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NEW SYNTHETIC METHODS USING β-KETO ESTERS AND SOME USEFUL APPLICATIONS IN NATURAL PRODUCTS SYNTHESES

by

FUK-WAH SUM

B.Sc., Chung Chi College, The Chinese University of Hong Kong, 1971

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to the required standard

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July, 1979

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Department of Chemistry

The University of British Columbia
2075 Wesbrook Place
Vancouver, Canada
V6T 1W5

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ABSTRACT

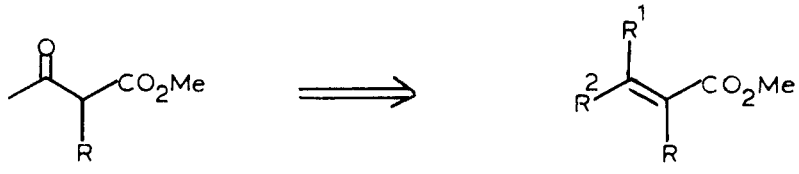
Results from studies on the cyclization of β-keto ester derivatives are presented. Electrophile- and acid-initiated cyclization of unsaturated β-keto esters, and the cyclization of epoxy β-keto esters provide interesting routes to some carbocyclic and heterocyclic compounds. Factors determining the predominance of C- or O-cyclization are discussed. The effect of olefin and epoxide substitution patterns on the reactivity and mode of cyclization was briefly investigated.

A novel stereospecific synthesis of substituted alkenes from β-keto esters was achieved, along with the extension of this method to β-diketones (equation i). Stereoselective synthesis of the E- and Z-enol phosphates of β-dicarbonyl compounds was developed. These enol phosphates reacted stereospecifically with lithium dialkylcuprates to give α,β-unsaturated carbonyl compounds. An efficient one-pot preparation of β,β-disubstituted-α,β-unsaturated esters from methyl acetoacetate based on these findings and the dianion chemistry of β-keto esters is also illustrated. The effect of a β-phosphoryloxy substituent on the reduction potential of an α,β-ethylenic carbonyl compound was estimated to be + 0.1 V. A plausible mechanism for the reaction between 1,3-dicarbonyl enol phosphates and lithium dialkylcuprates was proposed.

A convenient route to the cyclohexene derivative 248 is described. This compound represents a useful synthetic substrate for the synthesis of

several classes of natural products. The facile introduction of an isoprene unit, using methyl acetoacetate, in a stereoselective manner as indicated by equation ii is also demonstrated.

The syntheses of three natural products, viz., Latia luciferin (328), (E, E)-10-hydroxy-3,7-dimethyldeca-2,6-dienoic acid (335) and mokupalide (347) are presented, which illustrate some useful applications of the new synthetic methods developed. While the syntheses of 328 and 335 show improvements over the previous preparations of these compounds, the synthesis of mokupalide (347) represents the first synthetic approach to this compound.



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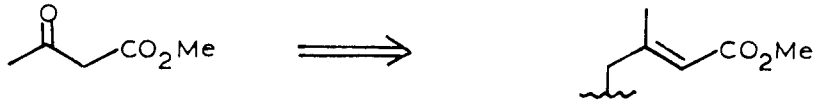

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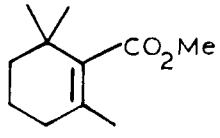

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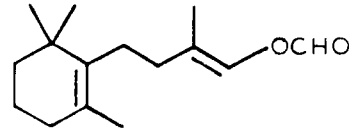

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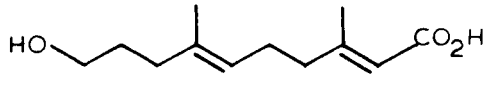

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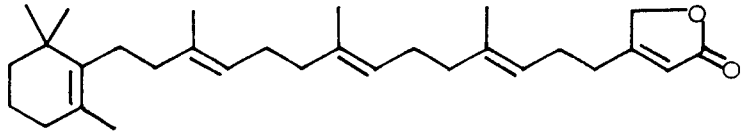

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LIST OF ABBREVIATIONS

^{13}CNMR	=	carbon-13 nuclear magnetic resonance
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DECP	=	diethyl chlorophosphate
DHP	=	dihydropyran
DIBAL	=	diisobutylaluminum hydride
DMF	=	dimethylformamide
eq	=	equivalent
ether	=	ethyl ether
HMPA	=	hexamethylphosphoramide
^{1}HNMR	=	proton nuclear magnetic resonance
IR	=	infrared
LAH	=	lithium aluminum hydride
NBS	=	N-bromosuccinimide
py	=	pyridine
THF	=	tetrahydrofuran
THP	=	2-tetrahydropyranyl
tlc	=	thin layer chromatography
TMEDA	=	N,N,N',N'-tetramethylethylenediamine
vpc	=	vapor-phase chromatography

Abbreviations for multiplicities of NMR signals:

br	=	broad	qn	=	quintet
s	=	singlet	dd	=	doublet of doublets
d	=	doublet	dt	=	doublet of triplets
t	=	triplet	m	=	multiplet
q	=	quartet			

ACKNOWLEDGMENTS

I find it most appropriate, first of all, to express my sincere thanks to Professor Larry Weiler for his advice and guidance during the course of this work.

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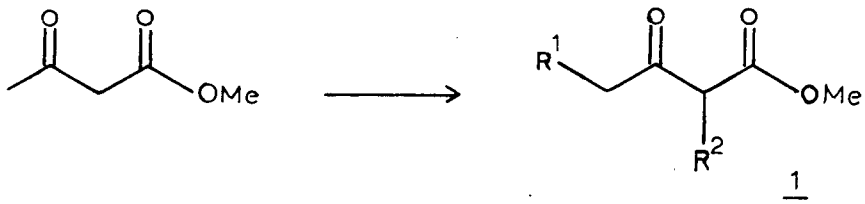
I would also like to thank Professor P. J. Scheuer and Dr. M. B. Yunker for kindly providing us with a sample of hydroxymokupalide, along with copies of experimental details for the identification of the mokupalides and the spectral data of mokupalide. Copies of the ^{1}HNMR and IR spectra, as well as a sample of methyl (E, E)-10-hydroxy-3,7-dimethyldeca-2,6-dienoate, obtained from Professor J. Meinwald and Dr. C. Semmelhack, are much appreciated.

The last but not the least is my special thanks to my wife, Phaik-Eng. My gratitude for her concern and encouragement throughout the years of my graduate studies is indescribable in words.

INTRODUCTION

Early investigations concerning the chemistry of the dianion of β-keto esters have provided new methodologies of considerable value in organic synthesis.[1] Since then, it has been a major interest in our laboratory to explore the use of simple β-keto esters as basic synthons in various synthetic tactics.

Functionalization of the α-carbon of a β-keto ester *via* reactions such as alkylation, acylation and Michael addition is well documented.[2] Selective reactions at the γ-carbon of the dianion of a β-keto ester[1] furnish the extension of the carbon skeleton at the γ-position of the molecule. By applying the above two synthetic possibilities to the simplest β-keto ester unit, namely, methyl acetoacetate, the following transformation (equation 1) can be readily accomplished. R^1 and R^2 in β-keto esters 1 represent

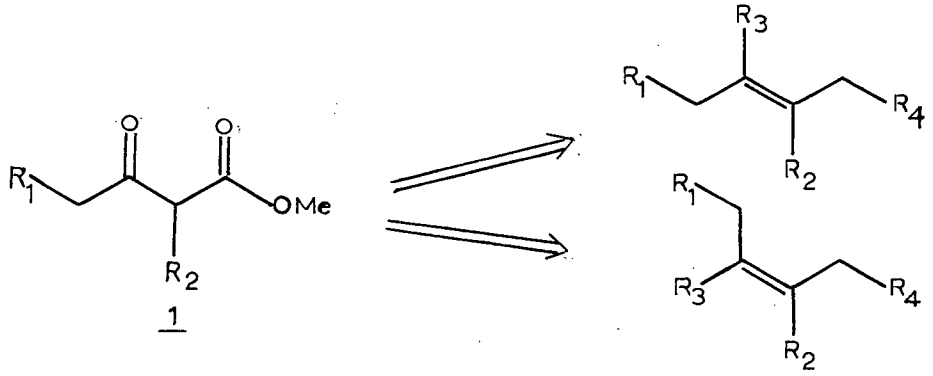


(1)

1

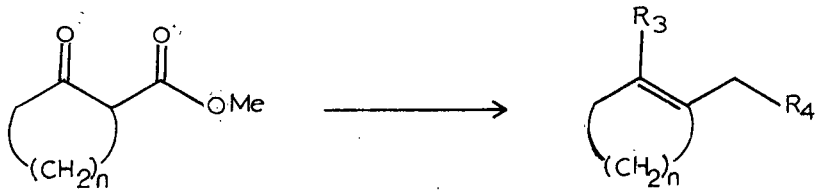
alkyl groups with or without functionalities. With access to compounds of type 1 secured, it would be of great synthetic value to establish ways to achieve extensions at the two carbonyl carbons. In fact, one of the reasons for adopting a β-keto ester as the basic synthetic substrate is the possible differentiation between the ketone and the ester functions, which would allow further structural elaboration.

A general and facile synthetic pathway leading to the overall transformations as illustrated in equation 2 would not only serve as a



(2)

stereospecific route to substituted alkenes, but would also constitute a useful method for extending carbon skeletons in organic synthesis. The same strategy could be applied to cyclic β-keto esters as shown in equation 3.



(3)

The aim of the work described in this dissertation was to develop two major synthetic methodologies based on β-keto esters, viz., ring formation reactions and stereospecific alkene synthesis, and to apply them to natural products synthesis. It is our modest hope that the results of our effort may find useful applications in modern organic chemistry.

In sections I and II, brief reviews of some aspects of carbocyclization methodologies and stereoselective alkene synthesis are given before

the respective presentations of our findings. Many of the reactions described in the introductions have been broadly used in modern organic synthesis. Some are included mainly for their elegance. The versatility as well as the limitation of those more general methods are discussed. The synthesis of several interesting natural products, demonstrating the utility of a combination of facile reactions involving β-keto esters, are presented in section III.

SECTION I: STUDIES ON CYCLIZATION REACTIONS OF β-KETO ESTERS

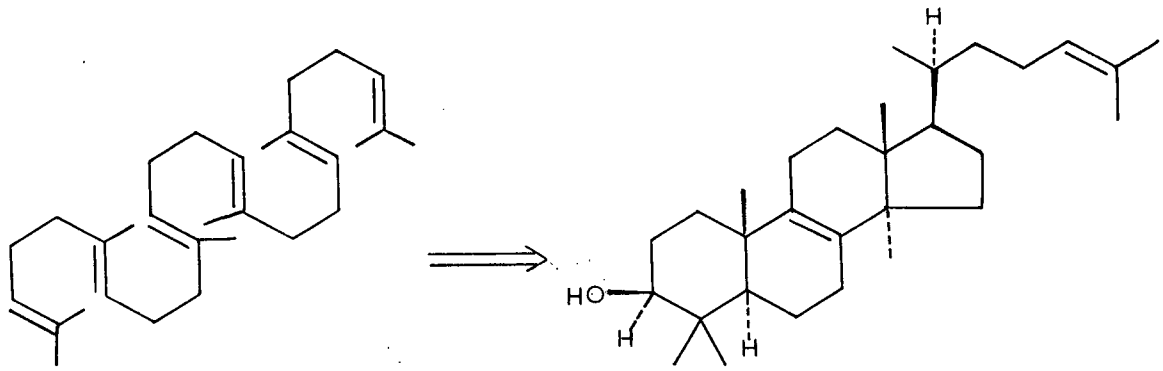
Introduction - Some Aspects of Cyclization Reactions

The creation of cyclic systems is often involved in the design of synthetic strategies. Ring structures either constitute part of the synthetic goal or serve to set up the specific stereochemistry of a molecule. Cyclization reactions are of particular interest to natural products synthesis owing to the ubiquitous existence of cyclic systems in various classes of natural products, e.g., alkaloids, insect hormones, terpenes and steroids.[3]

A ring can be formed either intermolecularly or intramolecularly. The former mode of ring formation falls into the category of cycloaddition reactions which embraces well-known reactions such as Diels-Alder reactions for the formation of six-membered rings, 1,3-dipolar addition for five-membered rings, [2 + 2] addition for four-membered rings and carbenoid addition for three-membered rings.[2] The category of intramolecular cyclization covers a broad and diverse spectrum of organic reactions with countless examples. Different types of reactions like alkylation, acylation, condensation, cycloaddition and electrophile-initiated alkene cyclizations have all been utilized. In fact, numerous novel reactions have been developed in the past few decades to synthesize ring systems which otherwise would be accessible only with great difficulty. Many of these new synthetic methods are interesting and challenging in their own right.

A. Acid-Catalyzed Cyclization of Polyenes

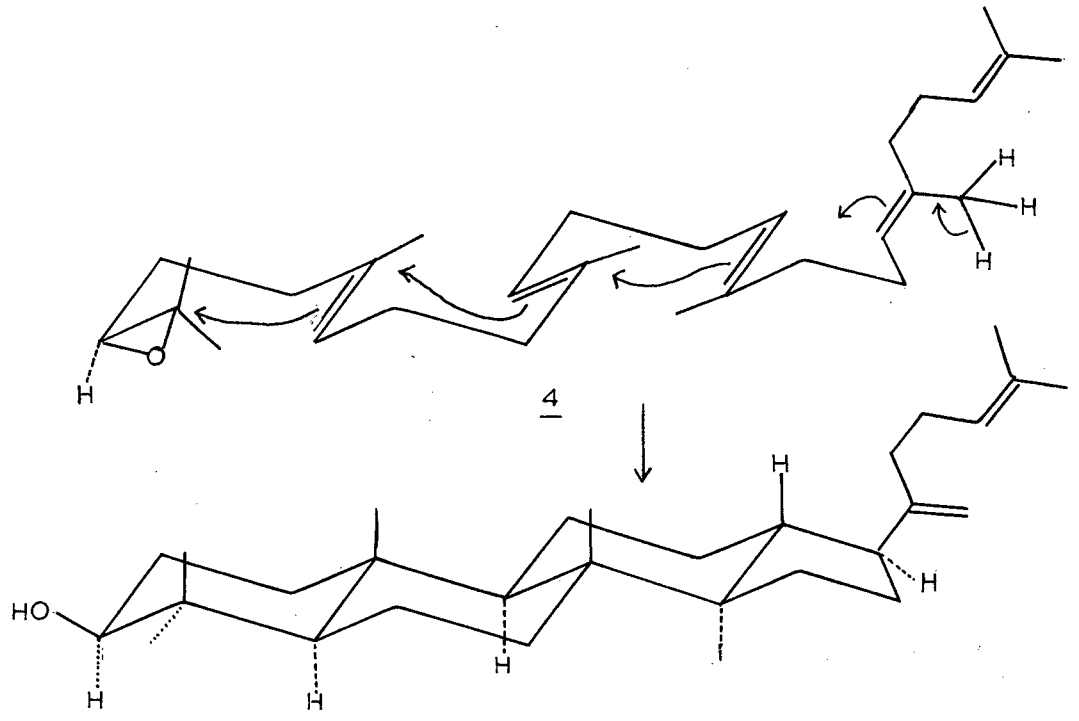
Of all the cyclization methods so far developed, few were more exciting than the biogenetic-type polyene cyclization pioneered by Stork[4] and Eschenmoser[5] in the mid-fifties, and later explored extensively by Johnson,[6] van Tamelen[7] and others.[8] The early studies were initiated by the ingenious proposals regarding the biogenesis of cholesterol from acetate.[9] At one stage of this biogenesis, squalene (2) was suggested to undergo enzyme catalyzed polycyclization to produce lanosterol (3). It is now well recognized that squalene or squalene 2,3-oxide is the biogenetic precursor of polycyclic



2 3

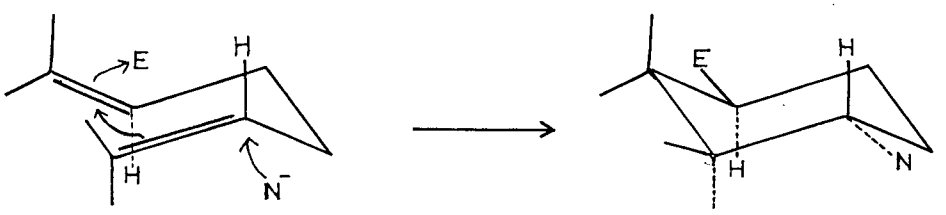
triterpenes.[9,10,11]

In 1955, Stork[4a] and Eschenmoser[5a] independently suggested that squalene-like polyolefins should have an intrinsic susceptibility to cyclize stereoselectively to a polycyclic system of definite stereochemical configuration. Thus the highly stereoselective biological cyclization of squalene could be rationalized on stereoelectronic grounds as illustrated below by the cyclization of squalene 2,3-oxide (4) to give dammaradienol (5).



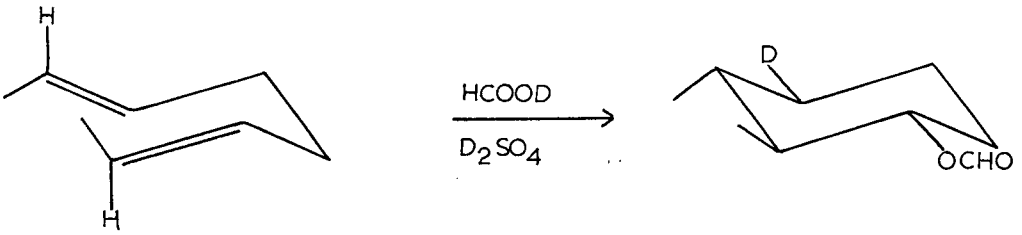
The squalene molecule was envisioned to align in such a way that trans-anti-parallel electrophilic additions to the olefinic bonds initiated by an incipient cationic centre at carbon-2 could occur through an all-chair conformation. An all-trans squalene would therefore lead to the all-trans fusion of the four rings in dammaradienol.

The Stork-Eschenmoser hypothesis postulates a concerted cyclization process. Applying it to the cationic cyclization of a 1,5-diene to form a cyclohexane system (equation 4), the entering electrophile (E) and



(4)

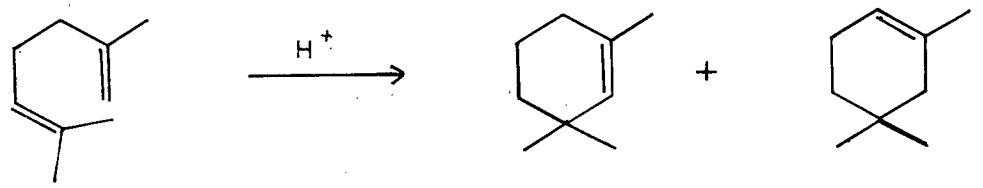
nucleophile (N) should be trans diequatorial in the products. Examples in accord with this hypothesis have been reported. Ulery and Richards[12] showed that treatment of diene 6 with deuteroformic and deuterosulfuric acids gave cyclohexyl formate 7 as the only cyclized product.



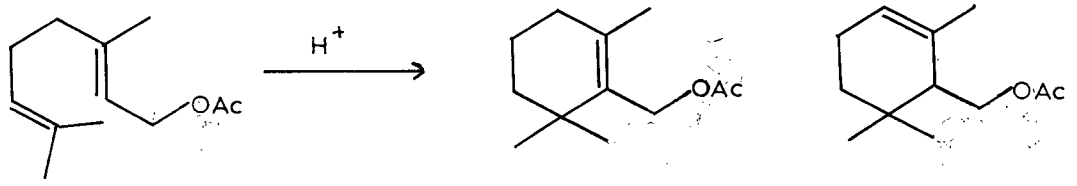
6 7

The biogenetic cyclization of squalene is intriguing to organic chemists for two main reasons, namely, the formation of polycyclic systems in one step and the complete stereochemical control over this process. A biomimetic approach to the total synthesis of polycyclic natural products, e.g., steroids and triterpenes, if successful, would be much more efficient than the conventional strategy of step-by-step annelations. Indeed, this concept has stimulated many investigations to develop similar but nonenzymic cyclizations in the laboratory. Results of these studies and their application to the synthesis of steroids and various terpenes have been reviewed.[6,7,8,13,14,15] Some noteworthy findings will be described below.

In a study which represented one of the earliest biogenetic-type synthesis of terpenes, cyclogeraniolenes (9) and cyclogeraniol acetates (11) were obtained by acid-catalyzed cyclization of geraniolene (8) and geraniol acetate (10), respectively.[16] Studies directed toward the bio-

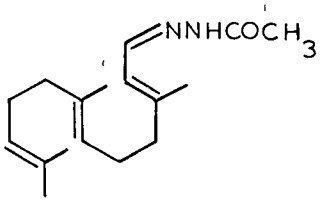


8 β-9 α-9



10 β-11 α-11

genetic-type cyclization of farnesol derivatives have provided an attractive route to decalin systems and related sesquiterpenes. Stoll et al. first reported the acid promoted cyclization of farnesol semicarbazone (12) to give α- and β-bicyclofarnesols (13).[17] Boron trifluoride catalyzed cyclization of farnesoic acid (14) to form the bicyclic compounds 16a and 16b was found to proceed via an isolable monocyclic intermediate 15.[4,18] This result suggests that similar intermediary monocyclic dienes are probably involved in other related cyclizations. Further evidence for the stepwise cyclization came from Eschenmoser's work.[19] When the (trans,



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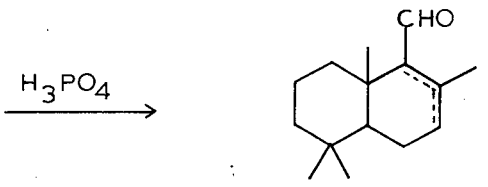

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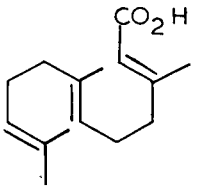

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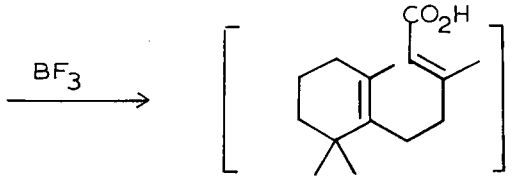

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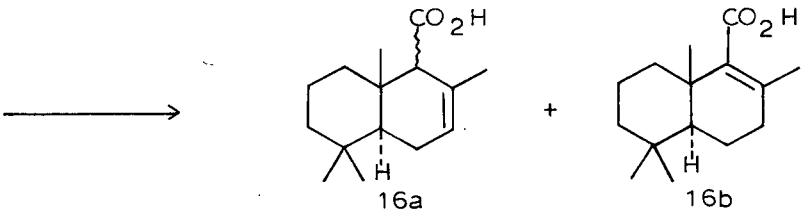
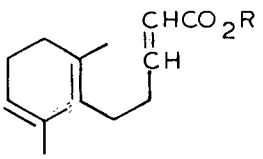
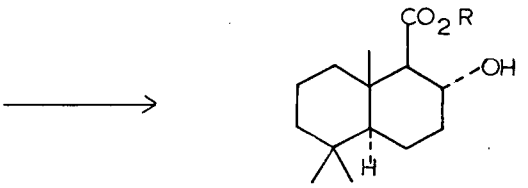


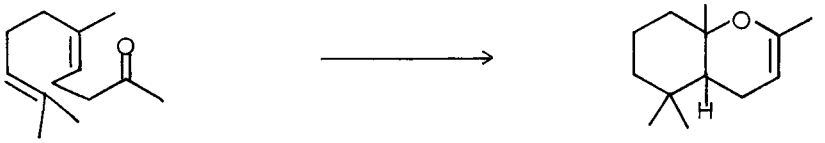
16a + 16b



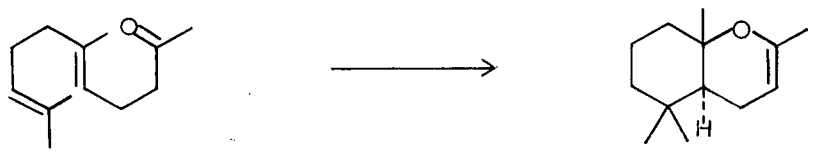
17 R = H 18 R = CH_3



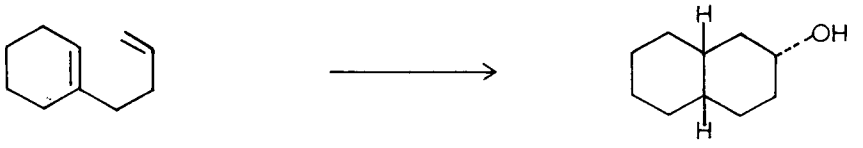
19 R = H 20 R = CH_3



21a 22a



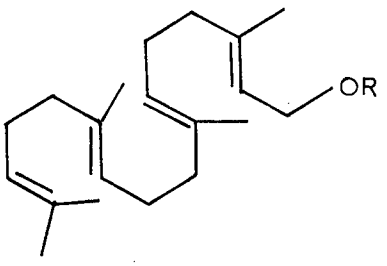
21b 22b



23 24

trans)-, (cis, trans)- and (trans, cis)-isomers of desmethyl farnesoic acid 17 and their methyl esters 18 were cyclized with sulfuric and formic acids, only trans fused products 19 and 20 were obtained. Cyclization of the (cis, trans)-isomer to a trans fused product is contrary to the Stork-Eschenmoser hypothesis which would predict cis fused products if the cyclizations were concerted. Monocyclic carbonium ions of sufficient lifetime must be involved to allow for the formation of the thermodynamically more stable trans-decalin system. The poor nucleophilicity of the olefinic bond conjugated to the carboxyl group may account for the non-concerted nature of this process. In fact, stereospecific cyclizations did occur in cases where the centre involved in terminating the ring closure process was not reduced in nucleophilicity. Smit et al. have shown that cis- and trans-geranyl acetone, (21a) and (21b), cyclized stereospecifically to the corresponding bicyclic ethers 22a and 22b.[20] Johnson also found that acid-catalyzed cyclization of diene 23 gave predominantly the cis-anti-decalol 24.[21]

Results of acid-promoted cyclization of geranylgeraniol derivatives 25 were unsatisfactory.[19] These reactions invariably led to complex



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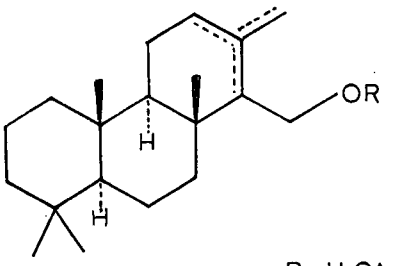


R = H, OAc

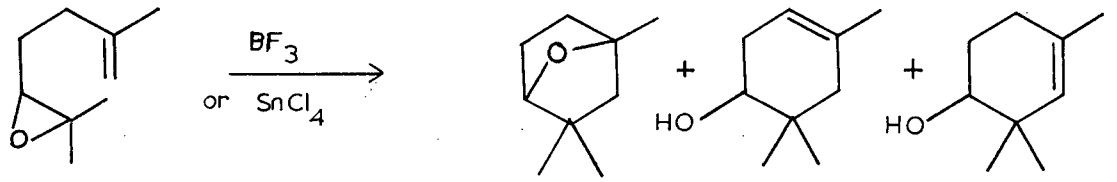
26

mixtures with very low yield of the desired tricyclic material 26. The difficulty appeared to arise from the indiscriminate protonation of various olefinic bonds, resulting in all sorts of cyclized products. In order to solve this problem, several groups of workers have searched to find more selective ways to initiate the cyclization of polyenic systems. The general concept is to incorporate into a polyenic molecule an appropriately disposed functional group which is capable of generating a cationic centre under conditions that would not otherwise affect the olefinic bonds. The use of polyenic epoxides,[7] sulfonate esters,[6] acetals[6] and allylic alcohols[6] have been studied extensively and have enjoyed great success in the synthesis of cyclic terpenes.

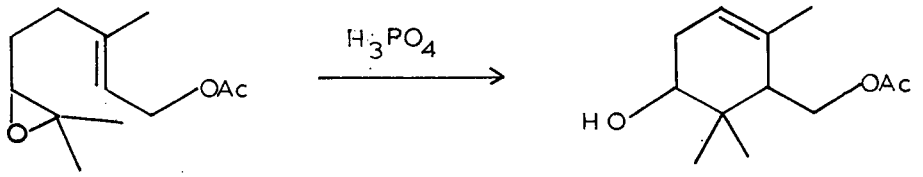
B. Cyclization of olefinic epoxides

Acid-catalyzed ring opening of an epoxide suitably placed in a polyenic molecule would generate a cationic centre to initiate cyclization and at the same time produce a hydroxy function in the cyclized product. Indeed, a host of 3-hydroxylated polycyclic terpenoids have been synthesized *via* stereoselective cyclization of terpene terminal epoxides.[7]

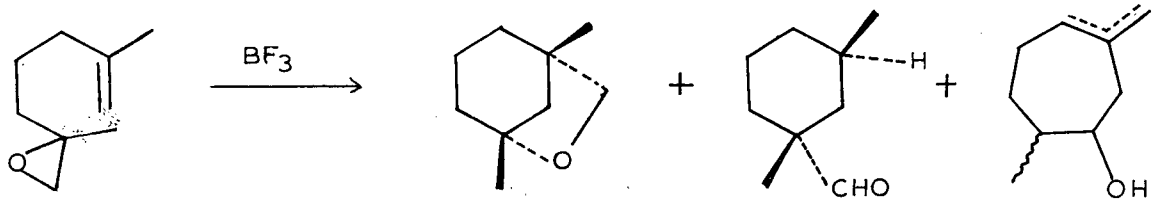
Simple monoenic epoxides were first put to test by Goldsmith and van Tamelen. Upon treatment with boron trifluoride or stannic chloride, geraniolene monoepoxide 27 afforded a mixture of bicyclic ether 28 and cyclohexenols 29a and 29b.[22] The epoxide of geranyl acetate, 30, was converted into the cyclohexenol 31 with phosphoric acid.[23] Mechanistically



27 28 29a 29b

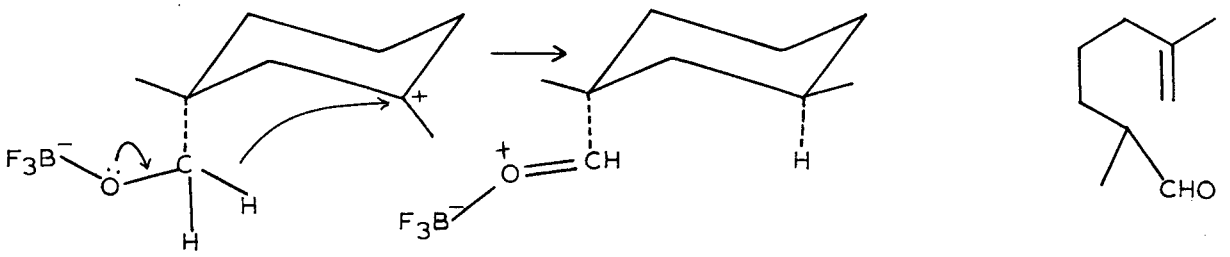


30 31



32 33 34 35

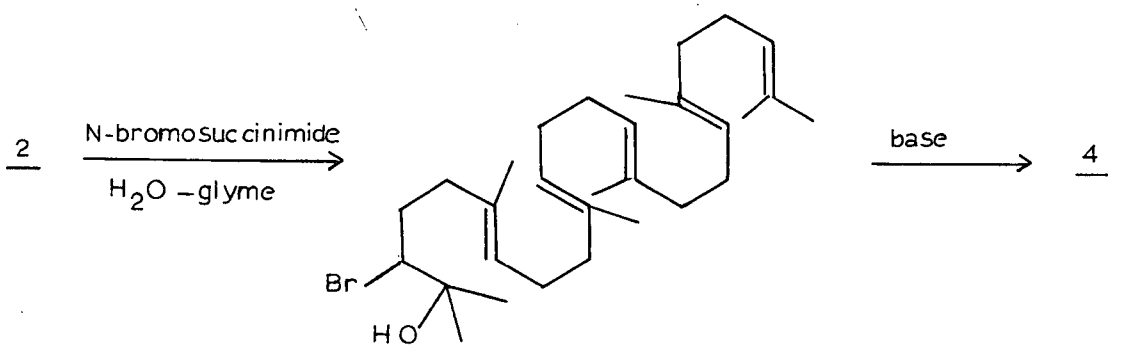
42% : 35% : 20%



I II 35a

interesting results were obtained from the reaction of epoxide 32 with boron trifluoride. Three cyclic products, 33, 34 and 35 were isolated.[24] Presumably, opening of the oxirane ring of 32 with participation of the olefinic bond gave rise to the bicyclic ether 33 and the aldehyde 34. Hydride transfer (I → II) was suggested to account for the formation of 34. An intermediary aldehyde 35a, derived from opening of the oxirane ring without participation of the olefinic bond, was apparently involved in the formation of 35.

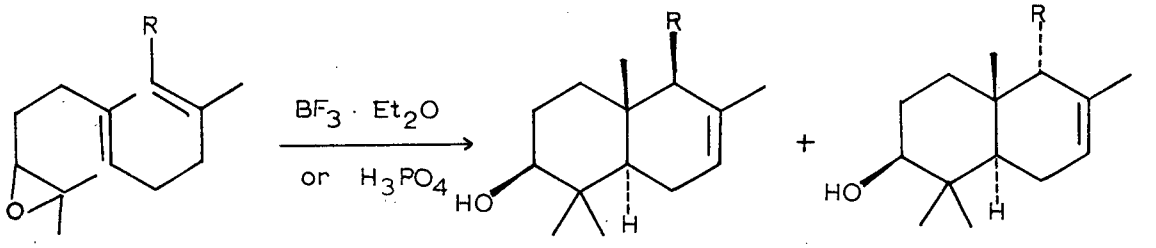
One serious problem concerning the utility of acyclic epoxypolyene cyclizations is the selective introduction of an epoxide function at the terminal olefinic bond of a polyenic system. To circumvent this difficulty, van Tamelen and coworkers developed a highly regioselective epoxidation method.[25] The procedure involves selective mono-bromohydrin formation using N-bromosuccinimide in aqueous glyme and subsequent treatment of the bromohydrin with base to form the epoxide. As illustrated by the conversion of squalene (2) to squalene 2,3-oxide (4), the selectivity for the formation of the terminal bromohydrin 36 was found to be greater than 95%. A plausible explanation for the high regioselectivity is that in a highly polar



36

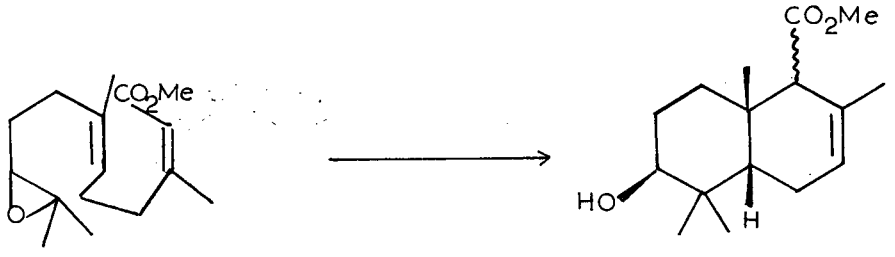
medium, a long chain polyenic molecule probably assumes a coiled conformation such that the internal carbon-carbon double bonds would be sterically shielded, leaving the terminal olefinic bonds exposed for reaction.

Epoxyfarnesyl derivatives, prepared by the above epoxidation method, have been investigated for polycyclization. Epoxides 37 and 39, on treatment with acids, cyclized to the bicyclic compounds 38a, 38b and 40a, 40b respectively. In each case, the ratio of the isomers formed varied according to the reaction conditions employed.[7a,26,27] These types of cyclizations have been shown to be stereospecific, in contrast to the results of acid-catalyzed cyclization of polyenes (vide supra). Thus the cis isomer of 39, viz., methyl trans, cis-10,11-oxidofarnesoate (41) was converted into the cis fused decalols 42 while epoxide 39 gave only the trans fused decalols 40a and 40b under acid catalysis.[27]



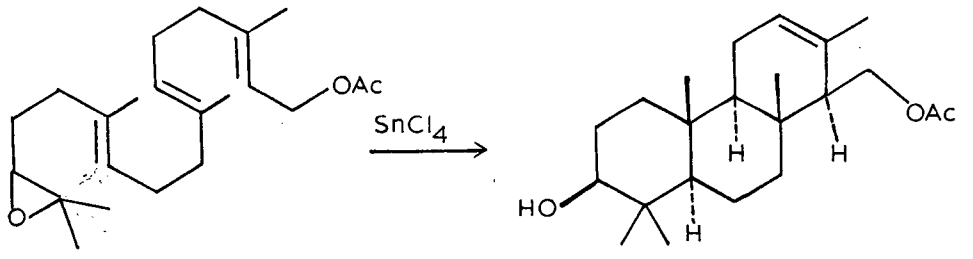
37 R = CH_2OAc 38a R = CH_2OAc 38b R = CH_2OAc

39 R = CO_2Me 40a R = CO_2Me 40b R = CO_2Me

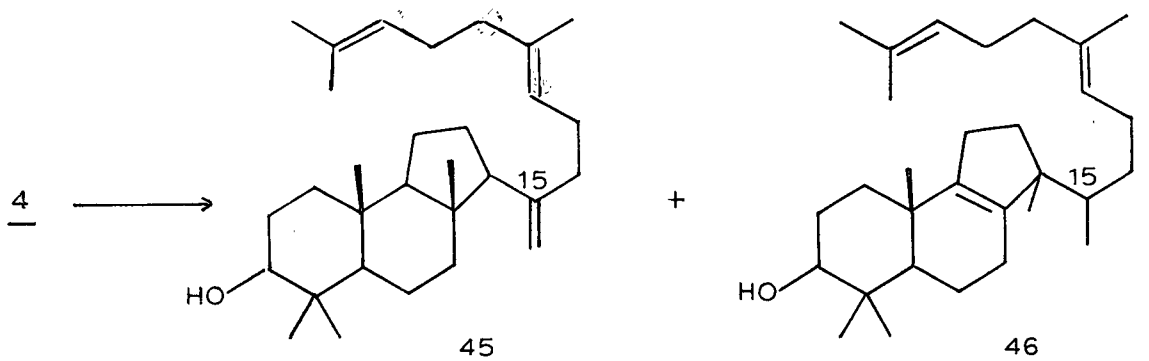


41 42

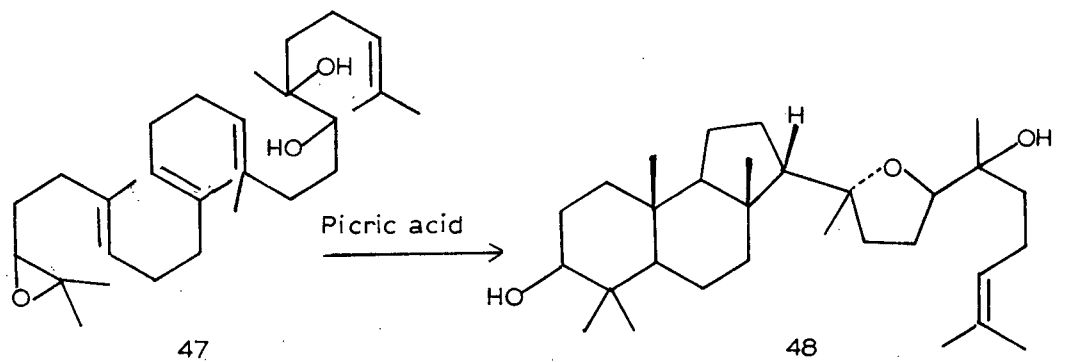
Extending the epoxypolyene cyclization to the tricyclic level, van Tamelen and Nadeau were able to isolate the tricyclic alcohol 44 from the stannic chloride catalyzed cyclization of epoxide 43.[28] When squalene 2,3-oxide (4) was subjected to similar reaction conditions, two tricyclic products, namely, the trienic alcohol 45 and the rearranged isomer 46 were obtained.[29] Formation of the five-membered C ring was apparently dictated by the development of the more stable cationic centre at carbon-15. Based on this finding, Sharpless accomplished the biogenetic-type synthesis of



43 44



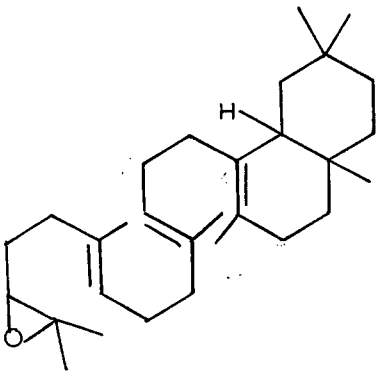
45 46



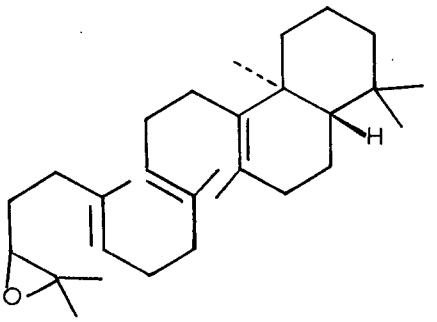
47 48

malabaricanediol (48) by preparing the epoxydiol 47 and cyclizing it with picric acid.[30]

Similar cyclizations have also been utilized in the total synthesis of the pentacyclic triterpenes, δ-amyrin (51)[31] and tetrahymanol (52)[32], with epoxides 49 and 50 as their corresponding acyclic precursors.



49



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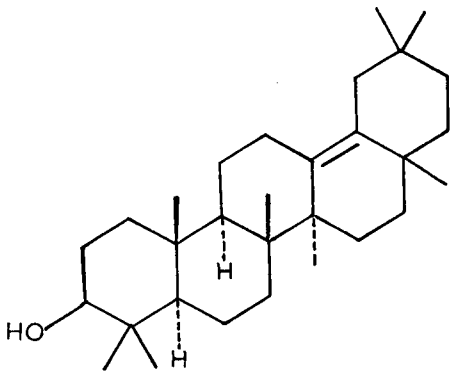

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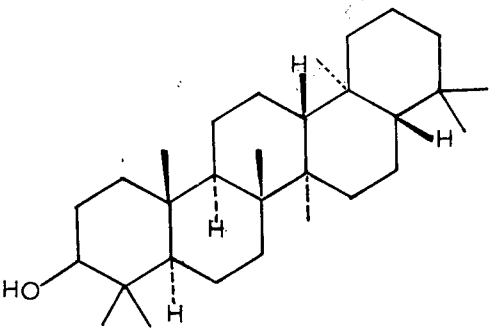
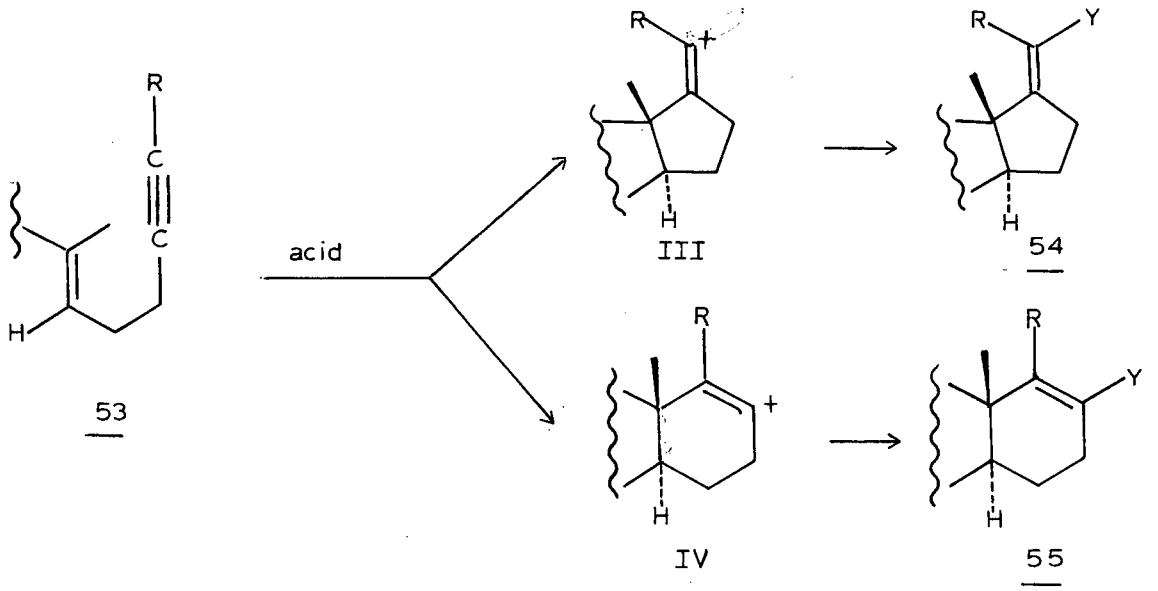


52

C. Cyclizations with Participation of Acetylenic Bonds

The acid-catalyzed cyclization of polyenes involving the participation of acetylenic bonds is a useful synthetic tool for constructing polycyclic systems, especially those possessing a five-membered ring moiety. Developed mainly by Johnson and coworkers,[6d,33] this type of cyclization can be generally represented by Scheme i. Compounds with partial structure

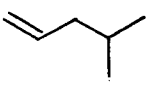
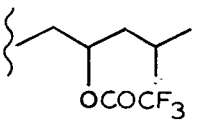
Scheme i



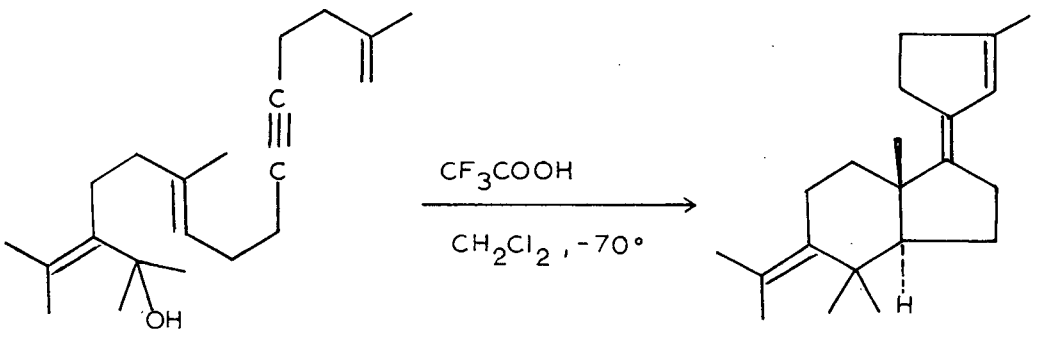
Y = nucleophiles (internal or external)

53 may cyclize to form either 54 or 55, via the corresponding intermediary cations III or IV, depending on the nature of R. It has been demonstrated that when R was an alkyl or aryl group, III predominated and when R was a

trialkylsilyl group, IV was favored. The vinylic cation III has been trapped by various external nucleophiles as listed below. Nucleophilic

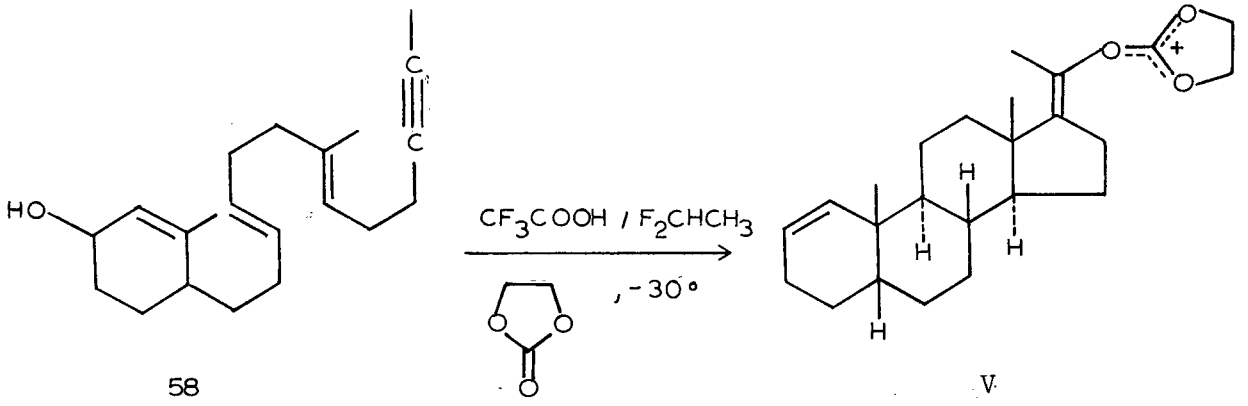
Acid, solvent	Y
Formic acid, pentane	-OCHO
1% Trifluoroacetic acid, acetonitrile	$-NHCOCH_3$
Stannic chloride, benzene	$-C_6H_5$
Trifluoroacetic acid, 	
Boron trifluoride, 1,1-dichloroethane	F

attack at the cationic centre of III by an internal olefinic bond has also been reported. Cyclization of alcohol 56 with trifluoroacetic acid at low temperature gave compound 57 in 70% yield.[34]

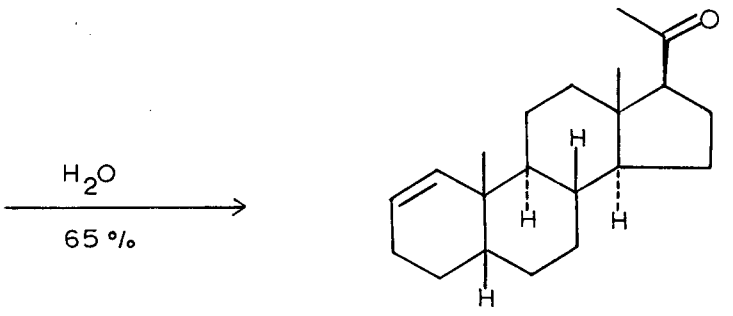


56 57

Polyene cyclizations with the participation of acetylenes have been successfully applied to the total synthesis of steroids. For example, the key step in a total synthesis of progesterone involved the conversion of alcohol 58 into the pregnenone (59) in the presence of trifluoroacetic acid and ethylene carbonate.[35] It was believed that ethylene carbonate served as a nucleophile to terminate the cyclization process by forming the stabilized cation V.

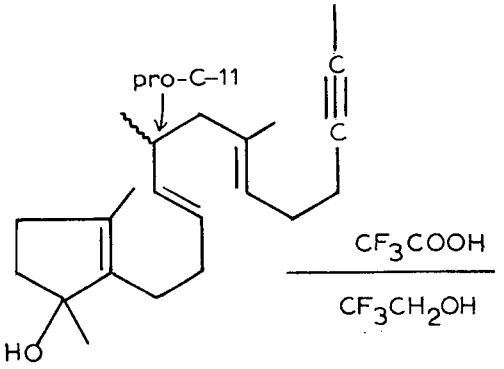


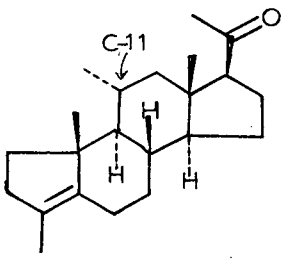
58 V



59

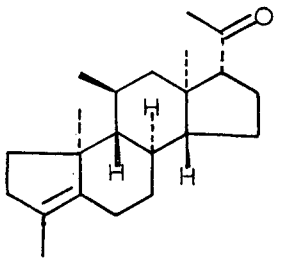
Results from application of similar cyclizations to the synthesis of C-11-substituted steroids indicated essentially complete stereochemical control by a chiral centre at pro-C-11 [1] of the polyene precursor in these processes. In theory, cyclization of the pro-C-11-methyl alcohols 60R and 60S would lead to two diastereomeric pairs of enantiomers 61a,b and 62a,b. The alcohol 60R with R configuration at pro-C-11 could cyclize to give 61a or 62a depending whether a back face or a front face attack on the cyclopentene ring occurred. Similarly alcohol 60S could cyclize to





61a

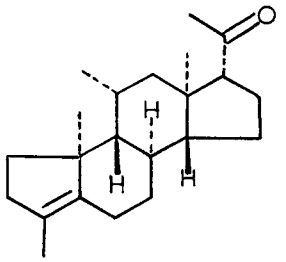
+



61b

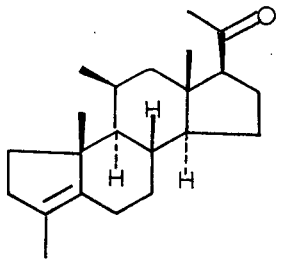
60R : R configuration at pro-C-11

60S : S configuration at pro-C-11



62a

+

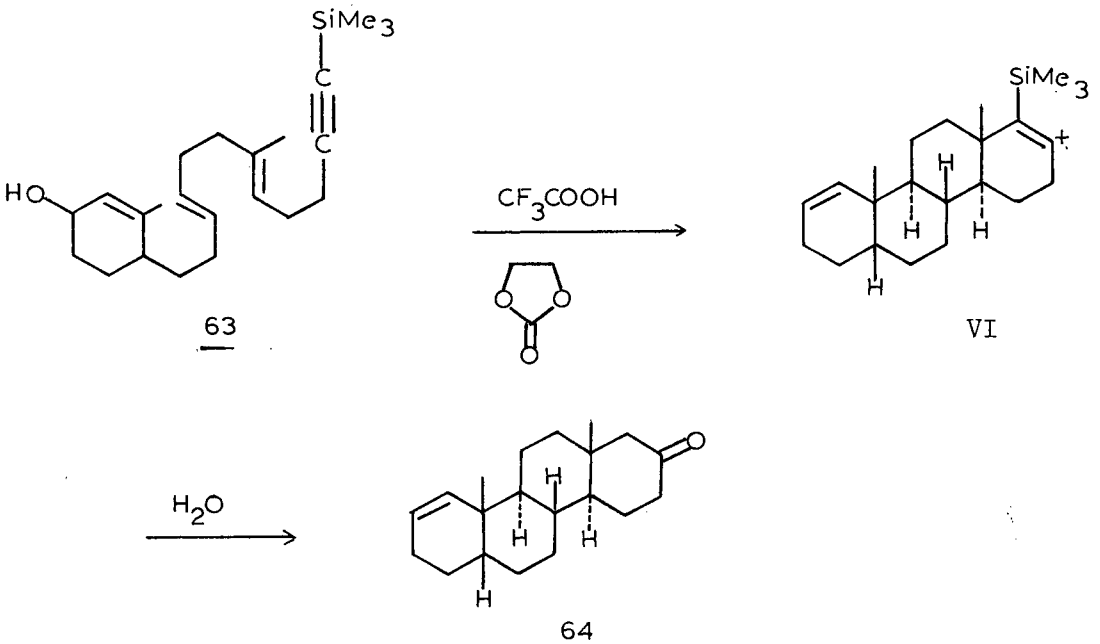


62b

(1). The term "pro-C-11" refers to the carbon which becomes C-11 in the steroid product.

form 61b or 62b. However, when alcohols 60R,S were treated with trifluoroacetic acid in trifluoroethanol, a racemic mixture of 61a and 61b was obtained in over 60% yield with no detectable amount of 62a and 62b.[36] Obviously, preference of the pro-C-11-methyl group to assume a pseudo-equatorial position during the cyclization dictated the stereochemical course. Thus 60R cyclized exclusively at the back face of the cyclopentene ring to give 61a with an equatorial C-11-methyl group, while 60S underwent exclusive front face attack on the cyclopentene ring to afford 61b. This asymmetric induction effected by a pro-C-11 chiral centre has been utilized in a total synthesis of optically active 11α-hydroxyprogesterone.[37]

Participation of the trimethylsilylacetylenic group in the cyclization of alcohol 63 resulted in the formation of a six-membered D ring in the steroid product 64.[33b] The stabilization of a positive charge by a β-silyl group[38] may account for the preferential formation of VI which, apparently, was the intermediate leading to ketone 64.

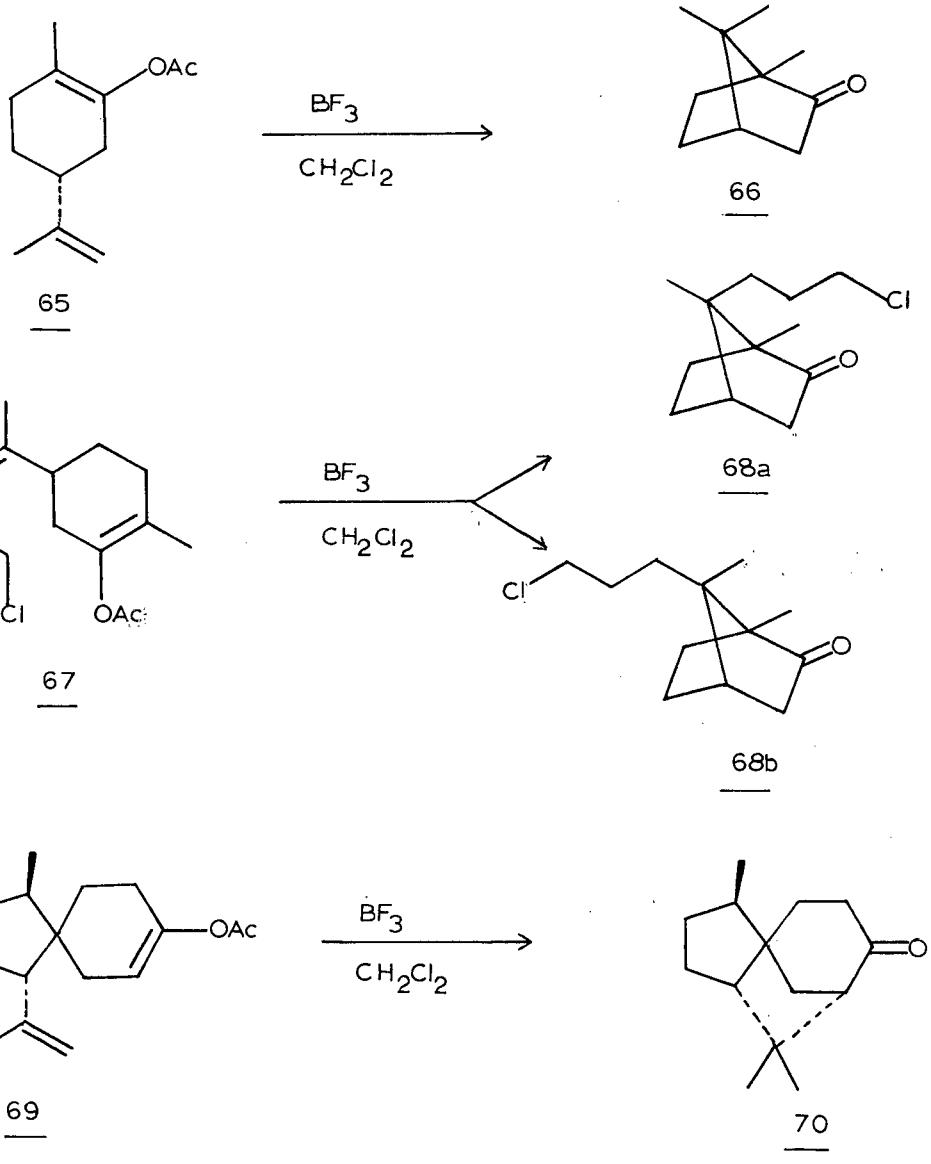


63 VI

64

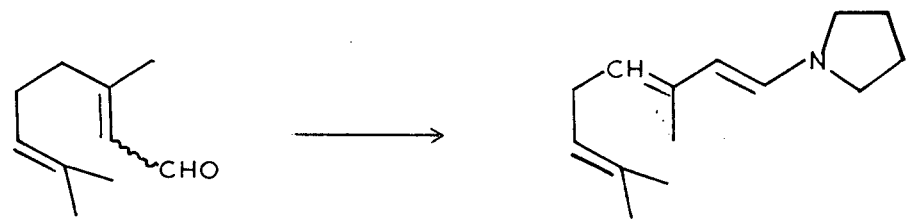
D. Cyclization via Enol Derivatives

Enol derivatives of ketones and aldehydes have been used successfully in several biogenetic-type cyclizations. Treatment of dihydrocarvone enolacetate (65) with boron trifluoride in dichloromethane gave camphor (66) in 90% yield.[39] This reaction was applied to the synthesis of campherenone and epicampherenone, in which enolacetate 67 was cyclized to

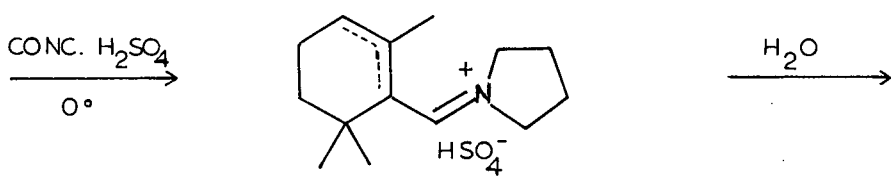


give a mixture of 68a and 68b.[40] Similarly, in the key step of a biogenetic type synthesis of cedrol, enolacetate 69 was converted into the tricyclic ketone 70.[41]

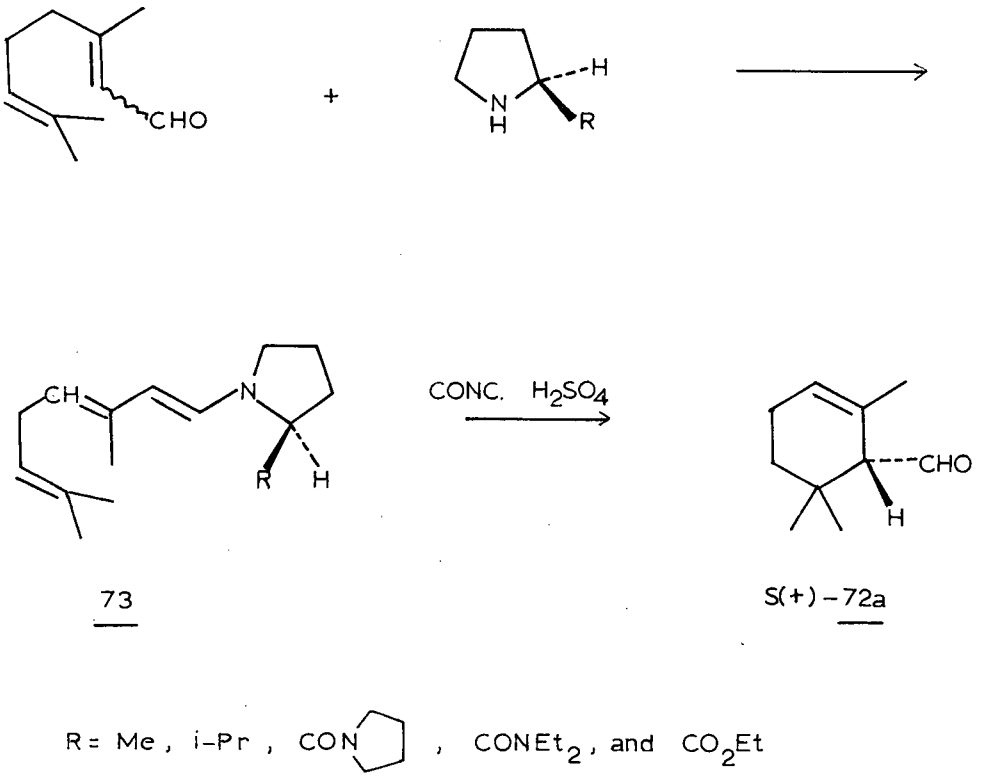
Recently, a group of Japanese workers developed a novel cyclization of citral via its enamine derivatives.[42] The citral pyrrolidine enamine 71, when treated with a mixture of concentrated sulfuric acid and water, gave α-cyclocitral (72a) in moderate yield, accompanied by only a trace amount of β-cyclocitral (72b). An asymmetric synthesis of



71



72a 72b



73

S(+)-72a

R = Me, i-Pr, CON⟨ ⟩, $CONEt_2$, and CO_2Et

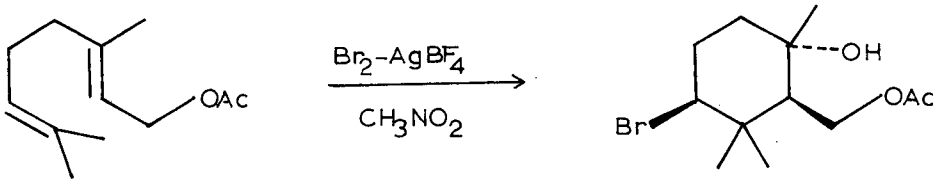
α-cyclocitral (S(+)-72a) was also accomplished by applying the same cyclization method to some chiral enamines of citral 73.

E. Electrophile-Initiated Cyclizations

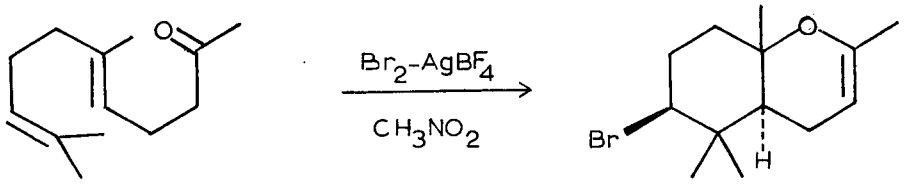
In the past decade, the rapidly growing number of bromine-containing terpenoids isolated from natural sources, especially marine organisms, has prompted many investigations to develop efficient synthesis of this class of compounds.[43] Of particular interest in this regard is the study on direct brominative ring closure of polyenes. A reagent

system developed by Faulkner for this purpose consisted of equivalent quantities of bromine and a Lewis acid mixed in a polar, aprotic solvent.[44] Cyclization of geranyl derivatives employing this method gave mediocre yields of the corresponding bromocyclogeranyl compounds. For example, treatment of geranyl acetate with an equimolar mixture of bromine and silver fluoroborate in nitromethane gave the bromo compound 74 in 20% yield. Under similar conditions, geranyl acetone afforded the vinyl ether 75 in the same yield.

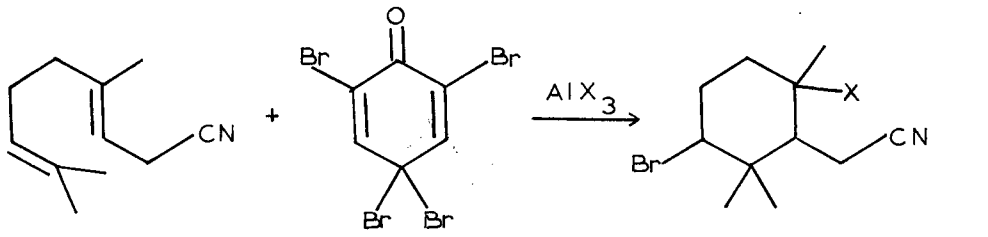
Kitahara and Kato used 2,4,4,6-tetrabromo-2,5-cyclohexadienone (77) as a mild source of bromine.[43,45] In the presence of this bromoketone and an aluminum halide, geranyl cyanide (76) was converted into the monocyclic compound 78 in about 15% yield. Although tetrabromoketone 77



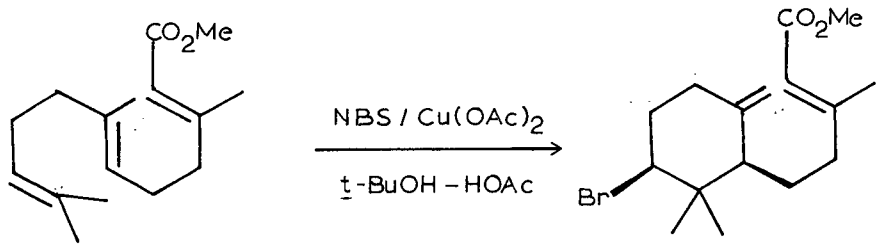
74



75



76 77 78 X = Br , Cl



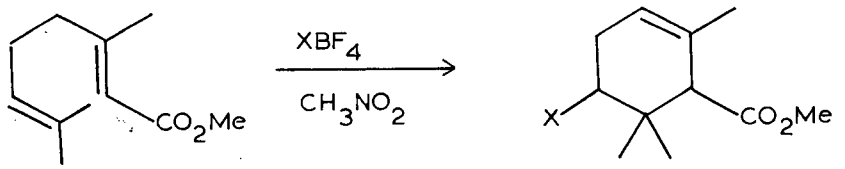
79

showed significant selectivity towards bromination of terminal olefinic bonds in polyene systems,[45b] the low yielding nature of the cyclization reactions limits its use in this respect.

Brominative cyclization was also effected by using N-bromosuccinimide and cupric acetate in t-butanol and acetic acid. The bromo compound 79 was obtained in 12% yield from methyl (trans, trans)-farnesoate by using this reagent system.[46]

Smit and coworkers investigated the electrophilic addition reactions of a wide variety of cationoid complexes of the type $X^+BF_4^-$ (X^+ =

RCO^+, R^+, NO_2^+ and RS^+) and accomplished, inter alia, the phenylsulfenium ion and the acylium ion initiated cyclizations of methyl geranate (equation 5) in 57 and 56% yields, respectively.[47]

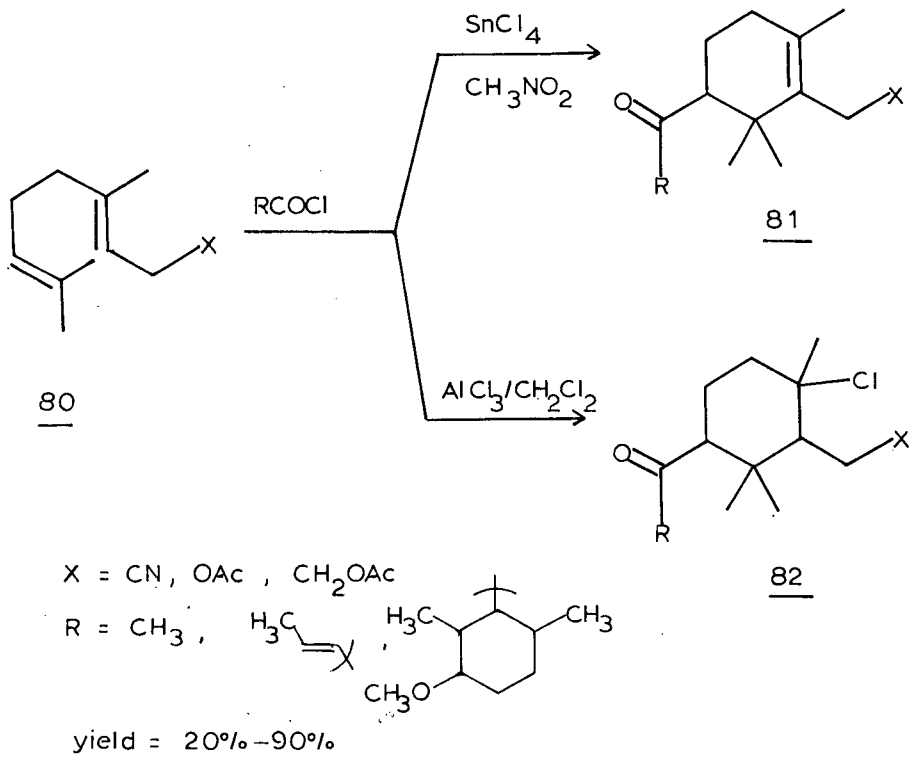


(5)

X = C_6H_5S-, $(CH_3)_3\overset{O}{\overset{\|}{C}}-$

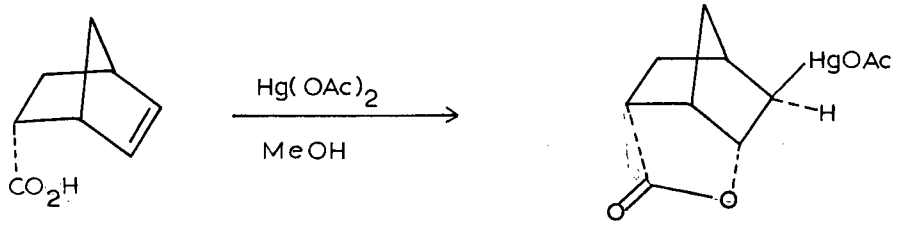
Another facile reagent system for promoting selective acylation of polyenes with concomitant ring closure was developed by Kitahara and co-

Scheme ii



workers.[48] Equimolar mixture of an acyl chloride and stannic chloride in nitromethane transformed the geranyl derivatives 80 to the corresponding unsaturated ketones 81. When aluminum chloride and dichloromethane were used instead of stannic chloride and nitromethane, the chloroketones 82 were obtained (Scheme ii).

Mercuric ion induced cyclization has been applied mainly to the synthesis of lactones and cyclic ethers as shown by the following examples (equations 6[49] and 7[50]). Goutarel and coworkers conducted a detailed study on the



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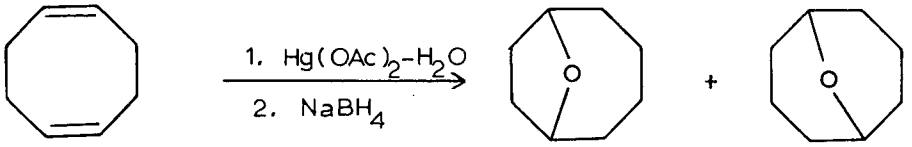
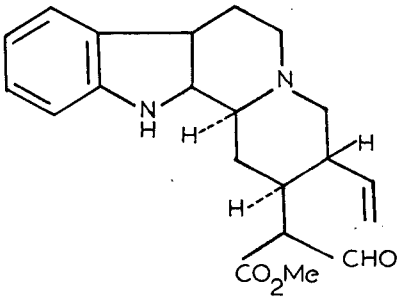


(7)

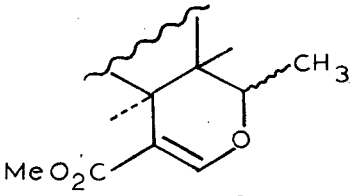
reactivity of the β-aldehydo ester group towards an internal olefinic bond activated by mercuration.[51] The mercurinium ion initiated cyclization of the alkaloid 83, followed by demercuration with sodium borohydride, gave a mixture of O- and C-cyclized products 84 and 85 in 20 and 45% yields, respectively.



83

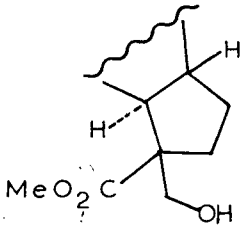
1. $Hg(OAc)_2$-HOAc

2. $NaBH_4$



84

+



85

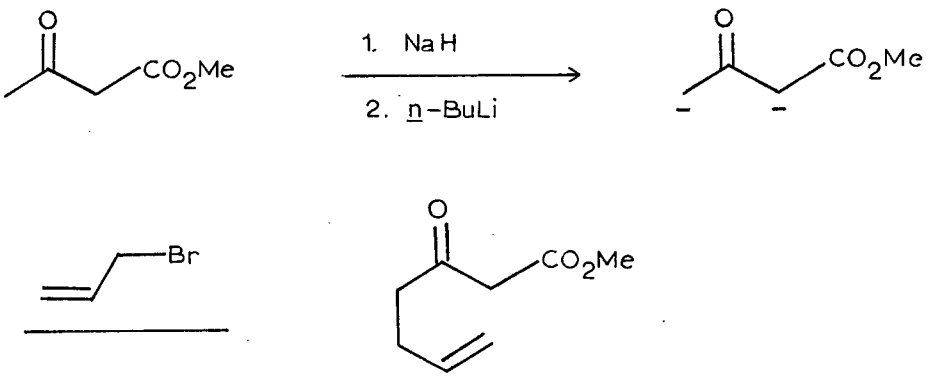
It is obvious from the foregoing survey on cyclization reactions that acid- and electrophile-initiated cyclizations of olefinic and epoxy substrates provide useful and efficient routes to cyclic systems. Although these methods have been investigated intensively, the utilization of enol type nucleophiles in similar reactions remains rather unexploited. In our continuing search for synthetic utilities of β-keto esters, we felt that the β-keto ester function would not only serve as a convenient internal nucleophile in cyclizations, but also provide useful functionalities in the cyclized products. The results of our study with the appropriate discussion are presented in the following part of this section.

Results and Discussion

A few examples of utilizing the β-keto ester function to construct ring systems have been reported in the past decade. Most of these cyclization reactions were applied to the synthesis of natural products, inter alia, jasmonoids and prostanoids. Among them are the cyclization of enamine[52] and α-diazo[53,54] derivatives of β-keto esters in the synthesis of prostaglandins; the intramolecular condensation of β,ε-diketo esters in the synthesis of jasmonoids;[55] and the intramolecular alkylation of β-keto ester enolates with π-allylpalladium complexes in the synthesis of humulene.[56] We have been interested in using acyclic β-keto esters as precursors to cyclic compounds, especially five- and six-membered ring systems. Results of our study on the cyclization of some unsaturated as well as some epoxy β-keto esters are described below.

Electrophile- and Acid-Initiated Cyclization of Unsaturated β-Keto Esters

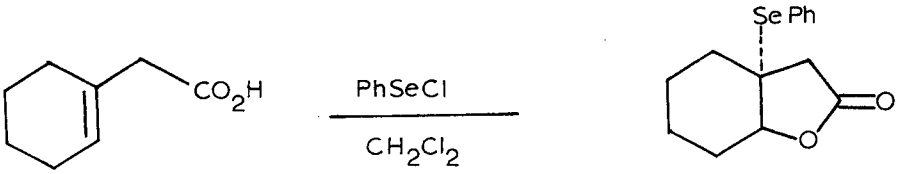
Cyclization of the alkenyl β-keto ester 86 was first investigated. This keto ester was prepared[1] in good yield by alkylation of the dianion of methyl acetoacetate with allyl bromide. Attempts to promote cyclization



86

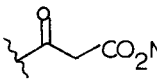
of 86 with acids proved to be futile. No significant reaction could be detected when 86 was treated with Lewis or protic acids at room temperature. Employment of more drastic conditions (e.g., refluxing temperatures and prolonged reaction times) merely led to polymerized and intractable mixtures.

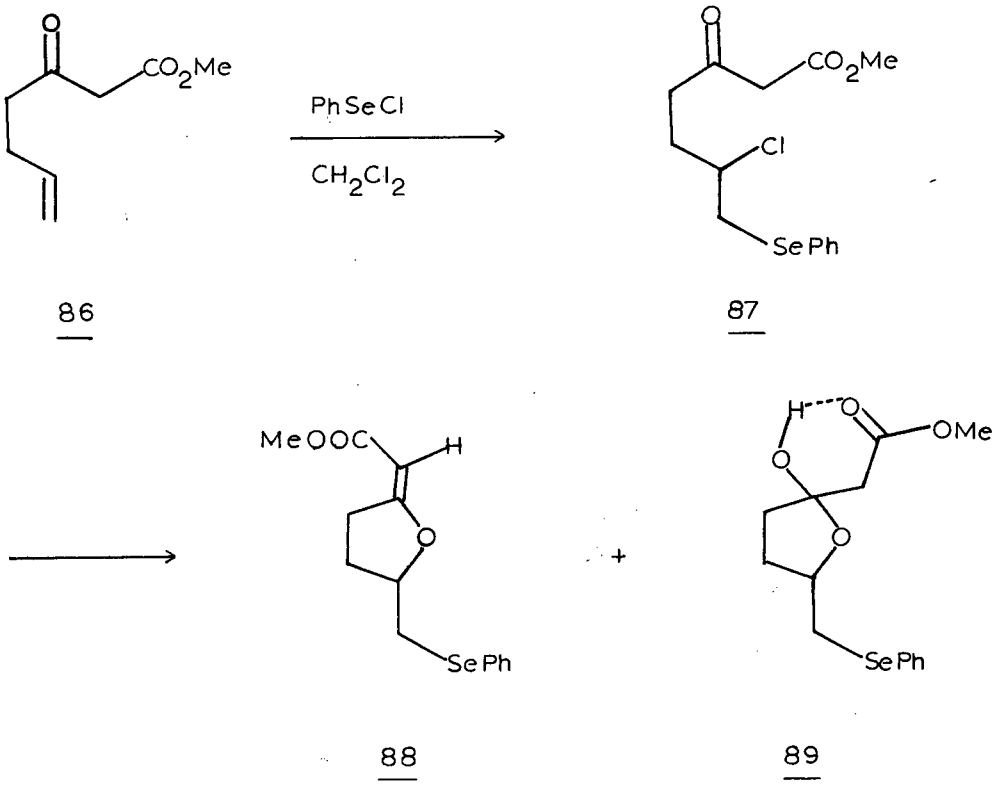
Bromonium ion initiated cyclization[44] of 86 invariably resulted in formation of mixtures of brominated material which were too complicated to have any synthetic value. Intrigued by the use of phenylselenenyl halides to effect lactonization of unsaturated acids[57] (e.g., equation 8), we studied the possibility of initiating cyclization of 86 with this reagent. Treatment of 86 with phenylselenenyl chloride in dichloromethane at different



(8)

temperatures gave only the addition product 87, in almost quantitative yield.

The structure of 87 was evident from its spectral data. IR absorptions at 1715 and 1740 cm^{-1}, a two-proton singlet at δ 3.38 in the ^{1}HNMR spectrum and mass fragment at m/e 101 in the mass spectrum of 87 affirmatively indicated the intact β-keto ester moiety (). Absence of vinyl proton absorptions in the ^{1}HNMR spectrum and a prominent molecular ion at m/e 348, corresponding to the parent mass of 87 (based on ^{35}Cl and ^{80}Se), in the mass spectrum were consistent with an addition product. Regiochemistry of the adduct 87 was assigned by analysis of its ^{1}HNMR spectrum,

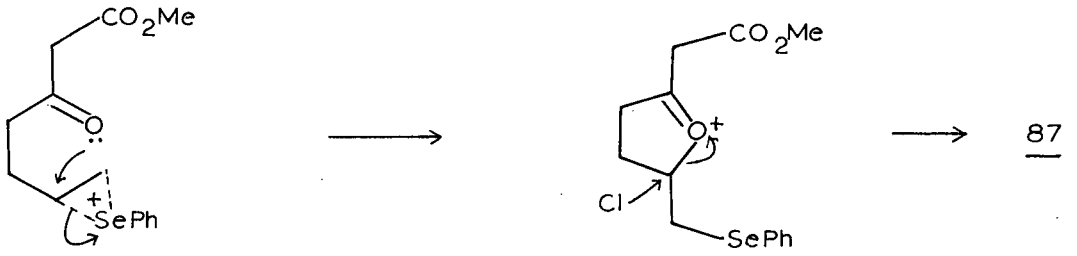


86 87 88 89

which showed a one-proton multiplet at δ 4.1 for the methine proton adjacent to chlorine and a two-proton broad doublet at δ 3.25 for the methylene protons on the carbon bearing the phenylselenenyl group. There were no peaks in the δ 3.4 to 3.6 region where the regioisomer of 87 would be expected to show absorptions.

Electrophilic addition of phenylselenenyl derivatives to olefins

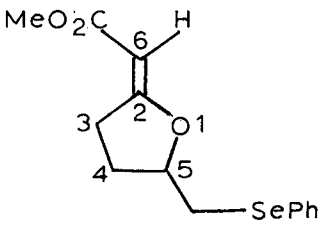
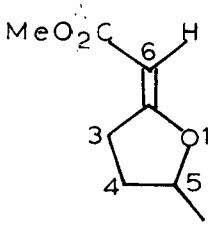
has been shown to be a facile process,[58] the mechanism of which is believed to involve an intermediate episeleniranium ion. In general, the regioselectivity of this type of addition to unsymmetrical olefins is low.[58,59] The unusually high regioselectivity observed in the addition of phenylselenenyl chloride to 86 might have arisen from intramolecular participation of the keto group as shown below.



Interestingly, when 87 was chromatographed with silica gel, cyclization took place and enol ether 88 was isolated in 68% yield along with 27% of hemiketal 89. The latter was presumably derived from hydration of 88.

The IR spectrum of 88 exhibited an absorption at 1700 cm^{-1} indicating the α,β-unsaturated ester function, and a remarkably intense peak at 1640 cm^{-1} characteristic of the double bond stretching of enol ethers. Presence of the phenylselenenyl group was shown by the mass spectrum (m/e 314: 312: 310: 309: 308: 306 = 11: 55: 27: 9: 10: 1; parent peaks of 88, characteristic family of peaks for Se due to natural isotopic abundance), as well as aromatic absorptions in the IR (1580, 1475 cm^{-1}) and ^{1}HNMR (δ 7.5, 7.2) spectra. The structure of 88 with the enol double bond in an E geometry was confirmed by comparing its IR and ^{1}HNMR data with those of compound 90[60,61] (Table 1). Preferential formation of the E isomer over the Z isomer of 88

Table 1. ^{1}HNMR and IR data of 88.

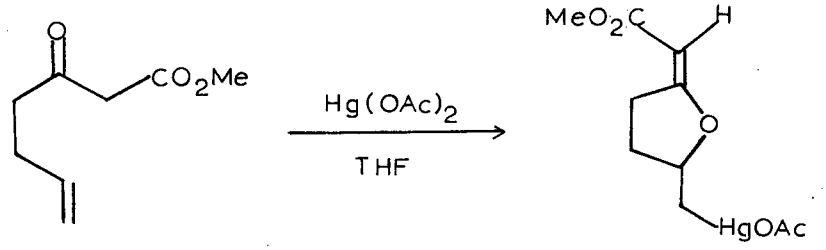
	 88	 90[60,61]
IR ($CHCl_3$):	1700 cm^{-1}	1700 cm^{-1}
	1640 cm^{-1}	1640 cm^{-1}
	1120 cm^{-1} (C-O-C)	1120 cm^{-1} (C-O-C)
^{1}HNMR ($CDCl_3$):	δ 5.17 (t, C-6H)	δ 5.2 (t, C-6H)
	4.52 (m, C-5H)	4.5 (m, C-5H)
	3.60 (s, CO_2CH_3)	3.60 (s, CO_2CH_3)
	3.2 (m, C-3H)	3.2 (m, C-3H)
	2.1 (m, C-4H)	2.2 (m, C-4H)

is attributed to the more stable orientation of dipole moments in the former molecule.

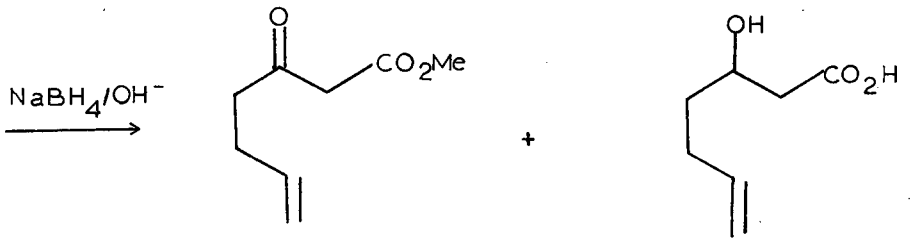
Hemiketal 89 was characterized by its spectroscopic properties. A two-proton singlet at δ 2.68 in the ^{1}HNMR spectrum revealed a methylene group between a tertiary carbon centre and a carbonyl function. The IR absorption at 3530 and 1720 cm^{-1} were consistent with an intramolecularly hydrogen bonded hydroxy ester moiety. The mass spectrum showed a parent

mass (based on ^{80}Se) at m/e 330 and a peak at m/e 312, probably arose from loss of H_2O. In fact, when 89 was heated to about 170° C under vacuum, dehydration occurred giving 88 as the distillate.

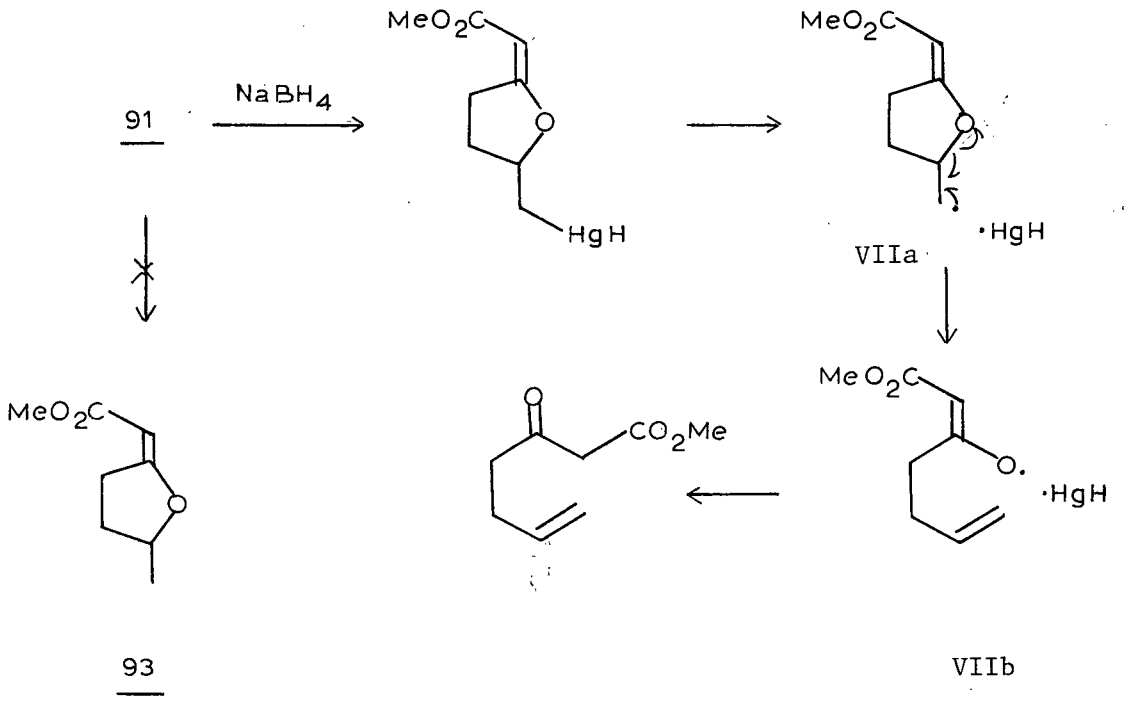
Mercuric salt promoted cyclization was also explored. Treatment of 86 with mercuric acetate in anhydrous tetrahydrofuran gave a crude product whose spectral data indicated the 0-cyclized mercurial compound 91 (IR: 1700, 1640 and 1565 cm^{-1}; ^{1}HNMR: δ 5.22 (br s), 4.6 (m), 3.62 (s), 2.23 (d),[62] 2.03 (s) and 1.6-3.4 (m)). Demercuration of 91 with sodium borohydride resulted in generation of the initial β-keto ester 86 and its reduction product, hydroxy acid 92. Failure to obtain the expected demercuration product 93 is possibly due to rearrangement of the intermediate radical[63] VIIa to VIIb.



86 91

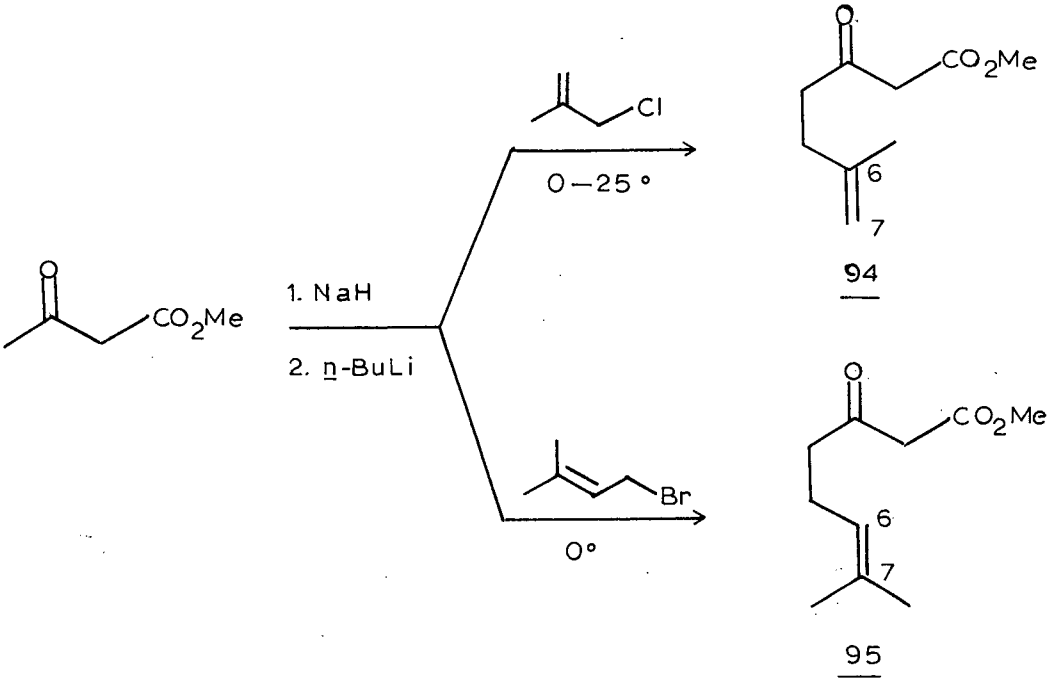


86 92

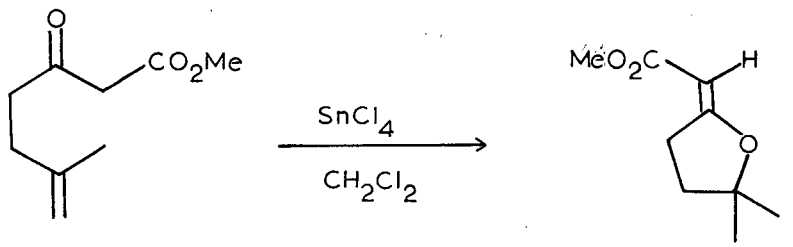


In order to study the effect of substitution at the C-6, C-7 olefinic bond on the cyclization of ε-alkenyl β-keto esters, compounds 94 and 95 were prepared and subjected to acid-induced cyclizations. These β-keto esters feature two interesting structural analogues of 86. In 94, the ease of development of a cationic centre at C-6 under acidic conditions is enhanced by the additional methyl group. With two methyl groups on C-7 in 95, the potential carbonium ion centre would be shifted from C-6 to C-7.

Alkylation of the dianion of methyl acetoacetate with 3-chloro-2-methylpropene and 1-bromo-3-methyl-2-butene afforded the β-keto esters 94 and 95 in 72 and 85% yields, respectively. In contrast to the inertness



of 86 towards acid-initiated cyclization, 94 was transformed cleanly into the cyclic enol ether 96 upon treatment with stannic chloride (ca. one equivalent) in dichloromethane at ambient temperature. Undoubtedly, the C-6 methyl group in 94 increases the reactivity of the olefinic bond towards



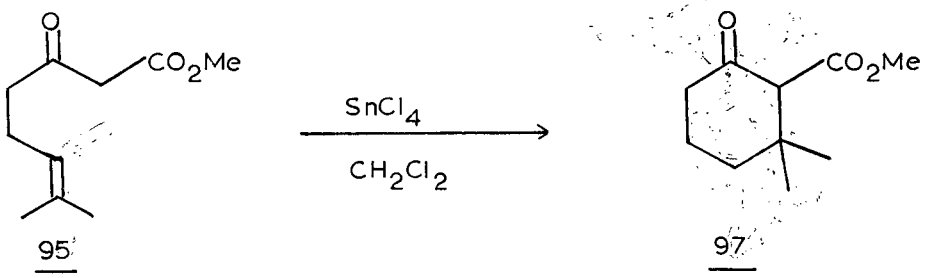
94 96

electrophilic reagents, in this case, H^+.

The structure of 96 was ascertained by comparing its spectroscopic properties with those of 90. Again, the Z isomer of 96 was not detected.

The α-furylidene acetate structure was readily recognized from the conspicuous IR absorptions at 1700, 1640 and 1120 cm^{-1}. That the molecule of 96 had a plane of symmetry was reflected in the ^{1}HNMR spectrum, which showed a six-proton singlet (δ 1.35) for the two methyl groups; a triplet (δ 5.17, J = 1.8 Hz) for the vinyl proton; a doublet of triplets (δ 3.15, J = 1.8, 7.6 Hz) for the allylic protons and a triplet (δ 1.87, J = 7.6 Hz) for the methylene group.

When 95 was exposed to stannic chloride in dichloromethane at room temperature, the C-cyclized compound 97, rather than an O-cyclized material analogous to 96, was obtained in almost quantitative yield. In the IR

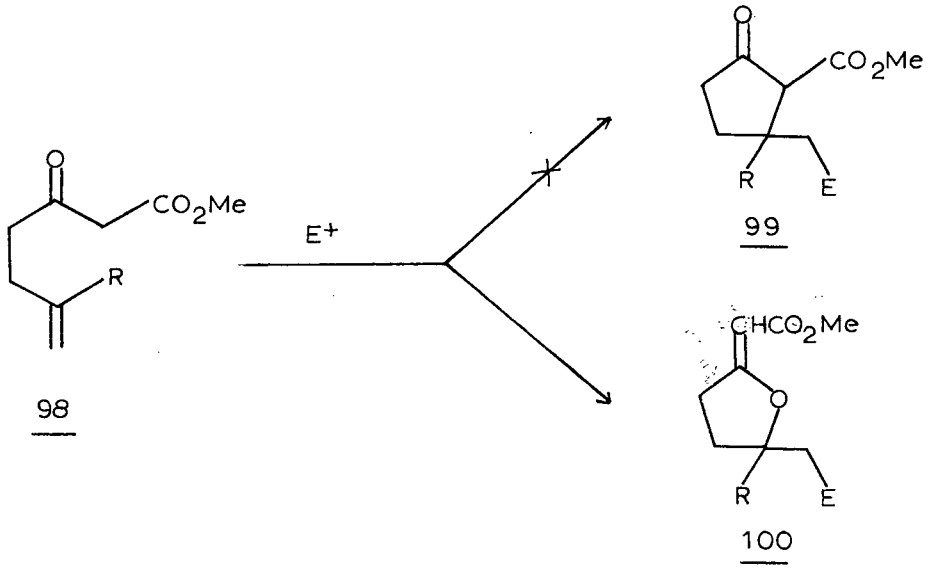


95 97

spectrum of 97, absorptions for a six-membered ring ketone (1710 cm^{-1}) and a normal ester (1730 cm^{-1}) were present. Two distinct three-proton singlets at δ 1.08 and 1.02 in the ^{1}HNMR spectrum revealed different environments for the two methyl groups. A one-proton singlet at δ 3.13 was assigned to the methine proton at the α-position of the β-keto ester. In the mass spectrum, a prominent peak at m/e 100 and the absence of notable mass fragments at m/e 101 (characteristic of β-keto esters unsubstituted at the α-position) provided further evidence for an α-substituted β-keto ester.[64] Based on the above analysis, the structure of 97 was established. The

chemical shift of the α-methine portion (δ 3.13) shows a slight upfield shift from the value normally observed (ca. δ 3.3-3.5) for protons of this type, indicating that it occupies an axial position. Other acids ($BF_3 \cdot Et_2O$, HCl) were also investigated for effecting the above cyclization and anhydrous stannic chloride was found to produce the most satisfactory result.

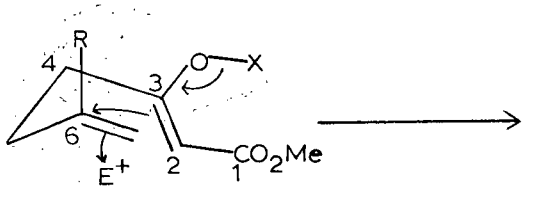
It is obvious from the above findings that in the electrophile-initiated cyclization of β-keto esters of type 98, there was a strong prefer-

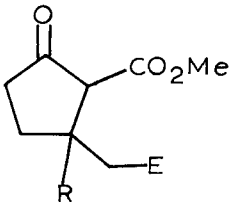


ence for formation of the O-cyclized compound 100 over the C-cyclized material 99. This predominance of O-cyclization might be rationalized on stereoelectronic grounds. Under electrophilic conditions, development of a cationic centre at C-6 is favored and would allow nucleophilic attack at this position. In principle, the ambident enol derivative of 98 may undergo intramolecular C-alkylation to give cyclopentanone 99, or O-alkylation to produce enol

ether 100 (Scheme iii). A study of molecular models shows that approach

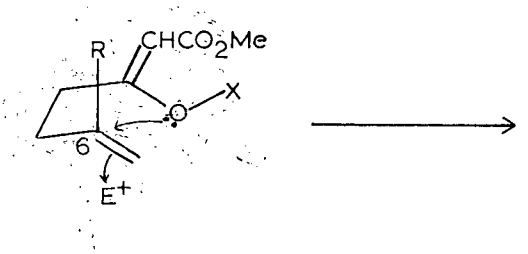
Scheme iii

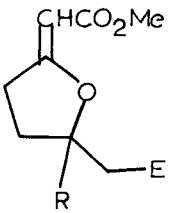




VIIIa

99





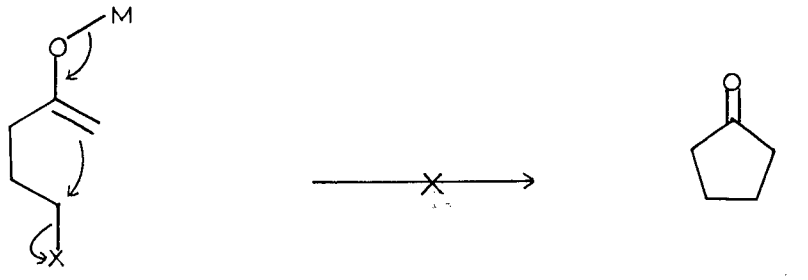
VIIIb

100

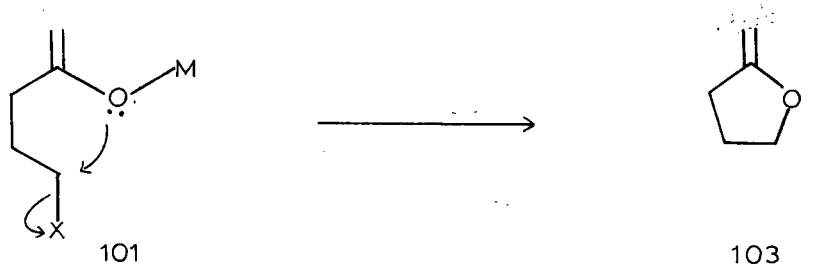
X = Lewis acid, H

of C-6 to C-2 perpendicular to the enol-plane (VIIIa) in order to attain sufficient orbital overlap in the transition state for C-cyclization, is sterically difficult. However, O-cyclization can be easily achieved by lining up C-6 with the lone pair of electrons on oxygen within the enol-plane (VIIIb). Thus, on the basis of stereoelectronic considerations, formation of enol ether 100 is feasible while that of 99 is disfavored.

