Insect Juvenile Hormone Activity of the Stereoisomers of Ethyl 3,7,11-Trimethyl-2,4-dodecadienoate

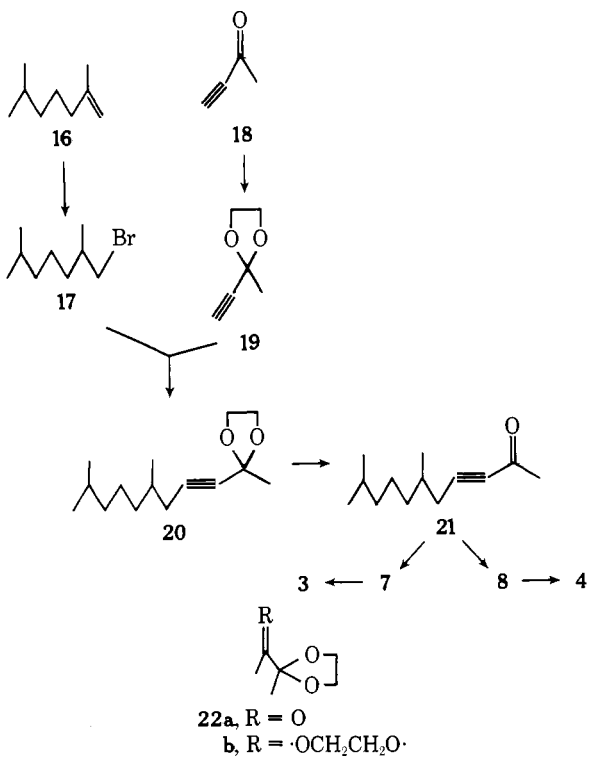
Clive A. Henrick,* W. Edward Willy, Barbara A. Garcia, and Gerardus B. Staal

All four possible stereoisomers of ethyl 3,7,11-trimethyl-2,4-dodecadienoate have been synthesized. Bioassay data on yellow fever mosquito (*Aedes aegypti*), greater wax moth (*Galleria mellonella*), yellow mealworm (*Tenebrio molitor*), house fly (*Musca domestica*), pea aphid (*Acyrthosiphon pisum*), and tobacco budworm (*Heliothis virescens*) for these and some related compounds are given. The 2*E*,4*E* stereoisomer 1 is the most biologically active of the four isomers.

We have recently described (Henrick et al., 1973) a new class of highly potent insect growth regulators (IGR's) with juvenile hormone activity, the alkyl 3,7,11-trimethyl-2,4-dodecadienoates. We wish to describe here the preparation of the 4*Z* stereoisomers, the properties of the four stereoisomers of ethyl 3,7,11-trimethyl-2,4-dodecadienoate, and some bioassay data for these and for some closely related compounds.

RESULTS AND DISCUSSION

The 2*E*,4*E* stereoisomer 1 and the 2*Z*,4*E* stereoisomer 2 were prepared as described elsewhere (Henrick et al., 1973; Henrick et al., 1975a). The 4*Z* isomers 3 and 4 were prepared from the corresponding 2-en-4-yne derivatives (Willy and Henrick, 1974). Thus, alkylation of the lithium salt of 19 with the bromide 17 in dimethyl sulfoxide containing *N,N,N′,N′*-tetramethylethylenediamine gave **20**. The bromide 17 was prepared from 2,6-dimethyl-1-heptene via hydroboration (Brown and Lane, 1970) and the intermediate dioxolane 19 was prepared by direct ketalization of 1-butyn-3-one (18). The reaction conditions in this ketalization reaction must be carefully controlled (see Experimental Section) to limit contamination of the product by the dioxolanes **22a** and **22b** (cf. Feugeas and Giusti, 1967; Giusti, 1972). Removal of the protecting group from **20** with acid gave **21**, which on reaction with the anion of triethyl phosphonoacetate in dimethylformamide gave (in 71% yield after distillation) a mixture of 7 and 8 in the ratio ca. 1:1. It is interesting to compare the stereochemical outcome of the last reaction with the results obtained with ketones such as geranylacetone, which give a mixture of *E* and *Z* isomers in the ratio 7:3, respectively, under these conditions (Anderson et al., 1972). Conjugated ketones such as 6,10-dimethyl-3-undecen-2-one give very poor yields of dienoic esters on reaction with the anion of triethyl phosphonoacetate under these conditions (Henrick et al., 1975b).



