A TOTAL SYNTHESIS OF (±)-*trans*-CHRYSANTHEMIC ACID

A Dissertation

Presented to

the Faculty of the Department of Chemistry

College of Natural Sciences and Mathematics

University of Houston

In Partial Fulfillment

of the Requirement for the Degree

Doctor of Philosophy

by

Theresa Ann Valdes

August 1976

To my mother and father

my brothers, Oscar and Raphael

and to Jessie....

ACKNOWLEDGEMENTS

I wish to express my gratitude to my research advisor Dr. S. C. Welch for suggesting and funding this research project, and for his guidance and patience during the course of this work.

I am also grateful to the members of my committee and to Dr. J. Cox for their support, their help and their time.

Very particularly, I am indebted to my lab partners Dr. P. Rao and Dr. J. W. Trotter for their suggestions and help; to Mr. Chou, Mr. Chayabunjonlerd and Mr. Walters for their cooperation and in a very special way to Dr. J. Han Kim and Mr. Ping Sun Chu without whose assistance and moral support this dissertation may not have been written.

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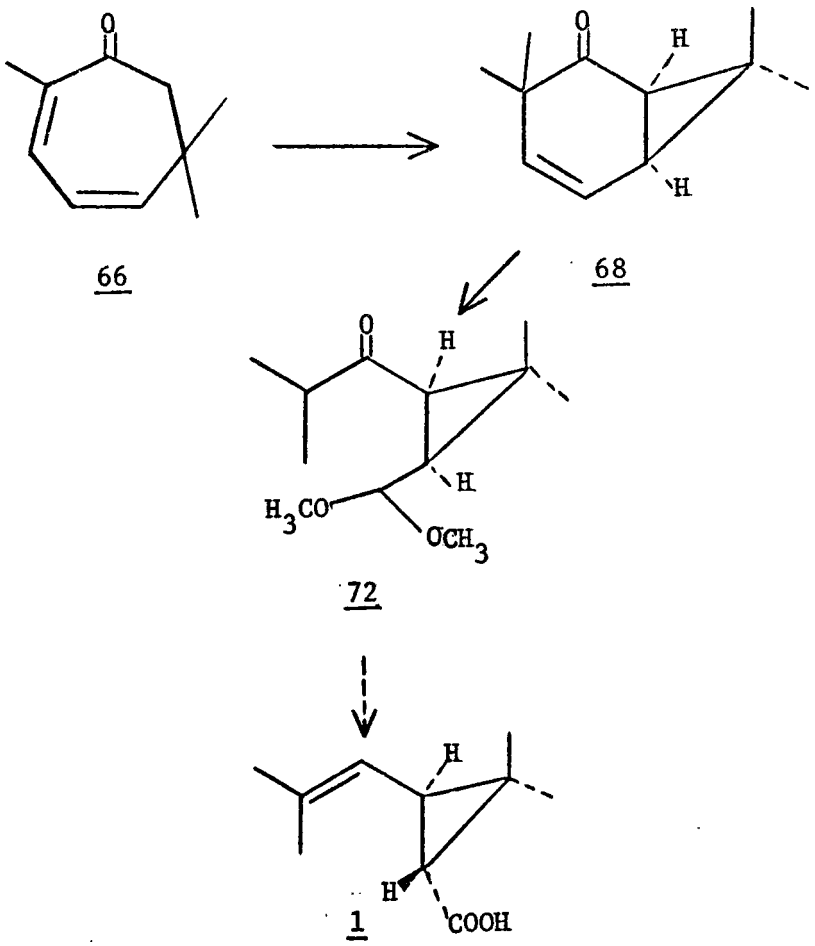
ABSTRACT

The total synthesis of (±)-trans-chrysanthemic acid (1) from eucarvone (66) via intermediate Δ^2-4-methylcaren-5-one (68)is discussed. The present synthetic scheme proceeds by ozonolysis of carenone 68 to a key intermediate, keto-acetal 73. Reductive elimination of the enol diethyl phosphate of acetal 73 leads to olefin aldehyde 58 which is ultimately oxidized to (±)-trans-chrysanthemic acid.



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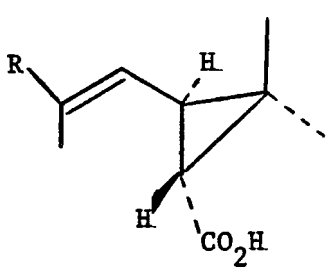
CHAPTER I

INTRODUCTION

INTRODUCTION

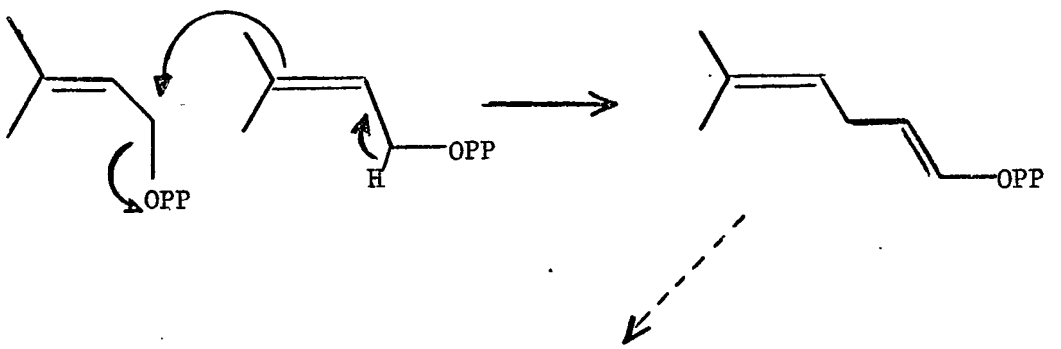
Monoterpenoid substances which are biogenetically derived from two isoprene units are widely distributed in a variety of living systems such as plants, microorganisms and insects. Some of these compounds exhibit important functions within living organisms, others show equally important external physiological activities. These substances derived from geranyl pyrophosphate make up a large family of compounds which are important components of the essential oils obtained from the leaves, roots and bark of various plants. They have pleasant odors and many are of some industrial importance. The monoterpenoids may be divided into three classes having zero, one or two rings. Other subdivisions are made on the basis of their carbon skeleton. The acyclic monoterpenoids are comparatively few in numbers, but they include some of the most important isolates in perfumery.

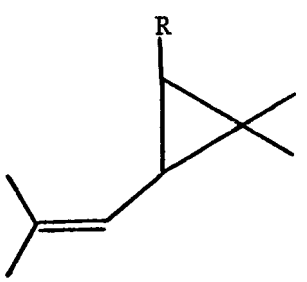
Some irregular monoterpenes whose carbon skeleton do not obey the isoprene rule are found in Compositae plants. Chrysanthemum monocarboxylic acid (1) and the related pyrethric acid (2) occur as insecticidal esters in Chrysanthemum cinerariaefolium[1,2]



1 R = CH_3 2 R = CO_2Me

The two acids represent the only examples of naturally occurring monocyclic monoterpenes containing cyclopropane ring structures.[3] The carbon frameworks in these monoterpenes are derived biogenetically by an unusual 'tail-to-middle' combination of iso-pentane units.[4] The resulting structure thus arises by the dimerization of two methallyl residues, with the added feature of a cyclization producing the three membered structure 3.





3

a: R = CH_2OPP; b: R = CH_2OH

The unusual linkage, and the analogous structure of chrysanthemum monocarboxylic acid to 'presqualene' has suggested a biogenetic relationship with irregular acyclic terpenes. Formal cleavage of the cyclopropane ring, in the three ways indicated (Fig. 1) leads to 3-ethyl-2,5-dimethylhexyl (santolinyl) (4), 2,5,5-trimethylheptyl (artemisyl) (5), and 2,3,6-trimethylheptyl (lavandulyl) (6), skeletons.[6]

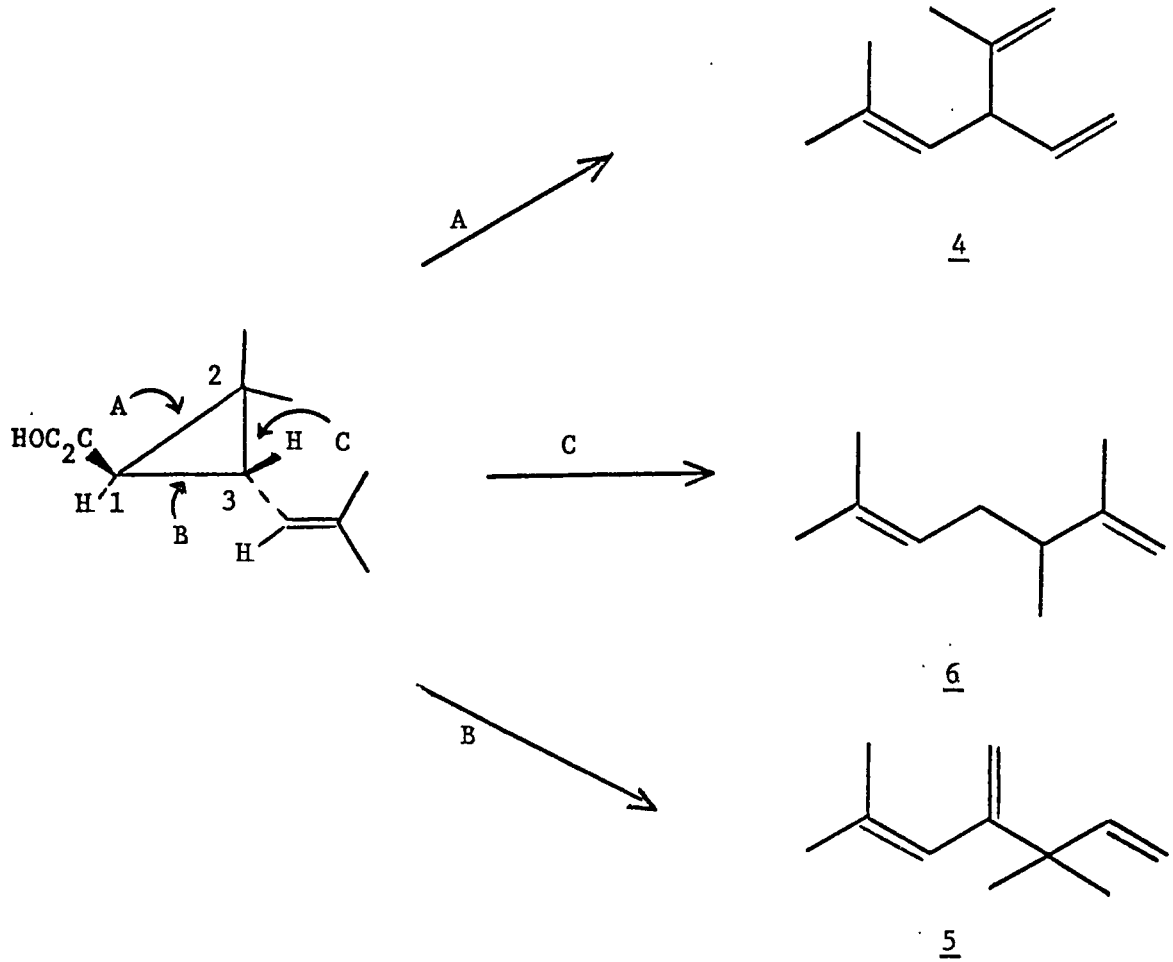
Several groups[7,8] have suggested the possibility that chrysanthemyl alcohol (3b), as its pyrophosphate, might give rise to a carbonium ion which could lead to artemisia compounds or santolina triene, and such types occur together in Santolina chamaecyparissus. However, by suitable adjustment of the functional groups in chrysanthemic acid (1) each of the bonds A - C can be made to rupture chemically in carbonium ion reactions leading to compounds having santolinyl, artemisyl and lavandulyl skeletons.[9]

Upon treatment of (±)-trans-dihydrochrysanthemyl alcohol (7), (R = R' = H) with thionyl chloride at 0° the 1,2-cleavage (A) occurs to yield the santolina diene (9). The same 1,2-rupture takes place upon distillation of the (±)-tertiary alcohol 8 (prepared by a Grignard reaction from (±)-trans-dihydrochrysanthemic ester). Decomposition leads to the formation of santolina diene (10). In each of these chemical examples, homoallylic carbonium-ion fission proceeds to the tertiary center causing 1,2-cleavage A.[6]

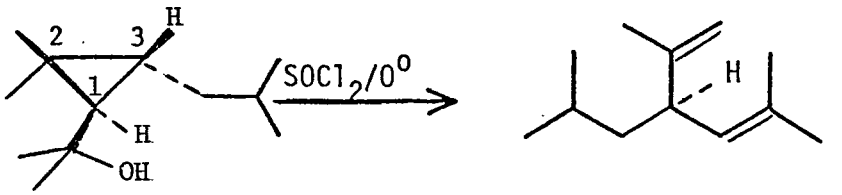
When the unsaturated 2-methylpropenyl side chain is unaltered the 1,3-cleavage B occurs in carbonium ion reactions. Both (±)-cis-(11) and (±)-trans-chrysanthemyl alcohol (12) and also the methyl ester 13

FIGURE I

BIOGENETIC RELATIONSHIP WITH IRREGULAR ACYCLIC TERPENES

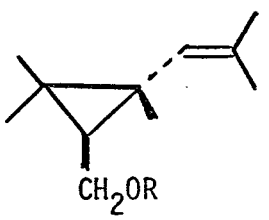


gave trans-artemisia triene (15)[10] when heated with p-toluenesulfonic acid in benzene. In this type of homoallylic cleavage 1,3-opening (B) to

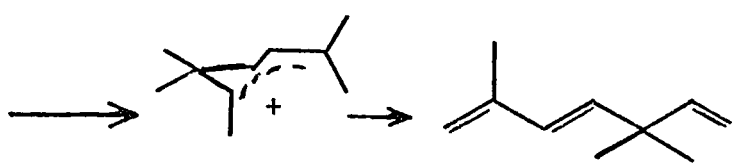


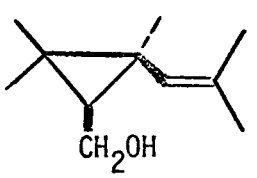
7 $R^1 = R^2 = H$; 8 $R^2 = R^1 = Me$ 9

10



12 R=H; 13 R=Me





11 14 15

give tertiary allylic cation 14 is preferred to the 1,2-opening found in the compounds with a saturated side-chain. The fact that only trans-triene 15 was obtained, whether cis- or trans-chrysanthemyl alcohol is used shows that a transition state leading to trans-3-olefin is much less hindered than that leading to cis-3-olefin. This is so in both cis- and trans-cyclopropanes, hindrance being caused by the gem-dimethyl groups in either case.

Rupture of the 2,3-cyclopropane bond (C) in chrysanthemyl systems can be induced, with carbonium-ion initiation, by suitable functional groups in the methylpropenyl side-chain to yield monoterpenes with a lavandulyl skeleton. Thus when the hydroxy-ester 16

(as either the cis- or the trans-isomer) is heated with p-toluenesulfonic acid the trans-triene ester 18 is formed in 60% yield.[12] A further example of the lavandulyl type of cleavage occurs when diol 17 is heated with p-toluenesulfonic acid in benzene. In this case cleavage A, B, and C are possible. Five components have been detected in reaction products, but under the conditions mentioned the major compound (47% of mixture) is product 19. A second substantial product (34%) is reported to be structure 20, derived by internal trapping of the carbonium ion.[13] (Fig. 2)

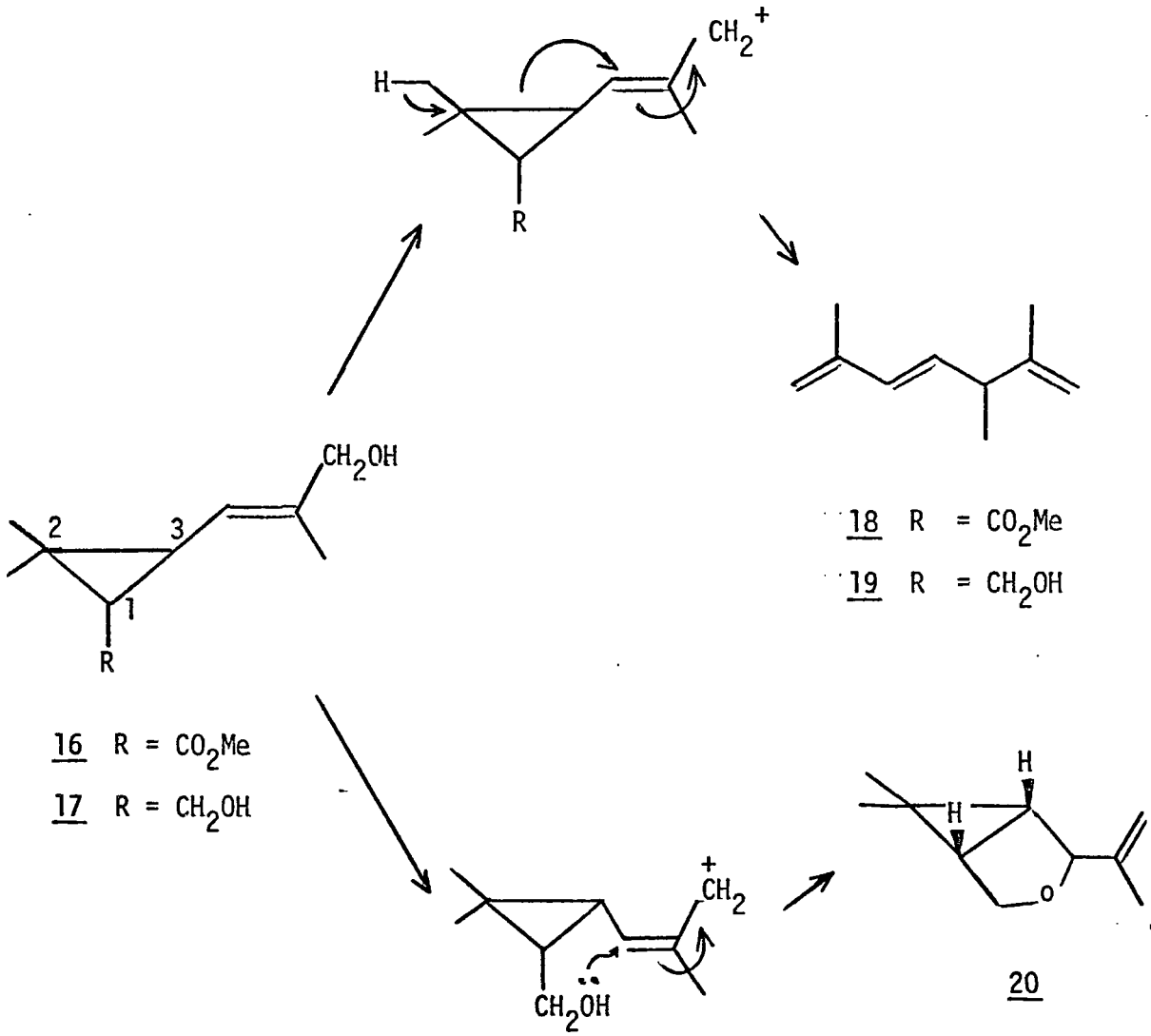
Other more recent reports[14,15] are also in accordance with, and their findings lend support to the suggested biogenetic pathways which link chrysanthemyl to the acyclic artemisyl, santolinyl and lavandulyl monoterpenes.

Furthermore, the results[16] of feeding experiments with ^{14}C chrysanthemic monocarboxylic acid in C. cinerariaefolium link the two acids 1 and 2, biogenetically and show that acid 2 (and the corresponding natural esters) can be derived from acid 1 (and the corresponding natural esters) in Nature by an oxidative-esterification sequence at the vinyl methyl group of acid 2.[16]

In 1924 Staudinger and Ruzicka[17] published results of a detailed chemical study of the insecticidal principles (pyrethins) of pyrethrum flowers and deduced that there were two kinds of esters, i.e., esters of (+)-trans-chrysanthemic acid (1) and (+)-trans-pyrethric acid (2). Six compounds are now recognized as being responsible for the insecticidal activity of pyrethrum extract: these naturally

FIGURE 2

LAVANDULYL CLEAVAGE

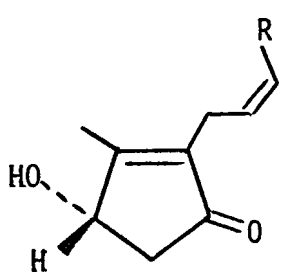


occurring esters, cinerin I (20), jasmolin I, (21), pyrethrin I, (22), are known collectively as "pyrethrin I's"; and cinerin II, (23), jasmolin II, (24), and pyrethrin II (25) grouped as the "pyrethrin II's".[18] (Fig. 3)

Degradation of the mixed esters gives a mixture of alcohols, the rethrolones, cinerolone, (26a), jamololone, (26b), pyrethrolone (26c) and of the acids chrysanthemic (1) and pyrethric (2).[19]

The pyrethrin family of insecticides, e,g, pyrethrin I (22), has attracted considerable attention.[19,20] The combination of insecticidal properties, knock-down effect, low mammalian toxicity and their ready biodegradability contrasts favorably with some of the more vilified methods of insect control. Hence, the chemical research on pyrethrins and their analogs has been pursued both, from the synthetic, as well as from their biological aspects.

