THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 1

JANUARY 10, 1975

Stereoselective Synthesis of Alkyl (2*E*, 4*E*)- and (2*Z*, 4*E*)-3,7,11-Trimethyl-2,4-dodecadienoates. Insect Growth Regulators with Juvenile Hormone Activity[1]

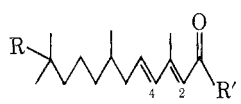
Clive A. Henrick,* W. Edward Willy, John W. Baum, Ted A. Baer, Barbara A. Garcia, Thomas A. Mastre, and Samuel M. Chang

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

Received July 30, 1974

A general synthetic method is described suitable for the preparation, in excellent overall yield, of alkyl (2*E*, 4*E*)- and (2*Z*, 4*E*)-3,7,11-trimethyl-2,4-dodecadienoates of high stereochemical purity. The method involves the condensation of dialkyl 3-methylglutaconates with the aldehydes **2** to give the diacids **4**. Decarboxylation (*via* **7**) affords the pure 2*Z*, 4*E* isomers **9** which are equilibrated with the 2*E*, 4*E* isomers **10**. The latter are then separated *via* their insoluble ammonium salts. Methods are discussed for the conversion of the 2*Z*, 4*E* stereoisomers to the 2*E*, 4*E* stereoisomers. Benzenethiol by itself is shown to be an excellent equilibration catalyst for olefins.

The alkyl 3,7,11-trimethyl-2,4-dodecadienoates[2,3] are potent insect growth regulators with juvenile hormone activity and their efficacy as control agents for several pest insect species has been demonstrated in large scale field tests. Zoecon Corporation has obtained an experimental use permit from the Environmental Protection Agency for compound **1a** (Altosid insect growth regulator; ZR-0515;



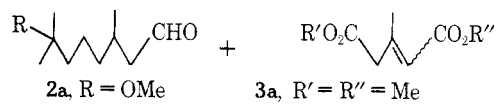
1a, R = OMe; R′ = $OCH(Me)_2$ (ZR-0515)
b, R = H; R′ = OEt (ZR-0512)
c, R = OMe; R′ = SEt (ZR-0619)
d, R = H; R′ = $OCH_2C{\equiv}CH$ (ZR-0777)
e, R = OH; R′ = OEt (ZR-0587)

methoprene; ENT 70460)[4] and we wish to describe here an outline of a procedure[5] which may be used to prepare **1a** and related compounds.

Since the 2*E*, 4*E* stereoisomer shows considerably higher biological activity than the other three possible stereoisomers,[2,6] a useful synthesis must produce principally this isomer as the final product. We also required a synthetic route that would be sufficiently versatile to enable us to prepare a variety of esters, thioesters, amides, and related analogs. We had initially investigated along with a phosphonate route[2,7] a variety of other methods[8] for the synthesis of **1a** and **1b** and related compounds. However, it soon became apparent that the glutaconate route described below was to be preferred.

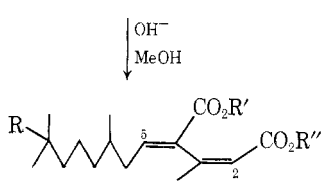
Any efficient synthesis of 3-methyl-2,4-dienoic acids could be applicable to the preparation of **1** since equilibration[8] of all four stereoisomers[6] of **1b** (or of the corresponding acids) with benzenethiol gives the same mixture containing *ca.* 65% of the 2*E*, 4*E* isomer, *ca.* 35% of the 2*Z*, 4*E* isomer, and only trace amounts of the two 4*Z* isomers. Furthermore, as demonstrated below, the 2*E*, 4*E* isomer can be readily separated from such an equilibrium mixture and the 2*Z*, 4*E* isomer can be recycled.

It has been known for some time that diethyl and dimethyl 3-methylglutaconates (**3**) condense with aliphatic and aromatic aldehydes under alkaline conditions (methanolic KOH) to give variable yields of 4-alkylidene (or 4-arylidene)-3-methylglutaconic acids.[9-12] The intermediate diacids, which were finally assigned[12] the "cis,cis" configuration (2*Z*, 4*E* as in **4**), have been decarboxylated, with inversion at C-4, to give (2*Z*, 4*E*)-3-methyl-2,4-dienoic



2a, R = OMe
b, R = H
c, R = OH

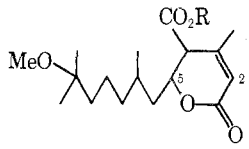
3a, R′ = R″ = Me
b, R′ = R″ = Et
c, R′ = Me; R″ = Et, R′ = Et; R″ = Me, and **3a**



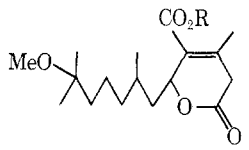
4a, R = OMe; R′ = R″ = Na
b, R = OMe; R′ = R″ = K
c, R = OMe; R′ = R″ = H
d, R = OMe; R′ = R″ = Et
e, R = OMe; R′ = Me; R″ = H
f, R = OMe; R′ = R″ = Me
g, R = OH; R′ = R″ = H
h, R = H; R′ = R″ = H

acids.[10-12] However, the reported yields have been highly variable and the reaction mechanisms of both the condensation and the decarboxylation steps have not been clarified.[12a] It was noted by Cawley[10b] that half-esters of the diacid may have been formed as intermediates in the conden-

sation and that both pure Z and E isomers of dimethyl 3-methylglutaconate gave the same diacid on condensation with cinnamaldehyde. Wiley and Ellert[11] found that on acidification of the condensation reaction product both diacids and the previously unnoticed isomeric carboxy-δ-lactones (assigned structures such as **5a**) were obtained. The

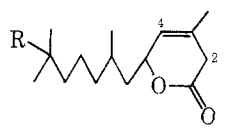


5a, R = H
b, R = Et
c, R = Me

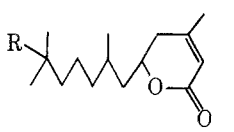


6a, R = H
b, R = Et
c, R = Me

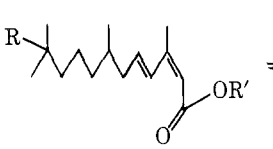
type of product obtained could apparently be correlated, by these authors, with the type of aldehyde used. Although the diacids were reported to decarboxylate by heating at 145–160° in quinoline alone,[10c] the preferred method of decarboxylation was found by Cawley, *et al.*,[10] to be heating with 2,4-dimethylpyridine in the presence of copper or cupric acetate at 90–120°. However, Wiley and Ellert[11] obtained poor yields of monoacid and/or δ-lactone under these conditions and preferred to decarboxylate in hot acetic acid to give δ-lactones, assigned the 5,6-dihydro-2-pyrone structure (*cf.* 8). We have investigated this reaction sequence in considerable detail and have developed it into a very useful general synthesis of (2*Z*, 4*E*)- and of (2*E*, 4*E*)-3-methyl-2,4-dienoic acids.



