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Ethyl (*E*)-3,5-Ethano-7,11-Dimethyl-2,4-Dodecadienoate, A New Insect Growth Regulator with Potent Juvenile Hormone Activity[1,2]

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A number of analogs of ethyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoate were prepared and bioassayed for juvenile hormone activity on the yellow-fever mosquito (*Aedes aegypti*), the greater wax moth (*Galleria mellonella*), the yellow mealworm (*Tenebrio molitor*), the house fly (*Musca domestica*), and the tobacco budworm (*Heliothis virescens*). The analog ethyl (*E*)-3,5-ethano-7,11-dimethyl-2,4-dodecadienoate (VI), containing a cyclopentene ring, showed remarkable potency on the above insect species. Since this compound possesses a fixed 3-s-*trans*-diene conformation it may provide some insight into the active conformation of bound 2,4-dienoate analogs.

The natural juvenile hormones of *Hyalophora cecropia*, which are produced and secreted by the corpora allata, have been identified as I and II (*1*). The hormones are responsible for the maintenance of juvenile characteristics during the larval molting. The compound III is also a naturally occurring juvenile hormone and was first isolated (along with II) from organ cultures of corpora cardiaca–allata complexes of *Manduca sexta* (*2*) (Fig. 1).

The racemic hormones I and II have been synthesized many times with varying degrees of stereoselectivity (*3*, *4*). Since the *E* configurations of the two double bonds in I and II are important for high biological activity (*3*), considerable effort has been expended in the development of stereoselective methods for the synthesis of such trisubstituted double bonds. Professor W. S. Johnson and co-workers have synthesized both I and II by stereoselective routes (*5–7*), and in the process they developed a

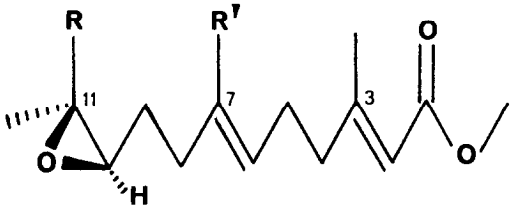

FIG. 1. I: R = R′ = CH_2CH_3 (JH I); II: R = CH_2CH_3, R′ = CH_3 (JH II); III: R = R′ = CH_3 (JH III).

[1] We dedicate this paper to Professor William S. Johnson with gratitude and appreciation for many stimulating discussions.

[2] Contribution No. 65 from the Research Laboratory, Zoecon Corporation.

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versatile method for the synthesis of trisubstituted double bonds, based on an *ortho*-ester Claisen rearrangement (*8*). The absolute configuration of I was established by Faulkner and Peterson (*4d*, *9*), by means of asymmetric synthesis, as 10*R*,11*S*. Other workers also arrived at the same conclusion by determination (*10*) of the chirality of the 10,11-diol derived from chiral I synthesized by Loew and Johnson (*11*) and also by asymmetric esterification of the diol prepared from natural I (*12*).

The natural juvenile hormones I, II, and III are, in general, not commercially useful for the control of insect populations. These compounds usually do not show high

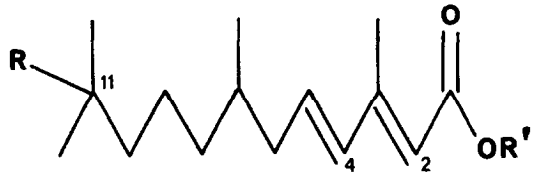
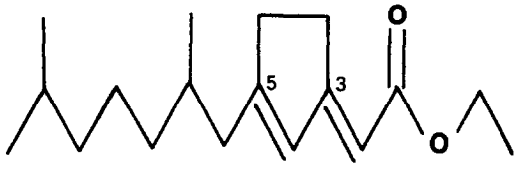


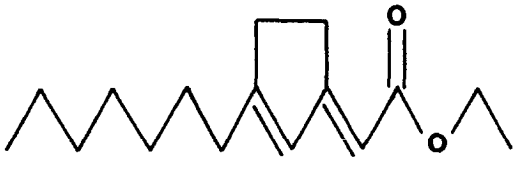
FIG. 2. IV: R = OCH_3, R' = $CH(CH_3)_2$; V: R = H, R' = CH_2CH_3.

potency on insect pest species, they have poor field stability, and their structural complexity has hindered the development of economically feasible syntheses. As a consequence, thousands of related compounds have been synthesized and bioassayed during the past decade in attempts to overcome these deficiencies. In general, the emphasis has been on the requirement of high biological activity, although in order to ensure that the analog is available when the target insect species reaches a sensitive stage in its life cycle, it is also necessary to develop compounds with sufficient field stability.

