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THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON PREZIZAANOIDS

BY

YOUSEF HAJIKARIMIAN

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF
MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1986

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Supervisor

Date JAN 31 1986

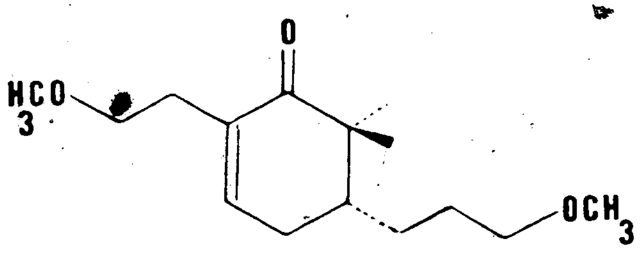
To my wife JACQUELINE

ABSTRACT

This thesis describes the preparation of the cyclohexenone diether i from which the bicyclic diketone ii can in principle be formed. The bicyclic diketone ii is considered to be a potential precursor of prezizaene iii and prezizanol iv.

In the route towards synthesis of the target cyclohexenone diether i, treatment of α-pinene oxide v with fused anhydrous zinc chloride afforded α-campholenic aldehyde vi. Wittig reaction of aldehyde vi with (methoxymethylene)triphenylphosphorane gave the vinyl ether vii. Selective hydrogenation of vii afforded the ether viii. Photooxygenation of the ether viii gave the enone ix. Treatment of the enone ix with sodium borohydride and cerous chloride afforded the allylic alcohol x. Direct conversion of ether viii to the allylic alcohol xi was achieved when viii was subjected to photooxygenation followed by reductive work-up using sodium borohydride. The allylic alcohol x underwent a claisen rearrangement with triethyl orthoacetate to give the unsaturated ester xii. Treatment of the ester xii with lithium aluminium hydride resulted in the formation of the alcohol xiii. Methylation of the alcohol xiii, using sodium hydride and methyl iodide, gave the diether xiv. Ozonolysis of xiv followed by reductive work-up using triphenylphosphine gave the keto aldehyde xv which, without

purification, was subjected to intramolecular aldol condensation with p-toluenesulfonic acid to form the target cyclohexenone diether i.



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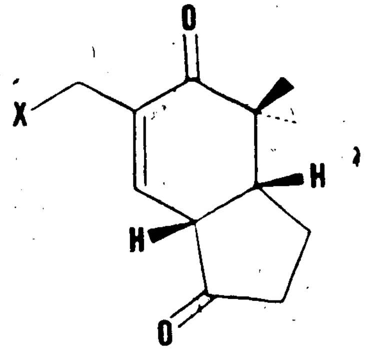
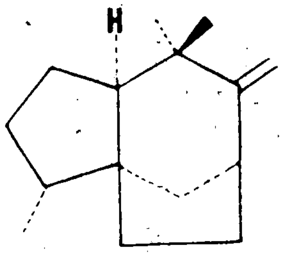


ii

X = –COOEt, etc.



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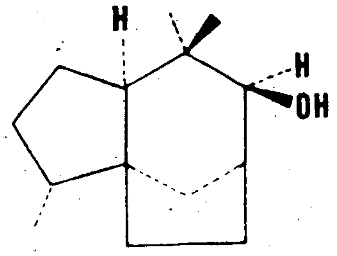

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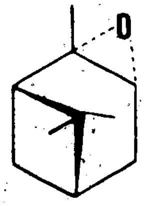

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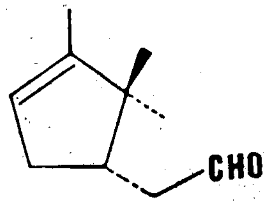

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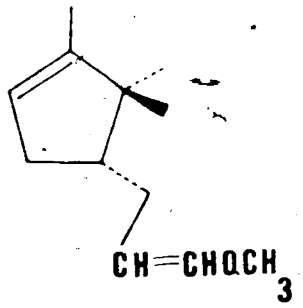

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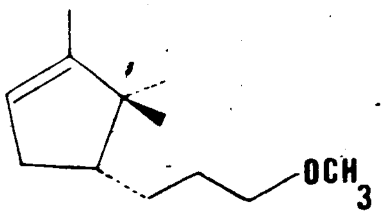

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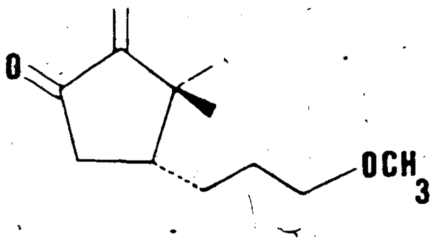

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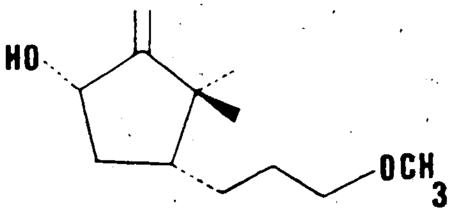

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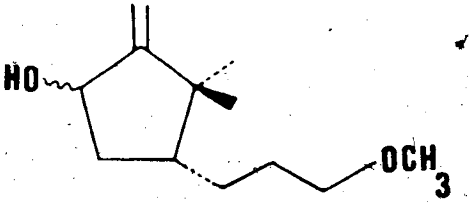

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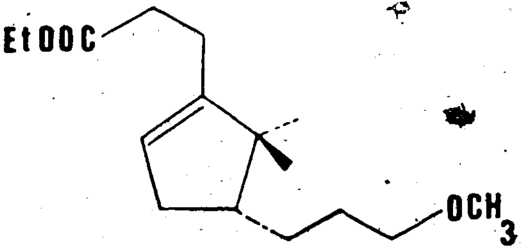

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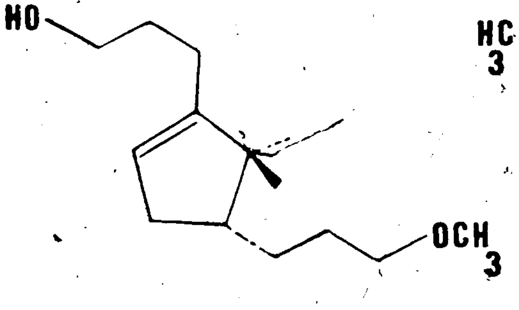

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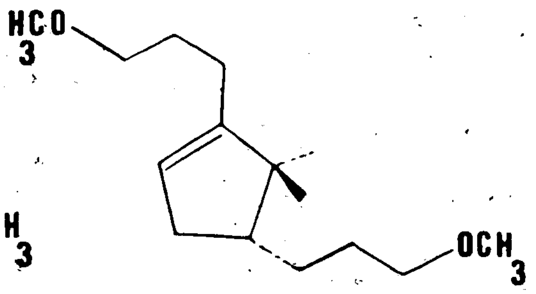

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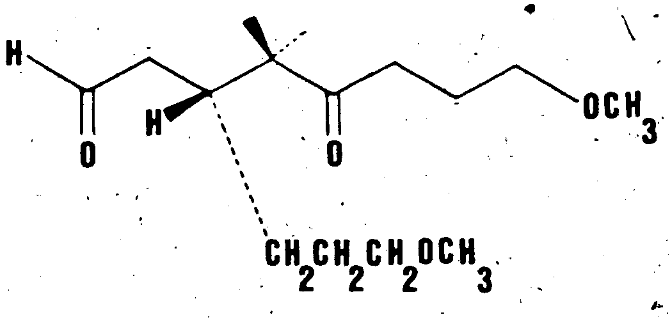

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CHAPTER I

INTRODUCTION

Oil of vetiver as an essential oil is found in the roots and rhizomes of the herbaceous plant *Vetiveria zizanoides*. This plant grows wild or is cultivated in East Africa, Central America, Indonesia, Ceylon and the Phillipines. Vetiver oil contains sesquiterpenes of varied structural types (1).

Among the intriguing components of this complex oil are zizaene (1) which is the parent hydrocarbon of a small group of tricyclic sesquiterpenes (2) as well as a number of additional compounds of the tricyclovetivane (or zizaane) skeleton (2). They are widely used as raw materials in the perfume industry (3).

Zizaane carbon skeleton is of biosynthetic interest as it represents a novel sesquiterpene framework. One of the first biogenetic hypotheses (4) (Scheme I) proposed in the study of the biosynthesis of zizaene (1), assumed hinesol (6), a spirovetivene sesquiterpene, as the intermediate. It is formed from farnesyl pyrophosphate (5) via a series of ring closures. Interaction of the double bond of hinesol (6) with the tertiary hydroxyl group will lead to the carbonium ion (7) which undergoes a rearrangement to give the tertiary carbonium ion (8) which, in turn, on deprotonation affords zizaene (1). The feasibility of this rearrangement (7→8) occurring *in vivo* was supported by the solvolysis of the mesylate (9) in refluxing pyridine/ triethylamine to give the ketone (10) possessing the tricyclovetivane ring structure (1).

Anderson and co-workers, in the course of their studies, had isolated additional members of the zizaane (tricyclovetivane) class of sesquiterpenes, which provided an unexpected connection with the constituents of the Alaska Yellow Cedar.

The Alaska Cedar had provided the missing spirane intermediates for two important classes of tricyclic sesquiterpenes: the cedranes and the tricyclovetivanes. The biogenetic sequence to the tricyclovetivanes runs parallel to that of the cedranes, however, they require intermediates of different relative and absolute stereochemistry (5-10).

The biosynthesis of cedrene (13) (Scheme II) involves formation of the intermediate cation (11) from farnesyl pyrophosphate (5). The isopropenyl group in this cation is cis relative to the double bond and this allows a facile Markovnikov addition to form the cation (12) which on deprotonation affords cedrene (13). The biogenetic sequence to zizaene (1) (Scheme III), however, involves formation of the cation (14) which is a diastereomer of (11), and in which steric constraint favours anti-Markovnikov cyclization to form carbocation (15).

During the examination of this biogenetic scheme, Andersen and co-workers noted the previously unknown skeleton of the carbocation (16). There was no reason to assume that other products such as the one formed as a result of direct deprotonation of (16) did not exist in vetiver oil and they set out to find these.

In 1970, the exomethylenic isomer of carbocation (16) was isolated in reasonable amounts as its dextrorotatory isomer and designated prezizaene (3) (11). The evidence for the structure assignment was provided by spectral data and optical properties. The discovery of prezizaene (3) was the key observation that allowed a decision between alternative biogenetic hypotheses for zizaane skeleton (2) and further supported the theory of the biosynthesis of zizaene (1) from the cation (16) as shown in scheme III.

The alternative biosynthetic proposal (Scheme I) was therefore dismissed since vetiver oil produces sesquiterpenes enantiomeric to hinesol (6) (9).

Further evidence was supplied by a series of successful chemical transformations mimicking the biogenetic process (12) (Scheme IV) carried out by Tomita and co-workers, who succeeded in the conversion of β-acoradiene (17) to (-)-prezizaene (4). Andersen and co-workers (2,9,11) also carried out chemical simulation studies involving acid catalyzed rearrangement of zizaene (1) and prezizaene (3) which confirmed the tendency for prezizaene (3) to undergo a

[1,2] methyl shift to give the carbon skeleton of zizaene (e.g. 8). Therefore, when prezizaene (3) and zizaene (1) were individually treated with sixty percent formic acid in tetrahydrofuran, each gave the same mixture of products possessing the zizaene skeleton. The same time course for the development of each product serves to confirm their structural and biogenetic relationship and, therefore, a common intermediate species for forming both the natural compounds in the biosynthetic process.

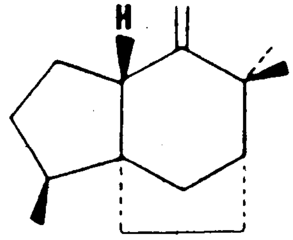
In 1976, Ghisalberti and co-workers (13) in an extension of their work on the constituents of *Eremophila* species presented evidence for the structure of four major components, all containing the tricyclo[6,2,1,$0^{1.5}$]-undecane skeleton namely; (-)-prezizaene (4), (-)-7-oxo-2,6,6,8-tetramethyltricyclo[6.2.1.$0^{1,5}$]-undecane (18), (-)-7α-hydroxy-2,6,6,8-tetramethyltricylo-[6.2.1.$0^{1.5}$] undecane (19), and 7-hydroxy-(-)-prezizaene (prezizanol) (20). The absolute sterochemistry of these sesquiterpenes was found to be antipodal to that of the zizaane sesquiterpenes found in vetiver oil. Since then, prezizaene (3) has been isolated from *Cupressus* *~~Semper~~virenes* and *Cupressus dupreziana* (14).

In 1978 Ganguly and co-workers (15), on their examination of Indian vetiver oil (Khus oil) from Moosanagar area in India, isolated 7α-hydroxy-(+)-prezizaene (21), a new tertiary alcohol designated as (+)-allokhusiol. This same alcohol was also isolated in 1981 by Nakanishi and co-workers (16) from Indonesian agarwood, Aquillaria sp., and was named jinkohol.

In 1980, Vettel and Coates carried out a total synthesis of prezizaene (4) and prezizanol (20). The eighteen-step synthesis (17) (Scheme V) from (+)-pulegone (22) gave the levoratatory isomer of prezizaene (4). The intramolecular ring expansion of the diazoethyl intermediate 24 to the isomeric methanoperhydroazulenones 25 and 26, formed in the ratio of 1:1.2 respectively, is considered to be the key step in this synthesis. Of the two isomers, only 26 possesses the required tricyclo[6.2.1.0$^{1.5}$]-undecane skeleton necessary for the subsequent conversion to prezizaene (4). The overall yield of the synthesis from the keto ester 23 was three percent.

A continuous interest in the zizaane family of sesquiterpenes at this laboratory, resulted in the total synthesis of (+)-zizanoic acid (27), (-)-epizizanoic acid (28), and (-)-khusimone (29) by Chan (18) in 1979, and in 1982, Naleway (19) carried out the synthesis of three cyclohexenone derivatives (30), (31) and (32), in an approach to the synthesis of the bicyclic diketone (33) which is considered as one of the potential precursors of prezizaene (4) and prezizanol (20).

