CHAPTER–I

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIP OF INSECT JUVENILE HORMONES

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ABSTRACT

With a brief introduction to insect juvenile hormones, important synthetic routes to Cecropia juvenile hormones and the relation between chemical structure and biological activity in this area has been reviewed. Biogenesis of Cecropia juvenile hormones has been discussed.

INTRODUCTION

Insect metamorphosis involves the transformation of sexually immature individuals into reproducing adults of different form and structure. In some insects, this development sequence consists of a series of larval stages followed by pupal stage and finally the adult, whereas others do not have a pupal stage, but molt directly from the larva to the adult. This three stage development of most insects is precisely controlled by the secretion of three hormones.[1]

Neurosecretory cells secrete the prothoracotropic hormone or brain hormone (BH) whose action on the prothoracic gland initiates the synthesis and release of the prothoracic gland hormone or moulting hormones (MH), i.e. Ecdysone, which induces the events associated with each molt. The third member of the trio is juvenile hormone (JH) which comes from two small glands called '<u>Corpora allata</u>', located behind an insect's brain, serves to maintain the juvenile (or larval) characteristics of the insect. The <u>Corpora allata</u> actually produce the JH and then control the amount of JH which enters the blood stream of the insect. If high concentrations circulate in the blood stream, the insect will remain sexually immature. The flow of the JH into the blood stream must stop if the larva is to metamorphose into a mature adult. During the adulthood of the insects, the JH also performs other functions, such as controlling the

sexual development, the production of sex attractants, the ability to reproduce and the ripening of the eggs from which the insects are born.

Karlson et al.[2] identified the hormone (Ecdysone) from silk worm pupae as a pentahydroxy cholestenone derivative. The detailed structure was derived from X-ray data[3] and confirmed by synthesis.[4] MHs from other sources whose structures have been elucidated resemble ecdysone closely, differing mainly in the pattern and number of hydroxyl groups. It appears that all arthropods employ essentially the same compound as the molting hormone.

In 1956 Williams[5] announced that the abdoman of the male silk moth, Platysamia cecropia L., is an exceptionally rich source of JH. Noting that topical application of JH caused insects to die without completing their development, Williams recognised the powerful insecticidal potential of 'JH-powerful', since insects could scarcely develop resistance to theor own hormones. It has been claimed that most mammalian tissues (including human placenta)[6], several micro-organisms,[7] and the parasite, Nosema,[8] all showed demonstrable JH-activity. Williams and Law,[9] went on to purify the original Cecropia extract some 50,000-fold, establishing that the major component of the material was the 9,10-epoxide of methyl hexadecanoate. Since synthetic (±)-cis and (±)-trans-

isomers were subsequently devoid of JH-activity, it was concluded that JH was but a minor portion of the purified active fraction.

The impressive team work of Roller et al. led first to a 10^5-fold purification of the Cecropia extract,[10] and thence to the elaboration and synthesis of the JH. By catalytic reduction (using 50 ug), oxidative cleavage (15 ug), and telling application of mass spectral analysis, the gross structure of JH was determined. From it's NMR spectrum (200 ug) and subsequent synthesis[11] of the racemates of four of the possible sixteen stereoisomers, Roller et al. were able to refine their earlier structural conclusions and deduce that JH is methyl-cis-10,11-epoxy-7-ethyl-3,11-dimethyl-trans,trans-2,6-tridecadienoate, (JH-I).[12]

Meyer, Schneiderman, Hanzmann and Ko established the presence of JH-II in their Cecropia oil extracts,[13] in which the ratio of JH-I: JH-II varied from 4:1 to 10:1. The structure of JH-II was confirmed by it's synthesis.[14]

Judy also reported the 3rd JH (JH-III)[14g] which is now considered to be the most abundant of the three JHs known so far.[14h]

SYNTHETIC APPROACHES

(±)-JH-I was pieced together for the first time in a non-stereoselective manner (Fig. 2), (overall yield: 0.05%), which consists essentially of two Wittig reactions and an epoxidation reaction with fractionations of the stereoisomers at appropriate stages.[15]

The first of a series of stereospecific synthesis was a beautifully conceived route[16] to the Roller intermediate 12. The synthesis (Fig. 3, overall yield: 4%) is based on sequential fragmentation of a bicyclic precursor 8, control of geometry therefore being transposed to a control of relative stereochemistry in cyclic systems (8 and 11).

The twelve-step Johnson synthesis[17] (Fig. 4), rests on Johnson's stereoselective modification of the Julia method for introducing trans-trisubstituted double bonds, a step which involves the rearrangement of a cyclopropyl carbinyl to the homoallylic system (14→15). While the overall yield is more respectable 10% or so; the final product is only about 90% pure.

A third stereospecific total synthesis of (±)-JH-I and (±)-JH-II, devised by Corey et al.[18] is again a fine example of imaginative chemistry. The route conceived embodies elegant

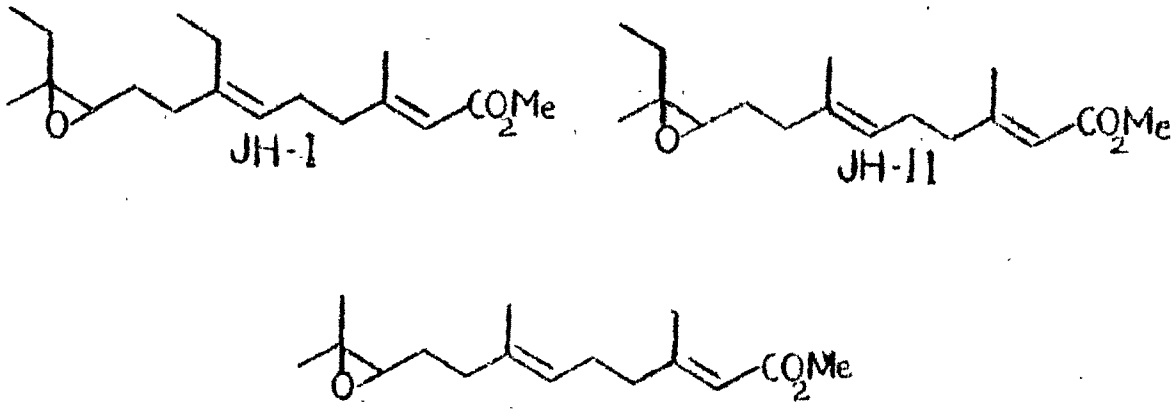
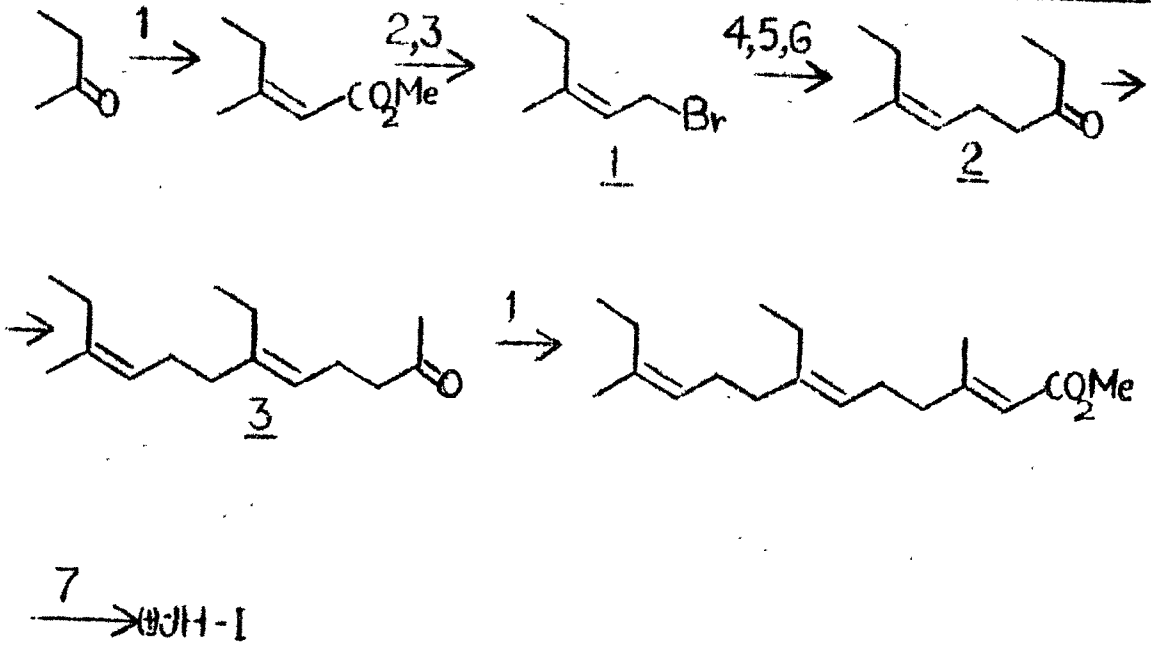
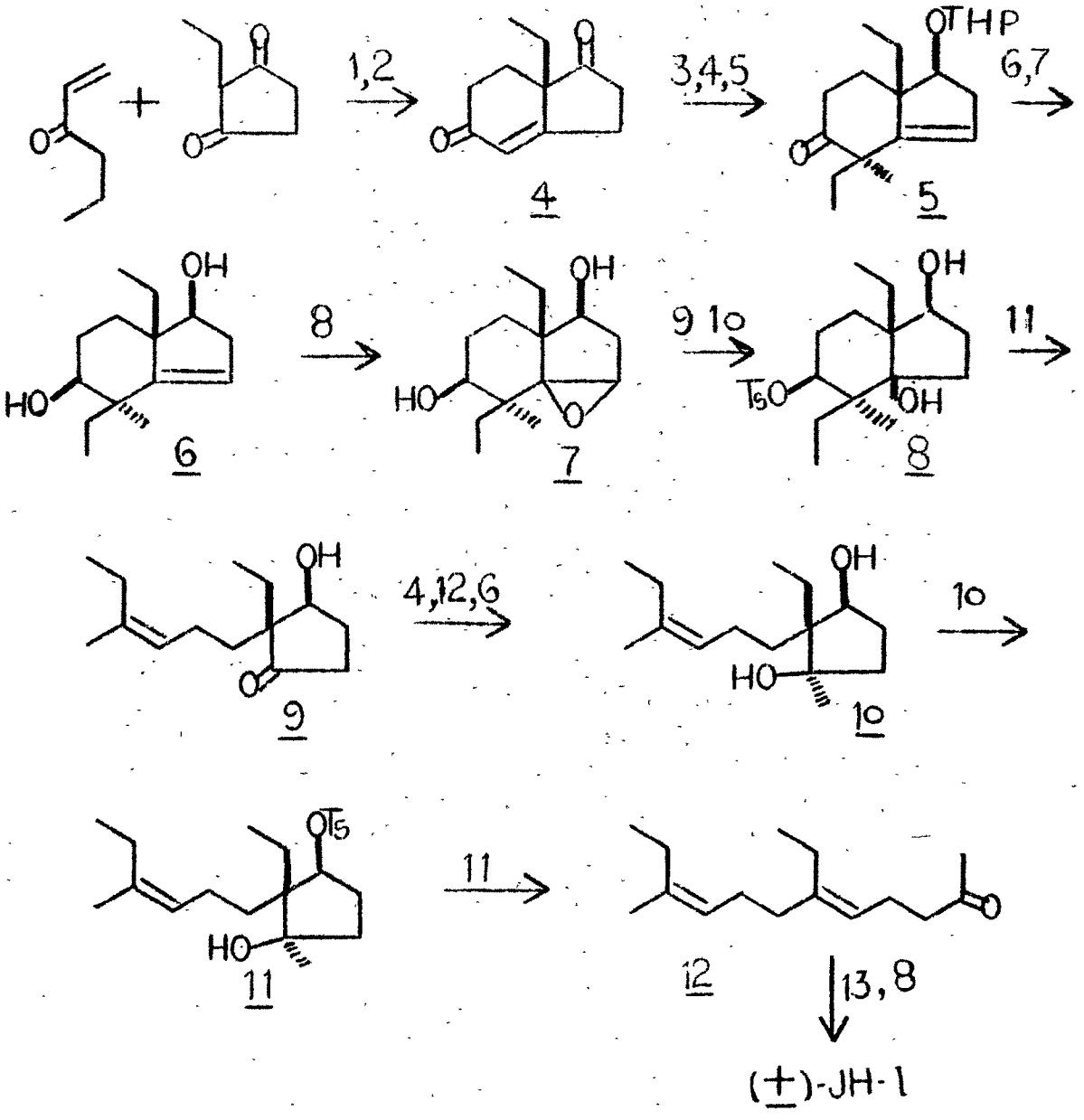