This argument is in accord with the rules for ring closure recently suggested by Baldwin.[6,5] It was proposed for the cyclization of enolate 101 that formation of 102 via intramolecular C-alkylation is disfavored while the



101 102

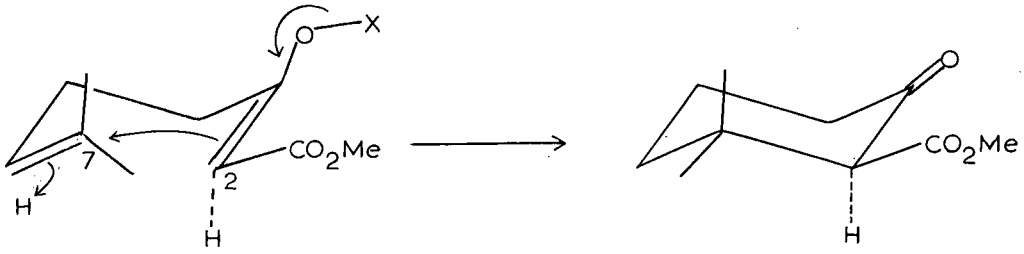


101 103

M = Metal ion ; X = leaving group

O-alkylation to give 103 is a favored process. Although a trigonal alkylating centre like C-6 in 98 was not discussed in this particular case, the pertinent stereoelectronic argument appears to agree with our observed results.

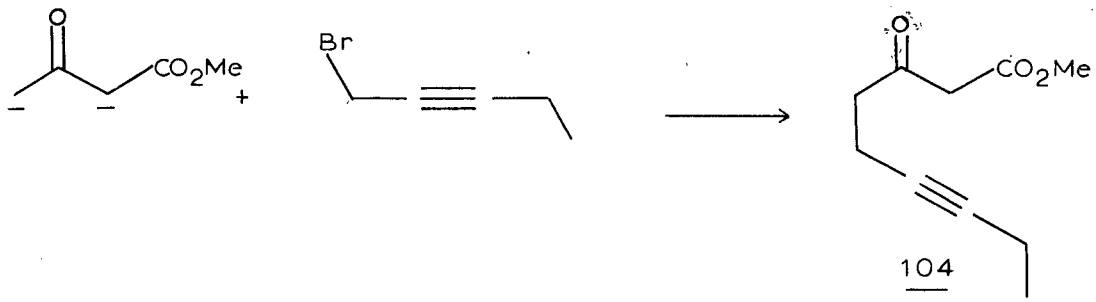
On the other hand, intramolecular C-alkylation at C-7 in 95 to form a six-membered ring (e.g., IX) is stereoelectronically facile. This accounts for the smooth transformation of 95 to the C-cyclized product by acid-catalyst.



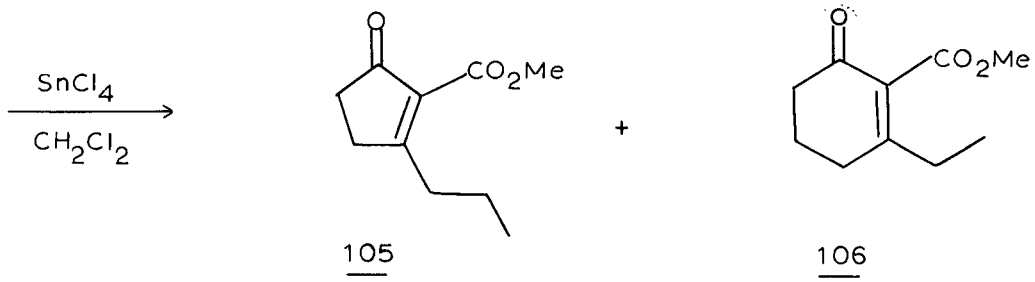
X= Lewis acid

97

Investigation on the acid-induced cyclization of the alkynyl β-keto ester 104 provided some interesting results. γ-Alkylation of the dianion of methyl acetoacetate with 1-bromo-2-pentyne[66] furnished the



104



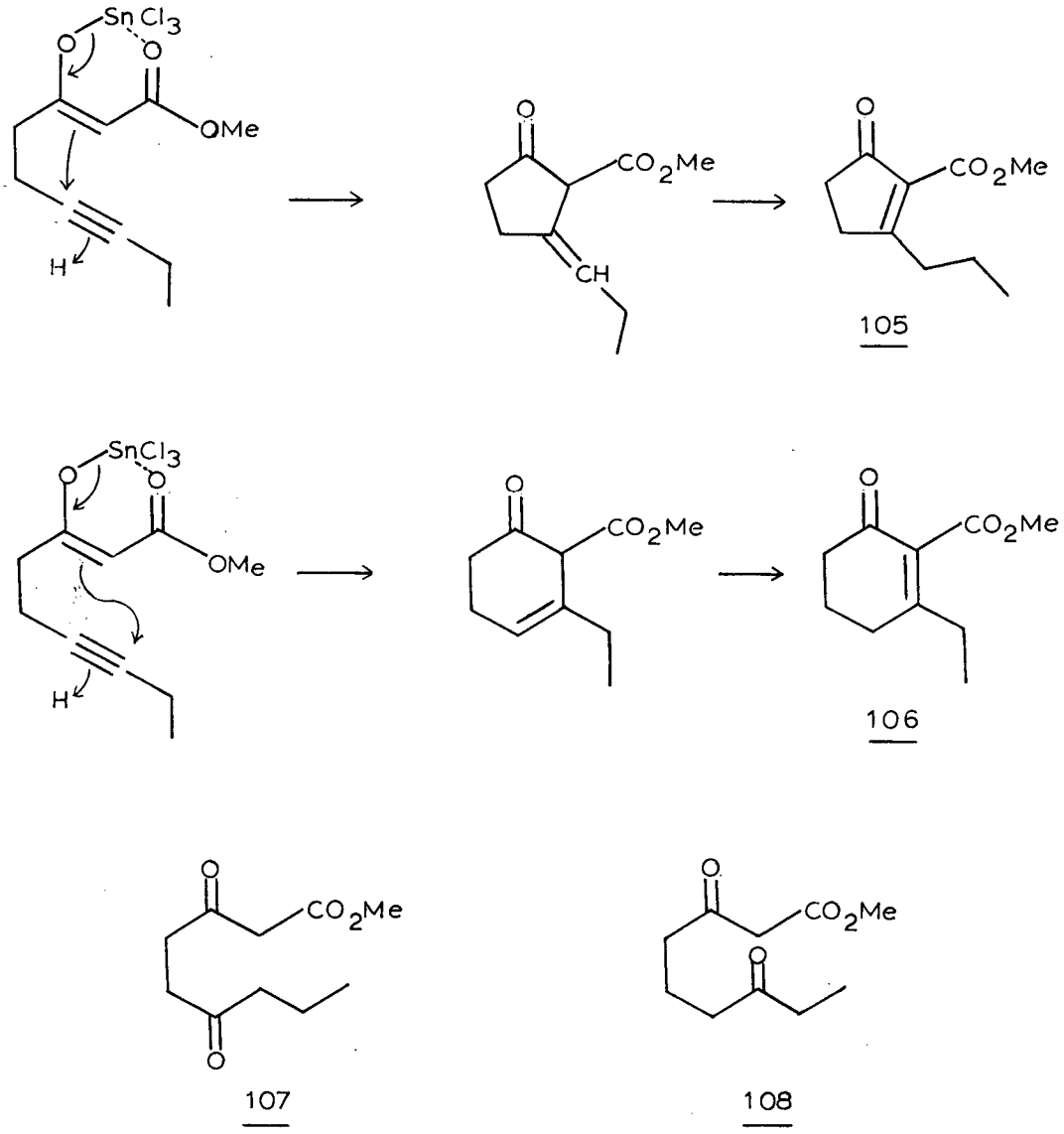
105 106

acetylene 104 in 87% yield. Treatment of 104 with anhydrous stannic chloride in dichloromethane at room temperature led to a mixture of two cyclic compounds in quantitative yield. After chromatographic separation, the two products were identified as the cyclopentenone 105 and the cyclohexenone 106, which were obtained in a ratio of ca. 2:1, respectively.

The IR spectrum of 105 exhibited absorptions at 1740, 1710 and 1625 cm^{-1} which were ascribable to the ester carbonyl, the conjugated five-membered ring ketone and the olefinic bond. Similarly, 106 had IR absorptions at 1730, 1675, and 1630 cm^{-1} for the corresponding ester, ketone and olefin groups. The high intensity of the 1625 and 1630 cm^{-1} peaks relative to ordinary olefinic absorptions was consistent with the conjugated structures. Apparently, the endocyclic double bonds in 105 and 106 conjugate to a greater extent with the keto groups than with the carbomethoxy side chains, causing little lowering in absorption frequency in the latter. Absence of absorptions for the α-protons of β-keto esters (δ 3.0-3.5) and presence of six-proton multiplets between δ 2.2 and 2.9 (region typical for chemical shifts of methylene protons adjacent to carbonyl and olefinic groups) in both ^{1}HNMR spectra supported the structural assignments. Existence of the n-propyl side chain in 105 and the ethyl group in 106 was also substantiated by the fragmentation patterns in their mass spectra.

The cycloalkenones 105 and 106 were believed to arise from direct intramolecular alkylation followed by isomerization of the olefinic bonds (Scheme iv). Although alternative mechanisms involving the intermediary ketones 107 and 108 could not be rigorously excluded, the direct cyclization

Scheme iv



route appears to be more plausible according to the following considerations. First, neither these tricarbonyl compounds, 107 and 108, nor their corresponding furan and pyran derivatives (expected side products from 107 and 108) were detected in the crude reaction product. Secondly, if hydration

of the acetylene in 104 occurred[2] without intramolecular participation of the β-keto ester, formation of essentially equal amounts of 107 and 108 would be expected, which should then lead to an approximately 1:1 proportion of the condensation products, 105 and 106. The observed 2:1 ratio for the generation of these compounds contradicts the above suggestion. Regioselective hydration with participation of the keto group[67] in 104 also seemed unlikely judging from the simplicity of the product mixture, which showed no sign of any O-cyclized derivatives at all.

It is interesting to note that 104 was found to be unreactive toward boron trifluoride etherate ($BF_3 \cdot Et_2O$) in benzene. Mainly starting material was recovered from the reaction mixture even after three days at room temperature. The cause for this marked change in reactivity with catalyst was not clear.

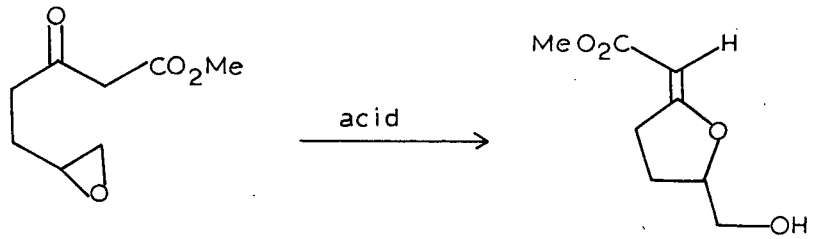
Cyclization of Epoxy β-Keto Esters

Successful utilization of the epoxide function to initiate cyclizations, especially those involving polyenes, has been demonstrated (see Introduction). We explored the cyclization of epoxy β-keto esters for two major reasons. The oxirane ring is capable of undergoing nucleophilic attack under both acidic and basic conditions, while, at the same time, the β-keto ester group can act as the nucleophilic component. This allows investigations into both acid- and base-catalyzed cyclizations. Moreover,

(2) Precautions were taken to avoid contact with moisture in carrying out these reactions.

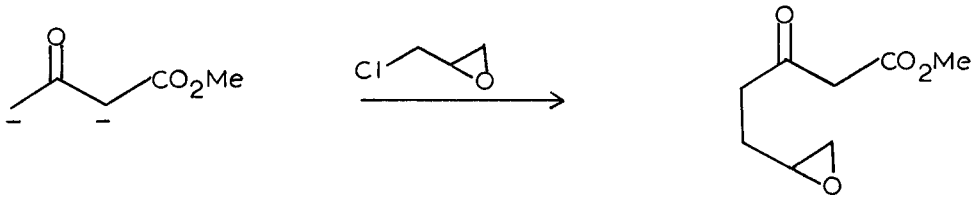
the hydroxy function which would result after cyclization would facilitate further synthetic elaboration.

Results secured earlier in our laboratory[68] indicated that acid-promoted cyclization of epoxide 109 gave predominantly the cyclic enol ether 110. The preparation of 109 via epoxidation of 86 was shown to be low yield-



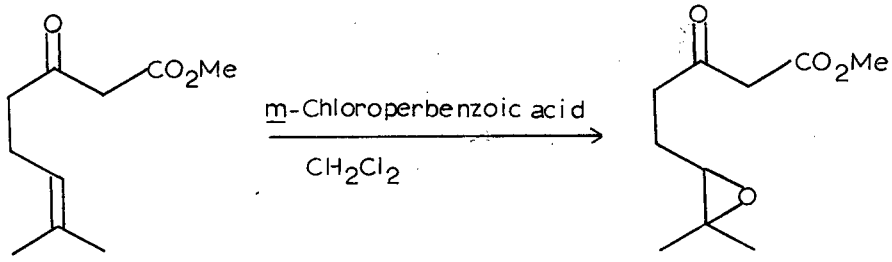
109 110

ing and sluggish.[68] However, this epoxide could be conveniently synthesized by γ-alkylation of the dianion of methyl acetoacetate with epichlorohydrin at 0° C.



109

To determine if the mode of ring closure could be controlled by alteration of the epoxide substitution pattern, reactions of the epoxy β-keto ester 111 with Lewis acids were examined. Despite the difficulties encountered in epoxidizing 86, epoxidation of 95 with m-chloroperbenzoic acid proceeded smoothly at 0° C to afford 111 in almost quantitative yield.

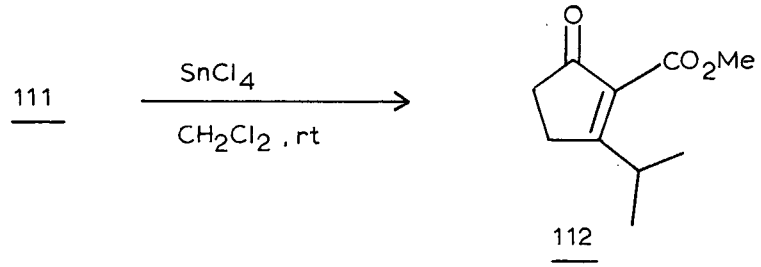


95 111

It was found necessary to buffer the reaction mixture with disodium hydrogen phosphate (Na_2HPO_4), owing to the highly acid-sensitive nature of 111.

Based on the facile C-cyclization of 95 to 97, it was anticipated that epoxide 111 might cyclize to give 113 under similar conditions. However, upon treatment with stannic chloride at ambient temperature, 111 was transformed cleanly to the cyclopentenone 112 after twenty-three hours.

The cross-conjugated cyclopentenone structure was confirmed by

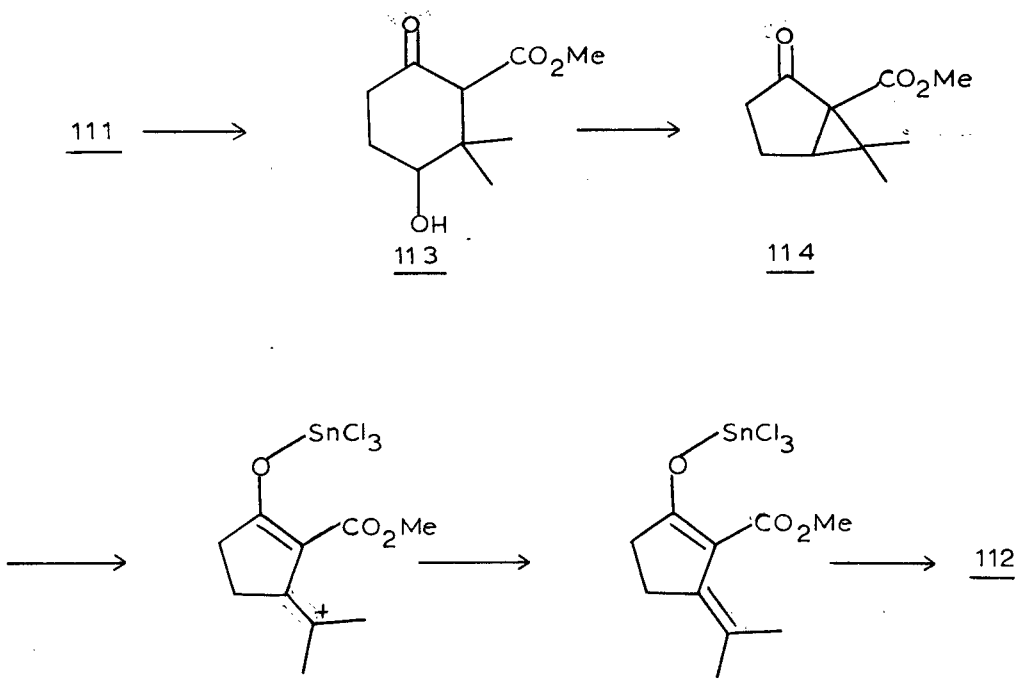


112

the IR absorptions at 1740, 1710 and 1620 cm^{-1} (cf. compound 105). A one-proton septet at δ 3.5 (J = 7 Hz) and a six-proton doublet at δ 1.17 (J = 7 Hz) in the ^{1}HNMR spectrum clearly indicated presence of the isopropyl group, which was further corroborated by the proton-proton decoupled spectra.

A possible mechanism for the formation of 112 was at first envisioned to involve initial C-cyclization to generate the cyclohexane derivative 113, which was transformed to 114, followed by cleavage of the cyclopropane ring (Scheme v). The conversion of 113 into 114, analogous

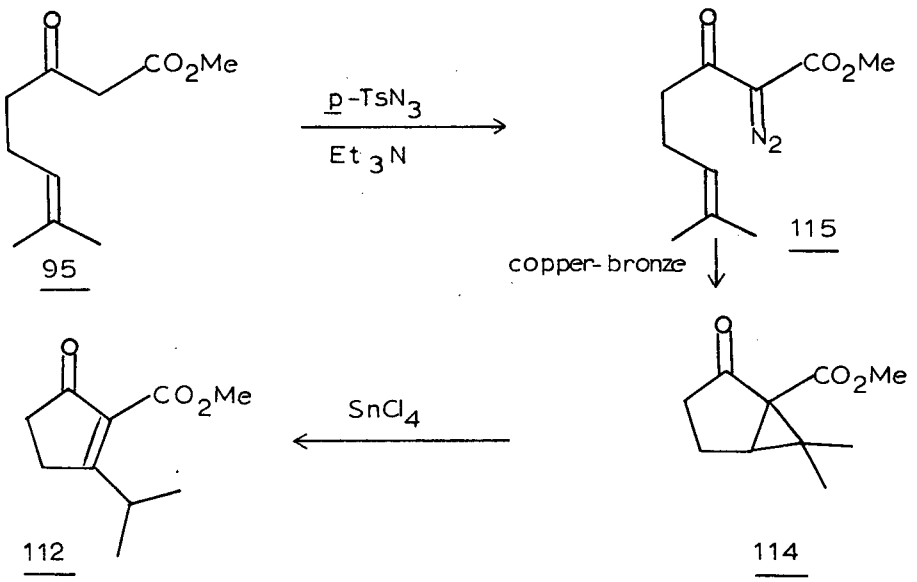
Scheme v



to the well known acid-catalyzed α-alkylation of β-keto esters with secondary alcohols,[69] seemed to be probable. To test the validity of the last transformation in Scheme v, the bicyclic compound 114, prepared by copper-

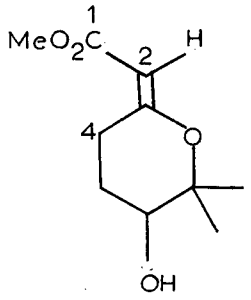
catalyzed cyclization[70] of α-diazo β-keto ester 115,[(3)] was allowed to react with stannic chloride in dichloromethane. Indeed, 112 was thus obtained in quantitative yield.

Even though the above mechanism looked convincing in terms of

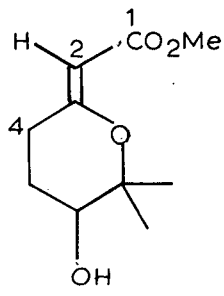


efficacy of the involved chemical transformations, attempts to isolate the suggested intermediates were unsuccessful. When the cyclization of 111 was conducted at low temperatures (-78° to 0° C) for a short period of time (30 min. to 1 hr), a mixture of 0-cyclized material 116, 117 and 118 were obtained in a ratio of ca. 15:5:3. Similar results were also observed for other Lewis acids ($BF_3 \cdot Et_2O$, $AlCl_3$) and solvent (CH_3CN). Structures of

(3) The α-diazo derivative was prepared by treating 95 with p-toluenesulfonyl azide and triethylamine in acetonitrile.[70] Compound 114 was synthesized via 115 in 71% yield from 95.



116



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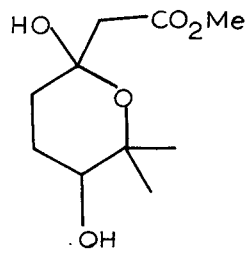
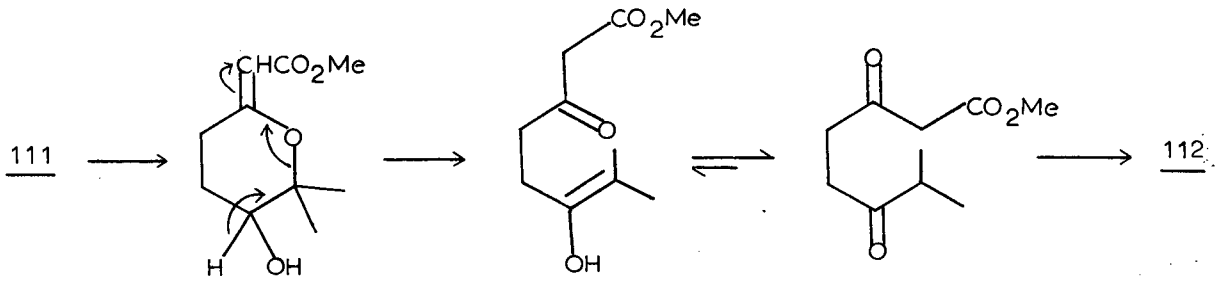


118

these compounds were verified by their spectral data. The carbomethoxy vinyl ether moiety in 116 and 117 was established by the characteristic IR absorptions at 1700 and 1640 cm^{-1}. Assignment of the E and the Z geometry for the olefinic bonds in 116 and 117 was based on analysis of their ^{1}HNMR spectra. The vinyl proton (C-2 H) and the allylic methylene protons (C-4 H) in 116 had chemical shifts at δ 5.27 and 3.07 respectively, while those in 117 were at δ 4.81 and 2.77. Due to their closer proximity to the ether oxygen and the carbomethoxy group, the C-2 and C-4 protons in the E isomer are expected to show lower field chemical shifts than their counterparts in the Z isomer.[71] Compound 116 was therefore identified as the E isomer and the Z geometry of 117 followed accordingly.

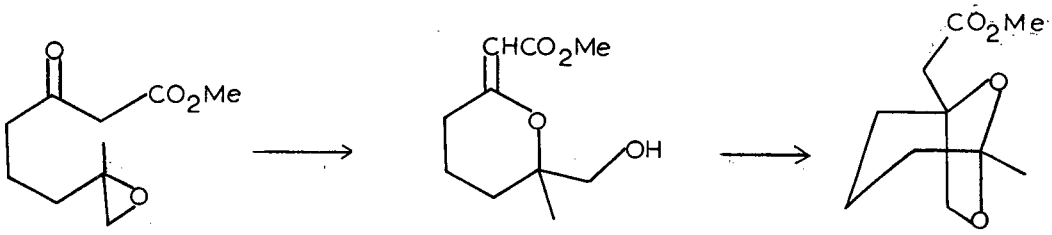
The isolation of 116 and 117 clearly implies their intermediary role during the transformation of 111 to 112. To depict the mechanism of this reaction would require a pathway to convert 116 or 117 to 112. It is most likely that, at elevated temperatures (e.g., room temperature), the initially formed O-cyclized species were cleaved to give a diketone, 119, which subsequently underwent intramolecular condensation and dehydration to yield 112. This proposal was substantiated by the conversion of 116



119

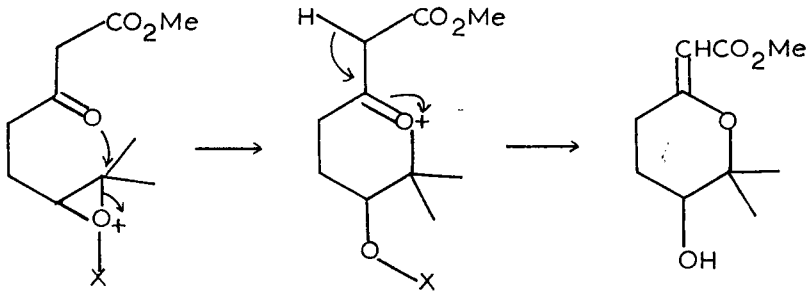
to 112 upon treatment with stannic chloride at room temperature. When the reaction time was shortened to 10 to 18 hours, evidence for the existence of the diketone 119 was also observed.

The readiness of epoxy β-keto esters in undergoing O-cyclization was illustrated by the mild conditions used to effect this process. The generality of this observation is supported by a recent report on the synthesis of frontalin.[72] Upon exposure to Lewis acid, epoxide 120 was transformed smoothly to the bicyclic ketal 121, presumably, via an O-cyclized intermediate X. The dominance of O-cyclization for epoxy

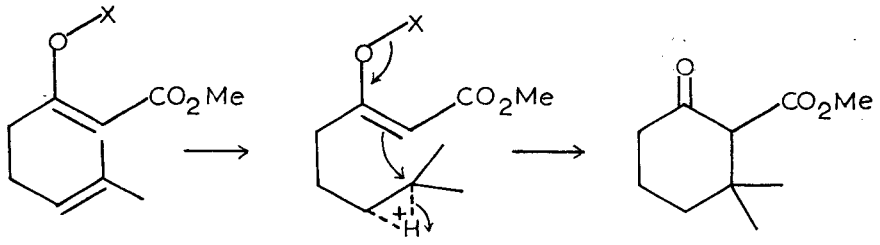


120 X 121

β-keto esters in contrast to the exclusive C-cyclization of 95 is noteworthy. Steric consideration offers little explanation. A promising rationalization could be conceived by assuming that the interaction between acids and the epoxide oxygen is faster than enolization of the β-keto ester. Opening of the activated oxirane ring with intramolecular participation of the keto group would then lead to the enol ether product (equation 9). For the alkenyl β-keto ester 95, enolization probably preceded protonation of the olefinic bond to allow for C-cyclization (equation 10).



(9)

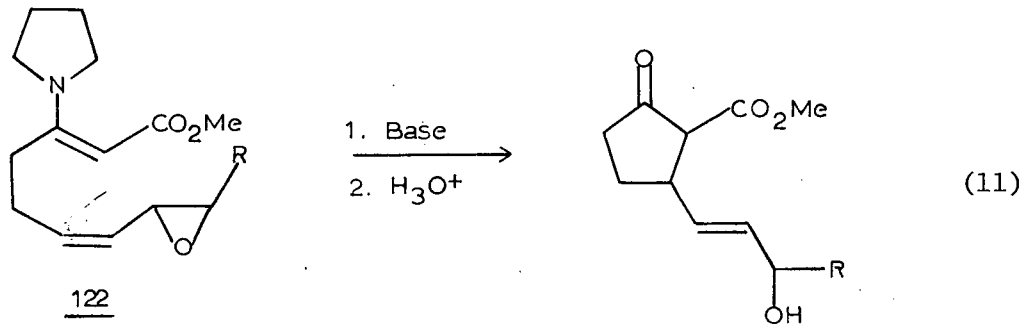


(10)

X = Lewis acid

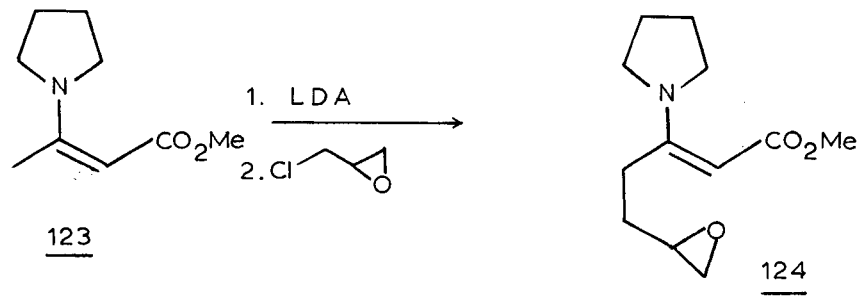
The principle of soft and hard acids and bases[73] may provide an explanation as well. The oxonium ion is a hard leaving group which prefers attack by hard nucleophiles such as oxygen atom, while a soft carbonium ion favors attack by a soft enol carbon.

According to results obtained by Martel et al.[52] and in our laboratory,[74] cyclization of enamines of type 122 through an S_N2' mechanism (equation 11) could be effected with sodium amide or lithium diisopropyl



122 (11)

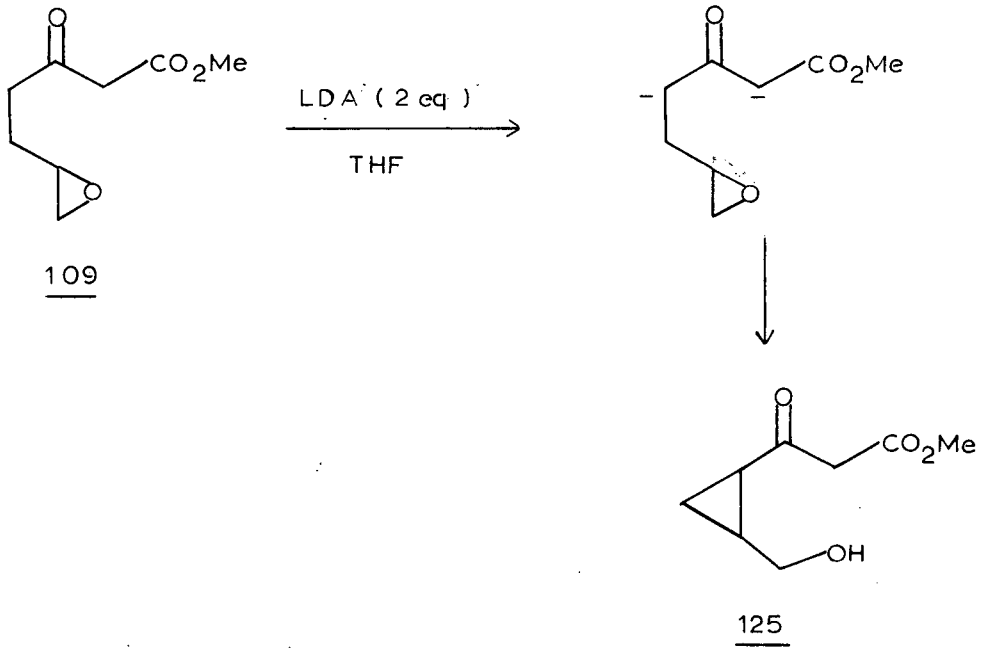
amide (LDA). The epoxy enamine 124 was prepared by γ-alkylation of 123 with epichlorohydrin. Attempts to cyclize 124 by using LDA or Lewis acids were unsatisfactory.



123 124

However, when epoxy β-keto ester 109 was treated with two equivalents of LDA in tetrahydrofuran, at 0° C, the cyclopropyl compound 125 was obtained in 50% yield. The dianion of the β-keto ester must be involved

in this reaction. Formation of 125 was not entirely unexpected since the γ-carbon of β-keto ester dianions is more reactive towards electrophiles than the other anionic sites. The preferred mode of cyclization giving the three-membered ring in this case is in agreement with the Baldwin's rules for ring closure.[65] The alternative mode of opening the epoxide, leading to a four-membered ring, is probably disfavored on stereoelectronic grounds.

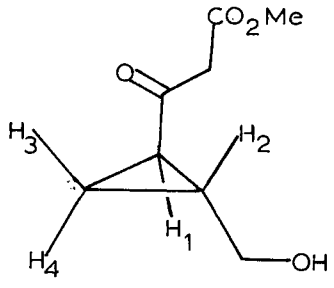


109

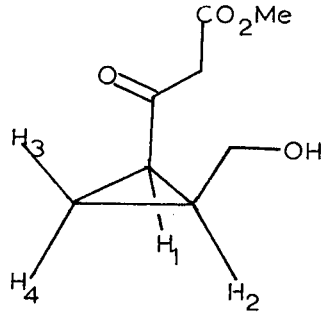
125

Presence of the cyclopropane structure was evident from the high field absorption pattern in the ^{1}HNMR spectrum and from the IR signal at 3050 cm^{-1}, ascribable to the methylene C-H stretching of cyclopropanes. IR bands at 1740 and 1700 cm^{-1} confirmed the β-keto ester structure in which the keto group is conjugated with a cyclopropyl moiety. The relative stereo-

chemistry in 125 was tentatively assigned as trans by the following considerations. The transition state leading to the trans isomer is sterically more favorable. The ^{1}HNMR spectrum of 125 exhibited four one-proton multiplets at δ 2.0, 1.7, 1.4 and 1.0 which were assigned to the cyclopropyl



trans-125



cis-125

protons H_1, H_2, H_3 and H_4, respectively. H_1, H_3 and H_4 in the cis and the trans isomers are expected to have similar chemical shifts. The chemical shift of H_2 would be close to that of H_4 in the cis isomer, and to that of H_1 in the trans isomer.[71] The observed pattern for these protons indicated the trans stereochemistry.

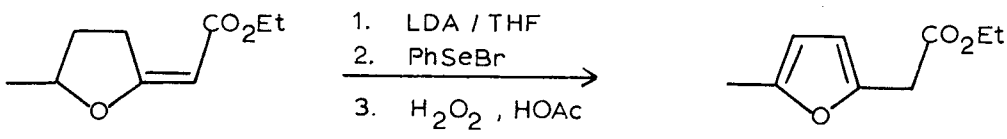
Conclusions

Although limited in variety, the β-keto ester derivatives used in this study serve as models for the cyclization of analogous, more complex β-keto esters. On the basis of the above results and the rules for ring closure suggested by Baldwin,[65] the following generalizations could be deduced. In the formation of five-membered rings from olefinic β-keto

esters, O-cyclization is favored over C-cyclization, whilst the latter process is preferred in the generation of six-membered rings. Under acidic conditions, epoxy β-keto esters have a prevailing tendency to O-cyclize. Finally, the mode and regiochemistry of the cyclization may be controlled by altering the substitution pattern of the olefin or the epoxide involved.

Despite the intense studies that have been conducted on cationic olefin cyclization (see Introduction), the range of nucleophilic multiple bonds utilized in most cases has been limited to simple olefins and acetylenes. The use of β-keto ester as the nucleophilic component offers the advantage of retaining useful functionalities in the cyclization product. Furthermore, suitably functionalized acyclic β-keto ester precursors are readily accessible.[1,2]

It is worth noting that some of the cyclization products reported in this study provide useful intermediates for synthesis. The utility of the cyclohexanone 97 has been demonstrated in the synthesis of basic units in natural products (see Section III). The O-cyclized products may serve as intermediates for the synthesis of heterocyclic compounds. In particular, the α-furylidene acetate derivatives could be transformed into substituted furans by employing the method developed by Bryson and Wilson.[75] As illustrated below, formation of the furan 127 from the furylidene acetate 126 involved



126 127

γ-phenylselenenylation of 126, followed by oxidation, and elimination of benzeneseleninic acid with concomitant double bond isomerization.[75]

SECTION II: ALKENE SYNTHESIS

Introduction - A Survey of Stereoselective Synthesis of Tri- and Tetrasubstituted Alkenes

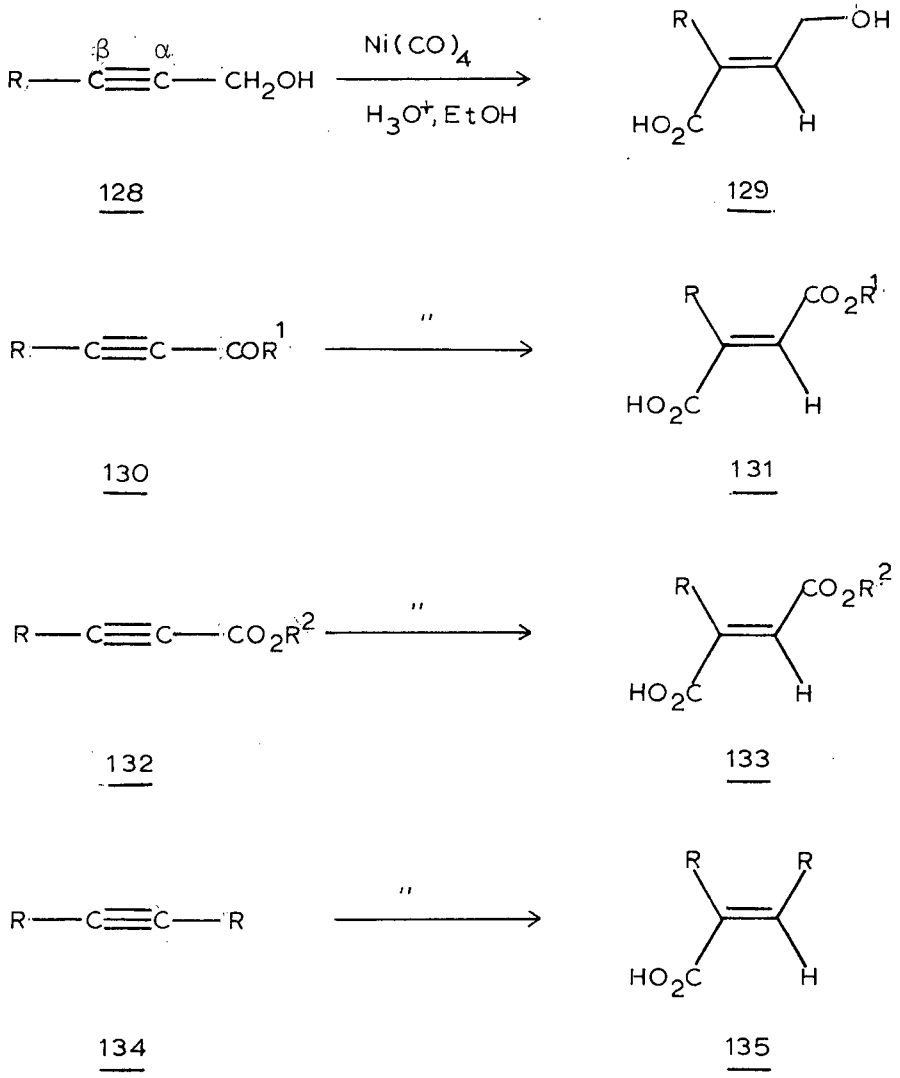
General and facile synthetic methods devised for the stereoselective formation of substituted alkenes play an important role in modern organic chemistry. The wide-spread occurrence of olefinic units in many classes of natural products is the major impetus to the development of these methods. Studies on polyene cyclizations also require stereoselective synthesis of alkenes. As can be seen from the above survey on polyene cyclizations, the stereochemistry of the cyclized products is often controlled by the geometry of the olefinic precursors. The activity of many insect hormones and pheromones is also governed by the configuration of the olefinic bonds in these substances. Hence, the access to stereochemically pure synthetic alkenes is of prime importance for investigations in these areas.

Mono- and disubstituted carbon-carbon double bonds are relatively easy to prepare, and control over the geometry of the latter does not impose much difficulty. The development of general and stereoselective synthesis of tri- and tetrasubstituted alkenes is synthetically challenging and has been the main goal of many organic chemists.

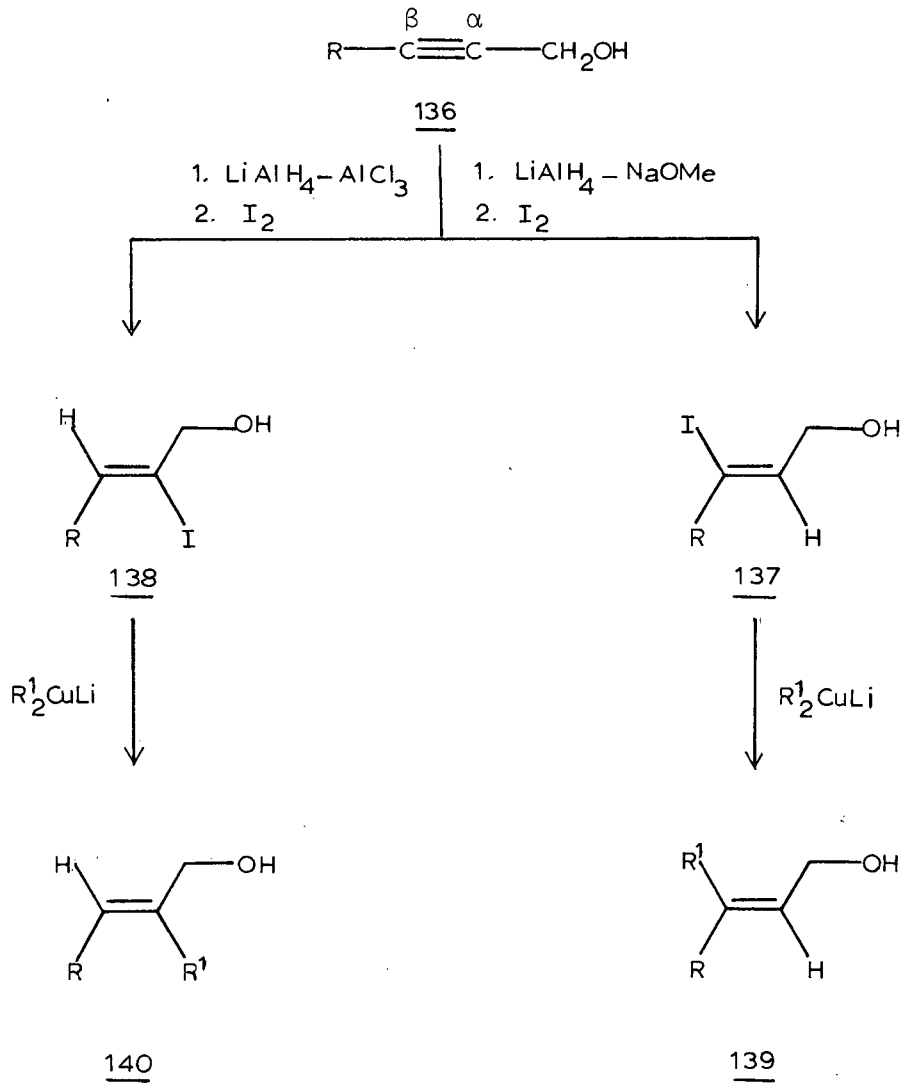
A. Synthesis via Addition to Acetylenes

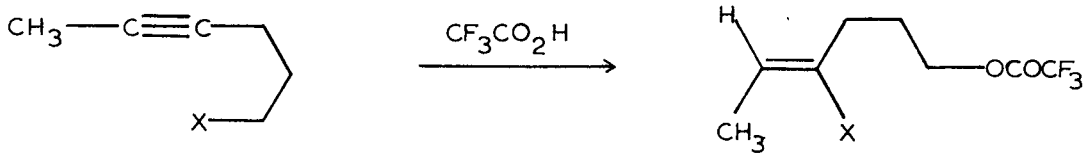
Successful use of acetylenes to synthesize trisubstituted alkenes was first reported by Reppe.[76] Propargylic alcohols 128, ketones 130 and

esters 132 underwent stereoselective addition of formic acid when treated with nickel tetracarbonyl, yielding the α,β-unsaturated acids 129, 131 and 133 respectively.[76,77] The carboxy group and the hydrogen were added in a cis manner with the former attached regioselectively to the β-carbon. Symmetrical acetylenes 134 gave alkenes 135 under similar conditions.



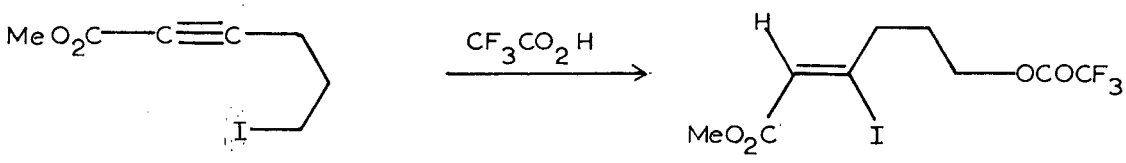
Alkylation of vinyl halides with lithium dialkylcuprates has been shown by Corey and Posner to occur with retention of configuration of the olefinic bond.[78] This reaction provides a synthetic route to substituted alkenes via vinyl halides which can be synthesized stereoselectively by many methods. Reduction of propargylic alcohols 136 with lithium aluminum-hydride, followed by addition of iodine, might lead to β-iodo alcohols 137 or α-iodo alcohols 138 depending on the conditions employed. Subsequent reactions of vinyl iodides 137 and 138 with lithium dialkylcuprates furnished stereospecifically the alkenes 139 and 140, respectively.[79]





141

X = Cl , I



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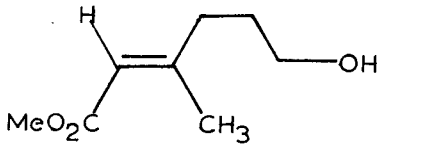
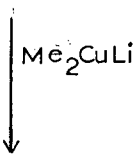


144



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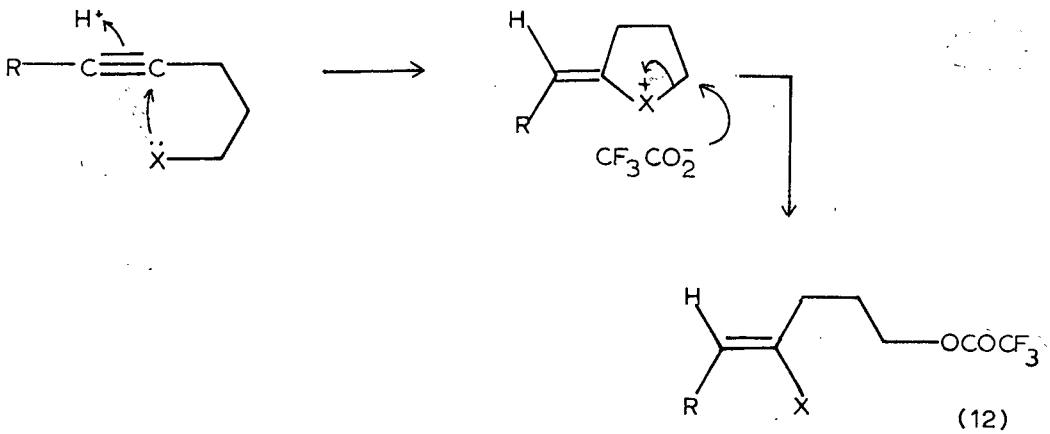
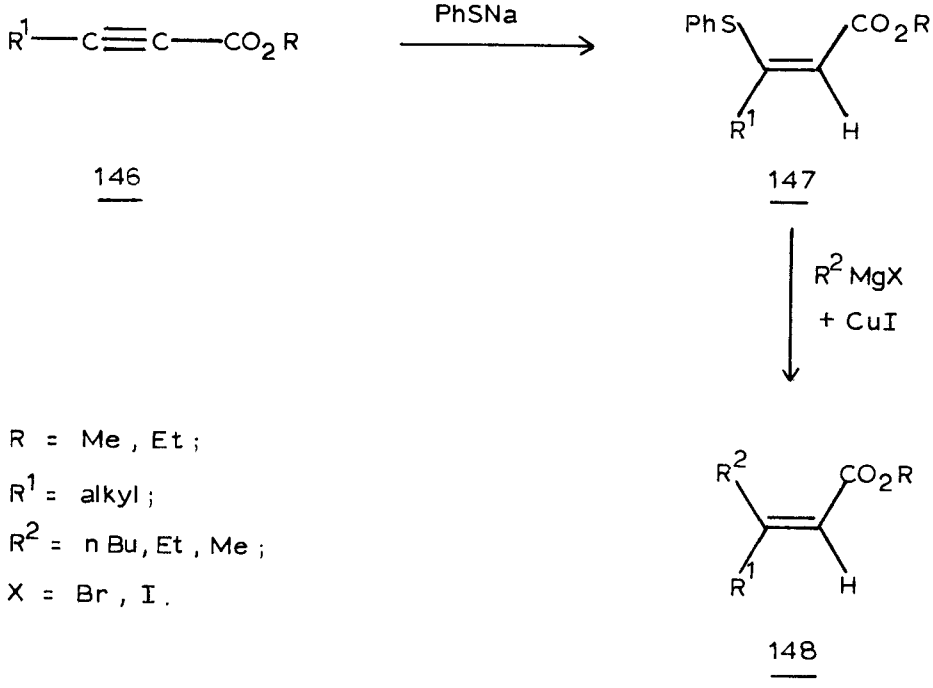


(12)

Another stereospecific route to vinyl halides was reported by Peterson et al.[80] The 1,4-halogen shift reaction of alkynyl halides 141 in trifluoroacetic acid gave predominantly the Z-vinyl halides 142. By applying this method to methyl 6-iodo-2-hexynoate (143), Bryson achieved the stereospecific synthesis of vinyl iodide 144, which was converted to the methyl E-hexenoate 145 by lithium dimethylcuprate.[81] A mechanism involving protonation of the acetylenic bond and synchronous participation of the halogen (equation 12) was proposed to account for the stereochemical outcome of these reactions.

Kobayashi et al. developed a stereoselective synthesis of trisubstituted alkenes, which involved trans addition of benzenethiol to an α,β-acetylenic ester, followed by displacement of the phenylthio group by an alkyl substituent with retention of configuration.[82] The selective formation of vinyl sulfide 147 was effected by treating 146 with sodium



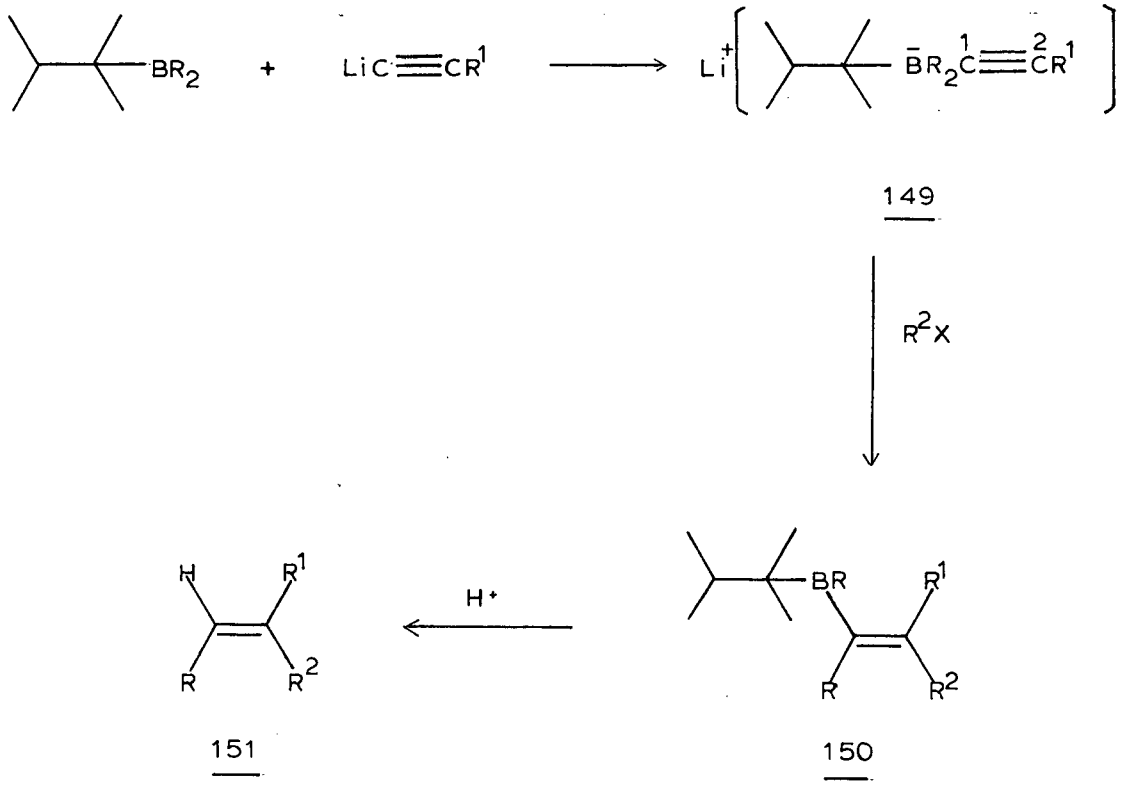
146 147

R = Me, Et;
R^1 = alkyl;
R^2 = n Bu, Et, Me;
X = Br, I.

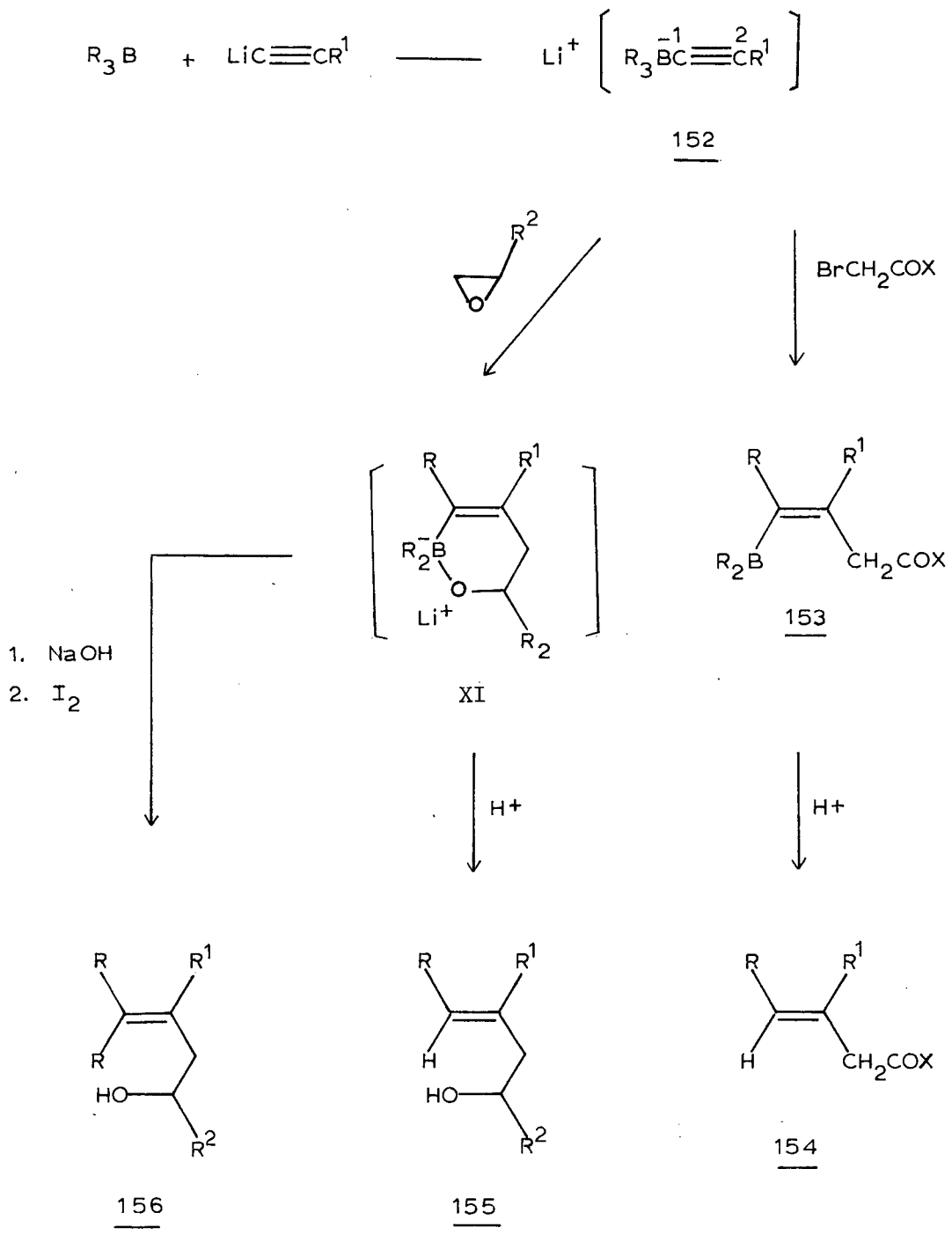
148

thiophenoxide in methanol and water. Reaction of 147 with Grignard reagents in the presence of cuprous iodide afforded α,β-unsaturated esters 148 in good yields.

Lithium 1-alkynyltrialkylborates (e.g., 149 and 152), which were readily prepared by treating lithium acetylides with trialkylboranes, underwent alkylation at C-2 with various alkylating agents accompanied by migration of an alkyl group from boron to C-1 of the acetylenic bond.[83] Acid-hydrolysis of the vinyl boranes thus formed led to trisubstituted alkenes. Pelter and coworkers[83] found that for simple alkylating agents, like alkyl



R = 1° alkyl ; R^1 = 1° alkyl ; R^2 = 1° alkyl, allyl, benzyl ; X = halides, etc.

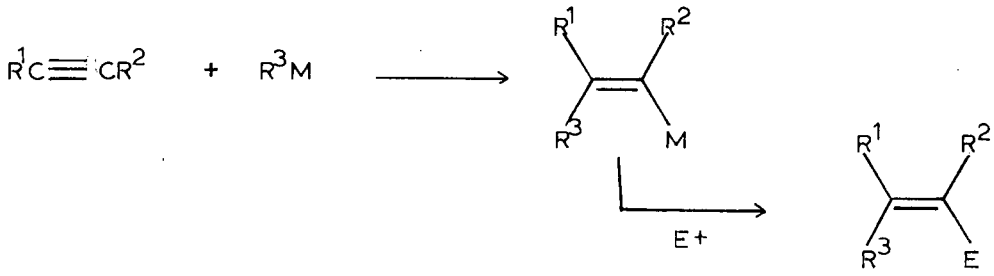


R = 1° and 2° alkyl ; R^1 = 1° alkyl ; R^2 = 1° alkyl, H ; X = Me, aryl, OEt.

halides, the alkylation-migration process (149 → 150) proceeded with higher stereoselectivity (ca. 90%) when a thexyl group was attached to boron in 149. In this case, the major vinylboranes 150 and the corresponding alkenes 151 were formed with the groups derived from the alkylating agent (R^2) and from boron (R) cis to each other.

Alkylation of borates 152 with α-bromocarbonyl compounds gave exclusively vinyl boranes 153 with the alkyl group from boron added trans to the alkylating agent.[84] Trisubstituted β,γ-unsaturated carbonyl compounds 154 were obtained from hydrolysis of 153 in ca. 70% yield. Treatment of 152 with epoxides gave intermediates which were believed to be cyclic borates XI. Of particular interest in this presumed formation of XI are the regioselective opening of monosubstituted epoxides and the stereoselective migration of the alkyl group from boron. Hydrolysis of XI with acetic acid afforded trisubstituted alkenes 155 in greater than 70% yield, while reaction with aqueous sodium hydroxide and then with iodine gave tetrasubstituted alkenes 156.[85]

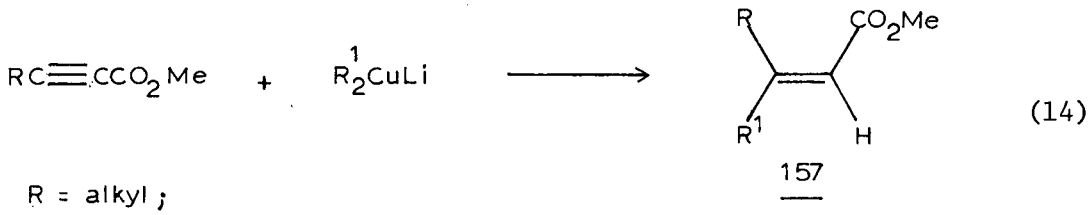
Although the aforementioned stereoselective synthesis of alkenes from acetylenes have their synthetic utility, the most commonly adopted method in this category is based on the addition of organometallic reagents to acetylenic bonds. Equation 13 (R^3 = alkyl groups; M = metallic ions



(13)

or complexes; E^+ = electrophilic species) is representative of this type of reaction. With a few exceptions (vide infra), the addition of R^3 and M generally occurs in a cis manner. Regioselectivity in these additions is controlled by the nature of the substituents R^1 and R^2. In the past decade, various reagents have been developed to serve the function of R^3M in equation 13. Those of general applicability are described below.

Conjugate addition of organocopper reagents to α,β-acetylenic carbonyl compounds has been a useful tool for the stereoselective synthesis of substituted alkenes. Additions of lithium dialkylcuprates to α,β-acetylenic esters were first reported by Corey[86] and Sidall[87] to give stereoselectively trisubstituted alkenes with an alkyl group from the cuprate added trans to the ester function (equation 14). A series of primary alkyl



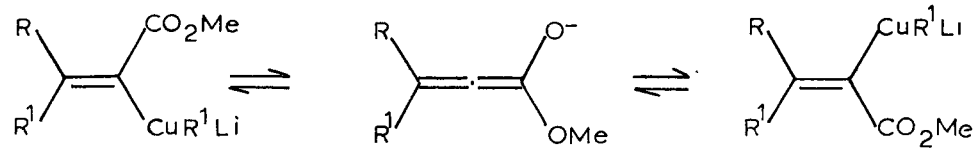
(14)

157

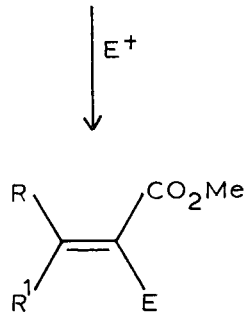
R = alkyl;

R^1 = Me, Et, n-Pr, n-Bu, n-heptyl.

groups (R^1) have been successfully transferred in this manner.[88,89] Low temperatures (-78° to -100°) are essential for obtaining high stereoselectivity (greater than 90%) and good yields (ca. 90%) for these reactions. Reported attempts to trap the intermediate vinylcopper species XII with alkylating agents were unsatisfactory. It was believed that the higher temperatures required for alkylation of XII caused isomerization to form



XII XIII



158a : E = I

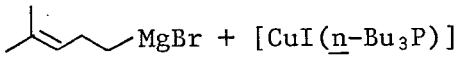
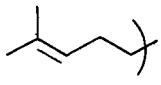
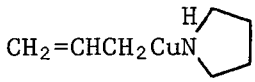
158b : E = Me

XIII. However, reactions of XII with iodine to give 158a, and with oxygen and excess lithium dimethylcuprate to form 158b have been accomplished.[86]

Organocopper reagents derived from mixing alkylmagnesium halides with the tri-n-butylphosphine copper (I) complex XIV (entries a and b, Table 2) or with cuprous halide and pyrolidine (entry c, Table 2), as well as mixed dialkylcuprates (entry d, Table 2) were also used for conjugate additions to α,β-acetylenic esters. Successful examples are listed in Table 2.[87,89]

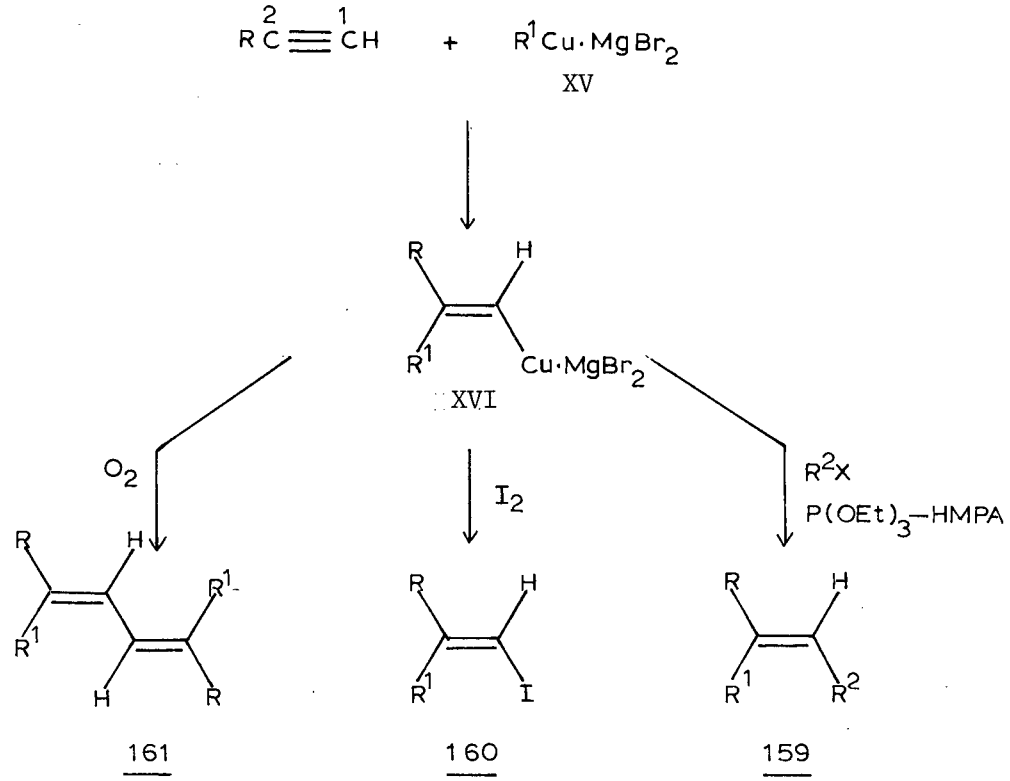
α,β-Acetylenic acids[89,90] and amides[89] also have been reported to undergo similar addition reactions with alkylcopper reagents, though the use of these reactions in alkene syntheses offers no distinct advantage over the use of acetylenic esters.

Table 2. Conjugate Addition of Organocopper Reagents to α,β-Acetylenic Esters.

Organocopper Reagents	157 R = CH_3 ; R^1 =
a.  XIV	
b. Cyclo-$C_5H_9CuP(n\text{-}Bu)_3$	cyclopentyl
c. 	allyl
d. $(t\text{-}BuCuCH_3)Li$	t-butyl

Normant and coworkers have conducted extensive studies on the addition of organocopper reagents to unactivated acetylenes. Their findings provide stereoselective routes to a variety of substituted alkenes.[91] Alkylcopper complexes XV, derived from the corresponding alkylmagnesium bromide and cuprous bromide, were shown to add across the triple bond of non-functionalized 1-alkynes in a cis manner and with copper attached regioselectively to C-1. The resultant vinylcopper complexes XVI could be alkylated with various alkylating agents in the presence of triethyl phosphite to give trisubstituted alkenes 159 in yields which ranged from 50 to 85%.[91a] Iodination and oxygen-promoted coupling of XVI gave vinyl iodides 160 and dienes 161, respectively, in 55 to 75% yields.[91b] The vinylcopper intermediates XVI retained their stereochemistry in all the above reactions as indicated in Scheme vi. Alkylation of XVI with 1-alkynyl halides 162 was effected in the presence of TMEDA, affording acetylenic alkenes 163 in good yields.[91c]

Scheme vi

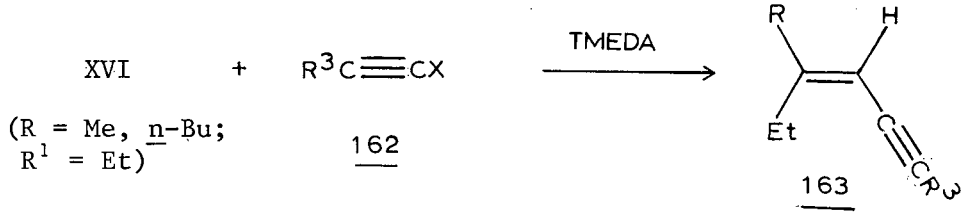


R = alkyl; R^1 = Et, n-Bu;

R^2X = alkyl iodides, allyl and benzyl bromides,

CH_3SCH_2Cl, $EtOCH_2Br$, $CH_3O_2C(CH_2)_3I$,

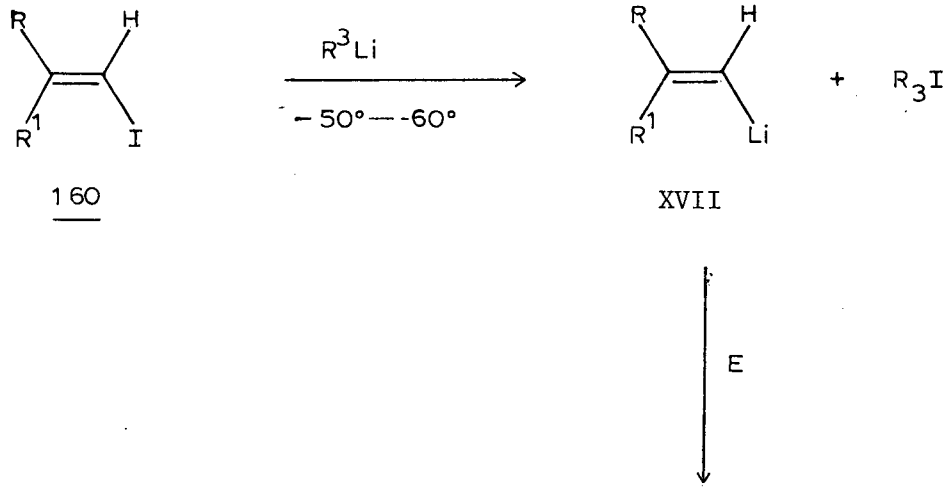
$ClCH_2CH_2OCH_2Br$, $ClCH_2CH_2OCH(CH_3)Br$.



X = I, Br; R^3 = alkyl, $-SiMe_3$, -SEt, $-CO_2Me$;

TMEDA = tetramethylethylenediamine

As an extension of the alkene syntheses shown in Scheme vi, vinyl iodides 160 were converted to functionalized trisubstituted alkenes via the vinyl lithium species XVII, which were formed stereospecifically by iodine-lithium exchange with alkyl lithium at low temperatures. Reactions of vinyl lithium XVII with reactive electrophilic compounds such as epoxides and aldehydes led to alkenes 164.[91e]



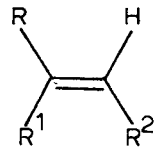
160 XVII

R^3 = Et, Bu

E =  ; CH_3CHO ; HCHO ; CO_2

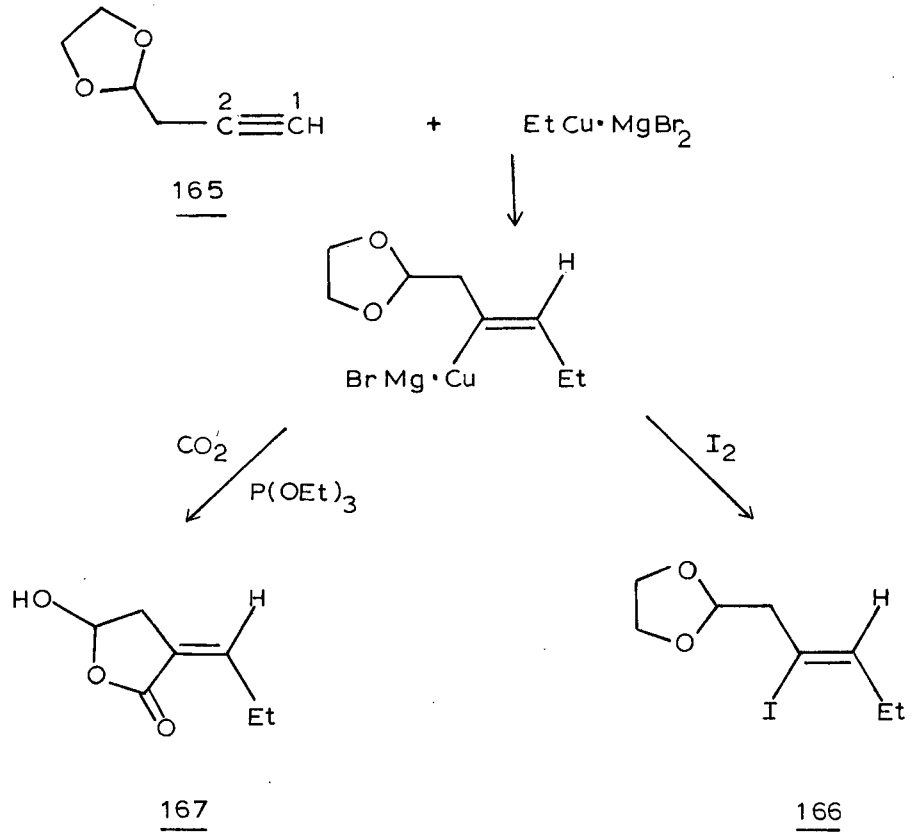
R^2 = $-CH_2CH_2OH$; $-CH(CH_3)OH$;

$-CH_2OH$; $-CO_2H$



164

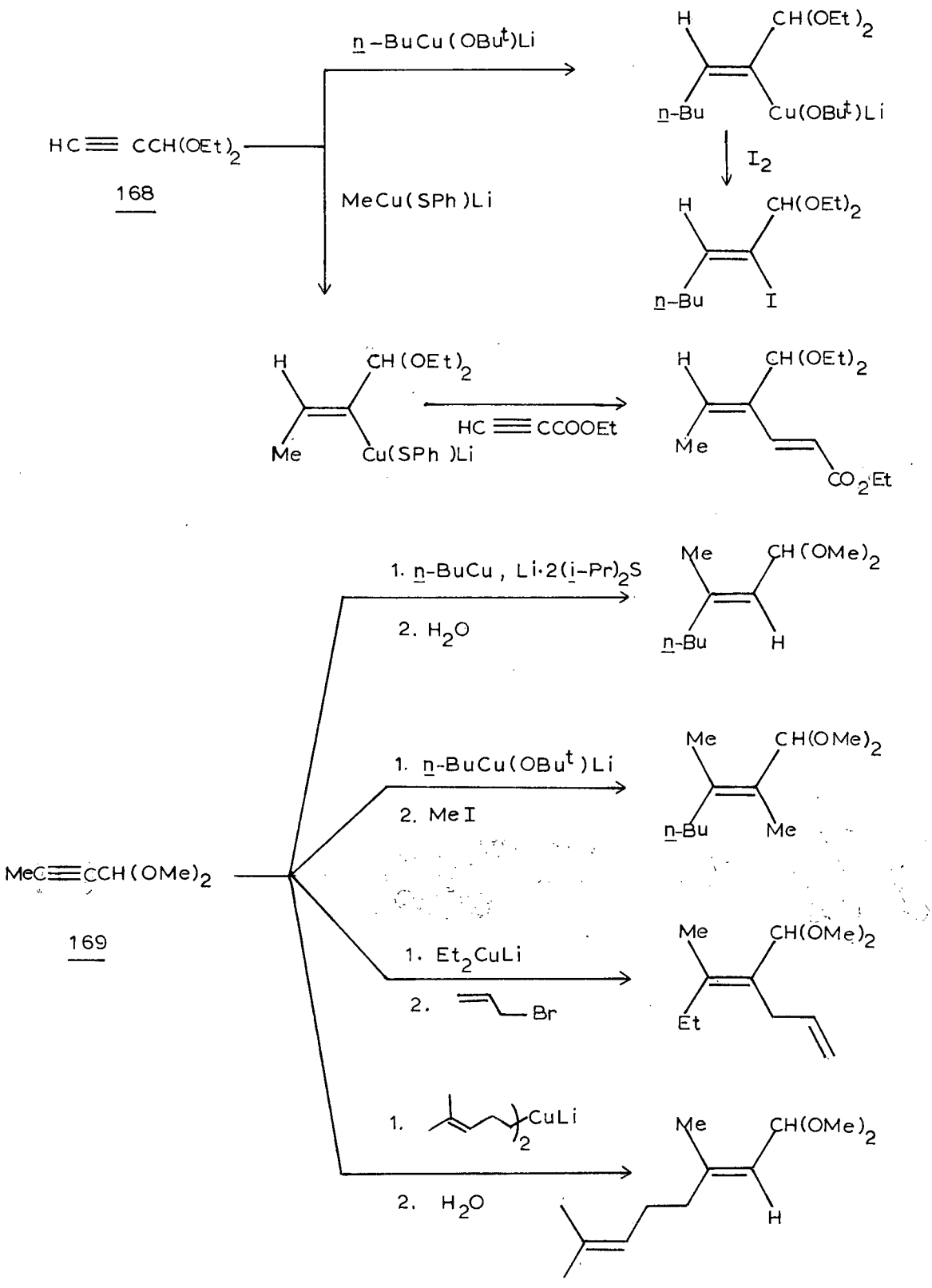
The addition of ethylcopper complex to the acetylenic acetal 165 was found to take a stereochemically different course. Although the ethyl group and copper still added cis to each other, the latter was bonded to C-2 instead of C-1.[91f] Participation of the acetal oxygen during the



167 166

addition was probably responsible for this prevailing regioselectivity. The vinylcopper intermediate underwent the usual iodination and carboxylation to furnish 166 and 167 in 61 and 55% yields, respectively. Similar results were observed for propargylic acetals 168 and 169. Examples that illustrate the application of this type of addition to the synthesis of tri- and tetrasubstituted alkenes are given in Scheme vii.[91d] The use of

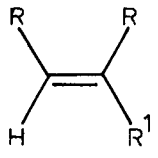
Scheme vii


n-BuCu(OBu^t)Li
HC≡CCH(OEt)2
168
MeCu(SPh)Li
H
CH(OEt)2
n-Bu
Cu(OBu^t)Li
I2
I
HC≡CCOOEt
Me
Cu(SPh)Li
CO2Et
1. n-BuCu, Li·2(i-Pr)2S
2. H2O
CH(OMe)2
1. n-BuCu(OBu^t)Li
2. MeI
1. Et2CuLi
2. Br
CuLi
MeC≡CCH(OMe)2
169

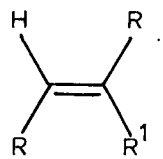
some heterocuprates, [RCuY]Li (Y = hetero ligand), which have been found superior to dialkylcuprates in many of these addition reactions are also illustrated.

The addition of alkylcopper complexes to acetylenes was further explored by Helquist and coworkers.[92] By using the dimethyl sulfide-cuprous bromide complex of Grignard reagents, XVIII, they obtained improved yields of the addition products with 1-alkynes. The vinylcopper complexes XIX so prepared were shown to undergo conjugate additions to α,β-unsaturated ketones, acylation with acetyl chloride, and alkylation with allyl bromide and ethylene oxide (Scheme viii).

Hydrometallation of acetylenes with hydride complexes of boron,[93a] aluminum,[93b] tin,[93c] and zirconium[93d] are well known. Use of this type of reaction to synthesize trisubstituted alkenes is limited by the generally low regioselectivity of the addition of these hydride complexes to unsymmetrical, disubstituted acetylenes. Nevertheless, trisubstituted alkenes of the general structure 170 and 171 can be derived from symmetrical acetylenes. A stereoselective route to these alkenes based on hydroalumination

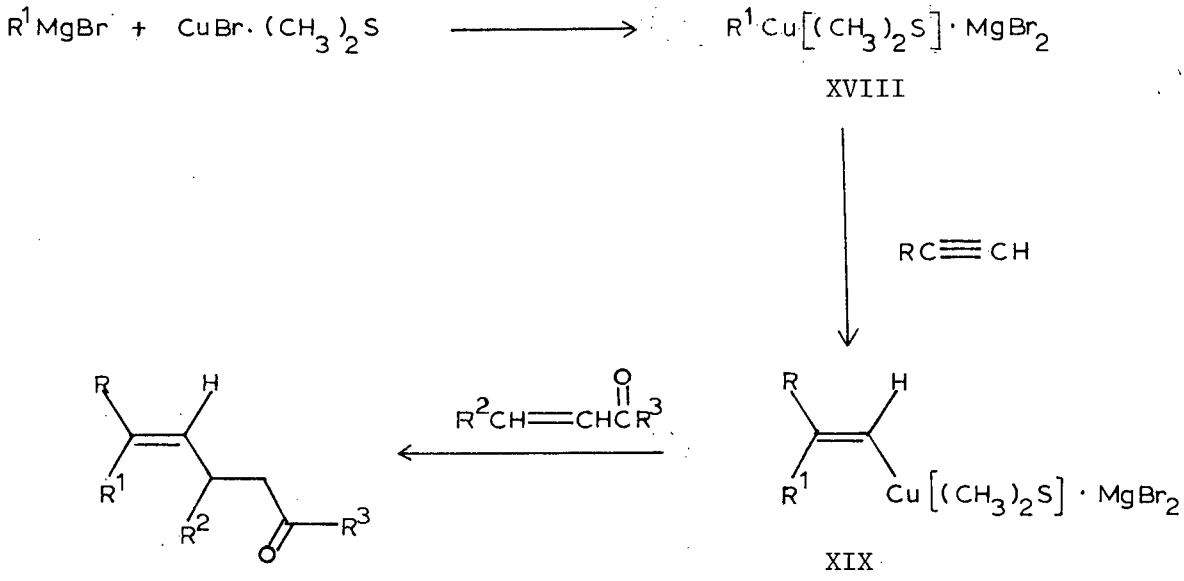


170



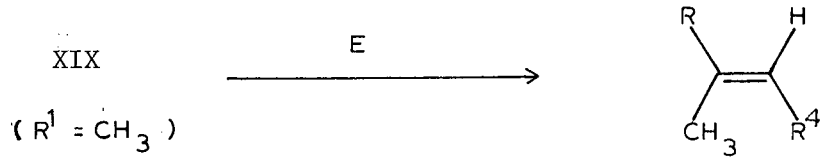
171

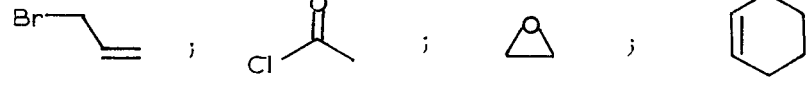
Scheme viii

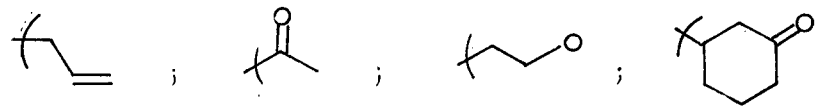


R = alkyl ; R^1 = alkyl ;

R^2, R^3 = alkyl , phenyl.



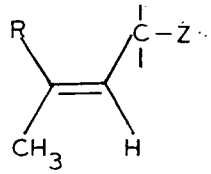
E = 

R^4 = 

was developed by Zweifel.[94] Diisobutylaluminum hydride was added to acetylenes 172 in a cis manner giving vinylalanes XX, which could undergo various reactions. Direct iodination of XX yielded vinyl iodides. Conversion of XX to the vinylalanates XXI with methyl lithium, followed by treatment with cyanogen, carbon dioxide, paraformaldehyde or allyl bromide[95] led to the corresponding functionalized alkenes (Scheme ix). All these reactions of vinylalanes XX and vinylalanates XXI proceeded in satisfactory yields and with retention of configurations.

Hydroalumination of disubstituted alkynes with lithium diisobutylmethylaluminum hydride occurred in a trans fashion, in contrast with the cis addition of diisobutylaluminum hydride.[95] The trans-vinylalanates XXII thus formed could also be transformed into trisubstituted alkenes via iodination, carboxylation and condensation as shown in Scheme ix.

Very recently, Negishi and coworkers reported a general procedure to synthesize functionalized E-3-methyl-2-alkenes 173 via carboalumination of terminal acetylenes.[96] Zirconocene dichloride (Cl_2ZrCp_2) catalyzed methyl-

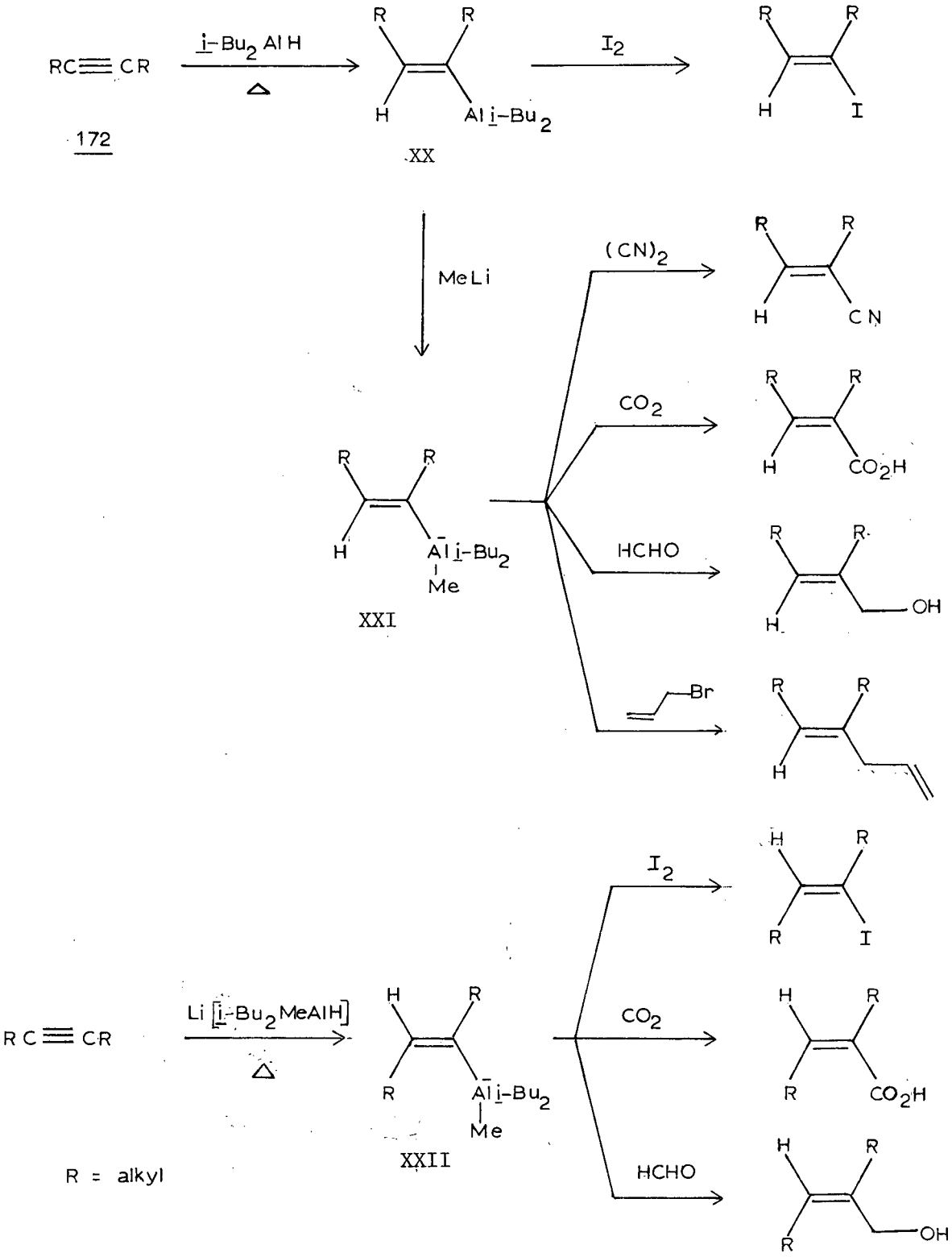


Z = oxo functional group

173

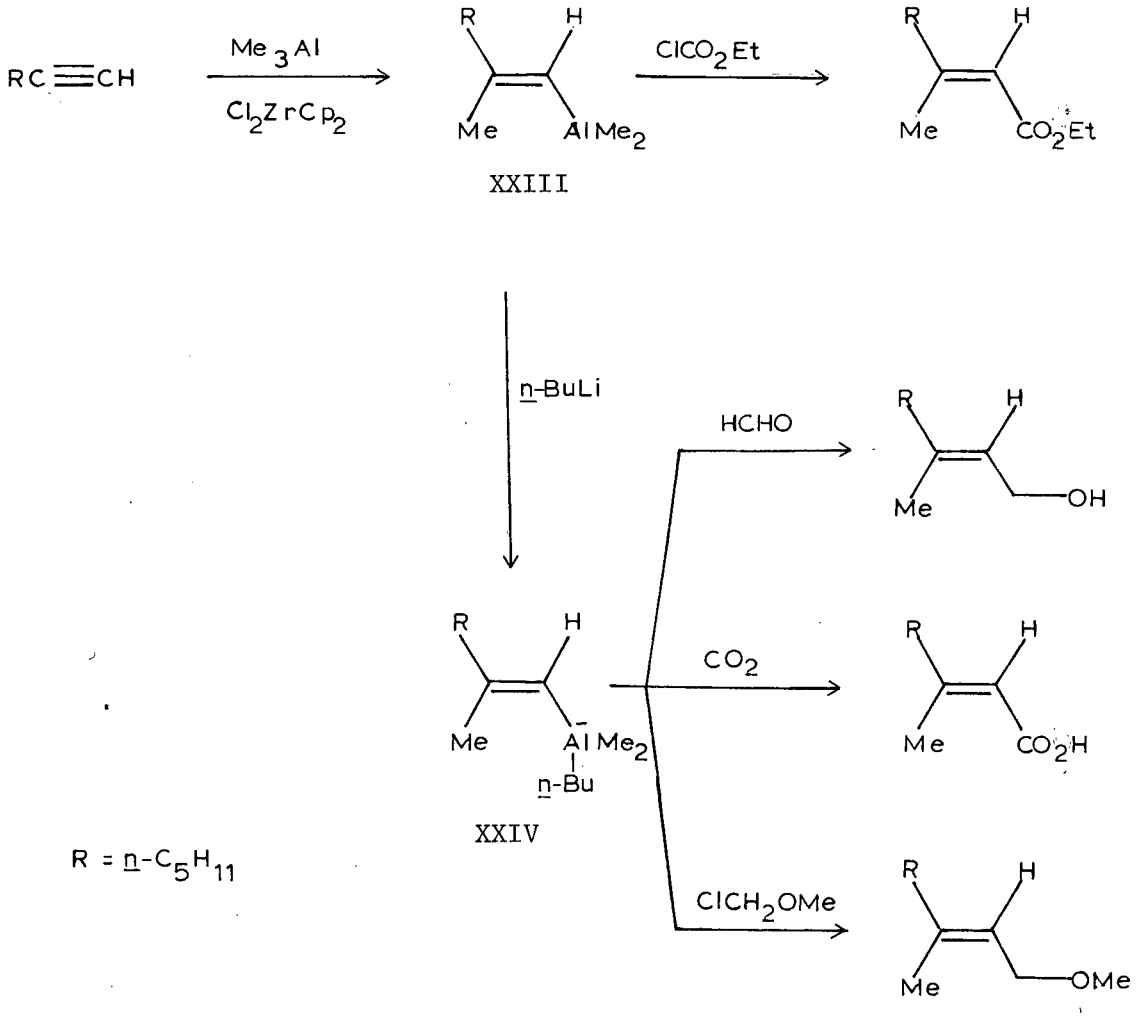
alumination of 1-alkynes with trimethylalane gave stereo- and regioselectively the E-2-methylalkenylalanes XXIII (ratio of terminal to internal alkenylalanes ca. 95:5). Treatment of vinylalanes XXIII, or the corresponding alanates XXIV, with the appropriate electrophilic reagents afforded the functionalized

Scheme ix


RC≡CR
172
i-Bu2AlH
△
R
R
H
Al i-Bu2
XX
I2
MeLi
(CN)2
CO2
HCHO
Br
CN
CO2H
OH
XXI
Me
Li [i-Bu2MeAlH]
XXII
R = alkyl

trisubstituted alkenes shown in Scheme x in satisfactory overall yields.

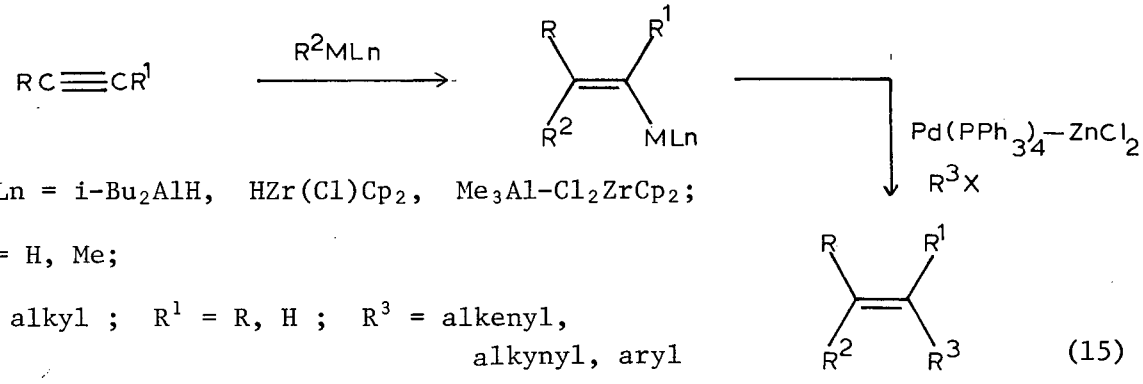
Scheme x



The fact that a host of differently functionalized alkenes 173 can be derived from the common intermediate XXIII enhances the utility of this method. However, two limitations should be noted, viz., it does not provide a route to the Z-isomer of 173 and it only allows the addition of a methyl

group to the acetylenes. An attempt to transfer an alkyl group other than methyl by using a trialkylalane-zirconocene dichloride system was reported unsuccessful.[96a]

The hydrometallated and carbometallated vinylic intermediates described above may also be coupled with vinyl, alkynyl or aryl halides, with both reactants retaining their stereochemistry. A double metal catalysis system, consisting of tetrakis(triphenylphosphine)-palladium (or nickel) and zinc(II)chloride, was developed by Negishi et al. for these coupling reactions (equation 15).[96b]

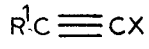


R^2MLn = i-Bu_2AlH, $HZr(Cl)Cp_2$, Me_3Al-Cl_2ZrCp_2;

R^2 = H, Me;

R = alkyl ; R^1 = R, H ; R^3 = alkenyl, alkynyl, aryl (15)

Hydroalumination of heterosubstituted acetylenes 174 with dialkylaluminum hydride has been studied in detail by Eisch and coworkers.[95,97] While their findings, in general, provide stereoselective routes to hetero-



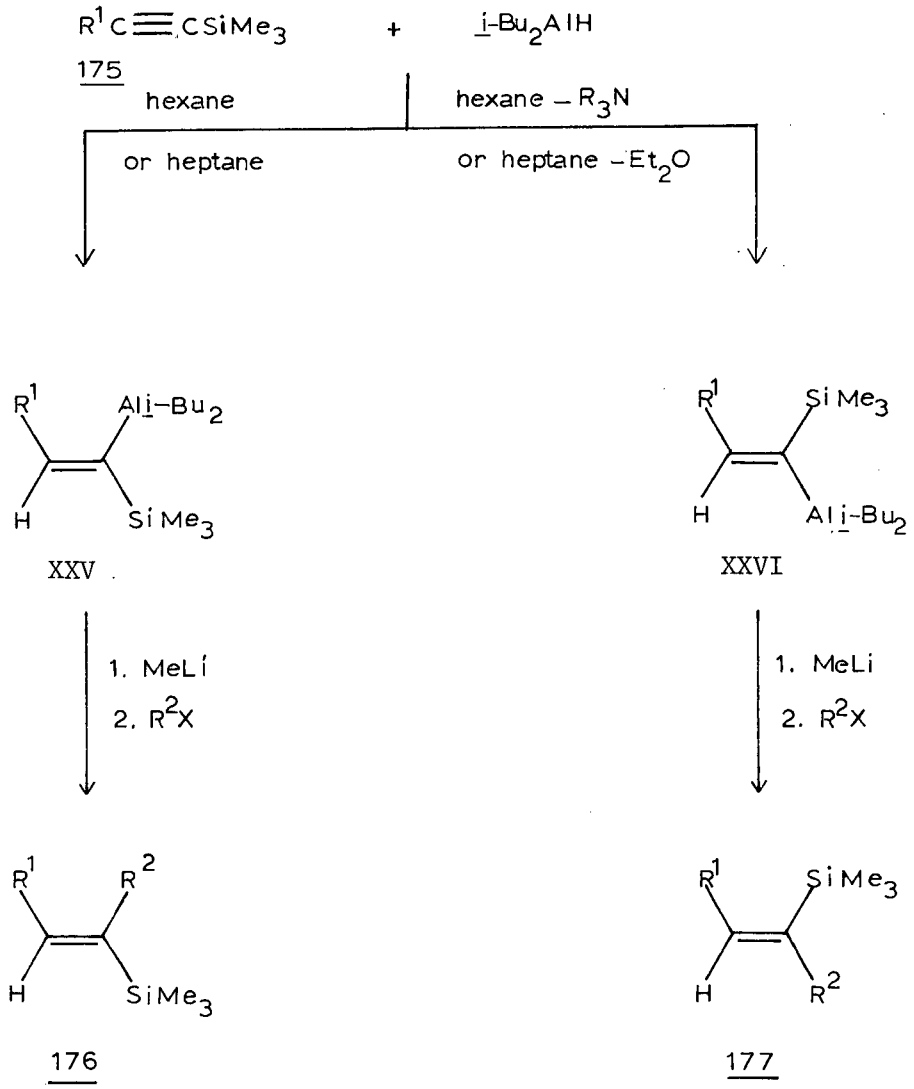
174

R^1 = alkyl, aryl ;

X = $-NR_2$, -OR, -SR, $-SiR_3$

vinylic compounds, such as vinylic ethers and sulfides, their work on silylacetylenes is of particular interest for alkenes synthesis. As shown in Scheme xi, trimethylsilylacetylenes 175 can be hydroaluminated stereo-

Scheme xi



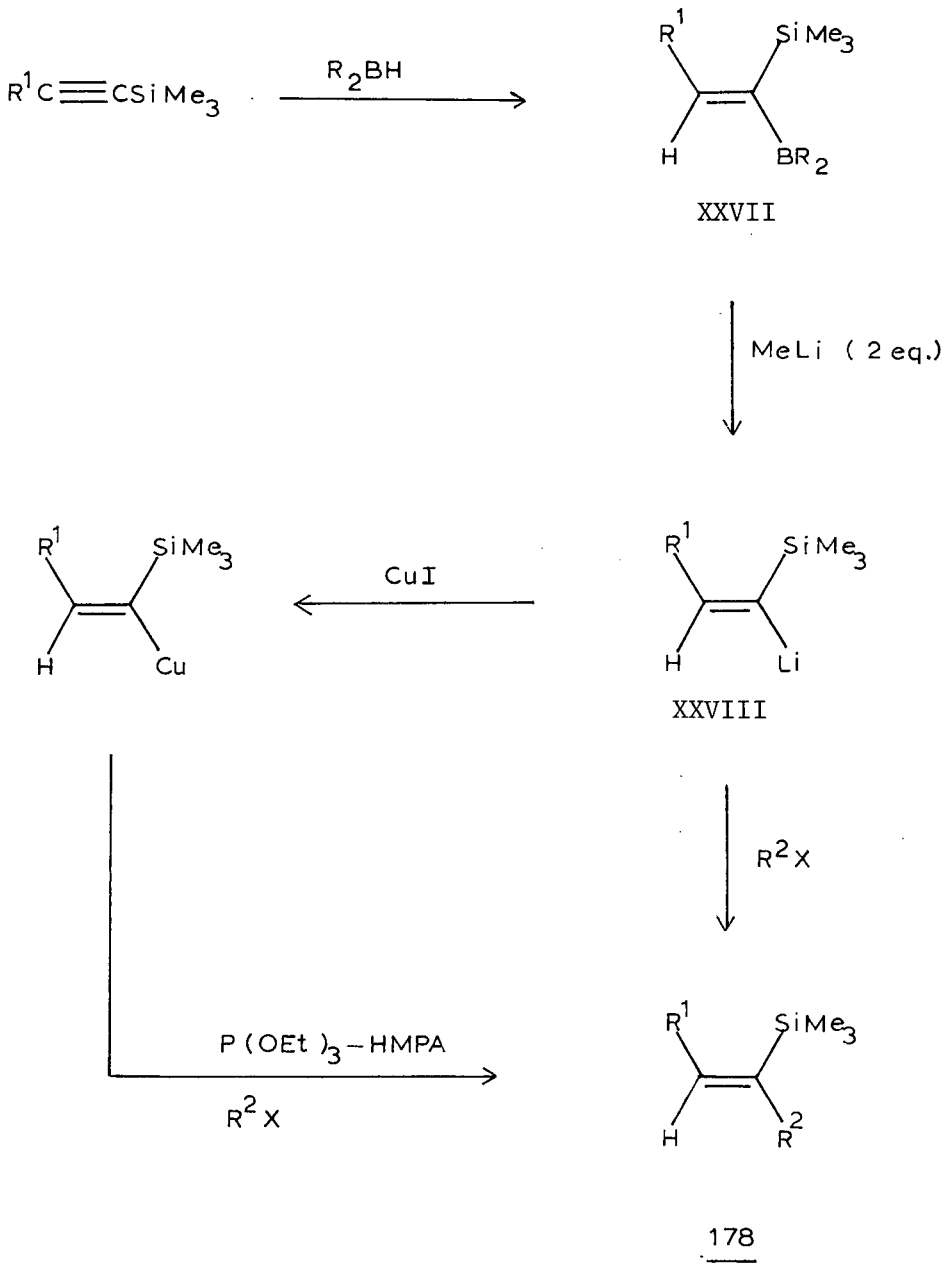
R^1 = alkyl, aryl ; R^2 = alkyl ; X = halogen.

selectively to the E-alkenylsilanes XXV or the Z-alkenylsilanes XXVI by conducting the reaction in the absence or presence of a Lewis base.[98] The regiochemistry of these addition reactions is controlled by the silyl group. Without any additional base, the addition of diisobutylaluminum hydride to 175 gave predominantly the trans adduct XXV, which was believed to arise from isomerization of the initially formed cis adduct XXVI. The isomerization is favored by steric considerations, and is probably assisted by the alumino and/or silyl group. Lewis bases coordinate with the aluminum and/or silicon atoms and hence retard the isomerization of the carbon-carbon double bond. A bulkier silyl group ($-SiEt_3$) was also found to favor the formation of XXV, supporting the isomerization mechanism.

