STUDIES RELATED TO THE INSECT CONTROL POTENTIAL OF THUJONE DERIVATIVES

by

J. BALSEVICH

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Department of Chemistry

The University of British Columbia
2075 Wesbrook Place
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V6T 1W5

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ABSTRACT

Treatment of cedar leaf oil with aqueous potassium permanganate resulted in the oxidative ring opening of thujone (VI), the major component of the leaf oil, to yield the crystalline α-thujaketonic acid (VII). This material because of its availability and interesting structure represented an attractive starting material for the synthesis of some novel analogs of possible insect controlling agents. Therefore, to achieve this goal the functionalization of the ketonic carbonyl of α-thujaketonic acid was studied. Treatment of the sodium salt of α-thujaketonic acid in dimethylsulfoxide with the phosphorane produced from either methyltriphenylphosphonium bromide or isopropyltriphenylphosphonium iodide yielded the methylene and isopropylidene derivatives of α-thujaketonic acid (XIII, XIV). These two compounds represented two novel analogs of chrysanthemic acid, a naturally occurring material of which numerous derivatives are known which possess insecticidal activity.

With the establishment of the conditions for the Wittig reaction of α-thujaketonic acid with a phosphonium salt, two routes for the synthesis of phosphonium salts which when coupled to α- or β-thujaketonic acid (XI, XII) would lead to insect hormone analogs, were studied. Thus, Horner reaction of 2-butanone with trimethylphos-

phonoacetate resulted in the preparation of cis and trans methyl 3-methyl-2-pentenoates (XX, XXI), which were separated by means of spinning band distillation. In the first sequence studied the separate isomers were elaborated via standard means to yield the cis and trans 7-methyl-6-nonene-3-ols (XXVI and XXXII) which possessed the desired carbon skeleton. However, upon conversion of the trans secondary alcohol (XXXII) to the iodide (XXXIII), and treatment of this iodide with triphenylphosphine, none of the desired trans 7-methyl-6-nonene-3-triphenyl-phosphonium iodide (XIX) was isolated. Therefore, the study of an alternate route for the synthesis of the desired cis and trans 7-methyl-6-nonene-3-triphenylphosphonium iodides (XVIII and XIX) was undertaken. Elaboration of cis methyl 3-methyl-2-pentenoate to cis 5-methyl-4-heptenetriphenylphosphonium iodide (XLVI) was achieved by standard means. Treatment of this phosphonium salt with n-butyllithium and ethyl iodide then yielded the desired cis 7-methyl-6-nonene-3-triphenylphosphonium iodide (XVIII).

TABLE OF CONTENTS

List of Illustrations

List of Tables

ACKNOWLEDGEMENTS

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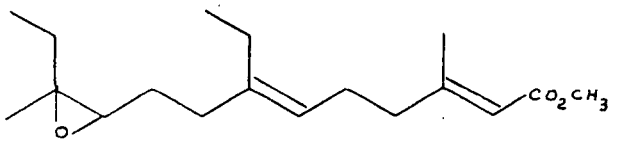
1. INTRODUCTION

1.1 GENERAL BACKGROUND

Insecticides have long been in use and have been invaluable in suppressing damage to agricultural products and to the health of man and animals. Concern over environmental aspects, and the ability of many insects to become immune to the various insecticides has created a general interest in developing alternative methods to existing chemical control agents.

It was in the mid-1930's that Sir Vincent Wigglesworth[1] showed that the molting and metamorphosis of Rhodnius prolixus nymphs were regulated by hormones. Since that time great strides have been made in deducing the hormonal aspects of a n insect's life cycle. In 1956, Professor Carroll Williams[2] at Harvard discovered that the abdomen of the adult male of Hyalophora cecropia was a rich source of juvenile hormone. With this discovery also came the realization that utilization of hormonal agents might be an effective way for controlling insect populations. In 1967, a major breakthrough occurred when Professor H. Roller and co-workers[3] at the University of Wisconsin elucidated the structure of the major cecropia juvenile hormone as methyl trans,trans,cis-10,

11-epoxy-7-ethyl-3,11-dimethyl2,6-tridecadienoate (I).



I

Since this time interest in the field of insect chemistry in general has been growing at a rapid rate, as can be attested to by the increasing number of publications.

1.2 HORMONAL CONTROL OF INSECT METAMORPHOSIS

Hormonal control over the development and maturation of the insect can be considered as regulated by three main groups of hormones (Fig. 1)[4]. The brain hormones (believed to be polypeptides) are secreted by neurosecretory cells in the protocerebrum and activate the prothoracic glands. The activated prothoracic glands are then believed to secrete one or several closely related steroids, the ecdysones (II).

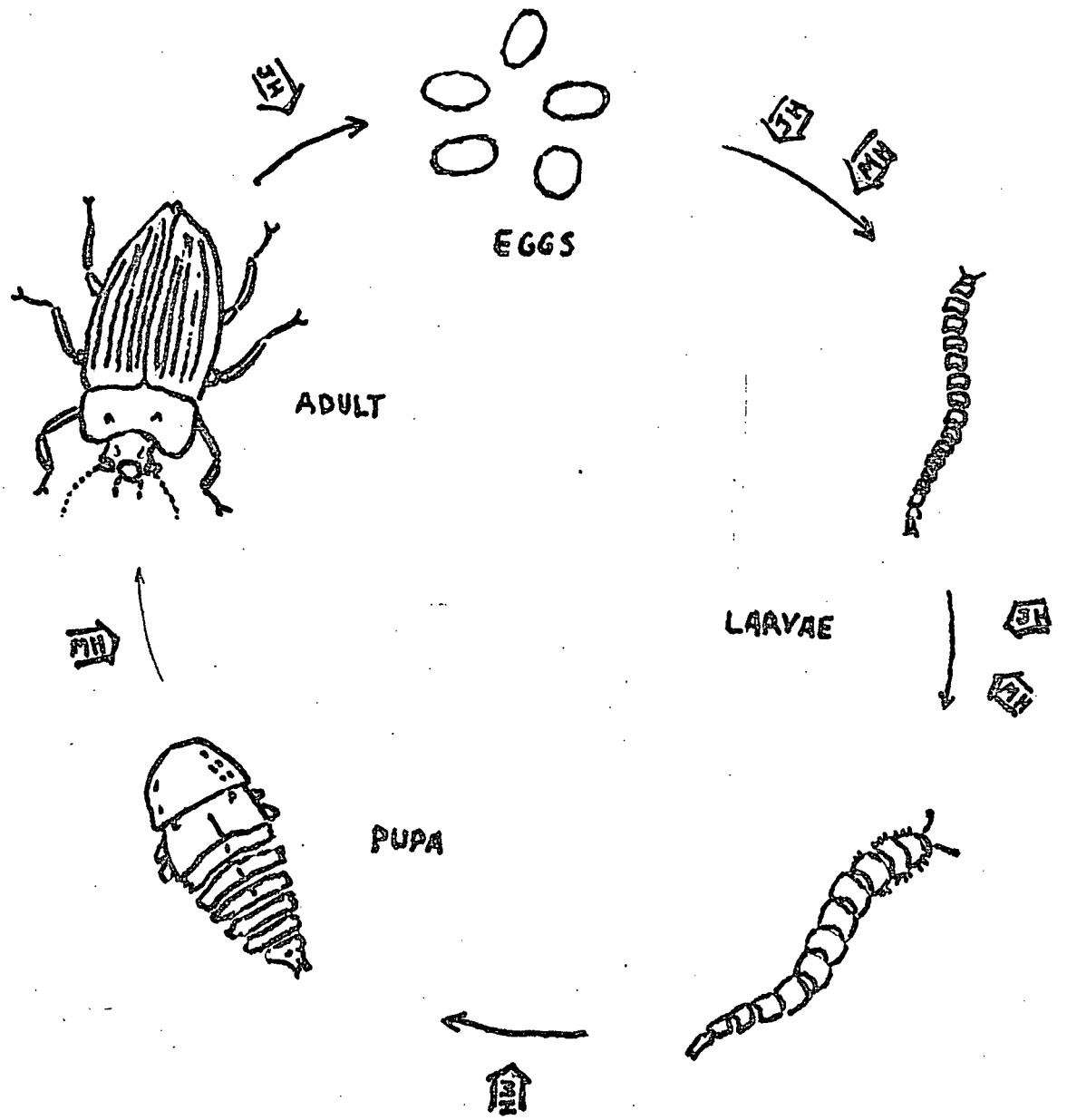
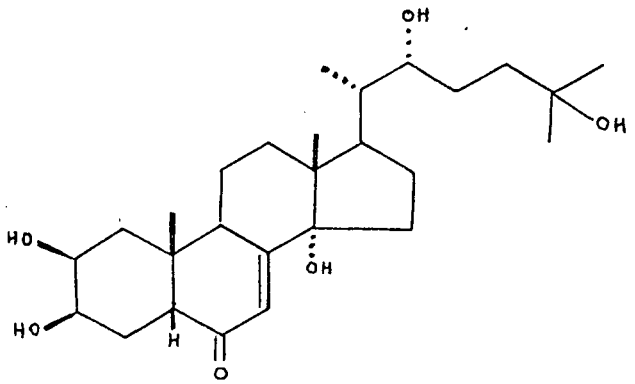


Fig. 1. Endocrine Regulation of Life Cycle of Yellow Mealworm.



II

These ecdysones, or their metabolic products then cause the insect to molt. The kind of cuticle secreted by the epidermal cells at each molt is then affected by a third group of hormones secreted by the corpora allata, the juvenile hormones (I). In the presence of juvenile hormone, the immature insect will remain in the same state. Thus, in the presence of both juvenile and molting hormones, the insect will molt, however the new cuticle secreted will be the same as the old one. At the end of a stage, for example, at the last larval instar, the concentration of juvenile hormone drops, and in the presence of molting hormone the insect will now molt into the next stage, either the pupa or adult. In the adult, juvenile hormone then plays a role in the development of the ovaries.

1.3 INSECT CONTROL POTENTIAL

Being able to disrupt the development and maturation cycle

of an insect leads to a possible means of controlling insect populations. Juvenile hormone must be present at certain times during the insect life cycle, and absent at others. The potential utilization of juvenile hormone compounds as insect controlling agents, rests in their application to the insect at an unfavourable time.

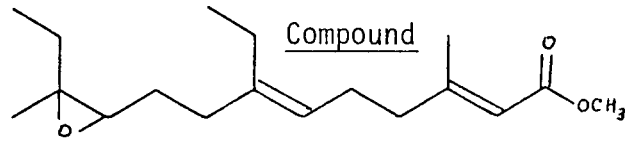
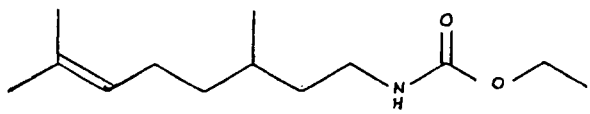
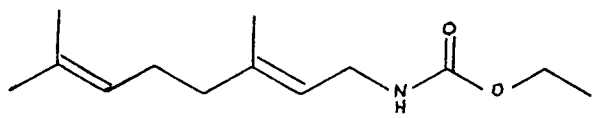
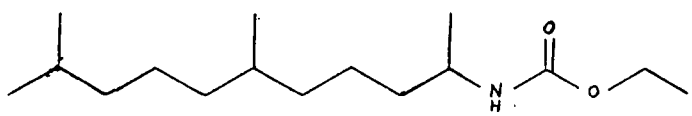
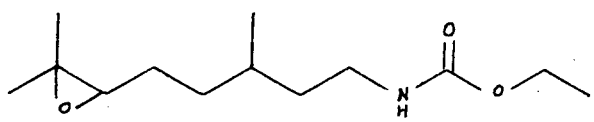
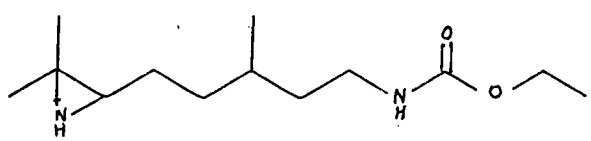
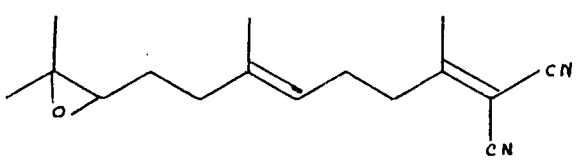
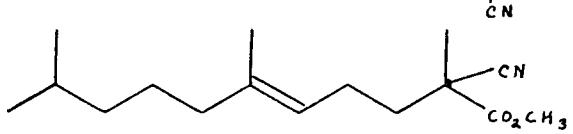
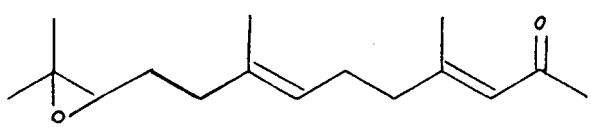
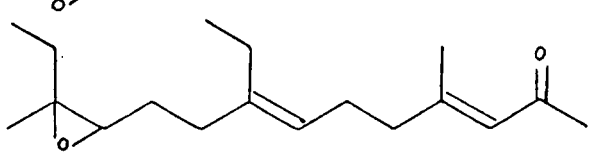
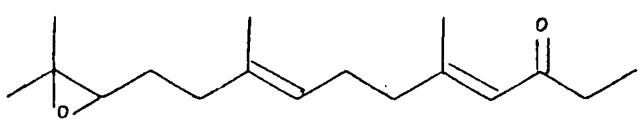
Juvenile hormones affect virtually all insects upon which they have been tested. In immature insects they produce a variety of morphogenetic effects. As well as determining the type of cuticle that the epidermal cells secrete in response to ecdysones, juvenile hormones also affect the development of internal organs such as the central nervous system, the glands, and the midgut, where they prevent maturation and metamorphosis.[5]

The use of natural juvenile hormones as insect controlling agents, however, has some drawbacks such as lack of species specificity and environmental instability. To overcome these problems and in order to try and define a structure-reactivity correlation, a number of analogs have been prepared.

Jacobson et al[6] prepared a number of compounds with terpenoid backbones to which various functional groups were attached (Table 1). The interesting finding was the high activity of compounds 9-11. But also of interest was the wide diversity of compounds which exhibited activity. Jacobson et al[6] also studied the effects of modifying unsaturation (Table 2) and the

Table 1

JH Activity of Various Compounds with Terpenoid Backbones on T. molitor

	Compound	Activity (µg)[a]
1.		0.03
2.		3.0
3.		3.0
4.		3.0
5.		0.1
6.		1.0
7.		1.0
8.		0.1
9.		0.03
10.		0.001
11.		0.001

[a]Dose required to give activity rating 1.0

epoxide functionality in a series of unsaturated esters (Table 3).

Table 2

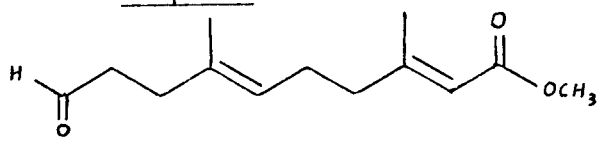
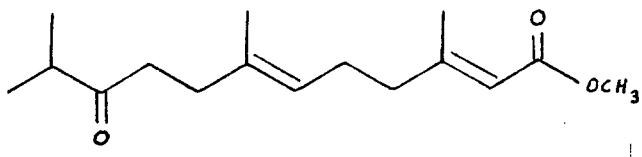
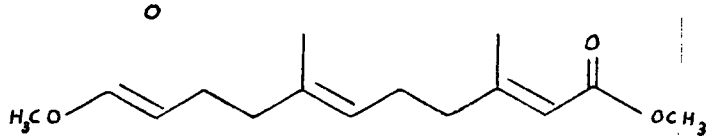
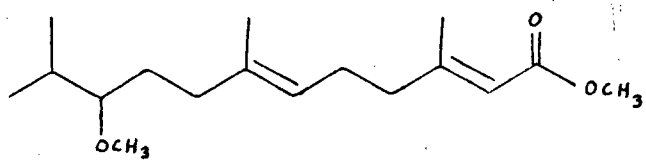
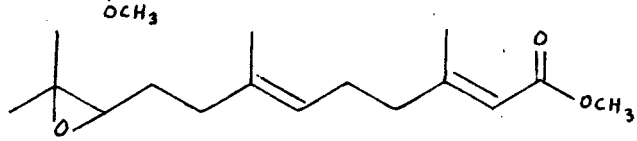
Effect of Modifying Methyl Juvenate Unsaturation on JH Activity in T. molitor

Compound	Activity (μg)[a]
Methyl laurate	> 10
Methyl 10,11-epoxyundecanoate	> 10
Methyl 10,11-epoxy-11-methyl-tridecanoate	> 10
Methyl 10,11-epoxy-11-methyl-dodecanoate	> 10
Methyl 3,7,11-trimethyldodecanoate	> 10
Methyl 10,11-epoxy-3,7,11-trimethyl-dodecanoate	> 10
Methyl 10,11-epoxy-3,7,11-trimethyl-2-dodecanoate	> 10
Methyl 10,11-epoxy-3,7,11-trimethyl-6-dodecanoate	> 10
Methyl farnesate 10,11-epoxide	0.031
Cecropia JH (mixed isomers)	0.01

[a] Dose required to give activity rating 1.0.

Table 3

Effect on JH Activity in T. molitor of Modification of the Epoxide End of Methyl Juvenate

	Compound	Activity (μg)[a]
1		10
2		25
3		10
4		15
5		0.06

[a]Dose required to give activity rating 1.0

Previous cyclization of juvenile hormone and methyl farnesate 10,11-epoxide under acid conditions had given both mono- and bicyclic acids whose esters were devoid of activity in T. molitor. Coupled with the results from Tables 2 and 3, it seems that unsaturation and the epoxide functionality are necessary for high activity.

Recently, White et al[7] have proposed an interesting hypothesis in attempting to rationalize structure-reactivity effects. On comparing molecular models it was revealed that the configuration

of compound I (Fig. 2) was such that the electronegative centres could be made to coincide with the distribution of similar groups in ecdysone (II), the hormone responsible for the initiation of molting in insects.

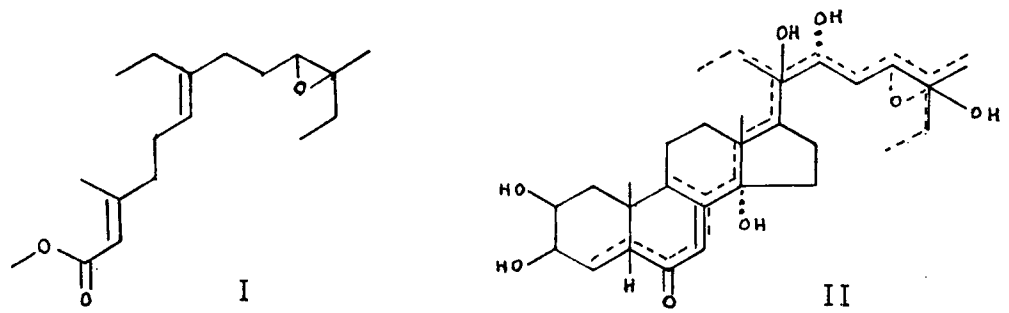
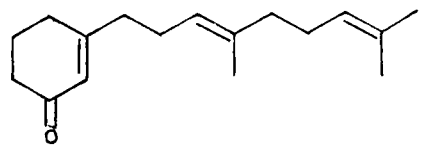
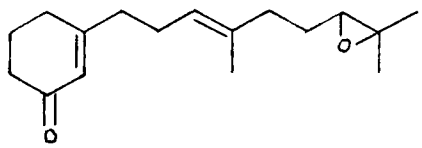
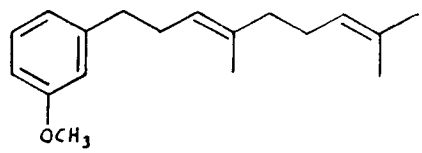
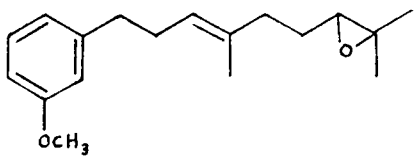
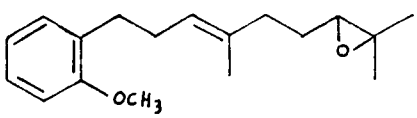
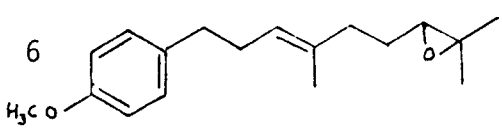


Fig. 2. Comparison of Electronegative Centers of Juvenile Hormone (I) with Ecdysone (II).

