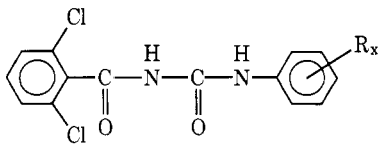
Table IV. Insecticidal Activities of  **, where R_x = electron attracting groups**

Compound no.	R_x	Test results: *Aëdes aegypti* L.	Test results: *Pieris brassicae* L.	Test results: *Leptinotarsa decemlineata* Say	mp, °C
1	4-$COCH_3$	±−	−	−	212
2	4-COC_6H_5	+−	++±−	±−	198
3	4-$COOC_2H_5$	−	−	−	197
4	4-CN	+++−	+++±−	±−	248
5	3,5-$(CN)_2$	±−	+±−	−	255
6	4-NO_2	±−	++±−	±±−	256
7	3-Cl, 4-NO_2	±−	−	−	>300
8	3-CF_3, 4-NO_2	−	−	−	>280
9	3-NO_2, 4-CH_3	−	+++±−	++−	256
10	2,4-$(NO_2)_2$	−	−	−	260
11	4-$N^+(CH_3)_3I^-$·1 aq	−	−	−	250
12	4-SO_2CH_3	−	+±−	−	222
13	4-SO_2-*n*-C_5H_{11}	−	+±−	−	166
14	4-$SO_2C_6H_5$	−	−	−	238
15	4-SO_2-(4-ClC_6H_4)	+++±−	+++±−	−	245
16	4-SO_2-(2,4,5-$Cl_3C_6H_2$)	−	−	−	265
17	4-SO_2NH_2	−	−	−	>270
18	4-$SO_2N(CH_3)_2$	−	±−	−	232
19	4-$SO_2N(n\text{-}C_3H_7)_2$	−	−	−	210

Applied concentrations in parts per million

Aëdes aegypti L. 1, 0.3, 0.1, 0.03, etc. + = 90–100% mortality

Pieris brassicae L. 100, 30, 10, 3, etc. ± = 50–89% mortality

Leptinotarsa decemlineata Say 100, 30, 10, 3, etc. − = 0–49% mortality

Speziale, A. J., Smith, L. R., *J. Org. Chem.* **27** (10), 3742 (1962).
van Daalen, J. J., Meltzer, J., Mulder, R., Wellinga, K., *Naturwissenschaften* **59** (7), 312 (1972).
Wellinga, K., Mulder, R., van Daalen, J. J., Part II: "Influence of the substitution pattern of the benzoyl moiety on the insecticidal activity," unpublished data, 1973.

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Alkyl 3,7,11-Trimethyl-2,4-dodecadienoates, A New Class of Potent Insect Growth Regulators with Juvenile Hormone Activity

Clive A. Henrick,* Gerardus B. Staal, and John B. Siddall

A new class of insect growth regulators with juvenile hormone activity, including isopropyl 11-methoxy-3,7,11-trimethyl-*trans*-2,*trans*-4-dodecadienoate and ethyl 3,7,11-trimethyl-*trans*-2,*trans*-4-dodecadienoate, has been synthesized and shown to be more potent and more stable than the known natural juvenile hormones. Bioassay data on yellow fever mosquito *(Aedes aegypti)*, greater wax moth *(Galleria mellonella)*, and yellow mealworm *(Tenebrio molitor)* for these and related compounds are given.

Insect growth regulators (IGR's) with juvenile hormone activity (Williams, 1956) may be used to interfere with essential life processes such as metamorphosis and adult emergence. Many insects are remarkably sensitive to the external application of suitable IGR's at certain critical stages in their life cycle. At present, the detailed biochemical consequences of such abnormal treatment are poorly understood; however, the morphological and developmental consequences are largely irreversible and therefore ultimately lethal to the target insects. The effects may be expressed by the occurrence of larval-pupal or

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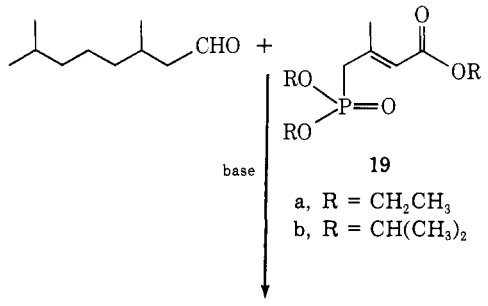
pupal–adult intermediates, defective reproductive organs, or abnormal embryogenesis. We wish to report the discovery of a new class of IGR's (alkyl 3,7,11-trimethyl-2,4-dodecadienoates), whose efficacy has been demonstrated in large-scale field tests.