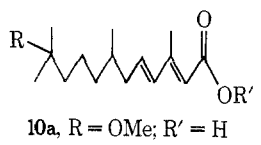
7a, R = OMe
b, R = H



8a, R = OMe
b, R = H



9a, R = OMe; R′ = H
b, R = H; R′ = H
c, R = OH; R′ = H
d, R = OMe; R′ = Me
e, R = OMe; R′ = Et
f, R = OMe; R′ = $CH(Me)_2$
g, R = H; R′ = Me

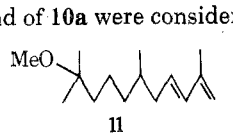


10a, R = OMe; R′ = H
b, R = H; R′ = H
c, R = OH; R′ = H
d, R = OMe; R′ = Me
e, R = OMe; R′ = Et
f, R = H; R′ = Me

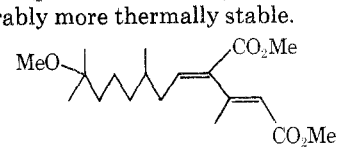
Results and Discussion

The condensation of dialkyl 3-methylglutaconates (**3**)[13] with the aldehydes **2** in the presence of excess alcoholic sodium or potassium hydroxide proceeded rapidly. For example, treatment of a mixture of **2a** and **3a** in dry methanol with sodium hydroxide in methanol and heating under reflux for 1 hr gave the precipitated disodium salt (**4a**) in 90% isolated yield (3.5–4 equiv of NaOH was required to obtain this optimum yield). Acidification of **4a** afforded the diacid **4c** which could be esterified to the stable diesters (**4d** and **f**). The free diacid lactonized readily to a mixture of **5a** and **6a** on heating or on standing at room temperature for long periods (*cf.* ref 11). The initial product of lactonization appeared to be mostly **6a**, with isomerization to **5a** occurring subsequently. However, under the above condensation conditions it was necessary to isolate the disodium or dipotassium salt by filtration, in order to obtain pure **4c**. Examination of the filtrate (after acidification) showed it to contain three additional diacid isomers of **4c** (see below). The presence of two 2*E* isomers (*ca.* 4% of the total condensation product) was detrimental as it was found that they did not decarboxylate readily in the following steps and hence contaminated the product or the recycle. It was found that the isomerization occurred subsequent to condensation (*cf.* ref 12a, c, and d) and thus could be avoided by modifying the reaction conditions. Thus addition of 1 equiv of 50% aqueous sodium hydroxide solution to a mixture of **2a** and **3a** in methanol at 5° followed by standing 1 hr at room temperature gave the half-ester **4e**. Addition of a further 2 equiv of sodium hydroxide in water and heating at 65° for 1 hr gave, after acidification, the diacid **4c** in 95% yield in >96% purity. The initial rapid formation of the half-ester indicated that **5c** (or **6c**) was probably an intermediate in the condensation reaction. On standing, the isolated half-ester lactonized to give a mixture of **5c** and **6c**. The initial product of lactonization of **4e** could be seen by nmr to be **6c**; however, subsequent isomerization to **5c** occurred readily on mild basic treatment and on chromatography of **6c** on silica gel tlc plates.

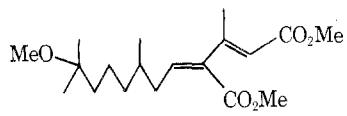
Decarboxylation of the diacid **4c** in the presence of 10% 2,4-dimethylpyridine began at 80° (neat or in toluene) and proceeded readily at 100° to a mixture of **7a**, **8a**, and **9a** with **7a** generally predominating (in toluene). In contrast to the published work,[10,11] it was found that *the presence (or absence) of a copper salt had no detectable effect* on the decarboxylation. It was possible to convert the diacid **4c** directly to the 2*Z*, 4*E* monoacid **9a** by prolonged heating at 100–130° using no solvent other than an excess of an organic base such as pyridine or 2,4-dimethylpyridine (*cf.* ref 10c). The initial decarboxylation took place readily but the subsequent conjugation and opening of the lactone ring to give **9a** was slow and often incomplete. These latter steps proceeded more rapidly in alcoholic sodium alkoxide[8,15] and hence it was found much more efficient to carry out the reaction in two steps (*cf.* ref 11). Thus the diacid **4c** was heated in toluene with 2,4-dimethylpyridine (0.1 equiv) at 100° until carbon dioxide evolution ceased, and then 1.1 equiv of sodium methoxide in methanol was added and the mixture heated at 70° for a further hour. This procedure gave the 2*Z*, 4*E* monoacid **9a** in >90% yield in high purity. The lactone acids **5a** and **6a**, which *were probably intermediates in the decarboxylation*, also gave **9a** under the above conditions (*cf.* ref 11). It was noted that although no decarboxylation occurred upon heating the diacid **4c** in excess 2 *N* NaOH, when the diacid was half-neutralized with aqueous NaOH and the solution heated to reflux (pH gradually increased from 6.5 to 8.5) a 50% yield of **9a** was obtained, along with 13% of the diene **11**, 9% of the lactone **8a**, and 20% of the starting diacid. Prolonged heating of the 2*Z*, 4*E* monoacid **9a** above 100° gave the diene **11** along with lesser amounts of **8a** (plus **7a**). The alkyl esters of **9a** and of **10a** were considerably more thermally stable.



11



12



13

The isomerization of the acid **9a** was studied with a variety of catalysts (see below). The best catalyst for equilibra-

tion was found to be benzenethiol. Thus heating the acid **9a** neat in the presence of 0.5–1.0% by weight of benzenethiol at 100° for 1–2 hr gave in 95% yield a mixture of 35% of **9a** and 65% of **10a.** It is particularly interesting that the presence of light or of AIBN [2,2′-azobis(isobutyronitrile)][16] was *not necessary* (see below).

We have already noted[2] that pure (2*E*,4*E*)-2,4-dienoic acids could be islated *via* their *S*-benzylisothiuronium salts. For purification of **10a** we now found that treatment of the isomerization mixture in ether (or in hexane, or dichloromethane for **10b** and **10c**) with anhydrous ammonia gas gave a crystalline precipitate of the pure 2*E*,4*E* ammonium salt which was collected. The filtrate from this procedure was recycled to the isomerization step above to convert the unprecipitated 2*Z*,4*E* acid to an equilibrium mixture of **9a** and **10a.** The ammonium salt was now acidified and the recovered pure 2*E*,4*E* acid converted *via* its acid chloride (prepared with thionyl chloride in dimethylformamide) into the corresponding ester or thioester (see Experimental Section). This overall scheme has been used to prepare pure **1a, b, c,** and **d** (purity 90–98% by internal standard glc analysis), *without any distillation of intermediates or final products.*

In connection with the isomerization of **9a** discussed above, we found that heating olefins without solvent with 0.5% by weight of benzenethiol at 100° was an excellent method for equilibration. The presence of a hydrocarbon solvent increased both the time required to reach equilibrium and the amount of benzenethiol which had to be used. We have used these conditions for equilibrating many olefins. For example, treating (*Z*)-11-tetradecen-1-yl acetate[17] with 1% by weight of benzenethiol for 1 hr at 100° followed by removal of the thiol by codistillation with a high boiling solvent, gave a mixture of the *Z* and *E* isomers in the ratio 25:75, respectively, in 92% yield. Other workers have reported the isomerization of olefins with thiyl radicals generated from benzenethiol in the presence of AIBN (at 65°).[16] It has been reported that when the benzenethiyl radicals were produced thermally (in the dark) from excess benzenethiol, diphenyl disulfide, or diphenyl sulfide it was necessary to heat to 200° in order to have a reasonable isomerization rate of (*Z,Z*)-1,8-cyclotetradecadiene.[18] These workers also noted that double bond migration occurred under these conditions whereas benzenethiyl radicals produced photochemically (λ >300 nm) from diphenyl disulfide (or from diphenyl sulfide) gave rapid equilibration at room temperature without double bond migration. Photochemical *Z–E* isomerization with diphenyl disulfide has been used successfully by other workers.[19–21]

The reversibility of the thiyl radical addition to the olefinic double bond,[22] especially in the case of a resonance-stabilized radical like benzenethiyl, is presumably the basis for the thiyl-catalyzed cis–trans isomerization discussed above. Even though the isomerization probably proceeds through a transitory radical adduct we did not detect any permanent thiol adduct in these reactions and our yields of pure products were always high. No polymerization or other decomposition took place during the benzenethiol-catalyzed isomerization.

