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The synthesis of insect juvenile hormones and their analogues

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ABSTRACT. **The methods of synthesis of insect juvenile hormones and their natural and synthetic analogues (juvenoids) are considered. Much attention is paid to juvenoids of the 2,4-dienoate class, including oxa and aza derivatives and cyclic and heterocyclic compounds, which display selective activity towards vairous forms of insect.**

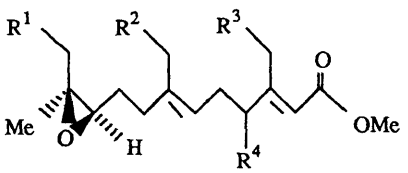
The bibliography contains 263 references.

Contents

I. Introduction 731
II. Synthesis of natural juvenile hormones 731
III. Synthesis of natural analogues of juvenile hormones 735
IV. Synthetic analogues of juvenile hormones 739

I. Introduction

It has been established in the last thirty years that certain terpenoid compounds, referred to as the juvenile hormones (JH), actively participate in the regulation of the development of insects at the larval stage.[1] Five native juvenile hormones have so far been isolated and identified, viz. JH-1, JH-II, JH-III, JH-0 and 4-Me-JH-I.[1–5]



JH-I ($R^1=R^2=Me$, $R^3=R^4=H$); JH-II ($R^1=Me$, $R^2=R^3=R^4=H$); JH-III ($R^1=R^2=R^3=R^4=H$); JH-O ($R^1=R^2=R^3=Me$, $R^4=H$); 4-Me-JH-I ($R^1=R^2=R^4=Me$, $R^3=H$).

The titre of JH in an insect at metamorphosis of the larva to the imago is close to zero. It was shown that the introduction of extraneous JH at this time seemingly affects the fate of a population due to disturbance of the natural cycle of insect development leading to a subsequent reduction in their number. This possible method of regulating the number of insects enables JH to be considered as insecticides of a new generation. They are ecologically safe and act exclusively upon Arthropods.

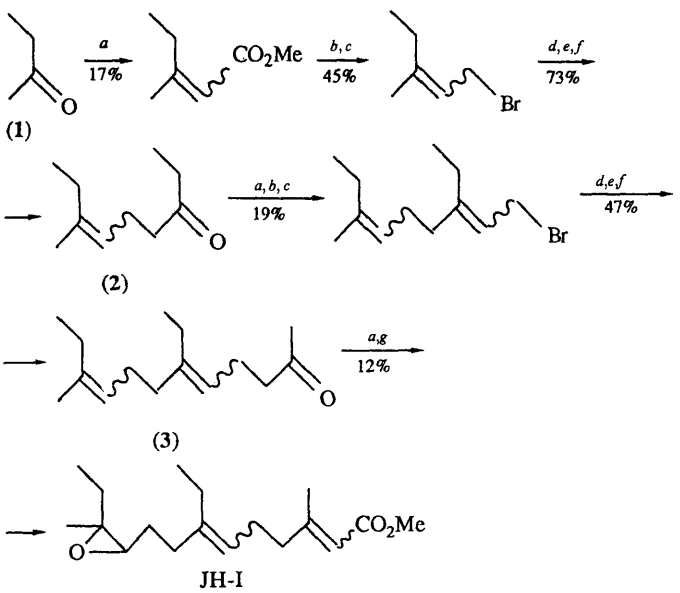
Since JH are present in insects in insignificantly small concentrations, their isolation from natural sources appears to be practically impossible and the only realistic route to obtain them is by chemical synthesis. The promise of the practical use of these regulators of insect development was marked by the discovery that JH action is possessed by certain natural compounds and by a whole series of synthetic compounds close in structure to the native JH. These analogues of the juvenile hormones (AJH) are known as juvenoids. Compounds have been discovered among the large number of AJH with JH activity significantly higher than that of the natural JH. Active juvenoids are found among compounds structurally close to the native JH and among compounds the structure of which only remotely suggests the structure of a JH.

Several monographs and reviews[6–16] have been devoted to the synthesis and study of the biological activity of JH and AJH. However they do not adequately reflect the information on the 2,4-dienoates, their oxa and aza derivatives and on the juvenoids containing hetero- and carbocycles. In addition, new reports of work in this area have recently appeared.

II. Synthesis of natural juvenile hormones

The phosphonate modification of the Wittig reaction, which is usually used to construct a trisubstituted double bond in the synthesis of JH, leads to a mixture of geometric isomers.[17,18] Thus the three-step condensation of trimethyl phosphonoacetate with the initial (**1**) and intermediate (**2**), (**3**) ketones gave JH as a mixture of (*Z*) and (*E*) isomers at the Δ^2 and Δ^6 bonds (Scheme 1).[19]

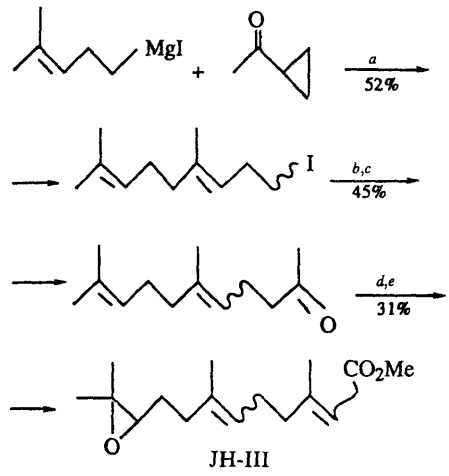
Scheme 1



a: $(MeO)_2P(O)CHCO_2Me$; *b*: $HAlH_4$; *c*: PBr_3; *d*: Mg; *e*: $MeCH_2COCH_2CO_2Et$; *f*: Δ; *g*: 3-$ClC_6H_4CO_3H$

A similar result was obtained in the synthesis of JH-III (Scheme 2).[20]

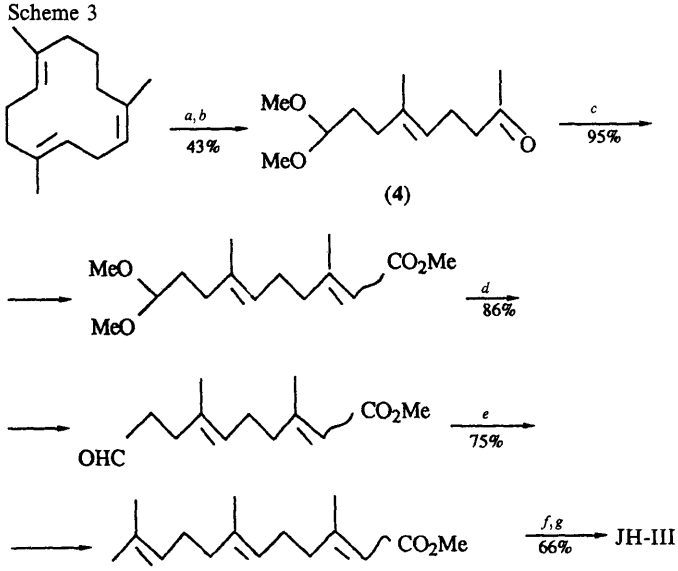
Scheme 2



a: H^+; *b*: Mg/Et_2O; *c*: Ac_2O, −70 °C; *d*: $(MeO)_2P(O)\overset{\ominus}{C}HCO_2Me$; *e*: NBS (*N*-bromosuccinimide)/K_2CO_3.

A mixture of geometric isomers at the Δ^2 bond is formed in the synthesis of JH-III via the selective ozonolysis of (1*E*, 5*E*, 9*E*)-trimethyl-1,5,9-cyclododecatriene and the Petersen reaction with the intermediate ketone (**4**) (Scheme 3).[21]

Scheme 3

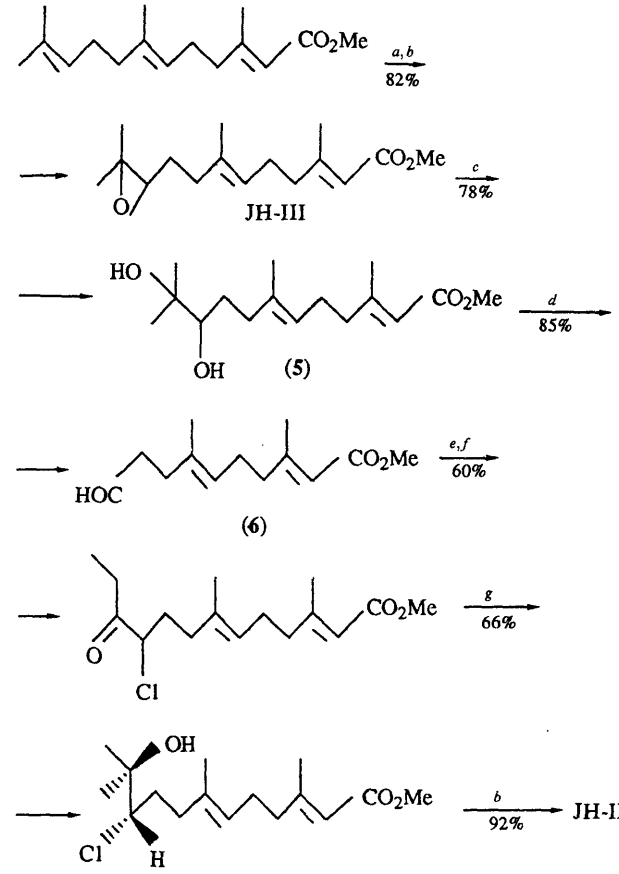


a: O_3/MeOH; *b*: MeOH/NH_4Cl; *c*: $Me_3SiCH_2CO_2Me$/iso-Pr_2NH; *d*: Py.TsOH/Me_2CO; *e*: $Me_2C{=}PPh_3$; *f*: NBS/THF; *g*: K_2CO_3/MeOH.

The individual (2*E*, 6*E*) isomers, which usually display higher activity than the other isomers,[22] were isolated by column chromatography.

Stereospecific syntheses of JH-II have been carried out from (*E*,*E*)-farnesol, methyl (*E*)-geranoate and methyl (*E*,*E*)-farnesenate [methyl (2*E*, 6*E*, 10*E*)-3,7,11-trimethyl-2,6,10-dodecanoate].[18,23] The epoxidation according to Van Tamelen[24] of the terminal double bond in methyl farnesenate gave JH-III. Subsequent opening of the epoxide to the glycol (**5**) and decomposition of the latter with sodium periodate led to the aldehyde (**6**), converted subsequently into the desired JH-II (Scheme 4).[18]

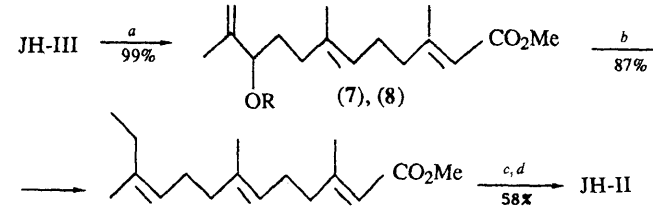
Scheme 4



a: NBS, *b*: K_2CO_3/MeOH; *c*: $HClO_4$; *d*: HIO_4; *b*: $MeCH_2C(OMe){=}PPh_3$; *f*: NCS(*N*-chlorosuccinimide); *g*: MeMgI.

It was established that on distillation JH-III is converted in high yield into the allyl alcohol (**7**), the acetate of which (**8**) is alkylated by lithium dimethylcuprate with the formation of JH-II (Scheme 5).[18,25]

Scheme 5



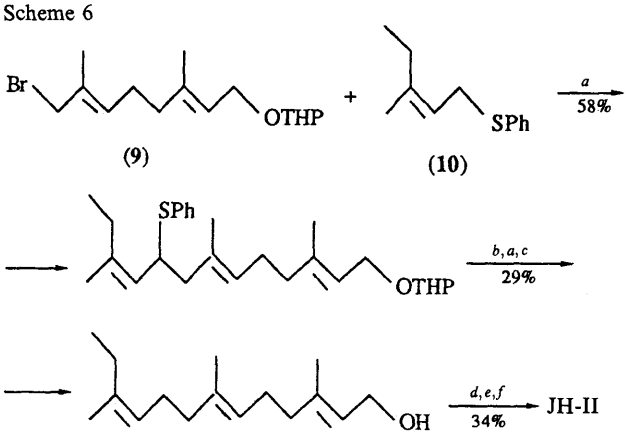
R = H(7), Ac(8).
a: Δ; *b*: Me_2CuLi; *c*: NBS; *d*: K_2CO_3/MeOH.

The syntheses of JH through alkylation of allyl substrates and the *syn*-addition of cuprates and organoaluminium reagents to acetylenes have been discussed in a review.[12] Much attention was paid in the

review to the stereospecific construction of trisubstituted alkenes using sulphur-containing intermediates in the synthesis of JH.

The key stage in one of the syntheses of racemic JH-II is the coupling of the allyl bromide (**9**) with the deprotonated allyl phenyl sulphide (**10**) (Scheme 6).[26,27]

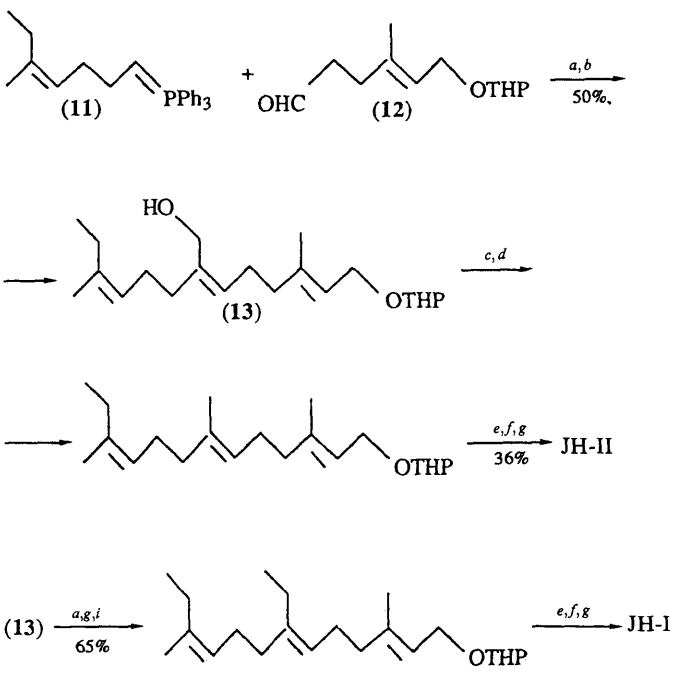
Scheme 6



THP – 2-tetrahydropyran-1-yl; *a*: n-BuLi; *b*: TsOH/MeOH; *c*: Li; *d*: MnO_2; *e*: MnO_2/NaCN/MeOH; *f*: 3-$ClC_6H_4CO_3H$.

Deprotonation of the intermediate in the reaction of phosphorane (**11**) with the aldehyde (**12**) and subsequent treatment with formaldehyde led to compound (**13**) the subsequent transformation of which gave the desired JH-II and JH-I (Scheme 7).[28]

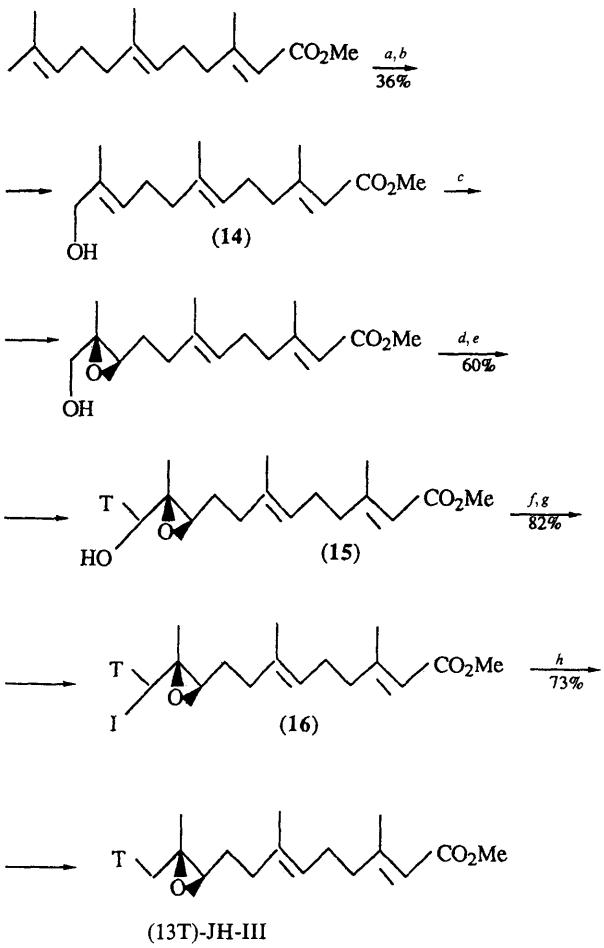
Scheme 7



a: n-BuLi; *b*: CH_2O; *c*: TsCl/Py; *d*: $LiAlH_4$; *e*: MnO_2; *f*: MnO_2/NaCN/MeOH; *g*: 3-$ClC_6H_4CO_3H$; *h*: $CH_2=PPh_3$; *i*: H_2O_2/EtOH/NH_2NH_2.

In 1970 it had already been established that the optically active natural JH have the (10*R*, 11*S*) configuration.[29] Subsequent investigations showed that the synthetic (+) enantiomers corresponding to that configuration displayed higher biological activity than the racemates.[30] One of the synthetic approaches to optically active JH is based on the Sharpless asymmetric epoxidation of allyl alcohols.[31,32] The synthesis of (10*R*, 11*S*)-JH-III containing tritium at C(13) is effected by the allylic oxidation of methyl farnesenate at the terminal position with subsequent asymmetric epoxidation of the resulting allyl alcohol (**14**). The tritiated hydroxy-epoxide (**15**) was deoxygenated via the iodide (**16**) to [13-T]-JH-III (Scheme 8).[33]

Scheme 8

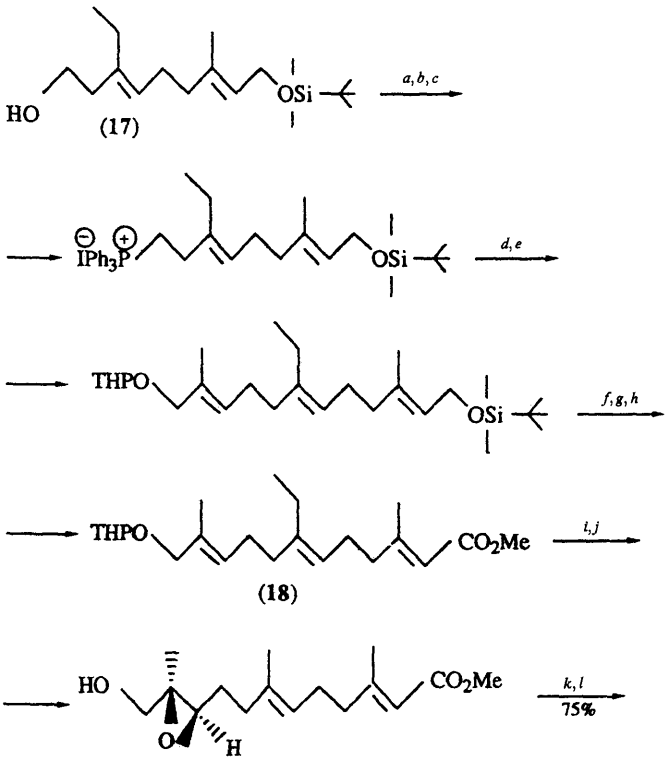


a: BuOOH/SeO_2; *b*: $NaBH_4$; *c*: (iso-PrO)$_4$Ti/t-BuOOH/iso-C_3H_7.OOCCH(OH)CH(OH).$COOC_3H_7$-iso; *d*: CrO_3/Py; *e*: $NaBT_4$; *f*: TsCl/Py; *g*: NaI/Me_2CO; *h*: $NaBH_3CN$.

The asymmetric epoxidation of the triene (**18**) also served as a key stage in the synthesis of optically active (10*R*, 11*S*)-JH-I from the homoallyl alcohol (**17**). Further transformations not affecting the chiral centre led to the (10*R*, 11*S*) enantiomer identical to the

natural JH or to its (12-D, 13-D) analogue.[34] The products obtained had high optical activity (95%) (Scheme 9).

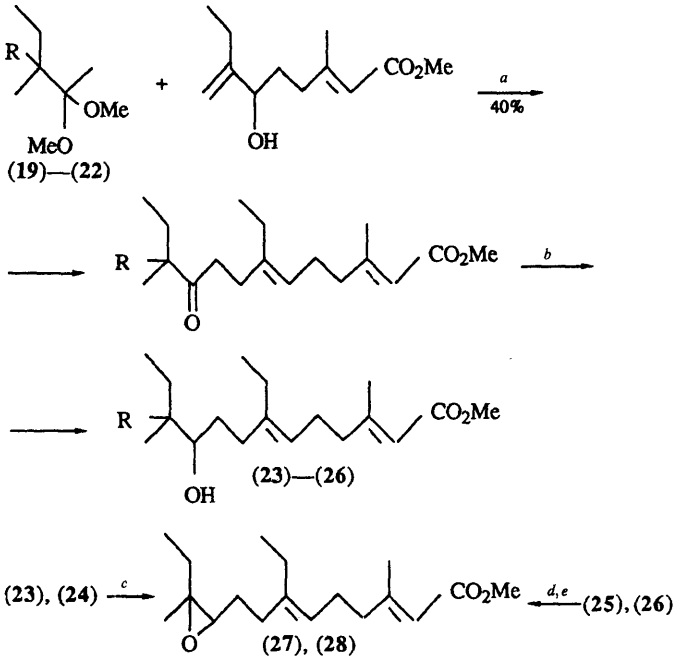
Scheme 9



a: TsCl/Py; *b*: NaI; *c*: Ph_3P; *d*: BuLi; *e*: $MeC(O)CH_2OTHP$; *f*: Bu_4NF; *g*: MnO_2; *h*: $MnO_2-NaCN-MeOH$; *i*: TsOH.Py.MeOH; *j*: t-BuOOH – CH_2Cl_2 – $Ti(OPr\text{-}iso)_4$ – $C_2H_5OOCCH(OH)CH(OH).COOC_2H_5$; *k*: CrO_3/Py; *l*: $Ph_3P=CH_2$; *m*: H_2 or D_2/$Rh(Ph_3P)_3Cl$.