Staudinger and Ruzicka[21] reported the synthesis of acids structurally related to chrysanthemic acid (1) and their esterification with pyrethrolone; also the synthesis of alcohols analogous to



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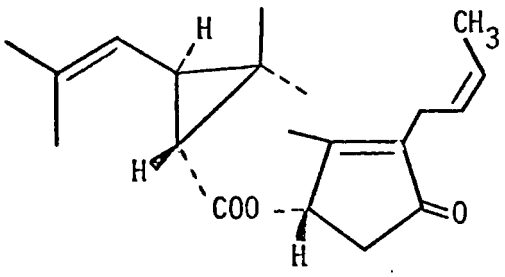
a: R = $-CH_3$

b: R = $-C_2H_5$

c: R = $-CH{=}CH_2$

FIGURE 3

ACTIVE INSECTICIDES OF PYRETHRUM EXTRACTS



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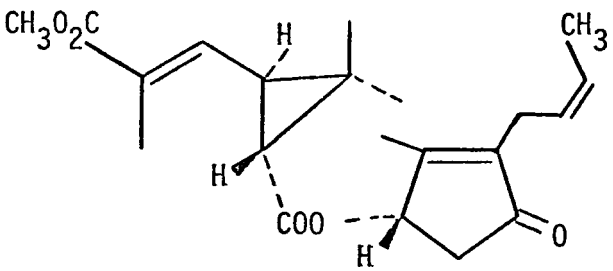

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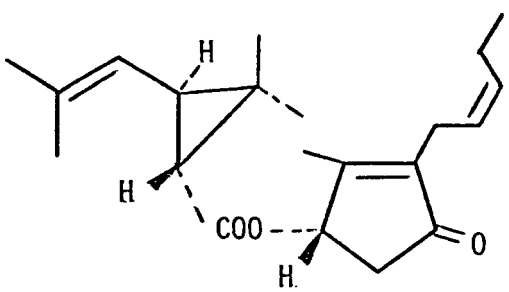

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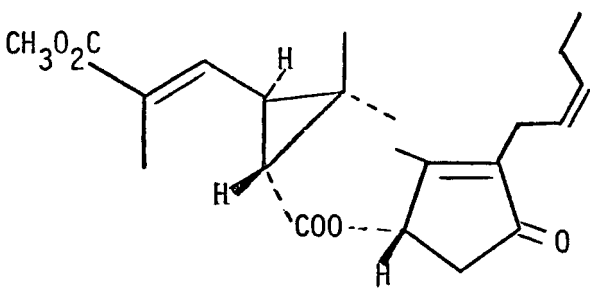

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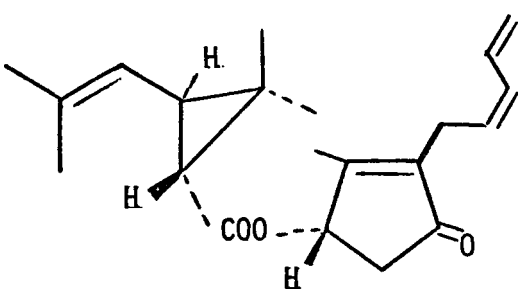

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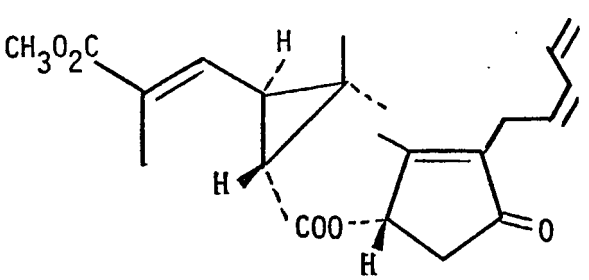

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pyrethrolone and their esterification with chrysanthemic acid. The result of biological studies on these synthetic esters showed that some of them possess toxicity comparable to the natural pyrethrin.

The synthesis of the chrysanthemic acid ester of allyl-rethrolone or allethrolone was reported by Schechter et al.[21] The acid ester known as "allethrin" was found to be as effective on Musca domestica L. (houseflies) as natural pyrethrins. "Allethrin" (26) is now produced commercially as a mixture of (±)-trans-and (±)-cis-chrysanthemic acid esters of (±)-allethrolone consisting of four racemates (eight isomers).

The marked difference in the toxicity of these stereoisomers to houseflies is directly related to the stereoisomerism of the ester.[22] (Table I)

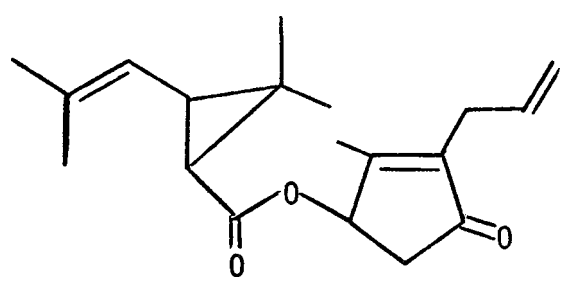

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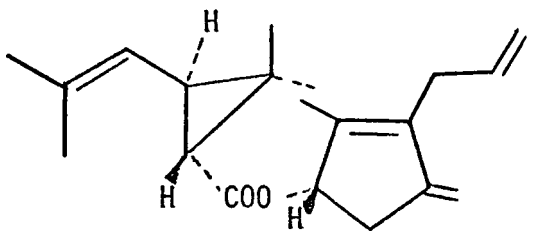
TABLE I

INSECTICIDAL ACTIVITY OF ISOMERS OF ALLETHRIN[23]

Alcohol Allethronyl	Acid chrysanthemate	Relative toxicity to *Musca domestica* L.
(+)	(+)-trans	100
(+)	(-)-trans	4
(-)	(+)-trans	17
(-)	(-)-trans	0.7
(+)	(+)-cis	53
(+)	(-)-cis	6
(-)	(+)-cis	10
(-)	(-)-cis	1.7

From this data, it is evident that the stereostructure of the acid moiety exerts more effect on toxicity than that of the alcohol moiety.

It is noteworthy that the most toxic allethrin, (+)-alcohol ester of (+)-trans-acid, has the same absolute configuration as natural pyrethrins.



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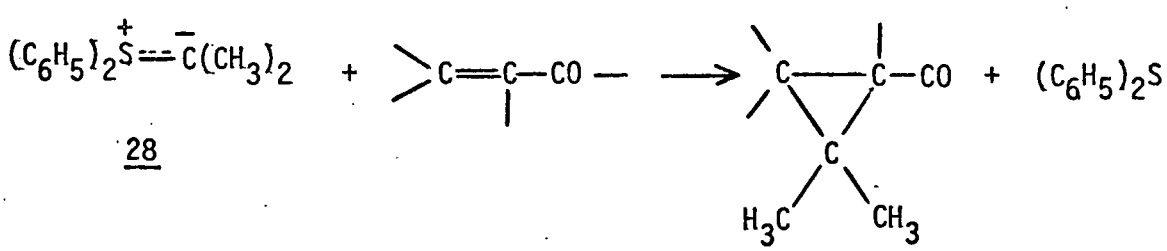
A more recent observation,[24] that simpler derivatives of (+)-trans-chrysanthemic acid (1) show even higher insecticidal activity than the natural esters, has focused attention on new synthetic approaches to this acid.

An ingenious and highly stereospecific approach to (±)-methyl trans-chrysanthemate has been reported by Corey and Jantelat[25] via a sulfur ylide. This method describes a novel and direct route to the gem-dimethylcyclopropane system using the reaction of the highly reactive sulfur ylide diphenylsulfonium isopropylide (28) with conjugated carbonyl compounds.



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Thus, reaction of the isopropylidene transfer reagent 28 with methyl 5-methyl-trans-2,4-hexadienoate (29), prepared by reaction of methallyl chloride, acetylene, and methanol in the presence of nickel carbonyl followed by treatment with sodium methoxide, cleanly affords (±)-methyl trans-chrysanthemate (30). (Figure 4)

Although other syntheses of the racemic acid have been reported,[26-28] and its resolution the subject of several patents,[29] a very attractive approach has been the conversion of (+) Δ^3-carene (31) to trans-chrysanthemic acid (1) by different methods. Carene (31) contained in considerable amounts in turpentine from Pinus sylvestris L. and Pinus Longifolia Roxb., had found no application in chemical synthesis until Matsui and coworkers[30] reported a selective synthesis of optically pure (+) and (-) trans-chrysanthemic acids from (31). (Figure 5) The transformation proceeds via a keto-aldehyde (32), previously obtained by Semmler and von Schiller[31] by ozonolysis of carene (31). (The same keto-aldehyde is later reported as the starting material in the synthesis of cis-homochrysanthemic acid by T. Sasaki and coworkers.[32]) Cyclization of keto-aldehyde 32 by aldol condensation in the presence of sodium acetate in acetic anhydride gave the conjugated ketone 33. Ozonolysis of enone 33 followed by aqueous alkaline hydrogen peroxide work-up yielded pure (+)-cis-homocaronic acid (34), which was converted to the anhydride 35 by heating in excess acetic anhydride. The anhydride was treated with two moles of methylmagnesium iodide in anhydrous ether. In the work-up the aqueous layer was acidified and extracted with ether. The ether extracts washed with 5% sodium carbonate and evaporated

FIGURE 4

COREY AND JANTELAT'S SYNTHESIS OF (±)-trans-CHRYSANTHEMIC ACID

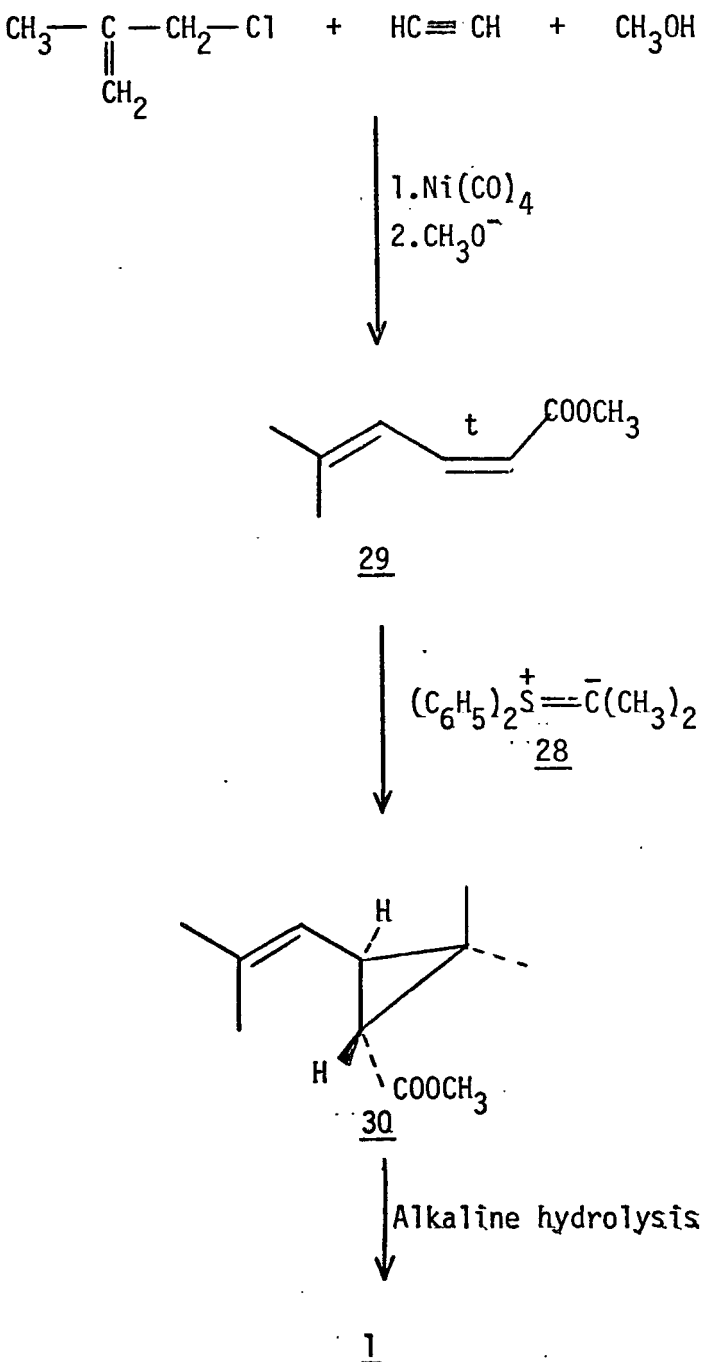
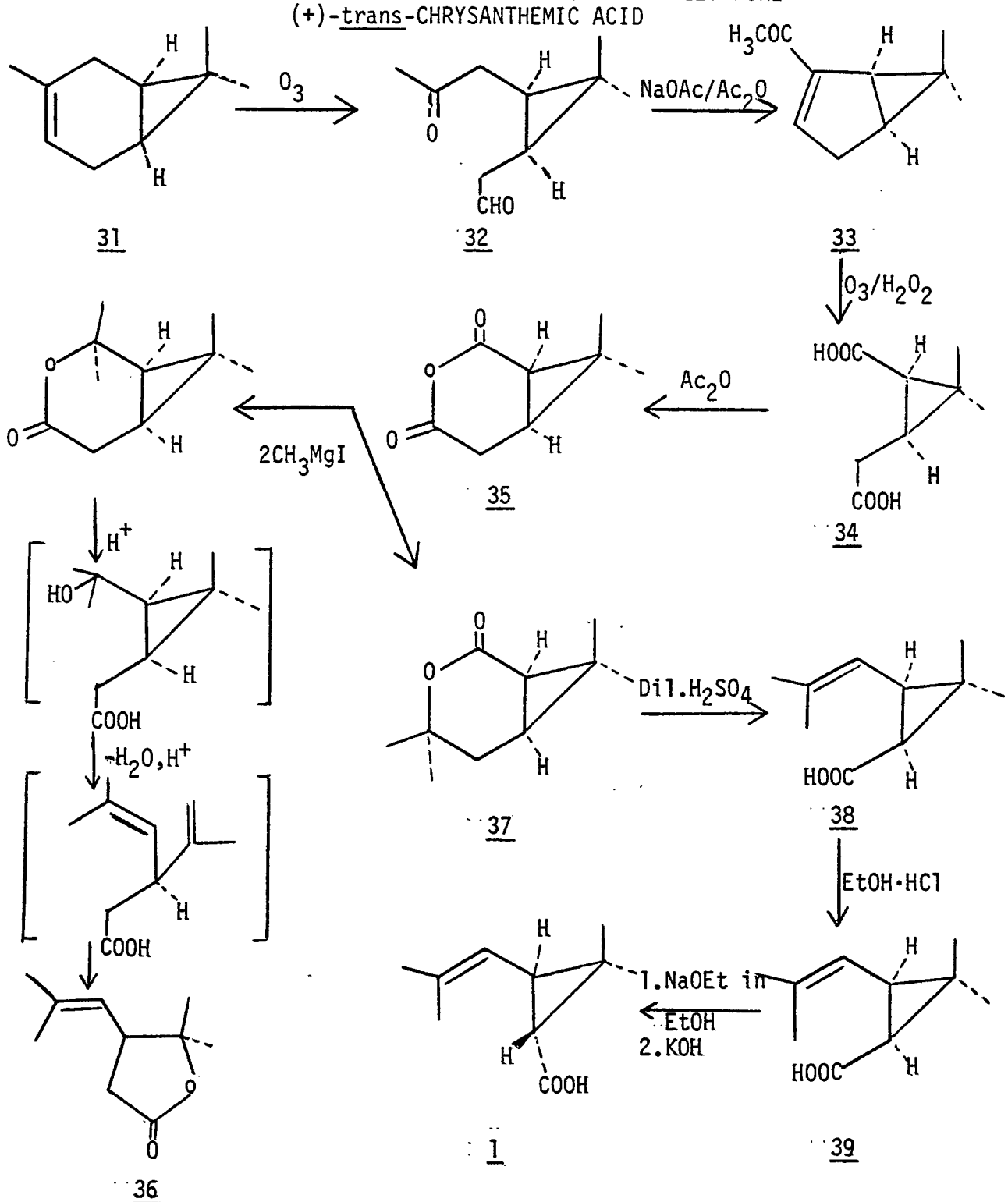


FIGURE 5

MATSUI AND COWORKERS' SYNTHESIS OF OPTICALLY PURE
(+)-trans-CHRYSANTHEMIC ACID

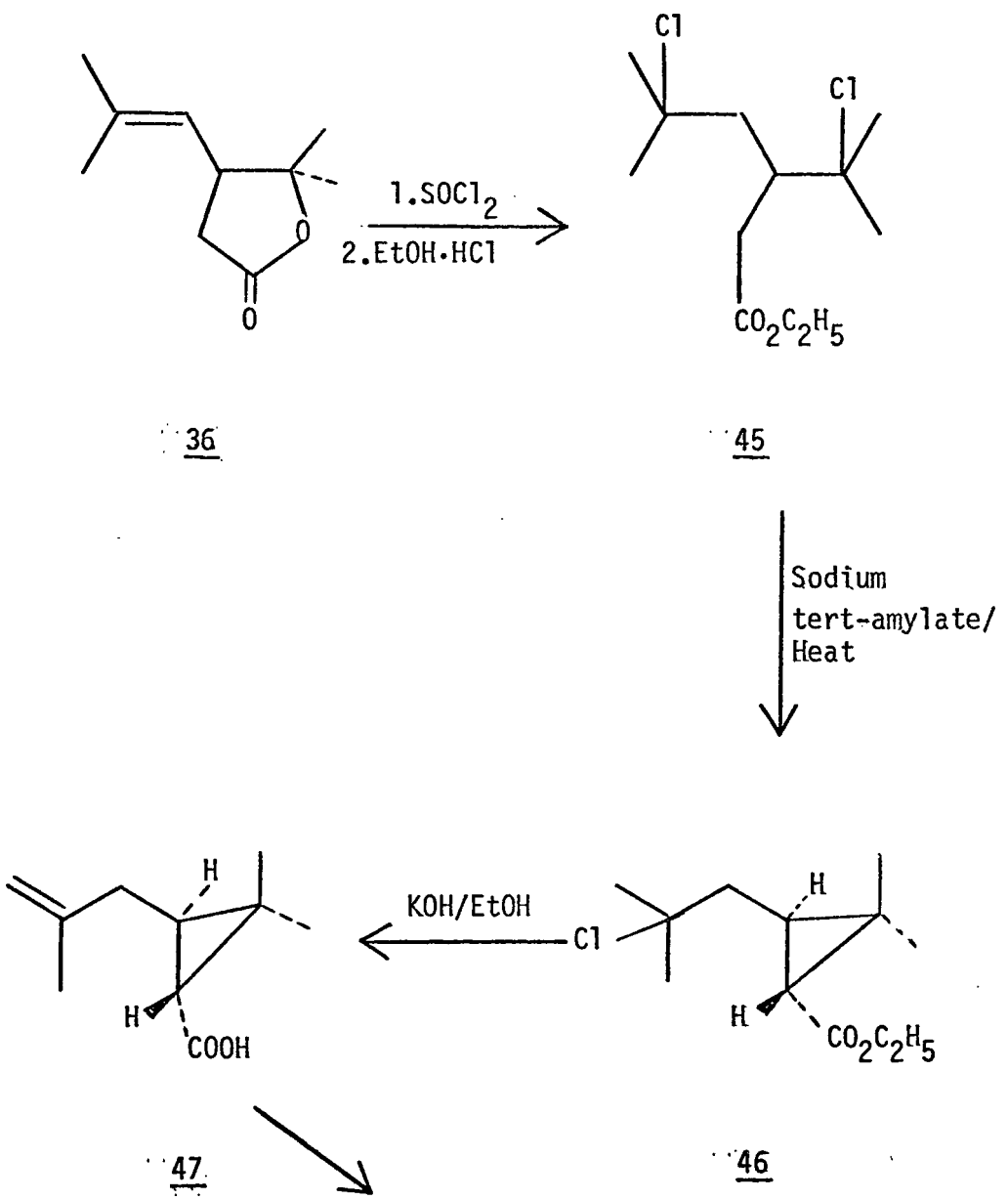


to yield the δ-lactone 36 . Acidification of the aqueous sodium carbonate layer from which lactone 36 was separated gave an oily viscous product which after refluxing with a catalytic amount of p-toluenesulfonic acid afforded δ-lactone 37 . Lactone 36 was found to be identical with (+)-pyrocine. Lactone 36 (Figure 6) has previously been utilized by the same authors in an earlier synthesis[33] of the same acid 1 following a procedure based upon the cyclization method of Julia[34] via intermediates 45 and 46. Lactone 37 was proven to be identical with authentic (-)-dihydrochrysanthemolactone earlier obtained by Harper's[35] method from (-)-cis-chrysanthemic acid. Treatment of compound 37 with dilute sulfuric acid according to the procedure accomplished by Harper[35] easily gave (-)-cis-chrysanthemic acid (38). Ethyl (-)-cis-chrysanthemate (39), prepared from intermediate 38 with 2% ethanolic hydrogen chloride, was treated with a catalytic amount of sodium ethoxide in absolute ethanol in a sealed tube at 180° C for two hours. Subsequent hydrolysis of the product with potassium hydroxide afforded optically pure (+)-trans-chrysanthemic acid (1).

