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Synthesis of compounds with juvenile hormone activity

K. MORI

Synthesis of bisabolene-type compounds

Our studies on juvenile hormones began in January, 1967, when I read Dr. Bowers's article (1) on the isolation and identification of juvabione (Ia). The parent acid of juvabione, that is, todomatuic acid (Ib) was originally isolated in 1940 from bisulfite-treated pulp oil of todomatsu (*Abies sachalinensis*) by Japanese chemists (2). Its correct plane structure was assigned by Momose in 1941 (3). We have already reported in detail the synthesis of its racemate (4). Then a synthesis of a mixture of dl-dehydrojuvabione (II) and its stereoisomer was accomplished starting from an intermediate employed in the synthesis of dl-juvabione (5). Demethyl-*ar*-juvabione (III) was prepared and shown to possess high juvenile hormone activity (6).

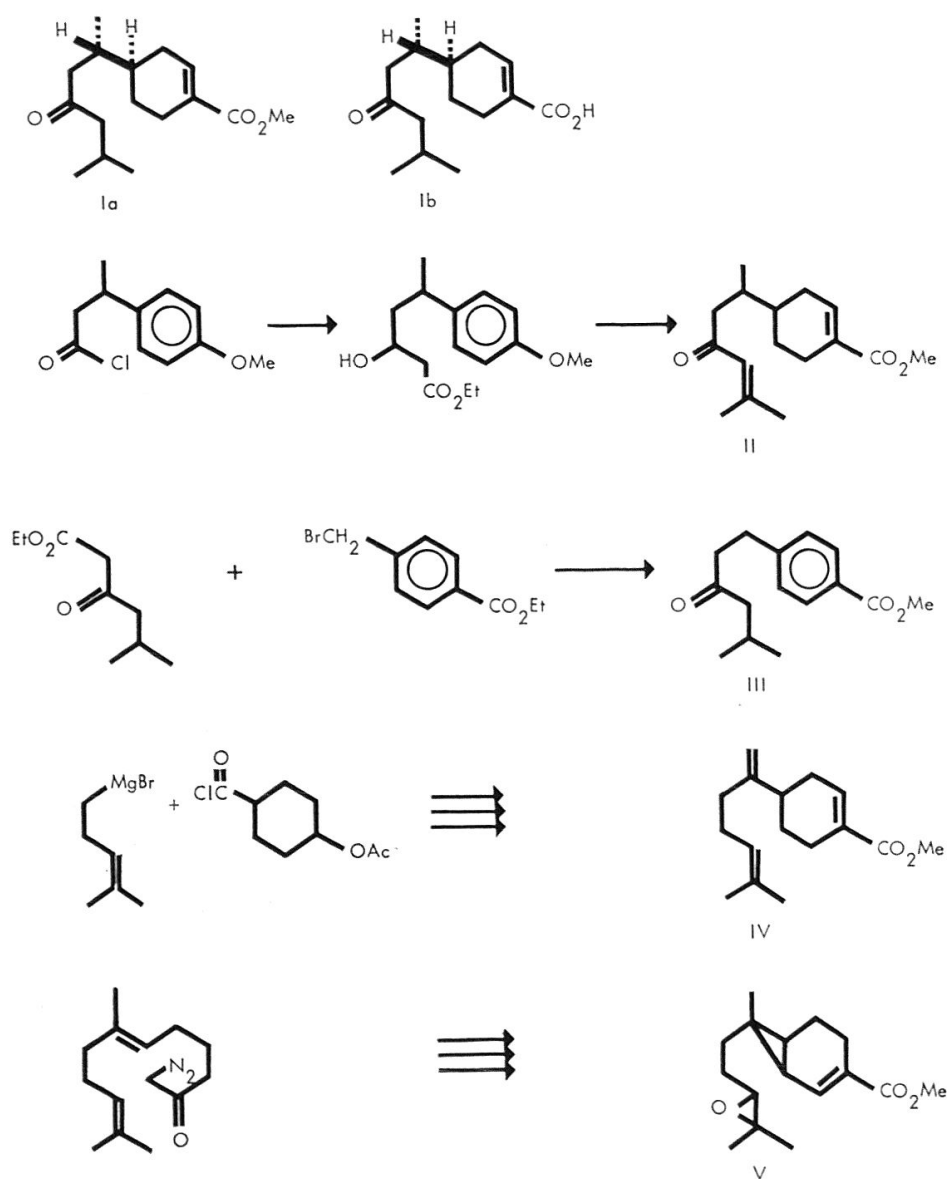
A simple β -bisabolene ester (IV) was also prepared by a multi-step synthesis (7). Compounds with sesquicarene skeleton such as V were obtained by intramolecular α -ketocarbene-olefin addition (Fig. 1) (8).

Figure 2 is the summary of our synthetic works on bisabolene-type sesquiterpene esters. Their juvenile hormone activity was tested on *Pyrrhocoris apterus* by Dr. W. S. Bowers. Racemic juvabione and dehydrojuvabione were also assayed by Dr. K. Sláma. Three compounds with sesquicarene skeleton were synthesized in the course of our work on sirenin (8). They, as well as dl-sirenin, were assayed on red cotton stainer, *Dysdercus koenigii*, by Dr. Bowers.

The first four compounds were very active and produced supernumerary nymphs at 10 μ g. The second four compounds were of intermediate activity at 10 μ g and produced nymphal-adult intermediates. Very little activity was exhibited by the next two compounds. At 10 μ g these two compounds produced adults with nymphal cuticle on the abdomen. The last two compounds were entirely inactive at 10 μ g and produced complete adults.

These results indicate that no clear-cut structure-activity relationship can be recognized at present. For example, demethyljuvabione (VI) (6) was inactive while its analogue with an aromatic ring (III) was quite active. Sirenin (VII), the plant sex hormone, was inactive (8).