Since many juvenile hormone mimics can be made to fit on the ecdysone skeleton, and possess a similar distribution of electronegative groups, the possibility of these two insect hormones having some common receptor sites might seem reasonable. In order to test their hypothesis, White et al[7] synthesized a number of compounds which would fit their hypothesis. The results are summarized in Table 4. The results from this study were quite promising. In agreement with other work it was noted that the epoxidized compounds were much more active than those lacking this functionality and also the trans olefins were more active than the cis. All the compounds were quite active, with the high activity of compound 4 being especially noteworthy as up until now

Table 4

Compound (mixed isomers except where otherwise stated)		Juvenile Hormone activity on *Rhodnius prolixus* Dose 10^a	19^b
1		29	
	cis		200
	trans	1.1	19
2		20	
	cis	20	>200
	trans	9	
3		0.3	10
	cis		>200
	trans		50
4		0.003	0.1
	cis	10	100
	trans	0.003	
5		>100	
6		5	100
Cecropia JH		1	

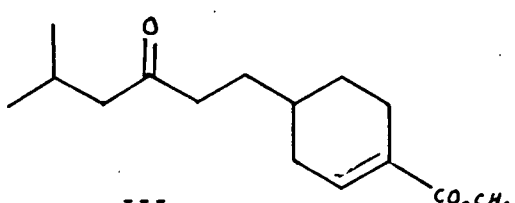
[a]Dose in µg required to give a score of 10, i.e. half-juvenalised;

[b]Dose in µg required to give a score of 19, i.e. complete supernumerary larva

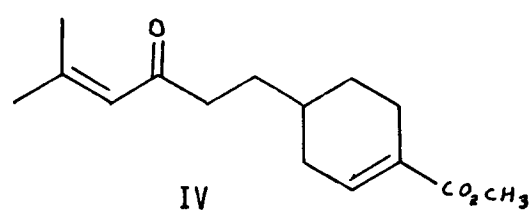
the C18 cecropia juvenile hormone had exhibited the highest activity in Rhodnius prolixus. Possible explanations for the high activity include its facility for cuticle penetration, its metabolic stability, its ability to interfere with the metabolic degradation of the natural hormone, or the structural similarity of compound 4 with the natural hormone.

1.4 SPECIFIC JUVENILE HORMONE ANALOGS

As mentioned earlier it was noted that one drawback of the natural cecropia juvenile hormone was its relative lack of species specifity. Analogs were hoped to provide a solution to this problem, and examples of species specific analogs are now known. Bowers et al[8] in 1967 isolated from the wood of the balsam fir (Abies balsamea l.) a compound (juvabione, III) which possessed a high degree of juvenile hormone activity against the species Pyrrhocoris apterus. Consequently dehydrojuvabione (IV) was isolated by Cerny et al[9] and also found to possess high



III



IV

activity in Pyr. apterus. The interesting finding here was that these two natural products did not exhibit noticeable activity against other species tested. A similar result was noted by Treadgold et al[10] who studied some esters of chrysanthemic acid (the acid portion of some naturally occurring pyrethroids). The results as tested on Dysdercus fasciatus are shown in table 5.

These compounds were also tested on the following insects: Rhodnius prolixus and Cimex lenticulus (Hemiptera Reduvidae and Cimicidae), Plutella xylostella (Lepidoptera), Phaedon cochlearire and Tenebrio molitor (Coleoptera), Aedes aegypti (Diptera), and Blatella germanica (Orthoptera). However, only in the case of D. fasciatus (Hemiptera Pyrrhocoridae) was juvenile hormone activity noted.

1.5 PHEROMONES

Although juvenile hormone analogs appear to have a bright future in the area of insect control, a number of other possibilities are also being explored and are of current interest. The use of insect pheromones is one of these areas. Pheromones can be classed as substances which are secreted to the outside environment by an animal and received by a second individual of the same species in which they release a specific reaction. Insect pheromones then, are compounds by which insects convey specific information. The effects of insect pheromones range widely from

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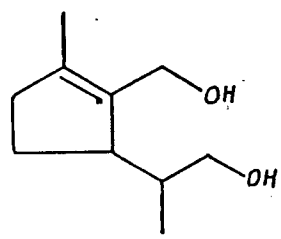
such applications as marking trails, exhibiting alarm, or for the purpose of attractancy. In contrast to insect hormones, pheromones are mostly species specific, as well as structure specific, with a slight structural modification often negating the activity of the compound (Table 6).[11]

Because of their high species-specificity and their high potencies (for example, the compound nematatabiol[12] which is the attractant pheromone of Chrysopa japana and Chrysopa septem-punctata is active in the amount of 10^{-6} µg.) pheromones are attractive candidates for use in controlling insect populations. The possible use of these compounds would likely have to be resolved for each specific insect problem.

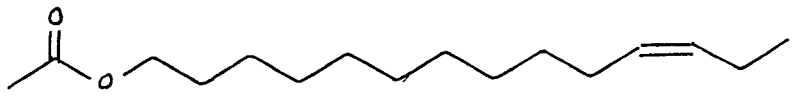


V, nematatabiol

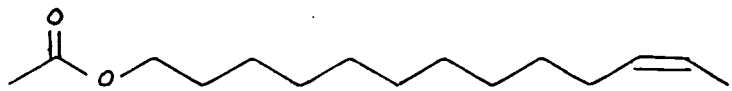
For example, a congregating pheromone could be used to attract a certain species of insects to a trap baited with a lethal compound or adhesive material which would prevent the insect from leaving, or alternatively, a sex attractant pheromone could be released into an infested area, thus masking the pheromone released by the insect and thus keeping the males and females from locating each

Table 6

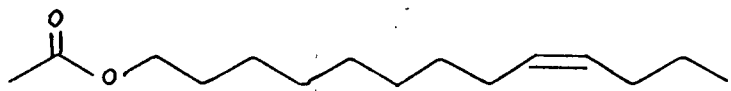
Effects of Structural Modification on Attraction of the Male Red-Banded Leaf Roller (Argyrotaenia velutinana)



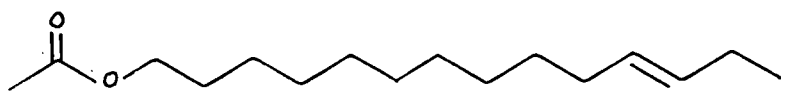
natural pheromone



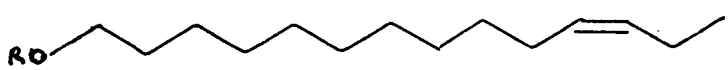
weak attractant



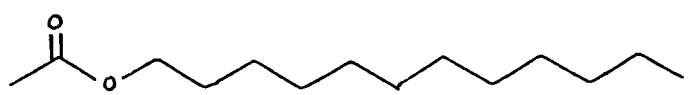
very weak attractant



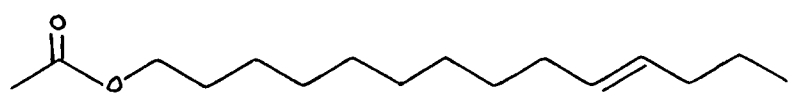
inhibitors



(R = H, CHO, EtCO)



synergist



inactive (both cis & trans)

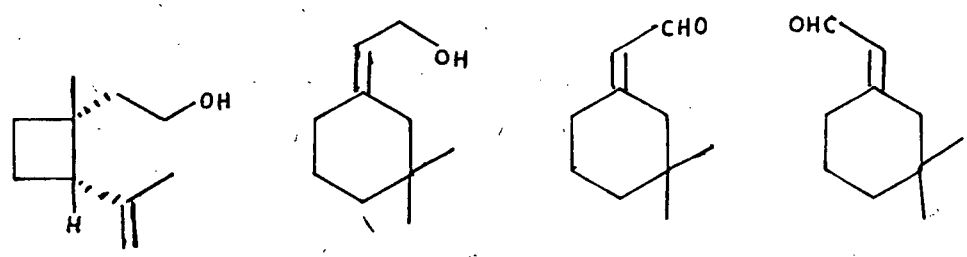
other for purposes of mating. Furthermore, because of the high potency of these compounds, this type of application would be technically feasible.

At present, chemically identified pheromones are known from only seven of the twenty-seven insect orders, but it would seem likely that intraspecific chemical communication may eventually be detected in every order.[13]

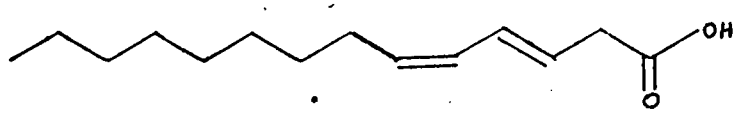
The structures of pheromones are quite diverse, but often they are derivatives of long chain slightly branched hydrocarbons (Table 7).[13]

Table 7

Structures of Some Insect Pheromones

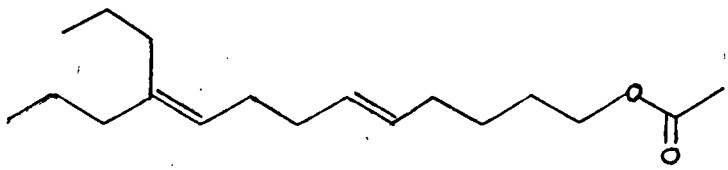


Female Sex Attractant of the Boll Weevil (Anthonomus grandis)

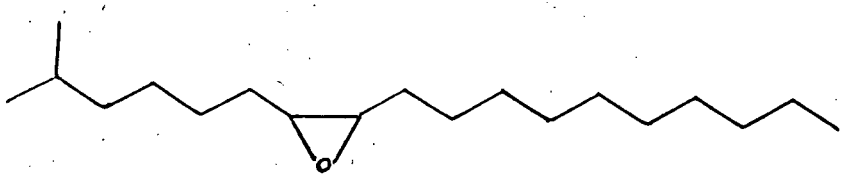


Sex Attractant of the Black Carpet Beetle (Attagenus megatoma)

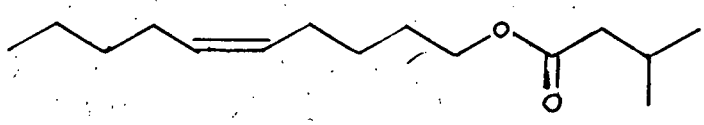
Table 7 continued



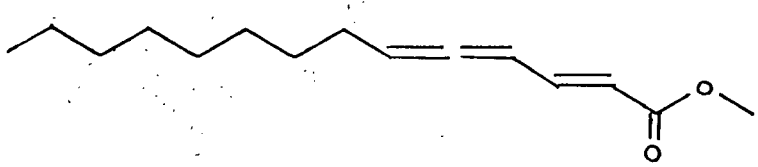
Female Sex Pheromone of the Pink Bollworm Moth (Pectinophora gossypiella)



Sex attractant of the Female Gypsy Moth (Porthetria dispor)



Sex Pheromone of the Female Pine Emperor Moth (Nudaurelia cytherea)

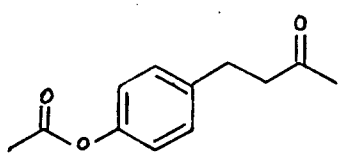
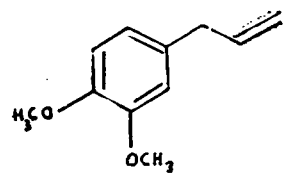
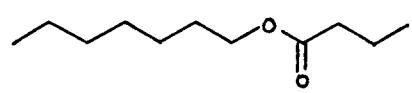
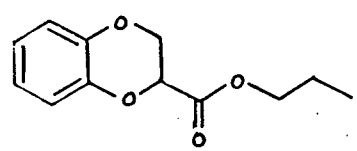
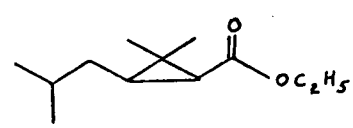


Sex Pheromone of the Bean Beetle (Acanthoscelides obtectus)

Besides these naturally occurring insect pheromones which have been isolated from insects, a number of synthetic compounds are known which possess pheromonal activity (Table 8).[14]

Table 8

Attractants Found by Volume Screening of Chemicals

Formula	Common or chemical name	Species attracted
	Cue-lure	Melon fly Dacus cucurbitae Coq.
	Methyl eugenol	Oriental fruit fly Dacus dorsalis (Hendel)
	Heptyl butyrate	Yellow jackets Vespula spp.
	Amlure	European chafer Amphimallon majalis (Raz.)
	Ethyl dihydrochrysanthemumate	Rhinoceros beetle Oryctes rhinoceros (L.)

The compounds listed in this table were found by mass testing of samples by the U.S.D.A. against various insect pests.

1.6 PYRETHROIDS

As was noted earlier, certain esters of chrysanthemic acid were noted to possess high juvenile hormone activity against D. fasciatus (Table 5), while the ethyl ester of dihydrochrysanthemic acid (compound 9, Table 8) was noted as a synthetic attractant of the rhinoceros beetle, Oryctes rhinoceros. It is also interesting to note that naturally occurring esters of chrysanthemic acid (pyrethroids) found in various plant sources are very toxic to insects.

Pyrethrum, which represents the dried flowers of Chrysanthemum cinerariaefolium, has been used as an insecticide from ancient times. The insecticidal activity of pyrethrum has been attributed to the action of the six constituents: pyrethrum I, pyrethrum II, cinerin I, cinerin II, jasmolin I, and jasmolin II (Table 9).[15]

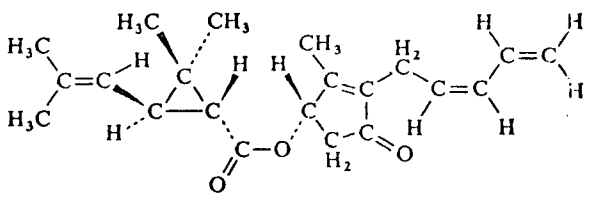
The insecticidal action of pyrethrins is due to their ability to paralyze insects. Knockdown occurs almost instantaneously at very low doses, with higher doses being required to kill the insect. A number of analogs have been prepared by either modifying the acid moeity and using the natural alcohol for esterification purposes (Table 10 and 11), or by using the natural acid portion, and using various alcohols to prepare the ester derivatives (Table 12).[15]

The use of benzyl alcohol, phthalimidocarbinol, and furylcarbinol were found to have good insecticidal activities. With

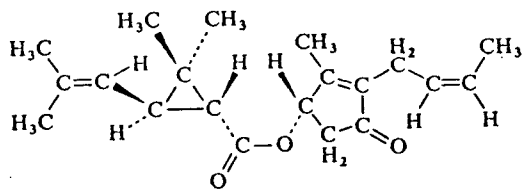
the natural alcohols, none of the esters of the modified acids were found to have insecticidal activities with comparable toxicity to that of pyrethrins until the discovery of 2,2,3,3-tetramethylcyclopropane-carboxylic acid by Matusi and Kitahara,[16] who synthesized various esters of this acid and found them to be nearly equal to chrysanthemates in their toxicity to insects.

Table 9

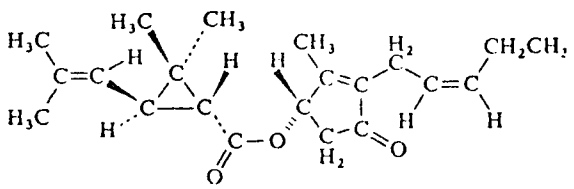
Structures of the Naturally Occurring Pyrethroids



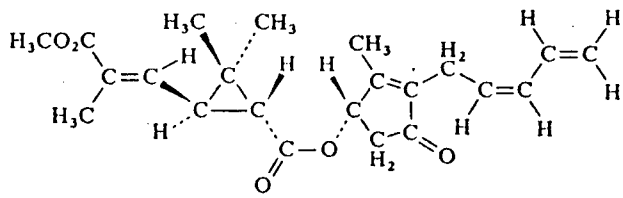
Pyrethrin I



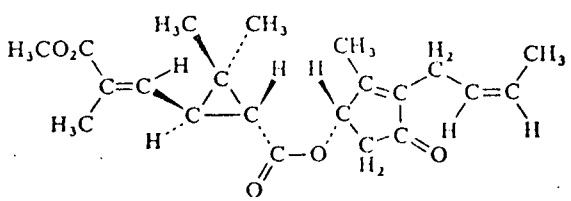
Cinerin I



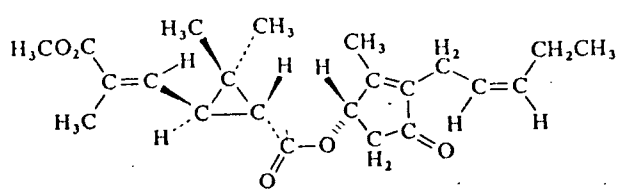
Jasmolin I



Pyrethrin II

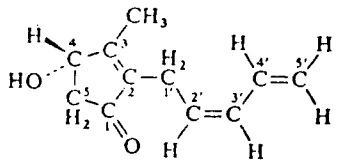


Cinerin II

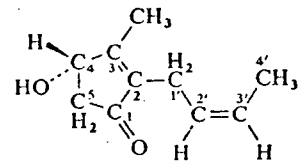


Jasmolin II

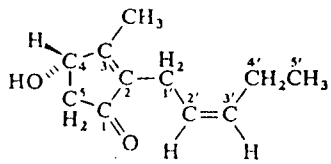
Table 9 continued:



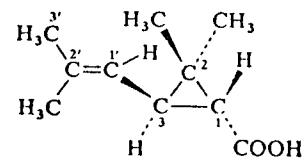
(+)-Pyrethrolone



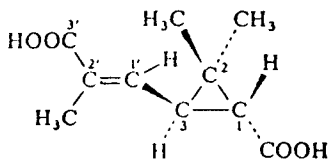
(+)-Cinerolone



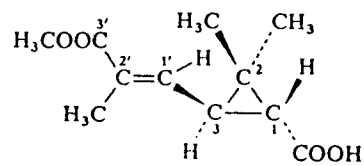
Jasmolone



(+)-*trans*-Chrysanthemic acid

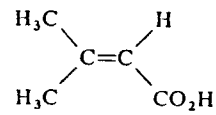
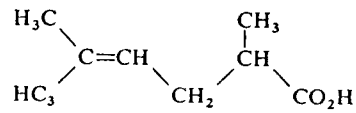
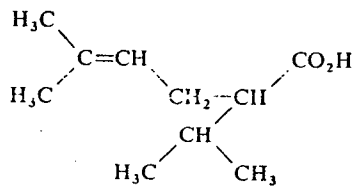
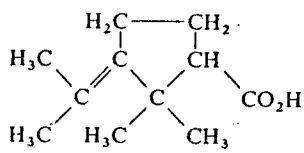
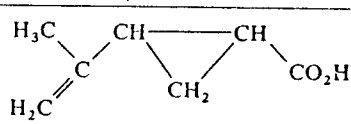
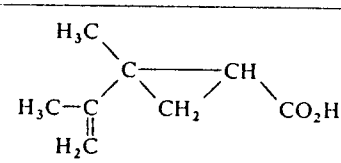


(+)-*trans*-Chrysanthemum dicarboxylic acid



(+)-*trans*-Pyrethric acid

TABLE 10 Toxicity of Natural Pyrethronyl Esters to the German Cockroach (*Blattella germanica* L.)