One class of highly potent insect growth regulators (IGRs) with juvenile hormone activity is the alkyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoates (*13–15*). The ability of several analogs of this group to interfere with the metamorphosis of the larvae and pupae of many insect species has been extensively studied (*16*). For example, methoprene (trademark Altosid IGR; ZR 515, IV) is highly effective in controlling many dipterous species by disrupting their metamorphosis, or at least by preventing the emergence of adults. Hydroprene (trademark Altozar IGR: ZR 512, V)



VI



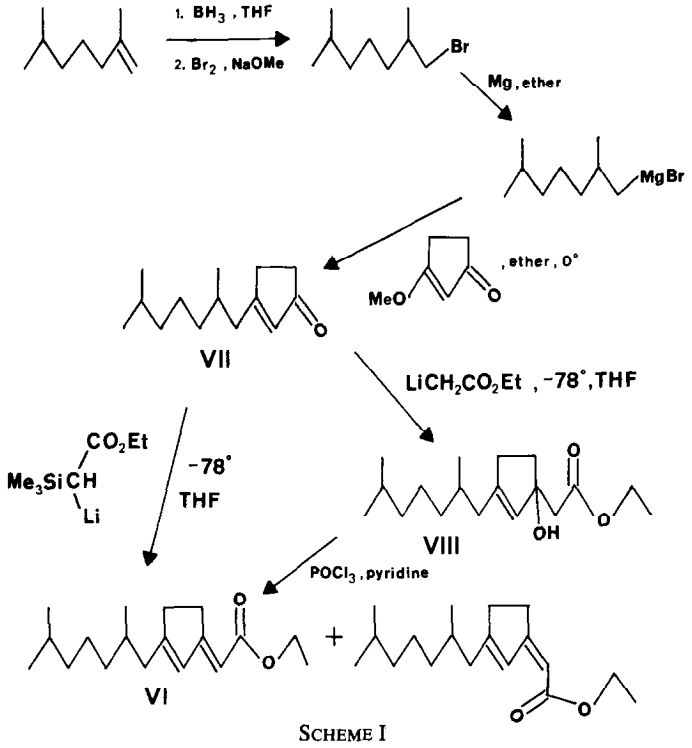
X

FIGURE 3

is very active on many insect species belonging to the orders Lepidoptera, Coleoptera, and Homoptera (Fig. 2). In previous papers we have discussed synthetic methods for the preparation of each of the four stereoisomers (*17*) and general synthetic routes to these compounds (*18*). We have also discussed detailed structure–biological activity relationships for this class of juvenile hormone analogs (*16, 17, 19*) including the considerable differences in biological activity observed for the 7*R* and 7*S* enantiomers of some of these 2,4-dienoates (*20*). We describe here the synthesis and biological activity of some racemic analogs with relatively rigid ring systems, including the remarkably active analog VI, which contains a cyclopentene ring and possesses a fixed 3-s-*trans*-diene conformation (*19, 21*) (Fig. 3).

SYNTHESIS

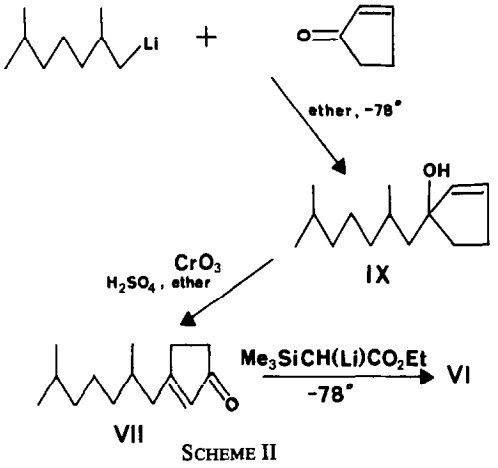
The cyclopentene analog VI was prepared as outlined in Scheme 1. Hydroboration of 2,6-dimethyl-1-heptene followed by treatment with bromine and sodium methoxide according to the procedure of Brown and Lane (*22*) gave 1-bromo-2,6-dimethylheptane



SCHEME I

which was then converted to its Grignard reagent. Reaction of 2,6-dimethylheptylmagnesium bromide with 3-methoxy-2-cyclopenten-1-one, followed by acidic hydrolysis, gave 3-(2,6-dimethylheptyl)-2-cyclopenten-1-one (VII) in low yield. Reaction of this enone VII with the lithium enolate of ethyl trimethylsilylactate (*23*) (generated with lithium diisopropylamide in tetrahydrofuran at −78°C) gave a mixture of the 2*E* isomer VI and the corresponding 2*Z* isomer in the ratio of 1 : 1. These isomers were then

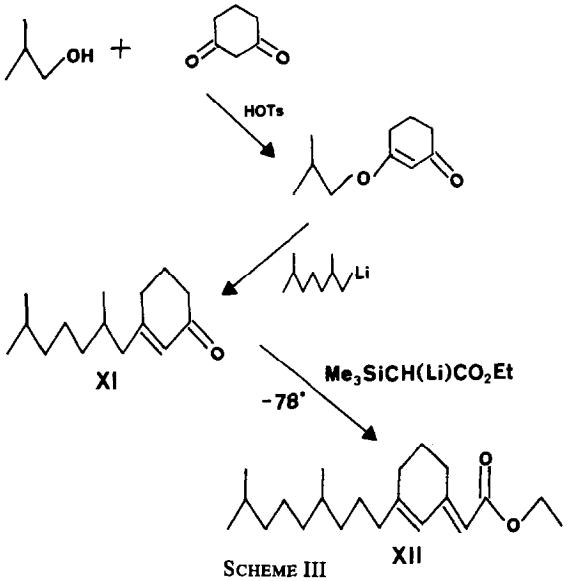
separated by preparative thin-layer chromatography (tlc) on silica gel. Alternatively, the enone VII was treated with ethyl lithioacetate (*24*) to give the hydroxy ester VIII which was then dehydrated with phosphoryl chloride in pyridine to give a mixture of the 2*E* and 2*Z* isomers along with decongugated isomers. The 2*E* isomer VI was isolated by preparative tlc as before.