RESULTS AND DISCUSSION

Successful pest management by IGR's requires that they possess at least the following properties: high potency in pest insects; moderate field stability without undue persistency; selectivity for target pest organisms; and structural simplicity for economically feasible synthesis. The natural juvenile hormones of *Hyalophora cecropia*, as identified by Röller *et al.* (1967) and by Meyer *et al.* (1968), appear to be deficient in all these properties. As a consequence, the search for better compounds has been intensive. Although hundreds of related compounds have been synthesized during the past decade, only a few have even approached the requirements necessary to achieve practical utility (*e.g.*, Bagley and Bauernfeind, 1972). The requirement for high potency is undoubtedly basic if a compound is to compete successfully with highly active conventional insecticides. The activity of an IGR has generally been cited only for a limited time during the most sensitive stage in the insect's life cycle. Detailed evaluation of IGR's in our laboratory, however, has revealed several subtle and delayed effects which contribute to population decline and which can only be assessed by studies carried through more than one generation of the insect. Direct comparison between current insecticides and IGR's is difficult, particularly when complex long-term effects on the total ecosystem are considered. Simple ID_{50} (Inhibition Dose) values (Table I), therefore, are not a satisfactory basis for making such a comparison between the two categories of control agents. However, such values do provide an accurate basis for making structure–activity correlations within each group of chemicals.

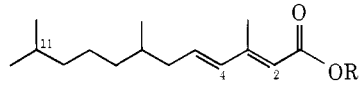
In order to ensure that the IGR is available when the target insect reaches a sensitive stage, it is necessary to develop compounds with sufficient field stability. A second aspect of structure–activity correlations concerns the relationship between the intrinsic activity, perhaps as a receptor fit, and stability within the organism; *i.e.*, resistance to metabolic breakdown. Insects are known to utilize metabolic mechanisms to destroy endogenous hormones. In our laboratory we found that the least stable structural groups in the natural cecropia hormone **1** under field conditions and *in vivo* were the epoxide group and the ester function (Siddall *et al.*, 1971; Slade and Zibitt, 1971, 1972). Furthermore, it had been observed by Röller and Dahm (1968) that the ethyl ester analog of the cecropia hormone **1** was more active on *Tenebrio molitor* than was the natural methyl ester; and in an *in vitro* incubation with diluted samples of hemolymph of *Manduca sexta* and of *Samia cynthia* it was found that the methyl ester **1** was hydrolyzed faster than the corresponding ethyl ester (Weirich and Wren, 1972). Therefore, the increased activity of the ethyl ester in *Tenebrio molitor* may be due to increased internal stability. We had also found that either the hydrolysis of the ester function of **1** to give the carboxylic acid or the hydration of the epoxide function resulted in the loss of most of the biological activity (Siddall *et al.*, 1971).

The considerations cited above led us to search for structural modifications which would maximize biological activity and eliminate the need for the labile epoxide and methyl ester functions. In modifying the structure of methyl 10,11-epoxyfarnesoate (**2**), we observed that saturation of the 6-ene double bond to give compounds such as **4** did not remove the biological activity (*cf.*, Wakabayashi *et al.*, 1969; Wigglesworth, 1969). Then it became clear (Table I) that in general *for 6,7-dihydro compounds*, the presence of a terminal epoxide (*e.g.*, **4**) or a double bond (*e.g.*, **3**) at the 10,11 position reduced the biological activity on the three insect species listed in Table I, compared with that of the corresponding 10,11 dihydro compound (*e.g.*, **6**). Furthermore, it was then found that introduction of an additional trans double bond to form a 2,4-dienoic ester enhanced the activity considerably and that again with this group of compounds the presence of either a 10,11-epoxide (*e.g.*, **10**) or a 10,11-olefin function (*e.g.*, **8** and **9**) in general decreased the activity relative to that of the corresponding 10,11-dihydro (*e.g.*, **15**) or the 11-methoxy analogs (*e.g.*, **12**). Thus, **12** has high activity on *Aedes aegypti*, but maximum activity was found with the isopropyl ester **13**.