Stereospecific syntheses of the (10*R*,11*S*) (**27**) and (10*R*,11*S*) (**28**) enantiomers of JH-I were effected from the optically active 2,2-dimethoxy-3-methylpentan-3-ols (**19**), (**20**) and 3-chloro-2,2-dimethoxy-3-methylpentanes (**21**) and (**22**). The optical purity of the JH obtained in these syntheses was 80–90% (Scheme 10).[35,36]

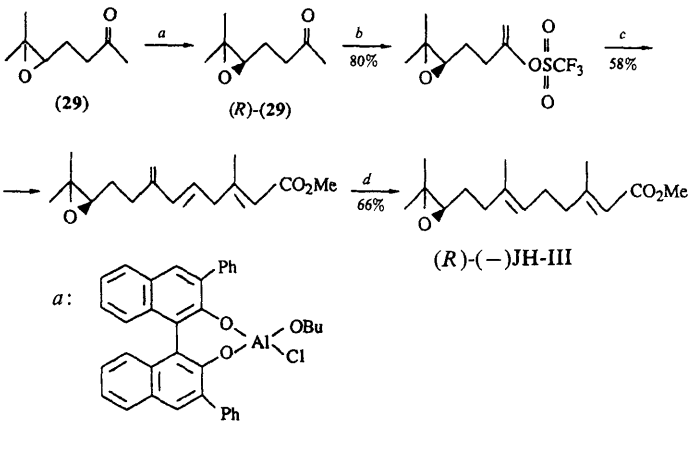
Scheme (10)



R = OH[(*R*)-(**19**), (*S*)-(**20**), (*R*,*R*)-(**23**), (*S*,*S*)-(**24**), (*R*,*S*)-(**27**)]; Cl[(*R*)-(**21**), (*S*)-(**22**), (*R*,*R*)-(**25**), (*S*,*S*)-(**26**), (*S*,*R*)-(**28**)].
a: Δ; *b*: $NaBH_4$; *c*: K_2CO_3/MeOH; *d*: TsCl/Py; *e*: MeONa/MeOH.

Kinetic resolution was used in the reaction of the racemic epoxide (**29**) with the optically active organoaluminium reagent in the synthesis of optically active JH-III.[37] Subsequent conversions of the chiral epoxide (*R*)-(**29**) led to (*R*)-(−)-JH-III (Scheme 11).[37]

Scheme 11



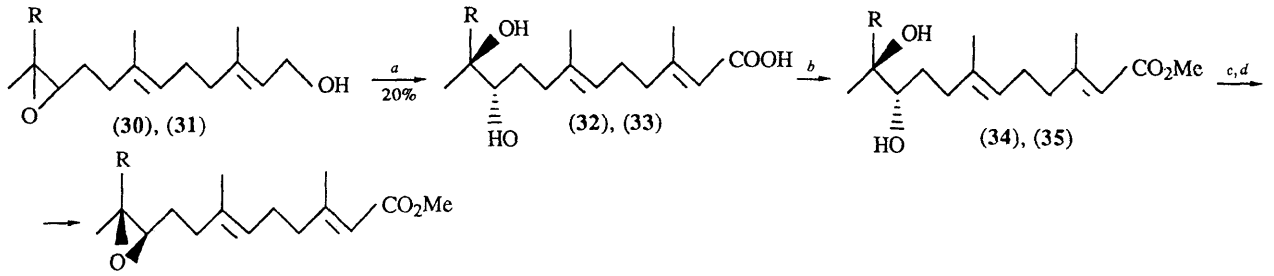
Enzymic reactions were used in the synthesis of optically active JH. Racemic 10,11-epoxyfarnesol (**30**) was converted by the action of a fungal culture of *Helminthosporium sativum* into (−)-*threo*-10,11-dihydroxyfarnesenic acid (**32**) which was then converted further into (10*R*)-JH-III through the ester (**34**).[38] Optically active (10*R*,11*S*)-JH-II was obtained similarly from homofarnesol (**31**) through the intermediates (**33**) and (**35**) (Scheme 12).[39]

The optically active (*R*)-diol (**34**) [containing < 5% (*S*)-isomer] was obtained from methyl farnesenate by treating it with the mould *Colletotrichum nicotianae*.[30] However the yield of the desired compound was low. It was more successful to synthesise enantiomerically pure JH-O, I, II, III from the chiral blocks (**38**) and (**39**) obtained by reduction of the diketones (**36**) and (**37**) with baker's yeast (*Pichia terricola*). The chiral ketones (**38**) and (**39**) were converted in eight steps into the corresponding phenylthio derivatives (**40**) and (**41**) by Baeyer-Villiger oxidation and subsequent ring opening. Further transformations of (**40**) and (**41**) led to enantiomerically pure JH (Scheme 13).[40–42]

III. Synthesis of natural analogues of juvenile hormones

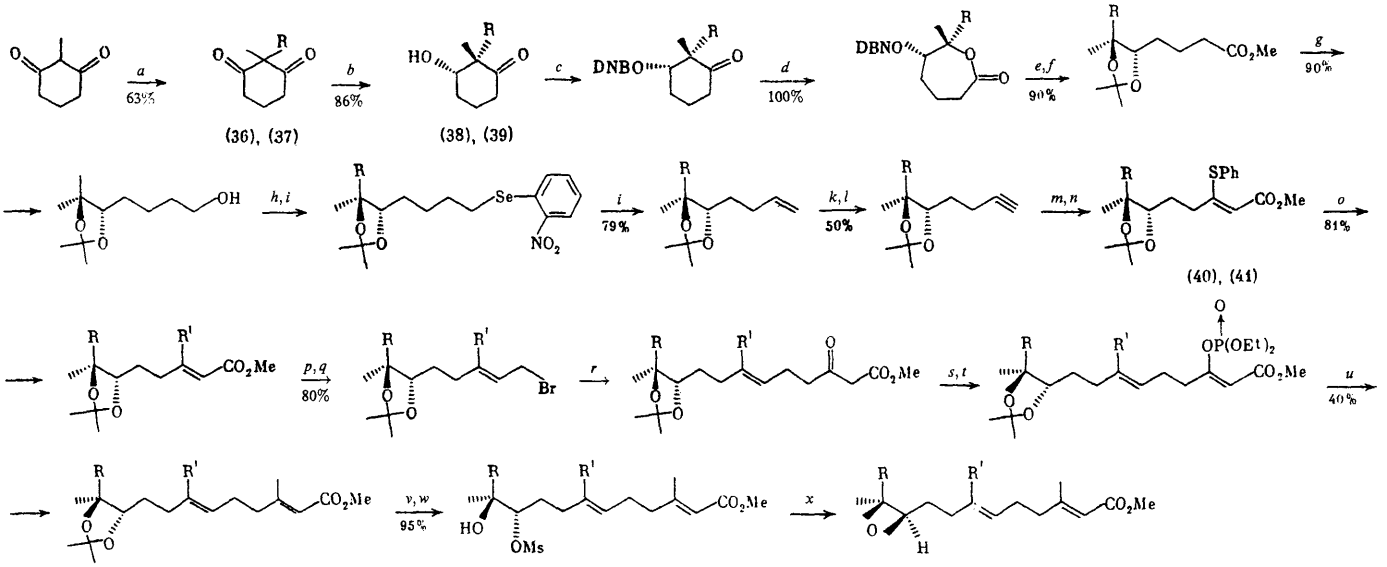
In 1975 an optically active compound was isolated from the North American rudbeckia (*Echinacea angustifolia*) which displayed juvenoid activity in relation to the yellow meal worm (*Tenebrio molitor*). This compound, called echinolone, was identified as (+)-(*E*)-10-hydroxy-4,10-dimethyl-4,11-dodecadien-2-one (**42**).[43]

Scheme 12



R = Me[(10*R*)-JH-II]; Et[(10*R*, 11*S*)-JH-II];
R = Me(**30**), (**32**), (**34**); Et(**31**), (**33**), (**35**);
a: Helm, sativum; *b*: CH_2N_2; *c*: MsCl/Py; *d*: KOH/MeOH.

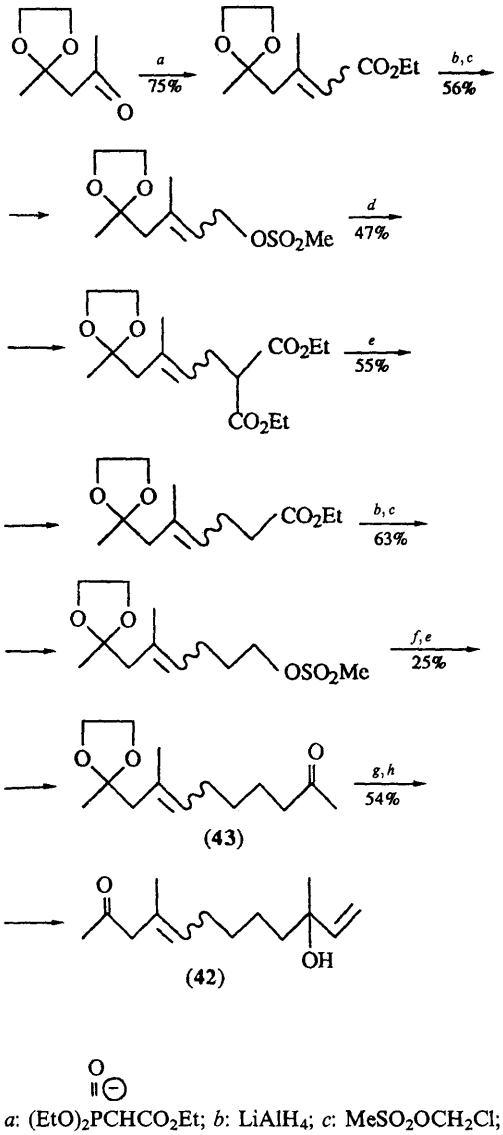
Scheme 13



DNB = 3,5-dinitrobenzoyl;
a: Rl/trilon B; *b*: Pichia tericola; *c*: DNB-Cl; *d*: $3\text{-}ClC_6H_4CO_3H/CH_2Cl_2$; *e*: K_2CO_3/MeOH; *f*: $Me_2C(ONe)_2$/TsOH; *g*: $LiAlH_4$; *h*: $o\text{-}(NO_2)C_6H_4SeCN$; *i*: $(n\text{-}Bu)_2P$; *j*: H_2O_2; *k*: Br_2; *l*: NaH_2/NH_2; *m*: $ClCO_2Me$/n-BuLi; *n*: PhSNa/MeOH; *o*: R^1MgBr/CuI/THF, −65 °C; *p*: $(iso\text{-}C_4H_9)_2AlH$; *q*: MeLi/TsCl/LiCl/HMPA; *r*: $MeCOC.HCO_2Me$; *s*: NaH; *t*: $(EtO)_2POCl$; *u*: MeCuLi; *v*: AcOH; *w*: $MsCl/Et_3N$; *x*: MeONa/MeOH.

Racemic echinolone is synthesised by a sequential build-up from the carbon skeleton of acetylacetone to the diketone monoacetal (**43**) using the Horner double bond reaction. The reaction of the ketoacetal (**43**) with vinylmagnesium bromide led to the desired (+)-echinolone as a mixture of geometric isomers (Scheme 14).[44]

Scheme 14

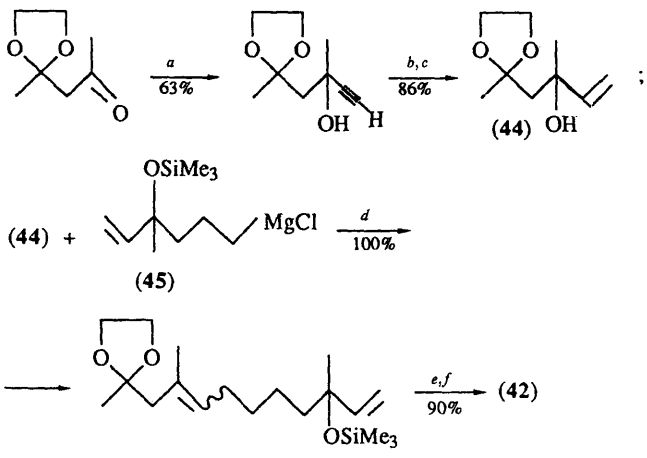


a: $(EtO)_2PCHCO_2Et$; *b*: $LiAlH_4$; *c*: $MeSO_2OCH_2Cl$; *d*: $CH_2(CO_2Et)_2$/NaH; *e*: Δ; *f*: $MeC(O)CH_2CO_2Et$/NaH; *g*: $CH_2=CHMgBr$; *h*: $H^{\oplus}$.

Another synthesis of a mixture (4:1) of the (*E*) and (*Z*) isomers of echinolone (**42**) was convergent with the key stage being the coupling of the two C_7 fragments (**44**) and (**45**).[45] The individual isomers were isolated by HPLC. It is interesting to note that the mixture of geometric isomers of echinolone proved to be more active than each of the individual isomers (Scheme 15).[45]

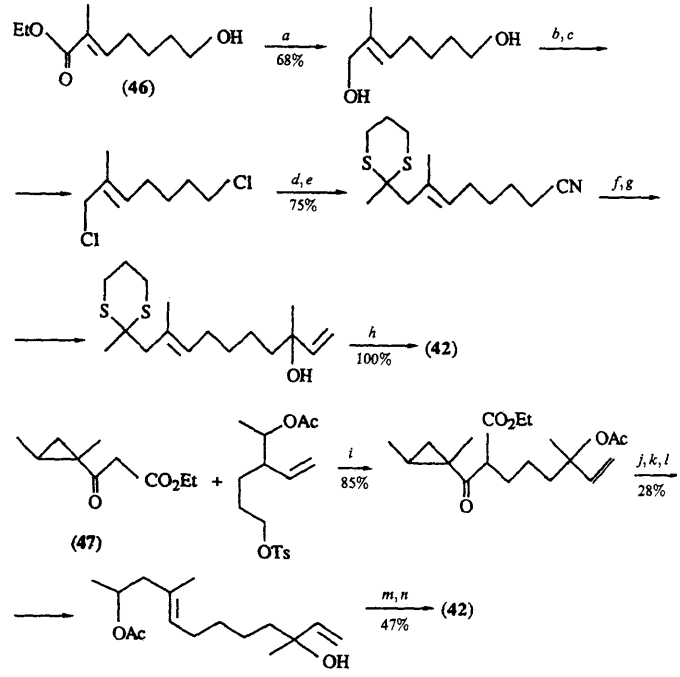
Schemes have been described for the synthesis of echinolone (**42**) from the unsaturated hydroxy-ester (**46**)[46] and from the ketoester (**47**) containing a cyclopropane fragment (Scheme 16).[47]

Scheme 15



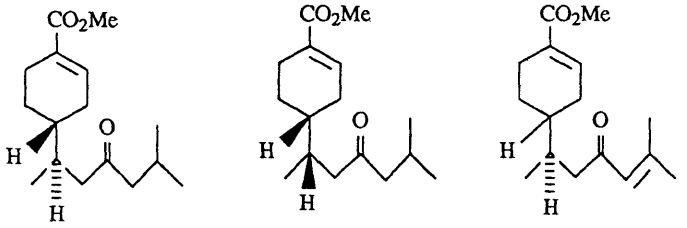
a: $CH\equiv CH/NH_3/KOH$; *b*: Ac_2O; *c*: Pd/ZnO; *d*: CuI/THF; *e*: HPLC; *f*: $H^{\oplus}$.

Scheme 16



a: $Na(OMe)_2(OEt)AlH$; *b*: $MeSO_2Cl/LiCl$; *c*: $Alk_4N^{\oplus}Cl^{\ominus}$; *d*: Me–C–Me (S S); *e*: NaCN; *f*: MeLi; *g*: $CH_2=CHMgBr$; *h*: $HgCl_2/CaCO_3$; *i*: NaH; *j*: $Ba(OH)_2$; *k*: $LiAlH_4$; *l*: HOAc; *m*: K_2CO_3 *n*: $CrO_3/Py/CH_2Cl_2$.

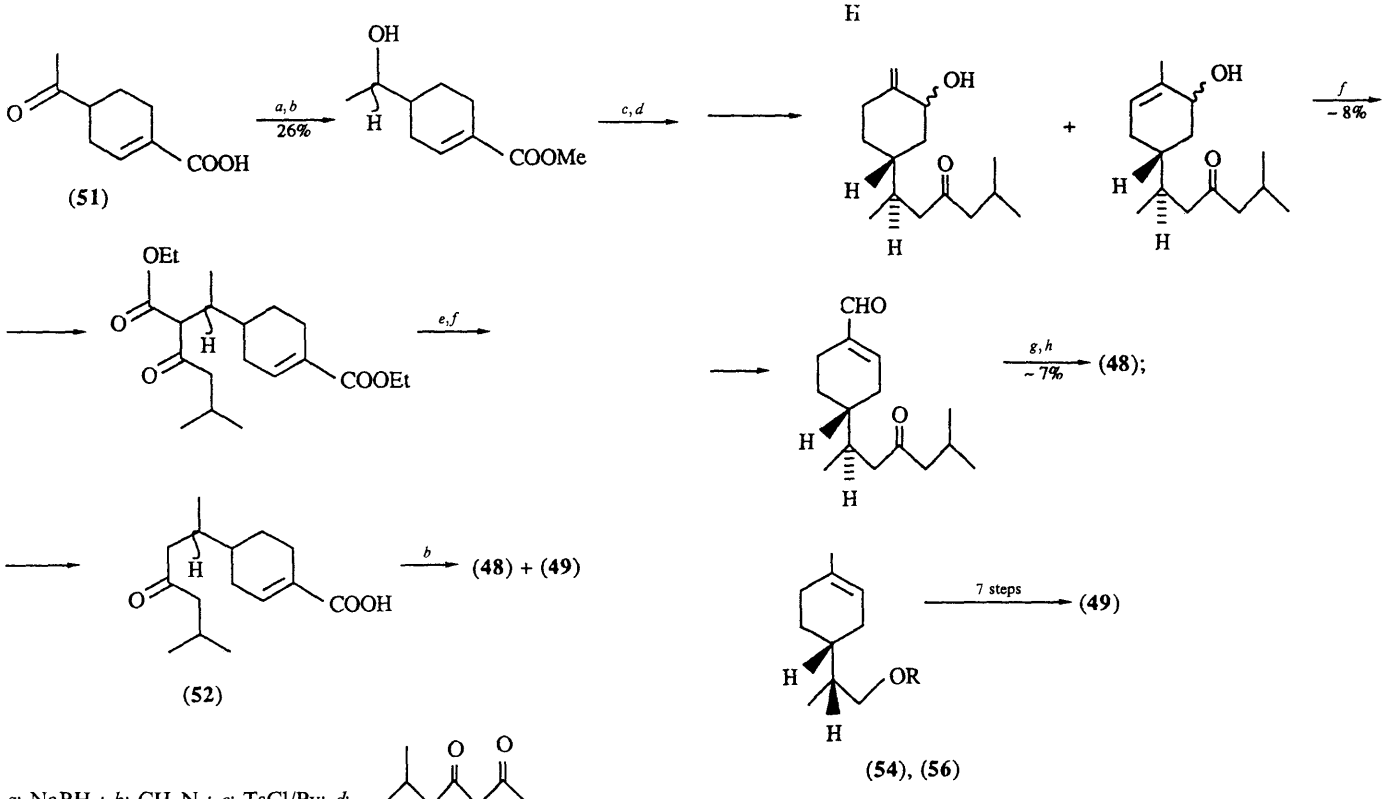
In 1965 Slama and Williams[48] discovered that paper from the wood of the balsam fir (*Abies balsamea*) possessed a JH action. The structure of the active compound proved to be identical to the methyl ester of (+)-todomatuic acid (**48**) with the (*R,R*) configuration at the asymmetric centres.[49,50] The new AJH was called juvabione. A compound of similar structure but with the (*R,S*) configuration was discovered in certain plants and was called epijuvabione (**49**).[51–53] One further active analogue, dehydrojuvabione (**50**), was isolated, together with (+)-juvabione, from Slovak fir.[54]



(**48**) (**49**) (**50**)

The shortest of the non-stereospecific routes proposed for synthesising a mixture of juvabione (**48**) and epijuvabione (**49**)[55–58] is that based on conversions of the methyl ester of 4-acetylcyclohexene-1-carboxylic acid (**51**) (Scheme 17).[58]

Scheme 17



a: $NaBH_4$; *b*: CH_2N_2; *c*: TsCl/Py; *d*:

e: KOH/EtOH; *f*: Δ.