In our studies, we undertook the synthesis of the cyclohexenone diether (<u>41</u>) from α-pinene epoxide (<u>34</u>). The cyclohexenone diether (<u>41</u>) can in principle be converted to the bicyclic diketone (<u>42</u>) which can act as a key intermediate towards the total synthesis of (–)-prezizaene (<u>4</u>) and prezizanol (<u>20</u>).



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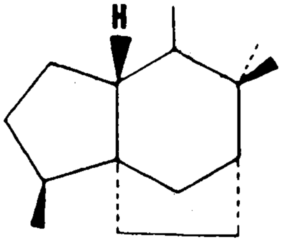

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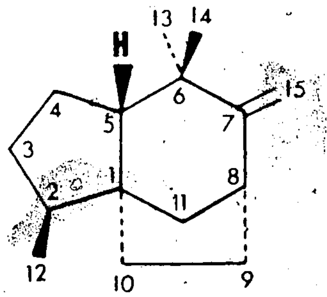

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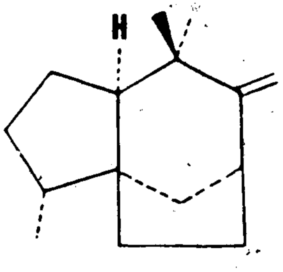

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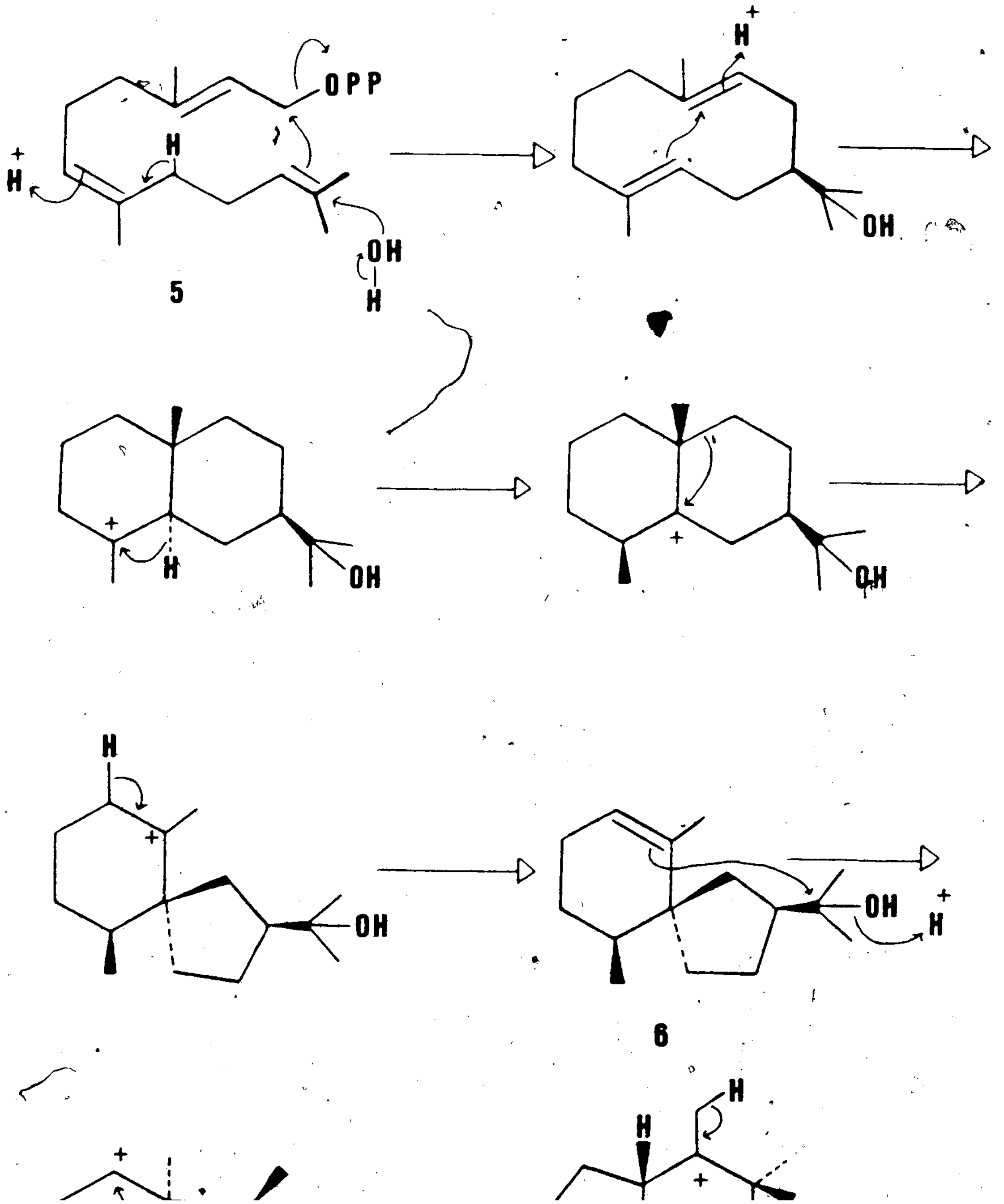

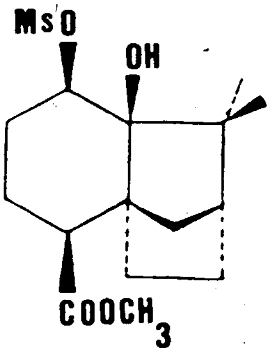

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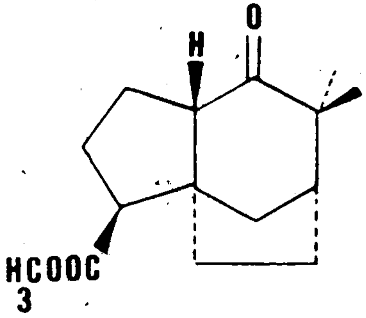

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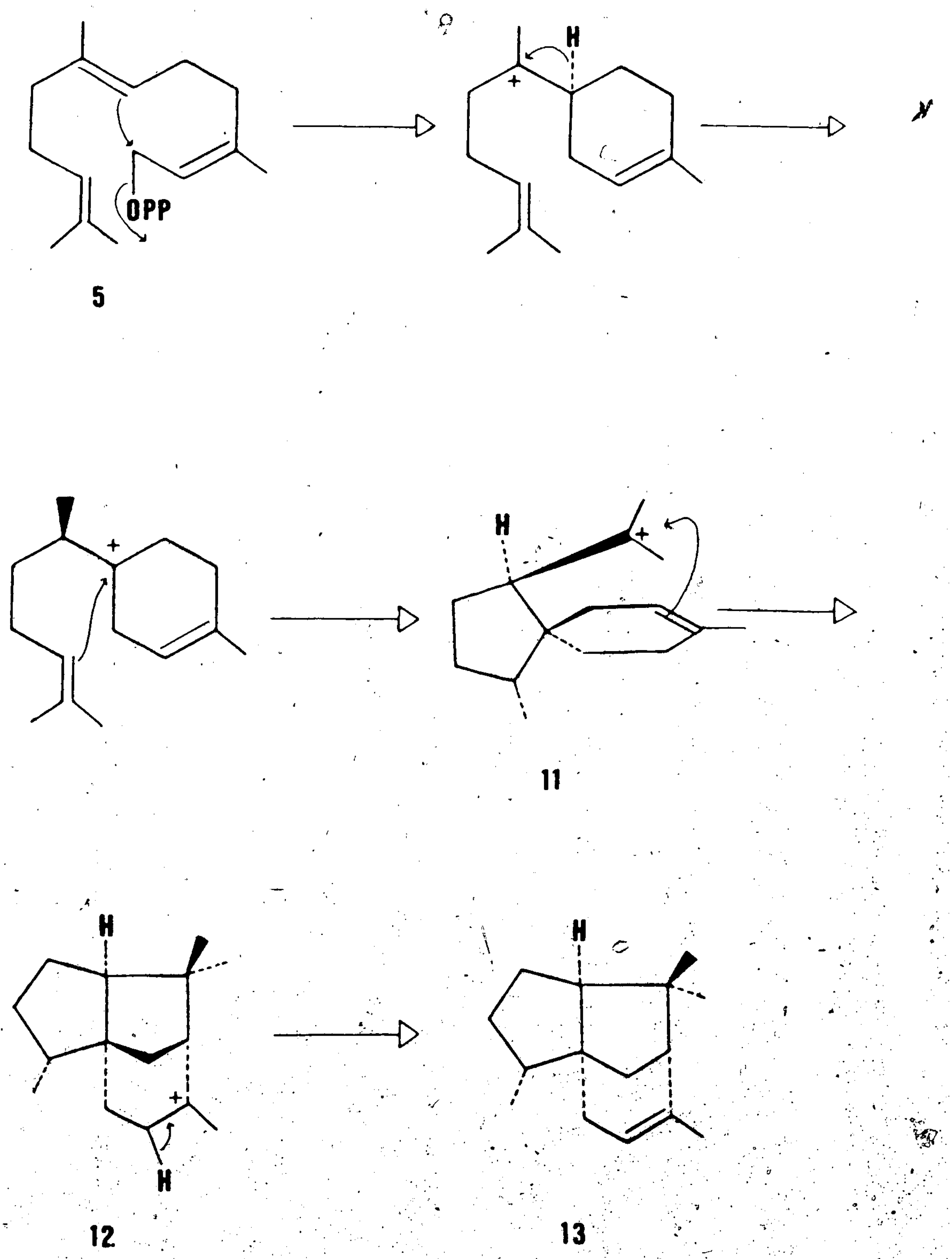

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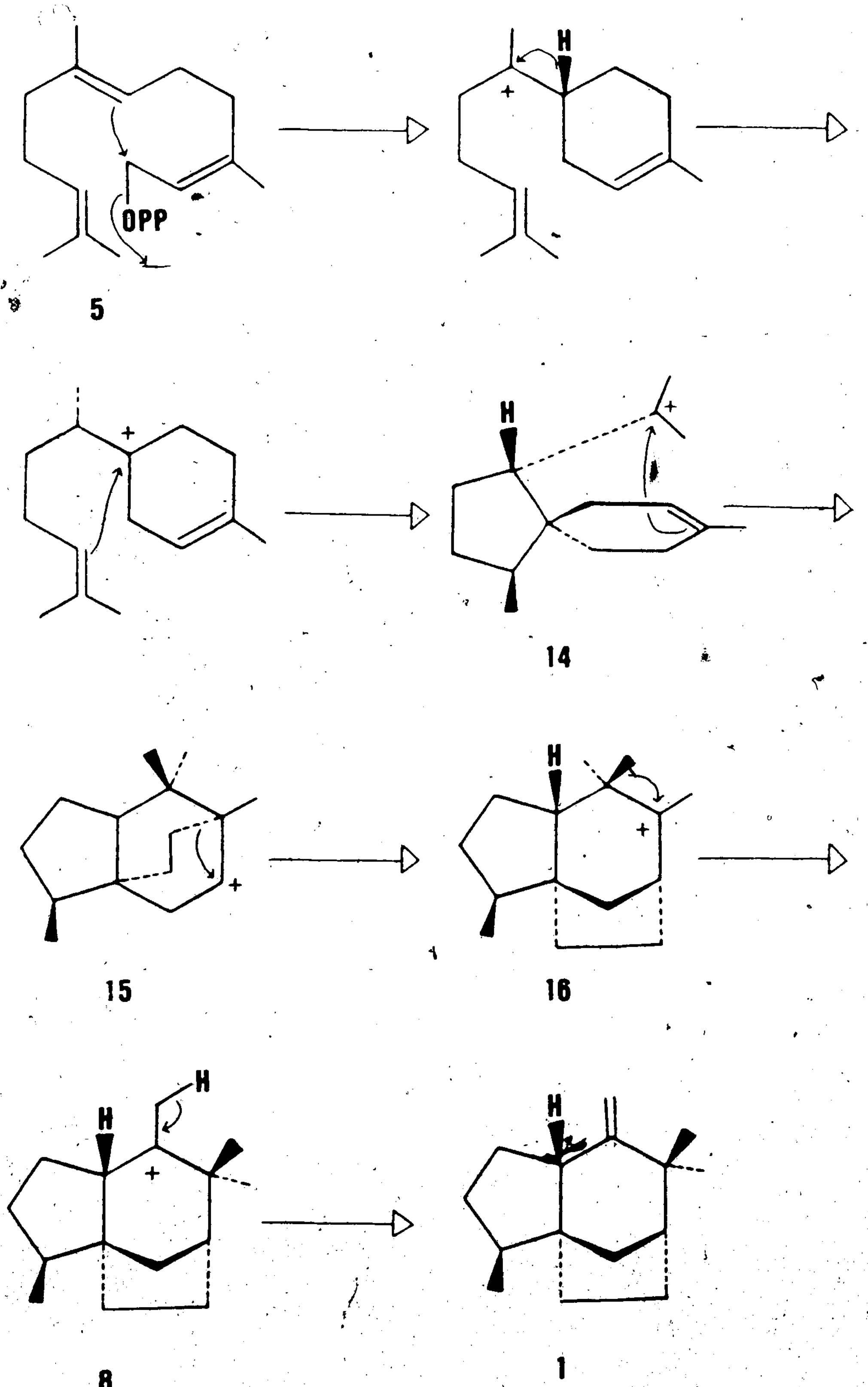