FIG. 1



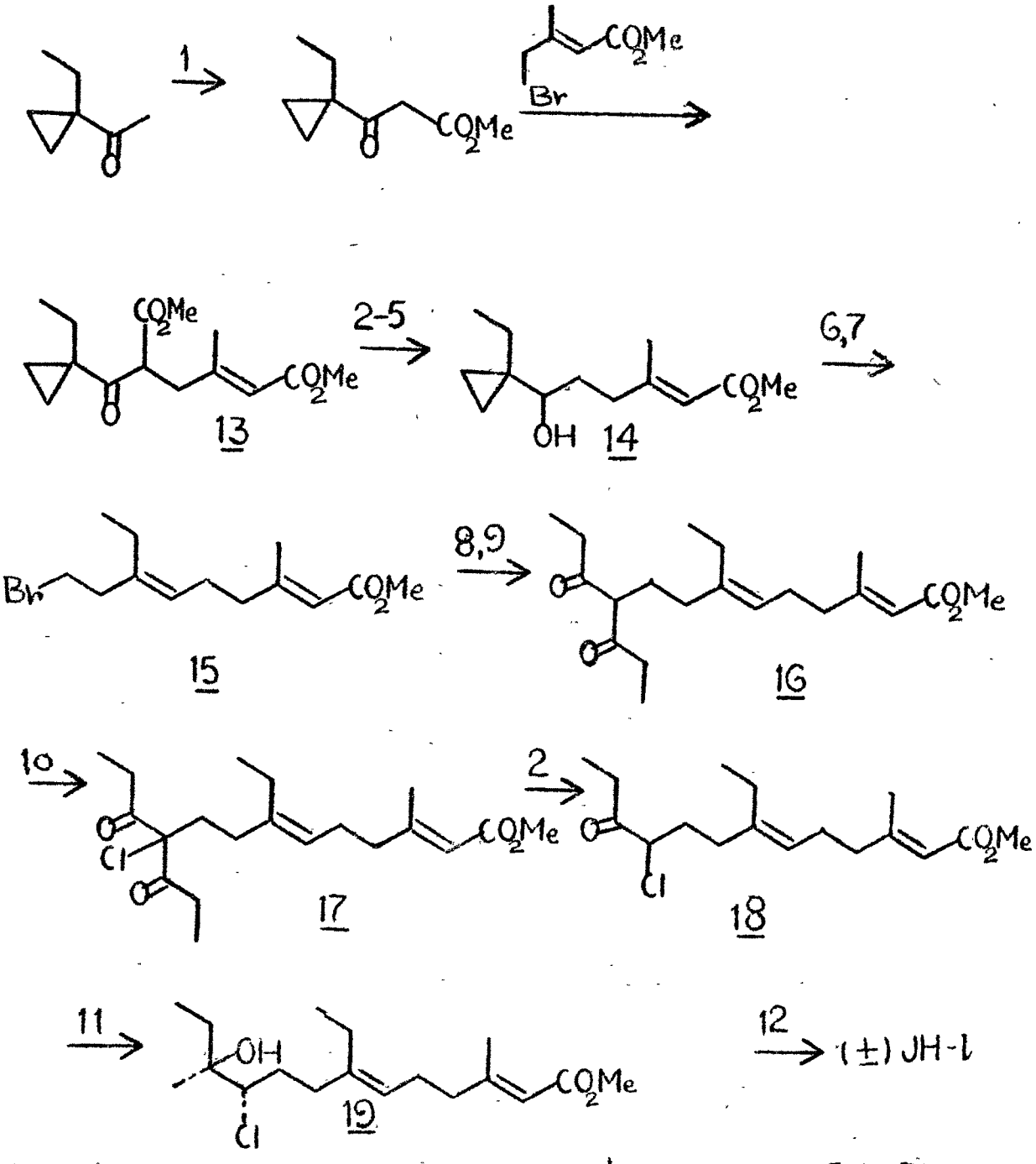
REAGENTS: 1. $(MeO)_2P(O)CH_2CO_2Me$, 2. LAH, 3. PBr_3, 4. NaOEt - $EtCOCH_2CO_2Et$, 5. NaOH, 6. H^+, 7. m-Cl-$PhCO_3H$

FIG. 2



REAGENTS: 1. Michael Addition, 2. PTS, 3. $NaBH_4$, 4. OH → OTHP, 5. CH_3I, 6. OTHP → OH, 7. $LiAlH(OBu^t)_3$, 8. m-Cl-$PhCO_3H$, 9. LAH, 10. TsCl, 11. NaH, 12. MeLi, 13. $(MeO)_2P(O)CH_2CO_2Me$

FIG. 3



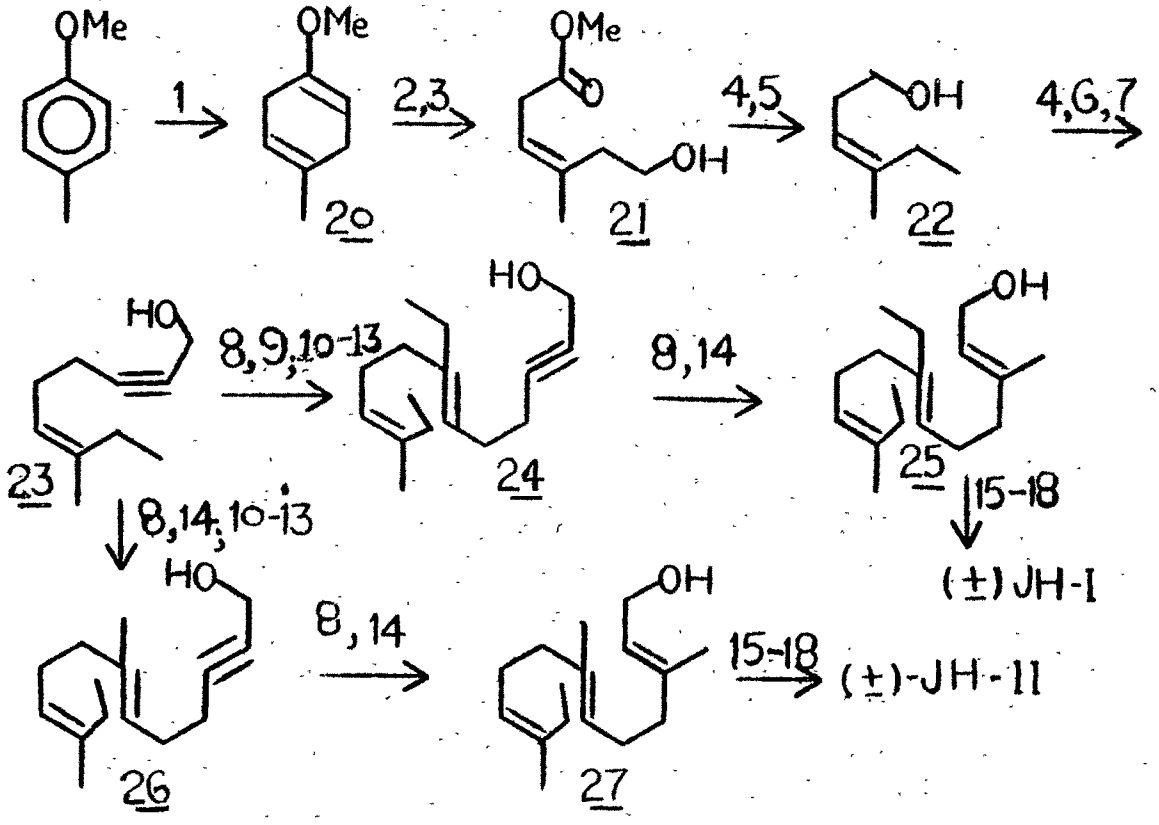
REAGENTS: 1. Me_2CO_3, 2. $Ba(OH)_2$, 3. H^+, 4. CH_2N_2, 5. $NaBH_4$, 6. PBr_3-LiBr, 7. ZnBr, 8: NaI / $(Me_2N)_3P(O)$, 9. Li-enolate of heptane-3,5-dione, 10. $CuCl_2$-LiCl, 11. $MeMgCl$, 12. K_2CO_3

FIG. 4

application of no less than five novel synthetic procedures, initially introduced by Corey. The essence of this synthesis (overall yield: 1%) is shown in Fig. 5. 20→21 ensures the cis-stereochemistry of the terminal bond, and hence the 10-epoxide. 23→24, 24→25, 23→26 and 26→27 involve the stereospecific conversion of propargylic alcohols into trisubstituted double bonds and 25→(±)-JH-I, and 27→(±)-JH-II offer the one-flask conversion of conjugated aldehyde into corresponding methyl ester and selective epoxidation at terminal double bond *via* bromohydrin formation.