Of the other catalysts[21] investigated for the equilibration of **9a** (and of **9b**) without solvent, it was found that Na_2S (20 mol %; 17 hr at 120°) and LiSCN (20 mol %; 22 hr at 120°) gave predominantly the lactone **8a.** Butadiene sulfone[20,21] (25 mol %; 7 hr at 120°) and ruthenium trichloride trihydrate (20 mol %; 2 hr at 120°) gave deconjugation to the 3,5-diene and some loss of the 11-methoxy group. Heating with thiobenzoic *S*-acid[20] (30 mol %; 24 hr at 120°), Al_2S_3 (20 mol %; 19 hr at 120°), or with diphenyl disulfide (20 mol % plus 10 mol % AIBN; 3 hr at 80°) gave slow isomerization without attainment of equilibrium under these conditions, whereas heating with dibenzyl disulfide (10 mol % plus 10 mol % AIBN; 3 hr at 80°) produced no change. Diphenyl disulfide did result in equilibration at a higher temperature (20 mol %; 5 hr at 120°), but benzenethiol, for comparison, gave rapid equilibrium *with* (5 mol % plus 1 mol % AIBN; 2 hr at 80°) *or without* (2 mol %; 1 hr at 100°) the use of AIBN. Heating with sulfur[21,23] (20 mol %; 25 hr at 115°) gave only partial isomerization. Heating with thioacetic *S*-acid (20 mol %; 6.5 hr at 120°) gave the equilibrium mixture (**9a:10a** in ratio 35:65, respectively) but the reaction was not as rapid or as clean as with benzenethiol and required considerably more catalyst. Treatment with thioglycolic acid (10% by weight; 22 hr at 100°) also gave the equilibrium mixture.

Isomerization of the esters **1a, 1b, 9e, 9f,** and **9g** was also investigated. Again benzenethiol was a satisfactory catalyst.[8] Thus heating either **1a** or **9f** with 1% by weight of benzenethiol and 0.5% AIBN at 80° for 2 hr gave a mixture of **1a** and **9f** in the ratio 67:33, respectively. Heating the 2*Z*,4*E* esters with alkoxides such as potassium *tert*-butoxide or sodium isopropoxide in dimethylformamide and also in 2-propanol for the latter gave very little isomerization, although addition of catalytic amounts of sodium ethoxide in ethanol to a solution of **1b** in dimethylformamide at 25° (overnight) did produce isomerization at C-2. Heating the ester **9g** (without solvent) with sulfur[21,23] (20 mol %; 4.5 hr at 115°) gave rapid equilibration to the 65:35 mixture of **10f** and **9g,** respectively. Sodium sulfide and also sodium hydrosulfide (20 mol %) gave equilibration after 20 hr at 115° (no solvent). Ruthenium trichloride (20 mol %; 48 hr at 115°) was slower and most other catalysts (no solvent; 115°) also gave either slow isomerization (*e.g.,* NaSMe, $LiSCH_3$, or $KSCH_3$), no isomerization (*e.g.,* KF or NaOMe), or caused decomposition (*e.g.,* I_2 or $PdCl_2$).

The configuration of the intermediate **4c** was assigned the 2*Z*,4*E* stereochemistry in agreement with previous assignments,[12] based on the following result. Methylation of the disodium salt **4a** with excess methyl iodide in dimethylformamide gave the dimethyl ester **4f.** Treatment of this diester with benzenethiol (10 mol % plus 0.05% AIBN) gave a mixture of three isomers (glc–ms) in the ratio 42:46:12. Partial separation by preparative tlc (and hplc) and examination of the nmr spectra enabled the assignment of the structures **4f, 12,** and **13,** respectively. The mixture of the two 2*E* isomers **12** and **13** could not be easily separated by preparative tlc but treatment of a mixture of **12** and **13** (in the ratio 78:22, respectively) with benzenethiol as above gave the same equilibrium mixture (**4f:12:13** in the ratio 40:48:12, respectively) as obtained from **4f.** In the nmr spectrum (CCl_4) of **4f** the 2-H absorbed at 5.85, the 5-H at 6.70, and the C-3 methyl group at 1.98 ppm. Similarly the 5-H of **12** absorbed at 6.76 whereas the C-3 methyl group absorbed at 2.22 ppm (*cf.* ref 2 and 6). In **13** and C-3 methyl group signal appeared at 2.27 but the signal due to the 5-H was shifted upfield to 6.08 ppm.[6,12]

The condensation of **3a** with **2a** using 4 equiv of sodium hydroxide *under reflux* gave mainly **4a** (90% yield) but the filtrate after the collection of the disodium salt **4a,** as mentioned above, contained (after acidification) three additional isomers of **4c,** in the ratio *ca.* 1:1:3. Methylation of the diacids with diazomethane and comparison with the isomerization products of **4f,** showed that one of the minor isomers was identical with **12,** and that a negligible amount of **13** was present. The major by-product diacid appeared to decarboxylate readily to give the same product as did **4c** and thus probably had the 2*Z* configuration (the other two

isomers did not decarboxylate readily). From an examination of the mass spectra of the dimethyl esters it appeared that both this major by-product isomer and the other minor isomer possessed 2,5-dienoate (or 3,5-dienoate) structures (both contained a major fragment at *m/e* 162 whereas **4f** and **12** had a typical strong peak at *m/e* 183 which was of low intensity in these two by-product isomers).

In conclusion the glutaconate route described above is a versatile general method for the preparation of (2*E*,4*E*)- and (2*Z*,4*E*)-3-methyl-2,4-dienoic acids, and of a variety of esters and related analogs. The chemical starting materials are readily available and the by-products are ecologically innocuous. The solid disodium salts (*e.g.*, **4a**) and the ammonium salts (of **10**) allow easy purification of the intermediates and thus the product esters are obtained in high purity without distillation. The process can be run in high concentrations and can be readily scaled up.

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 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. Solvents were dried over activated 4A molecular sieves.

Dimethyl 3-Methylglutaconate (3a). To a solution of 273 g (1.5 mol) of methyl isodehydracetate in 250 ml of dry methanol was added 34 g (0.16 mol) of 25% sodium methoxide in methanol, and the mixture was heated under reflux for 1 hr in a dry nitrogen atmosphere. The solvent was removed at reduced pressure and the residue was distilled *in vacuo* to give 232 g (90%) of **3a**, bp 100° (3 mm).

Substitution of 300 g (1.46 mol) of ethyl isodehydracetate for the methyl ester in the above reaction, gave 242 g (86.5%) of a fraction of mixed esters **3c** of 3-methylglutaconate, bp 99–115° (3 mm), which can be used directly in the condensation step. Diethyl 3-methylglutaconate was prepared, as above, from ethyl isodehydracetate with sodium ethoxide in dry ethanol.

Disodium (2*Z*,4*E*)-4-Carboxylato-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (4a). To a solution of 308 g (1.65 mol) of aldehyde **2a** and 284 g (1.65 mol) of dimethyl 3-methylglutaconate (**3a**) in 150 ml of dry methanol was added over 15 min with stirring, a solution of 267 g (6.68 mol; 4.05 equiv) of sodium hydroxide dissolved in 1.1 l. of dry methanol. The mixture was then heated under reflux for 1 hr and allowed to cool. The precipitate was filtered off, dried with suction, and then slurried in 1.8 l. of 2-propanol and the salt was collected by filtration. The filter cake was allowed to drain well and dried in a vacuum desiccator. The yield of the disodium salt **4a** was 529 g (90%). Ether can be used in place of 2-propanol to wash the salt (the solubility of **4a** in 2-propanol at room temperature was found to be 2.1 g/l.; the solubility in methanol was *ca.* 15 g/l.).