The individual epimers (**48**) and (**49**) were obtained by crystallisation of the semicarbazones of the corresponding ketoacids with subsequent esterification.[59,60]

A stereospecific synthesis of the individual (*R,R*)-(**48**) and (*R,S*)-(**49**) diastereomers of juvabione was achieved from the (*R,R*) (**53**) and (*R,S*) (**54**) alcohols, the optical activity of which was increased by fractional crystallisation of their 3,5-dinitrobenzoates (**55**) and (**56**) (Scheme 18).[61]

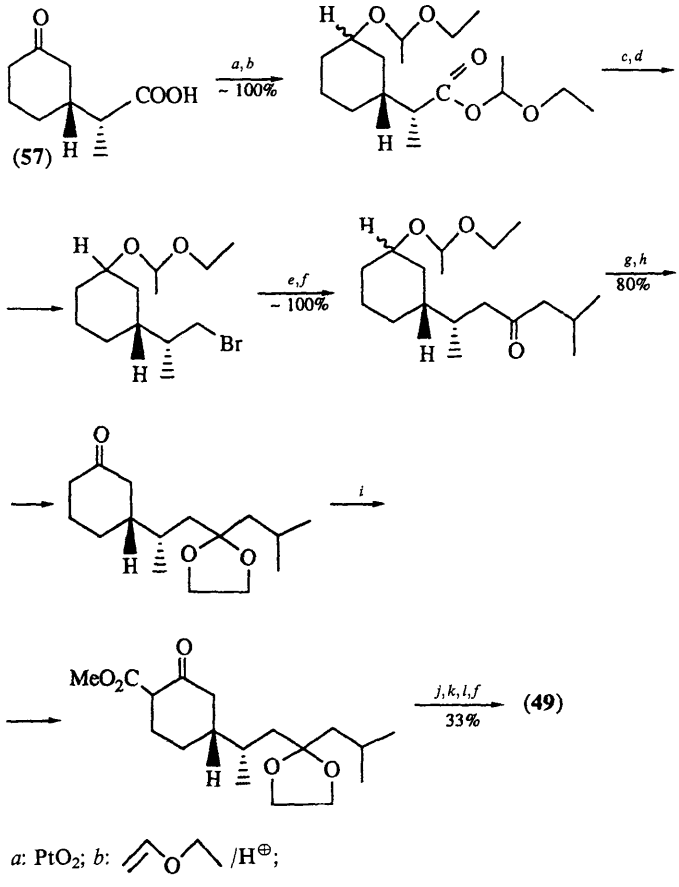
Scheme 18

R = H(**53**), (**54**), DNB (**55**), (**56**)

a: TsCl/Py; *b*: NaCN/DMSO; *c*: $(Me)_2CHCH_2Li$; *d*: $H_3O^{\oplus}$; *e*: $O_2/h\nu$; *f*: $Na_2Cr_2O_7/H_2SO_4$/HOAc; *g*: $AgNO_3$; *h*: CH_2N_2.

Two of the stereocontrolled syntheses lead to epijuvabione (**49**).[62,63] In one of them the optically active acid (**57**) serves as starting material (Scheme 19).[62]

Scheme 19

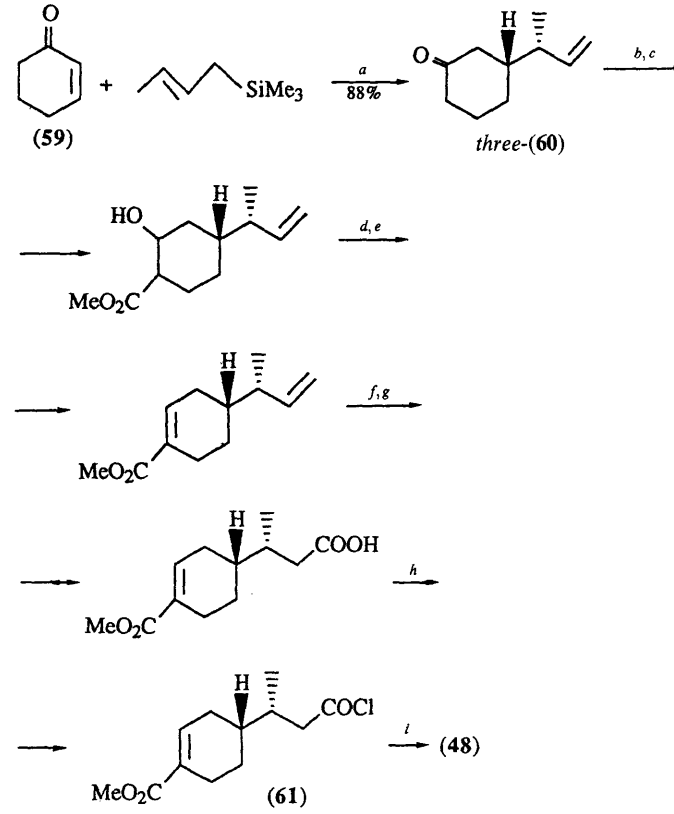


a: PtO_2; *b*: /$H^{\oplus}$; *c*: $LiAlH_4$; *d*: PBr_3; *e*: $(Me)_2CH(CH_2)_2CH(CN)(OH)^{\ominus}$; *f*: $H_3^{\oplus}O$; *g*: $(CH_2OH)_2/H^{\oplus}$; *h*: H_2CrO_4/Py; *i*: $(MeO)_2CO$/NaH; *j*: $NaBH_4$; *k*: TsCl/Py; *l*: MeONa/MeOH.

Another approach is based on a [3,3] sigmatropic rearrangement applied to the diastereomeric mixture (**58**) with the (*R*) configuration at one of the asymmetric carbon atoms (Scheme 20).[63]

The synthesis[64] of juvabione (**48**) is based on the stereoselective condensation of the enone (**59**) with (*trans*-2-butenyl)trimethylsilane in the presence of $TiCl_4$ leading to the product (**60**) of *threo* configuration, the methoxycarbonylation of which and subsequent transformation through the acid chloride (**61**) gave juvabione (**48**) (Scheme 21).

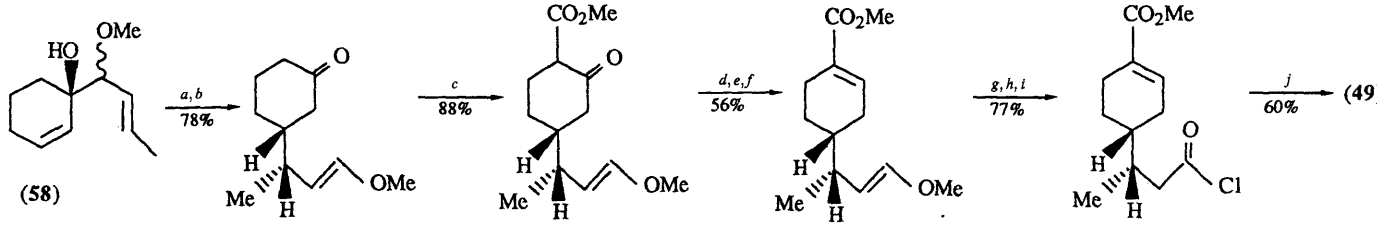
Scheme 21



a: $TiCl_4/CH_2Cl_2$; *b*: $(MeO)_2CO$/NaH; *c*: $NaBH_4$; *d*: MsCl; *e*: NaOH/MeOH; *f*: $(C_6H_{11})_2BH$/THF; *g*: CrO_3/H_2SO_4; *h*: $(COCl)_2$; *i*: $MeCHCH_2MgBr/Fe(acac)_2$.

The aromatic analogues corresponding to juvabione and epijuvabione have been isolated from natural sources. These are *ar*-juvabiones (**62**) and (**63**) which possess high JH activity.[65]

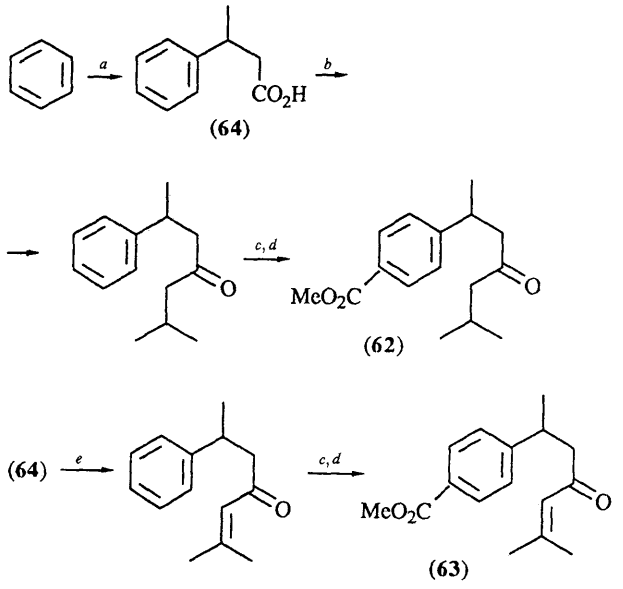
Scheme 20



a: KH, 110 °C; *b*: TLC; *c*: $(MeO)_2CO$/NaH; *d*: $NaBH_4$; *e*: MsCl; *f*: NaOMe/MeOH; *g*: $H^{\oplus}$; *h*: CrO_3/Me_2CO; *i*: $(COCl)_2$; *j*: $(iso\text{-}Bu)_2Cd$.

3-Phenylbutanoic acid (**64**) served as the key synthon in the synthesis of racemic (**62**) and (**63**) (Scheme 22).[66,67]

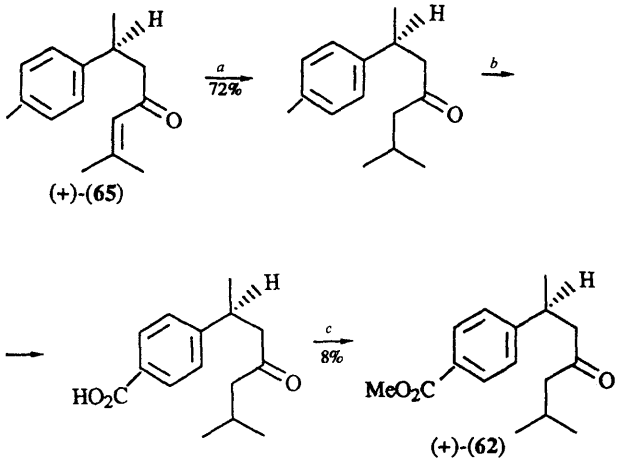
Scheme 22



a: MeHC=CHCOOH; *b*: Me_2CHCH_2Li; *c*: $(COCl)_2/AlCl_3$; *d*: MeOH; *e*: $Me_2C=CHLi$.

(+)-*ar*-Turmerone (**65**) was used for the synthesis of optically active (+)-*ar*-juvabione (**62**) (Scheme 23).[55]

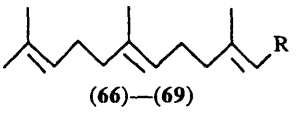
Scheme 23



a: H_2IPd-C; *b*: $CrO_3/AcOH$; *c*: MeOH/KOH/Me.

IV. Synthetic analogues of juvenile hormones

It was discovered in 1961[68] that farnesol (**66**) and farnesal (**67**) possess high juvenoid activity, comparable with that of the natural JH, but the methyl ester (**68**) and the diethylamide (**69**) of farnesenic acid proved to be even more active.[69–71]



(66)—(69)

R = CH_2OH (**66**), CHO (**67**), CO_2Me (**68**), $CONEt_2$ (**69**) .

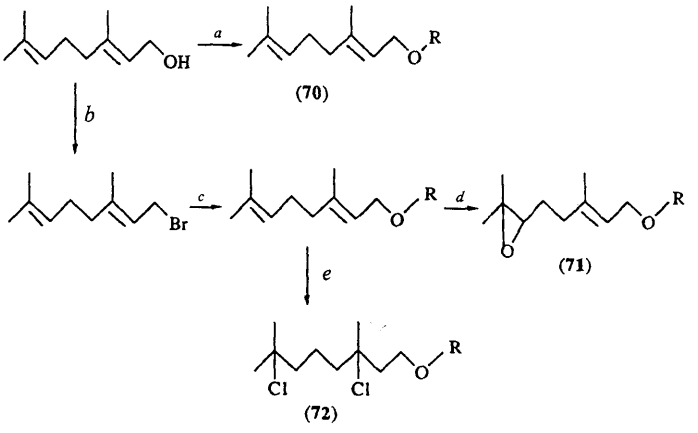
Intensive investigations then followed which were directed towards the search for active AJH and their synthesis. Several types of juvenoids emerged as a result of a widespread search. Highly active AJH were found chiefly among acyclic compounds with isoprenoid fragments in the chains, including derivatives of farnesenic acid and geraniol ethers. The most active juvenoids appeared among the esters of isoprenoid 2,4-dienoic acids (the 2,4-dienoates). Juvenoids of selective action were discovered among aliphatic compounds containing a heteroatom or a cyclic fragment in the carbon chain.

1. Acyclic juvenoids

a) Geraniol derivatives

When investigating the biological activity of alkyl ethers of geraniol (**70**), and of the epoxy (**71**) and dichloro (**72**) derivatives[72–74] in relation to the red cotton stainer bug (*Dysdercus koenigii*), it became apparent that the length of the alkyl chain (R) had considerable importance (the optimum was from four to six carbon atoms). Branching in the radical R causes a small increase in biological activity. Epoxydation of the terminal double bond in the geraniol portion of the molecule [compounds of the (**71**) series] reduces the juvenoid activity (Scheme 24).

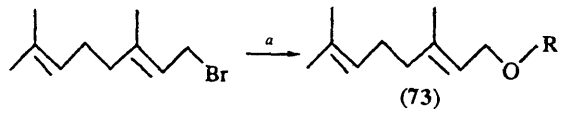
Scheme 24



R = n-Bu, CH_2CHMe_2, $(CH_2)_4Me$, $(CH_2)_2CHMe_2$, $CH_2CH=CMe_2$; *a*: $RBr/OH^{\ominus}$; *b*: PBr_3; *c*: RONa; *d*: $3\text{-}ClC_6H_4CO_3H$; *e*: HCl.

The most active were compounds with a total of 14–18 carbon atoms.[73] The geranyl ethers (**73**) or (**74**) were synthesised by the reaction of geranyl bromide with alcohols or geraniol with alkyl bromides in the presence of alkali (Scheme 25).[75–77]

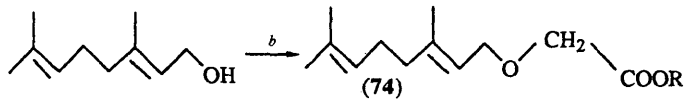
Scheme 25



(**73**)

R = $(CH_2)_2OMe$, $(CH_2)_2OCH_2Me$,

$(CH_2)_2O(CH_2)_2Me$, CH_2–CH(–)–OCH_2

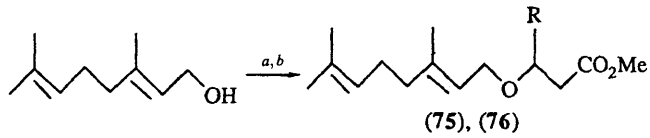


(**74**)

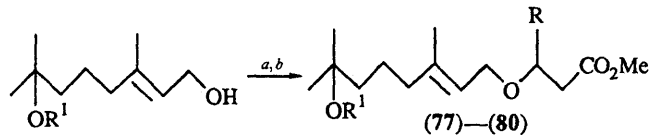
R = Me, Et, Pr, iso-Pr; *a*: $ROH/OH^{\ominus}$; *b*: $BrCH_2COOR/OH^{\ominus}$.

Catalytic addition of geraniol or of its 7-alkoxy derivatives to the activated double bond of methyl crotonate[74] or methyl 2-pentenoate[78,79] was used for the synthesis of compounds (**75**)–(**80**) (Scheme 26). It was noted that the introduction of methoxyl and ethoxyl groups at the terminal position of these compounds increases their JH activity.

Scheme 26



(**75**), (**76**)



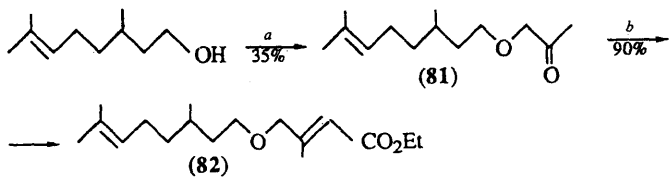
(**77**)—(**80**)

R = Me(**75**), (**77**), (**79**); Et (**76**), (**78**), (**80**);
R^1 = Me (**77**), (**80**); Et (**78**), (**79**);

a: R–CH=CH–$CO_2Me/OH^{\ominus}$; *b*: MeOH/TsOH.

An interesting approach to the synthesis of such a series of AJH is the olefination of compound (**81**), itself obtained by the reaction of citronellol with a diazoketone.[80–82] The ether (**82**), for example, was synthesised in this way (Scheme 27).

Scheme 27



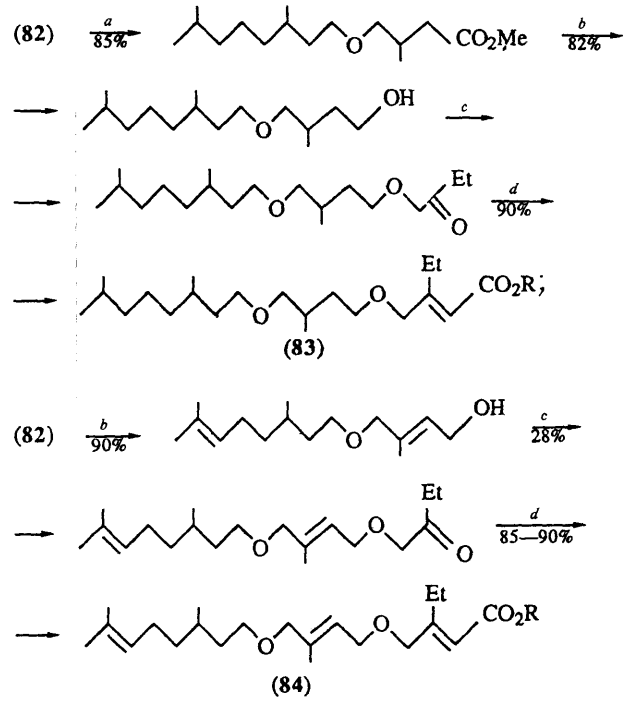
(**81**)

(**82**)

a: $MeC(O)CH_2N_2/BF_3$; *b*: $Ph_3P=CH_2CO_2Et$.

Transformations analogous to those carried out for compound (**82**) led to the ethers (**83**)[83–86] and (**84**)[84–86] with an oxygen atom in the alkyl chain of the citronellol derivative (Scheme 28).

Scheme 28

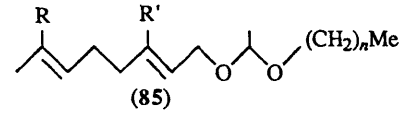


(**83**)

(**84**)

R = Me, Et, iso-Pr;
a: $H_2/Pd-C$; *b*: $LiAlH_4$; *c*: $EtC(O)CH_2N_2/BF_3$;
d: $Ph_3P=CHCO_2R$.

Some compounds of this series display a selective action. Compounds of the (**85**) series proved to be effective juvenoids in relation to the Mexican pea beetle.[87]



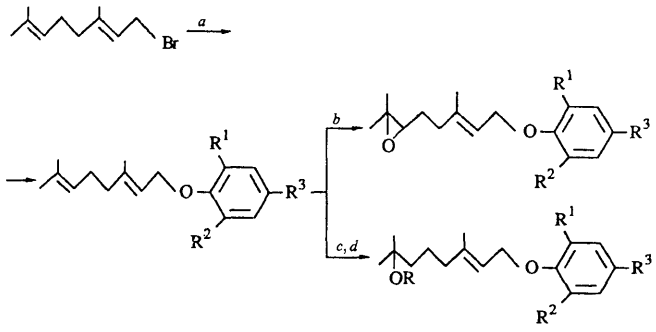
(**85**)

R, R' = Me, Et; *n* = 0, 1.

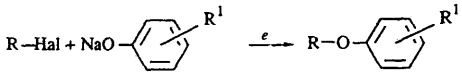
Juvenoids with a high morphogenetic effect were discovered in a series of phenyl ethers of geraniol and also their 6,7-epoxy, 7-hydroxy and 7-alkoxy derivatives.[9] The greatest effect on juvenoid activity was shown by substituents in the 4 and 2 positions of the phenyl group and also by hydroxyl and methoxyl groups in the 7 position of the chain.[88–110] Some of these compounds, containing for example ethyl, propyl and cyclopropyl groups in the 4 position of the phenyl ring, proved to be 100 or more times more active than the alkyl ethers of geraniol in relation to *Tenebrio molitor*, *Culex pipiens* and *Aedes aegypti*.[88,90,92,93,95] The greatest activity among

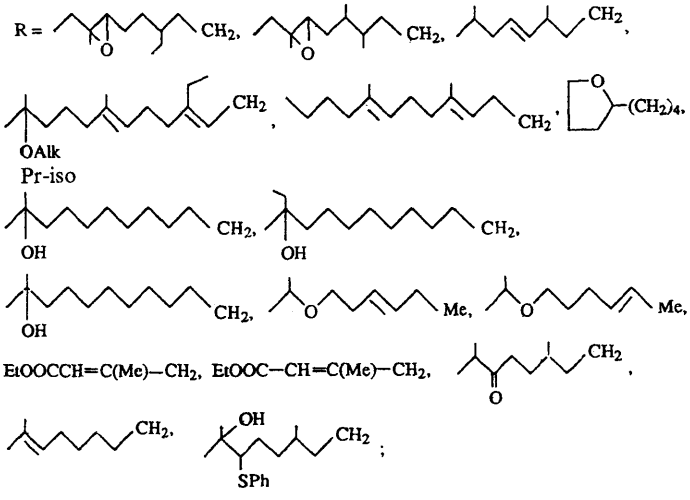
the 7-hydroxy and 7-methoxy derivatives is displayed by compounds with ring ethoxy and propoxy groups (Scheme 29).[88,93]

Scheme 29



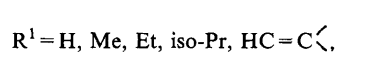
R = H, Me, Et, Pr, iso-Pr, CH_2Ph; R^1 = H, Me, iso-Pr, Cl, OMe; R^2 = H, Cl, NO_2; R^3 = H, Et, Pr, iso-Pr, CH_2-CH (O), CH(OH)Et, EtC = =NOH, CHO, MeCO, EtCO, OMe, SMe, NO_2, Cl;



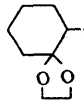
R = 

OAlk

Pr-iso

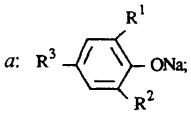


R^1 = H, Me, Et, iso-Pr, HC≡C,



CH_2, OMe, OCH(Me)(Et), CHO, C(O)Et,

F, Cl, Br, NO_2;

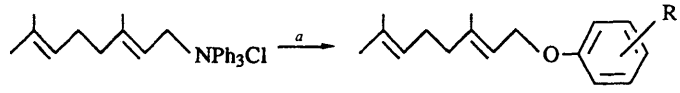


a: R^3, ONa; R^1, R^2

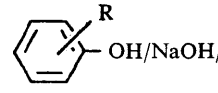
b: 3-$ClC_6H_4CO_3H$; *c*: $Hg(OAc)_2$;
d: $NaBH_4$/ROH; *e*: KOH/DMF.