	Acid	Activity[a]
		(−)
		(−)
		(−)
		(±)
		(++)
		(+)
cf.	Resynthesized pyrethrin I	(5+)

[a] Exposure by contact

TABLE 1] Insecticidal Activities of (±)-Allethronyl Esters

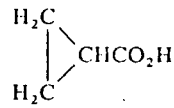
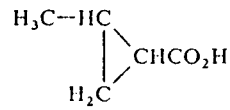
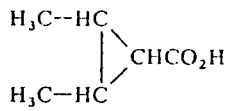
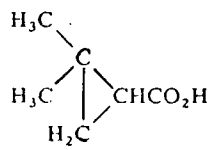
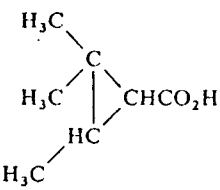
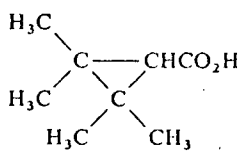
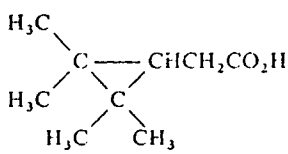
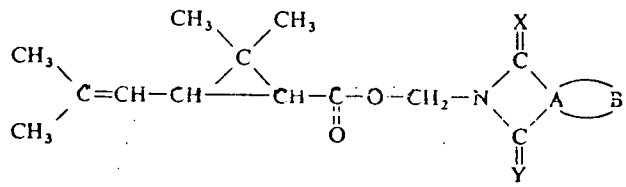
Acid	Relative activity[a] LC_{50} (mg/100 ml)	
	—	(−)
	>1000	(−)
	>1000	(−)
	920	(±)
	500	(+)
	135	(4+)
	>1000	(−)

TABLE 12 Insecticidal Activity of Imidomethyl Chrysanthemates



Chrysanthemate	Relative toxicity (LC_{50}) to *Musca domestica*[a]
Phthalimidomethyl (±)-cis, *trans*-	33
Monothiophthalimidomethyl (±)-*cis*, *trans*-	100
Dithiophthalimidomethyl (±)-*cis*, *trans*-	42
3,4,5,6-Tetrahydrophthalimidomethyl (±)-*cis*, *trans*- (Phthalthrin)	80
(+)-*trans*-Phthalthrin	170
1,2,3,4-Tetrahydrophthalimidomethyl (±)-*cis*, *trans*-	20
α,α′-Dimethylmaleimidomethyl (±)-*cis*, *trans*-	75
α-Methyl-α′-ethylmaleimidomethyl (±)-*cis*, *trans*-	38
α-Methyl-α′-phenylmaleimidomethyl (±)-*cis*, *trans*-	23
2,4-Dichlorophthalimidomethyl (±)-*cis*, *trans*-	34
Pyrethrins	100
Allethrin	50
2,6-Dimethyl-4-allyl-benzyl (±)-*cis*, *trans*-	188

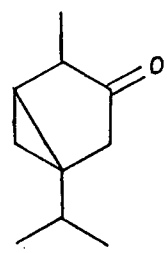
[a] Campbell turntable method

2. SCOPE OF PRESENT WORK

The previous discussion has provided a brief summary of the various areas of insect chemistry which have received some attention in the recent literature. Thus, it is clear that certain structural types provide biological activities of the juvenile hormone type, others possess insect repellency or attractancy properties, while still others reveal toxic properties reminiscent of the pyrethroid family. In many of these areas additional research is essential to provide a better understanding of structure-activity relationships and hopefully, to develop useful applications of such chemicals in insect control.

With these various objectives in mind, it was decided to initiate a synthetic program leading to various novel analogs of compounds within the above mentioned families and to subsequently evaluate their potential usefulness. It seemed particularly attractive to utilize, as starting materials for the synthetic program, some organic compounds which are presently regarded as waste byproducts in the pulp and paper industry. In this manner successful developments of the chemistry would stimulate useful applications of such waste products.

Of the various trees which are important in the forest industry of British Columbia, three species, the western red cedar, the douglas fir, and the western hemlock have been studied in regard to their chemical composition.[17] Of particular interest to us was the western red cedar tree of which the main component in the leaves and branches is the monoterpene thujone (VI). Currently, branches and leaves of trees are waste byproducts of the forest industry, and generally disposed of by burning or dumping methods, thus constituting a pollution hazard, as well as wasting a large portion of the tree.



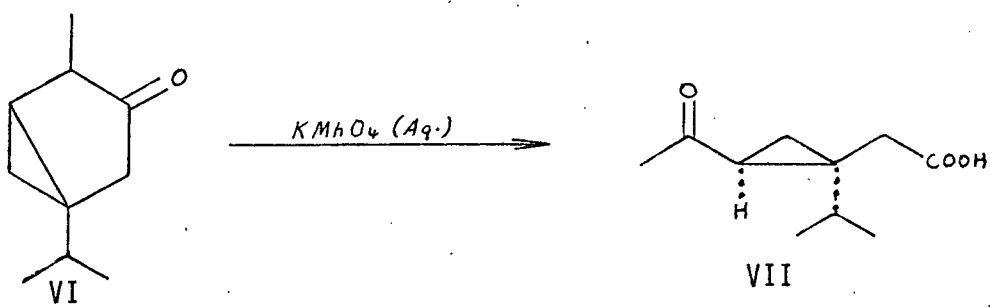
VI

Since thujone can be obtained from the leaves and branches by an economically viable steam distillation and fractionation process, and because of the attractive functionalities of thujone it was decided to study the possible usage of this material as a precursor to insect controlling agents.

3. DISCUSSION

3.1. α-THUJAKETONIC ACID

The treatment of cedar leaf oil* with aqueous potassium permanganate is a known reaction[18] which results in the oxidative ring opening of thujone to α-thujaketonic acid (VI → VII).



VI VII

During the oxidation, the chiral centre adjacent to the methyl group is lost, while the rest of the stereochemistry is fixed. Thus, only one product is obtained, with the stereochemistry about the cyclopropane ring established as having the iso-propyl group and hydrogen cis to each other.

Due to the central role that this material occupied in regards to some of the synthetic investigations its p.m.r. spectrum was recorded and analyzed for future reference. The spectrum contained

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* Cedar leaf oil was obtained through the courtesy of MacMillan Bloedel Research Ltd., and consisted of approximately 85% thujone and 12% terpenoid impurities.

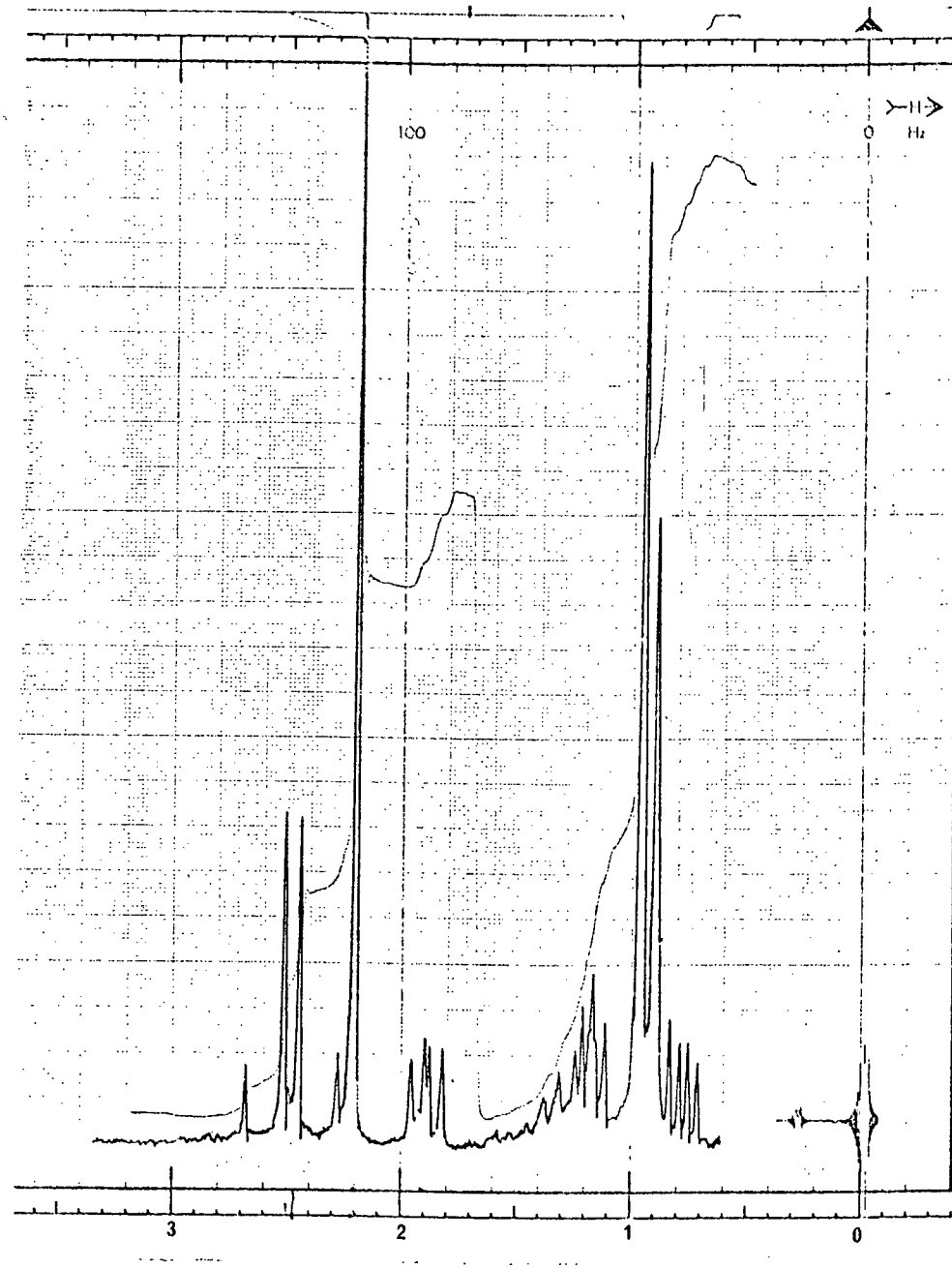
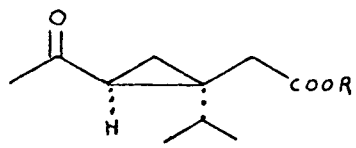


Fig. 3. P.M.R. Spectrum of α-Thujaketonic Acid.

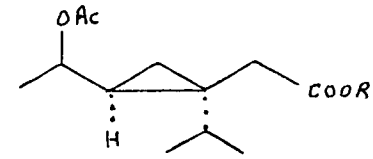
a three proton singlet at δ 2.22 which could be attributed to the methyl group adjacent to the ketonic carbonyl while at δ 0.94 occurred a six proton doublet (J = 5 Hz) which was assigned to the methyl protons of the iso-propyl group. The four line resonance centered at δ 2.49 was assigned to the methylene protons adjacent to the carboxylate group. These two protons were adjacent to a chiral centre and thus gave rise to the observed AB pattern (J = 17 Hz). Centered at δ 1.91 was a one proton doublet of doublets which was assigned to the proton on the cyclopropane ring adjacent to the ketonic carbonyl. This proton along with the methylene protons of the cyclopropane ring formed an ABX system. One of the cyclopropyl methylene protons gave rise to the doublet of doublets centered at δ 0.88. The other cyclopropyl proton and the methine proton of the isopropyl group then accounted for the multiplet which spanned the region δ 1.5 to δ 1.1.

3.2 SYNTHETIC OBJECTIVES

As was shown in the introduction, a number of insect controlling agents are derivatives of chrysanthemic acid, have a terpenoid backbone, or are branched long chain hydrocarbons. It was therefore hoped to find some general procedures for the elaboration of α-thujaketonic acid to produce a series of derivatives which would structurally resemble some of these active compounds. Previously[19], work had been done in this area to produce derivatives of the type (VIII + IX).



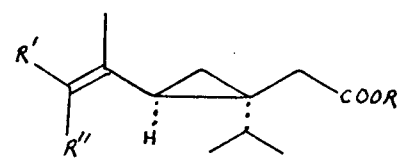
VIII



IX

The work described in this thesis was aimed at: 1.) the transformation of the ketonic carbonyl of α-thujaketonic acid to an olefinic linkage to produce derivaties of the type (X), and 2.) synthesis of suitable substances for subsequent coupling to α-thujaketonic acid at the ketonic carbonyl.

If the above objectives could be achieved with α-thujaketonic acid, then it would seem possible to produce an analogous series of derivatives with β-thujaketonic acid (XI, XII).



X

3.3 THE WITTIG REACTION

The Wittig reaction was deemed as the method of choice for the elaboration of the ketonic carbonyl of α-thujaketonic acid. With

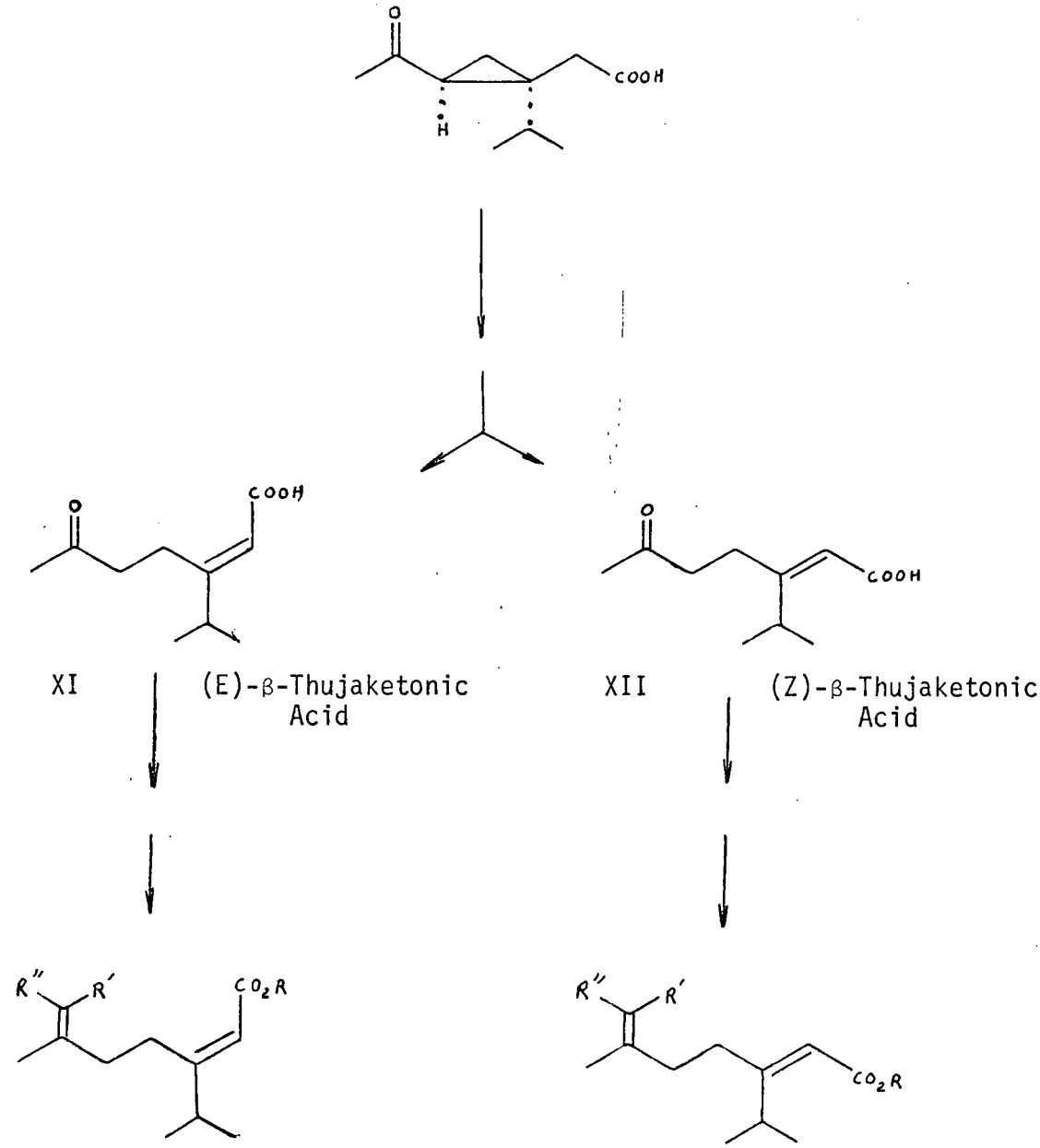
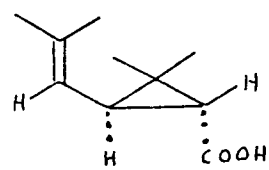


Fig. 4. Scheme for Elaboration of α-Thujaketonic Acid to Derivatives of β-Thujaketonic Acid.

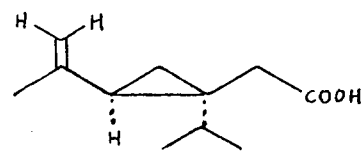
the Wittig reaction there is no ambiguity about the positioning of the double bond, and by use of suitable phosphonium salts a wide variety of side chains can be introduced. Therefore, a variety of conditions were studied in order to effect the desired transformation. The phosphonium salts used for the study were the commercially available methyltriphenylphosphonium bromide and the easily prepared isopropyl-triphenylphosphonium iodide. Successful application of the Wittig reaction with these phosphonium salts would then yield chrysanthemic acid-like compounds (Table 13).