The disodium salt was dissolved in 1.5 l. of water, acidified to pH 1 with 4 *N* sulfuric acid and the mixture was extracted with ether (3 × 1 l.). The combined organic layers were washed with water and brine and dried ($MgSO_4$) and the solvent was removed *in vacuo* to give **4c** (446 g) as a viscous oil: nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.13 (s, C-11 CH_3 + H-12), 2.05 (br s, C-3 CH_3), 3.22 (s, OCH_3), 5.97 (m, H-2), and 6.92 ppm (t, separation = 7.5 Hz, H-5). On standing at room temperature or on mild heating the diacid lactonized. Thus after standing 1 month, *ca.* 70% of the diacid had been converted to **6a** (and **5a**). Partial lactonization even occurred on removal of the ether solvent used to extract the diacid after acidification (the $CDCl_3$ nmr spectrum of **4c** above contained signals at 2.23 and 5.40 ppm due to **6a**). Extraction of the diacid into CCl_4 after acidification of the disodium salt, followed by washing with water and drying ($CaSO_4$), gave a pure *solution* of **4c** containing no lactone: nmr δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.08 (s, C-11 CH_3 + H-12), 2.01 (d, J = 1.3 Hz, C-3 CH_3), 3.10 (s, OCH_3), 5.85 (m, H-2), and 6.82 ppm (br t, "J" = 7.5 Hz, H-5).

Use of 4 equiv of potassium hydroxide in the above reaction gave the solid dipotassium salt **4b.**

Substitution of **2a** with 3,7-dimethyl-1-octanal (**2b**) or with 7-hydroxy-3,7-dimethyl-1-octanal (**2c**) in the above reaction gave the corresponding disodium salts in high yield (*ca.* 95%). The diacids recovered from these two salts solidified at room temperature.

If toluene was used in place of ether to extract the diacid after acidification, then the dried, filtered toluene extract could be used directly in the decarboxylation step.

Ethylation of the diacid **4c** with 1-ethyl-3-*p*-tolyltriazene[24] in ether and purification by silica gel preparative tlc gave the corresponding diethyl ester **4d:** bp (bath, short path) 146° (0.05 mm); ir (film) 1725, 1715, 1660, and 1635 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 + H-12), 2.00 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.18 (s, 3, OCH_3), 4.11 (q, 2, J = 7 Hz, OCH_2CH_3), 4.23 (q, 2, J = 7 Hz, OCH_2CH_3), 5.93 (m, 1, H-2), and 6.82 ppm (t, 1, separation = 7.5 Hz, H-5); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 368 (~0), 354 (~0), 291 (3), 290 (2), 244 (5), 229 (3), 211 (31), 183 (12), 167 (10), 73 (100).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.16; H, 9.96.

To 6.01 g (0.017 mol) of the disodium salt **4a** in 25 ml of dimethylformamide was added 9.6 g (0.068 mol) of methyl iodide and the solution heated at 56° for 8 hr under N_2. After cooling the mixture was poured into water and extracted with ether–hexane. The organic layer was washed with water, 10% Na_2CO_3, water, and brine and dried ($CaSO_4$). Removal of the solvent *in vacuo* gave 5.14 g (89% yield) of the dimethyl ester **4f:** bp (bath, short path) 130° (0.05 mm); nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.10 (s, C-11 CH_3 + H-12), 1.98 (d, J = 1.5 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.60 (s, CO_2CH_3), 3.70 (s, CO_2CH_3), 5.85 (m, H-2), and 6.70 ppm (t, "J" = 7.5 Hz, H-5); mass spectrum *m/e* (rel intensity) M^+ 340 (~0), 325 (2), 309 (~0), 308 (~0), 277 (3), 276 (3), 261 (7), 244 (10), 229 (8), 183 (60), 153 (18), 123 (8), 73 (100).

Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.94; H, 9.44.

Methylation of **4c** with diazomethane in ether, followed by purification by preparative tlc, also gave **4f.**

4-Ethoxycarbonyl-5-(6-methoxy-2,6-dimethylheptyl)-3-methyl-2-penten-5-olide (5b). Removal of the solvent from a sample of the diacid **4c,** which had been stored in ether solution at room temperature for 50 days, and examination of the residue by ir and nmr spectroscopy showed it to contain a considerable proportion of the lactone **5a** (and the 3-pentenolide isomer **6a**). A 2.15-g sample of this material was esterified with 1-ethyl-3-*p*-tolyltriazene[24] in ether. Chromatography on preparative thin-layer plates gave 0.50 g of the diester **4d** (upper band) and 0.50 g of **5b** (containing a small amount of **6b**): bp (bath, short path) 160° (0.05 mm); ir (CCl_4) 1740 and 1735 cm^{-1}; nmr ($CDCl_3$) δ 0.93 (d, J = 6 Hz, CH_3CH), 1.14 [s, $(CH_3)_2C$], 2.01 (d, J = 1.3 Hz, C-3 CH_3), 3.13 (m, H-4), 3.20 (s, OCH_3), 4.24 (q, J = 7 Hz, OCH_2CH_3), 4.28 (q, J = 7 Hz, OCH_2CH_3), 4.6 (br m, H-5), and 5.98 ppm (m, H-2); mass spectrum (20 eV) *m/e* (rel intensity) 325 (~0), 269 (~0), 183 (3), 73 (100).

Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 67.12; H, 9.58.

(2*Z*,4*E*)-4-Carboxy-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic Acid (4c). To a solution of 28.60 g (0.15 mol) of 3,7-dimethyl-7-methoxy-1-octanal (**2a**) and 28.32 g (0.15 mol) of dialkyl 3-methylglutaconate (analyzed mixture of methyl and ethyl esters) in 90 ml of methanol cooled in an ice–water bath was added, over 10 min, a solution of 12.0 g (0.15 mol) of 50% aqueous sodium hydroxide solution in 20 ml of methanol. After the mixture was stirred for 1 hr at room temperature, a solution of 12.0 g (0.30 mol) of sodium hydroxide in 48 ml of water was added and the reaction mixture was heated at 65° under reflux for 1 hr. After cooling, water was added and the mixture was extracted with hexane (discarded). The aqueous layer was acidified, and extracted with ether. The ether solution was washed with water and brine, dried ($MgSO_4$), and evaporated to give 44.71 g (95% yield) of **4c.** Methylation of a sample with diazomethane (before removal of the solvent) and glc analysis of the resulting diester **4f** indicated a purity of >96% by peak normalization. This product can be used directly in the decarboxylation step.

(2*Z*,4*E*)-11-Methoxy-4-methoxycarbonyl-3,7,11-trimethyl-2,4-dodecadienoic Acid (4e). To a solution of 2.86 g (15 mmol) of methoxycitronellal (**2a**) and 2.58 g (15 mmol) of dimethyl 3-methylglutaconate (**3a**) in 10 ml of dry methanol was added, with stirring and cooling in an ice–water bath, a solution of 1.2 g (15 mmol) of 50% aqueous sodium hydroxide solution in 2 ml of methanol.