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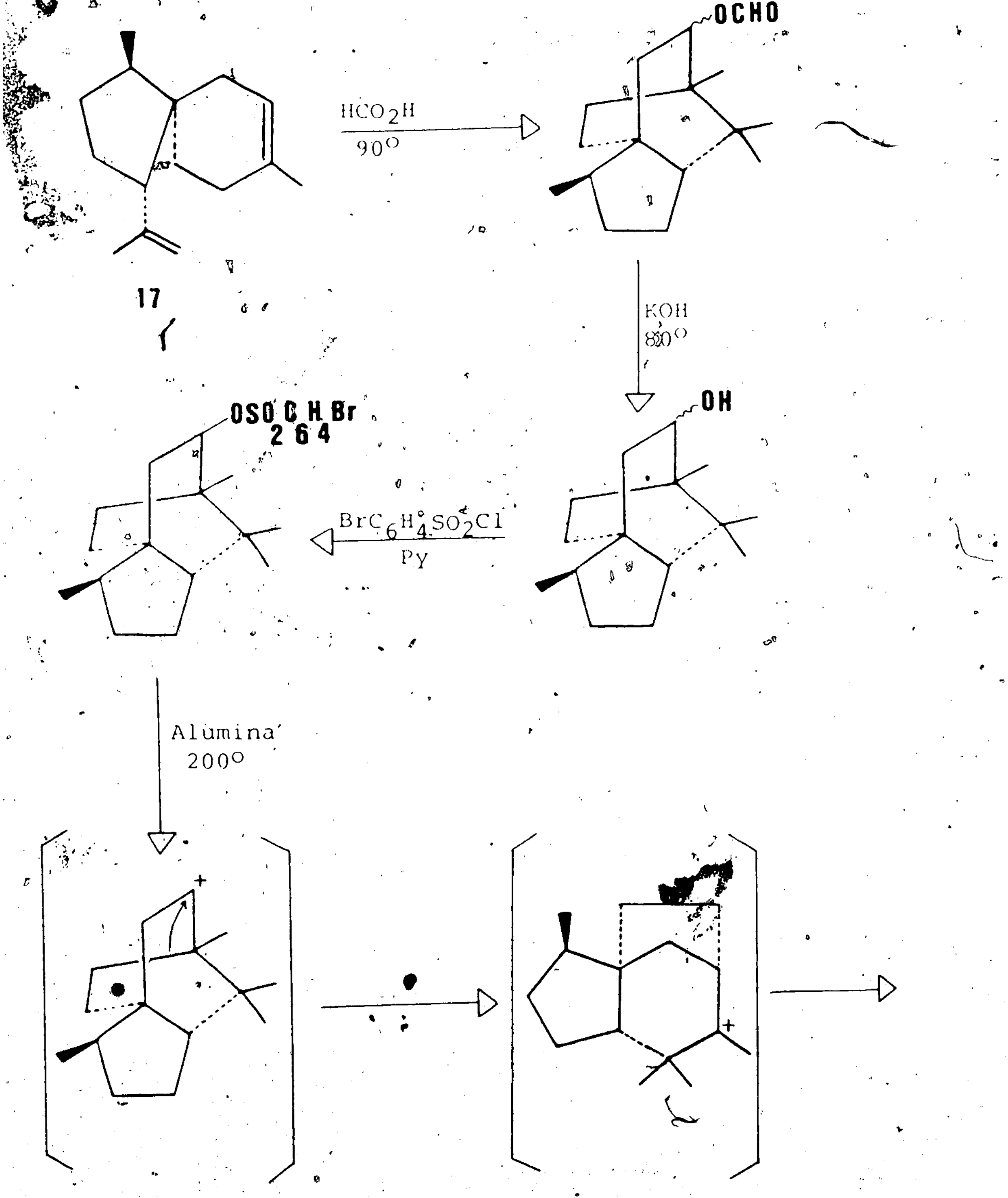
17
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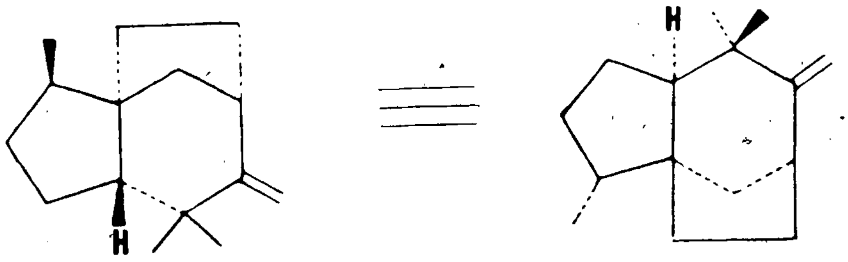
OCHO
KOH
80°
OH
BrC6H4SO2Cl
Py
OSO2C6H4Br
Alumina
200°
+
+



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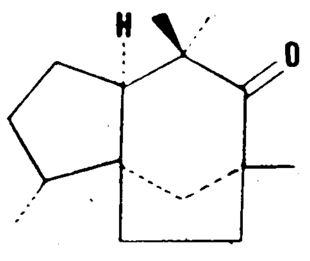

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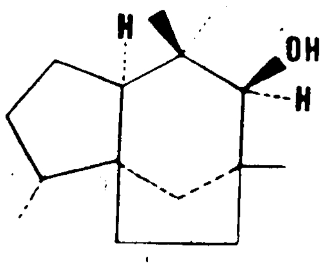

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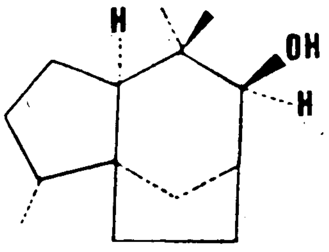

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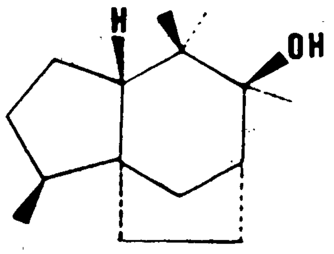

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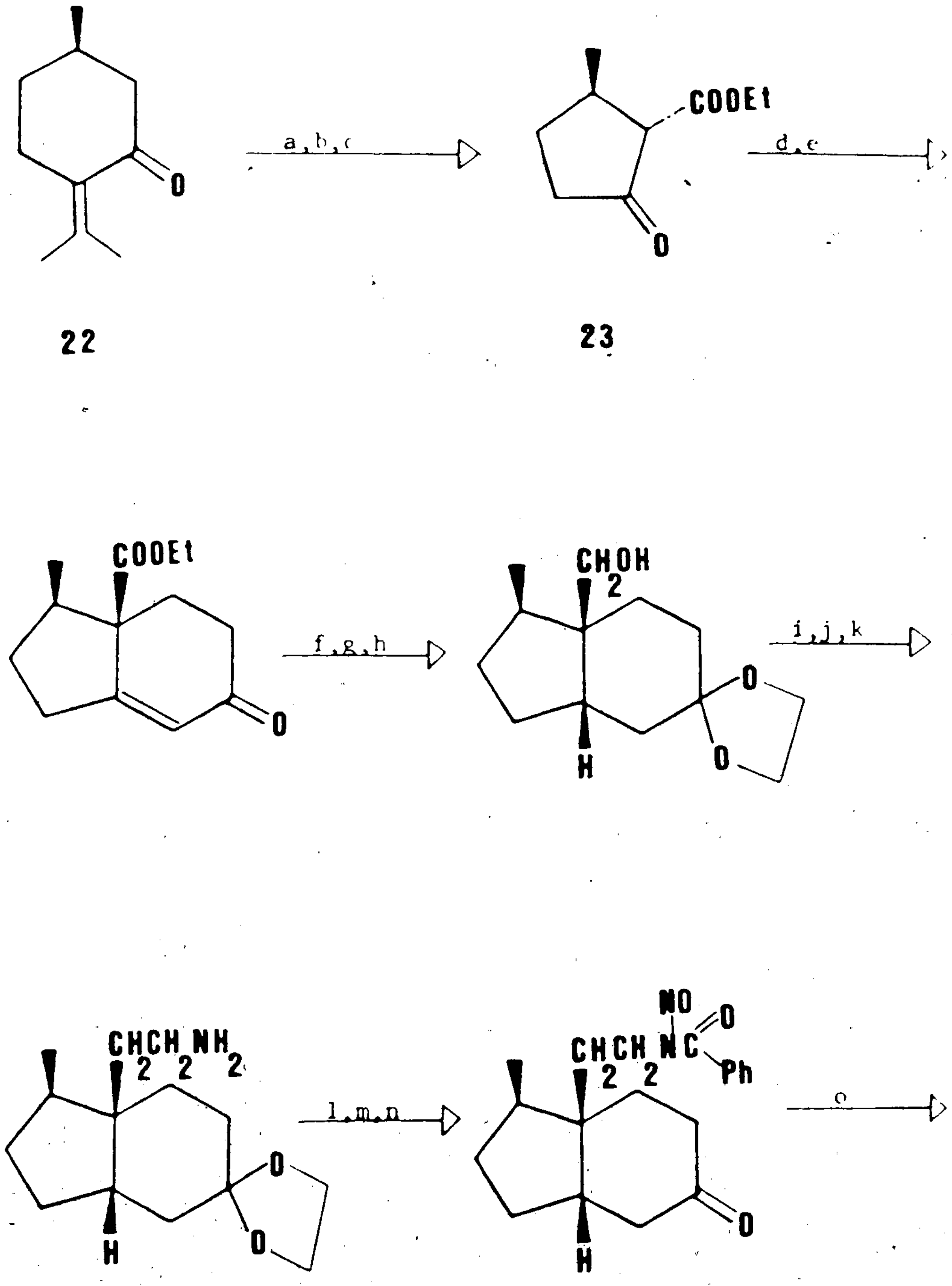

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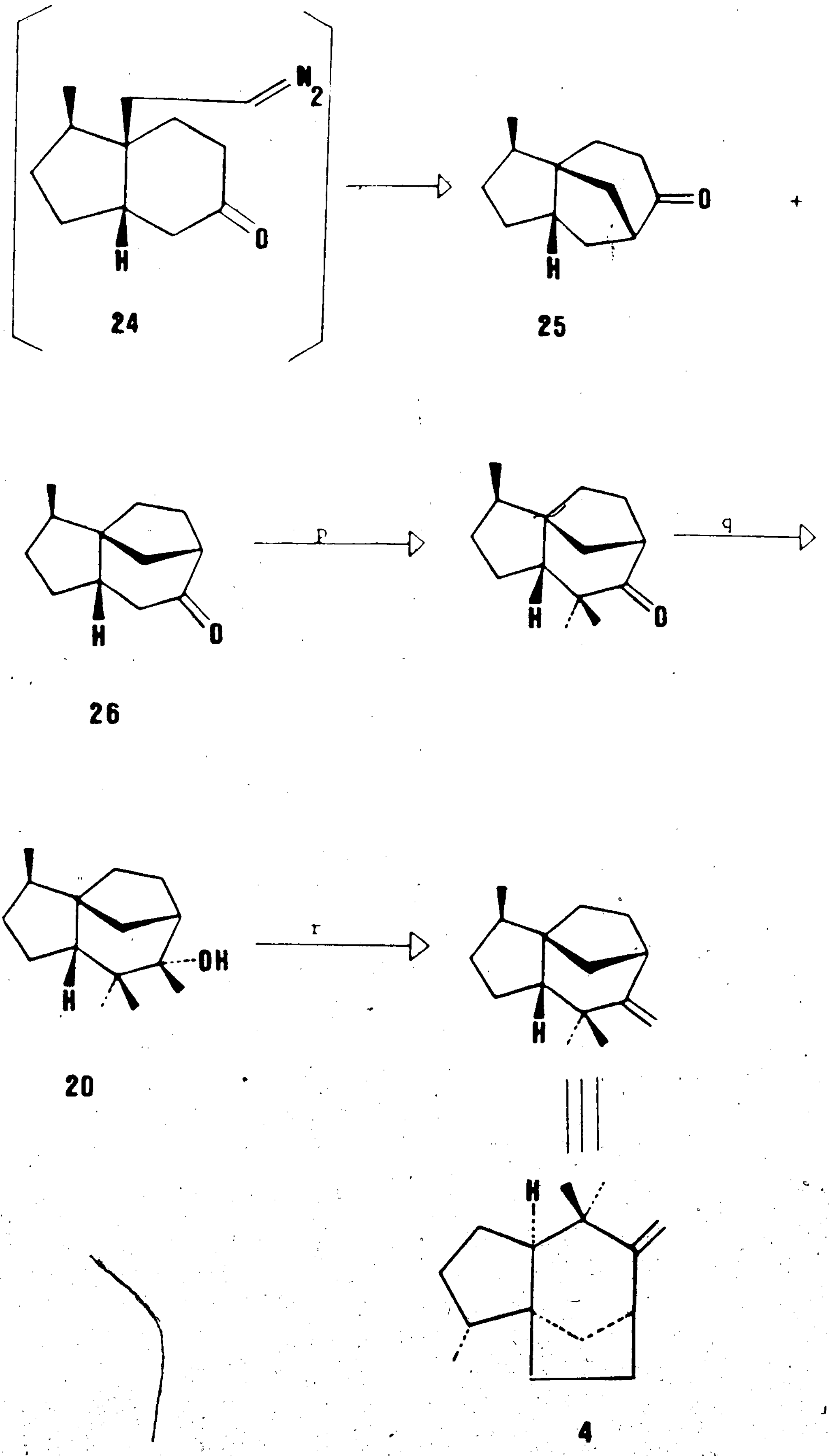

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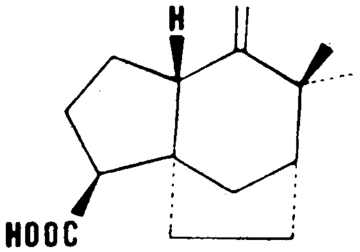
a = Br_2, Et_2O; b = NaOEt, Et_2O; c = O_3; d = MVK, Et_3N; e = Pyrrolidine, HOAC, H_2O; f = H_2, Pd/C; g = $(CH_2OH)_2$, H^+ h = $LiAlH_4$; i = CH_3SO_2Cl, Et_3N; j = NaCN, Et_4NCl; k = $LiAlH_4$; l = PhCOCl; m = H_3O^+; n = N_2O_4; O = KO^tBu, t-AmOH; p = KH, CH_3I; q = CH_3Li, Et_2O; r = CH_3SO_2Cl, Et_3N.