Table 13

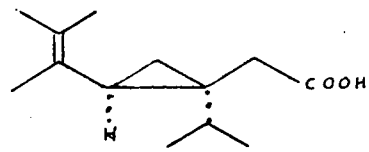
Structural Comparison of Methylene and Isopropylidene Derivatives of α-Thujaketonic Acid to Chrysanthemic Acid.



trans-Chrysanthemic Acid

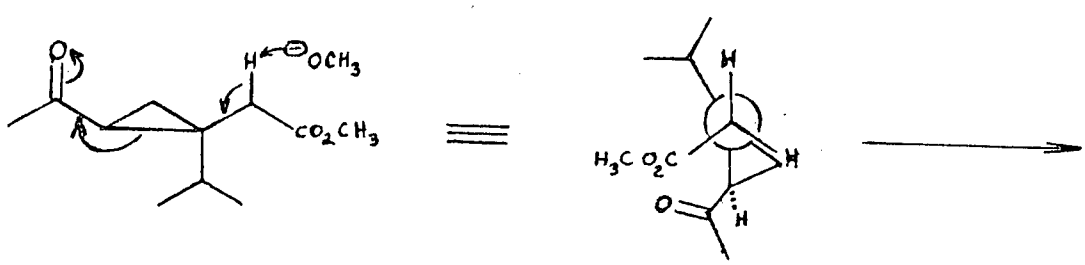


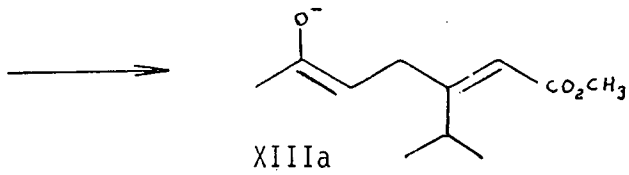
XIII, Methylene Derivative of α-thujaketonic Acid



XIV, Isopropylidene Derivative of α-thujaketonic Acid

The first attempts at the Wittig reaction were done on an ethereal mixture of α-thujaketonic acid and methyltriphenylphosphonium bromide using two equivalents of n-butyllithium. These reaction conditions however, led only to tarry decomposition products, perhaps obtained by indiscriminant attack of the base on the cyclopropyl ketone derivative. It was therefore decided to investigate the use of the methyl ester of α-thujaketonic acid as the starting material for the Wittig reaction. Using methanol as the solvent, and sodium methoxide as the base however gave back only starting material and ring opened material (XIIIa). The mechanism (Fig. 5) being visualized for this reaction involves attack of the base at the protons alpha to the carbomethoxy group, followed by ring opening to form the enolate of the methyl ester of β-thujaketonic acid.





XIIIa

Fig. 5. Proposed Mechanism for Ring Opening of α-Thujaketonic Acid under Basic Conditions.

Although the desired product was not obtained, the result was an interesting one. The ester thus obtained was believed to be the Z isomer due to the occurrence of a one proton septet (J = 7 Hz) at δ 4.0 (see below). Previously, the ring-opened acid having the E configuration (XI), was prepared in this laboratory by the treatment of α-thujaketonic acid with aqueous mineral acid.[20] The proposed mechanism is outlined below (Fig. 6).

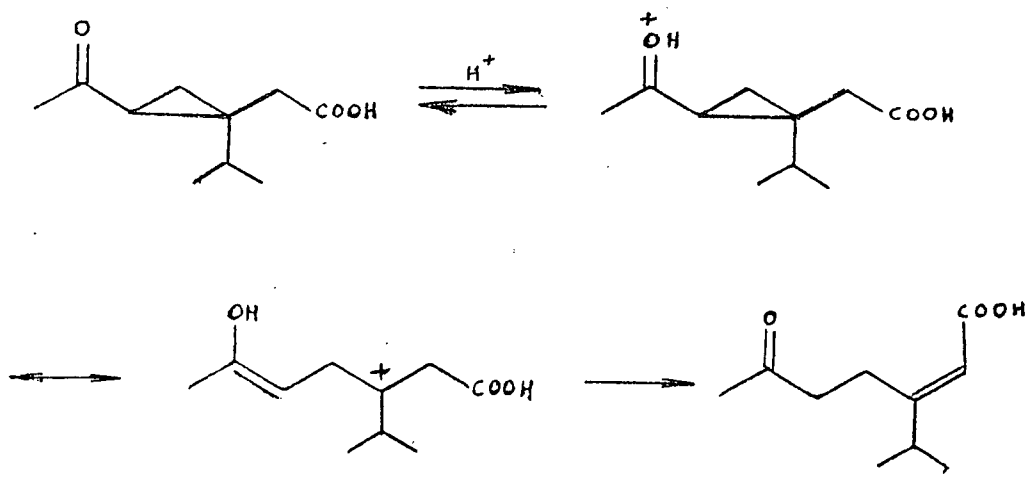
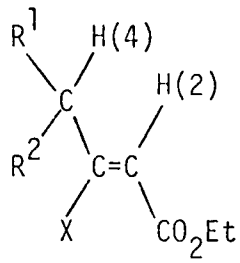


Fig. 6. Proposed Mechanism for Ring Opening of α-Thujaketonic Acid under Acidic Conditions.

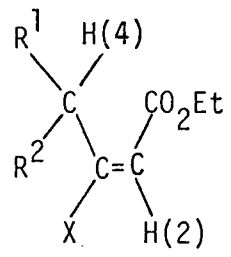
For a more direct comparison, the ring-opened acid obtained from the aqueous acid treatment was converted to the methyl ester. The p.m.r. spectra of the two methyl esters (Fig. 7a, 7b) were then compared. The spectra were quite similar except for two noticeable differences. In the case of the material obtained from the sodium methoxide reaction there was a one proton septet (J = 7 Hz) at δ 4.0 and the signal for the vinylic proton occurred at δ 5.4.

In the case of the methyl ester of the material obtained from the aqueous acid treatment, there was no septet at δ 4.0, and the signal of the vinylic proton came at δ 5.6. These observations corresponded to the results obtained by Pizzey et al[21] who studied the proton magnetic resonance spectra of a number of crotonic acid derivatives of the type XV + XVI.



trans

XV



cis

XVI

Their overall results (Table 14) indicated that in this type of a system the resonance of the proton(s) on C-4 which was cis to the carboethoxy group would occur at lower field than would the resonance of the proton(s) at C-4 if this group and the carboethoxy

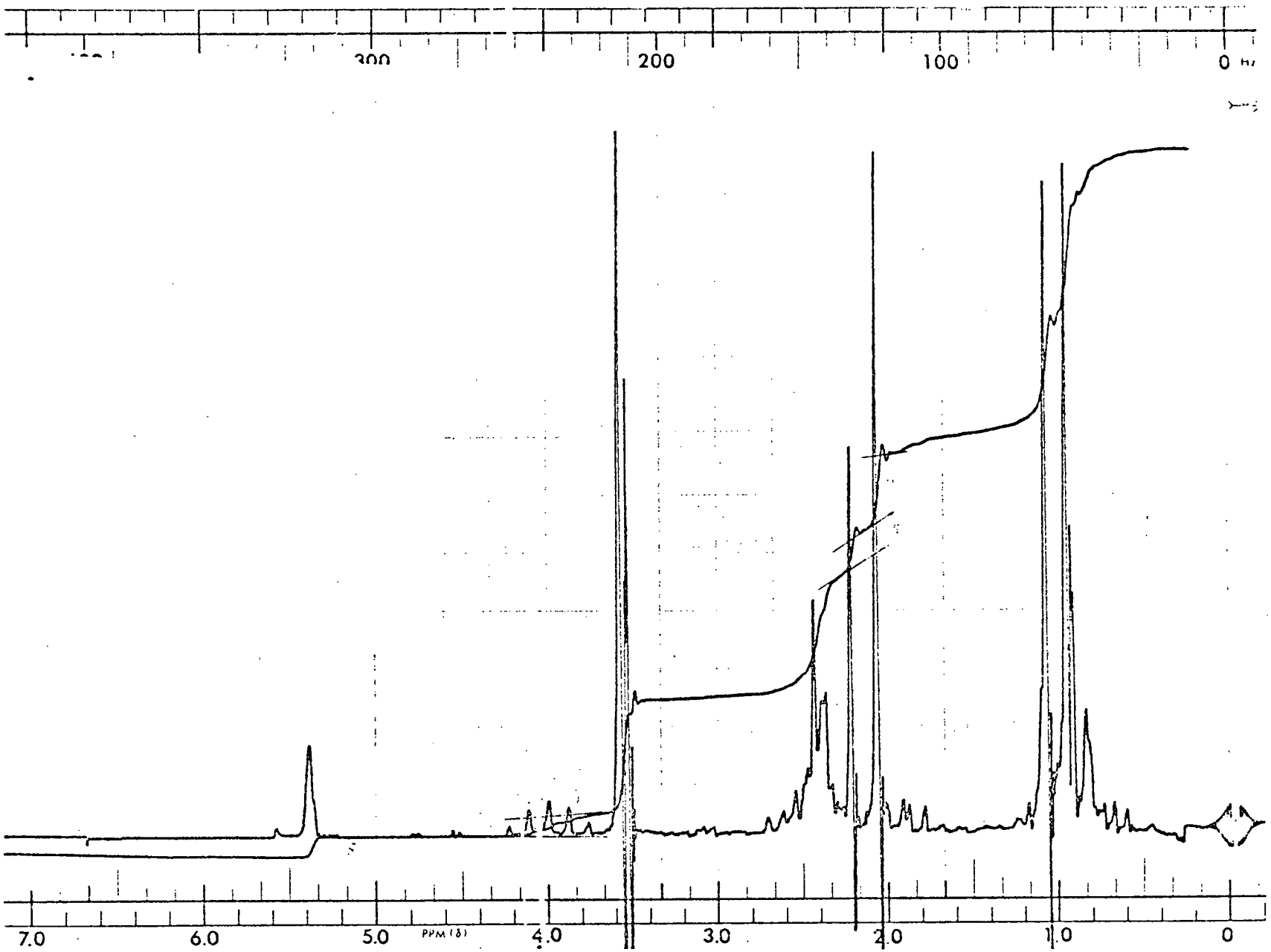


Fig. 7a. P.M.R. Spectrum of Methyl Ester of Ring Opened Material obtained from Sodium Methoxide Reaction (contains some α-thujaketonic acid).(Z-β-Thujaketonic Acid Methyl Ester)

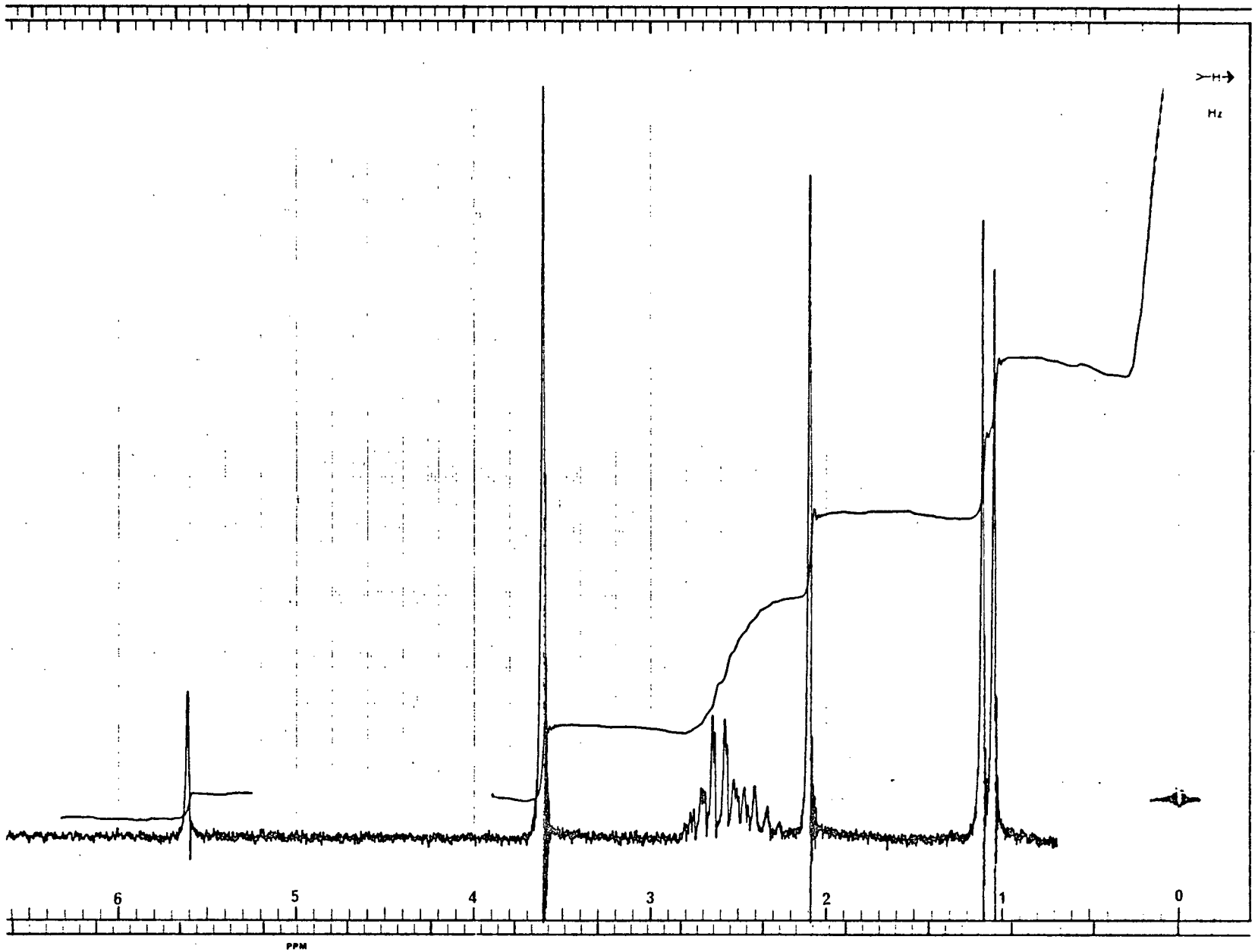


Fig. 7b. P.M.R. Spectrum of Methyl Ester of β-Thujaketonic Acid obtained from Aqueous Acid Treatment of α-Thujaketonic Acid. (E-β-Thujaketonic Acid Methyl Ester)

were trans. Also, it was noted that the resonance of the vinylic proton at C-2 occurred at lower field in the case of the trans ester as compared with cis.

Table 14

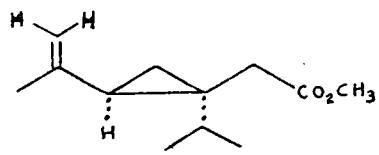
Chemical Shifts for Compounds of the Type

$R^1R^2CH\cdot C(X):CH\cdot CO_2Et$

	R^1	R^2	X	C:C-H(2)	C:C-C-H(4)
cis	H	H	Cl	δ 5.99	δ 2.51
trans	H	H	Cl	δ 6.04	δ 2.23
cis	H	H	S·Ph	δ 5.33	δ 2.42
trans	H	H	S·Ph	δ 5.86	δ 1.75
cis	H	H	S·mesityl	δ 4.81	δ 2.42
trans	H	H	S·mesityl	δ 5.82	δ 1.61
cis	H	H	Cl	δ 6.03	-
trans	H	H	Cl	δ 6.55	-

From these results it thus appeared that the ring opening of α-thujaketonic acid could be accomplished stereoselectively to provide either isomer. This was a pleasing result, however it was not investigated further, as the goal at this time was the study of the Wittig reaction.

Therefore, in considering more vigorous reaction conditions, it was decided to use the anion of dimethylsulfoxide as the base and dimethylsulfoxide as the solvent. Under these conditions (room temperature, 24 hours) only a poor recovery of the starting methyl ester contaminated with a small amount of ring-opened material was obtained. At elevated temperatures (100 C., 24 hours), no material soluble in the ether extract was recovered. Limited success was finally achieved by using sodium hydride in 1,2-dimethoxyethane, in which the methylene derivative (XVII) of the methyl ester of α-thujaketonic acid was obtained in 21% yield.



XVII

Under the same conditions employing isopropyltriphenylphosphonium iodide, no Wittig product could be detected and a 40% recovery of starting material was achieved.

From the results of these studies it seemed likely that the hindered nature of the ketonic carbonyl of α-thujaketonic acid was resulting in preferential nucleophilic attack by the phosphorane at the carbomethoxy group. Also, the hindered nature of the ketonic carbonyl was likely responsible for the basic removal of the protons adjacent to the carbomethoxy group thus resulting in the formation of ring-opened material. Therefore, to overcome these problems and eliminate the unwanted side reactions it would be necessary to decrease the acidity of the protons adjacent to the carbomethoxy group,

and also make the carbonyl of this function less electrophilic. It was therefore decided to work with the sodium salt of α-thujaketonic acid. Since, the in situ preparation of the lithium salt with n-butyllithium was not successful, it was decided to prepare the sodium salt by the action of methanolic sodium hydroxide, and then isolate this material. Due to solubility considerations and because of the claimed selectivity, dimethylsulfoxide was chosen as solvent.[22] Following the procedure of Corey et al[22], reaction of the dry sodium salt with methyltriphenylphosphonium bromide gave the desired methylene derivative (XIII) in about 90% yield. With isopropyltriphenylphosphonium iodide the corresponding isopropylidene derivative (XIV) was obtained in about 85% yield. The high yield of the isopropylidene derivative was especially noteworthy, as generally the yields of tetrasubstituted olefins from the Wittig reaction are not very good.[23] Thus, the first objective had now been realized.

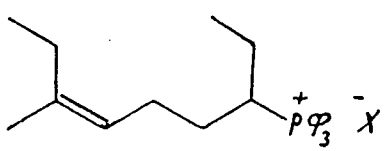
With the achievement of the desired functionalization of the ketonic carbonyl of α-thujaketonic acid it was now desired to find a general procedure for the esterification of the obtained olefinic acids.

Recently, Shaw et al[24] reported a simple convenient procedure for the quantitative esterification of carboxylic acids. Their method consisted of treating the acid in hexamethylphosphoramide with sodium hydroxide and an alkyl halide. This procedure was modified slightly in that the sodium salt of the olefinic acid was formed first by the action of methanolic sodium hydroxide. The salt was isolated,

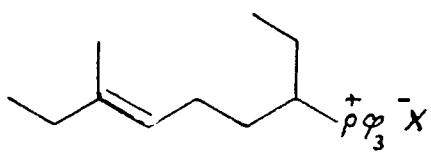
washed with petroleum ether; dried in vacuo; and then treated with an alkyl halide in hexamethylphosphoramide. Use of this procedure resulted in good yields of some simple ester derivatives. The results along with some spectroscopic data are summarized in Table 15.

3.4 ATTEMPTED PREPARATION OF APPROPRIATE PHOSPHONIUM INTERMEDIATES XVIII AND XIX.

With procedures for the Wittig reaction and subsequent esterification having been established there remained the final objective, which was the synthesis of suitable synthetic intermediates for the subsequent coupling with thujaketonic acid via the Wittig reaction. It was hoped that this approach would allow the preparation of a series of juvenile hormone analogs. To be specific, the target molecules were the phosphonium salts XVIII and XIX. The subsequent reaction of the phosphoranes derived from XVIII and XIX with α- and β-thujaketonic acids would then lead to materials which are structurally similar to the cecropia juvenile hormone (Table 16).



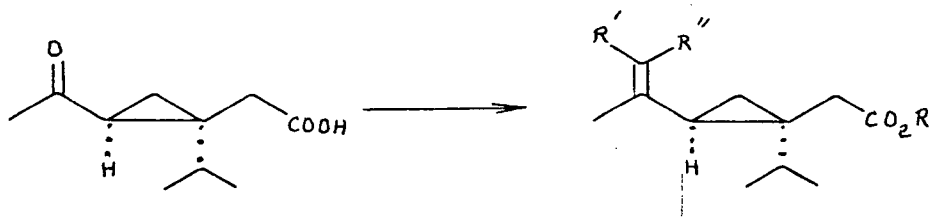
XVIII



XIX

Table 15

Overall Results for the Conversion of α-Thujaketonic Acid to Some Simple Olefinic Ester Derivatives.