SCHEME II

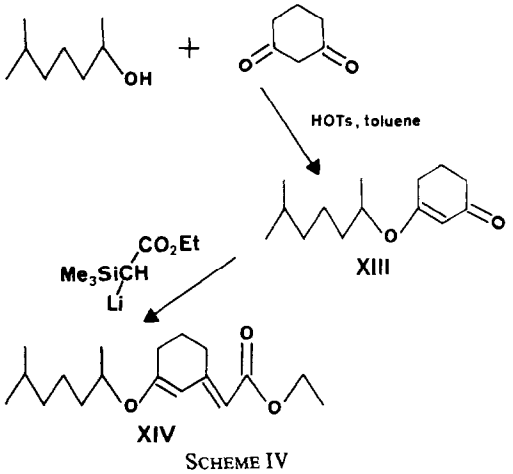
The enone VII could be prepared (Scheme 2) in much higher yield by the reaction of 2,6-dimethylheptyllithium with 2-cyclopenten-1-one to give IX followed by oxidative rearrangement of the allylic alcohol IX to VII with chromic acid (cf., *25*). The analog X was prepared by an analogous route starting with *n*-heptyllithium and 2-cyclopenten-1-one.

The analog XII was prepared in a similar manner (Scheme 3) by the reaction of 3-isobutoxy-2-cyclohexen-1-one with 2,6-dimethylheptyllithium in ether to give the enone XI, and then condensation of XI with ethyl lithiotrimethylsilylacetate. Purification of the product by preparative tlc gave the 2*E* isomer XII. Reaction of 1,5-dimethyl-



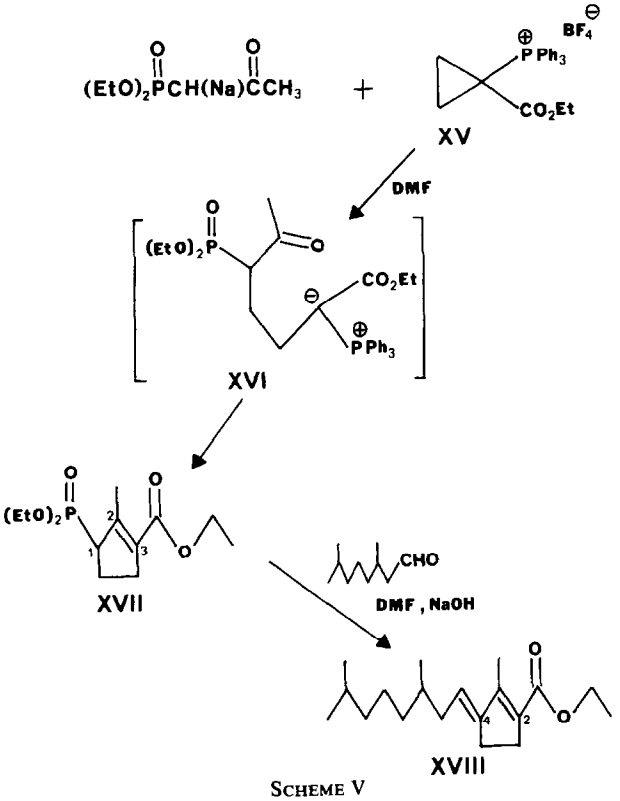
SCHEME III

hexanol and 1,3-cyclohexanedione in toluene in the presence of *p*-toluenesulfonic acid gave the enone XIII. Condensation of XIII with the lithium salt of ethyl trimethylsilylacetate then gave XIV (Scheme 4).



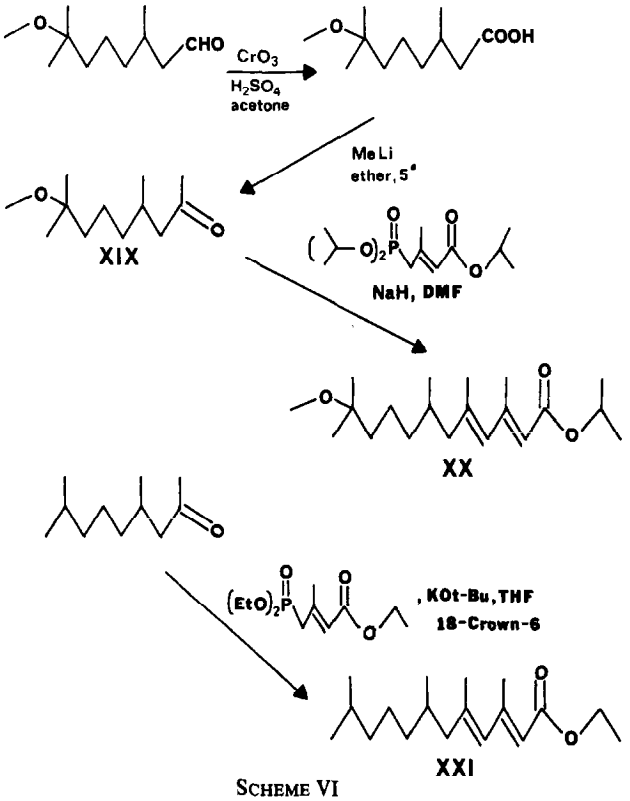
SCHEME IV

The cyclopentene analog XVIII was prepared as outlined in Scheme 5. Thus, reaction of 1-ethoxycarbonylcyclopropyltriphenylphosphonium fluoroborate XV with the anion of diethyl 2-oxopropylphosphonate gave the phosphonate XVII (cf. *26*). Condensation of the phosphonate XVII with 3,7-dimethyl-1-octanal then gave the ester XVIII.