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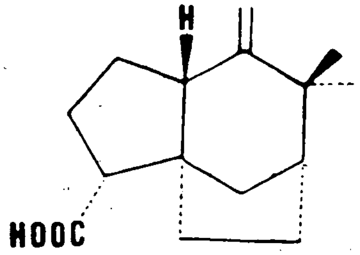

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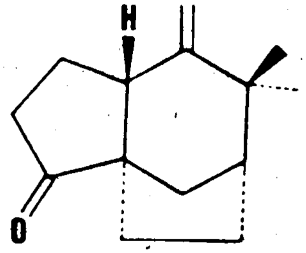

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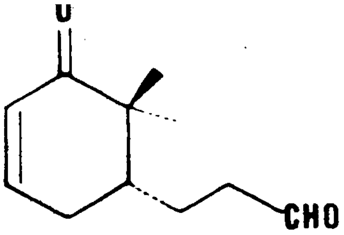

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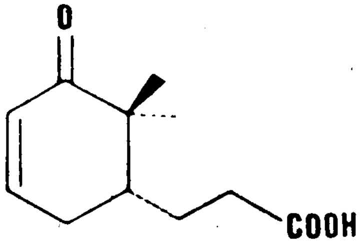

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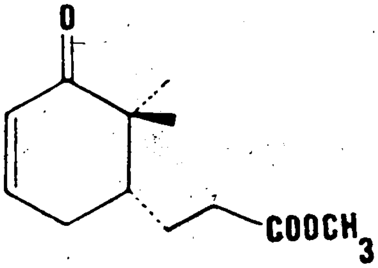

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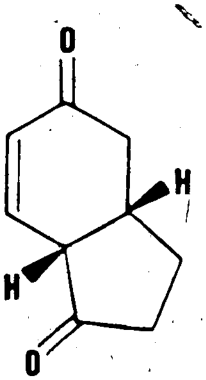

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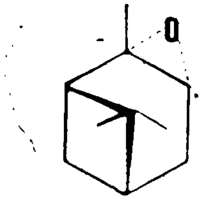

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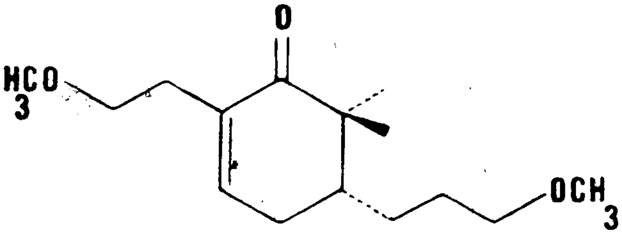

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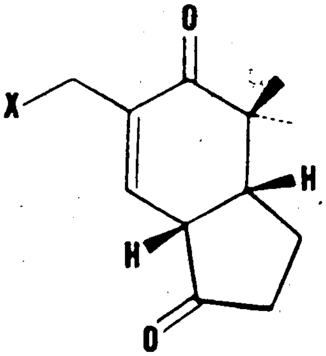


CHAPTER II

RESULTS AND DISCUSSION

In our studies directed towards the total synthesis of prezizaene (4), we focussed on the synthesis of the cyclohexenone diether (41). The diether (41) can in principle be used in order to synthesize the bicyclic diketone derivative (42) which is an appropriate potential precursor of prezizaene (4) and prezizanol (20).

From the retrosynthetic analysis (Scheme VI), it was recognized that a viable synthetic intermediate to the cyclohexenone diether (41) would be the cyclopentene, e.g. 35, of the campholenic family. This compound possesses not only the gem-dimethyl group and the correct stereochemistry at carbon adjacent to the geminal methyl groups similar to that found in the cyclohexenone diether (41), but also functionalities suitable for further modification. For example, after a Wittig reaction on the aldehyde functionality (35 → →37) and a suitable activation of the vinylic methyl group (37 → 38), followed by reduction (38 → 39) and the introduction of two carbon units via a rearrangement process (39 → 40), the cyclohexenone diether (41) could be formed by a subsequent ozonolysis followed by an intra-molecular aldol condensation (40 →41). The potential of α-pinene oxide (34) as a good source of the required starting material (35) was therefore recognized.

Towards the preparation of α-campholenic aldehyde (35), the commercially available α-pinene oxide (34) underwent an acid catalysed ring opening (20,21) with freshly fused zinc chloride in refluxing benzene to give aldehyde (35) in 80% yield. The ir spectrum showed characteristic absorption bands for an aldehyde at 2720 and 1727 cm^{-1} and for olefin at 1650 cm^{-1}. The nmr spectrum displayed a triplet (J=2 Hz) at δ 9.82 corresponding to the aldehydic proton and a broad singlet at δ5.26 for the vinylic proton. The protons of the vinylic methyl group displayed a multiplet at δ1.62 and those of the gem-dimethyl group showed sharp singlets at δ1.0 and δ0.79. The molecular ion peak in the mass spectrum at 152.1204 as well as elemental analysis, verified the $C_{10}H_{16}O$ molecular formula.

The extension of the side chain of aldehyde (35) by one carbon unit can conceivably be achieved by a Wittig reaction to form the vinyl ether (36). Towards this end, the aldehyde (35) was treated with (methoxymethyl)-triphenylphosphonium chloride and sodium hydride in a solution of dimethyl sulfoxide and benzene (22,23). The resulting vinyl ether (36), formed in 93% yield, was purified by distillation and flash chromatography. The nmr spectrum indicated the presence of both the cis and trans isomers of the vinyl ether (36) in a 1:1 ratio. The vinylic hydrogen adjacent to the methoxy group appeared as a doublet at δ6.30 (J=13 Hz) and as a doublet of triplets at δ5.88 (J=6 Hz, J=1½ Hz) corresponding to the *trans* and *cis* isomers respectively, and integrating for a total of one hydrogen. The other vinylic proton of the side chain appeared as a multiplet at δ4.72 and as a doublet of doublets at δ4.36 (J=13 Hz, J=6 Hz), integrating for a total of one hydrogen. The methoxy group appeared as two sharp singlets at δ3.58 and 3.50, integrating for a total of three hydrogens for the two isomers. The mass spectrum displayed a molecular ion peak at 180.1510 in agreement with the molecular formula $C_{12}H_{20}O$.

We then took advantage of the expected difference in reactivity of the two double bonds in vinyl ether (36) towards catalytic hydrogenation. The side chain double bond is expected to be hydrogenated selectively, forming a stable methyl ether moiety which should not interfere with further modifications of the ring system. Towards this end, vinyl ether (36) was subjected to hydrogenation with 5% palladium on carbon in ethyl acetate (24) at room temperature and atmospheric pressure. The reaction was carried out in the presence of one equivalent of potassium acetate, using glassware prewashed with ammonium hydroxide, in order to avoid formation of the byproduct, e.g. 43, resulting from the hydrolysis of the vinyl ether (36) and subsequent cyclization. Under these conditions, the desired ether (37) was formed in 97% yield. The ir spectrum of 37 displayed characteristic absorption bands for an olefin (1650 cm^{-1}) and an ether (1120 cm^{-1}). The nmr spectrum displayed a broad singlet at δ5.28 corresponding to the vinylic proton and a triplet (J=8 Hz) at δ3.44 for the two hydrogens adjacent to the methoxy group. A sharp singlet at δ3.40 was displayed corresponding to the three hydrogens of the methoxy group and the three hydrogens of the vinylic methyl group displayed a broad singlet at δ1.62. The geminal methyl groups were evident as singlets at δ1.0 and 0.80. The mass spectrum displayed a molecular ion peak at 182.1672 consistent with the molecular formula of $C_{12}H_{22}O$.

Having obtained the ether (<u>37</u>), we then turned our attention towards a suitable activation of the vinylic methyl group, the result of which would enable us to carry out the necessary rearrangement reaction in order to introduce two carbon units as in diether (<u>40</u>).

Towards this end, the ether (<u>37</u>) was subjected to photooxygenation (25) using dimethylaminopyridine and acetic anhydride along with pyridine and also tetraphenylporphine as the sensitizer. The reaction was carried out in methylene chloride as the solvent. Under these conditions, the enone (<u>38</u>) was formed in 50% yield. The ir spectrum showed the characteristic absorption bands for a carbonyl at 1730 cm^{-1} and for olefin at 1635 cm^{-1}. The nmr spectrum displayed two doublets (J=1 Hz), one at δ5.97 and the other at δ5.20, each integrating for one of the two vinylic protons. A triplet (J=7 Hz) at δ3.44 integrating for two hydrogens was assigned for the two protons adjacent to the methoxy group of the side chain. The hydrogens of the methoxy group appeared as a singlet at δ3.38. The two hydrogens on the carbon adjacent to the corbonyl group of the ring each appeared as a doublet of doublets, one at δ 2.54 (J=18 Hz, J=11 Hz) and the other at δ2.07 (J=18 Hz, J=7 Hz). The geminal methyls appeared as two sharp singlets at δ1.23 and 1.0. The mass spectrum showed a molecular ion peak at 196.1471 in agreement with the molecular formula of $C_{12}H_{20}O_2$.

Our next goal was to selectively reduce the carbonyl functionality of the conjugated enone (38) to the corresponding allylic alcohol (39). Towards this end, the enone (38) was treated with cerous chloride and sodium borohydride (26) in methanol at room temperature. The resulting allylic alcohol (39) was formed in 98% yield. In the ir spectrum, characteristic absorption bands were observed at 3420 (alcohol), 3080,1660 (olefin) and 1120 cm^{-1} (ether). The nmr spectrum displayed a doublet (J=2 Hz) at δ5.11 and another doublet (J=2½ Hz) at δ4.98, each integrating for one of the two vinylic protons. A triplet (J=6½ Hz) at δ3.4, integrating for two hydrogens, was assigned for the two protons adjacent to the methoxy group of the side chain. The hydrogens of the methoxy group were displayed as a sharp singlet at δ3.36, integrating for three protons and finally the two geminal methyls were each displayed as a sharp singlet at δ 1.6 and 0.92. The mass spectrum displayed a molecular ion peak at 198.1610 consistent with the molecular formula $C_{12}H_{22}O_2$.

The two step reaction sequence involving epoxidation of the olefinic bond of compound <u>37</u> followed by the base-induced ring-opening of the resulting epoxide (<u>44</u>) was also examined. Epoxidation of the compound <u>37</u> using m-chloroperbenzoic acid in dichloromethane afforded the epoxide (<u>44</u>) in 92% yield. The nmr spectrum displayed a doublet of triplets (J=6½ Hz, J=2½ Hz) at δ3.37, integrating for two protons and corresponding to the two hydrogens adjacent to the methoxy group of the side chain. The methoxy protons appeared as a sharp singlet at δ3.34, integrating for three hydrogens. A broad singlet at δ3.24, integrating for one proton was assigned to the hydrogen of the epoxide ring. The hydrogens of the methyl group on the carbon bearing the epoxide ring appeared as a singlet at δ 1.32, integrating for three protons. The hydrogens of the geminal methyl groups were displayed as two singlets, one at 1.0 and the other at 0.76. Although, the molecular ion peak was absent in the mass spectrum, the presence of a peak at m/e 183.1385 corresponding to the loss of a methyl group supported the assigned molecular formula of $C_{12}H_{22}O_2$.

Unfortunately, when the epoxide (<u>44</u>) was treated with lithium diisopropylamide in tetrahydrofuran, no allylic alcohol was formed but instead the starting material was recovered in each attempt.

The alternative approach of forming the allylic alcohol (<u>39</u>) directly by photooxygenation was also examined. Towards this end, the compound (<u>37</u>) was subjected to photooxygenation in methanol using methylene blue (27) as the sensitizer. This was followed by reduction of the resulting hydroperoxide with sodium borohydride. The reaction afforded the allylic alcohol (<u>45</u>) in 37% yield along with the formation of a substantial amount of an unidentifiable complex mixture. The ir spectrum of compound <u>45</u> showed characteristic absorption bands at 3420 (alcohol), 3095 (olefin) and 1125 cm^{-1} (ether). The nmr spectrum displayed two doublets, one at δ5.12 (J=2 Hz) and the other at δ4.97 (J=2 Hz), both integrating for a total of two protons and corresponding to the two vinylic protons. A multiplet at δ4.52, integrating for one proton, was assigned to the single allylic proton. The methoxy protons appeared as a singlet at δ3.32, integrating for three protons and finally two singlets were observed, one at δ1.13 and the other at δ0.81, each integrating for three protons and corresponding to the geminal methyl groups. The low yield of the conversion of <u>37</u> to <u>45</u>, as well as the long reaction time, prompted an investigation of the one-pot conversion of the compund <u>37</u> to the enone <u>38</u> (25) as explained before.

It has been established that allylic pivalates undergo efficient coupling with magnesium organocopper reagents (28) resulting in the predominant formation of an "S_N2'" - type product. This could enable us to introduce, on the vinylic carbon of the allylic alcohol (<u>39</u>), the two carbon units needed.

Towards this end, the allylic alcohol (<u>39</u>) was treated with trimethylacetyl chloride and pyridine (29) in ether to form the allylic pivalate (<u>46</u>) in 92% yield. The ir spectrum of <u>46</u> displayed characteristic absorption bands for a carbonyl (1735 cm^{-1}) and for an olefin (1660 cm^{-1}). The nmr spectrum displayed a doublet of doublets of doublets of doublets ($J=8\frac{1}{2}$, 8, $2\frac{1}{2}$, 2 Hz) at $\delta 5.48$, integrating for the one allylic proton. A doublet (J=2 Hz) was shown at $\delta 5.02$, integrating for one hydrogen and corresponding to one of the vinylic protons. The other vinylic proton was also displayed as a doublet ($J=2\frac{1}{2}$ Hz) at $\delta 4.98$, integrating for one hydrogen. The two protons adjacent to the methoxy group of the side chain appeared as a triplet (J=6 Hz) at $\delta 3.39$, integrating for two hydrogens. The methoxy hydrogens were displayed as a sharp singlet at $\delta 3.34$ integrating for three hydrogens. A sharp singlet at $\delta 1.20$ and integrating for nine protons was assigned to the methyls of the pivalyl group. The hydrogens of the two geminal methyls appeared as sharp singlets one at $\delta 1.08$ and the other at $\delta 0.94$. The mass spectrum displayed a molecular ion peak at 282.2209 in agreement with the molecular formula $C_{17}H_{30}O_3$.

Having formed the pivalate (46), we then attempted the suggested coupling reaction (28), using a 2:1 mixture of vinylmagnesium bromide and cuprous iodide in tetrahydrofuran. Unfortunately, none of the desired coupling product (47) was formed and the reaction led only to the recovery of the starting material.