Fig. 1

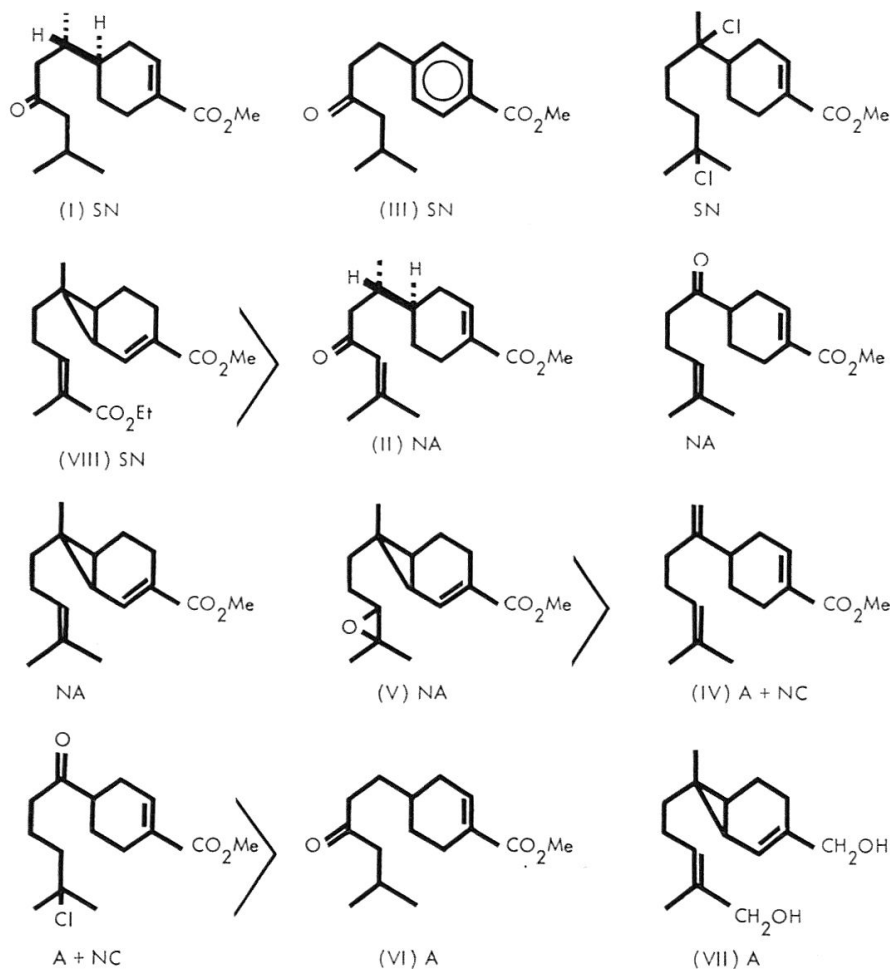


High activity was expected for the epoxy ester (V) with sesquicarene skeleton but its activity was weaker than that of the diester (VIII) (8).

An alternative approach to the stereospecific synthesis of C_{18} -*Cecropia* juvenile hormone

For a synthetic chemist, stereospecific syntheses of natural products are exciting challenges. In the case of the juvenile hormone this problem was solved by three independent groups headed by Dr. Corey, Dr. Siddall and Dr. Johnson, respectively.

Fig. 2
 JUVENILE HORMONE ACTIVITY OF BISABOLENE-TYPE COMPOUNDS on *Pyrrhocoris apterus* L. by topical treatment (10 μ g) of last instar nymphs



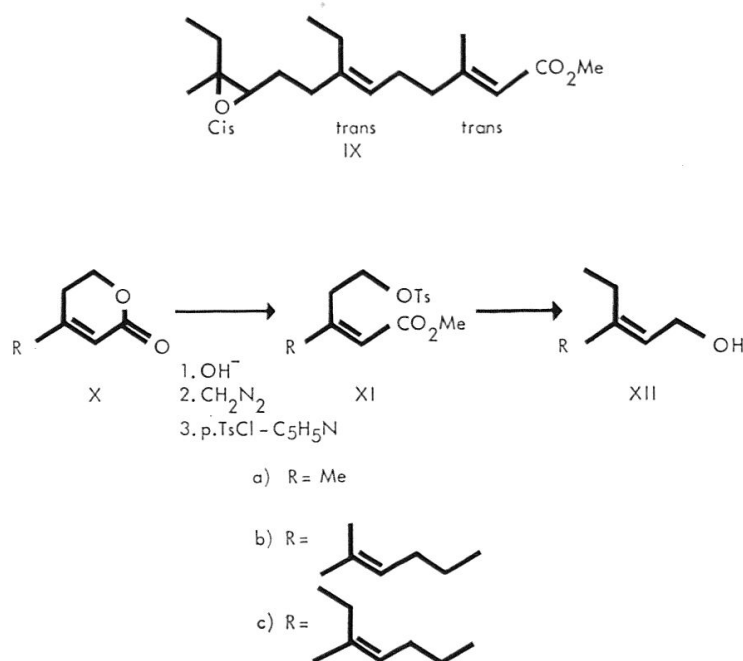
We report here a new approach to a stereospecific synthesis of *C*₁₈-*Cecropia* juvenile hormone (IX). At present we have obtained the *C*₁₂-*trans*, *cis*-alcohol (XIc).

The essence of our method lies in reductive conversion of α,β -unsaturated δ -lactones (X) into alcohols (XII) with retention of the geometry of the double bond via tosyloxy esters (XI) (Fig. 3).

The first example is the conversion of mevalonolactone (XVa) into the *cis*-*C*₆-alcohol (XIa, Fig. 4). This *C*₆-alcohol was previously obtained by Dahm, Trost and R  ller by a non-stereoselective synthesis involving separation of isomers (9).

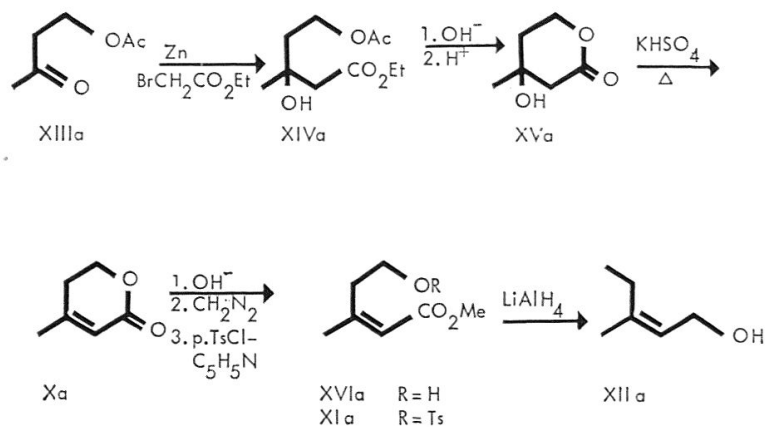
Fortunately the synthesis of methyl *cis*-5-hydroxy-3-methylpent-2-enoate (XVIa) had been recorded by Cornforth (10). We followed his method starting from 3-ketobutanol acetate (XIIIa). This ketone, upon Reformatsky reaction, gave a hydroxy ester (XIVa). This was

Fig. 3



hydrolyzed and cyclized to give mevalonolactone (XVa). Its dehydration took place readily when it was heated with potassium hydrogen sulfate to give an α,β -unsaturated δ -lactone [Xa, δ 2.00 (3H, s), 2.37 (2H, t, $J = 6$ Hz), 4.30 (2H, t, $J = 6$), 5.66 (1H, br. s) ppm]. This was hydrolyzed, methylated and tosylated to give crystalline tosyloxy ester (XIa), melting at $76-77^\circ$. Its reduction with lithium aluminum hydride yielded a gas-chromatographically homogeneous alcohol (XIIa, bp $74-76^\circ/26$ mm; n_D^{22} 1.4395) whose NMR spectrum supported the assigned structure [δ 1.01 (3H, t, $J = 7.5$ Hz), 1.72 (3H, s), 2.07 (2H, q, $J = 7.5$), 3.20 (1H, br., -OH), 3.98 (2H, d, $J = 7$), 5.29 (1H, t,