SCHEME V

The 3,5,7,11-tetramethyl analog XX was prepared (Scheme 6) by condensation of the ketone XIX with the anion of diisopropyl 3-isopropoxycarbonyl-2-propenyl-phosphonate (cf. *14*). This reaction proceeded in low yield and gave XX as a mixture of isomers. The analog XXI was prepared in much better yield by using modified condensation conditions (utilizing the potassium salt of the phosphonate and adding 18-crown-6) and careful purification gave the *E,E* isomer.



SCHEME VI

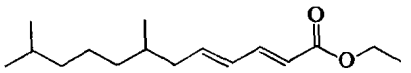
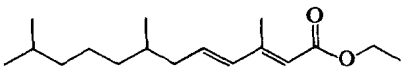
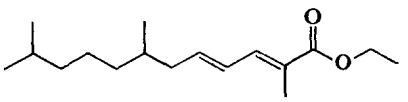
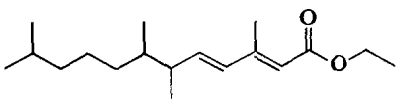
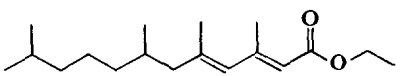
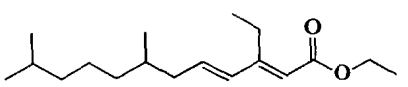
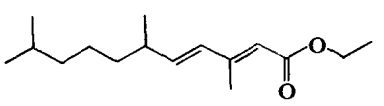
The C-3 ethyl analog XXIX (Table 2) was prepared by the condensation of 7-methoxy-3,7-dimethyl-1-octanal with diethyl 3-ethylglutaconate followed by decarboxylation, and isomerization (but without purification via the ammonium salt) as described previously for the preparation of IV (*18a*). The product was a mixture of the 2*E*,4*E* and 2*Z*,4*E* isomers in the ratio 56:42.

RESULTS AND DISCUSSION

In most juvenile hormone analogs the presence of alkyl branches along the carbon chain is very important for high biological activity, and compounds lacking two or more of the alkyl branches have very low insect activity (e.g., *16*, *27*). In the 2,4-dienoate compounds the addition of alkyl branches at C-7 and at C-11 markedly improves activity (*16*, *19*). However, the presence or absence of a methyl branch at C-3 is especially important in this series of analogs. The analog XXII, which lacks the C-3

TABLE 1

ID_{50} VALUES FOR SOME ETHYL ESTERS ON SENSITIVE SYNCHRONIZED INSTARS[a]

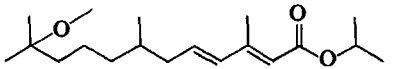
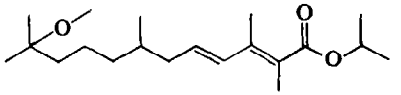
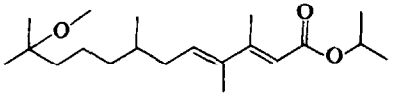
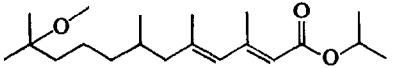
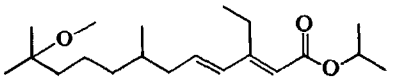
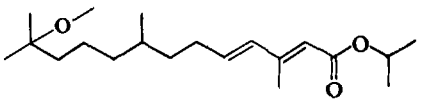
No.	Structure	*Aedes aegypti* (ppm)	*Galleria mellonella* (μg/pupa)	*Tenebrio molitor* (μg/pupa)	*Musca domestica* (μg/prepupa)	*Heliothis virescens* (ppm in medium)
XXII		4.9	4.4	34	57	200
V[b]		0.0078	0.040	0.25	18	0.30
XXIII		>0.01	>100	>100	>100	>300
XXIV		0.12	0.39	2.7	1.1	0.60
XXI		0.75	44		50	>1
XXV		0.053	5.0	4.4	31	13
XXVI		2.8	70	84	>100	>100

[a] Bioassays were performed as previously described (*14*, *17*).

[b] Hydroprene (trademark Altozar IGR; ZR 512).