It has also been long established that a number of allylic esters undergo [3,3] sigmatropic Claisen rearrangement as their silylketeneacetals to produce γ,δ-unsaturated acids in reasonably good yields (30). Subsequently, we proceeded to form the corresponding acetyl ester derivative (48) of the allylic alcohol (39) as explained below.

The allylic alcohol (39) was treated with pyridine and acetic anhydride in ether to form the corresponding allylic ester (48) in 96% yield. The ir spectrum showed characteristic absorption bands for a carbonyl (1730 cm^{-1}) and for an olefin (1655 cm^{-1}) as well as an ether (1120 cm^{-1}). In the nmr spectrum, there appeared a doublet of doublets of doublets of doublets ($J=8\frac{1}{2}$, 8, $2\frac{1}{2}$, 2 Hz) at δ 5.50, integrating for the one allylic proton. A doublet ($J=2$ Hz) was displayed at δ 5.06, integrating for one hydrogen and corresponding to one of the vinylic protons. The other vinylic proton was also shown as a doublet ($J=2\frac{1}{2}$ Hz) at δ5.02, integrating for one proton. A triplet

(J=6 Hz) at δ3.39 was assigned to the two protons adjacent to the methoxy group. The methoxy hydrogens appeared as a sharp singlet at δ3.34, followed by three more singlets, one at δ2.08 corresponding to the three hydrogens of the acetyl group and the other two at δ1.08 and δ0.94 for the geminal methyls. Although, the molecular ion peak was absent in the mass spectrum, the presence of a peak at m/e 180.1508 corresponding to the loss of an acetic acid molecule supported the assigned molecular formula of $C_{14}H_{24}O_3$.

The allylic ester (48) was then treated with lithium diisopropylamide and quenched with trimethylsilyl chloride. After refluxing the resulting mixture in tetrahydrofuran, none of the desired product (49) was formed and instead a substantial amount of starting material was recovered.

With no success in the previous two attempts in forming the desired rearranged compounds (47) or (49), we then turned our attention towards a simple version of the Claisen rearrangement developed by Johnson and co-workers (31), and to this end, the allylic alcohol (39) was treated with an excess of triethyl orthoacetate in the presence of a trace amount of propionic acid. The mixture was refluxed in xylene. The resulting unsaturated ester (50) was formed in 96% yield. The ir spectrum displayed characteristic absorption bands for an ester carbonyl (1730 cm^{-1}) and for an olefin (1640 cm^{-1}) as well as for an ether (1120 cm^{-1}).

In the nmr spectrum a broad singlet was shown at δ 5.26, integrating for the single vinylic proton of the ring. The two hydrogens on the carbon adjacent to the oxygen of the ester functionality appeared as a quartet (J=8 Hz) at 4.15, integrating for two protons. A triplet (J=8 Hz) at 3.42, integrating for two protons was assigned for the two hydrogens adjacent to the methoxy group. The three methoxy hydrogens appeared as a sharp singlet at δ 3.37. The three hydrogens of the methyl group of the ester functionality were displayed as a triplet (J=8 Hz) at δ1.25. Two sharp singlets corresponding to the geminal methyls appeared at 1.1 and 0.88 each integrating for three protons. The mass spectrum showed a molecular ion peak at 268.2037 and elemental analysis confirmed the molecular formula $C_{16}H_{28}O_3$.

In order to form the cyclohexenone ring system, the unsaturated ester (<u>50</u>) was subjected to ozonolysis. The expected product, keto aldehyde (<u>51</u>), could then undergo selective aldol condensation to give the cyclohexenone derivative (<u>52</u>).

However, upon ozonolysis of (<u>50</u>) in methanol followed by reductive work up, using methyl sulfide (32,33), the cyclic keto alcohol (<u>53</u>) was formed in 75% yield. The ir spectrum displayed characteristic absorption bands for an alcohol ($3420\ \text{cm}^{-1}$) and for an ester carbonyl (1730^{-1}) as well as the ketone carbonyl ($1705\ \text{cm}^{-1}$). In the nmr spectrum, a quartet (J=7 Hz) was displayed at δ4.14, integrating for two protons, corresponding to the two hydrogens on the carbon adjacent to the oxygen of the ester functionality. The methoxy protons of the side chain appeared as a singlet at δ3.31, integrating for three protons. A triplet (J=7 Hz) at δ1.26, integrating for three hydrogens was assigned to the methyl protons of the ester functionality and finally the two geminal methyl groups appeared as two close singlets, one at 1.10 and the other at 1.06, each integrating for three protons. The molecular ion peak at 300.1973, in the mass spectrum was consistent with the molecular formula $C_{16}H_{28}O_5$.

In an attempt to induce dehydration, the cyclic keto alcohol (53) was treated with d-10-camphorsulphonic acid in refluxing benzene with continuous removal of water. Unfortunately, the reaction yielded none of the desired cyclohexenone derivative (52), but instead a complex mixture of unidentifiable compounds was formed.

In a separate experiment, when the unsaturated ester (50) was subjected to ozonolysis in methanol-dichloromethane (1:1) as the solvent system, followed by reduction with triphenylphosphine (34), the reaction afforded mainly compound (54). Its structure was assigned on the basis of the following data. The nmr spectrum displayed a multiplet at δ4.43, integrating for one proton and corresponding to the single proton on the carbon bearing the two methoxy groups. A quartet (J=8 Hz) at δ4.15, integrating for two protons was observed and was assigned to the two hydrogens on the carbon adjacent to the oxygen of the ester functionality. A broad singlet appeared at δ3.35, integrating for eleven protons corresponding to the nine methoxy hydrogens as well as the two hydrogens on the carbon bearing the methoxy group of the side chain. A triplet (J=8 Hz) at δ1.25, integrating for three hydrogens was assigned to the methyl protons of the ester functionality. The hydrogens of the geminal methyl groups appeared as two sharp singlets, one at δ1.08 and the other at δ1.06. Although the molecular ion peak was absent in the mass spectrum, the presence of a peak at m/e 316.2213 corresponding to the loss of a formaldehyde molecule supported the assigned molecular formula of $C_{18}H_{34}O_6$. In the chemical ionization spectrum, a peak at m/e 364 corresponding to M + NH_4, further supported the molecular formula of $C_{18}H_{34}O_6$.

The formation of the compound (54), clearly indicated that methanol was responsible for its formation at some stage during the course of the reaction. In light of this observation, the unsaturated ester (50) was therefore subjected to ozonolysis using dichloromethane as the only solvent of the reaction. Reduction of the resulting ozonide using triphenylphosphine afforded a mixture of the keto aldehyde (51) and cyclic keto alcohol (53) in 70% yield. No attempt was made to separate these two compounds since our next step would involve the intramolecular aldol condensation in the presence of an acid in order to form the desired cyclohexenone derivative (52). The ir spectrum of this mixture showed a characteristic absorption band for alcohol at 3420 cm^{-1}. The nmr spectrum displayed a broad singlet at δ 9.89, integrating for the one aldehydic proton. A quartet (J=8 Hz) at δ 4.14, integrating for a total of four protons, was assigned to each of the two hydrogens on the carbon adjacent to the oxygen of the ester functionalities in the two compounds. Two close singlets at δ 3.34, integrating for a total of six protons were assigned to the six hydrogens of the two methoxy groups. A triplet (J=8 Hz) at δ 1.28 integrating for a total of six hydrogens and corresponding to the methyl hydrogens of the ester functionalities and finally the geminal methyl groups appeared as four singlets at δ 1.15, 1.12, 1.1 and 1.08, integrating for a total of twelve protons. The molecular ion peak at m/e 300.1936 in the mass spectrum was consistent with the assigned molecular formula of $C_{16}H_{28}O_5$. The mixture of the keto aldehyde (51) and the cyclic keto alcohol (53) was then treated with d-10-camphorsulphonic acid in refluxing benzene. The reaction yielded a substantial amount of unidentifiable complex mixture as well as two products in a very low yield, one of which was the desired cyclohexenone derivative (52) and the other a by-product (55), formed in an approximate ratio of 1:2 respectively. Their structures were assigned on the basis of the nmr spectrum, displaying for compound (52), a broad singlet at δ 6.70, integrating for the one vinylic proton. A quartet (J=8 Hz) at δ 4.14, integrating for a total of two protons was assigned to the two hydrogens on the carbon adjacent to the oxygen of the ester functionality. A singlet at δ 3.33 was displayed, integrating for the three methoxy hydrogens. The three methyl hydrogens of the ester functionality appeared as a triplet (J=8 Hz) at δ 1.23 and the two geminal methyl groups appeared at δ 1.16 and 0.98. The nmr spectrum of compound (55) displayed a doublet of doublets (J=9.5 Hz, J=3 Hz) at δ 6.42, integrating for one proton and corresponding to the vinylic proton β to the carbonyl group of the lactone ring. The vinylic proton α to the carbonyl group also appeared as a doublet of doublets (J=9.5 Hz, J=2 Hz) at δ 6.16. A doublet (J=1 Hz) at δ 5.73, integrating for one hydrogen was assigned to the vinylic proton γ to the carbonyl group. The single allylic proton at the ring junction appeared as a doublet (J=1 Hz) at δ 4.67. The two hydrogens on the carbon bearing the methoxy group appeared as a triplet (J=6 Hz) at δ 3.43 and the methoxy protons appeared as a singlet at δ 3.36 and finally the two geminal methyl groups appeared as singlets at δ 1.26 and 0.54.

In an attempt to examine the reproducibility of the ozonolysis reaction and to further examine different approaches for the cyclization of the products, thus obtained, to the desired cyclohexenone derivative (52), the unsaturated ester was subjected to ozonolysis in dichloromethane followed by reductive work-up using triphenylphosphine (34). The reaction resulted in the formation of the pure keto aldehyde (51) in 79% yield. The ir spectrum displayed characteristic absorption bands for an ester carbonyl (1733 cm^{-1}) and for the ketone and aldehyde carbonyls (1705 cm^{-1}). The nmr spectrum displayed a triplet (J=1½ Hz) at δ9.78 for the one aldehydic proton and a quartet (J=7 Hz) at δ4.13, integrating for the two protons on the carbon adjacent to the oxygen of the ester functionality. A singlet at δ3.32 was assigned to the three protons of the methoxy group. A triplet (J=7 Hz) at δ1.26, integrating for three methyl hydrogens of the ester functionality as well as two sharp singlets, each integrating for three protons, at δ1.14 and 1.08 corresponding to the geminal methyls were observed. The mass spectrum displayed a molecular ion peak at m/e 300.1942 in agreement with the assigned molecular formula of $C_{16}H_{28}O_5$.

A further attempt to induce cyclization of the keto aldehyde (51) to the cyclohexenone derivative (52) using the same procedure, namely, treatment with d-10-camphorsulphonic acid in refluxing benzene again led to the formation of a very small amount of the mixture of compound (52) and the by-product (55) as well as formation of a substantial amount of unidentifiable complex mixture. Other approaches such as treatment with camphorsulphonic acid in dichloromethane in the presence of sodium sulphate as drying agent at room temperature proved unsuccessful. Treatment of the keto aldehyde (51) with benzoic acid in the presence of triethylamine in refluxing xylene also led to the formation of an unidentifiable complex mixture. Treatment of the keto aldehyde (51) with sodium hydride in 1,2-dimethoxyethane also did not lead to the formation of the desired product. Suffice it to say that in all of the above approaches for cyclization, a substantial loss of the starting material occurred along with the hydrolysis of the ester functionality to the corresponding carboxylic acid.

In short, the transformation of the cyclopentene ring, present in compound (50), to a cyclohexenone ring system proved to be difficult, presumably due to the presence of the ester functionality in compound (50). Modification of this labile functional group to form an ether, via the corresponding alcohol, was deemed appropriate and towards this end, the unsaturated ester (50) was treated with lithium aluminium hydride in ether, resulting in the formation of the corresponding alcohol (56) in 97% yield. The ir spectrum displayed characteristic absorption bands for an alcohol (3420 cm^{-1}) and for an olefin (1640 cm^{-1}) as well as an ether (1130 cm^{-1}). In the nmr spectrum, a broad singlet at δ 5.32 was observed for the single vinylic proton. A triplet (J=6 Hz) at δ 3.71, integrating for one proton was assigned to the hydroxyl hydrogen. At δ3.44, integrating for two protons, appeared a triplet (J=7 Hz) corresponding to the two hydrogens on the carbon bearing the methoxy group. The three methoxy protons appeared as a singlet at δ 3.38 and finally the geminal methyl groups appeared as sharp singlets at δ 1.0 and 0.79, each integrating for three protons. The molecular ion peak in the mass spectrum at 226.1935 as well as elemental analysis, verified the $C_{14}H_{26}O_2$ molecular formula.

