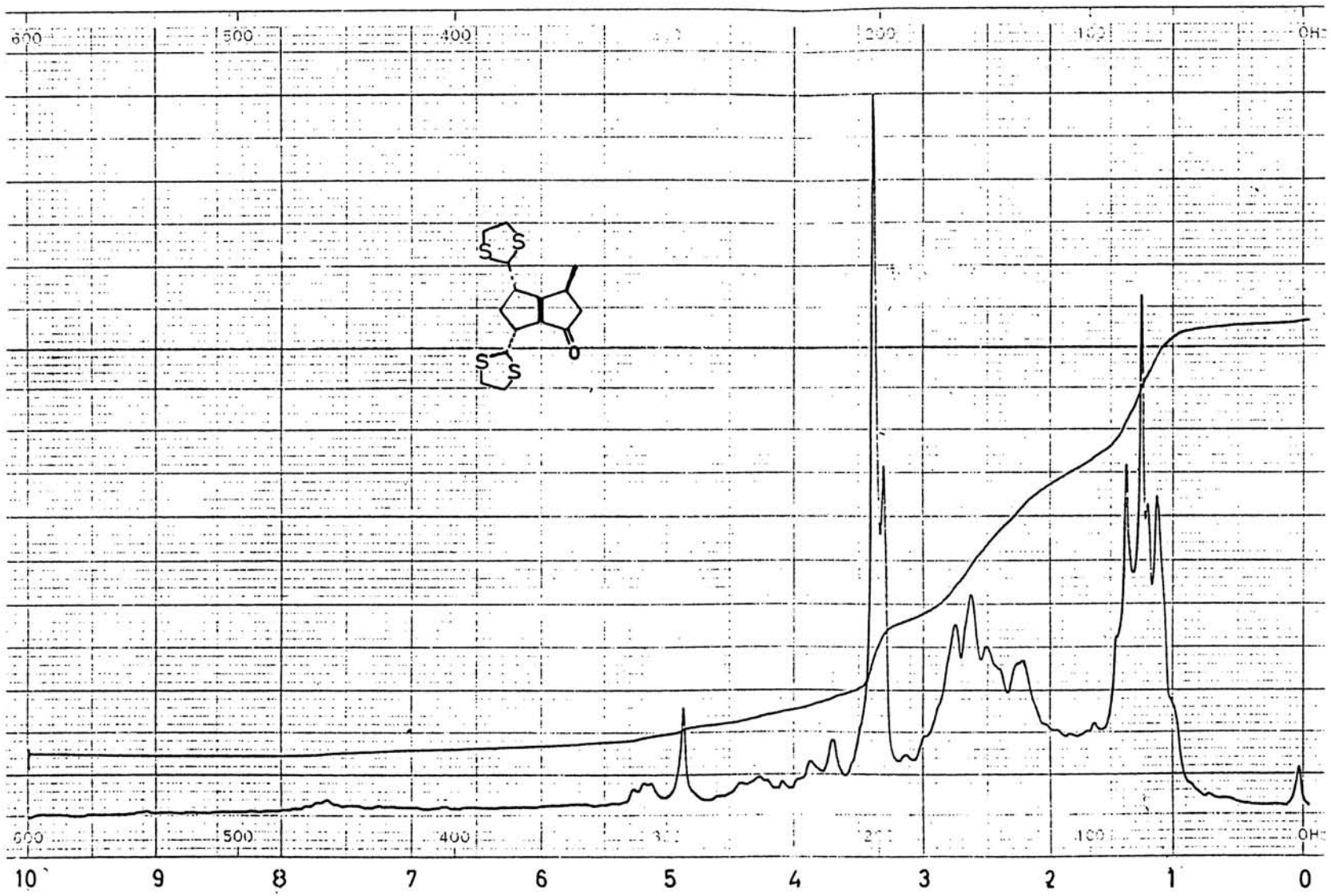
Oxidation using $KMnO_4$ or OsO_4 is generally carried out in aqueous condition or in polar solvents. Similarly periodate oxidations are also associated with water as a solvent or co-solvent. Hence isolation of products from the reaction medium is difficult and require a lot of effort. Considering these drawbacks of $KMnO_4$ periodate oxidation and toxicity of Os reagents quarternary ammonium permanganates[16] and quarternary ammonium periodates[17] are used now. Among the quarternary ammonium permanganates

cetyl trimethyl ammonium permanganate is the one widely used. It was prepared by mixing a saturated solutions of cetyl trimethyl ammonium bromide and $KMnO_4$ in water at 0°C. The solid formed was filtered and dried. Benzyl triethyl ammonium periodate is another reagent among quarternary ammonium periodates. It was prepared by adding a solution of $NaIO_4$ in water to a solution of benzyl triethyl ammonium chloride in water at 0°C. The precipitated reagent was filtered and dried in vacuo.

The double bond oxidation was attempted with above mentioned cetyltrimethyl ammonium permanganate and benzyl triethyl ammonium periodate in a mixture of CH_2Cl_2 and dioxane as solvent system. The aldehyde 10 isolated was only 75% IR spectrum showed absorptions at 2830 cm^{-1}, 2760 cm^{-1} and 1720 cm^{-1} and 'H NMR signals at δ 9.8 the aldehyde formation.

3.4 Conversion of aldehyde 10 to ketone 12

Conversion of two aldehyde groups in 10 to corresponding $-CH_3$ groups is the next step in the proposed scheme. Reduction of aldehyde to hydrocarbons is a very common reaction in synthetic organic chemistry. Several methods are available for this conversion.[18-20] In the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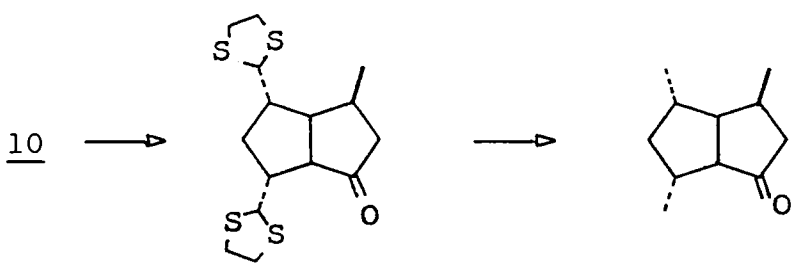
proposed scheme three routes were investigated. In the first method the two aldehyde groups in 10 were converted to thioketal 11 and reduction of this thioketal with Raney-Ni gave the expected ketone 12 (Scheme 5). 1,2-ethanedithiol was prepared in 60% yield[21] by treating ethylene dibromide with thiourea and treating the resulting



11 12

Scheme 5

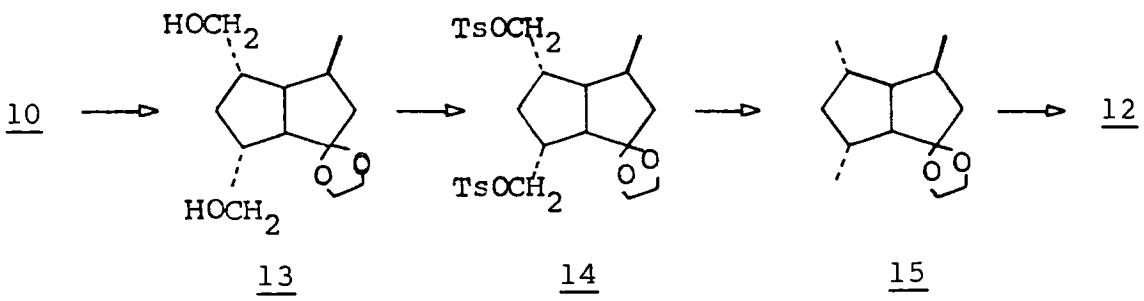
adduct with KOH. Thioketal 11 was prepared by adding 1,2-ethane dithiol to a solution of aldehyde 10 followed by catalytic amount of freshly distilled BF_3-etherate. Thioketal 11 was obtained in 70% yield which had 'H NMR signal at δ 3.4 as multiplet ($-S-CH_2-CH_2-S-$) and aldehyde signal at δ 9.8 in 10 was not present. In the IR spectrum absorption at 1740 cm^{-1} characteristic of C=O group was present. This is because of the removal of the ketal by BF_3 etherate. Absence of 'H NMR signal at δ 3.8 ($-OCH_2-CH_2-O-$) also confirmed the deketalization.

Raney-Nickel catalyst[22] (W2 grade) was prepared and the thioketal 11 was refluxed with it in dry ethanol. The ketone 12 was isolated from the reaction mixture in 80% yield.

As a desulphurization reagent the Raney-Ni has now been replaced by numerous heterogeneous nickel reagents[23,24] because of the tedious preparation, hazards in handling, difficulty in determining of the weight and necessity of large Ni/S ratio. Complete desulphurization of dithioketal can be effected in high yield with Nickel complex reducing agents [25]. Half desulphurization can be effectively achieved with 2,2'bipyridine modified nickel complex reducing agents.

For the present purpose the reagent was prepared by adding a solution of tertiaryamyl alcohol in dry THF to a mixture of nickel acetate and NaH in boiling THF. To the freshly prepared reagent the thioketal 11 was added and refluxed for 1 hour, and the product 12 was isolated in 60% yield. From the 'H NMR spectrum absence of signals at δ 3.4 multiplet ($-S-CH_2CH_2-S$) and formation of a broad signal at δ1.1-1.3 corresponding to three CH_3 groups confirmed the structure of 12. Structure was further confirmed by mass spectrum (m/z = 166 (M^+)).

In the second method the aldehyde groups of 10 were reduced to alcohols 13 and the -OH groups were converted to tosylate 14. Reduction of tosylate 14 with lithium aluminium hydride gave the ketal 15 which on deketalization afforded the ketone 12 (Scheme 6).



13 14 15

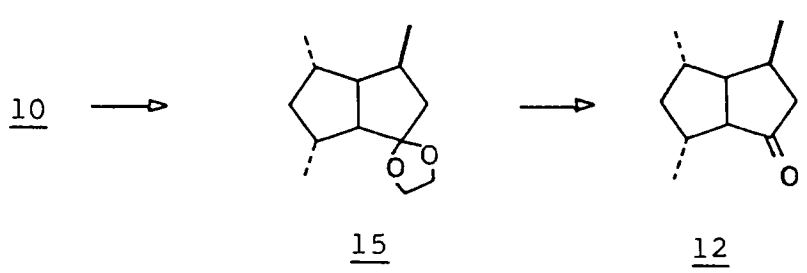
Scheme 6

Sodium borohydride was added slowly to a solution of aldehyde 10 in CH_3OH at 15°C. After the reaction, the mixture was quenched by adding to water and after work up the alcohol 13 was obtained in 80% yield. Formation of the alcohol was confirmed by appearance of IR absorption band at 3550 cm^{-1} and 1060 cm^{-1} and absence of aldehyde signals at 2830 cm^{-1}, 2760 cm^{-1} and 1720 cm^{-1}. ^1H NMR spectrum also confirmed the conversion of aldehyde by the absence of signal at δ 9.8. Without further purification the alcohol 13 was treated with a solution of p-toluene sulphonyl-

chloride in CH_2Cl_2 in presence of slightly excess dry triethylamine. After usual work up the residue was dried *in vacuo* to get the tosylate 14 in 95% yield.

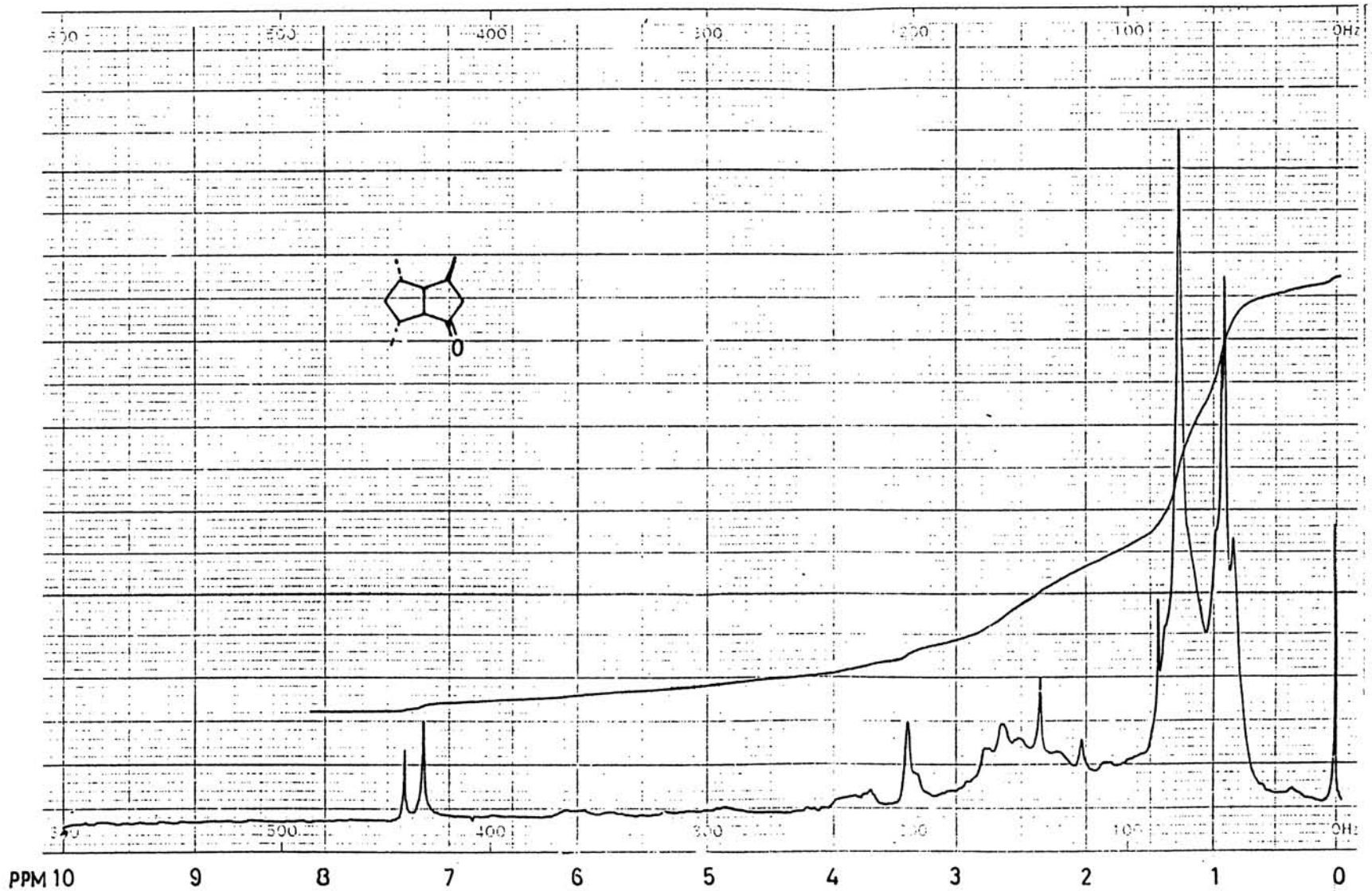
The dry and purified tosylate 14 was stirred with lithium aluminium hydride in refluxing ether for 15 hours. The reaction mixture was quenched by slow addition to ice water, extracted with ether and dried. Column chromatographic purification afforded the ketal 15 in 56% yield. The ketal group of 15 was removed by refluxing it with a solution of acetone and water in presence of little p-toluene sulphonic acid. The product 12 was obtained in 95% yield.

In the third method the conversion of aldehyde group of 10 to $-CH_3$ groups was accomplished by the Huang-Minlon modification[26] of Wolff-Kishner reduction[27] (Scheme 7).