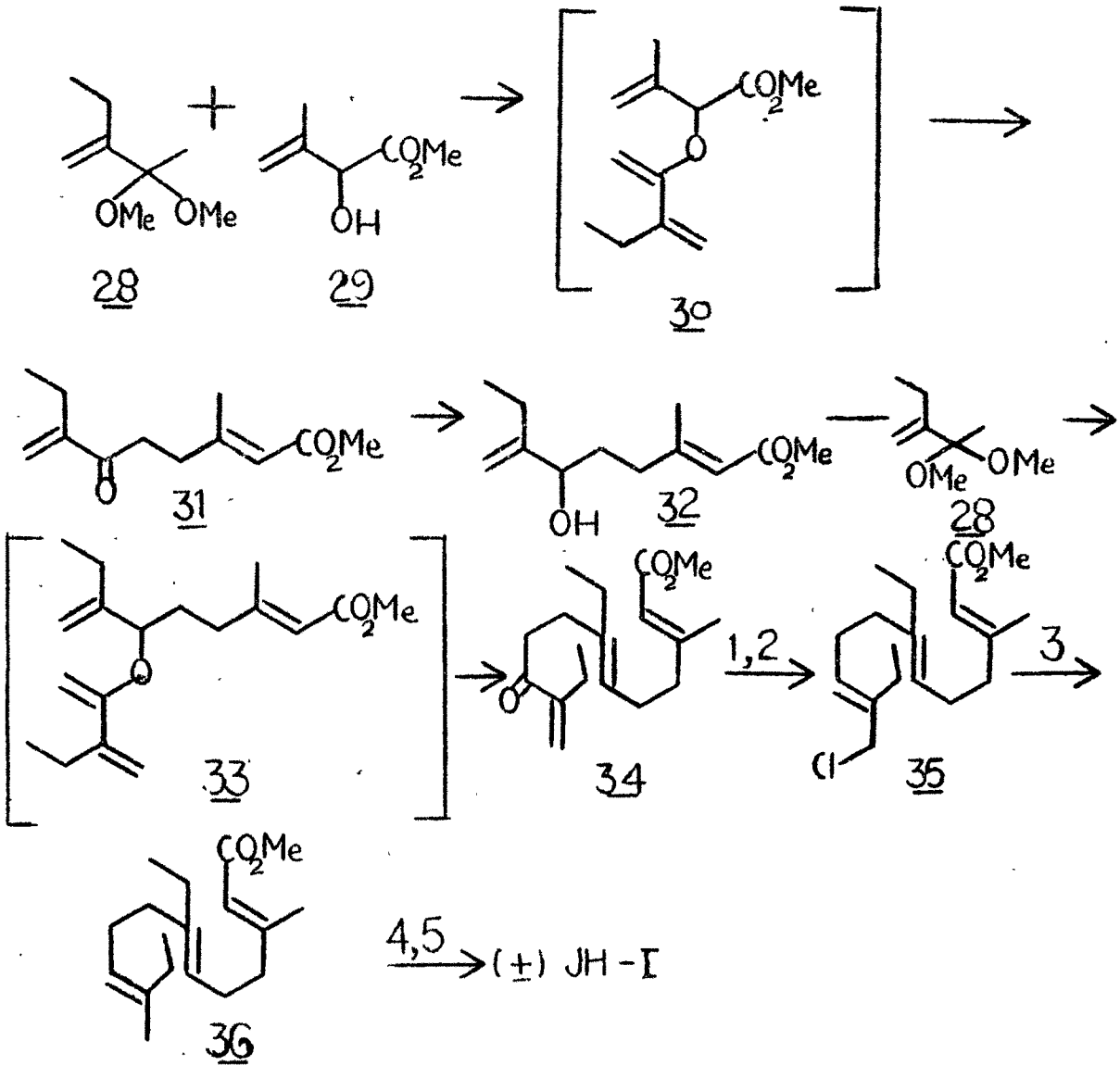
Johnson's route[19] involves Claisen rearrangement for the stereospecific formation of the trans-olefinic linkage as shown in the conversions 28 + 29→31 and 28 + 32→34 in Fig. 6. Rearrangement proceeds through the allylic ethers 30 and 33, which is produced in situ (Fig. 6).

A route of Corey *et al.*[20] involves the reaction of β-oxidophosphonium ylide 40 and paraformaldehyde as a key step. β-Oxidophosphonium ylide generated from the Wittig betaine (39) with Sec-Bu-Li reacts with carbonyl compounds to yield the trans-olefin (41) uncontaminated by stereoisomer, through a ,β,β′-dioxophosphonium ion intermediate. Both (±)-JH-I and (±)-JH-II were synthesized, stereospecifically from the common intermediate (41): (Fig. 7).



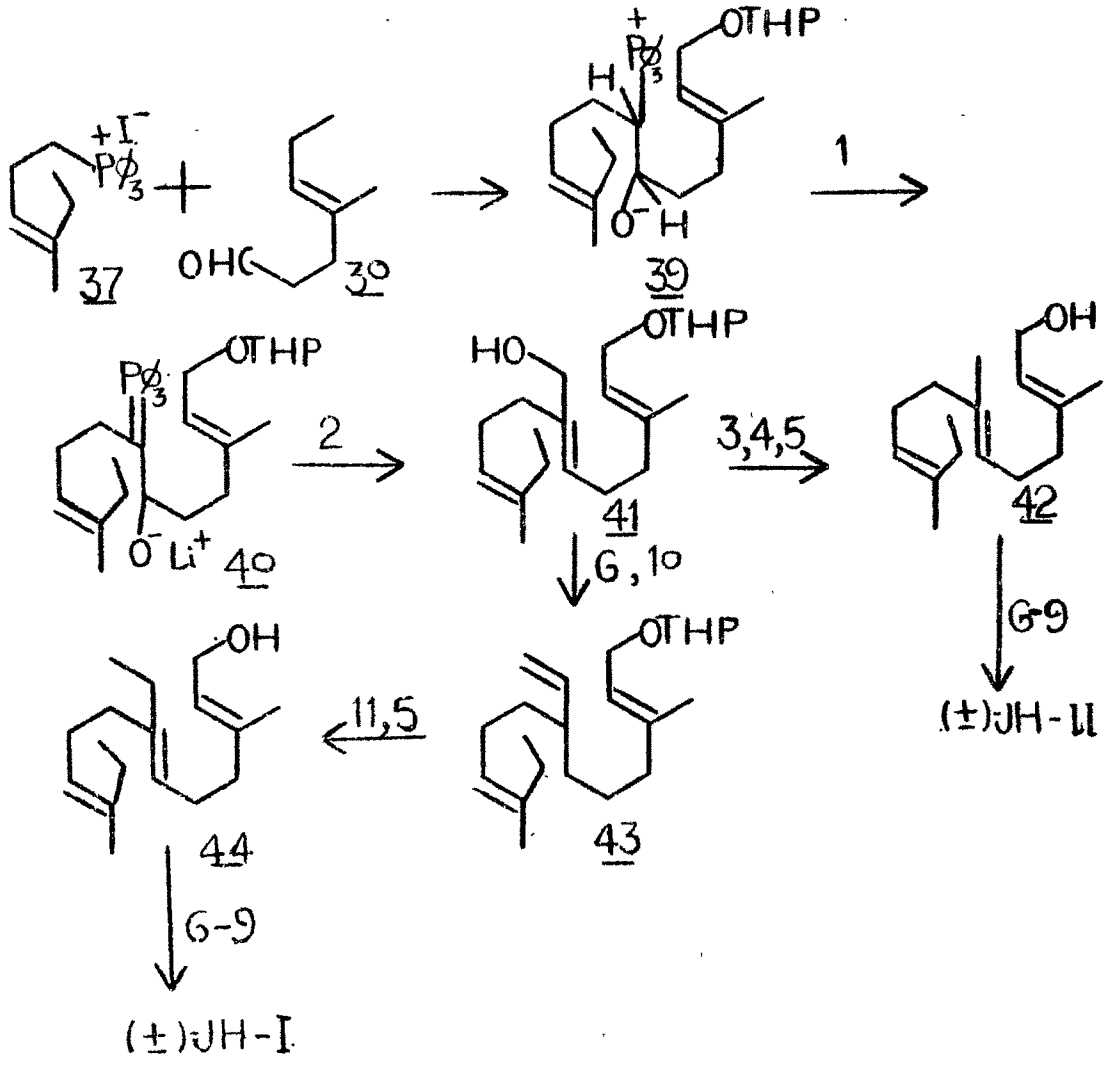
REAGENTS : 1. Birch Reduction, 2. O_3, 3. $NaBH_4$, 4. TsCl, 5. LAH, 6. $Li-C\equiv C-CH_2OTHP$, 7. H^+, 8. LAH/NaOMe/I_2, 9. Et_2LiCu, 10. PBr_3, 11. $Li\cdot CH_2C\equiv C.SiMe_3$, 12. $AgNO_3$/KCN, 13. BuLi then HCHO, 14. Me_2CuLi, 15. MnO_2, 16. CN^-/CH_3OH, 17. NBS/H_2O/THF, 18. $i\text{-}Pro^-$

FIG. 5



REAGENTS : 1. $NaBH_4$, 2. $SOCl_2$, 3. $NaBH_4$/DMSO,
4. NBS/H_2O/THF, 5. K_2CO_3/CH_3OH

FIG. 6



REAGENTS : 1. Sec-BuLi , 2. Paraformaldehyde , 3. Py./SO_3 , 4. LAH , 5. H^+ , 6. MnO_2 , 7. CN^-/MeOH , 8. NBS/THF/H_2O , 9. i-Pro^- , 10. $Ph_3P{=}CH_2$, 11. Diimide

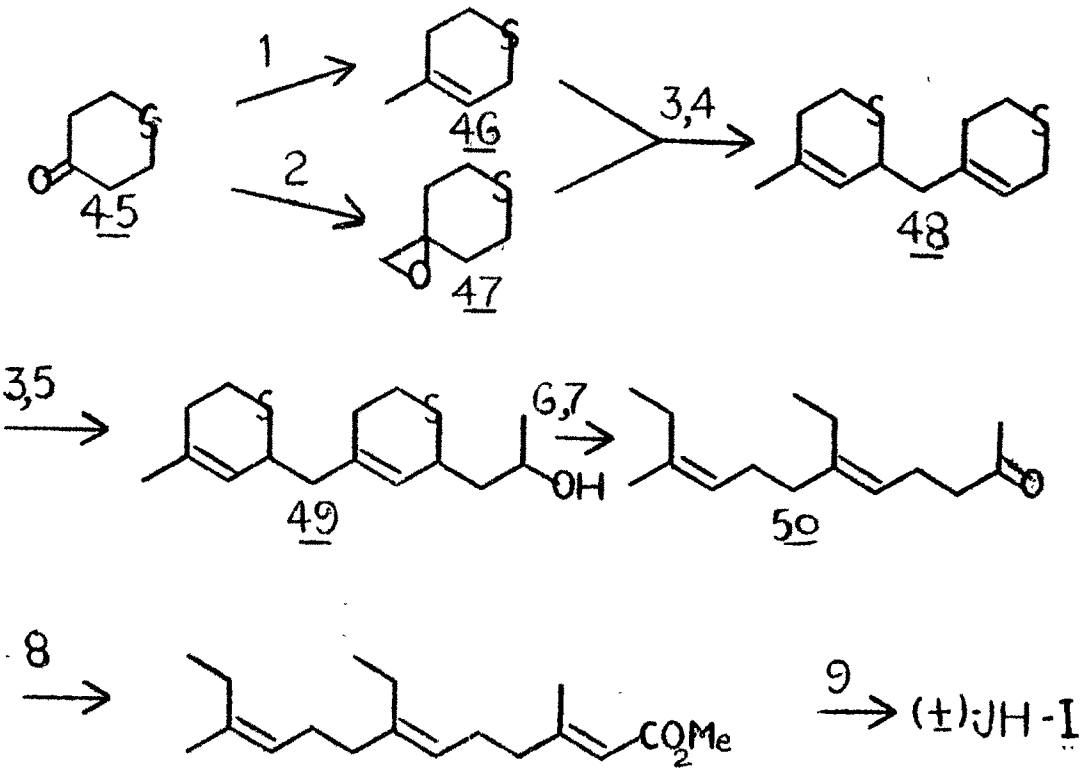
FIG. 7

Kondo et al.[21a] has also reported the stereospecific synthesis of Roller intermediate (50) which involves the condensation of two dihydropyrans (46) and (47), followed by reductive desulfurization (Fig. 8).

Most recent highly stereoselective route to (±)-JH-I is outlined in Fig. 9[21b], which involves highly stereoselective [2,3]-sigmatropic rearrangement of bis-alkoxy organometallic reagent like (56) to give Z-bis-homoallylic alcohol (57).