The method proposed for obtaining the phenyl ethers of geraniol is the reaction of the appropriate alkali metal phenoxide with geranyltriphenylammonium chloride (Scheme 30).[111,112]

Scheme 30

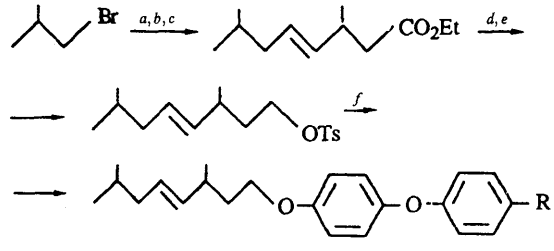


R = 3-Me, 4-Me, 4-Et, 3,4-Me_2, 4-iso-Pr, 2-iso-Pr, 5-Me, 2-OMe, 3-OMe, 4-NO_2, 4-Cl;

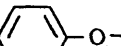
a: 

Juvenoid activity is increased significantly for the phenoxyphenyl ethers (Scheme 31).[113]

Scheme 31



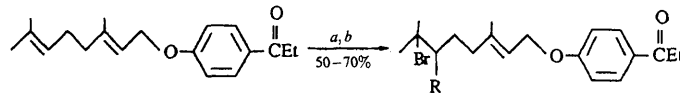
R = Bu, NO_2;

a: Mg; *b*: ; *c*: $MeC(OEt)_3$; *d*: $LiAlH_4$; *e*: TsCl/Py;

f:

The introduction of a halogen atom, a hydroxy or an alkoxy group into the terpene portion of the molecule did not change significantly the biological activity of the initial geraniol ether (Scheme 32).[114]

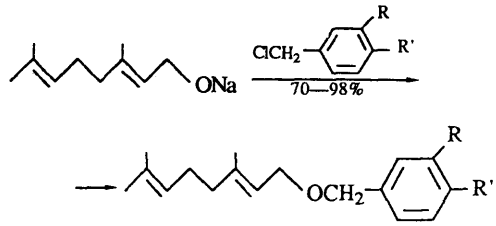
Scheme 32



R = OH, OMe, iso-Pr;
a: NBS; *b*: ROH.

Benzyl ethers of geraniol proved to be less active than phenyl ethers (Scheme 33).[115,116]

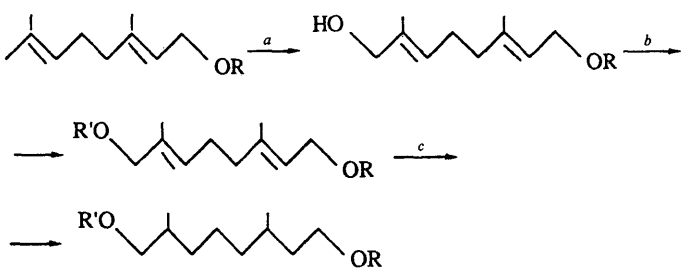
Scheme 33



R = H, OH, Cl; R' = H, CMe_3, OMe, OEt, SMe, SEt, Cl, Br.

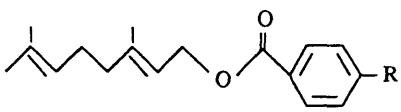
The diethers of (2*E*, 6*E*)-3,7-dimethyl-2,6-octadiene-1,8-diol and their tetrahydro derivatives shows high activity in relation to mosquitoes and the red cotton stainer bug (Scheme 34).[117]

Scheme 34



R = Me, Et, Ph, Bz, 4-MeC_6H_4; R′ = Me, Et, Ph, 4-ClPh, Bz, 4-MeC_6H_4; *a*: SeO_2; *b*: R′Hal – NaH; *c*: H_2/PtO_2 – Et.

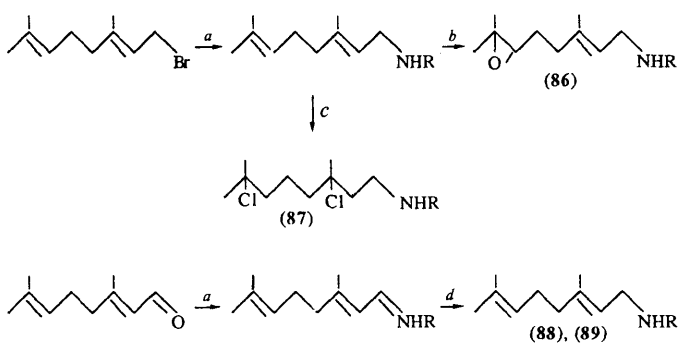
The geranyl esters of 4-substituted benzoic acids display high activity.[118]



R = OMe, Cl, NO_2.

The derivatives of geranylamine (**86**)–(**89**) have been investigated as potential juvenoids. However they proved to be less active than the corresponding oxygen-containing analogues (Scheme 35).[73,119]

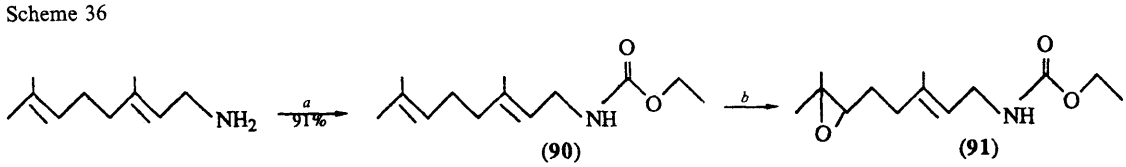
Scheme 35



R = C_nH_{2n+1} (n = 1 to 9) (**86**), (**87**); 4-$(EtO_2C)C_6H_4$ (**88**), 4-(HO_2C).C_6H_4 (**89**);
a: RNH_2; *b*: 3-$ClC_6H_4CO_3H$; *c*: HCl; *d*: KBH_4.

On the other hand the geranyl derivatives of carbamic acid (**90**) and (**91**), obtained by the reaction of ethyl chloroformate with geranylamine,[120] display high juvenoid activity in relation to the yellow meal worm (*Tenebrio molitor*) (Scheme 36).[120]

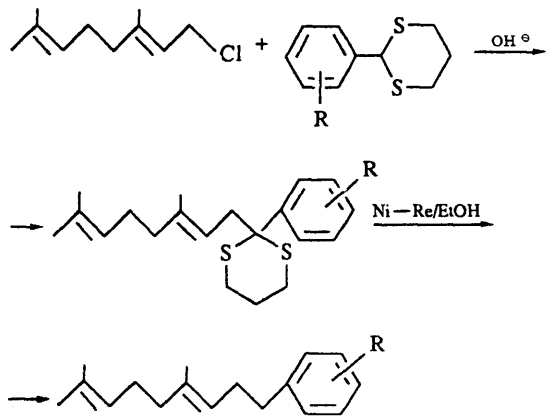
Scheme 36



a: $ClCO_2Et$; *b*: 3-$ClC_6H_4CO_3H$.

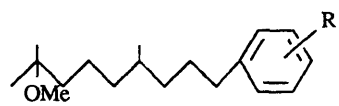
The reaction of geranyl chloride with dithiianes of substituted benzaldehydes and subsequent reduction of the dithiiane group gave geranyl benzyl derivatives (Scheme 37).[121]

Scheme 37



R = 3-Br, 4-Br, 4-F, 4,5-Cl_2, 4-CN, 4-CO_2Et, 4-NMe_2.

The methoxy substituted tetrahydro derivatives of the series (**92**)–(**94**) display high juvenoid activity against the house-fly.[122] Compound (**94**) proved to be the most active.

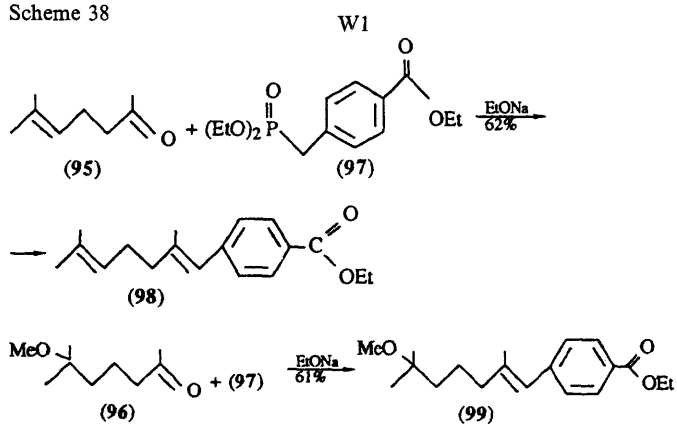


(**92**)—(**94**)

R = Et (**92**), Pr (**93**), iso-Pr (**94**).

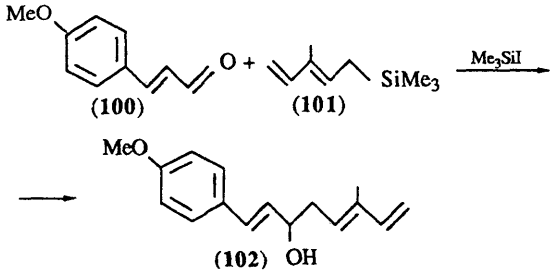
Compounds (**98**) and (**99**), obtained from ketones (**95**) and (**96**) and the phosphonate (**97**), display selective JH activity in relation to *Diptera* (Scheme 38).[123]

Scheme 38



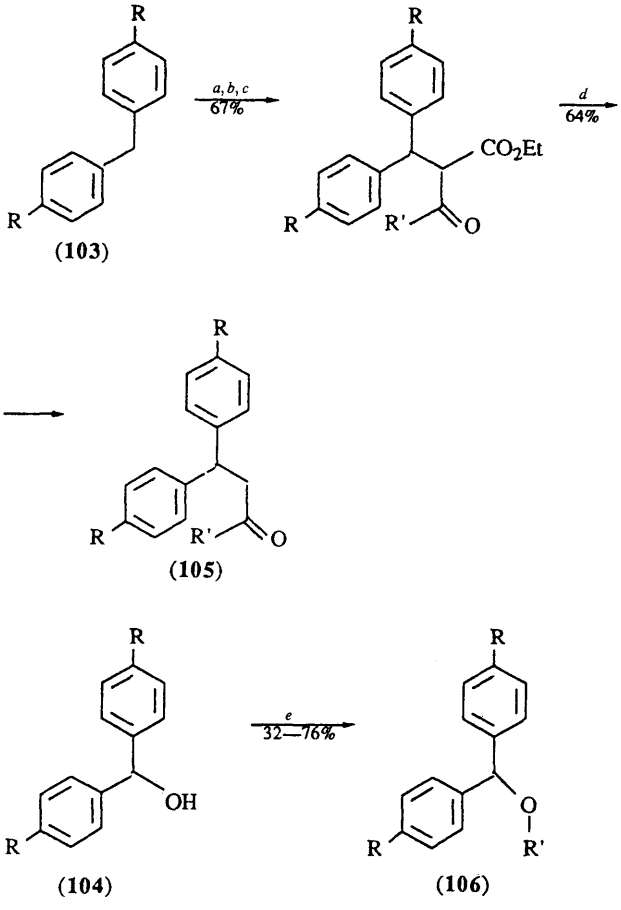
The product (**102**) from the reaction of 4-methoxycinnamaldehyde (**100**) and the allylsilane (**101**) shows juvenoid activity (Scheme 39).[124]

Scheme 39



The activity of the substituted diarylmethanes (**105**) and (**106**), synthesised[12] from the symmetrical diphenylmethanes (**103**) and (**104**), depends on the length of the alkyl chain R'. Compounds with eight carbon atoms in the side chain have the highest JH activity (Scheme 40).

Scheme 40

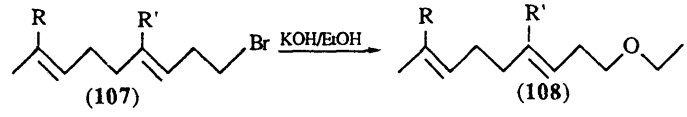


R = Cl, CO_2Me; R' = Me, Et, iso-Pr, iso-Bu, $COCCl_3$, $COCH_2CHMe_2$, $Me_2C{=}CH(CH_2)_2CH(Me)(CH_2)_2$;
a: NBS; *b*: R'CCH_2CO_2Et (R'C(=O)CH_2CO_2Et); *c*: K_2CO_3/DMF; *d*: NaCl–DMSO;
e: R'X/Py.

b) Oxa and aza derivatives

The interesting results obtained for geranyl ethers stimulated the search for active JH analogues in other compounds of the ether type referred to as oxa analogues of JH in the literature.[16] The oxa-AJH (**108**) were synthesised from the homologues of geranyl bromide (**107**) (Scheme 41).[126]

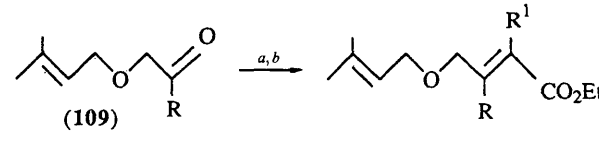
Scheme 41



R, R' = Me, Et, Pr.

However, compounds containing a Δ^2-double bond conjugated with the ester group were more promising. Compounds of this class with oxygen at various positions in the chain were synthesised. The 5-oxa analogues of JH were obtained, for example, by the Reformatsky reaction from the ketoethers (**109**) and α-haloacids with subsequent dehydration of the resulting β-hydroxyesters (Scheme 42).[127]

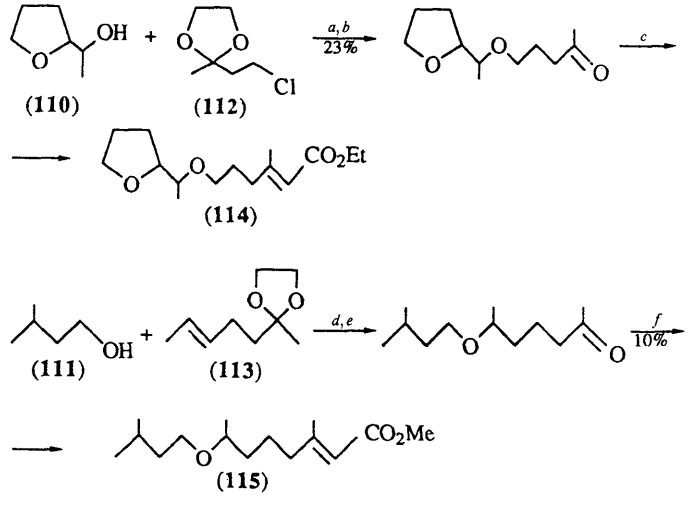
Scheme 42



R, R^1 = Me, Et, Pr;
a: $R^1CH_2(Br)COOEt$; *b*: $POCl_3$.

Compounds (**114**) and (**115**) were obtained by the reaction of the alcohols (**110**) and (**111**) with the acetals (**112**) and (**113**) respectively with subsequent Horner olefination (Scheme 43).[128,129]

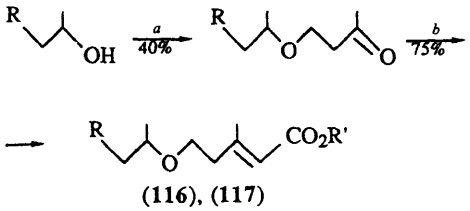
Scheme 43



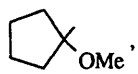
a: NaOH; *b*: H_3O^+; *c*: $(EtO)_2P(O)CHCO_2Et$; *d*: $NaBH_4$; *e*: TsOH;
f: $(MeO)_2P(O)CHCO_2Me$.

The key step in the synthesis of esters of the 6-oxa derivatives of (2*E*)-3,7-dimethyl-2-alkenoic acids (**116**) and (**117**) is the addition, catalysed by mercuric oxide and boron trifluoride etherate, of alcohols to methyl vinyl ketone with subsequent Horner olefination of the resulting ketones (Scheme 44).[130,131]

Scheme 44



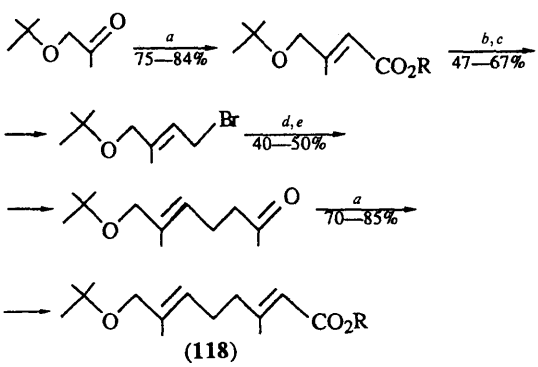
(**116**), (**117**)

(**116**): R = , R' = Me; (**117**): R = , R' = Et;

a: , $HgO/BF_3.Et_2O$; *b*: $(EtO)_2P(O)CHCO_2R'$.

9-Oxa derivatives of (2*E*,6*E*)-2,6-undecadienoic acid (**118**) have been synthesised using two olefination stages (Scheme 45).[132,133]

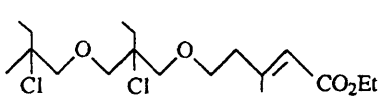
Scheme 45



(**118**)

R = Me, Et, iso-Pr;
a: $Ph_3P{=}CH_2CO_2R$; *b*: $LiAlH_4$; *c*: PBr_3; *d*: MeC(O)CH(Na)CO_2Et; *e*: Δ.

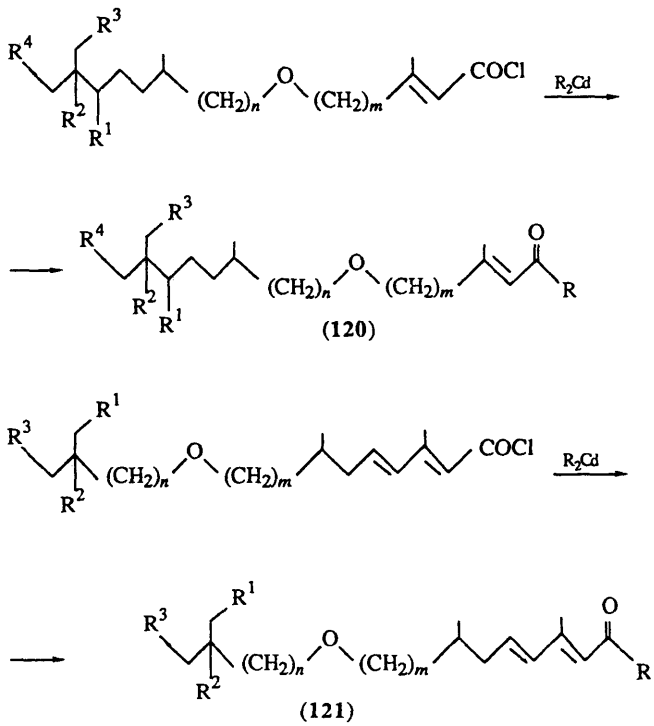
The juvenoid activity of compounds (**114**)–(**118**) proved to be less than that of the corresponding deoxy derivatives.[134] However some oxa derivatives show a selective action on particular species. Thus the ethyl ester of (2*E*)-8,12-dichloro-8-ethyl-12-methyl-6,10-dioxa-2-tetradecenoic acid (**119**) is an effective juvenoid in relation to *Dysdercus cingulatus*. The dose of compound enabling 50% intermediate forms to develop under standard conditions (specimens with part-larva part-pupa features) (UD_{50}) was 0.06 μg per specimen.[84]



(**119**)

Several mono- (**120**) and dienoketones (**121**) containing an oxygen atom in the main chain show high juvenoid activity towards the yellow meal worm, the domestic fly and *Eurygaster integriceps*.[135,136] These compounds were obtained by the reaction of the acid chlorides of the appropriate carboxylic acids with organocadmium compounds (Scheme 46).

Scheme 46



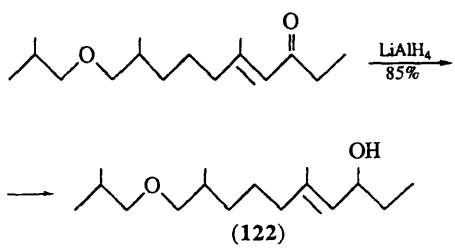
(**120**)

(**121**)

R, R^1, R^2, R^3, R^4 = H, Me, Et, Pr; m = 1,2; n = 0,1.