15 12

Scheme 7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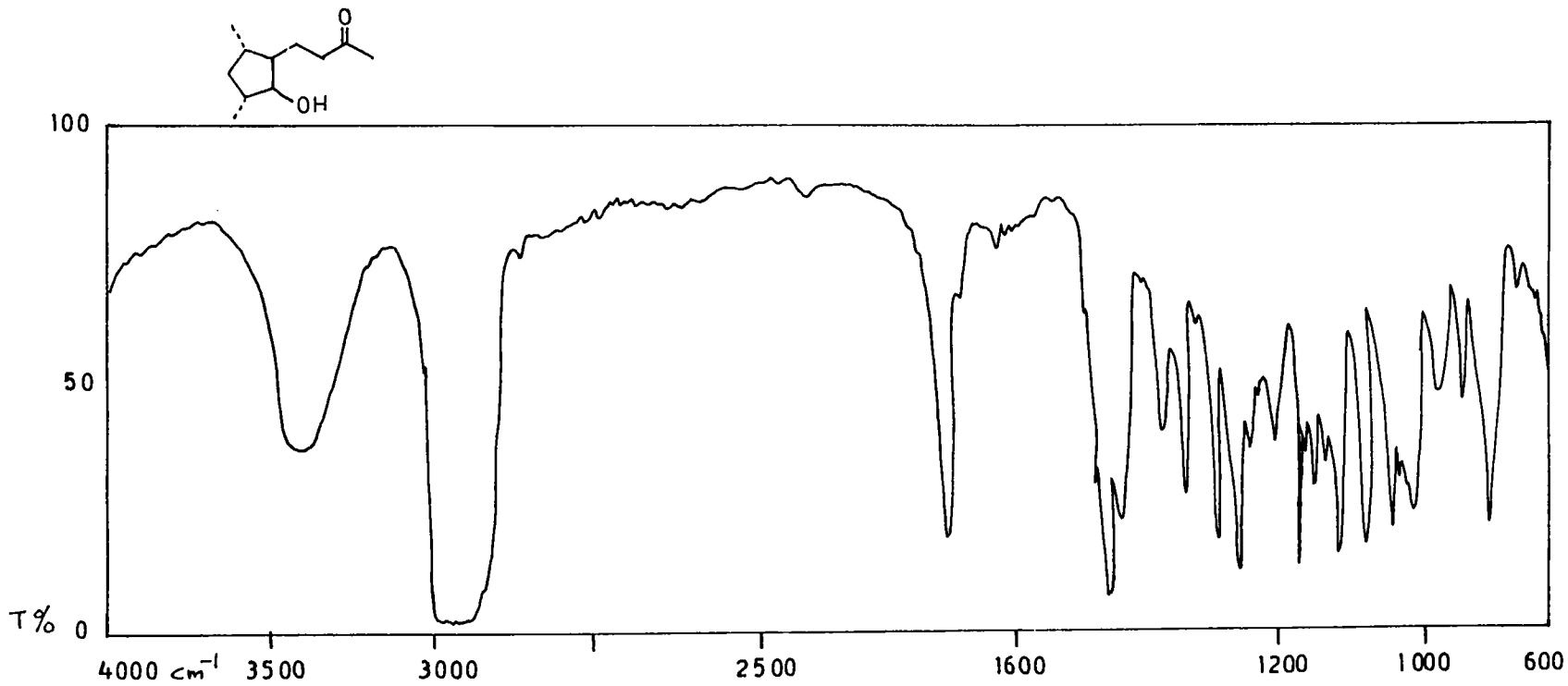
The dialdehyde 10 was refluxed with a mixture of diethylene glycol, hydrazine hydrate and powdered KOH for 4 hours. The reaction mixture was extracted with ether and evaporation of ether afforded the ketal 15 in 61% yield. The ketal group of 15 was removed by refluxing with p-toluene sulphonic acid in a mixture of acetone and water. The deketalised product 12 was obtained in 90% yield.

3.5 Baeyer-Villiger Oxidation of 12

Peracid oxidation of a ketone to an ester was first reported by Baeyer and Villiger [28]. For unsymmetrical ketones regioselectivity of oxygen insertion is decided by the migratory aptitude of groups on either side of the ketone. Besides this migratory aptitude some other factors like steric effects [29], hydrogen bonding capability of substituents [30], peracid employed etc. are also deciding the regioselectivity of oxygen insertion.

The ketone 12 was subjected to Baeyer-Villiger oxidation with a view to open the bicyclic ring by the hydrolysis of the lactone formed. By the mechanism of Baeyer-Villiger oxidation the migratory aptitude of bridge carbon is greater than the methylene carbon. Hence lactone 16 was preferred to 17 (Scheme 8).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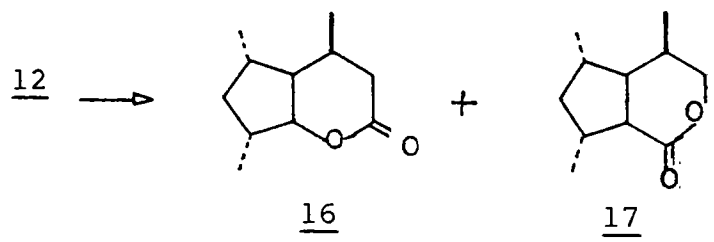
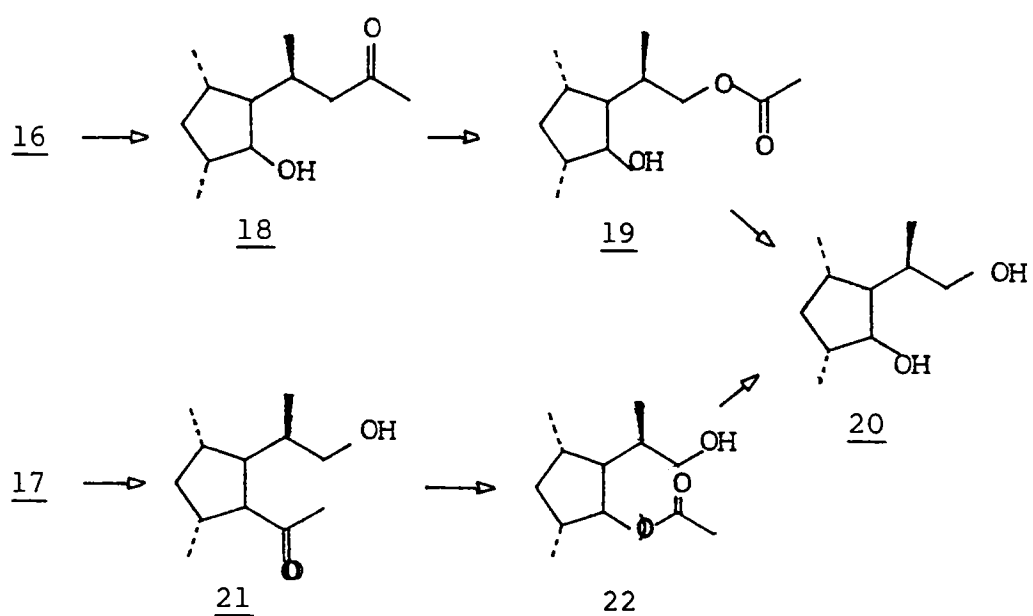


Scheme 8

But the proceeding schemes suggested that both products 16 and 17 can be converted to a single desired product 20 by a convergent step (Scheme 9). 'H NMR signal at δ2 as doublet for 2H and δ4.2 as multiplet for 1H (-OCH-) assigned for the structure of 16 and signals at

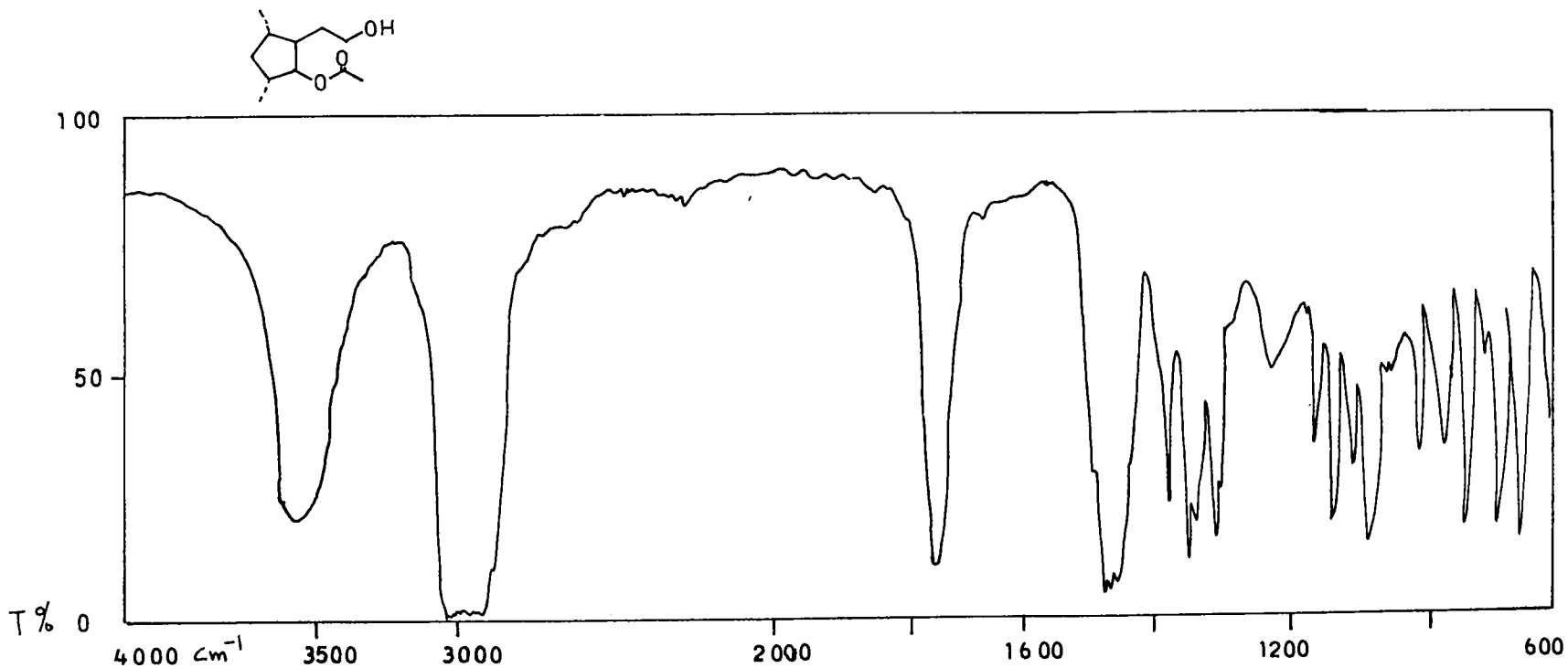


Scheme 9

§2.1 as multiplet for 1H (-$\overset{O}{\overset{\|}{C}}$-CH-) and δ4.1 as doublet for 2H confirmed the structure of 17. IR absorption peaks of 16 and 17 were almost same.

The cleavage of 16 and 17 were achieved treating with methyl lithium. Ether solution of methyl lithium was treated with lactone 16 at -50°C under N_2. The reaction mixture was quenched by pouring into ice water and subsequent work up yielded 90% of the methyl ketone 18. Similarly the methyl ketone 21 was prepared from 17 in 89% yield. Methyl ketone 18 was confirmed by IR absorptions at 3430 cm^{-1} (-OH group) and 1710 cm^{-1} (-C=O). 'H NMR spectrum showed signal at δ 2.1 as singlet for 3H (-$\overset{O}{\overset{\|}{C}}$-$CH_3$), Methyl ketone 21 was confirmed by the peaks at 3550 cm^{-1} (-OH) and 1710 cm^{-1} (C = O) of IR spectrum. The CH_3-$\overset{O}{\overset{\|}{C}}$- group of 21 was confirmed by 'H NMR signal at δ 2.1 as singlet for 3H.

The ketone 18 was subjected to Baeyer-Villiger oxidation using m-chloroperbenzoic acid buffered with $NaHCO_3$ in CH_2Cl_2. The acetate 19 was obtained exclusively in 91% yield. m-chloroperbenzoic acid oxidation of 21 gave 22 in 90% yield under same condition but with lesser time. IR spectrum of 19 showed absorptions at 3450 cm^{-1} (-OH),


OH
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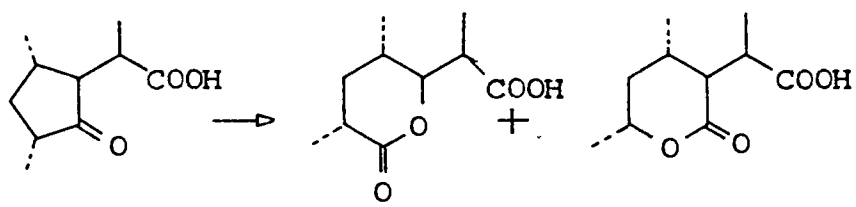
1735 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-O-$) and 1090 cm^{-1} (C-O). 'H NMR signals at δ2.1, as singlet for 3H ($-\overset{O}{\overset{\|}{C}}-CH_3$) and δ4.0 as doublet for 2H ($-O-CH_2-$) also confirmed the structure of 19. IR absorptions at 3550 cm^{-1}, 1735 cm^{-1} and 1100 cm^{-1} and 'H NMR spectrum signals at δ2.1 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$) and 4.1 (1H, m, -O-CH-) were assignable to the structure of 22.

The acetate 19 and 22 were hydrolysed with methanolic potassium hydroxide to get the alcohol 20 in 87% yield. The structure of 20 was confirmed by IR absorption at 3560 cm^{-1} , 3450 cm^{-1}, 2935 cm^{-1} and 1150 cm^{-1}.

The alcohol 20 was oxidised to keto acid 23 in 70% yield using chromic acid. Structure was confirmed by IR spectrum at 2500-3500 (broad band for -COOH), 1740 cm^{-1} and 1705 cm^{-1} (C = O). 'H NMR signal at δ10.9 also confirmed the compound 23.

3.6 Preparation of Prelog-Djerassi lactone

Synthesis of Prelog-Djerassi lactone (24) was accomplished by the Baeyer-Villiger oxidation of compound 23 (Scheme 10). Baeyer-Villiger oxidation has been used frequently in recent years for the oxidation of cyclic



23 24 25

Scheme 10

ketones to lactones, particularly in the synthesis of prostaglandin and macrocyclic lactones. In the case of unsymmetrical ketones the regioselectivity of oxidation is affected by the electronic properties of substituents at α or β to the carbonyl group.[31] Baeyer-Villiger oxidation studies on bicyclic [2.2.1] heptanones[32] showed that the product formation is enhanced by (1) electro-negativity of substituents at C-7, (2) H-bonding capability of substituent at C-5 and (3) the peracid employed.

Considering the case of compound 23 either side of the carbonyl group has a substituent and in one side a carboxyl group is present at β-position. It was expected that both products 24 and 25 can be formed with equal probability during peracid oxidation.

The keto acid 23 was treated with a mixture of m-chloroperbenzoic acid and disodium-hydrogen phosphate in CH_2Cl_2. After 20 hours of reaction the products were isolated by column chromatography using hexane-ethyl acetate mixture (5:1) to get Prelog-Djerassi lactone (24) in 47% yield. Structure was confirmed by 'H NMR spectrum signals at δ 1.0-1.3, (9H, m) for three CH_3 groups, δ 1.4-2.7 (5H, m), 4.3 (1H, m, -O-CH-), 11 (1H, br, $-\overset{O}{\overset{\|}{C}}OH$) IR spectrum has absorption at 2500-3500 cm^{-1}, 1735 cm^{-1}, 1705 cm^{-1}, 1190 cm^{-1} and 1100 cm^{-1}, mass spectrum m/z = 200 (M+).

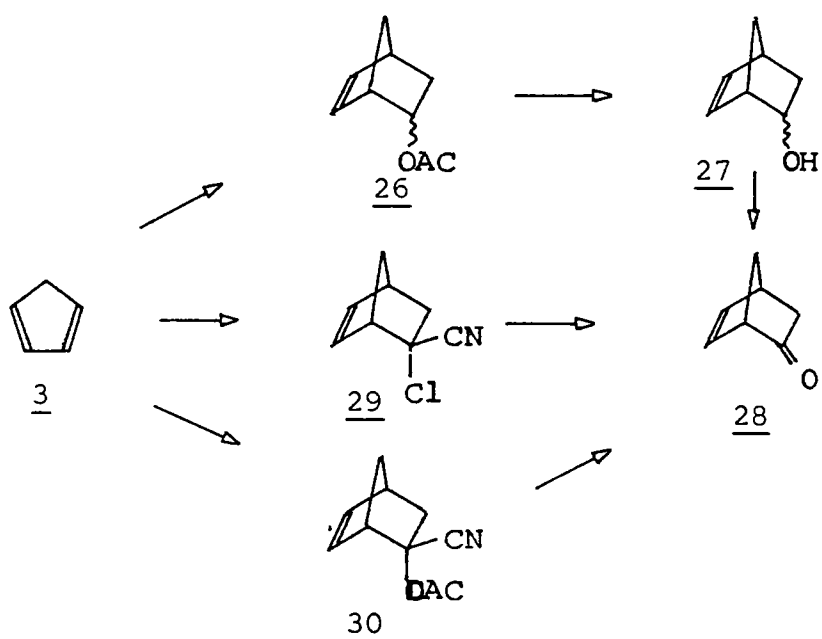
Baeyer-Villiger oxidation was attempted using various reagents like acetic anhydride/urea/H_2O_2/disodium hydrogen phosphate, peracatic acid/CH_3COONa, perbenzoic acid/Na_2HPO_4 and monoperphthalic acid/Na_2HPO_4. In all cases mixture of products were formed from which the lactone 24 was isolated by column chromatography.

3.7 Synthesis of dehydronorcamphor

Dehydronorcamphor (28) was prepared from cyclopentadiene (3) by Diels-Alder reaction with vinyl acetate followed by saponification and oxidation.

Different methods for the synthesis of dehydronor camphor are reported. All methods are based on Diels-Alder reaction of cyclopentadiene with different dienophiles (Scheme 11).