19

a, R = CH_2CH_3
b, R = $CH(CH_3)_2$



15, R = CH_2CH_3
16, R = $CH(CH_3)_2$

The 2,4-dienoates were synthesized by the reaction of dihydrocitronellal and related aldehydes with the phosphonates **19** (Davis *et al.*, 1966; Pattenden and Weedon, 1968; Stilz and Pommer, 1964, 1965). The dienes thus obtained were predominantly trans at C-2 and exclusively trans at C-4.

The compound **13** (Altosid insect growth regulator; Henrick and Siddall, 1972) is highly active on Diptera and shows great promise as a larvicide for the control of mosquitoes and flies. Its activity compares favorably in our laboratory bioassays with some of the commercially available mosquito larvicides (*e.g.*, Abate). The visible result of applying **13** to the water is the failure of viable normal adults to emerge from the pupal exuviae. In the case of mosquito field tests, rates of 0.5 to 2 oz per acre have given 100% control of mosquito larvae in waters ranging in depth from 4 in. to 15 ft and ranging in character from clear to highly contaminated with organic matter.

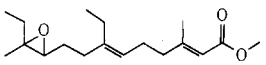
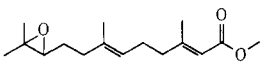
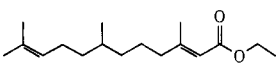
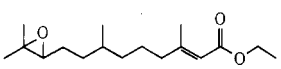
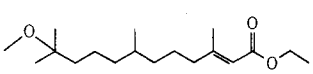
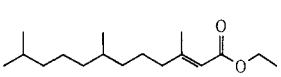
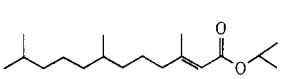
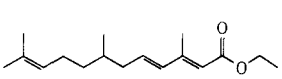
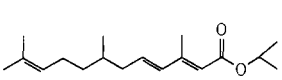
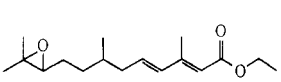
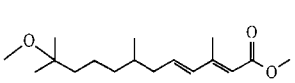
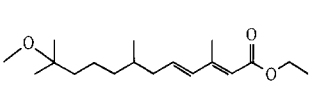
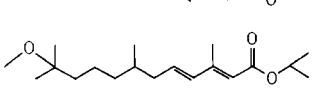
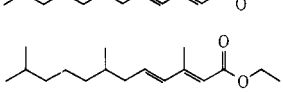
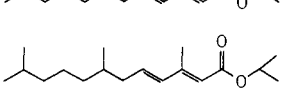
The compound **15** (Altozar insect growth regulator; Henrick, 1972) is highly active on Lepidoptera, some Coleoptera, and several Homoptera (particularly aphids and scale insects) but has low activity on Hymenoptera and Heteroptera.

Thus these 2,4-dienoates are highly active, even though they lack the terminal epoxy function that is essential for activity in the known natural juvenile hormones, and in most insects the activities of **13** and **15** are better than those of previously described analogs (*e.g.*, Bowers, 1968, 1969; Pallos *et al.*, 1971; Schwarz *et al.*, 1970; Sonnett *et al.*, 1972).

The *cis*-2,*trans*-4 isomers of **13** and **15** show much reduced biological activity, as do the carboxylic acids derived from **13** and **15**.

Permutations in the terminal functions appear to have large effects on the selectivity toward different insect orders. For example, the introduction of an 11-methoxy function into the ethyl ester **15** (to give **12**) enhances activity on *Aedes aegypti* but reduces activity on *Tenebrio molitor* (Table I). The replacement of an ethyl ester with

Table I. ID_{50} Values and Relative Potencies on Sensitive Synchronized Instars

	Structure	*Aedes aegypti*, ppm	Relative potency	*Galleria mellonella*, μg/pupa	Relative potency	*Tenebrio molitor*, μg/pupa	Relative potency
1		0.15	1.0	0.060	1.0	0.70	1.0
2[a]		0.34	0.44	9.8	0.0061	4.5	0.16
3		0.20	0.75	6.8	0.0088	12	0.058
4		0.29	0.52	6.7	0.0090	8.4	0.083
5		0.040	3.8	100	0.00060	95	0.0074
6		0.066	2.3	1.7	0.035	2.6	0.27
7		0.0046	33	>100	<0.0006	0.50	1.4
8		0.30	0.50	2.0	0.030	8.0	0.088
9		0.035	4.3	26	0.0023	0.52	1.4
10		0.18	0.83	0.86	0.070	34	0.021
11		0.020	7.5	0.082	0.73	36	0.019
12		0.0049	31	0.074	0.81	8.9	0.079
13[b]		0.00014	1070	1.1	0.055	0.0054	130
14		0.10	1.5	0.044	1.4	1.3	0.54
15[c]		0.014	11	0.047	1.3	0.29	2.4
16		0.0012	125	0.28	0.21	0.026	27