The reaction mixture was then stirred at room temperature for 1 hr, and then diluted with water and acidified with cold aqueous sulfuric acid, and then extracted with CCl_4. The organic layer was washed with water and dried ($MgSO_4$), to give a CCl_4 *solution* of pure **4e**; ir (CCl_4) 1730, 1700, 1660, 1635 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.08 (s, C-11 CH_3 + H-12), 2.00 (d, J = 1.3 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.70 (s, CO_2CH_3), 5.83 (m, H-2), and 6.67 ppm (t, "J" = 7.5 Hz, H-5). When the CCl_4 was removed *in vacuo* partial lactonization to **6c** occurred. The residue was dissolved in ether and the solution heated under reflux for 48 hr and the solvent removed *in vacuo*. The residue now contained a mixture of **4e** and **6c** in the ratio *ca.* 1:1 [the nmr spectrum in $CDCl_3$ showed peaks at 2.21 (C-3 CH_3) and 5.40 (H-5) due to **6c**]. When an aliquot of this material in ether was shaken with aqueous NH_4OH, the **6c** was converted mostly into **5c.** When the mixture of **4e** and **6c** above was chromatographed on silica gel preparative thin-layer plates, the recovered lactone fraction consisted of mostly **5c:** ir (CCl_4) 1735 and 1660 cm^{-1}; nmr (CCl_4) δ 0.93 and 0.97 (two d, J = 6 Hz, CH-CH_3), 1.10 [s, $(CH_3)_2C$], 1.99 (d, J = 1.3 Hz, C-3 CH_3), 3.03 (m, H-4), 3.12 (s, OCH_3), 3.76 (s, CO_2CH_3), 4.50 (br m, H-5), and 5.83 ppm (m, H-2).

Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 65.80; H, 9.03.

(2Z,4E)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoic Acid (9a). A solution of 104.0 g (333 mmol) of the diacid **4c** and 2.0 g (19 mmol) of 2,4-dimethylpyridine in 270 ml of dry toluene was heated, under nitrogen, at 100° until decarboxylation was complete (3 hr; the reaction was followed by tlc). The solution was cooled to 70°, purged with nitrogen, 82 g (380 mmol) of 25% sodium methoxide in methanol was added, and the resulting solution was held, under nitrogen at 70°, until reaction was complete (*ca.* 1 hr). To the cooled, stirred solution was added 500 ml of water and 30 ml of 1 N aqueous NaOH. After removal of the organic phase (discarded), the aqueous phase was acidified to pH 1 with 4 N sulfuric acid and extracted with 300 ml of hexane. The hexane extract was washed twice with water, once with brine, dried ($MgSO_4$), and the solvent was evaporated *in vacuo* up to 58° (1 mm) to give 83.5 g (93%) of (2Z,4E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid (**9a**) (analysis by glc showed a purity of 96%) as a yellow oil: ir ($CHCl_3$) 1685 (C=O), 1635, and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.13 (s, C-11 CH_3 + H-12), 2.01 (d, J = 1.3 Hz, C-3 CH_3), 3.17 (s, OCH_3), 5.63 (br s, H-2), 6.15 (d of t, J = 7 and 16 Hz, H-5), and 7.55 ppm (d, J = 16 Hz, H-4).

Methylation of a sample with diazomethane and analysis by glc showed it to contain <0.5% of the 2E,4E isomer **10d.**

To a solution of 2.0 g (0.0075 mol) of the acid **9a** in 10 ml dry ether, and 0.8 ml of thionyl chloride at 10°, was added 0.3 ml of dimethylformamide. The mixture was then allowed to warm to room temperature and was stirred for 1 hr. The upper layer of the now two-phase mixture was decanted and the solvent removed from it *in vacuo* (the lower phase was discarded). The residue was taken up in 15 ml of fresh ether and 2.3 g (0.038 mol) of 2-propanol was added. The mixture was then stirred at room temperature overnight, ether (45 ml) and water (50 ml) were added, and the mixture was made basic with aqueous 15% potassium carbonate solution. The organic layer was separated and washed twice with water, brine, and then dried ($CaSO_4$). Solvent removal *in vacuo* yielded 1.8 g (77%) of the isopropyl ester **9f:** bp (bath, short path) 136° (0.04 mm); nmr (CCl_4) δ 0.92 (d, J = 6 Hz, C-7 CH_3), 1.08 (s, C-11 CH_3 + H-12), 1.22 [d, J = 6 Hz, $OCH(CH_3)_2$], 1.95 (d, J = 1.3 Hz, C-3 CH_3), 3.08 (s, 3, OCH_3), 4.97 [m, 1, J = 6 Hz, $-OCH(CH_3)_2$], 5.50 (br s, H-2), 6.00 (d of t, J = 7 and 16 Hz, H-5), and 7.58 ppm (d, J = 16 Hz, H-4); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 310 (~0), 153 (25), 137 (15), 111 (40), 109 (15), and 73 (100).

Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.66; H, 10.97.

Decarboxylation of 4c to the Lactones 7a and 8a. To 12.95 g (0.0415 mol) of the diacid **4c** in 80 ml toluene was added 0.44 g (0.0041 mol) of 2,4-dimethylpridine. The solution was stirred and heated to 100° (evolution of CO_2 began at 80°) and held at 100° until CO_2 evolution ceased (*ca.* 90 min). The solvent was then removed *in vacuo* to give a residue of 10.5 g (94% yield) of a mixture of **7a, 8a,** and **9a** with the lactone **7a** predominating. Separation into acidic and neutral fractions and purification of a sample of the latter by preparative tlc gave the lactone **7a** (containing only a small amount of **8a**): nmr (CCl_4) δ 0.95 (d, J = 6 Hz, CH_3CH), 1.10 [s, $(CH_3)_2CO$], 1.80 (br s, C-3 CH_3), 2.83 (m, H-2), 3.10 (s, OCH_3), 4.87 (br m, H-5), and 5.50 ppm (m, H-4); mass spectrum (20 eV) *m/e* 254, 198, 197, 111, 109, 107, 97, 95, 81, 73 (base peak), 69, and 55.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.67; H, 10.38.

Repetition of the above experiment with the addition of cupric acetate monohydrate (0.002 mol) gave identical results.

Decarboxylation of 4c Directly to 9a. A mixture of 60.6 g (0.194 mol) of the diacid **4c,** 0.966 g (0.0048 mol) of cupric acetate monohydrate, and 187 g (1.7 mol) of dry 2,4-dimethylpyridine was heated at 80–85° until evolution of carbon dioxide ceased (*ca.* 1 hr). The temperature (oil bath) was then increased to 130° and held there for 1 hr. After cooling, ether and water were added and the mixture was then acidified with cold aqueous 3 N H_2SO_4. The aqueous layer was separated and extracted twice with ether. The combined ether layers were washed with aqueous saturated $CuSO_4$ solution, water, and brine and then dried ($CaSO_4$). Solvent removal *in vacuo* gave 50.8 g of a mixture of the lactones **7a** and **8a,** and the acid **9a** with the *acid* predominating.

Heating a sample of the diacid **4c** in excess pyridine as the solvent (no added copper salt) at 100° under a N_2 atmosphere for 2 hr gave a 20% yield of **7a** (plus some **8a**) and a 66% yield of **9a.** In general decarboxylation using 2,4-dimethylpyridine was found to be faster than when pyridine was used.