Cyclopentadiene (3) obtained by the cracking of dicyclopentadiene, was mixed with excess vinyl acetate and heated for 10 hours at 180°C. The products were fractionally distilled (73-75°C, 14 Torr) to get dehydro-norbornyl acetate (26) in 80% yield.[33] The structure of acetate was confirmed by IR absorptions at 1735 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-O-$) and 1110 cm^{-1} (C-O) and 'H NMR signals at δ 2 as 3H singlet ($-COCH_3$) and a multiplet of olefinic protons at 5.8. The acetate was hydrolysed with methanolic sodium



Scheme 11

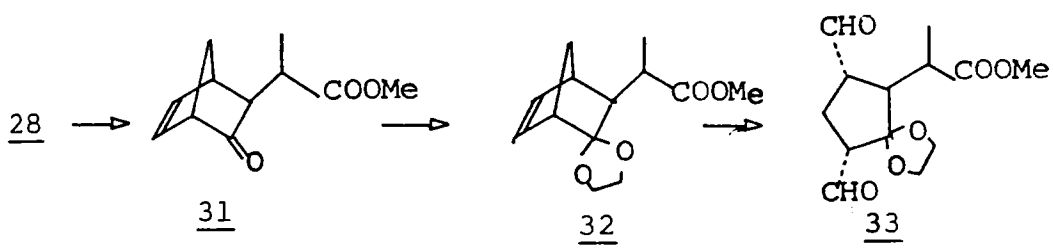
hydroxide to get alcohol 27 in 90% yield which had IR absorptions at 3400 cm^{-1}, 1250 cm^{-1} and 1100 cm^{-1} and 'H NMR signals at δ5.8 as multiplet for olefinic protons.

Dehydronorcamphor (28) was obtained by the chromic acid oxidation of dehydronorborneol. The oxidation was also carried out by pyridinium chlorochromate with better yield (85%). IR absorption at 1740 cm^{-1} (C=O) confirmed the formation of dehydronorcamphor.

In another method[34] dehydronorcamphor was prepared by Diels-Alder reaction of cyclopentadiene with 2-chloro acrylonitrile followed by treatment with potassium hydroxide. Formation of the adduct 29 was confirmed by the peak in IR spectrum at 2200 cm^{-1} (C≡N) and H'NMR signal at δ6.1 for olefinic protons. By a third method[35] α-acetoxy acrylonitrile was used as dienophile for the Diels-Alder reaction with cyclopentadiene. The product 30 was confirmed by IR absorption at 2200 cm^{-1} (C≡N) 1735 (-$\overset{O}{\overset{\|}{C}}$-O-) and 'H NMR signals at 2.1 as 3H singlet (-$\overset{O}{\overset{\|}{C}}$-$CH_3$) and 2H multiplet at 5.9 for olefinic protons. The dehydronorcamphor was obtained in 81% yield by the hydrolysis of cyanhydrin acetate with aqueous sodium hydroxide.[35]

3.8 Alkylation of dehydronorcamphor

The dehydronorcamphor (28) was alkylated at position-3 according to the proposed scheme using 2-chloromethyl propanoate as the alkylating agent. It was prepared by the esterification of 2-chloropropanoic acid. The alkylation was carried out using lithium diisopropylamide as base and the attack of alkylating group was specifically at exo-position. The product 31 was obtained in 55% yield (Scheme 12). The structure of 31 was confirmed by IR spectrum at 1745 cm^{-1} (C=O), 1735 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-O-), 1630 cm^{-1} (C=C) 1130 cm^{-1} (C-O) and ^1H NMR spectrum signals at δ 1.9 as multiplet for 1 endo-proton at C-3, 3.5 (3H, s) for $-OCH_3$ group and 6.1 as multiplet for olefinic protons.



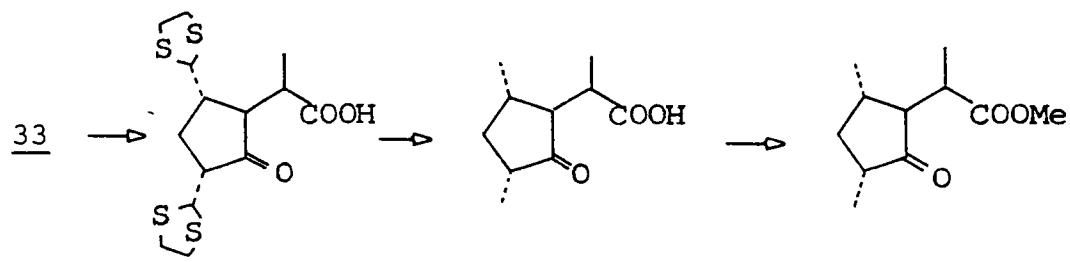
Scheme 12

The carbonyl group of 31 was protected as ethylene ketal 31. When preparation of the ketal 32 in the conventional method using ethylene glycol and p-toluene sulphonic acid was attempted, the yield obtained was less than 70%. However, the yield was considerably improved when the reaction was conducted with 10 mol % of pyridinium p-toluene sulphonate. When this method was adopted, the ketal 32 was obtained in 90% yield. The 'H NMR spectrum of 32 showed a singlet of 3H at δ3.8 ($-O-CH_2-CH_2O-$) and δ3.4 ($-OCH_3$).

The double bond of 32 was oxidised to dialdehyde 33 using osmium tetroxide and sodium meta periodate in dioxane-water system in 90% yield. The double bond oxidation was also carried out in nonaqueous medium using cetyl trimethyl ammonium permanganate and benzyl triethyl ammonium periodate to get the 33 in 68% yield. In IR spectrum the peaks at 2850 cm^{-1}, 2750 cm^{-1}, 1720 cm^{-1} and 'H NMR signal at δ9.8 were characteristic of aldehyde groups and presence of IR abdorption at 1735 cm^{-1}, 1100 cm^{-1} and 'H NMR signals at δ3.4 confirmed the ester group. The ketal group ($-OCH_2CH_2-O-$) was also confirmed by 'H NMR signal at δ3.8 as 4H singlet.

3.9 Preparation of thioketal 34 and ketoester 36

The aldehyde groups of 33 were converted to CH_3 groups. It is expected that these two CH_3 groups can function as the C-4 and C-6-CH_3 groups of Prelog-Djerassi lactone. Different methods were tried for the conversion of aldehyde to -CH_3 group. In one of the methods the two aldehyde groups were converted to thioketal 34 followed by reduction with Raney-Ni and esterification to get the keto ester 36 (Scheme 13). The aldehyde 33 was treated with



34 35 36

Scheme 13

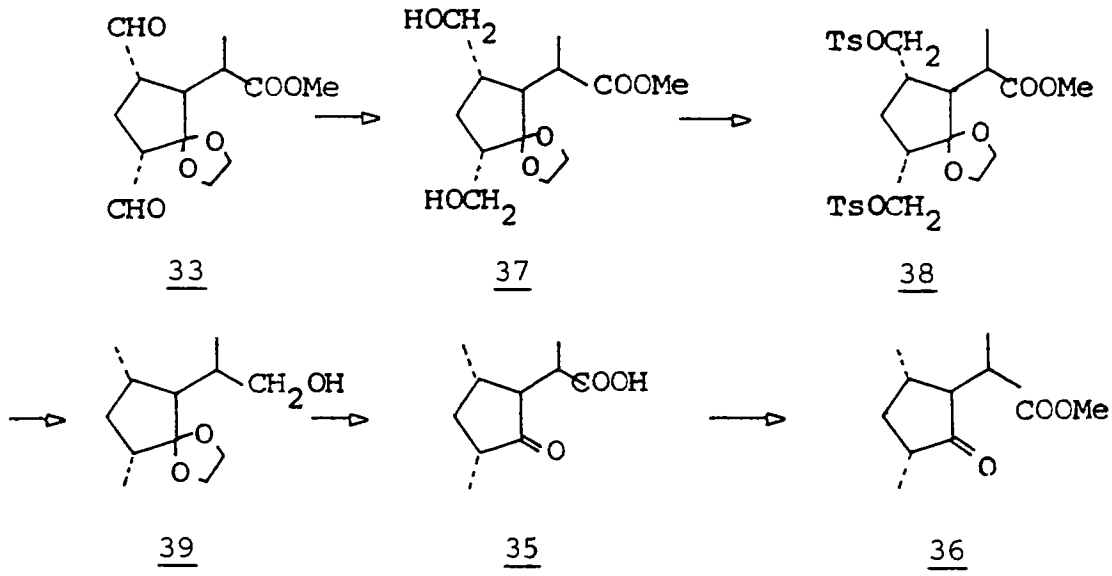
1,2 ethanedithiol and freshly prepared BF_3-etherate and stirred for 3 hours. The dithioketal 34 was isolated in 63% yield. The thioketal formation was confirmed by 'H NMR signal at δ 3.3 as multiplet for 8H. From the 'H NMR spectrum absence of signals at δ 3.5 (3H, s, -OCH_3) and δ 3.8

(4H, s, $-OCH_2CH_2O-$) and disappearance of peaks at 1735 cm^{-1} and 1100 cm^{-1} in IR spectrum revealed that the ester group and ketal group were removed from 33 during thioketal formation. Appearance of IR absorption at 1745 cm^{-1}, 2500-3500 cm^{-1} confirmed the formation of keto group and acid group in 34.

The thioketal 34 obtained was refluxed with freshly prepared Raney-Nickel catalyst in dry ethyl alcohol. After filtration of reaction mixture and evaporation of solvent afforded the keto acid 35 in 65% yield. The reduction of thioketal 34 was also performed with nickel containing complex reducing agent.[25] The structure of 35 was confirmed by disappearance of 8H multiplet at 3.3 for dithioketal. Presence of a broad IR absorption peak at 2500-3500 cm^{-1} (-COOH) and a sharp peak 1740 cm^{-1} (C=O) and 1705 cm^{-1} confirmed the structure of keto acid 35. The keto acid 35 was then esterified with dry methanol and p-toluene sulphonic acid to get 36 in 70% yield. IR spectrum showed peaks at 1735 cm^{-1} and 1110 cm^{-1} and ^1H NMR signal at 3.4 which confirm the ester formation.

In the second method the aldehyde 33 was reduced to alcohol by sodium borohydride in methyl alcohol. The

alcohol 37 was obtained in 90% yield (Scheme 14). The alcohol formation was confirmed by the peak in IR spectrum at 3550 cm^{-1}. The ester and ketal groups were retained in



33 37 38

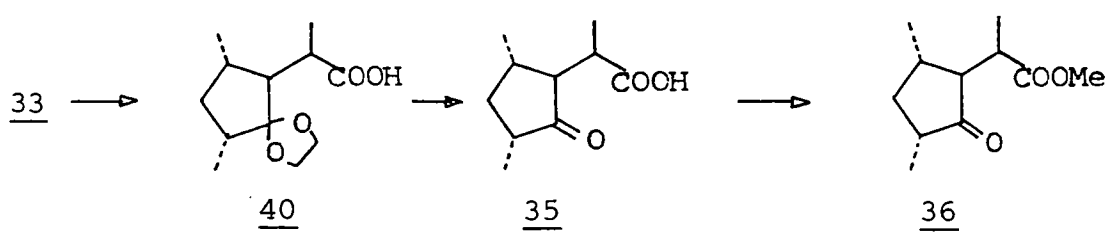
39 35 36

Scheme 14

the compound 37. Alcohol 37 was treated with p-toluene sulphonyl chloride in presence of dry triethylamine in CH_2Cl_2. The tosylate 38 obtained in 90% yield, was treated with lithium aluminium hydride in ether under reflux. The yield of product 39 obtained was only 55%. During the tosylate reduction the ester group present in 38 was also reduced to alcohol, (IR spectrum 3540 cm^{-1}) and ketal group remain unaffected. The alcohol 39 was then oxidised with

chromic acid to get keto acid 35 in 70% yield. The structure of 35 was confirmed by IR spectrum at 2700-3500 as a broad band (-COOH), 1740 cm^{-1} (C=O) and 1705 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-OH$), and 'H NMR spectrum with signals at δ10.8 (1H, br, -COOH). The keto and 35 was then converted to methyl ester 36.

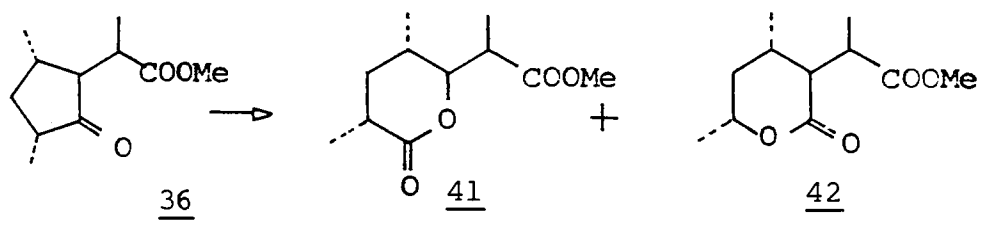
By a third method the aldehyde 33 was treated with hydrazine hydrate and potassium hydroxide in presence of diethylene glycol (Scheme 15). The product 40 was formed in 70% yield. During this reaction, the ester group was also hydrolysed to acid. The ketal group of 40 was removed by refluxing it with a mixture of acetone, water and p-toluenesulphonic acid to get 35. The deketalisation was confirmed by the absence of 'H NMR spectrum signal at δ3.8 (3H, s, $-OCH_2-CH_2O-$). The keto acid 35 was further converted to methylester 36.



40 35 36

Scheme 15

Finally, the keto ester 36 was subjected to Baeyer-Villiger oxidation to get the methyl ester of Prelog-Djerassi lactone (41) (Scheme 16). Different peracids were used for Baeyer-Villiger oxidation. With m-chloroperbenzoic acid buffered with $NaHCO_3$, keto ester 36



Scheme 16

gave a mixture of products and they were isolated by column chromatography to get the methyl ester 41 (57%) and 42 (34%). When the oxidation was carried out with acetic anhydride urea-H_2O_2 and disodium hydrogen phosphate 36 gave 41 (37%) and 42 (28%). With peracetic acid and CH_3COONa the keto ester 36 gave 41 (40%) and 42 (30%). Perbenzoic acid and monoperphthalic acid gave 41 in (50%) and (45%) and 42 in 25% and 36% respectively. Products were isolated by column chromatography using neutral aluminium oxide and hexane-ethyl acetate mixture (10:1).

Since the stereochemistry of methyl group at position-2 (C_2) of methyl ester 41 has not been defined, the ester 41 is actually a mixture of methyl ester of Prelog-Djerassi lactone and its epimer at C-2. The mixture can be separated by column chromatography. But there are reports of Baker's yeast mediated hydrolysis of α-substituted esters in which the stereochemistry of substituent at α-position is not known.[36] It is reported that the possibility of hydrolysis of such esters is decided by the stereochemistry of substituent at α-position. The ester having substituent with β-configuration will be hydrolysed and the other isomer will remain unhydrolysed. Thus Prelog-Djerassi lactone (24) can be separated from the mixture of methyl esters of Prelog-Djerassi lactone.

CHAPTER IV

EXPERIMENTAL

INTRODUCTION

The melting points determined in open capillary tubes are reported to degree celsius and are uncorrected. ^{1}HNMR Spectra (60 MHz) were obtained on a Hitachi R 600 FT NMR spectrometer and signals are reported in parts per million (δ) downfield, from TMS as internal standard (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad). IR spectra were recorded either on a Perkin Elmer 727 B spectrometer or Perkin Elmer 283 spectrometer (νmax cm^{-1}). Gas chromatographic analysis were carried out on a Hewlett Packard 5730 A gas chromatograph equipped with FID with N_2 as carrier gas (30 ml/min at ambient temperature) and using stainless steel columns (12 ft x 1/8 in; 6 ft x ¼ in) packed with 10% SE-30 or 5% carbowax on chromosorb (80/100). Mass spectra were recorded on a varian MAT CH 7 mass spectrometer. UV spectra were obtained using a Shimadzu model 160 A spectrophotometer in methanol. Thin layer chromatography was performed on glass plate coated with silica gel G. Unless otherwise specified, column chromatography was done with slurry packed silica gel (Qualigens or Sisco 60-120 and 100-200) columns. Moisture or oxygen sensitive reactions were carried out under an atmosphere of dry N_2. All solvents were dried using appropriate drying agents and distilled before use.

4.1 endo-Dicyclopentadiene (1)

Dicyclopentadiene (commercial grade) 100 ml was heated at reflux (170-180°C) under N_2 atmosphere in a 250 ml round bottomed flask equipped with Friedrichs Condenser, claisen head, thermometer, a gas inlet and a collection adaper. After discarding the Forerun the receiver was cooled in dry ice and cyclopentadiene distilling at 41°C was collected. Cyclopentadiene thus obtained in a tightly closed flask was placed in a refrigerator at 0°C for 3 days. By this time the whole cyclopentadiene monomer was slowly converted into endo-dicyclopentadiene. Finally, the endo-isomer was purified by distillation under reduced pressure (B.P. 59°C, 17 Torr).

4.2 exo-Dicyclopentene-bromide (4)

A mixture of endo-dicyclopentadiene (264 g, 2 mol) and 48% hydrobromic acid (650 gm) was stirred under N_2 at 75°C for 12 hours. The mixture was cooled, diluted with water and extracted with ether. Combined ether extracts were washed with 5% $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. After removal of ether, the product on distillation (B.P. 86-88°C, 0.1 Torr) gave a colourless liquid (372 g, 88%).