[a] Bowers *et al.* (1965). [b] Altosid Insect Growth Regulator (ZR-515). [c] Altozar Insect Growth Regulator (ZR-512).

an isopropyl ester (*e.g.*, **15** → **16** and **12** → **13**) increases activity on *Aedes aegypti* and on *Tenebrio molitor* but considerably decreases the measured activity on *Galleria mellonella*. Whether the selectivity is related to differences in the natural hormones and their receptors is only a matter of speculation at the present time.

The apparent absence of juvenile hormones in mammalian systems generated a speculation that insect growth regulators such as **13** and **15** might be free from toxic effects on mammals. In both single-dose acute studies and repeated-dose subacute studies, present results indicate very low toxicity to several mammalian species when these IGR's are administered by oral, dermal, and inhalation routes. Studies on teratogenicity, mutagenicity, and carcinogenicity are necessarily of longer duration and are still in progress.

Control of insects with a very short development cycle, particularly if damage by larvae is not a factor (as in mosquitoes), appears to be a logical first choice for the practical application of this novel type of control agent. This group of conjugated 2,4-dienoates combines high biological activity with several other desirable features that are essential for consideration of safe alternatives for pest control.

BIOASSAY PROCEDURES

Bioassays were performed on synchronized sensitive stages of three insect species representing different orders.

The activities were expressed as ID_{50} or IC_{50} values (dose or concentration required to produce 50% inhibition) which provide a quantitative basis for comparison of compounds.

Greater Wax Moth *(Galleria mellonella)* Pupae Less Than 24-hr Old. These pupae were collected after mature larvae from a mass colony were allowed to pupate in glass tubes treated with Siliclad (product of Clay Adams) solution (modification of a technique described by DeWilde *et al.*, 1968) and then freed of the cocoon with a dilute Chlorox solution. Starvation of mature larvae was employed to produce highly synchronous pupation. One microliter of acetone solution containing 100, 10, 1, 0.1, 0.01, or 0.001 μg of compound was applied to the mouthparts of each test pupa. Treated pupae were allowed to develop for 10 days at 31° and then scored for both retention of pupal characters and adult emergence. For the retention of pupal characters, the following scoring system was used: 0 = normal adult; 1 = minor pupal rudimentary mandibles only; 2 = as in 1, but also pupal cuticle patches at the base of the proboscis; 3 = extensive pupal cuticle formation at base of proboscis, slight pupal characters in intersegmental membranes in legs; 4 = proboscis entirely pupal, larger than normal, legs with extensive pupal zones; 5 = merging pupal bands on legs, specimen with only a few adult setae, essentially "a second pupa."

The graded-response score was calculated as a percentage of the maximum attainable ($n \times 5$) and plotted against the dose on semilogarithmic paper. The ID_{50} dose is taken from the intersection of this plotted line with the 50% effect level.

Yellow Mealworm *(Tenebrio molitor)* Pupae. Fresh pupae (within 24 hr) were collected and treated on the ventral surface with 1 μl of acetone solution of the test compound. The treated pupae were evaluated after 10 days at 25° for retention of such pupal characters as unpigmented cuticle, urigomphi, gin traps, and genitalia, using a graded score ranging from 0 to 4 (Bowers, 1968). The results were expressed and plotted as for the greater wax moth pupae.

Yellow Fever Mosquito *(Aedes aegypti)* Last Larval Instars. Fourth larval instars were selected from colonies maintained at 28° on a diet of liver powder. Three replicates of ten larvae each were transferred to disposable styrene tumblers containing 50 ml of tap water. Acetone solutions of test compounds were then added to the cups (50 μl per 50 ml of water) and liver powder was added as food. No difference in response was observed between animals treated in glass containers and those treated in plastic tumblers, and the volume of acetone used had no detectable effect on the viability or the response of larvae. The tumblers were fitted with an inverted funnel assembly to collect adults and prevent their drowning. After 5 days at 28°, the results were scored as the percentage of unemerged adults (including those which could only partially escape from the pupal cuticle), and plotted as cited above for the wax moth pupae.

For each compound, several assays, performed on different days with fresh dilutions, were averaged to obtain the data presented in Table I. Other assays not recorded here have confirmed that ovicidal and sterilizing activities were generally present and were correlated with morphogenetic activity in the same insect.