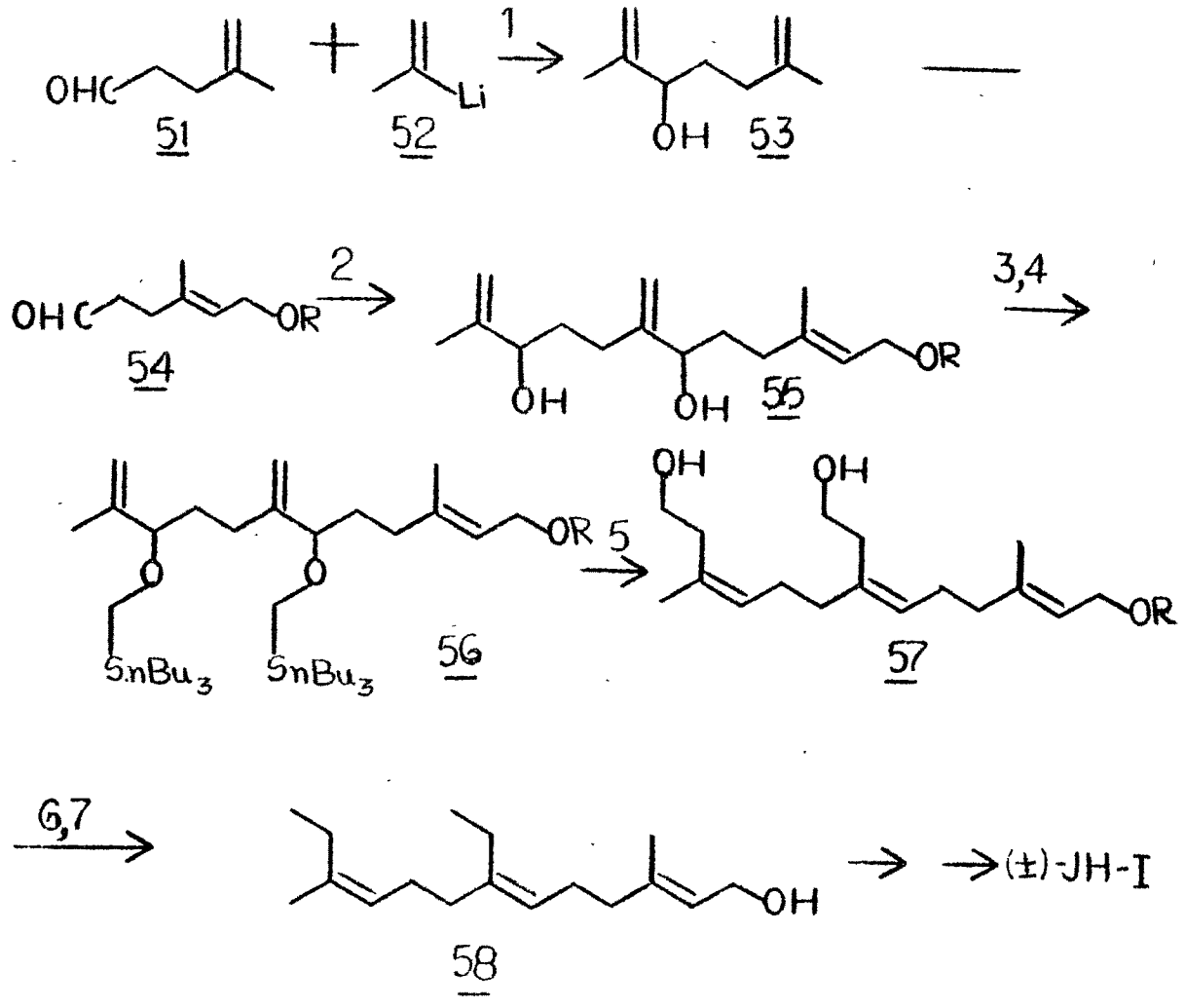
STRUCTURE ACTIVITY RELATIONSHIP

Because of the enormous variations in chemical structure and diversity of the species tested, there exist countless difficulties in determining relationship between chemical structure and biological activity in JH mimics. For example, relationships found in one species may be similar to those found in another, but may also be completely different.[22] Also, there is a lack of standard bioassay conditions. Even when a single species is used in bioassay, it is difficult to compare activities based on local epidermal effects with data on general morphological influence of JH-mimics. In addition, various compounds may have different dose response curves,[23,24] which makes it impossible to find a common denominator for data obtained with different techniques. Application methods, solvents and developmental stages employed also contribute to the problem.



REAGENTS : 1. $MeMgBr / MgSO_4$, 2. $Me_2\overset{O}{\uparrow}S=CH_2$, 3. n-BuLi / DABCO,
4. $SOCl_2$ / Py. , 5.  , 6. $Li / EtNH_2$, 7. CrO_3 / Py. ,
8. $(MeO)_2P(O)CH_2COOMe$, 9. m-Cl-$PhCO_3H$

FIG-8



REAGENTS : 1. THF, 2. t-BuLi/Ether , 3. KH/THF , 4. Bu_3SnCH_2I
5. BuLi/THF, 6. TsCl/Py., 7. LAH/Ether

FIG-9

PHYSICAL PROPERTIES OF JH-MIMICS

Most of the highly active JH-mimics are characterized by extremely low water solubility. On the other hand, the entirely non-polar compounds, such as hydrocarbons are, as a rule, inactive.[25,23] Thus, with respect to their solubility, the optimal JH-mimics possess very low polarity, but are not absolutely non-polar.

Lipophilic character of the JH-mimics, increases their ability to penetrate the lipoid layer of the insect epicuticle. However, some JH-mimics completely loss their activity when injected as aq. emulsions.[26]

MOLECULAR SIZE

Wakabayashi et al.[27], reported that aliphatic chain-lenth of fifteen carbon atoms was crucial for high JH-activity, when assayed on Tenebrio, but same may not be true for other species. For instance, JH-activity of some para-substituted aromatic esters (T-I) was lower than that of the corresponding p-halo (T-2), p-nitro (T-2), p-ethyl (T-2) and 3,4-methylene dioxy (T-3) derivatives, on Tenebrio, but it has shown a reversed order on Hemipterans.

Correlation between chain-length and JH-activity was also found in sesamax-type compounds (T-4 to T-6) shortening

or prolongation of the chain by a single or more carbon atoms led to decreased activity on Tenebrio.[28] The chainlength effect was also exemplified on 7-alkoxy geranyl ethers (T-7), the presence of an ethoxy or propoxy group led to an enormous increase in activity over the parent compound in Tenebrio (thousand times), while the presence of a butoxy group led to a drastic decrease in activity (hundred thousand times). On the other hand, the same compounds (T-7) could not show any change in activity on several Hemipteran species.

A broad tolerance in activity with respect to difference in chainlength was observed in certain species such as pyrrhocorids, e.g. juvabione or aromatic derivatives of juvabione with a shorter side chain were approximately equal in activity as aromaticgeranyl or farnesyl ethers with a longer side-chain (T-8, T-9).

The JH-activity of homologues of 3,7,11-trimethyl-2-dodecenic acid (T-10) remained almost unchanged when the chain was shortened by one carbon atom between the original C-7 and C-11 atoms (T-11). A considerable decrease or even loss of activity was observed after simultaneous shortening between both the C-7 and C-11 and also between C-3 and C-7 atoms of the original carbon chain (T-12).[22,29]

Thus, in general, one can say that specific change of distances between determined sensitive loci and chainlength of 14 to 16 $-CH_2-$ units[30,24,27,31] are important for biological activity.

SHAPE OF CARBON SKELETON

Most of the active compounds contain atleast a part of a branched carbon chain characteristic of isoprenoids. Each 4th carbon atom at the sequence (i.e. C-3, C-7, C-11) bears lower alkyl or other substituents (e.g. farnesol, geraniol, C_{18}-JH and C_{17}-JH). But some straight chain compounds without any branching such as certain saturated or unsaturated fatty acids[32], alcohols[33] (e.g. 1-tetradecanol), and ethers[34] (e.g. dodecylmethyl ether) also exhibited JH-activity. On the other hand, some JH-mimics with just one branched carbon atom in the side chain showed JH-activity.[35] Absence of branching at C-3 in some sesquiterpenoid derivatives, either decreased[27,36] or increased[37] the JH-activity, depending on additional features.

Comparison of JH-mimics derived from the parent farnesane with related aliphatic juvanoids indicates that:

a) it is not necessary that the branching alkyl be a methyl

b) it is not necessary that the branching occur exclusively at the usual C-3, C-7 and C-11 positions, and

c) the alkyl groups can be replaced by hydrogen or halogen atoms.

For example, C_{18}-JH and C_{17}-JH showed high JH-activity on Tenebrio,[27] Rhodnius,[24] and especially on Lepidoptera.[38] Replacements of ethyl and methyl groups at C-11 of C_{18}-JH and C_{17}-JH by ethyl,ethyl (T-13, T-14), n-propyl, methyl (T-15, T-16) increased the activity.[37] Incorporation of six-membered ring (T-17, T-18) also showed the activity on Tenebrio.[39] On the other hand, structural changes at C-3, C-6 and C-9 resulted into the loss of activity.[29]

Among the oxa-analogues of farnesoic acid, the C-3, C-8, C-12 branched derivatives, are as a rule less active, than those branched at the usual C-3, C-7, C-11 positions (T-19 to T-24). Presence of an additional alkyl group at C-11, increased the activity[29] (T-25, T-26). Introduction of an additional alkyl substutution at the positions other than C-3, C-7 and C-11 increased the activity on some insect species such as Graphosoma (T-27, T-28), but in other species did not increase the activity. Similarly, an additional subsitution at C-7, resulted in increased activity on Pyrrhocoridae, with simultaneous loss of activity on number of other insect species. Removal of the alkyl groups from both C-3 and C-7 positions, abolished the activity in Tenebrio.[39] However, some compounds with no substituents at C-3 (T-29, T-30) showed activity on Tenebrio or Tribolium.[37] Removal of alkyl substituents from C-1, abolished

the activity (T-31, T-32). Replacement of methyl groups at C-3 or C-7 by chlorine atom (T-33, T-34) did not change the activity.[30b,40] Sometimes branching at C-7 was not essential when it was present at C-3 (T-35). When the distance between the benzene ring and nearest side-chain substituent was considerably shortened in juvabione and related compounds (T-36 to T-41), the activity was limited to a few species or exclusively to Pyrrhocoridae.[22]

DOUBLE BONDS AND GEOMETRICAL ISOMERISM

Most of the JH-mimics including JH, based on farnesane skeleton contain double bonds at positions C-2:3, C-6:7 and C-10:11. Removal of all the three double bonds (T-42), either decreased or completely abolished the activity.[22,27,30c,39,41] Removal of $\Delta^{2,3}$-double bond destroyed the activity.[24,30c,41b] The presence of $\Delta^{6,7}$-double bond was not as essential as the $\Delta^{2,3}$-double bond.[24,30c,41b] It's absence either increased or decreased the JH-activity.[27,39,32] It's presence also determined the species specificity.[30c] The presence or absence of $\Delta^{10,11}$-double bond did not alter the activity. Assay of several JH-mimics[27,39,42] with one to four double bonds have revealed that a) increase in number of double bonds did not show much difference in activity on Pyrrhocoridae and Lygaeidae, but b) the activity increased in Tenebrionidae, Dermastidae, Acridiidae,[41b] and Pyralidae.[41a] Analogous oxa-esters also behaved in a similar way (T-43 to T-45). $\Delta^{6,7}$-and $\Delta^{10,11}$-Tetrahydro JH-mimics were less specific and

acted on diverse insect species.[30b]

Relationship between geometrical isomerism and JH-activity was first pointed out by Yamamoto and Jacobson.[43] This may be due to difference in shape of the molecule of the cis-and-trans-forms. Geometrical isomers of farnesol,[43] and C_{18}-cecropia-JH[23,24,42,44] exhibited great difference in JH-activity.

The trans-arrangement at $\Delta^{2,3}$-double bond was particularly important for high JH-activity. The trans-configuration at $\Delta^{6,7}$-double bond appeared less essential, while almost unimportant when at $\Delta^{10,11}$ for high activity.