Heating the lactone acid **5a** (containing some **6a**) in excess 2,4-dimethylpyridine for 2 hr at 100 to 120° gave a similar yield of a mixture of **7a, 8a,** and **9a.**

Opening of the Lactone 7a. A solution of 21.9 g (0.082 mol) of **7a** in 40 ml of ethanol was added to a solution of NaOEt (from 2.3 g of Na; 0.1 mol) in 100 ml of ethanol, and the solution stirred for 18 hr at room temperature. The ethanol was then removed *in vacuo,* and the residue was dissolved in water (150 ml) and extracted with ether (discarded). The aqueous phase was acidified (pH 1) with 4 N H_2SO_4 and extracted with ether. The ether extract was washed with water and brine and dried ($MgSO_4$) and the solvent removed to give 21.02 g (96% yield) of **9a.**

(2Z,4E)-3,7,11-Trimethyl-2,4-dodecadienoic Acid (9b). A solution of the lactone **7b** (1.065 g; 0.0045 mol) prepared from **4h** by the procedure given above for **7a,** in 5 ml of ethanol was added slowly to a solution of NaOEt (from 0.115 g of Na; 0.005 mol) in 7.5 ml ethanol at 5° under a N_2 atmosphere. After 20 hr at room temperature the solvent was removed *in vacuo,* water was added and the solution was extracted with ether (discarded). The aqueous phase was separated, acidified with aqueous HCl and the mixture was extracted with ether. The organic layer was washed with water and brine and dried (Na_2SO_4) and the solvent removed *in vacuo* to give 0.92 g (86% yield) of the acid **9b,** which crystallized on standing at room temperature, mp 28–30°. Recrystallization from pentane gave material with mp 31.5–32°: nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.03 (d, J = 1.3 Hz, C-3 CH_3), 5.63 (br s, H-2), 6.17 (d of t, J = 7 and 16 Hz, H-5), and 7.55 ppm (d, J = 16 Hz H-4).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.97; H, 11.02.

(2Z,4E)-11-Hydroxy-3,7,11-trimethyl-2,4-dodecadienoic Acid (9c). In an analogous sequence of reactions, condensation of **2c** with **3a** gave **4g.** Decarboxylation in 2,4-dimethylpyridine at 85–120°, and treatment of the isolated product with NaOEt in dry ethanol gave in similar yields (to above) the acid **9c:** ir (film) 1695 (C=O), 1635, and 1600 cm^{-1}; nmr ($CDCl_3$) δ 0.90 (d, J = 6 Hz, C-7 Me), 1.20 (s, C-11 CH_3 + H-12), 2.02 (br s, C-3 Me), 5.65 (br s, H-2), 6.17 (m, H-5), and 7.56 ppm (d, J = 16 Hz, H-4).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.36; H, 10.60.

This acid was best stored below 5° in sealed containers under N_2 or argon. Slightly impure samples were found to decompose readily at room temperature in air.

Decarboxylation of the Mono Salt of 4c. To 3.56 g (0.01 mol) of the disodium salt **4a** in 20 ml of water was added 2.77 ml (0.01 mol) of 3.60 N sulfuric acid (the pH of the resulting solution was 6.5). The solution was heated under reflux for 7 hr (after which time the pH was 8.5), and then allowed to stand overnight at room temperature. The mixture was made basic with 2 N sodium hydroxide and extracted with ether. The organic layer was washed with water and dried ($MgSO_4$) and the solvent removed to give 0.53 g of a colorless oil, which by tlc, glc, and nmr analysis was a 55:45 mixture of 11 and **8a,** respectively.

The aqueous phase was acidified with 3.6 N sulfuric acid and extracted three times with ether. The combined ether layers were dried ($MgSO_4$) and the solvent was removed. The residue (2.04 g) was composed of a 2:1 mixture of **9a** and the starting acid **4c,** respectively.

10-Methoxy-2,6,10-trimethyl-1,3-undecadiene (11). On heat-

ing a sample of the 2Z,4E acid **9a** at 120° without solvent both the lactone **8a** and the diene **11** began to appear. After 22 hr the three compounds **9a**, **8a**, and **11** were present in about equal amounts. At 150° the acid **9a** disappeared and the diene **11** began to predominate.

A 3.3-g sample of **9a** was heated without solvent at 130° for 27 hr under N_2. After the sample had cooled, the nmr spectrum (and the glc analysis of a diazomethane treated aliquot) showed the presence of a mixture of **11**, **8a**, and **9a**. A 1.85-g portion of this mixture was chromatographed on silica gel preparative thin-layer plates developed with ether–hexane (7:93). The upper band gave 0.45 g of the diene **11** (analysis by glc showed a purity of 96%): bp (bath, short path) 65° (0.04 mm); uv max (hexane) 230 nm (ϵ 25,600); ir (film) 3080, 1610, 970, and 885 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-6 CH_3), 1.10 (s, C-10 CH_3 + H-11), 1.82 (m, C-2 CH_3), 3.10 (s, OCH_3), 4.83 (br s, H-1), 5.57 (m, H-4), and 6.11 ppm (d, J = 16 Hz, H-3); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 224 (~0), 209 (1), 192 (6), 177 (7), 149 (16), 136 (8), 124 (13), 123 (23), 121 (13), 109 (20), 107 (27), 95 (10), 93 (15), 81 (20), 73 (100), 69 (27), and 55 (10).

Equilibration of the 2Z,4E Acid 9a. To 123 g (0.46 mol) of **9a** was added with stirring under N_2, 1.23 g (11 mmol) of benzenethiol and the mixture was heated at 100° in an oil bath for 1 hr (reaction was followed by glc analysis of diazomethane methylated aliquots). To the mixture was then added 60 g of odorless hydrocarbon solvent of bp 176–207° (Soltrol 130, from Phillips Petroleum Co) and the solution distilled *in vacuo* at 3 mm (up to 90°) to remove the benzenethiol. The residue was then cooled and to it was added hexane (100 ml), water (400 ml), and 37 g (0.55 mol) of 58% NH_4OH. After thorough mixing the aqueous layer was separated and acidified with 4 N H_2SO_4 and then was extracted with hexane. The organic layer was washed with water and brine and dried ($MgSO_4$) and the solvent removed at 1 mm (up to 60°) to give 117.3 g (95% yield) of a mixture containing 32% of **9a** and 65.4% of **10a** (determined by glc analysis of a diazomethane treated aliquot, on OV-101 or PDEAS).

In the equilibration reaction and during the benzenethiol removal, the temperature of the pot was kept below 102° to prevent any loss of **9a** by decarboxylation to **11**.

Under the same conditions **9b** and **9c** were equilibrated to the corresponding 65:35 mixtures of 2E,4E and 2Z,4E isomers, respectively.

Equilibrations of **9a** were also carried out using 5 mol % benzenethiol plus 1 mol % 2,2′-azobis(isobutyronitrile) with heating at 80° for 2 hr, to give a mixture of **9a:10a** in the ratio 32:68, respectively.

Equilibration of (Z)-11-Tetradecen-1-yl Acetate. A mixture of 10.36 g of (Z)-11-tetradecen-1-yl acetate[17] and 0.104 g of benzenethiol was heated in an oil bath at 100° with stirring for 80 min under a N_2 atmosphere. After cooling, 15 ml of Soltrol 130 (a mixture of hydrocarbons; bp 176–207°) was added and a Soltrol 130–benzenethiol mixture was distilled off *in vacuo* [max bp 54° (3.6 mm)]. The residue was chromatographed on silica gel (activity III; 200 g), and elution with 5% ether in hexane gave 9.35 g (90% yield) of pure 11-tetradecen-1-yl acetate, as a mixture of the E and Z isomers in the ratio of 75:25, respectively.

Similarly heating (Z)-8-dodecen-1-yl acetate[25] with 1% by weight of benzenethiol at 100° for 1 hr and working up as above gave a E:Z ratio of 77:23, respectively.

Ammonium (2E,4E)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoate. Over a stirred solution of 242.5 g (0.904 mol) of a 65:35 mixture of **10a:9a** (respectively) from equilibration, in 1.2 l. of diethyl ether, was passed dry NH_3 gas until the solution ceased to absorb the gas. After a further 2 hr stirring in a NH_3 atmosphere the mixture was filtered, and the collected solid was resuspended in 750 ml of fresh ether and the mixture was filtered again. Residual ether was removed from the salt under reduced pressure to give 130 g (0.46 mol) of the salt as a white solid. The ammonium salt slowly evolved NH_3 but was stable stored in air-tight containers.