Matsui and coworkers also describe the synthesis of (-)-trans-chrysanthemic acid (Figure VII) by treatment of keto-aldehyde 32 with sodium acetate, followed by separation from enone 33 to give the aldehyde enol-acetate 40. Ozonolysis of enol-acetate 40, followed by reductive work-up gave pure cyclopropyl keto-aldehyde 41. This aldehyde was easily oxidized with aqueous alkaline potassium permanganate to the corresponding carboxylic acid 42, which was esterified to ester

FIGURE 6

MATSUI AND COWORKERS' SYNTHESIS OF (±)-trans-CHRYSANTHEMIC ACID FROM (±) PYROCIN



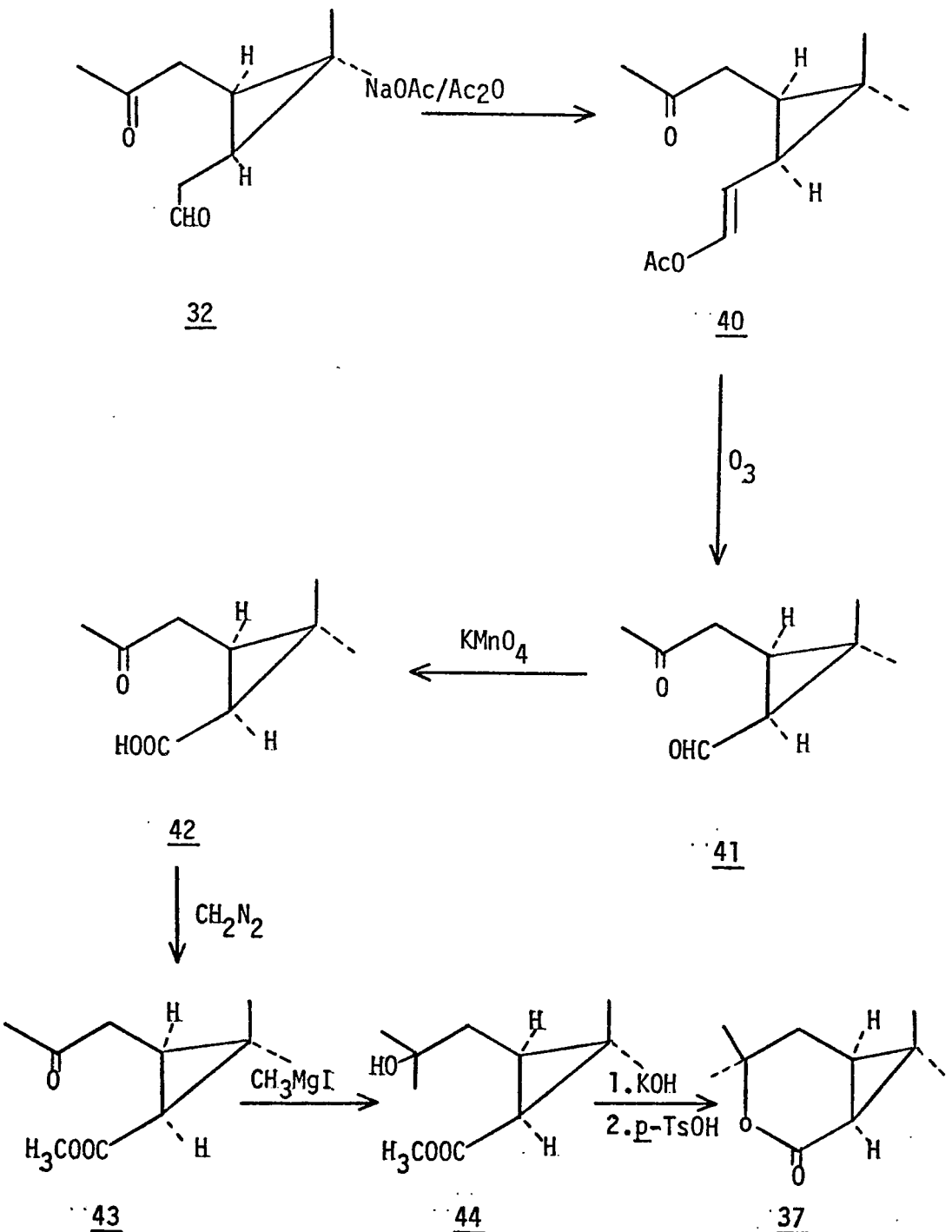
36 45

47 46

1

FIGURE 7

MATSUI AND COWORKERS' SYNTHESIS OF OPTICALLY PURE
(-)-trans-CHRYSANTHEMIC ACID



32 40 42 41 43 44 37

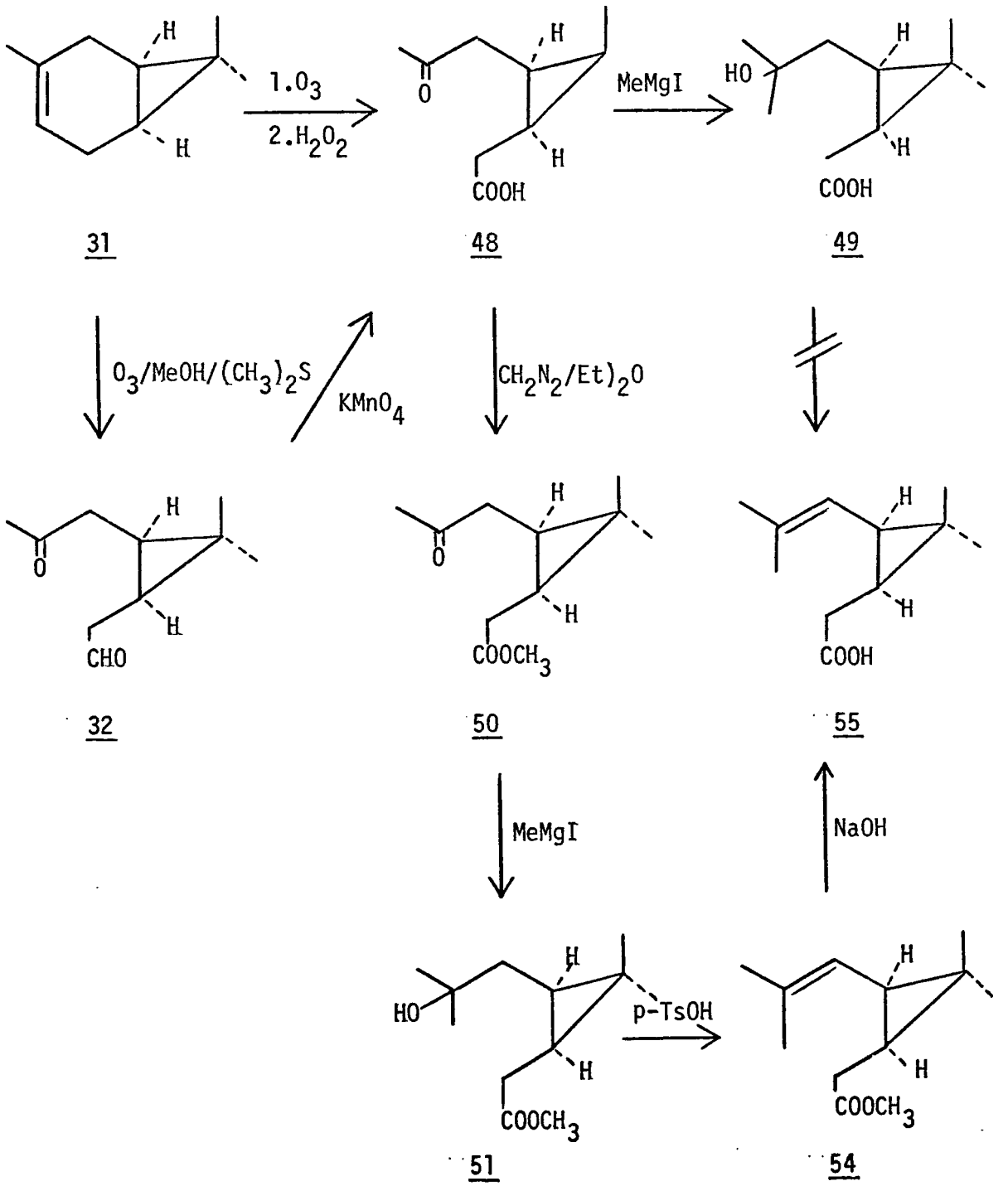
43 with ethereal diazomethane. Addition of methylmagnesium iodide to ester 43 afforded, after chromatographic separation, hydroxy ester 44. Hydrolysis of this compound with methanolic potassium hydroxide and subsequent lactonization of the acidic product with p-toluenesulfonic acid led to the formation of (+)-dihydrochrysanthemolactone (37). By the same procedure already mentioned lactone 37 was transformed to optically pure (-)-trans-chrysanthemic acid.

A later work by Matsui and coworkers[36] (Figure 7) reported the stereospecific synthesis of optically pure (+)-trans-chrysanthemic acid from Δ^3-carene (31) by the procedure formerly described by the authors using corresponding racemic compounds.

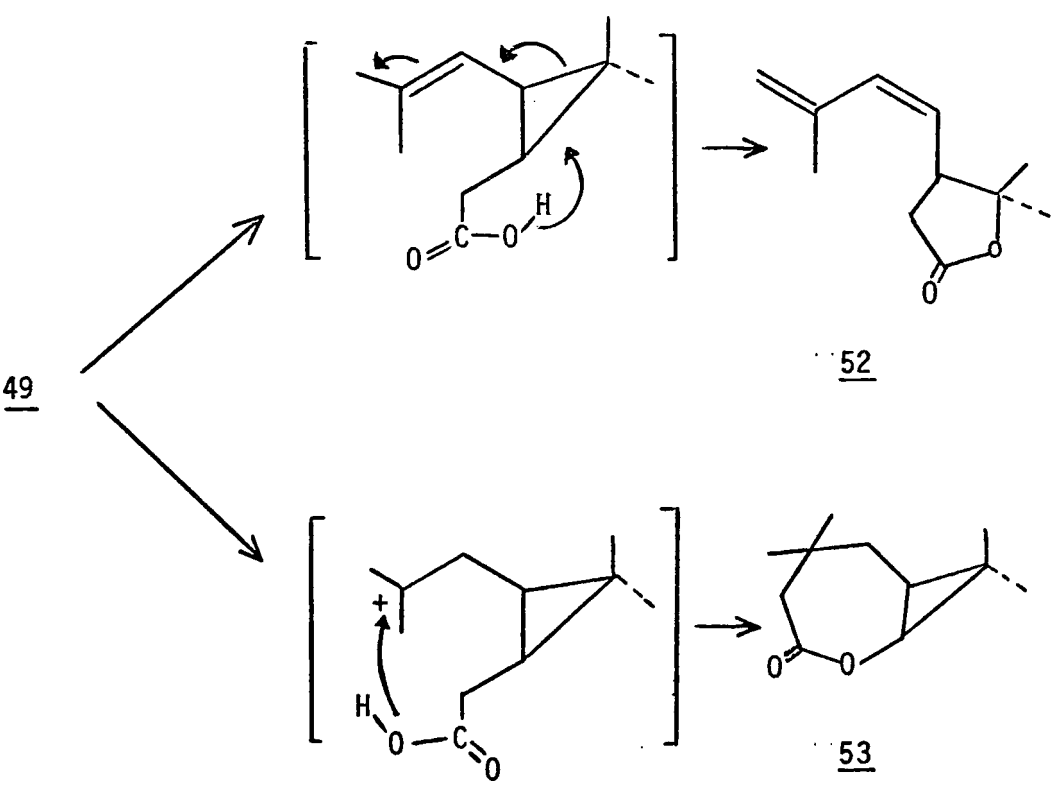
Sasaki and coworkers[32] have reported a synthesis of cis-homochrysanthemic acid from Δ^3-carene (31) via aldehyde 32 previously prepared by Matsui[30]. (Figure 8) The results of their work support some mechanistic explanations previously proposed by Matsui for the simultaneous cyclopropane-ring opening in the dehydration reaction of the hydroxy acid 49 or the hydroxy ester 51. By modification of the ozonolysis method of Semmler and Schiller[32] they obtained the keto-acid 48 directly from Δ^3-carene, but in low yield. Instead, keto-acid 48 was prepared via keto-aldehyde 32 by the procedure of Pappas and Keaveney.[37] This aldehyde was readily convertible to keto-acid 48 by the action of potassium permanganate. Keto ester 50 obtained from keto-acid 48 by esterification with diazomethane was converted to hydroxy-ester 51 by the Grignard reaction. The ester was also prepared by esterification of acid 49, which was similarly obtained in 90%

FIGURE 8

SASAKI AND COWORKERS' SYNTHESIS OF cis-HOMO-CHRYSANTHEMIC ACID



yield by Grignard reaction of the keto-acid with 2 equivalents of methylmagnesium iodide. The plan was to dehydrate the tertiary hydroxy group of intermediates (49) and (51) to give an isobutenyl group but treatment of alcohol 48 with a catalytic amount of p-toluenesulfonic acid resulted in opening of the cyclopropane ring to afford δ-lactone 52. However, when alcohol 48 was treated with phosphorus oxychloride in dry pyridine at 0°C the product was characterized as a seven-membered ring lactone 53. In all cases,[30] homochrysanthemic acid was shown to be more labile towards acid. The direct conversion of the hydroxy acid 49 to homochrysanthemic acid (55) has been reported to be unsuccessful. When the hydroxy ester 51 was heated with p-toluenesulfonic acid at reflux, the

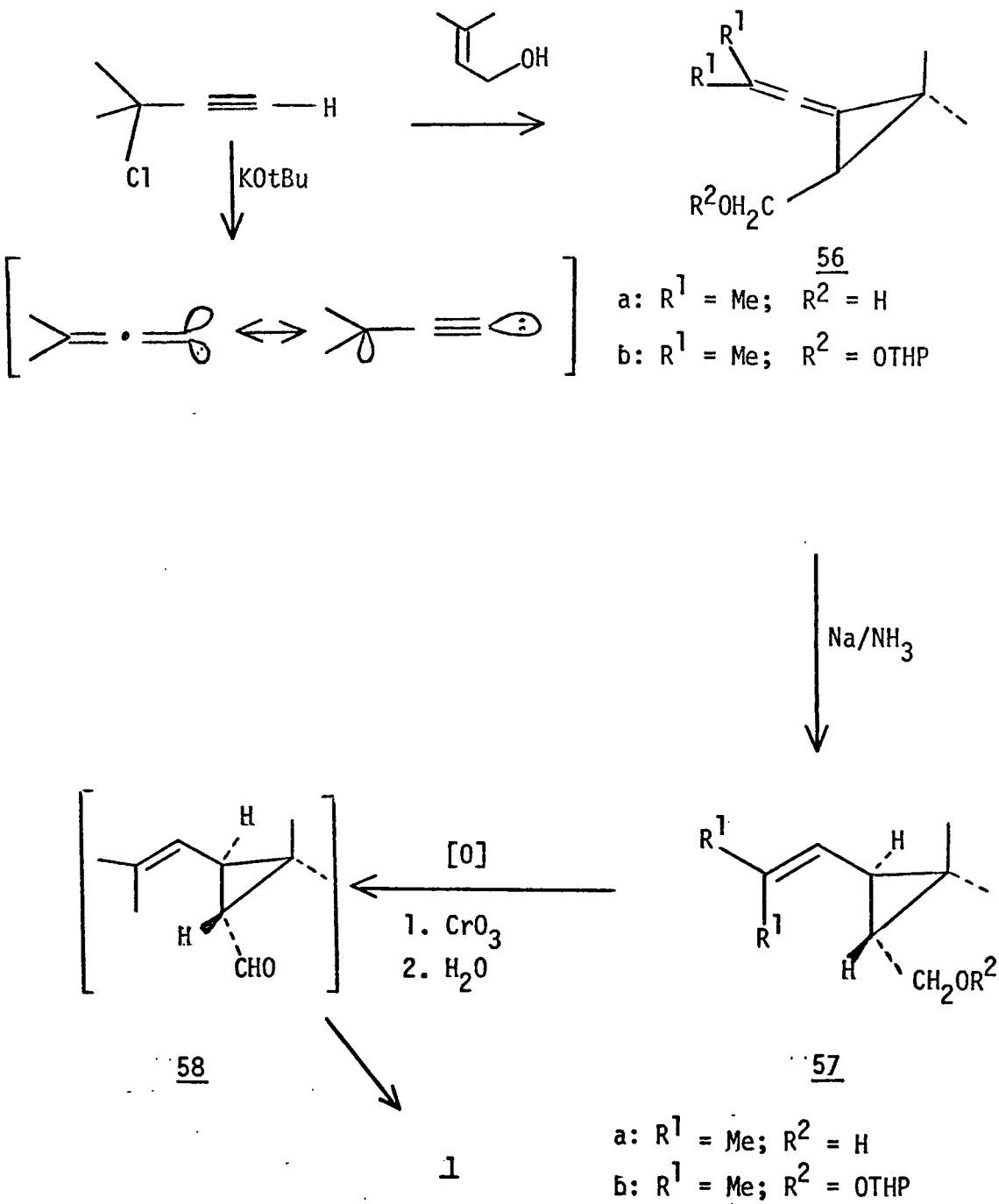


product was found to be a mixture of methyl homochrysanthemate (54) and homochrysanthemic acid (55), produced by hydrolysis of the former. The best method for dehydration of alcohol 51 is treatment with phosphorus oxychloride in dry pyridine at 0°C. Pure ester 54 was obtained in a 51% yield; the corresponding acid 55 was obtained by alkaline hydrolysis of ester 54.

Raphael and coworkers[38] (Figure 9) have reported a stereoselective route to trans-chrysanthemic acid via allene cyclopropane 56 generated by the base catalyzed interaction of 3-chloro-3-methylbut-1-yne and 3-methylbut-2-en-1-ol. The chloride was previously shown[39] to produce an allenyl carbene upon treatment with potassium tert-butoxide. The formation of this entity has been demonstrated by trapping with various ethyleneic hydrocarbons, whereby allene cyclopropanes are formed by electrophilic attack. It is reported that when the carbene acceptor is the double bond of 3-methylbut-2-en-1-ol there is produced allene cyclopropane 56 possessing precisely the carbon skeleton of chrysanthemic acid. The required regioselective reduction of allene 56 was achieved by treatment with sodium metal in liquid ammonia which gave chrysanthemyl alcohol 57 in high yield. The cis- and trans-diastereoisomers were formed in 25:75 ratio, respectively. The author's rationalization for this selectivity involves intramolecular participation of the pendant hydroxy-group, which is conveniently placed to affect proton transfer to the carbonionic center of an initially produced radical anion. Such a process would lead to trans-stereochemistry in the product. Support for this directing role

FIGURE 9

RAPHAEL AND COWORKERS' STEREOSELECTIVE SYNTHESIS OF
trans-CHRYSANTHEMIC ACID



of the hydroxy-group was demonstrated by the investigators by carrying out the reduction on the tetrahydropyranyl ether 57b . Reduction was again reported to be regioselective but no longer stereoselective. Hydrolysis of the product gave a 1:1 mixture of cis- and trans- chrysanthemyl alcohols. The oxidation of alcohol 57a at room temperature with chromium trioxide in pyridine gave the corresponding aldehyde 58, which was further oxidized to the carboxylic acid 1 by addition of water. Structural variations in the starting chloracetylene and allyl alcohol are reported to give analogues of chrysanthemic acid. This stereoselective synthesis exhibits the novel feature that both isoprenoid 'halves' of the molecule are derived from the same readily available starting material.