Fig. 4



with ethylene glycol in benzene in the presence of p-toluene-sulfonic acid to give a ketal (XIXb). Its reduction with lithium aluminum hydride gave an alcohol [XXb, δ 1.59 (3H, s), 1.65 (3H, s), 3.60 (2H, br.), 3.90 (4H, s), 5.04 (1H, br. t) ppm]. This was acetylated to give an acetate (XXIb, ν 1725 cm^{-1}). Then the ketal protective group was removed by acid hydrolysis to give an acetoxy ketone (XIIIb, ν 1730, 1705 cm^{-1}). We also prepared a bromoacetoxy ketone in the same manner (XIIIb, bromoacetyl instead of the acetyl group) and attempted an intramolecular Reformatsky reaction but it was unsuccessful. So we had to follow the same steps as used in the synthesis of *cis*-C₆-alcohol (XIIa). Conventional intermolecular Reformatsky reaction of the acetoxy ketone (XIIIb) with ethyl bromoacetate gave a hydroxy ester (XIVb) in a low yield. This was hydrolyzed and cyclized to the isoprenylogue of mevalonolactone [XVb, $\nu \sim 3400$, 1705 (br.) cm^{-1}]. Its dehydration afforded the desired δ -lactone (Xb) which showed expected NMR signals [δ 1.60 (3H, s), 1.68 (3H, s), 2.0–2.45 (6H), 4.28 (2H, t, $J = 6$), 5.02 (1H, br. s), 5.67 (1H, s) ppm]. This was converted into the desired *trans*-C₁₁-alcohol (XIIb) via an oily tosyloxy ester (XIb). The alcohol (XIIb) exhibited an NMR spectrum reasonably explained by the expected structure [bp 102–105°/6 mm; δ 1.00 (3H, t, $J = 7$), 1.60 (3H, s), 1.67 (3H, s), \sim 2.02 (6H, br.), 4.02 (2H, d, $J = 7$), 5.05 (1H, br., s), 5.30 (1H, t, $J = 7$) ppm]. The over-all yield of the alcohol was quite low at present. Further refinements in experimental conditions are necessary to improve the yield. Anyway, the *trans*-C₁₁-alcohol (XIIb) was synthesized stereospecifically.

In the same manner we have attempted the synthesis of the *trans*, *cis*-C₁₂-alcohol (XIIc) with two ethyl substituents. The starting material was the *cis*-C₆-alcohol (XIIa). The corresponding chloride was converted into *cis*-6-methyloct-5-en-2-one (XVIIc) by condensation with ethyl acetoacetate followed by hydrolysis and decarboxylation. Subsequent steps were familiar to us. The ketone (XVIIc) was carboethoxylated to a β -keto ester (XVIIIc). Its ketalization gave a ketal (XIXc). This yielded an alcohol (XXc) upon reduction and it was acetylated to give a ketal acetate (XXIc). The corresponding acetoxy ketone (XIIIc) was transformed into a hydroxy ester (XIVc) by the Reformatsky reaction. The hydroxy ester was hydrolyzed and cyclized to give a hydroxy lactone (XVc). This was dehydrated to afford a dihydro- α -pyrone (Xc). Its hydrolysis and the esterification of the resulting hydroxy acid gave a hydroxy ester (XVIc). The corresponding tosylate (XIc) was treated with lithium aluminum hydride to give the desired *trans*, *cis*-C₁₂-alcohol (XIIc). This was previously synthesized non-stereoselectively by Dahm, Trost and Röller (9) and stereospecifically by Corey and his co-workers (11). At present our synthetic material is somewhat impure but its NMR spectrum exhibited all the required signals.

The C₁₂-alcohol has been converted by the American chemists into C₁₈-*Cecropia* juvenile hormone in a stereospecific manner (11).

Non-stereoselective syntheses of the juvenile hormones and analogues

It seemed to be necessary to develop a new general method for the non-stereoselective synthesis of juvenile hormone analogues in order to clarify the effect of alkyl substituents (such as R, R', R'' and R''' in IX', Fig. 6) on biological activity. Before discussing this subject, we will review our previously reported synthesis of stereoisomeric mixtures of the juvenile hormones (12, 13). For example, a synthesis of methyl 14-homojuvenate (XXII) was accomplished as follows (Fig. 7) (13).

Fig. 6

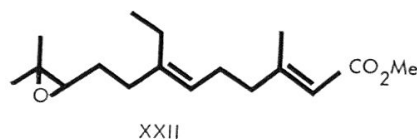
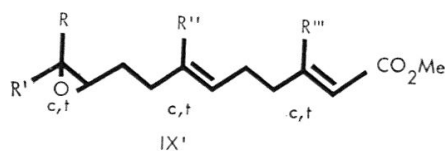
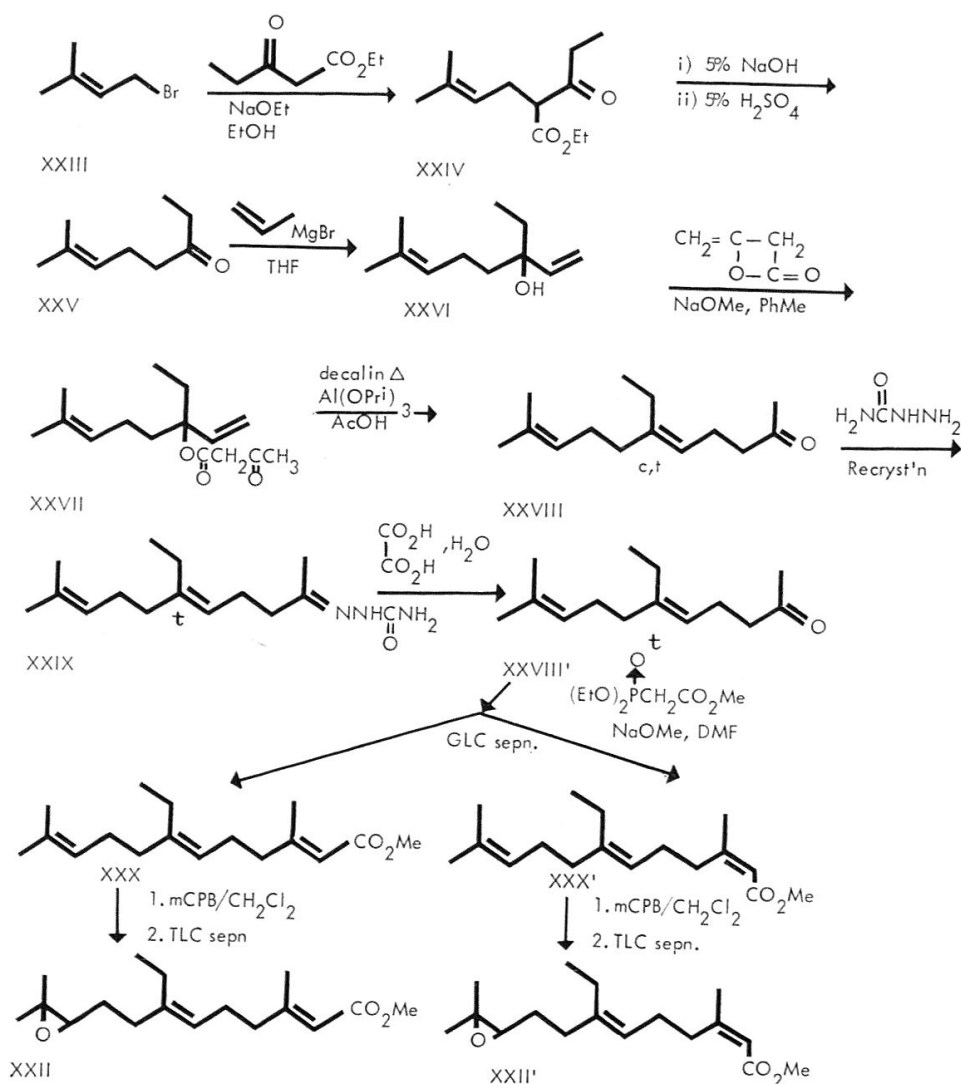