In general, trans-isomers possess more JH-activity than cis-isomers and should be considered in all cases, when JH-mimic contains an α,β-unsaturated[30b] or α,β-γ,δ-unsaturated[45] system (T-46 to T-48).

ROLE OF HETERO ATOMS

The common hetero atoms such as oxygen, nitrogen, chlorine and sulfur also influence the JH-activity.

(a) Hetero atoms as additional substituents on carbon chains

The presence of an oxygen atom in the form of an oxirane ring at 10,11-position greatly enhanced the JH-activity.[30b]

The presence of an alkyl group at C-11 (T-49) was not as effective as the 10,11-epoxy group or C-atom (T-50) at C-11 with respect to activity.[30d] Furthermore, presence of an oxygen atom at C-11 in the form of an alkoxy group or a nitrogen atom in the form of an azirane ring decreased the activity in many (but not in all) cases than the original epoxide derivatives.[27,45,46]

The presence of hetero atom at C-7 constituted one factor determining species specificity and selectivity of action. For example, JH-mimics with C-7 hetero atom lowered the JH-activity especially on Endopterygote insects[41a] and on Rhodnius[24,47], but greatly increased the activity on Pyrrhocoridae[30c] and did not alter the activity on Hemipteran family, Pentatomidae and abolished the activity on Tenebrio (T-51, T-52).

The presence of an epoxide oxygen at C-3 or C-7 unlike that at C-11, remarkably suppressed the activity on Tenebrio[42] and Rhodnius.[24] Substitution of hetero atoms (epoxide oxygen/ C-atom) at C-3 lowered the activity in Tenebrio and many other species but mostly did not affect the activity in Pyrrhocoridae.

(b) Hetro atoms as links connecting parts of the carbon chains:

The JH-mimics with hetero atom such as oxygen within the

chain had very low activity, e.g. farnesyl or geranyl ethers derived from the esters of β-hydroxy acids (T-53 to T-56). Replacement of C-5 by oxygen atom to form corresponding oxa-analogues gave the best JH-activity (T-57 to T-59), but the incorporation of extra oxygen atom to the basic skeleton without removing any $-CH_2-$group lowered the activity (T-60 to T-63). Introduction of two oxygen atoms into the basic chain (β-ethoxy or β-butoxy geranyl ethers) also exhibited JH-activity on Tenebrio and some other insect species[48] (T-64).

Introduction of nitrogen atom (terpenoid carbamates) in the basic skeleton also showed JH-activity[49] (T-65 to T-68).

Replacement of α-C-atom of the aromatic ring by hetero atoms such as oxygen, nitrogen or sulphur in the terpenoid aromatic JH-mimics enhanced the activity[27, 28b, 50] (T-69 to T-73). Replacement of oxygen by nitrogen or sulphur (T-71) did not alter the activity. Introduction of acetyl or methyl or trifluoro-acetyl groups on N could not change the activity (T-74). Replacement of $-CH_2-$ group (which is α to the N-atom) by -CO-group to form an amidic linkage, enhanced the activity only on pyrrhocorid bugs. This selectivity may be due to the characteristic amidic linkage. Replacement of t-butoxy carbonyl group by the pivaloyl group, which represented change of an urethane linkage to an amidic one led to an enormous increase in activity on the sensitive species.[51]

Aromatic ethers[28,35,48,52] with more than one etheric oxygen atoms also showed activity in Tenebrio and few other insects (T-78, T-79).

(c) Hetero atoms and hetero atom-containing groups as substituants on aromatic rings.

Introduction of hetero atom or hetero atom-containing groups in the meta-position of the aromatic ring increased the JH-activity[28b] (T-80 to T-82), but in the ortho-position either decreased or abolished the activity (T-83). Substitution at both ortho- and -meta-positions, other than usual methylene dioxy group increased the JH-activity in Tenebrio[28a] (T-84, T-85). Substitution in para-position also either decreased or abolished the activity. For example, while substitution of polar groups such as hydroxyl, amino, free carboxyl and sulfonyl amido groups (T-86) in the para-position completely abolished the activity, the alkoxy carbonyl group increased the activity on Hemipterans and Exopterygotes than on Tenebrio and other Endopterygotes. On the other hand para-substitution of halogen, nitro, methyl-thio and alkyl groups (T-86) and methylenedioxy group (T-87) showed more broad spectrum activity on various species.[34a]

(d) Hetero atoms as components of functional groups in acyclic juvenoids.

Most of the JH-mimics possessed functional groups containing oxygen and/or nitrogen atoms at the end of the chain. The presence of a free hydroxyl group (T-88), was too polar for

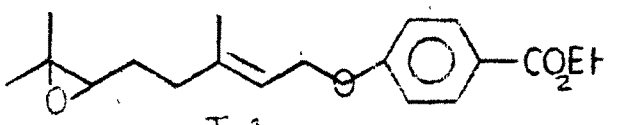
good JH-activity[26,30a,30b,34,38,49]. However, methoxy or ethoxy groups (T-89) were far better, especially on Tenebrio.[30a,34]

In ester series, ethyl ester had maximum activity,[22,24,30c 38, 41, 53] which decreased with increasing size of the ester group. The methyl keto analogues (T-90) increased the activity on Tenebrio, but decreased on flies.[52]

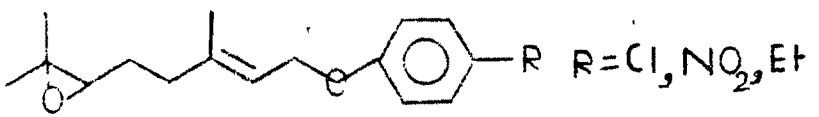
The α,β-unsaturated carboxylic acid amides, especially dialkylamides exhibited activity on Tenebrio.[42,54] The amines namely dimethyl or diethyl amines showed high activity than the corresponding hydroxy derivatives,[26,30a,34b] and low activity than the mentioned N,N-diethyl or dimethyl amides.[30b] On the other hand, diethyl amides exhibited high activity on Tenebrio and low activity on Hemipterans, but mono-ethyl amides were less specific and showed relatively high activity on both Tenebrio and Hemipterans.

OPTICAL ACTIVITY

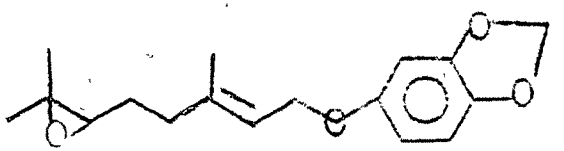
Studies on relationship between JH-activity and optical isomerism is limited. (+)-C_{18}-Cecropia-JH[55] was not 100% pure so that it is not clear whether it's activity was due to contamination with the native enantiomer. Essays on (+)-juvabione and it's enatiomer, (-)-juvabione as well as on the corresponding diastereoisomers (+)- and (-)-epijuvabione[56] did not show any major difference in the activity of the optical isomers.[57] On the other hand, the JH-activity of peptidic juvanoids was



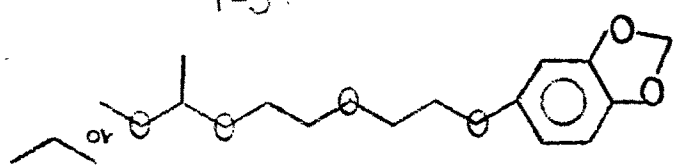
T-1



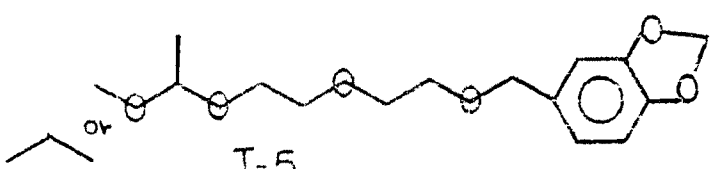
T-2



T-3



T-4



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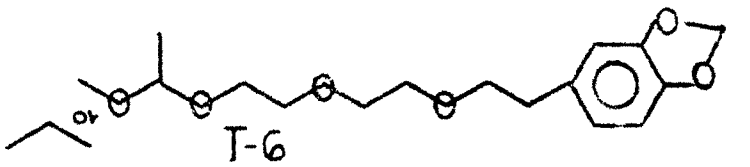

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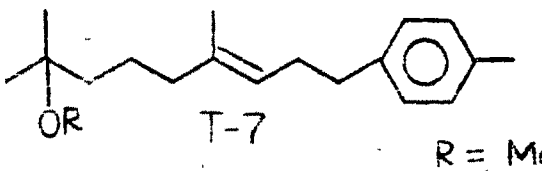
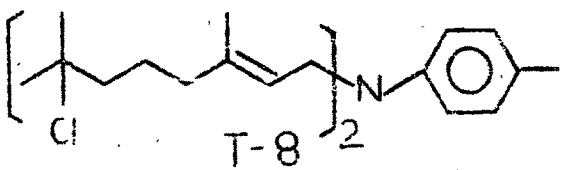


T-7

R = Me, Et, Pr, Bu



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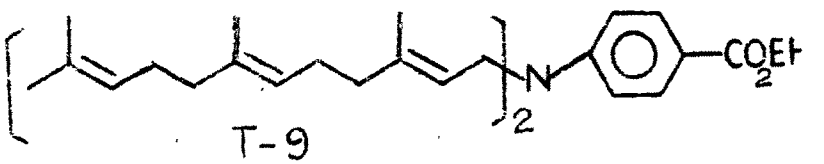
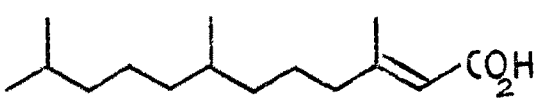
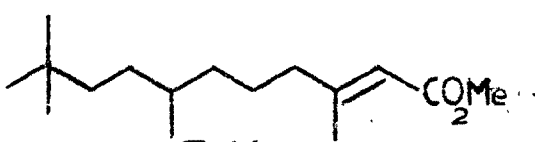


T-9



T-10



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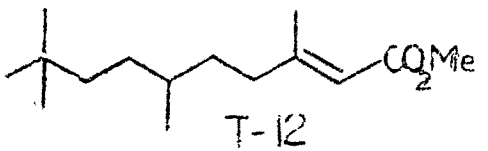

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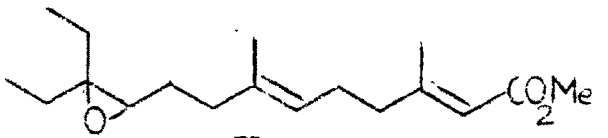

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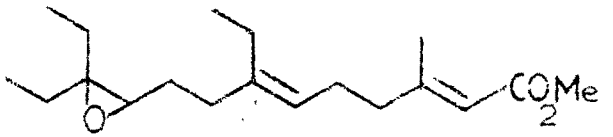
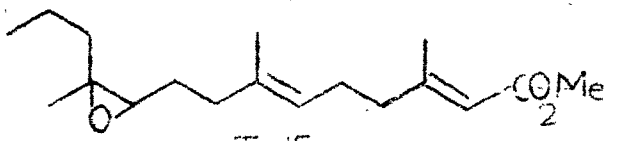
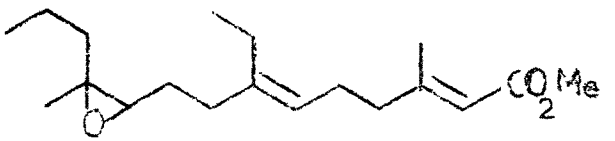