Recently Cocker and coworkers[40] (Figure 10) have reported a two-stage method to obtain cis-homocaronic acid (34) via ozonolysis (+)-4α-acetoxymethylcar-2-ene (59a) and (+)-4α-acetylcar-2-ene (59b), both readily obtainable in high yields from (+)- Δ^3-carene (31). Reaction of the ozonolysis products with alkaline hydrogen peroxide gave (+)-cis-homocaronic acid (34), which leads[37] to (-)-cis-chrysanthemic acid from which (+)-trans-chrysanthemic acid (1) is obtainable.[36]

Two new and more efficient routes for the conversion of the readily available (+)- Δ^3-carene into (+)-chrysanthemic acid, closely related in method, are described by Sobti and Dev[41] and Gopichand and coworkers.[42] (Figures 11 and 12) The pathway described by Sobti and Dev provides the key intermediate (-)-dihydrochrysanthemolactone (37)

FIGURE 10

COCKER AND COWORKERS TWO-STAGE SYNTHESIS OF
(+)-cis- HOMOCARONIC ACID

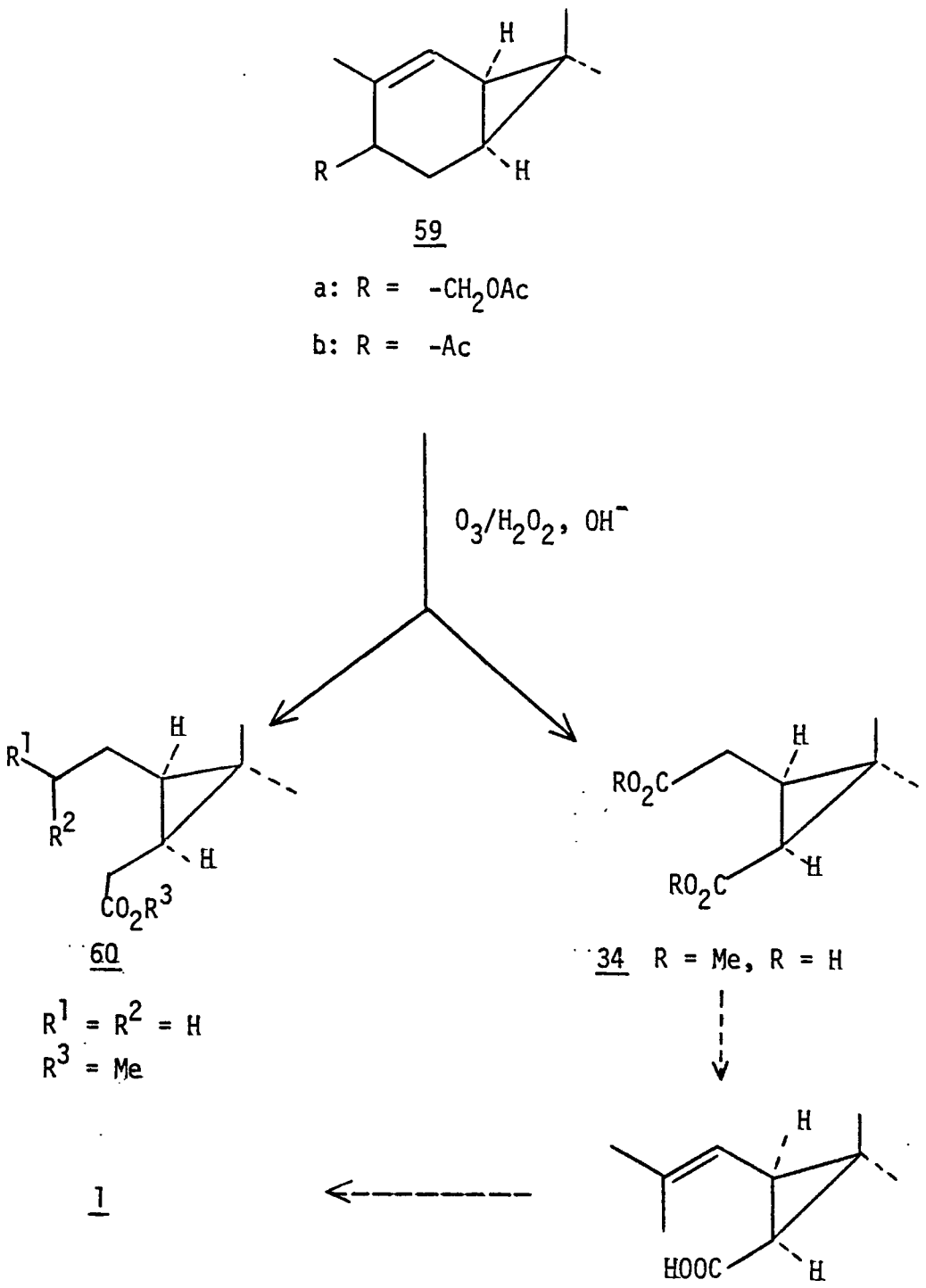
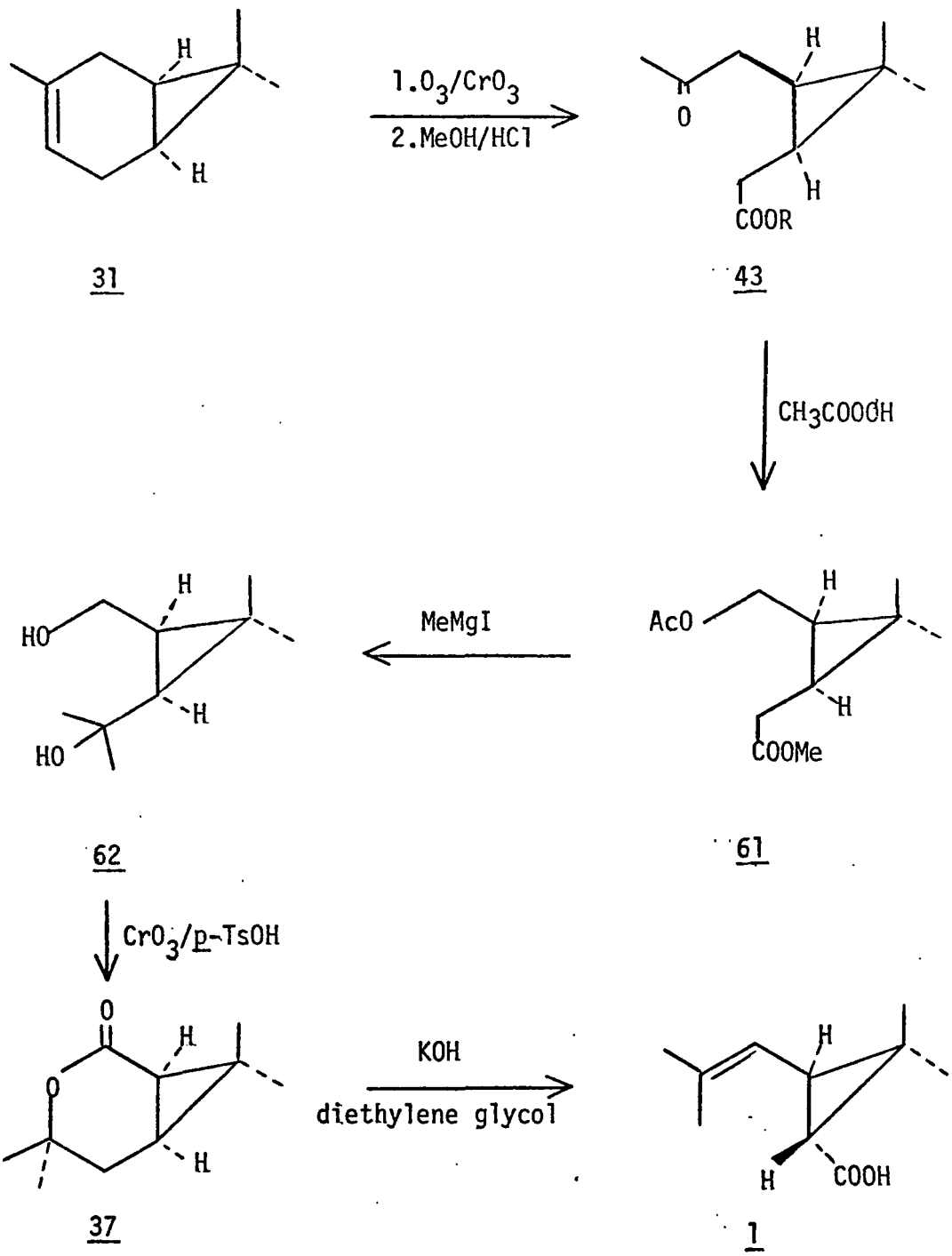


FIGURE 11

SOBTI AND DEV'S SYNTHESIS OF (±)-trans-CHRYSANTHEMIC ACID



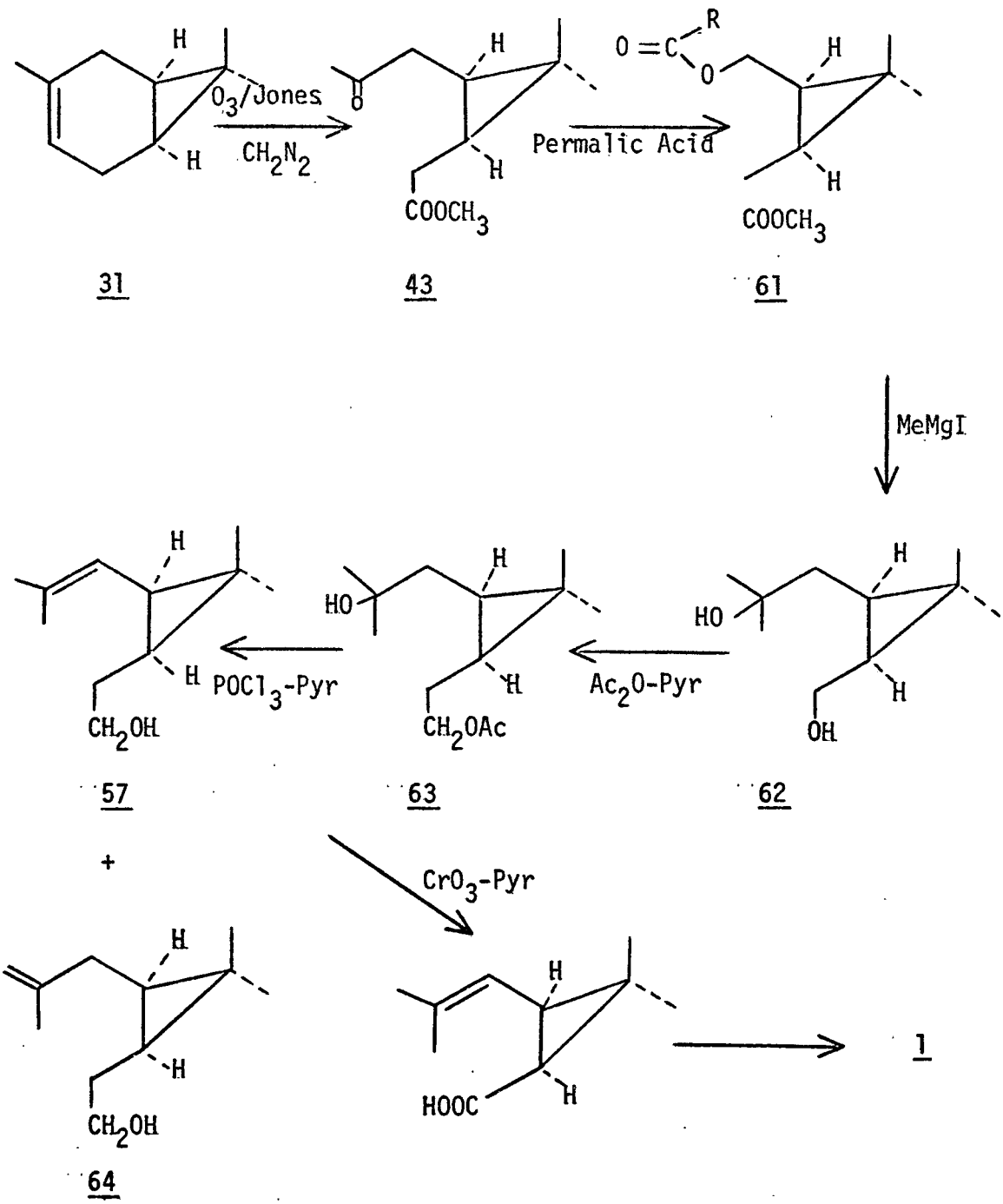
31 43 61 62 37 1

from the keto-ester 43 in over 35% yield, in contrast to the method of Matsui[30] which gives the same compound 37 from the ozonolysis of Δ^3-carene (31) in 16% yield. Moreover, the scheme describes a one-step conversion of the lactone 37 into (+)-trans-chrysanthemic acid (1). Previously, lactone 37 had been converted into cis-chrysanthemic acid, and this cis-acid (or the ester) ultimately epimerized to trans-compound 1.

The second route described by Gopichand and coworkers[42] (Figure 12) is developed via keto-ester 43, from the ozonolysis of carene (31), and ester acetate 61 intermediates. Baeyer-Villiger oxidation of the keto-ester 43 was attempted with the combination of boron trifluoride etherate and 90% hydrogen peroxide, the product obtained was not the expected ester acetate 61 but a δ-lactone 52. This product, probably derived by cleavage of the cyclopropane ring of the initial Baeyer-Villiger reaction product, had previously been identified by Matsui,[30] and the mechanism of such type cleavage had been observed by Sasaki and coworkers[32] when they attempted the conversion of the hydroxy acid 49 to cis-homochrysanthemic acid (55) by treatment with p-toluenesulfonic acid. Instead, ester-acetate 61 was successfully prepared in 90% yield by treatment with permalic acid. Addition of excess methylmagnesium iodide to ester 61 gave diol 62 which was converted to monoacetate 63 with acetic anhydride in pyridine. Dehydration of the tertiary alcohol in monoacetate 63 was effected by the same method employed by Sasaki,[32] by treatment with phosphorus oxychloride in dry pyridine at 0°C, and hydrolysis of the resulting product with methanolic sodium hydroxide solution. The resulting mixture was comprised of 80% chrysanthemyl

FIGURE 12

GOPICHAND AND COWORKERS' SYNTHESIS OF (-)-cis-CHRYSANTHEMIC ACID

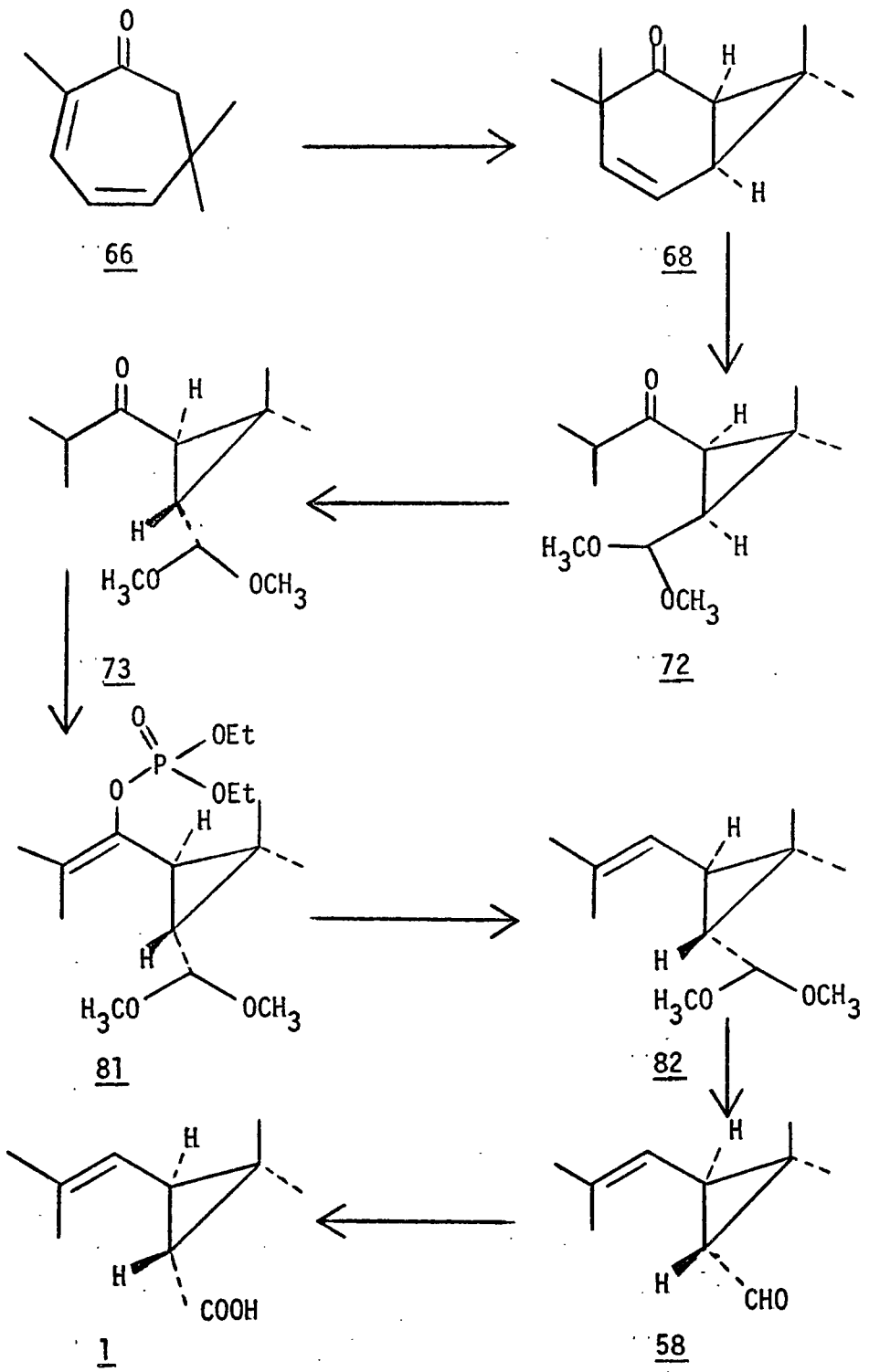


alcohol 57 and 20% of product 64 which has an exocyclic methylene double bond. Oxidation of alcohol 57 with chromium trioxide-pyridine gave (-)-cis-chrysanthemic acid. These are some of the key syntheses of trans-chrysanthemic acid (1) reported in the recent literature. For a complete list of syntheses see reference numbers 25 to 41 and 77 through 89.

The attention that has been focused on the ester of (±)-trans-chrysanthemic acid as the most potent insecticides reasonably justifies all reliable synthetic pathways that lead to the preparation of this compound. The starting material chosen for our total synthesis of (±)-trans-chrysanthemic acid is eucarvone (65). This material can be readily prepared from carvone via literature procedures.[43,44] The scheme for this synthesis (Figure 13) involves the conversion of enone 65 to the Δ^2-4-methylcaren-5-one (66). Ozonolysis of carenone 66, with a reductive work-up, and treatment with methanolic hydrogen chloride gives the keto-acetal 67. The generation of the enol phosphate ester 69 from the epimerized keto-acetal 68, followed by reductive elimination leads to olefin acetal 70. Removal of the acetal group affords aldehyde 71. Oxidation of aldehyde 71 produces the (±)-trans-acid chrysanthemic (1) and after esterification methyl-ester 30.