Conversion of the Z- and the E-alkenylalanes, XXV and XXVI, to their corresponding alanates with methyllithium, followed by treatment with alkyl halides led to the E- and the Z-alkenylsilanes, 176 and 177, respectively.[97,98] The major drawback of this synthetic method, as reported independently by Eisch and by Utimoto, is the low-yielding nature of some alkylation reactions of the alanates. Despite this limitation, it serves as a versatile route to trisubstituted alkenes since the trialkylsilyl groups of vinylsilanes can be replaced stereospecifically by a variety of electrophiles.[99]

Another approach to disubstituted vinylsilanes is the hydroboration of alkynylsilanes reported by Uchida et al.[100] Hydroboration of trimethylsilylacetylenes with dicyclohexylborane gave, regio- and stereoselectively, vinylboranes XXVII. Successive treatment of XXVII with methyl-

Scheme xii

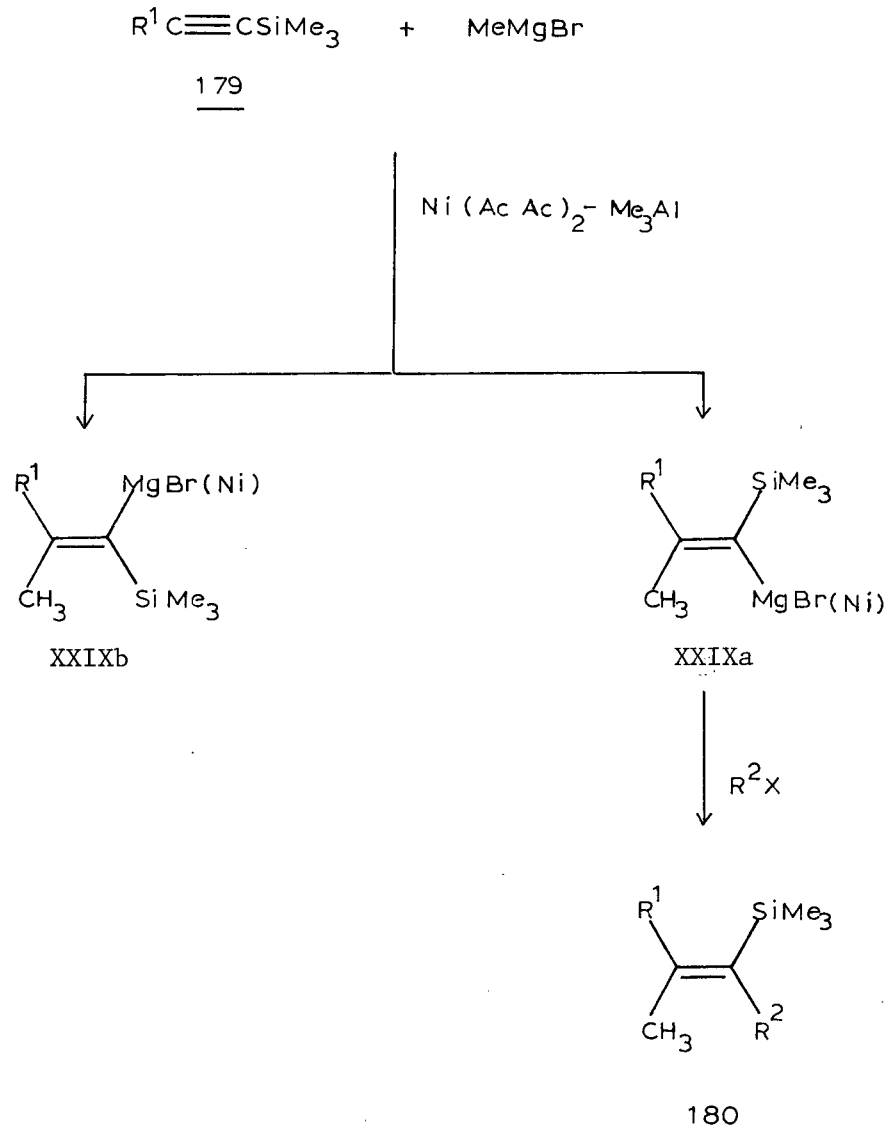


178

R^1 , R^2 = alkyl ; R = cyclohexyl ;

X = halides , tosylate.

Scheme xiii



R^1 = n-C_6H_{13}; AcAc = acetylacetonate;

R^2X = H_2O ; I_2 ; RCHO ; CO_2 ; alkyl halide

R^2 = H ; I ; RCHOH ; CO_2H ; alkyl

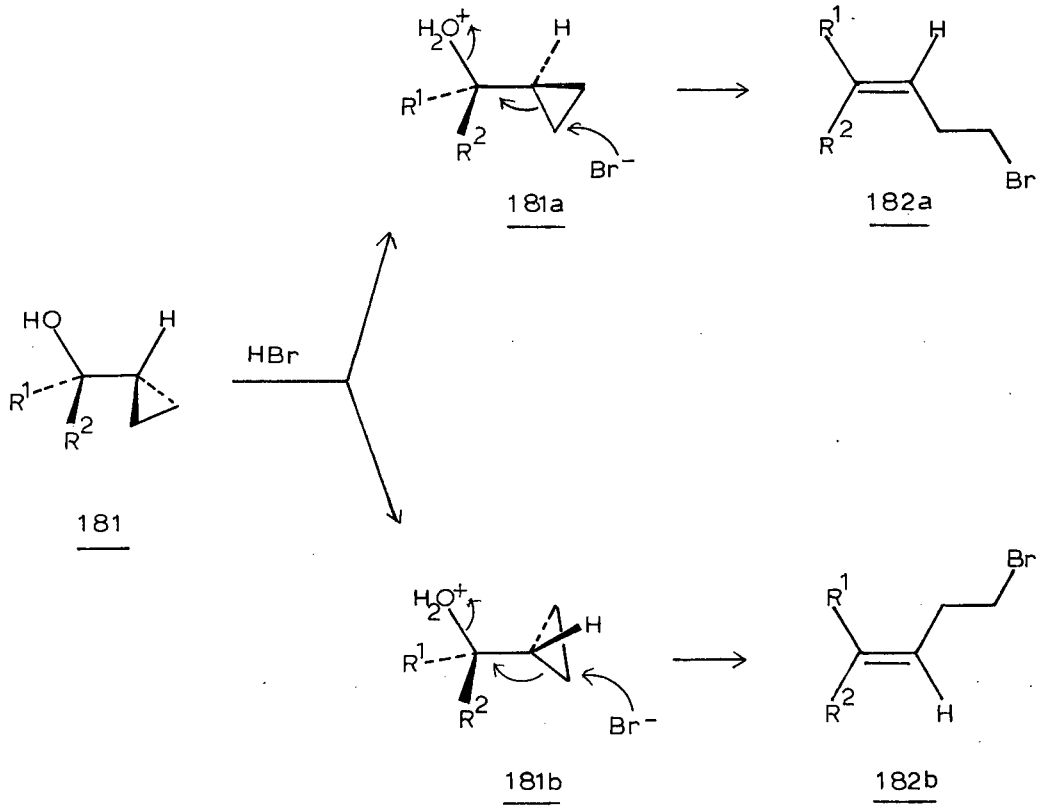
lithium, cuprous iodide and alkylating agents afforded Z-alkenylsilanes 178 in good yields. With more reactive alkyl halides (e.g., methyl iodide and allyl bromide), direct alkylations of the vinyllithium intermediate XXVIII have also given satisfactory results (Scheme xii).

Snider et al. developed another application of trimethylsilyl-acetylenes, which is of particular interest for the synthesis of tetra-substituted alkenes.[101] Carbometallation of 1-trimethylsilyl-1-octyne (179) with methylmagnesium bromide was effected by using a 1:1 mixture of nickel acetylacetonate and trimethylalane as catalyst. Under optimized conditions, a 9:1 mixture of vinylmetal complexes, XXIXa and XXIXb, were obtained in ca. 80% yield. The relatively high reactivity of these organometallic intermediates towards electrophilic reagents furnished the subsequent reactions (Scheme xiii) to give mainly trisubstituted vinylsilanes 180. Addition of ethylmagnesium bromide to 179, under similar conditions, was unsuccessful. The utility of this method, therefore, seems to be limited to the synthesis of methyl-substituted alkenes.

B. Synthesis Involving Ring Cleavages

Stereoselective formation of homoallylic bromides 182a,b via cleavage of α-cyclopropyl carbinols 181 was first reported by Julia.[102] The stereochemistry of the predominant olefinic product in these reactions can be predicted by considering the transition state conformations. An anti periplanar arrangement of the hydroxonium leaving group and the breaking carbon-carbon bond of the cyclopropyl ring is presumed in the transition state. As illustrated in Scheme xiv, when R^1 is bulkier than R^2, conforma-

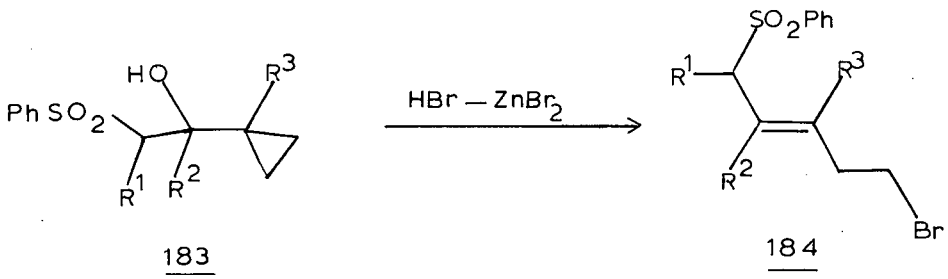
Scheme xiv



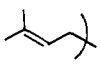
tion 181a prevails and 182a will be the major product. On the other hand, if R^1 is less bulky than R^2, conformation 181b will be favored, leading to predominant formation of 182b. Low stereoselectivity was observed when R^1 and R^2 were of similar bulkiness.[103]

Several modifications of the Julia synthesis have been developed to improve both the stereoselectivity and the versatility. Treatment of phenylsulfonyl alcohols 183 with hydrobromic acid and zinc(II)bromide

gave the E-alkenes 184 in greater than 83% yields, accompanied by only small amounts of the Z isomers.[104] The relatively large size of the phenylsulfonyl group undoubtedly enhances the stereoselectivity of these reactions (cf. Scheme xiv). Moreover, the phenylsulfonyl group also facilitates the preparation of the alcohol precursors 183 (i.e., condensation of the appro-

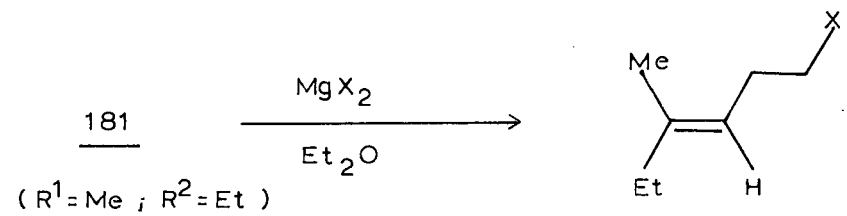


183 184

R^1 = H ,  ; R^2 = Me , Et ; R^3 = H , Me .

priate α-sulfonyl carbanion with alkyl cyclopropyl ketone), and further elaboration on the alkene products 184.

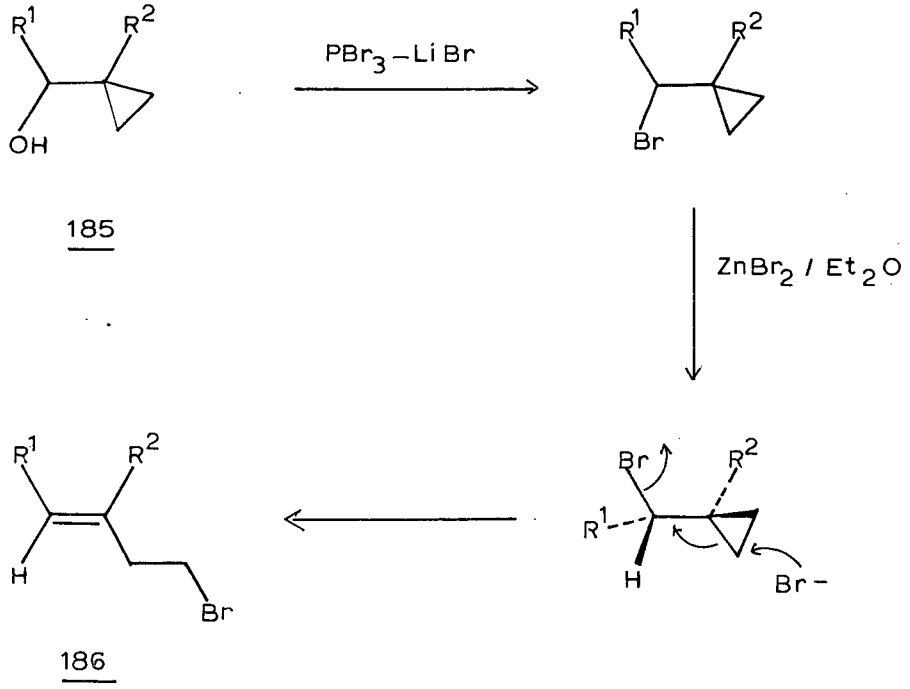
McCormick and Barton used magnesium halides to effect the following transformation (equation 16) with satisfactory selectivity.[105]



(16)

X = Br , I

Another variation of the Julia synthesis, developed by Johnson et al., also avoids the strong acid-conditions originally employed. Secondary alcohols 185, with a 1,1-disubstituted cyclopropyl moiety, were converted to trisubstituted alkenes 186 in good yield and in high stereoselectivity by bromination followed by reaction with zinc(II)bromide in ether.[106]

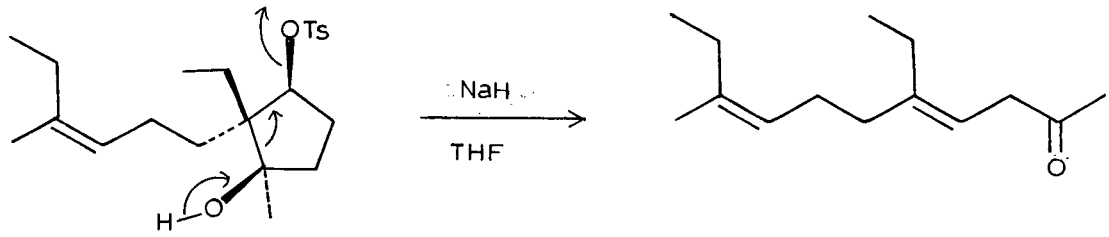


185

186

Synthesis of alkenes by stereospecific fragmentation of cyclic compounds has the advantage of complete control over stereochemistry. However, successful execution of this method requires facile, stereospecific synthesis of the cyclic precursors. Application of this methodology to the synthesis of acyclic alkenes is demonstrated by the fragmentation of

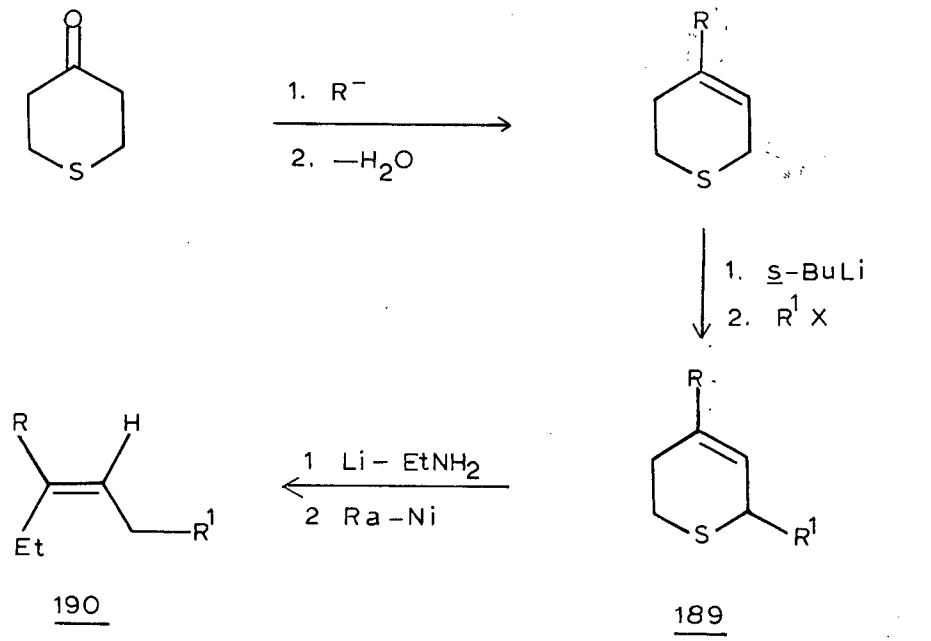
hydroxy tosylate 187 to dienic ketone 188.[107]



187 188

An alkene synthesis based on the cleavage of cyclic sulfides was reported by Stotter.[108] Substituted thiacyclohexenes 189 were prepared according to the sequence shown in Scheme xv. Reduction of 189 with lithium in ethylamine, followed by desulfurization using deactivated Raney nickel

Scheme xv

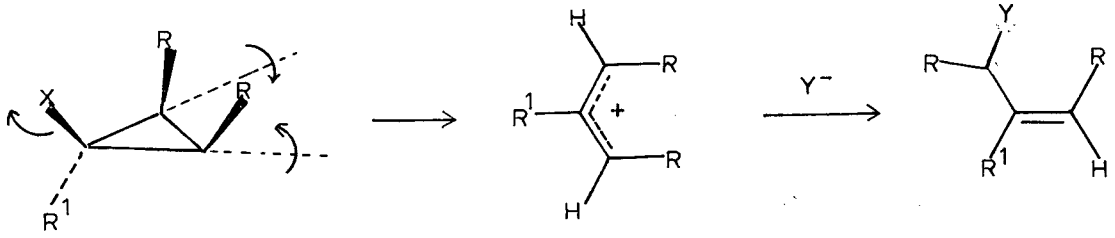


190 189

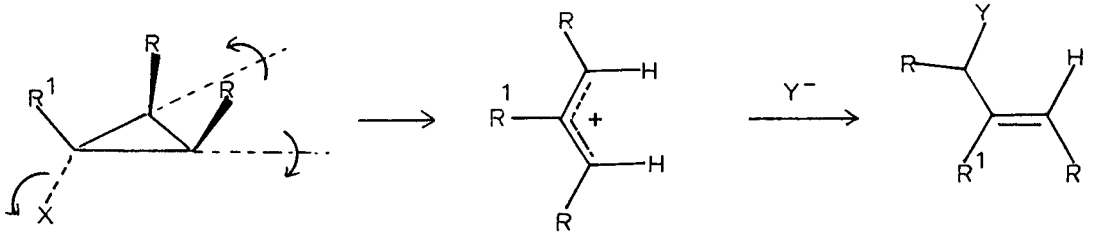
R^- = nucleophiles, e.g. MeMgBr R^1X = alkyl or allylic halides.

led to alkenes 190 with a cis ethyl substituent.

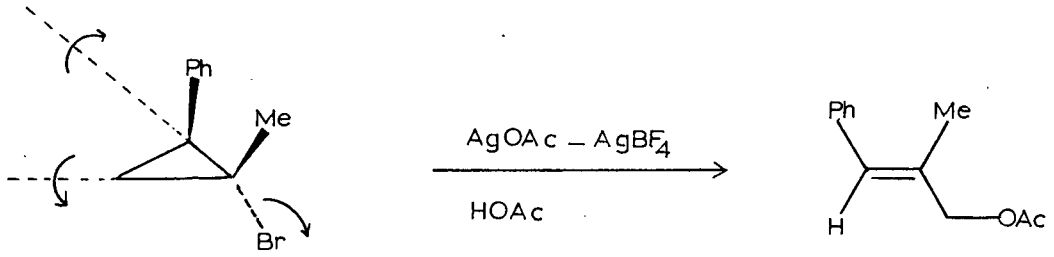
Symmetry-controlled electrocyclic opening of halogenocyclopropanes, e.g., 191a and 191b, occurs in a stereospecific manner,[109] forming allylic cations XXXa and XXXb which can be trapped by nucleophiles to give the corresponding alkenes 192a and 192b. For example, the cyclopropyl



191a XXXa 192a



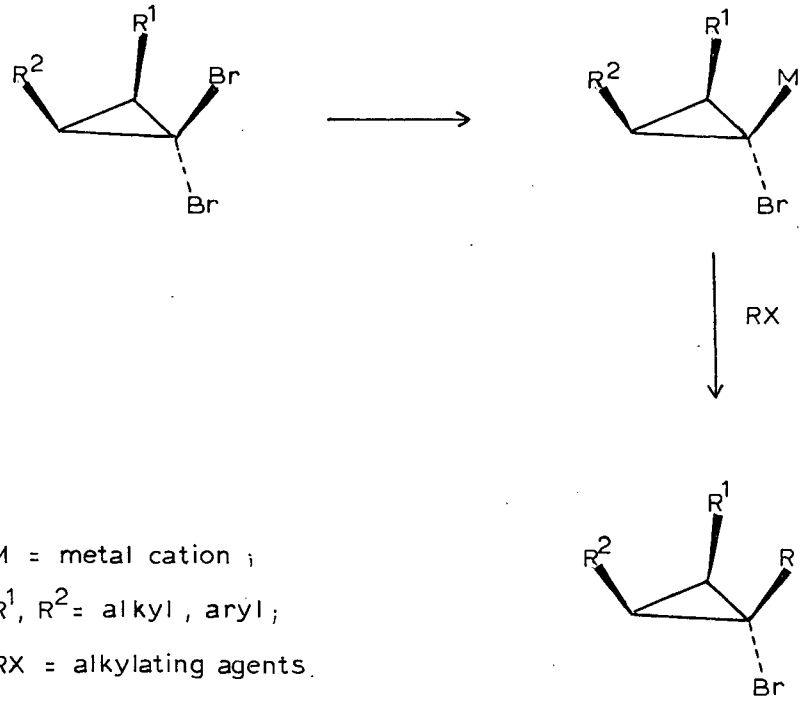
191b XXXb 192b



193 194

bromide 193 underwent electrocyclic opening to afford stereospecifically allylic acetate 194 in 74% yield.[110]

Stereoselective methods for achieving the following bromocyclopropane synthesis (equation 17) have been secured in the past few years.[110]



M = metal cation ;
R^1, R^2 = alkyl , aryl ;
RX = alkylating agents.

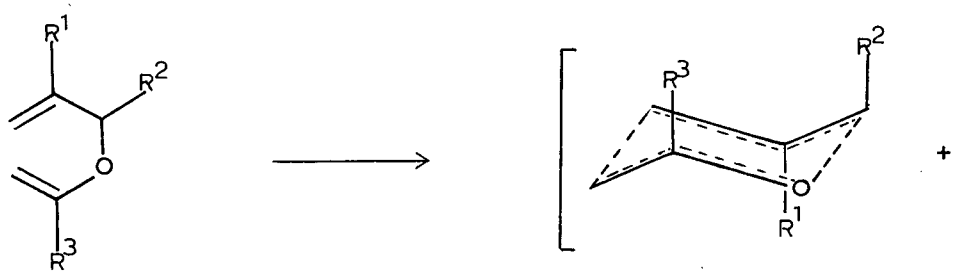
(17)

195

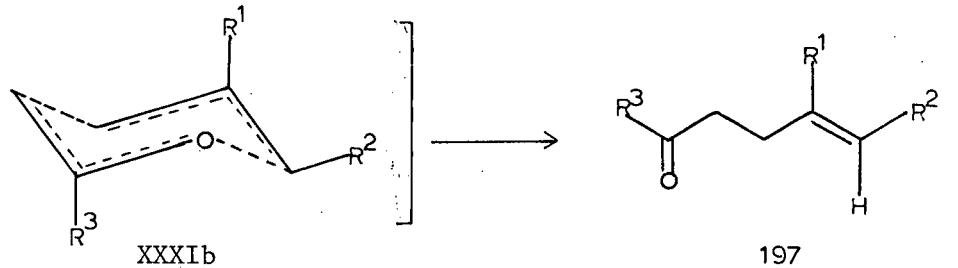
With these bromocyclopropanes 195 now readily accessible, the aforementioned stereospecific route to substituted alkenes will certainly become more attractive.

C. Synthesis via Sigmatropic Rearrangements

The Claisen type rearrangements have been broadly used for the stereoselective synthesis of trisubstituted alkenes.[111] In general, these reactions involve the [3,3]-sigmatropic rearrangement of allyl vinyl ethers as illustrated by equation 18. The rearrangement is believed to occur via



196 XXXIa



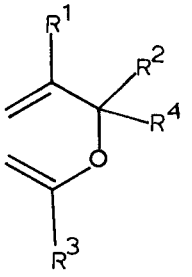
XXXIb 197

(18)

R^1, R^2 = alkyl ; R^3 = H, alkyl, OR, $OSiR_3$, NR_2.

a chair-like conformation in the transition state (e.g., XXXIa,b). Due to the pseudo-1,3-diaxial interaction between substituents R^2 and R^3 in conformation XXXIa, the alternative chair conformation XXXIb with R^2 in a pseudo-equatorial position, is more favorable. Consequently, the Claisen rearrangement of vinyl ether 196 gives predominantly the E-alkene 197. While the

degree of stereoselectivity may be enhanced by increasing the steric bulk of R^2 and/or R^3, vinyl ethers of allylic tertiary alcohols (e.g., 198) show poor stereoselectivity.[112] The side chain cis to H in alkene 197

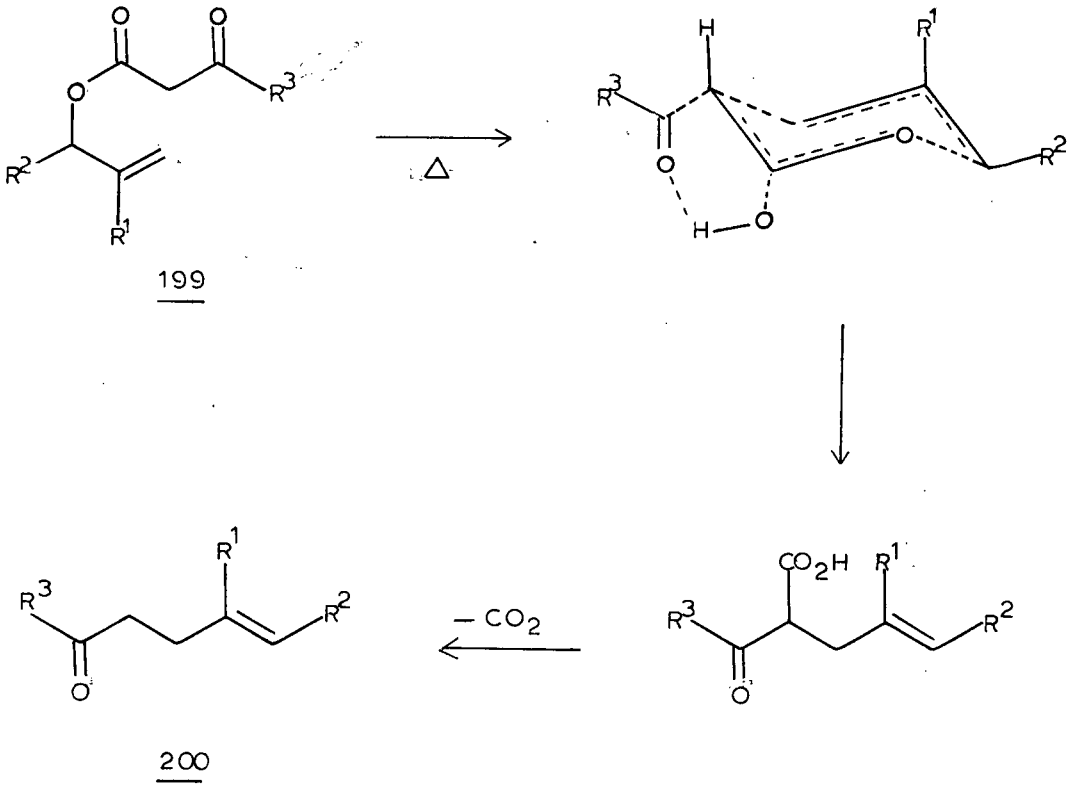


198 $R^2 \neq R^4 \neq H$

may contain an aldehyde,[113] ketone,[114] carboxylic ester,[115] acid[116] or amide[117] depending on the nature of R^3.

Another version of the Claisen rearrangement is the Carroll reaction which involves the thermal rearrangement of allyl acetoacetate derivatives and concomitant decarboxylation of the rearrangement products. The following transformation of allyl acetoacetate 199 ($R^1 = R^2 = CH_3$, $R^3 = H$), to alkene 200 ($R^1 = R^2 = CH_3$, $R^3 = H$; E:Z = 93:7) illustrates this process.[118]

The dianion of allyl dithioacetates 201 have been dialkylated successively at low temperature to give thioenol ether intermediates XXXII which, on warming to -25° C, underwent [3,3]-sigmatropic rearrangement to yield alkenes 202. The advantages of this procedure in alkene synthesis are that it allows for the facile introduction of R^2 and that the rearrangement can be achieved under mild conditions. The methyl thioester group of

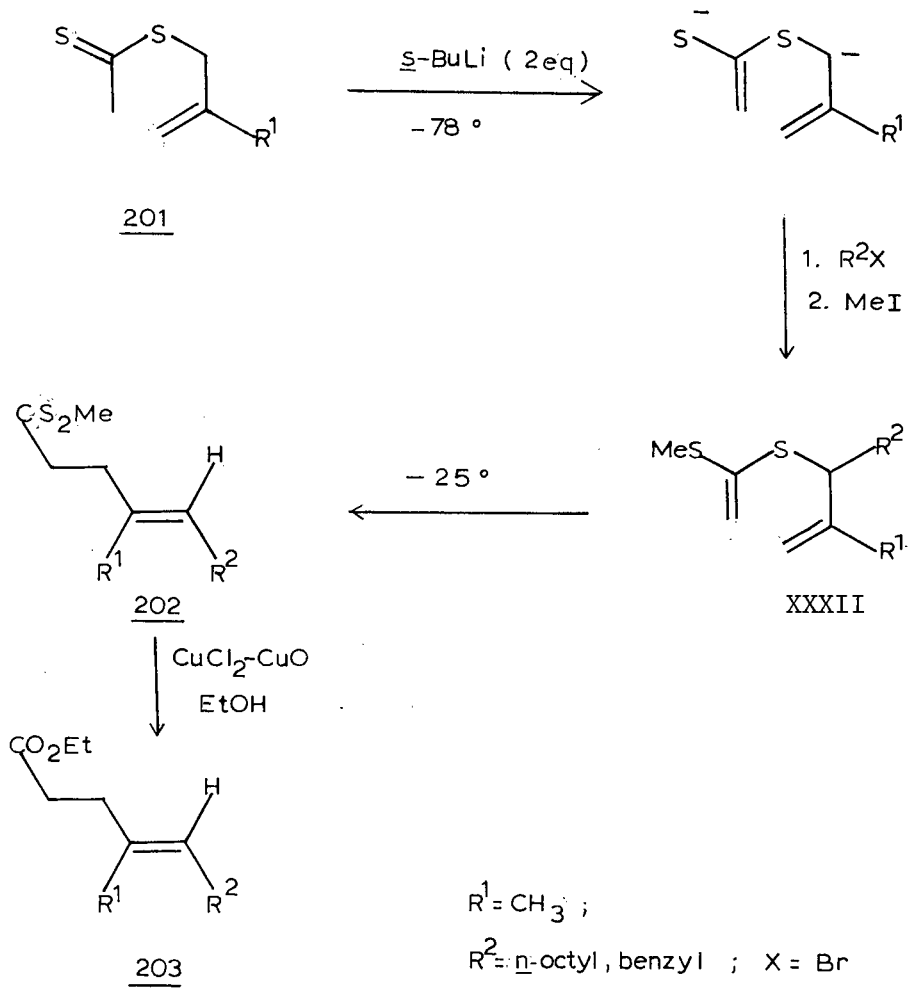


199

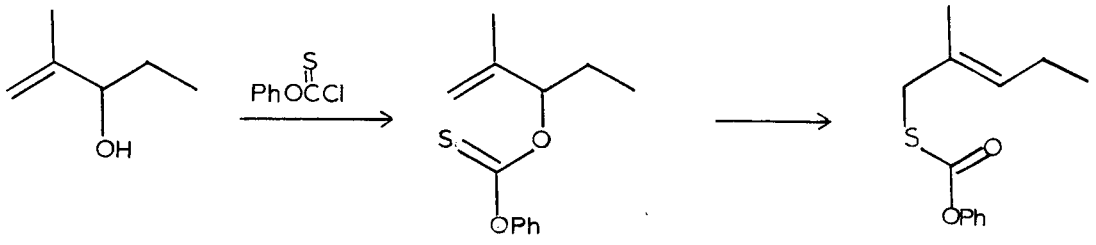
200

202 could be converted to the ethyl ester by treatment with cupric chloride in ethanol. Overall yields of 203 from 201 for the examples shown were 63 to 70% and stereoselectivities for the formation of the E isomers of 203 were greater than 98%.[119]

The rearrangement of allylic thionocarbonate XXXIII was reported by Faulkner.[120] When alcohol 204 was allowed to react with O-phenyl thionochlorocarbonate in pyridine, the allylic thiolcarbonate 205 was obtained in 67% yield with an E to Z isomer ratio of 96.5 : 3.5.



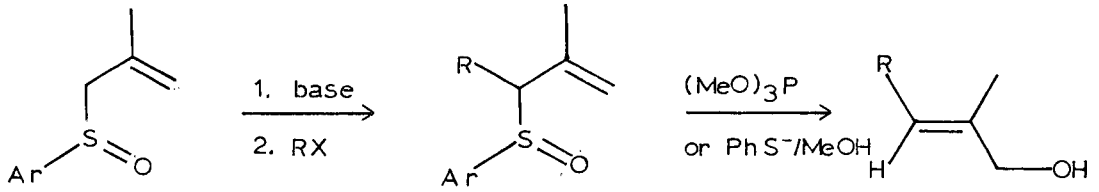
Stereoselective synthesis of trisubstituted alkenes via [2,3]-sigmatropic rearrangements have also been demonstrated. A stereoselective route to trisubstituted allylic alcohols based on the allylic sulfoxide-sulfenate interconversion was developed by Grieco[121] and Evans et al.[122] Scheme xvi illustrates the scope of this method. Sulfoxides 207 and 210 were



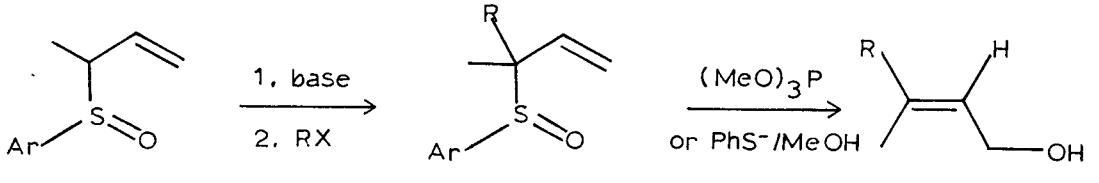
204 XXXIII 205

prepared by selective α-alkylation of the sulfoxide-stabilized allylic carbanions derived from 206 and 209 respectively. Transformation of these sulfoxides to the corresponding allylic alcohols, 208 and 211, was effected

Scheme xvi



206 207 208

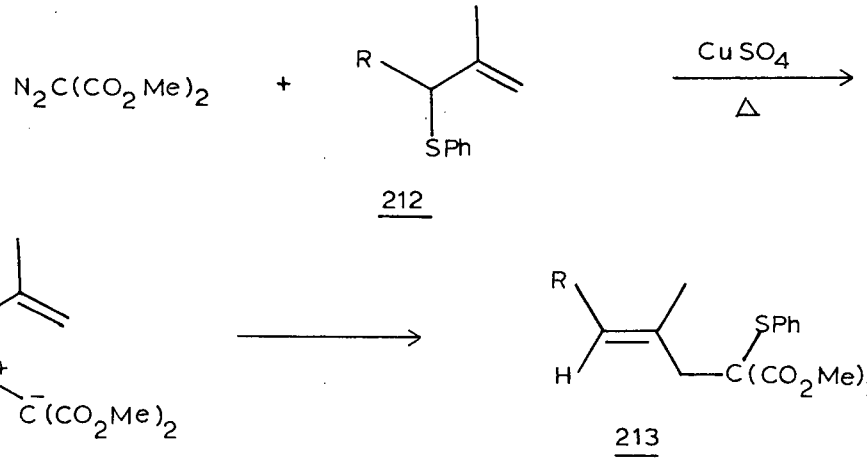


209 210 211

Ar = Ph , p-C_6H_4Me ; R = alkyl

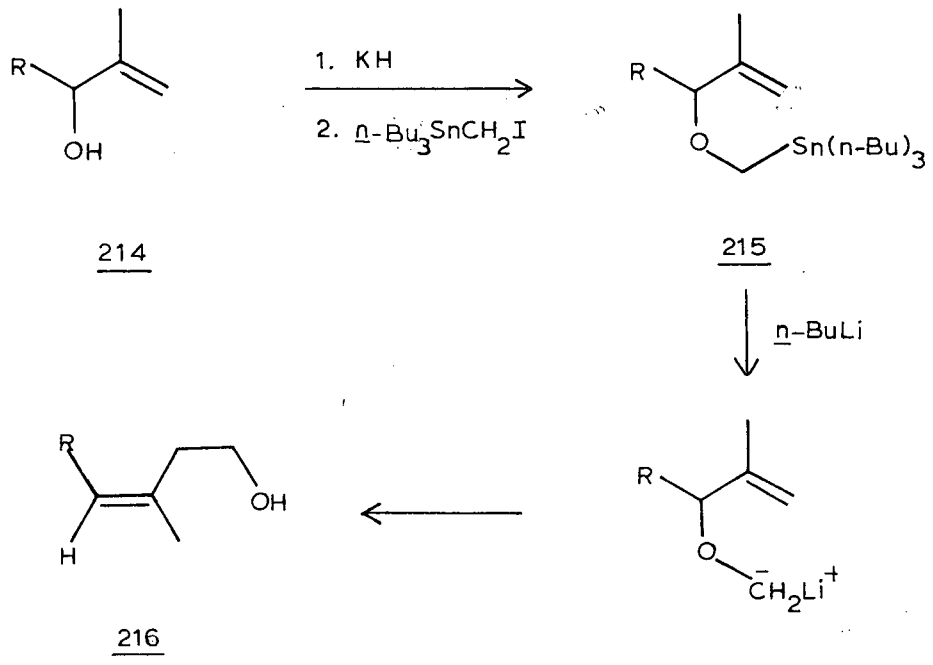
by trimethylphosphite or thiophenoxide in methanol. Satisfactory yields and stereoselectivities were reported for the overall conversions, 206 to 208 and 209 to 211.

α-Substituted methallylsulfonium ylides undergo [2,3]-sigmatropic rearrangements to give mainly E-trisubstituted alkenes.[123] By heating a mixture of methyl diazomalonate and α-substituted methallyl sulfide 212, in the presence of cupric sulfate, Grieco et al. obtained a 9:1 mixture of the E and Z isomers of alkene 213 in about 70% yield.[123]



R = n-Bu , Et.

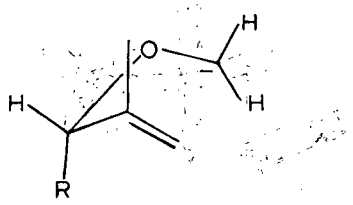
Recently, Still and Mitra reported the Wittig-type rearrangement[124] of allyl stannylmethyl ethers 215, generated by alkylating the anion of alcohols 214 with iodomethyltri-n-butyltin.[125] Unlike the previously described [2,3]- and [3,3]-sigmatropic rearrangements which generally give E-alkenes as the major product, the rearrangement of 215, upon treatment with n-butyllithium, gave the Z-alkenes 216 in greater than 95% stereoselectivity. The Z geometry of the predominant products indicates that



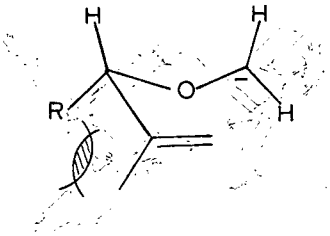
214 215 216

R = alkyl

conformation XXXIVa, with substituent R in a pseudo-axial position, is more favorable than conformation XXXIVb in the transition state of the rearrangement. This unusual preference was attributed to an early, more reactant-like transition state which would suffer significant steric interaction



XXXVa

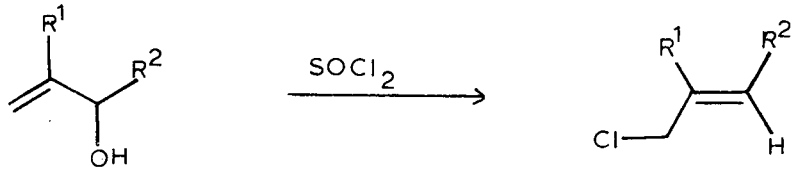


XXXVb

between R and the vinyl methyl group in adopting conformation XXXIVb.

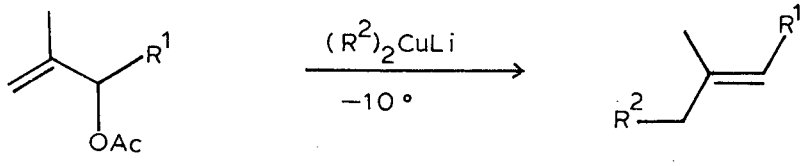
D. Synthesis Involving Allylic Rearrangements

Allylic alcohols 217, when treated with thionyl chloride, underwent chlorination with concomitant allylic rearrangement to afford trans allylic chlorides 218.[126] These reactions have been utilized to synthesize trisubstituted olefinic units of natural products with satisfactory stereoselectivity.[126b]



217 218

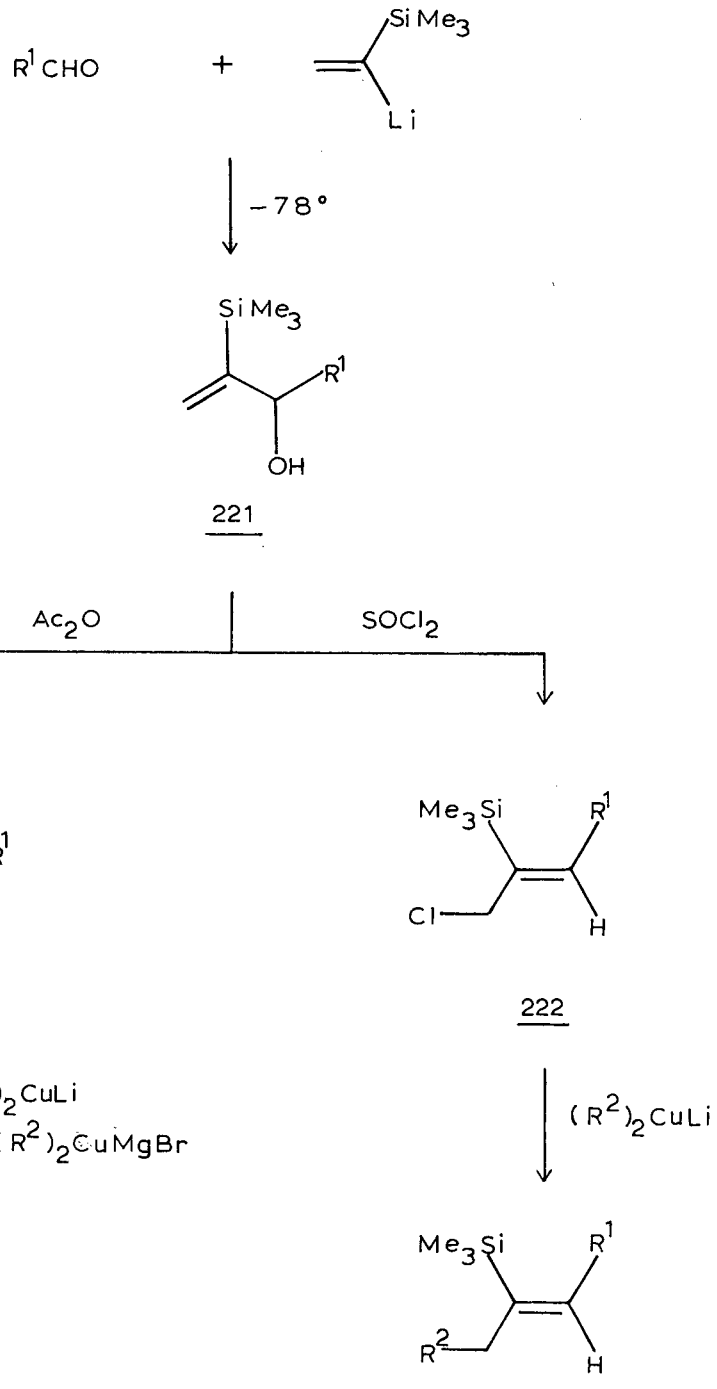
Alkylations of allylic acetates 219 with lithium dialkylcuprates also occurred with simultaneous allylic rearrangement, leading stereoselectively to the E-alkanes 220.[127]



219 220

By applying the above methods to allylic alcohols with a trimethylvinylsilane moiety, Mychajlowskij and Chan developed two stereoselective routes to trisubstituted alkenes.[128] As shown in Scheme xvii, alcohols 221, available from condensation of α-trimethylsilylvinyl lithium with aldehydes, were converted to allylic chlorides 222 (ca. 90% Z isomers) by treatment with

Scheme xvii



R^1 = alkyl, Ph ; R^2 = alkyl.

thionyl chloride. Direct displacement of chloride in 222 with lithium dialkylcuprates gave the corresponding Z-silylalkenes 223. On the other hand, conversion of alcohols 221 to their acetates 224 followed by reactions with lithium dialkylcuprates or dialkylcopper magnesium bromide complexes gave mainly the E-silylalkenes 225 (E : Z ca. 90:10). Stereoselectivity of the transformation of 224 to 225 is sensitive to the size of R^1 as well as the nature of the organocopper reagents. It was found that when R^1 was relatively less bulky (e.g., a primary alkyl group), selectivity would be much lower and could be improved by employing the less reactive dialkylcopper magnesium bromide reagents.

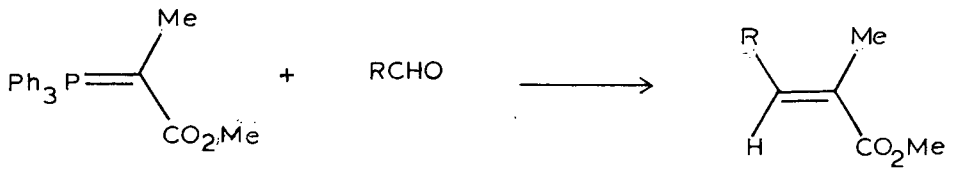
Since stereospecific replacements of the trimethylsilyl group of vinylsilanes are now well documented,[99] 223 and 225, obtainable from the common intermediate 221, could be further elaborated to give various trisubstituted alkenes.

E. Synthesis from Carbonyl Compounds

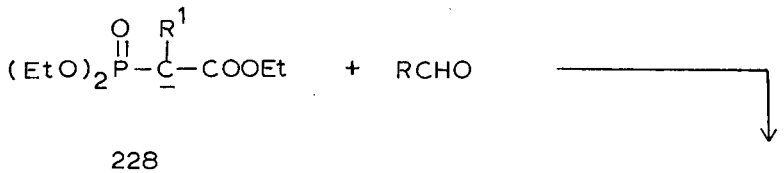
The Wittig reaction, in its original form,[129] has little synthetic value for the synthesis of tri- and tetrasubstituted alkenes owing to the lack of stereochemical control. Later investigations have led to a clearer understanding of its reaction mechanism and the introduction of several modifications which improved the yield as well as the stereochemistry of this type of reaction.[130]

The Wittig reaction of resonance-stabilized phosphorous ylides with aldehydes serves as a convenient route to trans-disubstituted alkenes.

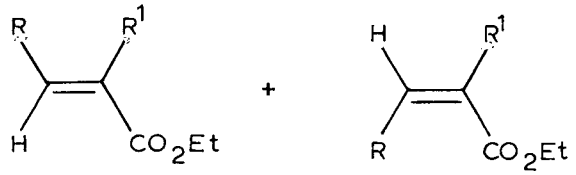
However, its use as a general stereoselective method for the synthesis of trisubstituted alkenes is far from satisfactory. Carbomethoxy ethylidene phosphorane 226 reacts with aldehydes to give mainly the E-alkenes 227 (e.g., when R = CH_3, E:Z = 95:5).[131] A more detailed study on the



226 227



228

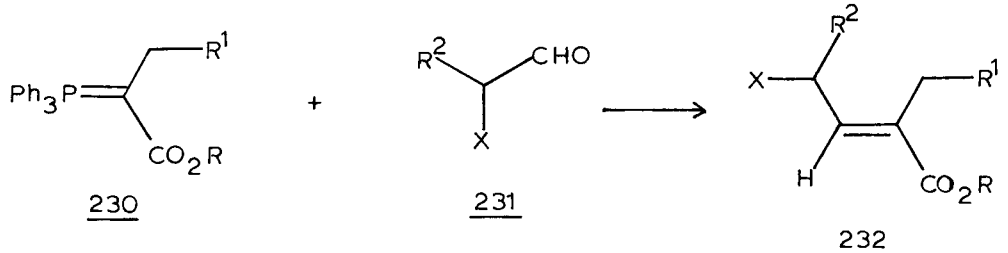


229a 229b

R^1 = CH_3 ;	R	=	CH_3	100	:	0
		=	C_2H_5	84	:	16
		=	$(CH_3)_2CH$	38-27	:	62-73
		=	$(CH_3)_3C$	50	:	50
R^1 = C_2H_5 ;	R	=	CH_3	82	:	18
		=	C_2H_5	59	:	41
		=	$(CH_3)_2CH$	10	:	84
		=	$(CH_3)_3C$	45	:	55

reaction of phosphonate carbanions 228 with aldehydes indicated that the proportion of the isomeric alkenes 229a,b formed was drastically affected by the size of R and R^1.[132] This erratic effect of R and R^1 on the stereochemical outcome of these reactions impairs their synthetic utility.

On the other hand, the reaction of carboalkoxy stabilized alkylidene phosphoranes 230 with α-haloaldehydes 231 showed remarkably high stereo-



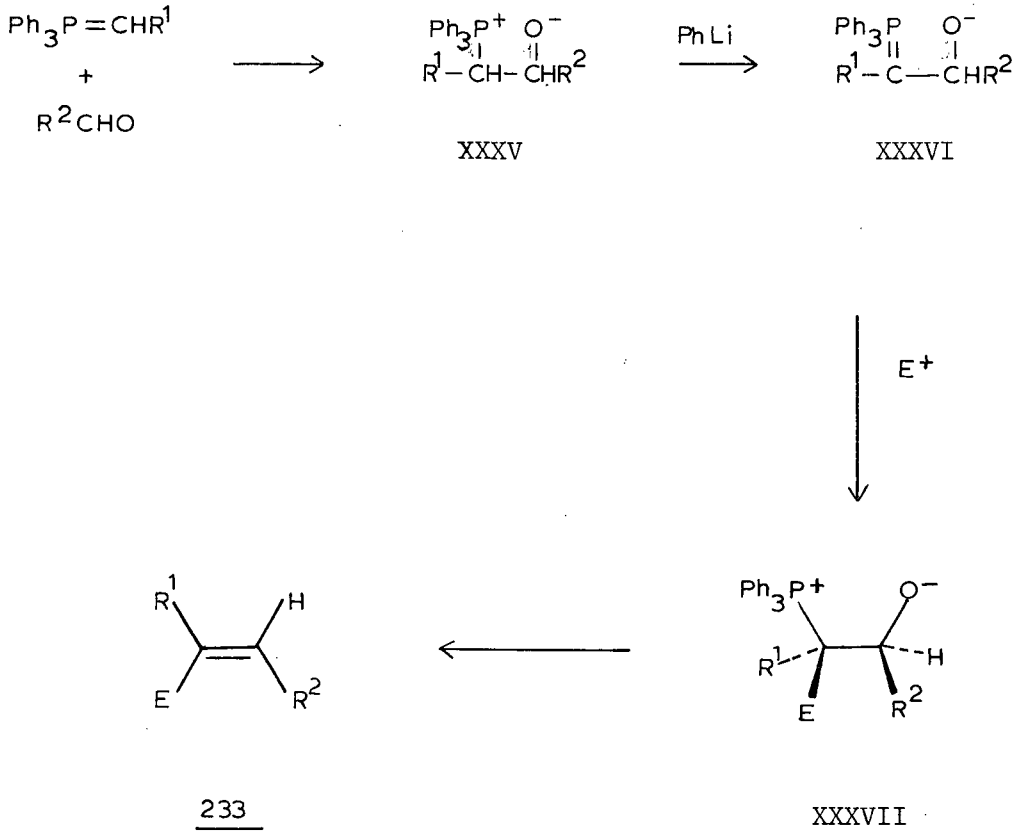
230 231 232

R = Me, t-Bu ; R^1 = H, Me, Et ;
R^2 = H, Me ; X = Br, Cl

selectivity. Stotter and Hill were able to observe stereoselective (greater than 92%) formation of the E-alkenes 232 in greater than 84% yield.[133]

Schlosser and Christmann[134] devised a modification of the Wittig reaction in which the intermediate betaine XXXV was deprotonated with phenyllithium to produce the β-oxido phosphonium ylide XXXVI. Subsequent reactions between XXXVI and a variety of electrophiles occurred stereospecifically, generating one major betaine diastereomer XXXVII which collapsed to give the E-alkene 233. For the electrophilic reagents listed in Scheme xviii, the corresponding alkenes 233 were obtained in poor to moderate yields but invariably with greater than 90% stereoselectivity. A similar synthetic study conducted by Corey et al.[136] showed that alkylating agents other than methyl iodide failed to react with the betaine intermediate XXXVI. However,

Scheme xviii



XXXV

XXXVI

233

XXXVII

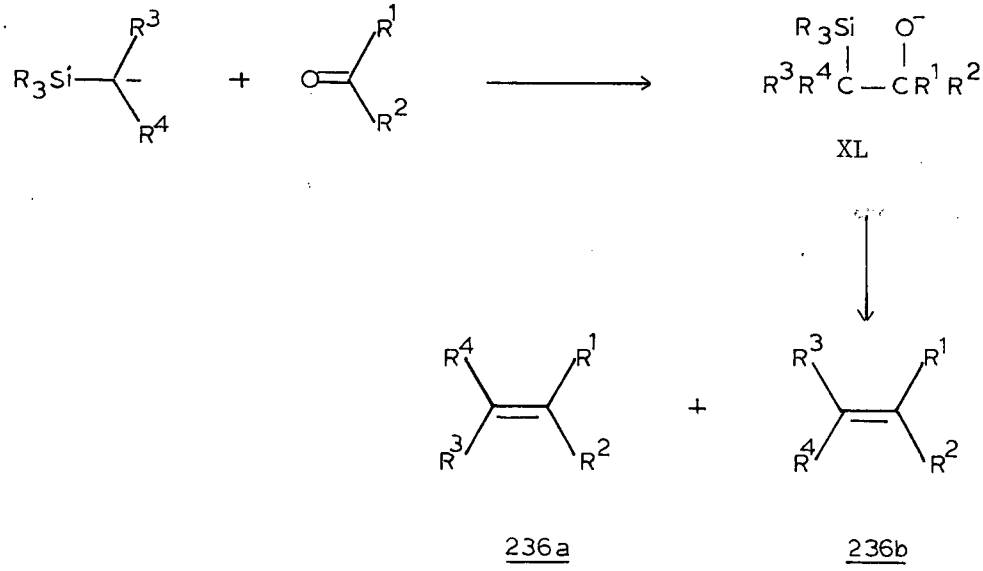
R^1 = alkyl ; R^2 = alkyl, aryl

Electrophilic reagent	E
CH_3I	CH_3
Br_2	Br
$FClO_3$	F
$Cl_2IC_6H_5$	Cl
$Hg(OAc)_2/Li\text{-}I_2$ [135]	I

by using paraformaldehyde as the electrophile in the last step of the above reaction sequence, they achieved a new approach to trisubstituted alkenes of type 234 (Scheme xix).[136] Betaine XXXVIII (R^1 = n-C_6H_{13}) derived from heptanal and ethylidenetriphenyl phosphorane was converted to β-oxido phosphonium ylide XXXIX by n-butyllithium at -78° C. Treatment of XXXIX with paraformaldehyde at 0° C gave E-1-hydroxy-2-methyl-2-nonene (234, R^1 = n-C_6H_{13}) in 73% yield overall.

In contrast to the above result, reaction of XXXIX with another molecule of aldehyde (≠ paraformaldehyde) produced predominantly alkene 235 having the oxygen originated in the second aldehyde eliminated. Although plausible rationalizations[136,137] for these stereochemical outcomes have been proposed, the exact mechanism is not yet clear.

The olefination of carbonyl compounds involving carbanions α to silicon (equation 19) bears certain similarity to the Wittig reaction. It has been shown by many investigations[99] that this class of reactions usually leads to mixtures of olefinic isomers. The lack of stereoselectivity is

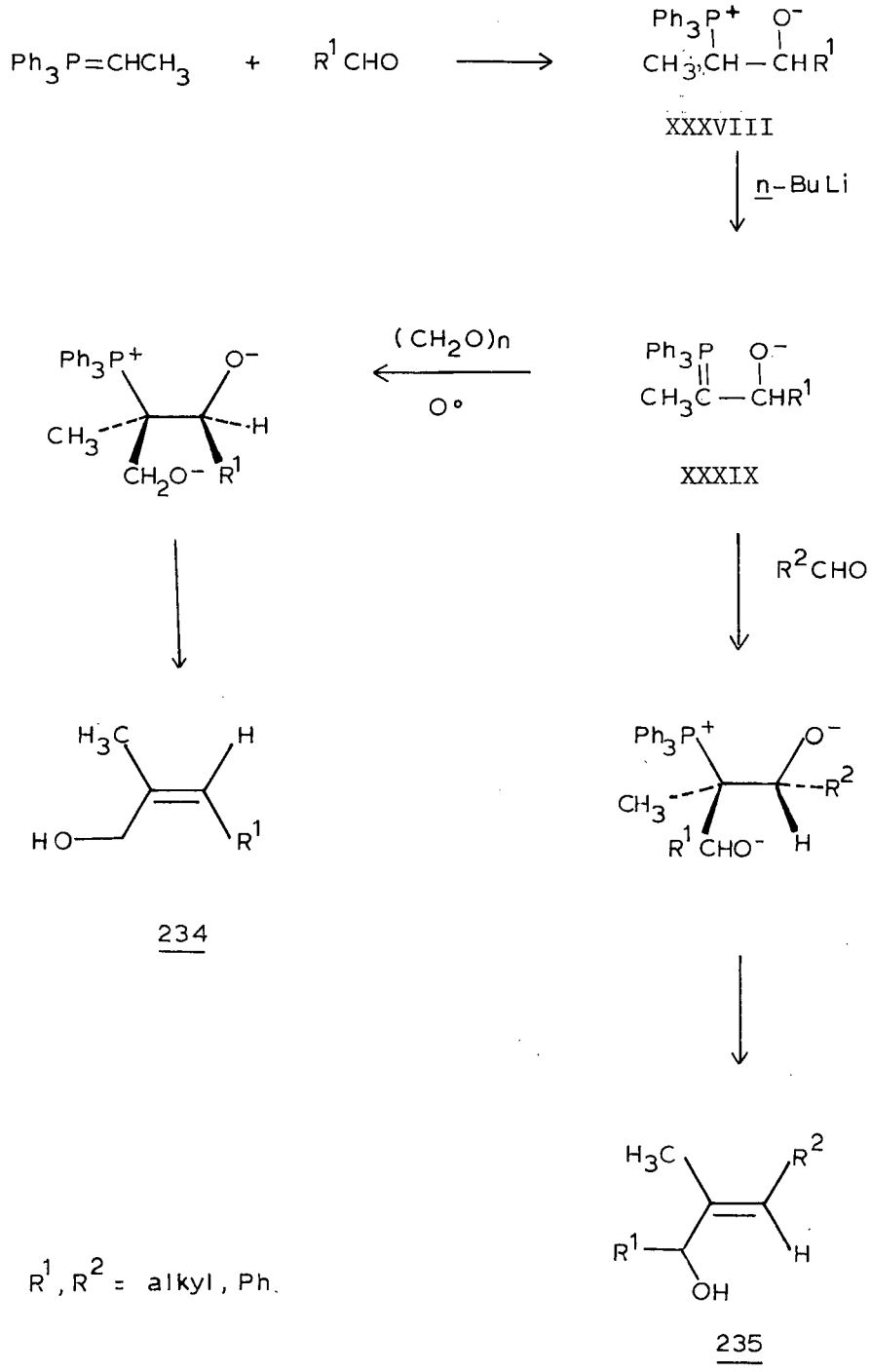


XL

(19)

236a + 236b

Scheme xix



R^1, R^2 = alkyl, Ph.

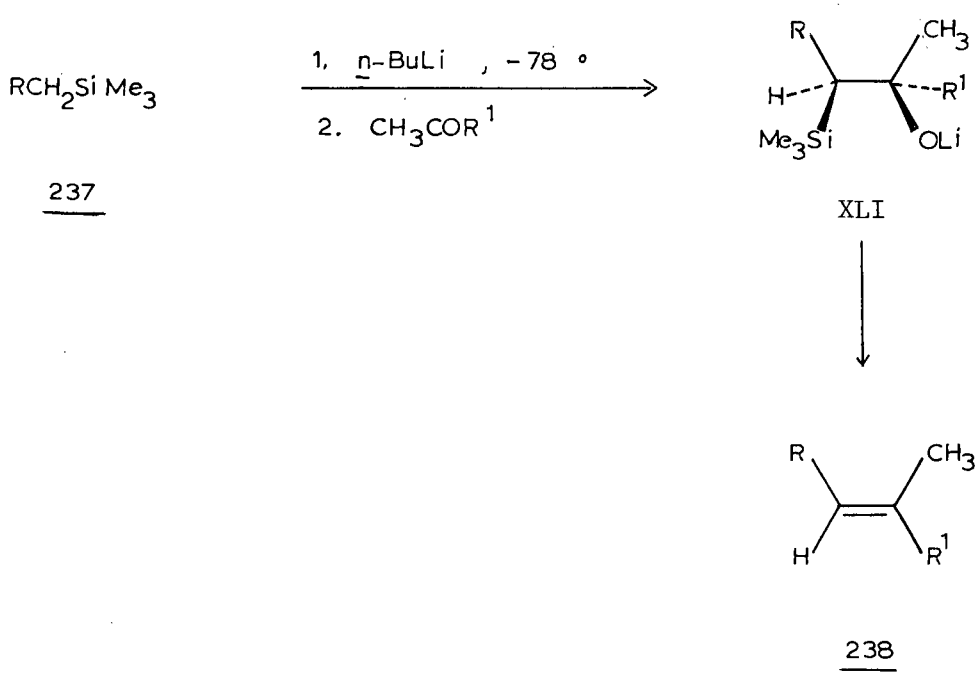
believed to arise from the irreversible formation of diastereomeric adducts XL which after elimination produce the corresponding isomeric alkenes 236a and 236b.

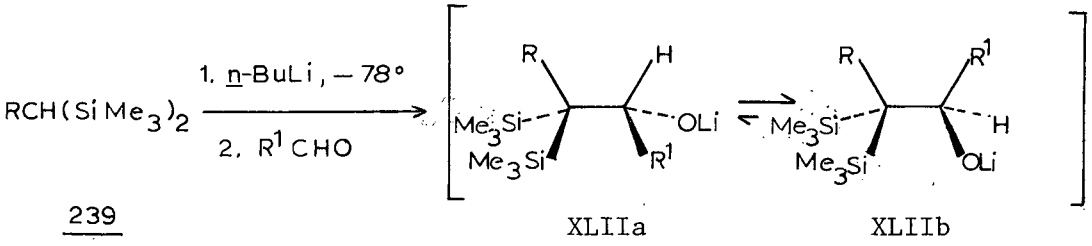
A solution to the selectivity problem was found by Sachdev[138] who utilized silyl carbanions stabilized with dihydro-1,3-oxazine. Thus, lithium carbanions derived from 2-(trimethylsilyl)methyl-5,6-dihydro-1,3-oxazine (237) and the bis-trimethylsilylmethyl derivative 239 reacted with unsymmetrical ketones and aldehydes, respectively, to afford alkenes 238 and vinylsilanes 240 in good yields and satisfactory stereoselectivities (Scheme xx). Since it has been proven that β-hydroxy silanes undergo elimination in a syn fashion,[139] preferential formation of the diastereomer XLI during the initial addition is obviously responsible for the selective generation of 238. Two conformers, XLIIa and XLIIb, of the adduct derived from 239 and the aldehyde (R^1CHO) are capable of syn elimination. Presumably, steric interaction between R^1 and the trimethylsilyl group is more severe than that between R^1 and R, so that elimination proceeding via conformer XLIIb is favored.

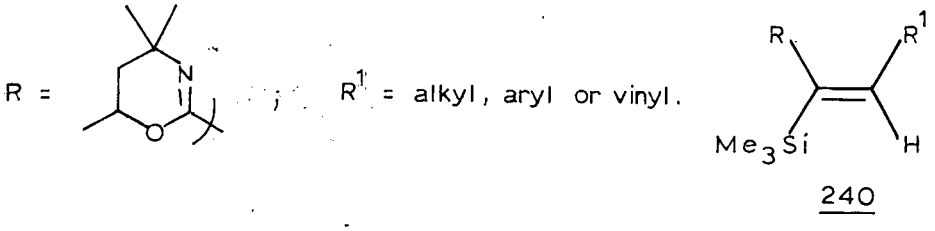
As methods for transforming the dihydro-1,3-oxazine group into an aldehyde or ketone are well established,[140] the R group in alkenes 238 and 240 may be regarded as a masked carbonyl functionality.

The addition of Grignard reagents to α-chloroketones or aldehydes has been demonstrated to occur in a stereospecific manner. On the basis of this finding, Cornforth introduced a general procedure for the stereospecific synthesis of substituted alkenes (Scheme xxi).[141] It was proposed that

Scheme xx

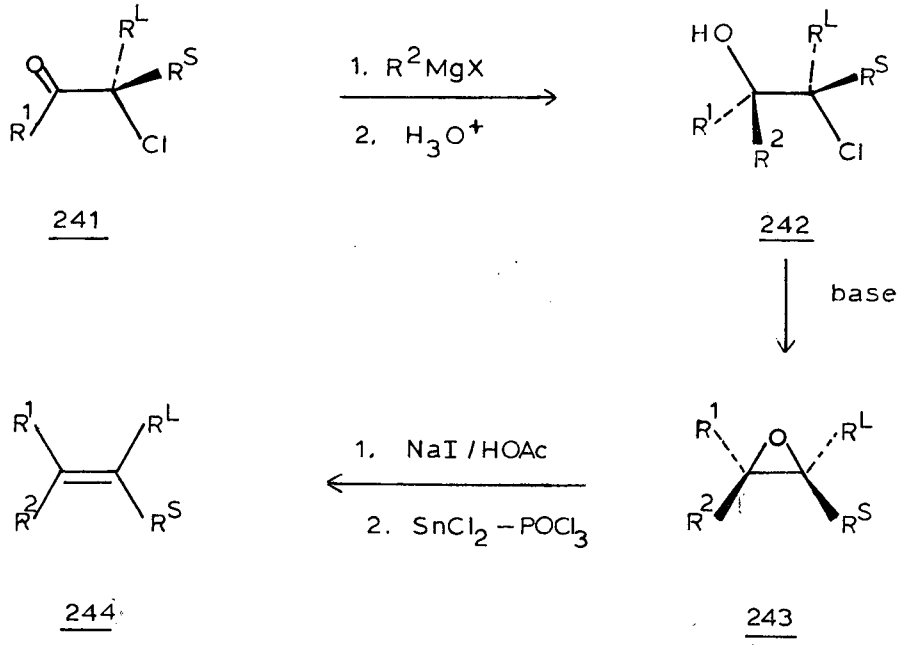

RCH2SiMe3
1. n-BuLi , -78 °
2. CH3COR1
237
R
CH3
H
R1
Me3Si
OLi
XLI
R
CH3
H
R1
238


RCH(SiMe3)2
1. n-BuLi, -78°
2. R1CHO
239
R
H
Me3Si
Me3Si
OLi
R1
XLIIa
R
R1
Me3Si
Me3Si
H
OLi
XLIIb


R =
N
O
R1 = alkyl, aryl or vinyl.
R
R1
Me3Si
H
240

chlorocarbonyl compound 241 prefers a conformation in which the carbonyl and chlorine groups are in an anti periplanar disposition. The steri-

Scheme xxi



241 242 243 244

R^L = large group ; R^S = small group ;

R^1 = alkyl or H; R^2 = alkyl

cally favored addition of Grignard reagent to the least hindered side of the carbonyl group would then lead to chlorohydrin 242 as the major diastereomer. Treatment of 242 with base gave epoxide 243 which could be deoxygenated stereospecifically to produce alkene 244 by a two-step reductive elimination sequence. This involved conversion of 243 to an iodohydrin using sodium iodide in buffered acetic acid, followed by stereospecific

reduction with stannous chloride and phosphorous oxychloride in pyridine.

As could be expected, the selective generation of 242 is affected by the relative sizes of R^L and R^S. Furthermore, successful execution of the Grignard addition also depends on the reaction temperature as well as the nature of the Grignard reagent and solvents used. These effects have been reported by Johnson and coworkers in a synthesis of Cecropia juvenile hormone. The stereospecificity of the Grignard addition employed was improved by lowering the reaction temperature and by changing the Grignard reagent from methylmagnesium iodide in ether to methylmagnesium chloride in THF.[103,106]

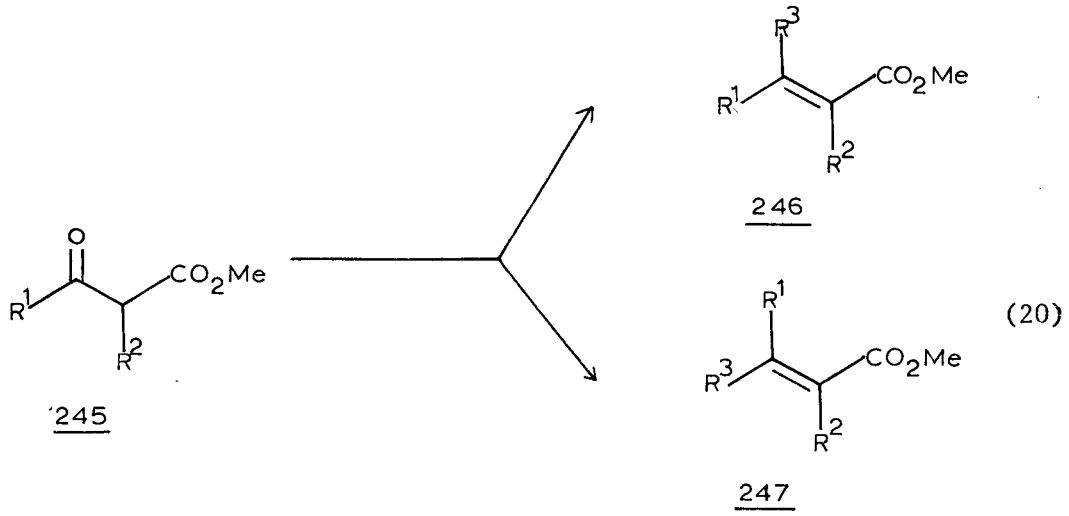
The above survey of stereoselective synthesis of substituted alkenes demonstrates the various strategies that have been generally adopted to form carbon-carbon double bonds. Whilst these methods have their own particular synthetic values, the scope of their utility are often limited in certain aspects. Using β-keto esters as precursors, we developed a facile and stereospecific route to substituted alkenes which may broaden the spectrum of alkene syntheses. The results of our work and comparison with related methods are described in the following part of this section.

Results and Discussion

The key steps in the design of synthetic strategies for olefinic compounds are often based on available methods for generating carbon-carbon double bonds that can fulfil the desired purpose. A useful alkene synthesis should not only facilitate definite olefinic geometry in a controllable manner, but also provide appropriate functionalities for further manipulation. The utility of a synthetic method is measured by a combination of its efficiency, the degree of stereochemical control and the accessibility of precursors. A scrutiny of the methodologies surveyed earlier reveals that very few alkene syntheses meet with all the above criteria. General and stereoselective routes to tetrasubstituted alkenes are especially scarce. Olefin synthesis *via* addition to acetylenes has been developed extensively and offers great versatility. Nevertheless, the main use of this methodology is limited to the synthesis of trisubstituted alkenes and obviously it is not applicable to small and medium-sized cycloalkenes.

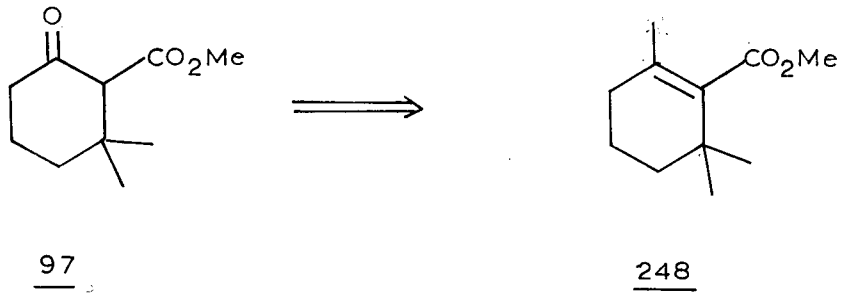
The β-keto ester function would be an ideal building block for olefinic units. A variety of β-keto esters of type 245 are readily attainable from methyl acetoacetate *via* well documented reactions.[1,2] Provided that an efficient and stereospecific method could be found which would transform 245 into 246 and 247, a host of substituted olefins could be synthesized with the carboalkoxy group as a useful handle for further elaboration.

Our interest in finding a synthetic pathway to effect the above transformation (equation 20) partially originated from the problems that occurred during an investigation aimed at converting the β-keto ester 97

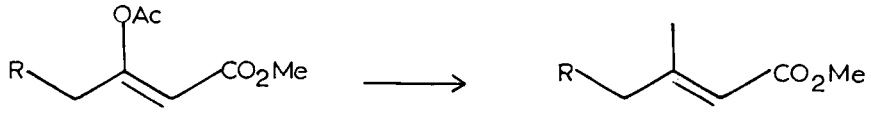


(20)

into the α,β-unsaturated ester 248. The latter portrays a valuable intermediate for the synthesis of several classes of natural products including vitamin A and carotenoids. Since 97 could be conveniently prepared from methyl acetoacetate, as described in Section I, this conversion would facilitate an efficient route to derivatives of structure 248. A thorough search of the literature revealed two synthetic reactions which closely resembled equation 20. Casey et al. reported the stereospecific reaction of β-acetoxy-α,β-ethylenic esters 249 with lithium dimethylcuprate, yielding β-methyl-α,β-ethylenic esters (equation 21).[142] Another method involves similar



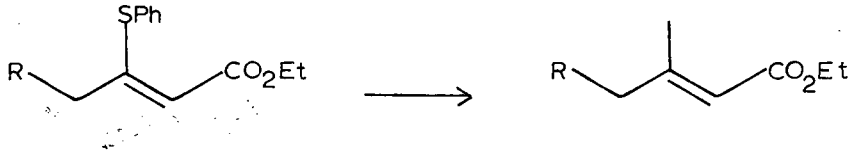
replacement of a phenylthio group in β-phenylthio-α,β-ethylenic esters



(21)

249

with a methyl group (equation 22). This has been achieved by treating the thio enol ether with either a large excess (10 equivalents) of lithium di-

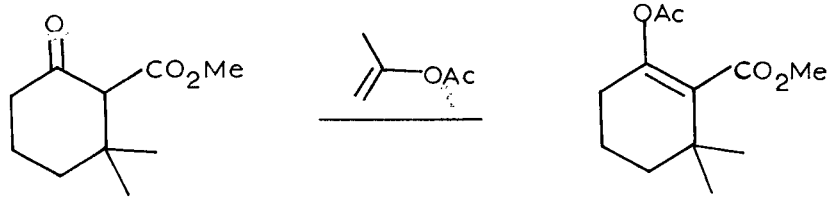


(22)

R = H or alkyl

methylcuprate,[143] or excess methylmagnesium iodide in the presence of cuprous iodide.[82]

Casey's method was first investigated. The keto ester 97 was converted into its enol acetate 250 by heating, under reflux, with a mixture of isopropenyl acetate (excess) and p-toluenesulfonic acid in benzene.[144]



97 250

Efforts to effect replacement of the acetoxy moiety in 250 with the methyl group of lithium dimethylcuprate failed completely. When the cuprate reaction

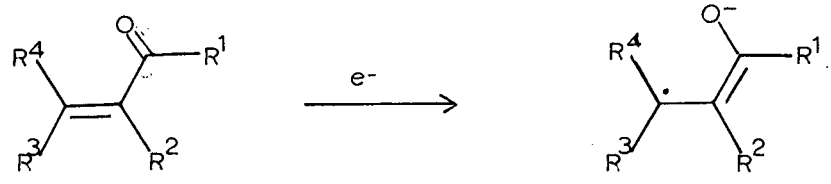
was carried out at low temperatures for a short period of time, the enol acetate was recovered. Employment at higher reaction temperatures or prolonged reaction time led to the regeneration of 97, apparently from cleavage of the acetate function.

The failure of 250 in undergoing a substitution reaction with lithium dimethylcuprate is not surprising in light of the theory proposed by House et al. for the conjugate addition of lithium dialkylcuprates to α,β-unsaturated carbonyl compounds.[145] It is believed that in the first stage of the above process, an electron is transferred from the cuprate reagent to the unsaturated carbonyl system (e.g., 251) producing an anion radical (e.g., XLIII). The conjugate addition is completed in the second stage which involves coupling of the anion radical with the cuprate radical and subsequent intramolecular migration of an alkyl group from the cuprate to the carbonyl substrate. The feasibility of the initial electron transfer will be determined by the electrode potential[(4)] (E_{red}) of the unsaturated carbonyl compounds and the electrode potential[(4)] (E_{ox}) of the cuprate reagents. A set of empirical rules has been suggested to estimate E_{red} of α,β-ethylenic carbonyl systems (Table 3).[145c] Based on these rules,

(4) Measured against a saturated calomel electrode in an aprotic solvent. The sign convention used for E_{red} and E_{ox} is associated with the following reaction:

$$\text{Oxidized reactant} + e^- \rightleftharpoons \text{Reduced reactant}$$

The most powerful reducing agents (cuprates) have the most negative E_{ox} while the most difficultly reduced carbonyl substrates have the most negative E_{red}.



251 XLIII

Table 3. Empirical Rules for Estimating the Reduction Potentials of α,β-Ethylenic Carbonyl Compounds.

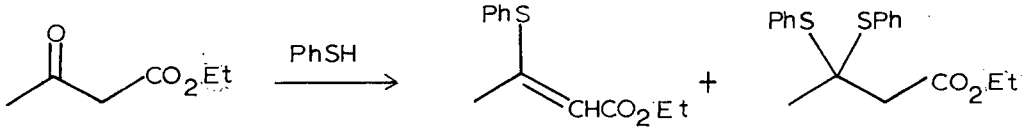
Base value for $R^1 = R^2 = R^3 = R^4 = H$: -1.9 Volt (V)

	Increment for E_{red} (V)		
Substituent	R^1	R^2	R^3 or R^4
alkyl group	-0.1	-0.1	-0.1
first alkoxy group	-0.3	0	-0.3
first phenyl group	+0.4	+0.1	+0.4

(R^3, R^4 = acetoxy has about the same effect as R^3, R^4 = H)[145a]

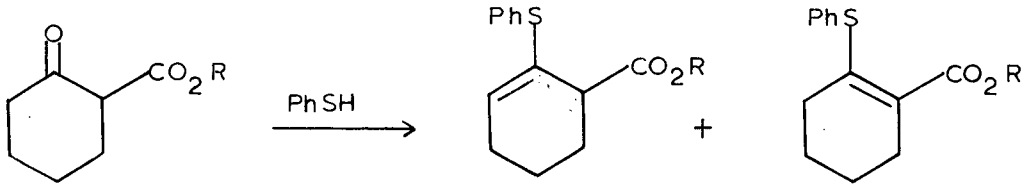
the calculated E_{red} for 250 is -2.4 V. Since it has been shown that in order to observe significant conjugate addition in the reaction of lithium dimethylcuprate with α,β-unsaturated compounds, E_{red} of the latter must be within the range of -1.3 to -2.3 V,[145b] the failure of 250 to couple with lithium dimethylcuprate is not totally unexpected. The results reported by Casey et al. obviously represented the limiting situation (E_{red} for 249 = -2.3 V) for successful coupling. In fact, no α-substituted esters were reported in their work.

The alternative route via the phenylthio enol ether of 97 was severely impaired by the inefficienty of available procedures for converting β-keto esters into their β-phenylthio-α,β-ethylenic derivatives. The p-toluenesulfonic acid catalyzed reaction of methyl acetoacetate with benzenethiol has been shown to give a mixture of thio enol ethers 252 and phenylthio ketal 253.[146] Application of similar reaction conditions to the

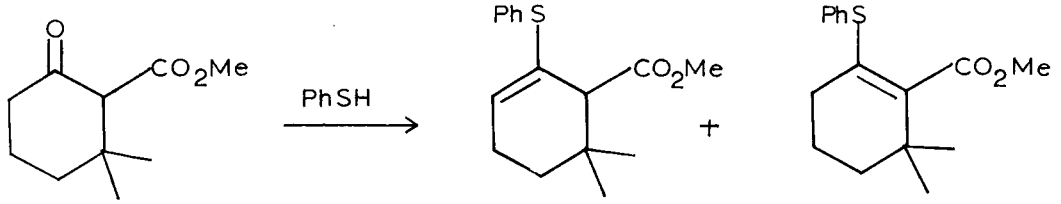


252 253

cyclic β-keto esters 254 and 97 led to mixtures of α,β- and β,γ-unsaturated esters. While about equal proportions of 255a and 255b were obtained from 254, the β,γ-unsaturated isomer 256a was the predominant product from 97 (256a:256b~4:1). As these reactions were conducted under equilibrium con-



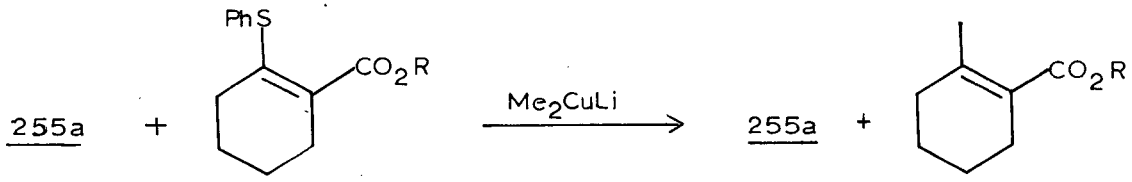
254 R = Me , Et 255a 255b



97 256a 256b

ditions, the observed formation of the non-conjugated esters clearly reflected that their stabilities are comparable to or even greater than the corresponding conjugated isomers. Steric effects and preference for more favorable disposition of dipole moments are presumably the cause of this phenomenon. Similar behavior of the enethiol derivatives of cyclic β-thioxo esters has been reported before.[147]

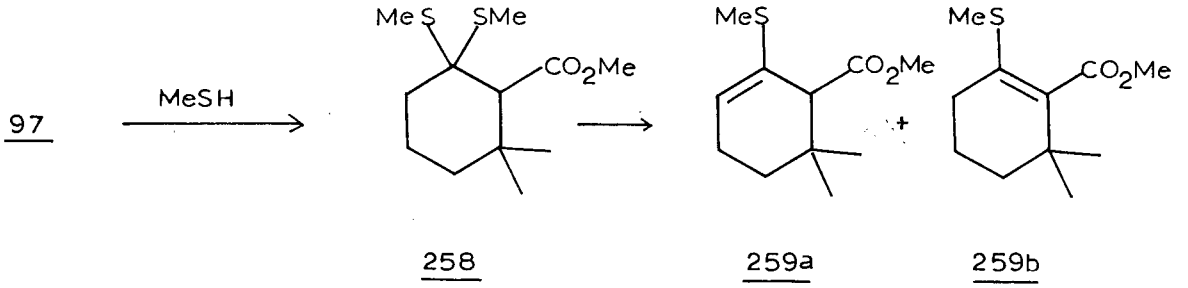
To test if the β-phenylthio-α,β-unsaturated ester 255b was adequate for coupling with cuprate reagents, a mixture[(5)] of 255a and 255b was treated with excess (ca. 4 equivalents) lithium dimethylcuprate in ether (0° C to room temperature). Indeed, the desired methylated product 257 was isolated together with recovered 255a.



255b 257

Since it was apparent that an efficient preparation of 256b from 97 was not feasible, attempts were made to synthesize the methyl derivative 259b. It was hoped that the smaller methyl group might lead to a greater proportion of the conjugated ester. Methylthio ketal 258 was prepared by treating 97 with excess methane thiol and zinc(II) chloride at -20° C.[148] Unfortunately, elimination of methane thiol from 258

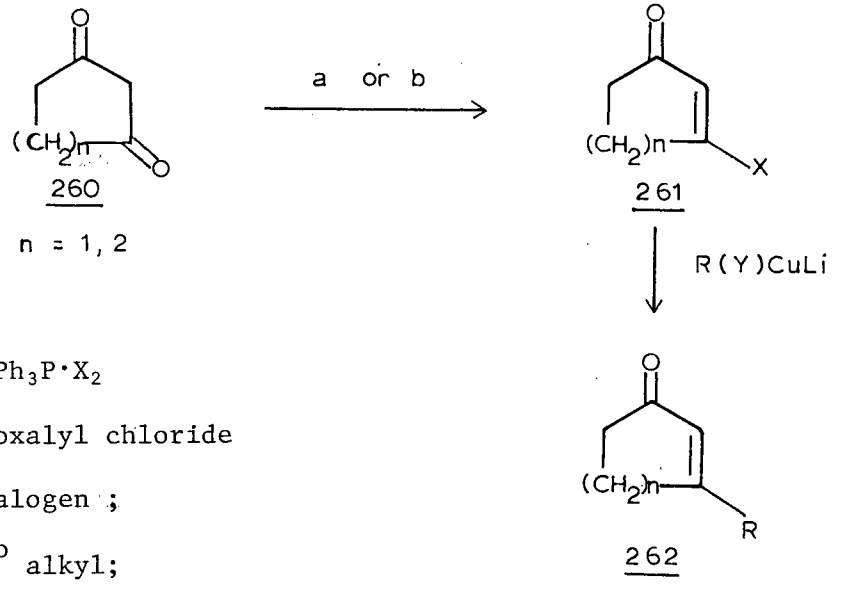
(5) This mixture was difficult to separate.



258 259a 259b

(with $HgCl_2$, methylating agents, or base) invariably gave the non-conjugated compound 259a with only insignificant amounts of 259b.

β-Halo enones 261 have been successfully transformed into the corresponding β-alkyl enones 262 by reaction with organocuprates.[149] Similar transformations of β-halo-α,β-ethylenic esters appeared promising. To our knowledge, direct synthesis of such β-halo derivatives from β-keto esters by an efficient and general method has not been recorded. Two most satis-



a: $Ph_3P \cdot X_2$

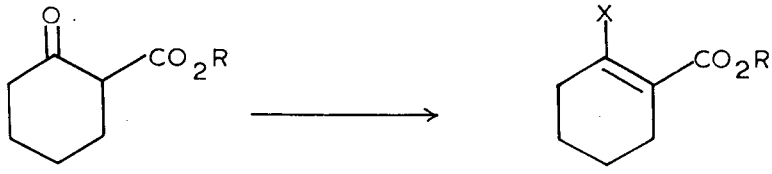
b: oxalyl chloride

X = halogen ;

R = 1^{o} alkyl;

Y = R or PhS

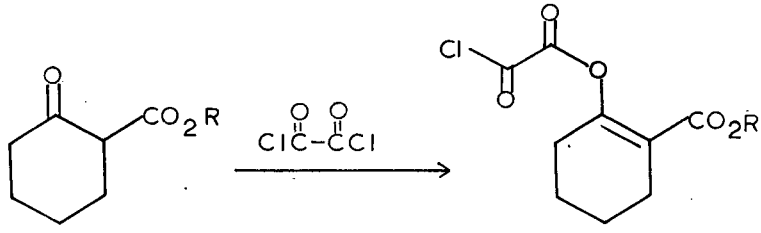
factory methods for preparing β-halo enones 261 from β-diketones 260 were applied to the conversion of 254 into 263. The procedure developed by Piers



254 263 X = halogen

and Nagakura,[150] which involved the use of triphenylphosphine dihalide complexes, was attempted without success.

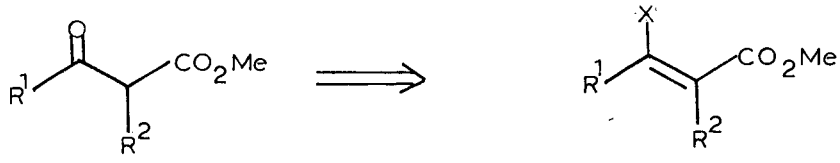
Clark and Heathcock accomplished the synthesis of β-chloro enones 261 (X = Cl) by treating β-diketones 260 with oxalyl chloride in refluxing chloroform.[151] However, when β-keto ester 254 was subjected to the same treatment, only the chlorooxalate ester 264 was isolated in ca. 70% yield.



254 264

The anticipated β-chloro-α,β-unsaturated ester was not detected. This result coincided with a later report by the above workers who showed that the oxalyl chloride procedure did not convert β-keto esters into β-chloro enoates.[152] The chlorooxalate derivative 264 (R = Et) was also observed in this latter case. Attempts to synthesize 263 (X = Cl) using thionyl chloride and other oxalyl chloride procedures[153] were unsuccessful.

Obviously, in order to effect transformation 20 (p. 110) and the analogous reaction for cyclic β-keto esters, a facile and efficient method was needed to convert β-keto esters into α,β-ethylenic esters 265, in which group X must be compatible with coupling reactions involving organocuprates. Although Casey's enol acetate route[142] succeeded for acyclic β-keto esters



245 265

without α-substituents, its utility is far from general. The acid and high temperature conditions required for stereoselective formation of the Z isomer of β-acetoxy-α,β-ethylenic esters prohibit the presence of acid-sensitive functionalities in the β-keto ester precursors. Furthermore, the stereoselectivities reported in some cases were not very high.

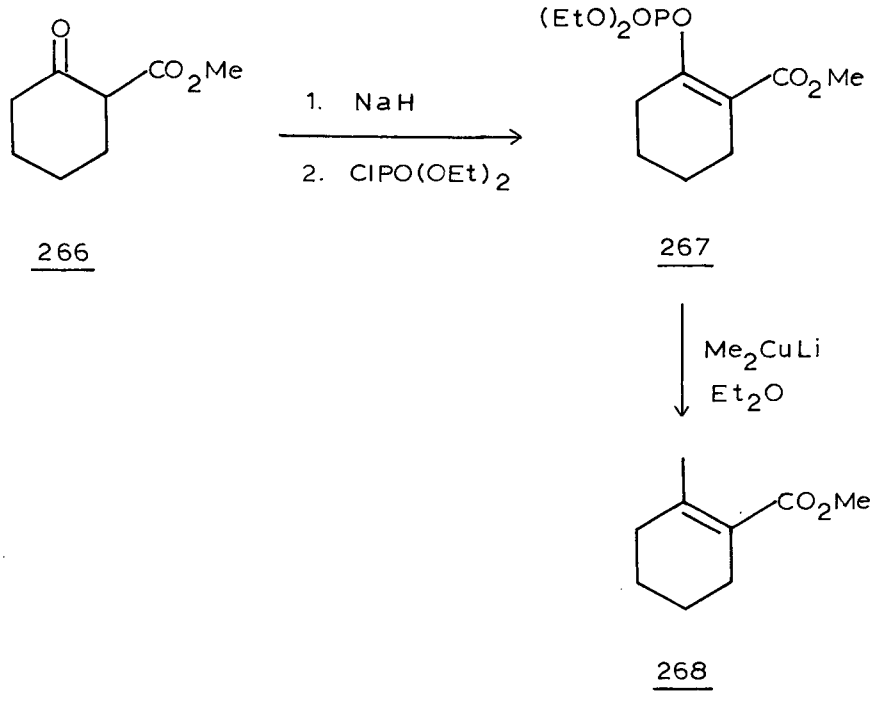
In conceiving potentially suitable candidates for group X in 265, the ease with which β-keto esters could be converted into their enolates was taken into account. It would be most convenient to generate 265 by trapping the enolate of 245 with some electrophile to form an appropriate leaving group at the β-position. The O-sulfonate and O-phosphate groups appeared to satisfy the above requisites. After several futile attempts to effect reaction between the enol methanesulfonate derivative of 254 (prepared from the enolate and methanesulfonyl chloride) and lithium dimethylcuprate, we turned our attention to the possibility of using enol phosphate derivatives.

It is well known that ketone enolates react readily with chlorophosphates to form enol phosphates, though similar reactions involving the enolates of β-dicarbonyl compounds has not been reported. The enol diethylphosphate esters derived from ketones have been reduced to olefins with lithium in ammonia/t-butanol,[154] indicating that the enol phosphate group is a reasonable electron acceptor. Blaszczak et al.[155] reported that the enol diphenylphosphate ester of some cyclohexanones and a methyl ketone reacted with lithium di-n-butylcuprate to give the corresponding n-butyl substituted olefins in fair yields. Reactions of the enol phosphate derivatives with lithium dimethylcuprate were unsatisfactory. However, we felt that conjugation of the enol phosphate function with a carboalkoxy group should improve the situation.

Synthesis and Reactions of Z-Enol Phosphates of β-Keto Esters

Our interest in exploiting the preparation and the synthetic utility of enol phosphates of β-keto esters started with the successful transformation of β-keto ester 266 into the α,β-unsaturated ester 268 via the enol phosphate intermediate 267.

Successive treatment of 266 with sodium hydride and diethyl chlorophosphate (DECP) in ether at ambient temperature afforded the enol phosphate 267 in quantitative yield. The α,β-ethylenic ester function in 267 was evident from its IR spectrum which showed absorptions at 1715 and 1660 cm^{-1}. Presence of the diethyl phosphate moiety was revealed by the intense IR absorptions at 1290 and 1030 cm^{-1}, characteristic of P = 0 and P-O-C stretch-



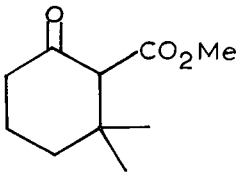
266 267 268

ings, respectively. A four-proton quintet (J = 7 Hz) at δ 4.15 and a six-proton triplet (J = 7 Hz) at δ 1.35 in the ^{1}HNMR spectrum provided further confirmation of the diethyl phosphate structure. The composition of 267 was corroborated by its mass spectral data.

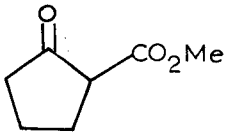
When the enol phosphate 267 was allowed to react with a slight excess of lithium dimethyl cuprate at 0° C, the desired β-methyl-α,β-ethylenic ester 268 was obtained in 94% yield.

Three other cyclic β-keto esters, viz., the substituted cyclohexane derivative 97, the five-membered ring system 269 and the cycloheptane system 270, were also smoothly converted into their corresponding β-methyl

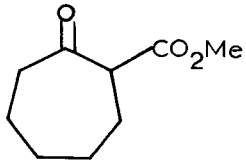
enoates by using the above enol phosphate formation and lithium dimethylcuprate coupling reaction sequence (Table 4). In all cases, the enol phosphates were obtained in essentially quantitative yield and could be used in the cuprate reactions without further purification.



97



269



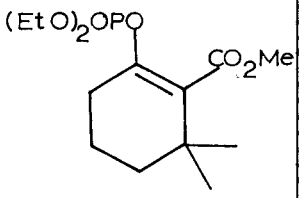
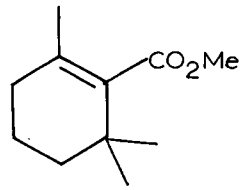
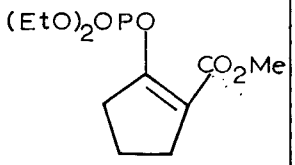
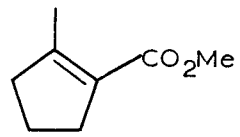
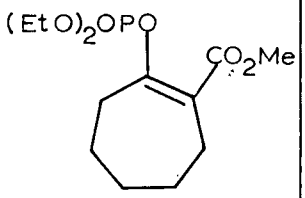
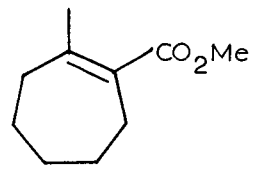
270

It should be noted that the two-step procedure described above could also be performed conveniently in one step without isolation of the enol phosphate intermediate. Thus, when enol phosphates generated _in situ_ from sodio β-keto esters and diethyl chlorophosphate were treated with lithium dimethylcuprate at the appropriate temperature, results similar to those acquired _via_ the two-step sequence were observed. The same applies to all the syntheses discussed herein involving enol phosphates derived from sodio β-keto esters.

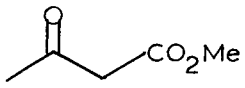
Extension of this methodology to acyclic β-keto esters provided a stereoselective route to substituted α,β-ethylenic esters. Results summarized in Table 5 for the following β-keto esters[6] serve to illustrate its synthetic utility. Acid-sensitive functionalities such as the

[6] 276 was prepared by alkylation of the dianion of methyl acetoacetate with ethyl iodide. The syntheses of 277 and 278 are shown in Section III.

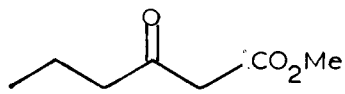
Table 4. Reactions of Enol Phosphates of Cyclic β-Keto Esters with Lithium Dimethylcuprate.

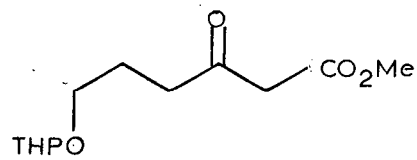
Cyclic β-Keto Ester	Enol Phosphate	Me_2CuLi (equivalents)	β-Methyl-α,β-unsaturated Ester (yield)[c]
97	 271	2 eq	 248 (92%)
269[a]	 272	3 eq	 274 (85%)
270[b]	 273	2 eq	 275 (98%)

a Prepared by carbomethoxylation of cyclopentanone.[156]
b Prepared by carbomethoxylation of cycloheptanone.[156]
c All yields are for isolated products and represent the overall yield from β-keto ester precursors.

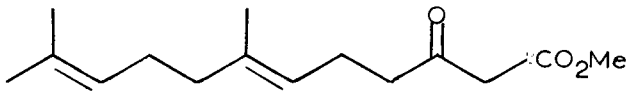


276

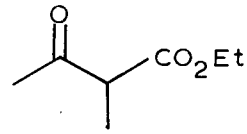




277



278

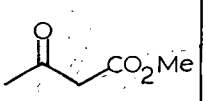
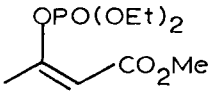
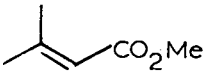
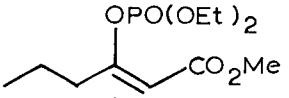
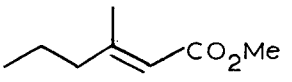
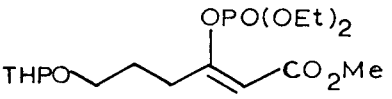
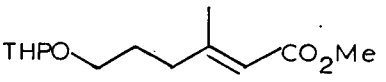
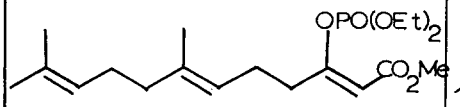
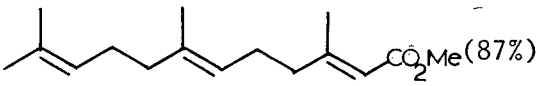
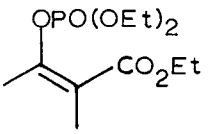
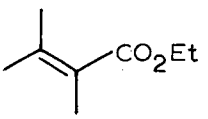


279

tetrahydropyranyl (THP) ether group in 277 are compatible with the conditions used to produce the enol phosphates. The efficient conversion of 279 to 289 demonstrated the applicability of this method to acyclic, α-substituted β-keto esters.

Enol phosphates 280 - 284 were prepared in almost quantitative yields by treating the respective β-keto ester precursors with sodium hydride and diethyl chlorophosphate in ether at 0^{o} C (or room temperature). All of these enol phosphates were characterized by spectroscopic and chromatographic analyses which invariably showed the presence of a single geometric isomer. The Z geometry of these enol phosphates was established on the basis of their ^{1}HNMR spectral data. The most distinct differences between the Z and the E isomers are the chemical shifts of the vinyl and vinyl methyl protons. A list of the chemical shifts for these protons abstracted from the ^{1}HNMR of 280 to 284, along with the corresponding data reported by Fukuto et al.[157]

Table 5. Reactions of Enol Phosphates of Acyclic β-Keto Esters with Lithium Dimethylcuprate.

Acyclic β-Keto Ester	Enol Phosphate	Cuprate Reaction Product (yield)[b] [a]
	 **280**	 **285** (83%)
276	 **281**	 **286** (83%)
277	 **282**	 **287** (82%)
278	 **283**	 **288** (87%)
279	 **284**	 **289** (85%)

[a] 1.5 to 2 equivalents of Me_2CuLi were used.