The oxa compound (**122**), obtained by reduction of the corresponding α,β-unsaturated ketone, displays high JH activity on the same insect species (Scheme 47).[137]

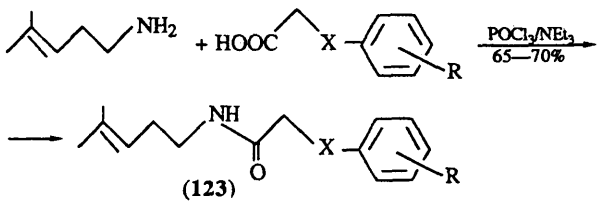
Scheme 47



(**122**)

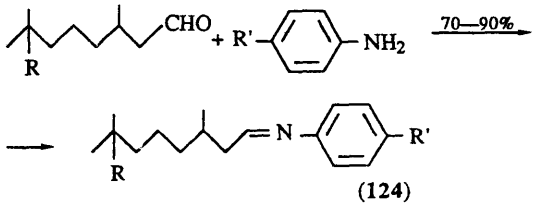
It was discovered that compounds (**123**)–(**128**), containing a nitrogen atom in the chain, display low juvenoid activity (Scheme 48).[138–140]

Scheme 48



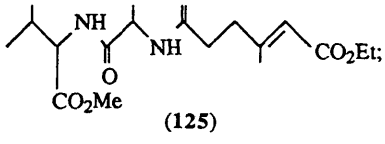
(**123**)

X = O, S; R = H, 4-Me, 4-Et, 2-Cl, 4-Cl, 4-Br.

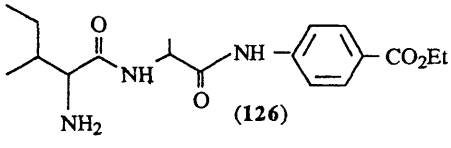


(**124**)

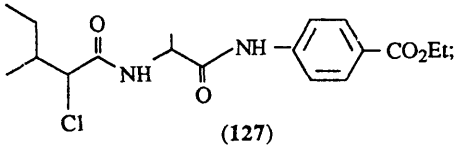
R = OH, OMe; R' = H, Me, Cl, CO_2H, NO_2.



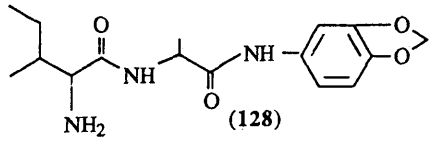
(**125**)



(**126**)



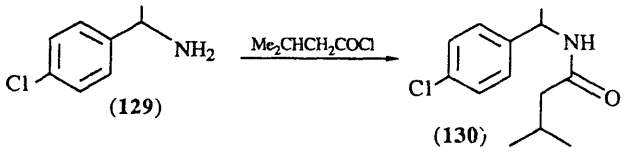
(**127**)



(**128**)

It was however established that the aza analogues of juvabione[141] display selectively high activity in relation to *Dysdercus fasciatus*. The most active proved to be compound (**130**) obtained by the acylation of the amine (**129**) (Scheme 49).

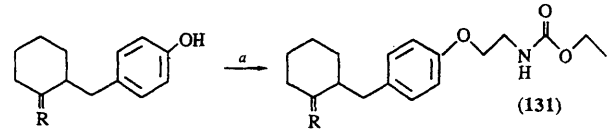
Scheme 49



(**129**) (**130**)

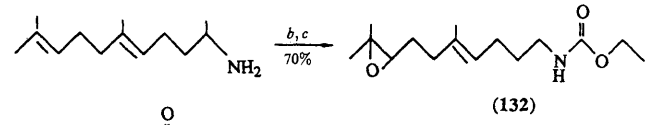
The compounds (**131**) and (**132**), containing oxygen and nitrogen atoms in the chain, display selective activity towards termites (Scheme 50).[142,143]

Scheme 50

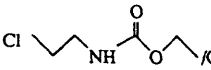


(**131**)

R = O (50%); OCH_2CH_2O (23%)

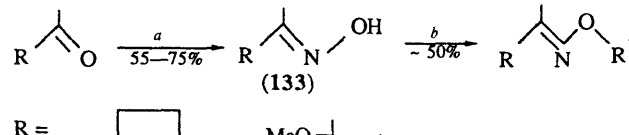


(**132**)

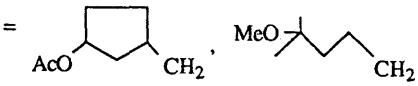
a: ; *b*: $ClCO_2Et$; *c*: $3\text{-}ClC_6H_4CO_3H$.

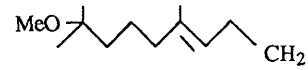
The reaction of oximes (**133**) and (**134**) with the appropriate halogen derivative[144–151] or chloroformate ester[143] may serve as an efficient method of obtaining juvenoids containing two heteroatoms, nitrogen and oxygen, in the same structure (Scheme 51).

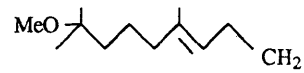
Scheme 51

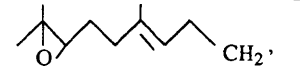


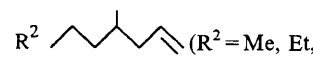
(**133**)

R = 

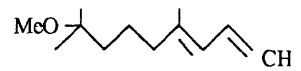
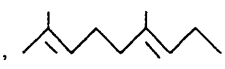


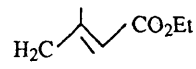
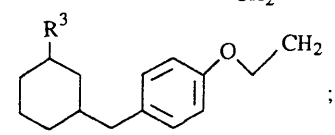




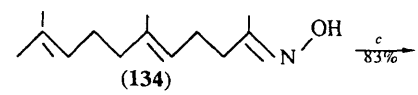


R^2 (R^2 = Me, Et, Pr, iso-Bu, MeC=CH, alkenyl)

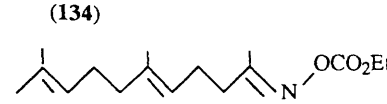
, ; R^1 = Alk,

, ;

R^3 = O, OH, OCH_2CH_2O.



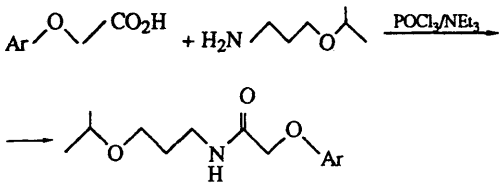
(**134**)



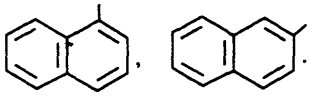
a: $H_2NOH.HCl$; *b*: Na/R'Br; *c*: $ClCO_2Et$.

Amides of unsaturated carboxylic acids with an oxygen atom in the chain, obtained by the reaction of acids with amines in the presence of $POCl_3$, display high JH activity in relation to the yellow meal worm (Scheme 52).[152–156]

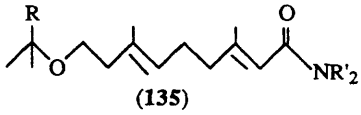
Scheme 52



Ar = 4-EtC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, 3-EC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4,



The JH activity of compounds of the (135) series is ~0.01 μg per specimen.[157]

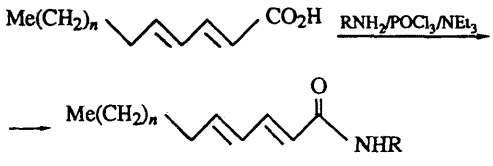


(135)

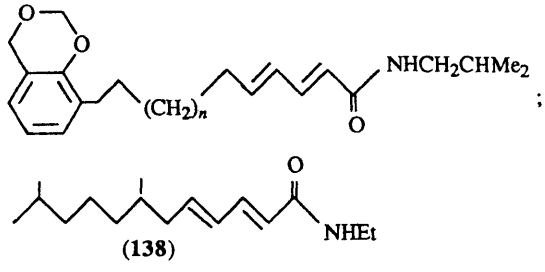
R, R′ = C_1-C_5-alkyl or C_2-C_5-alkenyl.

It was noted that the juvenoid activity of the amides was reduced in the series NR_2 > NHR > NH_2 (R = Alk, Ar)[9,158] and tertiary arylamides are more active than aliphatic amides. The amides of 2,4-dienoic acids are more active than the corresponding derivatives with isolated double bonds. A series of dienoates (136)–(138) was prepared, the action of which on *Callosobruchus maculatus*[159] and *Boophilus decoloratus*[160] exceeds that of methoprene (Scheme 53).

Scheme 53



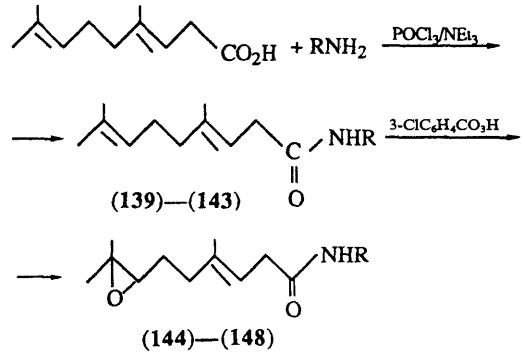
R = Me, Et, Pr, iso-Pr; n = 4 to 6.



(136), n = 5; (137), n = 3.

It was established that the epoxy derivatives (144)–(148) are more active than the initial amides (139)–(143) (Scheme 54).[155]

Scheme 54



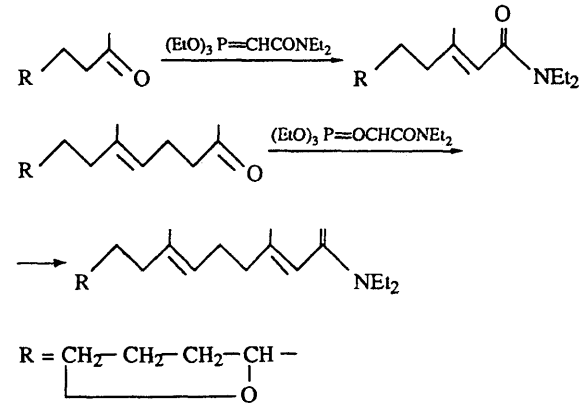
(139)—(143)

(144)—(148)

R = Ph (139), (144); 4-MeC_6H_4 (140), (145); 4-$MeOC_6H_4$ (141), (146); 4-$EtOC_6H_4$ (142), (147); 4-ClC_6H_4 (143), (148).

The Horner reaction is used for the synthesis of the α,β-unsaturated amides (Scheme 55).[152,153]

Scheme 55

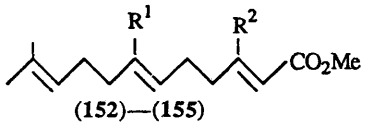


Highly active juvenoids of the amide type were obtained by the reaction of the corresponding alcohols with isocyanates,[161] or of amines with a chloroformate ester.[143,162] Compounds (149)–(151) display high activity towards the yellow meal worm (UD_{50} = 0.1 μg per specimen) but their activity in relation to *Dysdercus cingulatus* exceeds that of methoprene (UD_{50} = 0.008 and 0.04 μg per specimen respectively) (Scheme 56).

c) Derivatives of isoprenoid acids

Comparison of the methyl ester of farnesenic acid (152) and its C(3) and C(7) methylated analogues (153) and (154)[163] showed that the presence of the substituent at C(7) has little effect on juvenile hormone action but the absence of a methyl group at C(3) leads to an attenuating effect as indicated by the low activity of compound (154). On the other hand a stronger juvenoid is obtained by replacement of the methyl group at C(3) by trifluoromethyl [compound (155)].[164] It was also established that activity is increased in a series of farnesenic acid esters from methyl to propyl: CO_2Me < CO_2Et < CO_2Pr.[165,166] Replacement of the ester group

by amide reduces the juvenoid action of the obtained compound on *Bombyx mori* while the susceptibility of the yellow meal worm is increased.[167]

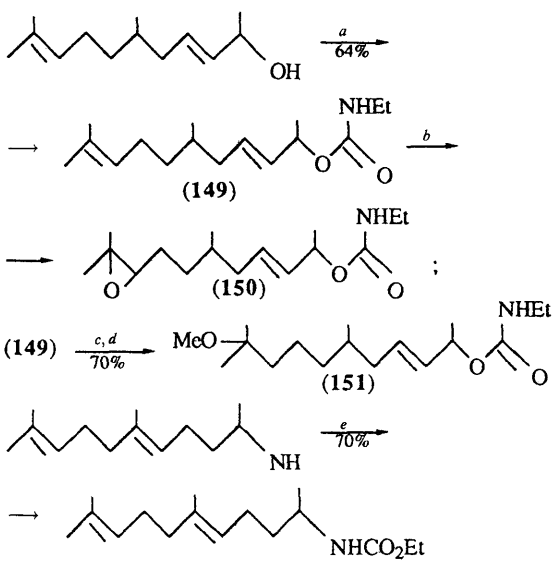


(152)—(155)

R^1 = H (153); Me (152), (154); CF_3 (155);
R^2 = H (154); Me (152), (153).

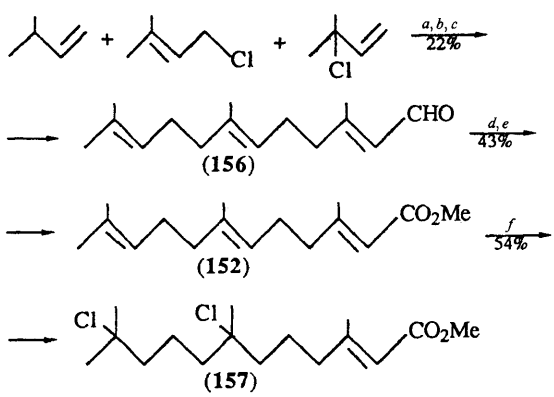
Methyl farnesenate (**152**) may be obtained mixed with other compounds by the telomerisation of isoprene, 1-chloro-3-methyl-2-butene and 3-chloro-3-methyl-1-butene with formaldehyde and subsequent oxidation of the aldehyde (**156**).[168] On treatment with hydrogen chloride the dichloride (**157**) is given and proved to be 1000 times more active in relation to *Antheraea polyphemus* than the natural JH (Scheme 57).[169]

Scheme 56



a: EtN=C=O; *b*: 3-$ClC_6H_4CO_3H$; *c*: $Hg(OAc)_2$; *d*: $NaBH_4$/NaOH; *e*: $ClCO_2Et$.

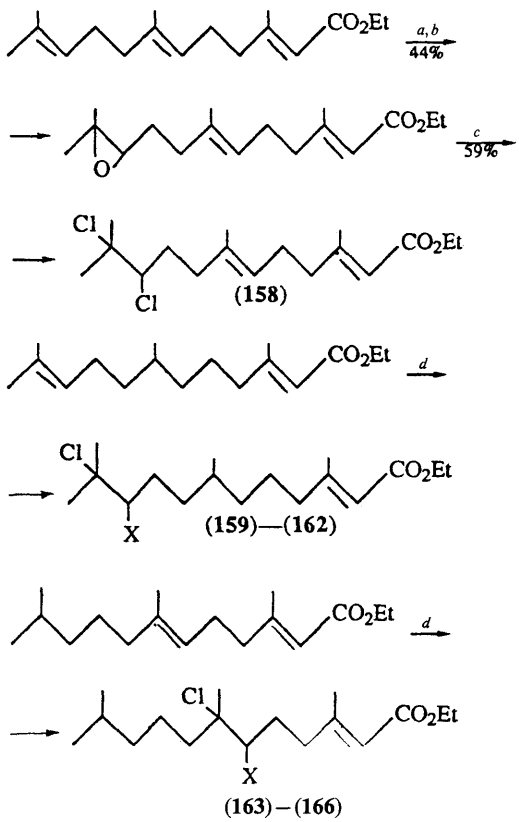
Scheme 57



a: $SnCl_4$; *b*: urofropin; *c*: CH_2O; *d*: $AgNO_2$; *e*: Me_2SO_4; *f*: HCl/MeOH.

It was shown that of the compounds (**159**)—(**166**) the activity of the 10,11-dichloro derivative (**158**) towards *Eurygaster integriceps* was greater than that of the 6,7- (**163**) and 7,11- (**157**) dichlorides. The thio analogues (**160**), (**161**), (**164**) and (**165**) were less active than the corresponding dichlorides (Scheme 58).[168,170]

Scheme 58



X = Cl (**159**), (**163**); SMe (**160**), (**164**); SPh (**161**), (**165**); 4-ClC_6H_4 (**162**), (**166**).
a: NBS; *b*: K_2CO_3; *c*: CCl_4/Ph_3P; *d*: $CuCl_2$/MeCN or RSCl.

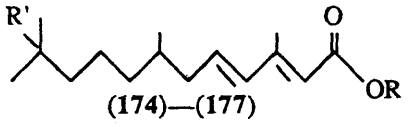
According to literature data[171] the presence of a fluorine atom in an organic compound inhibits its oxidative metabolism. This stimulated the synthesis of the fluorinated analogue (**169**) of JH-III. The fluorine-containing ester (**167**) served as starting material and was converted into the ester of 6-fluorogeranic acid (**168**) by a Claisen—Cope rearrangement. Further transformations led to the desired compound (**169**) (Scheme 59).[172]

The antipodes of the optically active juvenoids (**172**) and (**173**), which were obtained from the nitrile (**170**), possess different juvenoid activity in relation to *Dysdercus cingulatus*.[173,174] The racemic secondary alcohol (**171**), formed by the reaction of the nitrile (**170**) with propylmagnesium bromide was resolved into optical antipodes by Sharpless asymmetric epoxidation. Depending on whether (+) or (−) diisopropyl tartrate was used either the (*S*)-(−)- or the (*R*)-(+)-alcohol (**171**) respectively react and the unreacted (*R*)-(+) or (*S*)-(−) (**171**) enantiomer is isolated. The optical purity of the (*R*)-(+)-(**171**) and (*S*)-(−)-(**171**) alcohols was 88 and 74%

respectively. A Claisen rearrangement with an alkyl orthoformate in the presence of propionic acid[175] gave the juvenoids (172) and (173) of the (*R*) or (*S*) configuration (Scheme 60).[174]

Analogues of farnesenic acid of similar structure are comparable in juvenoid activity to the natural JH.[176–185] For example, a significant growth in JH activity was detected for esters of (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoic acid on changing from the α,β-enoates to the corresponding 2,4-dienoates.[1,186]

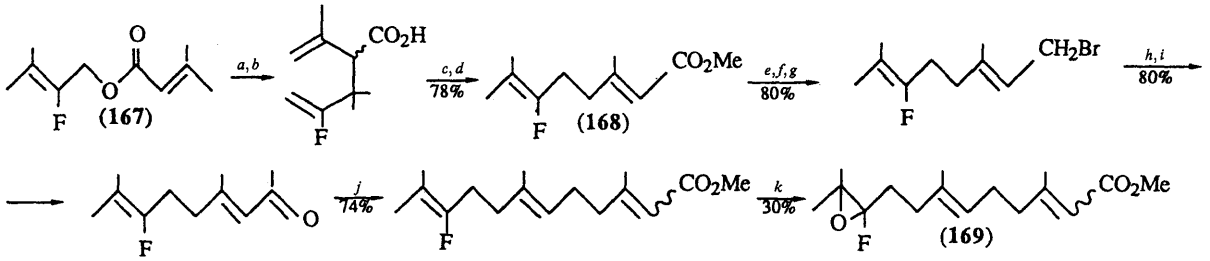
Compounds with very high juvenoid activity were found among the esters of (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoic acid. The ethyl ester (174) (hydroprene) and the propargyl ester (175) (kinoprene) are amongst these. The introduction of a methoxyl group at the 11 position of the isopropyl ester (176) gave an increase of almost one order of magnitude in juvenoid activity. Methoprene proved to be non-toxic to warm blooded animals and man. On the other hand this compound displayed high juvenoid activity towards the house ant *Monomorium pharaonis*,[187] the mosquito *Culex nigripalpus*,[188] the house-fly and the dung fly and also towards many agricultural pests of the orders *Lepidoptera* and *Hemiptera*.[13,189] The addition of 0.01% methoprene to bird feed led to 99% destruction of flies on poultry farms. Hydroprene (174)[189,190] and kinoprene (175)[189,191] are also of practical use.