EXPERIMENTAL SECTION

All substances described herein are racemic compounds; the prefix *dl* is omitted. Preparative thin-layer chromatography was carried out with Merck (Darmstadt) silica gel PF-254. 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 an Atlas CH-4 spectrometer, equipped with an E-4B ion source, at 70 eV ionization potential. Vapor-phase chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors.

Compounds 1 (Henrick *et al.*, 1972) and 2 (Anderson *et al.*, 1972) were prepared as described in the literature.

Ethyl 3,7,11-Trimethyl-*trans*-2,10-dodecadienoate (3). Pseudoionone (90 g) in 200 ml of ethanol was shaken with hydrogen at room temperature in the presence of 5% palladium-on-charcoal (400 mg) until 2 equiv of hydrogen were absorbed (35 hr; the reaction was followed by glc). The catalyst was filtered off and the solvent removed. Distillation *in vacuo* using a spinning-band column gave 65 g of pure 6,10-dimethyl-9-undecen-2-one, bp 80° (0.5 mm) (Teisseire and Corbier, 1963).

To a suspension of 17.5 g of sodium ethoxide in 125 ml of dimethylformamide under N_2 atmosphere was added 59 g of triethylphosphonoacetate over 30 min with cooling in ice water. 6,10-Dimethyl-9-undecen-2-one (50 g) was then added over 30 min, and the mixture was stirred for 24 hr at room temperature. The mixture was poured into brine and the product was isolated with hexane. Distillation *in vacuo* using a spinning-band column gave 25 g of pure **3** (trans at C-2) [bp 85° (0.01 mm)]: nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 2.17 (d, J = 1.5 Hz, C-3 CH_3), 5.13 (m, H-10), and 5.70 ppm (m, H-2).

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.63; H, 11.27.

To 1 g of **3** in 30 ml of dichloromethane, cooled in an ice water bath, was added portionwise a solution of 0.80 g of technical 85% *m*-chloroperoxybenzoic acid in 10 ml of dichloromethane. After 1 hr of being stirred at 10°, the mixture was filtered and the filtrate was washed with aqueous sodium sulfite, aqueous $NaHCO_3$, and brine, dried, and evaporated. The product was purified by preparative thin-layer chromatography (developed with hexane–ethyl acetate, 9:1) to give 0.80 g of **4** [bp (bath, short path) 90° (0.06 mm)]: nmr ($CDCl_3$) δ 0.87 (d, J = 6 Hz, C-7 CH_3), 2.14 (d, J = 1.5 Hz, C-3 CH_3), 2.67 (m, H-10), and 5.65 ppm (m, H-2).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.25; H, 10.77.

Ethyl 11-Methoxy-3,7,11-trimethyl-*trans*-2-dodecenoate (5). To 1.0 g (3.75 mmol) of **3** in 10 ml of dry methanol cooled in an ice water bath was added a suspension of 1.40 g (1.17 equiv) of mercuric acetate in 20 ml of dry methanol over 2 min. After being stirred for 1 hr at 5°, the mixture was warmed to room temperature and stirred for 2 hr. The methanol was *then removed in vacuo,* 10 ml of ethanol was added, the solution was cooled in an ice bath, and a solution of 1.5 g of NaOH in 2 ml of water and 10 ml of ethanol was added. Then solid sodium borohydride (0.6 g) was added portionwise and the mixture was stirred 1 hr at 5°. The mixture was poured into brine and extracted with ether to give 0.90 g of oil which was purified by thin-layer chromatography (developed with ether–hexane, 1:4) to give 0.50 g of **5** [bp (bath, short path) 85° (0.01 mm)]: nmr (CCl_4) δ 0.88 (d, 3, J = 6 Hz, C-7 CH_3), 1.08 (s, 6, C-11 CH_3), 2.15 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.10 (s, 3, OCH_3), 4.11 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), and 5.63 ppm (bs, 1, H-2).

Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.26; H, 11.35.

If the methanol is not removed *before* the addition of aqueous alkali in the above experiment, and the reduction is carried out directly in alkaline aqueous methanol, one obtains about 10% methyl ester as a transesterification byproduct.