The isomers 7 and 8 were separated by preparative TLC on silica gel and their configurations were assigned by NMR spectroscopy (cf. Wiley et al., 1962; Pattenden and Weedon, 1968). Each isomer was then hydrogenated in pentane over Lindlar catalyst (cf. Crombie, 1955; Wiley et al., 1962). Further purification by preparative TLC gave a sample of the 2*E*,4*Z* isomer 3 (containing, by GLC analysis, ca. 2% of 1) and a sample of the 2*Z*,4*Z* isomer 4 (containing ca. 1.4% of 2 and <1% of 1).

The NMR spectra of the four stereoisomers exhibit several distinctive features related to their configurations (cf. Wiley et al., 1962; Pattenden and Weedon, 1968; Kluge and Lillya, 1971; Leften and Gil-Av, 1972). Thus, the C-3 methyl group in 1 and in 3 absorbs (in CCl_4) at 2.26 and 2.23 ppm, respectively, whereas the C-3 methyl group in 2 and in 4 absorbs at 1.98 and 2.04 ppm, respectively. The downfield shift of the signal due to the C-3 methyl group when the 2-ene double bond is changed from cis to trans is presumably caused by the long-range anisotropic effect of the carbonyl group. The C-4 proton resonance in 2 and in 4 occurs downfield as a broadened doublet at 7.62 ppm (J = 16 Hz) and at 6.75 ppm (J = 12.5 Hz), respectively, whereas the C-4 proton in 3 absorbs at 5.93 ppm (d, J = 12.5 Hz) and in 1 the C-4 and C-5 protons are almost equivalent and absorb at 6.08 ppm. The large downfield shift of the C-4 proton signal in the spectrum of 2 when the 2-ene double bond is changed from trans to cis (i.e., 1 → 2) implies for 2 a predominantly planar (2*Z*)-dienoate with the *s-trans*-diene conformation.

The uv spectra (Table I) of the four stereoisomers are useful for partial assignment of conformations (cf. Eisner et al., 1953; Crombie, 1955; Allan et al., 1955; Kluge and Lillya, 1971). Thus, some loss of coplanarity of the chromophore is indicated in going from 1 to 2 and even greater loss in going to 3 and then to 4. In this context one observes in the NMR spectra that the C-4 proton in 4 is deshielded less by the ester group than is the C-4 proton in 2. All four isomers probably exist mainly in the 3-*s-trans*-diene conformations as drawn in Table II, and also possibly mainly in the *s-cis*-enoate conformations (cf. Kluge and Lillya, 1971).

The 4*Z* stereoisomers 3 and 4 are the least favored thermodynamically. We have shown elsewhere (Henrick et al.,

Research Laboratory, Zoecon Corporation, Palo Alto, California 94304.

Table I. Ultraviolet Spectral Data (in Hexane)

Isomer	λ_{max}, nm	ϵ
2*E*,4*E*-1	259	26,400
2*Z*,4*E*-2	262	20,900
2*E*,4*Z*-3	261.5	17,200
2*Z*,4*Z*-4	261	8,800

1975a,b) that equilibration of any of the four isomers with 1% by weight of benzenethiol gives an equilibrium mixture containing ca. 65% of the 2*E*,4*E* isomer **1** and 35% of the 2*Z*,4*E* isomer **2** with only traces (<1%) of the 4*Z* isomers **3** and **4**.

Biological Activity. The bioassay data for the four stereoisomers on several insect species are given in Table II. The 2*E*,4*E* isomer is the most active of the isomers and the biological activity is obviously very dependent upon the stereochemistry about both the C-2 and the C-4 double bonds. The critical dependence of biological activity on the 2*E* stereochemistry in the natural juvenile hormone **12** of *Hyalophora cecropia* has been demonstrated for several insect species (Dahm et al., 1968; Wigglesworth, 1969; Trost, 1970; Schwieter-Peyer, 1973). Similarly, for the isopropyl dienoate **5** (Henrick et al., 1973; Henrick et al., 1975a), the 2*Z*,4*E* isomer **6** is considerably less active (Table II) than the 2*E*,4*E* isomer **5**. In the less active 10,11-epoxy derivatives **14** and **15** (Henrick et al., 1973) the same correlation in general applies. It is interesting that the allenic ester **9** (Henrick et al., 1975b) shows negligible biological activity in these bioassays, although chemically it can be readily converted to **1**. The enynes **7** and **8** also have low biological activity. The activity of **7** is somewhat less than that found for the corresponding 4,5-saturated analog, ethyl (*E*)-3,7,11-trimethyl-2-dodecenoate (Henrick et al., 1973). The bioassay data for synthetic samples of the known natural juvenile hormones JH I (**12**), JH II (**11**), and JH III (**10**) (Judy et al., 1973) and for the analog JH 0 (**13**) (Anderson et al., 1975) are included in Table II for comparison purposes.