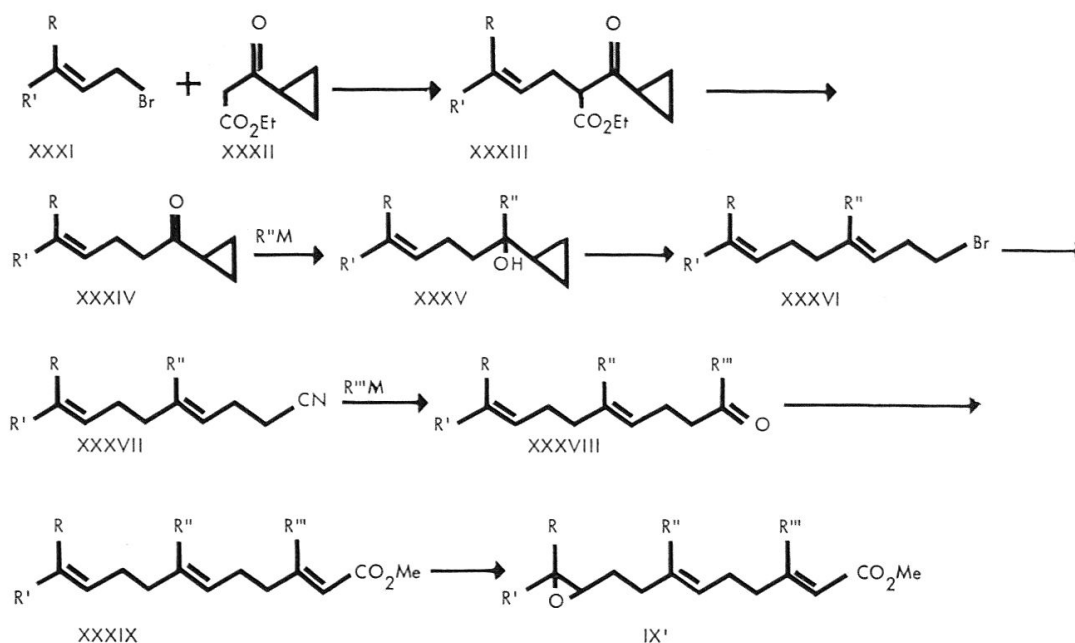
Fig. 7



Isoprenyl bromide (XXIII) was converted in the usual way to an ethyl ketone (XXV) via a β -keto ester (XXIV). The ketone (XXV) was treated with vinyl magnesium bromide to give a vinyl alcohol (XXVI). This was reacted with diketene. The resulting acetoacetate (XXVII) was pyrolyzed to give a mixture of *cis*- and *trans*-ketones (XXVIII). In our hands this Carroll reaction resulted in a low yield, that is, 36% yield of the ketone from the vinyl alcohol. Separation of the two stereoisomers was carried out by recrystallizing a crystalline semicarbazone (XXIX) of the *trans*-ketone. After regeneration by acid-hydrolysis, the *trans*-ketone (XXVIII') was obtained in 30% yield from the stereoisomeric mixture. The pure *trans*-ketone was treated with the phosphonoacetate carbanion. The resulting stereoisomeric mixture of esters (*cis*:*trans* = 1:4) were separated by preparative gas chromatography. The pure *trans*, *trans*- and *cis*, *trans*- esters (XXX and XXX') were separately epoxidized with *m*-chloroperbenzoic acid to give methyl 14-homojuvenate (XXII) and its stereoisomer (XXII'). In their NMR spectra the methyl group at C-3 of the *trans*-isomer absorbed at 2.12 ppm while that of the *cis*-isomer absorbed at 1.86 ppm.

Two drawbacks in this synthesis are the difficulty encountered in preparing a large amount of the necessary ethyl 3-oxopentanoate and the low yield observed in the Carroll reaction. This forced us to develop a new efficient route to the hormone. The new synthetic route was as follows (Fig. 8). An allyl bromide (XXXI) with alkyl groups, R and R', was condensed with a β -keto ester (XXXII) derived from methyl cyclopropyl ketone. The resulting substituted β -keto ester (XXXIII) was hydrolyzed and decarboxylated to give a cyclopropyl ketone

Fig. 8



(XXXIV). This was treated with an organometallic compound to introduce the third alkyl group R''.