Ethyl 3,7,11-Trimethyl-*trans*-2-dodecenoate (6). Geranylacetone (292 g) in 1 l. of ethanol was hydrogenated over 3 g of 5% palladium-on-charcoal at room temperature to give 6,10-dimethylundecan-2-one, which was reacted

with triethylphosphonoacetate as detailed above for the preparation of **3**. The crude **6** was distilled *in vacuo* using a spinning-band column to give the pure trans ester **6** [bp 92° (0.02 mm)]: nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.15 (d, J = 1.5 Hz, C-3 CH_3), and 5.68 ppm (m, H-2).

Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.20; H, 11.88.

To a solution of 15.8 g of **6** in 200 ml of ethanol and 50 ml of water was added 20 ml of 50% aqueous NaOH. After 20 hr at room temperature, the ethanol was removed *in vacuo*, water was added, and the mixture was extracted with ether (discarded). The aqueous layer was acidified, saturated with solid NaCl, and extracted with ether to give 13.4 g of acid. The crude acid was converted into its *S*-benzylisothiuronium salt, which was recrystallized from aqueous methanol. Regeneration with aqueous HCl–ether gave 4.5 g of the pure 3,7,11-trimethyl-*trans*-2-dodecenoic acid. To 2.11 g of this acid in benzene (40 ml) was added 1.0 ml of oxalyl chloride. After being stirred for 2 hr, the solvent was removed *in vacuo*, fresh benzene (30 ml) was added, followed by 10 ml of dry isopropyl alcohol. After 3 hr, the mixture was washed with water and brine, dried, and evaporated. Distillation gave the isopropyl ester **7**, [bp (bath, short path) 90° (0.01 mm)]: nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.13 (d, J = 1.5 Hz, C-3 CH_3), 4.97 [m, $OCH(CH_3)_2$], and 5.58 ppm (m, H-2).

Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.70; H, 11.99.

Ethyl 3,7,11-Trimethyl-*trans*-2,*trans*-4,10-dodecatrienoate (8). To a solution of 1 g of citronellal in 15 ml of dry dimethylformamide cooled in an ice bath under N_2 atmosphere was added 1.7 g of the phosphonate **19a** followed by dropwise addition of a solution of 0.44 g of sodium ethoxide (freshly prepared) in 3 ml of ethanol. After being stirred for 1 hr at room temperature, the solution was poured into brine and extracted with ether–hexane (1:1). The organic layer was washed with water and brine, dried ($CaSO_4$), and evaporated. The residue was purified by preparative thin-layer chromatography. Development of the silica plates with ether–hexane (1:9) gave two resolved bands. The upper band (0.25 g) was the *cis*-2,*trans*-4 isomer of **8** and the lower band (0.50 g) was the pure *trans*-2,*trans*-4 ester **8** [bp (bath, short path) 84° (0.01 mm)]: nmr (CCl_4) δ 0.90 (d, 3, J = 6 Hz, C-7 CH_3), 1.27 (t, J = 7 Hz, $CO_2CH_2CH_3$), 1.60 and 1.68 (2 s, 6, C-11 CH_3), 2.25 (d, 3, J = 1 Hz, C-3 CH_3), 4.13 (q, J = 7 Hz, $CO_2CH_2CH_3$), 5.07 (m, 1, H-10), 5.65 (br s, 1, H-2), and 6.08 ppm (m, 2, H-4 and H-5).

Selective epoxidation of 1.0 g of **8** in dichloromethane was carried out by the dropwise addition of 1 equiv of *m*-chloroperoxybenzoic acid in dichloromethane at 0°, as described above for the preparation of **4**. Purification by preparative thin-layer chromatography (developed with ether-hexane, 1:6) gave **10** [bp (bath, short path) 85° (0.01 mm)]: nmr (CCl_4) δ 0.92 (d, 3, J = 6 Hz, C-7 CH_3), 1.22 and 1.25 (2 s, 6, C-11 CH_3), 1.27 (t, J = 7 Hz, $CO_2CH_2CH_3$), 2.25 (d, 3, J = 1 Hz, C-3 CH_3), 2.50 (m, 1, H-10), 4.13 (q, J = 7 Hz, $CO_2CH_2CH_3$), 5.67 (br s, 1, H-2), and 6.10 ppm (m, 2, H-4 and H-5).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.91; H, 9.97.