It has been found (Quistad et al., 1975) from insect metabolism studies starting from the (2*E*,4*E*)-[5-^{14}C]dienoate **5**, that not only is **5** metabolized by *Aedes aegypti* (3rd and 4th instar larvae) and by *Musca domestica* larvae but also the starting dienoate recovered from the insects has undergone partial *isomerization at C-2 in the insect* to a mixture of **5** and **6**. Little isomerization (or metabolism) occurred in the control experiments run with media in the absence of larvae. These metabolism studies were run under similar conditions to the bioassays in Table II. In view of the very large differences in ID_{50} values observed between **5** and **6** in these two insect species, this implies that although these two insect species can rapidly isomerize the 2*E*,4*E* isomer at C-2 they *cannot rapidly isomerize the corresponding 2Z,4E isomer* at C-2. The metabolites of **5** which still contained the 2,4-diene group were also found in these studies to have undergone considerable isomerization at C-2.

In this context it has been shown previously (Weirich and Wren, 1973) that although **12**, the corresponding ethyl ester, and also **1** are hydrolyzed rapidly on incubation with dilute hemolymph of *Manduca sexta*, the corresponding 2*Z* isomer of **12** is not affected. However, these experiments were carried out with only short incubation times and the isopropyl ester **5** was also unaffected under these conditions. Weirich and Wren also showed that the JH esterases in the hemolymph of *Samia cynthia* and *Tenebrio molitor* have the same requirement for 2*E* configuration in **12**. Chemically both **1** and **2** can be readily equilibrated to the same 65:35 mixture of **1** and **2**, respectively (Henrick et al., 1975a). It has been also shown recently (Quistad et al., 1974) that the (2*E*,4*E*)-[5-^{14}C]dienoate **5** undergoes slow isomerization at C-2 on the leaf surface of alfalfa and rapid isomerization at C-2 under aqueous conditions in full sunlight (through Pyrex glass) to give a ca. 1:1 mixture of the isomers **5** and **6**. Photochemical *Z*–*E* isomerization of the α,β-double bond was essentially the only process observed in solution when the (2*E*,4*E*)-dienoate **1** or its 2*Z*,4*E* isomer **2** were directly irradiated (through a Pyrex filter), or irradiated in the presence of a suitable photosensitizer, with a medium-pressure mercury arc lamp (Henrick et al., 1975b).

BIOASSAY PROCEDURES

Bioassays were performed on synchronized sensitive stages of the six insect species. The activities were expressed as ID_{50} or IC_{50} values (dose or concentration required to produce 50% inhibition of metamorphosis) which provide a quantitative basis for comparison of compounds.

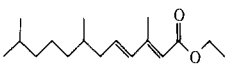
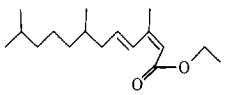
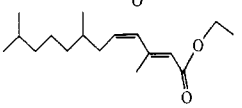
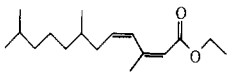
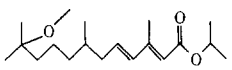
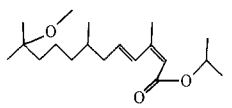
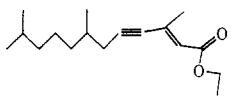
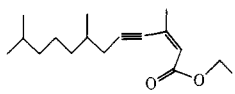
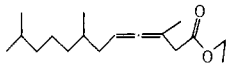
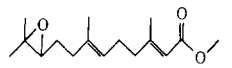
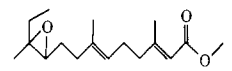
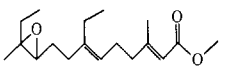
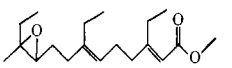
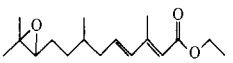
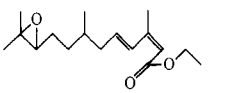
Procedures for bioassay on *Aedes aegypti* (last larval instars), *Galleria mellonella* (fresh pupae), and *Tenebrio molitor* (fresh pupae) have been previously described (Henrick et al., 1973).