T-14



T-15



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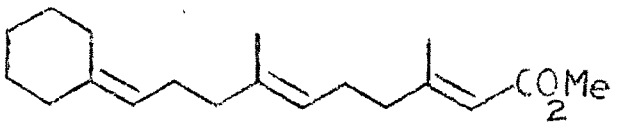

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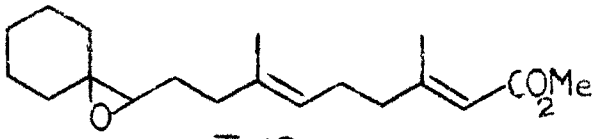

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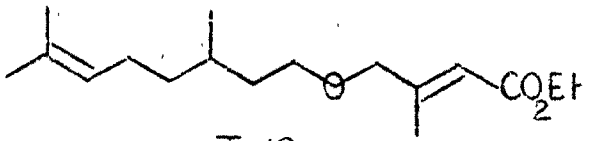

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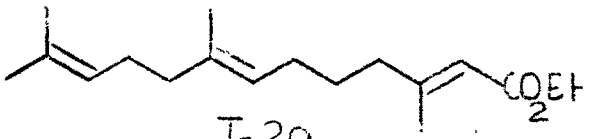

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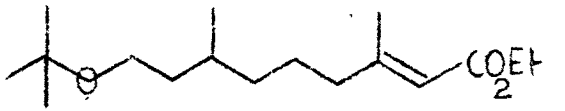

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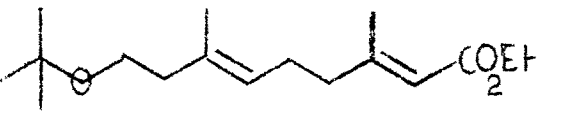

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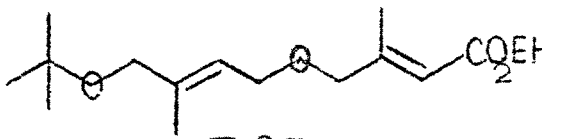

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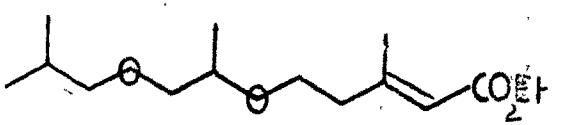

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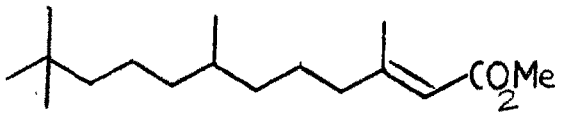

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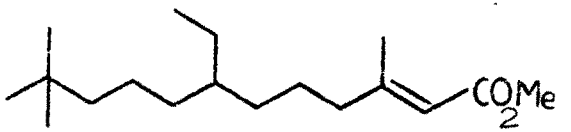

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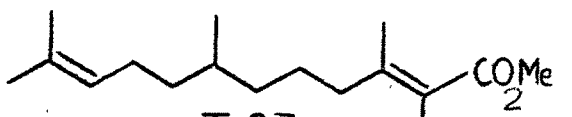

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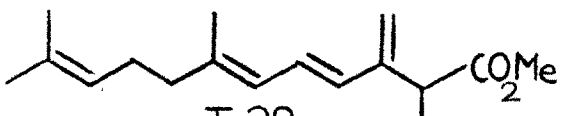

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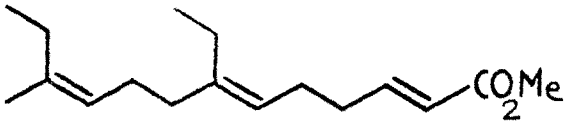

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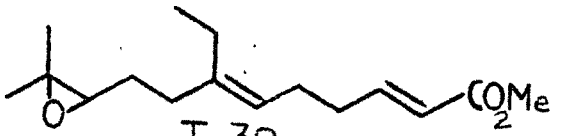

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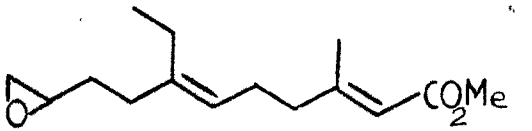
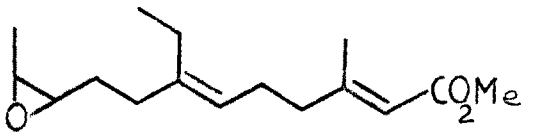
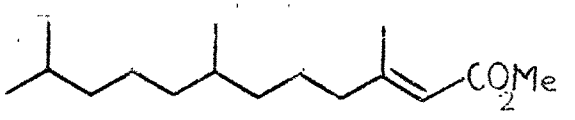


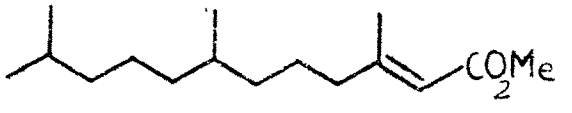
T-31



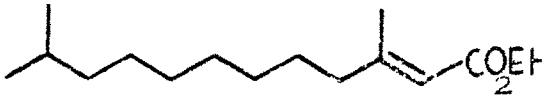
T-32



T-33



T-34



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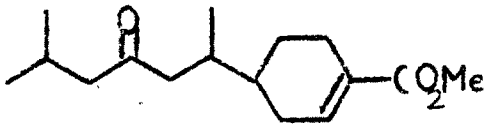
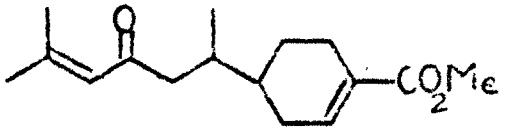


T-36



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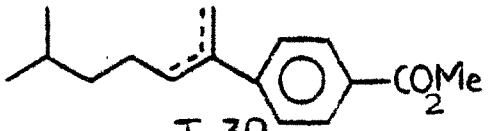

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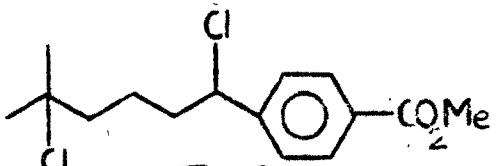

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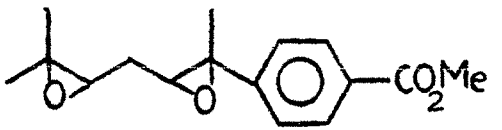

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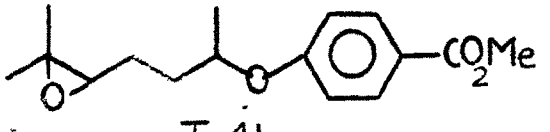

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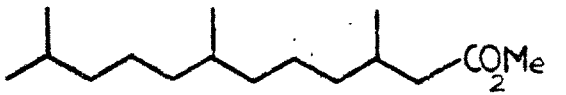
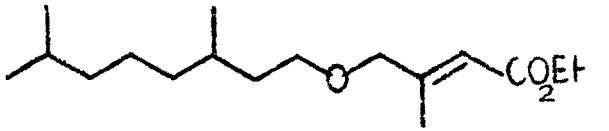
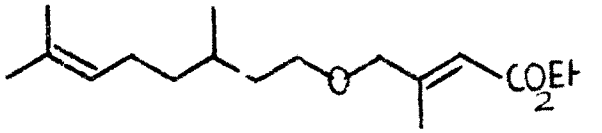