TABLE 2

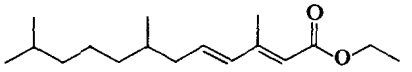
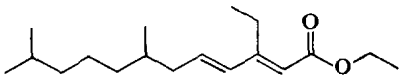
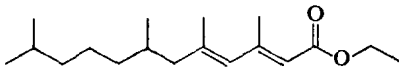
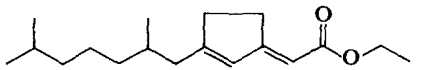
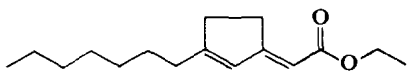
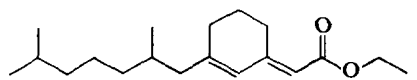
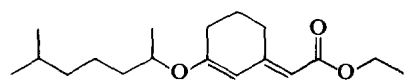
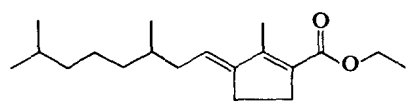
ID_{50} VALUES FOR SOME ISOPROPYL ESTERS ON SENSITIVE SYNCHRONIZED INSTARS

No.	Structure	*Aedes aegypti* (ppm)	*Galleria mellonella* (μg/pupa)	*Tenebrio molitor* (μg/pupa)	*Musca domestica* (μg/prepupa)	*Heliothis virescens* (ppm in medium)
IV[a]		0.00017	5.7	0.0040	0.0035	0.77
XXVII		0.0051	80	0.056	0.55	0.66
XXVIII		0.041	>100	0.68	1.4	13
XX		0.073	>100	1.5	0.40	>100
XXIX		0.024	>10	>0.1	>0.1	>10
XXX		>0.047	>10	>100	>0.2	>100

[a] Methoprene (trademark Altosid IGR; ZR 515).

TABLE 3

ID_{50} VALUES FOR SOME CYCLIC ANALOGS ON SENSITIVE SYNCHRONIZED INSTARS

No.	Structure	*Aedes aegypti* (ppm)	*Galleria mellonella* (μg/pupa)	*Tenebrio molitor* (μg/pupa)	*Musca domestica* (μg/prepupa)	*Heliothis virescens* (ppm in medium)
V		0.0078	0.040	0.25	18	0.30
XXV		0.053	5.0	4.4	31	13
XXI		0.75	44		50	>1
VI		0.0030	0.0029	0.0085	0.027	0.0085
X		—	30	—	—	>300
XII		0.21	>10	10	3.3	130
XIV		0.22	>100	>100	>100	>100
XVIII		>0.1	45	~100	>100	9.2

methyl group, shows considerably lower morphogenetic activity than does V (Table 1). In contrast, it has been found that the presence of a C-3 methyl group is *not* very important for analogs of methyl 10,11-epoxyfarnesoate (III). In this series of analogs, the morphogenetic activity on a number of insect species was found to be similar for compounds with H or methyl substituents at C-3 (with the 3-H analogs often showing higher activity) (*28*).

Movement of the C-3 methyl branch in V to C-2 to give compound XXIII (Table 1) essentially removes the morphogenetic activity. The analog XXIII is even less active than the 7,11-dimethyl compound XXII. In contrast, adding an additional methyl group at C-2 (compound XXVII vs compound IV, Table 2) merely reduces potency. The addition of an extra methyl group at C-4 (compound XXVIII vs compound IV, Table 2) greatly reduces the observed activity, as does the joining of these two branches to form a two-carbon bridge linking C-2 to C-4 as in compound XVIII (Table 3). Addition of an extra methyl group at C-5 (compounds XXI, Table 1 and XX, Table 2) also gives analogs which show much lower activity. Ethyl (2*E*,4*E*)-3,6,7,11-tetramethyl-2,4-dodecadienoate (XXIV; Table 1) shows higher activity on *Musca domestica* in comparison with that shown for V, but somewhat lower activity on the other insect species in Table 1.

When the C-3 methyl group in V is replaced an ethyl group to give XXV, the observed activity is considerably lower (Table 1) (cf. also XXIX, Table 2). *However, when the C-3 ethyl branch is joined to C-5 to form the compound VI containing a five-membered ring, a remarkable increase in the potency is observed* (Table 3). The cyclopentene analog VI is very active on all of the insect species in Table 3 (cf. V and XXV). The corresponding 2*Z* isomer shows, as expected (*17*), very low activity. Homologation of the ring in VI resulting in the analog XII, containing a six-membered ring, removes most of the morphogenetic activity (Table 3).

The juvenile hormone activity in the 2,4-dienoate series is very dependent on the isoprenoid nature of the carbon chain (*16*). Compounds such as XXVI (Table 1), with one less carbon atom between the first two methyl branches, and also analogs like XXX (Table 2), with one extra carbon atom between these branches, show very low activity. The cyclopentene analog X (Table 3), which lacks both the C-7 and the C-11 methyl groups, also has low activity.

The high morphogenetic activity shown by VI implies that the structure of this compound approaches the ideal combination of a reasonably planar active conformation of the carbon atoms 1 through 6 of the dienoate with appropriate but not excessive steric bulk in the region occupied by the C-3 methyl group of V. The compound VI possesses a fixed 3-s-*trans*-diene conformation, and its high activity suggests that the 2,4-dienoate analogs need to assume this conformation when bound to the active site.

EXPERIMENTAL

Bioassays were performed on synchronized sensitive stages of the five insect species and the activities are expressed as ID_{50} or IC_{50} values (dose or concentration required to produce 50% inhibition of metamorphosis). The bioassay procedures have been previously described (*14*, *17*). The responses were calculated as percentages of the

maximum attainable (fully larval characteristics) on a graded-response scale and plotted against the dose on semilogarithmic paper. The ID_{50} dose was taken from the intersection of this plotted line with the 50% effect level. For each compound, several assays performed on different days with fresh dilutions, were averaged to obtain the data given in the tables.