FIGURE 13

PLANNED SYNTHETIC SCHEME

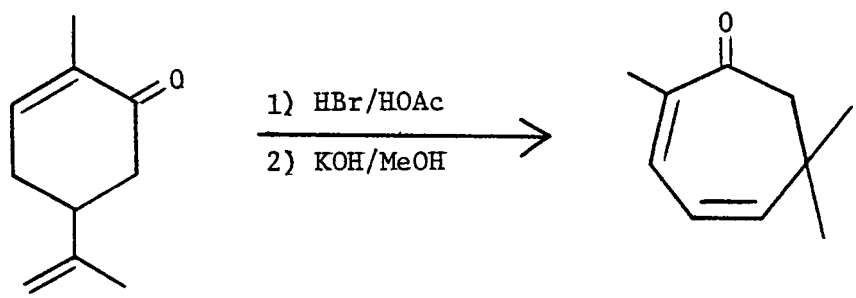


CHAPTER II

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Eucarvone can be prepared from carvone (65) in good yields.[43,44] Treatment of carvone with anhydrous hydrogen bromide in glacial acetic acid affords a monohydrobromide. When this crude monohydrobromide is allowed to react with potassium hydroxide in methanol, eucarvone (66) is formed in 65% yield. The reaction proceeds via an intramolecular alkylation to a carenone intermediate followed by fragmentation of the cyclopropyl ring in the presence of excess base. The mechanism of this reaction is well understood due to the work of van Tamelen and coworkers.[45]



65 66

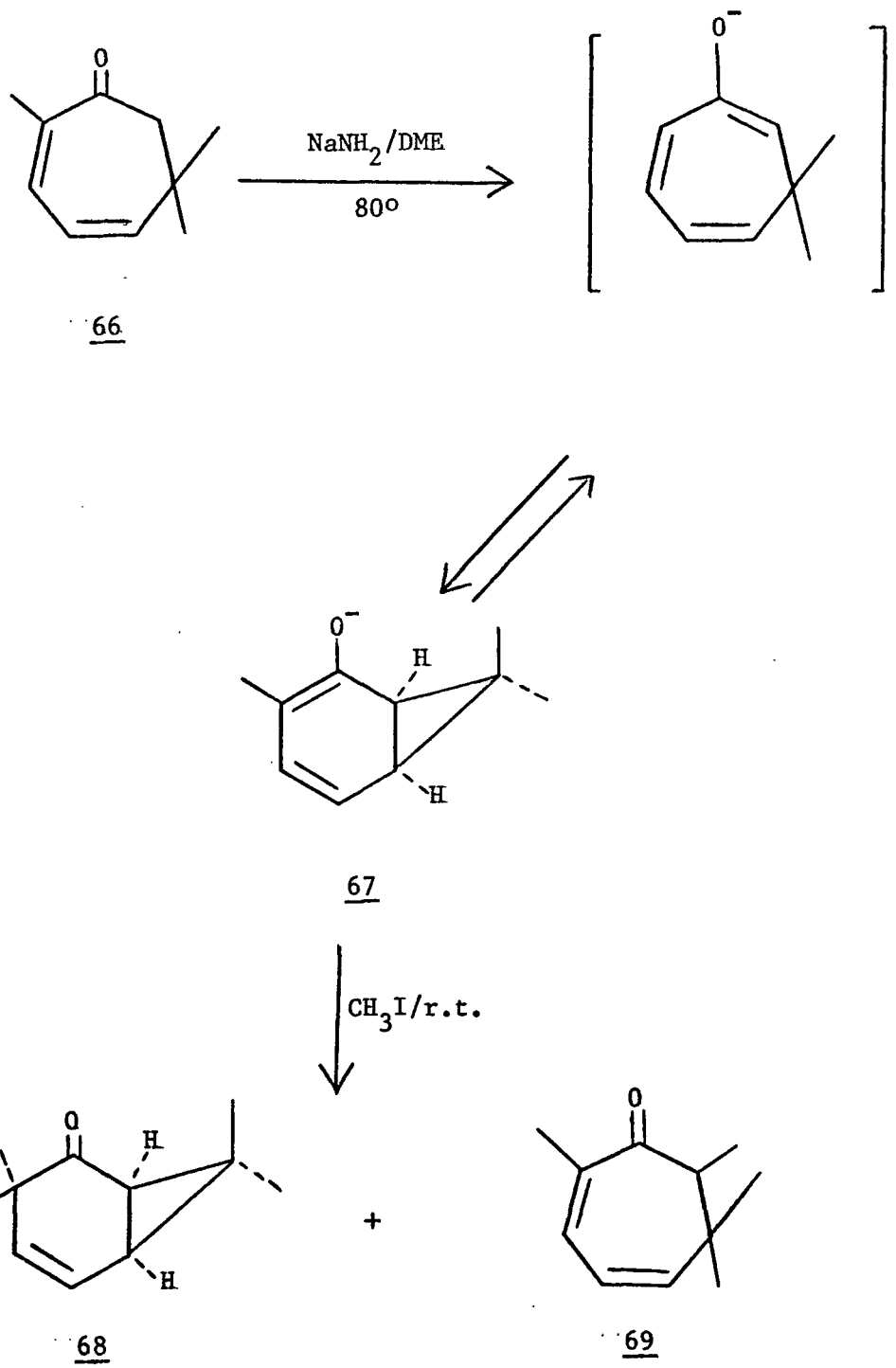
Alkylation of eucarvone (66) was expected to occur predominantly at α-position via bicyclic enolate anion 67. Alkylation of an unsymmetrical ketone such as dienone 66 is favored at this position when the corresponding

enolate anion is generated under thermodynamically controlled conditions.[46,47] This selectivity is due to the greater thermodynamic stability of the more substituted enolate. In addition, the alkylation must occur from the least hindered side of the molecule. In bicyclic enolate anion 67, one side in unhindered, but the other side is sterically hindered by one of the methyl groups at C_7. Since both effects favor alkylation at position 3, it seems reasonable that alkylation should proceed at that position with a high degree of regioselectivity. (Figure 14)

The enolate anion of eucarvone (66) was generated by stirring the dienone with sodium amide in 1,2-dimethoxyethane at reflux for two hours or until the evolution of ammonia had ceased. Alkylation of the enolate anion using methyl iodide gave a mixture consisting mainly of Δ^2-4-methylcaren-5-one (68) and 2,6,6,7-tetramethylcyclohepta-2,4-dienone (69) in a 4:1 ratio.[44] The structural assignment for carenone 68 was fully supported by spectral evidence. The nmr spectrum showed two quartets (5.72 δ) for the olefinic proton at C_5, as the X part of an ABX system; a doublet (5.48 δ) for the other olefinic proton at C_4; a multiplet (1.66 δ) for protons at C_1 and C_6 as the AB part of an ABX system. A carbonyl band (1695 cm^{-1}) and the characteristic gem-dimethyl absorptions (1375,' 1380 cm^{-1}) were present in the ir spectrum. The presence of the 2,4-dienone 69 was evidenced in the nmr spectrum by two multiplets (6.35 and 5.75 δ) due to the vinyl protons at C_3 and, C_4 and C_5 respectively; in the ir spectrum by a band indicative of a seven-membered ring ketone at 1660 cm^{-1}.

FIGURE 14

FORMATION OF Δ^2-4-METHYL CAREN-5-ONE



The seven-membered dienone 69 was selectively oxidized (Figure 15) using 4.0 equivalents of sodium chlorate with a catalytic amount of osmium tetraoxide in aqueous tert-butanol.[49] After 18 hours of reaction, dienone 69 had been totally oxidized to the conjugate keto-diol 70 and carenone 68 had remained unaltered. Bulb to bulb distillation afforded the separation of the pure unoxidized carenone 68 from the black tar-like diol 70, in an overall yield of 70.4% from eucarvone (66). This conversion was confirmed by the absence of the carbonyl absorption band of the seven-membered ketone (1660 cm^{-1}) in the ir spectrum, and the absence of the two multiplets (6.35 and 5.75 δ) in the nmr spectrum and also by glc analysis.

Keto-acetal 72 was synthesized via the ozonolysis procedure of Pappas and Keaveney.[37] The conversion of the enone 68 to the inter-

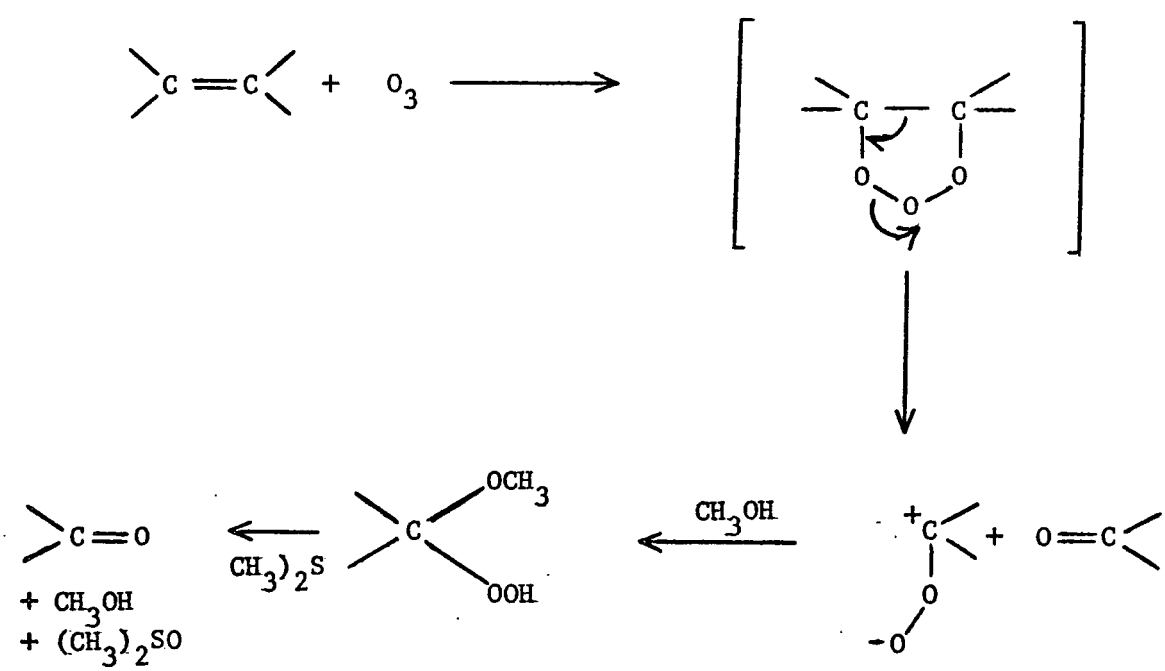
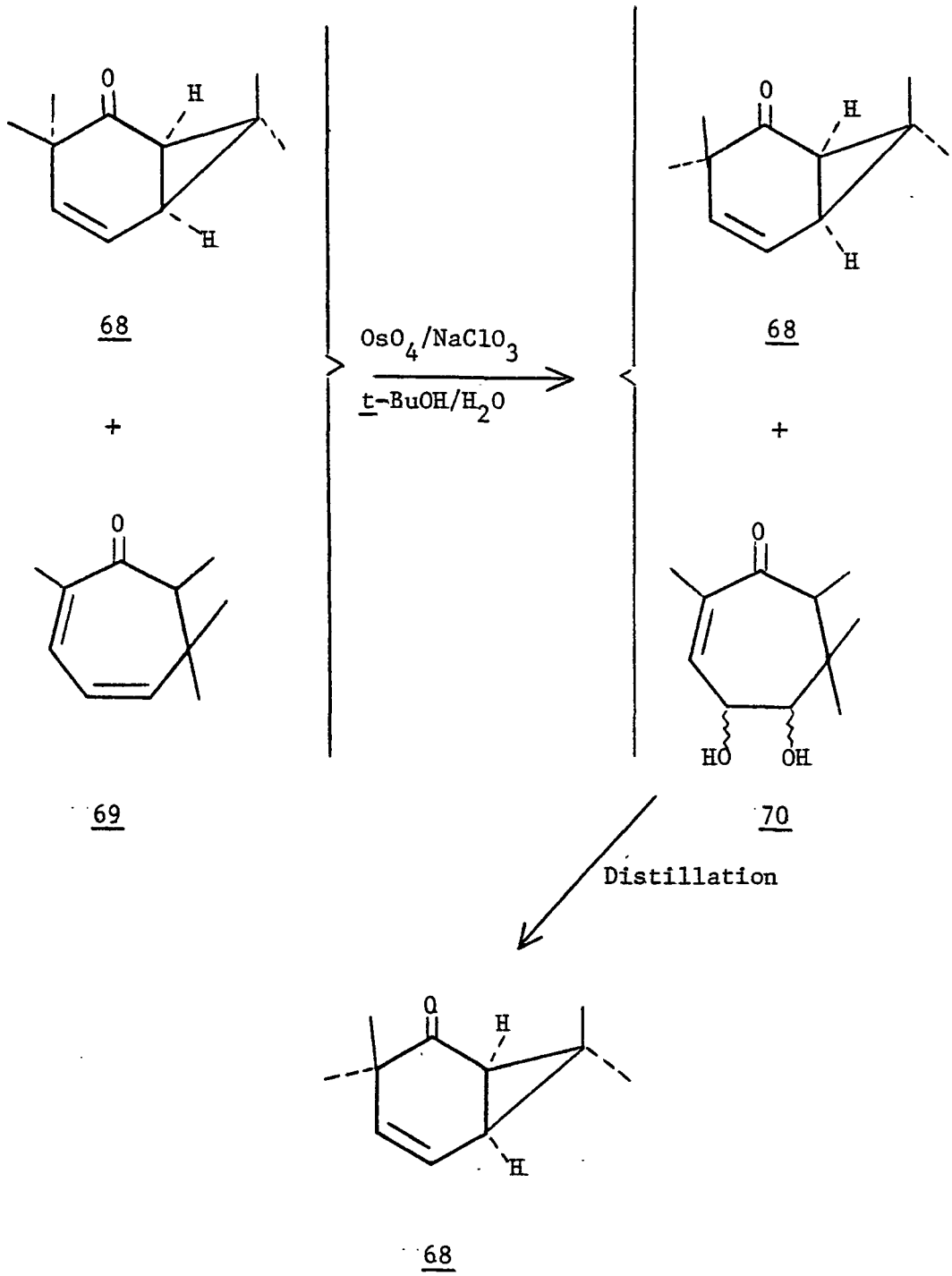


FIGURE 15

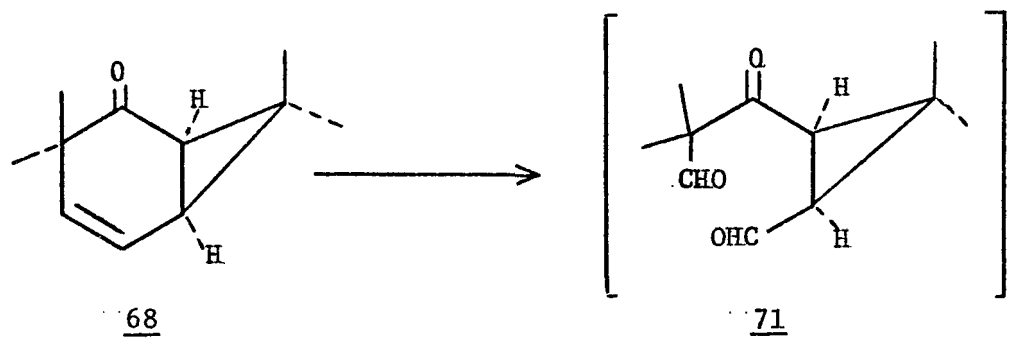
CLEAVAGE OF 2,6,6,7-TETRAMETHYLCYCLOHEPTA-2,4-DIENONE



mediate dialydehyde 71 by this method of oxidation involves the reduction of the immediate ozonide with dimethyl sulfide. It is understood that when addition of ozone to an olefin takes place in a protic solvent, such as methanol, the result is the formation of highly reactive hydroperoxides.[37] The use of dimethyl sulfide, in addition to the rapidity with which it reduces such hydroperoxides at low temperatures, is highly selective, e.g. carbonyl functions are not reduced. The reduction can be carried out under neutral conditions, any excess dimethyl sulfide easily removed by evaporation (bp 37°) and the by-products, methanol and dimethyl sulfoxide cause no purification problems.

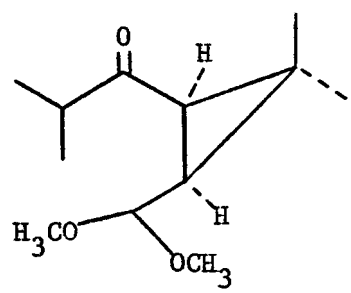
A colorless solution of enone 68 and absolute methanol was cooled to -60° in a Dry Ice-acetone bath and ozone-oxygen gas mixture was passed through the solution until the color had become a deep blue purple. While still at -60° the system was then stirred at -10° for one hour, then at ice-bath temperature at one hour and finally at room temperature. This method gives the intermediate dialdehyde 71 in a 93% crude yield. The formation of this intermediate was supported by ir bands indicative of a cyclopropyl ketone (1685 cm^{-1}) and cyclopropyl aldehyde (2820, 2700, and 1730 cm^{-1}). The nmr spectrum showed two signals for the methyl groups between two carbonyls (3.28 and 3.23 δ) and a singlet and multiplet signals (9.25 δ) indicative of two aldehyde functions.

Normally, the dialdehyde 71 was not isolated but converted at once to keto-acetal 72. The choice of a protecting group for the cyclopropyl aldehyde function required stability to neutral and alkaline reaction conditions, and ability to be removed under mild acid conditions.



68

71

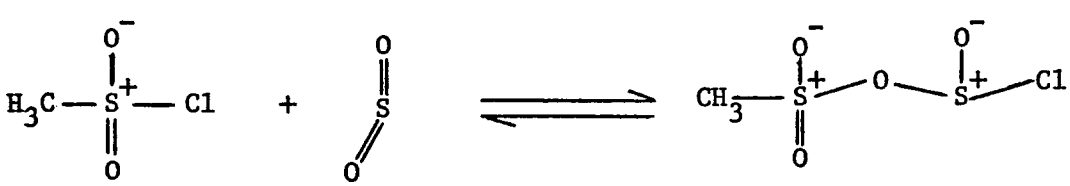


72

Formation of the dialkyl acetal was effected by an acid-catalyzed reaction with methanol as the alcoholic solvent,[50] that was conveniently carried out immediately after reductive work-up of the ozonolysis product with dimethyl sulfide. The crude reaction mixture was concentrated in-vacuo to one-third of its original volume and after addition of a catalytic amount of methanolic hydrogen chloride and a few crystals of anhydrous calcium sulfate, the reaction flask was stoppered and stored

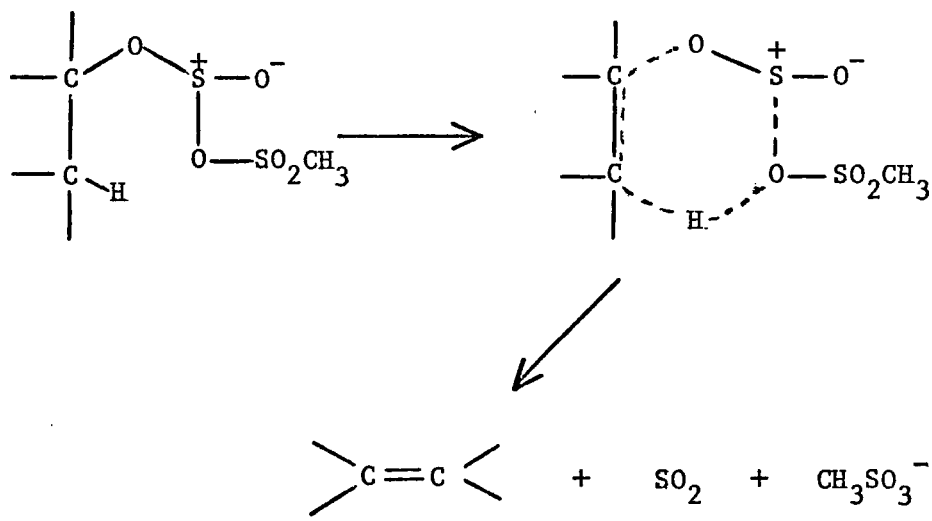
at 3° for 48 hours. Acetal formation and the simultaneous decarbonylation of the β-keto aldehyde function[51] afforded after careful chromatography keto-acetal 72 in 62.5% yield from enone 68. The conversion was confirmed on the basis of ir bands indicative of ketone carbonyl (1680 cm^{-1}), cyclopropyl (1460 cm^{-1}) and acetal (1180, 1120 and 1100 cm^{-1}); and the presence of two singlets (3.3 and 3.2 δ) corresponding to two acetal methyl groups, two singlets (1.1 and 1.0 δ) for the gem-dimethyl group and a singlet (1.2 δ) for the six protons corresponding to the isopropyl group, in the nmr spectrum.

Keto-acetal 72 was initially reduced to cyclopropyl carbinyl alcohol 74 using lithium aluminum hydride.[52,53] Subsequent dehydration of alcohol 74 was attempted by various methods that might lead to the formation of olefin acetal 82. The first attempt to dehydrate alcohol 74 was by the method of Hazen and Rosenberg[54] by treatment with mesyl chloride and sulfur dioxide. Their procedure suggests that mesyl chloride and sulfur dioxide react reversibly to form an unstable, reactive mixed anhydride of methane sulfonic acid and the hypothetical chlorosulfinic



acid. This reagent resembles methane sulfonyl chloride in its overall geometry except for the presence of only one oxygen or sulfur, whereas mesyl chloride possesses two oxygens.

This compound, being an acid chloride also reacts readily in the presence of base to form a labile ester whose decomposition may then proceed through a cyclic transition state to the olefin, methane sulfonate ion, and sulfur dioxide.



Mesyl chloride containing sulfur dioxide was added to a solution of alcohol 74, collidine and dimethylformamide at 10° with stirring. The reaction was allowed to proceed at room temperature until a light-colored precipitate had separated and the solution assumed a reddish hue. Hydrolysis of the mesyl chloride in excess water resulted in a mixture of

four products by tlc; a major product comprising 65% of the crude mixture and three other minor components. Spectral data of the crude product supports the rationalization that cyclopropyl carbinyl mesyl ester had undergone fragmentation and rearrangement. Ir bands characteristic of olefinic absorption (1650, 1645, 970, 960 and 890 cm^{-1}), and a multiplet (5.33 δ) due to more than one olefinic proton, in the nmr spectrum, supports this conclusion.