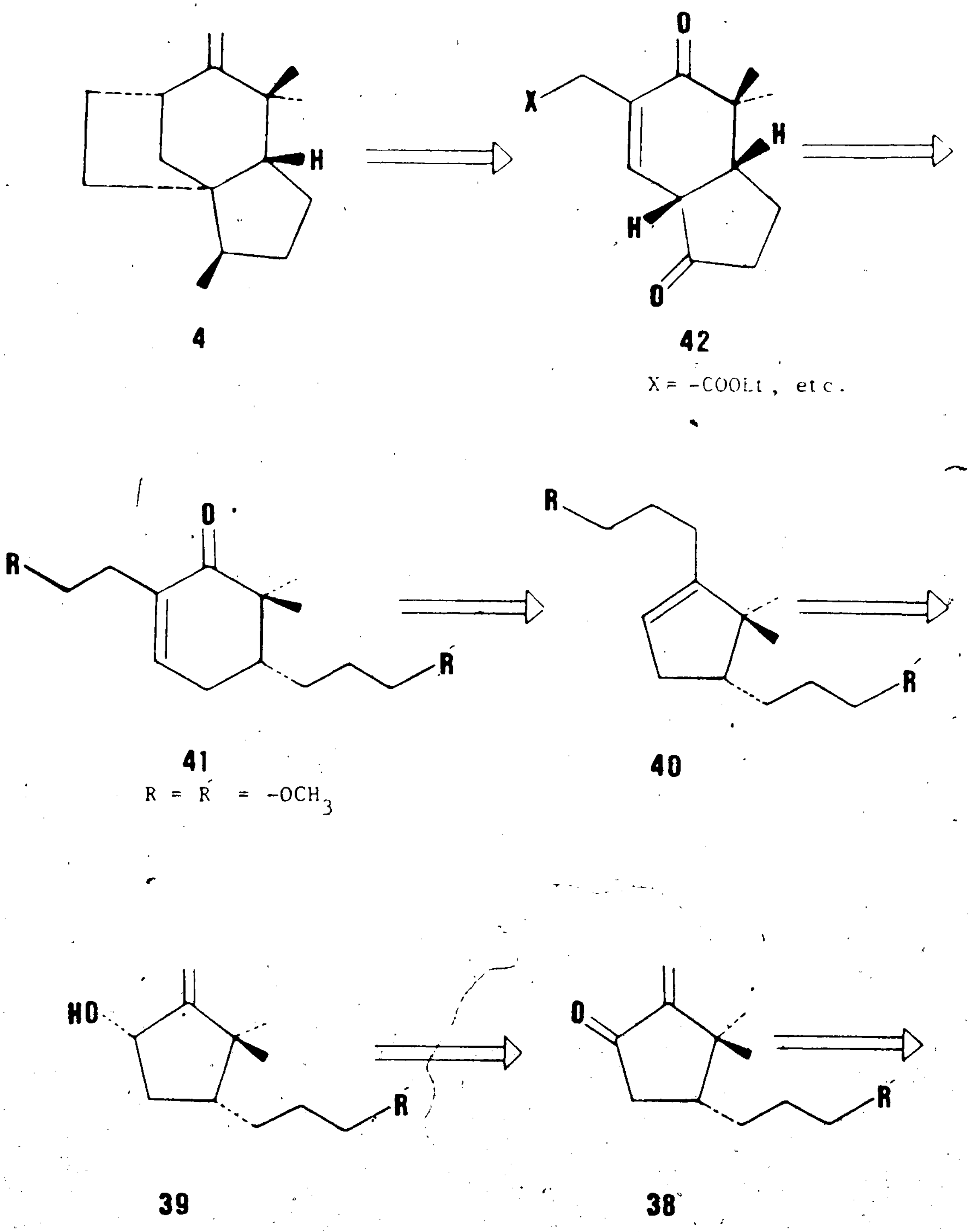
Methylation of the alcohol (<u>56</u>), using sodium hydride and methyl iodide in 1,2-dimethoxyethane afforded the ether (<u>40</u>) in 98% yield. The ir spectrum showed characteristic absorption bands for an olefin (1645 cm^{-1}) and for ether (1140 cm^{-1}). The nmr spectrum displayed a broad singlet at δ5.28, corresponding to the one vinylic proton. A quartet (J=6 Hz) at δ 3.42, integrating for a total of four protons, was assigned to the hydrogens on the carbons bearing the methoxy groups of the two side chains. The hydrogens of the two methoxy groups appeared as a broad singlet at δ3.38, integrating for a total of six protons and finally the geminal methyl groups were displayed as two singlets, one at δ 1.0 and the other at 0.78, each integrating for three protons. The molecular ion peak in the mass spectrum was displayed at m/e 240.2093 consistent with molecular formula of $C_{15}H_{28}O_2$, which was further verified by elemental analysis.

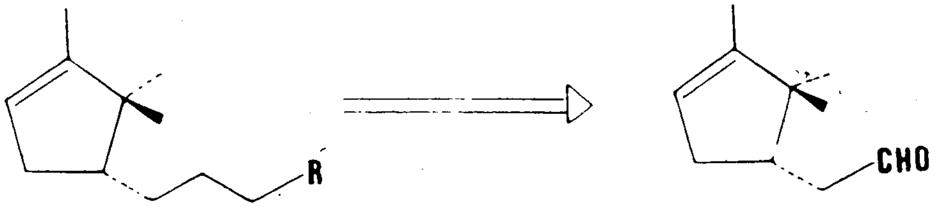
The ether (40) was then subjected to ozonolysis in dichloromethane followed by reductive work up with triphenylphosphine to give the keto aldehyde (58). This compound, without purification, was subjected to cyclization using d-10-camphorsulphonic acid in refluxing benzene to give the desired cyclohexenone diether (41) in 29% yield from ether (40). In an attempt to improve the yield of formation of the desired product (41), the crude keto aldehyde (58) was subjected to cyclization using p-toluenesulphonic acid in refluxing benzene. The desired cyclohexenone diether (41) was formed in 40% yield from ether (40). The ir spectrum displayed characteristic absorption bands for a ketone carbonyl (1670 cm^{-1}) and for ether (1120 cm^{-1}). In the nmr spectrum, a broad multiplet was observed at δ6.30, integrating for the single vinylic proton. The hydrogens of the two methoxy groups were displayed as two singlets, one at δ3.34 and the other at 3.30, each integrating for three protons and finally the geminal methyl groups appeared as singlets at δ1.15 and 0.95, each integrating for three protons. The molecular ion peak at 254.1871 in the mass spectrum as well as the elemental analysis verified the assigned molecular formula of $C_{15}H_{26}O_3$.

In conclusion, the preparation of the target cyclohexenone derivative (41) has been achieved from the levorotatory α-pinene oxide. Compound (41) can in principle be transformed into the bicyclic diketone (42), which is considered to be a potential synthetic precursor of (-)-prezizaene (4) and (-)-prezizanol (20). Towards the formation of this projected key intermediate, compound (41) can in principle be converted to the corresponding diol which upon oxidation to the diacid followed by esterification and subsequent cyclization could afford the compound (42).

Further studies are being carried out in this laboratory leading to the formation of the bicyclic diketone intermediate (42) on the way towards the total synthesis of prezizaene (4) and prezizanol (20).

SCHEME VI





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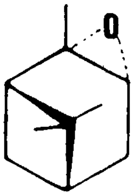

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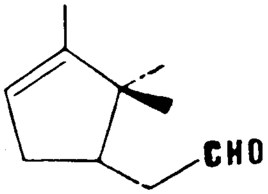

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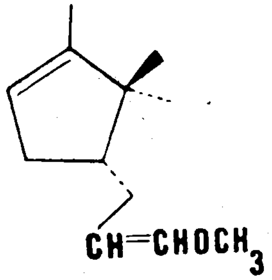

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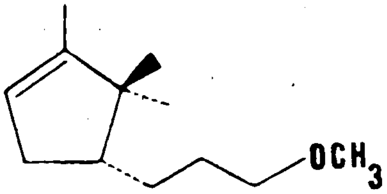

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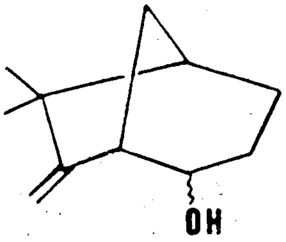

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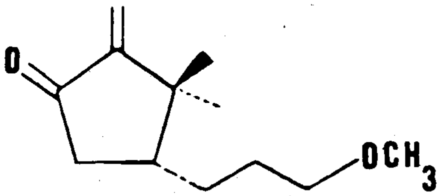

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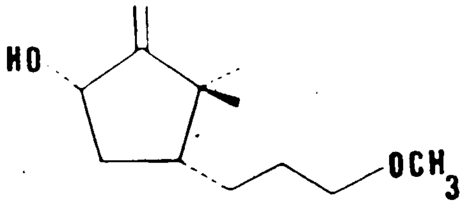

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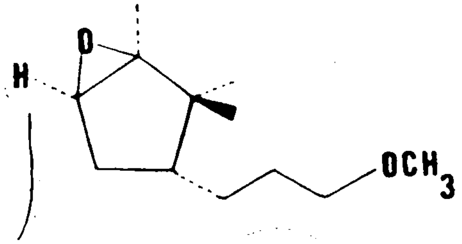

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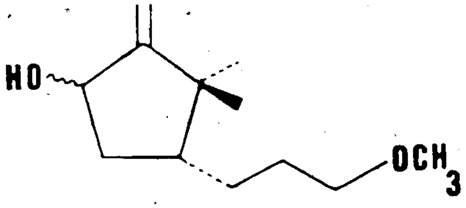

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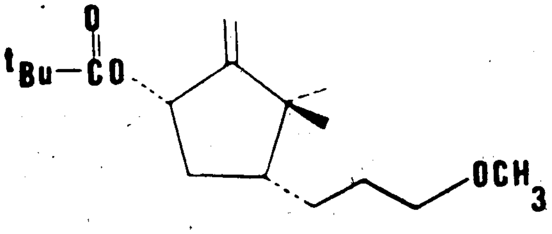

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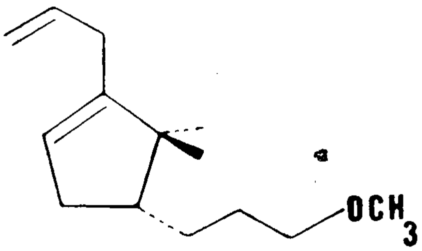

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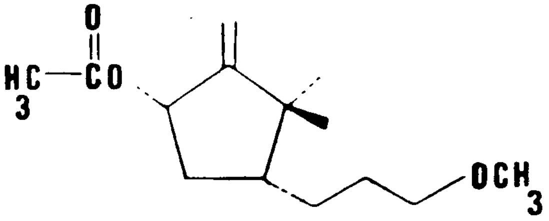

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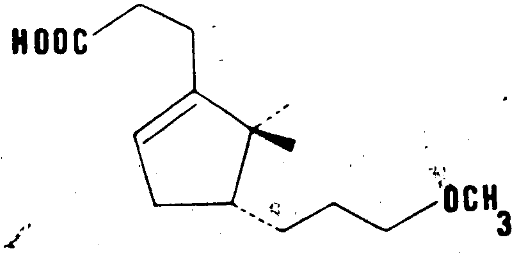

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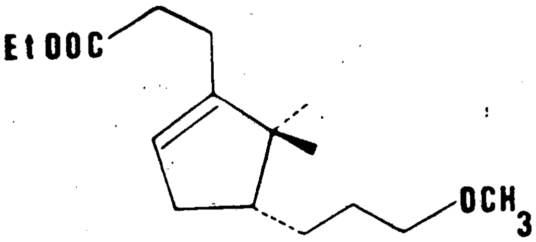

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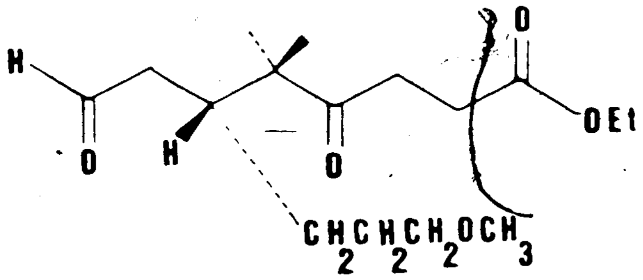
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O
H
O
O
OEt
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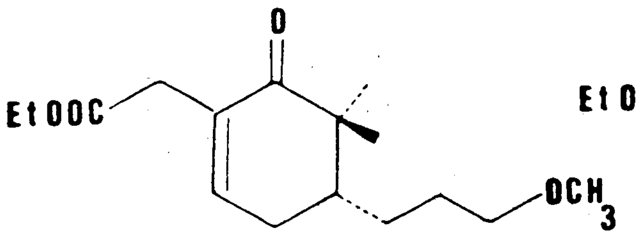
51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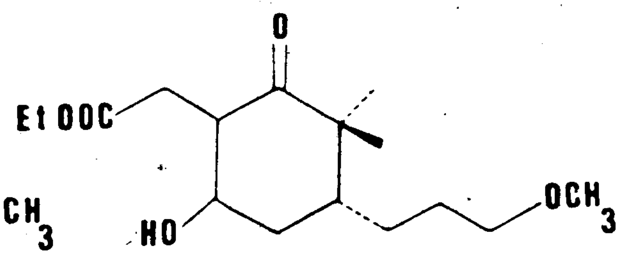
OCH3

52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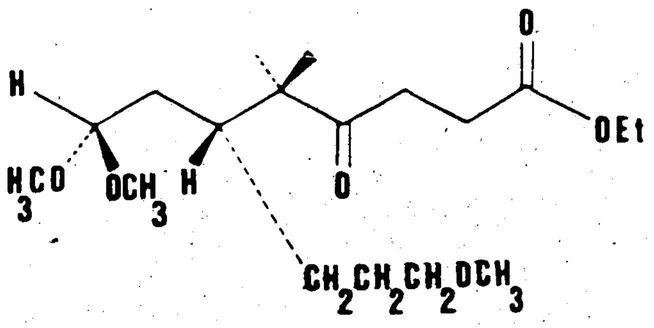
HO
OCH3

53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H
O
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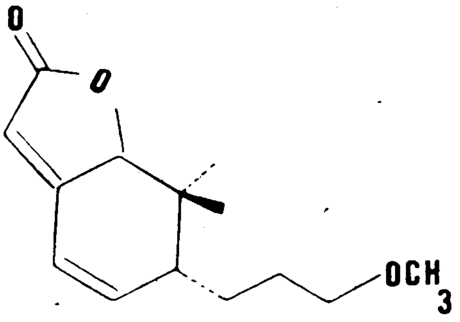
54



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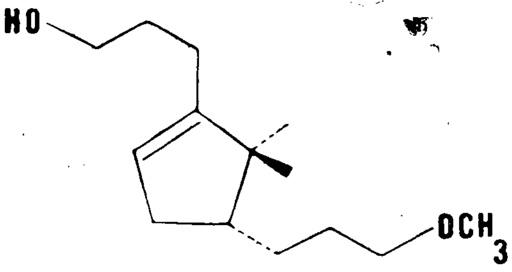

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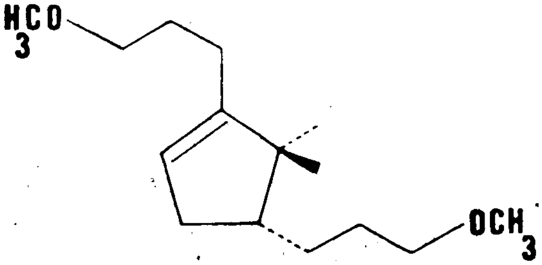