Compound R'	Compound R''	Alkylating Agent used for Esterification	% Yield[a] ν (C = O)	I.R. Data [cm^{-1}]	P.M.R. data Chemical Shift of C = C-CH_3
H	H	MeI	74	1741	δ 1.75
H	H	n-BuBr[b]	70	1735	δ 1.74
H	H	$H_2C = CN(CH_2)_2CH_2OTs$[b]	68	1735	δ 1.76
Me	Me	MeI	67	1740	δ 1.53, δ 1.62, δ 1.69
Me	Me	n-BuI[c]	65	1735	δ 1.52, δ 1.61, δ 1.70

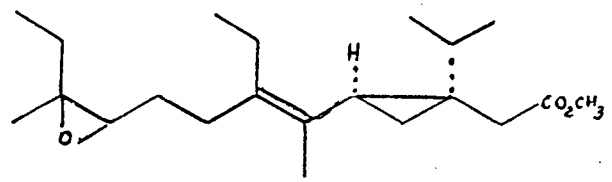
a refers to isolated yield of olefinic ester (X) based on α-thujaketonic acid.

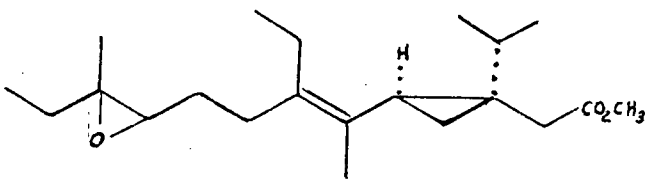
b catalytic amount of sodium iodide used in esterification reaction.

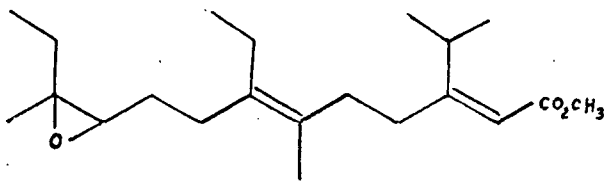
c prepared by Dr. A. Markus.

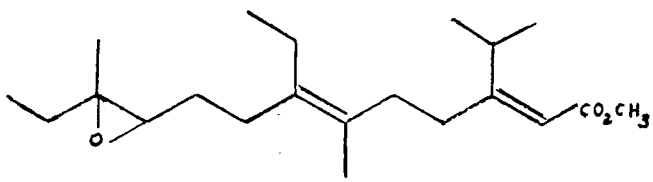
Table 16

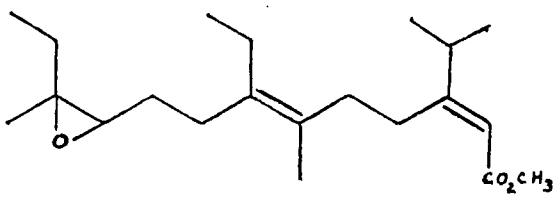
Structural Comparison of Juvenile Hormone with Possible Analogs Available from Thujaketonic Acid.

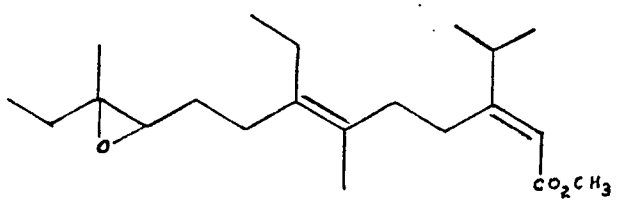


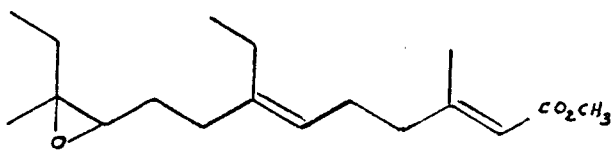






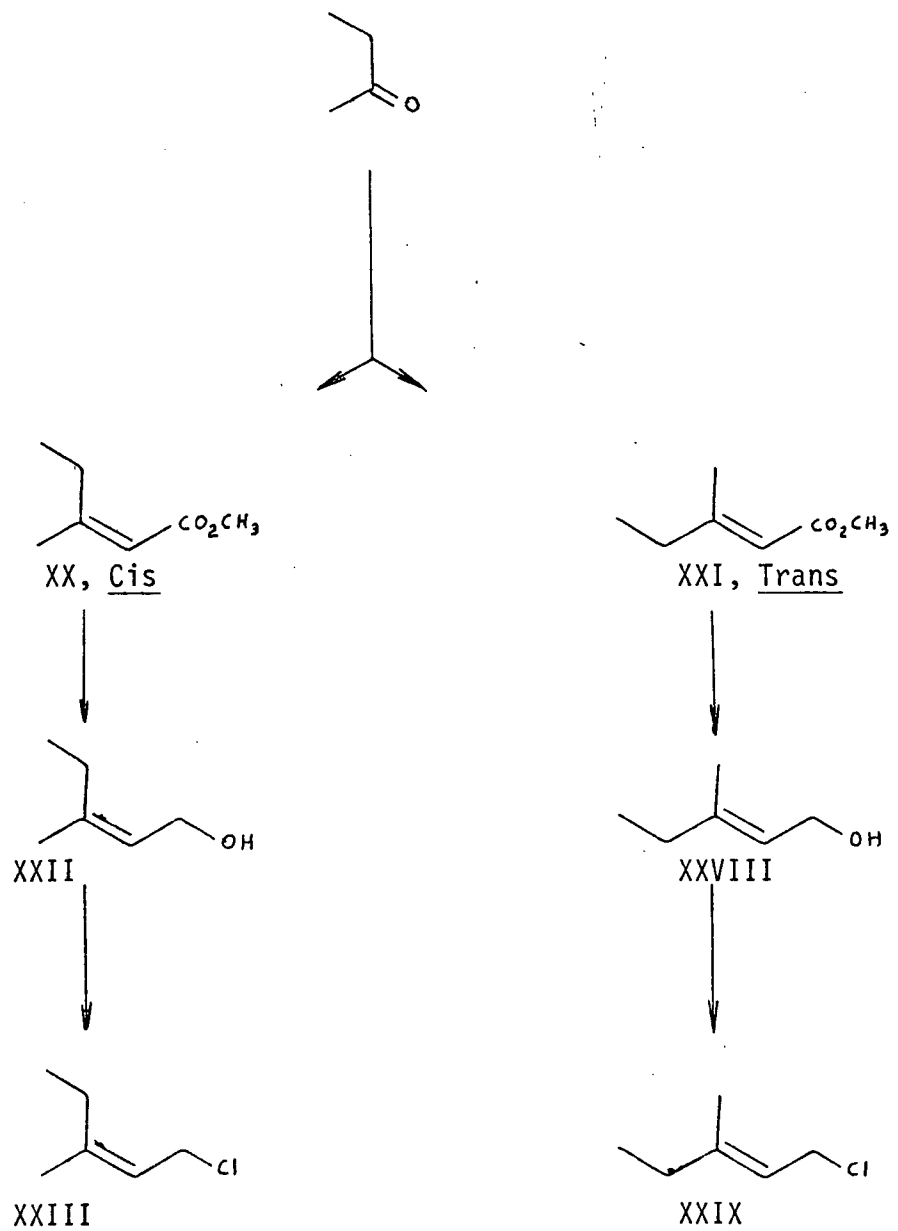


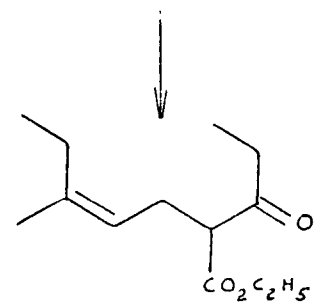




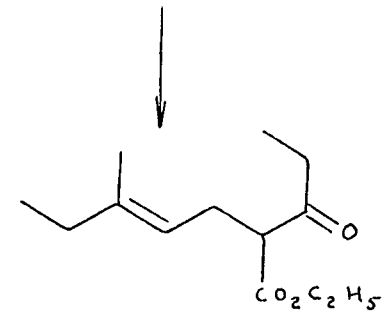
I, Juvenile Hormone

The synthetic scheme for the preparation of these phosphonium salts was based on a sequence used by Trost et al in their synthesis of the cecropia juvenile hormone.[25] The overall synthetic plan is shown in Fig. 8.

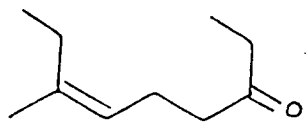




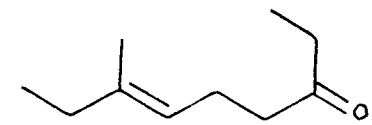
XXIV



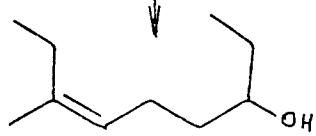
XXX



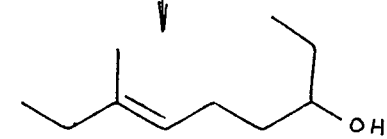
XXV



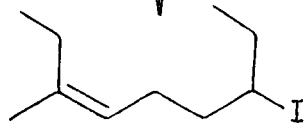
XXXI



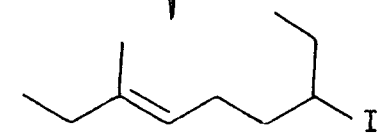
XXVI



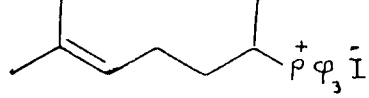
XXXII



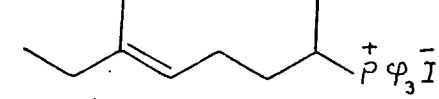
XXVII



XXXIII



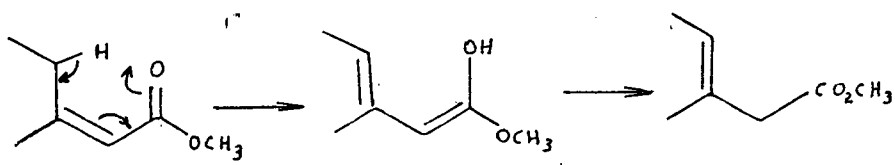
XVIII (X = I)



XIX (X = I)

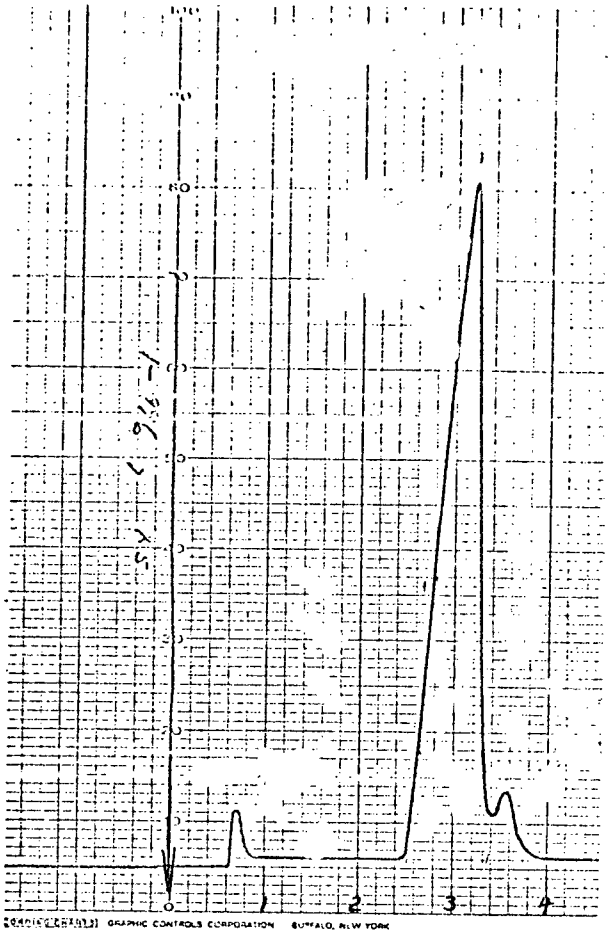
Fig. 8. Scheme for the Synthesis of the Desired Phosphonium Salts XVIII and XIX.

The first step in the sequence involved the reaction of trimethylphosphonacetate with methyl ethyl ketone. Cis- and trans-methyl 3-methyl-2-pentenoates (XX, XXI) were obtained in 18% and 37% yields respectively. These esters were separated from each other by spinning band distillation which generally resulted in the isolation of products which were 90-98% isomerically pure, as determined by gas chromatography (Fig. 9). The only complication during the separation of the two isomers was the thermal isomerization of the cis isomer to the β,γ-unsaturated product (XXXIV). This isomerization was more serious if larger quantities were separated so that longer time periods were necessary for the distillation. However, under normal separation conditions this isomerization was

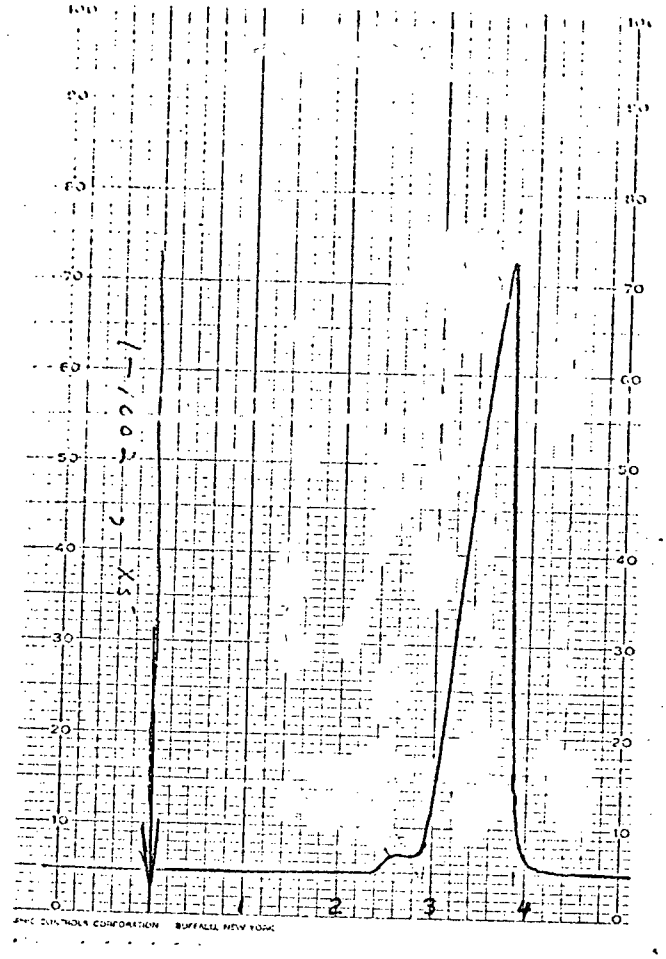


XX XXXIV

insignificant. With the separate isomers now available (Fig. 10a, 10b), the stereochemical integrity of the double bond in each isomer was assured, as the conditions for the following transformations would not likely result in any isomerization. Therefore, the separated isomers were subjected to a lithium aluminum hydride reduction, which resulted in the isolation of the desired allylic alcohols (XXII, XXVIII) in yields of 83% to 94%. The next step in the sequence was the conversion of the allylic alcohols to the corresponding allylic halides. Originally, Trost et al had used



cis (XX)



trans (XXI)

Fig. 9. Gas Chromatographic Traces of Cis and Trans Methyl 3-Methyl-2-Pentenoates.

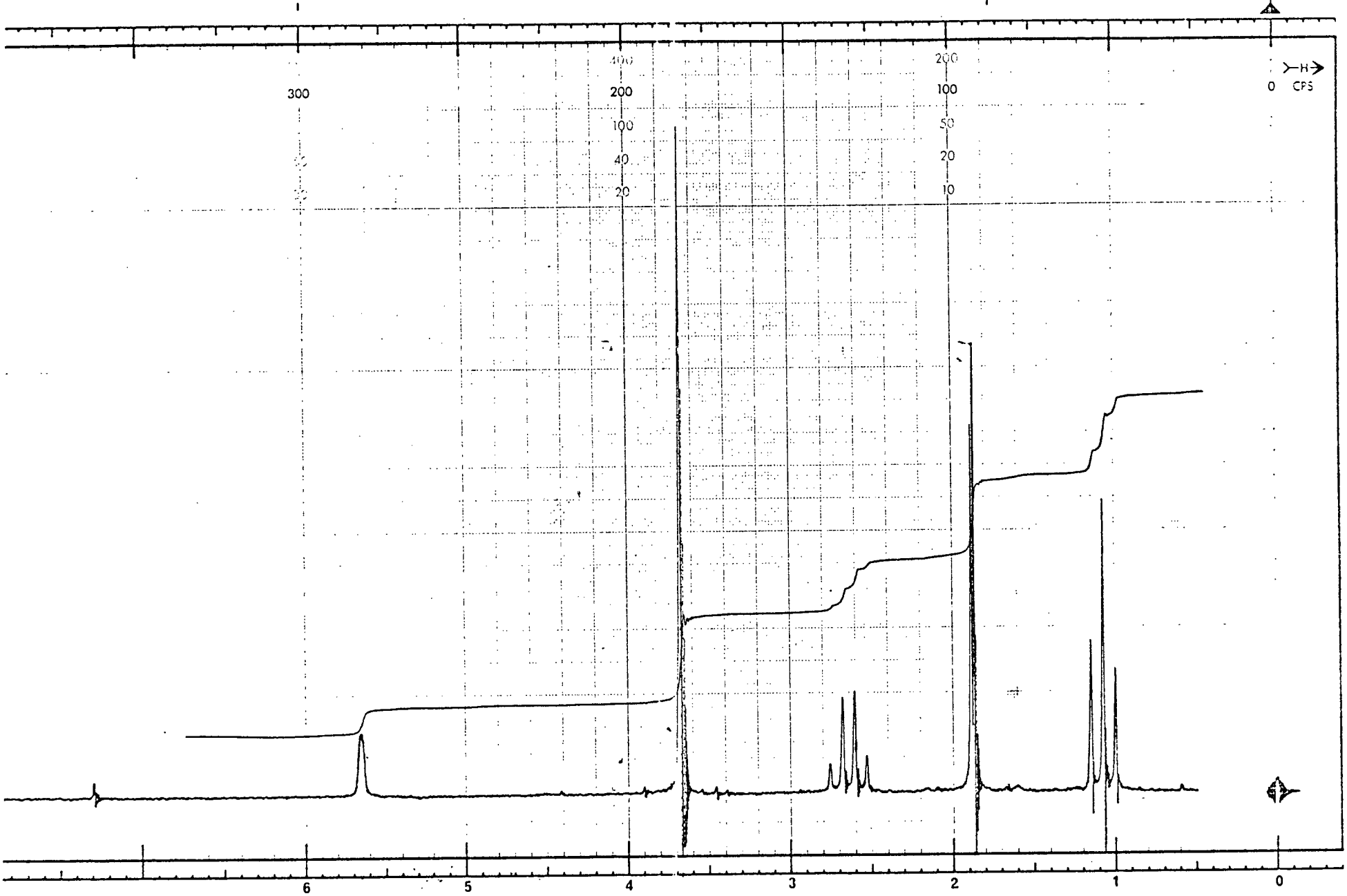


Fig. 10a. P.M.R. Spectrum of Cis Methyl 3-Methyl-2-Pentenoate (XX).