4.3 exo-Dicyclopentadiene (2)

A solution of potassium hydroxide (7.5 gm) in 95% ethanol (250 ml) was added to the bromide 4 (86 g, 0.4 mol) and the mixture was heated under reflux in N_2 for 24 hours. The mixture was cooled, diluted with water and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous Na_2SO_4. Removal of ether and vacuum distillation yielded exo-product along with 10% endo-product. A Vigreux column was attached and the dehydrobromination product was heated initially at 170°C and then at 190°C. The thermally less stable endo-dicyclopentadiene was converted to cyclopentadiene monomers and collected. The residue was distilled under reduced pressure (B.P. 63°C, 11 Torr) to give 2 as colourless liquid (118 g, 85%).

4.4 Tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-5-ol[3] (5)

Freshly distilled exo-dicyclopentadiene (2) (185 g, 1.4 mol) was dissolved in a mixture of dioxane (500 ml) and water (50 ml). Selenium dioxide (66.5 g, 0.6 mol) was added and the solution was heated under reflux for 3 hours. The resulting dark brown mixture was filtered from selenium and poured into two litres of water. The

heavy dark oil was drawn off and the aqueous solution was extracted with 200 ml of ether using a cont[illegible] ether extractor. Ether was removed and the residue was fractionally distilled (90°C, 5 mm) to give alcohol 5 (100.2 g, 57%).

IR (Neat) : 3450, 3050, 1050 cm^{-1}

^1H NMR ($CDCl_3$) : δ 5.8 (2H, m, -CH=CH-), 6.3 (2H, m, -CH=CH-)

4.5 Tricyclo[5.2.1.$0^{2,6}$]deca-3,8 diene-5-acetate[3] (6)

Freshly prepared exo-dicyclopentadiene (2) (50 g, 0.38 mol) was dissolved in acetic acid (50 ml) and a solution of selenium dioxide (18 g, 0.163 mol) in acetic acid (50 ml) was added to it with stirring. The reaction mixture was refluxed for 4 hours, cooled and diluted with ice water. The heavy dark oil was separated and the aqueous solution was extracted with ether (50 ml x 4). The combined organic solution was dried, evaporated and fractionally distilled 118-120°C, 15 mm) to get the acetate 6 (61 g, 85%).

IR (CCL_4) : 3010, 1735, 1100 cm^{-1}

^1H NMR ($CDCl_3$) : δ 2.1 (2H, s, $-\overset{O}{\overset{\|}{C}}CH_3$), 5.8 (2H, m, -CH=CH-)
6.3 (2H, m, -CH=CH-)

4.6 Tricyclo[5.2.1.$0^{2,6}$]deca-3,8 diene-5-ol (5)

A mixture of acetate 6 (40 g, 0.21 mol) in methyl alcohol (100 ml) and sodium hydroxide (12 g, 0.3 mol) dissolved in methyl alcohol (50 ml) were refluxed for 3 hours. The reaction mixture was cooled, diluted with water and extracted with ether (50 ml x 3). Combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was fractionally distilled to get alcohol 5 (21.8 g, 70%).

4.7 Tricyclo[5.2.1.$0^{2,6}$]deca-3,8 diene-5-one (7)

To a solution of alcohol 5 (14.8 g, 0.1 mol) in ether (100 ml) in a 500 ml round bottomed flask kept in ice bath, equipped with a thermometer and a stirrer. 8N chromic acid (60 ml) (Prepared by mixing chromium trioxide (15 g) and Con: H_2SO_4 (13 ml) in water (65 ml) was added from a dropping funnel. The reaction mixture was stirred for 2 hours keeping the temperature of the reaction mixture at 20°C. Sodium metabisulphite solution was added to reduce the excess oxidant. Ether layer was separated and washed with 5% $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. After evaporation of solvent the product was distilled (B.P. 82-87°C, 4 Torr) as a pale yellow oil

which crystallised on being cooled to room temperature. The product was finally purified by column chromatography using neutral alumina as absorbent and hexane-ethyl acetate (10:1) as eluent to get the ketone 7 (12 g, 82%).

IR (CCl_4) : 1720, 3010 cm^{-1}

'H NMR ($CDCl_3$) : δ6.3 (2H, m, -CH=CH-),7.2(2H,m,-CH=CH-CO-)

4.8 Tricyclo[5.2.1.$0^{2,6}$]deca-3,8 diene-5-one (7)-- Oppenaeur Oxidation

A mixture of alcohol 5 (22.2 g, 0.15 ml), p-benzoquinone (21.6 g, 0.2 mol) and aluminium ter:butoxide (36.2 g, 0.15 mol) in 200 ml dry benzene was stirred at 50°C for 6 hours. After the reaction, the reaction mixture was allowed to cool and decomposed with water. Aluminium hydroxide was filtered off and washed thoroughly with ether. The combined organic solution was extracted five times with 50 ml portions of 5% NaOH solution and then with to water neutrality and finally dried over anhydrous Na_2SO_4. After evaporation of solvent, the product was distilled under reduced pressure (82-87°C, 4 Torr) to a pale yellow oil which solidified on being cooled to room temperature. The crude product was purified by column chromatography using neutral alumina as adsorbent and

hexane-ethyl acetate (10:1) as eluent to get the ketone 7 (16.5 g, 75%).

4.9 Pyridinium chloro chromate (PCC)[5]

To 6M hydrochloric acid (45 ml, 0.26 mol), chromium trioxide (25 g, 0.25 mol) was added rapidly with stirring. After 5 minutes the homogeneous solution was cooled to 0°C and pyridine (19.77 g, 0.25 mol) was added over a period of 10 minutes. The mixture was cooled to 0°C and the yellow orange coloured solid formed was collected on a sintered glass funnel and dried in vacuo to get pyridinium chloro chromate (48.9 g, 81%).

4.10 Tricyclo[5.2.1.$0^{2,6}$] deca-3,8 diene-5-one (7)-- PCC Oxidation

To a solution of alcohol 5 (37 g, 0.25 mol) in dichloromethane (200 ml) in a 500 ml round bottomed flask equipped with a stirrer, pyridinium chlorochromate (107 g, 0.5 mol) was added in small portions for 30 minutes. After addition the reaction mixture was stirred for 3 hours keeping the temperature nearly at 20°C. Progress of the reaction was monitored by thin layer chromatography. When the reaction was complete, the reaction mixture was filtered and solvent was evaporated. The residue was

purified by column chromatography using neutral alumina as adsorbent and hexane-ethyl acetate (10:1) as eluent to get the ketone 7 (31 g, 85%).

4.11 Preparation of pyridinium dichromate[6]

To a cooled solution of chromiumtrioxide (100 g, 1 mol) in water (100 ml) at 20°C was added pyridine (80.6 ml, 1 mol) slowly with stirring. After 5 minutes the reaction mixture was diluted with acetone (400 ml) and cooled to -20°C. After 3 hours the precipitated orange crystals of pyridinium dichromate was filtered, washed with acetone and dried in vacuo (122 g, 68%).

4.12 [illegible]clo[5.2.1.$0^{2,6}$]deca-3,8 diene-5-one (7)

PDC oxidation

To a stirred solution of exo-dicyclopentadiene (2) (1.32 g, 0.01 mol) in benzene (20 ml) and celite (10 g) was added pyridinium dichromate (15 g, 0.04 mol) followed by the addition of 70% ter:butyl hydroperoxide (3.6 ml, 0.04 mol) at 10°C. After 15 minutes at 10°C, the reaction mixture was stirred for 5 hours at 25°C. Ether (20 ml) was added and the reaction mixture was filtered. The residue was again washed twice with 10 ml portion of ether.

Combined filtrate was evaporated and the residue was purified by column chromatography using neutral alumina as adsorbent and hexane-ethyl acetate (10:1) as eluent to get the ketone 7 (0.9 g, 61%).

4.13 β-3-methyl tricyclo[5.2.1.$0^{2,6}$]dec-8-en-5-one (8)— Lithium dimethyl cuprate method

Lithium dimethyl cuprate was prepared by adding methyl lithium (34.5 ml, 1.8 M) [(prepared from lithium (1.7 g, 0.24 mol) and methyl iodide (9 g, 0.06 mol) in anhydrous ether (40 ml)] in ether to a stirred suspension of cuprous iodide (11.9 g, 0.625 mol) in 100 ml dry ether at 0°C. A solution of ketone 7 (8.2 g, 0.056 mol) in 50 ml dry ether was added slowly into the cooled (-50°C) cuprate reagent over 30 minutes period. After the addition, the cooling bath was removed and stirring was continued for 30 minutes. The reaction mixture was slowly poured into 50 ml of rapidly stirring saturated NH_4Cl solution. A few millilitres of con: NH_3 was added to facilitate dissolution of the copper salts. The phases were separated and the aqueous phase was extracted with ether (20 ml x 3). The combined organic phase was washed with dilute NH_4OH and saturated NaCl solution. After being dried over anhydrous Na_2SO_4, the solvent was evaporated *in vacuo* to furnish

the crude ketone as yellow oil, which was purified by column chromatography using neutral alumina as adsorbent and hexane-ethyl acetate (15:1) as eluent to get 8 (8.7 g, 95%).

IR (Neat) : 1740, 1630, 3050 cm^{-1}

'H NMR ($CDCl_3$) : δ1.2 (3H, d, $-CH_3$), 6.3 (2H, m, -CH=CH)

4.14 β-3-methyl tricyclo[5.2.1.$0^{2,6}$]dec-8-en-5one (8)— Grignard reagent method

Methylmagnesium iodide was prepared from magnesium turnings (0.568 g, 0.023 mol) and methyl iodide (1.44 ml, 0.023 mol) in 20 ml of dry ether. The resulting solution was diluted with ether (40 ml) and cooled to 0°C, and cuprous iodide (0.168 g, 0.0008 mol) was added, followed by the dropwise addition of a solution of ketone 7 (2.7 g, 0.0185 mol) in ether (40 ml). After 30 minutes of addition, the cooling bath was removed and stirring was continued for 45 minutes. The reaction mixture was poured into saturated solution of NH_4Cl (50 ml). Concentrated NH_3 (2 ml) was added to facilitate dissolution of copper salts. Ether layer was separated and the aqueous layer was extracted with ether (25 ml x 3) and the combined organic layer was washed with dilute ammonium hydroxide and

saturated sodium chloride solution. Ether layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography using neutral alumina as adsorbent and hexane-ethyl acetate (15:1) as eluent to afford the ketone 8 (2.7 g, 90%).

4.15 β-3-methyl,5-ethylene dioxy tricyclo[5.2.1.$0^{2,6}$]dec-8-ene (9)

A mixture of ketone 8 (16.2 g, 0.1 mol), ethylene glycol (12.4 g, 0.2 mol) 20 mg of p-toluene sulphonic acid and benzene (50 ml) were refluxed using a Dean-Stark apparatus for 3 hours under N_2 atmosphere. The reaction mixture was cooled, diluted with water and extracted with ether (50 ml). The organic layer was washed with 5% sodiumbicarbonate solution, water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo and the product was purified by column chromatography using neutral alumina as adsorbent and hexane-ethyl acetate (20:1) as eluent to get the ketal 9 (19.6 g, 95%).

IR (Neat) : 1620, 1060 cm^{-1}

'H NMR ($CDCl_3$) : δ1.2 (3H, d, $-CH_3$), 3.8 (4H, s,$-OCH_2CH_2O-$)
6.3 (2H, m, -CH=CH-)

4.16 β-methyl-4-ethylenedioxy bicyclo[3.3.0^{1,5}] octane α6,8-dicarboxaldehyde (10)

To a stirred mixture of ketal 9 (15 g, 0.072 mol) dioxane (100 ml) and water (50 ml), Osmiumtetroxide (150 mg) was added followed by sodium metaperiodate (31.3 g, 0.144 mol) slowly with stirring and keeping the temperature at 20°C. The stirring was continued for 10 hours. After the reaction, the solid formed was filtered and washed with ether (20 ml x 3). The combined filtrate and washings were evaporated in vacuo to get the dialdehyde 10 (13.8 g, 80%).

IR (Neat) : 2830,2760, 1720 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.1 (3H, d, $-CH_3$), 3.8 (4H, s, $-OCH_2CH_2O-$)
9.8 (2H, d, 2-CHO).

4.17 Preparation of cetyl trimethyl ammonium permanganate[7]

To a stirred solution of potassium permanganate (3.168 g, 20 mmol) in water (100 ml) at 20°C was added, dropwise over 20 minutes, a solution of cetyl trimethyl ammoniumbromide (8.02 g, 22 mmol) in water (100 ml). A fine violet precipitate was formed immediately. Stirring was continued for 30 minutes, the precipitated product filtered, washed thoroughly with water and dried in a

desicator over phosphorous pentoxide *in vacuo* for 3 hours at room temperature to give the salt as a fluffy violet solid 6.5 g (80%).

4.18 Preparation of benzyl triethyl ammonium periodate[8]

Benzyl triethyl ammonium chloride (1.36 g, 0.006 mol) and sodium meta periodate (1.07 g, 0.006 mol) were dissolved in a minimum amount of water, respectively, and mixed at 0°C. The reaction mixture was stirred for 30 minutes and the precipitated product was filtered and dried under vacuum. The salt was then recrystallized from benzene-hexane mixture (2 g, 90%).

4.19 β-2-methyl-4-ethylenedioxy bicyclo[3.3.$0^{1,5}$] octane-6,8-dicarboxaldehyde (10)

A solution of cetyltrimethyl ammonium permanganate (4.04 g, 10 mmol) in dichloromethane (50 ml) was added dropwise to a stirred solution of ketal 9 (2.08 g, 10 mmol) in 30 ml dichloromethane at 20°C. Stirring was continued for one hour and the solvent was concentrated to half of its original volume. A solution of benzyl triethyl ammonium periodate (7.74 g, 20 mmol) in dioxane (40 ml) was added to the reaction mixture under N_2 at room temperature and stirred for 8 hours. After the reaction, the reaction

mixture was filtered. The residue and filtrate were extracted with ether (20 ml x 4) and the combined ether extracts were dried and evaporated *in vacuo* to get dialdehyde 10 (1.69 g, 70%).

4.20 Preparation of 1,2 Ethane dithiol[9]

A mixture of 95% C_2H_5OH (275 ml) and thio urea (60.9 g) were refluxed on a steambath until the solution is clear. The reaction mixture was cooled and added 1,2-ethylene dibromide (75.1 g) in one portion. The reaction become vigorous and it was controlled by cooling with ice water. After the reaction the isothiouronium salt formed was filtered and dried. Concentration of the mother liquor also yielded crude isothiouronium salt. A mixture of isothiouronium salt (25.5 g) and 85% potassium hydroxide (64 g in 136 ml water were placed in a 3-necked flask and boiled under reflux for 5 hours. NH_3 was evalued during the reaction. After the reaction N_2 was admitted to the flask and a cooled solution of H_2SO_4 (41.5 ml) in water (76 ml) was added dropwise until the reaction mixture became acidic. N_2 was cut off and steam was introduced to distil out the 1,2 ethane dithiol by steam distillation (22.5 g, 60%).

4.21 β-4-Methyl-6,8 (ethylene dithioxy methyl)-bicyclo [3.3.0^{1,5}] octan-2-one (11)

A mixture of ketal (30 g, 0.125 mol), 1,2-ethane dithiol (123.5 g, 0.25 mol) in $CHCl_3$ (20 ml) and freshly distilled boron trifluoride-etherate (2 ml) were stirred for 3 hours at 0°C. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with 5% sodium hydroxide solution, water and finally dried over anhydrous Na_2SO_4. Evaporation of solvent afforded thioketal 11 (30.4 g, 70%).

IR (CCl_4) : 1740 cm^{-1}

'H NMR ($CDCl_3$) : δ1.1 (3H, d, $-CH_3$), 3.4 (8H, m, 2 - SCH_2CH_2S-)

4.22 Preparation of Raney-Nickel catalyst (W_2)

To a solution of NaOH (19 g) in water (75 ml) in a 500 ml beaker equipped with an afficient stirrer, cooled in ice water at 10°C, was added Nickel-aluminium alloy (15 g) in small portions with stirring at such a rate that the temperature of the reaction mixture is below 25°C. After addition, the reaction mixture was heated on a water bath until the evolution of H_2 became slow. Distilled water was added to restore the original volume. The nickel was then

transferred to a stoppered graduated cylinder with the aid of distilled water and decanted the water again. A solution of NaOH (25 g) in water (250 ml) was added and the mixture was shaken thoroughly to disperse the catalyst and allowed to settle. The Ni suspension was then washed with distilled water until the washings are neutral to litmus. The washing process was then repeated with rectified spirit, absolute alcohol and stored the catalyst in a bottle filled with absolute ethanol.

4.23 β-4, α-6,8 trimethyl bicyclo[3.3.$0^{1,5}$]-octan-2-one(12)

A mixture of dithioketal 11 (10 g, 0.029 mol) in dry methyl alcohol (30 ml) and Raney-Nickel catalyst (W2, grade, 60 g) in absolute ethanol (100 ml) were refluxed with stirring for 3 hours. After the reaction, the reaction mixture was filtered and washed the Nickel catalyst with hot methanol and the combined washings and filtrate were evaporated. The residue was purified by column chromatography using silica gel (100-200 mesh) as adsorbent and hexane-ethyl acetate (10:1) as eluent to afford the ketone 12 (3.8 g, 80%).