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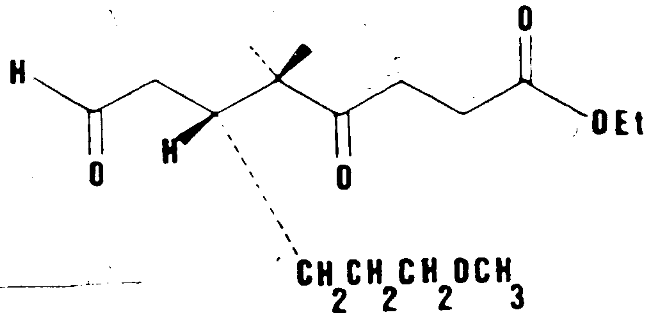
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H
O
O
OEt
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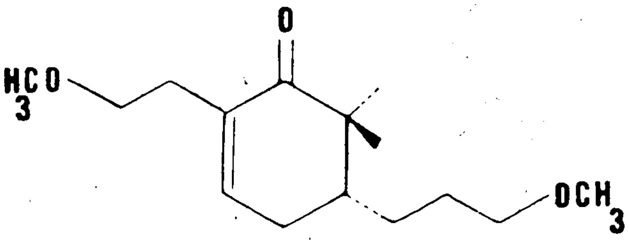
57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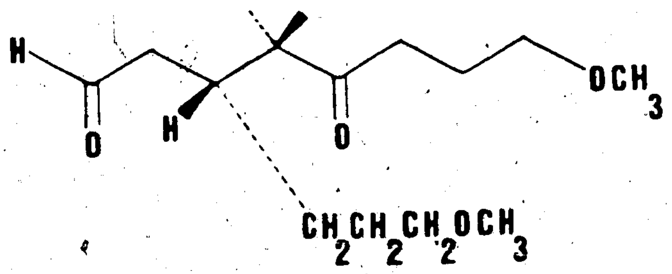
OCH3

41


H
O
H
O
OCH3
CH2CH2CH2OCH3

58

CHAPTER III

EXPERIMENTAL

General

Infrared (ir) spectra were obtained by using the Perkin-Elmer Model 457 spectrophotometer. Ir samples were run as thin films. Proton nuclear magnetic resonance (nmr) spectra were recorded on a Bruker W-200 or Bruker W-400 spectrometer using deuterated chloroform as solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: S = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra (MS) were recorded using A.E.I. model MS50 mass spectrometer. Elemental analyses were performed by the microanalytical laboratory of this department.

Materials

Benzene, diethyl ether (ether), 1,2-dimethoxyethane (DME) and xylene were freshly distilled over lithium aluminium hydride. Methanol was refluxed over magnesium turnings for 2-3 hrs and distilled. Dichloromethane, ethyl acetate, dimethyl sulfoxide (DMSO) and pyridine were freshly distilled over calcium hydride. α- Pinene epoxide was obtained from Aldrich Chemical Company. Ozone was generated with a Welsbach ozonator. Argon was purified by passing through a train of gas wash bottles containing sequentially, Fieser's solution (35), concentrated sulfuric acid and potassium hydroxide pellets. Silica gel, 0.040-0.063 mm particle size, 230-400 mesh ASTM was used as adsorbent for flash chromatography (36), and silica gel 60-120 mesh was used as adsorbent for column chromatography. Thin layer chromatography was carried out using Merck Art 5554 DC-alufolien TLC plates as well as Merck silica gel G.

6

α-Campholenic aldehyde (35)

Anhydrous zinc chloride (50 mg, 0.3676 mmole) was melted in a 50 ml 3-necked round-bottom flask under argon gas, to which was added a solution of α-pinene epoxide (95%, 1.928 g, 0.012 mole) in benzene (10 ml). The mixture was refluxed for three hours. The solvent was removed and molecular distillation of the residue in a kugelrohr apparatus (87°C/0.25 torr) gave the pure aldehyde 35 (1.54 g, 80% yield) with the following spectral data: ir 2720 and 1727 cm^{-1} (aldehyde) and 1650 cm^{-1} (olefin); nmr δ 9.82 (t, 1H, J=2 Hz, -CHO), 5.26 (br.S, 1H, -HC=), 1.62 (m, 3H, $CH_3C=$), 1.0 (S, 3H, $-CH_3$), 0.79 (S, 3H, $-CH_3$); MS M^+ 152.1204 (calcd. for $C_{10}H_{16}O$: 152.1201).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.88; H, 10.60;

Found: C, 78.71; H,10.38.

4-(3-Methoxy-2-propenyl)-1,5,5-trimethylcyclopentene (36)

A mixture of sodium hydride (4.53 g of 50% dispersion in oil; 0.094 mole) in dimethyl sulfoxide (49 ml) and benzene (80 ml) was refluxed for fifty minutes under Argon gas, to produce the methylsulfinyl carbanion. After allowing the mixture to come to room temperature, (methoxymethyl)-triphenylphosphonium chloride (35g, 0.102 mole) was added and the solution was stirred for ten minutes assuming the deep red colour of methoxymethylenetriphenylphosphorane solution. To this solution was added the aldehyde 35 (10g, 0.065 mole) in benzene (20 ml). After stirring for fifteen hours, the mixture was poured into ice-cold water (300 ml) and extracted with ether (4 x 100 ml). The org~~anic~~ solution was washed with saturated sodium chloride solution and the combined organic extract was dried (magnesium sulphate), filtered and concentrated. Molecular distillation of the residue using kugelrohr apparatus (90°C/0.4 torr) was carried out in order to remove triphenylphosphine oxide. The distillate was purified by flash chromatography on silica gel, using 20% ethyl acetate in petroleum ether. The product 36 (10.99 g, 93%) was a 1:1 mixture of the cis and trans isomers which gave the following spectral data: ir 1656 (olefin) and 1208 cm^{-1} (vinyl ether); nmr δ6.30; 5.88 (d, ½H, J=13 Hz; dt, ½H, J = 6 Hz, J = 1½ Hz, $-CH=C\underline{H}OCH_3$), 4.72; 4.36 (m, ½H; dd, ½H, J=13 Hz, J=6 Hz, $-C\underline{H}=CHOCH_3$), 3.58, 3.50 (both S, 3H, $-CH=CHOC\underline{H}_3$), 1.62 (m, 3H, $CH_3C=$), 1.0 (S, 3H, $-CH_3$), and 0.80 (m, 3H, $-CH_3$); MS M^+ 180.1510 (calcd. for $C_{12}H_{20}O$: 180.1515).

4-(3-Methoxypropyl)-1,5,5-trimethylcyclopentene (37)

Potassium acetate (0.33 g, 3.33 mmole) and 5% palladium on carbon (59 mg) were added to a solution of the vinyl ether 36 (599 mg, 3.33 mmole) in ethyl acetate (30 ml). The mixture was stirre[illegible]t room temperature under an atmosphere of hydrogen for ten hours. After filtering off the catalyst and removing the solvent, the crude product was purified by flash chromatography on silica gel, using 5% ether in petroleum ether to give the pure ether 37 (585 mg, 97% yield); ir 1650 (olefin) and 1120 cm^{-1} (ether); nmr 5.28 (br.S, 1H, $-HC=$), 3.44 (t, 2H, J=8 Hz, $-CH_2-C\underline{H}_2OCH_3$), 3.40 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.62 (br.S, 3H, $CH_3C=$), 1.0 (S, 3H, $-CH_3$), and 0.80 (S, 3H, $-CH_3$); MS M^+ 182.1672 (calcd. for $C_{12}H_{22}O$: 182.16716).

4-(3-Methoxypropyl)-3,3-dimethyl-2-methylidinecyclopentanone (38)

A solution of the ether 37 (0.5g, 2.74 mmole), acetic anhydride (0.27 ml, 2.83 mmole), pyridine (0.11 ml, 1.37

mmole), tetraphenylporphine (20 mg, 0.03 mmole) and dimethylaminopyridine (10 mg, 0.08 mmole) in dichloromethane (40 ml) was irradiated with two 200W tungsten light bulbs for 37 hours. During this period a gentle stream of oxygen was bubbled through the reaction mixture. The solution was diluted with dichloromethane and extracted with saturated sodium bicarbonate until basic (2 x 40 ml). The organic layer was then washed with 1.0 N solution of hydrochloric acid until it turned mint green and the aqueous washes were acidic (2 x 30 ml). Further extractions with saturated copper sulfate solution (80 ml) and saturated sodium chloride solution (80 ml) followed by drying with magnesium sulfate, filtering and concentration gave the crude residue which, on molecular distillation using kuglerohr apparatus (73°C/0.12 torr) and further purification by column chromatography on silica gel, using 20% ethyl acetate in petroleum ether, afforded the enone <u>38</u> (268 mg, 50% yield) giving the following spectral data: ir 1730 (ketone carbonyl) and 1635 cm^{-1} (olefin); nmr 5.97 (d, 1H, J=1 Hz, $=C\underline{H}H$), 5.20 (d, 1H, J=1 Hz, $=CH\underline{H}$), 3.44 (t, 2H, J=7 Hz, $-CH_2-C\underline{H}_2OCH_3$), 3.38 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 2.54 (dd, J=18 Hz, J=11 Hz, 1H, $-CO-CH\underline{H}$), 2.07 (dd, J=18 Hz, J=7 Hz, 1H, $-CO-C\underline{H}H$), 1.23 (S, 3H, $-CH_3$), and 1.0 (S, 3H, $-CH_3$); MS M^+ 196.1471 (calcd. for $C_{12}H_{20}O_2$; 196.1464).

4-(3-Methoxypropyl)-3,3-dimethyl-2-methylidinecyclopentanol (39)

A solution of the enone 38 (0.78 g, 4.0 mmole), cerous chloride (1.49 g, 6.04 mmole) in methanol (35 ml) was cooled to 10°C. Sodium borohydride (152 mg, 4.0 mmole) was added to this solution. The temperature was raised to 25°C and stirred for an additional two hours. The mixture was then quenched with aqueous solution of ammonium chloride (10 ml) and 1.0 N hydrochloric acid (5 ml). Extraction with dichloromethane (3 x 60 ml), drying, filtering and subsequent concentration gave an oily residue, which on flash chromatographic purification on silica gel, using 25% ethyl acetate in petroleum ether, afforded the pure allylic alcohol 39 (0.78 g, 98% yield): ir 3420 (alcohol), 1660 (olefin) and 1120 cm^{-1} (ether); nmr 5.12 (d, 1H, J=2 Hz, $=CH\underline{H}$), 4.97 (d, 1H, J=2½ Hz, $=C\underline{H}H$), 4.45 (m, 1H, $-\overset{|}{C}\underline{H}OH$), 3.40 (t, 2H, J=6½ Hz, $-CH_2-C\underline{H}_2OCH_3$), 3.36 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.06 (S, 3H, $-CH_3$), 0.93 (S, 3H, $-CH_3$); MS M^+ 198.1610 (calcd. for $C_{12}H_{22}O_2$; 198.16206).

1,2-Epoxy-4-(3-methoxypropyl)-2,3,3-trimethylcyclopentane (44)

To a solution of the ether 37 (0.127 g, 0.70 mmole) in dichloromethane (5 ml) was added a solution of *m*-chloroperbenzoic acid (0.17 g, 0.99 mmole) in dichloromethane

(10 ml). The mixture was stirred at room temperature for fourteen hours. An aqueous solution of 10% sodium sulfite (10 ml) was added to the reaction mixture and extracted with dichloromethane (3 x 20 ml). The organic solution was washed with an aqueous solution of 5% sodium bicarbonate (15 ml) and the aqueous solution extracted with dichloromethane (3 x 20 ml). The combined organic extract was dried, filtered and concentrated. The crude product upon purification by flash chromatography on silica gel, using 20% ethyl acetate in petroleum ether gave the epoxide <u>44</u> (0.12 g, 92% yield): nmr 3.37 (dt, J=6½ Hz, J=2½ Hz, 2H, $-CH_2C\underline{H}_2OCH_3$), 3.34 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 3.24 (br.S, 1H, $H\overset{O}{C-C}<$), 1.32 (S, 3H, $>C-CH_3$), 1.0 (S, 3H, $-CH_3$) and 0.76 (S, 3H, $-CH_3$); MS m/e 183.1385 (M^+-15; calcd. for $C_{12}H_{22}O_2$; 198.16206).

<u>4-(3-Methoxypropyl)-3,3-dimethyl-2-methylidinecyclopentanol (45)</u>

A solution of the ether <u>37</u> (0.21 g, 1.18 mmole) and methylene blue (12 mg) in methanol (25 ml) was irradiated with two 200W tungsten light bulbs for five days. During this period a moderate stream of oxygen was bubbled through the solution. The solution was cooled to 0°C and sodium borohydride (0.01 g, 0.44 mmole) was added. The resulting mixture was stirred for one hour, poured into ice-cold 2N aqueous hydrochloric acid solution (25 ml) and extracted with dichloromethane (3 x 35 ml). The organic solution was dried, filtered and concentrated to give the crude residue which was chromatographed on silica gel. Elution with 20% ethyl acetate in petroleum ether afforded the allylic alcohol 45 (0.08 g, 37% yield): ir 3420 cm^{-1} (alcohol), 3095 (olefin) and 1125 cm^{-1} (ether); nmr δ 5.12 (d, 1H, J=2 Hz, -CH=), 4.97 (d, 1H, J=2 Hz, -CH=), 4.52 (m, 1H, -$\underline{H}$COH-), 3.32 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.13 (S, 3H, $-CH_3$) and 0.81 (S, 3H, $-CH_3$).