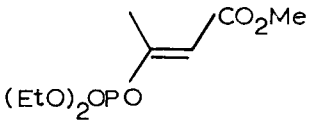
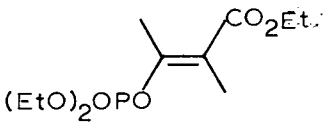
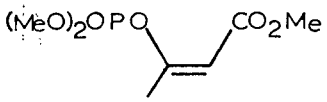
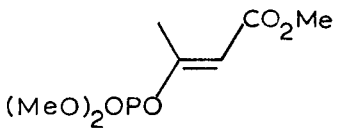
[b] All yields are for isolated products from β-keto ester precursors. In cases of **286**, **287** and **288**, the yields are for the purified E isomers.

for the E and Z isomers of methyl-3-(dimethylphosphoryloxy) crotonate (290) [7] are given in Table 6. The data for the E isomers of 280 and 284 (prepared in a later part of this section) are also presented for comparison. It is clear from the chemical shifts recorded for E- and Z-290 that the resonances of both the β-methyl protons and the vinyl proton occur at lower field in the E than in the Z isomer. While the deshielding effect on a β-methyl group cis to the carboalkoxy moiety of α,β-ethylenic esters is well known,[71,159] it is interesting to note the marked down-field shift of the vinyl proton caused by the phosphoryloxy group in the E isomer. The ^{1}HNMR data of 280 and 310 were in accord with the above findings and hence ascertained their structural assignments. The isomeric purities of 280 and 284 were further verified by combined vpc analyses (3% OV-17 column) of 280 with 310, and 284 with 311. The longer retention times detected for 280 and 284 were also consistent with the intrinsically higher polarity of the Z isomers. Although the E isomers of enol phosphate 281 and 283 were not available for comparison, judging from their ^{1}HNMR properties, and the fact that they were prepared in the same manner as 280, the Z geometry of these compounds was established.

Stereoselective formation of the Z-enol phosphates can be explained by considering the conformation of the sodium enolate of β-keto esters in solution. Since diethyl ether is not an effective solvent for

(7) The isomeric mixture of this compound has been prepared through the condensation of trimethyl phosphite and methyl 2-chloro-acetoacetate and this mixture is used as a wide spectrum insecticide.[158]

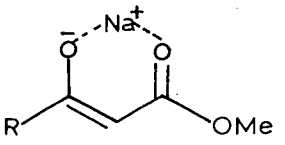
Table 6. Selected ^{1}HNMR Data of Enol Phosphates of Acyclic β-Keto Esters.

Enol Phosphate	Chemical Shift (δ)[a]	
	Vinyl H	β-Vinyl Methyl (or Methylene)
280	5.27	2.17 (d, J = 1.4 Hz)
281	5.28	2.37 (methylene)
282	5.33	2.53 (methylene)
283	5.30	2.40 (methylene)
284	1.83 (α-methyl)	2.10
	5.77	2.38 (s)
310		
	1.87 (α-methyl)	2.40
311		
	5.47	2.12 [b]
Z-290		
	5.76	2.32 [b]
E-290		

[a] Recorded in $CDCl_3$

[b] Recorded in CCl_4, reference 157.

solvating ionic species, the U-shaped enolate[160] XLIV, being capable of serving as a bidentate ligand for association with the sodium ion, is



XLIV

presumably the most favorable geometric orientation of the enolate. Trapping this enolate form with diethyl chlorophosphate leads to the Z-enol phosphate.

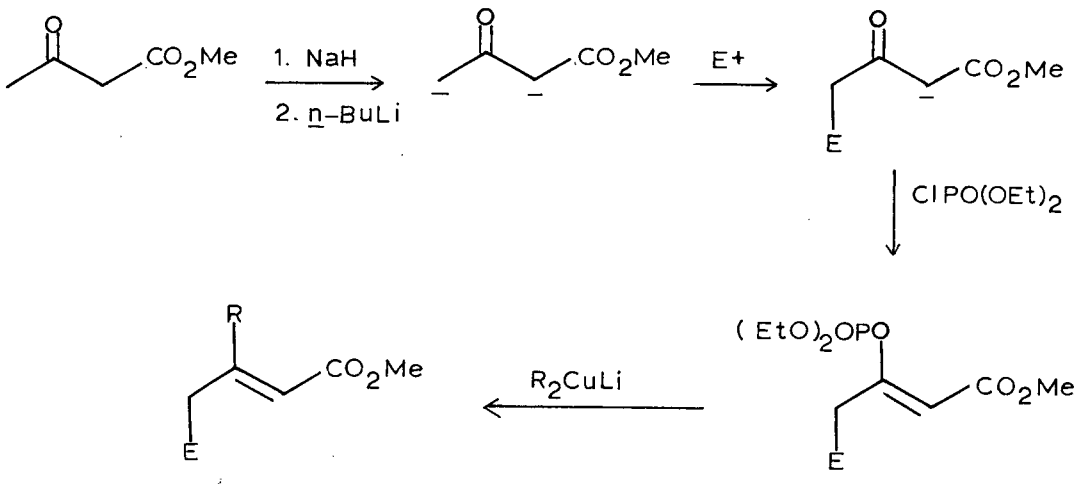
The enol phosphates listed in Table 6 were allowed to react with lithium dimethylcuprate at -78 to -47° C. The cuprate reactions of 280 and 284 were also conducted at 0° C without complication. In cases (e.g., 286 to 288) where geometric isomers might be produced, stereoselective formation of the E-alkene was observed. The E configuration of these products was readily discernible by the downfield shift of the β-methyl protons in the ^{1}HNMR. The absorptions ascribed to the β-methyl protons in compounds 286 to 288 appeared at around δ 2.1, which is the expected chemical shift for methyl protons cis to the carbomethoxy group in α,β-ethylenic esters.[71] The chemical shift of vinyl methyl protons trans to the ester function in similar compounds is usually at δ 1.8 to 1.9.[71] The structures of 287 and 288 were further verified by comparing their ^{1}HNMR data with those reported for analogous compounds.[81,82b]

The prevailing retention of geometry about the olefinic bond during replacement of the phosphoryloxy moiety by an alkyl group of lithium

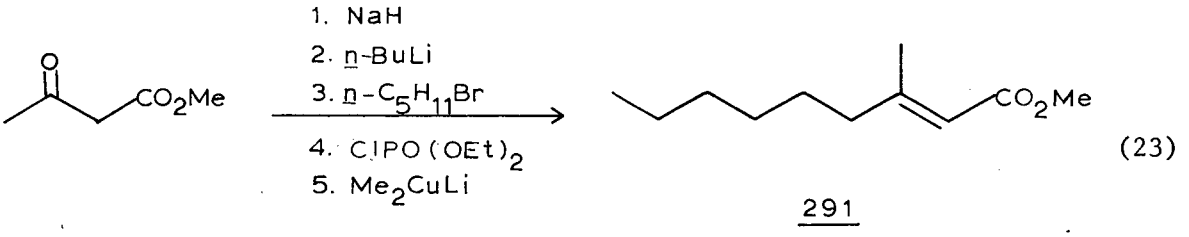
dialkycuprates could be rationalized in terms of a proposed mechanism for these reactions (see later part of this section). The proportion of the E compound in the crude reaction product in all cases was greater than 90%, as estimated from vpc and ^{1}HNMR analyses. According to results secured later, the stereoselectivity of the above reactions was believed to be substantially higher than that suggested by the estimation.

One of the merits in using the enol phosphate of β-keto esters as a synthetic intermediate arises from the mild and basic conditions under which they could be prepared. This was found particularly useful in conjunction with the reactions of β-keto ester dianions. The enolate of a β-keto ester, produced after trapping the dianion with electrophiles at the γ-carbon, may be quenched directly with diethyl chlorophosphate to give the γ-substituted enol phosphate (Scheme xxii). Subsequent reaction of the

Scheme xxii



enol phosphate thus generated, in situ, with lithium dialkylcuprates would then afford the corresponding β-disubstituted-α,β-ethylenic esters. To demonstrate that the above multi-step sequence can indeed be carried out in one single reaction mixture without the isolation of any intermediates, a one-pot procedure was developed to effect the overall transformation as shown in equation 23. The dianion of methyl acetoacetate in tetrahydrofuran was quenched sequentially with n-pentyl bromide and diethyl chlorophosphate.



(23)

291

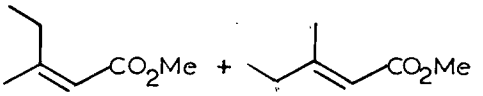
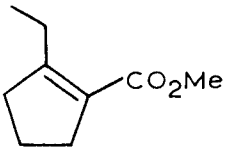
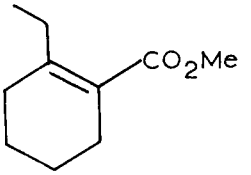
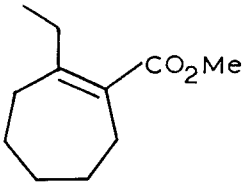
The resulting mixture was cooled to -47° C and treated with three equivalents of lithium dimethylcuprate (in ether) to afford 291 in 68% overall yield.

Reaction of enol phosphates with lithium diethyl- and di-n-butylcuprates

Lithium diethyl- and di-n-butylcuprates were used to explore the efficacy of replacing the phosphoryloxy group in enol phosphates with primary alkyl groups. Satisfactory results were obtained for a series of β-keto esters (Tables 7 and 8), indicating the general applicability of primary alkylcuprates in this olefin-forming reaction.

Due to the thermal instability of the dialkylcuprates, it was necessary to conduct the coupling reaction at very low temperatures. The reaction of enol phosphate 280 with lithium diethylcuprate yielded a mixture

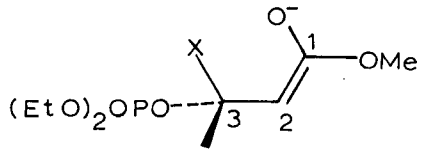
Table 7. Reactions of β-Keto Ester Enol Phosphates with Lithium Diethylcuprate.

Enol Phosphate	Product	Temperature (Et_2CuLi)	Yield
280	 Z-292 + E-292	-78° C (1.2 eq)	84% [a] Z:E = 1:1
		-98° C (2 eq)	90% [a] Z:E = 5:1
272	 293	-98° C (2 eq)	52%
		(3 eq)	70% [b]
267	 294	-98° C (2 eq)	79%
273	 295	-98° C (2 eq)	82%

[a] Yield and isomer ratio determined by vpc.

[b] Ethyl iodide was used to quench the reaction.

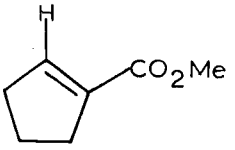
of E and Z olefins, 292. The ratio of these isomers appeared to be temperature dependent. Lowering of the reaction temperature from -78 to -98° C caused a significant increase in the relative proportion of Z-292 which was formed with retention of configuration. Further decrease in reaction temperature (-116° C) resulted in incomplete reaction (ca. 50% of the enol phosphate was recovered after 2 hours) and showed little improvement in stereoselectivity. The change in geometry about the olefinic bond may be attributed to intermediates of type XLV[145b] which can undergo rotation about the C_2-C_3 bond prior to elimination of the phosphoryloxy group.



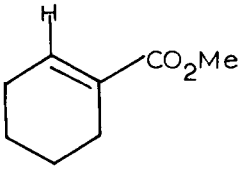
X = e^- or copper complex

XLV

The ring size of the cyclic enol phosphates seemed to have a slight influence on their reactions with lithium diethylcuprate. While 273 was converted cleanly to 295, the cuprate reaction products from 272 and 267 were contaminated with the reduced compounds 296 and 297 respectively.



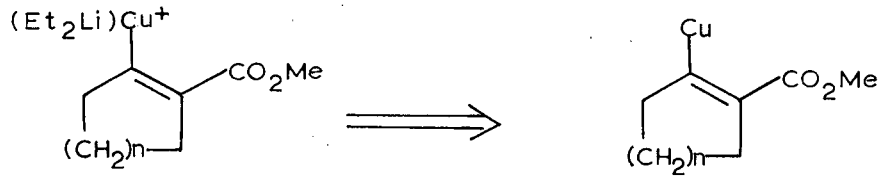
296



297

Such reduction products were probably derived from protonation of the vinyl-

copper species XLVII[161] which could be generated via decomposition of the coupled complex XLVI (see discussion on mechanism). The formation of



XLVI XLVII

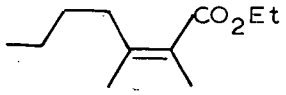
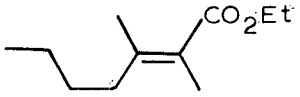
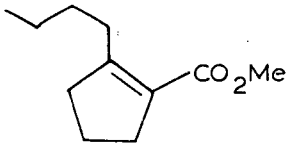
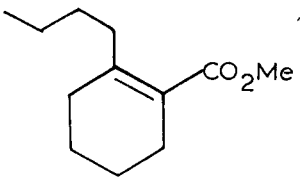
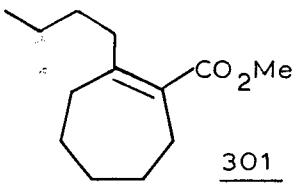
similar vinyl- and alkylcopper species in cuprate reactions has been reported previously.[161]

The side reaction was especially serious in the case of 272 and the situation could be remedied by quenching the reaction mixture with ethyl iodide. The desired ethylated product 293 was obtained in markedly improved yield by employing this modified procedure.

Enol phosphate 284 was smoothly converted to Z-298 in high stereoselectivity by treatment with lithium di-n-butylcuprate. Only a trace amount of the E isomer was detected. This result provides a stereoselective route to tetrasubstituted olefins.

Reduction products 296 and 297 were also observed in the reaction of 272 and 267 with lithium di-n-butylcuprate. Again, this complication could be circumvented by quenching the reaction with n-butyl bromide. Low temperature was also crucial in order to obtain the n-butyl substituted α,β-ethylenic esters in good yield. When the reactions were performed at -78° C, significant amounts of enone products, resulting from attack at the carbonyl of the ester function, were detected.

Table 8. Reactions of β-Keto Ester Enol Phosphates with Lithium Di-n-butylcuprate.

Enol Phosphate	Product [a]	Temperature (Additive) [b]	Isolated Yield
284	 Z-298	-98° C (n-BuBr) [c]	72%
	 E-298		2%
272	 299	-78° C	67%
		-98° C (n-BuBr)	81%
267	 300	-78° C	54%
		-98° C (n-BuBr)	73%
273	 301	-98° C (n-BuBr) [c]	81%

[a] 2 equivalents of $(n\text{-Bu})_2CuLi$ were used.

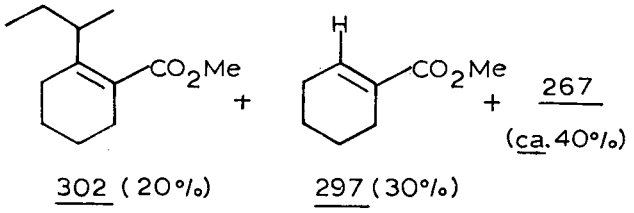
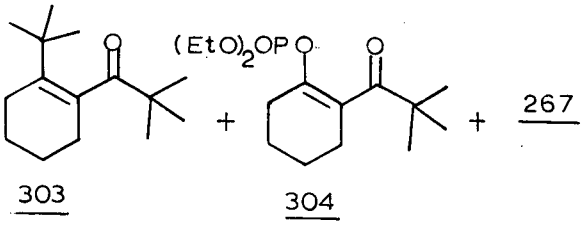
[b] Used to quench the reaction.

[c] n-BuBr was added merely as a precaution since we were unaware of any reduction products in these cases.

Reaction of enol phosphates with lithium di-sec-butyl- and di-t-butyl-cuprates

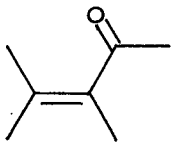
Reactions of the enol phosphate of β-keto esters with secondary and tertiary dialkylcuprates were complicated by the formation of reduction and 1,2-addition products. Typical results observed for enol phosphate 267 are described in Table 9. In the reaction of 267 with lithium di-sec-butylcuprate, the desired product 302 was obtained only in low yield

Table 9. Reactions of 267 with Lithium Di-sec-butylcuprate and Lithium Di-t-butylcuprate.

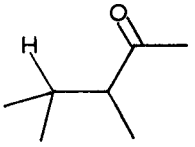
Enol Phosphate	Temperature	Cuprate	Products (Yield)
267	-63° C	sec-Bu_2CuLi (2 eq)	 302 (20%) 297 (30%) 267 (ca. 40%)
	-23° to -98° C	t-Bu_2CuLi (1.1 to 2 eq)	 303 304 267
	-47° C	4 eq	303 (80%)

along with substantial quantities of the reduction product 297 and unreacted enol phosphate. As sec-alkylcuprates are prone to decompose,[164] an enhanced rate of decomposition of intermediates such as XLVI (vide supra) may

explain the preponderant formation of 297 in this case. House and coworkers have observed the reduction product 306 in a study of the reaction between lithium di-sec-butylcuprate and enone 305.[145a] It was suggested that partial thermal decomposition of the cuprate reagent led



305



306

to the copper hydride species, (sec-Bu)HCuLi, which reduced the enone at a rate competitive with conjugate addition.

Treatment of 267 with one to two equivalents of lithium di-t-butylcuprate at temperatures ranging from -23° to -98° C gave varied proportions of 303, 304 and unreacted enol phosphate. The desired β-t-butyl-α,β-ethylenic ester was not detected in any of these runs. Formation of the keto enol phosphate 304 indicated that the ketone 303 was produced via an initial attack of a t-butyl anion on the methyl ester group to form 304, followed by coupling with excess lithium di-t-butylcuprate. Interestingly, when 267 was exposed to excess lithium di-t-butylcuprate, 303 was isolated in 80% yield - a result in support of the above concept. House et al.[145a] have shown that in the presence of small amounts of an impurity (presumably a Cu(II) contaminant in the Cu(I) salt used to prepare the cuprate), lithium di-t-butylcuprate may deteriorate to generate t-butyllithium which undergoes 1,2-addition with carbonyl functions. Such a side reaction became prominent when E_{red} of the enone substrate was more negative[(8)] than -2.1 V (E_{ox} of

[(8)] See footnote [(4)] on p. 112 for sign convention.

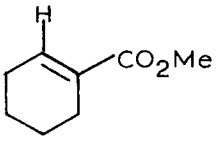
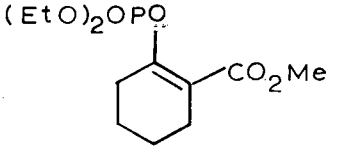
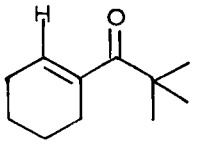
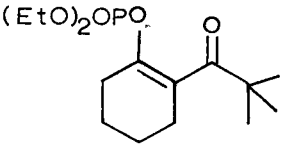
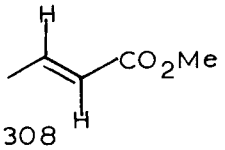
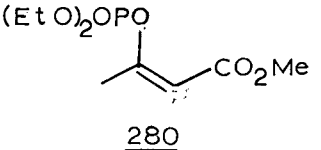
t-Bu_2CuLi), resulting in a slow reaction between the cuprate and the enone. Direct involvement of lithium di-t-butylcuprate in the 1,2-addition is also possible since conversion of certain esters into ketones using organocopper reagents has been reported.[162]

Effect of the β-phosphoryloxy group on E_{red} of α,β-ethylenic carbonyl compounds

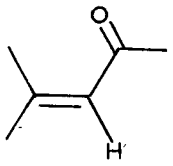
Results from the reaction between the enol phosphate of β-keto esters and lithium dialkylcuprates can be interpreted by means of a mechanism involving electron transfers as suggested by House[145] (cf. discussion on mechanism). As a consequence of this mechanistic view, the efficacy of the desired coupling reaction between an enol phosphate and a cuprate reagent is determined by the E_{red} of the former as well as the E_{ox} of the latter. Enol phosphates with E_{red} more negative than the E_{ox} of a lithium dialkylcuprate would fail to yield coupling products upon reaction with the cuprate. Under these circumstances, either the reactants are recovered or side reactions may occur giving rise to reduction and/or 1,2-addition products.

In order to accommodate all the results observed, the effect of a β-phosphoryloxy substituent on the E_{red} of α,β-ethylenic carbonyl systems was estimated to be ca. +0.1 V, according to House's rules (see Table 3).[145] This estimate was deduced from the following considerations. The E_{ox} of lithium dialkylcuprates[145] and the calculated E_{red} for the β-H analogs of enol phosphates 267, 304 and 280 are listed in Table 10. Since 267 coupled smoothly with lithium dimethylcuprate to give the β-methyl substituted ester, its E_{red} should not be more negative than -2.3 V. Hence, substitution of the β-hydrogen in 297 with a phosphoryloxy group causes a

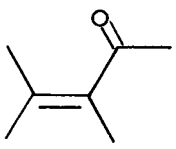
Table 10. Reduction Potentials of Some α,β-Ethylenic Carbonyl Compounds and Lithium Dialkylcuprates.

α,β-Ethylenic Carbonyl Compound (E_{red})	Enol Phosphate	Cuprate (E_{ox})
 297	(-2.4 V)	 267	Me_2CuLi (-2.3V)
 307	(-2.2 V)	 304	sec-Bu_2CuLi (-2.2 to -2.3 V)
 308	(-2.3 V)	 280	t-Bu_2CuLi (-2.1 V)

change ($\Delta E_{phosphate}$) no less than +0.1 V in E_{red}. The reaction of 280 with lithium di-t-butylcuprate was sluggish and the coupling product was not detected. This result limits $\Delta E_{phosphate}$ to be less than +0.2 V. House et al. have reported that enone 309 (E_{red} = -2.21 V) coupled satisfactorily with lithium di-sec-butylcuprate while enone 305 (E_{red} = -2.35 V) gave



309 (E_{red} = -2.21 V)



305 (E_{red} = -2.35 V)

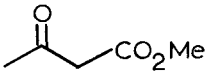
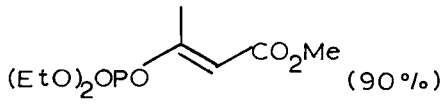
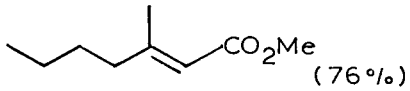
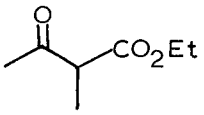
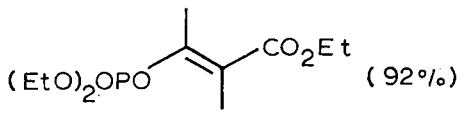
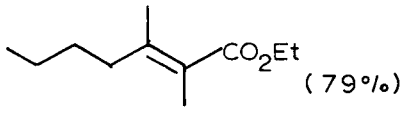
poor results (yields of conjugate addition product varied from 17 to 43%).[145a] The observed low yielding coupling of 267 with lithium di-sec-butylcuprate would be most consistent with a E_{red} value for 267 close to -2.3 V. Based on the foregoing argument, the appropriate magnitude for $\Delta E_{phosphate}$ was estimated to be +0.1 V.

Total failure of 267 to couple with lithium di-t-butylcuprate can now be explained by the fact that E_{red} of 267 (-2.3 V) is substantially more negative than -2.1 V. On the other hand, the keto enol phosphate 304 which has an estimated (assuming $\Delta E_{phosphate}$ = +0.1 V) E_{red} of -2.1 V, would be able to couple with lithium di-t-butylcuprate. This accounts for the efficient conversion of 267 into 303 by excess lithium di-t-butylcuprate, presumably via the intermediary 304.

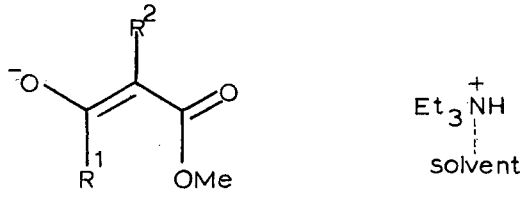
Synthesis and Reactions of the E-Enol Phosphate of Acyclic β-Keto Esters

A procedure for the stereoselective synthesis of E-β-phosphoryloxy-α,β-ethylenic esters was also developed. Treatment of acyclic β-keto esters with a slight excess of triethylamine and diethyl chlorophosphate in hexamethylphosphoramide at ambient temperature, for ca. 4 hr, afforded the corresponding E-enol phosphates in good yields (Table 11). Formation

Table 11. Reactions of E-Enol Phosphates of Acyclic β-Keto Esters with Lithium Di-n-butylcuprate.

β-Keto ester	Enol Phosphate (yield)	Product from Reaction with n-Bu_2CuLi (yield)
	 (90%)	 (76%)
279	310	312
	 (92%)	 (79%)
279	311	E-298

of the E isomers appeared to be exclusive according to vpc and ^{1}HNMR analyses (cf. Table 6). An adequate explanation for this stereoselectivity is offered by the following considerations. In a highly polar aprotic solvent such as hexamethylphosphoramide, the triethylammonium cation is strongly solvated and would be separated from the enolate anion of the acyclic β-keto ester. The most stable orientation of the free enolate is expected to be the W-shaped[160,163] (or E) conformation XLVIII, in which internal dipole-dipole repulsion is minimized. Reaction of diethyl chlorophosphate with this preferred form of the enolate gives the corresponding E-enol phosphate.



XLVIII

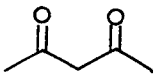
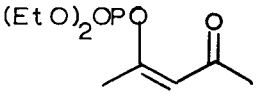
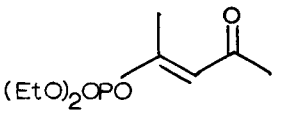
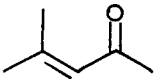
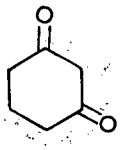
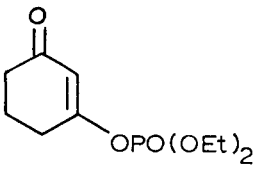
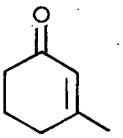
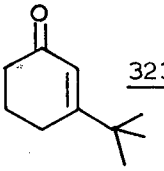
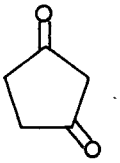
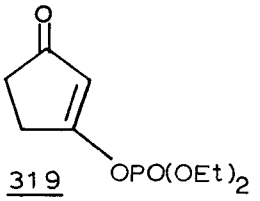
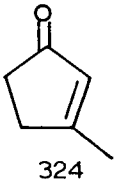
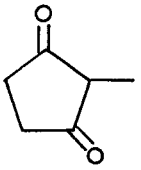
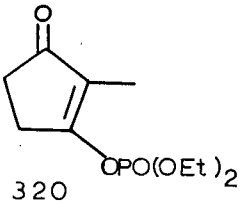
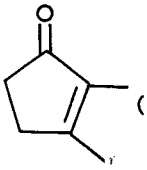
The enol phosphates 310 and 311 were converted stereoselectively into the α,β-unsaturated esters 312 and E-298 in 76 and 79% yields, respectively, upon exposure to two equivalents of lithium di-n-butylcuprate at -98° C. Only a trace amount (2.9%) of the Z isomer of 312 was obtained in the overall transformation from methyl acetoacetate, indicating a stereoselectivity of ca. 26:1 for the two-step sequence. The conversion of 279 into E-298 represents another stereoselective route to tetrasubstituted alkenes.

The stereoselective replacement of the phosphoryloxy group in both E- and Z-enol phosphates with retention of geometry about the olefinic bond demonstrated the stereospecificity of the coupling reactions between these enol phosphates and lithium dialkylcuprates. With the access to the E-enol phosphate of β-keto esters also secured, the versatility of the present alkene synthesis would be greatly enhanced.

Synthesis and Reactions of the Enol Phosphate of β-Diketones

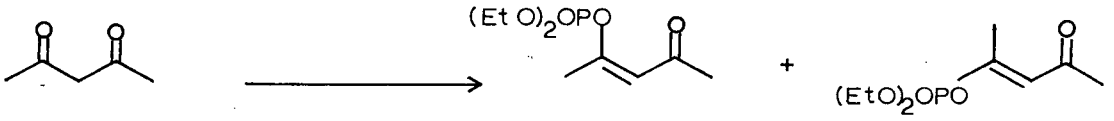
The foregoing methodology for synthesizing β-substituted-α,β-ethylenic esters has also been extended to symmetrical 1,3-diketones. Representative results are summarized in Table 12. The enol phosphates of these β-diketones were conveniently prepared, in excellent yields, either by the sodium hydride procedure mentioned earlier for β-keto esters, or by using triethylamine as base instead of sodium hydride. The latter procedure was found superior in cases (e.g., 315 and 316) where the diketones and their corresponding sodium enolates were insoluble in ether solvents (ether and THF).

Table 12. Reactions of β-Diketone Enol Phosphates with Lithium Dialkylcuprates.

β-Diketone	Enol Phosphate	Cuprate (equivalents)	Product (Yield)[a]
 313	 Z-317  E-317	Me_2CuLi (2 eq)	 (83%) 321
 314	 318	Me_2CuLi (1.1 eq)	 322 (92%)
		$t\text{-}Bu_2CuLi$ (2 eq)	 323 (83%)
 315	 319	Me_2CuLi (1.1 eq)	 (84%) 324
 316	 320	Me_2CuLi (2 eq)	 (74%) 325

[a] Overall yield of isolated product for the two-step sequence.

Some interesting results were observed during the preparation of the enol phosphates of acetylacetone (313), and are summarized below.



313 Z-317 E-317

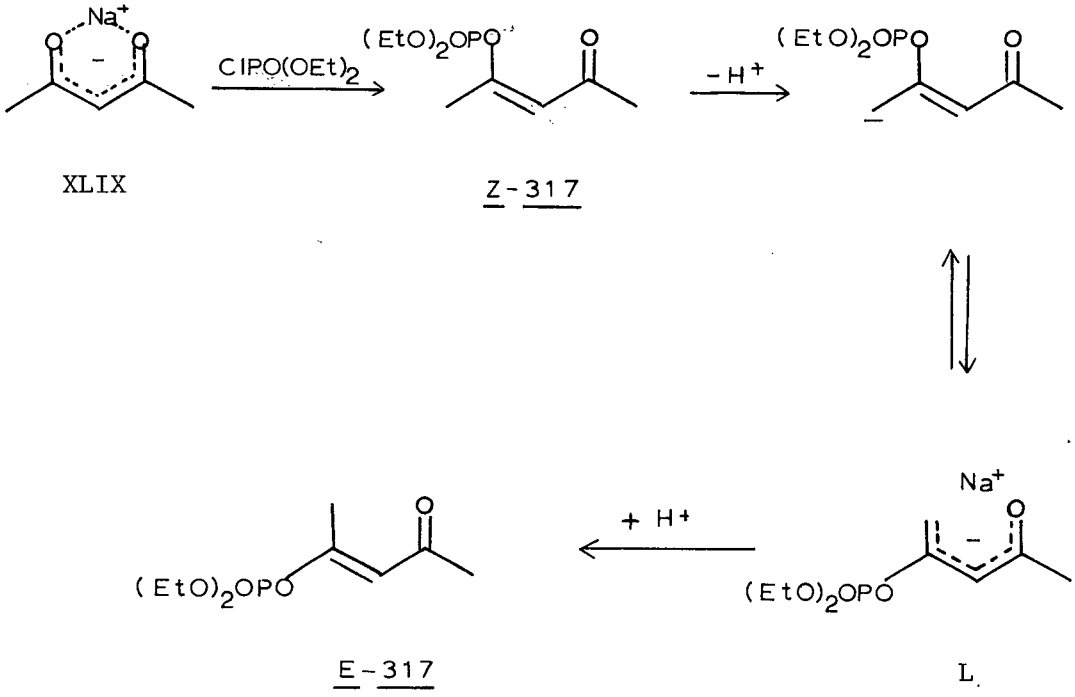
Reaction Conditions	Product Proportions
<1 eq NaH, 20 min, r.t.	100 : 0
1.1 eq NaH, 3 hr, r.t.	1 : 7
Et_3N/HMPA, 3 hr, r.t.	1 : 2.7

Table 13. Selected ^{1}HNMR Data of the E- and the Z-Enol Phosphates of Acetylacetone.

Enol Phosphate	Chemical Shift (δ)	
	Vinyl H	β-Methyl
Z - 317	5.42	2.17 (d, J = 1.2 Hz)
E - 317	6.17	2.33 (s)

When the procedure for the preparation of the Z-enol phosphate of acyclic β-keto esters (1.1 eq sodium hydride, 1.1 eq diethyl chlorophosphate, 3 hr at room temperature) was applied to 313, the E-enol phosphate, E-317, was obtained as the major product, accompanied by only a small quantity of the Z isomer. Structural assignments for E- and Z-317 were based on the

same argument as given earlier for the enol phosphates 280 and 310 (cf. Table 6), i.e., the vinyl and β-methyl protons in E-317 should have lower field chemical shifts than the corresponding protons in Z-317 (see Table 13 for ^{1}HNMR data of both isomers). This unusual predominant formation of the E-enol phosphate under the conditions described above was attributed to an isomerization of the Z isomer. It was speculated that the most favorable geometric orientation XLIX of the sodium enolate of 313 in ether initially led to formation of the Z-enol phosphate. However, in the presence of excess sodium hydride, Z-317 could be deprotonated and then isomerized to the presumably more stable sodium dienolate L. Subsequent protonation of L with another molecule of enol phosphate would give rise to E-317.



XLIX

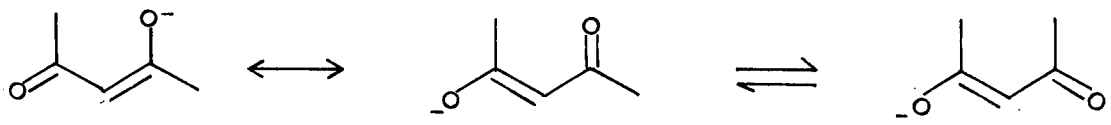
Z-317

E-317

L

In order to substantiate the above hypothesis, acetylacetone (313) was converted into its enolate with slightly less than one equivalent of sodium hydride, followed by treatment with diethyl chlorophosphate at room temperature for 20 min. Essentially pure Z-317 was thus obtained with no detectable contamination of the E isomer according to ^{1}HNMR and chromatographic analyses. In addition, by monitoring the amount of excess sodium hydride present and the time of reaction, we were able to observe varying proportions of the two isomers in agreement with the proposed isomerization mechanism. It is worth noting that the above results provide a common method for the stereoselective synthesis of both E- and Z-enol phosphates of acyclic 1,3-diketones. Employment of excess base and prolonged reaction time would afford predominantly the E-enol phosphate, while exclusive formation of the Z-enol phosphate could be achieved by ensuring the absence of any excess base.

The method which was proved successful in producing the E-enol phosphate of acyclic β-keto esters was also investigated for 1,3-diketones (vide supra). Treatment of acetylacetone with triethylamine (1.1 eq) and diethyl chlorophosphate (1.1 eq) in hexamethylphosphoramide for 3 hr at room temperature yielded a mixture of E- and Z-317 in a ratio of 2.5:1. This low stereoselectivity, in contrast with the exclusive formation of E-enol phosphates observed for β-keto esters under similar conditions, could be explained by the following considerations. Assuming that the free enolate of 313 exists mainly in planar conformations (to enable resonance stabilization) with minimized internal dipole-dipole repulsion, the major enolate forms leading to the enol phosphate products would be LIa,b and c.



LIa LIb LIc

The two conformers LIb and LIc both contribute to the formation of the E-enol phosphosphate. However, the enolate form LIa - another resonance form of LIb, with an Z geometric orientation, gives rise to the Z-enol phosphate. The above argument also briefly rationalizes the approximately two to one proportions of E- and Z-317 obtained.

The enol phosphates of β-diketones readily reacted with lithium dialkylcuprates to give the corresponding β-substituted-α,β-ethylenic ketones in good yields. It is interesting to note that 318 was smoothly converted into 323 upon treatment with lithium di-t-butylcuprate. This contrasts with the result observed for the β-keto ester enol phosphate 267 and is consistent with the suggested intermediary of 304 during the formation of 303 (see Table 9).

It is well known that organocuprates undergo conjugate addition to enones more easily than to enoate esters.[89] This can be attributed to the lower (i.e., less negative) E_{red} of enones than that of the analogous α,β-unsaturated esters (cf. Table 3). Assuming that the increment to E_{red} of α,β-ethylenic carbonyl compounds caused by a β-phosphoryloxy group is ca. +0.1 V (vide supra), even the most highly substituted β-diketone enol

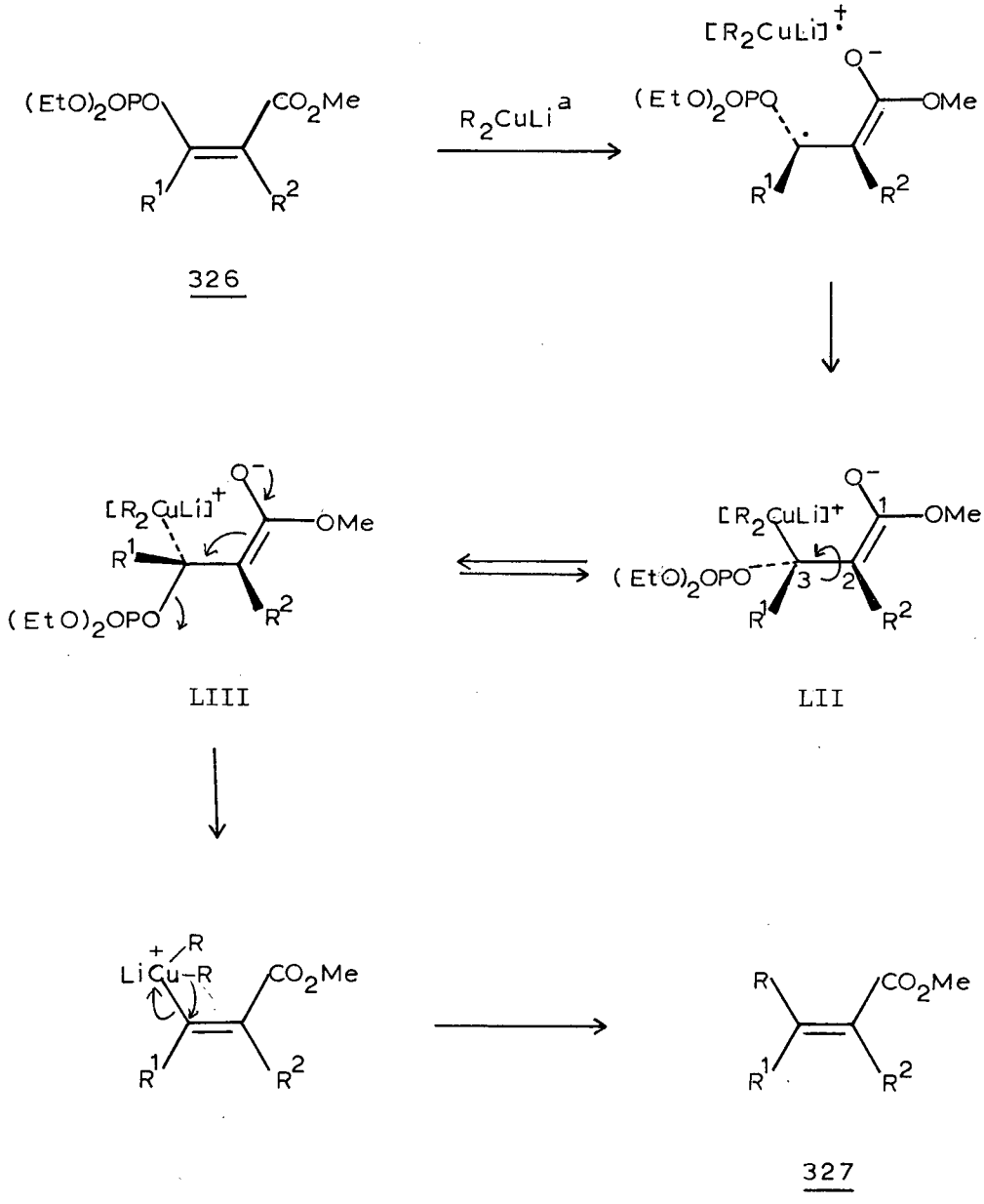
phosphates have E_{red} of ca. -2.1 V which is compatible with the E_{ox} of most lithium dialkylcuprates. This should broaden the scope of application of 1,3-dicarbonyl enol phosphates in synthesis.

Although coupling reactions of enol ethers,[143] enol sulfides,[143] enol acetates[142a] and enol halides[149,152] of β-diketones with cuprate reagents have been achieved previously, the stereoselective synthesis of the E and Z isomers of such derivatives for acyclic β-diketones[142a] and the reaction of the compounds with tertiary alkylcuprates[149] are rare. The present enol phosphate method not only provides a stereoselective route to the enol derivative of 1,3-diketones, but also extends the spectrum of reactions with cuprate reagents. The simplicity and efficiency in the preparation of 1,3-dicarbonyl enol phosphates and their ready reaction with lithium dialkylcuprates should render such approach to β-substituted enones attractive.

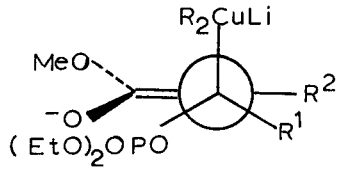
Mechanism and Scope of the Reaction of 1,3-Dicarbonyl Enol Phosphates with Lithium Dialkylcuprates

Based on the mechanism suggested by House for conjugate addition to unsaturated carbonyl compounds with cuprates,[145b] a four-stage mechanism was envisioned for the reaction between 1,3-dicarbonyl enol phosphates and lithium dialkylcuprates. As illustrated by the Z-enol phosphate 326 in Scheme xxiii, the first and second stages involve the transfer of an electron from the cuprate to the enol phosphate and the coupling of the resulting electron transfer complex to form intermediate LII. Expulsion of the phosphoryloxy moiety in LII, followed by rearrangement[145b] of group R from the

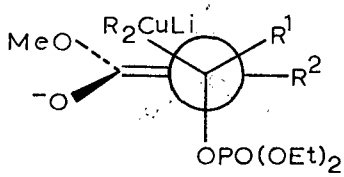
Scheme xxiii



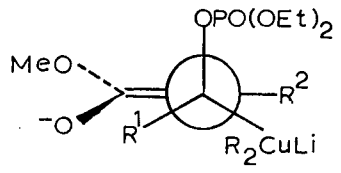
a It has been suggested that dialkylcuprates should be formulated as dimers, $R_4Cu_2Li_2$.[145b] The empirical formulas are adopted for simplicity.



LII



LIII



LIV

cuprate to the carbonyl substrate to give 327 constitute the third and final stages of the process. An anti periplanar arrangement of the leaving group and the enolate π-system is presumably required during elimination of the phosphoryloxy group. This could be achieved by a rotation about the C_2-C_3 bond in LII, either via mode A (60^o rotation) to give LIII or via mode B (120^o rotation) to give LIV. According to the principle of least motion,[165] the former conformational change leading to LIII is favored. Furthermore, a serious steric interaction arises in passing the bulky phosphate group through the enolate plane during the rotation from LII to LIV (mode B), and would disfavor such conformational change. Similar arguments also apply to the reaction between E-enol phosphates and lithium dialkylcuprates. The mechanism depicted above accounts for the retention of geometry about the olefinic bond observed in the cuprate reactions of 1,3-dicarbonyl enol phosphates.

The facile and highly stereoselective syntheses of E- and Z-enol phosphates of 1,3-dicarbonyl compounds and their stereospecific alkylations with lithium dialkylcuprates constitute a versatile and stereospecific route

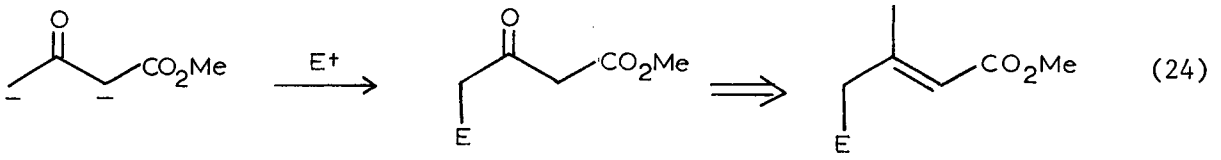
to substituted alkenes (equation 20). This alkene synthesis combined with the dianion chemistry of β-keto esters represent a useful synthetic tool. The utility of this methodology was partially demonstrated in the syntheses of natural products given in Section III.

The +0.1 V increment estimated for the effect of the phosphoryloxy substituent on E_{red} is of considerable value for determining the feasibility of a particular reaction between an enol phosphate and a lithium dialkylcuprate. Such assessments would enable the use of more effective cuprate reactions to accomplish the synthesis of more complex alkenes.

SECTION III: NATURAL PRODUCTS SYNTHESIS

Introduction

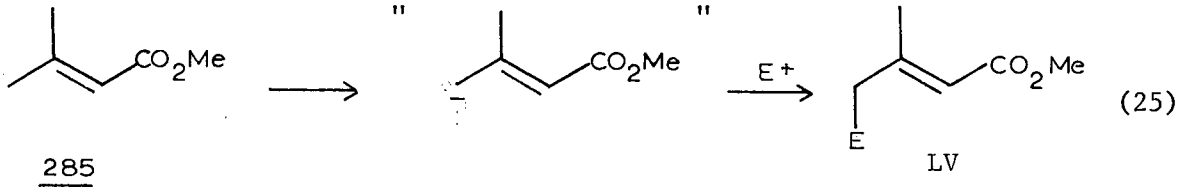
As stated in the introduction of this thesis, one of the ultimate goals of our continuing effort in exploring new synthetic methods based on β-keto esters is the successful application of these methods to the syntheses of natural products. To illustrate, in some aspects, the synthetic utility of the dianion chemistry of β-keto esters as well as the cyclization and olefin forming reactions developed earlier, we accomplished the stereoselective total syntheses of three natural products using a combination of the above methods. In the syntheses of these compounds, viz., Latia luciferin, (E, E)-10-hydroxy-3,7-dimethyldeca-2,6-dienoic acid and mokupalide, the basic methyl acetoacetate synthon was utilized repetitively and efficiently to construct more complex molecules. A convenient way to introduce stereoselectively the isoprene unit LV (equation 24) was also demonstrated. In principle, the overall transformation from methyl aceto-



(24)

LV

E = electrophile



(25)

E = electrophile

acetate to LV as shown by equation 24 is equivalent to the conceptual regio- and stereoselective γ-alkylation of the α,β-unsaturated ester 285 (equation 25).

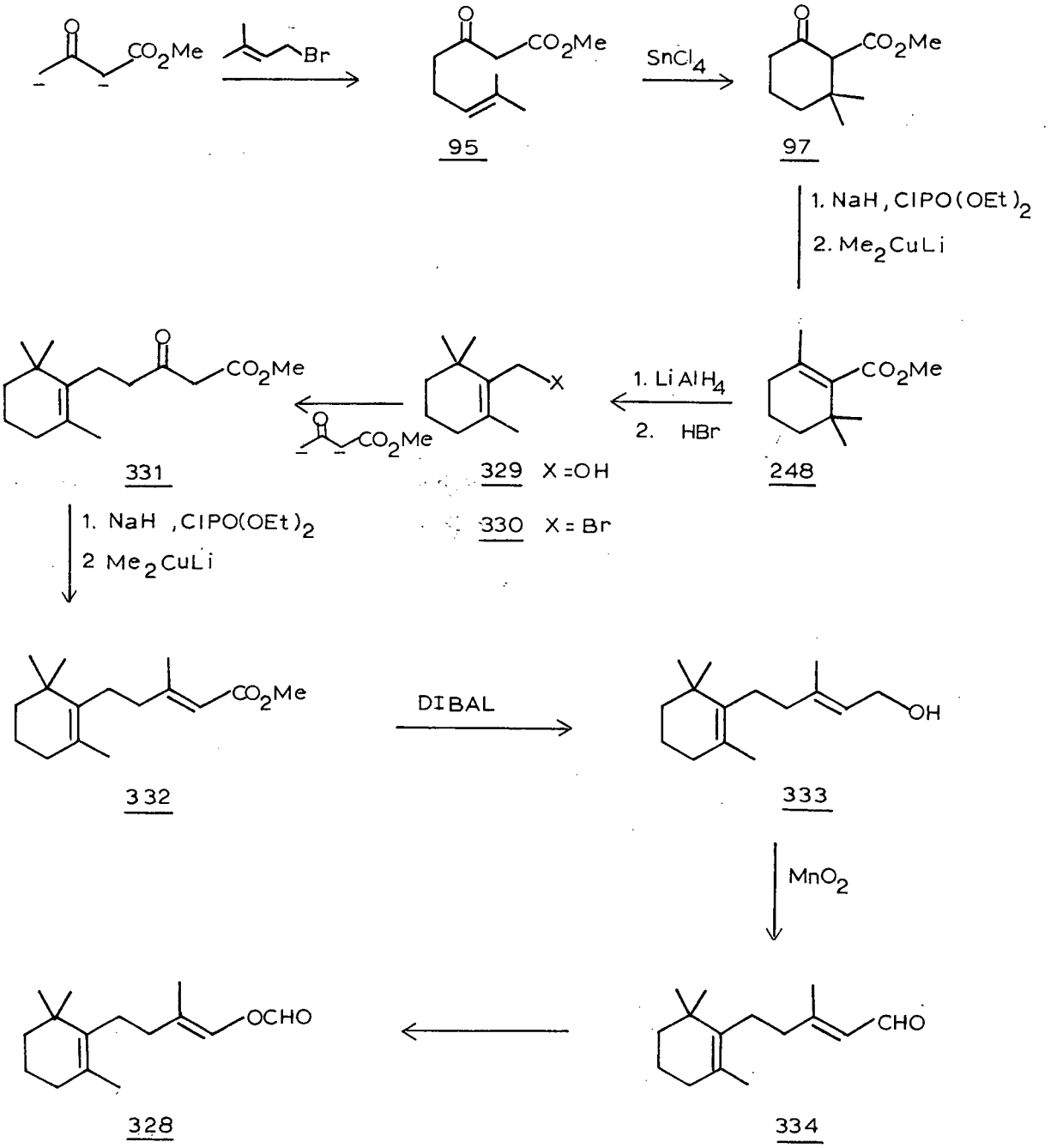
Results and Discussion

Synthesis of Latia Luciferin

Latia luciferin (328) is a specific substrate of the bioluminescence enzyme in the fresh water limpet Latia neriloides.[166] The side-chain olefin in natural luciferin has been shown to have the E geometry. Non-stereoselective synthesis of Latia luciferin, starting from β-ionone, have been reported by two groups.[167] Magnus and Roy accomplished a third synthesis of luciferin via an intermediary α,β-epoxysilane derived from dihydro-β-ionone.[168] The last route, though improved in terms of stereoselectivity over the previous methods, also gave a mixture of isomeric products containing ca. 10% of Z isomer.

A stereoselective synthesis of luciferin (328) was achieved, as shown in Scheme xxiv, by using methyl acetoacetate as a facile isoprene building block. Methyl β-cyclogeranate (248) was prepared by a sequence of

Scheme xxiv


CO2Me
Br
95
SnCl4
97
1. NaH, ClPO(OEt)2
2. Me2CuLi
248
1. LiAlH4
2. HBr
329 X=OH
330 X=Br
331
1. NaH, ClPO(OEt)2
2 Me2CuLi
332
DIBAL
333
MnO2
334
328
OCHO
CHO
OH

reactions described earlier (vide supra). Thus, the dianion of methyl acetoacetate was alkylated with dimethylallyl bromide to give 95 in 85% yield. Exposure of 95 to stannic chloride produced the cyclic β-keto ester 97 which, upon successive treatment with sodium hydride, diethyl chlorophosphate (DECP) and lithium dimethylcuprate afforded 248 in 89% yield from 95.

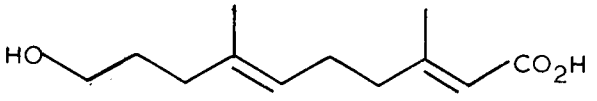
Ester 248 was reduced to alcohol 329[169] almost quantitatively with lithium aluminum hydride. Several methods were tried to convert the hydroxy group in 329 into a leaving group appropriate for dianion alkylation. While many procedures[170,171,172] failed to give satisfactory and reproducible results, it was found that the bromide 330 could be easily prepared, in over 80% yield, by treating 329 with concentrated hydrobromic acid[32] and n-pentane in a two-phase system at 0° C. The product so obtained was essentially pure according to spectroscopic analysis. Due to its thermal instability, bromide 330 was used, immediately after preparation, to alkylate the dianion of methyl acetoacetate to give 331 in ca. 80% yield. Conversion of 331 into its enol phosphate, followed by reaction with lithium dimethylcuprate (2 eq) at -78° C afforded the E-α,β-ethylenic ester 332 in 93% yield. No detectable amount of the Z isomer was observed by ^{1}HNMR and tlc analyses.

Diisobutylaluminum hydride reduction of 332 furnished the corresponding alcohol 333 which was then oxidized, with active manganese dioxide[173,174] in hexane, to the α,β-unsaturated aldehyde 334 in good yield. The spectral data of 334 were identical with those reported[167b] for the E isomer of this compound. Since aldehyde 334 has been stereoselectively transformed into the

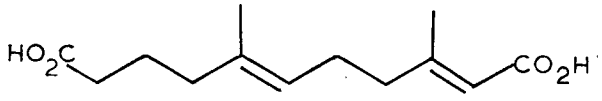
formate 328 using anhydrous hydrogen peroxide and selenium dioxide,[167b] the above stereoselective synthesis of 334 completed our approach to Latia luciferin (328).

Synthesis of (E, E)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoic Acid- A Major Component in the Hairpencil Secretion of the Male Monarch Butterfly

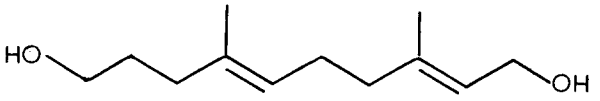
The major components in the hairpencil secretion of male danaid butterflies have been isolated and identified as a family of long chain unsaturated acids and alcohols.[175] Among them, the diol 337[176] from the queen butterfly (D. gilippus), and the hydroxy acid 335[177] and diacid 336[178] from the monarch butterfly (D. plexippus) represent three closely related compounds whose exact functions still remain unknown. Since it is a formidable task to acquire even minute quantities of these substances



335



336



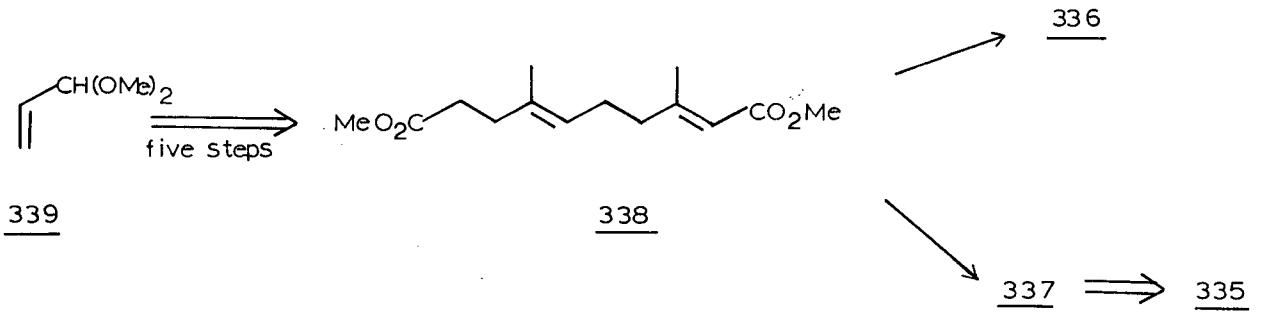
337

from the natural source, (9) elucidation of their biological activities

(9) It involved the extraction of thousands of butterfly hairpencils to obtain merely milligrams of these compounds.[175 - 178]

calls for *in vitro* preparation of the natural compounds.

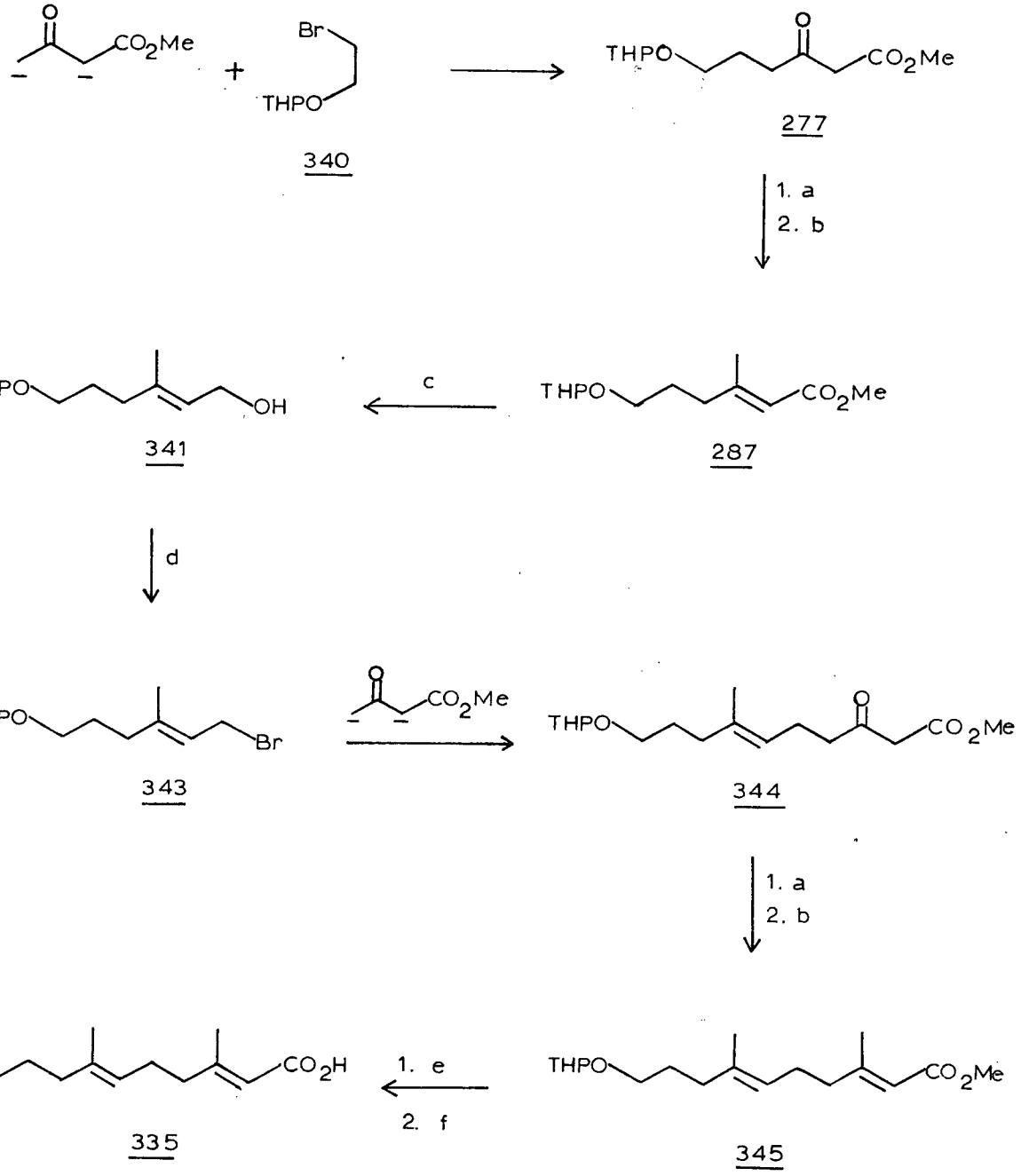
Partial syntheses of diol 337[176] and diacid 336[178] from *trans, trans*-farnesol have been reported by Meinwald *et al.*; however, details of these syntheses were not described. In a later publication, Meinwald and Johnson[179] jointly reported an improved route to 336 and 337 *via* the common intermediate, diester 338, prepared by a five-step sequence from acrolein dimethyl acetal (339). One serious drawback in the synthesis of 338 was the low stereoselectivity observed in a Wittig-type reaction. Hydroxy acid 335 was also synthesized in moderate yield from 337 by a two-step transformation which comprised a selective silver oxide oxidation. Katzenellenbogen and Christy[180] accomplished a stereoselective synthesis of diol 337,



in six steps from geraniol, using the [3,3]-sigmatropic rearrangement of an allyl siloxyvinyl ether intermediate as the key step. Unfortunately, this synthetic scheme was tarnished by a poor yielding ozonolysis reaction.

By employing the alkene synthesis developed earlier, we were able to synthesize hydroxy acid 335 in an efficient and highly stereoselective manner (Scheme xxv). Hydroxy acid 335 may be regarded as a precursor to

Scheme xxv



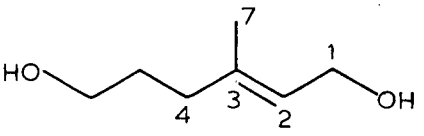
a : NaH, DECP ; b : Me_2CuLi : (2 eq) ;

c : $LiAlH_4$, Et_2o ; d : LiBr, n-BuLi, $MeSO_2Cl$;

e : OH^- , H_2O ; f : HCl, H_2O

both diacid 336 and diol 337. In fact, Meinwald and coworkers have shown that 335 could be converted into diacid 336[178] by the Cornforth oxidation method[181] and into diol 337[177] by reduction with lithium aluminum hydride.

The tetrahydropyranyl ether of 2-bromoethanol, 340, was allowed to react with two equivalents of the dianion of methyl acetoacetate to give 277 in 75% yield (based on 340 used). A lower yield (ca. 50%) of the desired product 277 and a significant amount (ca. 30%) of recovered 340 were observed when equivalent amounts of the two reactants were used. The β-keto ester 277 was then converted into its enol phosphate and treated with lithium dimethylcurpate at -78 to -47° C to produce the E-α,β-ethylenic ester 287 in greater than 82% yield. Subsequent reduction of the ester with lithium aluminum hydride afforded the allylic alcohol 341 in excellent yield. The ^{13}CNMR of diol 342, derived from cleavage (p-toluenesulfonic acid, methanol) of the tetrahydropyranyl ether protecting group in 341,

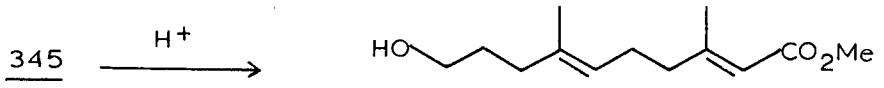


342

showed absorptions at δ 16.2 and 35.8 ppm, ascribable to C_7 and C_4 respectively. These chemical shifts were consistent with the data reported for such carbons in similar allylic alcohols with the E geometry[182] and provided additional evidence for the E configuration of the olefinic bond in ester 287.

Incorporation of the second isoprene moiety was effected by conversion of alcohol 341 into the corresponding bromide 343, followed by repetition of the foregoing reaction sequence of dianion alkylation, enol phosphate formation and lithium dimethylcuprate coupling. Several bromination methods[171,183] were found unsatisfactory for the preparation of bromide 343. However, the difficulty was circumvented by adopting Corey's procedure[170] which involved treating a mixture of alcohol 341 and lithium bromide in ether with n-butyllithium and methanesulfonyl chloride at -78° C to room temperature. The bromide 343, owing to its unstable nature, was used immediately to alkylate an excess of the dianion of methyl acetoacetate. β-Keto ester 344 was thus obtained in 70% yield overall from alcohol 341. Transformation of 344 into the dienic ester 345 was accomplished in 92% yield by utilizing the usual enol phosphate and cuprate coupling sequence. To complete the synthesis, ester 345 was hydrolyzed with aqueous base, and then treated with aqueous acid to give the desired hydroxy acid 335 in 91% yield. The spectral data of 335 were in excellent agreement with those originally reported for the natural compound.[177] As a final corroboration of the structural assignments, the tetrahydropyranyl ether protecting group in 345 was cleaved (p-toluenesulfonic acid, methanol) to give alcohol 346 whose spectroscopic and chromatographic properties were found to be identical with those of an authentic sample.[177,(10)]

(10) The spectra and a sample of the methyl ester of 335 were acquired from Dr. C. Semmelhack and Professor J. Meinwald.



346

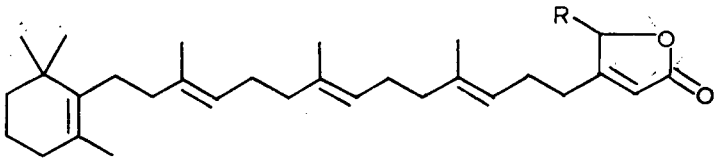
The above synthesis of 335 represents an improvement over the previous routes and demonstrates the synthetic utility of β-keto esters and their enol phosphates in the stereoselective synthesis of trisubstituted alkenes. It is also worth noting that during a large scale preparation, in which the intermediates 287, 341, 344 and 345 were purified simply by evaporative bulb-to-bulb distillation, the alcohol 346 obtained from 345 was found to have a 95% purity of the (E, E)-isomer by vpc analysis. This result implicated that each of the two enol phosphate formation and lithium dimethylcuprate coupling sequences produced at least 97% of the corresponding E-α,β-unsaturated ester.

Synthesis of Mokupalide - a Hexaprenoid from a Marine Sponge

Recent investigations in the chemistry of marine organisms have led to the discovery of numerous novel compounds, most of which have unique structural features.[184] In the past decade or so, the rapidly growing compilation of marine natural compounds has opened a new area in natural products chemistry.[185] The interesting biological activities of many of these compounds have attracted increased attention from organic chemists. In addition, the diversity as well as the novelty in their structure are of great

interest and provide a new challenge to synthetic chemists. The structural elucidation of many marine natural compounds with complex structures often requires total synthesis as an ultimate, unambiguous proof.

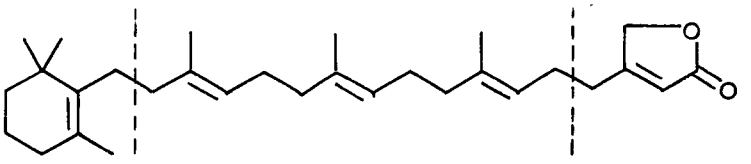
Recently, Scheuer and Yunker isolated from a Pacific marine sponge three novel hexaprenoids which were arbitrarily named mokupalide, hydroxymokupalide and acetoxymokupalide.[186] The mokupalides were shown to have structures 347 - 349 which contained an unusual array of six isoprene units joined together in a head-to-tail fashion. Our interest in exploring the



347 R = H ; 348 R = OH ; 349 R = OAc

synthetic utility of the newly developed β-keto ester chemistry prompted our effort to prepare mokupalide 347.

A brief examination of structure 347 revealed three major synthetic objectives, viz., construction of the cyclohexene moiety, stereoselective synthesis of the three olefinic linkages with E geometry and incorporation of the butenolide end group. Accordingly, the target molecule was envisioned to be composed of three units, A, B and C, as shown below.



A B C

The design of our synthetic route centred upon the separate syntheses of these individual units which were assembled at appropriate stages *via* carbon-carbon bond formation.

In devising the present synthesis, the mokupalide molecule was antithetically dissected into the butenolide C' and the hydrocarbon D (Figure 1). By employing suitable functionalities for W and Z, C' and D could be joined together to give, after removal of the extra functional groups, mokupalide (347). The combination of C' and D might be effected by alkylating the anion of C' with D or *vice versa*. Similarly, D could be derived from the cyclohexene derivative A' and the long chain triene B'. Based on the above considerations, the conceptual scheme depicted in Figure 1 was adopted.

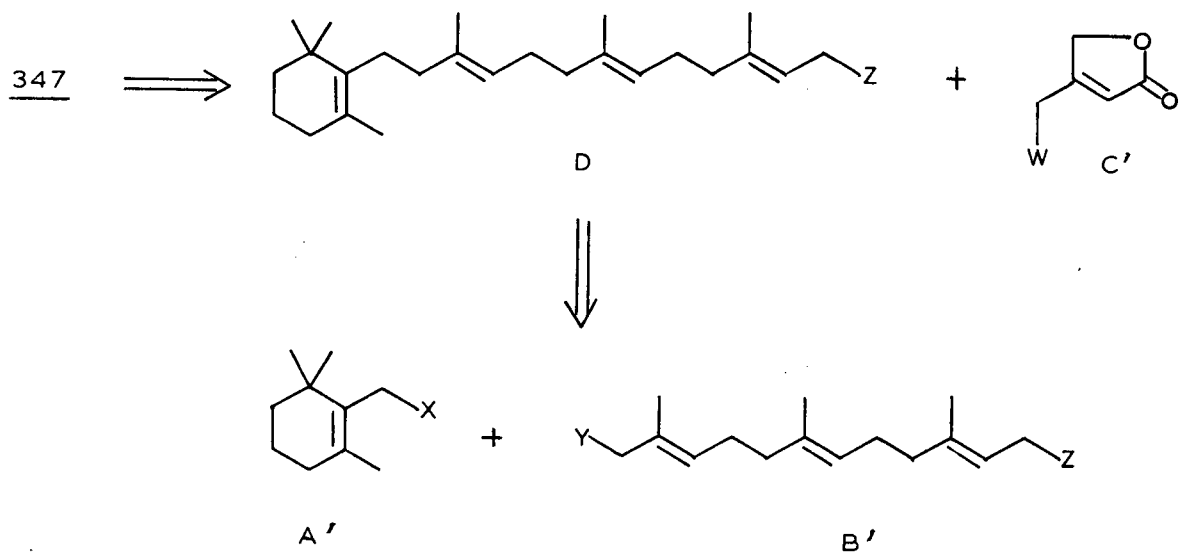
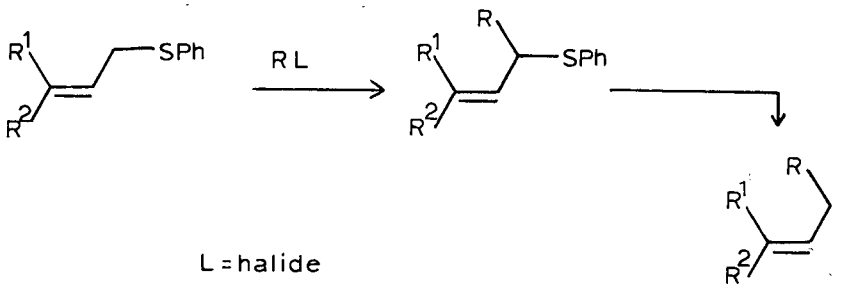


Figure 1. Strategy for the Synthesis of 347 .

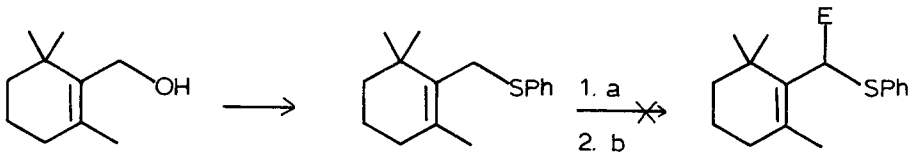
A preliminary study was undertaken to determine what functionality X (in A') might be in order to fulfil the desired purpose. A' was at first conceived as the nucleophile in the coupling with B'. The phenylthio group appeared to be an ideal candidate for X in this regard. The carbanion of allyl phenylthio ethers has been reported to undergo alkylation with alkyl halides.[187] Furthermore, the allylic phenylthio moiety could be readily removed by reductive cleavage.[187] This methodology (equation 26), developed by Biellmann and Ducep, has also been successfully



(26)

utilized by van Tamelen et al. in their juvenile hormone[188] and triterpene[32] syntheses.

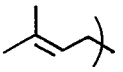
Sulfide 350 was synthesized in good yield by treating alcohol 329 (prepared as described before) sequentially with n-butyllithium, methanesulfonyl chloride and lithium thiophenoxide (generated from benzenthiol and n-butyllithium in THF).[188] To test the feasibility of carbanion alkylation of 350, 1-bromo-3-methyl-2-butene was used as a model alkylating agent. Exposure of 350 to a 1:1 mixture of methyllithium and diazabicyclo[2.2.2] octane (DABCO),[187] followed by treatment with dimethylallyl bromide, yielded



329 350

a = MeLi, DABCO, THF.

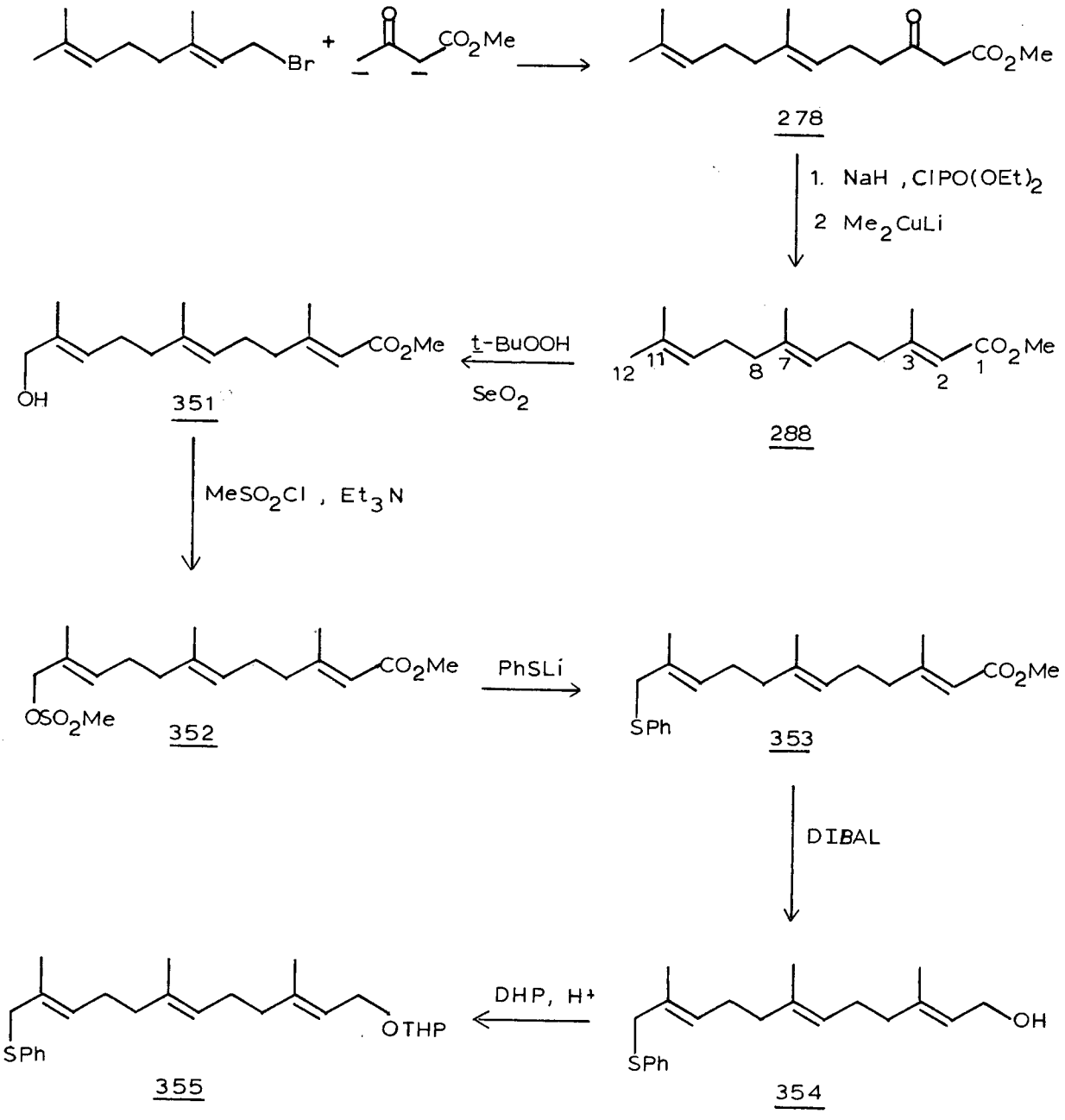
b = 1-bromo-3-methyl-2-butene or deuterium oxide

E =  or deuterium.

mainly recovered starting material. The failure in alkylation of 350 was found to arise from unsuccessful generation of the carbanion. This was shown by a series of investigations in which sulfide 350 was exposed to strong bases (MeLi, MeLi-DABCO, t-BuLi) under various conditions and subsequently quenched with deuterium oxide. In all cases, no significant deuterium incorporation was detected by spectroscopic analyses. Steric effect of the methyl groups was suspected to be the cause for the reluctance of 350 to form the allylic carbanion.

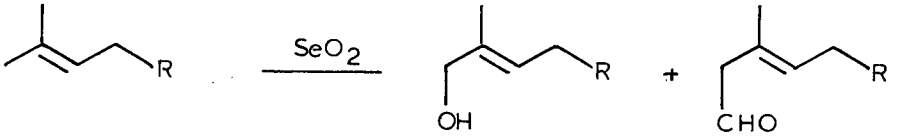
It was then decided to use bromide 330 as the alkylating agent and B' as the nucleophile in the first coupling step (see Figure 1). Following the same idea of using an allyl phenylsulfide carbanion in the alkylation step, sulfide 355 was conceived to play the role of B'. A stereoselective synthesis of 355 was achieved as described in Scheme xxvi. The dianion of methyl acetoacetate (1.2 eq) was alkylated with geranyl bromide

Scheme xxvi


Br
CO2Me
CO2Me
278
1. NaH , ClPO(OEt)2
2 Me2CuLi
OH
CO2Me
351
t-BuOOH
SeO2
12
11
8
7
3
2
1
CO2Me
288
MeSO2Cl , Et3N
OSO2Me
CO2Me
352
PhSLi
SPh
CO2Me
353
DIBAL
SPh
OH
354
DHP, H+
SPh
OTHP
355

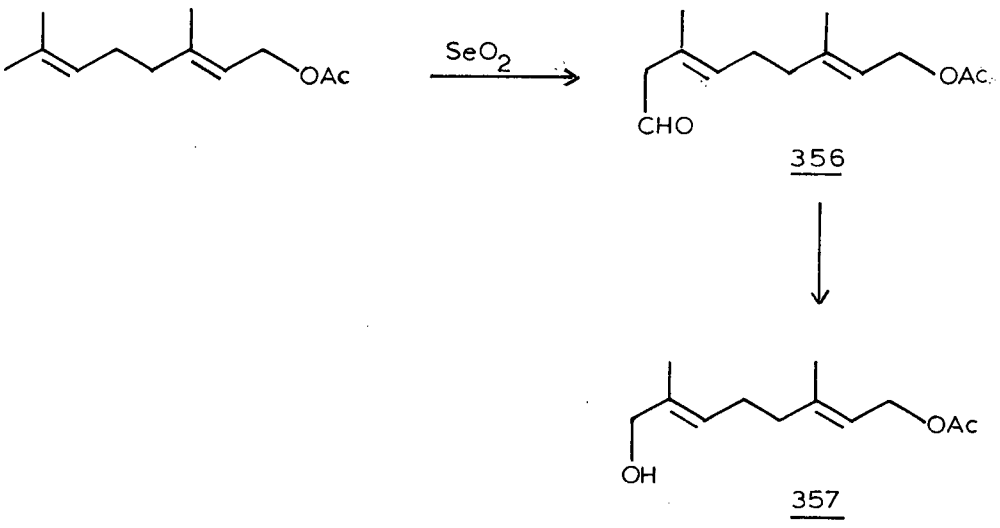
(prepared by phosphorous tribromide bromination of geraniol) to give 278 in 95% yield. The β-keto ester 278 was stereoselectively converted into the Z-enol phosphate which was coupled with lithium dimethylcuprate to afford (E, E)-methyl farnesoate (288). The above sequence invariably proceeded in greater than 90% yield and with greater than 98% stereoselectivity. This synthesis of (E, E)-methyl farnesoate showed marked improvement over a previous route reported by Kobayashi et al.[82b] via thio ethers derived from acetylenes.

The idea of regioselective oxidation was adopted for the selective functionalization of C-12 in 288. Regioselectivity in the allylic oxidation of olefins with selenium dioxide has been extensively demonstrated.[189] In general, trisubstituted olefins with terminal dimethyl groups can be oxidized to give predominantly E alcohols or aldehydes (equation 27). This method



(27)

has been used to convert geranyl acetate into the corresponding aldehyde 356[190] which after sodium borohydride reduction gave alcohol 357 in satisfactory yield (40%).[191] Theoretical considerations based on the reported findings[189] presaged plausible selective oxidation of C-12 in 288 with selenium dioxide. Electron deficiency of the C-2, C-3 double bond due to

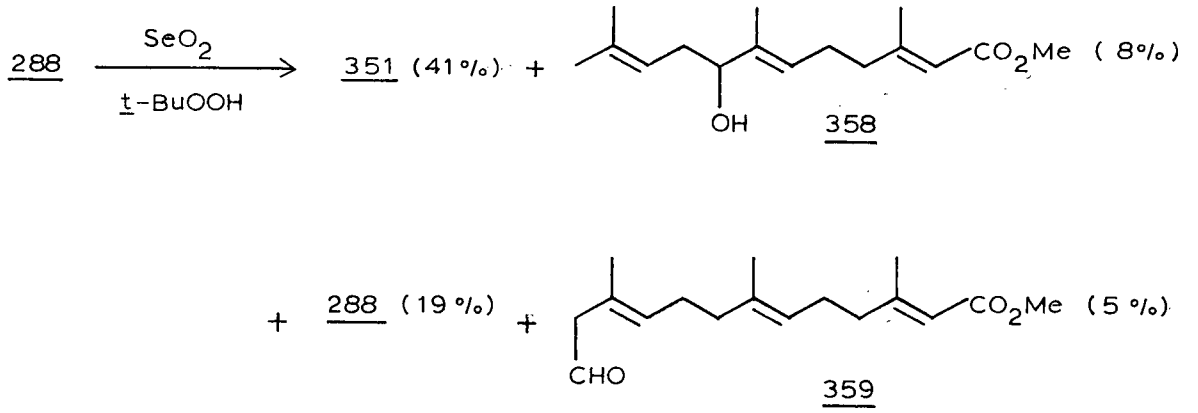


conjugation with carbomethoxy group would disfavor allylic oxidation at C-4. Oxidation at C-8 and C-12 are both mechanistically[189] favorable; however, the sterically less hindered C-12 is expected to be more susceptible to attack by the oxidizing agent.

The oxidation of 288 with selenium dioxide in refluxing ethanol[190] gave unsatisfactory results. A modified procedure, developed by Umbreit and Sharpless[192] involving t-butyl hydroperoxide and a catalytic (or stoichiometric) amount of selenium dioxide was then employed. It was hoped that the mild reaction conditions of this modification might alleviate the complications encountered in using excess selenium dioxide and refluxing ethanol. Indeed, by treating 288 with selenium dioxide (0.5 eq) and 70% t-butyl hydroperoxide [11] (2 eq) in dichloromethane (4.5 hr, 10° C), the allylic

[11] 90% t-BuOOH was used in the report by Sharpless et al.[192] However, we found that the commercial 70% t-BuOOH was also adequate.

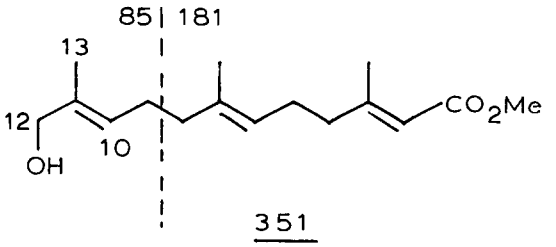
alcohol 351 was obtained in 41% yield along with the regioisomer 358 (8%), the aldehyde 359 (5%) and recovered 288 (19%). Careful monitoring



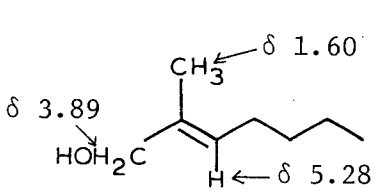
of the reaction conditions was crucial for good results as higher temperatures and prolonged reaction times led to significant formation of the aldehyde product and less efficient conversion into the desired alcohol 351.

The regiochemistry of the hydroxy group in structures 351 and 358 was established by analysis of their ^{1}HNMR and mass spectral data. The ^{1}HNMR spectrum of 351 (in CCl_4) showed absorptions at δ 1.60 (s, 3H), 3.83 (s, 2 H) and 5.25 (m, 1 H) which were ascribed to protons at C-13, C-12 and C-10 respectively. Comparison of these data with those reported for the analogous allylic alcohols E- and Z-360[121,189] (Figure 2, chemical shifts indicated were measured in CCl_4) confirmed the E geometry of the C-10 olefinic bond in 351. Prominent mass fragments at m/e 181 and 149 (181 - CH_4O) (see Figure 2) in the mass spectrum of 351 also supported the assigned terminal alcohol structure. Alcohol 358 exhibited a triplet

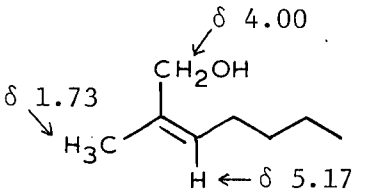
(J = 7 Hz) at δ 3.93 (1 H) and a multiplet at δ 5.3 (1 H) in its ^{1}HNMR spectrum, which were consistent with absorptions expected for protons at



351



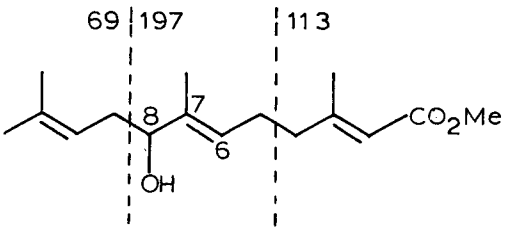
E-360



Z-360

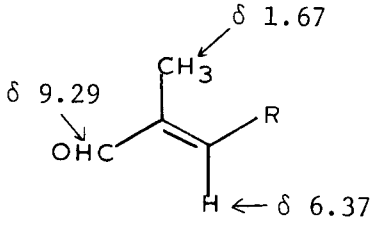
Figure 2. Some ^{1}HNMR and Mass Spectral Data Related to 351.

C-8 and C-6 in the suggested structure. The position of the hydroxy group in 358 was further substantiated by mass spectroscopy which showed major mass peaks at m/e 197, 165 (197 - CH_4O) and 113, corresponding to the



358

fragmentations illustrated above. The structure of aldehyde 359 was ascertained by comparing its ^{1}HNMR absorptions at δ 1.73 (s, 3H), 6.37 (m, 1H) and 9.3 (d, 1H), attributed to the C-13, C-10 and C-12 protons, with those recorded for structure 361.[120,193]

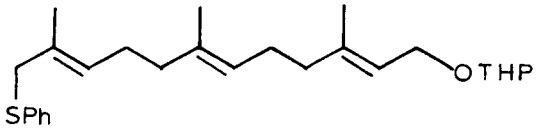


361

The allylic alcohol 351 was converted[172] into the corresponding mesylate 352, which was immediately treated with lithium thiophenoxide in tetrahydrofuran to give sulfide 353 in 93% overall yield. The ester function in 353 was reduced with diisobutylaluminum hydride at -23° C, and the resulting alcohol 354 was protected as the tetrahydropyranyl ether furnishing 355 in 95% yield.

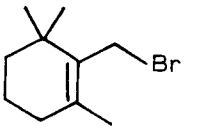
The two compounds 330 and 355, representing the subunits A' and B' (Figure 1), were assembled as shown in Scheme xxvii. The anion of 355, generated by n-butyllithium in the presence of DABCO[187] (THF, -23° C), was alkylated with bromide 330 to produce the α-alkylation product 362 in 75% yield. Biellmann and Ducep have shown that lithium in ethylamine was superior to other methods (Raney nickel, calcium-hexamine, and lithium in ammonia) for the reductive desulfurization of allylic sulfide in polyene molecules.[187]

Scheme xxvii

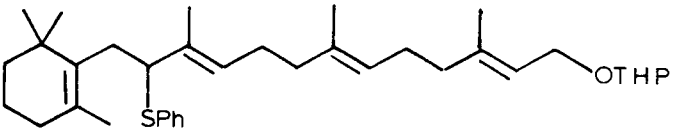


355

1. n-BuLi
DABCO
2.

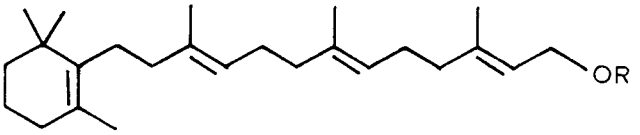


330



362

1. $NiCl_2$–$NaBH_4$, EtOH
2. H^+, MeOH

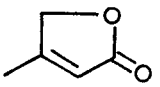


363 R = THP

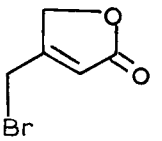
364 R = H

However, it is quite inconvenient to utilize this method in small scale reactions. A nickel catalyst, prepared from nickel (II) chloride and sodium borohydride,[12] has been developed by Truce and Roberts to desulfurize thioketals.[194] This so-called nickel boride reagent was later applied to reductively cleave benzylthio enol ethers.[195] The facility in the preparation and handling of this reagent intrigued our interest in testing its effectiveness in the desulfurization of the allylic sulfide 362. Indeed, when 362 was exposed to excess nickel boride in ethanol, the desulfurized compound 363 was obtained in ca. 72% yield. The hydroxy group was subsequently deprotected to give alcohol 364.

The bromination of 3-methyl-2-butenolide (365) to give bromide 366 was first envisioned as a possible route for the construction of the subunit C' (see Figure 1). According to results we had secured in an investigation related to steroidal cardenolides, N-bromosuccinimide (NBS) bromina-



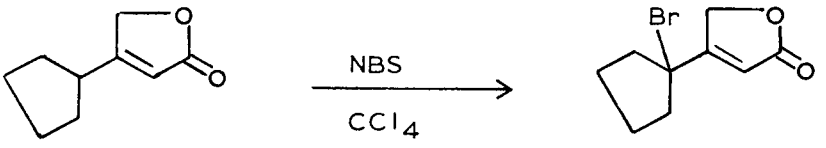
365



366

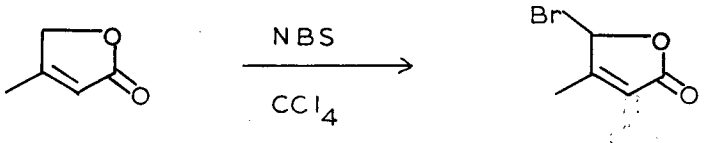
(12) The black precipitate prepared in this manner has been named "nickel boride."

tion of the model system 367 (prepared as described in Scheme xxviii) produced regioselectively the bromide 368 in 74% yield. Bromination of the butenolide moiety was not detected. Nevertheless, the NBS bromination



367 368

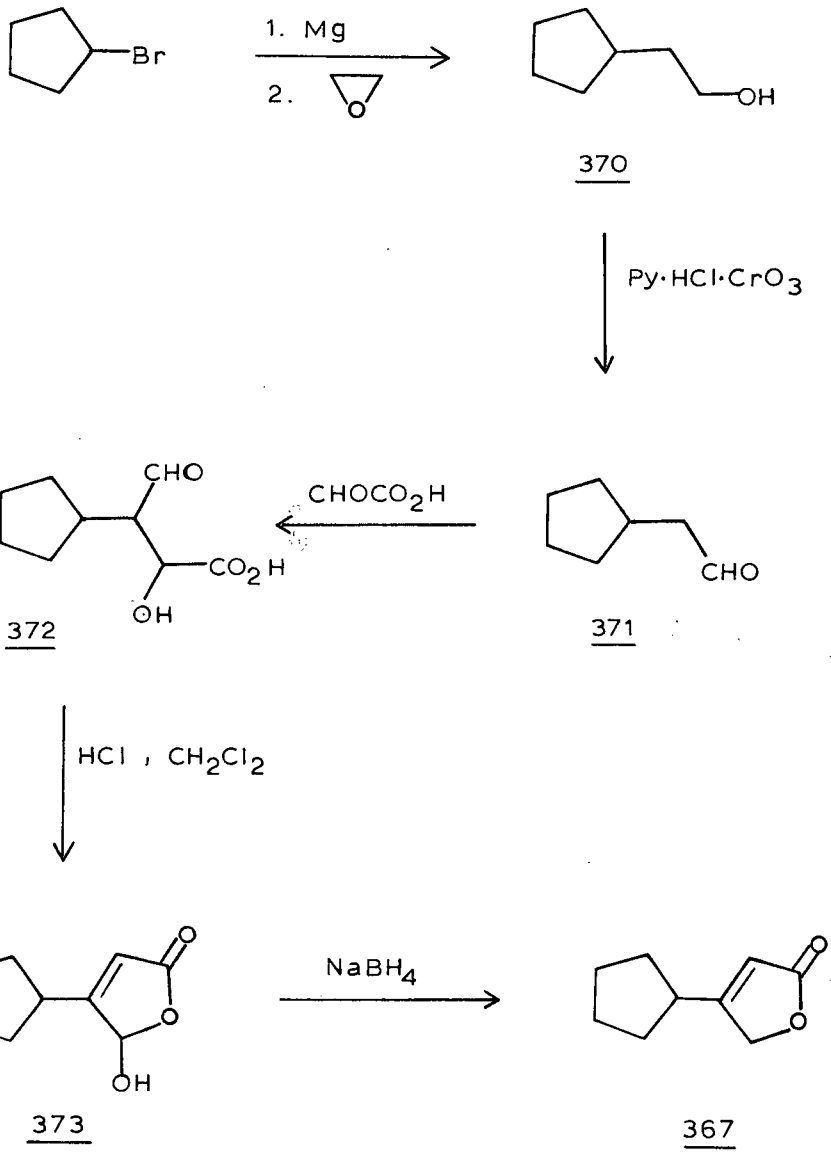
of 365 gave rise to bromobutenolide 369 instead of 366.[196] The remarkably different outcomes for 365 and 367 in this type of bromination probably reflects the difference in reactivity between primary, secondary and tertiary hydrogens towards free radical abstraction.[197]



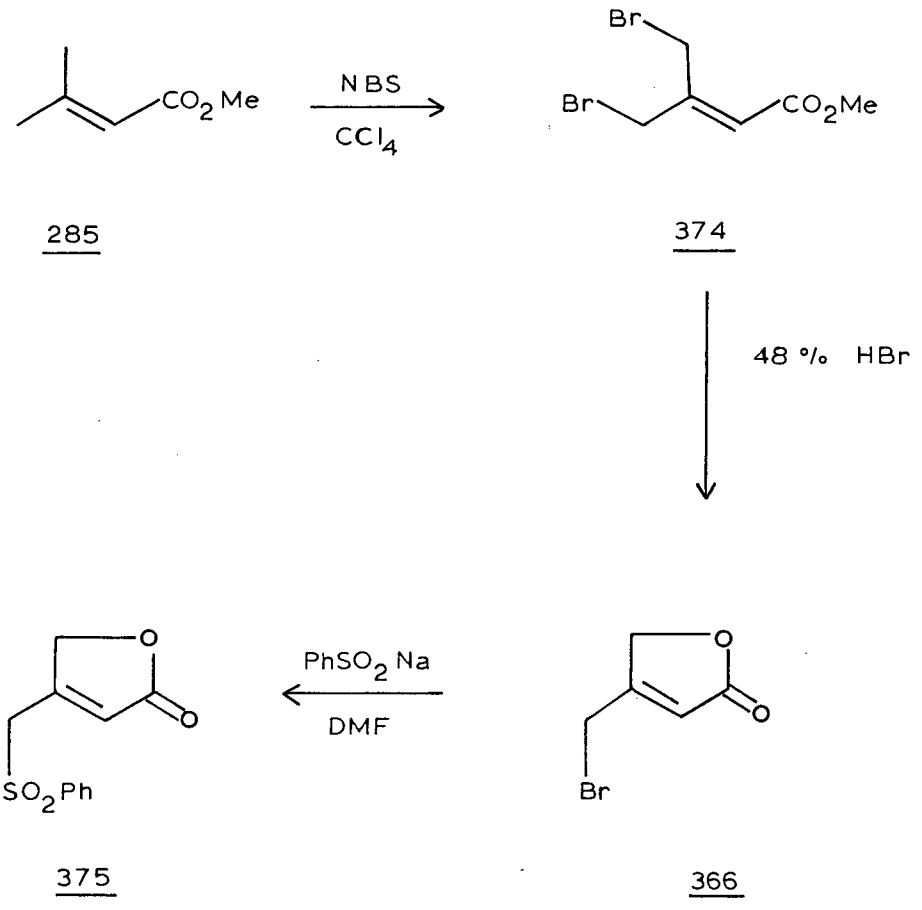
365 369

Since the preparation of a suitable C' unit from 365 seemed unlikely, a route to butenolide 366 (Scheme xxix) reported recently by Martin et al.[196] was adopted. Thus, methyl 3-methylbut-2-enoate (285) was brominated with NBS in carbon tetrachloride to give the dibromo ester 374, which was converted to bromo butenolide 366 with 48% hydrobromic acid in satisfactory overall yield.

Scheme xxviii



Scheme xxix

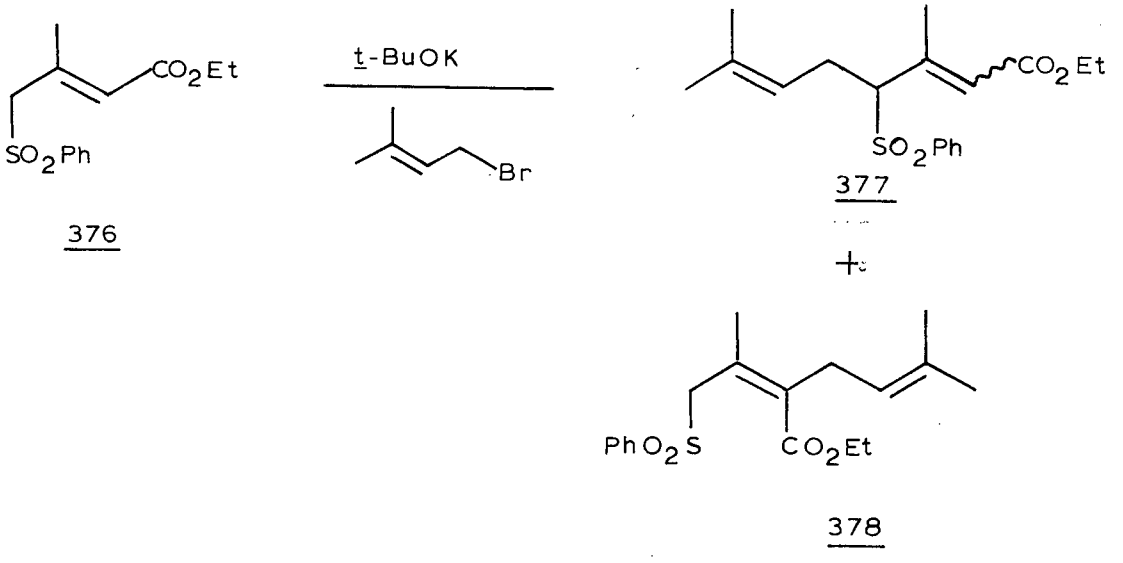


285 374 375 366

In a preliminary attempt to assemble the subunits D and C' (Figure 1), the carbanion of the phenylthio ether derived from 364 (-OH ⇒ SPh) was treated with the bromo butenolide 366. Only starting materials were recovered from this reaction. Presumably, proton exchange between the butenolide and the thio ether carbanion occurred faster than

the desired alkylation. On the basis of this result, it appeared more feasible to use C' as the nucleophile and D as the alkylating agent in the assembling process.

Julia and Arnould achieved the selective γ-alkylation of the α,β-unsaturated ester 376 with 1-bromo-3-methyl-2-butene, in tetrahydrofuran, using potassium t-butoxide as base.[198] The γ- and α-alkylation products, 377 (a mixture of E and Z isomers) and 378, were obtained in a ratio of 89:11. More recently, the anion of γ-phenylsulfonyl-α,β-unsaturated



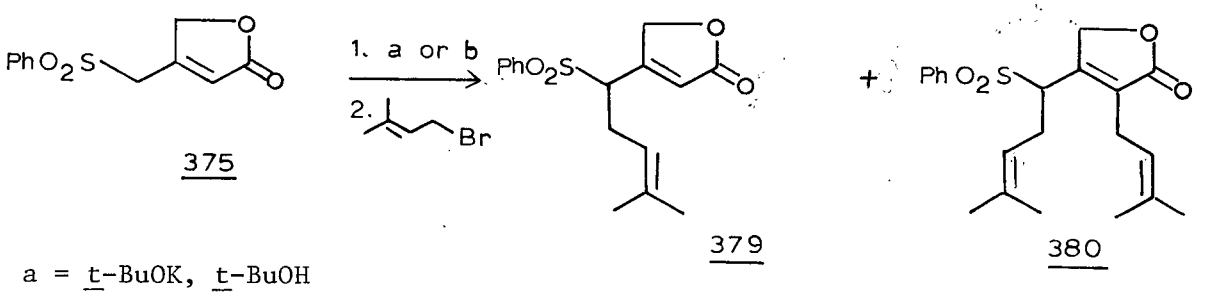
376

377

378

ketones were also reported to undergo selective γ-alkylations with alkyl halides in polar solvent systems.[199] The sulfonyl butenolide 375 was therefore chosen to introduce the butenolide end group in the final coupling step. Treatment of bromide 366 with sodium benzenesulfinate in dimethylformamide (DMF) at ambient temperature afforded the sulfone 375 in 85%

yield. Alkylation of the anion derived from 375 and sodium hydride[199a] (or potassium t-butoxide[199b]) in DMF (or t-butanol) invariably gave significant quantities of the dialkylated product 380. This complication was alleviated by employing an excess of the sulfonyl anion in the alkylation. With such modification, a markedly improved yield of the desired product 379 was attained.