The ether filtrates from above were combined and stirred with excess aqueous 4 N H_2SO_4. The organic layer was washed with water and brine and dried and the solvent removed to give a 116.3 g (0.43 mol) of residue (**9a** plus **10a**) which was recycled through the equilibration procedure.

The solubility of the ammonium salt of **10a** in dry ether, at 25°, was found to be 2.1 g/l., and the solubility in hexane was *ca.* 1 g/l.

In a like manner the ammonium salts of **10b** and **10c** were precipitated from dichloromethane.

(2E,4E)-3,7,11-Trimethyl-2,4-dodecadienoic Acid (10b). To a solution of 197 g (0.77 mol) of the ammonium salt of **10b** in 350 ml of water was added 850 ml of hexane and 275 g (0.1 mol) of 4 N H_2SO_4 with stirring. After 15 min the organic layer was washed with brine and dried ($CaSO_4$) and the solvent was removed to give 180 g (0.76 mol) of **10b** as a crystalline solid, mp 42–44° (lit.[2] mp 44°). Analysis by glc (of a diazomethane methylated sample) showed that the acid contained a negligible amount (<0.5%) of the 2Z,4E isomer **9b**.

Similarly recovery from the corresponding salts (as above) gave pure **10a**,[2] and also the pure 2E,4E acid **10c**: ir (film) 1697, 1635 and 1610 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.17 (s, C-11 CH_3 + H-12), 2.27 (d, J = 1 Hz, C-3 CH_3), 5.68 (m, H-2), and 6.03 ppm (m, H-4 and H-5).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.45; H, 10.03.

Methylation of **10c** with diazomethane gave methyl (2E,4E)-11-hydroxy-3,7,11-trimethyl-2,4-dodecadienoate: bp (bath, short path) 115° (0.04 mm); nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.18 (s, C-11 CH_3 + H-12), 2.26 (d, J = 1 Hz, C-3 CH_3), 3.67 (s, CO_2CH_3), 5.65 (br s, H-2), and 6.10 ppm (m, H-4 and H-5).

Ethylation of **10c** with diazoethane gave the corresponding ethyl ester **1e**: bp (bath, short path) 102° (0.01 mm).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71; O, 16.99. Found: C, 72.40; H, 10.77; O, 16.96.

Isopropyl (2E,4E)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoate (1a). To a solution of 285.4 g (1.0 mol) of the ammonium salt of **10a** in 450 ml of water was added 900 ml of hexane and 375 ml of 4 N H_2SO_4 with stirring. The organic layer was washed with brine and dried ($CaSO_4$) and the solvent was removed *in vacuo*. The dry residue was dissolved in 146 g (2 mol) of dimethylformamide under a N_2 atmosphere in an apparatus equipped with a reflux condenser, and 137 g (1.15 mol) of $SOCl_2$ was added (exothermic) dropwise with stirring, at such a rate that the temperature did not exceed 35°. After a further 1 hr at 35° the mixture was cooled and 350 ml of pentane was added (gas evolution occurred) followed by the dropwise addition of 81 g (1.35 mol) of 2-propanol (exothermic; temperature was controlled by the refluxing solvent). After a further 1 hr stirring, 400 ml of pentane was added followed by the slow addition of 300 ml of water, with cooling in a cold water bath. The organic phase was washed with 2 N NaOH, water, and brine and dried ($MgSO_4$) and the solvent removed to give 277 g (89% yield) of **1a**[2] (analysis by glc showed it to contain 95.1% of **1a** and 2.1% of the 2Z,4E isomer **9f**): bp 135–136° (0.06 mm).

Since the starting ammonium salt of **10a** contained negligible 2Z,4E isomer, a small amount of isomerization at C-2 obviously occurred under the above rather vigorous esterification conditions. Heating the acid chloride (above) at 110° for 2 hr with excess thionyl chloride caused equilibration at C-2.

S-Ethyl (2E,4E)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienethioate (1c). To a solution of 135 g (0.50 mol) of **10a** in 73 g (1.0 mol) of dimethylformamide under N_2 was added dropwise 68.5 g (0.58 mol) of $SOCl_2$ while maintaining the temperature at ≤35°. After a further 1 hr at 35° the mixture was cooled and 200 ml of pentane was added with stirring (gas evolution occurred). On settling, the lower dimethylformamide layer was drained off, additional pentane (250 ml) was added to the upper phase which was then cooled to 15°. To this solution was added slowly 34 g (0.55 mol) of ethanethiol followed by careful addition (exothermic) of 48 ml (0.60 mol) of pyridine dissolved in pentane (100 ml) with cooling to maintain the temperature below 30°. After the addition was completed the mixture was stirred for 1 hr at room temperature and then 300 ml of water was added. The organic phase was washed with 4 N H_2SO_4, water, 2 N NaOH, water, and brine and dried ($CaSO_4$) and the solvent removed to give 147 g (94% yield) of **1c**. Internal standard glc analysis gave a purity of 93% **1c**: bp 155–156° (0.09 mm); nmr (CCl_4) δ 0.88 (d, 3, J = 6 Hz, C-7 CH_3), 1.10 (s, 6, C-11 CH_3 + H-12), 1.27 (t, 3, J = 7.5 Hz, SCH_2CH_3), 2.24 (d, 3, J = 1 Hz, C-3 CH_3), 2.88 (q, 2, J = 7.5 Hz, SCH_2CH_3), 3.10 (s, 3, OCH_3), 5.90 (m, 1, H-2), and 6.10 ppm (m, 2, H-4 and H-5).

Anal. Calcd for $C_{18}H_{32}O_2S$: C, 69.19; H, 10.32. Found: C, 69.40; H, 10.35.

2-Propynyl (2E,4E)-3,7,11-Trimethyl-2,4-dodecadienoate (1d). To a solution of 85.4 g (0.36 mol) of **10b** in 52 g (0.71 mol) of dimethylformamide under N_2 was slowly added 48.8 g (0.41 mol) of $SOCl_2$ keeping the temperature ≤35°. After a further 1 hr at 35°, 300 ml of pentane was added to the cooled reaction mixture with stirring (gas evolution). The lower phase was discarded and then 27.5 g (0.49 mol) of 2-propyn-1-ol was slowly added (exothermic) to the upper pentane phase with cooling and stirring. After

the addition was completed the solution was stirred for an additional 1 hr at room temperature, then washed with water, 2 *N* NaOH, water, and brine and dried ($CaSO_4$) and the solvent was removed to give 97.8 g (98% yield) of crude product. Analysis by glc showed it to be 97.2% pure **1d:** bp (bath, short path) 121° (0.01 mm); ir (film) 1725, 1640, and 1615 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.31 (d, J = 1 Hz, C-3 CH_3), 2.45 (t, 1, J = 2.5 Hz, C≡CH), 4.74 (d, 2, J = 2.5 Hz, $OCH_2C{\equiv}CH$), 5.76 (m, 1, H-2), and 6.17 ppm (m, 2, H-4 and H-5).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.10; H, 10.12.