(174)—(177)

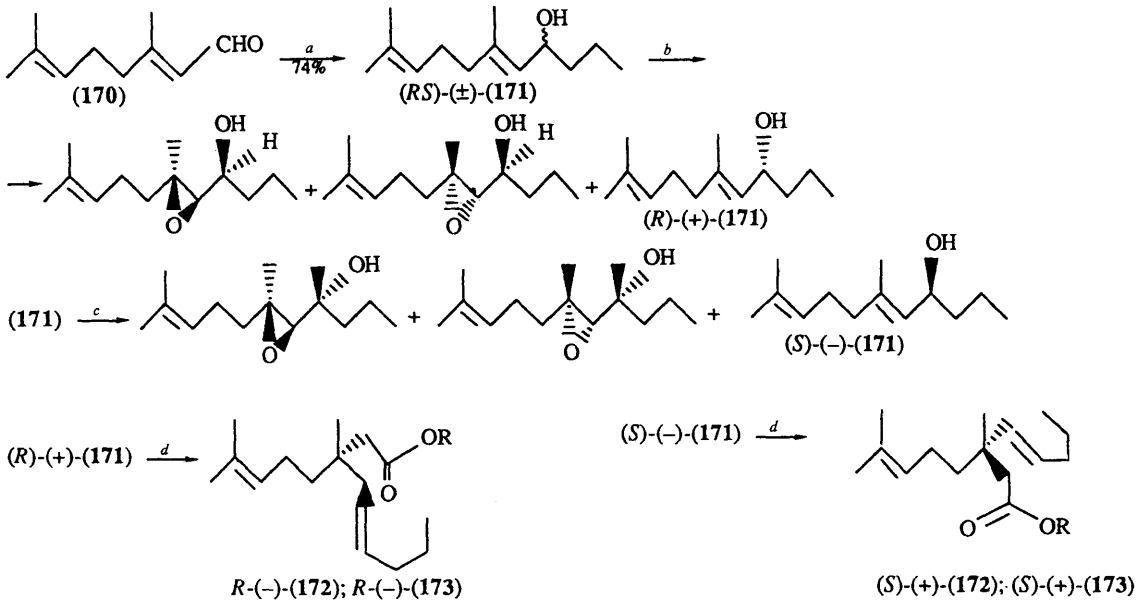
R = Et (174); $CH_2C{\equiv}CH$ (175); $CHMe_2$ (176), (177);
R' = H (174)—(176); OMe (177).

Scheme 59



a: LDA/THF, −75 °C; *b*: Me_3SiCl; *c*: DMFA, Δ; *d*: MeI/K_2CO_3/Me_2CO; *e*: $LiAlH_4$; *f*: $(CF_3CO)_2O$/Py; *g*: LiBr/THF; *h*: t-BuOK/Me.$COCH_2CO_2Et$; *i*: DMSO/H_2O/NaCl; *j*: $(MeO)_2P(O)CH_2CO_2Me$/NaH; *k*: 3-$ClC_6H_4CO_3H$.

Scheme 60



R = Me (172), Et (173);

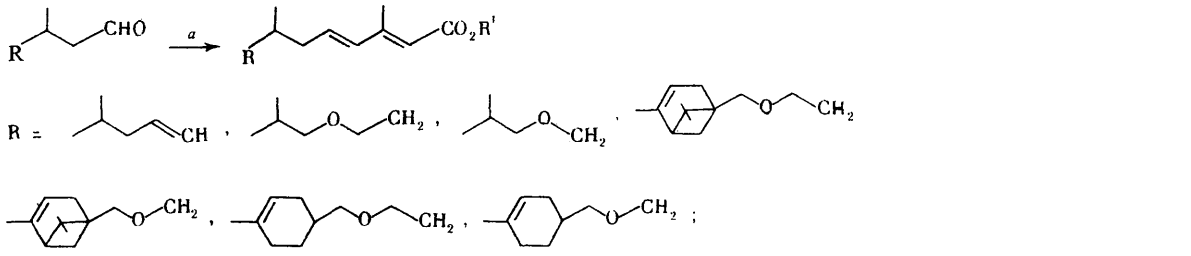
a: $Me(CH_2)_2MgBr$; *b*: t-BuOOH/(iso-OPr)$_4$Ti/(+)-PrOOCCH(OH)CH(OH)COOPr; *c*: t-BuOOH/(iso-OPr)$_4$Ti/(−)-PrOOCCH(OH)CH.(OH)COOPr; *d*: $MeC(OR)_3$/$MeCH_2COOH$.

The key stage in the synthesis of the 2,4-dienoates is usually the Emmons modification of the Wittig reaction (Scheme 61).[134,186,192–196]

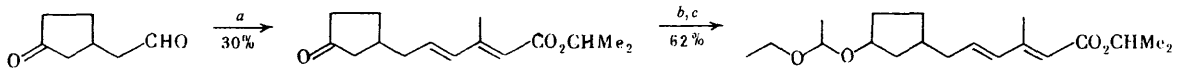
A review[13] has been devoted to the synthesis and properties of methoprene (**177**). Hydroprene (**174**), as a mixture of the (2*E*,4*E*) and (2*Z*,4*E*) isomers, was synthesised for the (2*E*) unsaturated ketone (**178**) and ethyl bromoacetate by the Reformatsky reaction,[197] using the Iotsich–Preobrazhenskii reagent[198] or by the reaction with acetic acid di-anion.[199]

The individual (2*E*,4*E*) isomer of the methyl ester (**181**) was obtained by elimination of acetic acid from the homoallyl acetate (**180**), which was itself obtained by the reaction of tetrahydrocitral (**179**) with the di-anion generated from 3-methyl-3-buten-1-ol (Scheme 63).[200]

Scheme 61

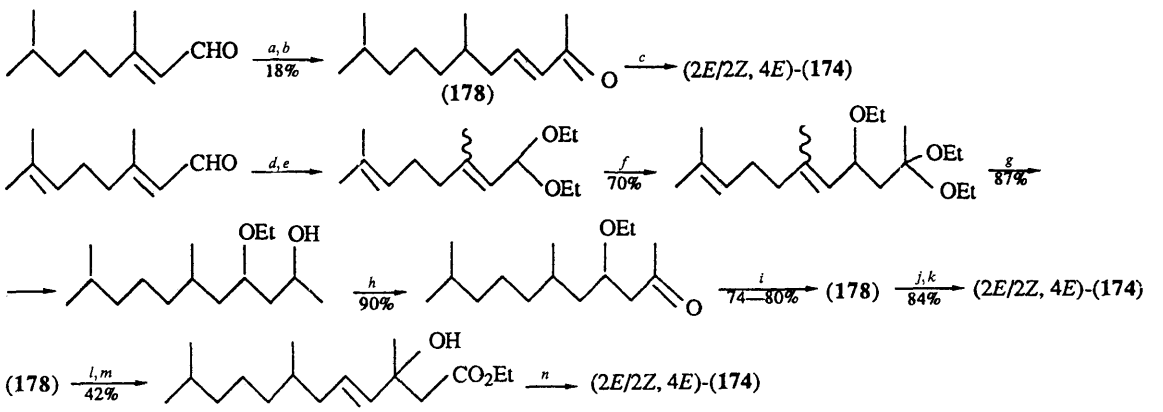


R^1 = OMe, OEt, iso-Pr, SEt.



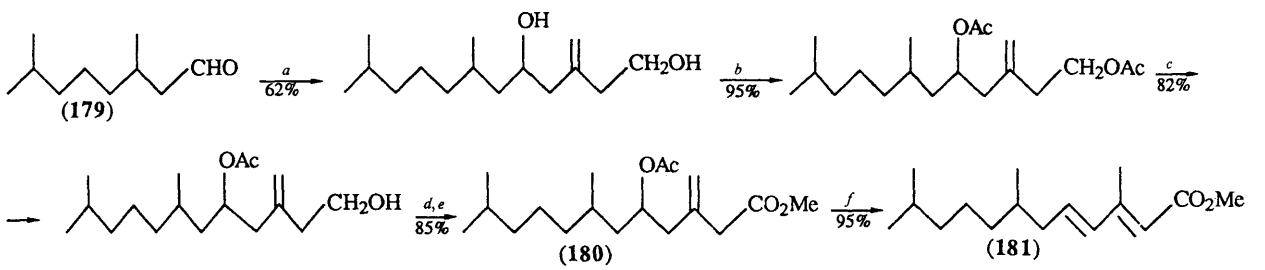
a: $(R'O)_2P(O)CHCMe{=}CHCO_2CHMe_2$; *b*: $NaBH_4$; *c*: $EtOCH{=}CH_2$.

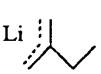
Scheme 62



a: Me_2CO; *b*: KOH/EtOH; *c*: $BrCH_2CO_2Et/Zn$; *d*: $HC(OEt)_3$; *e*: $HClO_4$; *f*: $CH_2{=}C(Me)OMe/ZnCl_2$; *g*: H_2/Ni; *h*: PY.CrO_3.HCl; *i*: Ts.OH/quinoline; *j*: HC≡COEt/EtMgBr; *k*: 10% H_2SO_4; *l*: $LiCH_2CO_2Li$; *m*: EtOH/$H^{\oplus}$; *n*: P_2O_5.

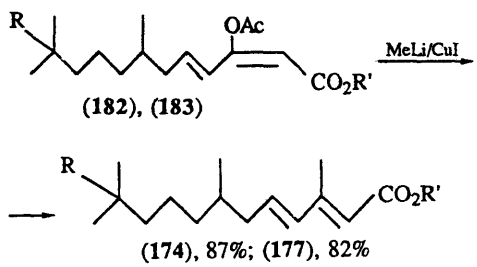
Scheme 63



a:  CH_2OLi; *b*: AcCl; *c*: $Na_2CO_2/EtOH$; *d*: CrO_3/Me_2CO; *e*: CH_2N_2; *f*: NaH.

Hydroprene (**174**) and methoprene (**177**) are obtained from compounds (**182**) and (**183**) by replacing the acetoxy group by methyl accompanied by isomerisation of the double bond (Scheme 64).[201]

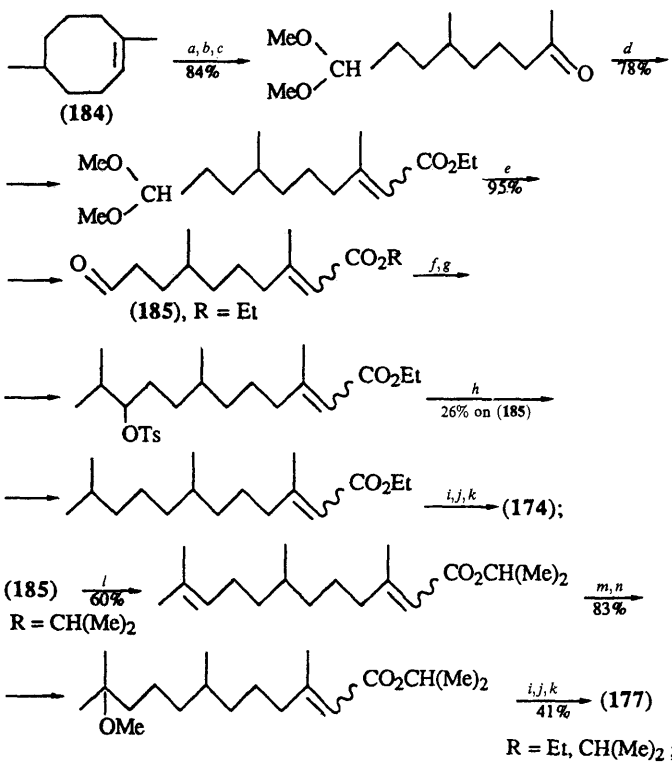
Scheme 64



R = H (174), (182); R = OMe (177), (183);
R' = Et (174), (182); $CHMe_2$ (177), (183).

A complete synthesis of hydroprene (**174**) and methoprene (**177**) was effected from the products of the ozonolysis of 1,5-dimethyl-1-cyclooctene (**184**).[202,203] The aldehyde (**185**) is the key synthon in both cases. The individual (2*E*,4*E*) isomers (**174**) and (**177**) were isolated by preparative HPLC (Scheme 65).

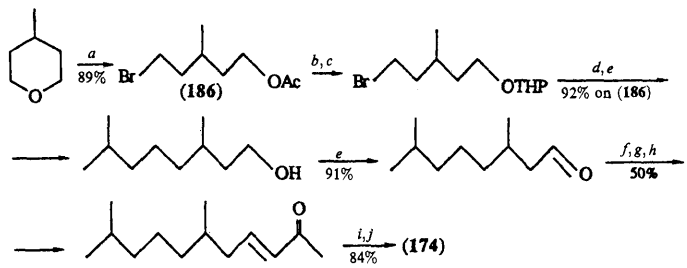
Scheme 65



a: O_3/MeOH; *b*: H_2/Pd–$CaCO_3$–PbO; *c*: NH_4Cl/MeOH; *d*: $(Me)_3$.$SiCH_2CO_2R$/$(iso\text{-}Pr)_2NH$; *e*: $H^{\oplus}$; *f*: $(Me)_2CHMgBr$; *g*: TsCl/Py; *h*: Zn/NaI/THF; *i*: NBS/$(BzO)_2$; *j*: Li_2CO_3/LiBr/DMF; *k*: HPLC; *l* $Me_2C{=}PPh_3$; *m*: $Hg(OAc)_2$/MeOH; *n*: $NaBH_4$/NaOH.

The synthon (**186**), readily available from 4-methyltetrahydropyran, was used for the preparation of hydropropene (**174**) (Scheme 66).[204]

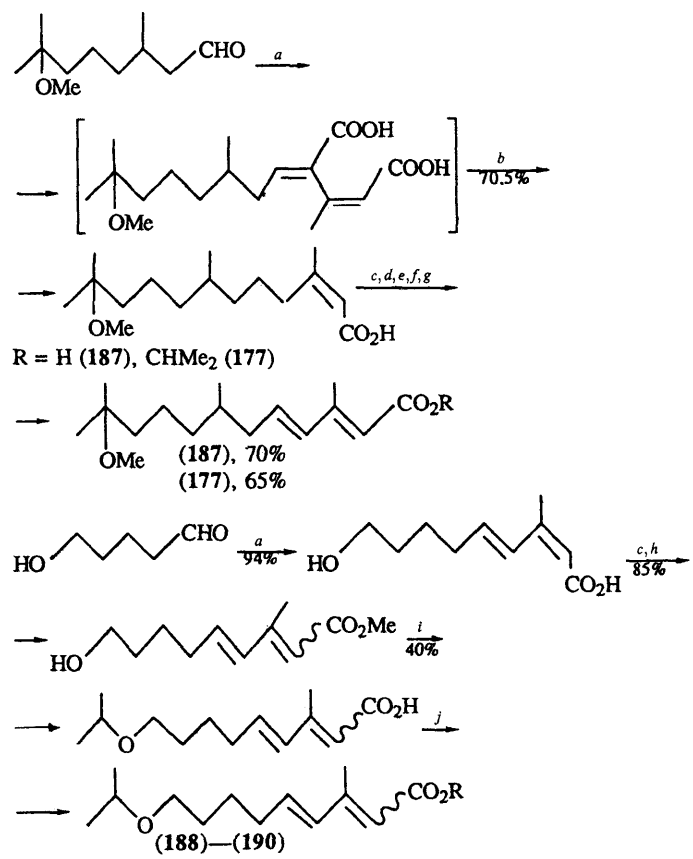
Scheme 66



a: AcBr/$ZnCl_2$; *b*: KOH/MeOH; *c*: DHP(3,4-dihydro-2H-pyran)/Ts.OH; *d*: Me_2CHCH_2MgBr; *e*: Py.CrO_3.HCl; *f*: $CH_2{=}CH{-}CH_2Mg$.Br; *g*: $O_2/PdCl_2/CuCl$; *h*: $H^{\oplus}$; *i*: $BrMgC{\equiv}COEt$; *j*: H_2SO_4.

The syntheses of methoprene (**177**) from 7-methoxycitronellal have been discussed.[13] The isolation of the (2*E*,4*E*) isomer was effected as the ammonium salt of the acid (**187**).[205,206] A similar methodology was used in the synthesis of the other 2,4-dienoates (**188**)–(**190**) (Scheme 67).[207,208]

Scheme 67

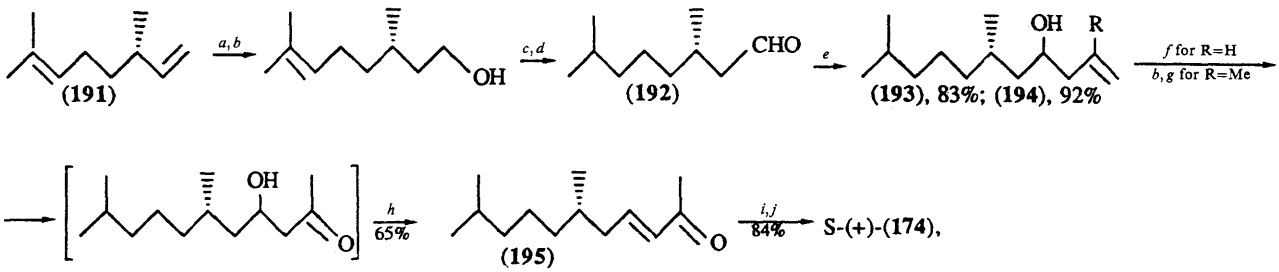


R = Me (188), 30%; $CHMe_2$ (189), 50%; $CH_2C{\equiv}CH$ (190), 58%;

a: EtO_2C  CO_2Et; *b*: Δ; *c*: PhSH; *d*: NH_3; *e*: $H^{\oplus}$; *f*: $SOCl_2$;

g: $Me_2CHOH/H^{\oplus}$; *h*: CH_2N_2; *i*: $Me_2CHBr/OH^{\ominus}$;
j: $C_6H_{11}NHC(OR){=}NC_6H_{11}$(R = Me, $CHMe_2$, $CH_2C{\equiv}CH$).

Scheme 68

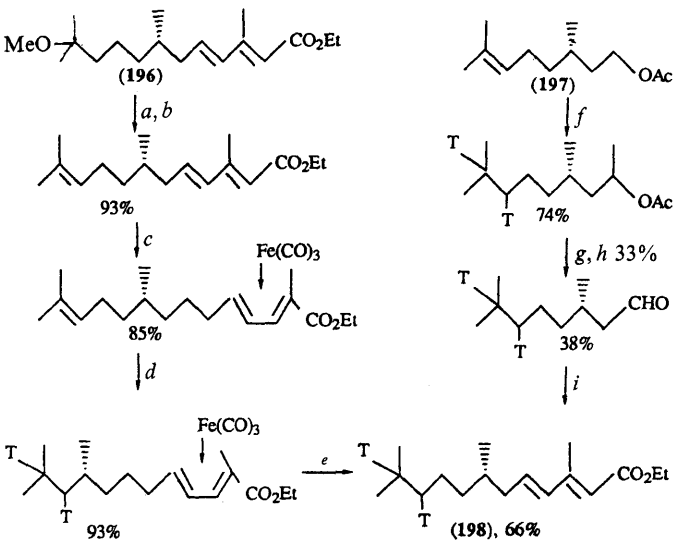


a: $(iso\text{-}Bu)_2AlH$; *b*: O_3/O_2; *c*: H_2-Pd/C; *d*: $Py.CrO_3.HCl$; *e*: $CH_2=C(R)-CH_2MgCl$; *f*: $O_2/PdCl_2-CuCl_2$; *g*: Me_2S; *h*: $H^{\oplus}$; *i*: $EtOC\equiv CH/Et.MgBr$; *j*: H_2SO_4.

It is known that the (7*S*)-(+) enantiomer of hydroprene (**174**) displays higher activity than the (7*R*)-(−) antipode.[209] Enantiomerically enriched hydroprene (**174**) (enantiomeric excess ~50%) is obtained from dihydromyrcene (**191**) through (*S*)-(+)-3,7-dimethyloctanal (**192**) which was treated with allyl- or methallylmagnesium chloride and gave the alcohols (**193**) or (**194**), each of which was converted into the conjugated ketone (**195**) then transformed by the usual route into the desired (*S*)-(+)-hydroprene (Scheme 68).[210]

The synthesis of 10,11-ditritiohydroprene (**198**), used for investigating the metabolism of juvenoids *in vivo*, was effected from the (*S*)-(+)-dienoate (**196**) in which the Δ^{10} double bond was tritiated after protecting the diene system as the iron carbonyl complex. Another route is based on tritiation of the double bond of (*S*)-(+)-citronellyl acetate (**197**) before constructing the diene system (Scheme 69).[211]

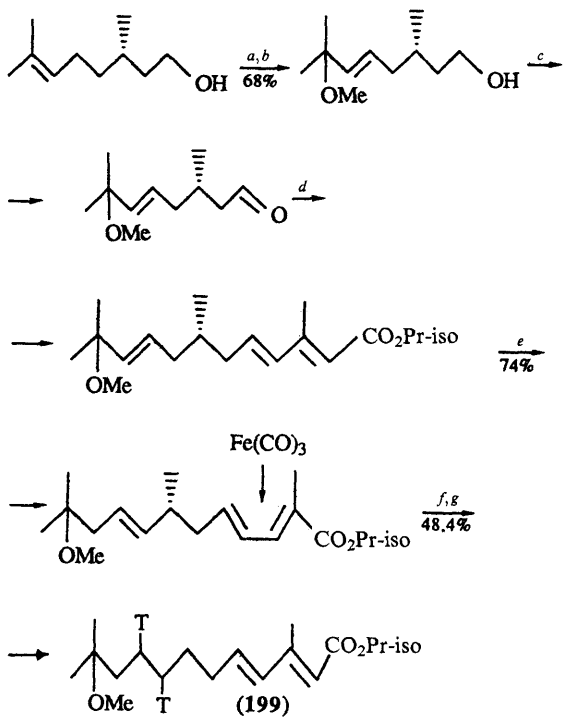
Scheme 69



a: NaOEt/EtOH; *b*: H_2SO_4; *c*: $Fe_3(CO)_{12}$; *d*: $T_2/Ph[Ph_3P]_3Cl$; *e*: $(NH_4)_2Ce(NO_3)_2$; *f*: T_2/Pd; *g*: NaOH/MeOH; *h*: CrO_3/Py; *i*: $Et_2.OCCH=C(Me)CH_2P(O)(OEt)_2$.