375 379 380

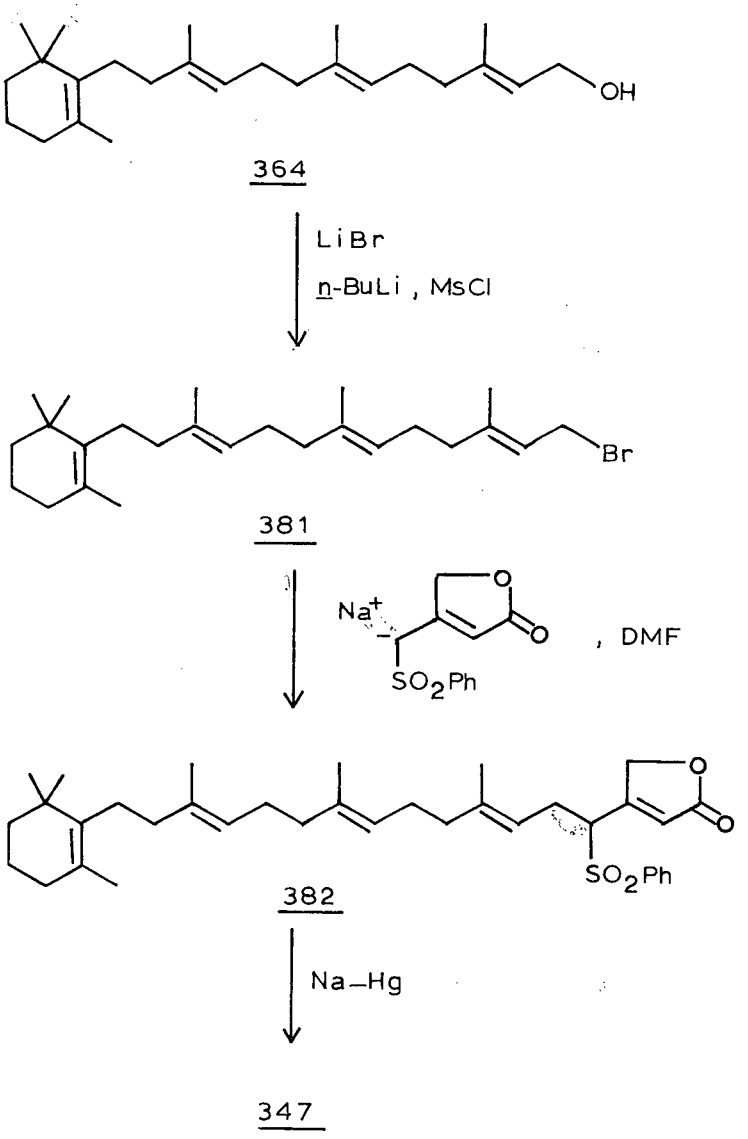
a = t-BuOK, t-BuOH

b = NaH, DMF (or THF-HMPA)

Scheme xxx illustrated the completion of the final assembling process in the synthesis of mokupalide (347). Alcohol 364 was converted into the bromide 381 via successive treatment with lithium bromide, n-butyllithium and methanesulfonyl chloride at -78 to 25° C.[170] This unstable bromide was immediately alkylated with an excess of the anion of sulfone 375 in DMF at room temperature to produce the coupled compound 382 in 60% yield from alcohol 364. The sulfonyl group in 382 was removed reductively with 6% sodium amalgam[200] in methanol at -10° C to give in greater than 80% yield of mokupalide (347). The IR, ^{1}HNMR and mass spectral data of this synthetic product were identical with those of the natural compound.[13]

[13] Copies of the spectra of mokupalide were obtained from Professor Scheuer and Dr. Yunker.

Scheme xxx



The above synthesis represents the first synthetic approach to mokupalide (347) which possibly can lead to hydroxymokupalide (348), and hence acetoxymokupalide (349), via functionalization of the butenolide moiety.

CONCLUSIONS

The syntheses of natural products presented in this thesis demonstrates the application of only limited aspects of the results from the cyclization study and the alkene synthesis. Potential utility of the findings other than those already employed still remains to be explored. While our exploitation of the scope of the new alkene synthesis is by no means thorough, possible extension of the present results to various cuprate reagents and other 1,3-dicarbonyl substrates, such as β-keto aldehydes and β-keto lactones, will certainly be the object of future investigations.

EXPERIMENTAL SECTION

All temperatures are stated in degrees centigrade. Melting points were determined on a Kofler hot stage microscope and are uncorrected. Kugelrohr distillations were performed by means of a Büchi Kugelrohr thermostat. Infrared spectra were recorded in chloroform solution (unless otherwise noted), on Perkin-Elmer Model 700 or 710B spectrophotometers, and were calibrated with the 1601 cm^{-1} band of polystyrene. Proton nuclear magnetic resonance spectra were recorded on Varian Model T-60, HA-100 or XL-100 spectrometers, in deuterochloroform solution unless otherwise specified. Chemical shifts are reported in the δ scale using tetramethylsilane as an internal standard. The multiplicity, coupling constants (if observable) and integrated peak area are indicated in parenthesis after each signal. Low resolution mass spectra were recorded on an Atlas CH-4B mass spectrometer, and high resolution mass measurements were obtained using an AEI MS-9 or MS-50 mass spectrometer. All instruments were operated at an ionizing potential of 70 eV. All mass measurements are reported in atomic mass units. Elemental microanalyses were performed by Mr. Peter Borda, University of British Columbia. The silica gel used was supplied by E. Merck. Silica Gel PF-254 was used for both analytical and preparative thin layer chromatography, whilst the grade 100-200 mesh ASTM was used for column chromatography. Visualization of spots or bands on tlc plates was accomplished by ultraviolet light and/or with iodine vapor staining. All solvent systems are expressed in ratios by volume (v/v). Vapor-phase chromatographic

analyses were conducted on a Hewlett-Packard Model 5830-A chromatograph using 6 ft. x 1/8 in. columns of 3% OV-17 or 3% OV-101.

The petroleum ether used has the boiling range 30-60°. Dry ethyl ether and tetrahydrofuran were obtained by distillation from lithium aluminum hydride. Dichloromethane and methanesulfonyl chloride were dried by distilling from phosphorous pentoxide. Dry dimethylformamide and hexamethylphosphoramide were obtained by refluxing over calcium hydride, followed by distillation under reduced pressure. Triethylamine was purified and dried by distilling from barium oxide. The anhydrous stannic chloride used was reagent grade material purchased from Fisher Scientific Company Ltd. Diethyl chlorophosphate supplied by Aldrich Chemical Company, Inc. was used directly without purification and was handled under dry nitrogen atmosphere at all times. Methyllithium (in ether), n-butyllithium (in hexane) and sec-butyllithium (in cyclohexane) were obtained from Aldrich Chemical Company, Inc., while ethyllithium (in benzene) and t-butyllithium (in pentane) were supplied by Alfa Division, Ventron Corporation. The alkyllithium solutions were standardized by titration against a 1.0 M solution of t-butanol in benzene, using 1,10-phenanthroline as indicator. Sodium hydride (from Alfa Division, Ventron Corporation) was weighed as a 50% dispersion in mineral oil and was washed with dry ether to remove the oil prior to use.

SECTION I

Preparation and Cyclization of Unsaturated β-Keto Esters

General Procedure for the Generation of the Dianion of β-Keto Esters.[1] - The β-keto ester, dissolved in dry tetrahydrofuran, was added to a suspension of sodium hydride (1.1 eq) in the same solvent under a dry nitrogen atmosphere, and with cooling in an ice bath. The resulting mixture was stirred at 0° for 15 min followed by dropwise addition of a solution of n-butyllithium (1.05 eq) in hexane. This dianion solution was stirred for another 15 - 20 min at 0° before use.

Methyl 3-Oxohept-6-enoate (86). - A dianion solution, prepared from 5.806 g (50 mmole) of methyl acetoacetate, 2.64 g (55 mmole) of sodium hydride (50% mineral oil) and 32.8 ml (52.5 mmole) of n-butyllithium (1.6 M in hexane), in 125 ml of dry tetrahydrofuran was treated with 7.26 g (60 mmole) of allyl bromide at 0°. The mixture was stirred for 5 min at the same temperature and for 20 min at room temperature. The reaction was then quenched with 100 ml of brine, 10 ml of concentrated hydrochloric acid and 100 ml of ethyl ether, and the aqueous phase was separated and extracted with 2 x 100 ml of ethyl ether. The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure gave 7.21 g of crude product which was distilled through a Vigreux column (3 cm) to afford 6.40 g (82%) of 86 as a colorless liquid: bp 77-78°/2.2 Torr (lit.[1] bp 99-100°/15 Torr); IR 1742, 1715 and 1640 cm^{-1}; ^{1}HNMR δ 2.03-2.8 (m, 4H), 3.42 (s, 2H), 3.70 (s, 3H), 4.77 - 5.17 (m, 2H) and 5.46-6.1 (m, 1H); mass spectrum m/e (rel intensity)

156(10), 124(18), 101(50), 83(36), 82(57), 69(32), 59(48), 57(15), 55(100), 54(45), 43(76), 42(20) and 41(27).

Methyl 6-Chloro-3-oxo-7-phenylselenenylheptanoate (87). - To a solution of 310 mg (1.62 mmole) of phenylselenenyl chloride in dry dichloromethane, kept at 0° and under a dry nitrogen atmosphere, was added 251 mg (1.61 mmole) of methyl 3-oxohept-6-enoate (86) with stirring. The resulting solution was maintained at 0° for 1 hr and then at room temperature for 30 min. The solvent was subsequently removed from the reaction mixture in vacuo to give 562 mg (ca. 100%) of crude 87 as an orange oil: IR 1742, 1715, 1580 and 1475 cm^{-1}; ^{1}HNMR δ 2.1 (m, 2H), 2.7 (m, 2H), 3.25 (br d, J = 4 Hz, 2H), 3.38 (s, 2H), 3.68 (s, 3H), 4.1 (m, 1H), 7.2 (m, 3H), and 7.5 (m, 2H); mass spectrum m/e (rel intensity) 348(11), 316(28), 314(79), 312(80), 311(29), 310(49), 309(17), 308(19), 234(22), 232(17), 159(26), 158(40), 157(100), 156(55), 155(70), 154(45), 153(23), 124(57), 123(72), 101(74), 95(22), 83(54), 82(82), 78(41), 77(76), 69(40), 59(60), 55(94), 54(41), 51(33), 43(45) and 41(25).

High Resolution Mass Measurement Calcd for $C_{14}H_{17}{}^{35}ClO_3{}^{80}Se$: 348.0026. Found: 348.0021.

Methyl α-(E-Tetrahydro-5-phenylselenenylmethyl-2-furylidene)-acetate (88) and Methyl α-(Tetrahydro-2-hydroxy-5-phenylselenenylmethyl-furan-2-yl)acetate (89). - The crude product 87 (560 mg) was chromatographed on a column of silica gel (100-200 mesh). Elution with a 10:1 mixture of carbon tetrachloride and ethyl ether gave two cyclized compounds, in order

of increasing retention time:- (a) 341 mg (68%) of 88: colorless liquid; IR 1700, 1640, 1580, 1475 and 1120 cm^{-1}; ^{1}HNMR δ 1.6-2.4 (m, 2H), 3.1 (br d, J = 4.4 Hz, 2H), 2.7-3.4 (m, 2H), 3.60 (s, 3H), 4.52 (m, 1H), 5.17 (t, J = 1.6 Hz, 1H), 7.2 (m, 3H) and 7.5 (m, 2H); mass spectrum m/e (rel intensity) 314(10.4), 312(52), 310(25.5), 309(8.5), 308(9.5), 306(0.9), 281(10), 280(9), 157(30), 155(71), 123(100), 101(26), 95(26), 91(15), 85(17), 81(20), 77(23), 69(32), 59(18), 55(33), and 51(14).

Anal. Calcd for $C_{14}H_{16}O_3Se$: C, 54.03; H, 5.18. Found: C, 53.80; H, 5.20.

(b) 144 mg (27%) of 89: colorless liquid; IR 3530, 1720, 1580 and 1475 cm^{-1}; ^{1}HNMR δ 1.53-2.3 (m, 4H), 2.68 (s, 2H), 3.0 (m, 2H), 3.67 (s, 3H), 4.33 (m, 1H), 7.2 (m, 3H) and 7.5 (m, 2H); mass spectrum m/e (rel intensity) 332(9.2), 330(47), 328(21.8), 327(7.5), 326(8.4), 324(0.8), 312(8), 256(14), 172(36), 170(20), 159(39), 157(21), 155(24), 149(14), 141(100), 127(23), 99(21), 91(16), 85(51) and 55(21).

High Resolution Mass Measurement Calcd for $C_{14}H_{18}O_4{}^{80}Se$: 330.0370. Found: 330.0351.

Reaction of Methyl 3-Oxohept-6-enoate (86) with Mercuric Acetate. - To a stirred suspension of 160 mg (0.5 mmole) of mercuric acetate in dry tetrahydrofuran (2 ml) was added 78 mg (0.5 mmole) of 86 in a small volume of the same solvent. The mixture turned into a solution in ca. 1 min and after ca. 30 min at room temperature, a gelatine-like suspension was formed. Stirring was continued for another 2 hr and then the solvent was removed

under reduced pressure. The residue was evaporated at high vacuum (0.05 Torr) for several hours at ambient temperature to give 179 mg of 91: yellow oil; IR 1700, 1640 and 1565 cm^{-1}; ^{1}HNMR δ 1.6-2.4 (m, ca. 2H), 2.03 (s, ca. 3H), 2.23 (d, J = 7 Hz, 2H), 2.6-3.4 (m, ca. 2H), 3.62 (s, 3H), 4.6 (m, 1H) and 5.22 (br s, 1H); mass spectrum m/e (rel intensity) 204(4), 202(17), 201(7), 200(13), 199(10), 198(6), 156(13), 155(9), 124(17), 123(8), 101(22), 83(15), 82(21), 69(14), 60(84), 59(16), 55(11), 45(100), 43(99).

Sodium Borohydride Reduction of Mercuration Product 91. - (i) The mercuration product prepared from 78 mg (0.5 mmole) of 86 in a similar manner as described above was treated in situ with a neutral solution of sodium borohydride (23 mg) in water. After 30 min at room temperature, the reaction mixture was quenched with dilute hydrochloric acid and ethyl ether. The organic solution was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of solvents gave 77 mg of crude material whose IR, ^{1}HNMR and mass spectral data and chromatographic property revealed the presence of mainly 86.

(ii) To 90 mg (ca. 0.25 mmole) of the crude product 91 in tetrahydrofuran (1 ml) was added a solution of sodium borohydride (23 mg, 0.6 mmole) in 3M sodium hydroxide (0.5 ml) at 0°. The resulting mixture was stirred for 30 min at 0° and 10 min at room temperature, followed by quenching with 5% hydrochloric acid and extraction with ethyl ether. The organic solution was dried over magnesium sulfate (anhydrous) and then evaporated

under reduced pressure to give 29 mg of residue. Preparative thin layer chromatography on silica gel with ethyl ether-carbon tetrachloride-acetic acid (1:1:trace amount) led to two major components: - (a) 8 mg (21%) of 86: (see spectral data described earlier).

(b) 16 mg (44%) of 3-hydroxy-6-heptenoic acid (92): colorless liquid; IR 3600-2800 (broad), 1710 and 1640 cm^{-1}; ^{1}HNMR δ 1.4-1.8 (m, 2H), 2.2 (m, 2H), 2.54 (d, J = 5 Hz, 2H), 4.1 (m, 1H), 4.92-5.22 (m, 2H), 5.7 (m, 1H) and 6.7 (br s, 2H, exchangeable with D_2O); mass spectrum m/e (rel intensity) 144(1), 126(31), 111(10), 102(20), 97(19), 89(46), 84(78), 81(98), 71(100), 67(66), 56(45) and 55(63).

High Resolution Mass Measurement Calcd for $C_7H_{12}O_3$: 144.0786. Found: 144.0793.

Methyl 6-Methyl-3-oxohept-6-enoate (94). - The dianion of methyl acetoacetate generated from 5.8 g (50 mmole) of methyl acetoacetate, 2.64 g (55 mmole) of sodium hydride (50% oil) and 32.8 ml (52.5 mmole) of n-butyl-lithium (1.6 M) in 100 ml of dry tetrahydrofuran, according to the general procedure, was allowed to react with 5.37 ml (55 mmole) of 3-chloro-2-methyl-propene for 2 hr at 0° and then for 0.5 hr at room temperature. The reaction mixture was worked up in the same manner as shown in the preparation of 86. The crude product (8.62 g) obtained was distilled through a Vigreux column (3 cm) to yield 6.12 g (72%) of 94, as a colorless liquid: bp 74-75°/1.0 Torr; IR 1745, 1720 and 1650 cm^{-1}; ^{1}HNMR δ 1.73 (s, 3H), 2.0-2.9 (m, 4H), 3.43 (s, 2H), 3.70 (s, 3H) and 4.65 (m, 2H); mass spectrum m/e

(rel intensity) 170(29), 152(40), 138(54), 127(24), 110(19), 101(67), 97(66), 96(71), 95(48), 93(39), 92(37), 85(30), 81(63), 70(53), 69(100), 68(70), 67(64), 59(73), 57(69), 55(74), 53(57), 43(76) and 41(81).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.46; H, 8.33.

Methyl 7-Methyl-3-oxooct-6-enoate (95). - A solution of the dianion of methyl acetoacetate in dry tetrahydrofuran (200 ml), prepared according to the general procedure from 11.6 g (0.1 mole) of methyl acetoacetate, 5.28 g (0.11 mole) of sodium hydride (50% oil) and 65.6 ml (0.105 mole) of n-butyllithium (1.6 M), was treated with 11.6 ml (0.1 mole) of 1-bromo-3-methyl-2-butene at 0°. The mixture was stirred for 1 hr 45 min at the same temperature and then worked up as described in the preparation of 86 to give 18.6 g of crude product. Distillation through a Vigreux column afforded 15.68 g (85%) of 95: bp 67-68°/0.1 Torr; IR 1745, 1718 and 1640 cm^{-1}; ^{1}HNMR δ 1.6 (s, 3H), 1.65 (s, 3H), 1.95-2.73 (m, 4H), 3.40 (s, 2H), 3.70 (s, 3H) and 5.0 (m, 1H); mass spectrum m/e (rel intensity) 184(13), 169(10), 166(15), 153(10), 149(24), 129(19), 116(27), 111(38), 110(35), 109(20), 101(42), 95(48), 83(36), 82(75), 74(100), 69(98), 67(64), 59(35), 55(45), 43(48) and 41(99).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.35; H, 8.96.

Methyl α-(E-Tetrahydro-5,5-dimethyl-2-furylidene)acetate (96). - To a solution of 528 mg (2.0 mmole) of anhydrous stannic chloride in dry dichloromethane (25 ml) was added 306 mg (1.8 mmole) of 94 at ambient temperature. The resulting solution was kept under a dry nitrogen atmosphere and stirred for 19 hr. The reaction mixture was then poured into 20 ml of ice-cold water and the aqueous phase was extracted with 3 x 20 ml of ethyl ether. The combined extracts were washed with water and brine until neutral, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 298 mg (97%) of crude material, which was reasonably pure by tlc and spectral analyses. Preparative thin layer chromatography of 160 mg of the crude product on silica gel with petroleum ether-ethyl ether (6:1) yielded 145 mg (88%) of 96: colorless liquid; bp (Kugelrohr distillation) 56-58°/0.8 Torr; IR 1700, 1640 and 1120 cm^{-1}; ^{1}HNMR δ 1.35 (s, 6H), 1.87 (t, J = 7.6 Hz, 2H), 3.15 (d t, J = 7.6 and 1.8 Hz, 2H), 3.60 (s, 3H) and 5.17 (t, J = 1.8 Hz, 1H); mass spectrum m/e (rel intensity) 170(65), 139(40), 138(19), 127(27), 110(10), 101(100), 96(23), 70(19), 69(32), 55(12), 43(13) and 41 (14).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.62; H, 8.41.

Methyl 2,2-Dimethyl-6-oxocyclohexanecarboxylate (97). - To a solution of 9.0 ml (77 mmole) of anhydrous stannic chloride in dry dichloromethane (200 ml), kept under a dry nitrogen atmosphere and cooled in an ice-bath, was added 12.88 g (70 mmole) of 95 dissolved in 15 ml of dichloromethane (dry). The resulting solution was stirred at room temperature for

18.5 hr and then poured into 100 ml of ice-cold water. The aqueous phase was extracted with 3 x 150 ml of ethyl ether, and the combined extracts were washed with 50% brine until neutral and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure gave rise to 12.9 g of crude product which contained essentially pure 97 according to its spectral and chromatographic data. Distillation of the crude material afforded 11.85 g (92%) of 97: bp 64-66°/0.1 Torr; IR 1750 (shoulder), 1730 and 1710 cm^{-1}; ^{1}HNMR δ 1.02 (s, 3H), 1.08 (s, 3H), 1.2-2.1 (m, 4H), 2.1-2.7 (m, 2H), 3.13 (s, 1H) and 3.65 (s, 3H); mass spectrum m/e (rel intensity) 184(26), 169(20), 153(38), 141(19), 137(53), 111(58), 100(68), 83(85), 74(74), 69(79), 55(100), 43(96) and 41(87).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.00; H, 8.55.

Methyl 3-Oxonon-6-ynoate (104). - The dianion of methyl acetoacetate in dry tetrahydrofuran (15 ml), generated from 348 mg (3 mmole) of methyl acetoacetate, 158 mg (3.3 mmole) of sodium hydride (50% oil) and 1.9 ml (3 mmole) of n-butyllithium (1.6 M) according to the usual procedure, was allowed to react with 294 mg (2 mmole) of 1-bromo-2-pentyne at 0° for 1.5 hr. The reaction mixture was worked up as indicated in the preparation of 86 to give 411 mg of crude product. Preparative thin layer chromatography on silica gel with petroleum ether-ethyl ether (5:1) yielded 77 mg (87% based on 1-bromo-2-pentyne used) of 104 from 100 mg of the crude material, as a colorless liquid: bp (Kugelrohr distillation) 98-100°/1.0 Torr; IR 1745 and 1720 cm^{-1}; ^{1}HNMR δ 1.08 (t, J = 7 Hz, 3H), 1.85-2.9 (m, 6H),

3.43 (s, 2H) and 3.70 (s, 3H); mass spectrum m/e (rel intensity) 182(27), 167(38), 154(32), 153(52), 123(45), 122(66), 109(100), 108(30), 107(32), 101(29), 81(41), 80(33), 79(49), 69(33), 67(17), 65(16), 59(44), 53(25) and 41(54).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.70; H, 7.64.

Cyclization of Methyl 3-Oxonon-6-ynoate (104). - A solution of 128 mg (0.49 mmole) of anhydrous stannic chloride in dry dichloromethane (5 ml) was kept under a dry nitrogen atmosphere and cooled in an ice-bath. To this was introduced 82 mg (0.45 mmole) of 104, and the resulting solution was stirred for 21.5 hr at room temperature. The reaction was quenched with ice-cold water (ca. 10 ml) and the aqueous layer was extracted with ethyl ether (ca. 20 ml). The ethereal extract was washed with 50% brine until neutral, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude material (84 mg) so obtained was chromatographed on silica gel with petroleum ether-ethyl ether (6:7) to give two cyclized products:- (a) 50 mg (61%) of methyl 2-n-propyl-5-oxocyclopentenecarboxylate (105): colorless liquid; R_f 0.22; bp (Kugelrohr distillation) 73-75°/ 0.05 Torr; IR 1740, 1710 and 1625 cm^{-1}; ^{1}HNMR δ 0.98 (t, J = 7 Hz, 3H), 1.2-2.0 (m, 2H), 2.27-2.93 (m, 6H) and 3.78 (s, 3H); mass spectrum m/e (rel intensity) 182(45), 151(67), 150(100), 135(79), 122(26), 109(12), 107(13), 95(14), 79(15), 55(14) and 41(18).

High Resolution Mass Measurement Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0941.

(b) 27 mg (33%) of methyl 2-ethyl-6-oxocyclohexenecarboxylate (106): colorless liquid; R_f 0.33; bp (Kugelrohr distillation) 66-68°/ 0.05 Torr; IR 1730, 1675 and 1630 cm^{-1}; ^{1}HNMR δ 1.13 (t, J = 7 Hz, 3H), 1.63-2.6 (m, 8H) and 3.78 (s, 3H); mass spectrum m/e (rel intensity) 182(29), 151(42), 150(100), 126(12), 122(55), 111(10), 96(17), 94(19), 55(20)and 41(16).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.98; H, 7.91.

Preparation and Reactions of Epoxy and α-Diazo β-Keto esters.

Methyl 6,7-Epoxy-7-methyl-3-oxooctanoate (111). - To a suspension of 199 mg (1.4 mmole) of anhydrous disodium hydrogen phosphate and 242 mg (1.4 mmole) of m-chloroperbenzoic acid (85%) in dry dichloromethane (4 ml) was added 184 mg (1 mmole) of methyl 7-methyl-3-oxooct-6-enoate (95) at 0° (this reaction was found notably exothermic). The resulting mixture was stirred at the same temperature for 20 min (reaction progress was monitored by tlc analysis, 1:1 petroleum ether-ethyl ether). The suspension was then filtered with suction and the residue was washed with a small volume of dichloromethane. The filtrate was diluted with ethyl ether (20 ml), washed with 10% sodium bisulfite, 10% sodium bicarbonate and brine, dried over anhydrous sodium sulfate and finally, evaporated in vacuo. The crude product (192 mg, 96%) of 111 so obtained was essentially pure by spectral and chromatographic analyses and was used in cyclization study without further purification. A sample for high resolution mass spectrum was purified by

Kugelrohr distillation at 82-85°/0.05 Torr: colorless oil; IR 1745 and 1720 cm^{-1}; ^{1}HNMR δ 1.28 (s, 6H), 1.8 (m, 2H), 2.7 (m, 3H), 3.45 (s, 2H) and 3.70 (s, 3H); mass spectrum m/e (rel intensity) 200(36), 185(15), 169(23), 159(12), 142(79), 141(51), 129(100), 127(43), 117(24), 116(24), 111(21), 110(15), 101(48), 99(22), 97(42), 85(46), 83(35), 74(41), 72(99), 71(36), 69(25), 59(73), 57(47), 55(54), 43(72) and 41(33).

High Resolution Mass Measurement Calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1048.

Methyl 2-Isopropyl-5-oxocyclopentenecarboxylate (112). - (a) From epoxide 111: A solution of 173 mg (0.86 mmole) of 111 in dry dichloromethane was added into a solution of 545 mg (2.1 mmole) of anhydrous stannic chloride in the same solvent (4 ml), at room temperature. After 23 hr, the reaction mixture was poured into ice-cold water (10 ml) and the aqueous phase was extracted with 2 x 15 ml of ethyl ether. The combined extracts were washed with 50% brine until neutral, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 180 mg of crude product. Distillation (Kugelrohr) at 94-98°/0.6 Torr afforded 135 mg (86%) of 112: colorless liquid; IR 1740, 1710 and 1620 cm^{-1}; ^{1}HNMR δ 1.17 (d, J = 7 Hz, 6H; collapsed into a broad singlet when irradiated at δ 3.5), 2.2-2.85 (m, 4H), 3.50 (septet, J = 7 Hz, 1H) and 3.80 (s, 3H); mass spectrum m/e (rel intensity) 182(15), 151(43), 150(100), 135(24), 122(18), 109(10), 107(11), 79(17), 55(11) and 41(10).

High Resolution Mass Measurement Calcd for $C_{10}H_{14}O_3$: 182.0942. Found: 182.0937.

(b) From Bicyclic Compound 114: To a solution of 116 mg (0.4 mmole) of anhydrous stannic chloride in dry dichloromethane was added 36 mg (0.2 mmole) of 114. The resulting mixture was stirred for 12 hr at room temperature and then worked up in the same manner as described above. The crude product isolated (36 mg, 100%) was homogeneous by tlc analysis, and had identical spectroscopic and chromatographic properties as 112 (vide supra).

Methyl 2-Diazo-7-methyl-3-oxooct-6-enoate (115). - To 5.52 g (30 mmole) of β-keto ester 95, dissolved in 50 ml of dry acetonitrile (distilled over P_2O_5), was added 4.2 ml (30 mmole) of anhydrous triethylamine. The solution was cooled in an ice-bath with constant stirring while a solution of 5.91 g (30 mmole) of p-toluenesulfonyl azide (prepared according to the procedure reported by Regitz et al.[70]) in dry acetonitrile (5 ml) was slowly introduced. The ice-bath was removed upon complete addition of p-toluenesulfonyl azide and stirring was continued for 4 hr at room temperature. The resulting solution was concentrated under reduced pressure (water aspirator; bath temperature 35°) to give a residue of oil and white solid, which was dissolved in 100 ml of ethyl ether. The ethereal solution was washed with 2 x 35 ml of 5% sodium hydroxide and 2 x 30 ml of brine and dried over anhydrous calcium sulfate. Removal of solvents and volatile materials in vacuo yielded 6.5 g (ca. 100%) of crude 115 which was directly used in the next copper-catalyzed cyclization reaction without any purification. This crude product (a pale yellow oil) was homogeneous by tlc and showed satisfactory spectral data: IR 2150, 1720, 1650 and 1435 cm^{-1}; ^{1}HNMR δ 1.65

(br s, 6H), 1.95-2.55(m, 2H), 2.57-3.05(m, 2H), 3.77 (s, 3H) and 5.05 (m, 1H); mass spectrum m/e (rel intensity) 210(8), 182(13), 167(15), 150(86), 135(100), 123(12), 122(20), 113(18), 109(13), 107(16), 82(26), 79(23), 69(43), 67(42), 59(18), 55(29), 53(19), 43(16) and 41(80).

High Resolution Mass Measurement Calcd for $C_{10}H_{14}N_2O_3$: 210.1004. Found: 210.0983.

Methyl 6,6-Dimethyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate (114).- A mixture of 6.4 g (ca. 29 mmole) of the crude α-diazo β-keto ester 115 and 2.0 g of copper-bronze (commercial grade from British Drug House) in 50 ml of dry benzene was heated under reflux for 30 hr. The suspension was filtered and the filtrate was evaporated under reduced pressure to give 5.6 g of crude product. Vacuum distillation through a short Vigreux column afforded 3.80 g (71% from 95) of 114 as a colorless oil: bp 72-73°/0.05 Torr; IR 1750 (shoulder) and 1720 cm^{-1}; ^{1}HNMR δ 1.2 (s, 3H), 1.23 (s, 3H), 1.5-2.6 (m, 5H) and 3.72 (s, 3H); mass spectrum m/e (rel intensity) 182(25), 151(39), 150(100), 141(21), 140(21), 135(26), 123(15), 122(27), 109(39), 108(17), 95(15), 94(12), 81(15), 79(20), 73(28), 67(14), 55(16), 53(14) and 41(24).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.97; H, 7.70.

Controlled Cyclization of Methyl 6,7-Epoxy-7-methyl-3-oxooctanoate (111). - To a solution of anhydrous stannic chloride (110 mg, 0.42 mmole) in dry dichloromethane (2 ml), kept under a dry nitrogen atmosphere and

cooled in an ice-bath, was added 76 mg (0.38 mmole) of epoxide 111. Progress of the reaction was traced by tlc analysis which revealed complete disappearance of starting material after 20 min at 0^{o}. The reaction mixture was then diluted with ice-cold water (5 ml) and ethyl ether (20 ml), and the organic phase was separated, washed with 50% brine until neutral and dried over anhydrous sodium sulfate. Evaporation of solvents under reduced pressure gave 69 mg of crude material, which upon chromatography on silica gel with ethyl ether yielded three cyclized products: - (a) 38 mg (51%) of methyl α-(E-tetrahydro-3-hydroxy-2,2-dimethyl-6-pyrylidene)acetate (116): colorless liquid; R_f 0.6; bp (Kugelrohr distillation) 92-95^{o}/0.05 Torr; IR 3500, 1700 and 1640 cm^{-1}; ^{1}HNMR δ 1.17 (s, 3H), 1.28 (s, 3H), 2.0 (m, 2H), 3.07 (m, 2H), 3.62 (s, 3H), 4.18 (t, J = 8 Hz, 1H) and 5.27 (t, J = 1.6 Hz, 1H); mass spectrum m/e (rel intensity) 200(9), 185(7), 169(15), 153(18), 142(100), 110(32), 99(34), 69(16), 59(33) and 43(22).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.91; H, 7.95.

(b) 12 mg (16%) of methyl α-(Z-tetrahydro-3-hydroxy-2,2-dimethyl-6-pyrylidene)acetate (117): colorless liquid; R_f 0.2; IR 3500, 1700 and 1650 cm^{-1}; ^{1}HNMR δ 1.18 (s, 3H), 1.36 (s, 3H), 2.0 (m, 2H), 2.77 (m, 2H), 3.63 (s, 3H), 4.37 (t, J = 7 Hz, 1H) and 4.81 (br s, 1H); mass spectrum m/e (rel intensity) 200(10), 185(7), 179(11), 169(17), 153(26), 151(16), 142(100), 127(11), 110(33), 109(16), 99(37), 86(26), 84(38), 69(15), 59(31) and 43(27).

High Resolution Mass Measurement Calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1046.

(c) 10 mg (11%) of methyl α-(tetrahydro-3,6-dihydroxy-2,2-dimethylpyran-6-yl)acetate (118): colorless oil; R_f 0.4; IR 3500 and 1720 cm^{-1}; ^{1}HNMR δ 1.11 (s, 3H), 1.25 (s, 3H), 1.7-2.4 (m, 4H), 2.79 (s, 2H), 3.76(s, 3H) and 4.05 (m, 1H); mass spectrum m/e (rel intensity) 218(4), 201(100), 200(10), 185(16), 183(64), 169(68), 159(21), 142(52), 141(53), 127(84), 116(27), 109(15), 101(40), 99(47), 85(47), 74(23), 72(16), 71(18), 69(17), 59(69), 57(23), 55(23), 43(71) and 41(20).

Methyl E-6,7-Epoxy-3-pyrrolidinohept-2-enoate (124). - A solution of 338 mg (2 mmole) of methyl E-3-pyrrolidinobut-2-enoate (123) (prepared from methyl acetoacetate and pyrrolidine) in 5 ml of dry tetrahydrofuran was cooled in a Dry Ice-chloroform bath (-60°) and kept under a dry nitrogen atmosphere. To this was added 1.25 ml (2 mmole) of n-butyllithium (1.6 M). The mixture was stirred at -60° for 5 min and then the bath temperature was raised to room temperature over 1 hr. The resulting light yellow solution was cooled to -60° again, followed by introduction of 278 mg (3 mmole) of epichlorohydrin (in ca. 1 ml of dry THF). After 20 min at -60°, the cooling bath was removed and stirring was continued for 4.5 hr. The mixture was finally poured into 15 ml of ice-cold brine and the aqueous phase was extracted with 3 x 20 ml ethyl ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 438 mg (97%) of crude product. Purification by Kugelrohr distillation afforded 383 mg (85%) of 124 as a colorless liquid. Vapor-phase chromatographic analysis (3% OV-17, column temperature 165°) showed one single compound: bp 95-98°/0.03 Torr; IR 2920, 1670, 1565 and 1150 cm^{-1}; ^{1}HNMR δ 1.5-2.2

(m, 6H), 2.3-3.5 (m, 9H), 3.57 (s, 3H) and 4.38 (s, 1H); mass spectrum m/e (rel intensity) 225(95), 208(20), 194(100), 182(43), 169(42), 168(73), 166(62), 152(66), 136(35), 124(23), 110(96), 96(37), 94(31), 84(35), 70(32), 55(26) and 41(32).

High Resolution Mass Measurement Calcd for $C_{12}H_{19}NO_3$: 225.1364. Found: 225.1361.

Methyl β-(2-Hydroxymethylcyclopropyl)-β-oxopropanoate (125). - A solution of lithium diisopropyl amide was generated by treating 0.29 ml (2.1 mmole) of anhydrous diisopropylamine in dry tetrahydrofuran (3 ml) with 1.25 ml (2.0 mmole) of n-butyllithium (1.6 M) at 0° for 20 min. This solution was then added dropwise, through a two-way needle with positive nitrogen pressure, into a solution of 172 mg (1 mmole) of methyl 6,7-epoxy-3-oxoheptanoate (109) in dry tetrahydrofuran (2 ml) which was cooled in an ice-bath and kept under a dry nitrogen atmosphere. The resulting suspension was stirred for 0.5 hr at 0° and 1 hr at room temperature. The reaction was quenched with ice-cold 5% hydrochloric acid (5 ml) and the aqueous phase was extracted with 3 x 10 ml of ethyl ether. The combined extracts were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 130 mg of crude material. Preparative thin layer chromatography on silica gel with carbon tetrachloride-ethyl ether (1:2) afforded 53 mg (50%) of 125 as the major component: colorless oil; R_f 0.2; bp (Kugelrohr distillation) $80\text{-}83^{\circ}/0.1$ Torr; IR 3550, 3050, 1740 and 1700 cm^{-1}; ^{1}HNMR δ 0.98 (m, 1H), 1.4 (m, 1H), 1.75 (m, 1H), 2.0 (m, 1H), 2.57 (br s, 1H, enchangeable with D_2O), 3.55 (s, 2H), 3.12-3.90 (m, 2H), and

3.70 (s, 3H); mass spectrum m/e (rel intensity) 172(25), 154(32), 153(17), 141(19), 129(20), 128(14), 116(77), 114(38), 112(21), 101(37), 99(100), 98(32), 97(46), 95(31), 94(27), 81(57), 74(29), 69(26), 59(28), 55(45), 43(40) and 41(37).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.85; H, 6.96.

SECTION II

Preliminary Studies

Methyl 2-Acetoxy-6,6-dimethyl-1-cyclohexenecarboxylate (250).- A mixture of 368 mg (2 mmole) of methyl 2,2-dimethyl-6-oxocyclohexanecarboxylate (97), 1.2 g (12 mmole) of isopropenyl acetate and catalytic amount (8 mg) of p-toluenesulfonic acid monohydrate in dry benzene (5 ml) was heated under reflux for 17 hr. The distillate was continuously removed and replaced by benzene by means of a Dean-Stark apparatus. The final mixture was cooled and concentrated under reduced pressure. The crude residue so obtained was Kugelrohr distilled at 80-85°/1.0 Torr to give 380 mg (84%) of 250 as a colorless liquid: IR 1755, 1720 and 1640 cm^{-1}; ^{1}HNMR δ 1.17 (s, 6H), 1.3-1.97 (m, 4H), 2.05 (s, 3H), 1.97-2.4 (m, 2H) and 3.67 (s, 3H); mass spectrum m/e (rel intensity) 226(7), 195(8), 194(9), 184(31), 169(72), 153(20), 152(12), 138(11), 137(100), 100(10), 96(10), 83(11), 81(10), 69(10), 55(18), 43(24) and 41(13).

High Resolution Mass Measurement Calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1209.

Ethyl and Methyl Esters of 2-Phenylthio-2-cyclohexenecarboxylic Acid and 2-Phenylthio-1-cyclohexenecarboxylic Acid, (255a) and (255b). - A mixture of 1.63 g (ca. 9.9 mmole) of ethyl 2-oxocyclohexanecarboxylate (mixture of 60% ethyl and 40% methyl esters; Aldrich) (254), 1.23 ml (12 mmole) of benzenethiol and 0.1 g of p-toluenesulfonic acid was heated under reflux in 15 ml of dry benzene. Reflux was continued for 20 hr with azeotropic

removal of water by means of a Dean-Stark apparatus. The mixture was then cooled and poured into 30 ml of 10% potassium carbonate solution, and extracted with 2 x 35 ml of ethyl ether. The combined extracts were washed with saturated potassium carbonate (20 ml) and brine (20 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product obtained was distilled (Kugelrohr) at 85-90°/0.2 Torr to yield 2.3 g (ca. 90%) of a mixture (ca. 1:1) of 255a and 255b: IR 3120, 1730 (due to 255a), 1690 (due to 255b), 1580, 1480, 1440, 1280, 1050 and 1020 cm^{-1}; ^{1}HNMR δ 1.3 (t, J = 7 Hz, ~1.8H), 1.4-2.5 (m, ~7H), 3.17 (m, ~0.5H, due to 255a), 3.57 (s, ~0.6H, due to 255a), 3.73 (s, ~0.6H, due to 255b), 4.2 (q, J = 7 Hz, ~1.2H), 6.2 (m, ~0.5H, due to 255b) and 7.0-7.5 (m, 5H); mass spectrum m/e (rel intensity) 264(5), 263(16), 262(100), 250(3), 249(9), 248(57), 218(15), 217(31), 216(25), 215(13), 189(38), 188(47), 187(28), 160(25), 153(40), 147(28), 139(24), 110(24), 109(23), 81(20), 79(71), 77(28), and 47(15).

Methyl 2-Phenylthio-6,6-dimethyl-2-cyclohexenecarboxylate (256a) and Methyl 2-Phenylthio-6,6-dimethyl-1-cyclohexenecarboxylate (256b). - A mixture of 920 mg (5 mmole) of methyl 2,2-dimethyl-6-oxocyclohexanecarboxylate (97), 0.52 ml (5 mmole) of benzenethiol and 50 mg of p-toluenesulfonic acid monohydrate was treated in the same manner as described above, giving rise to 1.358 g of crude material. Preparative thin layer chromatography of 150 mg of the crude product on silica gel with 10:1 petroleum ether-ethyl ether (developed three times) afforded two major components:- (a) 256a (96 mg, 63%): colorless oil; R_f 0.67; IR 1730, 1590, 1480, 1440 and 1160

cm^{-1}; ^{1}HNMR δ 0.9 (s, 3H), 0.95 (s, 3H), 1.2-2.0 (m, 2H), 2.0-2.4 (m, 2H), 2.78 (s, 1H), 3.57 (s, 3H), 6.22 (t, J = 4 Hz, 1H), and 7.2 (br s, 5H); mass spectrum m/e (rel intensity) 276(65), 261(17), 229(19), 217(14), 216(24), 201(37), 167(33), 161(7), 135(11), 123(14), 108(11), 107(100), 105(10), 91(12) and 41(11).

High Resolution Mass Measurement Calcd for $C_{16}H_{20}O_2S$: 276.1184. Found: 276.1185.

(b) 256b (25 mg, 16%): colorless oil; R_f 0.78; IR 1720, 1590, 1480, 1440, 1270 and 1060 cm^{-1}; ^{1}HNMR δ 1.18 (s, 6H), 1.3-1.9 (m, 4H), 2.1 (m, 2H), 3.73 (s, 3H) and 7.2 (m, 5H); mass spectrum m/e (rel intensity) 276(85), 261(84), 245(14), 229(100), 217(15), 201(14), 167(13) and 107(25).

High Resolution Mass Measurement Calcd for $C_{16}H_{20}O_2S$: 276.1184. Found: 276.1187.

Ethyl and Methyl esters of 2-Methyl-cyclohexenecarboxylic Acid (257). - A solution of lithium dimethylcuprate was generated by adding 2.26 ml (4 mmole) of methyllithium (1.77 M) to a suspension of 381 mg (2 mmole) of cuprous iodide in dry ethyl ether (5 ml) at 0°. To this solution, kept under dry nitrogen atmosphere, was added 155 mg (0.6 mmole) of a mixture of 255a and 255b (ca. 0.3 mmole of the conjugated isomer 255b). The resulting yellow suspension was stirred for 1 hr at 0° and 5 hr at room temperature. The reaction was quenched with 10% ammonium chloride (10 ml) and concentrated ammonium hydroxide (0.5 ml), and the aqueous phase was extracted with 20 ml of ethyl ether. The ether solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 105 mg of

crude product. Kugelrohr distillation yielded two different boiling fractions: - (a) 37 mg (76% based on 0.3 mmole of 255b) of 257: colorless liquid; bp 65-70°/0.2 Torr; IR 1700 and 1640 cm^{-1}; ^{1}HNMR δ 1.25 (t, J = 7 Hz, ~1.8H), 1.4-1.8 (m, 4H), 1.95 (br s, 3H), 1.8-2.4 (m, 4H), 3.68 (s, ~1.2H) and 4.1 (q, J = 7 Hz, ~1.2H); mass spectrum m/e (rel intensity) 168(90), 154(17), 140(23), 139(44), 123(88), 122(50), 95(100), 94(30), 93(37), 79(38), 77(20), 67(31), 55(19), 53(15) and 41(25).

(b) 56 mg of recovered 255a: bp 85-90°/0.2 Torr.

Methyl 2,2-Dimethyl-6,6-dimethylthio-cyclohexanecarboxylate (258). Approximately 3 ml of methanethiol was condensed into a septumed flask containing 544 mg (4 mmole) of anhydrous zinc chloride and 320 mg (1.7 mmole) of methyl 2,2-dimethy-6-oxocyclohexanecarboxylate (97), cooled at -20°. The resulting solution was stirred for 2 hr at -20° and 10 hr at room temperature. The reaction mixture was then poured into saturated sodium carbonate solution (20 ml) and extracted with 3 x 20 ml of ethyl ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 456 mg of crude product. Preparative tlc on silica gel with carbon tetrachloride-ethyl ether (15:1) afforded 85 mg (84% yield) of 258 from 101 mg of the crude product: colorless oil; bp (Kugelrohr distillation) 95-97°/0.05 Torr; IR 1730, 1435 and 1140 cm^{-1}; ^{1}HNMR δ 0.98 (s, 3H), 1.22 (s, 3H), 1.3-2.0 (m, 6H), 1.98 (s, 3H), 2.06 (s, 3H), 2.65 (s, 1H) and 3.64 (s, 3H); mass spectrum m/e (rel intensity) 262(3), 216 (11), 215(79), 214(11), 197(7), 183(29), 156(17), 155(100), 154(13), 139(16),

135(15), 107(34), 91(8), 69(14) and 41(8).

Anal. Calcd for $C_{12}H_{22}O_2S_2$: C, 54.92; H, 8.45. Found: C, 55.20; H, 8.40.

Methyl 6,6-Dimethyl-2-methylthio-2-cyclohexenecarboxylate (259a). - A mixture of 79 mg (ca. 0.3 mmole) of crude 258, 50 mg of mercuric chloride and 0.1 ml of anhydrous triethylamine was heated under reflux in xylene (3 ml) for 5 hr. The reaction mixture was then diluted with water (10 ml) and ethyl ether (20 ml). The organic solution was separated, washed with brine, and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure gave 67 mg of crude residue, which upon chromatography on silica gel with carbon tetrachloride-ethyl ether (15:1) afforded 47 mg (73% from 97) of 259a as a colorless liquid: R_f 0.5; IR 1730, 1640 and 1160 cm^{-1}; ^{1}HNMR δ 0.97 (s, 6H), 1.2-1.6 (m, 2H), 1.8-2.4 (m, 2H), 2.2 (s, 3H), 2.78 (br s, 1H), 3.65 (s, 3H) and 5.6 (t, J = 4 Hz, 1H); mass spectrum m/e (rel intensity) 214(39), 199(15), 167(20), 155(23), 154(81), 140(17), 139 (100), 127(13), 125(17), 107(34), 91(18) and 41(19).

High Resolution Mass Measurement Calcd for $C_{11}H_{18}O_2S$: 214.1027. Found: 214.1026.

Reaction of Ethyl (Methyl) 2-Oxocyclohexanecarboxylate (254) with Oxalyl Chloride. - To a solution of 254 (329 mg, ca.2 mmole) in dry chloroform (3 ml) was added 0.44 ml (5 mmole) of oxalyl chloride. The resulting solution was heated under reflux for 4.5 hr. Evaporation of solvent and volatile materials in vacuo, followed by distillation (Kugelrohr) gave 350 mg (70%) of 264 as a colorless oil: bp 85-89°/0.4 Torr (lit.[152]

bp 130°/1.5 Torr); IR 1790, 1745, 1720 and 1450 cm^{-1}; ^{1}HNMR δ 1.3 (t, J = 7 Hz, ~1.8H), 1.45-2.17 (m, 4H), 2.2-2.77 (m, 4H), 3.82 (s, ~1.2H) and 4.28 (q, J = 7 Hz, ~1.2H); mass spectrum m/e (rel intensity) 234(3), 232(9), 220(2), 218(6), 197(23), 187(27), 169(52), 151(49), 150(41), 141(43), 140(59), 127(81), 126(48), 124(56), 123(100), 113(90), 99(62), 95(43), 68(48), 67(32), 55(80), 44(72) and 41(57).

Preparation of Enol Phosphates of β-Keto Esters and their Reactions with Lithium Dialkylcuprates

General Procedure for the Preparation of the Z-Enol Phosphate of β-Keto Esters. - To a stirred suspension of sodium hydride (1.1 eq) in dry ethyl ether, kept under a dry nitrogen atmosphere and cooled in an ice-both, was added a solution of the β-keto ester (1.0 eq) in ethyl ether. After 15-20 min at 0° (or 10 min at room temperature), 1.1 eq of diethyl chlorophosphate was introduced and stirring was continued for 1-2 hr at 0° (or room temperature). (Progress of the reaction could be easily monitored by tlc. Although the β-keto ester enolate was usually found reacted within 30 min at 0°, the reaction was allowed to proceed for a longer period of time to ensure completeness of the transformation.) The enol phosphate was isolated from the reaction mixture by either of the following work-up procedures:

(a) (for less than 5mmole scale preparations) the reaction mixture was stirred with excess solid ammonium chloride for 20 min, filtered through celite, and the filtrate was concentrated in vacuo; or,

(b) (for larger than 5 mmole scale preparations) the reaction mixture was quenched with aqueous ammonium chloride and diluted with ethyl ether. The ether solution was then washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and evaporated under reduced pressure.

The crude enol phosphate so obtained, invariably in quantitative yield, was essentially pure by spectroscopic and chromatographic analyses, and was used directly in reactions with lithium dialkylcurpates.

Methyl 2-(Diethylphosporyloxy)cyclohexenecarboxylate (267): - IR 1715, 1660, 1290 and 1030 cm^{-1}; ^{1}HNMR δ 1.35 (t, J = 7 Hz, 6H), 1.6 (m, 4H), 2.3 (m, 4H), 3.68 (s, 3H) and 4.15 (qn, J = 7 Hz, 4H); mass spectrum m/e (rel intensity) 292(10), 260(67), 232(35), 204(100), 176(13), 55(14) and 41(11).

High Resolution Mass Measurement Calcd for $C_{12}H_{21}O_6P$: 292.1076. Found: 292.1087.

Methyl 2-(Diethylphosphoryloxy)-6,6-dimethylcyclohexenecarboxylate (271): IR 1725, 1680, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.15 (s, 6H), 1.2-1.9 (m, 4H), 1.32 (t, J = 7 Hz, 6H), 2.4 (m, 2H), 3.70 (s, 3H) and 4.10 (qn, J = 7 Hz, 4H); mass spectrum m/e (rel intensity) 320(7), 288 (100), 273(28), 260(25), 245(17), 232(24), 217(28), 137(10), 128(8) and 99(10).

High Resolution Mass Measurement Calcd for $C_{14}H_{25}O_6P$: 320.1389. Found: 320.1403.

Methyl 2-(Diethylphosphoryloxy)cyclopentenecarboxylate (272):- IR 1710, 1660, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.38 (t, J = 7 Hz, 6H), 1.95 (m, 2H), 2.3-3.0 (m, 4H), 3.67 (s, 3H) and 4.20 (qn, J = 7 Hz, 4H); mass spectrum m/e (rel intensity) 278(12), 246(60), 218(38), 190(100), 162(7), 141(7), 129(10), 113(14), 109(11), 101(17), 99(11), 81(8) and 55(15).

High Resolution Mass Measurement Calcd for $C_{11}H_{19}O_6P$: 278.0919. Found: 278.0918.

Methyl 2-(Diethylphosphoryloxy)cycloheptenecarboxylate (273):- IR 1718, 1660 (shoulder), 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.34 (t, J = 7 Hz, 6H), 1.7 (m, 6H), 2.2-2.8 (m, 4H), 3.71 (s, 3H), and 4.13 (qn, J = 7 Hz, 4H); mass spectrum m/e (rel intensity) 306(9), 274(100), 245(42), 218(50), 190(20), 155(21), 127(22), 113(9), 99(33), 55(15) and 41(13).

High Resolution Mass Measurement Calcd for $C_{13}H_{23}O_6P$: 306.1232. Found: 306.1242.

Methyl Z-3-(Diethylphosphoryloxy)but-2-enoate (280): - Vpc (3% OV-17 column, 140-150°) and ^{1}HNMR analyses showed pure Z-enol phosphate 280, with no detectable E isomer in the crude product. IR 1725, 1675, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.38 (t, J = 7 Hz, 6H), 2.17 (d, J = 1.4 Hz, 3H), 3.67 (s, 3H), 4.23 (qn, J = 7 Hz, 4H) and 5.27 (br s, 1H); mass spectrum m/e (rel intensity) 252(34), 220(70), 207(21), 192(53), 179(25), 164(70), 155(67), 127(64), 113(26), 109(26), 99(100), 67(30) and 43(36).

High Resolution Mass Measurement Calcd for $C_9H_{17}O_6P$: 252.0763. Found: 252.0739.

Methyl Z-3-(Diethylphosphoryloxy)hex-2-enoate (281): IR 1725, 1670, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 0.95 (t, J = 7 Hz, 3H), 1.35 (t, J = 7 Hz, 6H), 1.6 (m, 2H), 2.37 (m, 2H), 3.65 (s, 3H), 4.21 (qn, J = 7 Hz, 4H) and 5.28 (s, 1H); mass spectrum m/e (rel intensity) 280(20), 248(23), 220(23), 155(100), 127(5), 113(24), 101(38) and 99(51).

High Resolution Mass Measurement Calcd for $C_{11}H_{21}O_6P$: 280.1075. Found: 280.1075.

Methyl Z-3-(Diethylphosphoryloxy)-6-(2-tetrahydropyranyloxy)hex-2-enoate (282): IR 1725, 1670, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.36 (t, J = 7 Hz, 6H), 1.2-2.2 (m, 8H), 2.53 (br t, J = 7 Hz, 2H), 3.2-4.0 (m, 4H), 3.65 (s, 3H), 4.22 (qn, J = 7 Hz, 4H), 4.50 (m, 1H) and 5.33 (s, 1H); mass spectrum m/e (rel intensity) 380(0.1), 349(2), 296(5), 279(6), 251(8), 219(10), 155(100), 142(42), 127(18), 111(25), 99(20) and 85(17).

High Resolution Mass Measurement Calcd for $C_{15}H_{26}O_7P$ (P^+-OCH_3): 349.1416. Found: 349.1443.

Methyl (2Z, 6E)-3-(Diethylphosphoryloxy)-7,11-dimethyldodeca-2,6,10-trienoate (283): IR 1725, 1670, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.35 (t, J = 7 Hz, 6H), 1.60 (s, 6H), 1.67 (s, 3H), 1.7-2.3 (m, 6H), 2.4 (m, 2H), 3.65 (s, 3H), 4.23 (qn, J = 7 Hz, 4H), 5.0 (m, 2H) and 5.30 (s, 1H); mass spectrum m/e (rel intensity) 388(12), 357(5), 343(3), 319(4), 287(18), 252(25), 234(20), 220(28), 202(13), 192(14), 155(100), 127(50) and 99(63).

High Resolution Mass Measurement Calcd for $C_{19}H_{33}O_6P$: 388.2015. Found: 388.2024.

Ethyl Z-3-(Diethylphosphoryloxy)-2-methylbut-2-enoate (284): - ^{1}HNMR and vpc (3% OV-17 column, 160°) analyses indicated pure Z-enol phosphate 284, with no detectable E isomer in the crude product. IR 1720, 1660 (shoulder), 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.1-1.5 (m, 9H), 1.83 (m, 3H), 2.10 (m, 3H) and 3.85-4.4 (m, 6H); mass spectrum m/e (rel intensity) 280 (30), 234(75), 206(40), 178(50), 155(75), 150(25), 127(70), 109(15), 99 (100), 81(35), 70(20), 53(25), and 43(45).

High Resolution Mass Measurement Calcd for $C_{11}H_{21}O_6P$: 280.1076. Found: 280.1076.

Methyl 2-Oxocyclohexanecarboxylate (266).[156] - Into a 500 ml three-neck round bottomed flask was charged 22.5 g (0.47 mole) of sodium hydride (50% oil) and 120 ml of dry tetrahydrofuran. The flask was equipped with a reflux condenser and a pressure-equalized addition funnel, and the whole system was kept under a dry nitrogen atmosphere. Dimethyl carbonate (33.8 g, 0.38 mole) was then introduced and the mixture was heated to reflux with constant stirring. A solution of 14.7 g (0.15 mole) of cyclohexanone in dry tetrahydrofuran (40 ml) was added dropwise through the addition funnel and ca. 150 mg of potassium hydride (22.4% in oil) was introduced to initiate the reaction. After complete addition of cyclohexanone (over approximately 1 hr), the mixture was maintained refluxing for another 0.5 hr. Finally, the mixture was cooled in ice and quenched with 10% hydrochloric acid (100 ml) and brine (100 ml). The aqueous phase was extracted with 2 x 200 ml of chloroform and the combined organic solution was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. Vacuum distillation of the crude product gave 21.06 g (90%) of 266 as a colorless liquid: bp 39-40°/0.3 Torr (lit.[156] bp 68°/0.8 Torr); IR 1740 and 1715 cm^{-1} (due to the keto form), and 1655 and 1615 cm^{-1} (due to the enol form); ^{1}HNMR δ 1.4-2.5 (m, 8H), 3.3 (m, ~0.2H, due to the keto form), 3.70 (s, 3H) and 12.0 (s, ~0.8H, due to the enol form); mass spectrum m/e (rel intensity) 156(54), 128(24), 125(36), 124(100), 123(14), 100(22), 96(16), 87(14), 69(17), 68(55), 55(46) and 41(30).

Methyl 2-Oxocyclopentanecarboxylate (269).[156] - The above procedure was followed using 4.2 g (50 mmole) of cyclopentanone, 7.5 g (157 mmole) of sodium hydride (50% oil) and 10.5 ml (125 mmole) of dimethyl carbonate. Distillation of the crude product afforded 3.51 g (49%) of 269 as a colorless liquid: bp 80°/4.0 Torr; IR 1755, 1730, 1660 and 1620 cm^{-1}; ^{1}HNMR δ 1.7-2.6 (m, 6H), 3.13 (br t, J = 8 Hz, 1H) and 3.70 (s, 3H); mass spectrum m/e (rel intensity) 142(50), 114(76), 111(64), 110(70), 87(88), 83(22), 82(23), 69(10), 68(15), 59(14), 55(100) and 41(17).

Methyl 2-Oxocycloheptanecarboxylate (270). - The procedure used for the preparation of 266 was followed, starting from 7.5 g (157 mmole) of sodium hydride, 10.5 ml (125 mmole) of dimethylcarbonate and 5.6 g (50 mmole) of cycloheptanone. (The cycloheptanone in 20 ml of dry tetrahydrofuran was added over 2 hr and reflux was continued for another 4 hr before work-up.) The crude product was distilled to yield 7.59 g (89%) of 270 as a colorless liquid: bp 58°/0.1 Torr; IR 1740, 1705, 1640 and 1615 cm^{-1}; ^{1}HNMR δ 1.1-2.7 (m, 10H), 3.50 (m, ~0.8H, due to the keto form), 3.70 (two overlapping singlets, 3H) and 12.6 (s, ~0.2H, due to the enol

form); mass spectrum m/e (rel intensity) 170(53), 142(48), 139(40), 138(91), 127(12), 113(36), 110(56), 97(14), 87(37), 82(43), 74(32), 68(22), 67(21), 55(100) and 41(52).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.28; H, 8.37.

General Procedures for the Generation of Lithium Dialkylcuprate Reagents:-

Lithium Dimethylcuprate: Two equivalents of methyllithium (in ethyl ether) was added dropwise to a stirred suspension of 1 eq of cuprous iodide (purified according to Kauffman's procedure[202]) in dry ethyl ether at 0° and under a dry nitrogen atmosphere. The resulting light tan solution was used for coupling reaction at the appropriate temperature.

Lithium Diethylcuprate: Two equivalents of ethyllithium (in benzene) was added dropwise to a stirred suspension of cuprous iodide (1 eq) in anhydrous ethyl ether at -78° under nitrogen. The resulting black mixture was stirred for 20 min at -78° before use.

Lithium Di-n-butylcuprate: Two equivalents of n-butyllithium (in hexane) was added dropwise to a stirred suspension of cuprous iodide (1 eq) in dry ethyl ether at -47° under nitrogen. The resulting dark brown solution was maintained at -47° for 15 min before use.

Lithium Di-sec-butylcuprate: A solution of sec-butyllithium (2 eq) in cyclohexane was added slowly to a stirred suspension of cuprous iodide (1 eq) in anhydrous ethyl ether at -23° under nitrogen. The resulting dark black mixture was stirred at -23° for 15 min before use.

Lithium Di-t-butylcuprate: A solution of t-butyllithium (2 eq) in pentane was added dropwise to a stirred suspension of cuprous iodide (1 eq) in dry ethyl ether at -47° under nitrogen. The resulting black mixture was stirred at -47° for 20 min before use.

General Work-up Procedure for the Reactions of Enol Phosphates with Lithium Dialkylcuprates: The reaction mixture was poured into an ice-cold mixture of 50% aqueous ammonium chloride and concentrated ammonium hydroxide (ca. 5:1), and the aqueous phase was extracted with ethyl ether. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure.

Methyl 2-Methylcyclohexenecarboxylate (268). - A solution of enol phosphate 267 prepared in situ from 312 mg (2 mmole) of methyl 2-oxo-cyclohexanecarboxylate, 106 mg (2.2 mmole) of sodium hydride (50%) and 0.32 ml (2.2 mmole) of diethylchlorophosphate in 7 ml of ethyl ether (see general procedure) was added slowly into an ether solution of lithium dimethylcuprate (3 mmole) with cooling in an ice-bath. A deep purple color developed within seconds, and stirring was continued for 2 hr at 0°, and for another 2 hr with the ice-bath removed. The mixture was worked up according to the general

procedure to give 317 mg of crude material. Preparative tlc (silica gel, 50:3 carbon tetrachloride-ethyl ether of 110 mg of the crude product afforded 100 mg (94%) of 268: colorless liquid; bp (Kugelrohr distillation) 85-88°/20 Torr; IR 1705, 1640 and 1080 cm^{-1}; ^{1}HNMR δ 1.3-1.7 (m, 4H), 1.97 (br s, 3H), 1.8-2.4 (m, 4H) and 3.69 (s, 3H); mass spectrum m/e (rel intensity) 154(75), 139(10), 123(34), 122(32), 90(100), 89(33), 79(22) and 67(16).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.96; H, 9.31.

Methyl 2,6,6-Trimethylcyclohexenecarboxylate (248).- A solution of 9.3 g (30 mmole) of the enol phosphate 271 in dry ethyl ether (5 ml) was added to a stirred solution of lithium dimethylcuprate (60 mmole) in ethyl ether (150 ml) at 0°. The resulting dark purple mixture was maintained at 0° for 5 hr and then worked up according to the general procedure. The crude product (5.95 g) was distilled (Kugelrohr) to give 5.03 g (92%) of 248 as a colorless liquid: bp 81-83°/3.5 Torr; IR 1710, 1660 (weak) and 1070 cm^{-1}; ^{1}HNMR δ 1.08 (s, 6H), 1.2-2.1 (m, 6H), 1.64 (s, 3H) and 3.69 (s, 3H); mass spectrum m/e (rel intensity) 182(36), 167(80), 151(25), 135 (100), 123(67), 107(48), 81(9), 79(10) and 77(8).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.20; H, 9.87.

Methyl 2-Methylcyclopentenecarboxylate (274). - A solution of the enol phosphate 272 (1 mmole) in ethyl ether (5 ml) was prepared from

142 mg (1 mmole) of methyl 2-oxocyclopentanecarboxylate, 53 mg (1.1 mmole) of sodium hydride (50%) and 0.16 ml (1.1 mmole) of diethyl chlorophosphate according to the general procedure (2 hr, room temperature). This mixture was added directly into a solution of lithium dimethylcuprate (3 mmole) in ethyl ether (10 ml) at 0°. The resulting purple suspension was stirred at 0° for 2 hr and then at room temperature for about 1.5 hr. The crude product (169 mg) obtained after the usual work-up was chromatographed on silica gel with carbon tetrachloride-ethyl ether (50:3) to yield 119 mg (85%) of 274: colorless liquid; bp (Kugelrohr distillation) 81-83°/20 Torr; IR 1700, 1645, 1120 and 1060 cm^{-1}; ^{1}HNMR δ 1.4-2.2 (m, 2H), 2.10 (br s, 3H), 2.2-2.8 (m, 4H) and 3.69 (s, 3H); mass spectrum m/e (rel intensity) 140(95), 125 (30), 109(100) and 81(95).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.90.

Methyl 2-Methylcycloheptenecarboxylate (275). - A solution of the enol phosphate 273 (2 mmole) in ethyl ether was prepared from 340 mg (2 mmole) of methyl 2-oxocycloheptanoate, 106 mg (2.2 mmole) of sodium hydride and 0.32 ml (2.2 mmole) of diethyl chlorophosphate according to the general procedure (2 hr, room temperature). This mixture was added directly into an ether solution of lithium dimethylcuprate (4 mmole) at 0° and the resulting purple suspension was stirred for 2 hr at the same temperature. The cooling bath was then removed and stirring was continued for 2 hr. The reaction mixture was worked up as usual to give 366 mg of crude material. Preparative tlc (silica gel, 50:3 carbon tetrachloride-ethyl ether) of 184 mg of the crude product afforded 165 mg (98%) of 275 as a colorless liquid: bp (Kugelrohr

distillation) 78-80°/6 Torr; IR 1705, 1635, 1110 and 1040 cm^{-1}; ^{1}HNMR δ 1.2-1.9 (m, 6H), 1.99 (s, 3H), 2.0-2.6 (m, 4H) and 3.68 (s, 3H); mass spectrum m/e (rel intensity) 168(100), 153(15), 137(39), 136(36), 125(18), 109(72), 108(47), 93(41), 81(25), 79(22), 67(38), 55(18) and 41(25).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.55.

Methyl 3-Methylbut-2-enoate (285).[201] - To a solution of lithium dimethylcuprate (2 mmole) in ethyl ether, cooled at -23°, was added 252 mg (1 mmole) of the enol phosphate 280. The resulting purple mixture was stirred at -23° for 45 min and then worked up in the usual manner. The crude product (113 mg) isolated was Kugelrohr distilled at 79-82°/20 Torr, to give 97 mg (83%) of 285: IR 1715, 1655 and 1150 cm^{-1}; ^{1}HNMR δ 1.88 (s, 3H), 2.15 (s, 3H), 3.65 (s, 3H) and 5.63 (br s, 1H); mass spectrum m/e (rel intensity) 114(47), 83(100) and 55(45).

Methyl E-3-Methylhex-2-enoate (286). - An ether solution of lithium dimethylcuprate (2 mmole) was cooled to -78°, and to this was added 280 mg (1 mmole) of the enol phosphate 281. After 10 min at -78°, the temperature was raised to -47° and stirring was continued for 1.5 hr. The mixture was worked up in the usual manner to give 145 mg of crude product, which upon preparative tlc on silica gel with carbon tetrachloride-ethyl ether (50:3) furnished 118 mg (83%) of 286 containing pure E isomer by vpc (3% OV-17 column, 60°) and ^{1}HNMR analyses: colorless liquid; bp (Kugelrohr distillation) 89-91°/20 Torr; IR 1715, 1650 and 1155 cm^{-1}; ^{1}HNMR δ 0.88 (t, J = 7 Hz, 3H), 1.2-1.7 (m, 2H), 2.0 (m, 2H), 2.13 (d, J = 2 Hz, 3H), 3.63 (s, 3H)

and 5.60 (m, 1H); mass spectrum m/e (rel intensity) 142(45), 127(45), 126(40), 125(40), 111(99), 83(100), 69(35), 57(48), 55(55), 43(45) and 41(55).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.28; H, 10.12.

Methyl E-3-Methyl-6-(2-tetrahydropyranyloxy)hex-2-enoate (287). - To a solution of lithium dimethylcuprate (8.4 mmole) in ethyl ether, cooled at -47°, was added 1.6 g (4.2 mmole) of the enol phosphate 282 (dissolved in 2 ml of ether). The resulting reddish purple mixture was stirred at -47° for 2 hr and then worked up according to the general procedure. The crude product (1.02 g, ca. 100% yield) obtained was 97% pure in 287 by vpc analysis (3% OV-17 column, 150°). Preparative tlc (silica gel, 8:1 carbon tetrachloride-ethyl ether) of 90 mg of the crude product yielded 74 mg (82%) of 287 (pure by vpc and ^{1}HNMR analyses): colorless liquid; bp (Kugelrohr distillation) 110-112°/0.1 Torr; IR 1715, 1650, 1155 and 1030 cm^{-1}; ^{1}HNMR δ 1.2-2.4 (m, 10H), 2.13 (br s, 3H), 3.0-4.0 (m, 4H), 3.63 (s, 3H), 4.50 (m, 1H) and 5.63 (m, 1H); mass spectrum m/e (rel intensity) 242(0.1), 158(20), 141(8), 127(9), 112(6), 109(8), 85(100), 81(10) and 41(10).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.12. Found: C, 64.23; H, 9.24.

Methyl (2E, 6E)-3,7,11-Trimethyldodeca-2,6,10-trienoate (288). - To an ether (30 ml) solution of lithium dimethylcuprate (10 mmole), cooled at -78°, was added 1.94 g (5 mmole) of the enol phosphate 283 in 2 ml of

ethyl ether. The resulting orange-yellow suspension was stirred at -78° for 2 hr (mixture turned reddish brown at this stage) and then at -47° for 1 hr (mixture turned dark purple). The reaction mixture was worked up in the usual manner to give 1.23 g of crude product. Vpc analysis (3% OV-17 column, 160°) indicated a 93% purity of the desired (E, E)-isomer. Preparative tlc (silica gel, 50:3 carbon tetrachloride-ethyl ether) of 108 mg of the crude material afforded 96 mg (87%) of 288: bp (Kugelrohr distillation) 96-98°/0.02 Torr; IR 1715, 1650 and 1155 cm^{-1}; ^{1}HNMR δ 1.60 (s, 6H), 1.67 (s, 3H), 1.8-2.3 (m, 8H), 2.15 (d, J = 1.5 Hz, 3H), 3.65 (s, 3H), 5.0 (m, 2H), and 5.62 (br s, 1H); mass spectrum m/e (rel intensity) 250(35), 219(17), 207(20), 137(30), 136(32), 114(54), 81(43), 69(100) and 41(53).

High Resolution Mass Measurement Calcd for $C_{16}H_{26}O_2$: 250.1933. Found: 250.1929.

Ethyl 2,3-Dimethylbut-2-enoate (289). - To a solution of lithium dimethylcuprate (0.75 mmole) in ethyl ether (5 ml) was added 140 mg of the enol phosphate 284 at 0°. The resulting purple mixture was stirred for 1 hr at the same temperature and then worked up in the usual manner. The crude product (73 mg) was distilled (Kugelrohr) to give 60 mg (85%) of 289 as a colorless liquid: bp 86-88°/20 Torr; IR 1705, 1645 and 1105 cm^{-1}; ^{1}HNMR δ 1.27 (t, J = 7 Hz, 3H), 1.8 (br s, 6H), 1.97 (s, 3H), and 4.14 (q, J = 7 Hz, 2H); mass spectrum m/e (rel intensity) 142(100), 127(10), 114(20), 99(46), 97(88), 96(69), 69(57) and 41(65).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.46; H, 9.85.

"One-pot" Synthesis of Methyl E-3-Methylnon-2-enoate (291).- The dianion of methyl acetoacetate (116 mg, 1 mmole) in dry tetrahydrofuran (3 ml) was generated according to the general procedure and treated with 166 mg (1.1 mmole) of 1-bromopentane. The mixture was stirred at 0° for 10 min, warmed to room temperature for 25 min and then cooled to 0° again. Diethyl chlorophosphate (0.16 ml, 1.1 mmole) was introduced and the resulting mixture was warmed to room temperature and stirred for 2 hr. This enol phosphate mixture was cooled to -47° and then added, through a two-way needle, into an ether (10 ml) solution of lithium dimethylcuprate (3 mmole) maintained at the same temperature. Stirring was continued for 3.5 hr at -47° and the mixture was worked up in the usual manner. The crude product (177 mg) obtained was chromatographed on silica gel with carbon tetrachloride-ethyl ether (50:3) to yield 125 mg (68%) of 291 as a colorless liquid: bp (Kugelrohr) 108-110°/20 Torr; IR 1710, 1650 and 1155 cm^{-1}; ^{1}HNMR δ 0.87 (br t, J = 6 Hz, 3H), 1.1 - 1.8 (m, 8H), 1.8-2.3 (m, 2H), 2.13 (d, J = 1.8 Hz, 3H), 3.64 (s, 3H) and 5.60 (m, 1H); mass spectrum m/e (rel intensity) 184(16), 153(25), 127 (40), 114(100), 110(30), 83(20), 82(20), 55(18) and 41(17).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.59; H, 10.75.

Methyl 3-Methylpent-2-enoate (Z- and E-292).[203] - To a solution of lithium diethylcuprate (2 mmole) in ethyl ether (10 ml), cooled at -98°, was added 252 mg (1 mmole) of the enol phosphate 280. The resulting mixture, which developed a dark purple color within a few minutes, was stirred for 2 hr at -98°. The crude product (151 mg) obtained after the usual work-up procedure was Kugelrohr distilled at 75-78°/20 Torr to give 115 mg (90%) of

292 as a mixture of geometric isomers. Vpc (3% OV-17 column, 60°) and ^{1}HNMR analyses showed a 5:1 ratio of Z-292 and E-292 in the product (a 1:1 ratio was observed when the above reaction was carried out at -78°): IR 1715, 1655 and 1155 cm^{-1}; ^{1}HNMR δ 1.06 (t, J = 7 Hz, 3H, E + Z), 1.83 (d, J = 1.8 Hz, Z), 2.13 (d, J = 1.8 Hz, E), 1.9-2.3 (m, E), 2.61 (q, J = 7 Hz, Z), 3.63 (s, 3H, E + Z) and 5.58 (m, 1H, E + Z); mass spectrum m/e (rel intensity) 128(80), 97(100), 74(35), 43(32) and 41(55).

Methyl 2-Ethylcyclopentenecarboxylate (293). - To a solution of lithium diethylcuprate (3 mmole) in ethyl ether (15 ml) was added 278 mg (1 mmole) of the enol phosphate 272 at -98°. After stirring for 2 hr at the same temperature, 0.48 ml (6 mmole) of ethyl iodide was introduced. The cooling bath was removed and the mixture was stirred for another 15 min and then worked up in the usual manner. The crude product (156 mg) obtained was chromatographed on silica gel with carbon tetrachloride-ethyl ether (50:3) to give 108 mg (70%) of 293 as a colorless liquid: bp (Kugelrohr distillation) 108-110°/20 Torr; IR 1700, 1640 and 1120 cm^{-1}; ^{1}HNMR δ 1.01 (t, J = 7 Hz, 3H), 1.4-2.1 (m, 2H), 2.2-2.8 (m, 6H) and 3.68 (s, 3H); mass spectrum m/e (rel intensity) 154(100), 139(18), 123(92), 122(74), 95(88), 91(33), 79(33), 67(38), 55(25), 43(21) and 41(33).

High Resolution Mass Measurement Calcd for $C_9H_{14}O_2$: 154.0994. Found: 154.1000.

Methyl 2-Ethylcyclohexenecarboxylate (294). - The enol phosphate 267 (292 mg, 1 mmole) was treated with lithium diethylcuprate (2 mmole) in the same manner as described above. Preparative tlc (silica gel, 50:3 carbon

tetrachloride-ethyl ether) of the crude product (154 mg) afforded 132 mg (79%) of 294: colorless liquid; bp (Kugelrohr distillation) 89-91°/15 Torr; IR 1705, 1640 and 1080 cm^{-1}; ^{1}HNMR δ 1.03 (t, J = 7 Hz, 3H), 1.4-1.8 (m, 4H), 1.9-2.5 (m, 6H) and 3.68 (s, 3H); mass spectrum m/e (rel intensity) 168(100), 137(58), 136(84), 109(75), 79(46), 67(50), 55(22) and 41(30).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.80.

Methyl 2-Ethylcycloheptenecarboxylate (295).- The enol phosphate 273 (306 mg, 1 mmole) was treated with lithium diethylcuprate (2 mmole) in ethyl ether for 2 hr at -98° and then worked up in the usual fashion. The crude product (172 mg) was chromatographed on silica gel with 50:3 carbon tetrachloride-ethyl ether to yield 151 mg (82%) of 295 as a colorless liquid: bp (Kugelrohr) 111-113°/15 Torr; IR 1705, 1635 and 1110 cm^{-1}; ^{1}HNMR δ 1.04 (t, J = 7 Hz, 3H), 1.2-2.0 (m, 6H), 2.0-2.6 (m, 6H) and 3.68 (s, 3H); mass spectrum m/e (rel intensity) 182(100), 151(52), 150(88), 123(55), 122(43), 121(27), 108(27), 107(34), 93(80), 81(85), 79(41), 67(40), 55(38) and 41(46).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.70; H, 10.14.

Ethyl Z-2,3-Dimethylhept-2-enoate (Z-298). - To a solution of lithium di-n-butylcuprate (1 mmole) in ethyl ether (5 ml), cooled at -98°, was added 140 mg (0.5 mmole) of enol phosphate 284. The resulting dark purple mixture was stirred at -98° for 2.5 hr, followed by addition of 0.27 ml (2.5 mmole) of n-butyl bromide. The cooling bath was removed and stirring was continued for 20 min prior to the general work-up procedure. The crude

product (97 mg) obtained was chromatographed on silica gel with 50:3 carbon tetrachloride-ethyl ether to yield 66 mg (72%) of Z-298: colorless liquid; R_f 0.71; bp (Kugelrohr distillation) 95-97°/20 Torr; IR 1705, 1640 and 1105 cm^{-1}; ^{1}HNMR δ 0.90 (distorted t, 3H), 1.28 (t, J = 7 Hz, 3H), 1.0-1.6 (m, 4H), 1.77 (s, 3H), 1.83 (br s, 3H), 2.32 (br t, J = 6 Hz, 2H) and 4.13 (q, J = 7 Hz, 2H); mass spectrum m/e (rel intensity) 184(63), 169(17), 155(18), 139(100), 127(47), 109(80), 102(30), 69(48), 43(30) and 41(48).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.42; H, 10.98.

A small quantity (3.5 mg, 2%) of E-298 was also isolated from the tlc: R_f 0.63; IR 1700, 1640 and 1105 cm^{-1}; ^{1}HNMR δ 0.90 (distorted t, 3H), 1.28 (t, J = 7 Hz, 3H), 1.2-1.6 (m, 4H), 1.83 (br s, 3H), 1.98 (m, 3H), 2.1 (m, 2H), and 4.19 (q, J = 7 Hz, 2H); mass spectrum m/e (rel intensity) 184(17), 169(5), 155(5), 139(100), 127(10), 109(20), 102(9), 69(41), 55(22), 43(11) and 41(23).

High Resolution Mass Measurement Calcd for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1460.

Methyl 2-n-Butylcyclopentenecarboxylate (299). - The above procedure was followed using 278 mg (1 mmole) of enol phosphate 272, 2 mmole of lithium di-n-butylcuprate and 0.54 ml (5 mmole) of n-butyl bromide. Preparative tlc (silical gel, 10:1 carbon tetrachloride-ethyl ether) of the crude product (179 mg) gave 148 mg (81%) of 299 as a colorless liquid: bp (Kugelrohr distillation) 67-69°/0.9 Torr; IR 1700, 1640 and 1120 cm^{-1}; ^{1}HNMR δ 0.9 (distorted t, 3H), 1.0-2.1 (m, 6H), 2.2-2.8 (m, 6H) and 3.67

(s, 3H); mass spectrum m/e (rel intensity) 182(86), 153(100), 151(58), 140(50), 121(55), 93(40), 81(42), 79(30), 67(25) and 41(25).

High Resolution Mass Measurement Calcd for $C_{11}H_{18}O_2$: 182.1307. Found: 182.1278.

Methyl 2-n-Butylcyclohexenecarboxylate (300). - The procedure described in the preparation of Z-298 was repeated on 292 mg (1 mmole) of enol phosphate 267, 2 mmole of lithium di-n-butylcuprate and 0.54 ml (5 mmole) of n-butyl bromide. Preparative tlc (silica gel, 50:3 carbon tetrachloride-ethyl ether) of the crude product (193 mg) afforded 143 mg (73%) of 300 as a colorless liquid: bp (Kugelrohr distillation) 68-70°/0.7 Torr; IR 1705, 1635 and 1085 cm^{-1}; ^{1}HNMR δ 0.9 (distorted t, 3H), 1.1-1.9 (m, 8H), 2.0-2.6 (m, 6H) and 3.67 (s, 3H); mass spectrum m/e (rel intensity) 196(100), 165(99), 154(41), 135(85), 122(38), 107(50), 95(75), 94(65) and 79(66).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.20; H, 10.20.

Methyl 2-n-Butylcycloheptenecarboxylate (301). - The procedure described in the preparation of Z-298 was followed using 153 mg (0.5 mmole) of the enol phosphate 273 as starting material. The crude product (112 mg) obtained was chromatographed on silica gel (10:1 carbon tetrachloride-ethyl ether) to yield 85 mg (81%) of 301 as a colorless liquid: bp (Kugelrohr distillation) 73-75°/0.9 Torr; IR 1705, 1640 and 1110 cm^{-1}; ^{1}HNMR δ 0.9 (distorted t, 3H), 1.1-1.9 (m, 10H), 2.0-2.6 (m, 6H) and 3.69 (s, 3H); mass spectrum m/e (rel intensity) 210(100), 179(66), 168(31), 149(90), 136(30),

125(20), 121(38), 109(38), 108(42), 107(32), 95(56), 93(38), 81(25), 79(33), 67(30), 55(28) and 41(40).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.14; H, 10.44.

Reaction of Methyl 2-(Diethylphosphoryloxy)cyclohexenecarboxylate (267) with Lithium Di-sec-butylcuprate. - To a solution of lithium di-sec-butylcuprate (1 mmole) in ethyl ether (8 ml), cooled at -63°, was added 146 mg (0.5 mmole) of the enol phosphate 267. The resulting mixture was stirred at -63° for 2 hr and then worked up in the usual manner. The crude product (129 mg) was chromatographed on silica gel (50:3 carbon tetrachloride-ethyl ether) to give 58 mg (40%) of starting material 267 (R_f 0.08) and two products: - (a) methyl 2-sec-butylcyclohexenecarboxylate (302) (20 mg, 20%): colorless liquid; IR 1710 and 1635 cm^{-1}; ^{1}HNMR δ 0.90 (t, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 1.0-2.4 (m, 10H), 2.5-3.2 (sextet, J = 7 Hz, 1H), and 3.66 (s, 3H); mass spectrum m/e (rel intensity) 196(100), 167(55), 165(85), 149(60), 137(85), 128(34), 107(50), 81(32), 79(36) and 41(30). High Resolution Mass Measurement Calcd for $C_{12}H_{20}O_2$: 196.1463. Found: 196.1474.

(b) methyl cyclohexenecarboxylate (297) (22 mg, 31%): colorless liquid; IR 1705, 1650 and 1090 cm^{-1}; ^{1}HNMR δ 1.3-1.9 (m, 4H), 1.9-2.4 (m, 4H), 3.68 (s, 3H) and 6.9 (m, 1H); mass spectrum m/e (rel intensity) 140(58), 125(11), 109(44), 108(39), 97(10), 83(12), 81(100), 80(67), 79(46), 77(18), 53(25), and 41(29). High Resolution Mass Measurement Calcd for $C_8H_{12}O_2$: 140.0837. Found: 140.0833.

t-Butyl 2-t-Butyl-1-cyclohexenyl Ketone (303). - The enol phosphate 267 (146 mg, 0.5 mmole) was added to a solution of lithium di-t-butylcuprate (2 mmole) in ethyl ether (10 ml) at -47°. The resulting mixture was stirred at -47° for 1 hr, then warmed to -23° and maintained at this temperature for 1 hr 45 min. After the usual work-up procedure, 101 mg of crude product was obtained. Preparative tlc of this crude material on silica gel with 10:1 carbon tetrachloride-ethyl ether afforded 72 mg (80%) of 303 as a colorless oil: bp (Kugelrohr distillation) 68-70°/0.5 Torr; IR 1665 and 1625 cm^{-1}; ^{1}HNMR δ 1.03 (s, 9H), 1.24 (s, 9H), 1.4-1.8 (m, 4H), and 1.8-2.3 (m, 3H); mass spectrum m/e (rel intensity) 222(3), 207(8), 166(69), 165(100), 137(56), 121(18), 109(28), 107(47), 105(23), 95(94), 93(53), 91(65), 81(94), 79(86), 77(70), 69(51), 67(74), 65(29), 57(93), 55(75), 53(45), 43(40) and 41(99).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.79.

General Procedure for the Synthesis of the E-Enol Phosphate of Acyclic β-Keto Esters.- The β-keto ester (1 mmole) was dissolved in dry HMPA (1.5 ml) and the solution was cooled with a cold water-bath (ca.10°) and kept under a dry nitrogen atmosphere. Anhydrous triethylamine (0.15 ml, 1.1 mmole) was added, followed (after 15 min) by the introduction of 0.16 ml (1.1 mmole) of diethyl chlorophosphate. The resulting white suspension was stirred at room temperature for 3.5 hr and then diluted with 50% brine (10 ml) and ethyl ether (50 ml). The ether layer was washed with 3 x 10 ml of brine, dried over anhydrous magnesium sulfate and evaporated in vacuo.

The crude product so obtained was homogeneous by tlc (silica gel, ethyl ether) and vpc (3% OV-17 column, 150-160°) analyses. Only the E-enol phosphate was observed in the crude material (according to ^{1}HNMR) with no detectable quantity of the Z isomer.

Methyl E-3-(Diethylphosphoryloxy)but-2-enoate (310). - Prepared according to the general procedure from 116 mg (1 mmole) of methyl acetoacetate. The crude product (227 mg, 90%) was obtained as a colorless oil and had the following spectral properties: IR 1720, 1660, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.37 (t, J = 7 Hz, 6H), 2.38 (s, 3H), 3.67 (s, 3H), 4.17 (qn, J = 7 Hz, 4H) and 5.77 (br s, 1H); mass spectrum m/e (rel intensity) 252(34), 221(30), 220(95), 193(23), 192(72), 165(24), 164(95), 155(97), 127(100), 113(23), 99(88), 81(38), 67(40) and 43(46).

High Resolution Mass Measurement Calcd for $C_9H_{17}O_6P$: 252.0763. Found: 252.0766.

Ethyl E-3-(Diethylphosphoryloxy)-2-methylbut-2-enoate (311). - Prepared from 288 mg (2 mmole) of ethyl 2-methyl-3-oxobutanoate (279) by following the general procedure. The crude product (515 mg, 92%), obtained as a colorless oil, was characterized by the following spectral data: IR 1715, 1655, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.28 (t, J = 7 Hz, 3H), 1.37 (t, J = 7 Hz, 6H), 1.87 (t, J = 1.8 Hz, 3H), 2.40 (t, J = 1.8 Hz, 3H) and 3.9-4.4 (m, 6H); mass spectrum m/e (rel intensity) 280(31), 235(39), 234 (86), 207(10), 206(45), 179(11), 178(50), 155(94), 150(28), 127(73), 99(100), 81(15) and 43(16).

High Resolution Mass Measurement Calcd for $C_{11}H_{21}O_6P$: 280.1076. Found: 280.1075.

Methyl E-3-Methylhept-2-enoate (312). - The E-enol phosphate 310 (110 mg, 0.44 mmole) was treated with 0.88 mmole of lithium di-n-butylcuprate in the same manner as described on p. 218. Preparative tlc (silica gel, 50:3 carbon tetrachloride-ethyl ether) of the crude product (98 mg) afforded 52 mg (76%) of 312: R_f 0.60; bp (Kugelrohr distillation) 91-93°/20 Torr; IR 1715, 1650 and 1155 cm^{-1}; ^{1}HNMR δ 0.90 (distorted t, 3H), 1.1-1.8 (m, 4H), 2.13 (d, J = 2 Hz, 3H), 1.9-2.3 (m, 2H), 3.63 (s, 3H), and 5.60 (m, 1H); mass spectrum m/e (rel intensity) 156(25), 141(11), 127(43), 125(36), 114(100), 99(13), 96(15), 95(36), 86(12), 85(16), 83(43), 82(49), 69(17), 67(18), 55(41) and 41(36).

High Resolution Mass Measurement Calcd for $C_9H_{16}O_2$: 156.1150. Found: 156.1151.

Besides the major fraction of 312 a small quantity (2 mg, ca. 2.9%) of methyl Z-3-methylhept-2-enoate (Z-312) was also isolated from the tlc and was characterized by the following spectral data: IR 1715, 1650 and 1155 cm^{-1}; ^{1}HNMR (100 M Hz, FT) δ 0.9 (distorted t, 3H), 1.1-1.7 (m, 4H), 1.84 (d, J = 2 Hz, 3H), 2.58 (br t, J = 7 Hz, 2H), 3.63 (s, 3H) and 5.63 (br s, 1H).

Ethyl E-2,3-Dimethylhept-2-enoate (E-298). - The enol phosphate 311 (140 mg, 0.5 mmole) was allowed to react with 1.0 mmole of lithium di-n-butylcuprate in the same manner as described on p. 218. The crude product obtained was chromatographed on silica gel with 20:1 petroleum ether-ethyl ether to yield 73 mg (79%) of E-298: see p. 219 for spectral and analytical data.

Preparation of Enol Phosphates of β-Diketones and their Reactions with Lithium Dialkylcuprates

General Procedures for the Preparation of Enol Phosphates of β-Diketones:-

Method A: The β-diketone (1 eq) was dissolved in a small volume of dry ethyl ether (or THF) and added to a suspension of sodium hydride (1.1 eq) in ethyl ether at 0^{o} under nitrogen. After stirring for 0.5 - 1 hr at the same temperature, 1.1 eq of diethyl chlorophosphate was introduced. The resulting mixture was removed from the cooling bath and stirred for 3.5 hr. The enol phosphate was isolated from the reaction mixture by employing the work-up procedure (a) or (b), as described on p. 203.

Method B: To a suspension of the β-diketone (1 eq) in dry ethyl ether, under nitrogen, was added successively 1.1 eq of anhydrous triethylamine and 1.1 eq of diethyl chlorophosphate. The resulting mixture was stirred for 20 hr at room temperature. The final suspension was filtered and the precipitate was washed with small volumes of ethyl ether. The combined filtrate was washed with 10% aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure.

The crude enol phosphate so obtained was homogeneous by tlc analysis (with the exception of 317) and had satisfactory spectral data. This crude product was used directly in reactions with lithium dialkylcuprates without further purification.

Z-4-(Diethylphosphoryloxy)pent-3-en-2-one (Z-317). - To a suspension of 48 mg (1.0 mmole) of sodium hydride (50%) in dry ethyl ether (10 ml) was added 105 mg (1.05 mmole) of acetylacetone at 0°. The resulting white suspension was stirred for 20 min at the same temperature, followed by addition of 0.16 ml (1.1 mmole) of diethyl chlorophosphate. The ice-bath was then removed and stirring was continued for 20 min. The mixture was filtered through celite and the filtrate was evaporated in vacuo to give 220 mg (93% yield based on sodium hydride used) of Z-317 which was pure by tlc (ethyl ether) and ^{1}HNMR analyses: colorless liquid; IR 1700, 1650, 1275 and 1030 cm^{-1}; ^{1}HNMR δ 1.37 (t, J = 7 Hz, 6H), 2.17 (d, J = 1.2 Hz, 3H), 2.28 (s, 3H), 4.2 (qn, J = 7 Hz, 4H) and 5.42 (br s, 1H); mass spectrum m/e (rel intensity) 236(23), 221(5), 194(9), 193(10), 165(19), 155(100), 127(66), 99(35), 85(10), 82(10), 81(11), 67(19) and 43(57).

High Resolution Mass Measurement Calcd for $C_9H_{17}O_5P$: 236.0814. Found: 236.0834.

E-4-(Diethylphosphoryloxy)pent-3-en-2-one (E-317). - (a) To a solution of acetylacetone (200 mg, 2 mmole) in 2 ml of dry hexamethylphosphoramide, cooled at ca. 10°, was added successively 0.3 ml (2.2 mmole) of triethylamine (anhydrous) and 0.32 ml (2.2 mmole) of diethyl chlorophosphate. The resulting white suspension, kept under a dry nitrogen atmosphere, was stirred for 3 hr at room temperature. The final mixture was diluted with ethyl ether (80 ml), washed with 50% brine and dried over anhydrous magnesium sulfate. Removal of solvents in vacuo yielded 381 mg (81%) of crude product, the ^{1}HNMR spectrum of which indicated a 2.5:1 mixture of E-317 and Z-317. Preparative tlc of the crude product on silica gel with ethyl ether gave

107 mg (22.6%) of Z-317 (R_f 0.4; spectral data the same as those given above), and 263 (mg) 55.7%) of E-317: colorless liquid; R_f 0.6; IR 1695, 1615, 1280 and 1025 cm^{-1}; ^{1}HNMR δ 1.36 (t, J = 7 Hz, 6H), 2.17 (s, 3H), 2.33 (s, 3H), 4.15 (qn, J = 7 Hz, 4H) and 6.17 (br s, 1H); mass spectrum m/e (rel intensity) 236(27), 221(6), 193(9), 165(21), 155(100), 127(58), 100(28), 99(58), 85(23), 67(28) and 43(83).

High Resolution Mass Measurement Calcd for $C_9H_{17}O_5P$: 236.0814. Found: 236.0807.

(b) Acetylacetone was treated according to method A of the general procedures described above to give, in quantitative yield, a mixture of E-317 and Z-317 in a ratio of 7:1 (determined by vpc (3% OV-17 column, 150°) and ^{1}HNMR analyses).

3-(Diethylphosphoryloxy)-2-cyclohexenone (318). - The crude 318 was obtained in quantitative yield from cyclohexane-1,3-dione by using method A: pale yellow oil; IR 1675, 1630, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.37 (t, J = 7 Hz, 6H), 1.7-2.7 (m, 6H), 4.18 (qn, J = 7 Hz, 4H) and 5.87 (br s, 1H); mass spectrum m/e (rel intensity), 248(49), 235(14), 220(22), 192(22), 179(12), 164(17), 161(20), 155(73), 145(17), 130(50), 125(45), 104(34), 102(100), 99(49), and 67(45).

High Resolution Mass Measurement Calcd for $C_{10}H_{17}O_5P$: 248.0814. Found: 248.0790.

3-(Diethylphosphoryloxy)-2-cyclopentenone (319). - The crude enol phosphate 319 was obtained in quantitative yield from cyclopentane-1,3-dione by using method B: pale yellow oil; IR 1710, 1610, 1280 and 1030 cm^{-1}; ^{1}HNMR δ 1.38 (t, J = 7 Hz, 6H), 2.3-2.9 (m, 4H), 4.2 (m, 4H) and 5.78 (br s, 1H); mass spectrum m/e (rel intensity) 234(19), 179(19), 161(22), 145(60), 129(22), 117(78), 116(100), 99(19), 81(66), 53(85) and 45(22).

High Resolution Mass Measurement Calcd for $C_9H_{15}O_5P$: 234.0657. Found: 234.0649.

3-(Diethylphosphoryloxy)-2-methyl-2-cyclopentenone (320). - The enol phosphate 320 was obtained in quantitative yield from 2-methylcyclopentane-1,3-dione by using method B: pale yellow oil; IR 1710, 1660, 1280, and 1030 cm^{-1}; ^{1}HNMR δ 1.38 (t, J = 7 Hz, 6H), 1.67 (br s, 3H), 2.3-2.6 (m, 2H), 2.6-3.0 (m, 2H) and 4.22 (qn, J = 7 Hz, 4H); mass spectrum m/e (rel intensity) 248(5), 235(9), 179(8), 161(13), 145(85), 130(70), 119(45), 117 (100), 81(19), 67(55) and 45(28).

High Resolution Mass Measurement Calcd for $C_{10}H_{17}O_5P$: 248.0814. Found: 248.0817.

4-Methylpent-3-en-2-one (321). - A solution of lithium dimethylcuprate (2 mmole) in dry ethyl ether was cooled to -98° and to this was added 236 mg (1 mmole) of 317 (mixture of E and Z isomers). The resulting dark red suspension was stirred for 2.5 hr at the same temperature and then worked up by the usual procedure. Kugelrohr distillation of the crude product afforded 81 mg (83%) of 321: bp 128-130° (lit.[204] bp 129°); IR 1685 and

1615 cm^{-1}; ^{1}HNMR δ 1.85 (d, J = 2 Hz, 3H), 2.15 (s, 6H), and 6.02 (m, 1H).

3-Methyl-2-cyclohexenone (322).[149] - Enol phosphate 318 (248 mg, 1 mmole) was allowed to react with 1.1 mmole of lithium dimethylcuprate in 10 ml of dry ethyl ether at -78° for 3 hr. The crude product obtained after the usual work-up procedure was purified by preparative tlc (silica gel, 4:1 carbon tetrachloride-ethyl ether) to give 101 mg (92%) of 322: IR 1655 and 1630 cm^{-1}; ^{1}HNMR δ 1.95 (br s, 3H), 1.5-2.5 (m, 6H) and 5.80 (br s, 1H); mass spectrum m/e (rel intensity) 110(100), 82(93) and 54(38).

3-t-Butyl-2-cyclohexenone (323).[149] - To an ethyl ether solution (8 ml) of lithium di-t-butylcuprate (1.0 mmole) cooled at -78°, under nitrogen, was added 124 mg (0.5 mmole) of 318. The mixture was stirred for 3 hr at the same temperature and then worked up by the usual procedure. Preparative tlc of the crude product on silica gel (4:1 carbon tetrachloride-ethyl ether) afforded 63 mg (83%) of 323: IR 1655 and 1610 cm^{-1}; ^{1}HNMR δ 1.12 (s, 9H), 1.7-2.5 (m, 6H) and 5.88 (s, 1H); mass spectrum m/e (rel intensity) 152(78), 137(20), 124(60), 109(100), 96(90), 81(24), 67(20) and 41(22).

3-Methyl-2-cyclopentenone (324).[205] - Enol phosphate 319 (125 mg, 0.53 mmole) was treated with lithium dimethylcuprate (0.59 mmole) in dry ethyl ether for 3 hr 45 min at -78°. The reaction mixture was worked up in the usual manner to give 51 mg of crude product which was distilled (Kugelrohr) to yield 43 mg (84%) of 324: bp 76-78°/20 Torr (lit.[205] bp 74°/15 Torr); IR 1700, 1670 and 1620 cm^{-1}; ^{1}HNMR δ 2.13 (br s, 3H), 2.2-2.7 (m, 4H) and 5.87 (q, J = 1 Hz, 1H); mass spectrum m/e (rel intensity) 96 (100), 95(48), 81(64), 67(66), 53(60), 41(28) and 40(38).

2,3-Dimethyl-2-cyclopentenone (325).[206] - To a solution of lithium dimethylcuprate (1.28 mmole) in dry ethyl ether (5 ml) cooled at 0°, under nitrogen, was added 160 mg (0.64 mmole) of the enol phosphate 320. The resulting mixture was stirred for 2 hr at 0° and then worked up as usual. The crude product obtained was purified by preparative tlc (silica gel, 4:3 petroleum ether-ethyl ether) to afford 52 mg (74%) of 325: IR 1735 (weak), 1695 and 1650 cm^{-1}; ^{1}HNMR δ 1.68 (s, 3H), 2.03 (br s, 4H) and 2.38 (s, 3H); mass spectrum m/e (rel intensity) 110(100), 95(38), 67(71) and 41(16).

SECTION III

Synthesis of Latia Luciferin

β-Cyclogeraniol (329). - To a stirred suspension of lithium aluminum hydride (95%; 44 mg, 1.1 mmole) in anhydrous ethyl ether (4 ml) was added dropwise an ether solution of methyl β-cyclogeranate (248) (182 mg, 1.0 mmole) at room temperature. The resulting mixture was brought to reflux under a dry nitrogen atmosphere for 2 hr and then cooled in an ice-bath, followed by quenching with 0.4 ml of 5% aqueous sodium hydroxide. Stirring was continued for 30 min at room temperature and the resulting suspension was filtered through anhydrous magnesium sulfate. The residue was washed several times with ethyl ether and the combined filtrate was evaporated under reduced pressure to give 151 mg (98%) of 329 which was homogeneous on tlc (silica gel, 5:1 carbon tetrachloride-ethyl ether) and was 99% pure by vpc (3% OV-101 column) analysis. An analytical sample of 329 was obtained by Kugelrohr distillation of the crude material: bp 55-57°/0.2 Torr; mp 41°; IR 3670, 3500 and 1650 (weak) cm^{-1}; ^{1}HNMR δ 1.05 (s, 6H), 1.3-1.7 (m, 4H), 1.73 (s, 3H), 1.8-2.1 (m, 2H) and 4.10 (s, 2H); mass spectrum m/e (rel intensity) 154(28), 139(21), 136(32), 123(43), 121(100), 105(13), 93(30), 79(22) and 41(16).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.72; H, 11.91.

1-Bromomethyl-2,6,6-trimethyl-1-cyclohexene (330). - A prechilled solution of 48% hydrobromic acid (50 ml) was added to 1.222 g (7.9 mmole) of 329 with cooling in an ice-bath. The mixture, kept under nitrogen, was stirred for 10 min when 30 ml of n-pentane was introduced. Stirring was continued for 3 hr at 0°. The two-phase mixture was then poured into ice-cold water, and the aqueous layer was extracted with n-pentane. The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product 330 (1.402 g, 82%) so obtained was homogeneous by tlc analysis (silica gel, 6:1 carbon tetrachloride-ethyl ether) and had satisfactory spectral data: pale yellow oil; IR 1645 cm^{-1}; ^{1}HNMR δ 1.1 (s, 6H), 1.3-1.7 (m, 4H), 1.72 (s, 3H), 2.0 (m, 2H) and 4.02 (s, 2H); mass spectrum m/e (rel intensity) 137 (P^+-Br, 18), 136 (P^+-HBr, 49), 121(100), 107(21), 93(30) and 79(17).