1-Pivaloyloxy-4-(3-methoxypropyl)-3,3-dimethyl-2-methylidinecyclopentane (46)

To a mixture of the allylic alcohol 39 (770 mg, 3.88 mmole) and pyridine (1.87 ml, 23.19 mmole) in ether (25 ml) was added trimethylacetyl chloride (1.92 ml, 15.58 mmole), at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 30 minutes and at room temperature for 42 hours. The solution was then washed with water (60 ml) and the aqueous solution extracted with ether (3 x 50 ml). The organic solution was washed with an aqueous solution of 1.0 N hydrochloric acid (30 ml) followed by the extraction of the aqueous solution with ether (3 x 50 ml), drying with magnesium sulfate, filtering and concentration. Subsequent flash chromatography, using 15% ethyl acetate in petroleum ether, afforded an oily residue which on molecular distillation using kugelrohr apparatus (45°C/0.3 torr) gave the pure allylic pivalate 46 (998 mg, 91% yield): ir 1735 cm^{-1} (pivalate C=0), 1660 cm^{-1} (olefin) and 1130 cm^{-1} (ether); nmr δ 5.48 (d,d,d,d, 1H, J=8½, 8, 2½, 2 Hz, -C$\underline{H}$OCO-C$\lessgtr$), 5.02 (d, 1H, J=2 Hz, -C$\underline{H}$=), 4.98 (d, 1H, J=2½ Hz, -C$\underline{H}$=), 3.39 (t, 2H, J=6 Hz, $-CH_2-C\underline{H}_2OCH_3$), 3.34 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.20 (S, 9H, $(C\underline{H}_3)_3COO-$), 1.08 (S, 3H, $-CH_3$), and 0.94 (S, 3H, $-CH_3$); MS M^+ 282.2209 (calcd. for $C_{17}H_{30}O_3$; 282.2196).

1-Acetoxy-4-(3-methoxypropyl)-3,3-dimethyl-2-methylidinecyclopentane (48)

To a mixture of the allylic alcohol 39 (267 mg, 1.35 mmole) and pyridine (1.0 ml, 12.36 mmole) in ether (20 ml) was added acetic anhydride (0.5 ml, 5.29 mmole) at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 30 minutes and at room temperature for 20 hours. The solution was then diluted with water (50 ml) and extracted with ether (3 x 40 ml). The organic solution was washed with an aqueous solution of 1.0 N hydrochloric acid (20 ml) and the aqueous solution extracted with ether (3 x 40 ml). Drying, filtration, and concentration gave the crude product which was subjected to flash chromatography. Elution with 15% ethyl acetate in petroleum ether yielded the pure allylic acetate 48 (312 mg, 96% yield): ir 1730 cm^{-1} (acetate C=O), 1655 cm^{-1} (olefin) and 1120 cm^{-1} (ether); nmr 5.50 (dddd, 1H, J=8½, 8, 2½, 2 Hz, $-\overset{|}{C}\underline{H}OCO-CH_3$), 5.06 (d, 1H, J=2 Hz, -CH=), 5.02 (d, 1H, J=2½ Hz, -CH=), 3.39 (t, 2H, J=6 Hz, $-CH_2-C\underline{H}_2OCH_3$), 3.34 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 2.08 (S, 3H, CH_3-CO-), 1.08 (S, 3H, $-CH_3$), and 0.94 (S, 3H, $-CH_3$); MS m/e 180.1508 (M^+-60; calcd. for $C_{12}H_{20}O$; 180.1515).

1-(2-Carboethoxyethyl)-4-(3-methoxypropyl)-5,5-dimethylcyclopentene (50)

A mixture of the allylic alcohol 39 (0.4g, 2.02 mmole), triethyl orthoacetate (95%, 1.84 ml, 10.05 mmole), propionic acid (0.015 ml, 0.202 mmole) in xylene (10 ml) was refluxed for three hours with continuous removal of ethanol, using a Dean-Stark separator. The mixture was poured into water (20 ml) and extracted with dichloromethane (3 x 50 ml). The organic solution was dried over magnesium sulfate, filtered and concentrated. The residue, on purification by flash chromatography, using 15% ethyl acetate in petroleum ether, afforded the pure unsaturated ester 50 (0.52 g, 96% yield): ir 1730 cm^{-1} (ester carbonyl), 1640 cm^{-1} (olefin) and 1120 cm^{-1} (ether); nmr 5.25 (br.S, 1H, $-CH=$), 4.15 (q, 2H, J=8 Hz, $CH_3-C\underline{H}_2-O-$), 3.42 (t, 2H, J=6 Hz, $-CH_2-C\underline{H}_2OCH_3$), 3.37 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.25 (t, 3H, J=8 Hz, $C\underline{H}_3-CH_2O-$), 1.1 (S, 3H, $-CH_3$), and 0.88 (S, 3H, $-CH_3$); MS M$^+$ 268.2037 (calcd. for $C_{16}H_{28}O_3$; 268.2039).

Anal. Calcd. for $C_{16}H_{28}O_3$; C, 71.58; H, 10.52;
Found: C, 71.47; H, 10.26.

2-Carboethoxymethyl-3-hydroxy-5-(3-methoxypropyl)-6,6-dimethylcyclohexanone (53)

At -78°C, ozone (condition: E=80V, air inlet = 8 psi, ozone outlet = 0.06 psi) was allowed to pass through a solution of the unsaturated ester 50 (40 mg, 0.149 mmole) in methanol (12 ml) until a light blue colour was retained (3 minutes). Dimethyl sulfide (0.2 ml, 2.72 mmole) was added to the solution under an argon atmosphere. The mixture was allowed to warm to 25°C and stirred for two hours. Removing of the solvent, followed by flash chromatography, using 30% ethyl acetate in petroleum ether, afforded the cyclic keto alcohol 53 (33.5 mg, 75% yield): ir 3420 cm^{-1} (alcohol), 1730 cm^{-1} (ester C=O), and 1705 cm^{-1} (ketone C=O); nmr δ 4.14 (q, 2H, J=7 Hz, $CH_3-C\underline{H}_2-OCO-$), 3.31 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.26 (t, 3H, J=7 Hz,

$C\underline{H}_3$-CH_2-OCO-), 1.10 (S, 3H, -CH_3) and 1.07 (S, 3H, -CH_3); MS M^+ 300.1937 (calcd. for $C_{16}H_{28}O_5$; 300.19374).

2-Carboethoxymethyl-5-(3-methoxypropyl)-6,6-dimethyl-2-cyclohexenone (52) and Lactone (55)

To a solution of the ketoaldehyde 51 and the alcohol 53 (40 mg, 0.133 mmole) in benzene (5 ml) was added d-10-camphorsulfonic acid (10 mg, 0.043 mmole). The mixture was refluxed for nineteen hours under an argon atmosphere with continuous removal of water using a Dean-Stark water separator. The reaction mixture was diluted with water (20 ml) and extracted with ether (3 x 20 ml). The organic solution was washed with saturated aqueous solution of sodium bicarbonate (30 ml), dried, filtered and concentrated. Flash chromatography of the residue, using 25% ethyl acetate in petroleum ether, afforded the cyclohexenone derivative 52 (3 mg, 8% yield) and the lactone by-product 55 (4.8 mg, 15% yield).

The following nmr data were obtained for compound 52: δ6.70 (br.S, 1H, =$C\underline{H}$-), 4.14 (q, 2H, J=8 Hz, CH_3-$C\underline{H}_2$-OCO-), 3.33 (S, 3H, -CH_2-CH_2-$C\underline{H}_3$), 1.23 (t, 3H, J=8 Hz, $C\underline{H}_3$-CH_2-OCO-), 1.16 (S, 3H, -CH_3), and 0.98 (S, 3H, -CH_3).

The following nmr data were obtained for compound 55: δ6.42 (dd, 1H, J=9.5 Hz, J=3 Hz, =-$C\underline{H}$=), 6.16 (dd, 1H, J=9.5 Hz, J=2 Hz, =$C\underline{H}$-CH-), 5.73 (d, 1H, J=1 Hz, -CO$\underline{H}$C=), 4.67 (d, 1H, J=1 Hz, $>C\underline{H}-O-$), 3.43 (t, 2H, J=6 Hz, $-CH_2-C\underline{H}_2-OCH_3$), 3.36 (S, 3H, $-CH_2-CH_2-OC\underline{H}_3$), 1.26 (S, 3H, $-CH_3$) and 0.54 (S, 3H, $-CH_3$).

Ethyl 10-methoxy-5,5-dimethyl-4-oxo-7-(2-oxoethyl)-nonanoate (51)

At -78°C, ozone (conditions: E=80V, air inlet=8 psi, ozone outlet = 0.06 psi) was allowed to pass through a solution of the unsaturated ester 50 (54 mg, 0.2 mmole) in dichloromethane (10 ml) until a light blue colour was retained (3.0 minutes). Triphenylphosphine (78 mg, 0.29 mmole) was added to the solution under an argon atmosphere. The mixture was allowed to warm to 25°C and stirred for eighteen hours. Removal of the solvent and subsequent flash chromatography, using 30% ethyl acetate in petroleum ether, gave the pure keto aldehyde 51 (48 mg, 79% yield): ir 1735 cm^{-1} (ester C=O), 1705 cm^{-1} (ketone and aldehyde C=O), and 1120 cm^{-1} (ether); nmr 9.78 (t, 1H, J=1½ Hz, -CHO), 4.13 (q, 2H, J=7 Hz, $CH_3-C\underline{H}_2OCO-$), 3.32 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.26 (t, 3H, J=7 Hz, $C\underline{H}_3-CH_2OCO-$), 1.14 (S, 3H, $-CH_3$), and 1.08 (S, 3H, $-CH_3$); MS M^+ 300.1942[illegible] (calcd. for $C_{16}H_{28}O_5$: 300.19374).

1-(3-Hydroxypropyl)-4-(3-methoxypropyl)-5,5-dimethylcyclopentene (56)

To a solution of the unsaturated ester 50 (279 mg, 1.04 mmole) in ether (15 ml) at -30°C, was added lithium aluminium hydride (95%, 63 mg, 1.66 mmole). The mixture was stirred for six hours under an argon atmosphere. The temperature was then brought to 0°C. Water (0.063 ml), 15% aqueous solution of sodium hydroxide (0.063 ml) and again water (0.19 ml) were added to the ethereal solution. The mixture was then filtered, dried with magnesium sulfate and concentrated. Flash chromatography, using 30% ethyl acetate in petroleum ether, yielded the pure alcohol 56 (227 mg, 97% yield): ir 3410 cm^{-1} (alcohol), 1640 cm^{-1} (olefin) and 1130 cm^{-1} (ether); nmr 5.32 (br.S, 1H, -HC=), 3.71 (t, 1H, J=6 Hz, $-CH_2O\underline{H}$), 3.44 (t, 2H, J=7 Hz, $-CH_2C\underline{H}_2OCH_3$), 3.38 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.0 (S, 3H, $-CH_3$), and 0.79 (S, 3H, $-CH_3$); MS M^+ 226.1935 (calcd. for $C_{14}H_{26}O_2$: 226.19338).

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.27; H, 11.58;
Found: C, 73.90; H, 11.67.

1,4-Bis(3-methoxypropyl)-5,5-dimethylcyclopentene (40)

To a solution of the alcohol 56 (217 mg, 0.963 mmole) in 1,2-dimethoxyethane (14 ml) were added sodium hydride (84 mg, 3.53 mmole) and methyl iodide (0.23 ml, 3.69 mmole).

The mixture was stirred at 25°C for ten hours under an argon atmosphere, followed by addition of water (20 ml) and extraction with ether (3 x 50 ml). The organic solution was washed with saturated aqueous solution of sodium bicarbonate (50 ml) followed by extraction of the aqueous solution with ether (3 x 50 ml). The extracts were combined, dried with magnesium sulfate, filtered and concentrated. Flash chromatography, using 10% ethyl acetate in petroleum ether, afforded the pure diether <u>40</u> (226 mg, 98% yield): ir 1645 cm cm^{-1} (olefin) and 1140 cm^{-1} (ether); nmr 5.28 (br.S, 1H, -HC=), 3.42 (q, 4H, J=6 Hz, 2 x $-CH_2-C\underline{H}_2OCH_3$), 3.38 (br.S, 6H, 2 x $-CH_2-CH_2OC\underline{H}_3$), 1.0 (S, 3H, $-CH_3$), and 0.78 (S, 3H, $-CH_3$); MS M^+ 240.2093 (calcd. for $C_{15}H_{28}O_2$; 240.20904).

<u>Anal</u>. Calcd. for $C_{15}H_{28}O_2$: C, 74.93; H, 11.75;
Found: C, 74.87; H, 11.66.

<u>2-(2-Methoxyethyl)-5-(3-methoxypropyl)-6,6-dimethyl-2-cyclohexenone (41)</u>

At -78°C, ozone (condition: E=80V; air inlet = 8 psi, ozone outlet = 0.06 psi) was allowed to pass through a solution of the diether <u>40</u> (135 mg, 0.56 mmole) in dichloromethane (15 ml) until a light blue colour was retained (5 minutes). Triphenylphosphine (0.73 g, 2.78 mmole) was added to the solution under an argon atmosphere.

The mixture was allowed to warm to 25°C and stirred for four hours. After removal of the solvent, the crude keto aldehyde <u>58</u>, without purification, was dissolved in benzene (15 ml). *p*-Toluenesulfonic acid (215 mg, 1.24 mmole) was added and the mixture refluxed for two hours with continuous removal of water using a Dean-Stark water separator. The reaction mixture was diluted with water (50 ml) and extracted with diethyl ether (4 x 40 ml). The organic solution was washed with saturated aqueous solution of sodium bicarbonate (40 ml), dried with magnesium sulfate, filtered and concentrated. Flash chromatography, using 20% ethyl acetate in petroleum ether, afforded the pure enone <u>41</u> (58 mg, 40% yield): ir 1670 cm^{-1} (ketone C=O) and 1120 cm^{-1} (ether); nmr 6.30 (br.m, 1H, -HC=), 3.34 (S, 3H, $-CH_2-CH_2OC\underline{H}_3$), 1.15 (S, 3H, $-CH_3$), and 0.95 (S, 3H, $-CH_3$); MS M^+ 254.1871 (calcd. for $C_{15}H_{26}O_3$: 254.18828).

<u>Anal.</u> Calcd. for $C_{15}H_{26}O_3$: C, 70.81; H, 10.30;

Found: C, 70.98; H, 10.15.

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