IR (Neat) : 1740 cm^{-1}

'H NMR ($CDCl_3$) : δ 1.0-1.2 (9H, m, $3CH_3$)

4.24 β-4, α-6,8-trimethyl bicyclo[3.3.$0^{1,5}$]octan-2-one (12)

Tertiary amyl alcohol (3.52 g, 0.04 mol) in dry THF (20 ml) was added dropwise to a suspension of sodium hydride (3.36 g, 0.14 mol) and nickel acetate (3.54 g, 0.02 mol) in refluxing THF (50 ml). After 2 hours the dithioketal 11 (6 g, 0.017 mol) in THF (50 ml) was added slowly and refluxed for 2 hours. The reaction mixture was cooled and slowly added to water with stirring and extracted with ether. Solvent was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel 100-200, hexane-ethyl acetate 10%) to get the ketone 12 (3.6 g, 60%).

4.25 β-2-Methyl-4-ethylene dioxy - 6,8-(hydroxy methyl) bicyclo[3.3.$0^{1,5}$]-octane (13)

Under stirring and ice cooling a solution of dialdehyde 10 (15 g, 0.063 mol) in CH_3OH (50 ml) was added in drops to a suspension of $NaBH_4$ (4.8 g, 0.126 mol) in CH_3OH (50 ml). The mixture was stirred for 2 hours at 10°C. After the reaction, the solvent was evaporated *in vacuo* and the residue was diluted with water and extracted 3 times with ether. Combined ether solution was washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to get the alcohol 13 (13.7 g, 90%).

IR (CCl_4) : 3550, 1060 cm^{-1}

'H NMR ($CDCl_3$) : δ 3.8 (4H, s, $-OCH_2-CH_2-O-$),
3.6 (4H, m, $2(-CH_2OH)$)

4.26 β-2-Methyl 4-ethylene dioxy 6,8 (α-tosyl methyl)-bicyclo[3.3.$0^{1,5}$] octane (14)

To a stirred and cooled solution of alcohol 13 (10 g, 0.04 mol) and triethylamine (12 g, 0.12 mol) in anhydrous CH_2Cl_2 (10 ml) was added a solution of p-toluene sulphonyl chloride (17.1 g, 0.09 mol) in CH_2Cl_2 (20 ml) during 30 minutes at 5°C. The mixture was stirred at 5°C for 2.5 hours and was added to ice water. The organic layer was washed with saturated NH_4Cl solution, dried and concentrated in vacuo to get tosylate 14 (21.5 g, 95%).

'H NMR ($CDCl_3$) : δ 3.8 (4H, s, $-OCH_2CH_2O-$)
7.5 (m, 2 phenyl groups)

4.27 β-2,α-6,8 Trimethyl,4-ethylene dioxy bicyclo [3.3.$0^{1,5}$] octane (15)

To a magnetically stirred suspension of lithium aluminium hydride (5.32 g, 0.14 mol) in dry ether was added dropwise to a solution of the tosylate 14 (33 g, 0.06 mol) in ether (80 ml). After refluxing for 15 hours the excess

lithium aluminium hydride was destroyed by slow addition of reaction mixture to ice water. The residue was filtered out, ether solution was washed with water and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification by column chromatograph using silica gel (60-120 mesh) as adsorbent and hexyl-ethyl acetate (10:1) gave the ketal 15 (17 g, 56%).

^1H NMR ($CDCl_3$) : δ 3.8 (4H, s, $-O-CH_2-CH_2-O$)
1.0-1.3 (9H, m, $3CH_3$)

4.28 β-2, α-6,8 Trimethyl-4-ethylene dioxy bicyclo-[3.3.0^{1,5}] octane (15)

Hydrazine hydrate (43.5 g, 0.86 mol) was added to a mixture of the dialdehyde 10 (13.1 g, 0.055 mol), powdered KOH (37.6 g, 0.66 mol) and diethylene glycol (60 ml) and refluxed for 4 hours. After adding water (125 ml) to the cold solution the reaction mixture was extracted with ether and the ether layer was then washed with water until the washings became neutral. It was then washed with brine, water and dried over Na_2SO_4. The ether solution was finally concentrated *in vacuo* and the crude product obtained was purified by column chromatography on

silica gel (100-200 mesh) as adsorbent and hexane-ethyl acetate (10:1) as eluent to get the ketal 15 (7 g, 61%).

4.29 β-4,α-6,8-Trimethyl-bicyclo[3.3.0^{1,5}]octan-2-one (12)

A mixture of ketal 15 (10.5 g, 0.05 mol), p-toluene sulphonic acid (50 mg) and aqueous acetone (5:1, 100 ml) was gently refluxed over a water bath for 5 hours. The mixture was cooled, washed with 1% $NaHCO_3$ solution, water and dried over Na_2SO_4 and concentrated *in vacuo* to get the ketone 12 (7.8 g, 95%).

IR (Neat) : 1740 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.0-1.2 (9H, m, $3CH_3$)

4.30 Baeyer-Villiger oxidation of β-4, α-6,8 Trimethyl-bicyclo[3.3.0^{1,5}]octan-2-one (12)

To a mixture of ketone 12 (2.0 g, 0.012 mol) in methylene chloride (40 ml) and sodium hydrogen carbonate (6.3 g, 0.075 mol) was added *m*-chloroperbenzoic acid (3.45 g, 0.02 mol). The mixture was stirred at room temperature for 16 hours. After the reaction, the reaction mixture was filtered and the excess peracid was decomposed by washing the filtrate with aqueous 10% sodium meta-bisulphite. The organic phase was washed with saturated

sodium bicarbonate solution, water, dried over anhydrous Na_2SO_4 and evaporated to get a mixture of products. The products were isolated by column chromatography using silica gel (100-200 mesh) as adsorbent and hexane-ethyl acetate (10:1) as eluent to get 16 (1.42 g, 65%) and 17 (0.54 g, 25%).

Compound: 16

IR (CCl_4) : 1745, 1450, 1060 cm^{-1}

'H NMR ($CDCl_3$) : δ 1.0-1.4 (9H, m, 3 $-CH_3$)
2 (2H, d, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 4.2 (1H, m, -OCH-)

Compound: 17

IR (CCl_4) : 1745, 1455, 1055 cm^{-1}

'H NMR ($CDCl_3$) : δ 0.9-1.2 (9H, m, 3 $-CH_3$)
2.1 (1H, m, $-\overset{O}{\overset{\|}{C}}-\overset{|}{C}H$), 4.1(2H, d, $-O-CH_2-$)

4.31 Baeyer-Villiger oxidation of β-4, α-6,8 trimethyl bicyclo[3.3.$0^{1,5}$]-octan-2-one (12)

Acetic anhydride (2.04 g, 20 mmol) was added dropwise to a stirred mixture of urea-H_2O_2 reagent 3.9 g, 0.04 mol), disodium hydrogen phosphate (9.8 g, 0.07 mol) and ketone 12 (1.33 g, 0.008 mol) in CH_2Cl_2 (40 ml) at 0°C. The mixture was warmed to room temperature and stirred for

10 hours. A saturated solution of sodiumbicarbonate was added to neutralise the acid present and the aqueous layer was extracted with CH_2Cl_2. Combined organic layer was washed with water, dried over Na_2SO_4 and solvent was evaporated. The residue was chromatographed using silica gel (100-200 mesh) and hexane-ethyl acetate mixture (10:1) to afford a mixture of products 16 (0.73 g, 50%) and 17 (0.36 g, 25%).

4.32 β-5, α-7,9-Trimethyl, 2-oxa-bicyclo[4.3.0^{1,6}]-octan-3-one (16)

To a solution of ketone 12 (1.67 g, 0.01 mol) in glacial acetic acid (15 ml) containing sodium acetate (6.75 g, 0.08 mol) was treated with hydrogen peroxide (30% in water, 3 ml). After 22 hours at room temperature sodium metabisulphite solution was added to decompose the free peracid. The aqueous solution was extracted with chloroform and the chloroform extracts were washed with water, saturated sodium hydrogen carbonate solution. The aqueous extracts were back extracted with chloroform and the combined organic solution was dried over Na_2SO_4 and evaporated *in vacuo* to get the lactone 16 (1.2 g, 66%) as the major product and it was purified by column chromatography using silica gel (100-200 mesh) and hexane ethyl acetate (10:1).

4.33 Preparation of perbenzoic acid[12]

In a 500 ml Erlanmeyer flask metallic sodium (5.2 g, 0.22 gm atom) was dissolved in absolute methyl alcohol (100 ml) with moderate cooling and finally the reaction mixture was cooled to -5°C. A solution of pure benzoylperoxide (Benzoylperoxide was purified by dissolving in $CHCl_3$ at room temperature and adding twice the volume of methyl alcohol) 50 g, 0.21 mol) in $CHCl_3$ (200 ml) was prepared at 0°C and added without delay to the sodium methoxide solution with stirring and cooling at such a rate that the temperature did not rise above 0°C. The mixture was kept for 5 minutes at -5°C with continuous stirring. The reaction mixture was then transferred to 1 litre separating funnel and extracted with water (500 ml) containing ice. The $CHCl_3$ layer was separated and the aqueous layer was extracted twice with $CHCl_3$ to remove the methyl benzoate. The aqueous layer containing sodium salt of perbenzoic acid was treated with 1N H_2SO_4 (220 ml) and the liberated perbenzoic acid was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water dried over anhydrous Na_2SO_4 and evaporated <u>in vacuo</u> to get solid perbenzoic acid (24 g, 82%).

4.34 Baeyer-Villiger oxidation of β-2,α-6,8-trimethyl bicyclo[3.3.$0^{1,5}$]octan-2-one (12)

Perbenzoic acid (1.52 g, 0.011 mol) in methylene chloride (30 ml) was introduced to a mixture of ketone 12 (1.325 g, 0.008 mol) in methylene chloride (10 ml) and solid sodium hydrogen carbonate (1.1 g), while maintaining the reaction temperature at 20°C. After stirring for 20 hours at room temperature, the reaction mixture was diluted with water, organic phase was separated and treated with saturated sodium metabisulphite solution. Organic layer was washed with water, dried over Na_2SO_4 and concentrated to get a mixture of products. The products were isolated by column chromatography using silica gel (100-200 mesh) and hexane ethyl acetate (10:1) to get 16 (0.725 g, 50%) and 17 (0.425 g, 30%).

4.35 Preparation of mono perphthalic acid[13]

To a cooled solution of sodium hydroxide (125 ml, 15%) at -10°C in a 500 ml R.B flask equipped with a mechanical stirrer, was added 30% H_2O_2 (52.5 ml) in one portion. Keeping the temperature at -10°C, pure phthalic anhydride (37.5 g) was added with stirring. After the addition a cooled solution of H_2SO_4 (20%, 120 ml) was added. The reaction mixture was filtered through a glass

wool into a separating funnel and extracted with ether (3 times). Combines ether solution was treated with saturated $(NH_4)_2SO_4$ solution, water and dried over Na_2SO_4. Ether was evaporated *in vacuo* to get the peracid (30 g, 70%).

4.36 Baeyer-Villiger oxidation of β-2,α-6,8-trimethyl bicyclo[3.3.0^{1,5}]octan-2-one (12)

To a mixture of ketone 12 (2.5 g, 0.015 mol) and sodium hydrogen carbonate (2 g) in dichloromethane (30 ml) a solution of monoperphthalic acid (4.08 g, 0.023 mol) in ether (20 ml) was added. The reaction mixture was stirred at 20°C for 16 hours. The reaction mixture was filtered and the filtrate was washed with saturated sodium meta-bisulphite solution, sodium hydrogen carbonate solution and water. The aqueous washings were back extracted with methylene chloride and the combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give a mixture of products. The products were isolated by column chromatography using silica gel (100-200 mesh) and hexane-ethyl acetate (10:1) to get 16 (1.78 g, 65%) and 17 (0.55 g, 20%).

4.37 α-3,5-Dimethyl-2-(β-4 methyl-2-oxo-4-butyl)-cyclopentan -1-ol (18)

To a solution of lactone 16 (1.83 g, 0.01 mol) in dry ether (10 ml) in a 3-necked flask fitted with a magnetic stirrer, thermometer, cooled to -50°C was added ether solution of methyl lithium (6.5 ml, 1.5 mol) slowly maintaining the temperature at -50°C under N_2. The reaction mixture was stirred for 30 minutes and brought to room temperature. It was then poured to ice water and stirred for 15 minutes. Organic layer was separated, washed with NH_4Cl solution, water and dried over Na_2SO_4. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (100-200 mesh) and hexane-ethyl acetate (8:1) to afford 18 (1.78 g, 90%).

IR (CCl_4) : 3430, 1710 cm^{-1}

'H NMR ($CDCl_3$) : δ 2.1 (3H, s, $-CO-CH_3$)

4.38 1-Acetyl α-3,5 dimethyl-2-(2-β-methyl-hydroxy 2-ethyl)cyclopentane (21)

To a solution of lactone 17 (1.22 g, 0.007 mol) in dry ether (10 ml) at -50°C in a 3-necked flask fitted with a magnetic stirrer and thermometer, was added ether solution solution of methyl lithium 4.3 ml, 1.5 M) slowly

keeping the temperature at -50°C under N_2. The reaction mixture was stirred for 30 minutes and brought to room temperature, and poured into ice water with stirring. Stirring was continued for 15 minutes. Organic layer was separated, washed with NH_4Cl solution, water and dried over Na_2SO_4. Solvent was removed *in vacuo* and the residue was purified by column chromatography using silica gel (100-200 mesh) and hexane-ethyl acetate (8:1) to get 21 (1.17 g, 89%).

IR (CCl_4) : 3550, 1710 cm^{-1}

'H NMR ($CDCl_3$) : δ 2.1 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$)

4.39 2(1-hydroxy α-3,5 dimethyl)cyclopentyl-β-2-methyl ethyl acetate (19)

To a mixture of ketone 18 (2.2 g, 0.011 mol) in methylene chloride (50 ml) was added sodium-hydrogen carbonate (5.0 g, 0.06 mol) and m-chloroperbenzoic acid (2.76 g, 0.016 mol). The mixture was stirred at room temperature for 45 hours. After the reaction the excess peracid was decomposed by washing with aqueous 10% sodium metabisulphite. Organic layer was separated and washed with saturated sodium hydrogen carbonate solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated

under reduced pressure and the product was purified by column chromatography using silica gel (100-200 mesh) and hexane-ethyl acetate (12:1) to get the acetate 19 (2.16 g, 91%).

IR (CCl_4) : 3450, 1735, 1090 cm^{-1}

'H NMR ($CDCl_3$) : δ 2.1 (3H, s, $-COCH_3$), 4.0 (2H, d, $-O-CH_2$).

4.40 2(1-Acetoxy α-3,5 dimethyl)cyclopentyl-β-2-methyl ethanol (22)

To a mixture of ketone 21 (1.2 g, 0.004 mol) in methylene chloride (20 ml) was added sodium-hydrogen carbonate (0.1 mol) and m-chloroperbenzoic acid (2.8 g, 0.009 mol). The reaction mixture was stirred at room temperature for 38 hours. After the reaction the excess peracid was decomposed by washing with aqueous 10% sodium meta-bisulphite. Organic layer was separated and washed with saturated sodium hydrogen carbonate solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated in vacuo and the product was purified by column chromatography on silica gel (100-200 mesh) and hexane-ethyl acetate (12.1) as eluent to get the acetale 22 (1.16 g, 90%).

IR (CCl_4) : 3550, 1735, 1100 cm^{-1}

'H NMR ($CDCl_3$) : δ 2.1 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 4.1(1H, m, -O-CH).

4.41 2(1-hydroxy α-3,5 dimethyl)cyclopentyl β-2-methyl 2-ethanol (20)

A mixture of lactones 19 and 22 (1.8 g, 0.008 mol) and potassium hydroxide (0.9 g, 0.016 mol) in dry methyl alcohol (15 ml) were refluxed for 2 hours. The reaction mixture was added to 50 ml of ice water with stirring and acidified with dilute hydrochloric acid. The reaction mixture was extracted with ether (20 ml x 4) and the combined ether solution was washed with water, dried over anhydrous Na_2SO_4 and evaporated to yield 1.26 g (87%) of the alcohol 20.

IR (CCl_4) : 3560, 3450, 2935, 1150 cm^{-1}

4.42 2(1-oxo α-3,5-dimethyl cyclopentyl β-2 methyl-2-acetic acid (23)

To a solution of alcohol 20 (2 g, 0.011 mol) in ether (20 ml) in a 250 ml round bottomed flask kept in ice bath equipped with a thermometer and stirrer, 8 N chromic acid (20 ml) was added from a dropping funnel. The reaction mixture was stirred for 5 hours keeping the temperature of the reaction mixture at 20°C. After the reaction, sodium metabisulphite solution was added to eliminate the excess oxidant. Ether layer was separated

and the aqueous solution was extracted with ether (20 ml x 3) and the combined ether solution was washed with 5% sodium hydrogen carbonate, water and dried over anhydrous Na_2SO_4. Solvent was evaporated *in vacuo* and the residue was purified by column chromatography using neutral aluminium oxide as adsorbent and hexane-ethyl acetate (5:1) as eluent to get the keto acid 23 (1.48 g, 70%).