House Fly (*Musca domestica*). Full grown larvae of a milk, yeast, and agar diet adapted SCR strain of house flies that had left the breeding medium searching for a pupation site ("wandering larvae") were collected and placed in plastic petri dishes on filter paper disks. Individual larvae, while still mobile, were topically treated with compounds serially diluted in acetone (1 μl per larva, 20 larvae per dose level). The paper disks were removed the following day and the results were evaluated after 7 days (at 30°), when all the controls had emerged as adults. The typical IGR effect was nonemergence of adults, although pupariation was generally not affected. Standard insecticides usually killed the larvae before pupariation. The percentage of nonemerged flies, corrected for nonemergence in acetone treated controls, was calculated and the ID_{50} determined by interpolation on semilogarithmic paper. The ID_{50} values given were usually determined from the averages of at least two replicates.

Pea Aphid (*Acyrthosiphon pisum*) **2nd and 3rd Instar Nymphs.** Young pea plants were infested with adult pea aphids which were allowed to reproduce for 24 hr, then the adults were removed. The offspring were maintained on the same plants (25°, 16-hr photophase, fluorescent light) for 3 more days, to reach the 2nd or 3rd nymphal instar. Fresh pea seedlings, 12 days old, were sprayed until runoff with a fine mist of emulsions of the test compounds in water with 0.1% Tween 20. This emulsifier was chosen because of the absence of direct toxic effects on aphids as noted with many other emulsifiers. The test concentrations were chosen so as to bracket the median effective dose (ID_{50}), usually in a logarithmic dilution series. The plants were allowed to dry for 1 hr, after which the 2nd or 3rd instar nymphs were transferred to them and confined in small cages with fine mesh nylon screening. Test plants with aphids were kept under the conditions mentioned above for 6 days, after which effects were evaluated by the following graded scoring system: 0 = normal adult with elongated cauda, sclerotized genital plate and functional genital pore; 1 = intermediates with nearly adult cauda but with occluded genital pore; 2 = extra nymphal instars with nymphal cauda, no genital pore and usually a congestion of fully grown embryos. (Under the test conditions primarily apteriform nymphs are produced; therefore, wing metamorphosis was not evaluated).

The graded-response score was calculated as a percentage of the maximum attainable. The ID_{50} was determined by interpolation on semilogarithmic paper (dead nymphs, not being a typical IGR effect, were excluded from the

Table II. ID_{50} Values on Sensitive Synchronized Instars

No.	Structure	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa	*Musca domestica*, μg/prepupa	*Acyrthosiphon pisum*, % active ingredient in spray	*Heliothis virescens*, ppm in medium
1[a,b]		0.0078	0.040	0.25	18	0.0039	0.30
2[b,c]		0.59 (0.30[d])	34	4.9	>100		2.7
3[e]		0.14	8.6	13	26	>0.01	
4[f]		0.11	7.6	22	36	>0.01	
5[b,g]		0.00025	1.1	0.0040	0.0056	0.0054	0.77
6[h,i]		0.018	>100	1.9	1.2		>100
7		0.36	84	13	2.5	>0.1	>100
8		>10	>100	>100	>100	>0.01	>100
9[j]		>10	73	>100	>100		>100
10[k]		0.35	12.0	4.5	>100	>0.1	>100
11[k]		0.26	0.13	4.3	>100	0.035	>100
12[l]		0.15	0.060	0.70	>100		24
13[m]		1.0	1.0	0.15	>100		>100
14[b]		0.18	2.4	26	23		>10
15[b]		1.8	79	15	>100		

[a] Altozar Insect Growth Regulator (ZR 0512). [b] Henrick et al., 1973. [c] Contains <0.4% of 1 (purity by GLC, 99.6%). [d] This bioassay was run on a sample containing 2% of 1. [e] Contains 2% of 1. [f] Contains 1.4% of 2 and <1% of the isomer 1. [g] Altosid Insect Growth Regulator (ZR 0515). [h] Contains ≤0.5% of 5 (purity by GLC, 99.2%). [i] Henrick et al., 1975a. [j] Henrick et al., 1975b. [k] Anderson et al., 1972. [l] Henrick et al., 1972. [m] Anderson et al., 1975.

score). In each test every dose was replicated 2 times with 10 nymphs each. Every test series was usually repeated at least once on a different day. The figures presented are the averages of the replicates.