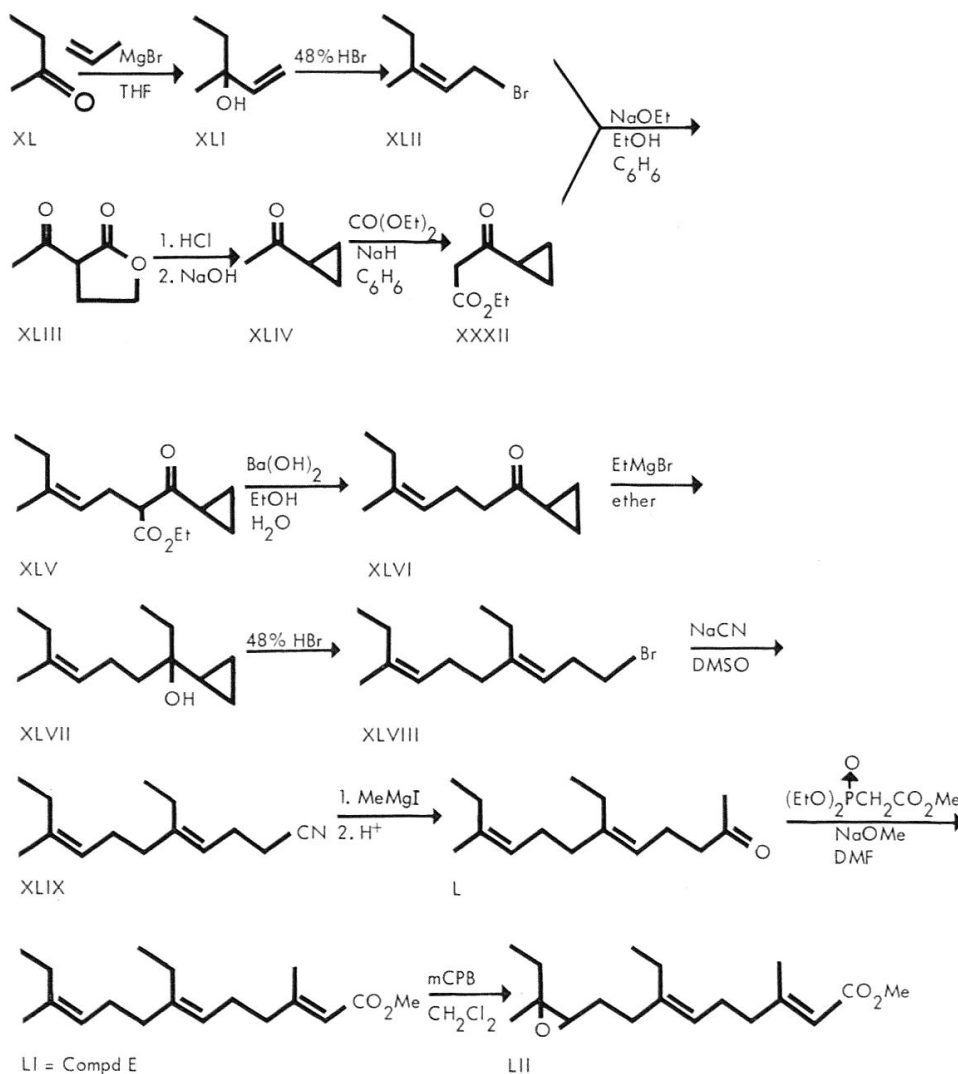
The cyclopropyl alcohol (XXXV) thus obtained was cleaved with hydrobromic acid to give an aliphatic bromide (XXXVI) as described by Julia (14). This gave a nitrile (XXXVII) when treated with sodium cyanide. Then an organometallic reagent R'''M was added to it to give a ketone (XXXVIII) after acid hydrolysis.

We could thus easily control the introduction of the four alkyl substituents. The latter half of our synthetic procedure (XXXV \rightarrow XXXVIII) coincides with the procedure described by Braun, Jacobson, Wakabayashi and their co-workers (15).

The ketone (XXXVIII) was converted into an unsaturated ester (XXXIX) by the Wadworth-Emmons modification of the Wittig reaction. Direct epoxidation with *m*-chloroperbenzoic acid or indirect epoxidation via bromohydrin afforded an epoxy ester (IX'). The direct epoxidation was more convenient for the preparative purpose.

We will illustrate our synthetic method choosing the C₁₈-*Cecropia* hormone for example (Fig. 9). Methyl ethyl ketone (XL) was condensed with vinyl magnesium bromide to give a vinyl alcohol (XLI). This was treated with hydrobromic acid to give a bromide (XLII). Another starting material was α -acetyl- γ -butyrolactone (XLIII). This was converted into methyl cyclopropyl ketone (XLIV) by the standard method. Its carbethoxylation afforded the β -keto ester (XXXII) in good yield. Alkylation of the β -keto ester with the bromide (XLII) gave a substituted β -keto ester (XLV). This was hydrolyzed and decarboxylated by heating under reflux with aqueous ethanolic barium hydroxide. The resulting cyclopropyl ketone [XLVI, ν 1690 cm⁻¹; δ 0.7–1.3 (4H), 0.99 (3H, t, *J* = 7), 1.61 (2.2H, s), 1.65 (0.8H, s), 5.04 (1H, t, *J* = 6) ppm; *trans* : *cis* = 2.7 : 1] was treated with ethyl magnesium bromide to give an alcohol (XLVII). The cleavage of the cyclopropane ring took place readily to give a bromide (XLVIII). Then the bromide (XLVIII) was treated with sodium cyanide in DMSO to give a nitrile (XLIX). This was treated with methyl magnesium iodide followed by dilute hydrochloric acid to give a methyl ketone [L, ν 1710 cm⁻¹, *trans* : *cis* (middle double bond) = 1.2 : 1] as a stereoisomeric mixture. Condensation of the ketone (L) in DMF with methyl diethyl phosphonoacetate in the presence of sodium methoxide afforded the C₁₈-unsaturated ester [LI, bp 130–142°/0.2 mm; δ 0.97 (6H, t, *J* = 7), 1.57 (2.2H, s), 1.64 (0.8H, s), 2.13 (s), 1.80–2.20 (~15H), 3.60 (3H, s), 5.01 (2H, br.), 5.56 (1H, s) ppm]. We could obtain 8.5 g of this material starting from about 30 g of the C₆-bromide (XLII) within 10 days. *m*-Chloroperbenzoic acid in methylene chloride smoothly oxidized the unsaturated ester to give a stereoisomeric mixture of C₁₈-*Cecropia* juvenile hormone [LII, bp 130–145°/0.2 mm, δ 0.97 (6H, t, *J* = 7), 1.16 (3H, s), 2.12 (s), 1.20–2.20 (~15H), 2.50 (1H, br.), 3.60 (3H, s), 5.05 (1H, br., s), 5.55 (0.7H, s), 5.60 (0.3H, s) ppm; Δ^2 *trans* : *cis* = 3 : 1]

Fig. 9



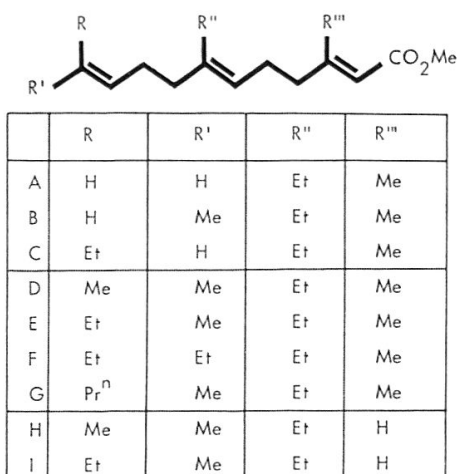
as the main product. The minor products were the position-isomeric epoxide and the diepoxide.