IR (CCl_4) : 2500-3500, 1740, 1705 cm^{-1}

'H NMR ($CDCl_3$) : δ10.9 (1H, br, -COOH), 2.0-2.2(2H,m,-$COCH_3$)

4.43 Baeyer-Villiger oxidation of 2(1-oxo α-3,5 dimethyl) cyclopentyl β-2 methyl-2-acetic acid (23)

A mixture of 23 (1.0 g, 0.005 mol) and disodium hydrogen phosphate (10.65 g, 0.075 mol) in CH_2Cl_2 (50 mol) was cooled in ice water and stirred magnetically. To this was added m-chloroperbenzoic acid (2.0 g, 0.012 mol) in small portions over 15 minutes. The reaction mixture was stirred for 20 hours at 25°C under N_2. A saturated solution of $NaHSO_3$ was added followed by $NaHCO_3$ (8 g) and stirred for 1 hour. Insoluble material was filtered and the filtrate was evaporated to a pale yellow solid which was chromatographed on silica gel (100-200 mesh) using hexane-ethyl acetate mixture (5:1) to afford a mixture of products 24 (0.5 g, 47%) and 25 (0.43 g, 40%).

Compound 24

IR (CCl_4) : 3500-2700, 1735, 1705, 1460, 1190 cm^{-1}

'H NMR ($CDCl_3$) : δ 1-1.3 (9H, m, CH_3 at C_2, C_4 and C_6), 4.5 (1H, m, H-3), 10.8 (1H, br, COOH).

MS : m/z 200 (M^+)

Anal : Cacld for $C_{10}H_{16}O_4$; C, 60; H, 8

Found : C, 60.8; H, 8.2

Compound 25

IR (CCl_4) : 3500-2700, 1735, 1710, 1470, 1130 cm^{-1}

'H NMR ($CDCl_3$) : δ 1.0-1.3 (9H, m, $3CH_3$, 4.1 (1H, m), 10.9 (1H, br, -COOH).

MS : m/z 200 (M^+)

Anal : Calcd for $C_{10}H_{16}O_4$; C, 60. ; H, 8

Found: C, 60.2, H, 8.1

4.44 Baeyer-Villiger oxidation of 2-(1-oxo-α-3,5 dimethyl) pentyl β-2 methyl-2-acetic acid (23)

Acetic anhydride (1.22 g, 12 mmol) was added dropwise to a stirred mixture of urea -H_2O_2 reagent (2.28 g, 0.024 mol), disodium hydrogen phosphate (5.68 g, 0.04 mol)

and keto acid 23 (0.88 g, 0.0048 mol) in CH_2Cl_2 (60 ml) at 0°C. The mixture was warmed to room temperature and stirred for 15 hours. A saturated solution of $NaHCO_3$ was added to neutralise the acid present and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over Na_2SO_4 and evaporated to get a mixture of products by TLC and was separated by column chromatography using silica gel (100-200 mesh) and hexane-ethyl acetate (5:1) to afford 24 (0.41 g, 43%) 25 (0.36 g, 39%).

4.45 Baeyer-Villiger oxidation of 2(1-oxo ∝-3,5dimethyl) cyclopentyl β-2 methyl 2-acetic acid (23)

To a solution of keto acid 23 (0.6 g, 0.0032 mol) in glacial acetic acid (10 ml) containing sodium acetate 1.72 g, 0.021 mol) was added hydrogenperoxide (1 ml, 30%). Reaction mixture was stirred for 24 hours at room temperature. A saturated solution of sodium metabisulphite was added to decompose the excess per acid and the solution was extracted with chloroform (10 ml x 3). Combined organic layer was washed with saturated sodium bicarbonate solution, water, dried over Na_2SO_4 and evaporated in vacuo to afford a solid which was purified by column chromatography using silica gel (100-200 mesh) and hexane-ethyl

acetate mixture (5:1) resulted a mixture of products 24 (0.38 g, 58%) and 25 (0.14 g, 21%).

4.46 Baeyer-Villiger oxidation of 2(1-oxo-α3,5-dimethyl) cyclopentyl β-2-methyl-2-acetic acid (23)

To a mixture of keto acid 23 (0.5 g, 0.002 mol) and disodium hydrogen phosphate (5.3 g, 0.037 mol) in dichlorcmethane (50 ml) was added perbenzoic acid (0.82 g, 0.006 mol) in dichloromethane (10 ml) with stirring and keeping the temperature at 20°C. After stirring for 18 hours at room temperature the reaction mixture was diluted with water and organic layer was separated. Organic layer was washed with saturated sodium metabisulphite solution, 5% sodium bicarbonate solution, water and dried over sodium sulphate. The residue left after the evaporation of solvent in vacuo was chromatographed on silica gel (100-200) and hexane-ethyl acetate mixture (5:1) to afford a mixture of products 24 (0.24 g, 44%) and 25 (0.21 g, 39%).

4.47 Baeyer-Villiger oxidation of 2(1-oxo α-3,5-dimethyl) cyclopentyl β-2-methyl-2-acetic acid (23)

To a mixture of keto acid 23, (0.5 g, 0.002 mol) and disodium hydrogen phosphate (5.3 g, 0.0375 mol) in

dichloromethane (30 ml) was added a solution of monoperphthalic acid (1 g, 0.006 mol) in ether (5 ml) with stirring at 20°C. The reaction mixture was stirred for 17 hours at room temperature, diluted with water and filtered. The filtrate was washed with saturated solution of sodium meta-bisulphite, sodiumbicarbonate, water, dried over sodium sulphate and evaporated *in vacuo*. The residue was purified by column chromatography using silica gel (100-200) and a mixture of hexane and ethyl acetate (5:1) to afford the lactones *24* (0.23 g, 42%) and *25* (0.2 g, 37%).

4.48 Cyclopentadiene[14]

Dicyclopentadiene (commercial grade 100 ml) was heated at reflux (170-180°C) under nitrogen atmosphere in a 250 ml round bottomed flask equipped with Friedrich's condenser, Claisen head, thermometer, a gas inlet and a collection adapter. After discarding the forerun (5 ml), the receiver was cooled in freezing mixture and cyclopentadiene distilling at 41°C was collected. A slight positive pressure of N_2 was maintained throughout the distillation to prevent moisture from enetering the system. Cyclopentadiene thus obtained was used immediately for further reaction.

4.49 Bicyclo[2.2.1]hept-5-en-2-acetate (26)[15]

Freshly prepared cyclopentadiene (3) (50 g, 0.75 mol) was mixed with excess vinyl acetate (129 g, 1.5 mol) in a heavy glass sealed tube and heated in a furnace at 180°C for 10 hours. After the reaction the tube was opened and the contents were fractionally distilled (73-75°C, 14 mm) to get the acetate 26 (121 g, 80%) and it was purified by column chromatography using silica gel (60-120 mesh) adsorbent and hexane-ethyl acetate (20:1) as eluent.

IR (CCl_4) : 3010, 1730, 1100 cm^{-1}

^1H NMR ($CDCl_3$) : δ2.0 (3H, s, $-\overset{O}{\overset{\|}{C}}CH_3$), 5.8 (2H, m, -CH=CH-)

4.50 Bicyclo[2.2.1]hept-5-en-2-ol (27)

A solution of acetate 26 (100 g, 0.66 mol) in methyl alcohol (300 ml) was refluxed with methanolic solution of potassium hydroxide (39.2 g, 0.7 mol) for 3 hours. Progress of the reaction was monitored by thin layer chromatography. After the reaction the reaction mixture was poured into ice water with stirring. The organic layer was separated and the aqueous layer was extracted with ether (50 ml x 4). Combined organic

solution was washed with water, dried over Na_2SO_4 and evaporated. The crude alcohol was purified by crystallization from petroleum ether (35-40) to get the alcohol 27 (65 g, 90%).

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

'H NMR ($CDCl_3$) : δ 5.8 (2H, m, -CH=CH-)

4.51 Bicyclo[2.2.1]hept-5-en-2-one (28)

To a solution of alcohol 27 (40 g, 0.36 mol) in ether (100 ml) at 0°C was added 8N chromic acid (300 ml) (Prepared by mixing 70 g of CrO_3 in 200 ml water with 61 ml con. H_2SO_4 and diluted with 100 ml water) slowly with stirring. The reaction mixture was stirred for 3 hours at 10°C. After the reaction a solution of sodium metabisulphite was added to reduce the excess oxidising agent. Ether layer was separated and the aqueous layer was extracted with ether (30 ml x 3). Combined ether layer was washed with saturated sodium bicarbonate solution, water and dried over anhydrous sodium sulphate. Ether was evaporated *in vacuo* and the crude ketone was purified by column chromatography using neutral alumina as adsorbent and hexane-ethyl acetate (10:1) as eluent to afford 28 (31.4 g, 80%).

IR (CCl_4) : 1740, 1630 cm^{-1}

'H NMR ($CDCl_3$) : δ 6 (2H, m, -CH=CH-)

4.52 Bicyclo[2.2.1]hept-5-en-2-one (28) - PCC oxidation

To a solution of alcohol 27 (35 g, 0.32 mol) in CH_2Cl_2 (300 ml), freshly prepared pyridinium chlorochromate (137 g, 0.63 mol) was added slowly with stirring and keeping the temperature below 25°C. The reaction mixture was stirred for 2 hours. After the reaction, reaction mixture was filtered and the residue was washed with CH_2Cl_2 (50 ml x 2) and the combined filtrate and washings were evaporated under reduced pressure. The residue purified by column chromatography using neutral aluminium oxide and hexane ethyl acetate (10:1) to afford the ketone 28 (29 g, 85%).

4.53 2-Chloro-2-cyano-bicyclo[2.2.1]hept-5-ene (29)[16]

To a mixture of freshly prepared cyclopentadiene (3) (30 g, 2.45 mol) and catalytic amount of cupric fluoroborate at 0°C was added excess 2-chloro-acrylonitrile (196 g, 2.25 mol) and the reaction mixture was stirred at 0°C. The resulting product was fractionally distilled to get the adduct 29 (62.7 g, 90%).

IR (Neat) : 2200 cm^{-1}

'H NMR ($CDCl_3$) : δ 6.1 (2H, m, -CH=CH-)

4.54 Bicyclo[2.2.1]hept-5-ene-2-one (28)

To a solution of nitrile 29 (50 g, 0.33 mol) in dimethylsulphoxide (150 ml) was added a hot aqueous solution of potassium hydroxide (46.2 g, 0.83 mol) and the reaction mixture was stirred for 10 hours at 30°C. When the reaction was complete, the reaction mixture was diluted with water and extracted with ether (50 ml x 3). The combined ether extracts were washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography using neutral aluminium oxide and hexane-ethyl acetate (10:1) to get the ketone 28 (25 g, 70%).

4.55 2-Cyano-2-acetoxy bicyclo[2.2.1]hept-5-ene (30)[17]

A mixture of cyclopentadiene (3) (13 g, 0.197 mol) and α-acetoxy acrylonitrile (17 g, 0.153 mol) was heated at 100°C for 3 hours. The mixture was kept overnight at room temperature and fractionally distilled (132-137°C, 18 Torr) to get 30 (16.8 g, 62%).

IR (CCl_4) : 2250, 1735, 1620, 1110 cm^{-1}

'H NMR ($CDCl_3$) : δ 2.1 (3H, s, $-COCH_3$), 5.9 (2H, m, -CH=CH-)

4.56 Bicyclo[2.2.1]hept-5-en-2-one (28)[17]

A mixture of cyanhydrin acetate (30) (7 g, 0.04 mol) and sodium hydroxide (20 g, 0.5 mol) in water (200 ml) were heated under reflux for 2 hours and then steam distilled. The distillate was saturated with potassium carbonate and extracted with ether (20 ml x 3). Combined ether layer was washed withw ater, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography using neutral alumina and hexane-ethyl acetate (10:1) to get the ketone 28 (3.5 g, 81%).

4.57 2-Chloro-methyl propanoate

Freshly distilled 2-chloropropanoic acid (50 g, 0.46 mol) was refluxed with dry methyl alcohol (32 g, 1 mol) containing 50 mg of *p*-toluene sulphonic acid in a 250 ml round bottomed flask for 3 hours. The reaction mixture was cooled, diluted with water and the organic layer was separated. The aqueous layer was washed with ether and the combined organic layers were washed with saturated sodiumbicarbonate, water and dried over sodium sulphate. Solvent was removed under reduced pressure and the residue fractionally distilled to get the methyl ester (48 g, 85%).

4.58 Methyl 3(2-oxo-bicyclo[2.2.1]hept-5-en)2-propanoate(31)

To a suspension of lithium powder (0.58 g, 0.027 mol) in dry tetrahydrofuran (5 ml) at -50°C, was added n-butylbromide (2.48 g, 0.01 mol) in dry tetrahydrofuran (55 ml) and stirred for 20 minutes under N_2. A solution of diisopropylamine (1.4 g, 0.01 mol) in dry tetrahydrofuran (5 ml) was added dropwise with stirring, keeping the reaction mixture cooled in dry ice. After 30 minutes the ketone 28 (1.08 g, 0.01 mol) in dry tetrahydrofuran (5 ml) was added, stirred for 1 hour and methyl -chloropropanoate (2.9 g, 0.024 mol) in dry tetrahydrofuran (5 ml) was added. Stirring was continued for 2 hours by keeping the temperature at -50°C. After two hours the reaction mixture was warmed to room temperature and poured into ice water containing pentane (20 ml). The organic layer was separated and the aqueous layer was extracted with pentane (10 ml x 2). The combined extracts were washed with NaCl solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated *in vacuo* and residue was purified by column chromatography on neutral aluminium oxide and hexane-ethyl acetate (10:1) to get the keto ester 31 (1.84 g, 55%).

IR (Neat) : 1730, 1745 cm^{-1}

^1H NMR ($CDCl_3$) : δ 6.1 (2H, m, -CH=CH-), 3.5 (3H, s, $-OCH_3$)

4.59 Methyl 3(2-ethylenedioxy-bicyclo[2.2.1] hept-5-en) 2-propanoate (32)

A mixture of the ketoester 31 (15 g, 0.07 mol), ethylene glycol (6.2 g, 0.1 mol) and pyridinium-p-toluene sulphonate (prepared by adding dry pyridine to p-toluene sulphonic acid (1.3 g) in dry ether and washing the excess pyridine with dry ether) was taken in benzene (60 ml) and was heated at reflux using a Dean-Stark apparatus for 3 hours under N_2 atmosphere. The reaction mixture was cooled and washed with 10% sodium bicarbonate, water and dried over anhydrous sodiumsulphate. Benzene was removed *in vacuo* and the crude ketal was purified by column chromatography using neutral aluminium oxide and hexane-ethyl acetate (12:1) to give the ketal 32 (16.5 g, 90%).

IR (CCl_4) : 1730, 1100 cm^{-1}

'H NMR ($CDCl_3$) : δ 6.1 (2H, m, -CH=CH-),
3.8 (4H, s, $-OCH_2-CH_2-O$), 3.4 (3H,s, $-OCH_3$)

4.60 Cleavage of ketal ester 32

Under stirring and protection from light, osmium tetroxide (90 mg) was added to a solution of ketal 32 (10 g, 0.042 mol) in a mixture of dioxan (80 ml) and water (40 ml) and stirred for 15 minutes at 20°C. After 15

minutes a solution of sodium meta-periodate (18.3 g, 0.084 mol) in water (50 mol) was added and stirred overnight. The reaction mixture was filtered and the residue and filtrate were extracted with ether and the combined ether extracts were washed with brine, water and dried over Na_2SO_4. Solvent was evaporated *in vacuo* to get the dialdehyde 33 (10.2 g, 90%).

IR (CCl_4) : 2850, 2750, 1730, 1720 cm^{-1}

'H NMR ($CDCl_3$) : δ 3.4 (3H, s, $-OCH_3$),
9.8 (2H, d, -CHO).

4.61 Cleavage of ketal ester 32 — Second method

A solution of cetyltrimethyl ammonium permanganate (4.04 g, 10 mmol) in dichloromethane (50 ml) was added dropwise to a stirred solution of ketal 32 (2.37 g, 0.010 ml) in dichloromethane (20 ml) at 20°C. Stirring was continued for one hour and the solvent was concentrated to half of its original volume. A solution of benzyl triethyl ammoniumperiodate (7.74 g, 0.02 mol) in dioxane (40 ml) was added to the reaction mixture under N_2 atmosphere and the reaction mixture was stirred for 10 hours. The reaction mixture was filtered and the filtrate and residue were

extracted with dichloromethane and the combined organic solution was dried over sodium sulphate and evaporated *in vacuo* to get dialdehyde 33 (1.83 g, 68%).