Tobacco Budworm (*Heliothis virescens*). Larvae were reared in mass culture on a modified Van der Zandt artificial diet based on agar, lima beans, split peas, torula yeast plus vitamins, minerals, and bacteriostatic additives. Compounds to be tested were mixed as acetone solutions with this diet while it was still warm and not yet solidified (7.5 ml of medium in 15-ml tubes). Unfed first instar larvae were collected from the mass rearing and distributed in the glass tubes (one larva per tube, 15 tubes per dose level). The tubes with larvae were then capped with a firm cotton plug and placed on racks in a culture room at 25° and 16-hr photophase (low intensity fluorescent light). The normal interval until pupation under these conditions was ca. 16 days.

Typically, IGR effects did not become apparent before metamorphosis to the pupae, although it was noted that a deep red color could usually be noticed in the larvae long before morphogenetic effects became apparent if effective

IGR concentrations were present in the medium. Broad-spectrum insecticides usually killed the larvae at the moment they came into contact with the treated medium or when they had just started feeding.

Individual specimens were preserved in ethanol within a few days after pupation and stored until the entire series was thus preserved. The test results were then evaluated with the following scoring system: 0 = normal pupa; 1 = pupa of normal shape and appearance except for very minor abnormalities such as minute rudiments of larval mouthparts, larval tubercles, etc. (the ultimate viability of these pupa was not investigated); 2 = unviable intermediates between larvae and pupae ranging from almost perfect supernumerary larval instars (frequently with some pupal cuticle on the antennae only) to pupae with pronounced prolegs, patches of larval cuticle, etc. These intermediates invariably showed a delayed development. The graded-response score was calculated as a percentage of the maximum attainable. ID_{50} doses were determined by interpolation on semilogarithmic paper. Dead larvae were generally excluded from the score, unless death was obviously a consequence of morphogenetic abnormalities and the specimens could be scored as above.

It should be noted that field efficacy cannot be automatically deduced from these tests with continuous exposure in an enclosed situation. The data given should, however, provide a measure of relative activities.

EXPERIMENTAL SECTION

All substances described herein are racemic compounds; the prefix *dl* is omitted. Preparative thin-layer chromatography was carried out on 1 m × 20 cm plates coated with 1.3 mm of 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 a Varian Mat CH-7 spectrometer, at 20 or 70 eV ionization potential. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. All solvents were dried over activated 4A molecular sieves, and most reactions were carried out under a nitrogen atmosphere.

1-Bromo-2,6-dimethylheptane (17). Hydroboration of 2,6-dimethyl-1-heptene (from Chemical Samples Co.) followed by treatment with bromine and sodium methoxide, according to the procedure of Brown and Lane (1970), gave, after distillation, a 70% yield of 1-bromo-2,6-dimethylheptane (**17**), bp 48° (0.08 mm).

2-Ethynyl-2-methyl-1,3-dioxolane (19). To 25.0 g (0.367 mol) of 1-butyn-3-one (**18**) (from Chemical Samples Co.), 23.3 g (0.375 mol) of ethylene glycol, and 190 ml of dichloromethane contained in a 300-ml flask fitted with a water collection trap (for solvents heavier than water) and condenser, was added 3.0 g of *p*-toluenesulfonic acid monohydrate. The mixture was boiled for 4.5 hr, at which time 5.1 ml (theoretical 6.6 ml) of water had been collected in the trap. The reaction mixture was then treated with solid sodium bicarbonate and filtered, and the solvent was removed and the residue short path distilled to give 21.0 g (51% yield) of **19**, bp 36–40° (18 mm) [lit. Giusti (1972) bp 41° (23 mm)].

Two by-product dioxolanes were also identified in the crude product by GLC–mass spectra: 2-acetyl-2-methyl-1,3-dioxolane (**22a**) [mass spectrum (70 eV) *m/e* (rel intensity) 115 (4), 103 (7), 102 (5), 87 (6), 73 (70), 58 (10), 45 (48), and 43 (100)] and bis-2,2,3,3-(ethylenedioxy)butane (**22b**) [mass spectrum (70 eV) *m/e* (rel intensity) 159 (9), 129 (9), 87 (100), 73 (67), 45 (14), 43 (40)].