A similar approach was used in the synthesis of 8,9-ditritiomethoprene (**199**) used as a tracer for characterising protein receptors in insects (Scheme 70).[212]

Scheme 70

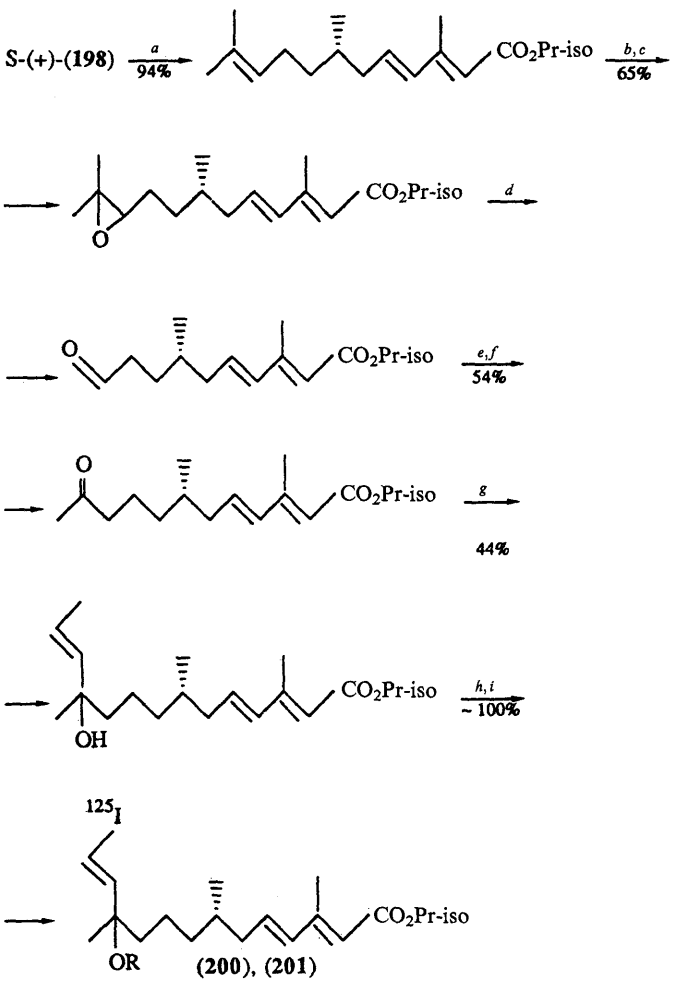


a: NBS/MeOH; *b*: $Ph_3CK/CH_2(OMe)_2$; *c*: $Py.CrO_3.HCl$; *d*: $(iso\text{-}PrO)_2P(O)CH_2CH(Me)=CHCO_2Pr\text{-}iso$; *e*: $Fe(CO)_{12}$; *f*: $T_2/Rh-C$; *g*: $Ce(NH_4)_2(NO_3)_2$.

In order to study the mechanism of binding juvenoids to protein, an iodomethyl group labelled with radioactive ^{125}I, which is stable to metabolism, was introduced into the methoprene molecule

[compounds (200) and (201)].[213] The resulting analogue (201) proved to be four times as active as methoprene (Scheme 71).

Scheme 71

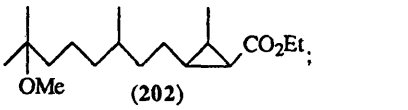


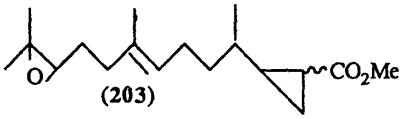
R = H(200), Me (201);
a: H_2SO_4; *b*: NBS; *c*: K_2CO_3; *d*: H_2IO_6; *e*: $Ph_3P=C(Me)OMe$; *f*: $H^{\oplus}$/MeOH; *g*: (*E*)-$Bu_3SnCH=CHSnBu_2$, BuLi/THF; *h*: $Na^{125}I/H_2O_2$/AcOH; *i*: $NaHSO_3$.

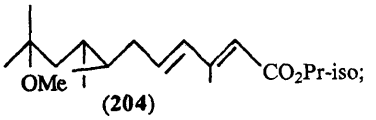
2. Juvenoids containing cyclic residues in the carbon chain

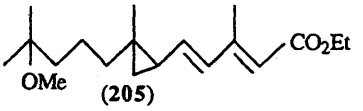
a) Juvenoids containing carbon rings

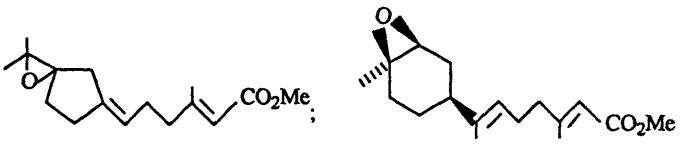
Compounds containing cyclic residues in various parts of the carbon chain of the AJH molecule have been synthesised with the aim of studying the mechanism of action and of searching for new active juvenoids. It was established that the introduction of a cyclopropane ring into the head portion of the molecule [compounds (202), (203)[214,215]] or its heart [compounds (204), (205)[216,217]] did not change the biological activity while the presence of an alicycle in the tail portion of the molecule [compounds (206)–(209)] reduces JH activity compared with the corresponding compounds containing no cyclic fragments.[218–221]

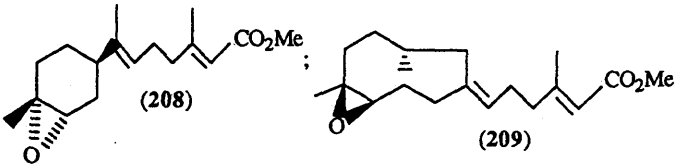






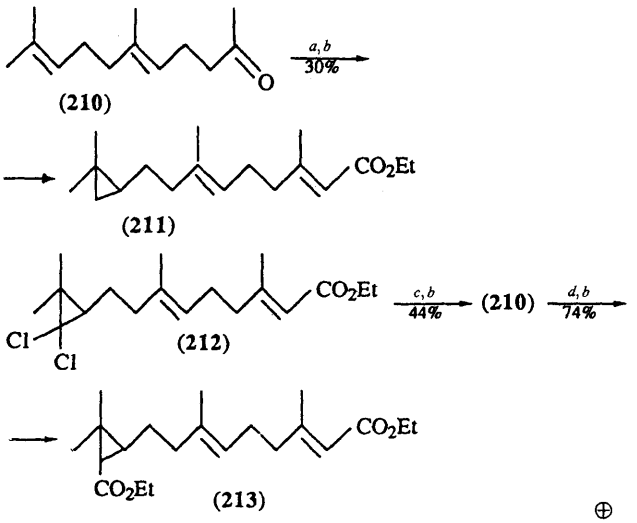






Compounds (211)–(213) were obtained by the cyclopropanation of geranylacetone (210) and subsequent Horner olefination (Scheme 72).[221]

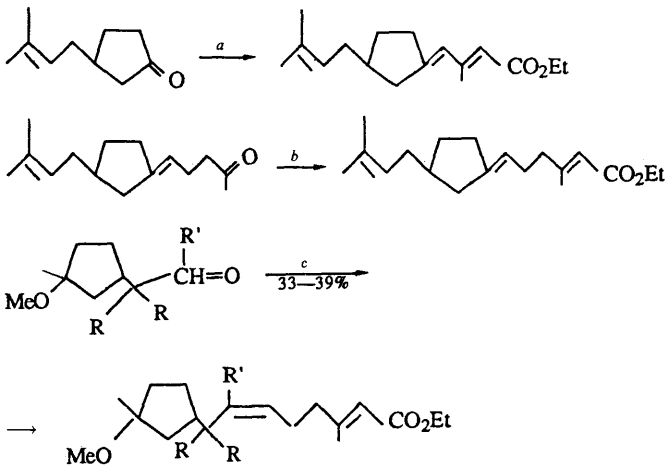
Scheme 72



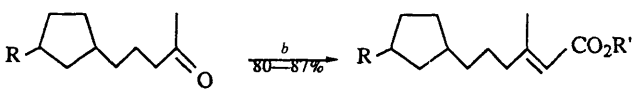
a: $CH_2I_2/Zn/CuO$; *b*: $(EtO)_2P(O)CH_2CO_2Et$; *c*: $CHCl_3/Et_3BuNCl^{\ominus}$; *d*: $EtO_2CCH_2N_2$.

A typical route for the synthesis of juvenoids containing a carbocyclic residue is the olefination of cyclic ketones or ketones and aldehydes containing a cyclic fragment in the carbon chain (Scheme 73).[222–232]

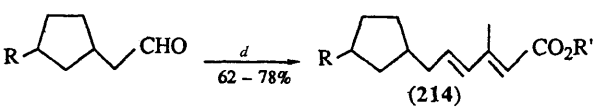
Scheme 73



R = H, Me; R' = H, Me;

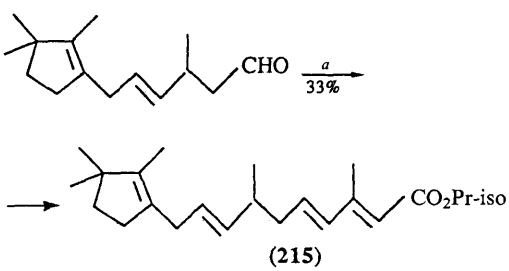


R = $CH(Me)_2$; $C(Me)_3$; $HOCMe_2$; R' = Et, $CHMe_2$;

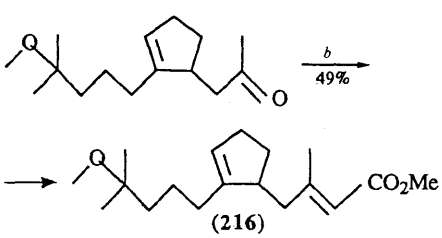


(214)

R = OAc, $MeC(OMe)-CH_2-CH_2$; R' = Et, Pr-iso;

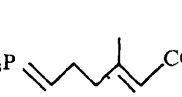


(215)



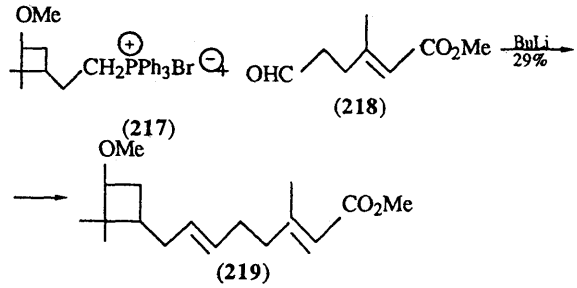
(216)

a: $(EtO)_2P(O)CHC(Me)=CHCO_2Et$, *b*: $(EtO)_2P(O)CHCO_2Et$;

c: Ph_3P  ; *d*: $Br^{\ominus}(Ph_3)PC$ 

The juvenoid (**219**) was obtained by the reaction of the aldehyde (**218**) with the phosphonium salt (**217**) containing a cyclobutane residue (Scheme 74).[233]

Scheme 74

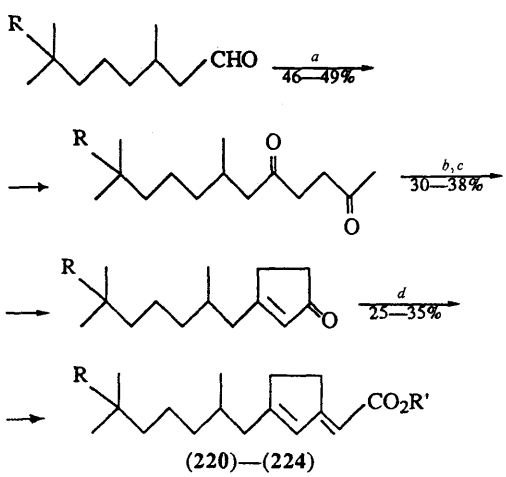


(219)

It may be concluded from the existing literature data that AJH containing an alicyclic residue possess lower juvenoid activity than compounds without these fragments. The dienoates (**214**) do not have significant advantages over the unconjugated or α,β-unsaturated esters. The presence of a double bond in a cyclopentane ring does not increase biological activity [compounds (**215**), (**216**)]. Juvenoids containing cyclobutane rings proved to be selectively active towards *Tribolium costaneum*.[233,234]

The ethyl bridge between atoms C(3) and C(5) in the 2,4-dienoates (**220**)–(**224**) leads to high morphogenetic activity, two to three times greater than the activity of methoprene (**177**) and hydroprene (**174**) on the pupa of the Cabbage White butterfly (*Pieris brassicae*).[235–237] The methoxy derivatives of the 2,4-dienoates of this series are selectively active towards *Diptera*, while compounds without the methoxy group display higher activity towards *Lepidoptera* (Scheme 75).[236]

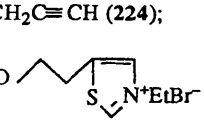
Scheme 75



(220)—(224)

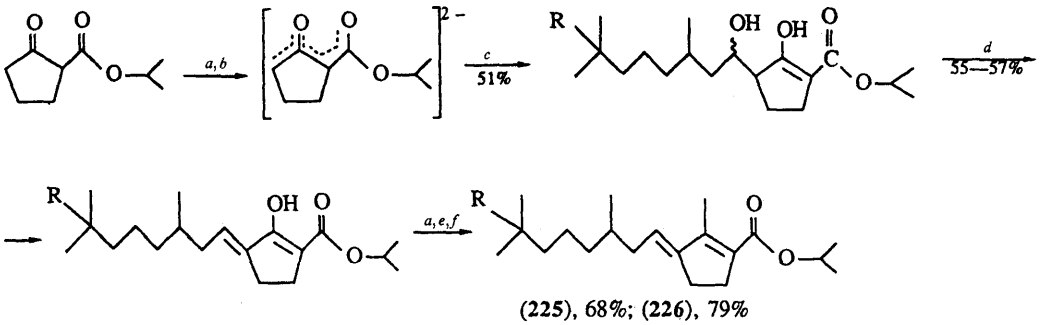
R = H (**220**), (**221**); OMe (**222**)—(**224**); R' = H (**220**), (**222**);

$CHMe_2$ (**221**), (**223**); $CH_2C{\equiv}CH$ (**224**);

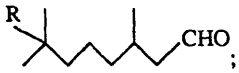
a: $H_2C=CHC(O)Me/HO$  ; *b*: iso-$PrNH_2$; *c*: NaH;

d: $Me_3SiCH_2CO_2R'$ or $(R^1O)_2P(O)CH_2CO_2R^1$.

Scheme 76



R = H (225), OMe (226);

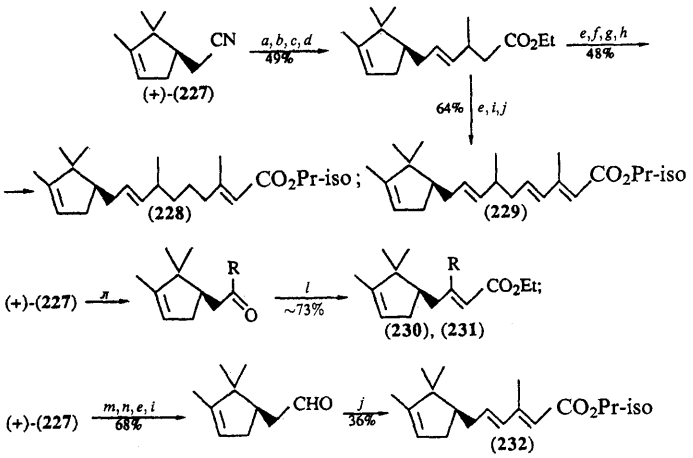
a: NaH; b: AlkLi; c:  ; d: HCl; e: Et_2PCl; f: $LiCuAlk_2$.

The following route is proposed for the synthesis of 2,4-dienoates (225) and (226) with an ethylene bridge between the C(2) and C(4) atoms (Scheme 76).[238]

The optically active compounds (228)–(232), obtained from (+)-1-cyanomethyl-2,2,3-trimethyl-3-cyclopentane (227), displayed higher juvenoid activity than the corresponding racemates (Scheme 77).[239,240]

Juvenoids of medium activity (234) and (235), containing a cyclobutane ring, were obtained by the partial ozonolysis of caryophyllene (233) (Scheme 78).[241]

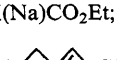
Scheme 77



R = Me (230), Et (231);

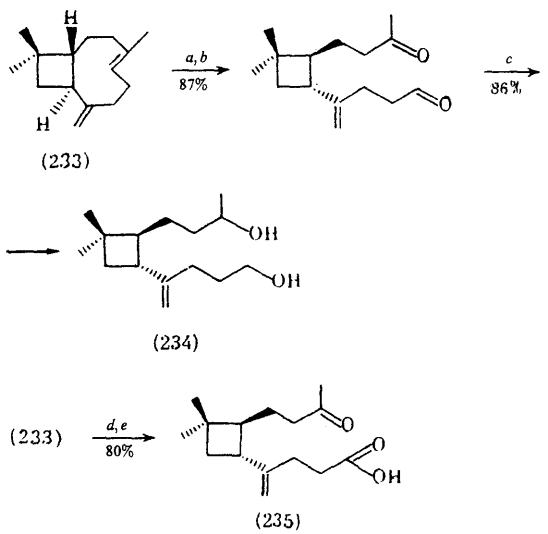
a: $CH_2=CHMgBr$; b: $Et_3N/EtOH$; c: iso-BuAlH; d: $MeC(OEt)_3$;

e: $LiAlH_4$; f: PBr_3; g: $AcCH(Na)CO_2Et$; h: $(EtO)_2P(O)\overset{\ominus}{C}HCO_2Pr$-iso;

i: $Py.CrO_3.HCl$; j: $(EtO)_2P(O)$CO_2Pr-iso; k: RMgX;

l: $(EtO)_2P(O)\overset{\ominus}{C}HCO_2Et$; m: KOH/H_2O; n: TsOH/EtOH.

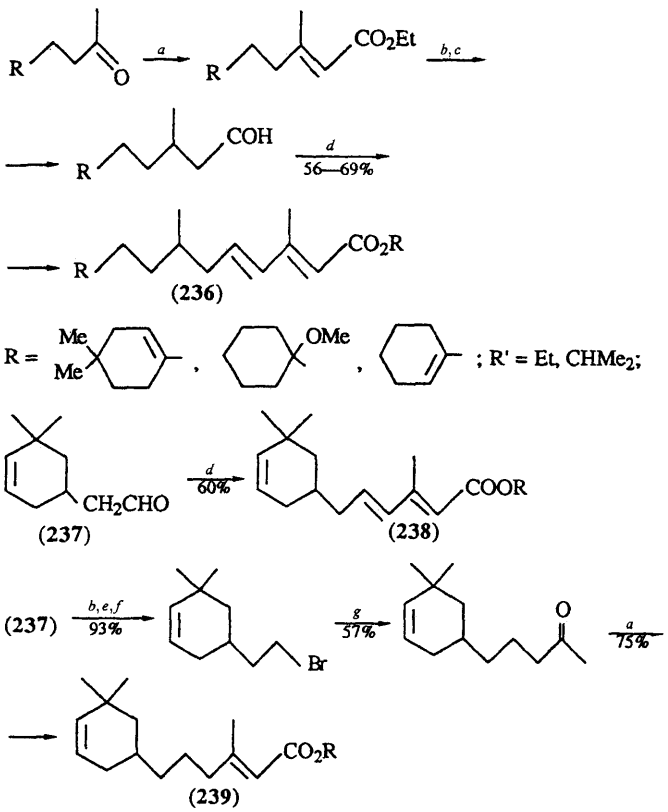
Scheme 78



a: $O_3/MeOH$; b: $H_2/Pd.CaCO_3.PbO$; c: $NaBH_4$; d: $O_3/AcOH$; e; AcOH/AcONa.

The juvenoids (**236**) with a six-membered ring, like the related compounds (**238**)–(**241**) obtained from the aldehyde (**237**), are not active towards the yellow meal worm and are ten times less active than their acyclic analogues towards *Dysdercus cingulatus* (Scheme 79).[123,217,242–245]

Scheme 79



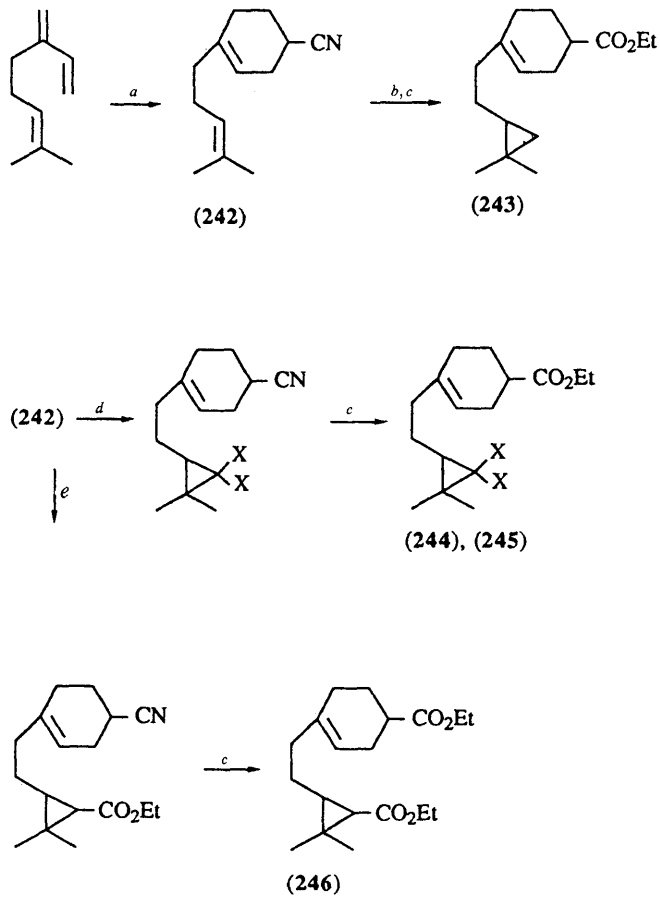
a: $(EtO)_2P(O)C^{\ominus}HCO_2Et$; *b*: $LiAlH_4$; *c*: $CrO_3.Py$;

d: $(EtO)_2P(O)\overset{\ominus}{C}(CO_2R')$;

e: TsCl/Py; *f*: LiBr/acetone; *g*: $AcOC^{\ominus}HCO_2Et$; *h*: $4\text{-}XC_6H_4ONa$; *i*; NaH.