Similar epoxidation of the *cis*-2 isomer gave ethyl 10,11-epoxy-3,7-dimethyl-*cis*-2,*trans*-4-dodecadienoate [bp (bath, short path) 84° (0.01 mm)]: nmr (CCl_4) δ 0.93 (d, J = 6 Hz, C-7 CH_3), 1.22 (s, 3, C-11 CH_3), 1.23 (s, 3, C-11 CH_3), 1.25 (t, J = 7 Hz, $CO_2CH_2CH_3$), 1.97 (d, J = 1 Hz, C-3 CH_3), 2.52 (m, 1, H-10), 4.10 (q, J = 7 Hz, $CO_2CH_2CH_3$), 5.55 (br s, 1, H-2), 5.72–6.38 (m, 1, H-5), and 7.61 ppm (d, J = 16 Hz, H-4).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.65; H, 9.90.

Isopropyl 3,7,11-Trimethyl-*trans*-2,*trans*-4,10-dodecatrienoate (9). To a solution of 50 g (0.325 mol) of citronellal and 99.5 g (0.325 mol) of diisopropyl 3-isopropoxycarbonyl-2-methyl-2-propenyl phosphonate (**19b**) in 200 ml of dry dimethylformamide, cooled in an ice bath under N_2 atmosphere, was added 13 g (0.325 mol) of finely ground sodium hydroxide in one portion. After being stirred overnight at room temperature, the reaction mixture was poured into hexane–water. The hexane layer was washed with brine, dried, and evaporated to give crude **9**. The product was filtered through a column of Florisil (5X weight) in hexane and the resulting ester (60 g) was distilled *in vacuo* to give 45 g of **9** (ratio of *cis*-2,*trans*-4:*trans*-2,*trans*-4 was *ca.* 1:3) [bp 98° (0.03 mm)]: nmr ($CDCl_3$) δ 0.89 (d, J = 6 Hz, C-7 CH_3), 1.26 [d, J = 6 Hz, $OCH(CH_3)_2$], 1.98 (d, J = 1.0 Hz, C-3 CH_3-*cis*), 2.28 (d, J = 1.0 Hz, C-3 CH_3-*trans*), 5.10 [m, $OCH(CH_3)_2$], 5.73 (m, H-2), 6.15 (m, H-4-*trans* and H-5), and 7.67 ppm (d, J = 16 Hz, H-4-*cis*); mass spectrum (70 eV) m/e 278 (M^+).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.38; H, 10.73.

Ethyl 11-Methoxy-3,7,11-trimethyl-*trans*-2,*trans*-4-dodecadienoate (12). 7-Methoxy-3,7-dimethyloctan-1-al (50 g) was reacted with **19a** in dimethylformamide as described above for the preparation of **8** to give crude **12**. In this case no separation of the two isomers at C-2 was observed on preparative thin-layer chromatography, so the product was hydrolyzed as described below under the preparation of **15**. Purification by recrystallization of the *S*-benzylisothiuronium salt (from methanol) and regeneration with aqueous HCl–ether gave the pure *trans*-2,*trans*-4-dienoic acid (crystalline at 0°, remelts at room temperature).

Ethylation of the acid with diazoethane in ether gave **12** [bp (bath, short path) 100° (0.03 mm)]: ir (film) 1710, 1638, and 1613 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 3, J = 6 Hz, C-7 CH_3), 1.15 (s, 6, C-11 CH_3), 1.28 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 2.28 (d, 3, J = 1 Hz, C-3 CH_3), 3.20 (s, 3, OCH_3), 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.72 (br s, 1, H-2), and 6.12 ppm (m, H-4 and H-5).

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.78; H, 10.71.

Methylation of the acid with diazomethane in ether gave **11** [bp (bath, short path) 80° (0.03 mm)]: ir (film) 1718, 1638, and 1614 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 3, J = 6 Hz, C-7 CH_3), 1.13 (s, 6, C-11 CH_3), 2.28 (d, 3, J = 1 Hz, C-3 CH_3), 3.18 (s, OCH_3), 3.72 (s, CO_2CH_3), 5.72 (br s, 1, H-2), and 6.13 ppm (m, H-4 and H-5).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.43; H, 10.57.