Nine unsaturated esters were synthesized by this method. R'' was fixed as ethyl and other alkyl substituents, R , R' and R''' , were varied to yield three groups of compounds (Fig. 10).

The first group (A, B and C) consists of compounds with one or no alkyl substituent at the terminal position. The second group (D, E, F and G) consists of compounds with two alkyl substituents at the terminal position. The third group (H and I) consists of two compounds lacking in a methyl substituent at C-3.

Compound C was synthesized from pent-2-ynyl bromide (LIII). The acetylenic ester (LIV) was hydrogenated over palladium-barium sulfate to give a *cis*-olefin [LV = compd. C, bp 113–125°/0.15 mm ;

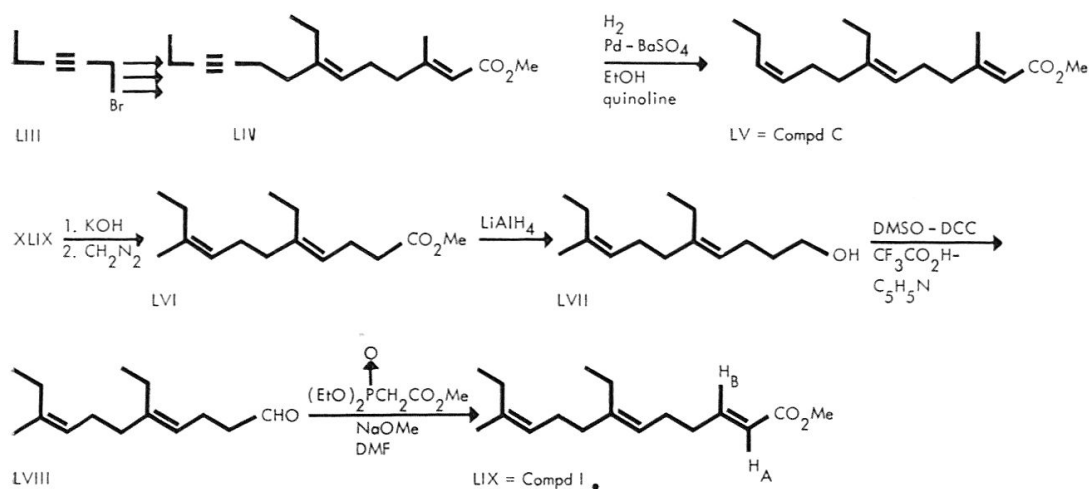
Fig. 10



δ 0.95 (6H, t, $J = 7$), 2.10 (s), 1.8–2.2 ($\sim 15\text{H}$), 3.58 (3H, s), 5.00 (1H, br., s), 5.22 (2H), 5.53 (1H, s) ppm]. This was epoxidized to give a mixture of epoxides. Judging from its NMR spectrum the major product was not the desired 10,11-epoxide but 6,7-epoxide (Fig. 11).

Compound I was synthesized as follows. The nitrile (XLIX) was hydrolyzed, methylated and reduced to give an alcohol (LVII). Its Pfitzner-Moffatt oxidation gave an aldehyde (LVIII). This, upon modified Wittig reaction, yielded an unsaturated ester [LIX = Compd. I, bp 105–107°/0.1 mm; δ 1.00 (6H, t, $J = 7$), 1.60 (2.2H, s), 1.67 (0.8H, s), 1.8–2.3 ($\sim 12\text{H}$), 3.68 (3H, s), 5.05 (2H, br.), 5.57 (H_A , d, $J = 16$), 6.88 (H_B , td, $J = 16$, $J' = 7$) ppm] in rather low yield. Epoxidation by *m*-chloroperbenzoic acid gave methyl 13-nor-12,14-dihomojuvenate as major product (Fig. 11).

Fig. 11



The bioassays of nine synthetic materials were kindly carried out by Drs. T. Mitsui and J. Fukami of Laboratory of Insect Toxicology, Institute of Physical and Chemical Research, Saitama, Japan.

Each compound was diluted with ethanol to 0.2 to 200 mg/ml and 0.5 μ l/pupa was applied topically to the ventral side of the abdomen of 10 to 20 pupae (within 24 hr-old) of the yellow mealworm (*Tenebrio molitor* L.) and rust-red flour beetle (*Tribolium castaneum* Herbst).

The treated pupae were then held until they molted normally to the adult stage or until morphological changes characteristic of juvenile hormone activity were noted. About 7 to 9 days at 27° were necessary.

Observations were made on five points as follows: pupal cuticle on abdomen, wholly pupal wing lobes, retention of gin trap and urogomphi and pupal genitalia. Each character was scored as one. Thus, perfect adult is scored as zero. The maximum score five is obtained by a complete second pupa or completely pupal-adult intermediate.

Average rating was calculated by multiplying the number of pupae by their numerical activity ratings and dividing the sum by the number of insects tested. The dead insects were excluded.

Table 1 shows the results obtained with *Tenebrio molitor*. Methyl *trans*, *trans*-farnesoate was used as the reference material. Compounds with one or no alkyl substituent at the terminal position were less active than methyl farnesoate, although methyl 15-nor-12,14-dihomofarnesoate (compd. C) showed considerable activity. Among compounds with two alkyl substituents those with higher alkyl groups were more active than methyl 12,14-dihomofarnesoate (compd. E). Two 13-nor compounds (H and I) exhibited higher activity than the parent compounds (D and E).

Table 2 shows the biological activity of epoxy esters. For convenience the oxirane group was assumed to be entirely at 10,11-position, although the major components of the esters of first group were 6,7-epoxides.

Here again compounds belonging to the first group were less active than methyl juvenate. Among compounds with two alkyl substituents, ethyl-ethyl (F') and n-propyl-methyl (G') compounds were shown to be more active than the C₁₈-*Cecropia* hormone (E'). Two 13-nor compounds (H' and I') exhibited higher activity than the parent compounds.

Table 3 shows the results obtained with *Tribolium castaneum*. In this case application of greater dose of the material caused death of the insects.

Compounds with one or no alkyl substituent showed considerable activity. The highest activity was observed with ethyl-ethyl (F) and n-propyl-methyl (G) compounds. The 13-nor compounds (H and I) were also quite active.

The activity of methyl juvenate and its homologues on *Tribolium castaneum* was summarized in Table 4.

Table 1

JUVENILE HORMONE ACTIVITY on *Tenebrio molitor* L.