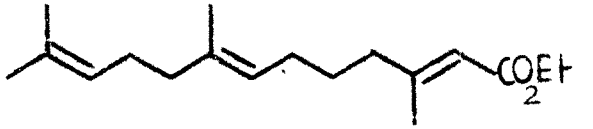
T-42



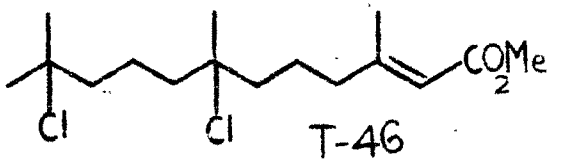
T-43



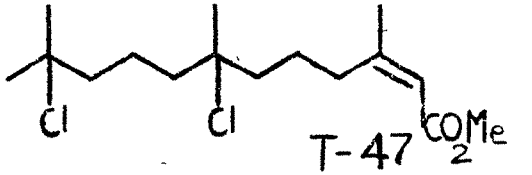
T-44



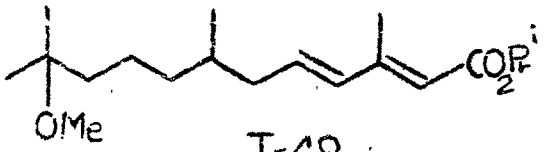
T-45



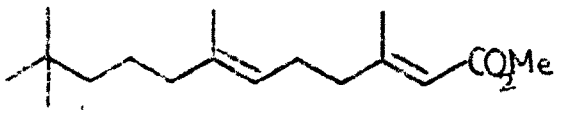
T-46



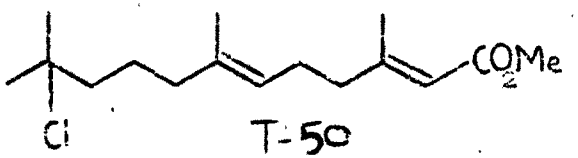
T-47



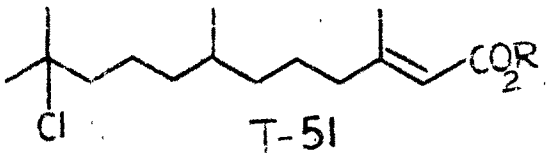
T-48



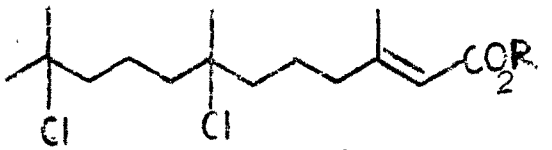
T-49



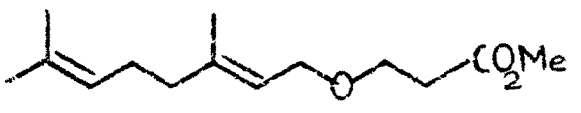
T-50



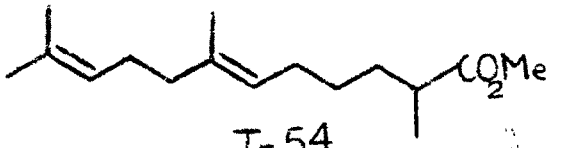
T-51 R = Me, Et



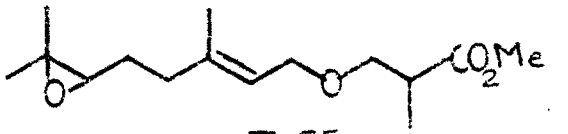
T-52



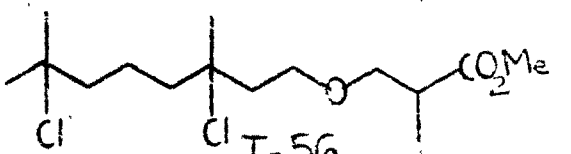
T-53



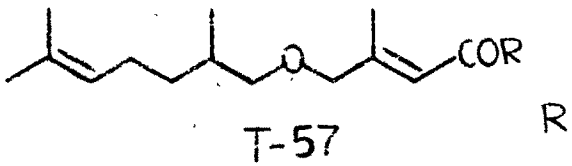
T-54



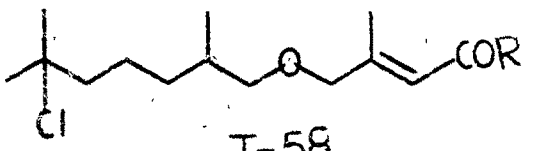
T-55



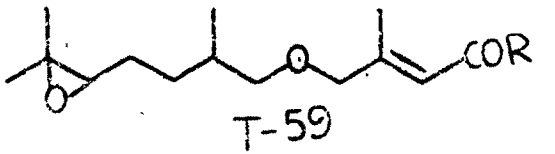
T-56



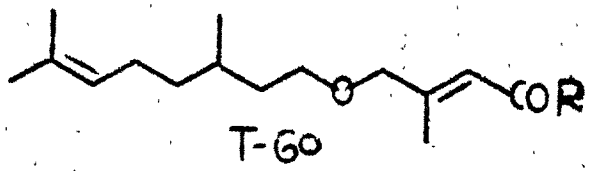
T-57 R = OEt, NEt2



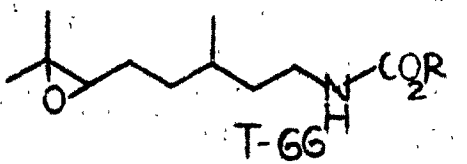
T-58



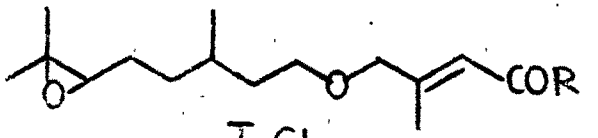
T-59



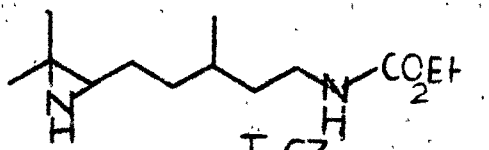
T-60 R = OEt, NEt_2



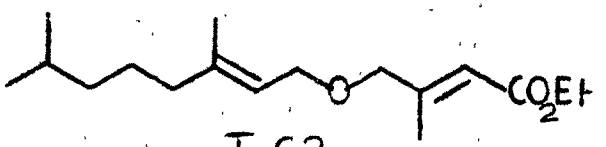
T-66 R = Et, Ph



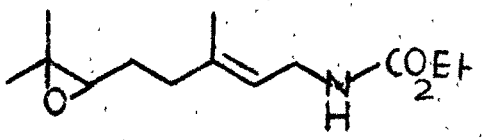
T-61



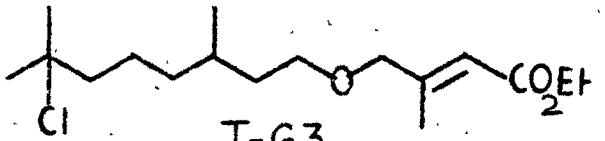
T-67



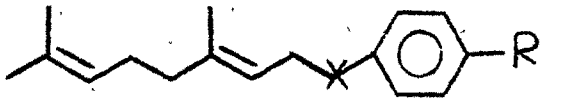
T-62



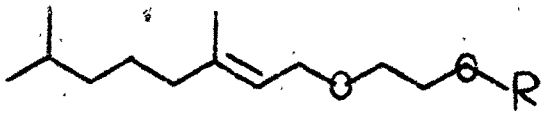
T-68



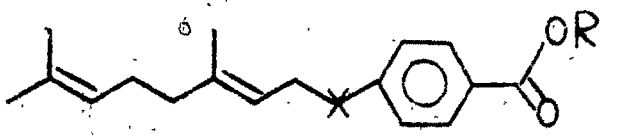
T-63



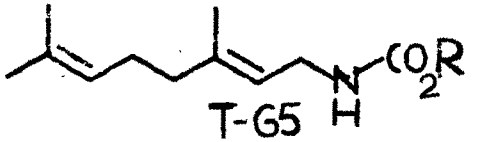
T-69 R = H, OH, NO_2



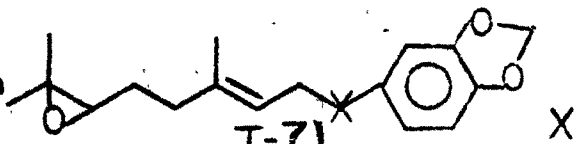
T-64 R = Et, Bu



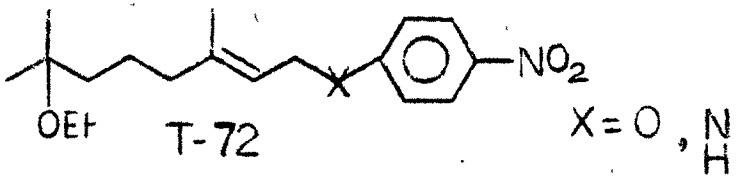
T-70 R = Me, Et



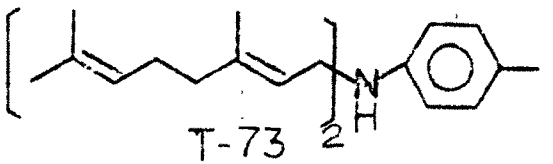
T-65 R = Ph, m-Cl-Ph



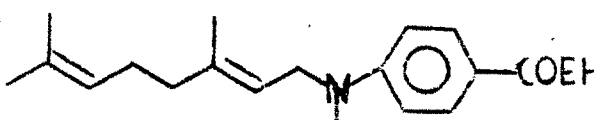
T-71 X = O, NH, S



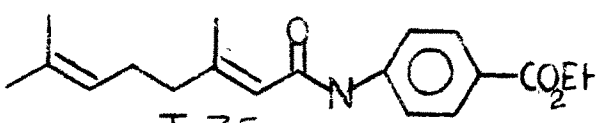
T-72



T-73

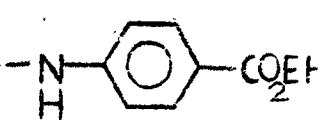


T-74 R R = Me, COMe, COF_3



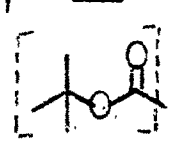
T-75

R-L-Ala-

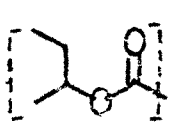


T-76

R = (L) Boc =

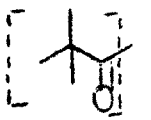


(S) Boc =

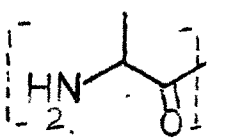


α-Cib =

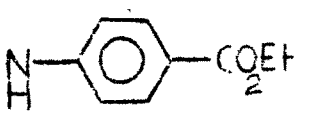
Piv =



Ala =

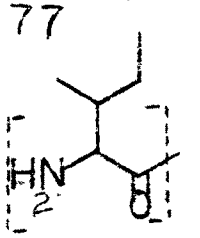


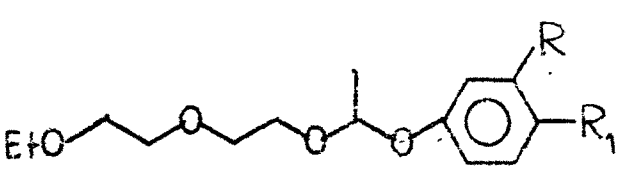
Piv-L-Ile-



T-77

Ile =





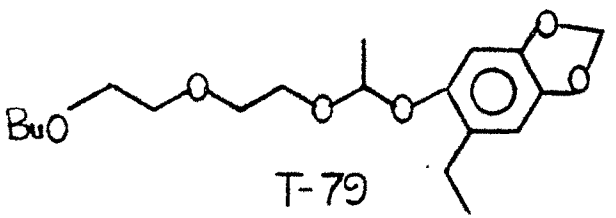
T-78

R= R_1= Cl

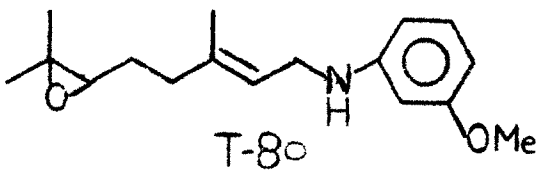
R= R_1= Me

R= H , R_1=Me

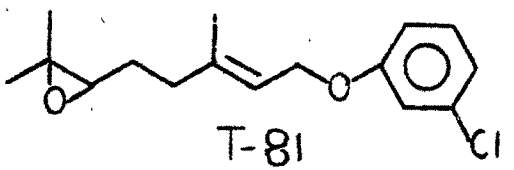
R =H, R_1= Br, SMe



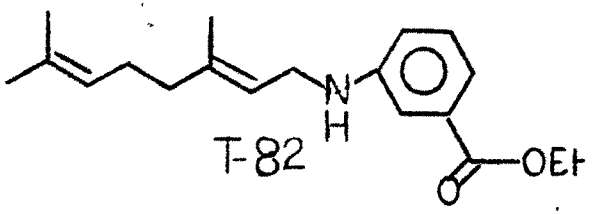
T-79



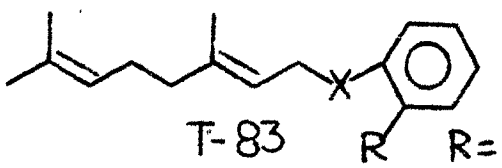
T-80



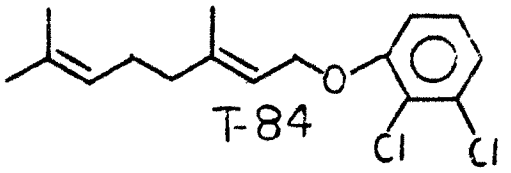
T-81



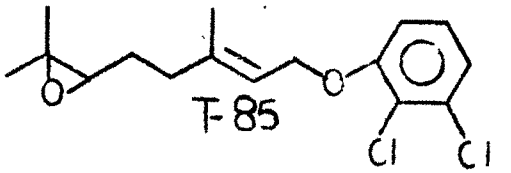
T-82



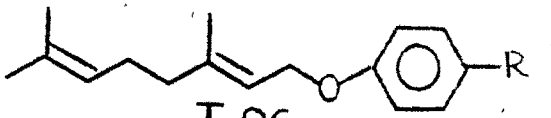
T-83 X = O, NH R = NO_2, CO_2Et



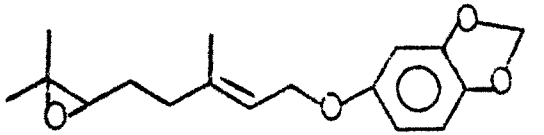
T-84



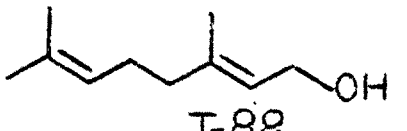
T-85



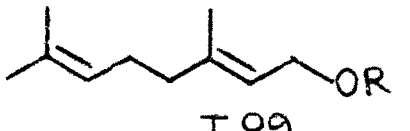
T-86 R = OH, CO_2H, Cl, CO_2Et, Br, NO_2, SMe



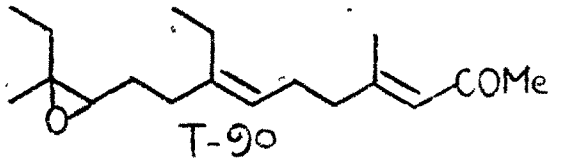
T-87



T-88



T-89 R = Me, Et



T-90

strictly dependent on the L-configuration of the central amino acid, but D-configuration led to the loss of activity.[30b,57] Thus, spatial arrangement of the peptidic chain and the considerable rigidity of the whole molecule appears to constitute one of the most important factors in determining the activity of peptidic JH-mimics.