Preparative thin-layer chromatography (tlc) was carried out on 1-m × 20-cm plates coated with 1.3 mm of Merck (Darmstadt) silica gel PF-254. The nmr spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200G spectrophotometer. Mass spectra were measured on a Varian Mat CH-7 spectrometer, at a 20-eV ionization potential. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett–Packard instruments equipped with hydrogen flame ionization detectors.

All the new compounds mentioned gave satisfactory elemental analyses and/or were characterized by their nmr, ir, and mass spectra. All of the substances described in this paper were racemic compounds.

The synthesis of compounds I to V (*3*, *14*) and XXII to XXX (except for XXIX) have been previously described (*16*, *19*).

3-(2,6-Dimethylheptyl)-2-cyclopenten-1-one (VII)

(a) Hydroboration of 2,6-dimethyl-1-heptene in tetrahydrofuran followed by treatment with bromine and sodium methoxide in methanol according to the procedure of Brown and Lane (*22*) gave, after distillation, a 70% yield of 1-bromo-2,6-dimethylheptane, bp 48°C (0.08 mm).

A solution of 9.03 g (43.6 mmol) of 1-bromo-2,6-dimethylheptane in 20 ml of diethyl ether was added dropwise to a mixture of 1.7 g of magnesium turnings and 10 ml of ether with stirring, and the mixture was then heated for 3 hr under reflux. The final concentration of Grignard was found (by titration) to be 0.98 *M* (75% yield).

To a solution of 3.0 g (31 mmol) of 1,3-cyclopentanedione in 300 ml of ether at 0°C was added 100 mmol of diazomethane in 600 ml of ether, the mixture was stirred for 45 min at 0°C, and then the solvent was removed *in vacuo*. Distillation of the residue gave 3.16 g (92% yield) of 3-methoxy-2-cyclopenten-1-one, bp 90°C (2.5 mm).

A solution of 3.19 g (28 mmol) of 3-methoxy-2-cyclopenten-1-one in 30 ml of ether was added dropwise at 0°C over 1.5 hr to 41 mmol of the above Grignard reagent in ether. The reaction mixture was stirred at 25°C for 24 hr and then treated at 0°C with 150 ml of 1 *N* aqueous H_2SO_4. After the mixture had been stirred for a further 4 hr at room temperature, ether was added, the organic phase was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude product was distilled, and the distillate was chromatographed on silica gel preparative thin-layer plates to give 0.75 g (13% yield) of the enone VII: bp (bath, short path) 75°C (0.03 mm); nmr ($CDCl_3$), δ 0.88 [d, 6, $J = 6$ Hz, $(CH_3)_2CH$], 0.92 (d, 3, $J = 6$ Hz, (CH_3CH)], and 5.97 ppm (bs, 1, C*H*=C); mass spectrum (20 eV) *m/e* (rel intensity), M^+ 208 (6), 123 (86), 97 (100), and 57 (91).

(b) To 14.4 g (0.10 mol) of 2,6-dimethyl-1-heptanol in 200 ml of benzene was added 22 g (0.19 mol) of thionyl chloride and 0.1 ml of *N,N*-dimethylformamide, and the mixture was heated under reflux for 6 hr. After cooling, the solution was decanted from the insoluble material, and the solvent was removed from it *in vacuo*. Distillation of the residue gave 11.2 g of 1-chloro-2,6-dimethylheptane, which was treated with 1.05 g of

lithium wire (1% sodium) in 70 ml ether at −10°C under argon, and the mixture was stirred at −10 to 0°C for 4 hr. The concentration of lithio reagent was found (by titration) to be 0.90 *M*.

To a solution of 3.8 g (46 mmol) of 2-cyclopenten-1-one in 40 ml of ether at −78° under argon was added 45 ml (41 mmol) of the above 2,6-dimethylheptyllithium solution, and the mixture was allowed to warm to room temperature with stirring. The mixture was then poured into water, the organic phase was washed with water and dried, and the solvent was removed *in vacuo*. The resulting crude alcohol IX was dissolved in 80 ml of ether and stirred at 0°C with 30 ml of 1 *M* CrO_3 in 5% aqueous H_2SO_4 (cf. *25*) for 15 min. Water and ether were then added, the organic phase was washed with aqueous $NaHCO_3$ and dried, and the solvent was removed *in vacuo*. The residue (5.2 g) was purified by preparative tlc on silica gel (developed with 15% ethyl acetate in hexane) to give, after distillation, 3.1 g of VII.