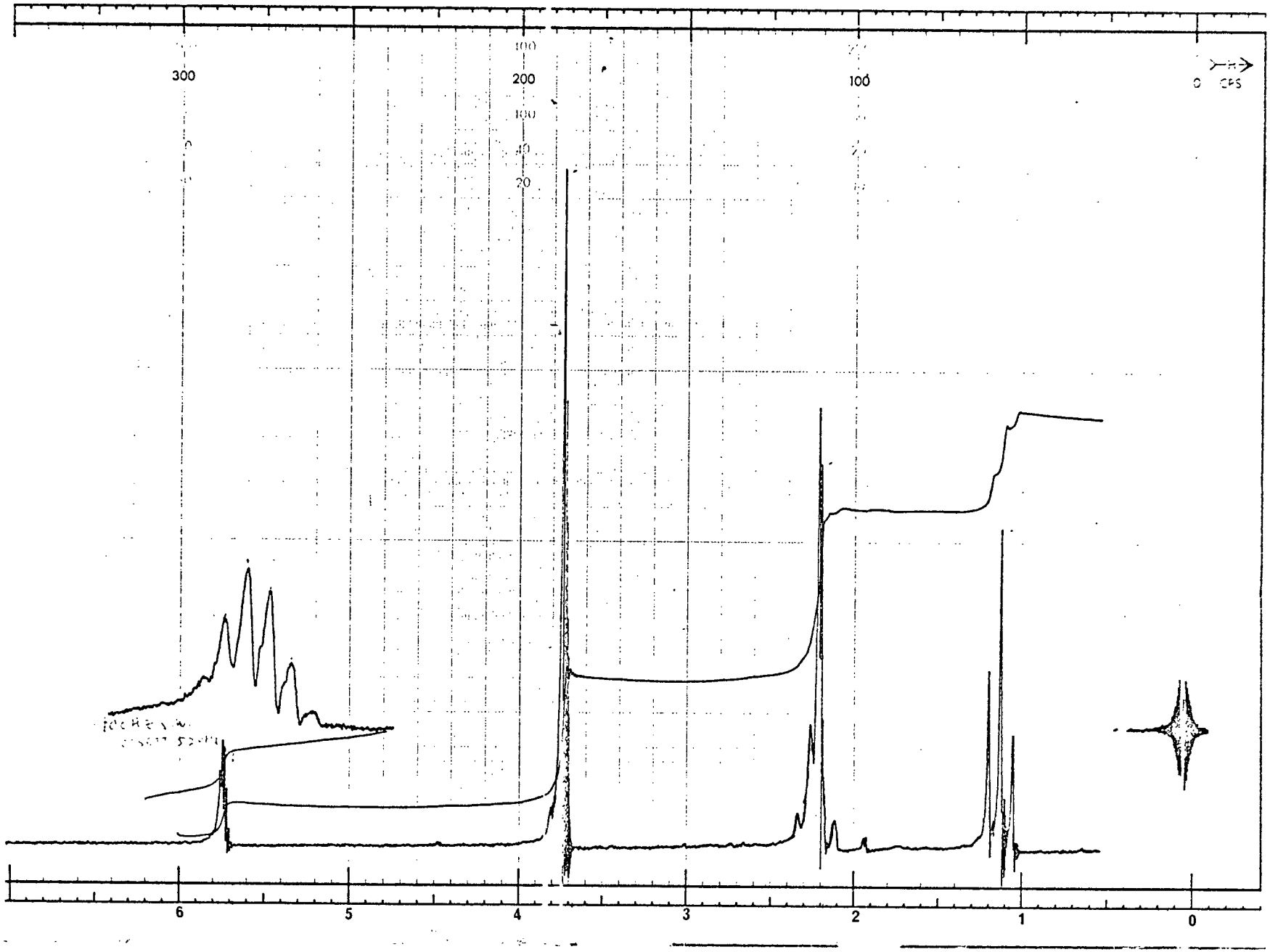


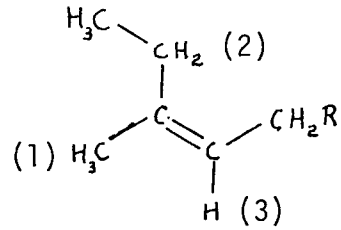
Fig. 10b. P.M.R. Spectrum of Trans Methyl-3-Methyl-2-Pentenoate (XXI).

phosphorus tribromide for this conversion, however, this procedure was abandoned in favor of a procedure used by Stork et al[26] to form allylic chlorides which were not contaminated with rearrangement products. Since the desired allylic chlorides were found to be unstable as well as difficult to handle because of their volatility, they were not isolated, but rather they were treated directly with the anion of ethyl 3-oxo-pentanoate.[27] The desired monoalkylated β-ketoesters (XXIV, XXX) were then isolated in 39% to 44% yield by means of fractional distillation. Subsequent saponification and decarboxylation of the β-ketoesters gave the resultant ketones (XXV, XXXI) in about 80% to 90% yield. The ketones were then smoothly reduced with sodium borohydride in ethanol to afford the cis and trans alcohols (XXVI, XXXII) in 90% to 95% yield. A comparison of the p.m.r. spectra of the products obtained to this point confirmed that the integrity of the double bond in the two isomers had been retained (Table 17). At this point, due to its greater availability, only the trans isomer was used. Thus, the trans olefinic alcohol (XXXII) was converted to the olefinic iodide (XXXIII) by the action of triphenylphosphite diiodide in ether.[28] However, on treatment of the iodide with triphenylphosphine none of the desired phosphonium salt (XIX) was obtained.

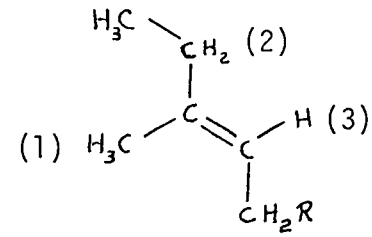
This conclusion was reached on the basis of the p.m.r. spectrum of the polar products obtained from the reaction. The p.m.r. spectrum of the desired phosphonium salt (XIX) would be expected to exhibit resonances at approximately δ 7.5 (15 H, ϕ_3P^+-), δ 5.0 (2 H,

Table 17

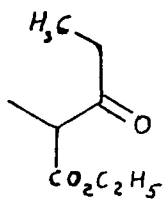
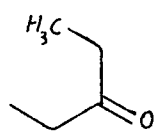
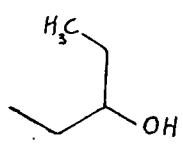
Comparison of Some P.M.R. Data for Compounds of the Type XL and XLI.



XL, cis



XLI, trans

	R	chemical shifts, δ		
		C = C-CH_3(1)	C = C-CH_2(2)	C = C-H(3)
cis	—OH	1.70	2.05	5.31
trans		1.68	2.04	5.37
cis		1.62	2.02	4.89
trans		1.61	1.95	4.97
cis		1.63	2.03	5.00
trans		1.58	1.94	4.97
cis		1.62	2.01	5.01
trans		1.60	1.98	5.09

$C{=}C\langle^{/}_{H}$ and $>C\langle^{P^+}_{H}$) and δ 2.5 to δ 0.8 (17 H). The p.m.r. spectrum of the obtained polar material had no resonance around the region δ 4.0 to δ 6.0 and although resonances occurred in the δ 7.5 and δ 1.0 to δ 2.5 regions, the ratio of the intensities of these resonances was about 2.5:1 respectively. As a further check to ascertain whether any of the desired phosphonium salt was present, the polar products from the reaction were used in a Wittig reaction with the sodium salt of α-thujaketonic acid. From this reaction however only a quantitative recovery of α-thujaketonic acid was obtained.

From these results it seemed that perhaps elimination and/or cyclization reactions (Fig. 11) might be occurring preferentially to the desired substitution reaction.

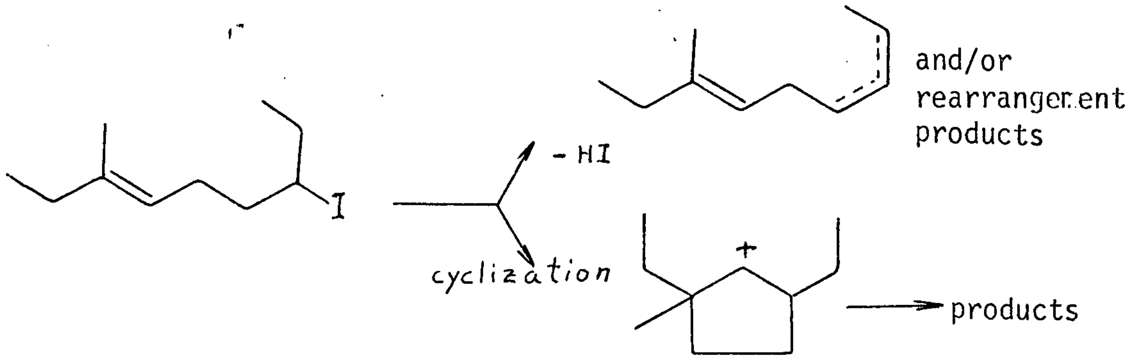
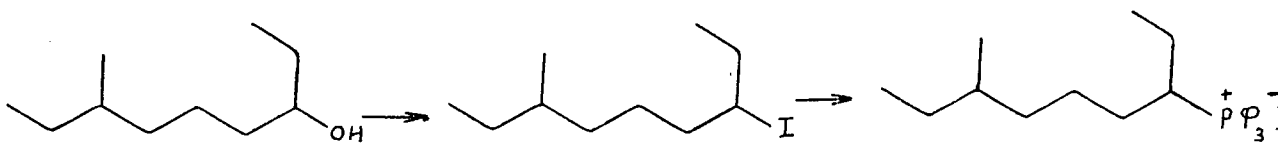


Fig. 11. Possible Side Reactions Competing with Phosphonium Salt Formation.

If the double bond of the olefinic iodide (XXXIII) was interfering with the formation of the desired phosphonium salt then perhaps the desired phosphonium salt (XIX) could be obtained by protecting the double bond prior to the reaction of the iodide with triphenylphosphine. In order to check whether this might be a viable

pathway to the desired product it was decided to hydrogenate the olefinic alcohol (XXXII), convert this saturated alcohol (XXXV) to the saturated iodide (XXXVI) and then treat this iodide with triphenylphosphine (Fig. 12). To this end, the unsaturated decanol (XXXII) was reduced with hydrogen in the presence of a palladium catalyst. The saturated alcohol (XXXV) was then converted to the saturated iodide (XXXVI) in the manner previously described. Treatment of this iodide with triphenylphosphine however did not give any detectable amount of the desired phosphonium salt (XXXVII).



XXXV XXXVI XXXVII

Fig. 12. Scheme for the Preparation of Phosphonium Salt XXXVII.

From these results it could not be ascertained whether the double bond in the unsaturated iodide (XXXIII) was responsible for the formation of unwanted side-products, however, it did appear as though elimination was probably much more favorable than substitution. Because of these results it was decided that the original synthetic scheme would not be practical and was abandoned.

3.5 ALTERNATE ROUTES FOR THE SYNTHESIS OF THE DESIRED PHOSPHONIUM SALTS XVIII AND XIX.

The formation of phosphonium salts from primary halides proceeds much more readily than from secondary halides.[29] Therefore

it would seem reasonable to form the desired phosphonium salts via reaction with the suitable primary halide followed by alkylation with another primary halide. This type of strategy is revealed in the two routes shown in Fig. 13.

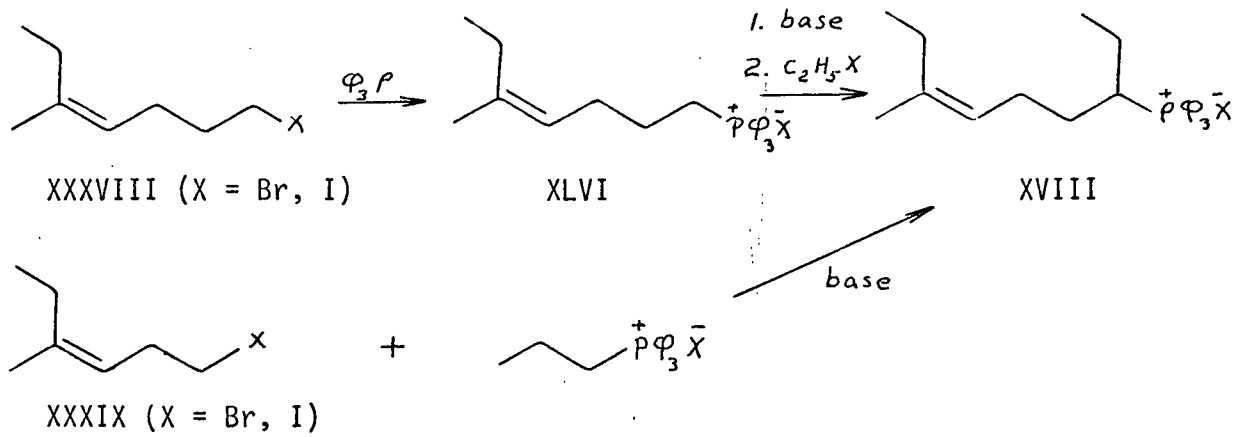


Fig. 13. Alternate Routes for Synthesis of the Desired Phosphonium Salts XVIII and XIX.

In the first method, the olefinic halide (XXXVIII) could be prepared by modifying the previous scheme as shown in Fig. 14.

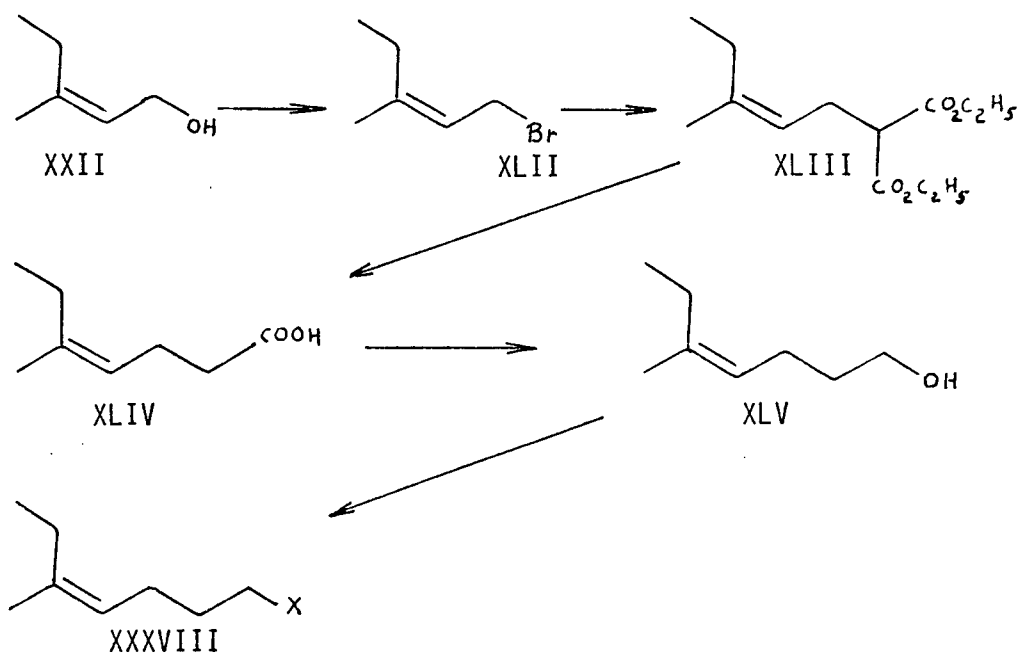


Fig. 14. Proposed Scheme for Synthesis of Olefinic Halide XXXVIII.

In the second route the olefinic halide (XXXIX) used for alkylating the n-propylphosphonium salt is a known compound which has been prepared by Corey et al[30], as outlined in Fig. 15.

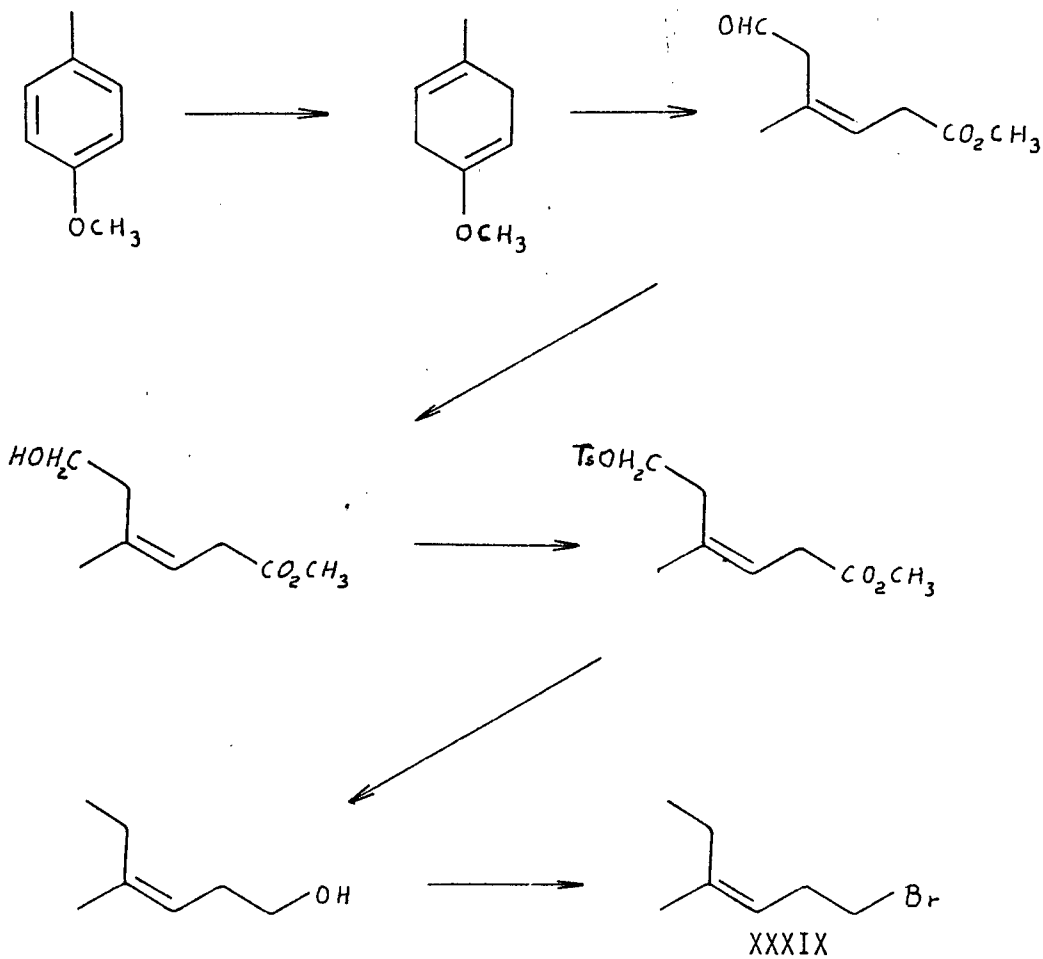
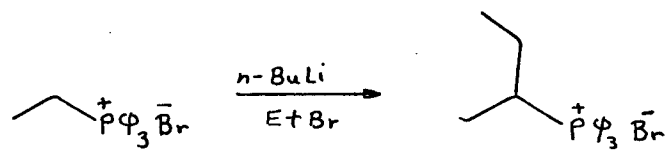


Fig. 15. Outline of Corey's Synthesis of 1-Bromo-4-Methyl-3-Hexene (XXXIX).

3.6 PRELIMINARY INVESTIGATION OF AN ALTERNATE ROUTE FOR THE SYNTHESIS OF THE DESIRED PHOSPHONIUM SALTS XVIII AND XIX

Due to the availability of the allylic alcohol XXII it was decided to test the feasibility of the first proposed alternate route for the synthesis of the desired phosphonium salts XVIII and XIX.