BIOGENESIS

Two conceivable modes of biogenesis must be considered. One route involves simple homologation of a farnesol derivative utilizing methonine as outlined in Fig. 10. Such one-carbon transfer reactions are well-documented in fatty acid and steroid biogenesis.[58] This route also provides an attractive rationale for the stereochemistry of JH. The enzyme (or enzyme system) responsible for homologation of C-7 methyl most likely is the same (or atleast has the same stereochemical requirements) as the enzyme (or enzyme system) responsible for terminal methyl homologation. Thus, the terminal methyl group that bears a cis-relationshp to the aliphatic chain leading to the trans, trans,-cis-isomer should be involved since it occupies an environment similar to the C-7 methyl. This stereochemistry does represent that of the natural product. Isolation of the 10,11-epoxide corresponding to 4 (Fig. 10) from Hyalophora cecropia suggests the correctness of this scheme.

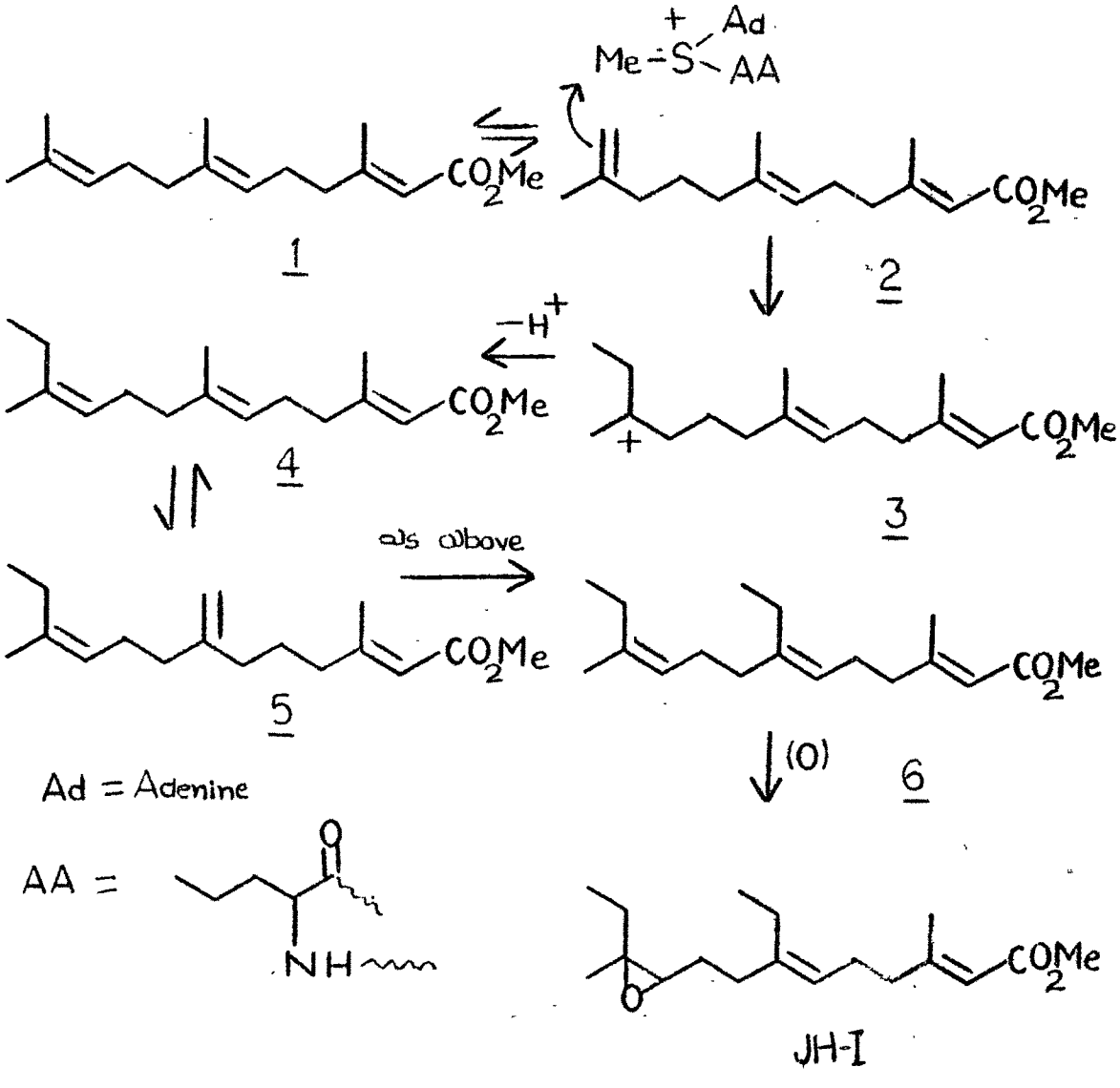
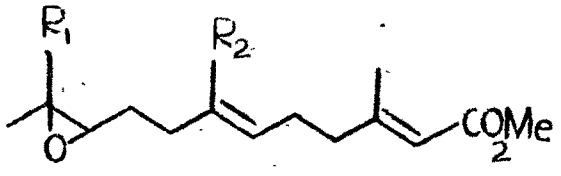


FIG. 10

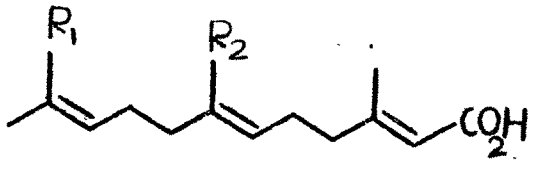
The more recent route involves a homomevalonate unit in biogenesis. Previous studies on three species of giant silk moths had revealed the occurance of two juvenile hormones JH-I and JH-II. A new hormone JH-III has now been reported in organ cultures of Corpora allata from Manduca sexta, where it co-occurs with JH-II.[60] This hormone JH-III may also be the major JH of Schistocerca vaga[61] and Schistocerca gregaria.[62] Radioactive acetate, mevalonate, and propionate are incorporated by organ cultures of Corpora allata from Menduca sexta into JH-II, whereas acetate and mevalonate, but not propionate, are incorporated into JH-III.[63] Following partial degradation of the product hormone JH-III, a possible biogenesis of JH was suggested (Fig. 12). When Corpora allata from Schistocerca gregaria were cultured with either [^{3}H]-trans,trans-farnesenic acid (IV) or [^{3}H]-trans,trans,cis-bishomofarnesenic acid (V) and [methyl-^{14}C]methionine, the corresponding doubly labelled methyl 10,11-epoxyesters, JH-III or JH-I were produced. Some indication was also obtained that esterification may precede expoxidation under the conditions employed. However, the epoxy acid (VI) was esterified, yielding JH-I, in another insect.[64] Some lack of enzyme substrate specificity is indicated by the preliminary identification of JH-III, as the only detectable JH in Schistocerca gregaria.[62] A cell free system of the corpous allatam - corpus cardiacum complex from Manduca sexta has been reported, which catalyses formation of labelled JHs from endogenous precursors and [methyl-^{3}H]-S-adenosyl-L-methionine.[65]



JH I : $R_1 = R_2 = Et$

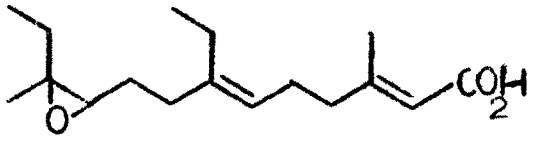
JH II : $R_1 = Et$, $R_2 = Me$

JH III : $R_1 = R_2 = Me$



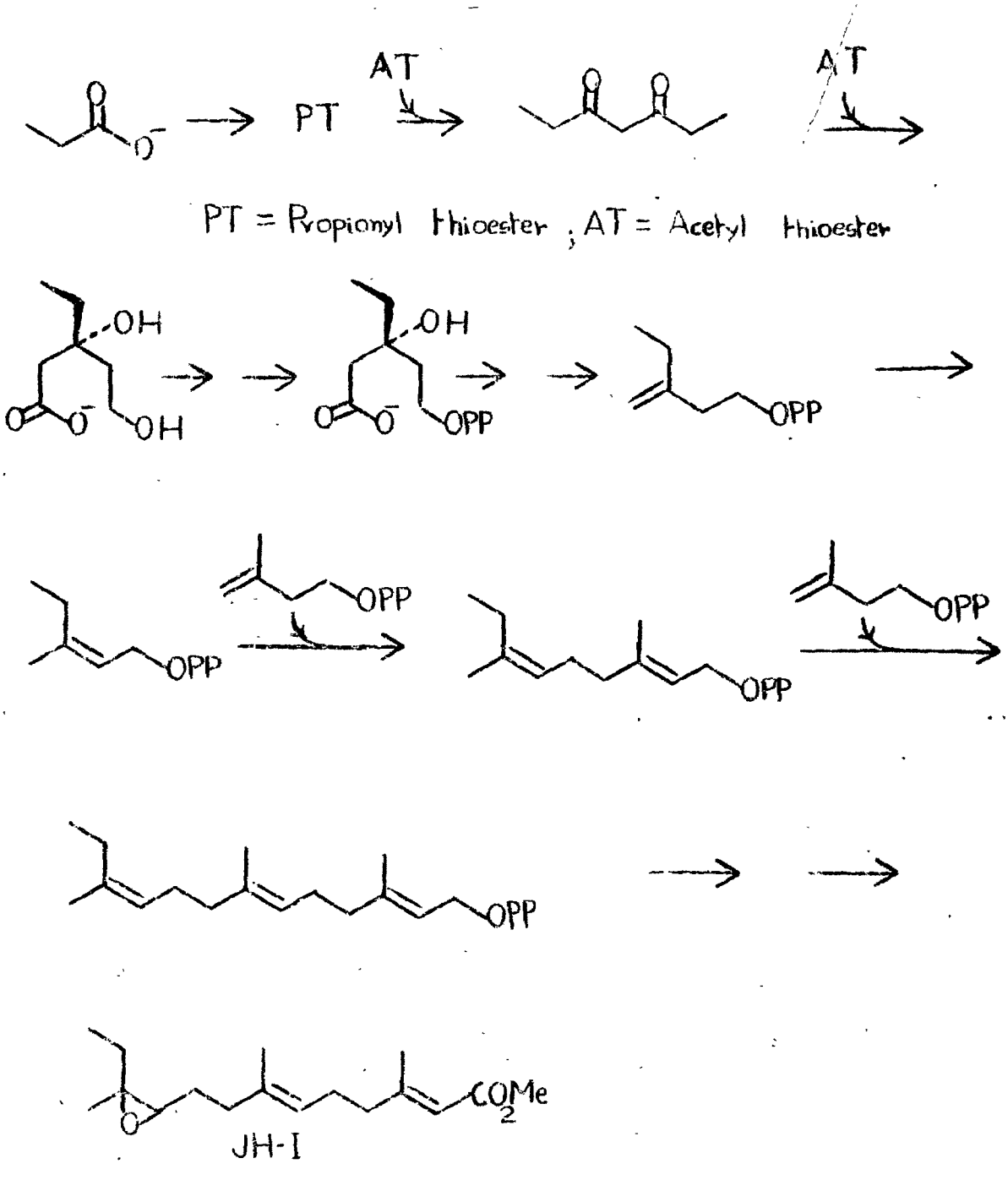
IV : $R_1 = R_2 = Me$

V : $R_1 = R_2 = Et$



VI

FIG. 11



Intermediate thioesters could be formed from either coenzyme A or an acyl-carrier protein

FIG. 12

The major metabolites of JH-I in many insects include the corresponding acid (VI), the acid-diol formed by hydration of the epoxide ring, and conjugated polar metabolites.[66] The substrate specificity[67] and developmental changes during development[68] of the insect JH-esterase activity has been reported. This enzyme activity has been suggested to be involved in control of the hormone titre.[68,69]

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