Ketalization of **18** using refluxing benzene (2 hr) in place of the dichloromethane under the above conditions gave a mixture of **19**, **22a**, and **22b** in approximately equal amounts.

2,2-Ethylenedioxy-6,10-dimethyl-3-undecyne (20). To a mixture of 25 ml of ether, 25 ml of tetrahydrofuran, and 58.5 ml (0.091 mol) of a 1.55 *M* *n*-butyllithium in hexane solution, at −70°, was added dropwise a mixture of 10.7 g (0.095 mol) of the dioxolane **19**, in 25 ml of ether and 25 ml of tetrahydrofuran over a period of 1 hr. The mixture was stirred at −70° for an additional 1 hr, then at −35° for 0.5 hr, at which time a white solid had formed. 1-Bromo-2,6-dimethylheptane [(**17**); 19.7 g (0.095 mol)] in 15 ml of ether and 15 ml of tetrahydrofuran was then added dropwise, at −35°, over a period of 1 hr. The reaction temperature was raised to 0° and dimethyl sulfoxide (150 ml) followed by *N,N,N′,N′*-tetramethylethylenediamine [1.10 g (0.0095 mol)] were then added. The cooling bath was removed and the mixture was stirred, at room temperature overnight, and then poured into a mixture of 400 ml of saturated aqueous NH_4Cl and 400 g of ice. The mixture was extracted thoroughly with hexane. The combined organic layers were washed with water and brine, and then dried ($CaSO_4$). Solvent removal in vacuo gave 14.8 g of **20:** bp (bath, short path) 60° (0.01 mm); ir (film) 2270 cm^{-1}; NMR (CCl_4) δ 0.88 (d, J = 6 Hz, C-10 CH_3 + H-11), 0.97 (d, C-6 CH_3), 1.58 (s, H-1), 2.12 (br d, H-5), and 3.93 ppm (br s, OCH_2CH_2O); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 238 (4), 223 (74), 153 (91), 139 (11), 126 (100), 113 (47), 99 (30), 87 (79), 83 (47), 81 (24), 71 (18), 69 (30), 57 (34), 55 (26), 43 (54).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.39; H, 10.81.

6,10-Dimethyl-3-undecyn-2-one (21). A mixture of 14.0 g (0.059 mol) of the ketal **20,** 45 ml of *p*-dioxane, 1.5 ml of water, and 0.5 ml of concentrated H_2SO_4 was heated at 40° for 4.5 hr, then neutralized with aqueous saturated $NaHCO_3$. Water was then added and the mixture was extracted with hexane. The combined organic layers were washed with brine and then dried ($CaSO_4$). Solvent removal yielded 10.8 g of crude product which was distilled yielding 8.38 g (73% yield) of ketone **21:** bp 60–61° (0.01 mm); ir (film) 2240 (C≡C), 1680 cm^{-1} (C=O); NMR (CCl_4) δ 0.88 (d, J = 6 Hz, C-10 CH_3 + H-11), 1.02 (d, J = 6 Hz, C-6 CH_3), 2.25 (s, H-1), and 2.29 ppm (br d, H-5); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 194 (~0), 179 (7), 151 (8), 137 (9), 123 (13), 109 (22), 95 (29), 82 (100), 71 (37), 57 (49), 43 (47).