Methyl 3-Oxo-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pentanoate (331). - The dianion of methyl acetoacetate (102 mg, 0.88 mmole) in tetrahydrofuran was generated according to the general procedure (see p. 181). To this dianion solution, cooled in an ice-bath, was added 174 mg (0.8 mmole) of the crude bromide 330. The resulting yellow suspension was stirred for 1 hr 45 min at 0° and then worked up in the usual manner (see p. 181). The crude product (181 mg) obtained was chromatographed on silica gel with 5:1 petroleum ether-ethyl ether to afford 160 mg (79.5%) of 331 as a colorless liquid: IR 1745, 1715, 1655 and 1635 cm^{-1}; ^{1}HNMR δ 0.97 (s, 6H), 1.3-1.7 (m, 4H), 1.55 (s, 3H), 1.7-2.8 (m, 6H), 3.40 (s, 2H) and 3.68 (s, 3H);

mass spectrum m/e (rel intensity) 252(33), 234(47), 221(33), 220(94), 163 (51), 159(82), 145(94), 137(66), 136(93), 129(53), 123(90), 121(100), 119 (50), 107(82), 105(75), 95(91), 93(94), 91(77), 81(90), 79(86), 69(58), 67(61), 59(50), 55(90), 43(72) and 41(98).

High Resolution Mass Measurement Calcd for $C_{15}H_{24}O_3$: 252.1726. Found: 252.1726.

Methyl E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pent-2-enoate (332). - The Z-enol phosphate of 331 (72 mg, 0.28 mmole) in ethyl ether was prepared in the same manner as described on p. 203. This enol phosphate solution was syringed into a solution of lithium dimethylcuprate (0.56 mmole) in dry ethyl ether (3 ml), cooled at -78°. The resulting purple mixture was stirred at -78° for 2 hr and then warmed to -47° over 2 hr. The reaction mixture was worked up according to the usual procedure (see p. 210) to give 110 mg of crude product which, after preparative tlc (silica gel, 20:1 carbon tetrachloride-ethyl ether) purification, furnished 65 mg (93%) of 332: colorless liquid; bp (Kugelrohr distillation) 86-88°/ 0.02 Torr; IR 1715 and 1650 cm^{-1}; ^{1}HNMR δ 1.0 (s, 6H), 1.2-1.7 (m, 4H), 1.57 (s, 3H), 1.7-2.1 (m, 2H), 2.13 (d, J = 1.5 Hz, 3H), 2.17 (br s, 4H), 3.63 (s, 3H) and 5.61 (br s, 1H); mass spectrum m/e (rel intensity) 250(10), 219(4), 176(5), 138(13), 137(100), 121(9), 114(40), 95(30), 81(15) and 41(10).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.80; H, 10.40.

E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pent-2-en-1-ol (333). - To a solution of 43 mg (0.17 mmole of the ester 332 in dry hexane (2 ml) was added 0.36 ml (0.36 mmole) of diisobutylaluminum hydride (1 M in hexane) at -78°. The mixture was stirred under nitrogen for 2 hr at the same temperature, followed by quenching with saturated aqueous ammonium chloride. After warming up to room temperature, the resulting cloudy suspension was acidified with 10% hydrochloric acid until the aqueous layer turned clear. The aqueous phase was extracted with ethyl ether and the ether solution was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product (38 mg, 100%) obtained was homogeneous by tlc (silica gel, 5:1 petroleum ether-ethyl ether) analysis and showed essentially pure 333 in the ^{1}HNMR spectrum. Preparative tlc of the crude product gave an analytical sample of 333 (36.5 mg, 97%): colorless oil; bp (Kugelrohr distillation) 93-95°/0.05 Torr; IR 3650, 3500 and 1670 cm^{-1}; ^{1}HNMR δ 1.0 (s, 6H), 1.2-2.2 (m, 6H), 1.6 (s, 3H), 1.7 (s, 3H), 2.06 (br s, 4H), 4.1 (br d, J = 7 Hz, 2H) and 5.37 (br t, J = 7 Hz, 1H); mass spectrum m/e (rel intensity) 222(6), 204(14), 191(11), 189(12), 149(25), 138(27), 137(96), 136(72), 123(40), 121(66), 119(42), 109(48), 107(56), 105(53), 95(100), 93(79), 91(73), 81(98), 79(79), 77(65), 69(78), 67(84), 65(40), 57(74), 55(86), 53(51), 44(93), 43(77) and 41(98).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.00; H, 11.72.

E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-pentenal (334).[167b] - To a stirred suspension of 340 mg of active manganese dioxide (prepared by Attenburrow's method[173]) in dry hexane was added 32 mg (0.14 mmole) of alcohol 333 at 0°. Stirring was continued for 1.5 hr at 0° and 0.5 hr at room temperature. The mixture was then filtered through Celite and the residue was eluted with n-pentane. The combined filtrate was evaporated under reduced pressure to give 31 mg (98%) of crude 334 which was homogeneous by tlc analysis (silica gel, 10:1 petroleum ether-ethyl ether) and showed satisfactory spectral data: IR 1670 and 1635 cm^{-1}; ^{1}HNMR δ 1.02 (s, 6H), 1.2-1.7 (m, 4H), 1.6 (s, 3H), 1.7-2.1 (m, 2H), 2.2 (br s, 7H), 5.83 (br d, J = 7 Hz, 1H) and 9.13 (d, J = 8 Hz, 1H); mass spectrum m/e (rel intensity) 220(1), 219(2), 191(5), 177(10), 153(17), 139(16), 137(56), 135(34), 125(22), 123(45), 121(39), 119(23), 111(42), 109(63), 107(50), 95(73), 93(55), 91(46), 81(64), 79(50), 77(39), 71(51), 69(71), 67(66), 55(74), 43(100) and 41(75).

Synthesis of (E, E)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoic Acid (335)

Methyl 3-Oxo-6-(2-tetrahydropyranyloxy)hexanoate (277). - A solution of the dianion of methyl acetoacetate was generated in the same manner as described on p. 181 from 6.96 g (60 mmole) of methyl acetoacetate, 3.02 g (63 mmole) of sodium hydride (50%) and 37.5 ml (60 mmole) of n-butyllithium (1.6 M) in 130 ml of dry tetrahydrofuran. To this solution, cooled in an ice-bath, was added 6.27 g (30 mmole) of 2-bromoethanol tetrahydropyranyl ether (340) (prepared from 2-bromoethanol[207]). The resulting yellow suspen-

sion was stirred for 2 hr at 0° and then poured into 200 ml of ice-cold saturated ammonium chloride solution. The aqueous phase was extracted with 2 x 200 ml of ethyl ether and the combined organic solution was washed with brine and dried over anhydrous sodium sulfate. The crude product obtained after removal of solvents was Kugelrohr distilled to yield 5.456 g (75%) of 277 as a colorless oil: bp 116-118°/0.1 Torr; IR 1745, 1715, 1655, 1630, 1440 and 1030 cm^{-1}; ^{1}HNMR δ 1.2-2.2 (m, 8H), 2.63 (t, J = 7 Hz, 2H), 3.45 (s, 2H), 3.2-4.1 (m, 4H), 3.71 (s, 3H), and 4.5 (m, 1H); mass spectrum m/e (rel intensity) 244(2), 190(4), 159(8), 143(65), 142(65), 111(89), 101(38), 85(99), 84(67), 83(32), 69(100), 55(71) and 41(40).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.80; H, 8.27.

Methyl E-3-Methyl-6-(2-tetrahydropyranyloxy)hex-2-enoate (287). - See p. 214 for preparation and spectral data.

E-3-Methyl-6-(2-tetrahydropyranyloxy)hex-2-en-1-ol (341). - A solution of 3.63 g (15 mmole) of ester 287 in dry ethyl ether (10 ml) was added dropwise to a suspension of 374 mg (9.38 mmole) of lithium aluminum hydride in 60 ml of ethyl ether (anhydrous) at room temperature with constant stirring. The mixture, kept under nitrogen, was heated under reflux for 1 hr. About 4 ml of 5% aqueous sodium hydroxide was then introduced and stirring was continued for 45 min. The resulting suspension was filtered through anhydrous sodium sulfate and the residue was eluted with more ethyl ether. The combined filtrate was concentrated under reduced pressure to give 3.161 g (98%) of crude 341 which was very pure by tlc (silica gel, 1:1 carbon tetrachloride-ethyl ether) and spectroscopic analyses. Purification of the

crude product by Kugelrohr distillation furnished 2.983 g (93%) of 341: colorless oil; bp 98-100°/0.05 Torr; IR 3670, 3500 and 1670 cm^{-1}; ^{1}HNMR δ 1.2-2.3 (m, 11H), 1.67 (s, 3H), 3.1-3.9 (m, 4H), 4.09 (d, J = 7 Hz, 2H), 4.50 (m, 1H) and 5.38 (br t, J = 7 Hz, 1H); mass spectrum m/e (rel intensity) 214(0.5), 196(1), 130(5), 112(6), 101(10), 97(11), 85(100), 84(20), 69(10), 67(14), 57(15), 55(15), 43(14) and 41(25).

High Resolution Mass Measurement Calcd for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1579.

E-1-Bromo-3-methyl-6-(2-tetrahydropyranyloxy)-2-hexene (343). - A mixture of alcohol 341 (1.498 g, 7.0 mmole) and anhydrous lithium bromide (1.97 g, 22.7 mmole) in dry ethyl ether (70 ml) was cooled at -78° and kept under nitrogen. To this stirred mixture was added 4.4 ml (7.0 mmole) of n-butyllithium (1.6 M in hexene), followed (after 20 min) by 0.57 ml (7.35 mmole) of methanesulfonyl chloride. The resulting mixture was warmed to -10° over 1 hr, maintained at -10° for 0.5 hr and then stirred for 6 hr without the cooling bath. The final suspension was poured into 30 ml of ice-cold 5% aqueous sodium bicarbonate and the aqueous phase was separated and extracted with 30 ml of ethyl ether. The combined ether solution was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude bromide 343 (1.914 g, 99%), obtained as a slightly tan oil, showed satisfactory spectral data: IR 1660, 1120, and 1030 cm^{-1}; ^{1}HNMR δ 1.1-2.4 (m, 10H), 1.72 (s, 3H), 3.1-3.9 (m, 4H), 3.95 (d, J = 8 Hz, 2H), 4.52 (m, 1H), and 5.5 (br t, J = 8 Hz, 1H); mass spectrum m/e (rel intensity) 122(P-C_5H_9O-Br, 11), 98(13), 97(100), 85(33), 84(77),

83(38), 71(12), 69(13), 67(16), 56(24), 55(93), 54(21), 43(45) and 41(34). Since bromide 343 was sensitive to distillation and chromatographic purification conditions (the crude material decomposed quite rapidly on standing at room temperature), no satisfactory analytical data could be obtained.

Methyl E-7-Methyl-3-oxo-10-(2-tetrahydropyranyloxy)dec-6-enoate (344). - A solution of the dianion of methyl acetoacetate (2.436 g, 21 mmole) in dry tetrahydrofuran (50 ml) was prepared according to the general procedure (p. 181). To this was added 1.91 g (6.9 mmole) of crude bromide 343 (prepared above) at 0^{o}. The resulting yellow suspension was stirred for 2 hr at the same temperature and then worked up in the same way as shown on p. 236. Kugelrohr distillation of the crude product obtained gave 1.529 g (71%) of the alkylation product 344: bp $120-122^{o}$/0.04 Torr; IR 1745 and 1715 cm^{-1}; ^{1}HNMR δ 1.2-2.7 (m, 14H), 1.63 (s, 3H), 3.1-3.9 (m, 4H), 3.4 (s, 2H), 3.71 (s, 3H), 4.52 (m, 1H), and 5.05 (m, 1H); mass spectrum m/e (rel intensity) 312(0.8), 248(10), 228(7), 220(5), 210(4), 206(4), 192(7), 170(5), 164(5), 155(14), 152(5), 149(5), 143(15), 130(6), 127(7) 101(9), 95(11), 94(15), 85(83), 84(83), 83(40), 69(20), 67(14), 56(35), 55(100), 54(32), 43(35) and 41(35).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.38; H, 9.20.

Methyl (E, E)-3,7-Dimethyl-10-(2-tetrahydropyranyloxy)deca-2,6-dienoate (345). - The enol phosphate of β-keto ester 344 (230 mg, 0.737 mmole) was generated in 5 ml of dry ethyl ether by the procedure described on p. 203. This enol phosphate mixture was added through a two-way needle

into an ether solution of lithium dimethylcuprate (1.48 mmole), cooled at -78°. The resulting orange-yellow suspension was stirred for 0.5 hr at -78° and then for 2 hr at -47° (reaction mixture turned purple after 20 min at -47°). The reaction mixture was worked up in the usual manner (p. 210) to give 260 mg of crude product, which upon preparative tlc (silica gel, 4:1 carbon tetrachloride-ethyl ether) afforded 210 mg (92%) of 345 as a colorless liquid: bp (Kugelrohr distillation) 108-110°/0.04 Torr; IR 1710 and 1650 cm^{-1}; ^{1}HNMR δ 1.1-2.5 (m, 14H), 1.61 (s, 3H), 2.14 (d, J = 1.4 Hz, 3H), 3.1-4.0 (m, 4H), 3.64 (s, 3H), 4.52 (m, 1H), 5.05 (m, 1H) and 5.61 (m, 1H); mass spectrum m/e (rel intensity) 310(0.6), 279(0.7), 278(0.7), 227(4), 226(11), 196(5), 195(6), 194(4), 149(5), 121(4), 114(18), 95(43), 85(100), 84(12), 83(14), 67(12), 55(16), 43(11) and 41(14).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.80; H, 9.92.

Methyl (E, E)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoate (346). - The tetrahydropyranyloxy ester 345 (200 mg, 0.64 mmole) and 10 mg of p-toluenesulfonic acid were dissolved in 10 ml of dry methanol and stirred for 2 hr at room temperature. The solution was then concentrated under reduced pressure and the residue was diluted with ethyl ether, washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation in vacuo yielded 143 mg (99%) of hydroxy ester 346 which was identical with an authentic sample (see footnote (10), p. 155) by vpc (3% OV-17 column, 150°) as well as tlc (silica gel, 1:1 carbon tetrachloride-ethyl ether) analyses. The spectral properties of 346 were in excellent

agreement with those of the authentic material: IR (CH_2Cl_2) 3670, 1715, 1650, 1220 and 1150 cm^{-1}; ^{1}HNMR δ 1.2-2.4 (m, 9H), 1.61 (s, 3H), 2.14 (d, J = 1.4 Hz, 3H), 3.56 (t, J = 6 Hz, 2H), 3.64 (s, 3H), 5.06 (m, 1H) and 5.60 (br s, 1H); mass spectrum m/e (rel intensity) 226(6), 208(3), 196(10), 195(10), 194(8), 167(11), 166(10), 114(50), 95(100), 85(29), 83(22), 82(18), 69(24), 67(30), 55(29), 43(16) and 41(28).

(E, E)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoic acid (335). - To a solution of 42 mg (0.135 mmole) of ester 345 in methanol (2 ml) was added 1 ml of 5% aqueous sodium hydroxide. After stirring for 3 hr at 60°, the methanol was evaporated under reduced pressure and the aqueous solution was acidified with 5% hydrochloric acid. Dioxane was introduced (ca. 2 ml) until a homogeneous solution was formed, which was stirred for 1 hr at room temperature. The resulting mixture was saturated with sodium chloride and extracted with ethyl ether. The ether solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was partitioned between 10% aqueous sodium bicarbonate and chloroform. Acidification of the bicarbonate phase with concentrated hydrochloric acid, followed by extraction with ethyl ether, and drying (anhydrous sodium sulfate) and evaporation of the ether extracts furnished 26 mg (91%) of hydroxy acid 335. The spectral data of this synthetic material were in excellent agreement with those reported previously for the natural compound[177]: IR 3600, 3400-2600 (broad), 1690 and 1640 cm^{-1}; ^{1}HNMR δ 1.2-2.4 (m, 8H), 1.6 (s, 3H), 2.15 (s, 3H), 3.58 (t, J = 6 Hz, 2H), 5.05 (m, 1H), 5.62 (m, 1H) and 6.73 (br s, 2H, exchangeable with D_2O); mass spectrum m/e (rel intensity) 212(2), 195(10), 194(13),

166(11), 135(10), 125(12), 113(14), 111(15), 100(18), 97(17), 96(16), 95(94), 85(100), 69(16), 67(24), 55(26), 43(52) and 41(27).

High Resolution Mass Measurement Calcd for $C_{12}H_{20}O_3$: 212.1412. Found: 212.1429.

Synthesis of Mokupalide (347)

2,6,6-Trimethyl-1-phenylthiomethyl-1-cyclohexene (350). - To a stirred solution of alcohol 329 (271 mg, 1.76 mmole) in dry tetrahydrofuran (8 ml) was added 1.1 ml (1.76 mmole) of n-butyllithium (1.6 M in hexane), under nitrogen, at -23°. After 20 min, 0.14 ml (1.86 mmole) of methanesulfonyl chloride was introduced and the mixture was warmed to 0° over 30 min. Stirring was continued for 1 hr at 0°, followed by the addition of a THF solution (4 ml) of lithium thiophenoxide (1.95 mmole, generated from 0.2 ml of benzenethiol and 1.2 ml of n-butyllithium). The resulting mixture was stirred for 1 hr at 0° and then 3 hr at room temperature. The final reaction mixture was diluted with ethyl ether, washed with 10% aqueous sodium hydroxide and brine, and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure gave 389 mg of crude product, which was chromatographed on a short column of silica gel (100-200 mesh) with carbon tetrachloride to yield 363 mg (84%) of 350: IR 1585, 1480 and 1440 cm^{-1}; ^{1}HNMR δ 1.09 (s, 6H), 1.2-1.7 (m, 4H), 1.73 (s, 3H), 1.95 (m, 2H), 3.58 (s, 2H) and 7.18 (m, 5H); mass spectrum m/e (rel intensity) 246(36), 218(18), 137(100), 136(59) 121(41), 110(30), 109(30), 95(58), 81(33), 69(25) and 41(27).

Anal. Calcd for $C_{16}H_{22}S$: C, 77.99; H, 9.00. Found: C, 77.89; H, 9.02.

Methyl (6E)-7,11-Dimethyl-3-oxododeca-6,10-dienoate (278). - The dianion of methyl acetoacetate (6.96 g, 60 mmole) in tetrahydrofuran (100 ml) was prepared in the usual manner (p. 181). Geranyl bromide (10.85 g, 50 mmole) was added to this dianion solution at 0° and the yellow suspension formed was stirred for 1 hr at the same temperature. Work-up of the reaction mixture by the usual procedure (p. 181) led to 12.8 g of crude product, which was purified by Kugelrohr distillation to give 11.97 g (95% based on geranyl bromide used) of the β-keto ester 278 as a colorless liquid: bp 90-92°/0.02 Torr; IR 1745, 1715, 1650 and 1630 cm^{-1}; ^{1}HNMR δ 1.62 (s, 6H), 1.67 (s, 3H), 1.97 (br s, 4H), 2.0-2.7 (m, 4H), 3.38 (s, 2H), 3.70 (s, 3H) and 5.02 (m, 2H); mass spectrum m/e (rel intensity) 252(25), 234(18), 209 (13), 191(16), 151(17), 137(16), 136(53), 129(29), 123(27), 121(28), 116(24), 110(17), 109(100), 107(18), 105(26), 101(36), 95(28), 93(25), 81(47), 69(86), 55(22) and 41(53).

High Resolution Mass Measurement Calcd for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1740.

Methyl (2E, 6E)-3,7,11-Trimethyldodeca-2,6,10-trienoate (288). - See p. 214 for preparation and spectral data.

Methyl (E, E, E)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trienoate (351). - A suspension of 5.58 g (0.05 mole) of selenium dioxide (99.4%) in dichloromethane (250 ml) was stirred with 28.7 ml (0.2 mole) of 70% t-butyl-hydroperoxide for 30 min at room temperature in the dark. The resulting briefly homogeneous solution was cooled to 10°, followed by the addition of 25.0 g (0.1 mole) of 288. The mixture was stirred for 4.5 hr at 10° and

then diluted with 150 ml dichloromethane. The organic solution was washed with 10% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude material obtained was chromatographed on silica gel (100-200 mesh) with 3:1 petroleum ether-ethyl ether to give the following components, in order of elution: (a) starting material 288 (4.750 g, 19%);

(b) methyl (E, E, E)-3,7,11-trimethyl-12-oxododeca-2,6,10-trienoate (359) (1.327 g, 5%): colorless oil; IR 1690 and 1650 cm^{-1}; ^{1}HNMR δ 1.62 (s, 3H), 1.73 (s, 3H), 2.15 (s, 3H), 2.0-2.4 (m, 8H), 3.64 (s, 3H), 5.07 (m, 1H), 5.60 (m, 1H), 6.37 (m, 1H) and 9.30 (d, J = 1 Hz, 1H); mass spectrum m/e (rel intensity) 264(4), 233(6), 232(6), 181(18), 165(19), 157(28), 155(28), 151(27), 141(32), 127(53), 125(62), 121(51), 114(100), 113(31), 97(65), 95(99), 83(44), 69(32) and 55(54). High Resolution Mass Measurement Calcd for $C_{16}H_{24}O_3$: 264.1726. Found: 264.1728.

(c) methyl (2E, 6E)-8-hydroxy-3,7,11-trimethyldodeca-2,6,10-trienoate (358) (2.128 g, 8%): colorless oil; IR 3600, 1710 and 1650 cm^{-1}; ^{1}HNMR δ 1.63 (s, 6H), 1.70 (s, 3H), 2.17 (s, 3H), 1.9-2.6 (m, 7H), 3.63 (s, 3H), 3.93 (t, J = 7 Hz, 1H), 5.03 (m, 1H), 5.3 (m, 1H) and 5.60 (m, 1H); mass spectrum m/e (rel intensity) 266(1), 248(2), 235(2), 197(24), 166(14), 165(100), 147(7), 138(5) (metastable peak = $(165)^2/197$), 137(11), 135(9), 118(14), 113(10), 108(21), 106(17), 94(12), 92(17), 90(9), 83(16), 70(29), 69(18), 55(23), 43(16) and 41(30). High Resolution Mass Measurement Calcd for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1870.

(d) 351 (10.906 g, 41%): colorless oil; IR 3550, 1715 and 1650 cm^{-1}; ^{1}HNMR δ 1.60 (s, 3H), 1.63 (s, 3H), 1.8-2.3 (m, 9H), 2.13 (d, J = 1.2 Hz, 3H), 3.63 (s, 3H), 3.94 (s, 2H), 5.05 (m, 1H), 5.30 (m, 1H) and 5.60 (m, 1H); ^{1}HNMR (in CCl_4) δ 1.60 (s, 6H), 1.8-2.3 (m, 8H), 2.09 (d, J = 1.2 Hz, 3H), 3.15 (br s, 1H, exchangeable with D_2O), 3.58 (s, 3H), 3.83 (s, 2H), 4.95 (m, 1H), 5.25 (m, 1H) and 5.51 (m, 1H); mass spectrum m/e (rel intensity) 266(4), 248(7), 234(12), 181(31), 164(30), 149(38), 135(50), 125(40), 123(28), 121(100), 114(87), 109(43), 107(66), 105(36), 97(31), 95(68), 93(90), 81(63), 69(50), 67(50), 55(68), 43(62) and 41(60). High Resolution Mass Measurement Calcd for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1861.

Methyl (E, E, E)-12-Methanesulfonyloxy-3,7,11-trimethyldodeca-2,6,10-trienoate (352). - To a solution of 1.09 g (4.1 mmole) of the alcohol 351 in dry dichloromethane (35 ml), cooled at -10° and kept under nitrogen, was added successively 0.86 ml (6.15 mmole) of anhydrous triethylamine and 0.35 ml (4.51 mmole) of methanesulfonyl chloride. The resulting suspension was stirred for 2.5 hr at -10°, and then poured into 15 ml of ice-cold water. The organic layer was separated, washed with ice-cold 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure yielded 1.410 g (100%) of crude 352 as a pale yellow oil which was homogeneous by tlc analysis (silica gel, 5:1 carbon tetrachloride-ethyl ether), and showed satisfactory spectral data: IR 1710, 1650, 1360, 1170 and 1150 cm^{-1}; ^{1}HNMR δ 1.59 (s, 3H), 1.70 (s, 3H), 2.13 (d, J = 1.2 Hz, 3H), 1.9-2.3 (m, 8H), 2.95 (s, 3H), 3.65 (s, 3H), 4.54 (s, 2H), 5.03 (m, 1H),5.2-5.7 (m, 2H);

mass spectrum m/e (rel intensity) 344(2), 248(34), 217(10), 189(12), 136(19), 135(100), 134(35), 133(22), 121(36), 119(38), 114(51), 109(24), 107(83), 105(35), 96(33), 93(76), 91(31), 81(32), 79(47), 67(25), 55(44), 43(26) and 41(34).

High Resolution Mass Measurement Calcd for $C_{17}H_{28}O_5S$: 344.1658. Found: 344.1669.

Methyl (E, E, E)-3,7,11-Trimethyl-12-phenylthiododeca-2,6,10-trienoate (353). - A solution of benzenethiol (0.46 ml, 4.5 mmole) in dry tetrahydrofuran (15 ml) was allowed to react with 2.58 ml (4.5 mmole) of methyllithium (1.75 M in ether) for 20 min at 0°, under a dry nitrogen atmosphere. To the resultant lithium thiophenoxide solution was added 1.35 g (3.9 mmole) of 352 and the mixture was stirred for 4 hr at 0°. The reaction mixture was then diluted with ethyl ether and water. The organic solution was separated, washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The ^{1}HNMR spectrum of the crude product so obtained (1.44 g) showed essentially pure 353. Preparative tlc (silica gel, 6:1 carbon tetrachloride-ethyl ether) purification of 62 mg of the crude material gave 56 mg (93%) of 353 as a colorless liquid: IR 1710, 1650, 1585, 1440 and 1150 cm^{-1}; ^{1}HNMR δ 1.56 (s, 3H), 1.72 (s, 3H), 1.8-2.3 (m, 8H), 2.14 (d, J = 1.6 Hz, 3H), 3.45 (s, 2H), 3.63 (s, 3H), 5.07 (m, 2H), 5.60 (m, 1H) and 6.9-7.4 (m, 5H); mass spectrum m/e (rel intensity) 359(25), 358(100), 249(10), 218(17), 217(14), 189(25), 177(46), 176(57), 149(16), 135(66), 121(43) 109(40), 107(33), 95(18), 93(24), 81(25), 79(16), 69(18), 67(22), 55(26), 43(20) and 41(29).

High Resolution Mass Measurement Calcd for $C_{22}H_{30}O_2S$: 358.1966. Found: 358.1956.

(E, E, E)-3,7,11-Trimethyl-12-phenylthiododeca-2,6,10-trien-1-ol (354). - To a solution of 1.181 g (3.3 mmole) of 353 in dry ethyl ether (45 ml), cooled at -23° and kept under nitrogen, was added 9.9 ml (9.9 mmole) of diisobutylaluminum hydride (1 M in hexane). The resulting mixture was stirred for 1 hr 50 min at -23° and then quenched with 2 ml of methanol. The cooling bath was removed, and after 20 min, the mixture was treated with 10% aqueous hydrochloric acid until the aqueous layer turned clear. The ether solution was separated, washed with brine, and dried over anhydrous magnesium sulfate. Evaporation of solvents under reduced pressure afforded 1.080 g (99%) of crude 354 which was essentially pure by tlc (silica gel) and ^{1}HNMR analyses. Satisfactory elemental microanalysis was obtained on a tlc purified (silica gel, 4:1 carbon tetrachloride-ethyl ether) sample: colorless oil; bp (Kugelrohr distillation) 145-147°/0.1 Torr; IR 3650, 3500, 1665, 1585 and 1440 cm^{-1}; ^{1}HNMR δ 1.55 (s, 3H), 1.66 (s, 3H), 1.71 (s, 3H), 1.8-2.3 (m, 9H), 3.45 (s, 2H), 4.09 (d, J = 7 Hz, 2H), 4.8-5.5 (m, 3H) and 6.9-7.4 (m, 5H); mass spectrum m/e (rel intensity) 330(29), 312(10), 221(32), 220(19), 203(46), 177(100), 176(28), 163(30), 147(30), 135(88), 134(63), 121(54), 110(67), 109(89), 107(78), 95(42), 93(72), 81(73), 69(55), 68(45), 67(70), 55(60), 43(45) and 41(75).

Anal. Calcd for $C_{21}H_{30}OS$: C, 76.31; H, 9.15. Found: C, 76.64; H, 9.21.

(E, E, E)-1-(2-Tetrahydropyranyloxy)-3,7,11-trimethyl-12-phenylthio-2,6,10-dodecatriene (355). - A mixture of 1.026 g (3.1 mmole) of crude 354, 391 mg (4.65 mmole) of dihydropyran and a catalytic amount (10 mg) of p-toluenesulfonic acid in dry dichloromethane (45 ml) was stirred for 2 hr at room temperature. The resulting solution was diluted with ethyl ether, washed with 10% aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate. Removal of solvents under reduced pressure gave 1.285 g of crude material, which after column chromatography (silica gel 100-200 mesh, 6:1 petroleum ether-ethyl ether) furnished 1.232 g (95% yield from 353) of 355: colorless liquid; IR 1670, 1585, and 1440 cm^{-1}; ^{1}HNMR δ 1.56 (s, 3H), 1.67 (s, 3H), 1.72 (s, 3H), 1.3-1.8 (m, 6H), 1.8-2.2 (m, 8H), 3.44 (s, 2H), 3.5-4.2 (m, 4H), 4.56 (m, 1H), 5.1 (m, 3H) and 6.97-7.33 (m, 5H); mass spectrum m/e (rel intensity) 414(10), 329(10), 202(20), 176(23), 134(28), 123(15), 121(15), 110(21), 109(25), 107(22), 93(16), 86(21), 85(100), 81(23), 69(18), 67(37), 57(36), 55(32), 43(40) and 41(42).

High Resolution Mass Measurement Calcd for $C_{26}H_{38}O_2S$: 414.2593. Found: 414.2582.

(E, E, E)-13-(2-Tetrahydropyranyloxy)-3,7,11-trimethyl-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-phenylthio-3,7,11-tridecatriene (362). - A solution of 1.656 g (4 mmole) of 355 and 448 mg (4 mmole) of diazabicyclo-[2.2.2]octane in dry tetrahydrofuran (25 ml) was kept under nitrogen and cooled to -23°. To this was added 3.75 ml (6 mmole) of n-butyllithium (1.6 M in hexane) and the resulting orange solution was stirred for 3 hr at -23°. A solution of bromide 330 (1.302 g, 6 mmole) in dry tetrahydrofuran

(2 ml) was then introduced. The light yellow suspension formed was stirred at -23° for 3 hr and warmed to 0° over 50 min. The reaction was worked up by quenching with 20 ml of water and extracting the aqueous phase with 2 x 25 ml of ethyl ether. The ether extracts were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 2.781 g of crude material, which showed one major spot (besides a fast moving component) on tlc. Purification of 100 mg of the crude product by preparative tlc (silica gel, 10:1 petroleum ether-ethyl ether) afforded 59 mg (75%) of 362 as a colorless oil: IR 1670, 1585 and 1440 cm^{-1}; ^{1}HNMR δ 0.98 (s, 3H), 1.05 (s, 3H), 1.51 (s, 3H), 1.66 (br s, 9H), 1.2-2.4 (m, 22H), 3.4-4.2 (m, 5H), 4.57 (m, 1H), 4.75-5.47 (m, 3H) and 6.93-7.33 (m, 5H); mass spectrum m/e (rel intensity) 550(0.5), 449(2), 440(3), 413(5), 355(11), 338 (14), 329(16), 311(46), 270(15), 255(15), 243(26), 219(32), 203(75), 202(72), 189(61), 187(60), 177(69), 175(64), 173(59), 163(71), 161(74), 159(70), 149(73), 147(79), 145(74), 135(87), 123(84), 119(81), 110(93), 109(96), 107(80), 105(80), 95(84), 93(81), 91(79), 85(96), 84(94), 69(88), 67(85), 57(89), 55(96), 43(100) and 41(88).

High Resolution Mass Measurement Calcd for $C_{36}H_{54}O_2S$: 550.3844. Found: 550.3839.

(E, E, E)-13-(2-Tetrahydropyranyloxy)-3,7,11-trimethyl-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7,11-tridecatriene (363). - To a solution of nickel (II) chloride hexahydrate (29.13 g, 122 mmole) in 400 ml of absolute ethanol, cooled in an ice-bath, was added simultaneously a solution of 362 (1.760 g, 3.2 mmole) in ethanol (40 ml) and a solution of sodium borohydride

(3.948 g, 102 mmole) in water with vigorous stirring. The addition was completed over 20 min, and the resulting black suspension was removed from the cooling bath and stirred for 26 hr at room temperature. The reaction mixture was then filtered through Celite and the precipitate was washed with ethanol. The combined filtrate was evaporated under reduced pressure and the residue was dissolved in ethyl ether. The ether solution was washed with brine and dried over anhydrous magnesium sulfate. The crude product obtained after removal of solvents was chromatographed on a silica gel (100-200 mesh) column with 20:1 petroleum ether-ethyl ether to give 1.018 g (72%) of 363 as a colorless oil: IR 1670 and 1450 cm^{-1}; ^{1}HNMR δ 1.0 (s, 6H), 1.2-2.3 (m, 36H), 3.4-4.2 (m, 4H), 4.57 (m, 1H) and 4.8-5.5 (m, 3H); mass spectrum m/e (rel intensity) 442(4), 358(5), 357(4), 340(15), 203(10), 189(8), 177(7), 161(6), 147(8), 137(73), 135(12), 123(14), 121(18), 119(11), 109(14), 107(15), 95(36), 93(18), 85(100), 81(35), 69(13), 67(15), 57(17), 55(16) and 41(17).

High Resolution Mass Measurement Calcd for $C_{30}H_{50}O_2$: 442.3811. Found: 442.3796.

(E, E, E)-13-Hydroxy-3,7,11-trimethyl-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7,11-tridecatriene (364). - A solution of 363 (486 mg, 1.1 mmole) and p-toluenesulfonic acid (20 mg) in 60 ml of methanol-tetrahydrofuran (5:1) was stirred for 24 hr at room temperature. The solution was then concentrated under reduced pressure to ca. 1 ml, diluted with ethyl ether, and washed with saturated aqueous sodium bicarbonate. After drying over anhydrous magnesium sulfate and removal of solvents, the residue was evaporated in vacuo to afford 395 mg (quantitative yield) of 364,

which was homogeneous by tlc (silica gel) analysis: colorless liquid; IR 3650, 3500, 1670 and 1450 cm^{-1}; ^{1}HNMR δ 0.98 (s, 6H), 1.2-2.3 (m, 30H), 4.1 (d, J = 7 Hz, 2H) and 4.8-5.5 (m, 3H); mass spectrum m/e (rel intensity) 358(12), 340(10), 204(13), 203(9), 189(9), 177(12), 161(8), 149(8), 147(11), 138(15), 137(100), 136(15), 135(16), 133(16), 123(20), 121(24), 119(14), 109(16), 107(16), 95(23), 81(25), 69(14), 55(16) and 41(15).

High Resolution Mass Measurement Calcd for $C_{25}H_{42}O$: 358.3235. Found: 358.3220.

3-Phenylsulfonylmethyl-2-butenolide (375). - Anhydrous sodium benzenesulfinate (1.15 g, 7.0 mmole) and 1.03 g (5.8 mmole) of 3-bromomethyl-2-butenolide (366) (prepared in the same manner as described by Martin et al.[196]) were dissolved in 10 ml of dry dimethylformamide. The orange-brown solution formed was stirred for 2 hr at room temperature under a dry nitrogen atmosphere. The reaction mixture was worked up by adding 20 ml of water and extracting the solution with 4 x 30 ml of chloroform-n-pentane (1:1). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Removal of residual dimethylformamide in vacuo gave 1.35 g of crude 375 (solid) which was essentially pure by tlc (silica gel) and ^{1}HNMR analyses. Recrystallization from dichloromethane-ethyl ether-n-pentane yielded 1.18 g (85%) of 375 as colorless flakes: mp 125°; IR 1795, 1760, 1650, 1335, 1175 and 1160 cm^{-1}; ^{1}HNMR δ 4.17 (s, 2H), 4.87 (br s, 2H), 5.83 (br s, 1H) and 7.4-7.9 (m, 5H); mass spectrum m/e (rel intensity) 238(54), 141(100), 126(15), 125(28), 97(29), 77(99), 68(16), 67(16) and 51(27).

Anal. Calcd for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46. Found: C, 55.31; H, 4.14; S, 13.22.

(E, E, E)-13-Bromo-3,7,11-trimethyl-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7,11-tridecatriene (381). - To a mixture of 364 (425 mg, 1.19 mmole) and anhydrous lithium bromide (413 mg, 4.76 mmole) in 25 ml of dry ethyl ether, cooled at -78° and kept under nitrogen, was added 0.86 ml (1.31 mmole) of n-butyllithium (1.52 M in hexane) with stirring. After 30 min at the same temperature, 0.1 ml (1.31 mmole) of methanesulfonyl chloride was introduced. The mixture was warmed to -10° over 1 hr, maintained at -10° for 30 min and then at room temperature for 6 hr. The resulting suspension was poured into ice-cold water and the aqueous phase was extracted with 2 x 50 ml of ethyl ether-n-pentane (1:1). The combined organic solution was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude bromide 381 (463 mg, 92%) obtained was used directly in the next alkylation step without any purification. Satisfactory spectral data were observed for this crude material (a slightly tan oil): IR 1665, 1455, 1380 and 1180 cm^{-1}; ^{1}HNMR δ 0.98 (s, 6H), 1.2-2.3 (m, 30H), 3.95 (d, J = 8 Hz, 2H) and 4.7-5.57 (m, 3H); mass spectrum m/e (rel intensity) 422(7), 420(7), 341(6), 340(8), 204(15), 203(9), 189(10), 177(12), 149(10), 147(10), 138(15), 137(100), 136(15), 135(13), 123(18), 121(21), 119(13), 109(16), 107(18), 105(12), 95(36), 81(24), 69(13), 67(13), 55(15) and 41(13).

High Resolution Mass Measurement Calcd for $C_{25}H_{41}{}^{81}Br$ and $C_{25}H_{41}{}^{79}Br$: 422.2371 and 420.2391. Found: 422.2399 and 420.2391.

3-[(E, E, E)-4,8,12-Trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1-phenylsulfonyl-3,7,11-tetradecatrien-1-yl]-2-butenolide (382). - To a stirred suspension of 144 mg (3.0 mmole of sodium hydride (50%) in dry dimethylformamide (20 ml) was added 714 mg (3.0 mmole) of sulfone 375 (dissolved in 1 ml of dimethylformamide) at 0°, under nitrogen. The cooling bath was removed, and an orange-yellow solution was formed after 30 min. To this solution was introduced 460 mg (ca. 1.19 mmole) of the crude bromide 381 and the resulting mixture was stirred for 4 hr at room temperature. The reaction was quenched with ice-cold 5% hydrochloric acid 40 ml and the mixture was extracted with 3 x 60 ml of ethyl ether-petroleum ether (1:1). The combined extracts were washed with 2 x 40 ml of 50% brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give 572 mg of crude product. Purification of 100 mg of the crude material by preparative tlc (silica gel, 2:3 petroleum ether-ethyl ether) afforded 72 mg (60% yield from alcohol 364) of 382 as a thick, colorless oil: IR 1792, 1760, 1640, 1330 and 1150 cm^{-1}; ^{1}HNMR δ 1.0 (s, 6H), 1.1-2.2 (m, 30H), 2.7 (m, 2H), 4.0 (m, 1H), 4.8 (d, J = 1.5 Hz, 2H), 4.6-5.2 (m, 3H), 5.8 (m, 1H) and 7.3-7.9 (m, 5H); mass spectrum m/e (rel intensity) 578(15), 441(3), 435(2), 300(10), 244(18), 237(47), 188(19), 176(21), 164(19), 163(19), 148(18), 146(20), 136(100), 135(38), 134(33), 132(24), 122(34), 120(45), 118(36), 108(37), 106(40), 104(30), 94(60), 81(95), 69(97), 57(40), 55(51) and 41(89).

High Resolution Mass Measurement Calcd for $C_{36}H_{50}O_4S$: 578.3430. Found: 578.3435.

Mokupalide (347). - A mixture of 382 (29 mg, 0.05 mmole) and disodium hydrogen phosphate (28 mg, 0.2 mmole) was dissolved in 5 ml of dry methanol. To this solution, cooled at -10° and kept under nitrogen, was added 75 mg (0.2 mmole) of 6% sodium amalgam (prepared according to the procedure reported by McDonald and Reineke[213]) in one portion. The resulting mixture was stirred for 20 min at -10°, followed by quenching with saturated aqueous ammonium chloride and extraction with ethyl ether. The combined extracts were washed with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The crude residue obtained was chromatographed on silica gel with 1:1 petroleum ether-ethyl ether to furnish 18 mg (82%) of mokupalide (347)[186]: IR 1790, 1755, 1645 and 1450 cm^{-1}; ^{1}HNMR δ 0.99 (s, 6H), 1.1-2.2 (m, 32H), 2.4 (m, 2H), 4.65 (d, J = 1.5 Hz, 2H), 5.05 (m, 3H) and 5.78 (m, 1H); mass spectrum m/e (rel intensity) 438(23), 423(5), 395(3), 296(5), 278(4), 245(5), 217(5), 204(12), 189(11), 177(24), 161(13), 149(28), 137(100), 136(36), 135(36), 133(28), 123(32), 121(52), 119(27), 110(29), 108(37), 98(46), 95(65), 93(41), 91(25), 81(83), 79(31), 69(65), 67(32), 57(40), 55(54), 43(28) and 41(52).

High Resolution Mass Measurement Calcd for $C_{30}H_{46}O_2$: 438.3497. Found: 438.3519.

3-(4-Methyl-1-phenylsulfonyl-3-penten-1-yl)-2-butenolide (379). - 3-Phenylsulfonylmethyl-2-butenolide (375) (48 mg, 0.2 mmole) was alkylated with 1-bromo-3-methyl-2-butene (15 mg, 0.1 mmole) in the same manner as described in the preparation of 382. Preparative tlc (silica gel, 5:1

ethyl ether-petroleum ether) of the crude product (27 mg) gave 22 mg (72% yield based on the bromide used) of 379 as colorless flakes (crystallized from petroleum ether-ethyl ether): mp 96°; IR 1792, 1760, 1640, 1595, 1455, 1330 and 1150 cm^{-1}; ^{1}HNMR δ 1.57 (s, 3H), 1.63 (s, 3H), 2.7 (m, 2H), 4.0 (m, 1H), 4.80 (br s, 2H), 4.6-5.0 (m, 1H), 5.8 (m, 1H) and 7.3-7.9 (m, 5H); mass spectrum m/e (rel intensity) 306(8), 238(15), 181(8), 165 (100), 164(100), 137(12), 136(13), 121(33), 120(24), 119(27), 109(17), 107(23), 105(44), 93(28), 91(30), 77(36), 69(29) and 41(38).

Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.73; H, 5.92; S, 10.46. Found: C, 62.65; H, 5.97; S, 10.38.

When approximately 1:1 ratios of 375 and 1-bromo-3-methyl-2-butene were used in the alkylation under various conditions (t-BuOK, t-BuOH; NaH, THF-HMPA; or NaH, DMF), the mono-alkylation product 379 was obtained in 40-50% yields.

Synthesis and Bromination of 3-Cyclopentyl-2-butenolide (367)

2-Cyclopentylethanol (370). - Prepared in 25% yield by the procedure reported by Yohe and Adams[208]: bp 80-82°/11 Torr (lit.[208] bp 80-81°/11 Torr); IR 3650 and 3500 cm^{-1}; ^{1}HNMR δ 0.9-2.0 (m, 11H), 2.2 (s, 1H, exchangeable with D_2O) and 3.58 (t, J = 6 Hz, 2H).

2-Cyclopentylacetaldehyde (371). - A 500 ml round-bottom flask equipped with a magnetic bar and a drying tube (anhydrous calcium sulfate) was charged with 21.7 g (101 mmole) of pyridinium chlorochromate[209] and 300 ml of dry dichloromethane. To the resulting deep red solution was added

7.65 g (67.1 mmole) of cyclopentylethanol (370) over 5 min. A black precipitate was formed within a few minutes and the mixture was stirred for 2 hr at room temperature. The reaction was worked up by filtering through a short pad of Florisil and washing the residue with 2 x 150 ml of ethyl ether. The combined filtrate was washed with 250 ml of 5% hydrochloric acid, 250 ml of 10% aqueous sodium bicarbonate and 250 ml of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product thus obtained was distilled to give 5.41 g (72%) of 2-cyclopentylacetaldehyde: bp 53-54°/12 Torr (lit.[210] bp 53°/12 Torr); IR 2750 and 1720 cm^{-1}; ^{1}HNMR δ 0.9-2.1 (m, 9H), 2.43 (m, 2H) and 9.8 (t, J = 2 Hz, 1H).

Condensation of 2-Cyclopentylacetaldehyde (371) with Glyoxylic Acid.[211] - To a solution of 4.14 g (37 mmole) of 2-cyclopentylacetaldehyde in 400 ml of methanol-water (1:1) was added 8.40 g (114 mmole) of glyoxylic acid hydrate in one portion, followed by 5.50 g (136 mmole) of sodium hydroxide pellets in several portions. The resulting solution was stirred for 22 hr at room temperature and then acidified with glacial acetic acid to pH 6. The solution was extracted with 3 x 200 ml of ethyl ether, and the extracts were washed with 300 ml of brine and dried over anhydrous magnesium sulfate. After removal of solvents and vacuum drying, a white solid residue (4.9 g) was obtained. The spectral data of this material indicated the presence of the hydroxy acid 372, along with some dehydrated product and some butenolide. This crude mixture was used directly in the subsequent reaction.

3-Cyclopentyl-4-hydroxy-2-butenolide (373). - The crude product (4.00 g) acquired from the above reaction was dissolved in 180 ml of dichloromethane saturated with anhydrous hydrogen chloride. The solution was stirred for 5 hr at room temperature, and then diluted with 100 ml of ethyl ether, washed with 75 ml each of 10% aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. The crude product obtained after removal of solvents was distilled (Kugelrohr) to give 3.73 g (73% yield from 2-cyclopentyl-acetaldehyde) of 373 as a colorless oil: bp 100-103°/0.6 Torr; IR 3650, 3400, 1760 and 1640 cm^{-1}; ^{1}HNMR δ 1.4-2.4 (m, 8H), 2.8 (m, 1H), 5.3 (br s, 1H, exchangeable with D_2O), 5.72 (br s, 1H) and 6.00 (s, 1H); mass spectrum m/e (rel intensity) 168(0.6), 150(5), 139(4), 122(100), 100 (51), 94(28) and 79(21).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.30.

3-Cyclopentyl-2-butenolide (367). - To a solution of 3.65 g (21.7 mmole) of 373 and 3 g of sodium hydroxide in 250 ml of methanol-water (1:1) was added 2.5 g (65.1 mmole) of sodium borohydride with stirring at room temperature.[212] After 2 hr, the reaction mixture was acidified with concentrated hydrochloric acid to pH 1 and extracted with 2 x 200 ml of ethyl ether. The combined extracts were washed with 100 ml each of 10% aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. Evaporation of solvents gave 3.20 g of liquid residue which upon Kugelrohr distillation afforded 3.01 g (91%) of 367: colorless oil; bp 108-110°/0.8 Torr; IR 1785, 1745, 1640, 1040, 1030, 895 and 860 cm^{-1}; ^{1}HNMR δ 1.2-2.2 (m, 8H), 2.8 (m, 1H), 4.78 (d, J = 2 Hz, 2H) and 5.82

(q, J = 2 Hz, 1H); mass spectrum m/e (rel intensity) 152(60), 123(100), 107(67), 95(35), 93(43), 69(53), 68(75), 67(75), 60(70), 55(75) and 41(70).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.95.

3-(1-Bromocyclopentyl)-2-butenolide (368). - A mixture of 367 (31 mg, 0.02 mmole), N-bromosuccinimide (36 mg, 0.2 mmole) and a small crystal of azobis(isobutyronitrile) was stirred in 2 ml of dry carbon tetrachloride in a 5 ml round-bottom flask fitted with a condenser and a drying tube (anhydrous calcium sulfate). The mixture was exposed to a 275 W sun lamp with a filter (Corning no. 7380, λ>340 nm) for 45 min. The resulting suspension was filtered and the filtrate was evaporated to give a solid residue. Recrystallization from isopropyl ether-ethyl ether yielded 34 mg (74%) of 368 as colorless plates: mp 69-70°; IR 1795, 1760, 1635, 1050, 895 and 860 cm^{-1}; ^{1}HNMR δ 1.6-2.6 (m, 8H), 5.08 (d, J = 2 Hz, 2H) and 6.00 (t, J = 2 Hz, 1H); mass spectrum m/e (rel intensity) 231(0.3), 229(0.4), 167(2), 151(100), 123(20), 107(12), 105(9), 95(10), 93(12), 91(7) and 67(8).

Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.76; Br, 34.60. Found: C, 46.77; H, 4.86; Br, 34.40.

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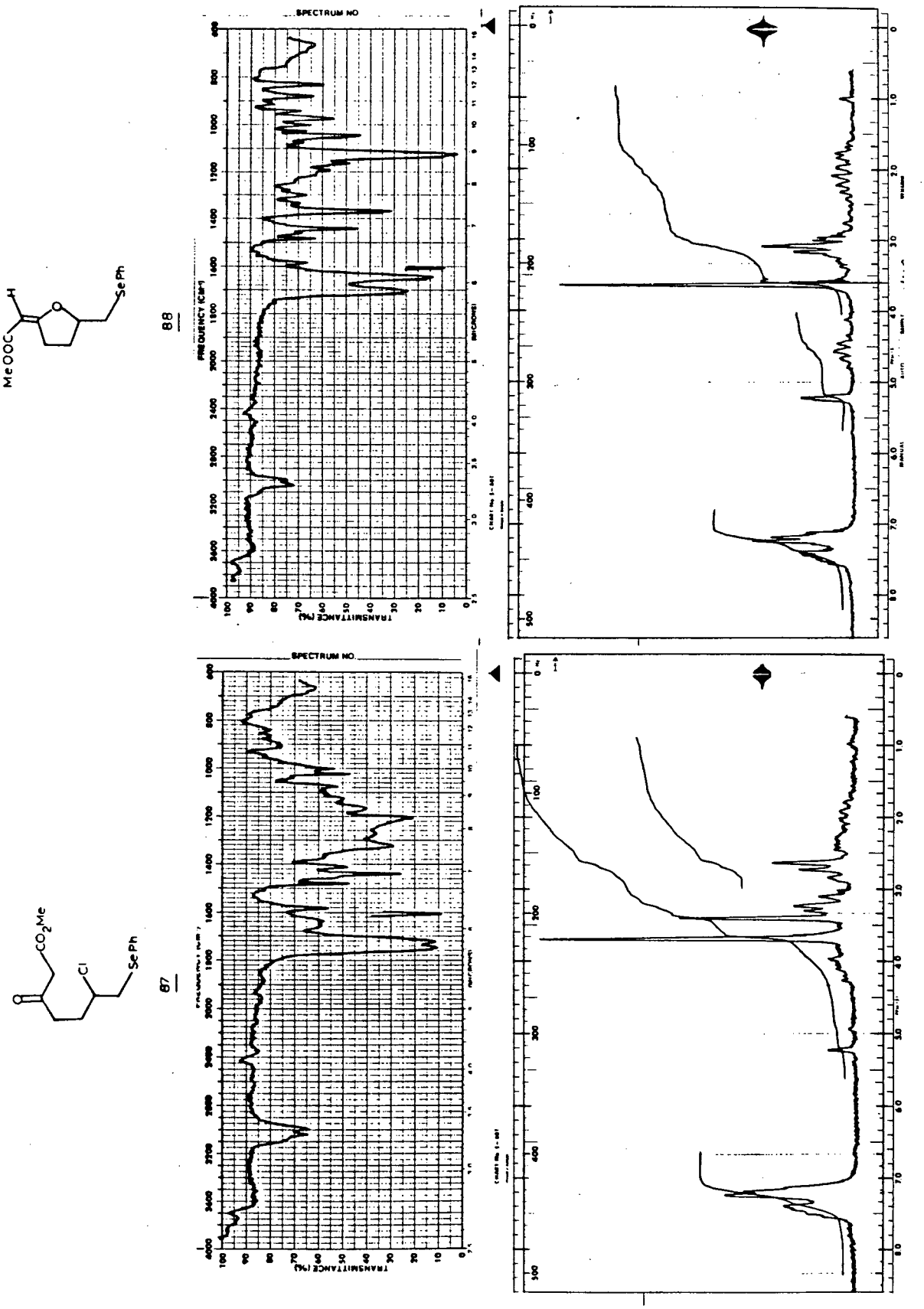
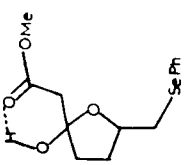
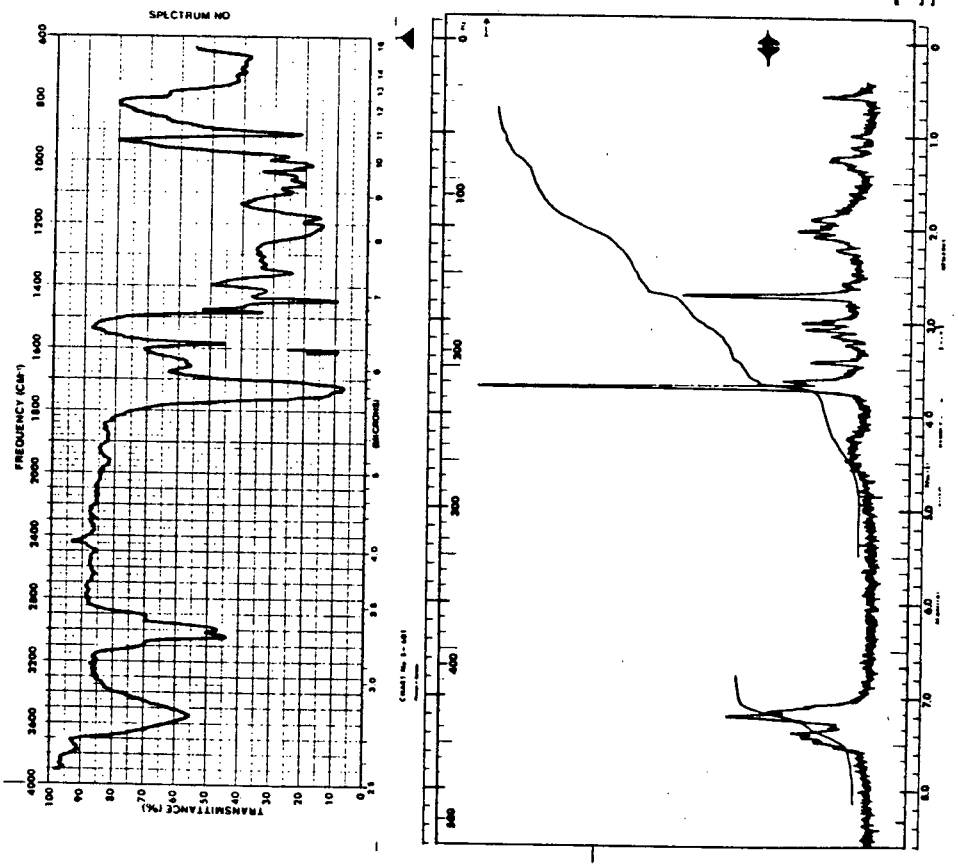
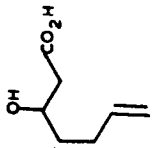
SPECTRAL APPENDIX


MeOOC
SePh
88
SPECTRUM NO
TRANSMITTANCE (%)
FREQUENCY (CM⁻¹)
CO2Me
Cl
SePh
87
SPECTRUM NO.
TRANSMITTANCE (%)

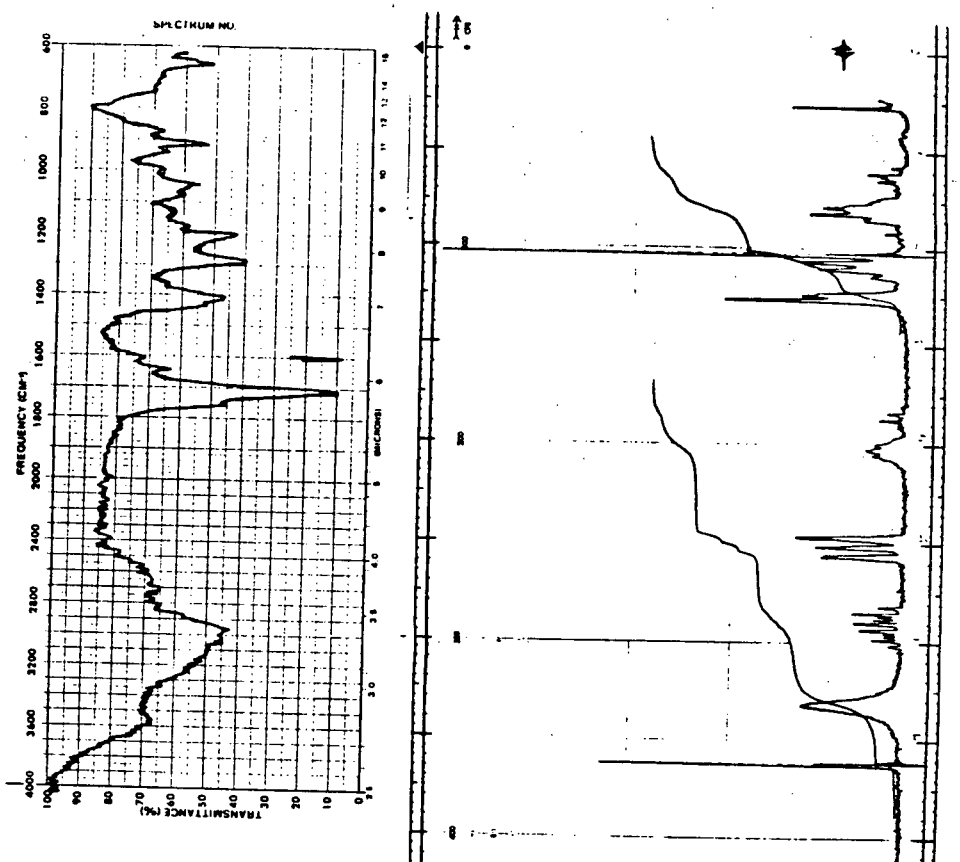

OMe
SePh

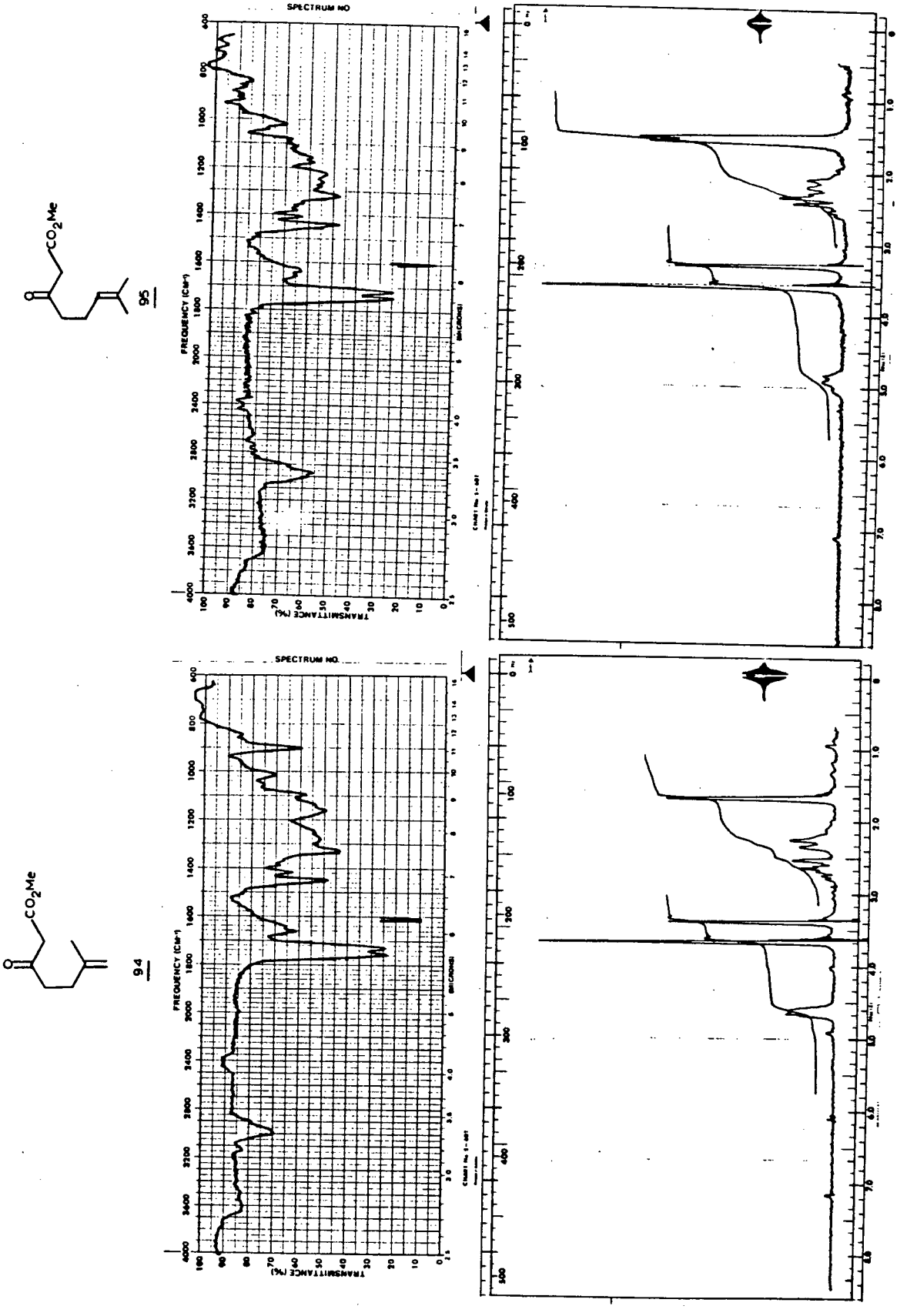
89

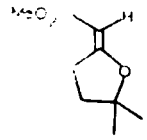

SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)


OH
CO2H

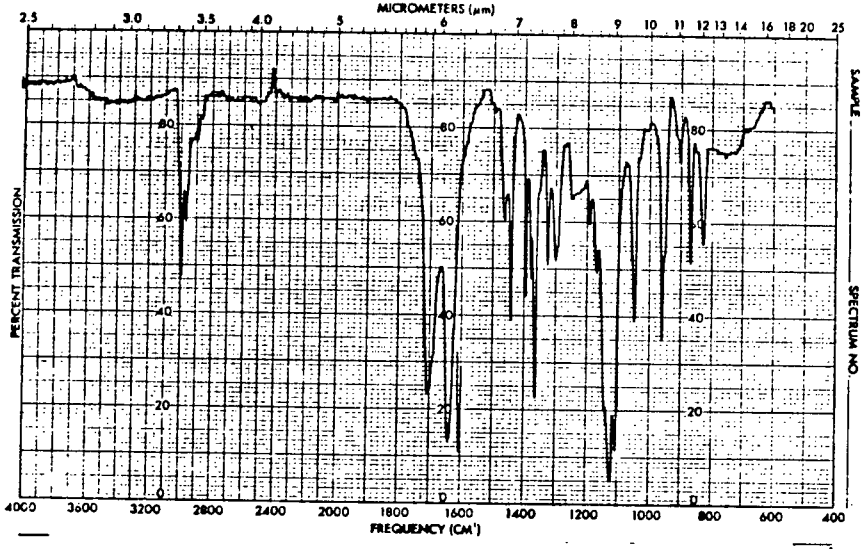
92

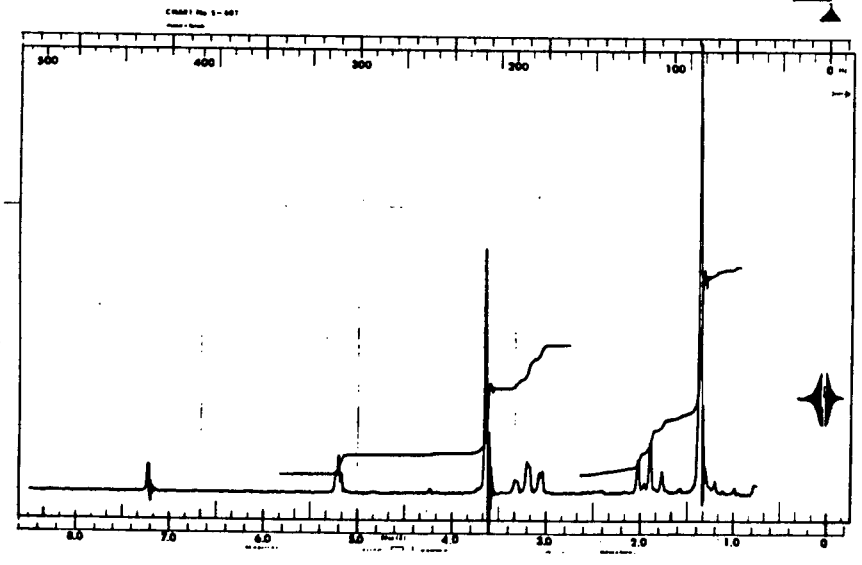

SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

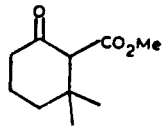

CO2Me
94
CO2Me
95
SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)



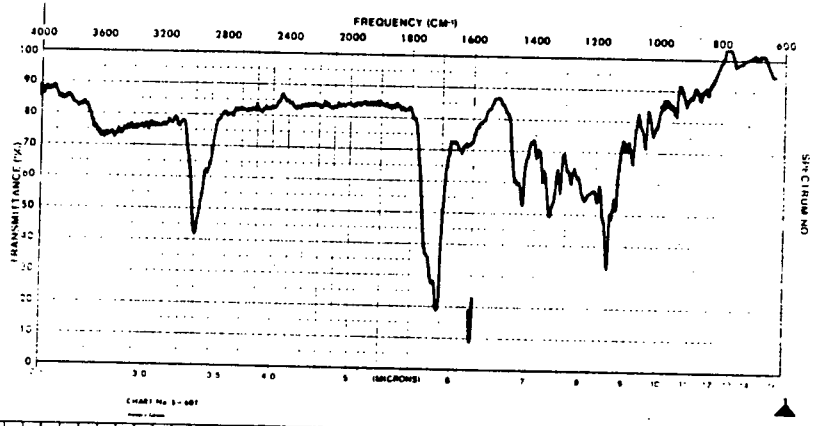
96

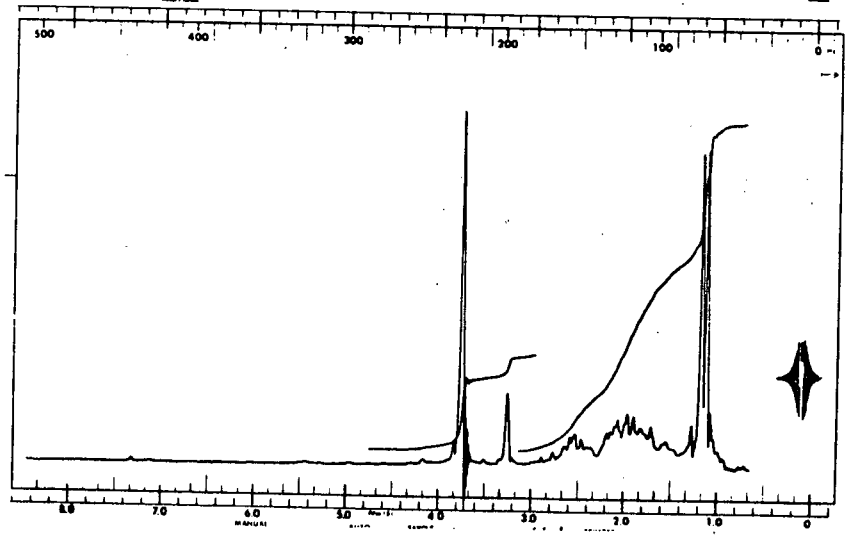

MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.

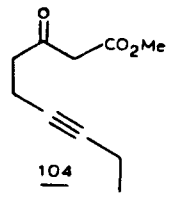



CO2Me

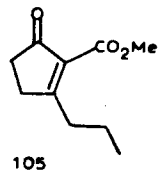
97


FREQUENCY (CM⁻¹)
TRANSMITTANCE (%)
SPECTRUM NO.

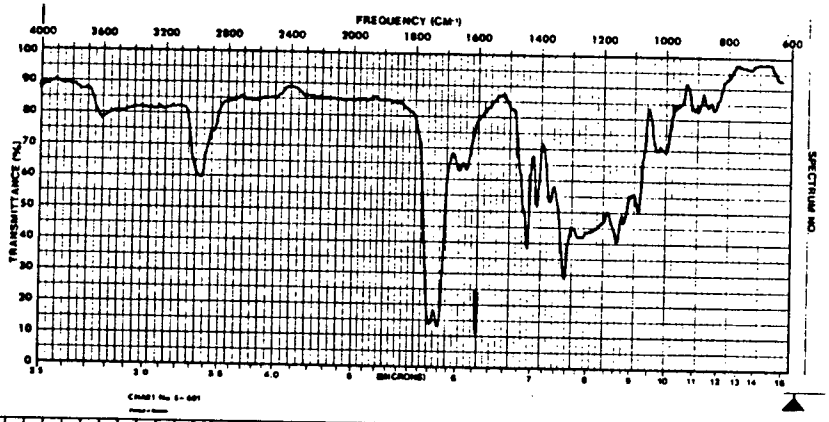


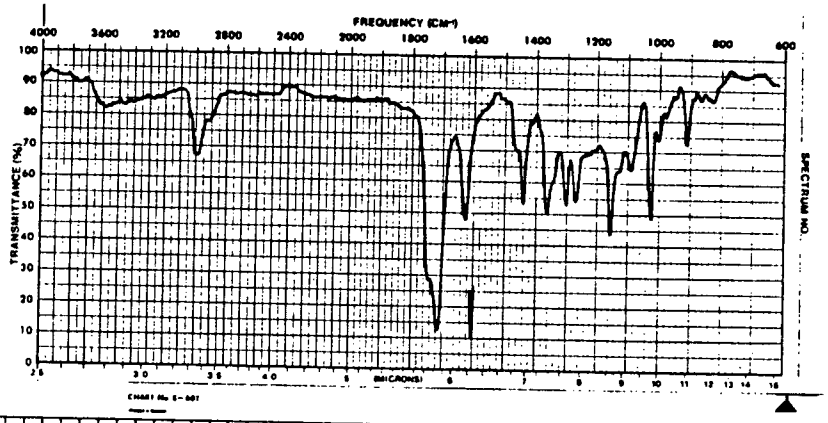

O
CO2Me

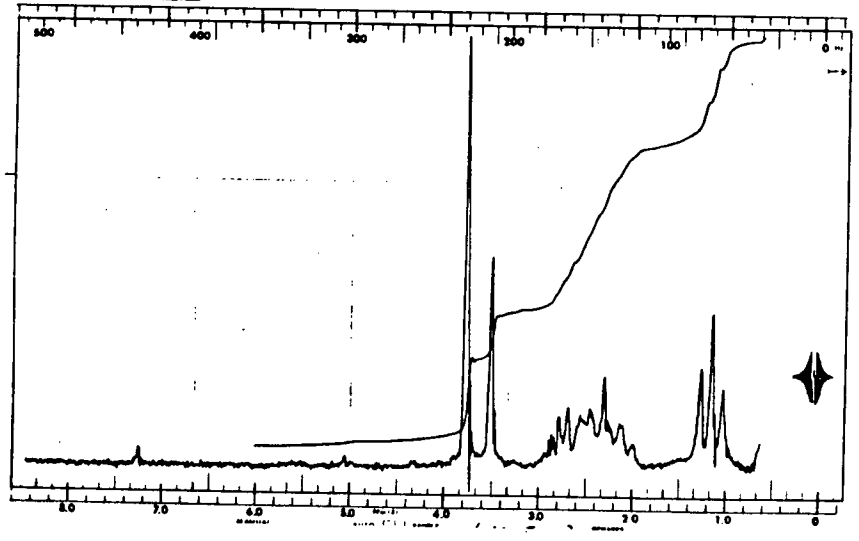
104

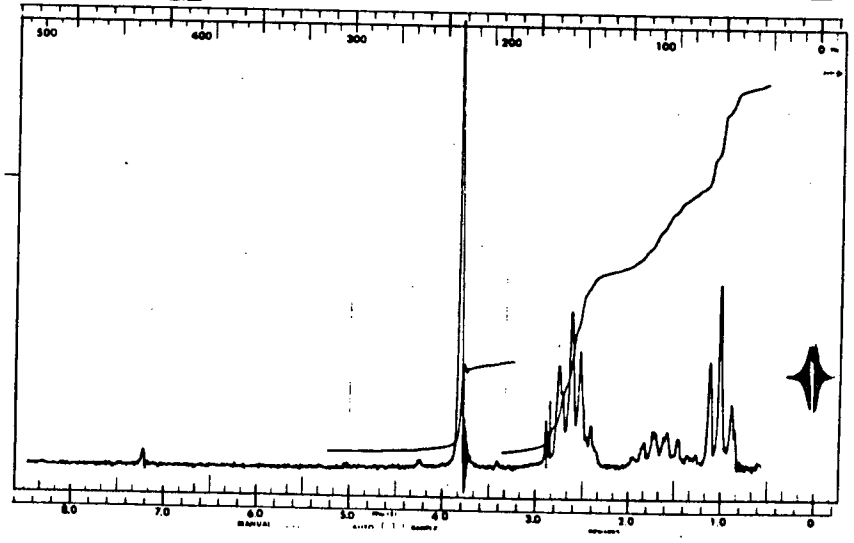

O
CO2Me

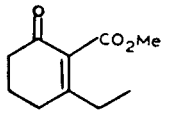
105


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO.
WAVELENGTH (MICRONS)

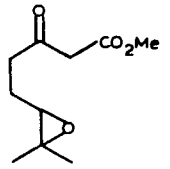

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO.
WAVELENGTH (MICRONS)



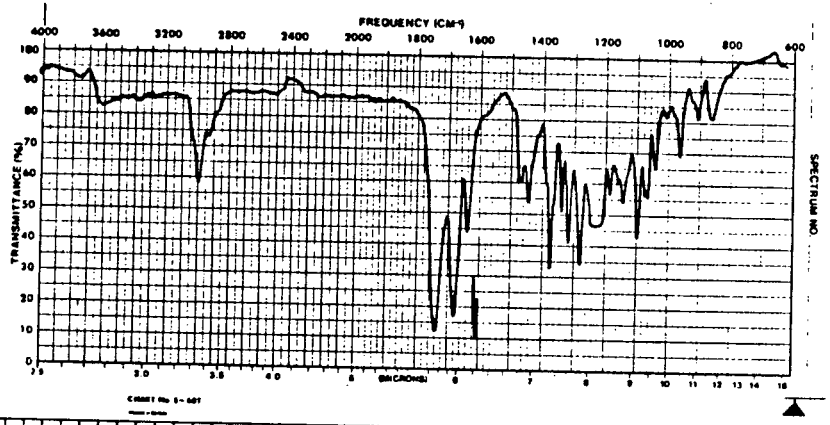


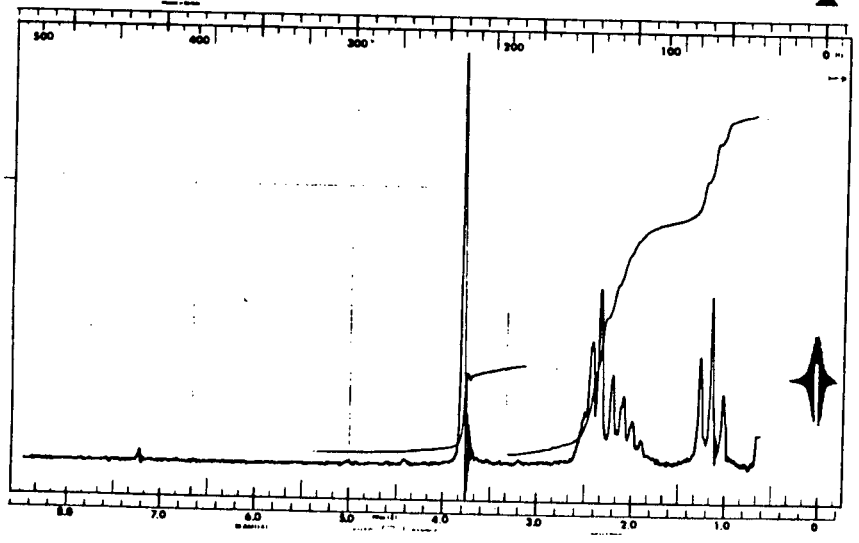

CO2Me

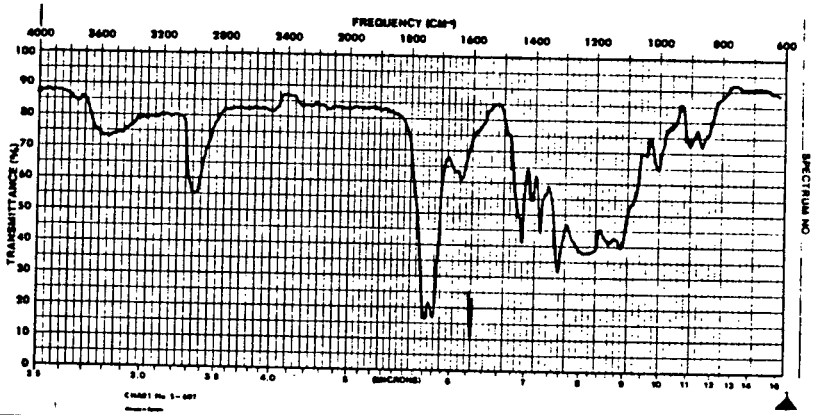
106

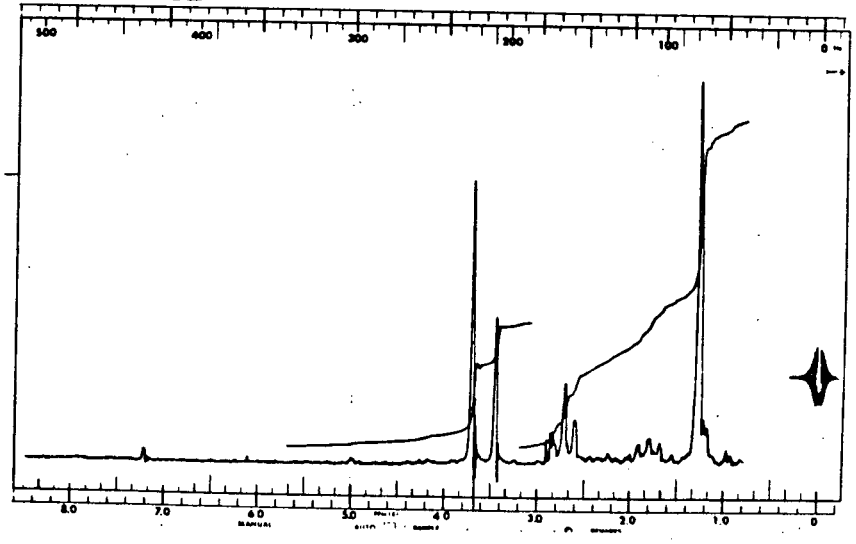

CO2Me

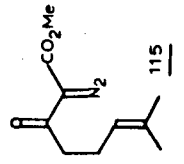
111


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

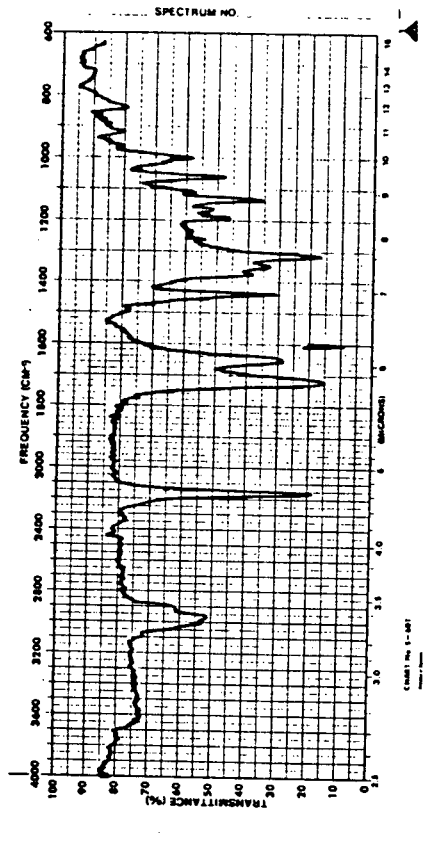


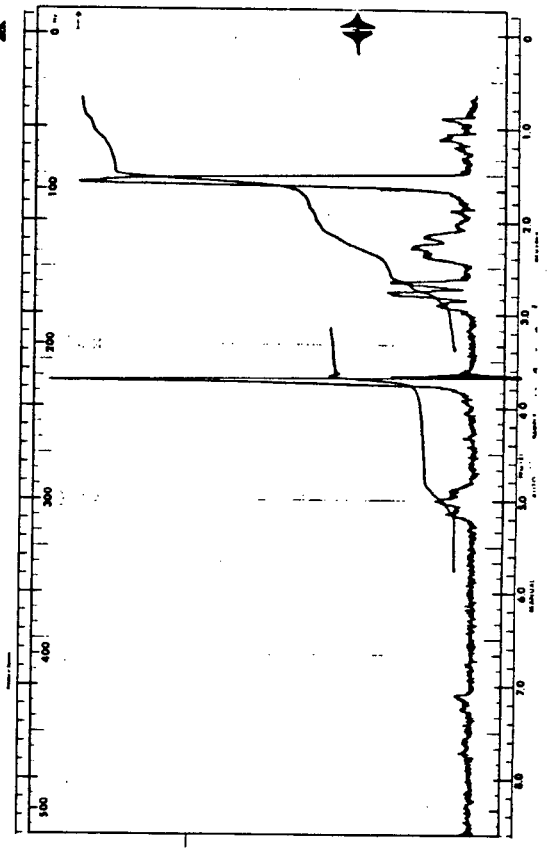

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

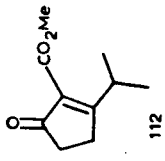



CO2Me
N2
O

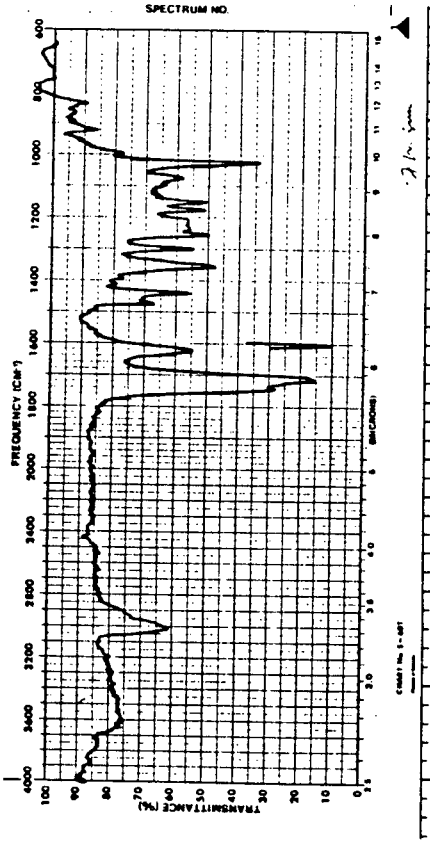
115

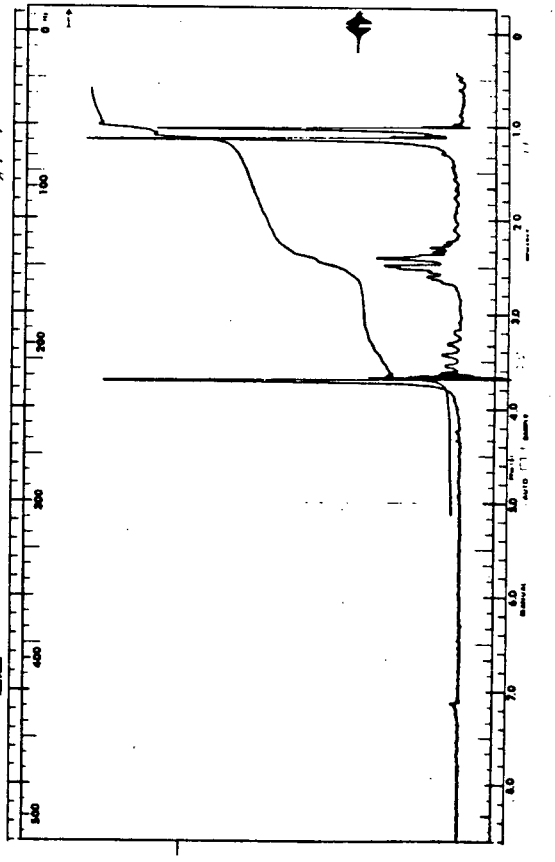

SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

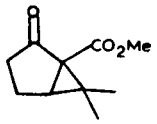



CO2Me
O

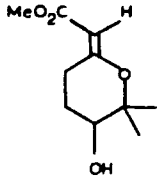
112


SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

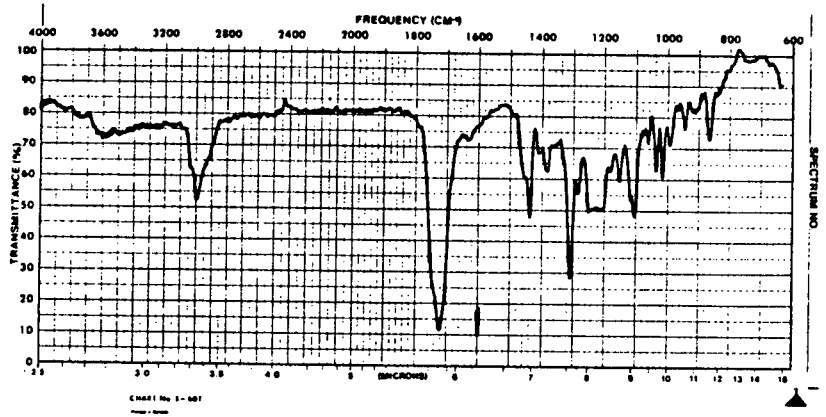


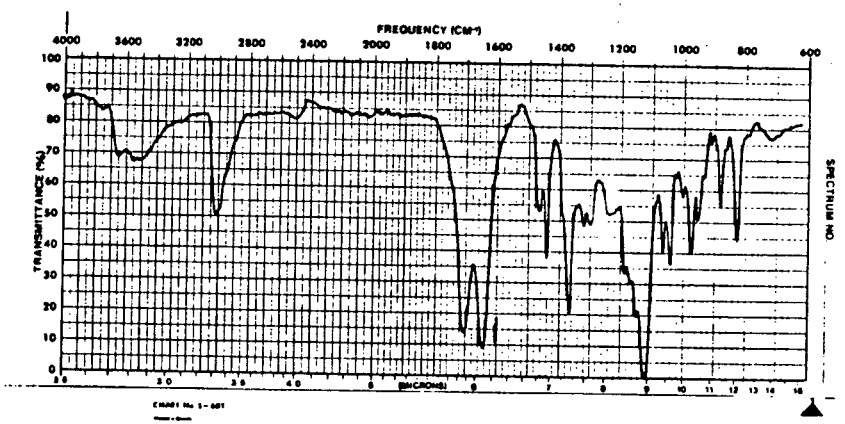

CO_2Me

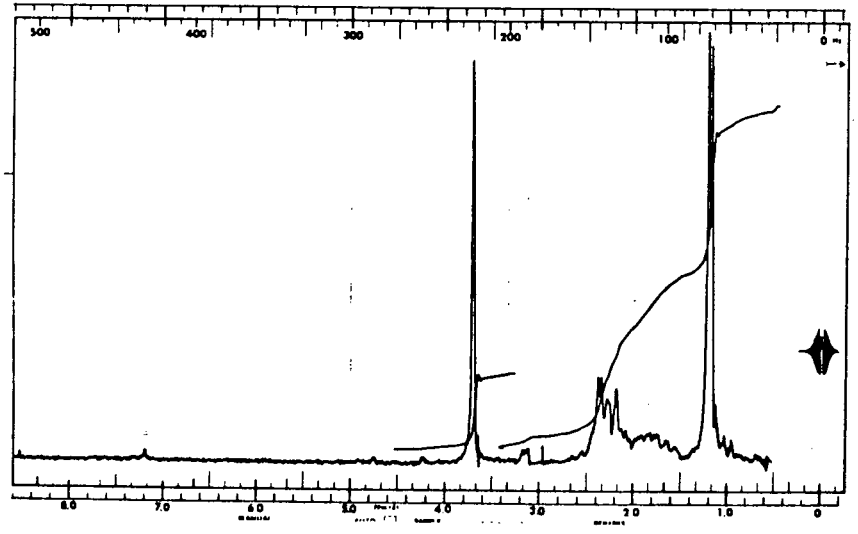
114

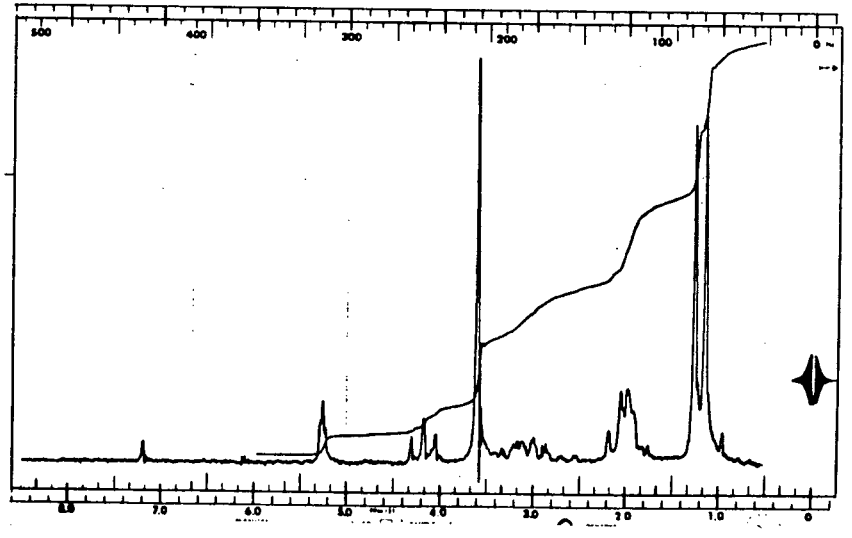

MeO_2C
H
O
OH

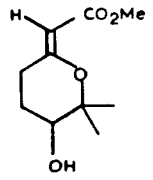
116


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.

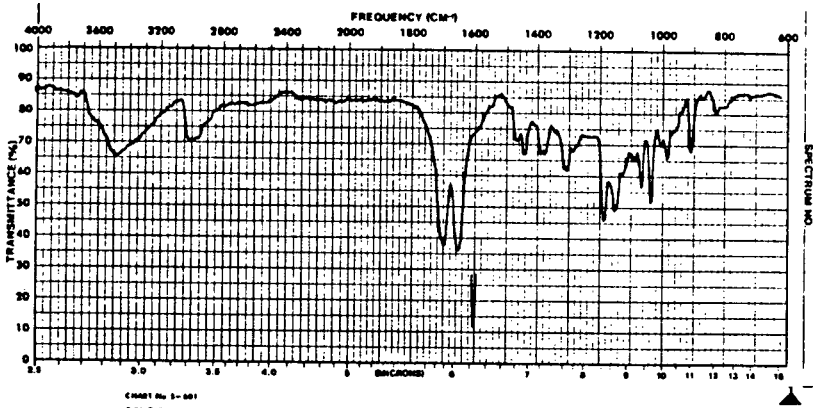

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.

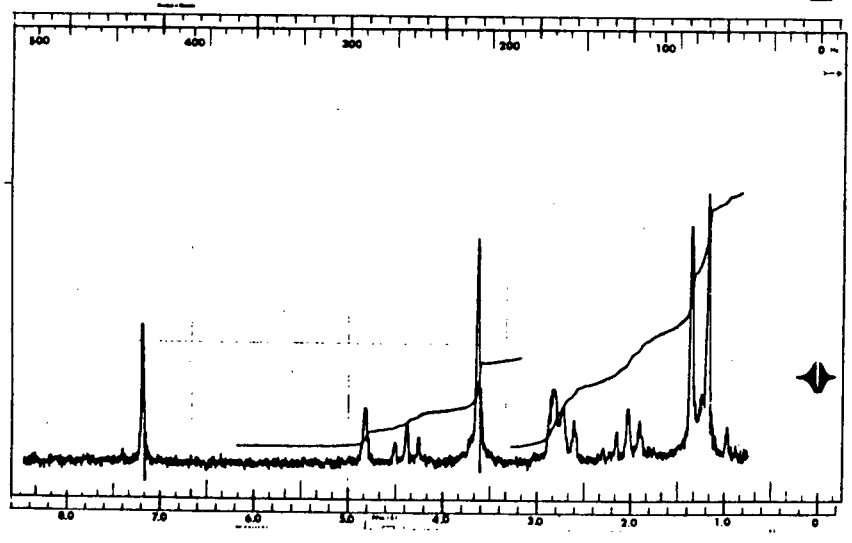


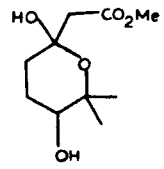



H
CO2Me
O
OH

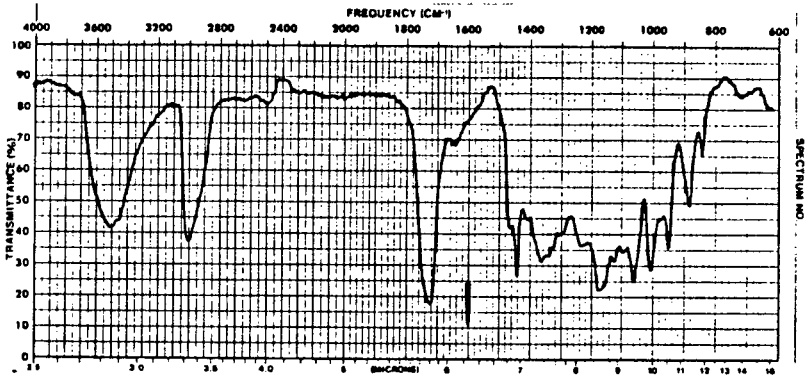
117

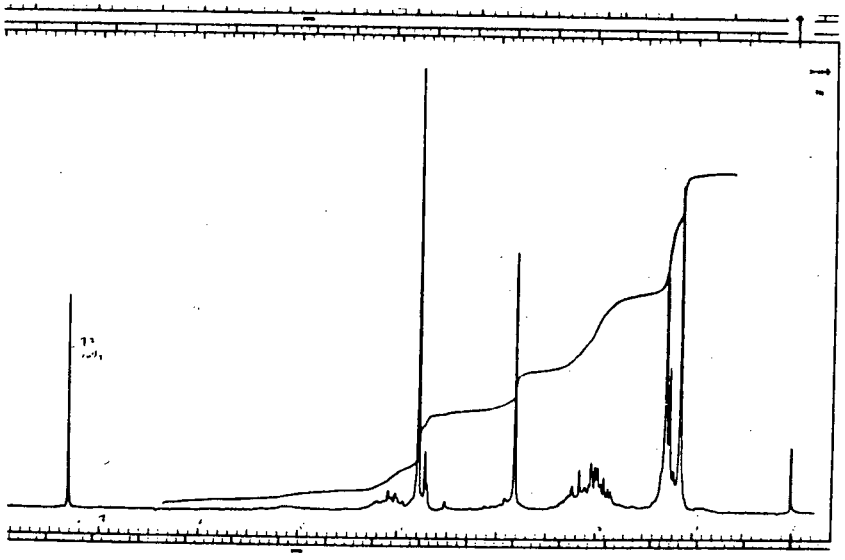

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.

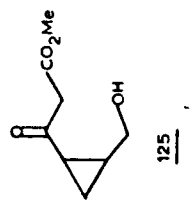



HO
CO2Me
O
OH

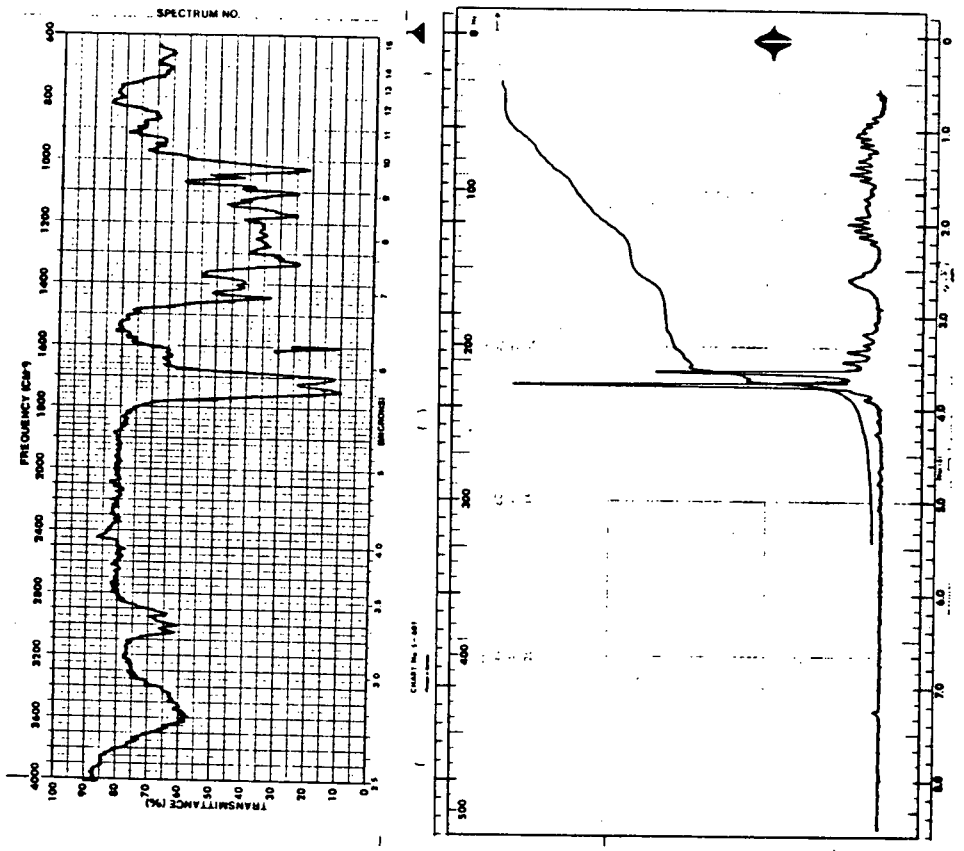
118

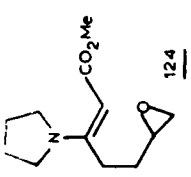

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.