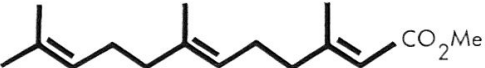
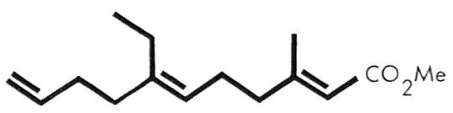
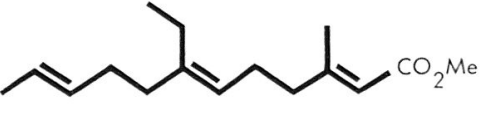
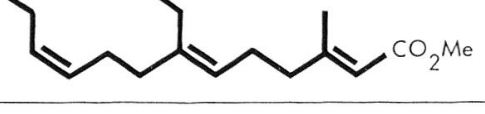
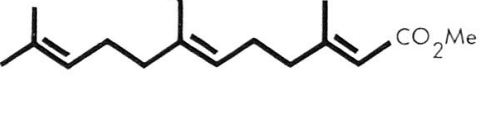
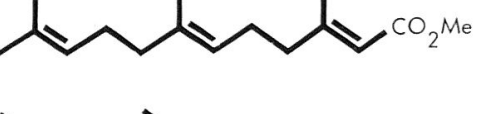
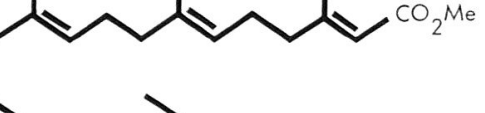
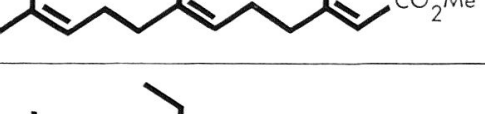
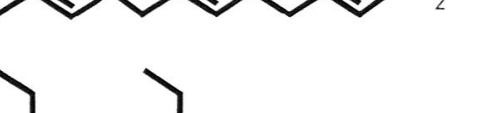

Compounds		μg		
		100	10	1
A		5.0	0.6	0.1
		0.1	—	—
		1.2	0	—
		4.8	0.2	0.3
D		5.0	0.6	0
E		5.0	1.9	0.4
F		5.0	3.7	0.4
G		5.0	5.0	0.1
H		5.0	1.2	0.4
I		5.0	5.0	0.7

Table 2

JUVENILE HORMONE ACTIVITY on *Tenebrio molitor* L.

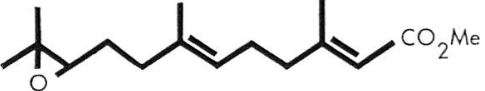
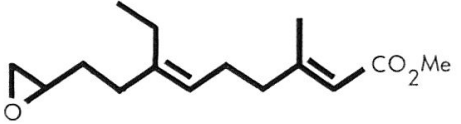
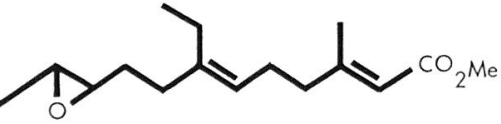
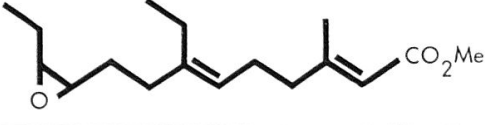
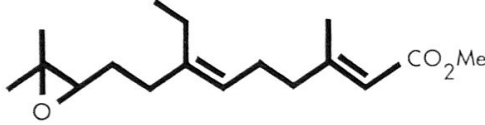
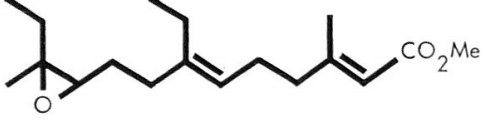
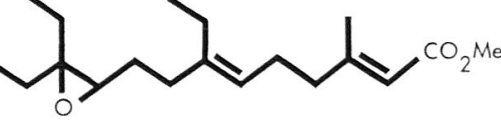
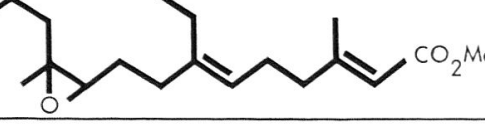
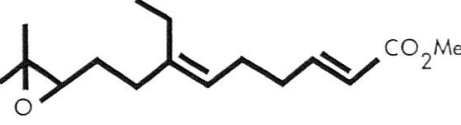
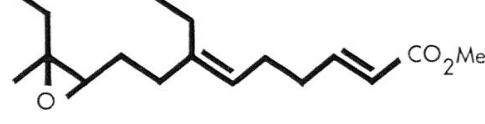
Compounds		μg		
		100	10	1
		4.8	5.0	0.2
A'		0.5	—	—
B'		2.3	0.1	—
C'		3.8	0.6	0.1
D'		5.0	4.8	0.1
E'		5.0	5.0	0.7
F'		5.0	5.0	3.0
G'		5.0	5.0	1.4
H'		5.0	5.0	0.8
I'		5.0	4.0	4.9

Table 3


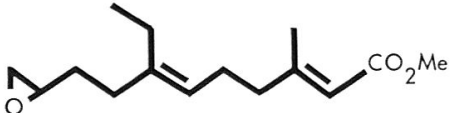
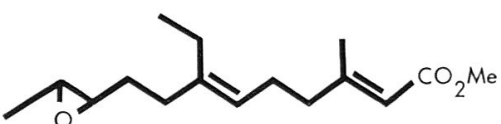
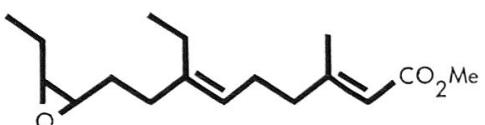
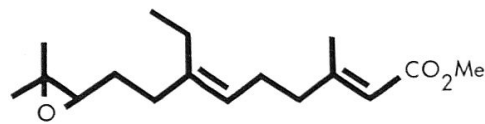
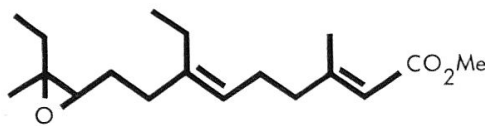
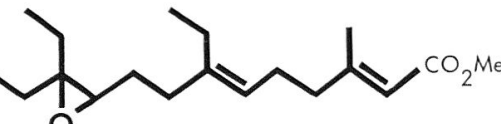
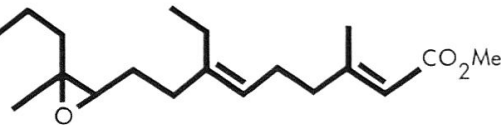
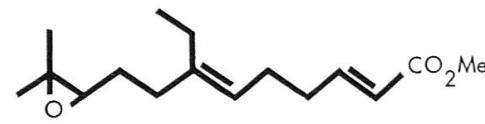
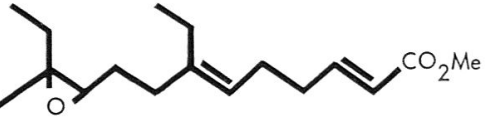
JUVENILE HORMONE ACTIVITY on *Tribolium castaneum* Herbst