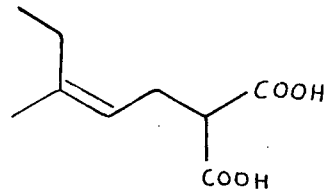
Since an important step of the alternate route was the alkylation of a primary phosphonium salt (XLVI) with a primary alkyl halide, a model reaction involving ethyltriphenylphosphonium bromide was studied in this laboratory by Dr. S. Morehead. It was found that sec-butyltriphenylphosphonium bromide (XLVIII) could be obtained by treating the ethyltriphenylphosphonium bromide with n-butyllithium and ethyl bromide in diethyl ether (XLVII → XLVIII).



XLVII XLVIII

This result was encouraging and also noteworthy in that Trippett and co-workers[31] had reported that the action of triphenylphosphine on sec-butyl bromide yielded only elimination products.

Therefore, to achieve the desired goal, the cis allylic alcohol XXII (Fig. 14) was converted to the known allylic bromide[32] XLII by the action of phosphorous tribromide in ether. This allylic bromide was then used in the alkylation of diethylmalonate to yield this cis diester XLIII. Saponification of the diester with aqueous potassium hydroxide gave the cis diacid XLIIIa as a white crystalline



XLIIIa

solid. The yield of this diacid based upon the allylic alcohol XX was 52%. Upon heating the diacid XLIIIa or upon refluxing it dilute sulphuric acid a mixture of products was obtained which analyzed for an emperical formula of $C_8H_{14}O_2$. The mass spectrum obtained on this mixture further substantiated the analysis by having 142(10%) as the highest molecular ion recorded. From the proton magnetic resonance spectrum it could be ascertained that the desired cis olefinic acid XLIV was present as well as a side product which contained no olefinic or acid proton. Since the infrared spectrum contained two carbonyl stretches (1725 cm^{-1}, 1700 cm^{-1}) it appeared as if the side product was a lactone. Reduction of the decarboxylation reaction mixture with lithium aluminum hydride yielded a mixture of alcohols which were separated by vacuum distillation. The lower boiling alcohol (100°C at 12 torr) was found to be the desired olefinic alcohol XLV, while the higher boiling alcohol (140°C at 12 torr) was determined to be a saturated diol by means of its proton magnetic resonance spectrum, infrared spectrum, and mass spectrum. Also, since the proton magnetic resonance spectrum indicated the presence of a primary alcohol (3.63, 2H, mult.), but no secondary alcohol it there seemed likely that the decarboxylation of the cis diacid XLIIIa yielded the δ-lactone XLVII (Fig. 16) as a major side-product which would then account for the observed products obtained from the lithium aluminum hydride reduction.

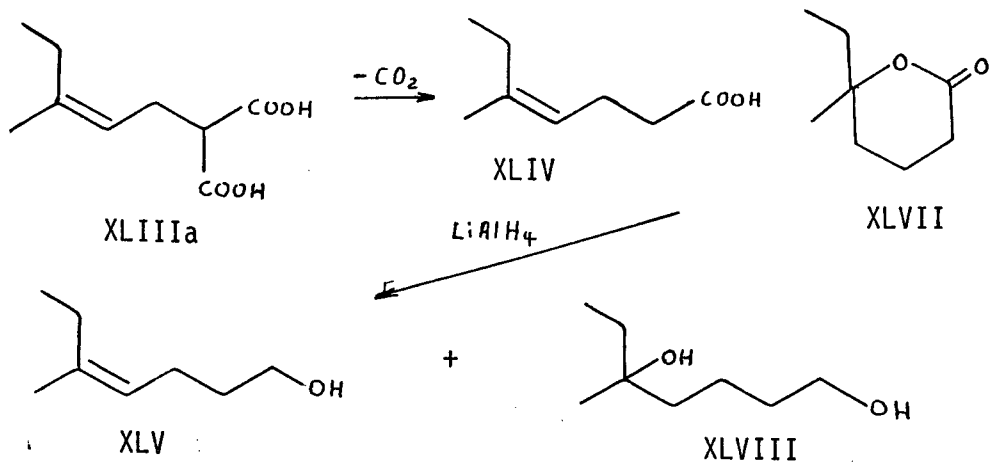


Fig. 16. Products Obtained From the Lithium Aluminum Hydride Reduction of the Decarboxylation Reaction Mixture Obtained From the Cis Diacid XLIIIa.

Although the above mentioned side reaction resulted in a substantial lowering of the yield of the synthetic sequence, the desired cis alcohol XLV was obtainable in pure form and was carried further. Treatment of this alcohol with triphenylphosphite diiodide resulted in the formation of the olefinic iodide XXXVIII (X = I) which was then converted to the desired primary phosphonium salt XLVI by the action of triphenylphosphine in refluxing ethyl acetate. The structure of this phosphonium salt was definitely established from the combustion analysis ($C_{26}H_{30}PI$), proton magnetic resonance spectrum (δ 3.62, 2H, multiplet, $\overset{H}{>}C\overset{H}{<}_{P\phi_3}^{+}$), and the mass spectrum (373, 11%, M^+-I).

With the desired functionality having been introduced, the remaining task of elaborating the carbon skeleton to produce the desired phosphonium salt XVIII was then achieved by treatment of the primary phosphonium salt with n-butyllithium and ethyl iodide in ethyl ether.

3.7 OVERALL RESULTS

In summary, the work done towards this thesis has resulted in the determination of the reaction conditions for the successful Wittig reaction of α-thujaketonic acid (VII), thus providing a means for the possible elaboration of α-thujaketonic acid to novel analogues of known insect controlling agents. Also, it was determined that α-thujaketonic acid could be ring-opened stereoselectively to afford either (E)- or (Z)-β-thujaketonic acid which in turn could be used as starting materials for the preparation of a complementary series of analogues. Finally, two routes for the synthesis of the desired phosphonium salts XVIII and XIX, which when coupled with thujaketonic acid via the Wittig reaction would lead to juvenile hormone analogs, were studied.

In the first route the desired carbon skeleton was obtained, however, attempted functionalizations to produce the desired phosphonium salt failed. In the second route a primary phosphonium salt (XLVI) was formed and the carbon skeleton was elaborated to provide one of the target phosphonium salts (XVIII).

4. EXPERIMENTAL

The separation of the cis and trans methyl 3-methyl-2-pentenoates (XX, XXI) was achieved on a Nester-Faust auto-annular spinning band still. The still was equipped with a 90 cm teflon shaft, and the separation was achieved at atmospheric pressure by using a boil up rate of about 12 drops/min. and a takeoff ratio of about 30:1. The progress of the distillation was monitored by means of gas chromatography, using a Carle model 8000 gas chromatograph. The column used was a 1/8" x 6' stainless steel column which was packed with 3.1 g of 5% by weight Ethofat 60/25 on 90-100 mesh Anakrom ABS. Helium was used as the carrier gas. With a column temperature of about 111°C and a flow rate of about 25 ml/min. the cis isomer had a retention time of about 3.20 min., while the trans isomer had a retention time of about 3.68 min.

The α-thujaketonic acid (VI) used was prepared from cedar leaf oil by using the method of Thompson[20]. The cedar leaf oil used was supplied by MacMillan Bloedel Research Ltd., and generally consisted of approximately 88% thujone and 12% terpenoid impurity.

Products obtained were generally characterized by the boiling point (B.P.) infrared spectrum (I.R.), proton magnetic resonance spectrum (P.M.R.), mass spectrum (M.S.), and analysis. Except for the cis and trans methyl 3-methyl-2-pentanoates and the cis 1-bromo-3-methyl-2-pentene, no physical or spectral data for any of the compounds prepared had been published.

Boiling points were generally determined during distillation or by using the micro-boiling point method (Siwoloboff's method) as described in Vogel[33].

Infrared spectra were recorded on the Perkin-Elmer model 710 spectrophotometer. Polystyrene was used as the calibrant and the samples were run as neat liquids between salts. The position of the desorption was recorded in wavenumbers (cm^{-1}).

Proton magnetic resonance spectra were obtained from either the Varian model XL-100 or HA-100 spectrometer. Tetramethylsilane was used as the internal standard, and carbon tetrachloride was used as the solvent. Peaks obtained from the spectra were recorded in the delta (δ) scale.

Mass spectra obtained were all low resolution and were run on the Varian/MAT model CH4B spectrometer. The electron energy generally used was 70 eV.

Combustion analyses obtained were performed by Mr. P. Borda.

The adsorbent generally used for column chromatographic purposes was Shawinigan Alumina (adsorption: 0.550-0.750 mg./gm. of ortho-nitroaniline).

Cis and Trans Methyl 3-Methyl-2-Pentenoates (XX and XXI)

To a slurry of sodium hydride (29.4 g of 50% suspension, 0.60 moles) in dry 1,2-dimethoxyethane (1.2ℓ) at 0°C - 5°C (ice-water bath) was added trimethylphosphonoacetate (109.3 g, 0.60 moles). At

the end of the addition (ca. 30 min) the resultant thick slurry was stirred (Hershberg stirrer) at room temperature for a further hour. At this point a solution of 2-butanone (43.6 g, 0.60 moles) in 1,2-dimethoxyethane (100 ml) was added at a dropwise rate. At the end of this addition (ca. 20 min.) the reaction mixture was allowed to stir at room temperature for 20 hours at which point water (300 ml) was added. The aqueous portion was separated and extracted with ether (3 x 100 ml). The organic portions were combined and washed with brine (2 x 100 ml), dried over sodium sulphate, and the solvents were removed by simple atmospheric distillation. The crude esters were then purified by vacuum distillation (15 torr) and separated by spinning bond distillation to give the cis ester (XX) (11.6g) in about 95% isomeric purity, the trans ester (XXI) (21.0 g) in about 97% isomeric purity, and a 25:75 mixture of the cis and trans esters (10.7 g). The yield for this reaction was 43.3 g or 56%.

The cis ester had a boiling point of 148°C at atmospheric pressure. IR: 1718 ($\overset{O}{\overset{\|}{C}}OCH_3$), 1642 (C=C). PMR: 1.07 (3H, triplet, J - 7.5 Hz, CH_3CH_2), 1.87 (3H, doublet, J = 1.4 Hz, CH_3-C=C), 2.64 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 3.67 (3H, singlet, $\overset{O}{\overset{\|}{C}}$-$OCH_3$), 5.64 (1H, multiplet, C=C-H). MS: M^+ 128 (50%), 97 (71%), 28 (100%). Analysis: calculated for $C_7H_{12}O_2$: C, 65.58; H, 9.44; found: C, 65.38; H, 9.37.

The trans ester had a boiling point of 155°C at atmospheric pressure. IR: 1719 ($\overset{O}{\overset{\|}{C}}$-$OCH_3$), 1646 (C=C). PMR: 1.07 (3H, triplet, J = 7.5 Hz, CH_3CH_2), 2.16 (3H, doublet, J = 1.3 Hz, CH_3-C=C), 2.18 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 3.68 (3H, singlet, $\overset{O}{\overset{\|}{C}}$-$OCH_3$), 5.68 (1H,

quartet, J = 1.3 Hz, C=C-H). MS: M^+ 128 (18%), 97 (28%), 43 (100%). Analysis: calculated for $C_7H_{12}O_2$: C, 65.58, H, 9.44; found: C, 65.61; H, 9.41.

Trans 3-Methyl-2-Pentene-1-ol (XXVIII)

To a slurry of lithium aluminum hydride (16.7 g, 0.43 moles) in anhydrous ether (300 ml) at 0-5°C (ice-water bath) was added a solution of the trans ester (XXI) (36.6 g, 0.29 moles) in anhydrous ether (50 ml). At the end of the addition (ca. 30 min) the reaction mixture was allowed to stir at room temperature for a further 5 hours, at which point the excess lithium aluminum hydride was decomposed by the cautious addition of water (15 ml) followed by aqueous 10% NaOH (20 ml) and a further portion of water (50 ml). The reaction mixture was then filtered (Buchner funnel) and the white granular salts were washed thoroughly with ether (200 ml). The filtrate was then dried over potash, the solvent was removed by flash evaporation and the crude product was distilled under vacuum (12-20 torr) to give the purified material (XXVII) as a colorless liquid. The boiling point of the alcohol was 160°C at atmospheric pressure. IR: 3356 (OH), 1666 (C=C). PMR: 1.02 (3H, triplet, J = 7.5 Hz, CH_3CH_2), 1.68 (3H, broad singlet, CH_3-C=C), 2.04 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 4.16 (2H, doublet, J = 7.0 Hz, CH_2OH), 5.37 (1H, triplet of quartets, J = 7.0 & 1.4 Hz, C=C-H). MS: M^+ 100 (19%), 71 (100%). Analysis: calculated for $C_6H_{12}O$: C, 71.95; H, 12.08; found: C, 72.20; H, 12.20.

Cis 3-Methyl-2-Pentene-1-ol (XXII)

Treatment of the cis ester (XX) (36.0 g, 0.28 moles) in anhydrous ether (300 ml) with lithium aluminum hydride (16.7 g, 0.43 moles) as above gave the desired cis allylic alcohol (XXII) (24.3 g, 0.25 moles) as a colorless liquid. The boiling point at atmospheric pressure was 153°C. IR: 3370 (OH), 1667 (C=C). PMR: 1.02 (3H, triplet, J - 7.5 Hz, CH_3CH_2), 1.70 (3H, broad singlet, CH_3-C=C), 2.05 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 4.01 (2H, doublet, J = 7.0 Hz, CH_2OH), 5.31 (1H, triplet, J = 7.0 Hz, C=C-H). MS: M^+ 100 (8%), 71 (39%), 31 (100%). Analysis: calculated for $C_6H_{12}O$: C, 71.95; H, 12.08; found: C, 72.15; H, 11.94.

Trans 3-Oxo-4-Carboethoxy-7-Methyl-6-Nonene (XXX)

To a solution of the trans allylic alcohol (XXVIII) (20.0 g, 0.20 moles) in anhydrous ether (30 ml) and dry hexamethylphosphoramide (50 ml) under nitrogen was added an ethereal solution of methyllithium (115 ml of a 1.8 M solution, 0.21 mole). This resultant solution was then added to a cooled mixture (ice-water bath) of methanesulphonyl chloride (28.6 g, 0.25 moles) and anhydrous lithium chloride (17.0 g, 0.40 moles) in anhydrous ether (200 ml) under nitrogen. At the end of the addition (ca. 35 min) the reaction was stirred at room temperature for a further 6 hours, at which point the anion of ethyl 3-oxo-pentanoate (prepared from 27.3 g (0.19 moles) of ethyl-3-oxo-pentanoate[27], 4.37 g

(0.19 moles) of sodium) in absolute ethanol (150 ml) was added. At the end of the addition (ca. 5 min.) the reaction mixture was allowed to stir at room temperature for 24 hours. At this point the reaction mixture was concentrated in vacuo and taken up in water (300 ml) and extracted with ligroin (3 x 125 mls). The organic portions were combined, washed with water (3 x 40 ml), and dried over sodium sulphate. After removal of the solvents by flash evaporation the remaining mixture was subjected to a vacuum distillation and filtration through alumina (ca. 300 g) using petroleum ether (65-100) as the eluent. The desired trans β-ketoester (XXX) (20.0 g, 89 mmoles) was obtained as a colorless liquid. The boiling point at 30 torr was 159°C. IR: 1736 ($\overset{O}{\overset{\|}{C}}$-OEt), 1716 (C=O), 1666 (C=C). PMR: 0.95 (3H, triplet, J = 7.5 Hz, CH_3CH_2), 161 (3H, broad singlet, CH_3-C=C), 1.95 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 3.28 (1H, triplet, J = 7.5 Hz, $\overset{H}{\underset{CO_2Et}{C-C=O}}$), 4.97 (1H, multiplet, C=C-H). MS: M^+ 226 (7%), 169 (36%), 123 (100%). Analysis: calculated for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; found: C, 68.92; H, 9.82.

Cis 3-Oxo-4-Carboethoxy-7-Methyl-6-Nonene (XXIV)

Treatment of the cis allylic alcohol (XXII) (24 g, 0.24 moles) as above gave the desired cis β-ketoester (XXIV) (21.0 g, 93 mmoles) as a colorless liquid. The boiling point at atmospheric pressure was 258°C. IR: 1740 ($\overset{O}{\overset{\|}{C}}$-OEt), 1708 (C=O). PMR: 0.94 (3H, triplet, J = 7.5 Hz, CH_3CH_2), 1.62 (3H, broad singlet, CH_3-C=C), 2.02 (2H, quartet,

J = 7.5 Hz, CH_3CH_2), 3.23 (1H, triplet, J = 7.1 Hz), 4.89 (1H, triplet, J = 7.1 Hz, C=C-H). MS: M^+ 226 (15%), 169 (43%), 123 (100%). Analysis: calculated for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; found: C, 69.09; H, 9.80.

Trans 3-Oxo-7-Methyl-6-Nonene (XXXI)

A mixture of the trans β-ketoester (XXX) (20.0 g, 89 mmoles) and 5% aqueous NaOH (150 ml, 0.19 moles) were stirred at room temperature for a period of 26 hours. At the end of this time the reaction mixture was washed with ligroin (1 x 30 ml) and made just acidic (RH paper) with 3M H_2SO_4. Steam distillation of this mixture was followed by extraction of the distillate with ligroin (3 x 100 ml). The organic portions were combined, dried over sodium sulphate, and the solvents removed by flash evaporation. Subsequent vacuum distillation (12-20 torr) gave the desired trans ketone (XXXI) (12.0 g, 78 mmoles) as a colorless liquid. The boiling point at atmospheric pressure was 206°C. IR: 1712 (c=o), 1668 (C=C). PMR: 0.94 (3H, triplet, J = 7.3 Hz, CH_3CH_2), 1.58 (3H, broad singlet, CH_3-C=C), 1.94 (2H, quartet, J = 7.3 Hz, CH_3CH_2), 4.97 (1H, multiplet, C=C-H). MS: M^+ 154 (14%), 82 (69%), 55 (100%). Analysis: calculated for $C_{10}H_{18}O$: C, 77.87; H, 11.97; found: C, 77.77; H, 11.60.

Cis 3-Oxo-7-Methyl-6-Nonene (XXV)

Treatment of the cis β-ketoester (XXIV) (20.0 g, 89 mmoles) as above gave the desired cis ketone (XXV) (11.8 g, 77 mmmoles) as a colorless liquid. The boiling point at atmospheric pressure was 202°C. IR: 1709 (c=o), 1670 (C=C). PMR: 0.96 (3H, triplet, J = 7.5 Hz, CH_3CH_2), 1.63 (3H, broad singlet, CH_3-C=C), 2.03 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 5.00 (1H, multiplet, C=C-H). MS: M^+ 154 (27%), 82 (93%), 57 (100%). Analysis: calculated for $C_{10}H_{18}O$: C, 77.87; H, 11.76; found: C, 78.12, H, 11.52.

Trans 7-Methyl-6-Nonene-3-ol (XXXII)

To a slurry of sodium borohydride (4.0 g, 105 mmoles) in 95% ethanol (350 ml) was added the trans ketone (XXXI) (16.2 g, 105 mmoles) in 95% ethanol (30 ml). At the end of the addition (ca. 20 min.) the reaction was allowed to stir at room temperature for a further 3 hours, at which point the ethanol was removed by flash evaporation and the resultant residue was taken up in water (100 ml). This resultant mixture was then extracted with ether (3 x 75 ml). The combined organic extracts were then washed with brine (2 x 20 ml) and dried over potash. The ether was then removed by flash evaporation and the crude product was distilled in vacuo (23 torr) to give the desired trans alcohol (XXXII) (15.7 g, 100 mmoles) as a colorless liquid. The boiling point at 23 torr

was 114°C. IR: 3360 (OH), 1666 (C=C). PMR: 0.97 (3H, triplet, J = 7.0 Hz, CH_3CH_2), 1.60 (3H, broad singlet, CH_3-C=C), 1.98 (2H, quartet, J = 7.0 Hz, CH_3CH_2), 3.43 (1H, multiplet, $>C<^{H}_{OH}$), 5.09 (1H, triplet of quartets, J = 7.0 & 1.3 Hz). MS: M^+ 156 (13%), 138 (19%), 109 (100%). Analysis: calculated for $C_{10}H_{20}O$: C, 76.86; H, 12.90; found: C, 76.60; H, 12.98.