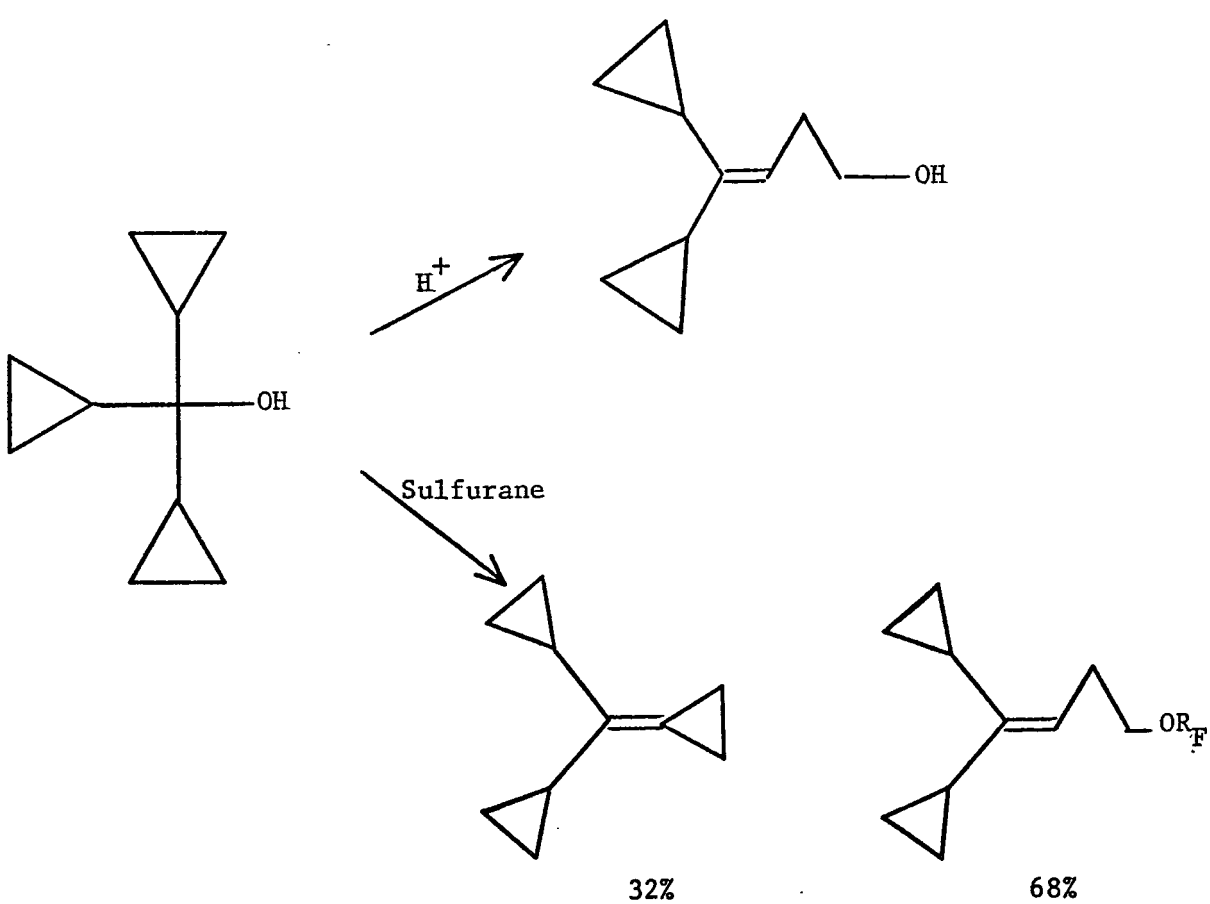
Mesylation and dehydromesylation of alcohol 74 was again attempted with some modifications[55,56] based on the previous methods. The procedure of Crossland and Servis[55] deviates from the previous method by the use of triethylamine as base and methylene chloride as solvent. Also the mechanistic course of the reaction deviates from the usual nucleophilic addition of the alcohol to the sulfonyl group. The alcohol actually undergoes to the sulfene derived from mesyl chloride by E2 elimination of hydrogen chloride[57] by triethylamine. The reagent has a small steric requirement, the nucleophilicity of the alcohol is unimportant, and the conditions are sufficiently mild that even very reactive systems may be esterified. The limiting factor, however, seems to be the stability of the product and intermediates.

Mesyl chloride was added dropwise to a solution of alcohol 74 in methylene chloride containing a 50% molar excess of triethylamine at 0° to 10° over a period of 5 - 10 minutes. After formation of the mesylate was complete (monitored by tlc), collidine was added and the flask immersed all at once to a preheated (100°) oil bath and the reaction stirred for two hours. The resulting product that was isolated showed the exact same

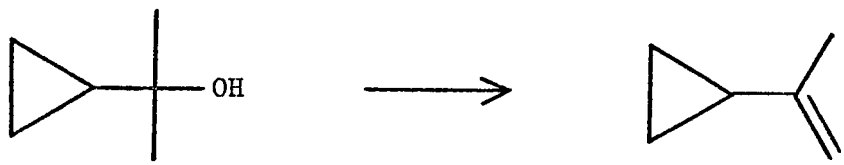
spectral characteristics as those of the major product obtained by the previous method.

Recent evidence[58,59] of the synthetic utility of sulfurances in the conversion of alcohols to alkenes prompted still another attempt to dehydrate cyclopropyl carbinyl alcohol 74 to the corresponding olefin acetal 82 via a dialkoxydiphenyl sulfurane reagent.

Attempts to dehydrate systems like tricyclopropylcarbinol using acidic catalysts have led only to ring-opened products,[60] however, Arhart and Martin[58] have reported formation of a tricyclopropyl olefin in 32% yield by the use of a dialkoxydiphenyl sulfurane reagent.



Moreover, dimethylcyclopropyl carbinol, which would form a less stable carbonium ion, and whose carbon framework resembles that of alcohol 74, affords the unrearranged olefin upon dehydration with the sulfurane reagent in quantitative yield.

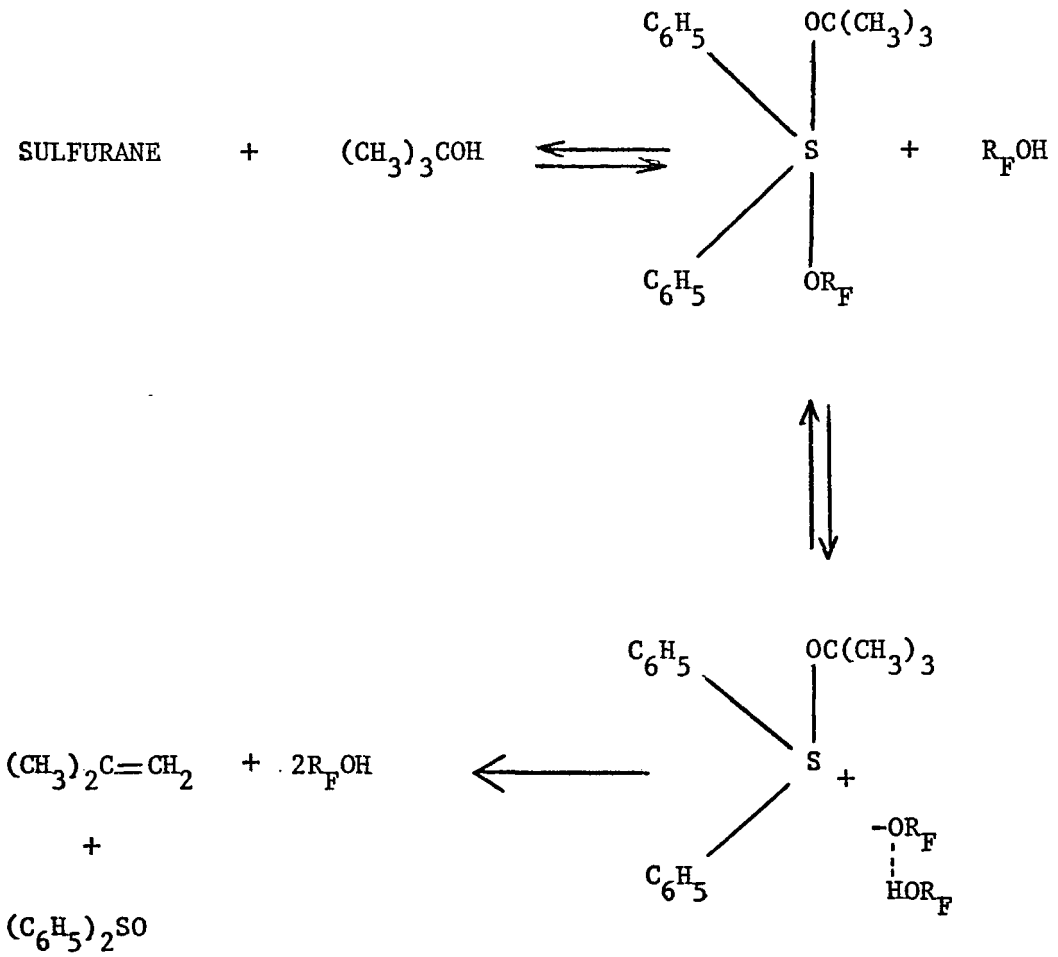


All of the alcohols studied by Arhart and Martin[58] appear to exchange rapidly (Figure 16) with the alkoxy ligands of the sulfurane reagent. This exchange is followed by a very rapid elimination reaction. Evidence for the rapid equilibration of the alkoxy ligants in the first step of this mechanism was seen in both ^{19}F and ^{1}H low - temperature nmr spectra of dehydration reaction mixture of the more slowly eliminating secondary alcohols.[61]

Addition of hexafluoro-2-phenyl-2-propanol to an 86% aqueous solution of potassium hydroxide was concentrated to a syrup by vacuum distillation. Further evacuation with a vacuum pump while heating to 140° gave the white solid potassium hexafluoro-2-phenyl-2-propoxide. Addition of diphenyl sulfide to a stirred suspension of the alkoxide in carbon tetrachloride was followed by subsequent addition of bromine to

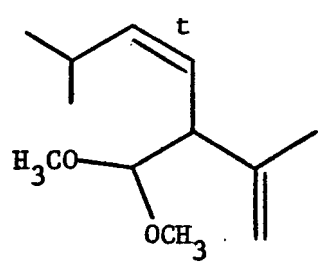
FIGURE 16

SULFURANE ALKOXY EXCHANGE MECHANISM



to give a red-brown mixture which gradually faded to a pale yellow. Removal of potassium bromide under a nitrogen atmosphere and concentration in-vacuo gave the crude sulfurane as slightly yellow crystals.[62]

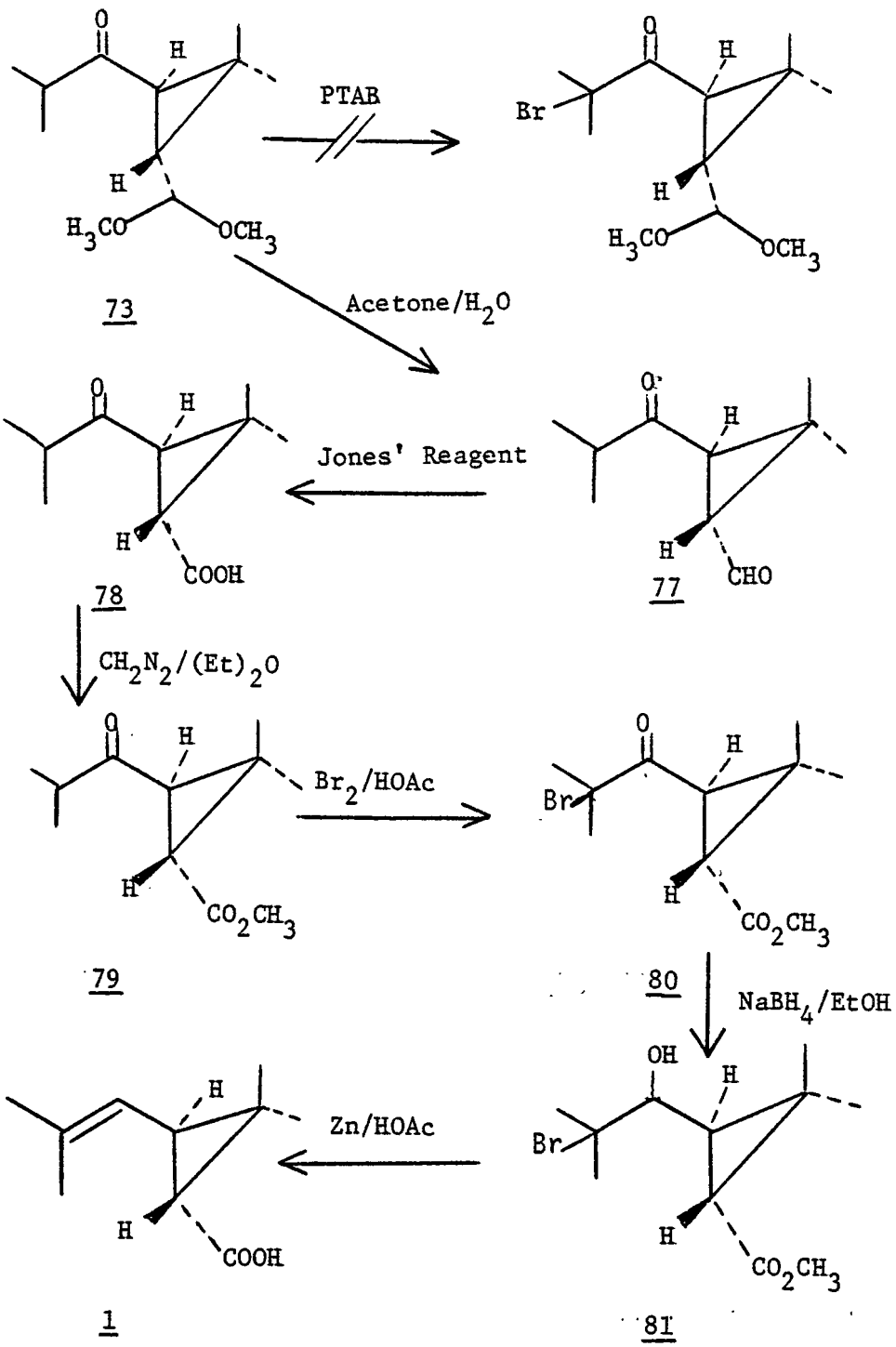
An excess of hexafluoro-2-phenyl-2-propoxy diphenyl sulfurane was added at room temperature under a nitrogen atmosphere to a stirred solution of cyclopropyl carbinyl alcohol 74 and d-chloroform. The reaction which takes place instantaneously gave a single product by tlc. The spectral data of this product were identical to that of the major product from the previous dehydration experiments, thus supporting the conclusion that in each experiment the fragmentation and rearrangement of the cyclopropyl ring had proceeded by the same mechanistic course. Investigation of which bond was ruptured in the cyclopropyl ring and the course of its rearrangement was not pursued. But on the basis of these spectral data it seems feasible to propose a structure such as diene 74a to this product. Due to these failures to contruct the isobutylene framework of (±)-trans-chrysanthemic acid by dehydration of intermediate 74, a different approach was then explored. (Figure 17)



74a

FIGURE 17

ALTERNATE SCHEME



Keto-acetal 72 was then epimerized by heating in tert-butanol in the presence of a catalytic amount of potassium tert-butoxide just before reflux. After 48 hours the thermodynamically more stable isomer 73 was obtained in quantitative yield. This structure was confirmed in the nmr spectrum by the shift of the acetal proton signal up field (4.2 δ) when removed from the deshielding environment of the carbonyl function in the less sterically hindered epimer.

Addition of water to a stirred solution of epimerized keto-acetal 73 in acetone afforded keto-aldehyde 77 in quantitative yield. Structural assignment was made on the basis of ir bands indicative of a cyclopropyl ketone (1690 cm^{-1}) and cyclopropyl aldehyde (2860, 2720, and 1730 cm^{-1}); and the presence of the aldehyde signal (9.25 δ, J = 2 Hz) in the nmr spectrum.

Treatment of aldehyde 77 with Jones' reagent[63,64] added dropwise at 0° with rapid stirring at room temperature for 30 minutes gave the carboxylic acid 78 in 83% yield. The conversion was confirmed by the presence of carboxylic acid bands (3060 and 1690 cm^{-1}) in the ir; and an acid proton (11.4 δ) in the nmr. Anhydrous diazomethane in ether was added dropwise at 0° to an ethereal solution of the resulting carboxylic acid 78. The mixture was stirred at 0° for 30 minutes and at room temperature for 30 minutes. After quenching, and removal of excess reagent and solvent methyl ester 79 was isolated in 94% yield. The structure was supported by ir bands indicative of cyclopropyl ketone (1690 cm^{-1}) and ester carbonyl (1730 cm^{-1}); and the nmr signal (3.63 δ) for the carbomethoxy protons.

Conversion of methyl ester 79 to α-bromo ketone 80 was initially attempted using phenyltrimethylammonium perbromide.[65] The result of this reaction was a mixture of products comprising three major components, due probably, to the three available α-carbonyl positions in the starting material. Alternatively, keto-ester 79 was brominated with bromine in acetic acid.[66] Chromatography of the crude material after work-up afforded α-bromo ketone 80 in 58% yield. The structure was confirmed in the ir spectrum by the shift of the cyclopropyl ketone carbonyl stretching frequency (1700 cm^{-1}), due to the bromine substitution on the carbon atom adjacent to the carbonyl group; in the nmr spectrum, by the absence of the signal corresponding to the α-methine proton.

The final stages of this approach called for the conversion of the α-bromo ketone 80 to the intermediate bromohydrin 81. Despite the failures previously encountered to generate a double bond via the cyclopropyl carbinyl alcohol 74, other elimination procedures via a bromohydrin intermediate seemed feasible and have been well documented.[67-69] To this effect, cyclopropyl ketone 80 was selectively reduced with 2 equivalents of sodium borohydride in methanol at 25°.[70] After chromatography of the crude product bromohydrin 81 was obtained in 85% yield. This conversion was confirmed by an ir band indicative of an alcohol (3475 cm^{-1}); and an nmr signal of one hydroxy-methine proton (3.2 δ).

At this point in our research, the successful preparation of the diethyl enol phosphate of tetrahydroeucarvone diverted our attention from the scheme under investigation. Reduction of the phosphonate intermediate with excess lithium in a mixture of monoethylamine and tert-butanol

led to the corresponding olefin in high yield.[70,71] The efficiency of this sequence focused our attention on the preparation of an enol diethyl phosphate intermediate from the epimerized keto-acetal 73 (Figure 18)

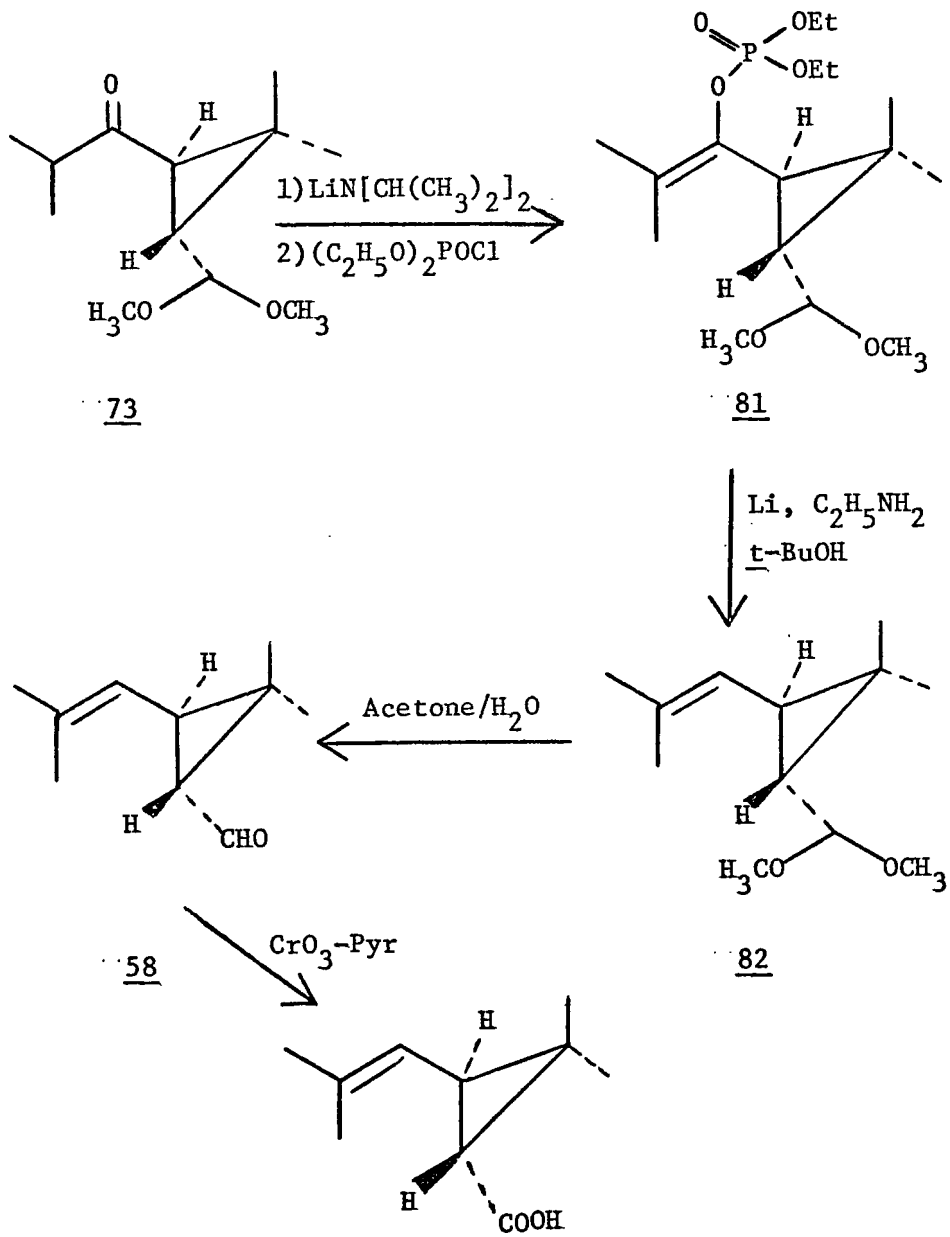
Formation of the required phosphonate might logically result from the interaction of an enolate anion and a suitable phosphorylating agent such as diethyl phosphorochloridate or tetramethyldiamidophosphoro chloridate. In either case structural selectivity would depend on the generation of the enolate anion. Enol phosphates can be prepared from α-bromo ketones via the Perkow reaction[72] but we thought to accomplish the total synthesis in a limited number of steps by choosing acetal 73 as the starting intermediate for this last stage.