Compounds		μg		
		100	10	1
A			0.8	0
		4.0 (D*70%)	—	—
		4.3 (D 65%)	1.8	—
		4.1 (D 60%)	3.7	0.2
D		4.6 (D 65%)	4.4	0.3
E		D	5.0	1.0
F		4.7 (D 45%)	4.8	5.0
G		5.0 (D 55%)	4.8	5.0
H			5.0	1.1
I			5.0	2.2

*D = death

Table 4

JUVENILE HORMONE ACTIVITY on *Tribolium castaneum* Herbst

Compounds		μg		
		100	10	1
A'		5.0	2.3	
		3.0 (D 30%)	2.4	
		3.7 (D 55%)	1.7	
		4.3 (D 65%)	3.6	0
D'		4.6 (D 50%)	4.9	3.4
E'		4.9 (D 45%)	5.0	4.2
F'		4.6 (D 45%)	5.0	4.8
G'		4.7 (D 65%)	4.9	5.0
H'		5.0	5.0	3.3
I'		5.0	5.0	5.0

Here again compounds belonging to the first group showed considerable activity. The higher activity was observed with ethyl-ethyl (F'), propyl-methyl (G') and ethyl-ethyl 13-nor-compounds (I'). Since syntheses of compounds belonging to the first and second groups were carried out in entirely the same manner, these differences in biological activity were taken to mean the effect of terminal alkyl substituents on biological activity.

These results led us to the following conclusions.

1. Compounds with one or no alkyl substituent at the terminal position were less active.
2. Compounds with two ethyl groups or n-propyl and methyl groups at the terminal position were more active than the *C₁₈-Cecropia* juvenile hormone.
3. Removal of the methyl group at position 3 does not decrease but rather increases the activity.

Our investigations on the effect of alkyl substituents on biological activity are still continuing. We are planning to synthesize more 13-nor compounds by a different route. Synthesis of 13,14-bisnor compounds are also planned to see whether the alkyl substituent at C-7 is necessary for the activity or not.

Compounds were also applied topically to the ventral side of 10 pupae (within 24 hr-old) of rice stem borer (*Chilo suppressalis* Walker). The treated pupae were then held at 27° for about 10 days. Normal pupae ecdysis to adult after about 7 days. Morphological changes characteristic of JH activity are not yet well studied, but most of the treated pupae were observed to fail molting to adult moths by 10–100 µg of juvenile hormones.

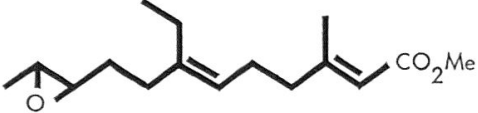
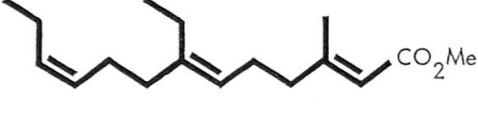
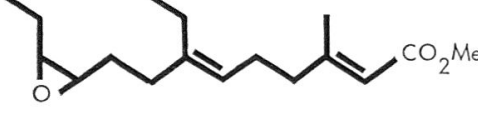
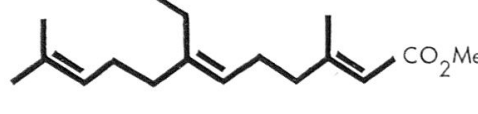
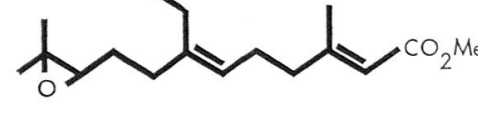
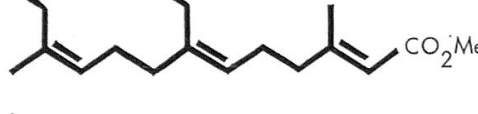
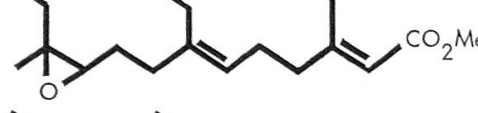
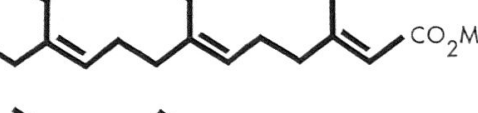
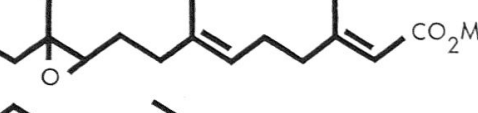
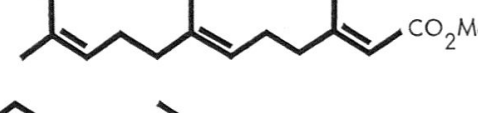
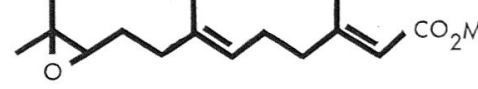
Dr. T. Ohtaki of National Institute of Health, Japan, kindly tested the activity of our material on mosquito, *Culex pipiens*. The juvenile hormone analogues were suspended in water with emulsifier. Thirty of late third instar larvae of *Culex pipiens* were transferred to trays which contained 200 ml of juvenile hormone suspension.

At the concentration of 10 ppm almost all of the unsaturated esters were quite active and killed the test insects. The n-propyl-methyl compound (G) was the most active. It is to be noted that in this case the epoxy esters were less active than the unsaturated esters.

The effect of the juvenile hormones on silkworm, *Bombyx mori*, was studied by Dr. Ohtaki. A large cocoon was spun by a normal fifth instar larva. A small one was spun by an allatectomized fourth instar larva. When juvenile hormone was applied to this allatectomized fourth instar larva one more larval molt was induced and the insect spun a cocoon of normal size. The necessary dose for 50% induction of larval molt was 0.6~14 µg by injection.

Table 5

TOXICITY on *Culex pipiens* LARVAE (per cent mortality)

Compounds		ppm		
		10	1	0.1
B'		97.5	0	1.3%
C		91.4	79.2	0
C'		88.6	0	—
D		97.5	37.6	0
D'		98.4	14.0	0
E			35.0	23.4
E'		97.4	14.8	16.1
F		97.5	41.6	31.2
F'		81.4	9.1	15.5
G		100.0	48.0	7.1
G'		100.0	13.7	1.3

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