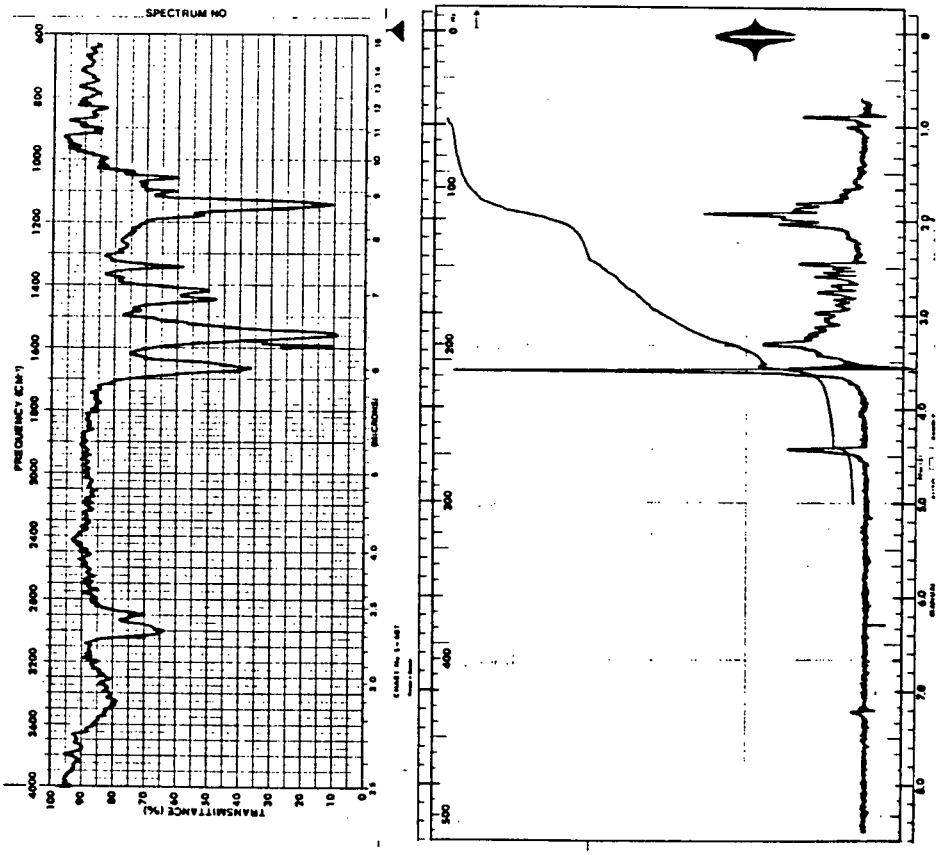

CO2Me
OH

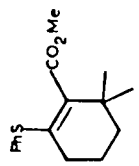
125


SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

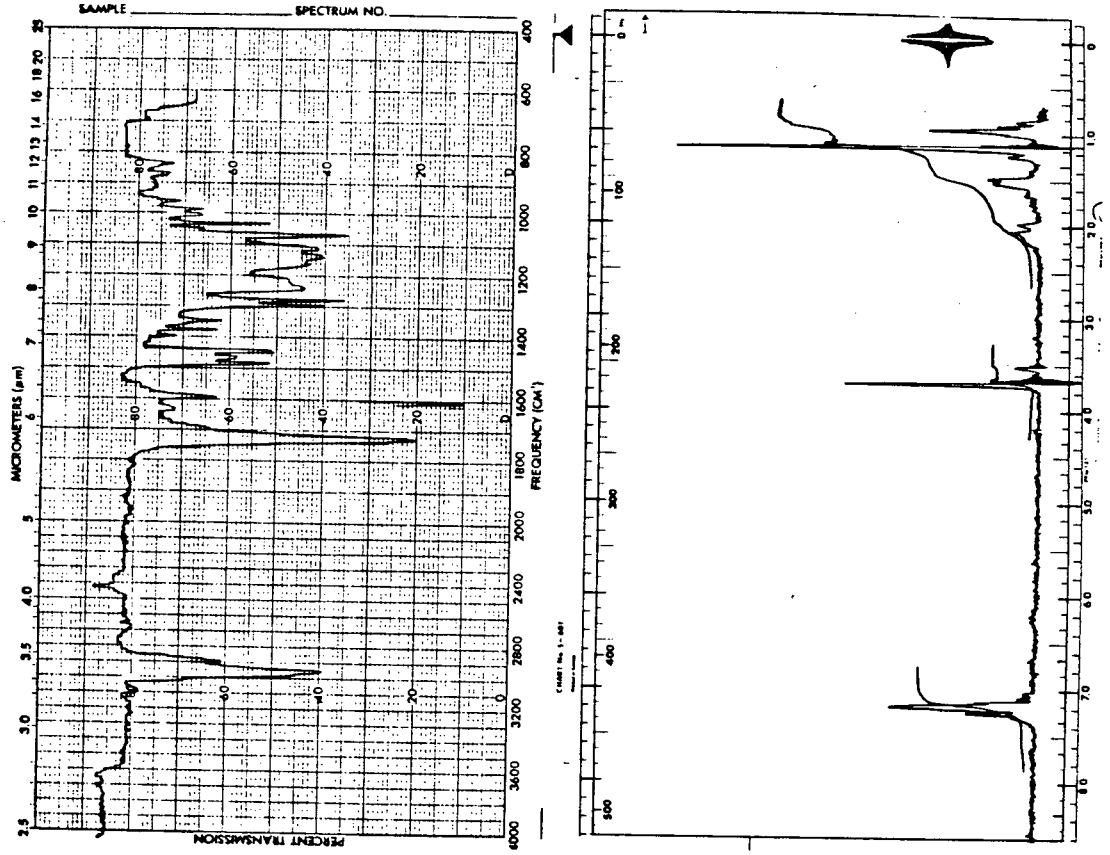

CO2Me
N

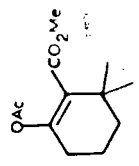
124


SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)

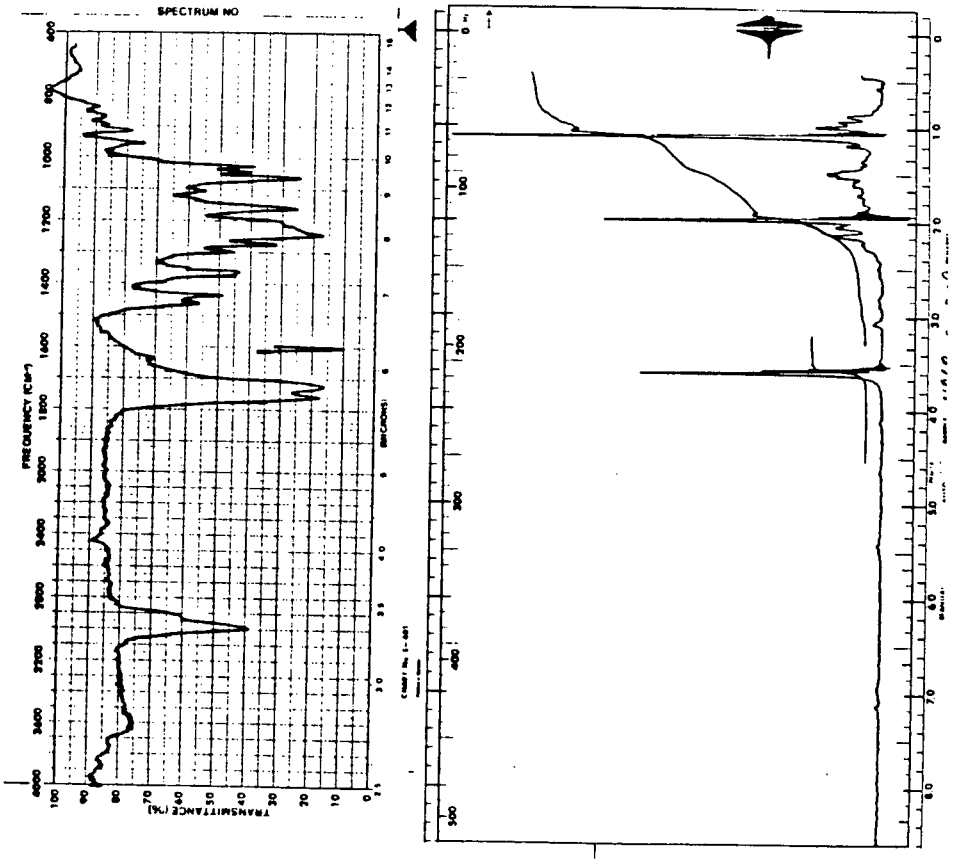


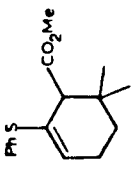
256b


SAMPLE
SPECTRUM NO.
PERCENT TRANSMISSION
MICROMETERS (μm)
FREQUENCY (CM⁻¹)

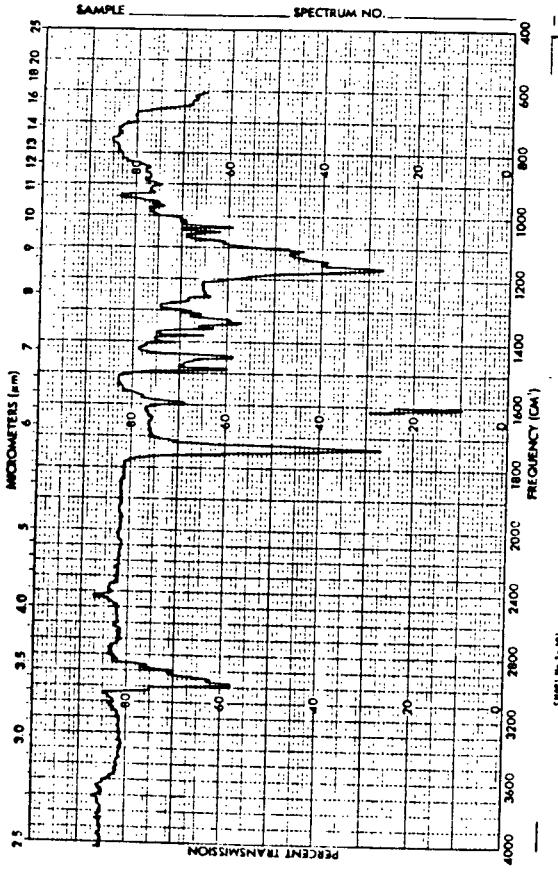


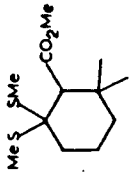
250


SPECTRUM NO
TRANSMITTANCE (%)
FREQUENCY (CM⁻¹)

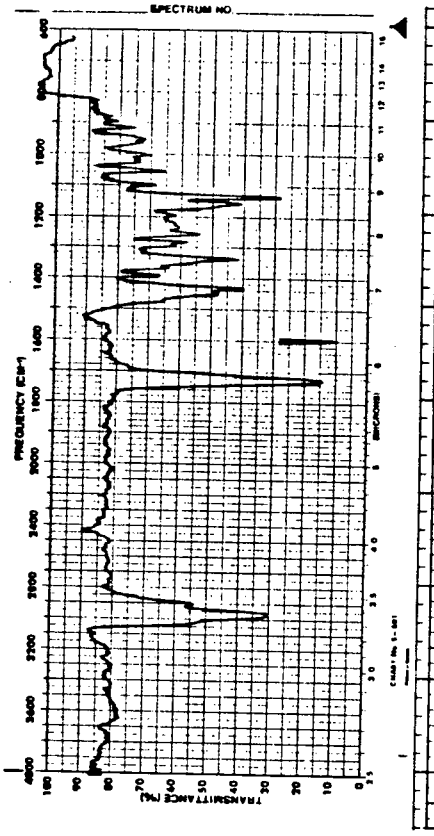


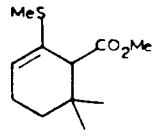
256a


SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION

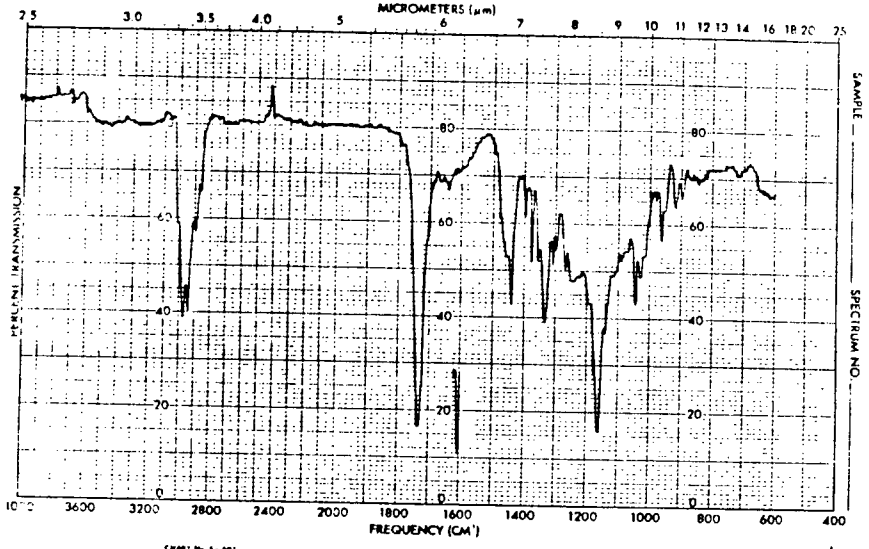


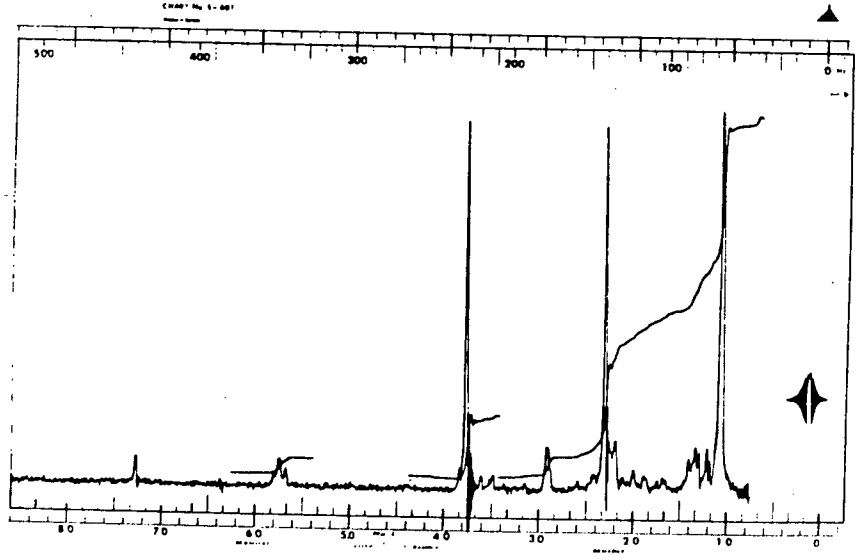
258

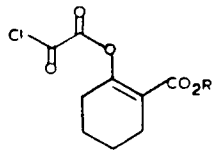

SPECTRUM NO.
FREQUENCY (CM⁻¹)
TRANSMITTANCE (%)


MeS
CO2Me

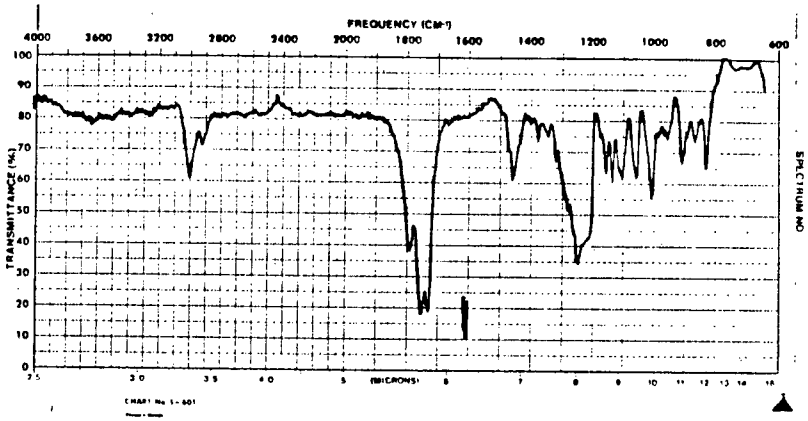
259a

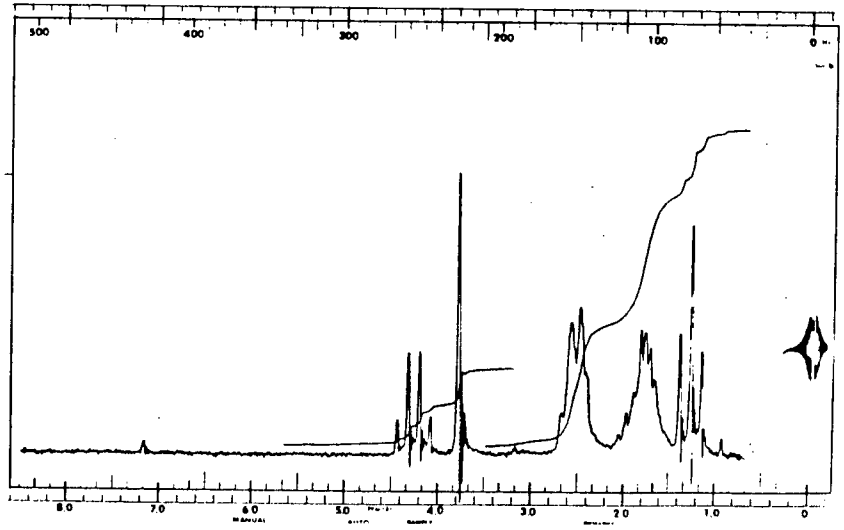

MICROMETERS (μm)
FREQUENCY (CM')
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.

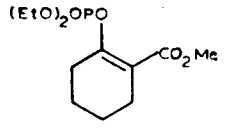



Cl
CO2R

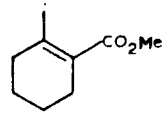
264


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS
SPECTRUM NO

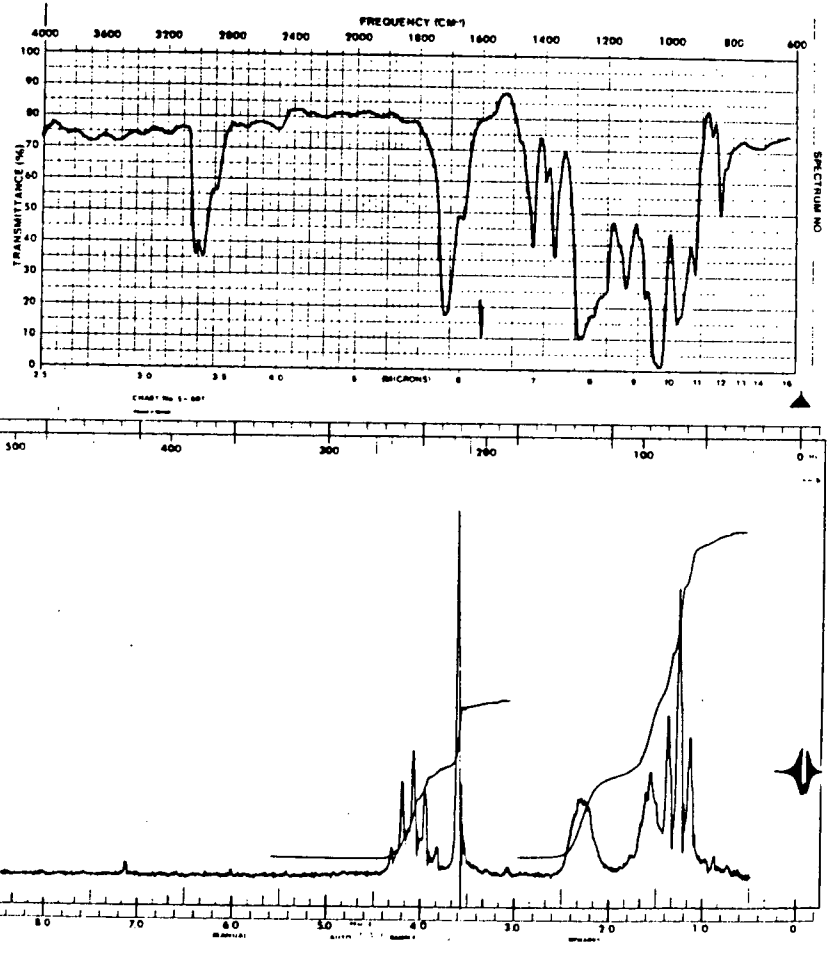


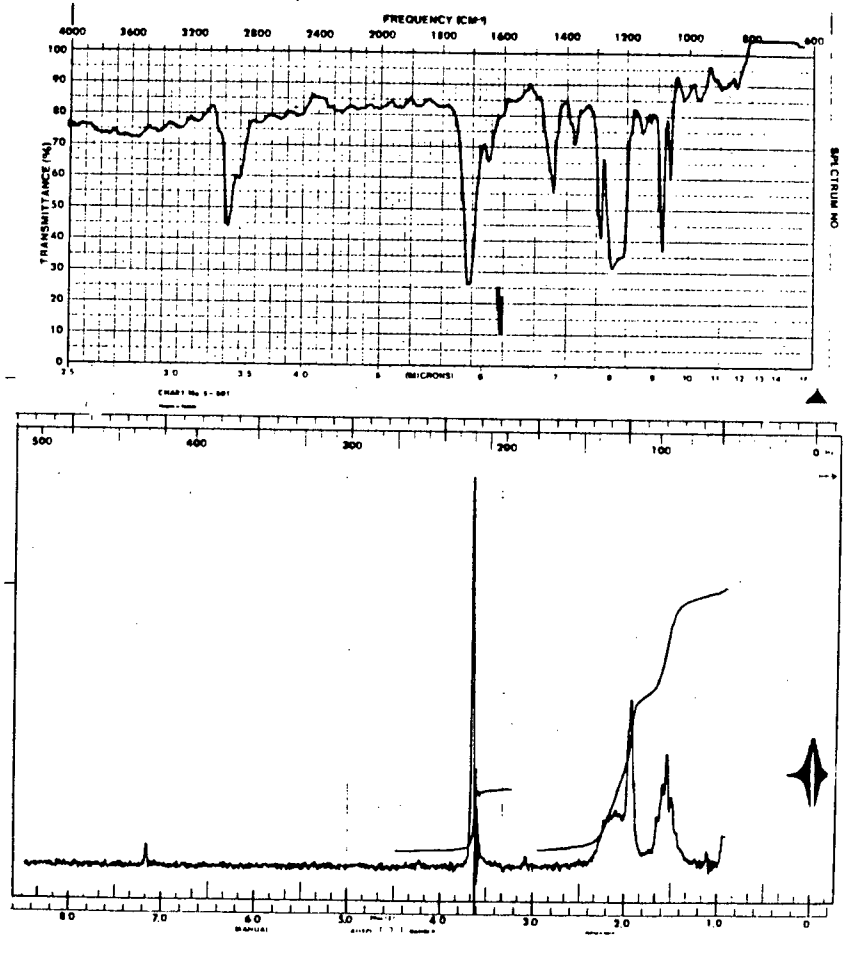

(EtO)2OPO
CO2Me

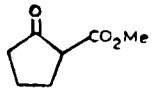
267


CO2Me

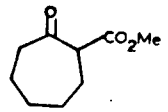
268


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

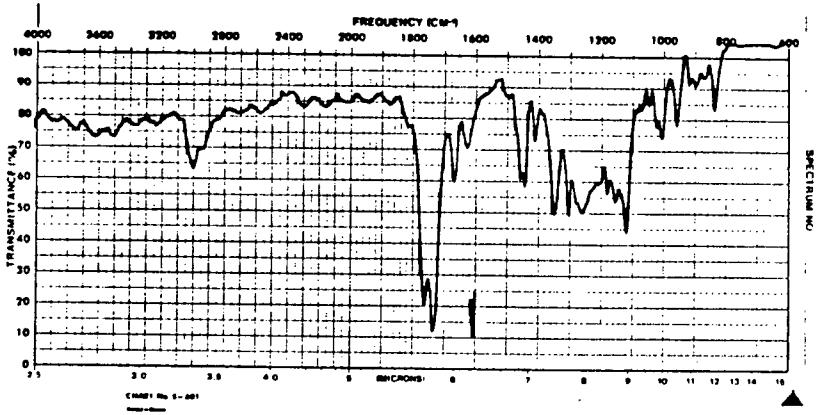

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

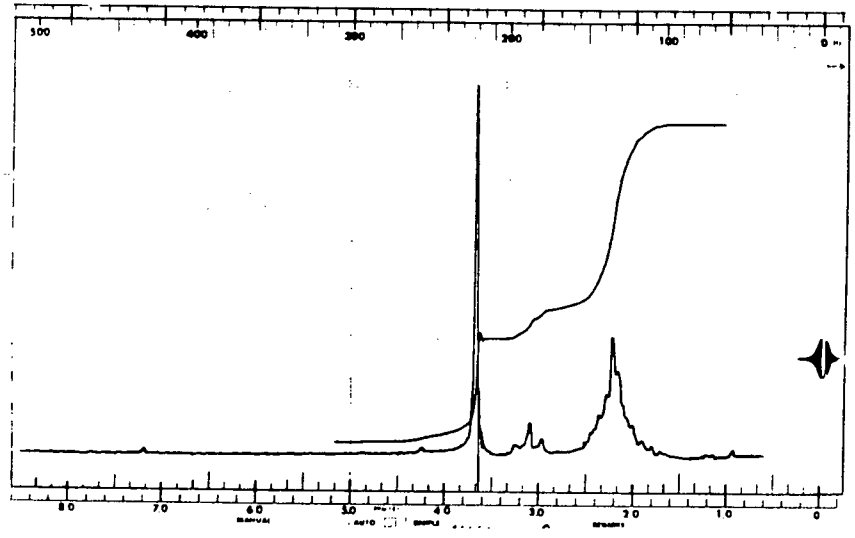

O
CO2Me

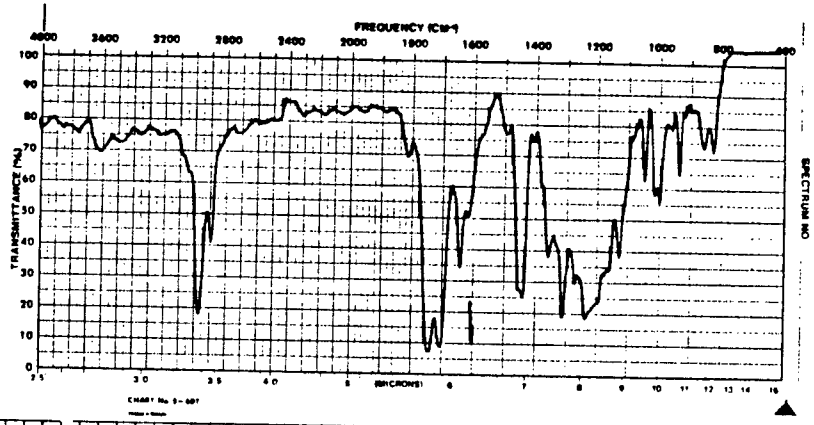
269

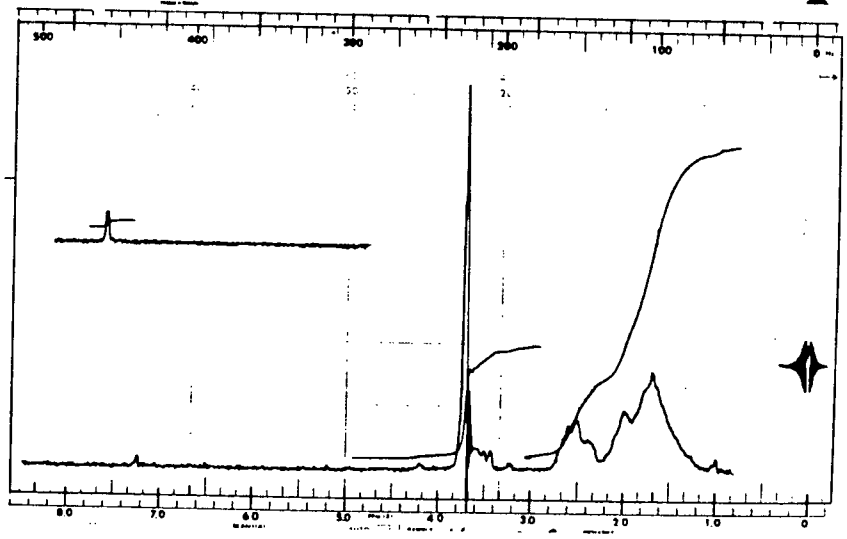

O
CO2Me

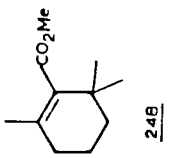
270


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO
MICRONS

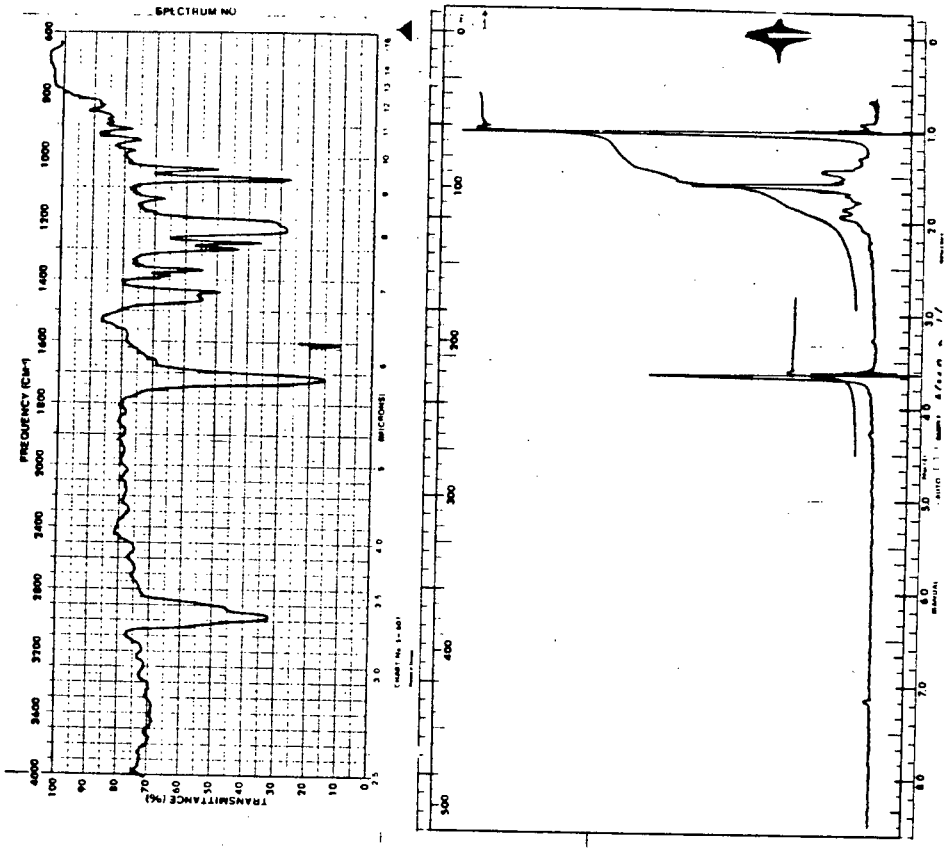


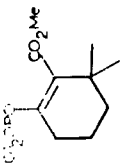

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO
MICRONS



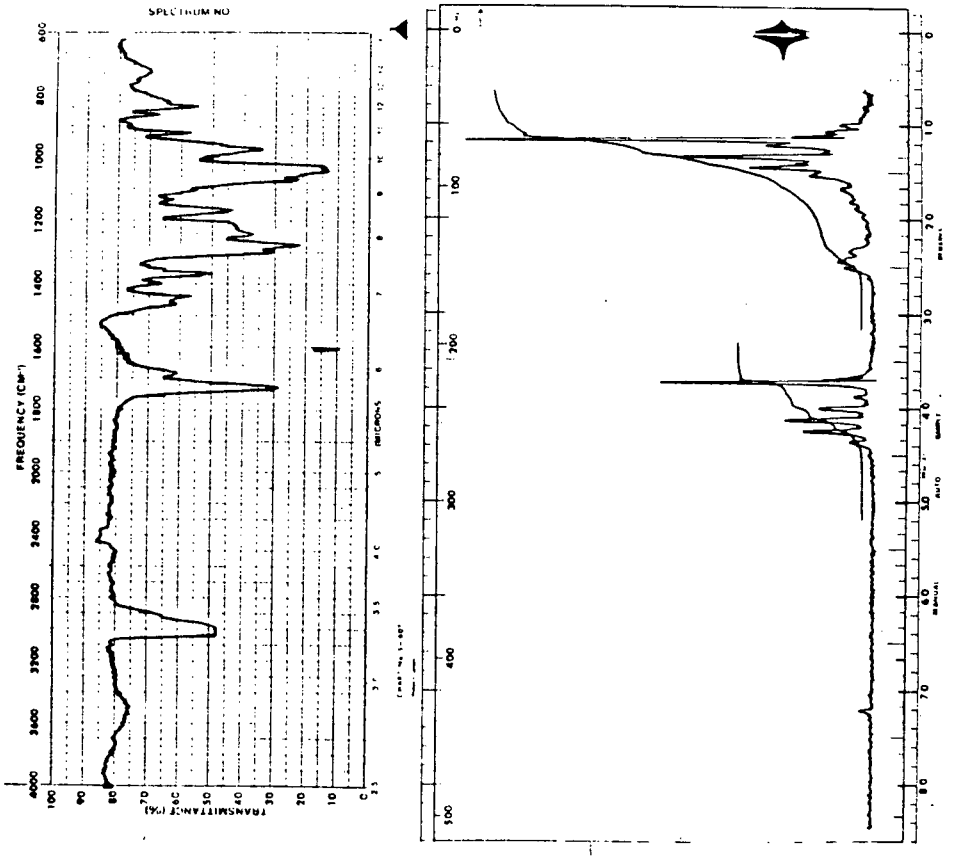

CO2Me

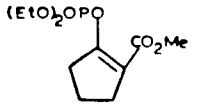
248


SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)

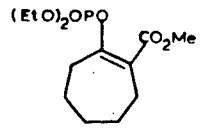

CO2Me

271

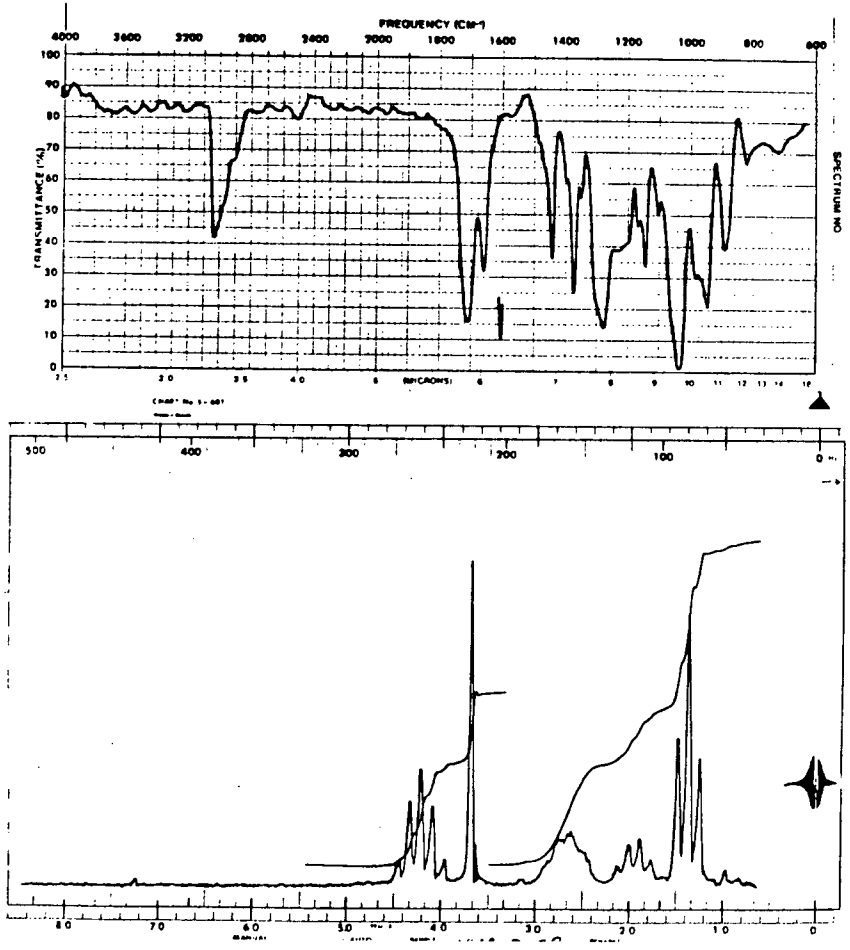

SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)

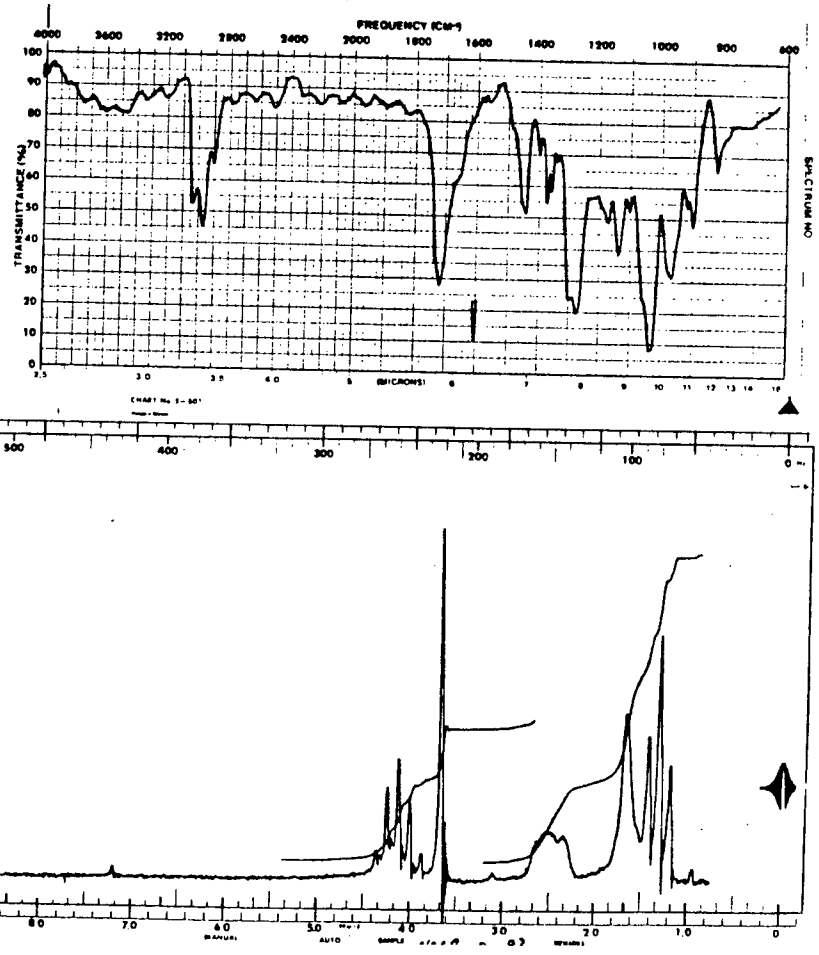

(EtO)2OPO
CO2Me

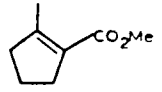
272


(EtO)2OPO
CO2Me

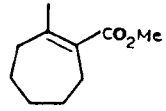
273


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO.

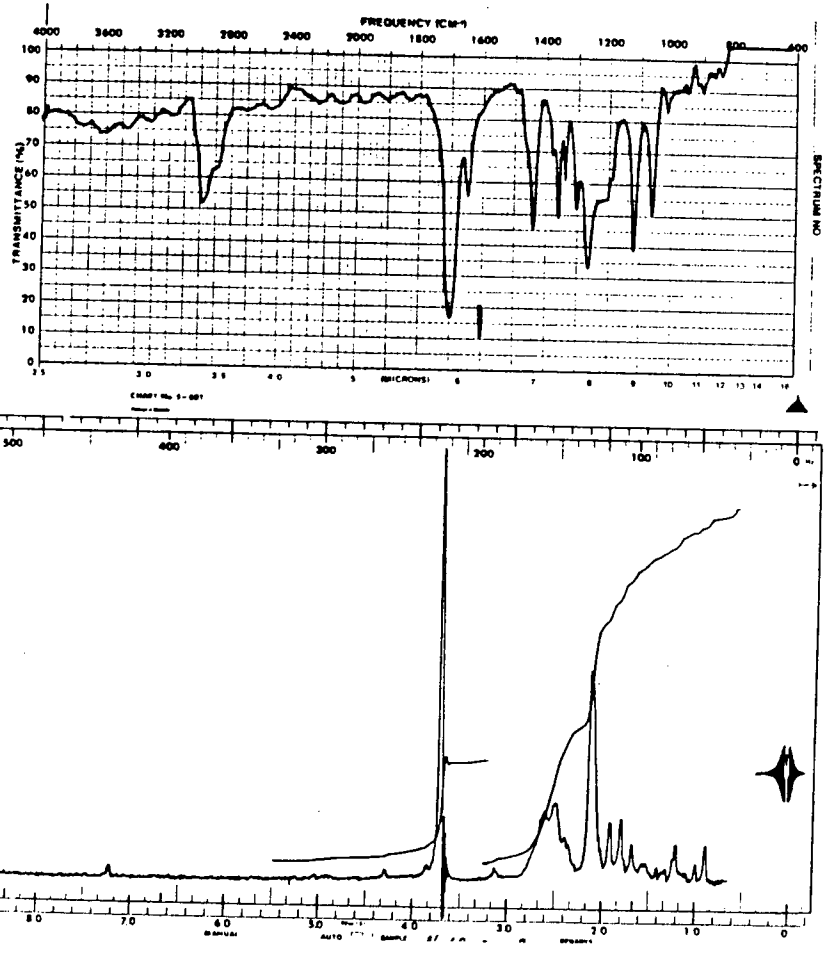

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO.

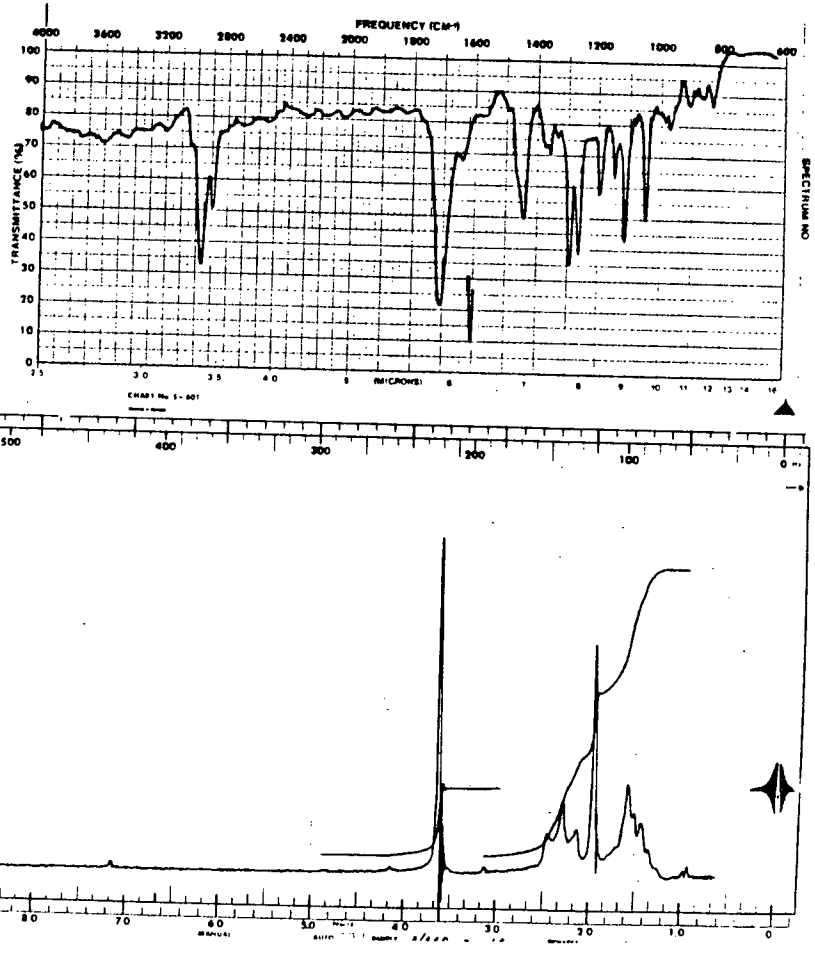

CO2Me

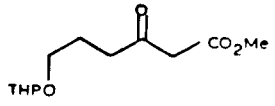
274


CO2Me

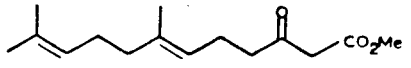
275


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

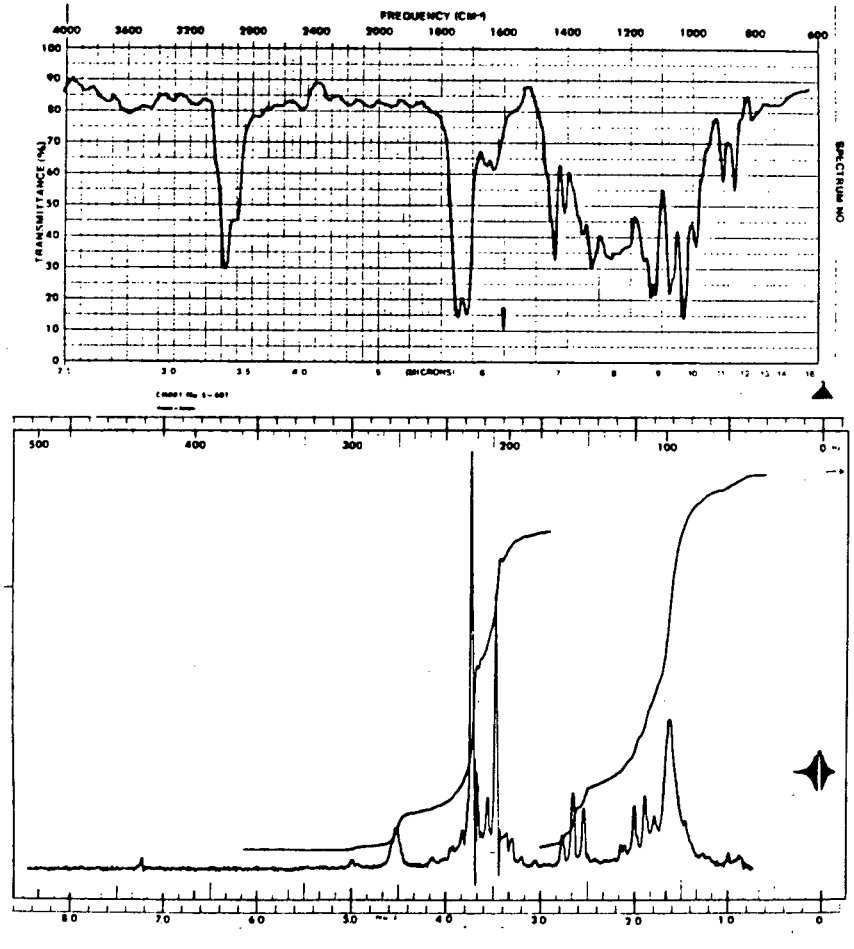

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

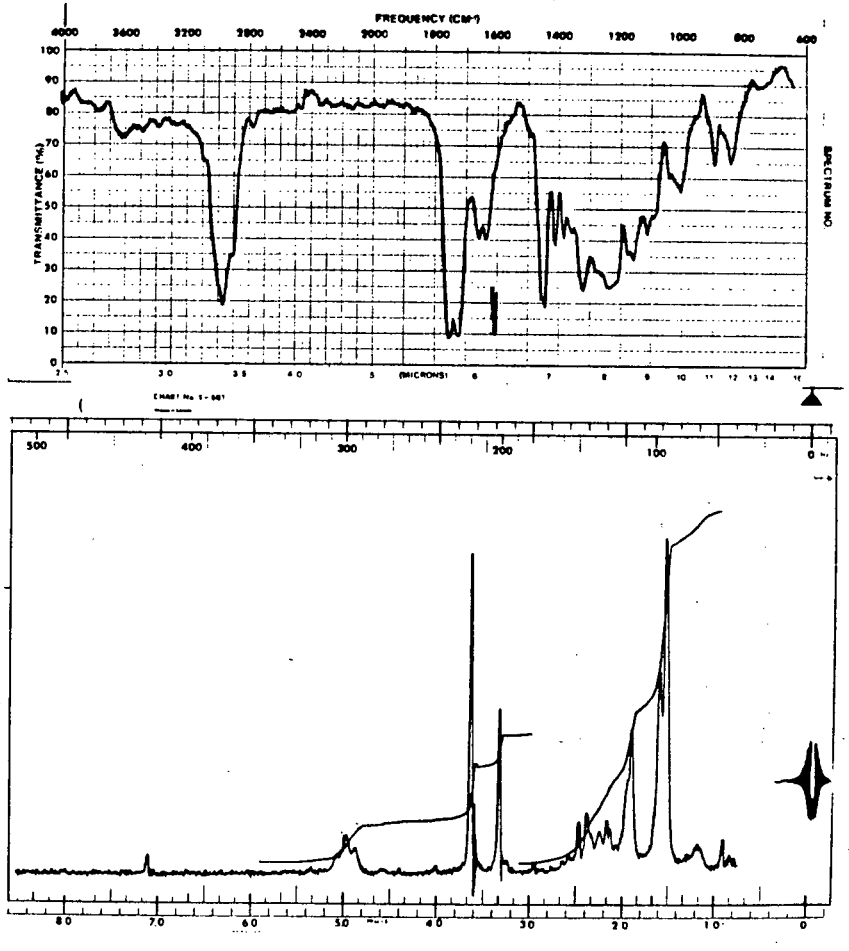

CO2Me
THPO

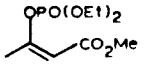
277


CO2Me

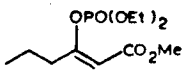
278


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO
(MICRONS)

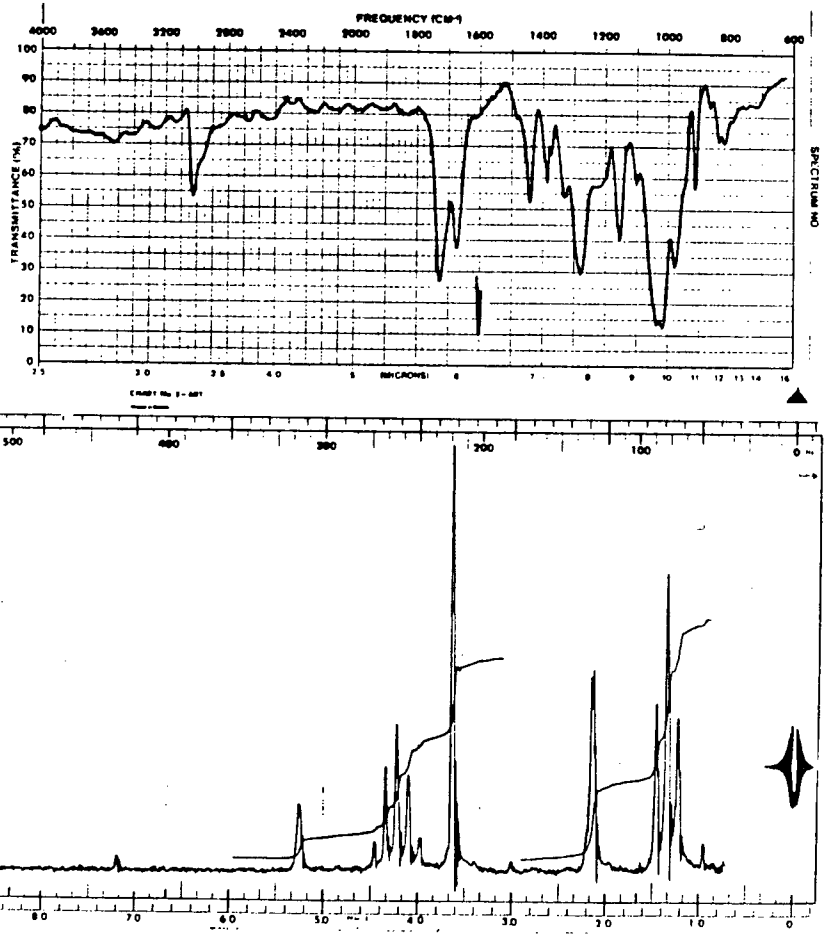

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO
(MICRONS)

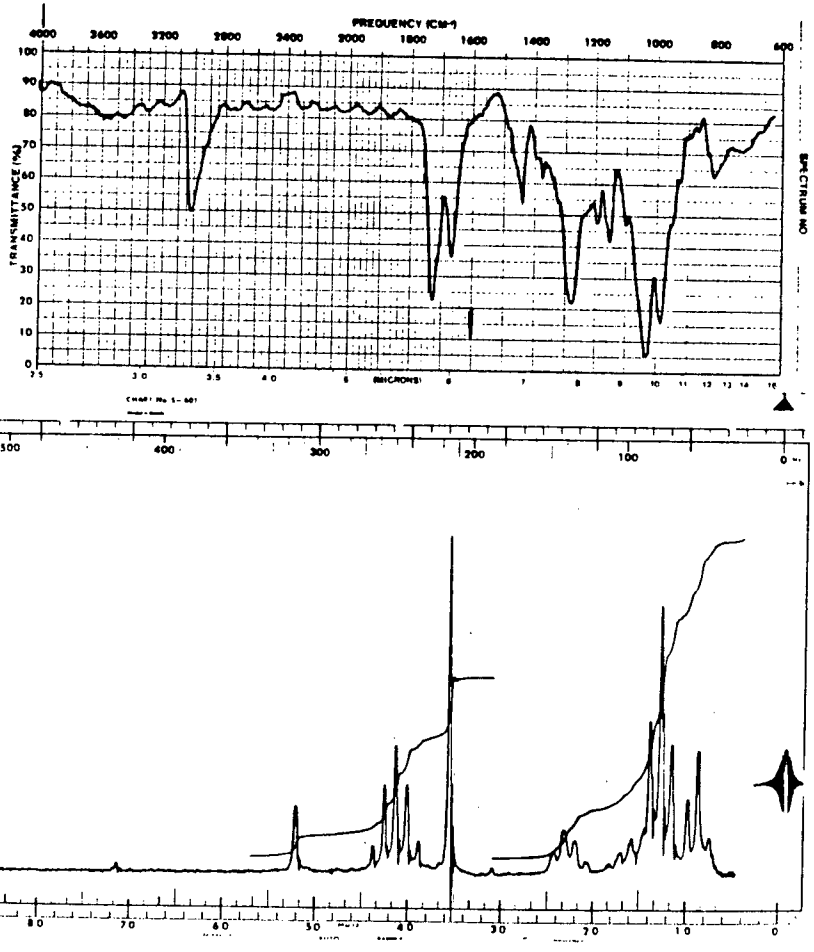

OPO(OEt)2
CO2Me

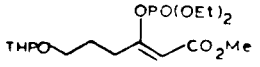
280


OPO(OEt)2
CO2Me

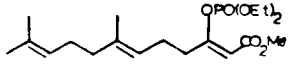
281


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

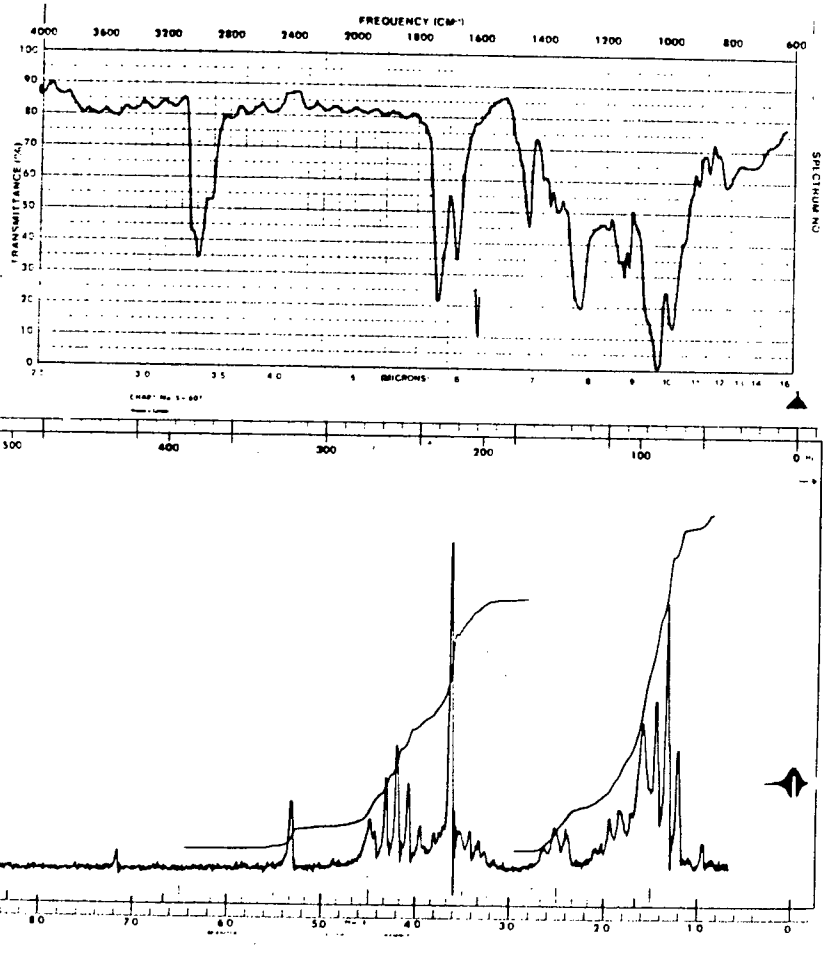

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

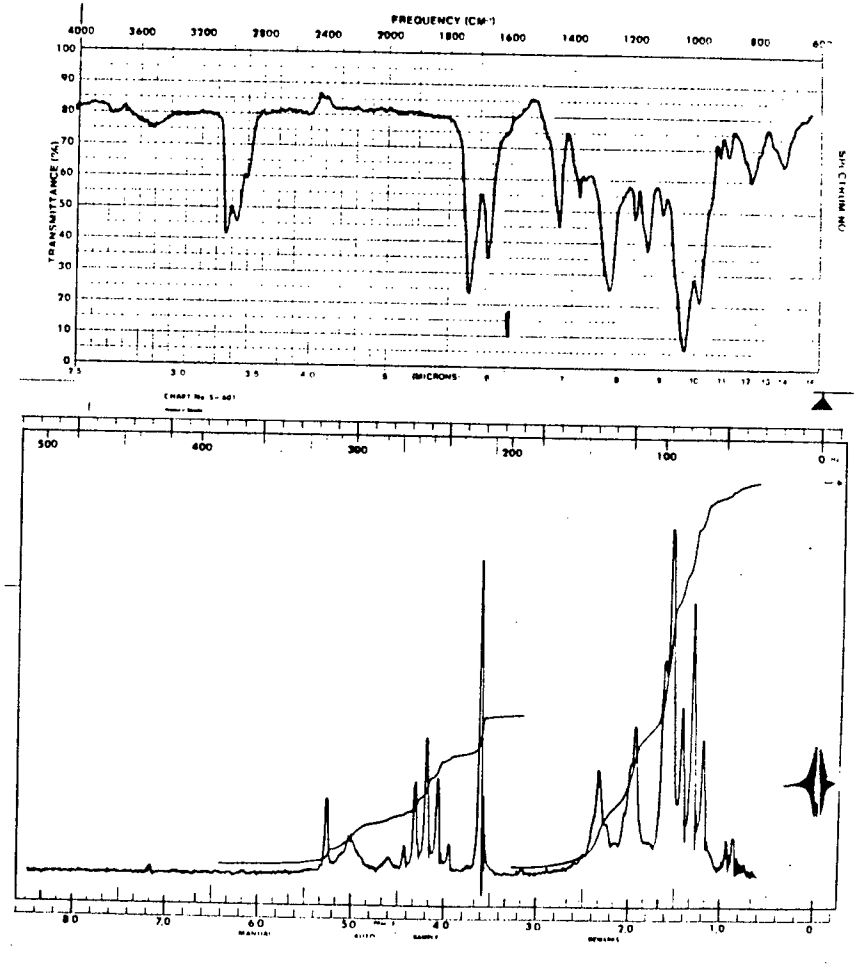

OPO(OEt)2
THPO
CO2Me

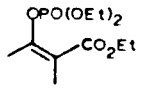
282


OPO(OEt)2
CO2Me

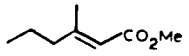
283


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS
SPECTRUM NO

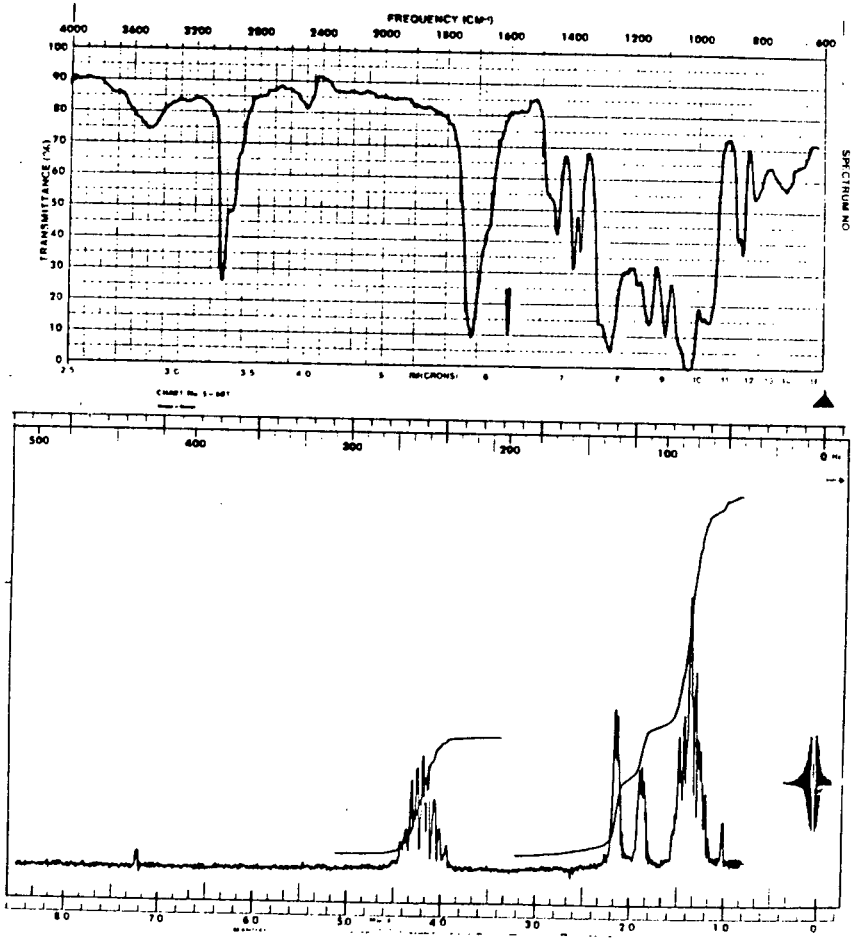

FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS
SPECTRUM NO

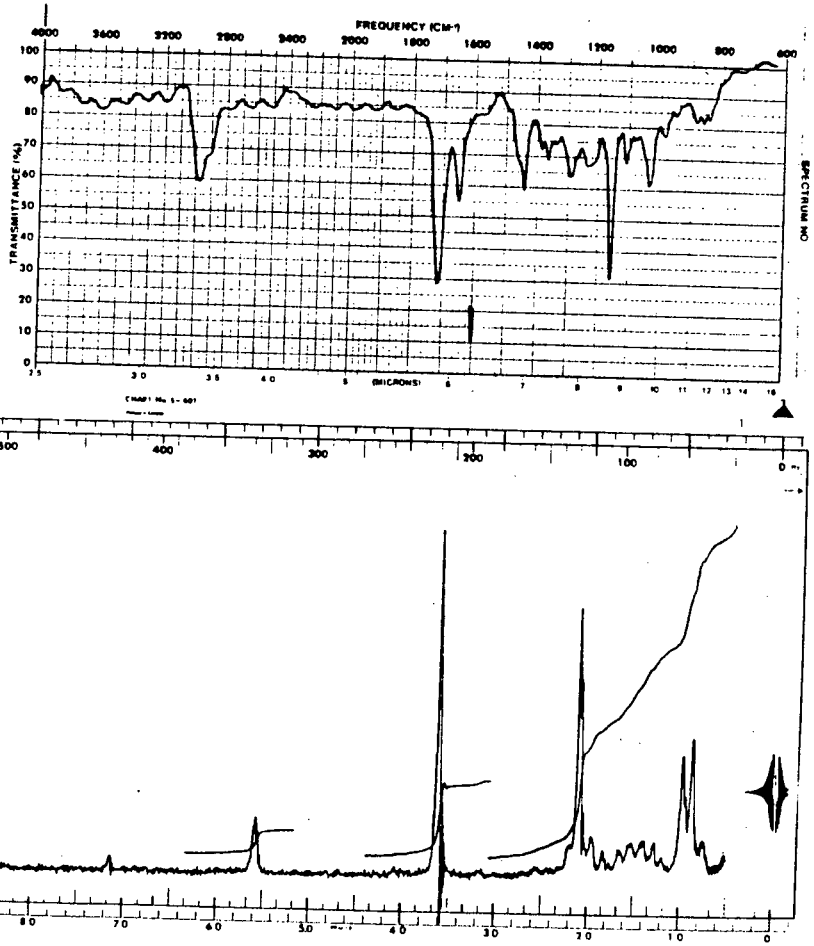

OPO(OEt)2
CO2Et

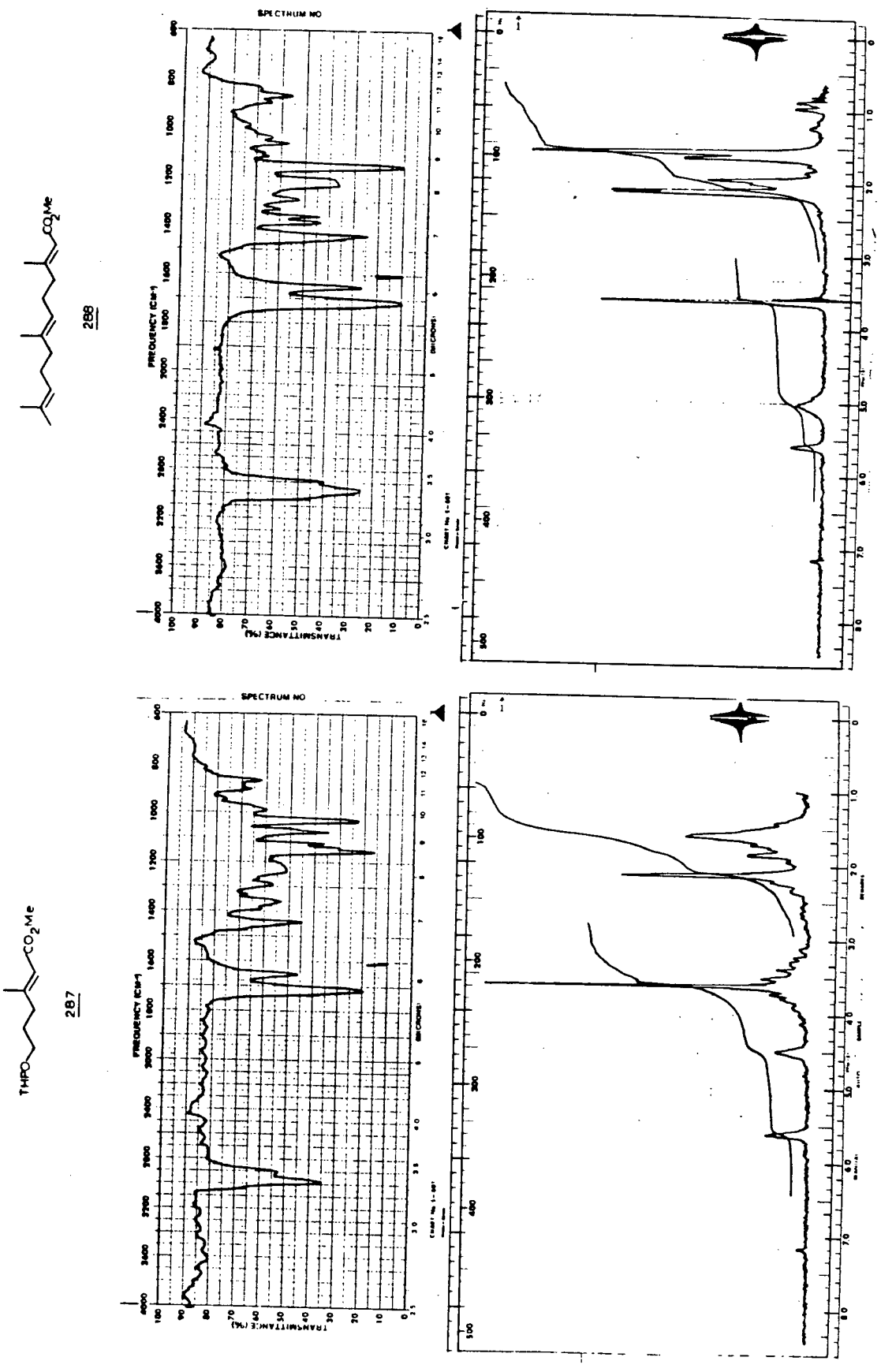
284


CO2Me

286

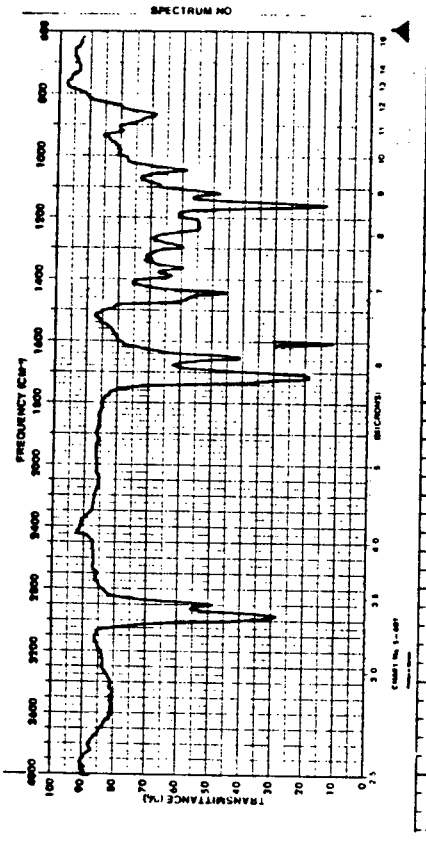

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO
(MICRONS)

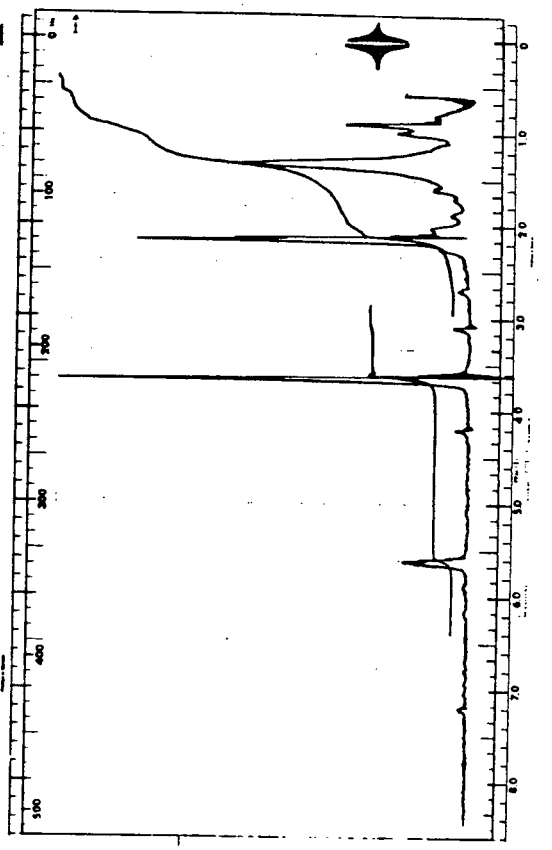

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO
(MICRONS)

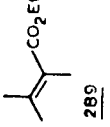

THPO
CO2Me
287
CO2Me
288
SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)
SECONDS


CO2Me

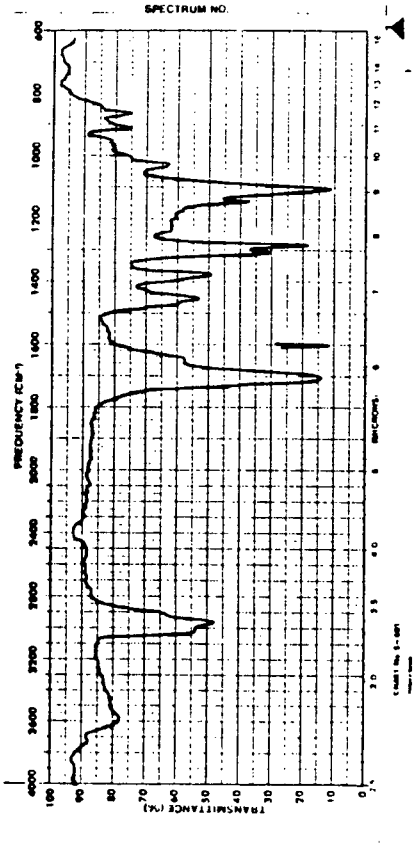
291

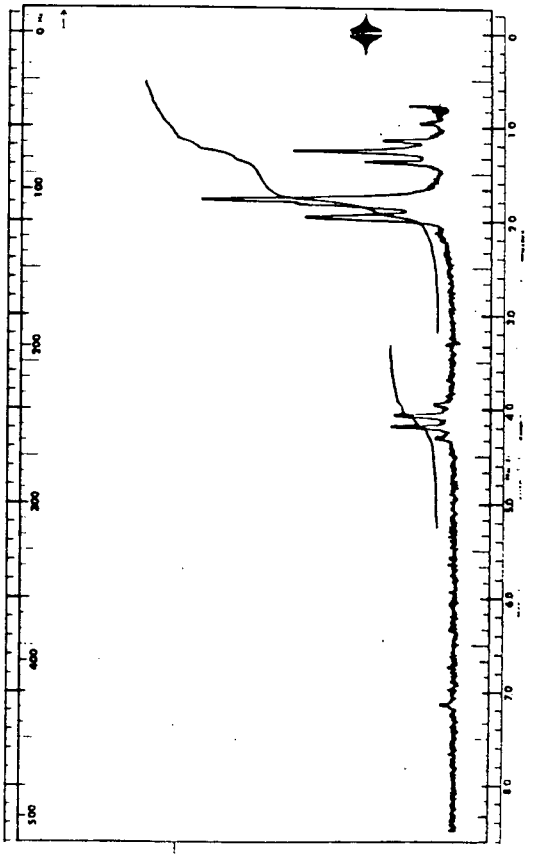

SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)

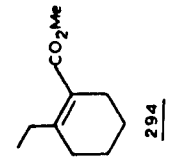



CO2Et

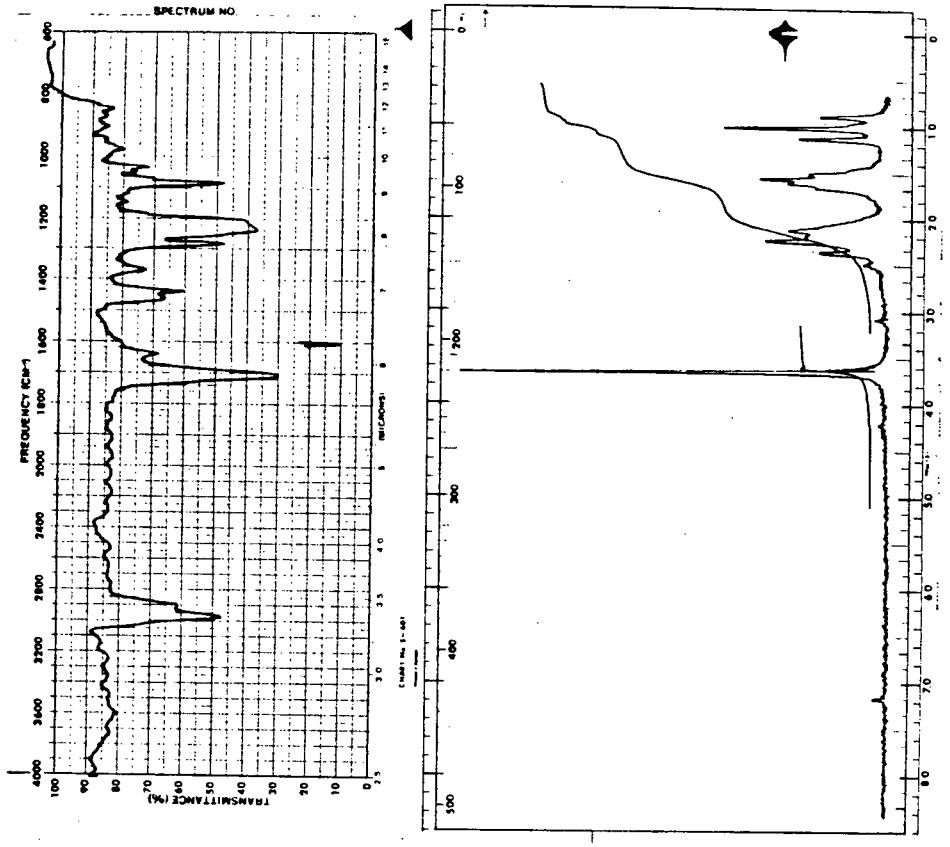
289

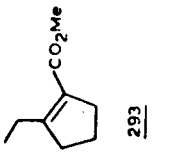

SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)



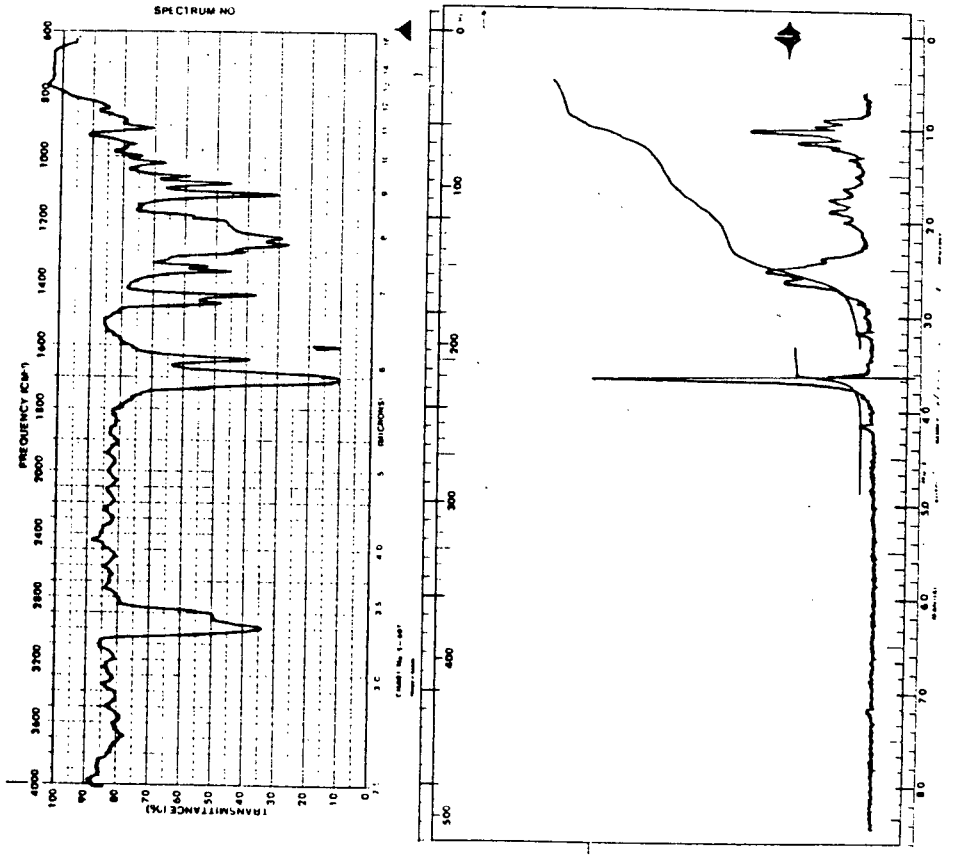

CO2Me

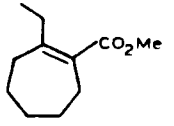
294


SPECTRUM NO.
FREQUENCY (CM-1)
MICRONS
TRANSMITTANCE (%)


CO2Me

293


SPECTRUM NO.
FREQUENCY (CM-1)
MICRONS
TRANSMITTANCE (%)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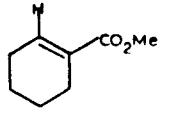
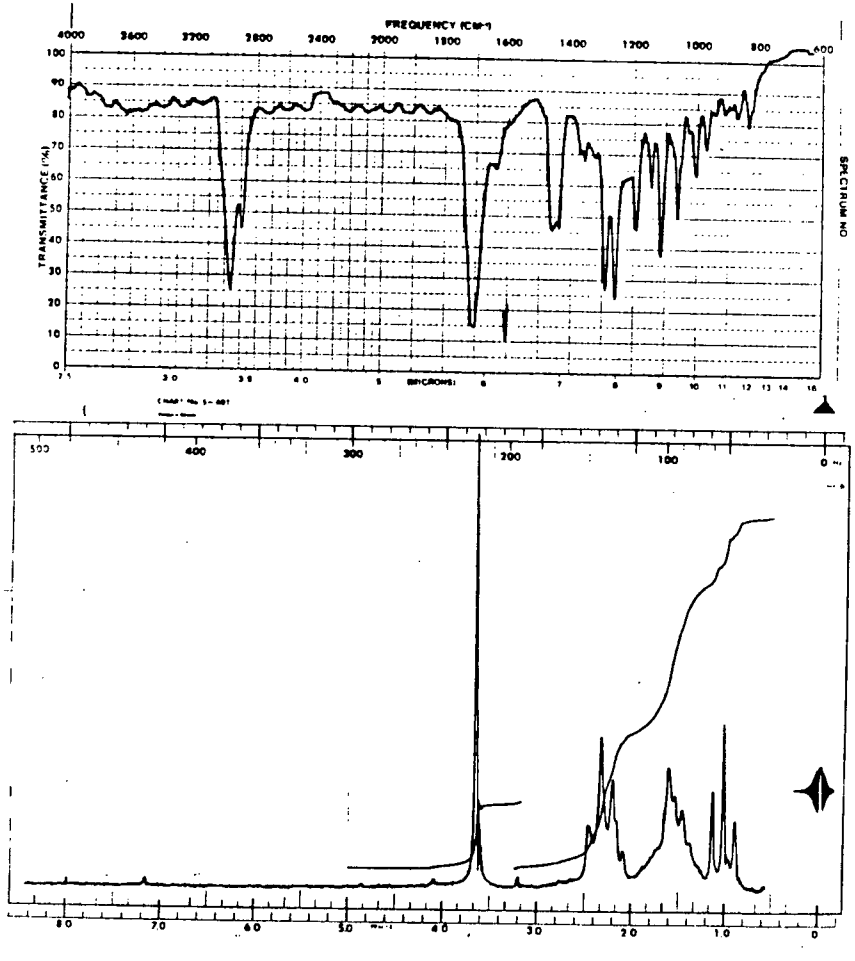
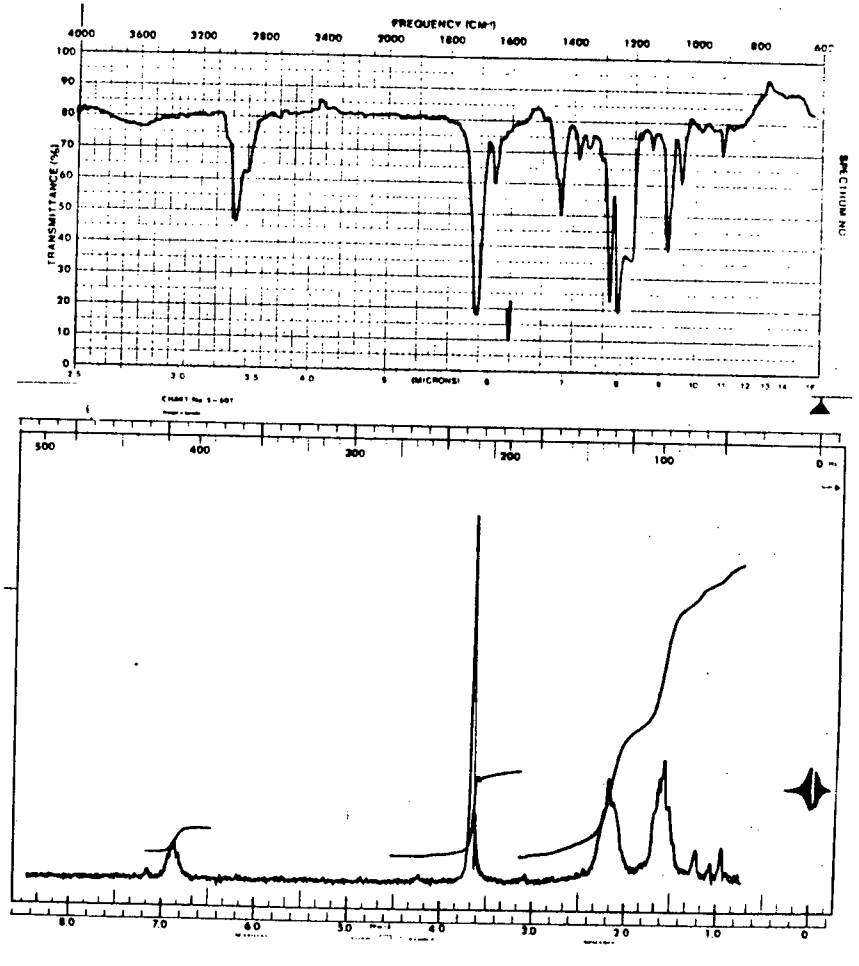
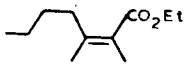
295


CO2Me

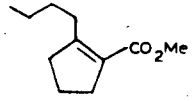
297


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS
SPECTRUM NO

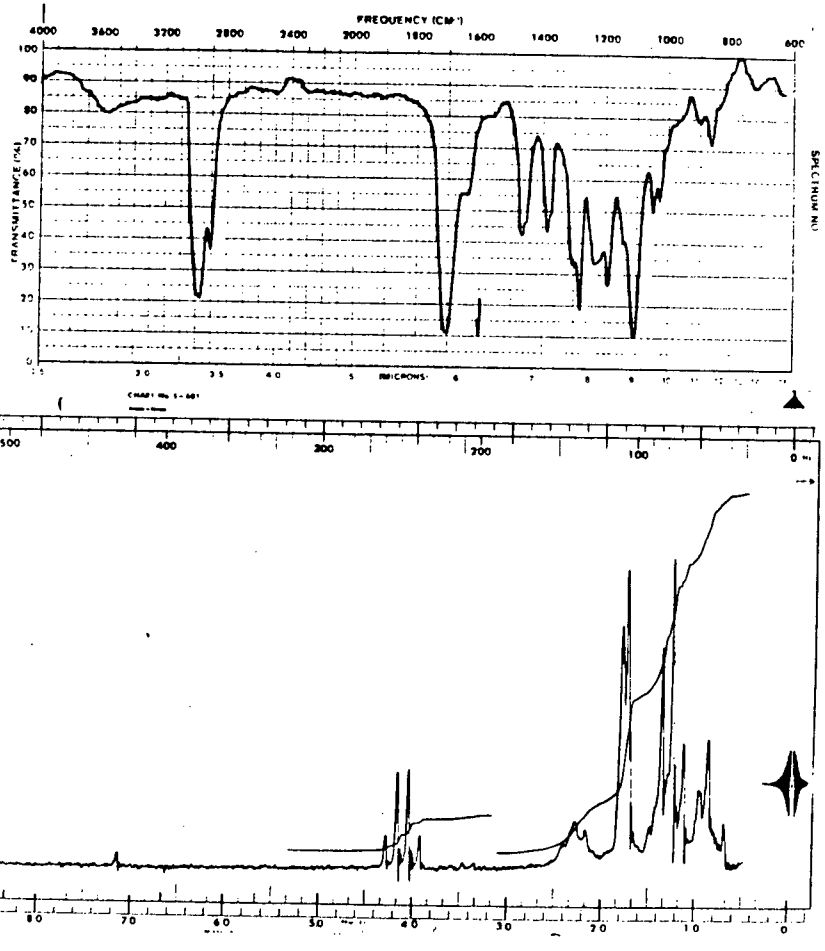

FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS
SPECTRUM NO

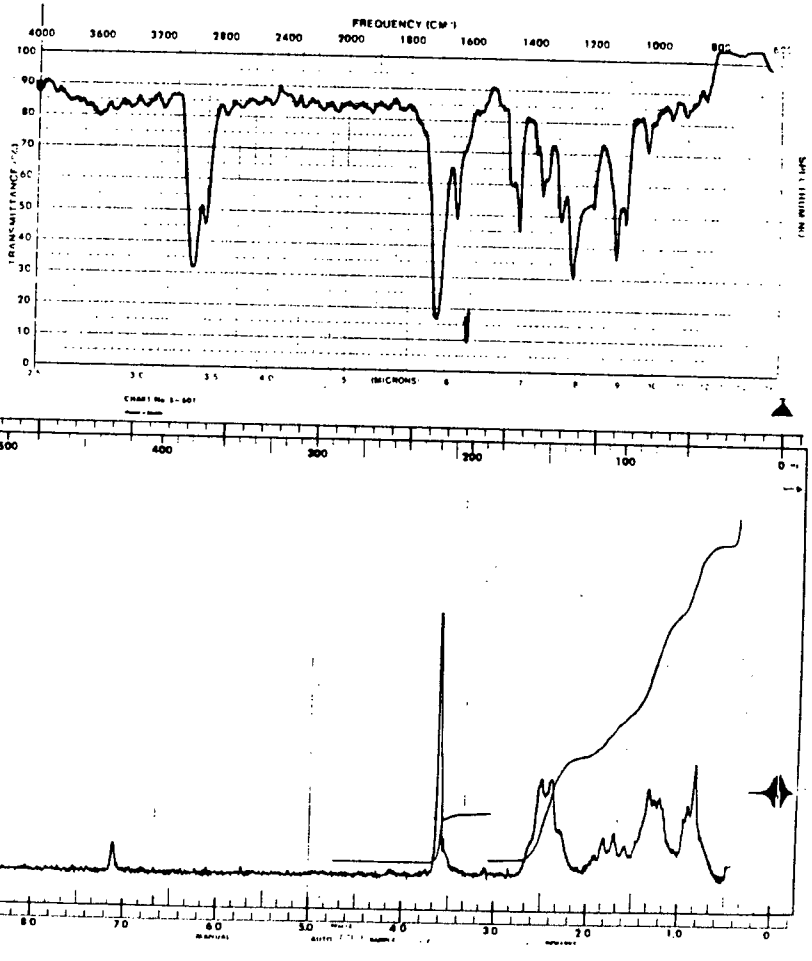

CO2Et

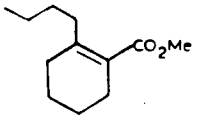
Z-298


CO2Me

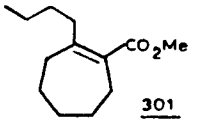
299


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS

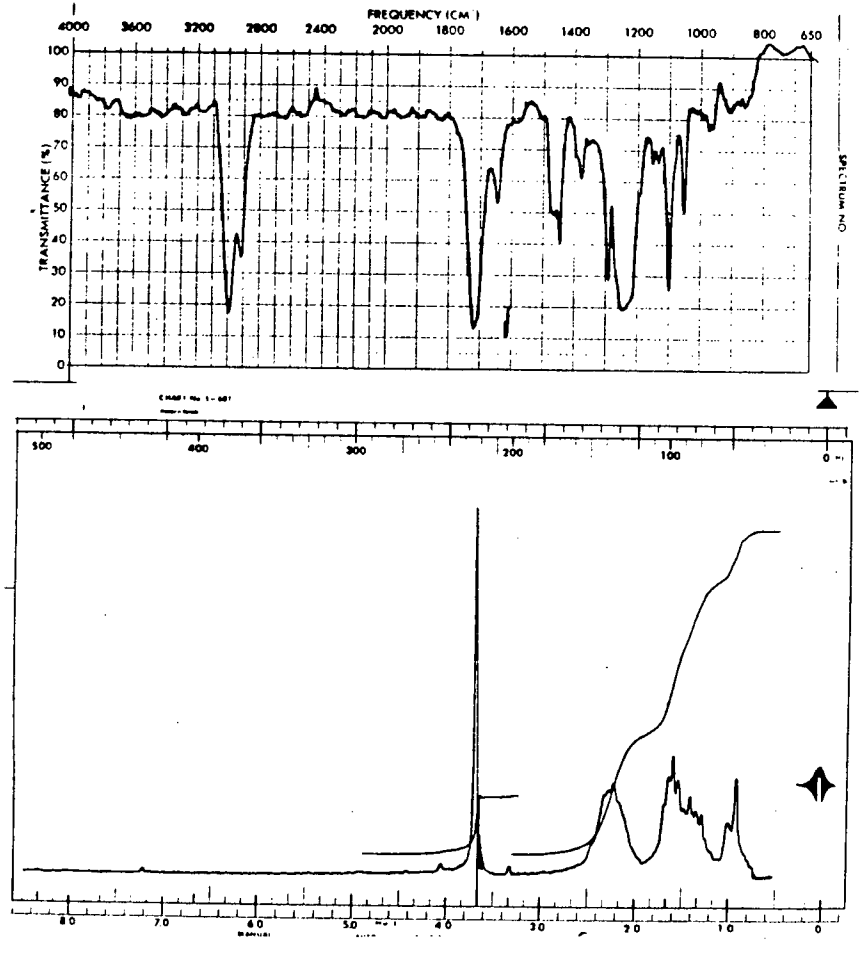

FREQUENCY (CM-1)
MICRONS

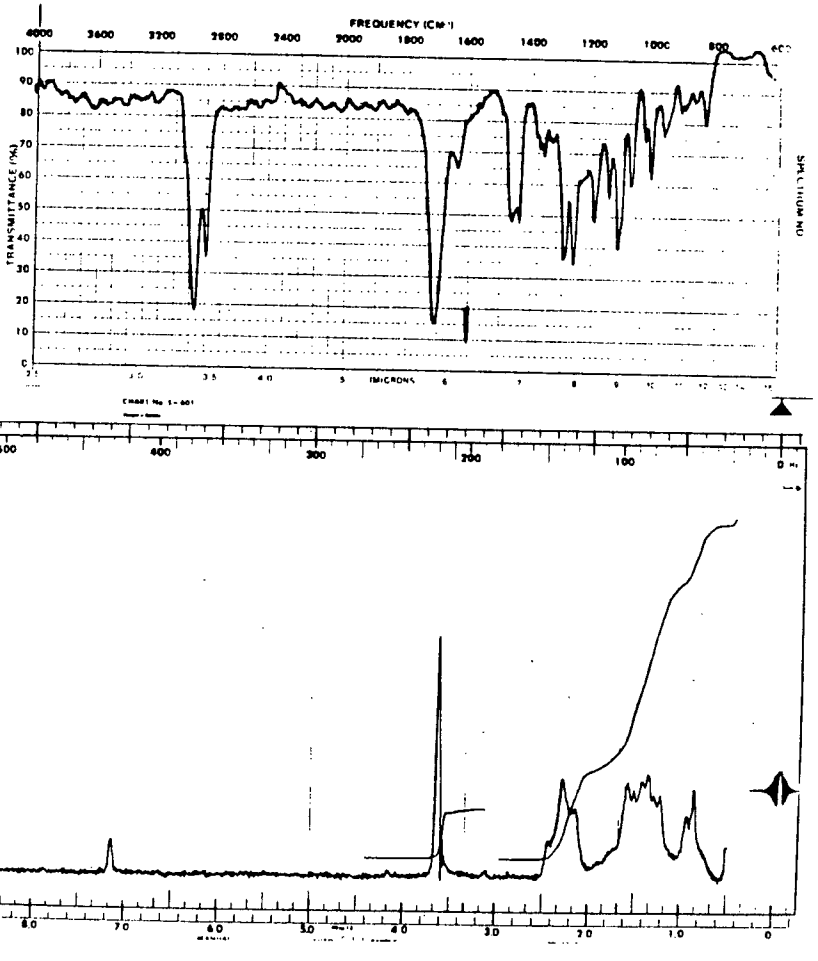

CO2Me

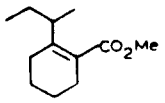
300


CO2Me

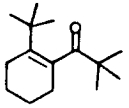
301


FREQUENCY (CM-1)
TRANSMITTANCE (%)

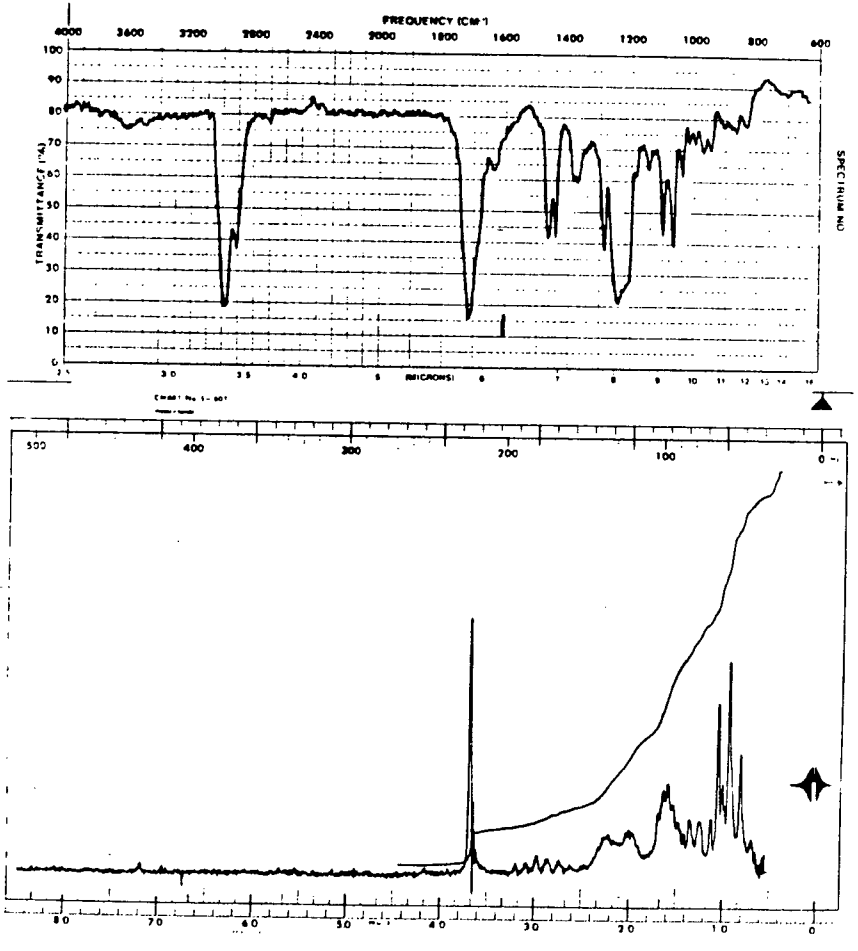

FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS

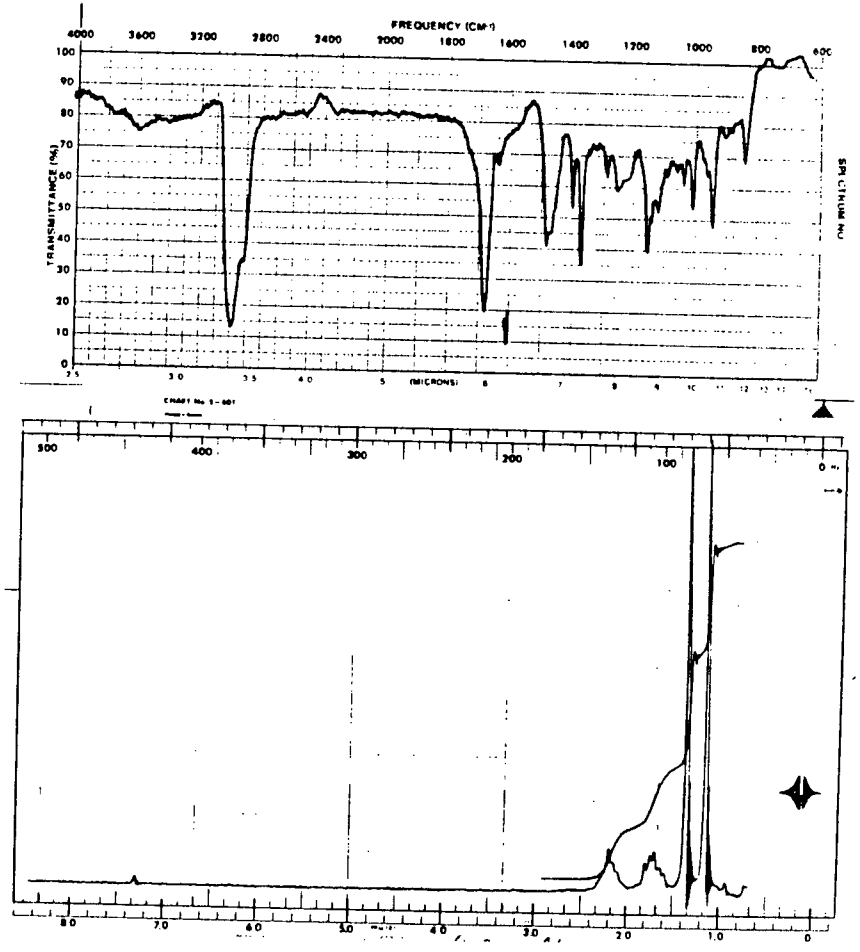

CO2Me

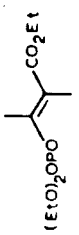
302



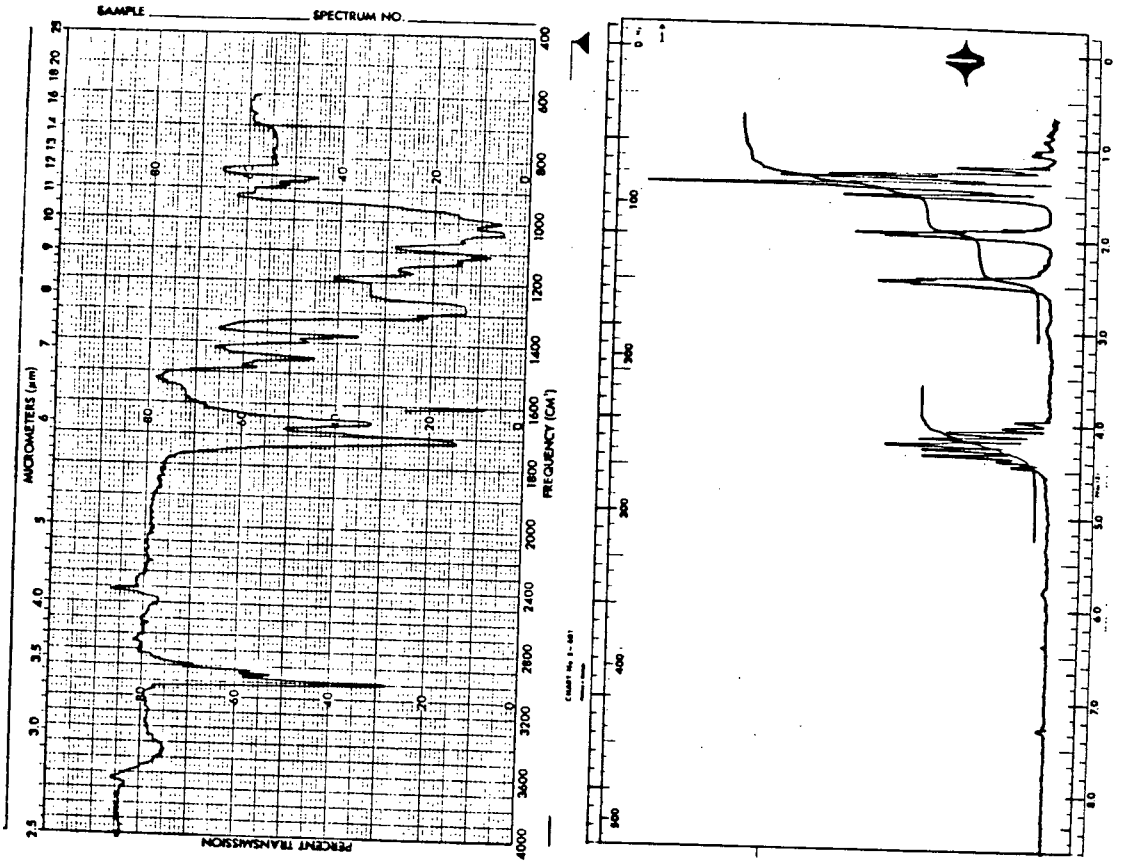
303

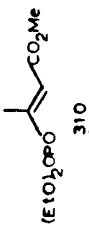

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
(MICRONS)


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
(MICRONS)

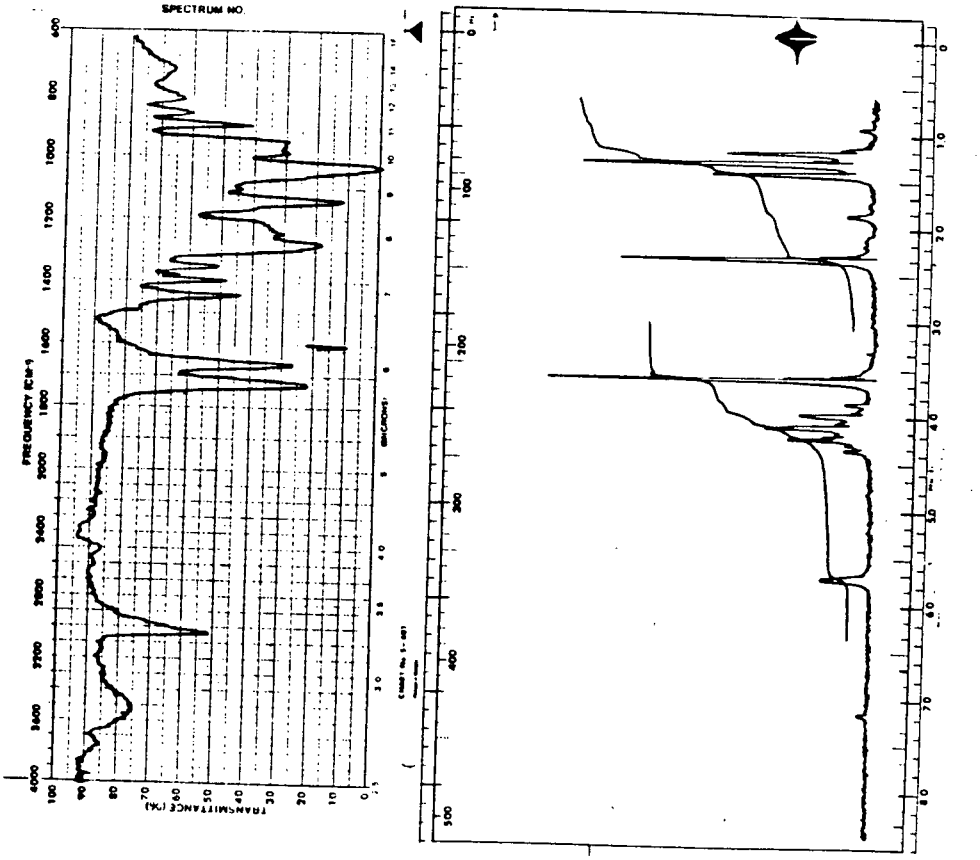


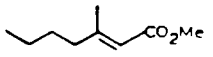
311


SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION

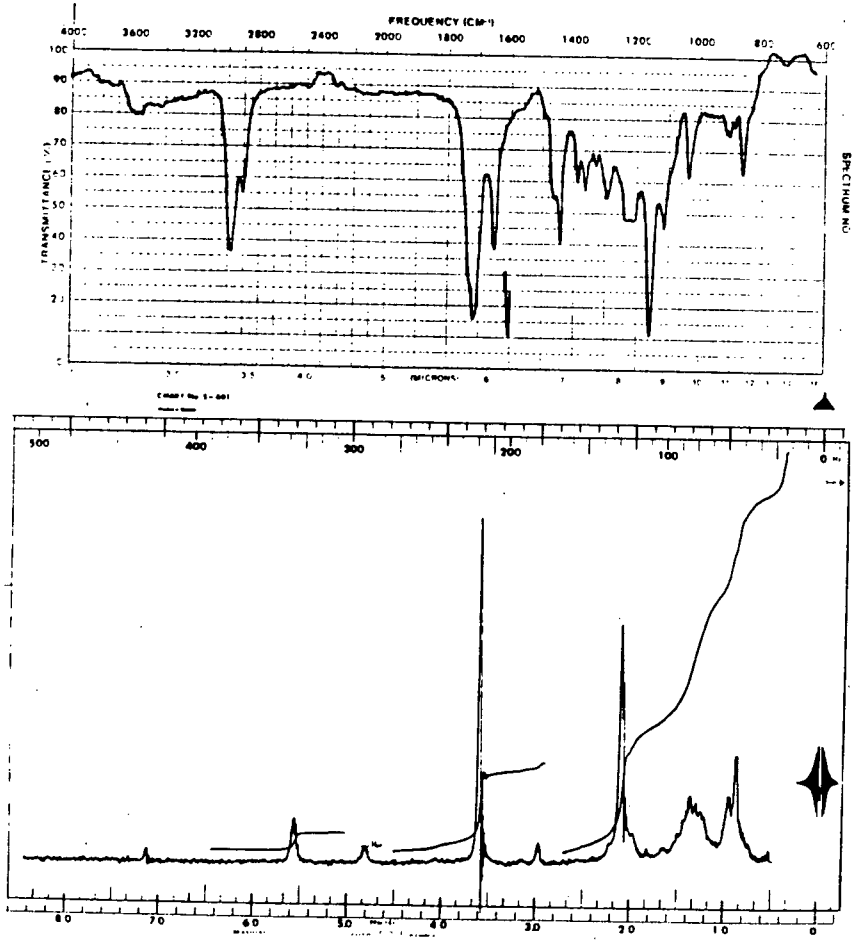


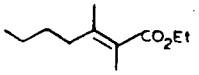
310


SPECTRUM NO.
FREQUENCY (CM⁻¹)
MICRONS
TRANSMITTANCE (%)

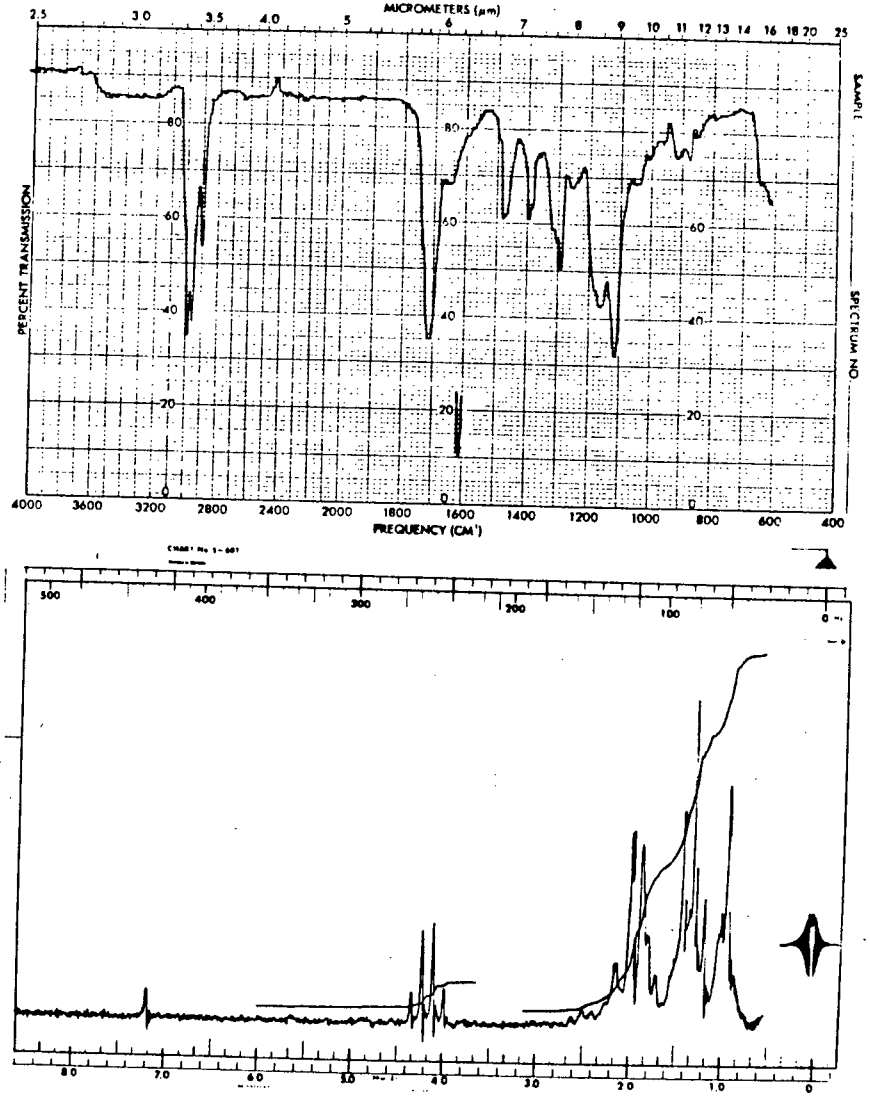

CO2Me

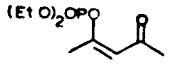
312


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.