4.62 Preparation of dithioketal 34

A mixture of dialdehyde 33 (15 g, 0.56 mol), 1,2-ethanedithiol (10.5 g, 0.11 mol) in $CHCl_3$ (10 ml) and freshly distilled borontrifluoride etherate (2 ml) were stirred for 3 hours at 10°C. The reaction mixture was diluted with water and extracted with ether. Ether layer was washed with 5% sodium hydroxide solution, water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get thioketal 34 (13.6 g, 65%).

IR (CCl_4) : 3500-2500, 1745, 1705 cm^{-1}

^1H NMR ($CDCl_3$) : δ 3.3 (8H, m, 2-SCH_2-CH_2-s-),
10.8 (1H, s, -COOH).

4.63 Methyl 2-(1-oxo-α-3,5-dimethyl)cyclopentyl-2-propanoate (35) — Reduction with Raney-nickel

A mixture of dithioketal (2 g, 0.005 mol) in dry methyl alcohol (15 ml) and freshly prepared Raney-nickel catalyst (W.2 grade, 10 g) in absolute ethyl alcohol (100 ml) were refluxed with stirring for 3 hours. After

the reaction the reaction mixture was filtered and washed the nickel catalyst with hot methyl alcohol and the combined washings and filtrate were evaporated *in vacuo* and the crude acid was purified by column chromatography using silica gel (100-200 mesh) and hexane-ethyl acetate (10:1) to afford the keto acid 35 (0.68 g, 65%).

IR (Neat) : 1740, 1705 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.1-1.2 (9H, m), 10.8 (1H, br, -COOH)

4.64 Methyl-2-(1-oxo 3,5-dimethyl)cyclopentyl 2-propanoate (35) — Reduction with complex reducing agent

A solution of tertiary amyl alcohol (2g, 0.02 mol) in dry tetrahydrofuran (15 ml) was added dropwise to a suspension of sodium hydride (1.68 g, 0.07 mol) and nickel acetate (1.77 g, 0.01 mol) in refluxing tetrahydrofuran (20 ml). After two hours the dithioketal 34 (3.21 g, 0.008 mol) in tetrahydrofuran (25 ml) was added slowly and refluxed for 2 hours. The reaction mixture was cooled and slowly added to water with stirring and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by column chromatography using silica gel (100-200 mesh) and hexane-ethyl acetate (10:1) to get keto acid 35 (1 g, 65%).

4.65 Methyl 2-(1-oxo-α-3,5 dimethyl)cyclopentyl-2-propanoate (36)

A mixture of keto acid 35 (2 g, 0.0087 mol) in dry methyl alcohol (20 ml) and p-toluene sulphonic acid (30 mg) were refluxed for 3 hours. The reaction mixture was cooled, diluted with water and extracted with ether. Ether layer was washed with 5% sodium bicarbonate solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue was purified by column chromatography using neutral aluminium oxide and hexane-ethyl acetate (10:1) to give the keto ester 36 (1.2 g, 70%).

IR (CCl_4) : 1740, 1725, 1100 cm^{-1}

^1H NMR ($CDCl_3$) : δ 3.4 (3H, s, $-OCH_3$)

4.66 Methyl-2(1-ethylenedioxy α-3,5-dihydroxy methyl) cyclopentyl-2-propanoate (37)

A solution of dialdehyde 33 (2.25 g, 0.0075 mol) in methyl alcohol (15 ml) was added in drops to a suspension of sodiumborohydride (0.57 g, 0.015 mol) in methyl alcohol (10 ml). The mixture was stirred for 2 hours at 10°C. After the reaction, half of the solvent was evaporated and the mixture was diluted with water and

extracted with ether (20 ml x 3). Combined ether extracts were washed with water, dried over anhydrous Na_2SO_4 and on evaporation yielded the alcohol 37 (2.05 g, 90%).

IR (CCl_4) : 3550, 1735 cm^{-1}

'H NMR ($CDCl_3$) : δ 3.4 (3H, s, $-OCH_3$),
3.8 (4H, s, $-O-CH_2-CH_2-O-$)

4.67 Methyl-2(1-ethylene dioxy α-3,5 ditosyl methyl) cyclopentyl-2-propanoate (38)

To a solution of alcohol 37 (2 g, 0.007 mol) and triethyl amine (2.2 g, 0.022 mol) in anhydrous CH_2Cl_2 (10 ml) at 10°C, was added a solution of p-toluene sulphonyl chloride (3.1 g, 0.016 mol) in CH_2Cl_2 (20 ml) during 30 minutes. The mixture was stirred at 10°C for 2 hours and was added to ice water. The organic layer was washed with saturated NH_4Cl solution, water, dried over Na_2SO_4 and concentrated *in vacuo* to get tosylate 38 (3.83 g, 90%).

'H NMR ($CDCl_3$) : δ 7.3 (8H, m, Phenyl), 3.4 (3H, s, $-OCH_3$),
3.8 (4H, s, $-OCH_2-CH_2-O-$)

4.68 2-(1-ethylene dioxy ∝-3,5 dimethyl)cyclopentyl-2-propan-1-ol (39)

To a suspension of lithium aluminium hydride (0.532 g, 0.014 mol) in dry ether was added dropwise a solution of tosylate 38 (2 g, 0.0034 mol) in dry ether (20 ml). After refluxing for 12 hours the excess lithium luminium hydride was destroyed by slow addition of the reaction mixture to ice water. The residue was filtered and the ether solution was washed with water, dried over Na_2SO_4. Solvent was in vacuo to get the alcohol 39 (0.42 g, 55%).

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

'H NMR ($CDCl_3$) : δ 3.8 (3H, s, $-OCH_2-CH_2-O-$)

4.69 2-(1-oxo-∝3,5 dimethyl)cyclopentyl-2-propanoic acid (35)

To a solution of alcohol 39 (2 g, 0.009 mol) in ether (50 ml) 8N chromic acid (10 ml) was added slowly with stirring and keeping the temperature of reaction mixture at 10°C. Stirring was continued for 2 hours. Ether layer was separated and the aqueous layer was extracted with ether (20 ml x 3). Combined ether layer was washed with saturated metabisulphite solution, sodiumbicarbonate

solution, water and dried over Na_2SO_4. After evaporation of the solvent the residue was chromatographed on neutral aluminium oxide and a mixture of hexane-ethyl acetate (4:1) to afford the acid 35 (1.48 g, 70%).

IR (CCl_4) : 3500-2700, 1745 cm^{-1}

'H NMR ($CDCl_3$) : δ10.8 (1H, s, -COOH)

4.70 2(1-ethylene dioxy α-3,5 dimethyl) cyclopentyl-2-propanoic acid (40)

Hydrazene hydrate (4 g, 0.12 mol) was added to a mixture of aldehyde 33 (2.1 g, 0.008 mol) powdered potassium hydroxide (5.1 g, 0.09 mol) and ethylene glycol (8 ml). The mixture was refluxed for 4 hours, cooled and diluted with ice cold water. The solution was neutralised with dil. HCl and made it slightly acidic and extracted with ether (50 ml x 3) and the ether solution was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give ketal 40 (1.28 g, 70%0.

IR (CCl_4) : 3500-2500, 1705 cm^{-1}

'H NMR ($CDCl_3$) : δ 3.8 (4H, s, $-OCH_2-CH_2-O-$),
10.9 (1H, s, -COOH).

4.71 2(1-oxo-α3,5 dimethyl) cyclopentyl-2-propanoic acid (35)

A mixture of ketal 40 (1.83 g, 0.008 mol) p-toluene sulphonic acid (10 mg) and aqueous acetone (5:1, 20 ml) were gently refluxed over a water bath for 5 hours. The mixture was cooled, treated with 1% sodiumbicarbonate solution and acetone was removed under reduced pressure. The residue was extracted with ether (20 ml x 3) and the ether extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to get the keto acid 35 (1.3 gm, 85%).

IR (CCl_4) : 3500-2700, 1745 cm^{-1}

'H NMR ($CDCl_3$) : δ 10.9 (1H, br, -COOH).

4.72 Baeyer-Villiger oxidation of methyl 2-(1-oxoα-3,5 dimethyl) cyclopentyl 2-propanoate (36)

To a mixture of keto ester 36 (1.0 g, 0.005 mol) in CH_2Cl_2 (10 ml) was added sodiumbicarbonate (2.5 g, 0.03 mol) and m-chloroperbenzoic acid (1.38 g, 0.008 mol). The mixture was stirred for 18 hours at room temperature. Reaction mixture was filtered and excess peracid was decomposed by washing the filtrate with 10% sodium meta bisulphite solution. Organic layer was separated and

washed with $NaHCO_3$ solution, water, dried over Na_2SO_4 and evaporated *in vacuo* to get a solid. Column chromatographic purification of the solid using neutral alumina and hexane-ethyl acetate mixture afforded a mixture of products as 41 (0.6 g, 57%) and 42 (0.36 g, 34%).

Compound 41

^1H NMR($CdCl_3$): δ 1-1.3 (9H,m), 4.3 (1H,m), 3.4 (3H, S, $-OCH_3$)

MS: M/Z 214 (M^+)

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68, H, 8.41.
Found: C, 61.92, H, 8.54

Compound 42

^1H NMR ($CDCl_3$): δ 0.9-1.3 (9H, m), 4 (1H, m) 3.4 (3H, S, $-OCH_3$)

MS: M/Z 214 (M^+)

Anal: Calcd for $C_{11}H_{18}O_4$ C, 61.68, H, 8.41.
Found: C 61.98, H, 8.61.

4.73 Baeyer-Villiger oxidation of methyl-2-(1-oxo-3,5 dimethyl) cyclopentyl-2-propanoate (36)

Acetic anhydride (1.67 g, 0.016 mol) was added dropwise to a stirred mixture of urea $-H_2O_2$ reagent (3.1 g, 0.033 mol), disodium hydrogen phosphate (8 g, 0.057 mol) and keto ester 36 (1.3 g, 0.007 mol) in CH_2Cl_2 (20 ml) at

0°C. The mixture was warmed to room temperature and stirred for 12 hours. A saturated solution of sodium bicarbonate was added to neutralize the acid present and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography using neutral alumina and hexane-ethyl acetate (10:1) to get the lactones 41 (0.52 g, 37%) and 42 (0.49, 28%).

4.74 Baeyer-Villiger oxidation of methyl-2-(1-oxo-α-3,5 dimethyl) cyclopentyl-2-propanoate (36)

To a solution of keto ester 36 (0.759, 0.004 mol) in glacial acetic acid (5 ml) containing sodium acetate (4 g, 0.049 mol) was treated with hydrogen peroxide (30% in water, 1 ml). After 24 hours at room temperature sodium metabisulphite solution was added to decompose the excess peracid. The reaction mixture was extracted with chloroform and the chloroform layer was washed with saturated sodium bicarbonate solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated *in vacuo* and the residue was purified by column chromatography using neutral alumina and hexane-ethylacetate (10:1) to get a mixture of products 41 (0.33 g, 40%) and 42 (0.24 g, 30%).

4.75 Baeyer-Villiger oxidation of methyl-2(1-oxo-∝3,5 dimethyl) cyclopentyl-2-propanoate (36)

Perbenzoic acid (0.89 g, 0.007 mol) in CH_2Cl_2 (10 ml) was added to a mixture of keto ester 36 (1.0 g, 0.005 mol) in CH_2Cl_2 (10 ml) and sodium bicarbonate (0.65, 0.007 mol) while keeping the reaction temperature at 25°C. After stirring for 20 hours at room temperature, the reaction mixture was diluted with water, organic phase was separated and treated with saturated sodium metabisulphite solution followed by water and dried over Na_2SO_4. On evaporation of solvent in vacuo yielded pale yellow solid which was purified by column chromatography using neutral aluminium oxide and hexane-ethyl acetate (10:1) to get the lactone 41 (0.54 g, 50%) and 42 (0.27 g, 25%).

4.76 Baeyer-Villiger oxidation of methyl-2-(1-oxo-∝-3,5 dimethyl) cyclopentyl-2-propanoate (36)

To a mixture of keto ester 36 (0.75 g, 0.0038 mol) and sodium bicarbonate (0.63 g, 0.0075 mol) in dichloromethane (10 ml), a solution of monoperphthalic acid (1.125 g, 0.0063 mol) in ether (10 ml) was added. The reaction mixture was stirred for 18 hours at room temperature. After the reaction, the reaction mixture was

filtered and the filtrate was washed with sodium metabisulphite solution (10%), water and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography using neutral alumina and hexane ethylacetate (10:1) mixture as eluent to get lactones 41 (0.36 g, 45%) and 42 (0.275 g, 36%).

CHAPTER V

CONCLUSION

Prelog-Djerassi lactone has been a focus of attention for the chemists since its isolation as a degradation product of macrolide antibiotics like Narbomycin and Methymycin. Its importance in the synthesis of macrolide antibiotics was first demonstrated by Masamune in the synthesis of Methymycin and since then there have been a number of preparations of Prelog-Djerassi lactone in recemic as well as in optically active forms. In the present work two methods were developed for the synthesis of recemic Prelog-Djerassi lactone.

In the first method the starting material exo-dicyclopentadiene was subjected to selenium dioxide oxidation in dioxane-water system to get exo-dicyclopentadienol (5). The same alcohol was also obtained in better yield by the acetic acid mediated selenium dioxide oxidation of exo-dicyclopentadiene. The above alcohol was oxidised to exo-dicyclopentadienone (7) using oxidants like chromic acid, PCC, P-beznoquinone-Aluminium t-butoxide etc. and best result was obtained with PCC. Treatment of the exo-dicyclopentadienone with dimethyl copper lithium or Cu^{+} ion catalysed CH_3MgI, afforded β-3-methyl-tricyclo[5.2.1.$0^{2,6}$]dec-8-3n-5-one (8). Better stereoselectivity and yield were achieved with dimethyl

copper lithium. Carbonyl group of β-3-methyl tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-5-one (8) was protected and the double bond was oxidatively cleaved to B-2-methyl-4-ethylenedioxy-bicyclo[3.3.$0^{1,5}$]octane-6,8-dicarboxaldehyde (10). Aldehyde groups of this compound were converted to methyl groups by different methods. In the first method the aldehyde groups were converted to corresponding thioketal 11 and it was reduced to methyl groups by Raney-Ni. By the second method the aldehyde groups were reduced to alcohol 13 and then converted to tosylate 14 using P-toluenesulphonyl chloride. Reduction of the tosylate groups with lithium aluminium hydride afforded the methyl groups. In the third method the conversion of aldehyde groups to methyl groups was achieved by reduction with hydrazine hydrate. Adopting all these methods, the product obtained was β-4-α-6,8-trimethyl bicyclo[3.3.$0^{1,5}$]octan-2-one (12). This ketone was subjected to Baeyer-Villiger oxidation and the lactones 16 and 17 obtained as expected were isolated and treated with methyl lithium to get the corresponding methyl ketones 18 and 21. The methyl ketones were again subjected to Baeyer-Villiger oxidation followed by hydrolysis and oxidation leading to the formation of 2-(1-oxo-α-3,5-dimethyl) cyclopentyl-β-2-methylacetic acid (23). Baeyer-Villiger oxidation of this keto acid gave a

mixture of lactones from which the expected Prelog-Djerassi lactone (24) was separated by column chromatography.

In the second method of Prelog-Djerassi lactone synthesis, dehydronorcamphor (28) was used as the starting material. The dehydronorcamphor was prepared by the Diels-Alder reaction of cyclopentadiene with dienophiles vinyl acetate, α-chloroacrylonitrile and α-acetoxyacrylo nitrile. The dehydronorcamphor was subjected to α-alkylation using methyl ester of α-chloropropanoic acid as the alkylating agent. The carbonyl group of this alkylated product 31 was protected and treated with $OsO_4/NaIO_4$ or cetyltrimethyl ammonium permanganate/Benzyltriethylammonium periodate to get 1-ethylenedioxy-2-(2-methyl propanoate) cyclopentan-α-3,5-dicarboxaldehyde (33). The aldehyde groups of the above compound were converted to methyl groups by adopting the methods as described in the first method for the synthesis of Prelog-Djerassi lactone. The product obtained was 2-(1-oxo-α-3,5-dimethyl) cyclopentyl-2-propanoic acid (35). The acid group was esterified and the keto ester 36 obtained was subjected to Baeyer-Villiger oxidation to get a mixture of lactones from which methyl ester of Prelog-Djerassi lactone 41 was isolated. Since the stereo-chemistry of the C-2 methyl group of methyl ester 41 is not

known the ester itself is a mixture of methyl esters of Prelog-Djerassi lactone and its C-2 epimer. By analogy With what is reported in the literature, it is hoped that from the mixture of methyl esters, the expected Prelog-Djerassi lactone can be separated by Baker's yeast mediated hydrolysis. By this process the methyl ester with β-methyl group will be hydrolysed and the other will remain unhydrolysed.

REFERENCES

Chapter I

1. R.Anilker, D.Dvornik, K.Gubler, H.Heusser and V.Prelog, Helv. Chim. Acta., 39, 1785 (1956).

2. C.Djerassi and J.A.Zderic, J. Am. Chem. Soc. 78, 6390 (1956).

3. H.Brockmann and W.Henkel, Naturwissen Schaften, 37, 138 (1950).

4. P.F.Wiley, K.Gerzon, E.H.Flynn, M.V.Sigal, Jr., O.Weaver, U.C.Quarck, R.R.Chauvelte and R.Monahan, J.Am. Chem. Soc., 79, 6062 (1957).