Cis 7-Methyl-6-Nonene-3-ol (XXVI)

Treatment of the cis ketone (XXV) (4.0 g, 26 mmoles) as above gave the desired cis alcohol (XXVI) (3.7 g, 24 mmoles) as a colorless liquid. The boiling point at atmospheric pressure was 210°C. IR: 3400 (OH). PMR: 0.94 (3H, triplet, J = 7.2 Hz, CH_3CH_2), 1.62 (3H, broad singlet, CH_3-C=C), 2.01 (2H, quartet, J = 7.2 Hz, CH_3CH_2), 3.44 (1H, multiplet, $>C<^{OH}_{H}$), 5.01 (1H, triplet, J = 7.0 Hz, C=C-H). MS: M^+ 156 (8%), 138 (15%), 109 (100%). Analysis: calculated for $C_{10}H_{20}O$: C, 76.86; H, 12.90; found: C, 76.56; H, 12.85.

Trans 3-Iodo-7-Methyl-6-Nonene (XXXIII)

To a cooled (ice-water bath) solution of iodine (12.7 g, 50 mmoles) in anhydrous ether (250 ml) under nitrogen was added triphenylphosphite (15.5 g, 50 mmoles) in anhydrous ether (50 mls). At the end of the addition (ca. 30 min.) the reaction mixture was allowed to stir at room temperature for a further 17 hours. At this point the trans

alcohol (XXXII) (7.50 g, 48 mmoles) in ether (25 ml) was added, (ca. 10 min.) and the mixture was allowed to stir for a further hour at room temperature at which point the reaction mixture was concentrated in vacuo to about 1/4 of its volume, and eluted through neutral alumina (200 g) using petroleum ether (65-110) as the eluent. After removal of the solvent by flash evaporation the desired trans iodide (XXXIII) (10.2 g, 38 mmoles) was obtained as a colorless liquid. The boiling point at atmospheric pressure was 230°C (d). IR: 1668 (C=C). PMR: 0.95 (3H, triplet, J = 7 Hz, CH_3CH_2), 1.60 (3H, broad singlet, CH_3-C=C), 3.96 (1H, multiplet, $\rangle C\langle^{H}_{I}$), 5.02 (1H, multiplet, C=C-H). MS: M^+ 266 (26%), 138 (32%), 55 (100%). Analysis: calculated for $C_{10}H_{19}I$: C, 45.13; H, 7.20; found: C, 45.50; H, 7.20.

7-Methyl-3-Nonanol (XXXV)

A solution of the trans alcohol (XXXIII) (1.56 g, 10 mmoles) in absolute ethanol (130 ml) was hydrogenated (360 ml H_2) at atmospheric pressure in the presence of palladium (10% Pd/C). After filtration through celite and removal of the solvent by flash evaporation the residue was eluted through neutral alumina (10 g) using petroleum ether (65-110) as the solvent. Removal of the solvent by flash evaporation yielded the desired saturated alcohol (XXXV) (1.0 g, 63 mmoles as a colorless liquid. The boiling point at atmospheric pressure was 206°C. IR: 3400 (OH). PMR: 3.38 (1H, multiplet, $\rangle C\langle^{OH}_{H}$). MS: M^+ 158 (0%), 140 (7%), 129 (31%), 59 (100%). Analysis: calculated for $C_{10}H_{22}O$: C, 75.88; H, 14.01; found: C, 75.60; H, 13.85.

3-Iodo-7-Methyl-Nonane (XXXVI)

The saturated alcohol (XXXV) (600 mg., 3.8 mmoles) was treated with triphenylphosphite diiodide as before (compound XXXIII). From this reaction was obtained the saturated iodide (XXXVI) (804 mg., 3.0 mmoles) as a colorless liquid. The boiling point at atmospheric pressure was 224°C. (dec.). P.M.R.: 1.01 (3H, triplet, J = 7.0 Hz, CH_3CH_2), 3.97 (1H, multiplet, $C\begin{smallmatrix}I\\H\end{smallmatrix}$). M.S.: M^+ 268 (2%), 141 (100%). Analysis: calculated for $C_{10}H_{21}I$: C, 44.79; H, 7.89; found: C, 47.88; H, 8.25.

Methylene Derivative of α-Thujaketonic Acid (XIII)

A mixture of sodium hydride (1.6 g. of a 50% suspension in mineral oil, 53 mmoles) and dry dimethylsulfoxide (60 ml) were heated (under nitrogen atmosphere) at 70-80°C. for 45 min. At the end of this time the reaction mixture was allowed to cool to room temperature at which point a solution of methyltriphenylphosphonium bromide (10.5 g., 29 mmoles) in dry dimethylsulfoxide (50 ml) was added. This mixture was stirred for a further 10 min. at room temperature and then cooled to near 0°C. (ice-water bath) at which point the sodium salt of α-thujaketonic acid (VII) (5.9 g., 29 mmoles) was added. The resultant slurry was allowed to stir at room temperature for 20 hours at which point it was taken up in water (200 ml) and washed with methylene chloride (2 x 30 ml). The aqueous portion was then made just acidic with 3M H_2SO_4 and was extracted with ligroin (3 x 100 ml). The organic portions were combined

and washed with water (3 x 30 ml), dried over sodium sulphate, and the solvent was then removed by flash evaporation to give the methylene derivative of α-thujaketonic acid as a pale yellow oil. The boiling point at atmospheric pressure was 250°C. IR: 1613 (C=C). PMR: 1.73 (3H, singlet, CH_3-C=C), 4.54 (1H, broad singlet, C=C-H), 4.81 (1H, broad singlet, C=C-H). MS: M^+ 182 (48%), 139 (82%), 69 (100%). Analysis: calculated for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; found: C, 72.20; H, 9.91.

Isopropylidene Derivative of α-Thujaketonic Acid (XIV)

Treatment of the sodium salt of α-thujaketonic acid (1.9 g., 9.2 mmoles) with the phosphorane formed from isopropyltriphenylphosphonium iodide (3.1 g., 9.3 mmoles) as described above gave the desired isopropylidene derivative (1.7 g., 8.1 mmoles) as a light yellow liquid. IR: 1703 (C=O). PMR: 0.96 (6H, doublet, J = 7.0 Hz), 1.57 (3H, broad singlet, C=C-CH_3), 1.64 (3H, broad singlet, C=C-CH_3), 1.71 (3H, broad singlet, C=C-CH_3). MS: M^+ 210 (68%), 167 (85%), 121 (100%). Analysis: calculated for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54; found: C, 74.04; H, 10.29.

Methyl Ester of the Methylene Derivative of α-Thujaketonic Acid (XVII)

A mixture of the sodium salt of the methylene derivative of α-thujaketonic acid (XIII) (4.5 g., 22 mmoles) and methyl iodide (3.8 g.,

27 mmoles) in hexamethylphosphoramide (40 ml) was stirred for 27 hours at room temperature. At the end of this time the reaction mixture was poured into water (120 ml) and extracted with ligroin (3 x 60 ml). The organic portions were combined and washed with a saturated sodium bicarbonate solution (1 x 25 ml) and water (3 x 25 ml). After drying over sodium sulfate and removal of the solvent by flash evaporation, the desired methyl ester was obtained as a colorless liquid (4.0 g., 20 mmoles). The boiling point at atmospheric pressure was 212°C. IR: 1741 (C=O), 1645 (C=C). PMR: 1.84 (3H, singlet, $C=C-CH_3$), 3.62 (3H, singlet, OCH_3). MS: M^+ 196 (11%), 107 (67%), 69 (100%). Analysis: calculated for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20; found: C, 73.28; H, 10.20.

n-Butyl Ester of the Methylene Derivative of α-Thujaketonic Acid (X) (R = n-butyl, R'=R"=H).

A mixture of the sodium salt of the methylene derivative of α-thujaketonic acid (XIII) (4.4 g., 24 mmoles), n-butyl bromide (13.7 g., 100 mmoles), and a catalytic amount of sodium iodide in hexamethylphosphoromide was stirred at room temperature for 48 hours. At the end of this time the reaction mixture was treated as above to give the desired n-butyl ester (5.1 g., 21 mmoles) as a colorless liquid. The boiling point at atmospheric pressure was 268°C. IR: 1735 (C=O), 1644 (C=C). PMR: 1.74 (3H, singlet, $C=C-CH_3$), 3.94 (2H, triplet, J = 7.0 Hz, OCH_2-). MS: M^+ 238 (32%), 121 (83%), 41 (100%). Analysis: calculated

for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99; found: C, 75.41; H, 10.97.

1-Pentenyl Ester of the Methylene Derivative of α-Thujaketonic Acid (X) (R = $-CH_2CH_2CH_2CH=CH_2$, R'=R"=H)

A mixture of the sodium salt of the methylene derivative of α-thujaketonic acid (4.4 g., 24 mmoles), 5-O-tosyl-1-pentene (5.0 g., 21 mmoles), and a catalytic amount of sodium iodide in hexamethylphosphoramide were stirred at room temperature for a period of 48 hours. At the end of this time the reaction mixture was treated as above to give the desired 1-pentenyl ester (4.6 g., 19 mmoles) as a light yellow liquid. The boiling point at atmospheric pressure was 277°C. IR: 1735 (C=O), 1613 (C=C). PMR: 1.76 (3H, singlet, $C=C-CH_3$), 3.97 (2H, triplet, J = 6.5 Hz, OCH_2-). MS: M^+ 250 (27%), 121 (82%), 41 (100%). Analysis: calculated for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47; found: C, 76.48; H, 10.46.

Methyl Ester of the Isopropylidene Derivative of α-Thujaketonic Acid (X) (R = R'=R"=CH_3)

A mixture of the sodium salt of the isopropylidene derivative of α-thujaketonic acid (XIV) (4.5 g., 19 mmoles) and methyl iodide (3.27 g., 23 mmoles) in hexamethylphosphoromide (40 ml) were stirred at room temperature for a period of 24 hours. At the end of this time the reaction mixture was worked up as before giving the desired methyl ester (3.8 g., 17 mmoles) as a colorless liquid. The boiling point

at 0.1 torr was 62°C. IR: 1740 (C=O). PMR: 1.53 (3H, broad singlet, $C=C-CH_3$), 1.62 (3H, broad singlet, $C=C-CH_3$), 1.69 (3H, broad singlet, $C=C-CH_3$), 3.72 (3H, singlet, OCH_3). MS: M^+ 224 (37%), 121 (100%), 107 (93%). Analysis: calculated for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78; found: C, 74.68; H, 10.72.

n-Butyl Ester of the Isopropylidene Derivative of α-Thujaketonic Acid (R = n-butyl, $R'=R''=CH_3$)

A mixture of the sodium salt of the isopropylidene derivative of α-thujaketonic acid (XIV) 4.5 g., 19 mmoles) and n-butyl iodide (4.2 g., 23 mmoles) in hexamethylphosphoramide (40 ml) was stirred at room temperature for a period of 48 hours. At the end of this time the reaction mixture was worked up as before giving the desired n-butyl ester (4.3 g., 16 mmoles) as a pale yellow liquid. The boiling point at 0.1 torr was 70°C. IR: 1735 (C=O). PMR: 1.52 (3H, broad singlet, $C=C-CH_3$), 1.61 (3H, broad singlet, $C=C-CH_3$), 1.70 (3H, broad singlet, $C=C-CH_3$), 3.92 (2H, triplet, J = 6.5 Hz,-CH_2O-). MS: M^+ 266 (27%), 121 (62%), 43 (100%). Analysis: calculated for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35; found: C, 76.35: H, 11.29.

Cis 5-Methyl-4-Heptene-1,3-Dioicacid (XLIIIa)

To a freshly prepared solution of sodium ethoxide in ethanol (1.90 g. of sodium, 83 mmoles, in 300 ml of absolute ethanol)

was added diethyl malonate (13.9 g., 87 mmoles). To this stirred mixture was added a solution of the cis allylic bromide[32] (XLII) (13.5 g., 83 mmoles) in anhydrous ether (30 ml). This resultant mixture was then allowed to stir at room temperature for a period of two hours. At this point the solvents were removed by flash evaporation and the resultant slurry was taken up in water (100 ml) and extracted with ether (3 x 100 ml). The ethereal portion was dried (sodium sulfate) and the solvent was removed by flash evaporation. The remaining oil was then treated with an aqueous potassium hydroxide solution (180 ml of a 10% solution, 0.33 moles). This mixture was stirred at room temperature for a period of 20 hours at which point it was washed with ether (1 x 40 ml), made just acidic with sulphuric acid, and extracted with methylene chloride (3 x 75 ml). The organic portions were combined and dried (sodium sulfate). The solvent was then removed by flash evaporation yielding an oil which crystallized on standing. Recrystallization from ligroin/benzene gave the cis diacid (10.2 g., 55 mmoles) as a white crystalline solid. The melting point of the diacid was 92-94°C. PMR: 0.97 (3H, triplet, J = 7.5 Hz., CH_3CH_2), 1.70 (3H, broad singlet, C=C-CH_3), 2.08 (2H, quartet, J = 7.5 Hz, CH_3CH_2), 3.45 (1H, triplet, J = 7.5 Hz. $H-C(COOH)_2$), 5.09 (1H, broad triplet, J = 7.5 Hz., C=C-H). MS: M^+ 186 (11%), 82 (100%), 55 (53%). Analysis: calculated for $C_9H_{14}O_4$: C, 58.05; H, 7.58; found: C, 57.78, H, 7.39.

Cis 5-Methyl-4-Heptenoic Acid (XLIV)

The cis diacid (XLIIIa) (10.2 g., 55 mmoles) was placed in a claisen flask and heated to 140°C in vacuo (12 torr). A mixture of the monoacid (XLIV) and an isomeric lactone (XLVII) (6.2 g., 44 mmoles) were collected as they distilled over (116°C. at 12 torr). IR (of mixture): 1725 (C=O of lactone), 1700 (C=O of acid). PMR: 1.67 (3H, broad singlet, $C=C-CH_3$), 5.09 (1H, multiplet, C=C-H). MS: M^+ 142 (11%). Analysis: calculated for $C_8H_{14}O_2$: C, 67.57; H, 9.92; found: C, 67.32; H, 10.00.

Cis 5-Methyl-4-Hepten-1-ol (XLV)

The decarboxylation reaction mixture from above (4.3 g., 30 mmoles) was treated with lithium aluminum hydride (1.7 g., 45 mmoles) in anhydrous ether (50 ml). This mixture was stirred at room temperature for a period of 18 hours at which point the excess lithium aluminum hydride was destroyed by the cautious addition of a 5% aqueous sodium hydroxide solution (4 ml) and water (8 ml). The reaction mixture was filtered (Buchner funnel) and the white granular precipitate was washed with ether (3 x 20 ml). The ethereal portion was dried (potash) and the solvent removed by flash evaporation. The remaining oil was subjected to a vacuum distillation from which was obtained the desired olefinic alcohol (XLV) (B.P. 100°C. at 12 torr) (0.96 g., 7.5 mmoles)

and a saturated diol (XLVIII) (B.P. 140°C at 12 torr) (2.6 g., 18 mmoles). IR: 3400 cm^{-1} (OH). PMR: 0.96 (3H, triplet, J = 7.5 Hz., CH_3CH_2), 1.66 (3H, broad singlet, C=C-CH_3), 3.51 (2H, triplet, J = 7.0 Hz., CH_2OH), 5.03 (1H, multiplet, C=C-H). MS: M^+ 128 (43%), 81 (50%), 55 (100%). Analysis: calculated for $C_8H_{16}O$: C, 74.94; H, 12.58; found: C, 74.93; H, 12.75.

Cis 1-Iodo-5-Methyl-4-Heptene (XXXVIII) (X = I).

Treatment of the cis olefinic alcohol (XLV) (294 mg., 2.3 mmoles) with triphenylphosphite diiodide (2.4 mmoles) as before (compound XXXIII) gave the desired cis olefinic iodide (328 mg., 1.4 mmoles) as a colorless liquid. PMR: 0.98 (3H, triplet, J = 7.5 Hz, CH_3CH_2), 2.64 (3H, broad singlet, C=C-CH_3), 3.16 (2H, triplet, J = 6.5 Hz, CH_2I), 5.00 (1H, multiplet, C=C-H). Analysis: calculated for $C_8H_{15}I$: C, 40.35; H, 6.35; found: C, 37.54; H, 5.93.

Cis 5-Methyl-4-Heptenetriphenylphosphonium Iodide (XLVI)

A solution of the olefinic iodide (XXXVIII) (750 mg., 3.2 mmoles) and triphenylphosphine (865 mg., 3.3 mmoles) in ethyl acetate (5 ml) was heated at reflux for 17 hours. At the end of this time the reaction mixture was allowed to cool to room temperature, at which point 10 ml of anhydrous ether was added. Decanting off of the solvent left behind an amber syrup which crystallized as needles

(940 mg., 1.9 mmoles) upon standing with ethyl acetate. The melting point of the phosphonium salt was 148-155°C. PMR: 1.60 (3H, broad singlet, C=C-CH_3), 3.62 (2H, multiplet, $>C<^{H}_{\overset{+}{P}\phi_3}$), 5.09 (1H, multiplet, C=C-H), 7.85 (15H, multiplet, $-\overset{+}{P}\phi_3$). MS: 373 (11%), 372 (10%), 262 (100%). Analysis: calculated for $C_{26}H_{30}PI$: C, 62.41; H, 6.04; I, 25.36; found: C, 62.65; H, 6.12; I. 25.20.

Cis 7-Methyl-6-Nonene-3-Triphenylphosphonium Iodide (XVIII)

To a slurry of cis 5-methyl-4-heptenetriphenylphosphonium iodide (XLVI) 100 mg., 0.2 mmoles) in anhydrous ether (1 ml) was added (nitrogen atmosphere) a 0.2 M solution of n-butyllithium in ether (1 ml, 0.2 mmoles). This mixture was allowed to stir at room temperature for 15 min. at which point a solution of ethyl iodide (31.2 mg., 0.2 mmoles) in anhydrous ether (1 ml) was added. This mixture was then stirred for 15 hours at room temperature at which point the solvent was removed in vacuo. The resultant semisolid material was taken up in methylene chloride (10 ml) and filtered. The methylene chloride was removed in vacuo and the resultant syrop was allowed to stand with ethyl acetate (1 ml) from which was obtained the desired phosphonium salt (XVIII) as a white crystalline powder (64 mg., 0.12 mmoles). The melting point of the salt was 108-112°C. PMR: 0.94 (3H, triplet, J = 7.5 Hz, CH_2CH_3), 1.22 (3H, triplet, J = 7.0 Hz, CH_2CH_3), 1.53 (3H, broad singlet, C=C-CH_3), 4.58 (1H, multiplet, $>C<^{\overset{+}{P}\phi_3}_{H}$), 5.00 (1H, multiplet, C=C-H). MS: 401 (1.5%), 400 (2%), 262 (100%).

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