To a solution of lithium diisopropylamide prepared from diisopropylamine and methyl lithium under a nitrogen atmosphere was added dropwise at -60° a solution of keto-acetal 73 and tetrahydrofuran. The stirred solution was allowed to come to room temperature, then cooled again to -60° and diethyl chlorophosphate was added dropwise. The resulting yellow solution was allowed to warm to room temperature and then stirred for 1.5 hours. The product was isolated by ether extraction including a base wash to avoid any acetal cleavage that might occur due to traces of acid. Chromatography and distillation of the crude product gave enol phosphate ester 81 in 62% yield. The structure was confirmed by ir bands indicative of an enol (1688 cm^{-1}) and acetal (1180, 1100 and 1050 cm^{-1}).

A solution of lithium wire and dry monoethylamine was stirred for 30 minutes and then a solution of enol phosphate in dry tert-butanol was injected all at once with a syringe with constant stirring. After

FIGURE 18

LAST STAGE OF SYNTHESIS



the blue solution had stirred for an additional 30 minutes the excess lithium was carefully decomposed with methanol and most the monoethylamine allowed to evaporate. The grey residue was carefully treated with water and the crude olefin acetal 82 isolated by ether extraction including a base wash to safeguard the acetal moity. Chromatography and distillation of the crude material gave pure olefin acetal 82 in 81% yield.[73,74]

The efficiency of the second stage of this reduction process suggested that the entire sequence might be carried out without isolation of the intermediate diethyl enol phosphate 81.[72] The possibility to combine these two synthetic steps would make the scheme quite useful and more attractive. However, when the crude reaction mixture from the initial phosphorylation of the keto-acetal 73 was directly reduced with lithium in monoethylamine and tert-butanol, the desired olefinic intermediate 82 was isolated after chromatography in only 17% yield. Confirmation of the structure was based on the presence of ir bands indicative of an olefin (1705 and 980 cm^{-1}) and acetal (1180, 1110 and 1050 cm^{-1}); and nmr peaks indicative of one olefinic proton (4.8 δ, J = 7 Hz).

Removal of the dimethyl acetal moity from olefin 82 was accomplished by the same acid-catalyzed method previously employed on keto-acetal 73 in an earlier scheme. The yield obtained from olefin 82 was also quantitative. Spectral data, ir bands indicative of cyclopropyl aldehyde (2850, 2720 and 1715 cm^{-1}) and of an endomethylene (980 cm^{-1}); and an aldehyde signal (9.9 δ, J = 5 Hz) in the nmr spectrum, support the structure. This data, for olefin aldehyde 58, were in exact agreement with that reported for the same structure by Raphael and coworkers[38]

in their earlier synthesis of (±)-trans-chrysanthemic acid (1).

Oxidation of aldehyde 58 to (±)-trans-chrysanthemic acid proved to be less successful than anticipated. In an initial attempt, Jones' reagent[63,64] was added dropwise at 0° to an acetone solution of aldehyde 58, and the reaction mixture stirred for 30 minutes. At this time some aldehyde still remained unoxidized, so an additional aliquot of oxidizing reagent was added and the reaction mixture stirred for an additional 30 minutes. Following work-up and preparative layer chromatography, (±)-trans-chrysanthemic acid was isolated in 28% yield.

A more satisfactory yield was obtained when silver oxide was used to affect the oxidation.[75,76] A tetrahydrofuran solution of olefin aldehyde 58 was added to freshly precipitated silver oxide and water. Four drops of 50% sodium hydroxide was added, and the mixture allowed to stir for 36 hours. Work-up and distillation of the crude product afforded the acid 1 in an improved yield of 34%.

The best results were obtained when olefin aldehyde was oxidized by the chromium trioxide-pyridine procedure.[38,42] Chromium trioxide was carefully added to pyridine with rapid stirring at 0°. To this slurry was then added a pyridine solution of aldehyde 58, followed by a catalytic amount of water. The reaction mixture was then stirred at room temperature for 4 days. The desired acid 1 was obtained after chromatography and distillation of the crude product in 42.3% yield.

A systematic approach to alter reaction conditions in each method of oxidation was undertaken in an attempt to improve the yield of this last synthetic step. However, in no case was the yield of the

acid greater than in the chromium trioxide-pyridine method as described. In addition, a variety of unidentified products were formed in each reaction.

The acidic product that was isolated from each of the described procedures exhibited identical spectral properties (ir, nmr, gc, tlc) with a sample of authentic trans-chrysanthemic acid which was obtained by the equilibration and hydrolysis of the ethyl chrysanthemumate[32] (Aldrich[12,819-8]). Ethereal diazomethane was added to each of the samples of trans-chrysanthemic acid and the resulting methyl esters were also compared (ir, nmr, gc, tlc) and found to exhibit identical characteristics. These spectral data are also in agreement with those previously reported.[20,25,38]

CHAPTER III

CONCLUSIONS

CONCLUSIONS

Three separate synthetic routes to the construction of (±)-trans-chrysanthemic acid (1) are described from a key intermediate, the epimerized keto-acetal 73. The preparation of this ketone from the readily available eucarvone was successfully accomplished by trapping the thermodynamically more stable bicyclic enolate anion 67 with methyl iodide. Ozonolysis of carenone 68 by the methods of Pappas and Keaveney represents a key step in the synthesis. This oxidation method yields a dialdehyde intermediate which was not normally isolated in view of the ability exhibited by the β-keto-aldehyde function to undergo decarbonylation. The carbon framework of keto-acetal 73 has essentially all the structural features of the desired acid 1.

A lot of time and effort was devoted to introduce the double bond by dehydration of the cyclopropyl carbinyl alcohol 74. Despite the variety of methods attempted, this approach resulted in fragmentation and rearrangement of the cyclopropane ring in each instance.

In an alternate scheme, we though to circumvent this difficulty by utilizing well-documented reductive elimination procedures on a bromohydrin intermediate 80, devised from epimerized keto-acetal 73. The successful formation of a enol diethyl phosphate intermediate from tetrahydroeucarvone, and the efficient reductive elimination of this intermediate to the corresponding olefin derivative, led to new modifications on the proposed syntheic scheme.

Our efforts were now diverted to the synthesis of diethyl enol phosphate 81 from keto-acetal 73. The efficiency of this reaction, coupled

with the high yields of the subsequent reduction of the enol phosphate intermediate to olefin acetal 82, provided us with an attractive and efficient route to (±)-trans-chrysanthemic acid. The total synthesis of this acid have thus be been accomplished in a limited number of synthetic steps.

CHAPTER IV

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined on a Nalge No. 500 and/or Buchi melting point apparatus and are uncorrected. All boiling points are uncorrected. Analyses were performed by P.C.R. Inc. Laboratories, Incorporated, Gainsville, Florida and Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Analytical gas phase chromatography (glc) was performed using the following types of columns and flow rates:

A. 6-foot, stainless steel, 1/8 inch column, packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian); flow rate 15 ml/min. at ambient temperature.

B. 6-foot, stainless steel, 1/8 inch column, packed with 5% FFAP on Varaport-30, 80/100 mesh (Varian); flow rate 15 ml/min. at ambient temperature.

C. 6-foot, stainless steel, 1/8 inch column, packed with 5% OV-17 on Varaport 30, 80/100 mesh (Varian); flow rate 15 ml/min. at ambient temperature.

Silica gel PF 254 + 366 (E. Merck No. 7748) and silica gel 60 (E. Merck No. 7734, 70-230 mesh) available from Brinkmann Instruments was used for thin layer and column chromatography, respectively.

Infrared (ir) spectra were recorded on a Perkin-Elmer Model 337 or 700 spectrophotometer. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10 mm sodium chloride cells. Liquid samples were taken as thin films between sodium chloride plates.

Nuclear magnetic resonance (nmr) spectra were measured on a Varian Associates Model T-60, HA-100, or EM-390 spectrometer. The following abbreviations are used to describe nmr spectral bands reported in the experimental section: broad (b), singlet (s), doublet (d) doublet of doublets (dd) doublet of multiples (dm), triplet (t), quartet (q), AB quartet (AB), multiplet (m), and δ (parts per million, ppm) downfield from tetramethylsilane.

High resolution mass spectra (HRMS) were obtained on a CEC Model 21-110-B spectrometer under the supervision of Dr. R. Grigsby, Department of Chemistry, Texas A & M University, College Station, Texas. Medium resolution mass spectra (MRMS) were obtained on a Perkin Elmer RMU-6H.

Finally for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120° for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider. - The term "pet-ether" refers to Baker "Analyzed Reagent" bp 30-60°.

Eucarvone (66)[43,44]- Freshly distilled carvone (65); 200 g, 1.33 mole) was slowly added to a solution of anhydrous hydrogen bromide (295 g, 3.66 mole) in glacial acetic acid (1.0 l) at 5 to 10° with rapid stirring and efficient cooling. The cooling bath was removed and stirring continued for 15 minutes.

The resulting orange solution was poured into water (2 l), the lower layer separated and the aqueous layer extracted with ether (3X). The combined ethereal extracts were washed with water (3X), saturated

potassium bicarbonate solution until basic to litmus paper and finally with water until neutral. The organic solution was dried (Na_2SO_4), then added dropwise to a well-stirred and cooled solution of potassium hydroxide (145 g) and anhydrous methanol (550 ml).

After completion of the addition, the resulting suspension was stirred at reflux for 15 minutes, then poured into ice-sulfuric acid. The yellow liquid was separated and the aqueous layer was extracted with ether (3X). The combined ethereal extracts were washed with 10% sodium hydroxide (3X) to remove the carvacrol, and with water until neutral; and then dried (Na_2SO_4), concentrated in vacuo, and distilled to give 130 g (65%) of eucarvone (66); bp 46-49° (1.5 mm) [lit. — 81.5 - 84.0° (8 mm)]; ir (film) 3010 (CH=CH), 1660 (CO), 1385, 1365 (gem-CH_3), and 728 cm^{-1} (CH=CH); nmr (CCl_4) δ 5.5 - 6.54 (m, 3, CH=CH), 2.57 (s, 2, $COCH_2$), 1.85 (d, 3, J = 1.8 Hz, CH_3C =), and 1.06 ppm (s, 6, gem-CH_3)

Δ²-4-Methylcaren-5-one (68)[44,48] - Preparation of Sodioeucarvone. A suspension of finely powdered sodium amide (3.77 g 96.5 mmole, 25 - 80% excess) in 125 ml of refluxing anhydrous 1,2-dimethoxyethane was treated all at once with eucarvone (66) (9.90 g, 65.9 mmole) in dry 1,2-dimethoxyethane (25ml) under nitrogen with stirring. The evolution of ammonia was swift at the start. The progress of the reaction was followed by titration of the ammonia evolved, and the refluxing was discontinued when the ammonia evolution had substantially ceased (1 - 3 hrs.). To the cooled sodioeucarvone solution was added with stirring at 10°, methyl

iodide (15.6 g, 110 mmole). No reaction occurred at this temperature, so the cooling bath was removed. When the reaction was checked again an hour later the solution had turned light-yellow brown and the internal temperature was 38°. Stirring at room temperature was continued for an additional two hours, then the solution was acidified with glacial acetic acid. A small amount of solid potassium bicarbonate was added to destroy excess acetic acid, and one liter of saturated sodium chloride solution was added. This solution was extracted with ether (3 X 100 ml), the combined ethereal extracts are washed with water (4 X 100 ml) and saturated sodium chloride solution (150 ml), and then dried (Na_2SO_4) and the solvent removed in-vacuo. Distillation gave 9.95g (92%) of pale yellow mixture of methyl carenone 68, and 2,6,6,7-tetramethylcylcohepta-2,4-dienone (69) in a 4:1 ratio ; bp 82 - 84° (0.8mm); ir (film) 1695 (CO) methyl carenone; 1665 (CO) cyclohepta-2-4-dienone , 1007 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 5.72 (2 q, 5H as the X part of an ABX system, $J_{4,5}$ = 10 Hz), 5.48 (d, 4H), 1.66 (m, 2H, 1-and 6-H as the AB part of an ABX system, $J_{1,6}$ = 7, $J_{5,6}$ = 4, $J_{1,5}$ = 1 Hz), 1.24, 1.06, 1.03, and 0.95 (4s, 3-,3-,7-, and 7-CH_3). The impurity 2,6,6,7-tetramethylcyclohepta-2,4-dienone, appears at δ 6.35 ppm (m, 3-H); glc analysis on column A (column temp. 115°), retention time 5.24 and 20.40 min. shows a ratio of 4:1, respectively.

The impurity was removed by the following procedure.[49] A solution of the distilled mixture (10.0 g, 60.9 mmole), water (400 ml), tert-butanol (200 ml), sodium chlorate (34.20 g, 159.8 mmole) and a catalytic amount of osmium tetraoxide (0.005 g/ml, 4 ml) was placed in

a 1.0-l flask. The solution was stirred at room temperature and the selective cleavage of the cychoheptadienone impurity was monitored by glc analysis on column A (column temp. 115°). After 18 hrs. the resulting pale yellow solution was taken up in an equal volume of water (600 ml) and extracted with dichloromethane (6X 100 ml). The combined organic extracts were washed with water (2X 100 ml) and saturated sodium chloride solution (150 ml); and then dried ($MgSO_4$), and concentrated in vacuo to yield 9.84 g of a darker yellow crude oil. Distillation of the crude product gave 7.04 g (70.4%) of pure methylcarenone 68; bp 66-70° (6 mm); ir (film) 1696 (CO), 1007 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 5.74 (2q, 5-H) as the X part of an ABX system, $J_{4,5}$ = 10 Hz), 5.5 (d, 4-H), 1.66 (m, 2 -H, 1- and 6-H as the AB part of an ABX system, $J_{1,6}$ = 7, $J_{5,6}$ = 4, $J_{1,5}$ = 1 Hz), 1.24, 1.04, 1.03 and 0.95 ppm (4s, 3,-3,-7, and 7-CH_3); glc analysis on column A (column temp 115°, retention time 5.25 min) and spectroscopic evidence show the methylcarenone (68) to be at least 99.6% pure.

(±)-cis-3-Isobutyryl-2,2-dimethylcyclopropanecarboxaldehyde dimethyl acetal (72)[37] - A solution of methyl carenone 68, (6.34 g, 38.7 mmole) in absolute methanol (150 ml) was placed in a 250-ml gas washing bottle equipped with a coarse posority disk. The gas washing bottle was immerged in a Dry Ice-acetone bath (-70°) and ozone was bubbled through the solution (6-7 psi O_2, 90ev, and .02 flow rate) from a Wellsback Corporation ozonator apparatus, style T-23, Serial No. 344. After 35 min. the clear solution had turned a deep blue purple color.

The ozone inlet was then removed and nitrogen was bubbled through the the blue purple solution for 15 min. to remove any excess ozone. The solution was transferred to a 1-l round bottomed flask, stirred, and allowed to warm to room temperature while methyl sulfide (2 equivalents or until it gave a negative potassium starch-iodide test) was added. This reaction mixture was concentrated in-vacuo to approximately one-third its original volume and a catalytic amount of methanolic hydrogen chloride was added (1 ml) with a few crystals of anhydrous calcium sulfate (white Drierite, 8 mesh). The flask was stoppered and left standing in a refrigerator at 3^{o}. After 48 hours the solution was diluted with ether (100 ml), shaken with a small amount of solud sodium bicarbonate to remove any traces of acid, washed with water (3X 40 ml), and then dried (Na_2SO_4 - 1 drop of pyridine), filtered (Na_2SO_4) and concentrated in-vacuo to give 7.85 g (95%) of a crude product. A portion of the crude product (0.265 g) was chromatographed immediately before use on silica gel (30 g, 70-230 mesh, E. Merck) in a 2.5 cm diameter column. A solution 30% ether - 70% pet-ether (with a few drops of pyridine) was used to develop the column, taking 15-ml sized fractions. Fractions 12-18 gave 0.211 g (62.5%) of pure keto-acetal 72 as a colorless oil; bp 40 - 42^{o} (6 mm); ir (film) 1680 (CO), 1370, 1380 (gem-CH_3), 1460 (cyclopropyl), 1100, 1098, and 1180 cm^{-1} (acetal); nmr (CCl_4) δ 4.8 (d, 1, J = 9 Hz, C<u>H</u>-$(OCH_3)_2$), 3.3 and 3.2 (2s, 6, -CH-$(O\underline{CH_3})_2$), 1.0 (d, 6, J = 7 Hz, isopropyl), 1.25 (bs, 6, gem-$\underline{CH_3}$) and 1.8 ppm (d, 1, J = 8 Hz,-COC<u>H</u>); HR mass spectral data are presented in Table II.

TABLE II

Mass Spectral Data[a] for

(±)-cis-Isobutyryl-2,2-dimethylcyclopropanecarboxaldehyde dimethyl acetal

m/e	I[b]	m/e	I[b]
124	1	139	89
184	2	125	7
183	18	121	3
182	4	113	3
171	2	112	23
167	5	111	19
143	3	110	2
142	6	109	3
141	2	107	6
140	9	99	5
98	4	75	100
97	34	74	7
96	5	73	94
95	5	72	5
88	6	71	89
86	4	78	2
85	2	69	13
83	5	68	2

TABLE II CONTINUED

m/e	I[b]	m/e	I[b]
82	2	67	15
81	15	66	1
80	3	59	9
79	20	58	6
79	8	57	25
76	1	55	3
53	7		
51	2		
47	23		
45	7		
44	3		
43	88		
42	5		
41	55		
40	4		
39	19		
31	9		
29	7		
27	23		

[a]Mass spectrum taken on CEC 21-110B

[b]Relative abundance

Anal. Calcd for $C_{12}H_{22}O_3$: ($M^+ - OCH_3$, Peak at 214 too weak for high resolution measurement); 183.139309; found: 183.138495 (MS) 4.4 ppm error.

(±)-trans-3-Isobutyryl-2,2-dimethylcyclopropanecarboxaldehyde dimethyl acetal (73)[52,53]

A catalytic amount of potassium tert-butoxide (26.2 mg, 0.233 mmole) was placed in a 25 ml round bottomed flask and dissolved in dry tert-butanol (10 ml, freshly distilled from calcium hydride). Keto acetal 72 (250 mg, 1.17 mmole) in dry tert-butanol (3 ml) was added all at once. The resulting light yellow solution was allowed to stir at gentle reflux (90 ± 5°) for forty-eight hours. The resulting yellow solution was taken up in water (40 ml) and extracted with ether (5X 15 ml). The combined ethereal extracts were washed with water (2X 15 ml) and saturated sodium chloride solution (20 ml), and then dried over (Na_2SO_4), filtered (Na_2SO_4) and concentrated in-vacuo. The remaining traces of tert-butanol were removed by co-distillation in-vacuo with benzene (3X 40 ml containing a trace of pyridine) to give 248.4 mg pale yellow crude oil. Distillation of the crude product afforded 241 mg (96%) of colorless epimerized keto-acetal 73; bp 40° (5 mm, bulb to bulb, external temperature), ir (film) 1690 (CO), 1370, 1380 (gem-CH_3), 1190, 1103 1050 (acetal), 1460 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 4.2 (d, 1, J = 6 Hz, CH-$(OCH_3)_2$), 3.25 3.23 (2s, 6, -CH-$(OCH_3)_2$), 1.2 (d, 6, isopropyl), and 1.0 ppm (bs, 6, gem-CH_3); MR mass spectral data are presented in Table III.