Ethyl 3,7,11-Trimethyl-2-dodecen-4-ynoate (7 and 8). To a mixture of 1.02 g (0.043 mol) of sodium hydride and 100 ml of dimethylformamide at 24° was added dropwise 9.75 g (0.044 mol) of triethyl phosphonoacetate over a period of 20 min. Stirring was continued for a further 1 hr (until gas evolution ceased), and then 8.0 g (0.041 mol) of the ketone **21** was added dropwise over a period of 15 min. After another 40 min the mixture was poured into 700 ml of ice-cold saturated aqueous NH_4Cl. The mixture was extracted with ether–hexane (1:1) and the combined organic layers were washed with brine and then dried ($CaSO_4$). Solvent removal yielded 10.2 g of crude product (76% purity by GLC; ratio of **7**:**8** was 1:1) from which the stereoisomers **7** and **8** were isolated by preparative TLC. We obtained 2.61 g of the *E* stereoisomer **7:** bp (bath, short path) 90° (0.04 mm); ir (film) 2240 (C≡C), 1715 (C=O), and 1620 cm^{-1}; NMR (CCl_4) δ 0.88 (d, J = 6 Hz, C-11 CH_3 + H-12), 0.98 (d, J = 6 Hz, C-7 CH_3), 1.27 (t, J = 7 Hz, OCH_2CH_3), 2.26 (d, J = 1.5 Hz, C-3 Me), 4.13 (q, J = 7 Hz, OCH_2CH_3), and 5.92 ppm (br s, H-2); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 264 (~0), 249 (3), 236 (2), 219 (16), 179 (39), 161 (20), 151 (44), 139 (25), 137 (15), 124 (100), 123 (67), 111 (22), 107 (24), 95 (24), 81 (28), 71 (25), 69 (31), 57 (45), 55 (13), 43 (40).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 76.98; H, 10.61.

Also we obtained 2.49 g of the *Z* stereoisomer **8**: bp (bath, short path) 90° (0.04 mm); ir (film) 2250 (C≡C), 1730, 1710 (C=O), and 1620 cm^{-1}; NMR (CCl_4) δ 0.88 (d, J = 6 Hz, C-11 CH_3 + H-12), 1.03 (d, J = 6 Hz, C-7 CH_3), 1.27 (t, J = 7 Hz, OCH_2CH_3), 2.00 (d, J = 1.5 Hz, C-3 Me), 2.34 (br d, $J \simeq$ 5.5 Hz, H-6), 4.13 (q, J = 7 Hz, OCH_2CH_3), and 5.85 ppm (br s, H-2); the mass spectrum of **8** was essentially identical with that obtained from **7**.

Ethyl (2*E*,4*Z*)-3,7,11-Trimethyl-2,4-dodecadienoate (3). A mixture of the ester **7** [0.500 g (0.00189 mol)], 15 ml of pentane, 1 drop of synthetic quinoline, and 0.14 g of Lindlar catalyst was stirred at 24° under a slight positive pressure of H_2 until nearly the theoretical amount (ca. 42 ml; 1 equiv) of hydrogen had been taken up. The hydrogenation was then interrupted and a small amount of Celite was added and the mixture was filtered. Pentane (100 ml) was added to the filtrate which was washed with 2 *N* sulfuric acid, water, and brine, and then dried ($CaSO_4$). Solvent removal in vacuo yielded 0.45 g of crude product which was purified by preparative tlc yielding 0.25 g of ester **3** (analysis by GLC showed the presence of 2% of **1**): bp (bath, short path) 90–95° (0.04 mm); ir (film) 1720 (C=O) and 1640 cm^{-1}; NMR (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 1.27 (t, J = 7 Hz, OCH_2CH_3), 2.23 (d, J = 1.2 Hz, C-3 Me), 4.11 (q, J = 7 Hz, OCH_2CH_3), 5.57 (br m, H-5), 5.63 (br s, H-2), and 5.93 ppm (br d, J = 12.5 Hz, H-4); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 266 (7), 221 (9), 181 (9), 178 (12), 139 (100), 111 (31), 107 (40), 95 (19), 81 (35), 71 (18), 57 (27), 43 (21).

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.45; H, 11.18.

Ethyl (2*Z*,4*Z*)-3,7,11-Trimethyl-2,4-dodecadienoate (4). Ester **8** [0.72 g (0.00273 mol)] was hydrogenated and the product was purified in the same manner as described above for the preparation of **3**. There was obtained 0.60 g of crude product which after TLC purification gave 0.35 g of ester **4** (analysis by GLC showed the presence of 1.4% of **2** and less than 1% of **1**): bp (bath, short path) 90° (0.04 mm); ir (film) 1720 (C=O) and 1635 cm^{-1}; NMR (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 1.25 (t, J = 7 Hz, OCH_2CH_3), 2.04 (d, J = 1 Hz, C-3 Me), 4.09 (q, J = 7 Hz, OCH_2CH_3), 5.57 (br m, H-5), 5.62 (br s, H-2), and 6.75 ppm (br d, J = 12.5 Hz, H-4); the mass spectrum of **4** was identical with that obtained from **3**.

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.43; H, 11.33.

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