To 0.50 g of the above acid in dry benzene (10 ml) was added with stirring 0.17 ml of oxalyl chloride. After 3 hr at room temperature, 2 ml of isopropyl alcohol was added. After a further 3 hr, the organic layer was washed with water and brine, dried, and evaporated. The residue was purified by preparative thin-layer chromatography (developed in ether–hexane, 1:4) to give 0.30 g of **13** [bp (bath, short path) 90° (0.010 mm)]: nmr (CCl_4) δ 0.90 (d, 3, J = 6 Hz, C-7 CH_3), 1.10 (s, 6, C-11 CH_3), 1.25 [d, 6, J = 6 Hz, $OCH(CH_3)_2$], 2.26 (d, 3, J = 1 Hz, C-3 CH_3), 3.12 (s, 3, OCH_3), 5.00 [m, $OCH(CH_3)_2$], 5.62 (m, 1, H-2), and 6.08 ppm (m, H-4 and H-5); mass spectrum (70 eV) m/e 295 ($M - CH_3$), 278 ($M - CH_3OH$), 251, 73 (base peak), 55, no molecular ion.

Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.41; H, 10.98.

Ethyl 3,7,11-Trimethyl-*trans*-2,*trans*-4-dodecadienoate (15). Dihydrocitronellal was reacted with the phosphonate **19a** as described above for the preparation of **8**.

Chromatography of the product on silica gel thin-layer plates (developed with ether–hexane, 1:19) gave two resolved bands. The lower band afforded the trans,trans isomer **15** [bp (bath, short path) 95° (0.03 mm)]: uv max (hexane) 262 nm (ϵ 28,300); ir (film) 1715, 1640, and 1615 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + 12H), 1.27 (t, J = 7 Hz, $CO_2CH_2CH_3$), 2.26 (d, J = 1.1 Hz, C-3 CH_3), 4.13 (q, J = 7 Hz, $CO_2CH_2CH_3$), 5.67 (br s, H-2), and 6.08 ppm (m, H-4 and H-5).

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.52; H, 11.17.

The upper band gave the *cis*-2,*trans*-4 isomer [bp (bath, short path) 90° (0.01 mm)]: uv max (hexane) 264 nm (ϵ 17,900); nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + 12H), 1.27 (t, J = 7 Hz, $CO_2CH_2CH_3$), 1.98 (d, J = 1.2 Hz, C-3 CH_3), 4.11 (q, J = 7 Hz, $CO_2CH_2CH_3$), 5.57 (br s, H-2), 6.05 (br m, H-5), and 7.62 ppm (d, J = 16 Hz, H-4).

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.48; H, 11.21.

46.5 grams of the crude product from the phosphonate reaction above (**15** + *cis*-2,*trans*-4 isomer) was dissolved in 350 ml of ethanol and 105 ml of water, 70 ml of 50% aqueous NaOH was added, and the mixture was heated under reflux for 20 hr. The ethanol was removed *in vacuo*, water was added, and the residue was extracted with ether (discarded). Acidification of the aqueous layer and isolation with ether gave the crude acid. Purification *via* the *S*-benzylisothiuronium salt gave 3,7,11-trimethyl-*trans*-2,*trans*-4-dodecadienoic acid: mp 44° (from aqueous methanol).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.45; H, 10.85.

Methylation of a sample of this acid with diazomethane in ether gave **14** [bp (bath, short path) 95° (0.3 mm)]: ir (film) 1717, 1637, and 1614 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + 12-H), 2.28 (d, J = 1 Hz, C-3 CH_3), 3.73 (s, $COOCH_3$), 5.73 (m, H-2), and 6.13 ppm (m, H-4 + H-5).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.93; H, 10.99.

Conversion of a sample of the acid to the acid chloride with oxalyl chloride in benzene and addition of isopropyl alcohol as described above for **7** gave **16** [bp (bath, short path) 80° (0.005 mm)]: nmr (CCl_4) δ 0.88 (d, 9, J = 6 Hz, C-7 and C-11 CH_3), 1.25 [d, 6, J = 6 Hz, $OCH(CH_3)_2$], 2.25 (d, 3, J = 1 Hz, C-3 CH_3), 5.00 [m, $OCH(CH_3)_2$], 5.62 (m, 1, H-2), and 6.07 ppm (m, H-4 and H-5); mass spectrum (70 eV) m/e 280 (M^+), 238 (M − C_3H_6), 221 and 111 (base peak).

Diethyl 3-Ethoxycarbonyl-2-methyl-2-propenyl Phosphonate (19a). The phosphonate **19a** was prepared as described in the literature (Davis *et al.*, 1966; Pattenden and Weedon, 1968; Stilz and Pommer, 1964, 1965). In the above experiments it made little difference whether the pure *trans*-phosphonate or a mixture of *cis*- and *trans*-phosphonates was used. The triisopropyl phosphonate **19b,** bp 140° (2 mm), was prepared by the same procedure as was **19a.**

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