Ethyl (E)-3,5-Ethano-7,11-dimethyl-2,4-dodecadienoate (VI)

(a) To a solution of 2.82 ml of diisopropylamine in 40 ml of tetrahydrofuran at 0°C under N_2 was slowly added 12.5 ml (0.020 mol) of 1.6 *M* *n*-butyllithium in hexane solution. The mixture was stirred at 0°C for 1 hr, and at room temperature for 3 hr. To this solution, cooled to −78°C, was added 3.65 g of ethyl trimethylsilylacetate (cf. *23*) and after stirring 10 min at −78°C, 2.02 g (0.010 mol) of the enone VII in 10 ml of tetrahydrofuran was added. After stirring at −78°C for 1 hr, followed by 3 hr at −25°C, the mixture was allowed to warm to room temperature and then poured into water and extracted with hexane. The organic layer was washed with aqueous 1 *N* H_2SO_4, aqueous $NaHCO_3$, and water and dried, and the solvent was removed *in vacuo*. The residual product (2.8 g) was shown by glc analysis to be a 1:1 mixture of the 2*E* isomer VI and the corresponding 2*Z* isomer. Purification by preparative tlc on silica gel (developed with 3% ethyl acetate in hexane) gave 0.85 g of the pure VI (glc analysis showed it to contain a 99:1 ratio of the 2*E*:2*Z* isomers); bp (bath, short path) 135°C (0.05 mm); uv max (hexane), 284 nm (ε 24 800); ir (film), 1708, 1628, and 1605 cm^{-1}; nmr ($CDCl_3$), δ 0.88 (d, 9, *J* = 6 Hz, C-7 CH_3, C-11 CH_3 + H-12), 1.28 (t, 3, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.18 (q, 2, *J* = 7 Hz, $CO_2CH_2CH_3$), 5.65 (br s, 1, H-2), and 6.02 ppm (br s, 1, H-4); mass spectrum (20 eV) *m/e* (rel intensity), M^+ 278 (12), 232 (10), and 166 (100).

(b) To 10 ml of dry tetrahydrofuran at −10°C was added 2.28 ml (3.8 mmol) of 1.67 *M* *n*-butyllithium in hexane followed by 0.39 g (3.85 mmol) of diisopropylamine. After cooling to −78°C, 0.133 g (3.8 mmol) of ethyl acetate was added over 15 min, and the solution was stirred for an additional 30 min. The enone VII (0.79 g; 3.8 mmol) was then added and after stirring for 45 min, 5 ml of 10% aqueous HCl was added. After warming to room temperature, pentane was added, the organic phase was washed with saturated aqueous NaCl and dried, and the solvent was removed *in vacuo* to give 0.90 g of VIII: nmr ($CDCl_3$), δ 0.88 [d, 6, *J* = 6 Hz, $(CH_3)_2CH$], 0.92 (d, 3, *J* = 6 Hz, CH_3CH), 1.26 (t, 3, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.16 (q, 2, *J* = 7 Hz, $CO_2CH_2CH_3$), and 5.98 ppm (br s, 1, CH=C). The crude VIII (0.90 g; 3.04 mmol) was dissolved in 3 ml of pyridine at 0°C, 0.8 ml of phosphoryl chloride was added, and the mixture was stirred for 30 min at 0°C followed by 17 hr at 25°C. The mixture was then cooled in an ice bath, poured into ice-water, and extracted with ether. The organic layer was washed with 10% aqueous HCl, 5% aqueous $NaHCO_3$, and brine and dried (Na_2SO_4), and the

solvent removed to give 0.90 g of product. Analysis by glc showed the presence of 30% of the *E* isomer VI, 35% of the corresponding *Z* isomer, and 30% of deconjugated isomers. Purification by preparative tlc on silica gel (developed with 4% ethyl acetate in hexane) gave 0.21 g of the pure *E* isomer VI.

The analog X (Table 3) was prepared starting with *n*-heptyllithium and 2-cyclopenten-1-one in a manner analogous to that described above (Scheme 2) for the synthesis of VI.

Ethyl (E)-3,5-Propano-7,11-dimethyl-2,4-dodecadienoate (XII)

This analog was prepared in a manner similar to that described above for VI. Thus 3-isobutoxy-2-cyclohexen-1-one was prepared by heating under reflux a mixture of isobutyl alcohol and 1,3-cyclohexanedione in benzene with *p*-toluenesulfonic acid under conditions of continuous removal of water. To a solution of 3.8 g of this enone in ether (50 ml) at −78°C under argon was added 25 ml of 0.9 *M* 2.6-dimethylheptyllithium in ether, and the mixture was allowed to warm to room temperature and then was poured into cold 5% aqueous H_2SO_4, and the mixture was stirred for 10 min at 0°C. Working up the organic phase in the normal manner gave 2.3 g of the enone XI: bp (bath, short path) 95°C (0.05 mm). A solution of 2.2 g (10 mmol) of XI in 10 ml of tetrahydrofuran was added to a solution of the lithium salt of ethyl trimethylsilylactate (20 mmol) in tetrahydrofuran at −78°C [prepared as described above under the preparation (a) of VI]. Working up in the same manner as described above gave a 1 : 1 mixture of the 2*E* isomer XII and the corresponding 2*Z* isomer. Purification by preparative tlc then gave the 2*E* isomer XII (glc analysis showed it to contain a 96 : 4 ratio of the 2*E* : 2*Z* isomers): bp (bath, short path) 135°C (0.05 mm); uv max (hexane), 282 nm (ε 25 200); nmr (CCl_4), δ 5.45 (br s, 1, H-2) and 5.88 ppm (br s, 1, H-4).