TABLE III

Mass Spectral Data[a] for

(±)-trans-3-Isobutyryl-2,2-dimethylcyclopropanecarboxaldehyde dimethyl acetal

m/e	I[b]	m/e	I[b]
214	4	123	6
203	5	122	9
184	5	118	4
183	40	116	5
182	17	115	6
177	6	114	11
175	11	113	39
171	11	112	38
155	14	111	9
143	6	110	14
142	6	109	8
141	8	108	60
140	13	106	4
139	100	102	9
135	8	101	8
130	3	100	32
128	14	99	6
127	2	98	48

TABLE III (continued)

m/e	I^b	m/e	I^b
126	19	97	14
124	7	96	14
92	10	67	23
91	4	65	6
90	47	61	21
89	95	59	20
88	5	58	37
87	5	57	6
86	12	56	8
84	15	55	37
83	11	53	19
82	30	51	5
81	10	47	25
80	33	45	41
78	13	44	21
77	19	43	81
76	96	42	12
75	13	41	86
74	90	39	29
73	8	32	56

TABLE III (continued)

m/e	I[b]	m/e	I[b]
72	95	31	51
71	41	30	5
70	25	29	51
69	5	28	78

[a]Mass spectrum taken on Perkin Elmer RMU-6H

[b]Relative abundance

(±)-trans-3-(1-Hydroxy-2-methylpropenyl)-2,2-dimethylcyclopropane carboxaldehyde dimethyl acetal, diethyl phosphate (81)[70,71,72]

A few crystals of bipyridine (used as an indicator) were placed in an oven-dried 25-ml round bottomed flask and the system flushed with nitrogen. The reaction flask was charged with anhydrous tetrahydrofuran (5 ml, freshly distilled from lithium aluminum hydride) and methyl lithium (0.372 ml, 1.1 equivalents, 0.770 mmole). The resulting deep red solution was cooled to -40° in a Dry Ice-acetone bath and allowed to stir for 5 to 10 minutes. Freshly distilled (0.113 ml, 1.15 equivalents, 0.806 mmole) was added dropwise to the cooled solution with stirring as the formation of lithium diisopropylamide was evidenced by the gaseous evolution of methane. Stirring was continued for 0.5 hours and the temperature allowed to rise to 0°. The solution was again cooled to -78° and a solution of keto acetal 73 (.150 g, .70 mmole) in anhydrous tetrahydrofuran (3 ml) was added all at once.

The resulting solution which had now turned yellow orange was further stirred for 0.75 hours and the temperature was allowed to rise to 0°. At this time the Dry Ice-acetone bath was replaced and diethyl chlorophosphate (0.094 ml, 1.1 equivalents, 0.771 mmole) was added. The reaction mixture was stirred at room temperature for one hour, and the solution turned pale yellow color. The reaction mixture was poured into ice-water (40 ml) and extracted with ether (4X 25 ml). The combined ethereal extracts were washed with water (4X 20 ml), and saturated sodium chloride solution, and then dried (Na_2SO_4), filtered (Na_2SO_4) and concentrated in-vacuo to yield 0.1722 g of a colorless oil. Preparative thin

layer chromatography on a 20 X 20 cm silica gel plate using 90% ether-10% pet-ether eluent (with a drop of pyridine) gave 0.1524 g (62%) of enol phosphate 81; (R_f 0.34); bp 90-94° (2 mm); ir (film) 1688 (C=C), 1370, 1380 (gem-CH_3), 1180, 1100, 1050 (acetal), 1460(cyclopropyl), and 1260 cm^{-1} (P-(O-C)$_2$); nmr (CCl_4) δ 4.08 (m, 5, C$\underline{H}$(OCH_3)$_2$ and P(O$\underline{CH_2}$-)$_2$), 3.3 and 3.24 (s,s, 6, CH(O$\underline{CH_3}$)$_2$), 1.71 (bs, 6, (CH_3)$_2$C=C), 1.33 (t, 6, P(O$CH_2\underline{CH_3}$)$_2$), 1.1 and 1.05 ppm (s,s, 6, gem-CH_3). The HR mass spectral data are presented in Table IV.

Anal. Calcd. for $C_{16}H_{31}O_6P$: (M^+ -OCH_3, Peak at 350 too weak for high resolution measurement): 319.167414; Found: 319.168674 (MS), 3.9 ppm error.

(±)-trans-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde dimethyl acetal (82)[73,74]

Two 50-ml three-necked flasks connected in series were fitted with stirring bars, Dewar condensers (in the middle neck) and stopcocks. The entire apparatus was oven-dried, assembled while hot and cooled under a positive nitrogen flow which entered the first flask, swept the entire system and was flushed out of a soda lime tube at the top of the Dewar condensers. The stopcock between the first and second flask was closed and commercial monoethylamine was introduced into the first flask and allowed to sweep this part of the system prior to condensation. The condenser was filled with a Dry Ice-acetone slurry, stirring was started and the monoethylamine was dried by the addition of several pieces of lithium metal, ca. 5 mg (quickly rinsed with hexane to remove mineral

TABLE IV

Mass Spectral Data[a] for

(±)-trans-3-(1-Hydroxy-2-methylpropenyl)-2,2-dimethylcyclopropane carboxaldehyde dimethyl acetal, diethyl phosphate

m/e	I[b]	m/e	I[b]
350	2	163	5
320	3	155	32
319	17	153	4
318	43	151	7
304	2	150	26
303	2	149	94
290	3	141	3
286	2	135	11
278	4	134	8
217	1	133	31
196	1	132	14
195	2	131	6
182	2	127	19
181	7	125	10
180	2	124	89
170	3	123	17
169	32	122	26
167	6	121	29
165	44	120	4
164	95	119	12

TABLE IV (continued)

m/e	I[b]	m/e	I[b]
117	8	79	22
113	8	78	6
111	4	77	21
110	4	76	18
109	46	75	100
108	11	73	56
107	83	71	6
106	9	70	3
105	25	69	9
103	3	67	8
99	45	66	3
98	2	59	6
97	6	55	13
95	4	53	12
93	16	47	18
92	7	45	19
91	38	43	15
85	3	42	6
83	7	41	41
82	5	39	11
81	22		
80	5		

[a]Mass spectrum taken on CEC 21-110B

[b]Relative abundance.

oil, and dried quickly with a towel). After the blue color persisted for 30 minutes the stopcock connecting the second flask was opened and the freshly dried monoethylamine allowed to flush the rest of the system. The condenser of the second flask was then filled with Dry Ice-acetone slurry and sufficient amine (25 ml) allowed to distil from the first flask. Freshly cut lithium wire (80 mg, 11 mg-at, 16 equivalents) was introduced into the flask with stirring, and stirring continued for 20 minutes to allow dissolution of the metal. While stirring was continued a solution of enol phosphonate (256 mg, 0.731 mmole) in dry tert-butanol (0.27 ml freshly distilled from calcium hydride) and dry ether (1 ml freshly distilled from lithium aluminum hydride) was added all at once. The blue colored reaction mixture was stirred for 5 minutes and then carefully quenched with ethyl alcohol (2 to 5 ml). The Dewar condenser was removed and the excess monoethylamine was allowed to evaporate. The reaction mixture was transferred to a separatory funnel with a mixture of ether (50 ml) and water (50 ml), shaken, and the ether layer separated. The water layer was taken up in an equal volume of saturated sodium chloride solution and extracted with ether (3X 25 ml), and then dried (Na_2SO_4), filtered (Na_2SO_4) and concentrated in-vacuo to give 0.1245 g of a colorless oil. This crude product was chromatographed on silica gel (14 g, 70-230 mesh, E. Merck) in a 1.0 cm diameter column using 15% ether - 85% pet-ether to develop the column, taking 7-ml sized fractions. Fractions 5 - 7 gave 0.118 g (81%) of pure olefin acetal 82; bp 48 - 51° (4 mm, external temperature); ir (film) 1670 (C=C), 1460 (cyclopropyl), 1375, 1360 (gem-CH_3), 1180, 1125, 1050 (acetal) 970 cm^{-1} (endomethylene); nmr (CCl_4) δ 4.8 (dm, 1, J = 7 Hz C=CH), 4.1 (d, 1, J = 6 Hz, $CHC(CH_3)_2$), 3.2

(s, 6, $(OCH_3)_2$), 1.7 (s, 6, $(CH_3)_2C=C$), 1.1, 1.0 ppm (s,s, 6, gem-CH_3). The MR mass spectral data are presented in Table V.

Anal. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18

Found: C, 72.68; H, 11.24

(±)-trans-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde (58)[63]

Olefin acetal 88, (100 mg, .50 mmole) dissolved in reagent acetone (5 ml) was placed in a 10-ml round bottomed flask. Water (about 2 drops) was added and the solution stirred at room temperature while the progress of the acetal removal reaction was monitored by tlc (R_f 0.63 (acetal) - 0.39 (aldehyde) using 5% ether - 95% pet-ether to develop the slides.)

After 12 hours of stirring the reaction mixture was taken up in water (20 ml) and extracted with ether (4X 10 ml). The combined ether extracts were dried (Na_2SO_4), filtered ($MgSO_4$) and concentrated in-vacuo at room temperature, to yield 79.4 mg (98%) of colorless olefin aldehyde 58; bp 38-40° (5 mm, external temperature); ir (CCl_4) 2850,2720 (-CHO) 1705 (-CHO), 1440 (cyclopropyl), 1375 (gem-CH_3) and 975 cm^{-1} (endomethylene); nmr (CCl_4) δ 9.5 (d, 1, J = 5 Hz, -CHO), 4.9 (dm, 1, J = 7 Hz, HC=C), 1.72 (s, 6, $(CH_3)_2C=C$), 1.3, 1.2 ppm (s, s, 6, gem-CH_3). The HR mass spectral data are presented in Table VI.

Anal. Calcd. for $C_{10}H_{16}O$: 152.120110; Found: 152.119776

2.9 ppm error.

TABLE V

Mass Spectral Data[a] for

(±)-trans-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde dimethyl acetal

m/e	I[b]	m/e	I[b]
198	2	79	4
167	3	77	6
166	2	76	7
151	3	75	100
135	4	74	62
125	3	73	53
124	2	67	6
123	7	59	79
121	3	55	5
120	2	47	9
119	4	45	77
110	2	43	76
109	4	42	5
107	4	41	68
99	4	39	7
95	3	32	2
93	4	31	57
91	5	30	97
86	3	27	58
81	6	26	44

[a]Mass Spectrum taken on Perkin Elmer RMU-6H

[b]Relative abundance.

TABLE VI

Mass Spectral Data[a] for

(±)-trans-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde

m/e	I[b]	m/e	I[b]
152	12	95	18
150	1	94	2
138	2	93	12
137	8	91	18
135	2	84	4
125	4	83	2
124	11	82	8
123	100	81	73
122	2	80	4
121	3	79	19
119	3	77	13
111	5	72	6
110	4	69	26
109	14	68	10
108	6	67	36
107	13	66	8
105	4	59	8
98	2	58	2
97	8	57	7
96	6	56	4

TABLE VI (continued)

m/e	I[b]
55	32
53	20
51	8
43	39
42	8
41	64
39	40
24	14
23	12
22	26

[a]Mass spectum taken on CEC 21-110B.
[b]Relative abundance.

(±)-trans-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylic acid (1)

Method A[38,42] - Chromium trioxide (1.0 g, 10 mmole) was added carefully to pyridine (10 ml) in a 25-ml round bottomed flask at 0°C. The olefin aldehyde 58 (380 mg, 2.5 mmole) in pyridine (3 ml) was added in one portion, followed by a catalytic amount of water (5 drops). The mixture was stirred at room temperature. The slow oxidation of aldehyde 58 to the acid 1 was monitored by thin layer chromatography, by taking small aliquots of the mixture and diluting it in ether-water (3:1) prior to spotting the plate. Ether - pet-ether (70:30, respectively) was used to develop the silica gel slides (Rf 0.89, aldehyde; 0.32, acid). After 78 hours the mixture was poured into water (25 ml) and ether (5 ml). The reaction mixture was acidified with 10% hydrochloric acid solution until the pH reached 3-4 (approximated by litmus paper), the product was then extracted with ether (3X 50 ml). In another run the reaction mixture was diluted with dichloromethane (20 ml) and passed through a 16 cm X 3 cm diameter column of silica gel-celite (1:1) and the column was rinsed with dichloromethane (5X 25 ml). The combined organic extracts, in either case, were washed with saturated sodium chloride solution, and then dried (Na_2SO_4), filtered ($MgSO_4$) and concentrated in-vacuo to give 189 mg of the crude product as a viscous, syrup-like, colorless oil. Bulb to bulb distillation afforded 178 mg (42.3%) of pure acid 1; bp 97 - 99° (6 mm, external temperature). The product failed to crystallize even after storing in the refrigerator (3°) overnight. Crystallization was induced by taking up a sample (50 mg) of the above distilled product in an ethyl acetate-pet-ether (5 ml 10:1 ratio, respectively).

Removal of the solvent afforded 48 mg of a white, crystalline solid, which was further recrystallized from the same ethyl acetate-pet-ether solvent system; mp 47 - 49° [lit. 46 - 48°] [25] ; ir(CCl_4) 2960 (COOH), 1690 (CO), 1740 weak shoulder (H- bonding of dimer), 1375 (gem-CH_3), 850 cm^{-1} (endo C=CH); nmr (CCl_4) δ 4.86 (dm, 1, J = 8 Hz, HC=C), 2.0 (dd, 1, J = 8 Hz, J = 5 Hz -C=CH-CH), 1.73 (s, 6,$(CH_3)_2$C=C), 1.33, 1.16 (s, s, 6, gem-CH_3), 1.33 ppm (d, 1, J = 5 Hz).

Method B[75,76] - Excess Jones' reagent (0.3 ml) was added dropwise to a solution of olefin aldehyde 58 (51.4 mg, .337 mmole) in anhydrous reagent acetone (3 ml) at 0° (ice bath). After 30 minutes the reaction mixture was checked by tlc (silica gel slides) developed using 30% ether - 70% pet-ether solvent system. The presence of a spot with a high Rf of 0.83 indicated the presence of unoxidized aldehyde. There was also one other unidentified spot of Rf 0.45 besides the acid spot (Rf 0.3). Additional Jones reagent (0.1 ml) was added and the stirring continued at 0°. After 30 minutes the ice-bath was removed and the solution stired at room temperature for an additional 30 minutes. At this time the excess Jones' reagent was quenched with isopropanol (1 ml) added dropwise. The mixture was poured into water (10 ml) and extracted with ether (10 X 5 ml). The ethereal extracts were washed with water (2X 5 ml) and saturated sodium chloride solution (5 ml), and then dried (Na_2SO_4), filtered ($MgSO_4$) and concentrated in-vacuo to give 40.4 mg of a colorless viscous oil. Preparative thin layer chromatography on a 10 X 20 cm silica gel plate using 30% ether - 70% pet-ether eluent gave 16 mg of the acid 1, (28%) and 16.4 mg of an unidentified material (Rf0.3,

acid - 0.41 other product) whose nmr spectrum lacked the doublet at δ 4.8, and the singlet at δ 1.73, characteristic signals of the vinyl H (C=C<u>H</u>) and the isopropylidene 6 H $(CH_3)_2C=$), respectively.

The pure acid fraction was crystallized from ethyl acetate-pet-ether (10:1) solvent system; mp 45 - 47°.

Method C[64,65] - A solution of silver nitrate (1.7 g, 0.1 mole) in water (50 ml) in a 100-ml flask was treated dropwise, with stirring, with a solution of 80% sodium hydroxide (4.0 g, 0.1 mole) water (5.0 ml). The mixture was stirred for 10 minutes and the brown precipitate (silver oxide) was collected by decantation on a 6-cm Buchner funnel with suction and washed free of nitrates with water (3X 20 ml). The wet, freshly precipitated silver oxide was transferred to a 50-ml round bottomed flask, covered with water (2 ml) and stirred. Olefin aldehyde <u>58</u>, (224 mg, 1.47 mmole) in tetrahydrofuran (20 ml) was added all at once followed by addition of 50% solution of sodium hydroxide (4 drops). After stirring for 36 hours the reaction mixture was taken up in ether (50 ml) and the aqueous separated. The ether portion was washed with 10% sodium hydroxide solution (5X 20 ml), water (2X 15 ml), and saturated sodium chloride solution (15 ml), and then dried (Na_2SO_4), filtered ($MgSO_4$) and concentrated <u>in-vacuo</u> to give 118 mg of a crude product. The combined aqueous layer was cooled to 0° and acidified with concentrated hydrochloric acid (2-4 drops) and extracted with ehter (4X 25 ml). The combined ether portion was washed with water (2X 15 ml) and saturated sodium chloride solution (15 ml) and then concentrated <u>in-vacuo</u> to give 95.4 mg of a viscous, colorless oil. Distillation of the crude product afforded 83.4 mg (34%) of the

pure acid; bp 96 - 99° (6 mm, external temperature). The other 118.2 mg of crude product obtained from the neutral fraction comprised 48% of the theoretical yield and was recognized by the nmr doublet at δ 9.4 as a mixture of unoxidized aldehyde 58 and an unidentified third product. The pure acid 1 obtained by this method was crystallized by ethyl acetate-pet-ether (10:1) solvent system; mp 47 - 49°. The spectral data of this acid sample are identical to those observed for the other samples obtained *via* method A and B.

The above acid sample (80 mg, .476 mmole) was transformed to its methyl ester by dissolving in ether (10 ml) and adding an ethereal solution of diazomethane at 0° in small increments until the yellow color persisted. The solution was maintained at 0° for 30 minutes then allowed to rise to room temperature. Excess of diazomethane was quenched with glacial acetic acid (2 drops) then the solution was added to an equal volume of ether (15 ml) and washed with water (2X 10 ml). The ether layer was separated and then dried (Na_2SO_4), filtered ($MgSO_4$) and concentrated *in-vacuo* to give 82 mg of a slightly yellow oil. Distillation of this crude product gave 79 mg (92%) of methyl ester 83 bp 86 - 90° (12 mm, external temperature). [lit. 90 - 92° (12 mm)][25]; ir (film) 1730 (CO), 1435 (cyclopropyl), 1375, 1350 cm^{-1} (gem-CH_3); nmr (CCl_4) 4.8 (dm, 1, J = 8 Hz, HC=C), 3.62 (s, 3, H_3CCO-), 1.73 (s, 6,$(CH_3)_2C=$), 2.0 (dd, 1, J = 7, 8 Hz - C=CH-CH), 1.23, 1.1 (s, s, 6, gem-CH_3) 1.26 ppm (d, 1, J = 7).

Synthetic (±)-trans-chrysanthemic acid was found to have identical retention times to a sample of authentic trans-chrysanthemic acid which was obtained by the equilibration and hydrolysis of ethyl chrysanthemumate[32] [Aldrich 12,819-8]. The methyl esters were also compared. Glc data on separate and coinjected samples of the acid and the ester, and tlc data of separate samples and a mixture are listed below:

Trans-Chrysanthemic Acid

Column	Column Temperature	Retention time in minutes
B	135°	4.5
A	130°	6.0

Trans-Chrysanthemic Acid Methyl Ester

D	90°	8.5
E	80°	11.5
F	60°	25.3

Trans-Chrysanthemic Acid

Solvent System	R_f Value
70%-30% Pet-Ether - Ether	.38
80%-20% Pet-Ether - Ethyl Acetate	.35
60%-40% Pet-Ether- Ethyl Acetate	.48

Trans-Chrysanthemic Acid Methyl Ester

Solvent System	R_f Value
15%-85% Ethyl Acetate - Pet-Ether	.64
10%-80% Ethyl Acetate - Pet-Ether	.55
95%-5% Pet-Ether - Ether	.48

*Columns

D. 6-foot, stainless steel, 1/8 inch column, packed with 20% OV-101 on Chromosorb G, 80/100 mesh; flow rate 15 ml/min. at ambient temperature.

E. 6-foot, stainless steel, 1/8 inch column, packed with 5% SE-30 on Chromosorb W, 60/80 mesh; flow rate 15 ml/min. at ambient temperature.

F. 5-foot, stainless steel, 1/8 inch column, packed with 1.5% OV-101 on Chromosorb G, 100/120 mesh, flow rate 15 ml/min. at ambient temperature.

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