The compounds (**243**)–(**246**) obtained from compound (**242**) and containing cyclohexene and cyclopropane fragments proved to be active towards *Dysdercus koenigii* (Scheme 80).[246]

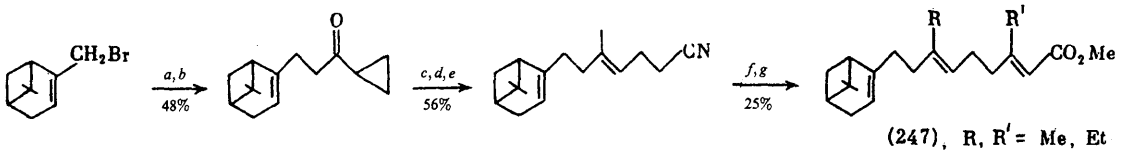
Scheme 80



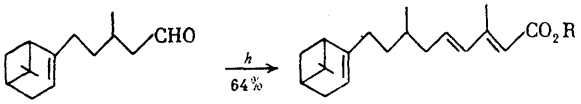
a: $CH_2{=}CH{-}CN$; *b*: CH_2I_2/Zn, Cu; *c*: EtOH, H_2O, HCl; *d*: $CHX_3/(C_6H_5CH_2)Et_3N^{\oplus}Cl^{\ominus}$; *e*: $H_2NCHCO_2Et/CuSO_4$.

Several AJH have been synthesised with pinene (**247**) and (**248**) and norbornene (**249**) bicyclic fragments.[217,247–249] The AJH (**251**)–(**253**) were synthesised from camphene (**250**) (Scheme 81).

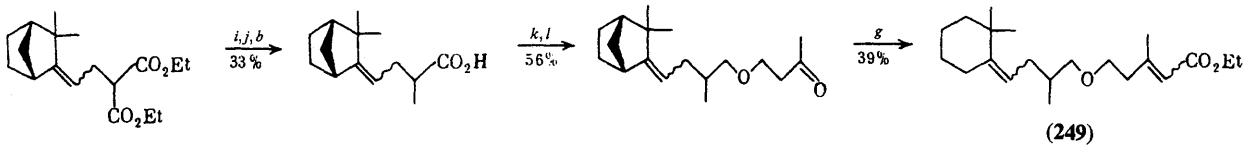
Scheme 81



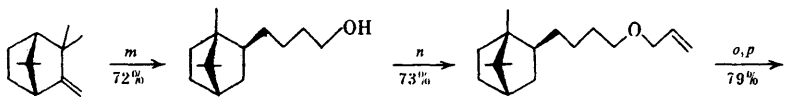
(247), R, R' = Me, Et



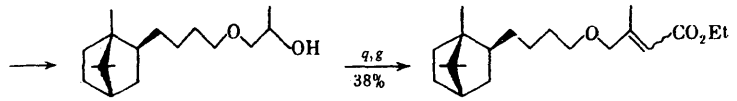
(248), R = Et, $CHMe_2$



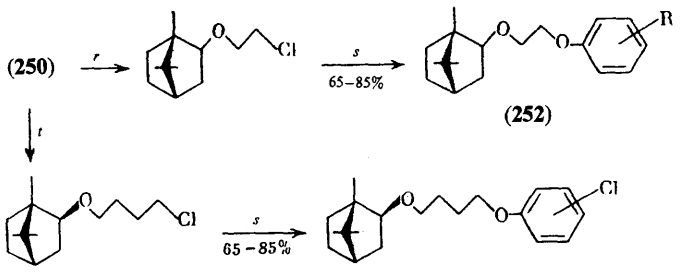
(249)



(250)



(251)



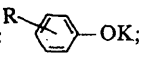
R = 4-Et; 2-iso-Pr; 2-Me; 4-iso-Pr; 2-Me; 4-Ac; 4-Cl; 4-Br; 2,4,6-Cl_3; 4-NO

a: $EtO_2CCH_2\overset{O}{\overset{\|}{C}}/EtONa$; *b*: Δ; *c*: RMgI; *d*: HBr; *e*: NaCN; *f*: R_1MgBr;

g: $(EtO)_2\overset{\ominus}{P}(O)CHCO_2Me$; *h*: $(EtO)_2\overset{\ominus}{P}(O)CH-C(CH_3)=CHCO_2R$;

i: Na/MeI; *j*: $OH^{\ominus}$; *k*: $LiAlH_4$; *l*; $CH_2=CH-C(O)-Me$;

m: $HO(CH_2)_3OH/HClO_4$; *n*: $CH_2=CH-CH_2I$; *o*: $Hg(OAc)_2$;

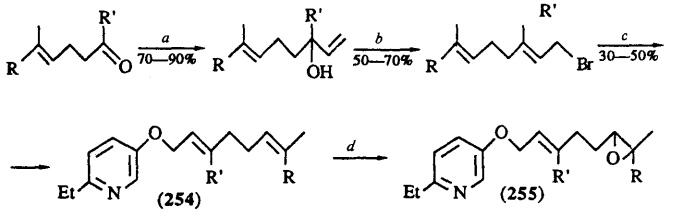
p: $NaBH_4/OH^{\ominus}$; *q*: CrO_3/Py; *r*: $HO(CH_2)_2Cl/HClO_4$; *s*: 

t: $HO(CH_2)_4Cl/HClO_4$.

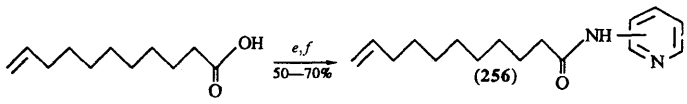
b) Juvenoids containing heterocycles

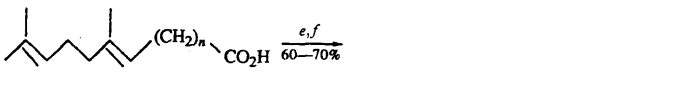
Compounds containing heterocycles have been investigated as AJH. The AJH (**254**)–(**257**) have been obtained with a pyridine ring in the molecule and also compound (**258**) containing a pyrrolidine ring as well (Scheme 82).[250–252]

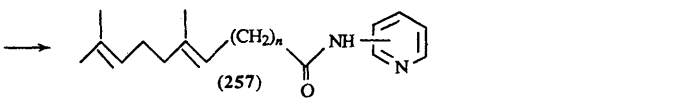
Scheme 82



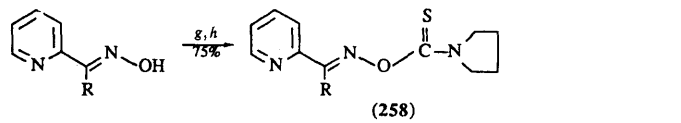
R = $Me(CH_2)_2$, $Me(CH_2)_3$; R' = Me, Et;



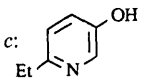




n = 0,1



R = Me, Me_2CH;

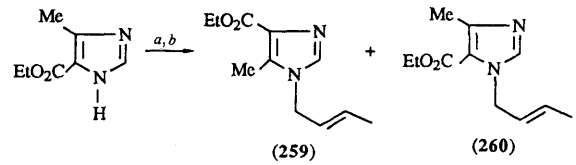
a: $CH_2=CHMgBr$; *b*: HBr; *c*:  ; *d*: $3\text{-}ClC_6H_4CO_3H$; *e*: $SOCl_2$;

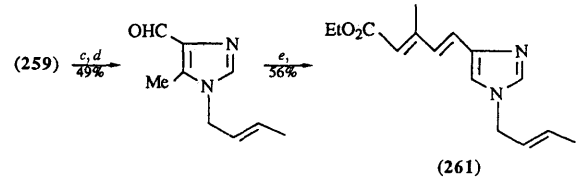
f:  ; *g*: $CSCl_2/Et_3N$; *h*: .

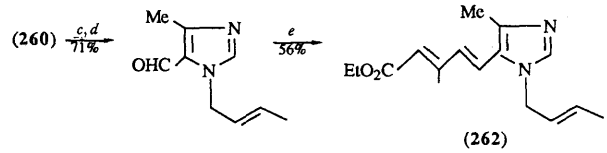
It was established that the introduction of a pyridine ring reduced JH activity significantly. A similar result was obtained for the imidazole derivatives (**261**) and (**262**) synthesised from compounds (**259**) and (**260**) (Scheme 83).[157,253]

Highly active AJH have been discovered among compounds (**263**)–(**266**) containing oxygen in the heterocycle and also for compounds (**267**) and (**268**) containing both nitrogen and oxygen in the rings (Scheme 84).[254,255]

Scheme 83

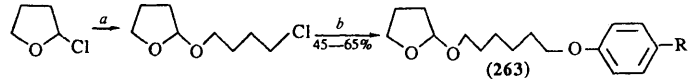




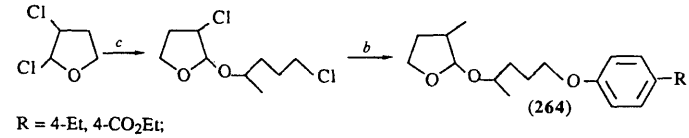


a: NaH; *b*: $Me_2C=CH-CH_2Cl$; *c*: $LiAlH_4$; *d*: MnO_2; *e*: $(EtO)_2-\overset{\ominus}{C}H.-C(Me)=CHCO_2Et$.

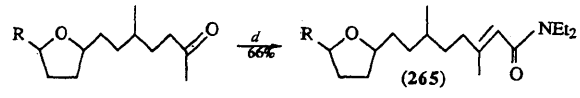
Scheme 84

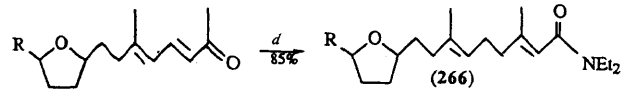


R = 4-H, 3-Me, 4-OMe, 4-SMe, 4-COMe, 4-COEt, 4-CO_2Me, 4-CO_2Et, 4-Cl, 4-NO_2.

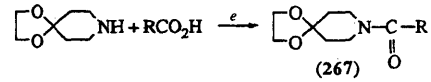


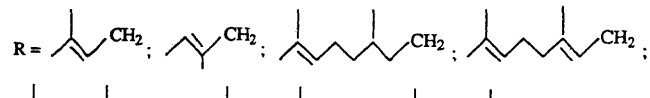
R = 4-Et, 4-CO_2Et;

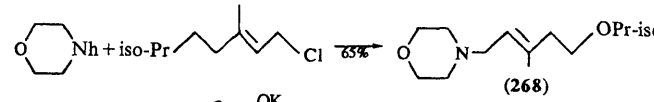


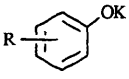
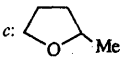


R= H, Me;



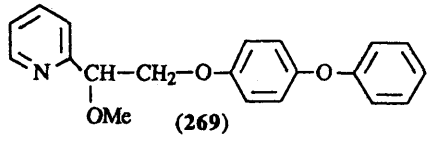




a: $HO(CH_2)_4Cl$; *b*: R- ; *c*: $/ZnCl_2$; *d*: $(EtO)_2P(O)\overset{\ominus}{C}HCONEt_2$;

e: $Ph_2P(O)Cl$.

It turned out that the JH activity of compound (**269**) exceeded that of methoprene (**177**) in relation to *Aedes aegypti, Galleria mellonella, Tenebrio molitor* and *Musca domestica*.[256]

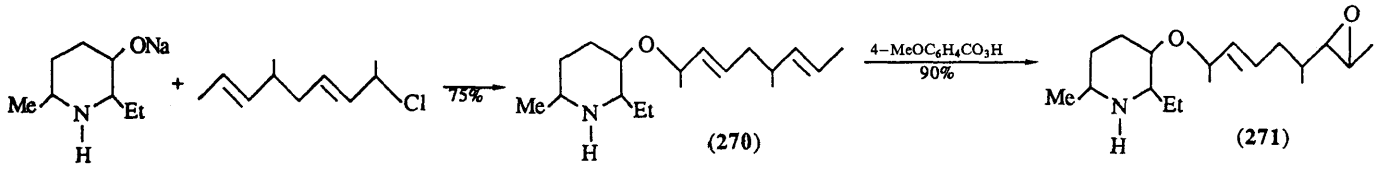


(**269**)

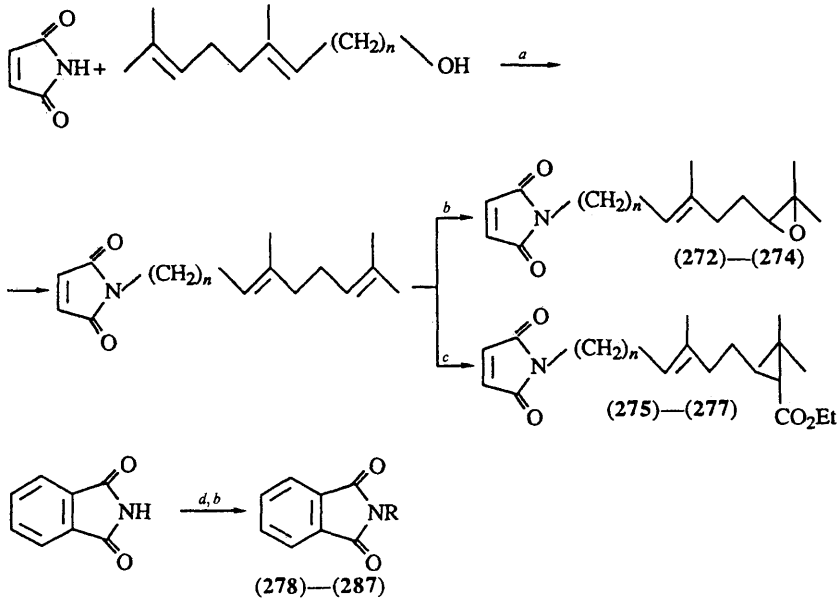
Oxa-AJH containing a piperidine ring (**270**) and (**271**) displayed selective activity towards *Coleoptera* (Scheme 85).[257]

Of the other AJH containing nitrogen heterocycles it is necessary to mention the derivatives of maleimide (**272**)–(**277**) and phthalimide (**278**)–(**287**).[258,259] Compounds (**278**)–(**287**) were tested for JH activity against *Dysdercus koenigii* and proved to be 1.5–2 times more active than methyl faranesenate (**152**). Compounds (**283**)–(**287**), containing an epoxy group in the isoprenoid group R, display higher activity (Scheme 86).

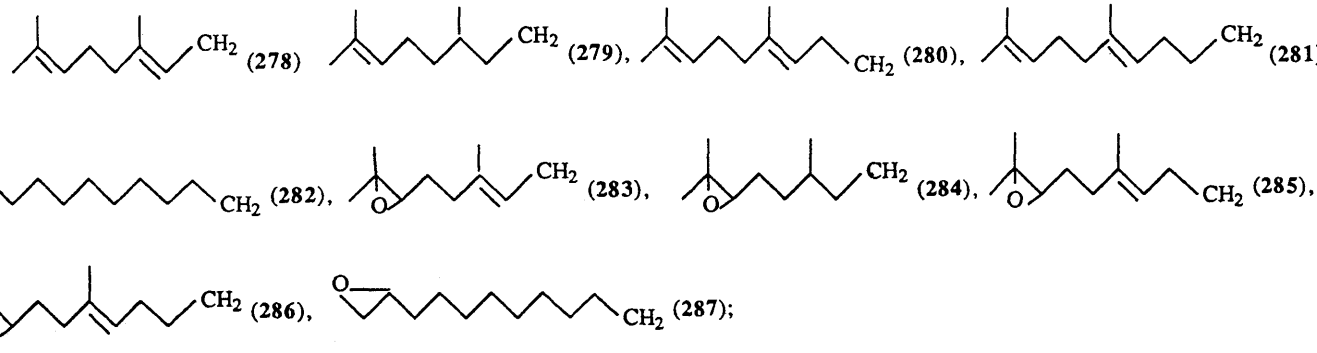
Scheme 85



Scheme 86

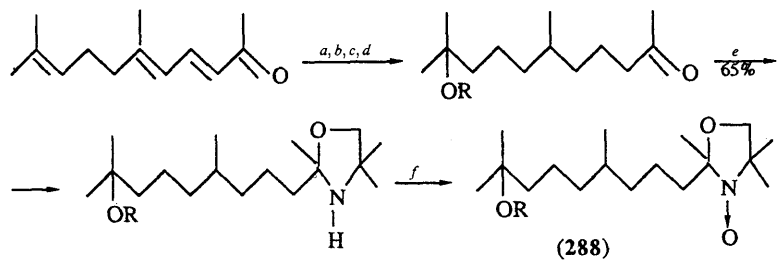


n = 1 (**272**), (**275**); 2 (**273**), (**276**); 3 (**274**), (**277**);

R = 

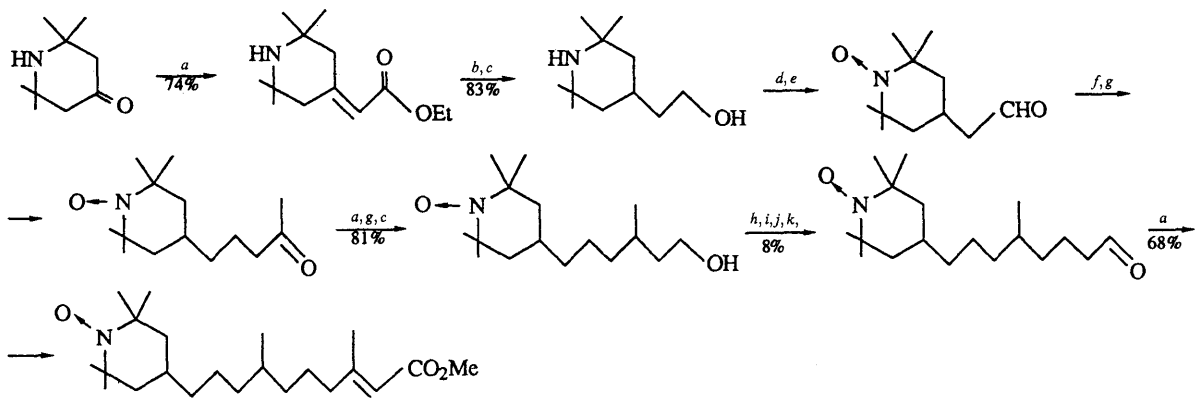
a: $PhP/N_2(CO_2Et)_2$; *b*: $3\text{-}ClC_6H_4CO_3H$; *c*: $N_2C(CO_2Et)_2$; *d*: ROH/PPh_3; $N_2(CO_2Et)_2$.

Scheme 87



(288)

R = Me, Et;
a: Ni–Re; *b*: $Hg(OAc)_2/ROH$; *c*: $NaOH/NaBH_4$; *d*: CrO_3; *e*: $Me(NH_2)_2C-CH_2OH$; *f*: $3\text{-}Cl-C_6H_4CO_3H$.

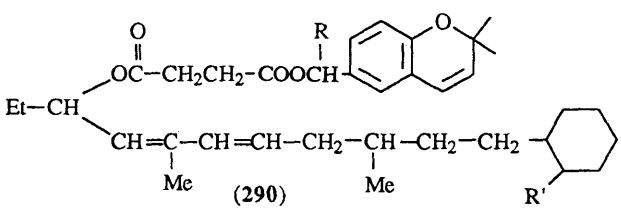


(289)

a: $(EtO)_2P(O)^{\ominus}CHCO_2Et$; *b*: $H_2/Ni-Re$; *c*: $LiAlH_4$; *d*: H_2O_2; *e*: CrO_3/Py; *f*: $Ph_3P=CHCH_2C(O)Me$; *g*: $H_2/Pd-BaSO_4$; *h*: TsCl/Py; *i*: NaI/. .acetone; *j*: $MeC(O)CH_2CO_2Et$; *k*: Δ.

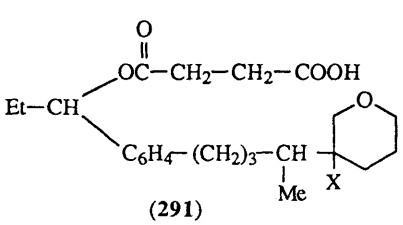
AJH with stable nitroxyl radicals in oxazolidine (**288**)[260] or piperidine (**289**)[261] rings have been synthesised and display high juvenoid activity (Scheme 87).[260,261]

The mixed succinic acid esters (**290**) and (**291**) proved to be active analogues of JH.[262,263]



(290)

R = Me, Et, Pr; R′ = H, Me, Et, Pr, iso-Pr:



(291)

X = H, Cl

To date, stereospecific methods of synthesising the natural juvenile hormones have been developed. Active analogues of the juvenile hormones, such as farnesal, methyl farnesenate, echinolone and juvabione, have been isolated from natural sources. The discovery in nature of JH analogues has stimulated investigation of the synthesis and study of the biological activity of compounds of various structures. Highly active juvenoids have become apparent in various classes of organic compounds. The most active juvenoids were found among the isoprenoid 2,4-dienoates and the aryl ethers of geraniol. The search for highly active and readily available JH analogues has been actively pursued since juvenoids are already recommended as effective and ecologically safe agents for regulating the insect population and an extension of their use for this purpose must be expected.

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