Dienoate (XIV)

A mixture of 13 g of 1,5-dimethyl-1-hexanol, 11.2 g of 1,3-cyclohexanedione, and 100 mg of *p*-toluenesulfonic acid in 100 ml of toluene was heated under reflux with continuous removal of water via a Dean–Stark trap. After cooling, the mixture was treated with solid $NaHCO_3$, and the solution was washed with 10% aqueous NaOH and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Distillation of the residue *in vacuo* gave XIII; bp (bath, short path) 125°C (0.05 mm).

A solution of 20 mmol of the lithium enolate of ethyl trimethylsilylacetate was prepared at −78°C in tetrahydrofuran as described above under the preparation of VI. Then 2.2 g of the enone XIII in 10 ml of tetrahydrofuran was added, and the mixture was stirred for 1 hr at −78°, 1 hr at −25°, and then 1 hr at room temperature. The mixture was then poured into cold water and extracted with ether–hexane (1 : 1). The organic phase was washed with aqueous $NaHCO_3$ and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Distillation of the residue gave 1.0 g of XIV; bp (bath, short path) 135°C (0.05 mm): Glc and nmr analysis showed the sample to contain the 2*E* isomer and the corresponding 2*Z* isomer in the ratio 35 : 65, respectively.

Ethyl 2,4-Ethano-3,7,11-trimethyl-2,4-dodecadienoate (XVIII)

To a suspension of 0.47 g of oil-free sodium hydride in 30 ml of dry *N,N*-dimethylformamide at 25°C was added 3.2 g of diethyl 2-oxopropylphosphonate in 10 ml of *N,N*-dimethylformamide. The mixture was stirred under N_2 until the evolution of H_2

ceased, and then 7.5 g of dry 1-ethoxycarbonylcyclopropyltriphenylphosphonium fluoroborate (*26*) was added in one portion. The mixture was then heated at 55–60°C for 18 hr, and the cooled mixture was poured into water and extracted with ether several times. The combined organic layers were washed with saturated brine and dried, and the solvent was removed *in vacuo*. The residue was extracted with hexane, the hexane extracts were filtered, and the solvent was removed from the filtrate. The residue was then distilled to give 2.3 g of the crude phosphonate XVII: bp (kugelrohr) 120°C (0.15 mm).[4]

To a mixture of 1.16 g of the phosphonate XVII, 0.80 g of 3,7-dimethyl-1-octanal in 15 ml of *N,N*-dimethylformamide was added 200 mg of finely ground NaOH (cf. *14*, *16*), and the mixture was stirred at room temperature for 5 hr. The mixture was then poured into water and extracted with hexane, the organic phase was washed with water and dried, and the solvent was removed *in vacuo*. The residue (1.1 g) was purified by preparative tlc (developed with 2% ethyl acetate in hexane) followed by vacuum distillation to give 0.21 g of XVIII (one isomer by glc analysis): nmr (CCl_4), δ 0.90 (d, 9, $J = 6$ Hz, C-7 CH_3, C-11 CH_3 + H-12), 1.30 (t, 3, $J = 7$ Hz, $CO_2CH_2CH_3$), 2.10 (br s, 1, C-3 CH_3), 4.18 (q, 2, $J = 7$ Hz, $CO_2CH_2CH_3$), and 5.60 ppm (br t, 1, J = ca. 7 Hz, H-5); mass spectrum (20 eV) *m/e* (rel intensity), M^+ 292 (15), 247 (9), 219 (3), 179 (95), 161 (100), 151 (23), 137 (15), 133 (17), 107 (20), and 105 (30).

3,5,7,11-Tetramethyl Analogs XX and XXI

7-Methoxy-3,7-dimethyloctanoic acid was treated with two equivalents of methyllithium in ether at 5°C to give a 92% yield of 8-methoxy-4,8-dimethyl-2-octanone (XIX). Condensation of this ketone with the anion (generated with sodium hydride) of diisopropyl 3-isopropoxycarbonyl-2-methyl-2-propenylphosphonate (cf. *14*) in *N,N*-dimethylformamide (7 days at 85°C) gave in 10% yield the dienoate XX as a mixture of isomers: bp (bath, short path) 115°C (0.10 mm). A glc analysis indicated that the sample contained ca. 44% of the 2*E*,4*E* isomer.

The analog XXI was prepared by a modified procedure in better yield. Thus, to a solution of 11 g of diethyl 3-ethoxycarbonyl-2-methyl-2-propenylphosphonate in 50 ml of tetrahydrofuran at 0°C was added 23.5 ml (40 mmol) of a 1.7 *M* solution of potassium *t*-butoxide in tetrahydrofuran. Then 7 g (42 mmol) of 4,8-dimethyl-2-octanone in 10 ml of tetrahydrofuran was added followed by 7 ml of hexamethylphosphoramide and 500 mg of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane). This mixture was heated under reflux for 60 hr and after cooling was poured into water and extracted with ether–hexane (1 : 1). The organic layer was washed with water and dried, and the solvent was removed. The residue was distilled *in vacuo* and the fraction of bp 104–105°C (0.05 mm) was further purified by preparative tlc to give the 2*E*,4*E* isomer XXI: nmr ($CDCl_3$), δ 1.83 (br s, 3, C-5 CH_3), 2.27 (br s, 3, C-3 CH_3), and 5.72 ppm (br s, 1, H-4).

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[4] The phosphonate XVII is a mixture of the 1- and 2-ene isomers.

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