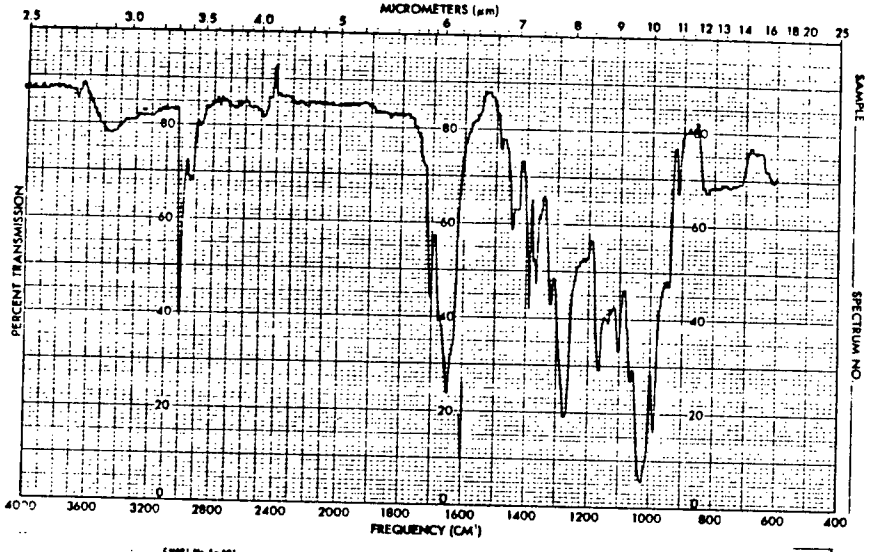

CO2Et

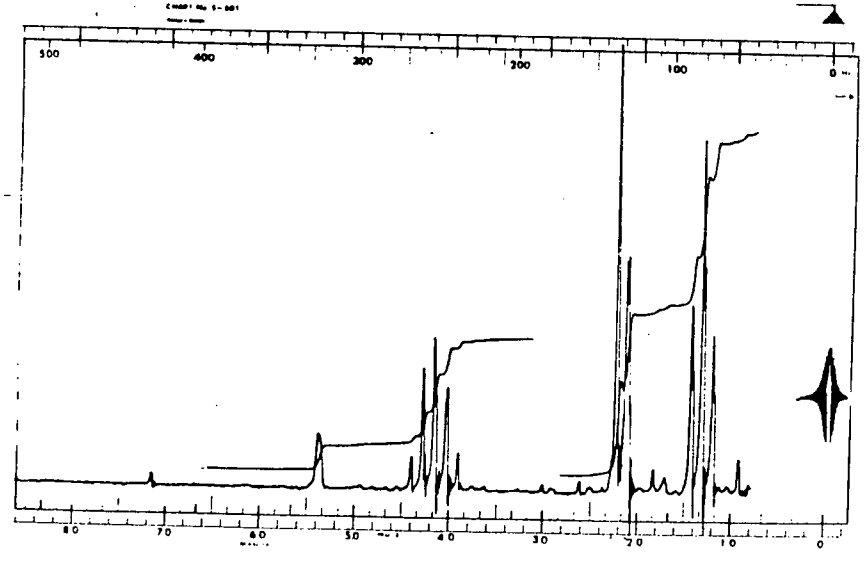
E-298

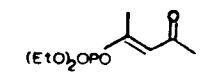

MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM-1)
SAMPLE
SPECTRUM NO.



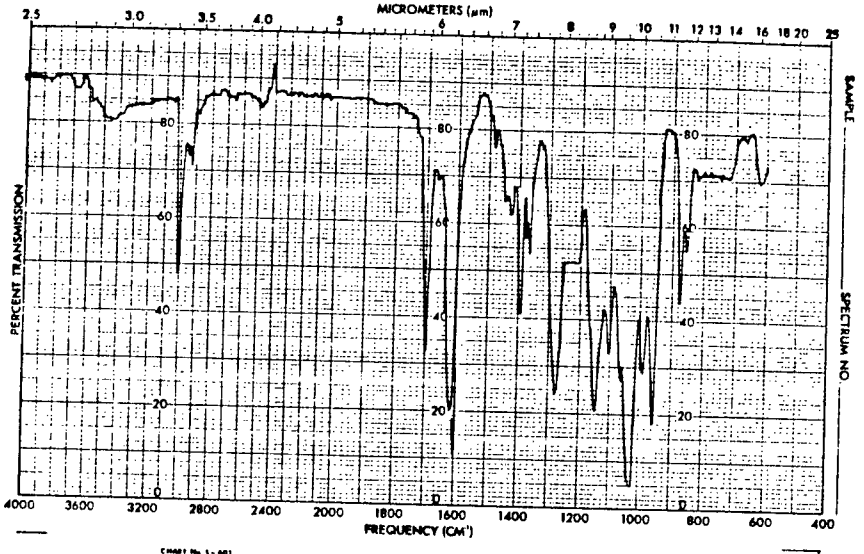
Z-317

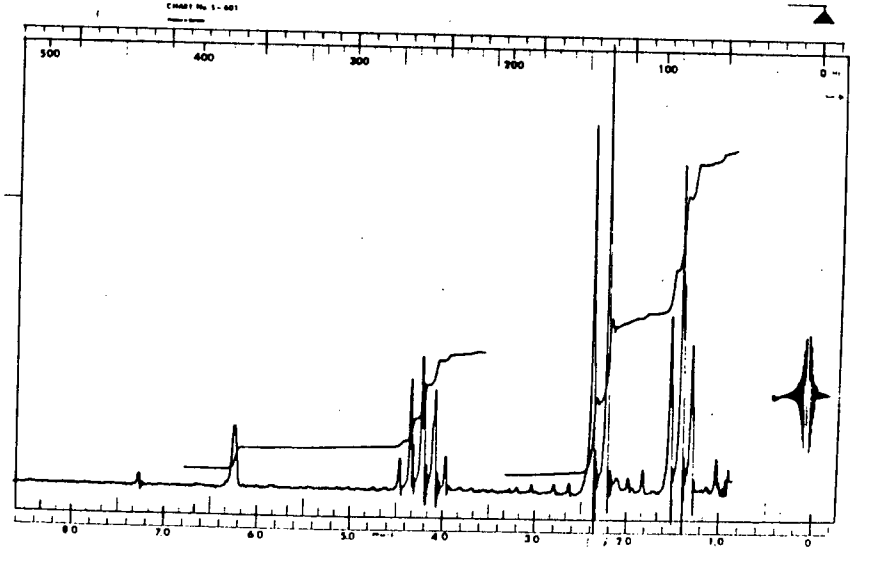

MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.

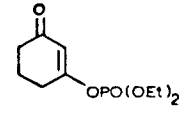




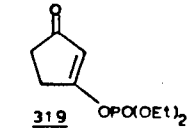
E-317


MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.

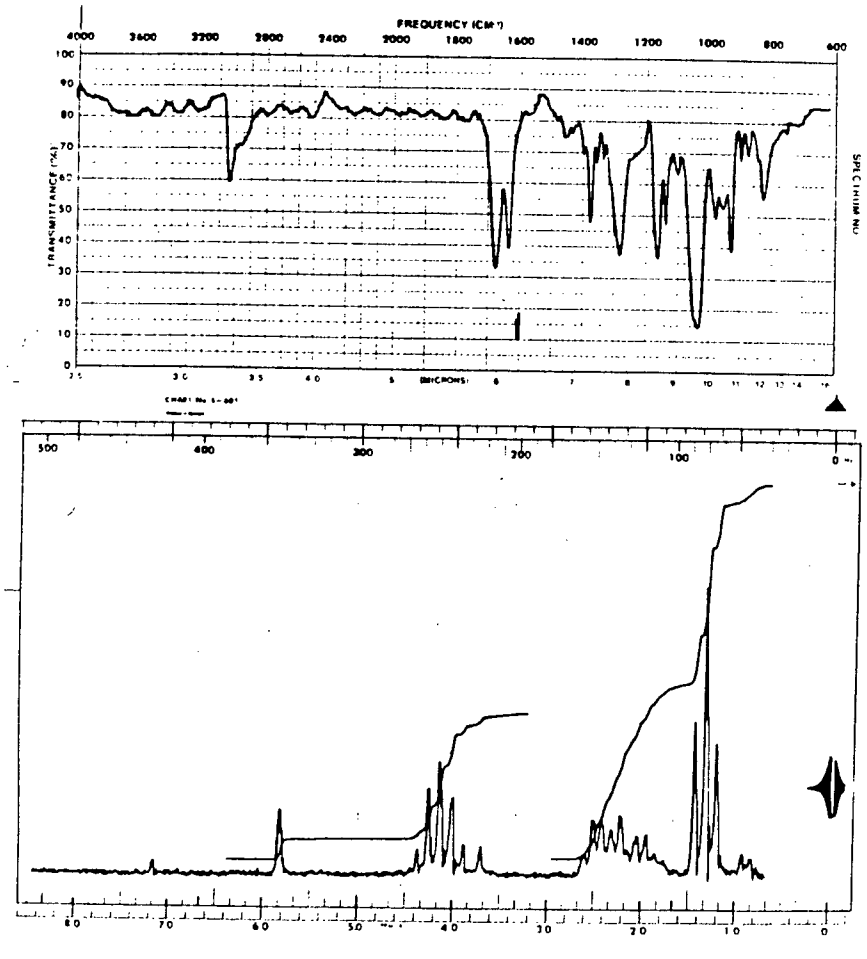


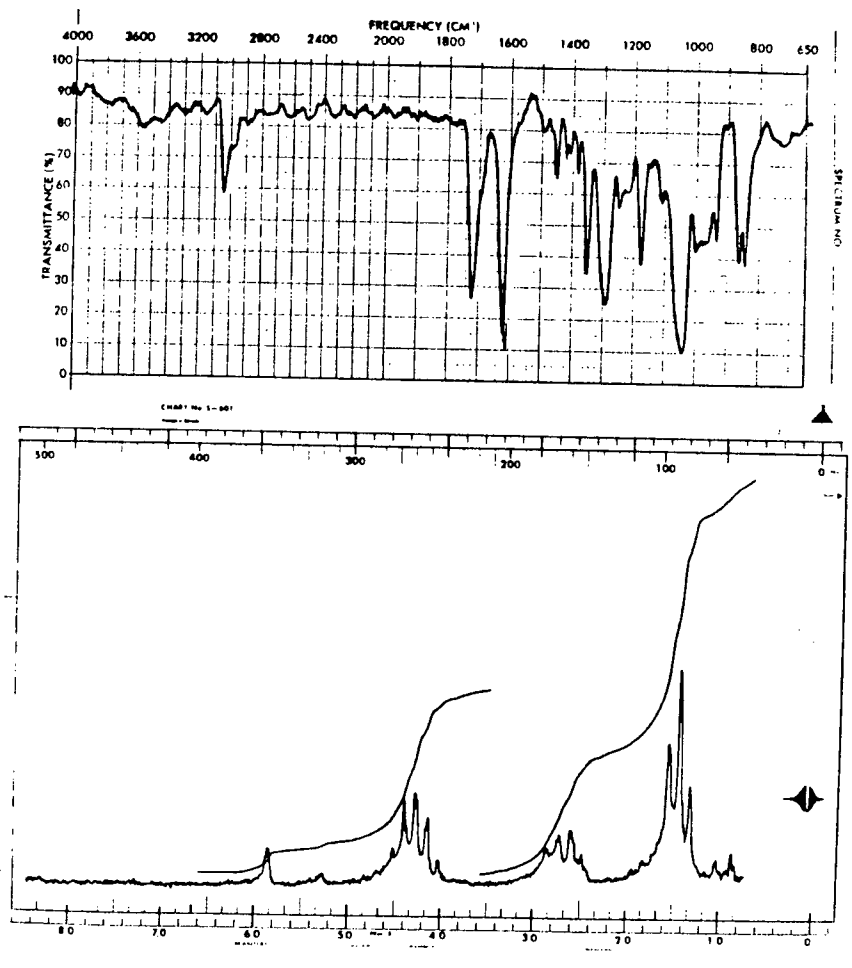

OPO(OEt)2

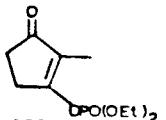
318


OPO(OEt)2

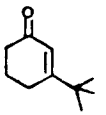
319


FREQUENCY (CM⁻¹)
TRANSMITTANCE (%)
MICRONS

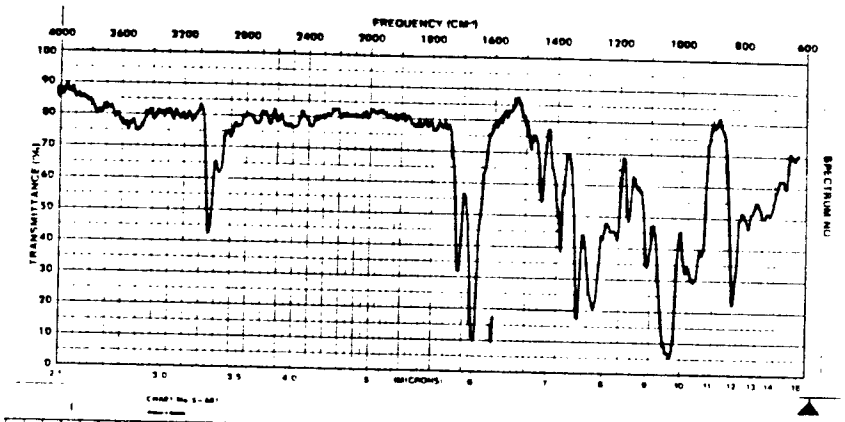

FREQUENCY (CM⁻¹)
TRANSMITTANCE (%)

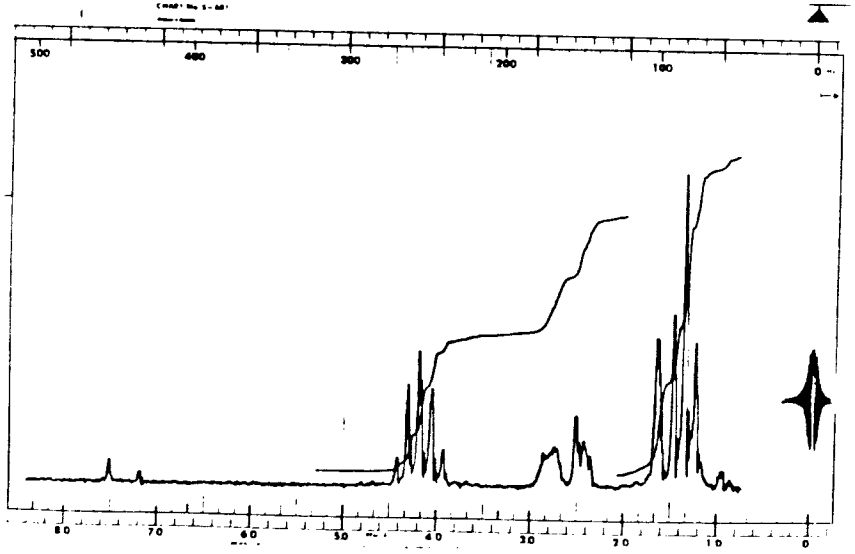

O
OPO(OEt)2

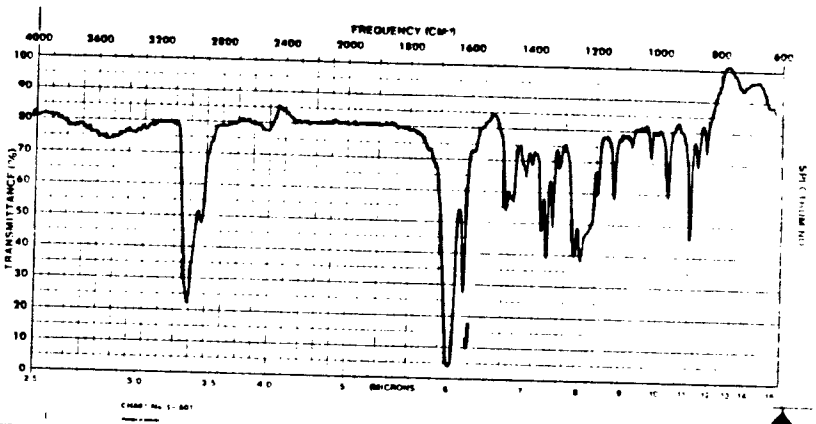
320

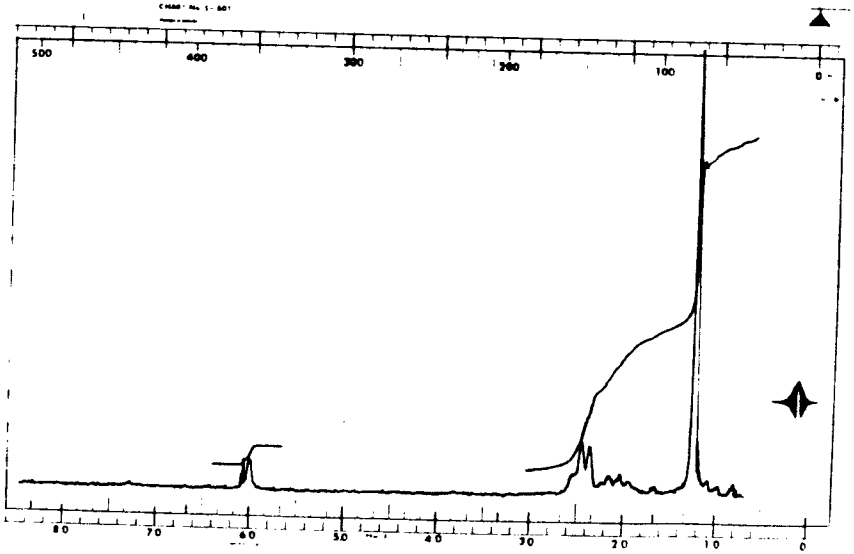

O

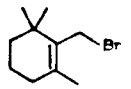
323


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
MICRONS

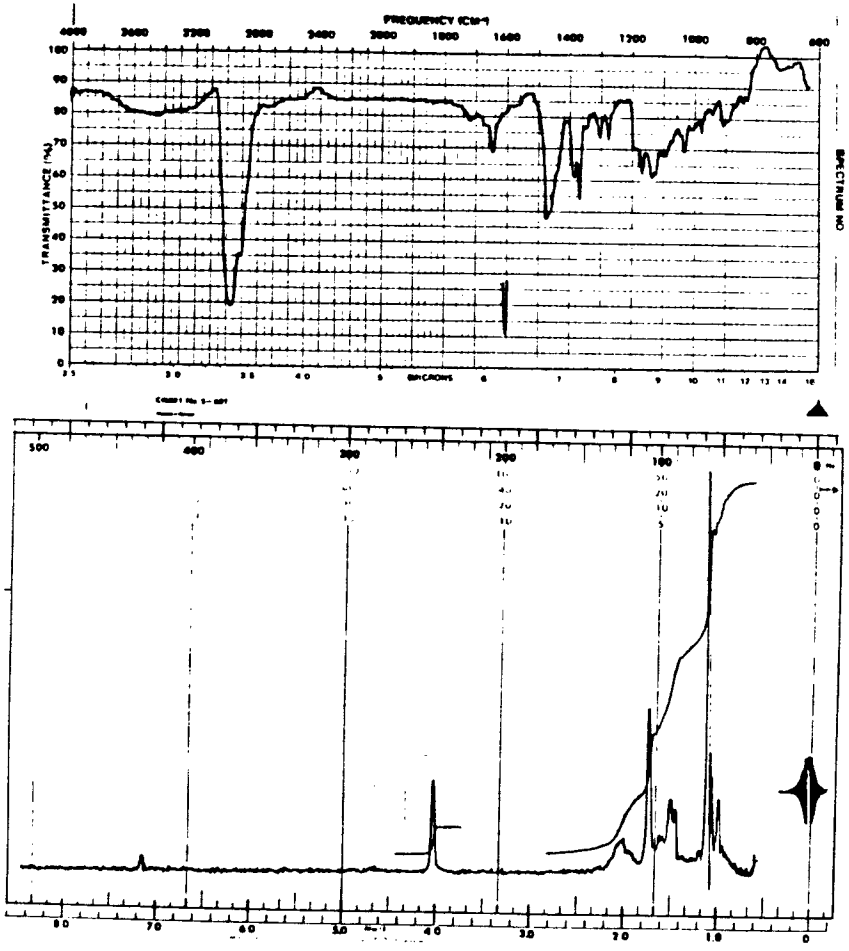


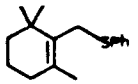

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
MICRONS



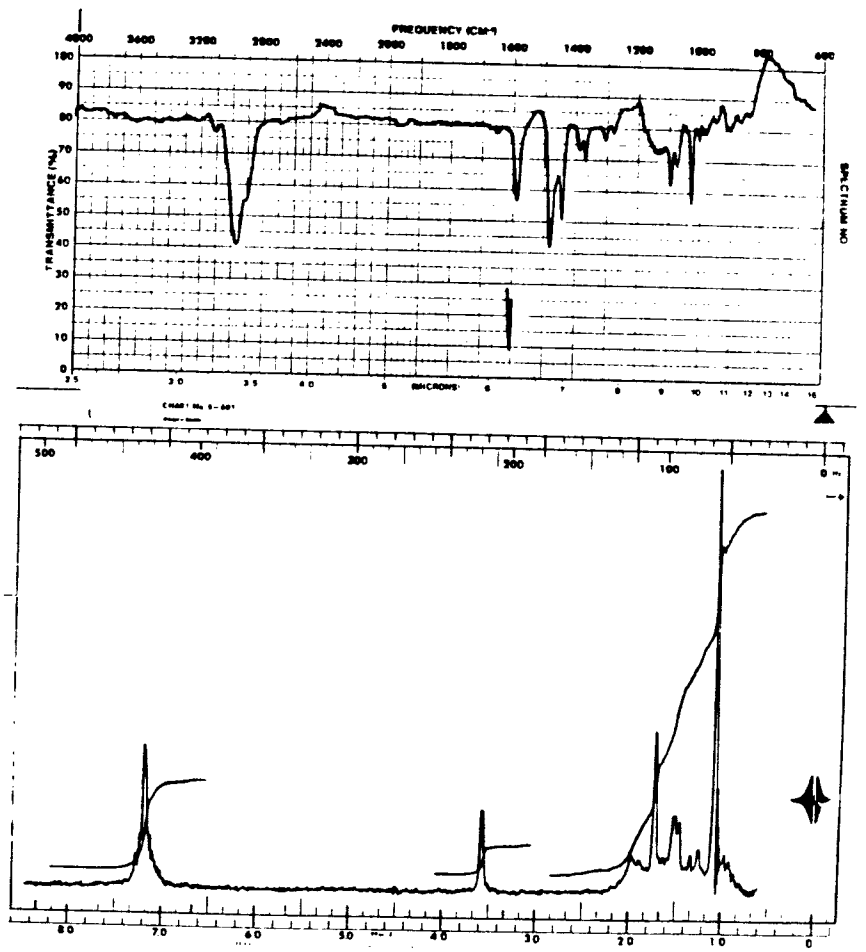

Br

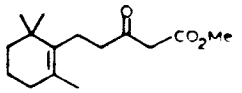
330


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO

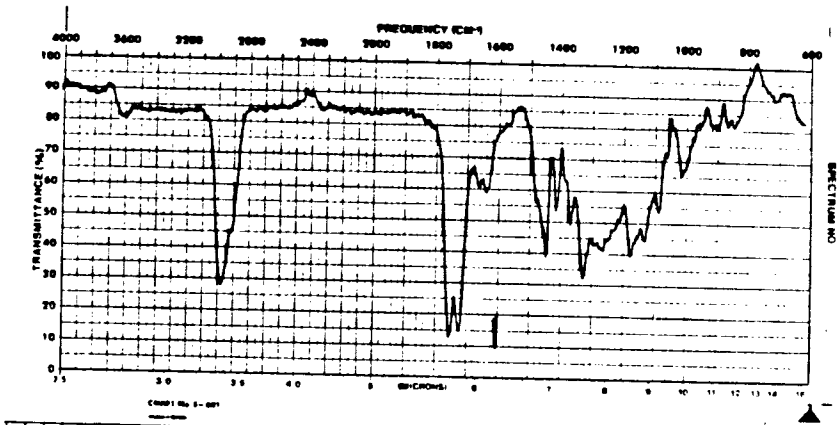

SPh

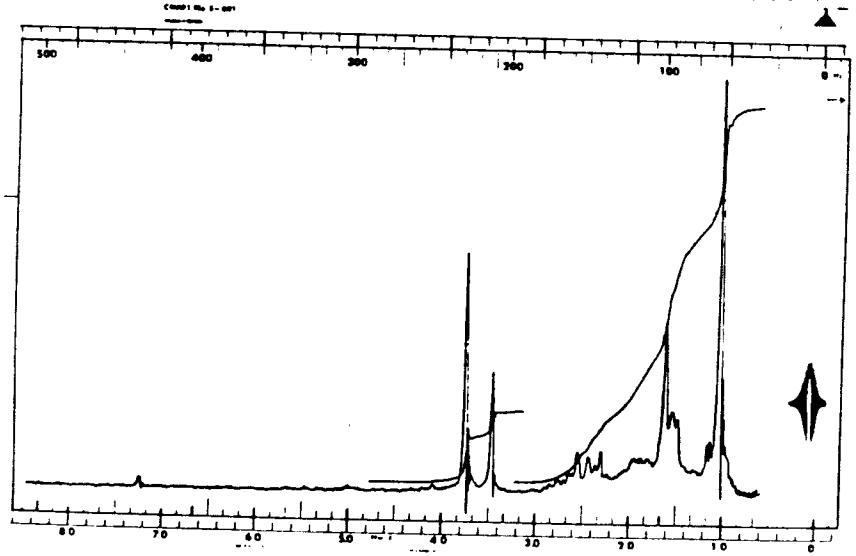
350

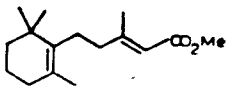

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO


CO2Me

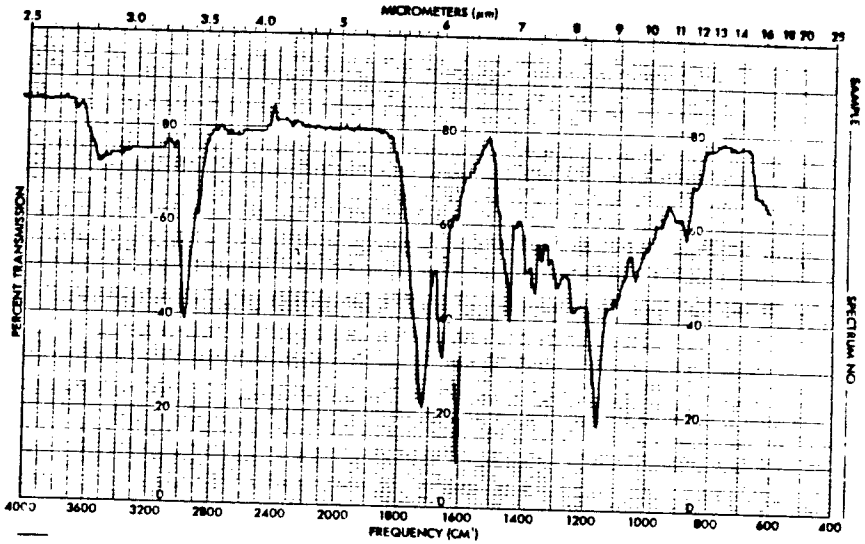
331

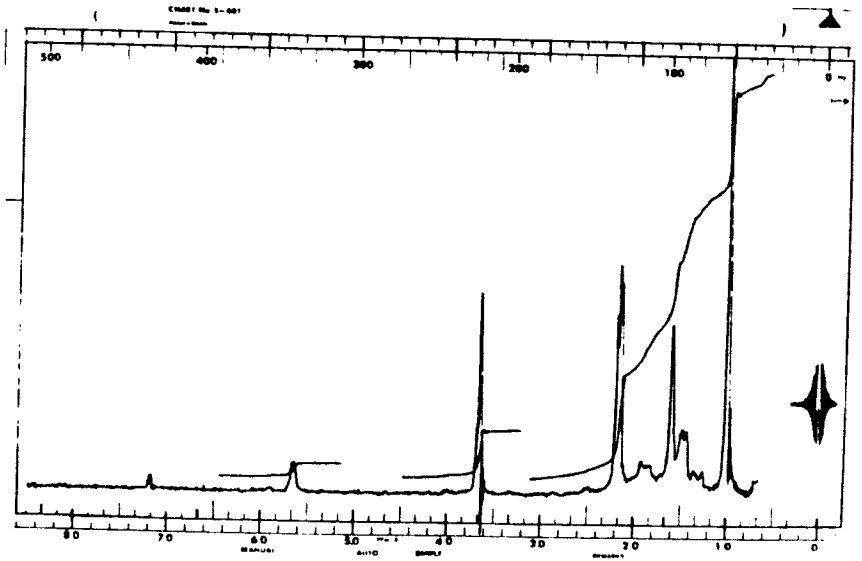

FREQUENCY (CM-1)
TRANSMITTANCE (%)

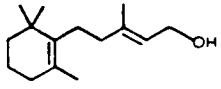



CO2Me

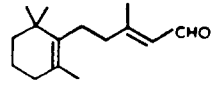
332


MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM-1)
SAMPLE
SPECTRUM NO

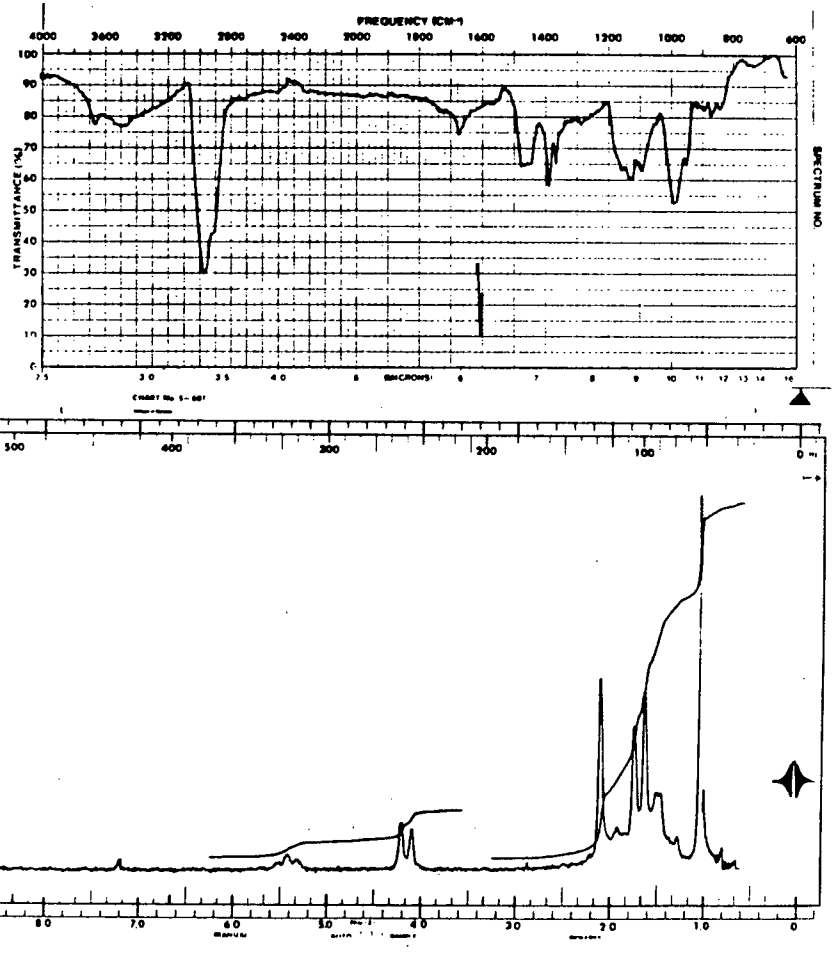


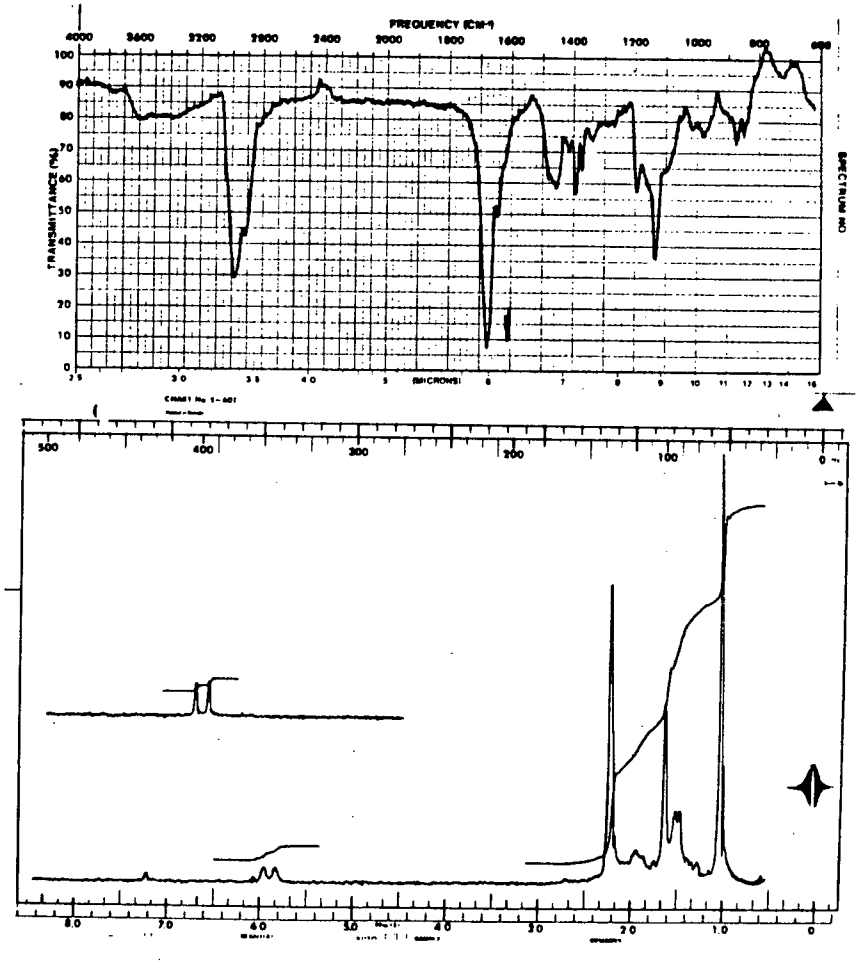

OH

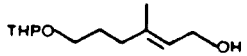
333


CHO

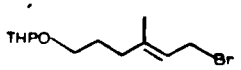
334


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.
MICRONS

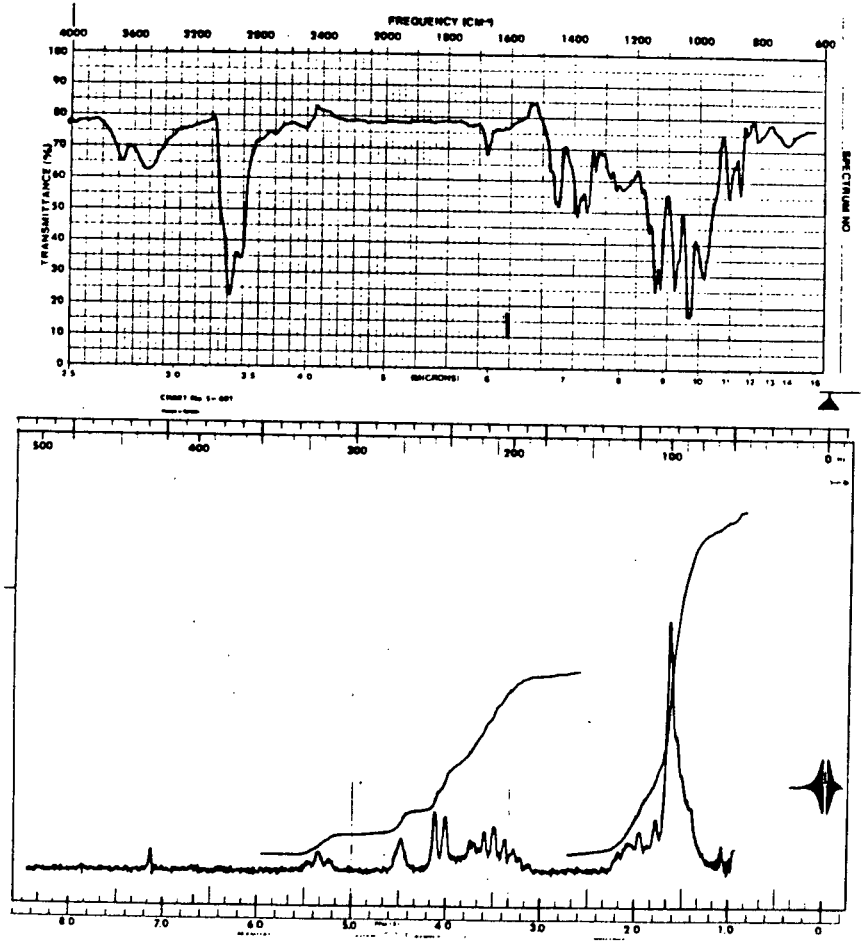

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.
MICRONS

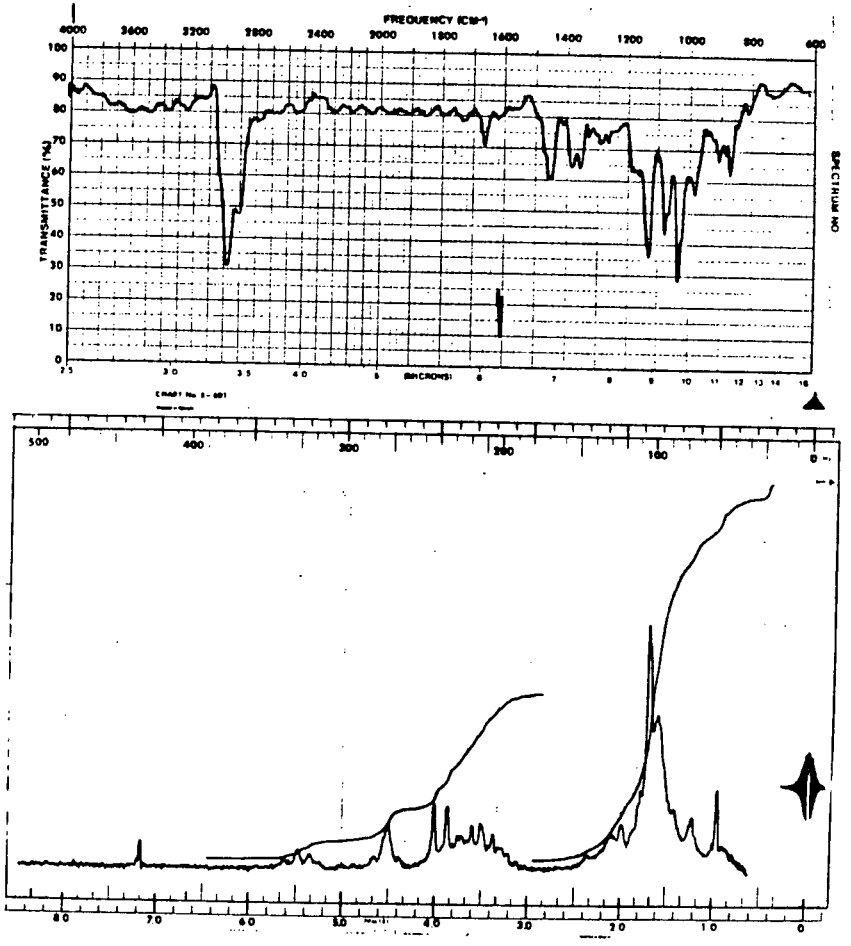

THPO
OH

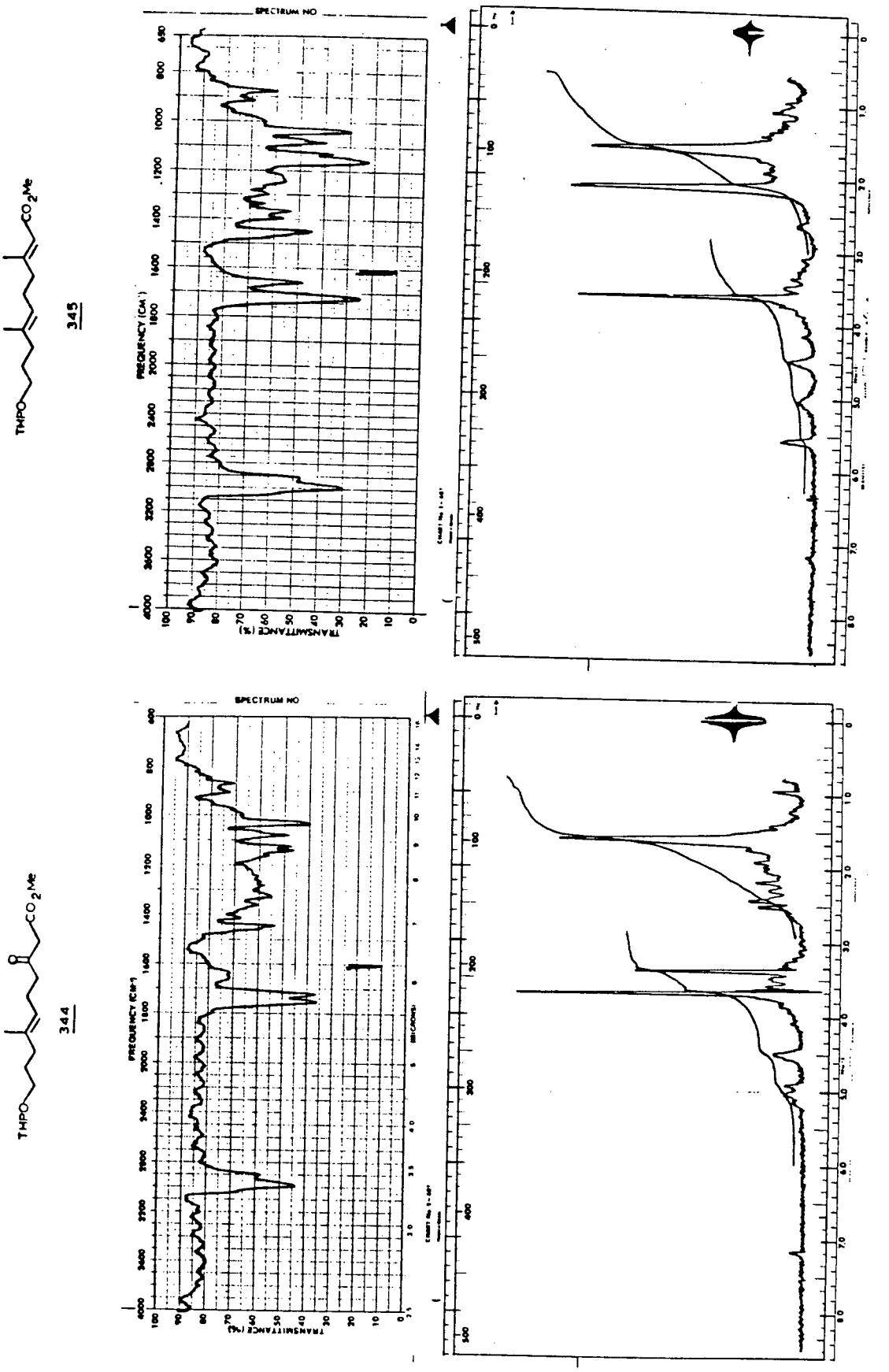
341

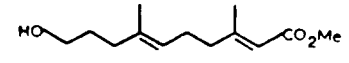

THPO
Br

343

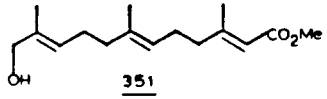

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO

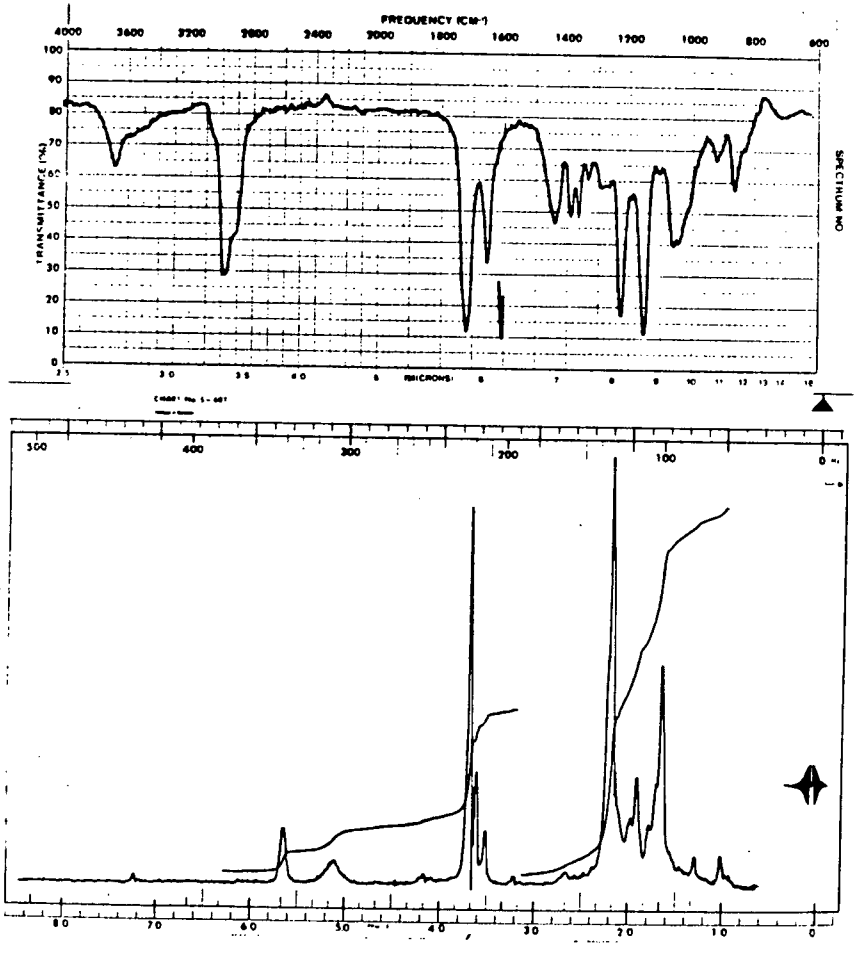

THPO
CO2Me
345
THPO
CO2Me
344
SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)

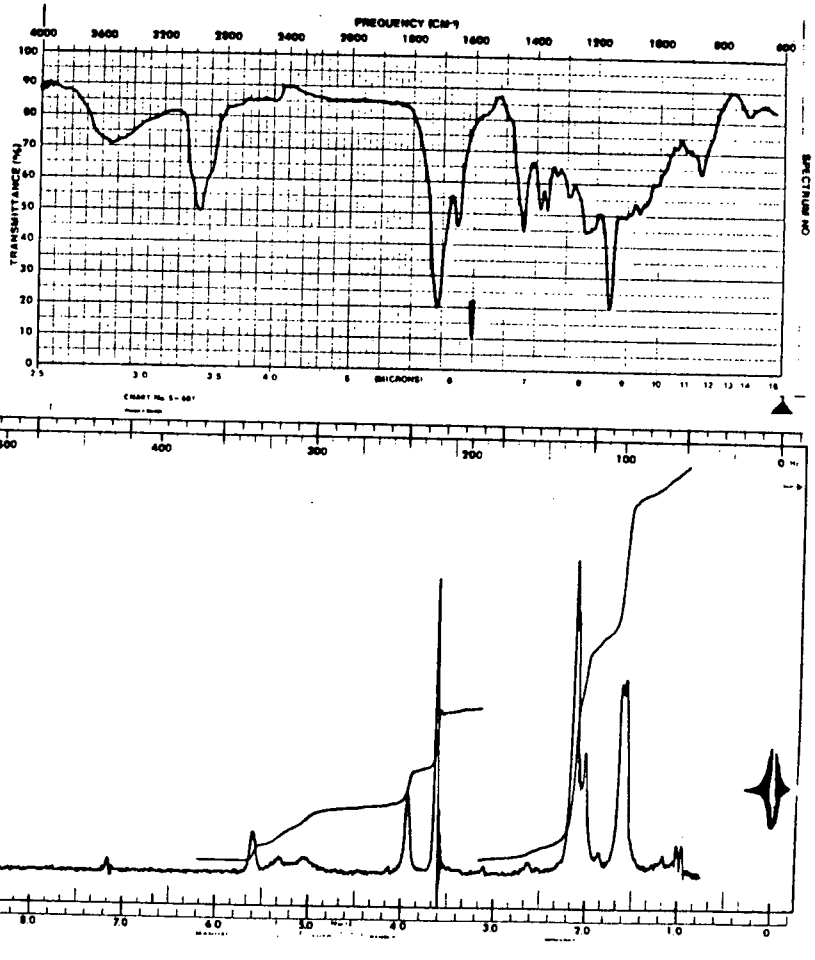

HO
CO2Me

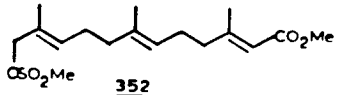
346


CO2Me
OH

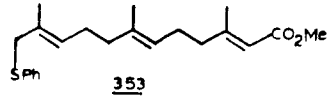
351


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO

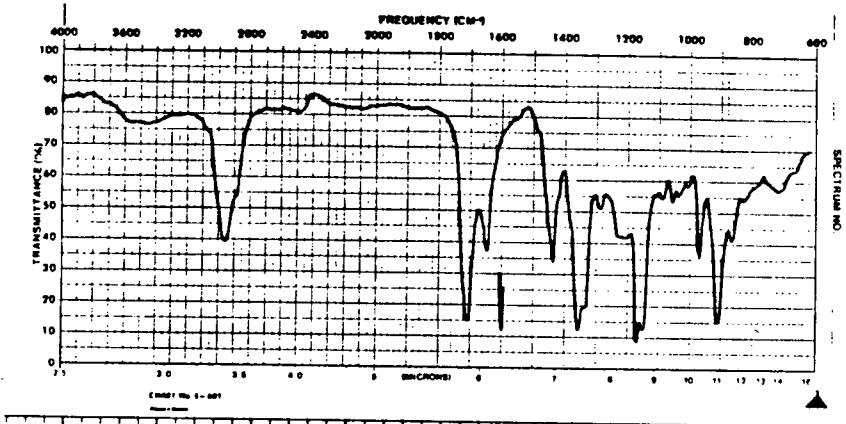

FREQUENCY (Cm-1)
TRANSMITTANCE (%)
SPECTRUM NO

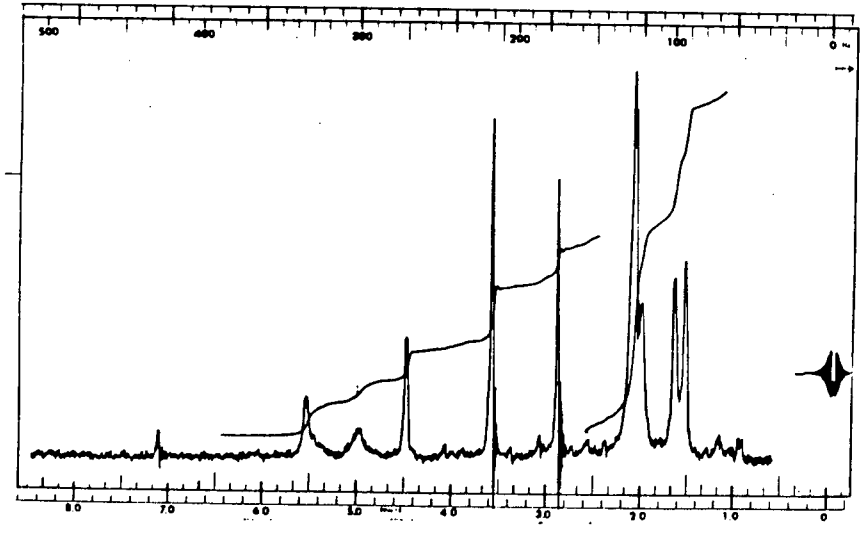

CO2Me
OSO2Me

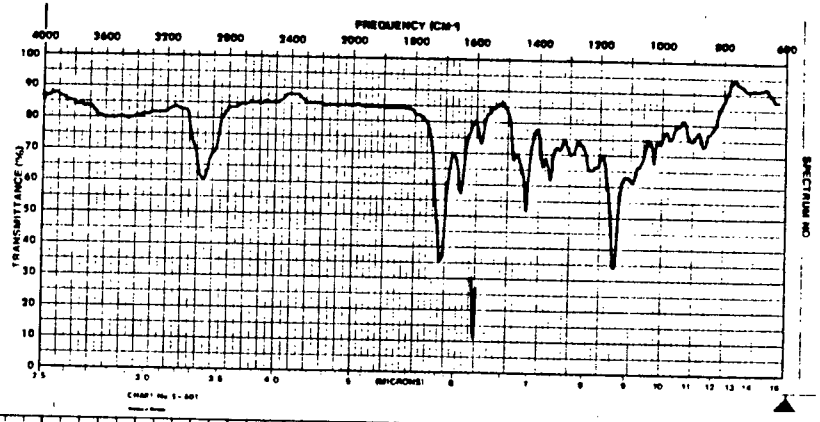
352

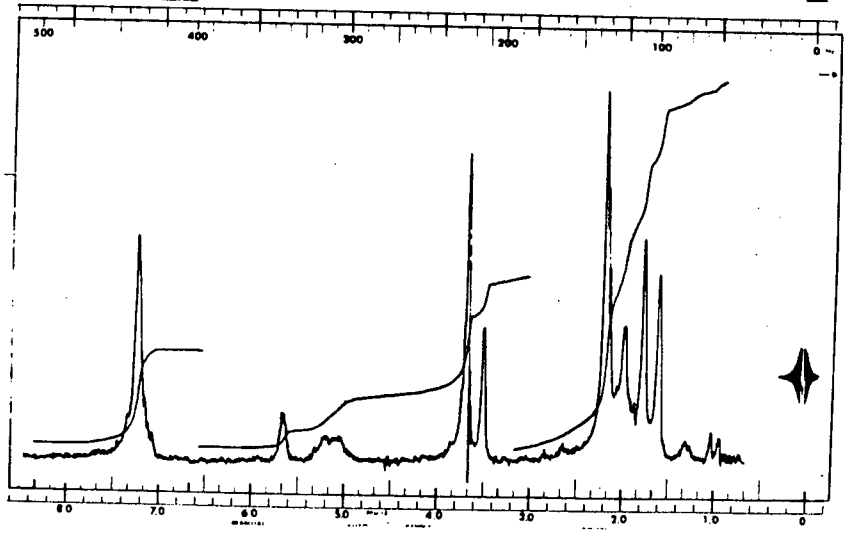

CO2Me
SPh

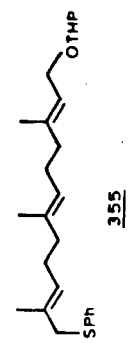
353


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.

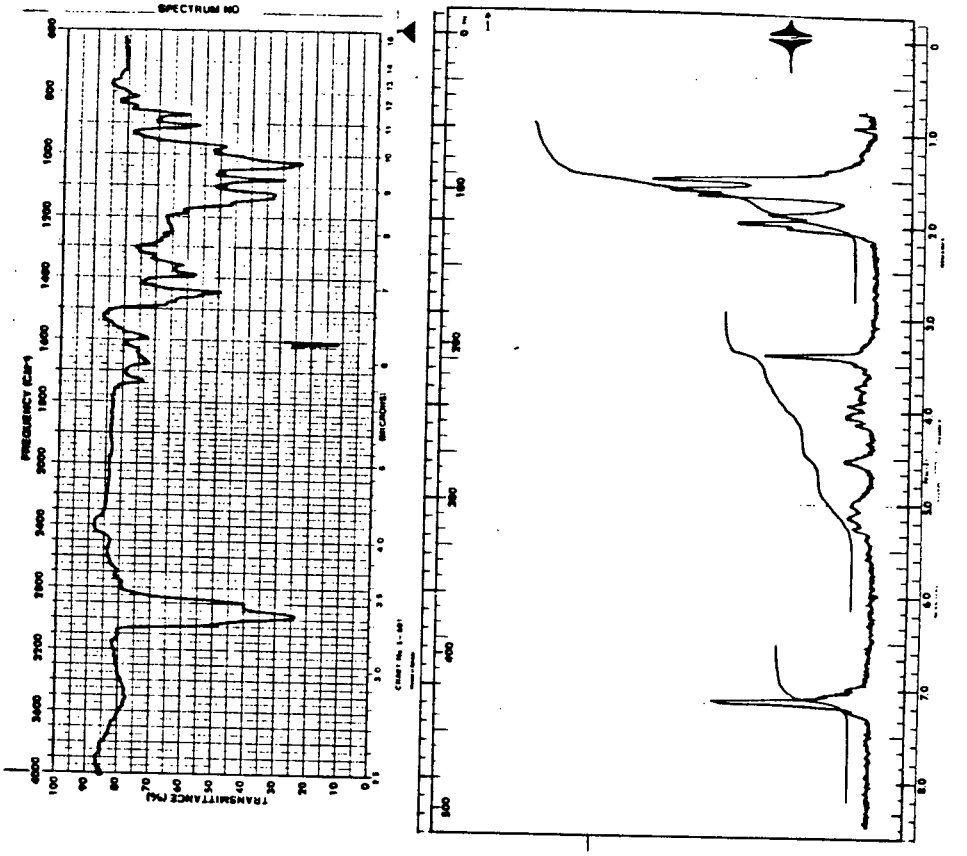


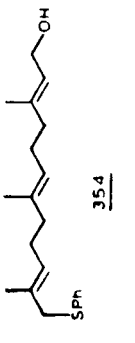

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.



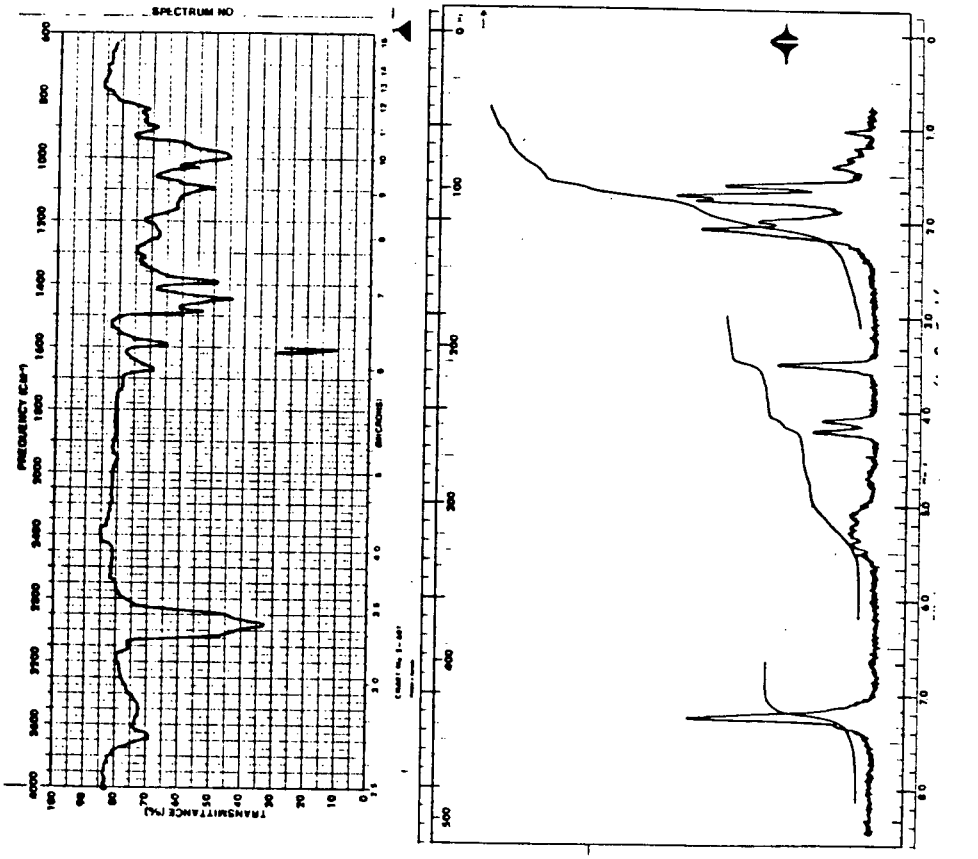

OTHP
SPh

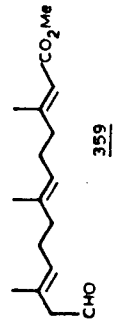
355


SPECTRUM NO
TRANSMITTANCE (%)
FREQUENCY (CM-1)

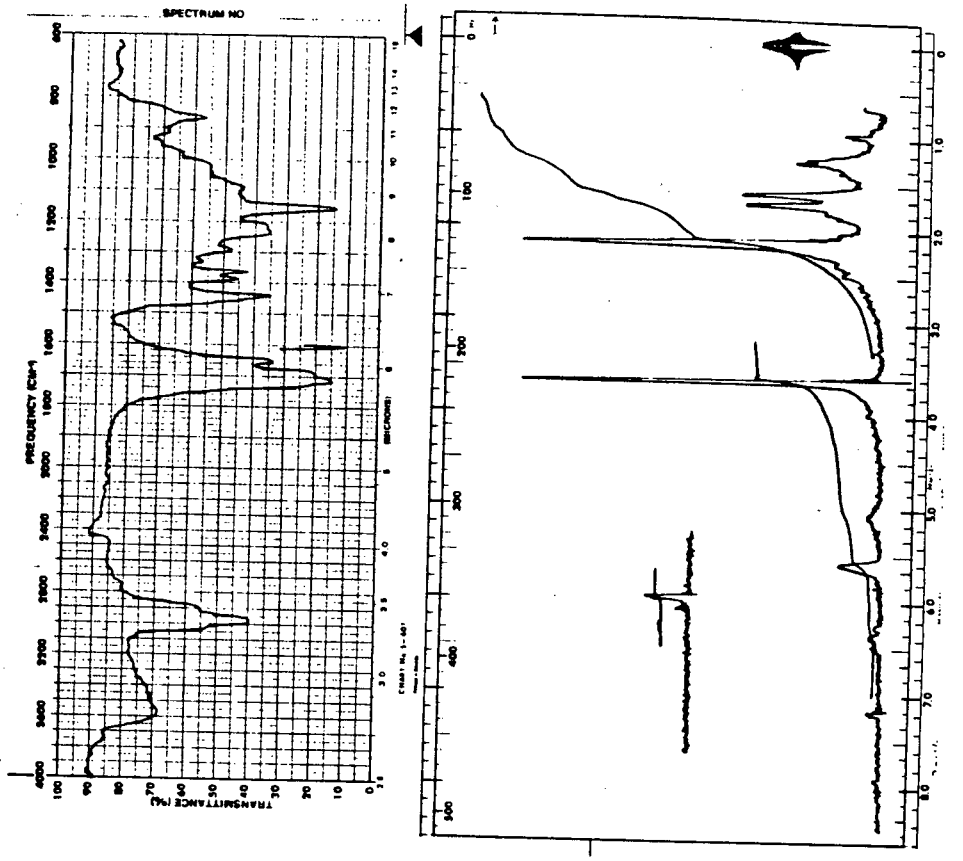

OH
SPh

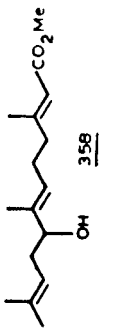
354


SPECTRUM NO
TRANSMITTANCE (%)
FREQUENCY (CM-1)

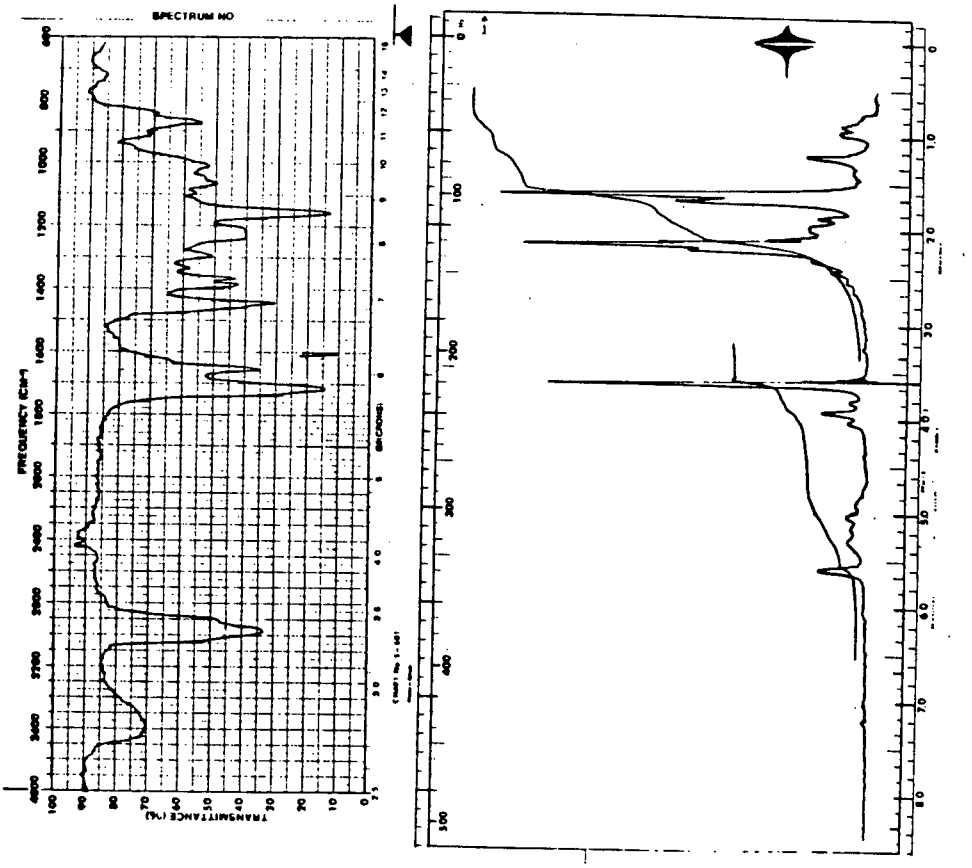

CO2Me
CHO

359


SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)


CO2Me
OH

358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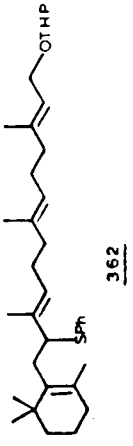
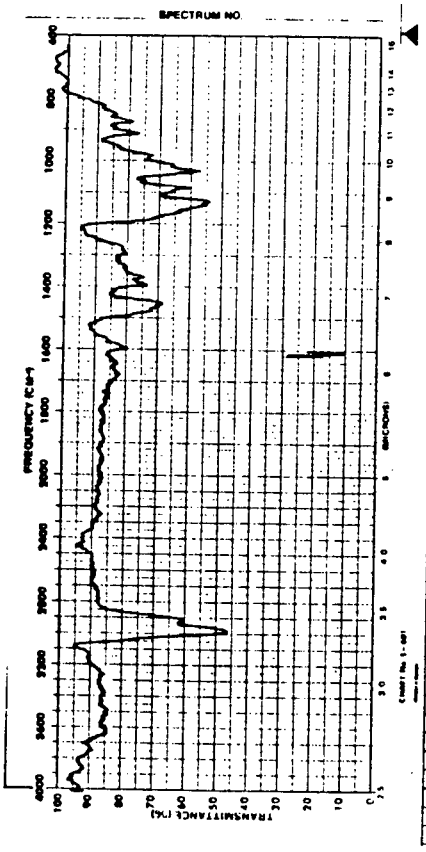
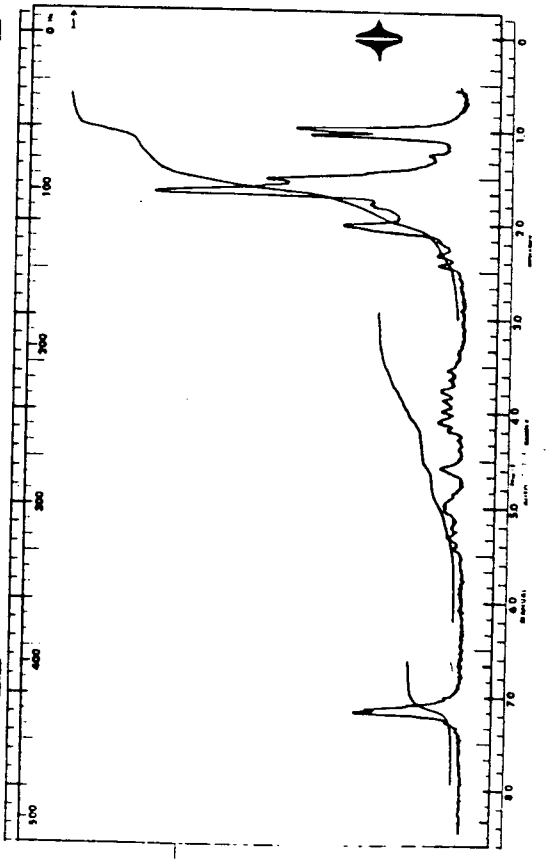
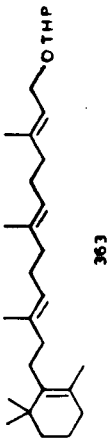
FREQUENCY (CM-1)
TRANSMITTANCE (%)


OTHP
SPh

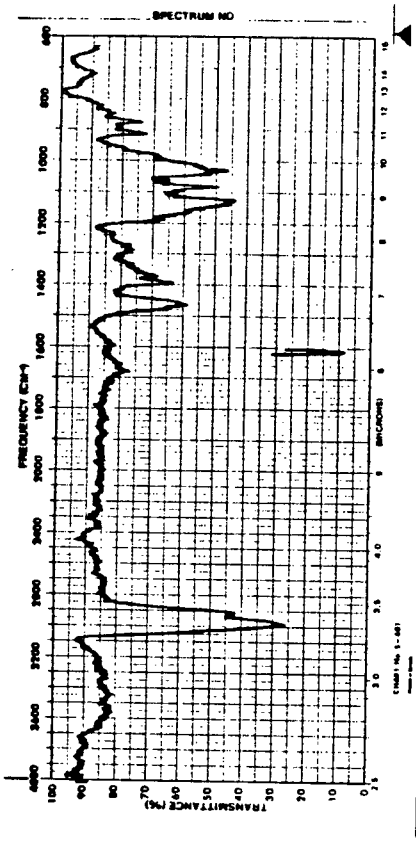
362

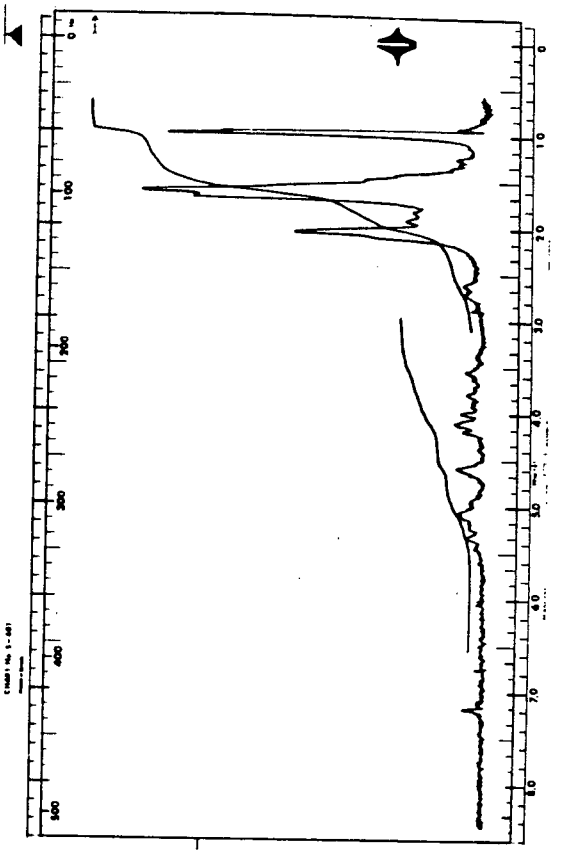

SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

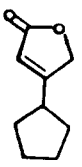



OTHP

363


SPECTRUM NO
FREQUENCY (CM-1)
TRANSMITTANCE (%)





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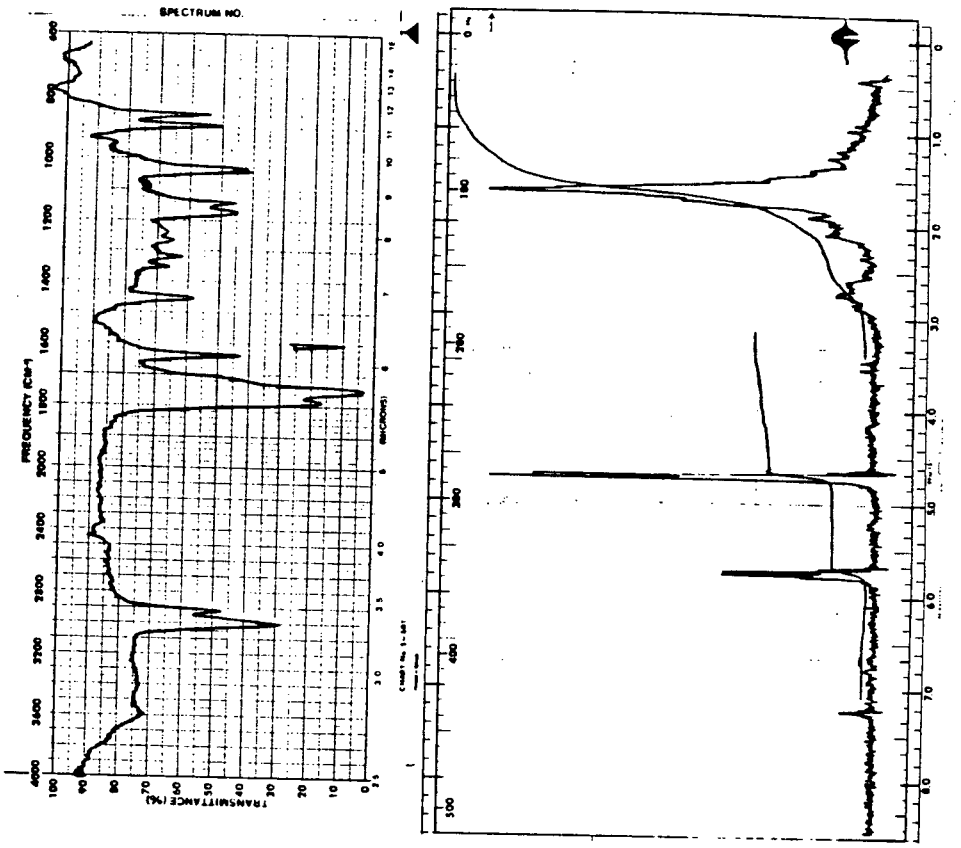
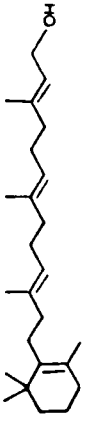
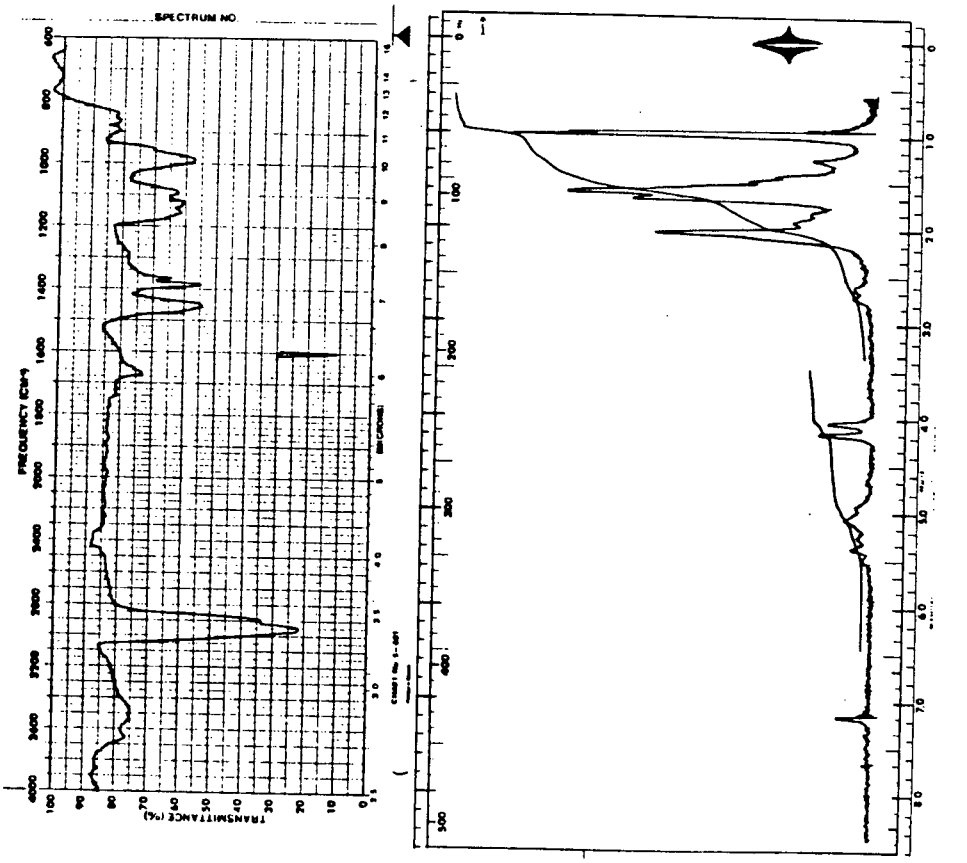
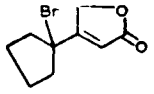

SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

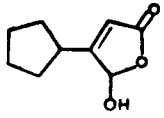


364

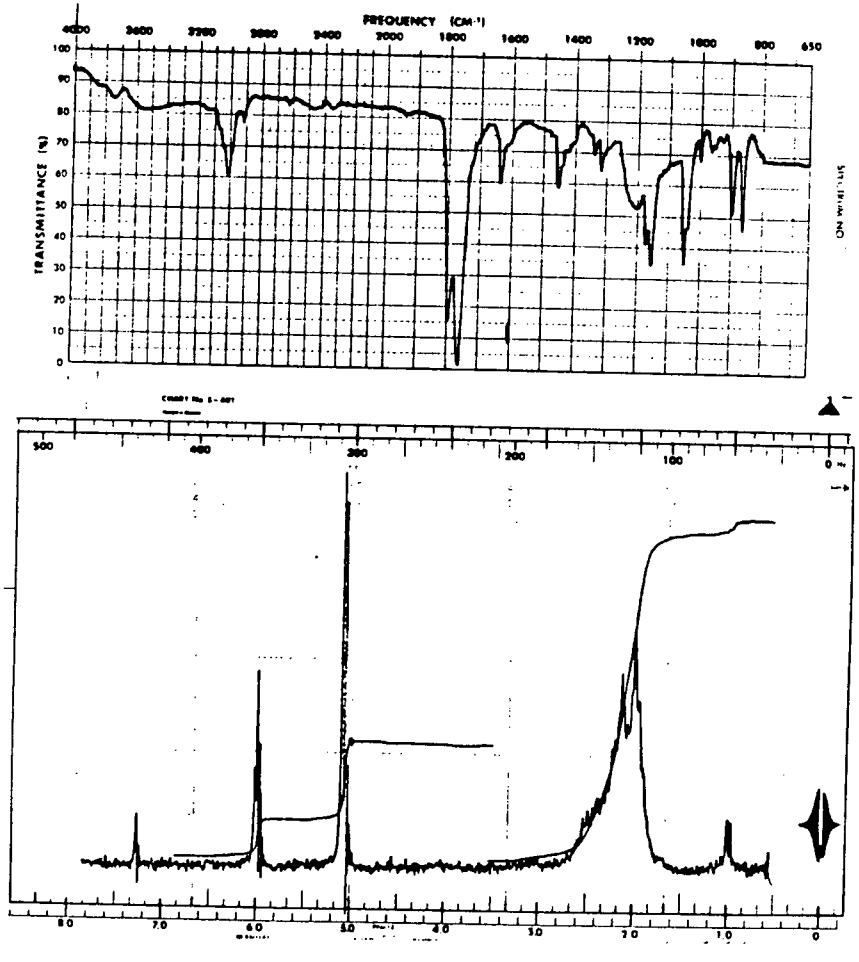

SPECTRUM NO.
FREQUENCY (CM-1)
TRANSMITTANCE (%)

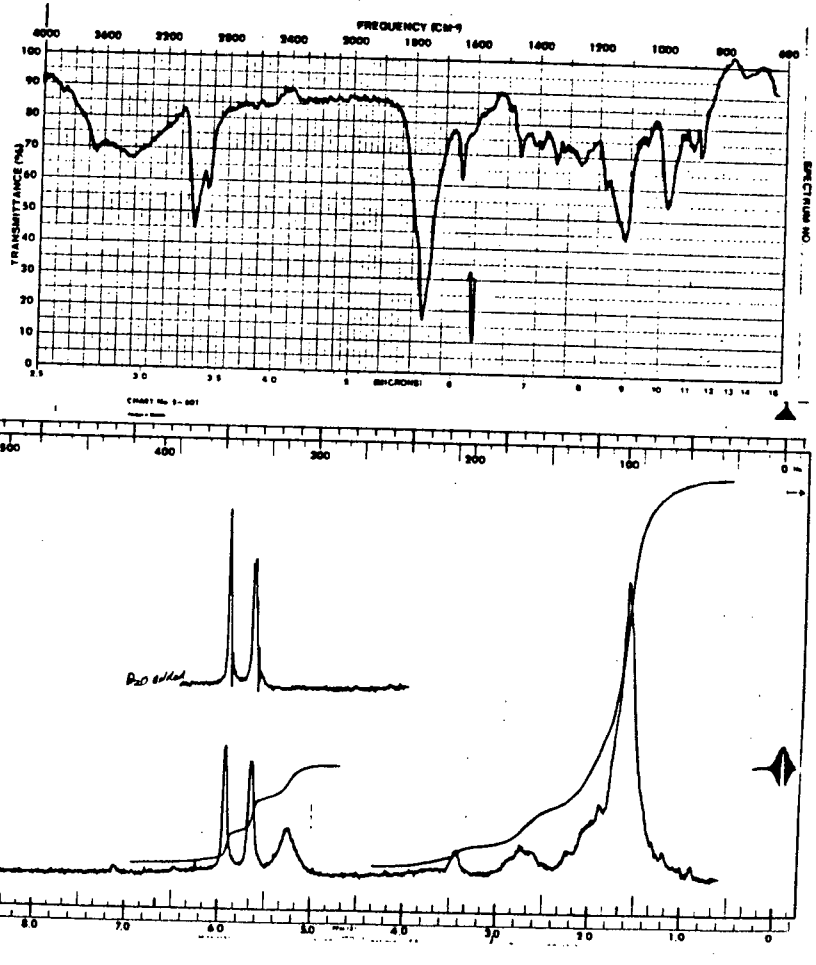

Br
O
O

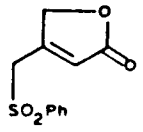
368


O
O
OH

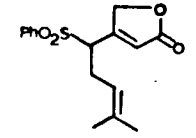
373


FREQUENCY (CM-1)
TRANSMITTANCE (%)

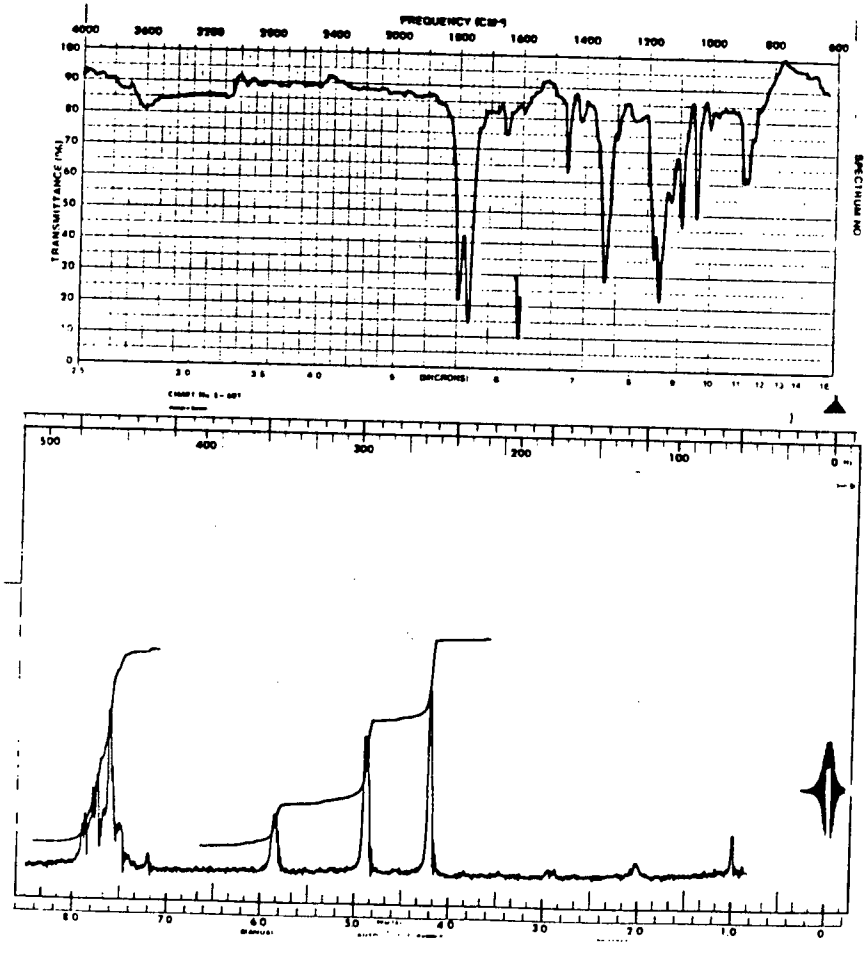

FREQUENCY (CM-1)
TRANSMITTANCE (%)
D2O added

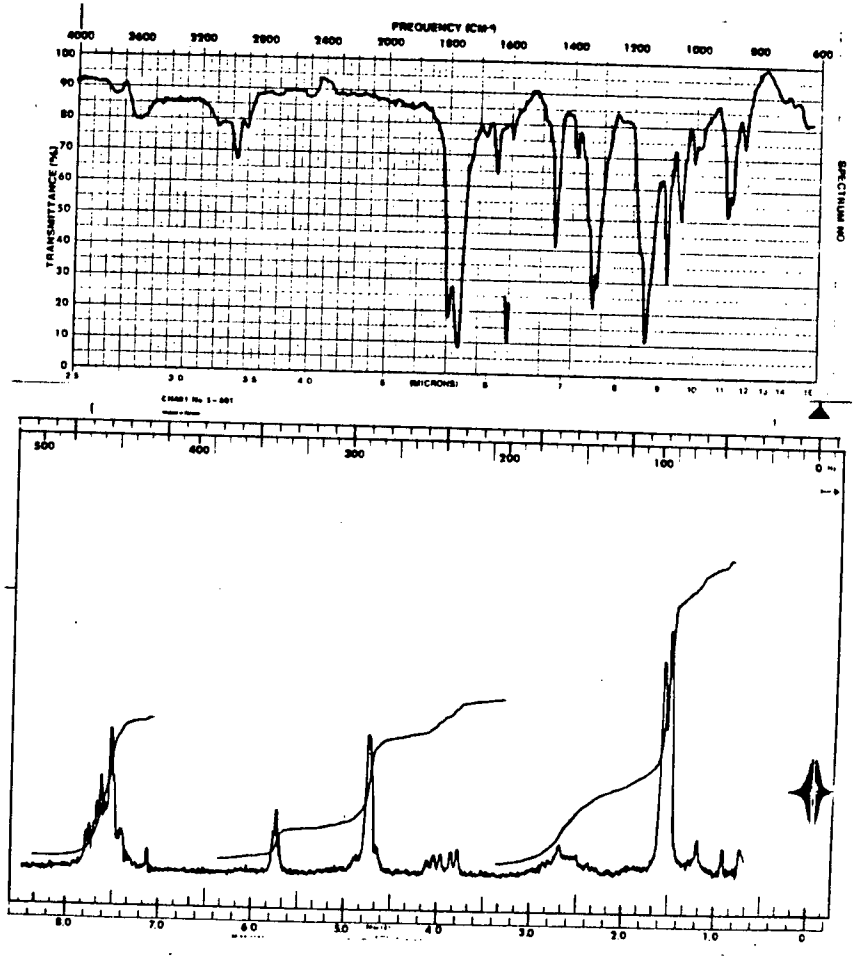

O
O
SO_2Ph

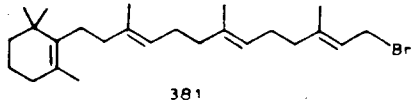
375


PhO_2S
O
O

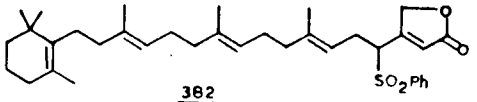
379


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO
MICRONS

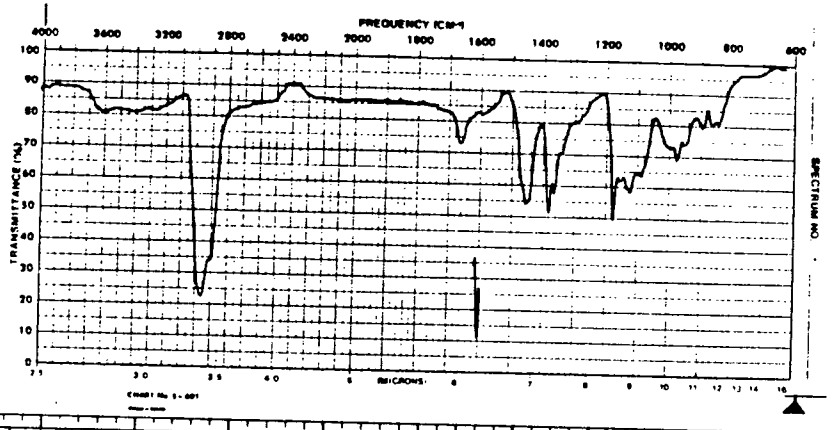

FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO
MICRONS

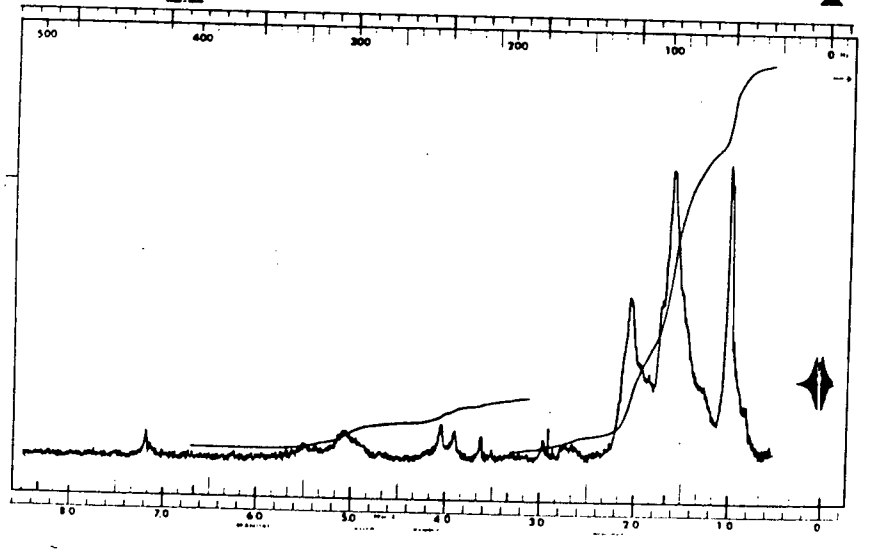

Br

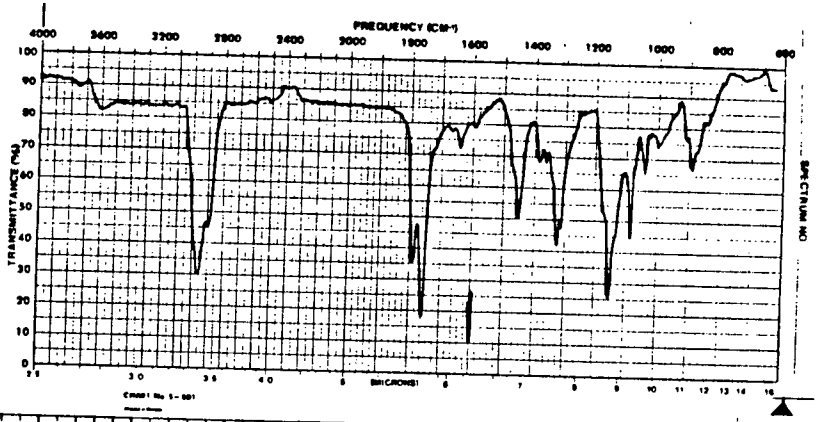
381


SO2Ph

382


FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.




FREQUENCY (CM-1)
TRANSMITTANCE (%)
SPECTRUM NO.