5. P.F.Wiley, M.V.Sigal, Jr., O.Weaver, R.Monahan and K.Gerzon, J. Am. Chem. Soc., 79, 6070 (1957).

6. R.B.Woodward, Angew, Chem. 69, 50 (1957).

7. M.E.Kuehne and B.W.Benson, J. Am. Chem. Soc., 87, 4660 (1965).

8. H.Brockmann, R.Oster, Chem. Ber., 90, 605 (1957).

9. H.Muxfeldt, S.Shrader, P.Hansen and H.Brockmann, J. Am. Chem. Soc., 90, 4748 (1968).

10. S.M.Kupchan, Y.Komada, W.A.Court, G.J.Thomas R.C.Haltiwanger and R.F.Bryan, J. Am. Chem. Soc., 94, 1354 (1972).

11. V.Prelog and W.Oppolzer, Chim. Acta, 56, 2279 (1973).

12. R.B.Morin and M.Gorman, Tetrahedron Lett., 2339 (1964).

13. W.Keller-Schierlein and Fortschr, Chem. Org. Naturst., 30, 313 (1973).

14. W.Keller-Schierlein, H.Gerlach and Fortschr, Chem. Org. Naturst., 26, 161 (1968).

15. H.Gerlach and V.Prelog, Justus Leibig Aun. Chem. 121, 669 (1963).

16. W.Oppolzer and V.Prelog, Helv. Chim. Acta., 56 2287 (1973).

17. K.L.Rinehart, Jr., Acc. Chem. Res., 5, 57 (1972).

18. M.T.Shipchandler, Heterocycles, 3, 471 (1975); C.A.Peters and R.N.Hurd, J. Med. Chem., 18, 215 (1975).

19. H.D.Munro, O.C.Musgrave and P.Templeton, J. Chem. Soc. c, 947 (1967).

20. S.Nozoe, K.Hirai, K.Tsuda, K.Ishibashi, M.Shirasaka and J.F.Grove, Tetrahedron Lett., 4675 (1965).

21. S.Inouye, Sci. Rep. Meiji Seika Kaisha., 13, 100 (1973).

22. S.Omura, A.Nakagawa, H.Takeshima and J.Miyasawa, J. Antibiot., 29, 316 (1976).

23. H.Griesebach, In "Antibiotics and Other Secondary Metabolites", R. Hutter, T.Leisinger, J.Nuesch and W.Wehrili (Eds), Academic, London, p.113 (1978).

24. J.Birch, C.Djerassi and J.D.Ducher, J. Chem. Soc., 5274 (1964).

25. S.M.Friedman, S.M.Kaneda and J.W.Corcoran, J.Biol. Chem. 239, 2386 (1964).

26. D.Srinivasan and P.R.Srinivasan, Biochemistry, 6, 3111 (1967).

27. M.Vramoto, N.Otake, L.Cary and M.Tanabe, J. Am. Chem. Sco., 100, 3616 (1978).

28. A.M.Walter and L.Heilmeyer, "Die Makrolid Antibiotika", Georg Thieme Verlag, Stuttgart, p.473 (1975).

29. S.Omura, C.Kitao and H.Hamada, Chem. Pharm. Bull. 27, 176 (1979).

30. J.W.Corcoran, "Drug Action and Drug Resistance in Bacteria", University Park Press, p.177 (1971).

31. N.L.Oleinick, Antibiotics IV, Springer, New York, p.396 (1975).

32. J.M.Wilhelm, N.L.Oleinick and J.W.Corcoran, Antimicrob. Agents, Chemother., 236 (1968).

33. K.L.Arora, J.Majer, M.R.Chevellier and J.W.Corcoran, 11th Interscience Conference on "Antimicrobial Agents and Chemotherapy", Atlantic City (1971).

34. L.D.Bergelson and S.G.Batrakov, Izv. Akad. Nauk SSSR, Ser. Khim., 1259 (1963).

35. R.W.Rickards and R.M.Smith, Tetrahedron Lett., 1025 (1970).

36. M.Yamaguchi, J.Inanaga, T.Katsuki, S.Takimoto, S.Ouchita, K.Inone, A.Nakaru, M.Soga and N.Okukada, Symp. Chem. Nat. Prod., 21st, 324 (1978).

37. S.Masamune, C.U.Kim, E.Kenneth, G.O.Spessard, P.E.Georghiou and G.S.Bates, J. Am. Chem. Soc., 97 3512 (1975).

38. L.G.Cannel, Tetrahedron Lett., 5967 (1966).

39. H.Kono and J.Hooz, Org. Synth., 53 77 (1973); G.Zweifel and H.C.Brown, Org. React., 13, 1 (1963).

40. D.M.Wieland and C.R.Johnson, J. Am. Chem. Soc., 93, 3047 (1971).

41. S.Masamune, P.A.Rossy and G.S.Bates, J. Am. Chem. Soc., 95, 6452 (1973).

42. R.U.Lemieux and E.Von Rudloff, Can. J. Chem., 33, 1701 (1955).

43. J.D.White and Y.Fukuyama, J. Am. Chem. Soc., 101, 226 (1979).

44. G.Stork and V.Nair, J. Am. Chem. Soc., 101, 1315 (1979).

45. H.C.Brown and S.Krishnamurthy, J. Am. Chem. Soc., 94, 7159 (1972).

46. S.Masamune, M.Hirama, D.S.Garvey and L.D.Lu, Tetrahedron Lett., 41, 3937 (1979).

47. P.A.Grieco, Y.Ohfune, Y.Yokayama and W.Owens, J. Am. Chem. Soc., 101, 4749 (1979).

48. P.A.Bartlett and J.L.Adams, J. Am. Chem. Soc., 102, 337 (1980).

49. D.S.Morgans, Tetrahedron Lett., 22, 3721 (1981).

50. W.C.Still and K.R.Shaw, Tetrahedron Lett., 22, 3725 (1981).

51. S.Sarosz and B.F.Reid, Tetrahedron Lett., 22, 2533 (1981).

52. S.Danishefsky, N.Kato, D.Askin and J.F.Kerwin, J. Am. Chem. Soc., 104, 360 (1982).

53. R.J.Ferrier, J. Am. Chem. Soc., 5443 (1964).

54. P.M.Wovkulich and M.R.Vskokovic, J. Org. Chem., 47, 1600 (1982).

55. R.H.Schlessinger and M.A.Poss, J. Am. Chem. Soc., 104, 357 (1982).

56. T.R.Hoye, D.R.Peck and T.A.Swanson, J. Am. Chem. Soc., 106, 2738 (1984).

57. M.Yamaguchi, M.Honda and T.Katsuki, Tetrahedron Lett., 25, 3857 (1984).

58. C.Santelli, Tetrahedron Lett., 25, 4371 (1984).

59. P.G.M.Wuts, M.L.Obrzut and P.A.Thompson, Tetrahedron Lett., 25, 4051 (1984).

60. Y.Yamamoto, H.Yatagai, Y.Ishihara, N.Maeda and K.Maruyama, Tetrahedron, 40, 2239 (1984).

61. I.Fleming and H.Fun, Tetrahedron Lett., 26, 397 (1985).

62. T.Nakai, Y.Veno, N.Sayo, E.Kitahara and E.Nakai, Chem. Lett., 1725 (1985).

63. Y.Ueno and G.Stork, J. Am. Chem. Soc., 104, 5564 (1982).

64. M.Isobe, Y.Ichikawa and T.Goto, Tetrahedron Lett., 22, 4287 (1981).

65. R.E.Ireland and J.P.Daub, J. Am. Chem. Soc., 46, 479 (1981).

66. D.A.Evans and J.Bartroli, Tetrahdedon Lett., 23, 807 (1982).

67. Y.Nagoa, T.Inove, K.Hashimoto, Y.Hagiwara and M.Ochiai, J. Chem. Soc. Chem. Commun., 1419 (1985).

68. D.J.S.Tsai and M.Midland, J. Am. Chem. Soc., 107, 3915 (1984).

69. F.E.Ziegler and R.T.Wester, Tetrahedron Lett., 27, 1225 (1986).

70. P.Deslongchamps and C.Moreau, Can. J. Chem., 49, 2465 (1971).

71. S.F.Martin and D.E.Guinn, J. Org. Chem., 52, 5588 (1987).

72. A.J.Pearson, Y.Lai, W.Lu and A.Pinkerton, J. Org. Chem., 54, 3882 (1989).

73. M.Santelli and S.Hacini, Tetrahedron, 45, 6449 (1989).

Chapter II

1. R.Anliker, D.Dvornik, K.Gubler, H.Heusser and V.Prelog, Helv. Chim. Acta., 39, 1785 (1956).

2. C.Djerassi and J.A.Zderic, J. Am. Chem. Soc., 78, 6390 (1956).

3. P.A.Bartlett, Tetrahedron, 36, 54 (1980).

4. S.Masamune, C.U.Kim, E.Kenneth, G.O.Spessard, P.E.Georghiou and G.S.Bates, J. Am. Chem. Soc., 97, 3512 (1975).

5. M.Yamaguchi, T.Katsuki and M.Honda, Tetrahedron Lett., 25, 3857 (1984).

6. P.A Bartlett and J.L.Adams, J. Am. Chem. Soc., 102, 337 (1980).

7. D.J.Morgans, Tetrahedron Lett., 22, 3721 (1981).

8. S.Danishefsky, N.Katom D.Askin and J.F.Kerwin, J. Am. Chem. Soc., 104, 360 (1982).

9. L.Ghosez, R.Montaigne, A.Roussel and P.Mollet, Tetrahedron, 27, 626 (1971).

10. G.L.Nelson and C.L.Kuo, Synthesis, 105 (1975).

11. M.Rosenblum, J. Am. Chem. Soc., 79, 3179 (1957).

12. J.Wisha and A.Zarecki, Tetrahedron Lett., 3059 (1974).

13. M.E.Jung and R.W.Brown, Tetrahedron Lett., 2771 (1976).

14. E.J.Corey and C.U.Kim, Tetrahedron Lett., 287 (1974).

15. L.F.Fieser and M.Fieser, "Reagents for Organic Synthesis", Wiley, New York, 142 (1967).

16. S.Chandrasekaran and N.Chidambaram, J. Org. Chem., 52, 5048 (1987).

17. C.H.Heathcock, T.C.Germroth and S.L.Graham, J. Org. Chem., 44, 4481 (1979).

18. G.R.Pettit, Organic Reactions, Vol.12, Cope A.C. (ed.), John Wiley and Sons, Inc., 356 (1966).

19. Todd, Org. React., 4, 378 (1948).

20. E.Clemmensen, Chem. Ber., 46, 1837 (1913).

21. a. E.J.Corey, N.M.Weinshenker, T.K.Shaaf and W.Huber, J. Am. Soc. 91, 5675 (1969).
b. E.J.Corey and H.E.Ensley, J. Am. Chem. Soc., 97, 6908 (1976).

22. K.Alder and H.F.Richert, Ann., 543, 1 (1940).

23. E.J.Corey and N.M.Weinshenker, J. Am. Chem. Soc., 91, 5675 (1969).

24. P.D.Bartlett and B.E.Tate, J. Am. Chem. Soc., 78, 2473 (1955).

25. R.Csuk and B.I.Glanzer, Chem. Rev., 91, 49 (1991).

Chapter III

1. J.J.Patridge, N.K.Chandha and M.R.Uskokovic, Org. Synth., 63, 44 (1985).

2. L.Ghosez, R.Montaigne, A.Roussel and P.Mollet, Tetrahedron, 27, 626 (1971).

3. G.L.Nelson and C.L.Kuo, Synthesis, 105 (1975).

4. M.Rosenblum, J. Am. Chem. Soc., 79, 3179 (1956).

5. D.C.Kleinfelter and P.R.Schleyer, Org. Synth. Coll. Vol.5, 582 (1973).

6. L.F.Fiesor and M.Fieser, "Reagents for Organic Synthesis", Wiley, New York, 142 (1967).

7. H.C.Brown, C.P.Garg and K.T.Liu, J. Org. Chem., 36, 387 (1971).

8. E.J.Corey and J.W.Suggs, Tetrahedron Lett., 2647 (1975).

9. H.Hock and F.Depke, Ber., 84, 356 (1951).

10. S.Chandrasekaran and N.Chidambaram, J. Org. Chem., 52, 5048 (1987).

11. E.J.Corey and G.Schmidt, Tetrahedron Lett., 399 (1979).

12. H.O.House and J.M.Wilkins, J. Org. Chem., 43, 2443 (1978).

13. G.Stork and V.Nair, J. Am. Chem. Soc., 101, 1315 (1979).

14. J.D.White and Y.Fukuyama, J. Am. Chem. Soc., 101, 228 (1979).

15. H.O.House, C.Y.Chu, J.M.Wilkins and J.M.Umen, J. Org. Chem., 40, 1460 (1975).

16. V.Bhushan, R.Rathore and S.Chandrasekaran, Synthesis, 431 (1984).

17. K.Inomata, Y. Nakayama and H.Kotake, Bull. Chem. Soc., Jpn., 53, 565 (1980).

18. E.Clemmensen, Chem. Ber., 46, 1837 (1913).

19. G.R.Pettit, Org. React. Vol.12, A.C. Cope, Ed., John Wiley and Sons, Inc. 356 (1966).

20. Todd, Org. React., 4, 378 (1948).

21. J.Speziale, Org. Synth. Coll. Vol.4, 401 (1963).

22. B.S.Furniss, A.J.Hannaford, V.Rogers, P.W.G.Smith and A.T.Tatchell, "Vogel's Text Book of Practical Organic Chemistry", 4th edn., ELBS, London, p.303 (1979).

23. M.R.Everby and R.D.Waigh, Synth. Commun., 16, 779 (1986).

24. R.K.Dieter, Tetrahedron, 42, 3029 (1986).

25. S.Becker, Y.Fort and P.Caubere, J. Org. Chem., 55, 6194 (1990).

26. Huang-Minlon, J. Am. Chem. Soc., 68, 2487 (1946).

27. a. Kishner, J. Russ. Phys. Chem. Soc., 43, 582 (1911).
b. Wolff, Ann., 394, 86 (1912).

28. A.V.Baeyer and V.Villiger, Chem. Ber., 32, 8625 (1899).

29. M.A.Winnick and V.Stoute, Can. J. Chem. 51, 2788 (1973).

30. Z.Grudzinski and S.M.Roberts, J. Chem. Soc. Perkin I, 1182 (1978).

31. R.Noyori, T.Sato and H.Kobayashi, Bull. Chem. Soc. Jpn., 56, 2661 (1983).

32. R.Peel and J.K.Sutherland, J. Chem. Soc. Chem. Commun., 131 (1974).

33. K.Alder and H.F.Richart, Ann., 543, 1 (1940).

34. E.J.Corey and N.M.Weinshenker, J. Am. Chem. Soc., 91, 5675 (1969).

35. P.D.Bartlett and B.E.Tate, J. Am. Chem. Soc., 78, 2473 (1955).

36. R.Csuk and B.I.Glanzer, Chem. Rev., 91, 49 (1991).

Chapter IV

1. L.Ghosez, R.Montaigne, A.Roussel and P.Mollet, Tetrahedron, 27, 626 (1971).

2. G.L.Nelson and C.L.Kuo, Synthesis, 105 (1975).

3. M.Rosenblum, J. Am. Chem. Soc., 79, 3179 (1956).

4. H.Hock and F.Depke, Ber., 84, 356 (1951).

5. E.J.Corey and J.W.Suggs, Tetrahedron Lett., 2647 (1975).

6. E.J.Corey and G.Schmidt, Tetrahedron Lett., 399 (1979).

7. S.Chandrasekaran, R.Rathore and V.Bhushan, Synthesis, 431 (1984).

8. K.Inomata, Y.Nakayama and H.Kotake, Bull. Chem. Soc. JPA., 53, 565 (1980).

9. J.Speziale, Org. Synth. Coll. Vol.4, 401 (1963).

10. B.S.Furniss, A.J.Hannaford, V.Rogers, P.W.G.Smith and A.T.Tatchell, "Vogel's text book of practical organic chemistry", 4th Ed., ELBS, London, p.303 (1979).

11. H.Heaney, M.S.Cooper, A.J.Newbold and W.R.Sanderson, Synlett., 533 (1990)

12. L.S.Silbert, E.Siegel and D.Swern, Org. Synth. Coll., 5, 904 (1975).

13. G.B.Payne, Org. Synth. Coll., 5, 805 (1973).

14. J.J.Patridge, N.K.Chandha and M.R.Uskokovic, Org. Synth., 63, 44 (1985).

15. K.Alder and H.F.Richert, Ann., 543, 1 (1940).

16. E.J.Corey and N.M.Weinshenker, J. Am. Chem. Soc., 91, 5675 (1969).

17. P.D.Barlett and B.E.Tate, J. Am. Chem. Soc., 78, 2473 (1955).