Substitution of dry ethanol for 2-propyn-1-ol in the above preparation gave **1b.**[2]

Isomerization of Dimethyl Ester 4f. To 2.01 g of the ester **4f** was added 0.065 g of benzenethiol and 0.045 g of 2,2′-azobis(isobutyronitrile) [AIBN] and the mixture heated at 88° for 2.25 hr under N_2. Analysis by glc showed the presence of 48% of **4f,** 34% of the isomer **12,** and 13% of the isomer **13.** A further 0.065 g of benzenethiol and 0.049 g of AIBN were added and the mixture was heated at 88° for 2 hr. Glc analysis now showed the presence of 42% of **4f,** 46% of **12,** and 12% of **13.** Further addition of 0.065 g of benzenethiol and 0.048 g of AIBN and heating again at 85° for 2 hr did not produce any further change in the isomer ratio. No evidence was seen (nmr and glc) for the presence of the fourth possible isomer (2*Z*,4*Z*). The product was chromatographed on preparative thin-layer silica gel plates (1.5 mm thick) developed with ether–hexane (3:7). The lower band gave the starting ester **4f** and the upper band gave 0.70 g of a mixture of **12** and **13** in the ratio 78:22, respectively. Attempted separation of a portion of this mixture by hp liquid chromatography on LiChrosorb (20 μ, lm) in ether–pentane (1:4) gave two fractions, the first containing **12** and **13** in the ratio 31:69 and the second fraction containing **12** and **13** in the ratio 89:11, respectively. **12:** nmr (CCl_4) δ 0.93 (d, J = 6 Hz, C-7 CH_3), 1.10 (s, C-11 CH_3 + H-12), 2.22 (d, J = 1.5 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.70 (s, CO_2CH_3), 3.73 (s, CO_2CH_3), 5.54 (m, H-2), and 6.76 ppm (t, "J" = 7.5 Hz, H-5).

13: nmr (CCl_4) δ 0.93 (d, J = 6 Hz, C-7 CH_3), 1.10 (s, C-11 CH_3 + H-12), 2.27 (d, J = 1.5 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.66 (s, CO_2CH_3), 3.76 (s, CO_2CH_3), 5.62 (m, H-2), and 6.08 ppm (t, "J" = 7.5 Hz, H-5).

The mass spectra of **12** and **13** (obtained from glc–ms) were almost identical with that obtained from **4f.**

To 0.20 g of a mixture of **12** and **13** (in the ratio 78:22, respectively) were added 0.007 g of benzenethiol and 0.006 g of AIBN and the mixture was heated at 80° for 2 hr under N_2. A further 0.007 g of benzenethiol and 0.006 g of AIBN were added and the mixture heated again at 80° for 2 hr. Glc analysis (after removal of the benzenethiol in high vacuum) showed the presence of 40% of **4f,** 48% of **12,** and 12% of **13.**

Acknowledgment. We thank Loren L. Dunham for invaluable technical assistance.

Registry No.—**1a,** 41205-06-5; **1c,** 53023-54-4; **1d,** 53023-55-5; **1e,** 53023-56-6; **2a,** 53023-57-7; **3a,** 52313-87-8; **3b,** 924-59-4; **3c** (R′ = Me, R″ = Et), 53023-58-8; **3c** (R′ = Et, R″ = Me), 53092-54-9; **4a,** 53023-59-9; **4c,** 53023-60-2; **4d,** 53023-61-3; **4e,** 53023-62-4; **4f,** 53023-63-5; **5a,** 52313-83-4; **5b,** 53092-48-1; **5c,** 53092-49-2; **6c,** 53023-64-6; **7a,** 52313-82-3; **7b,** 52313-78-7; **8a,** 52313-85-6; **9a,** 53023-65-7; **9a** NH_3 salt, 53042-19-6; **9b,** 53092-50-5; **9c,** 53092-51-6; **9f,** 53108-97-7; **10a,** 53092-52-7; **10a** NH_3 salt, 53023-66-8; **10b,** 53023-67-9; **10b** NH_3 salt, 53023-68-0; **10c,** 53092-53-8; **10c** NH_3 salt, 53154-32-8; **10c** methyl ester, 53154-33-9; **11,** 53023-69-1; **12,** 53023-70-4; **13,** 53023-71-5; methyl isodehydracetate, 41264-06-6; ethyl isodehydracetate, 3385-34-0; 1-ethyl-3-*p*-tolyltriazene, 50707-40-9; (*Z*)-11-tetradecen-1-yl acetate, 20711-10-8; (*E*)-11-tetradecen-1-yl acetate, 33189-72-9; (*Z*)-8-dodecen-1-yl acetate, 28079-04-1; (*E*)-8-dodecen-1-yl acetate, 38363-29-0; 2-propanol, 67-63-0; 2-propyn-1-ol, 107-19-7.

References and Notes

(1) Contribution No. 24 from the Research Laboratory of Zoecon Corporation.
(2) C. A. Henrick, G. B. Staal, and J. B. Siddall, *J. Agr. Food Chem.*, **21,** 354 (1973).
(3) S. G. Nassar, G. B. Staal, and N. I. Armanious, *J. Econ. Ent.*, **66,** 847 (1973); G. B. Staal, S. Nassar, and J. W. Martin, *ibid.*, **66,** 851 (1973).
(4) C. A. Henrick and J. B. Siddall, Belgian Patent 778,242 (Jan 19, 1972); see also C. A. Henrick, Belgian Patent 778,241 (Jan 19, 1972).
(5) C. A. Henrick, U. S. Patent 3,773,793 (Nov 20, 1973); German Patent 2,332,601 (Feb 28, 1974); U. S. Patent 3,818,047 (June 18, 1974).
(6) C. A. Henrick, W. E. Willy, B. A. Garcia, and G. B. Staal, *J. Agr. Food Chem.*, submitted for publication.
(7) W. Stilz and H. Pommer, U. S. Patents 3,163,669 (Dec 29, 1964); 3,177,226 (April 6, 1965).
(8) C. A. Henrick, W. E. Willy, D. R. McKean, E. Baggiolini, and J. B. Siddall, *J. Org. Chem.*, **40,** 8 (1975).
(9) F. Feist and O. Beyer, *Justus Liebigs Ann. Chem.*, **345,** 117 (1906) (these authors describe the preparation of 4-carboxy-3-methyl-5-phenyl-2,4-pentadienoic acid); C. D. Hurd and J. L. Abernethy, *J. Amer. Chem. Soc.*, **63,** 976 (1941); V. Petrow and O. Stephenson, *J. Chem. Soc.*, 1310 (1950).
(10) (a) C. D. Robeson, J. D. Cawley, L. Weisler, M. H. Stern, C. C. Eddinger, and A. J. Chechak, *J. Amer. Chem. Soc.*, **77,** 4111 (1955); (b) J. D. Cawley, *ibid.*, **77,** 4125 (1955); (c) J. D. Cawley and D. R. Nelan, *ibid.*, **77,** 4130 (1955); C. D. Robeson and J. D. Cawley, British Patent 701,807 (Jan 6, 1954); C. D. Robeson and J. D. Cawley, U. S. Patents 2,709,711 and 2,709,712 (May 31, 1955).
(11) R. H. Wiley and H. G. Ellert, *J. Amer. Chem. Soc.*, **79,** 2266 (1957).
(12) (a) R. H. Wiley, *J. Chem. Soc.*, 3831 (1958); (b) R. H. Wiley, E. Imoto, R. P. Houghton, and P. Veeravagu, *J. Amer. Chem. Soc.*, **82,** 1413 (1960); (c) R. H. Wiley, P. F. G. Nau, and T. H. Crawford, *J. Org. Chem.*, **26,** 4285 (1961); (d) R. H. Wiley, P. F. G. Nau, H. C. van der Plas, and T. H. Crawford, *J. Org. Chem.*, **27,** 1991 (1962).
(13) Dialkyl 3-methylglutaconates were prepared from the alkyl isodehydracetate[14] with a catalytic amount of sodium alkoxide in refluxing alcohol (see Experimental Section); *cf.* D. S. Young and G. F. Rodgers, U. S. Patent 2,673,212 (March 23, 1954); *Chem. Abstr.*, **49,** 4710*d* (1955).
(14) The alkyl isodehydracetates were prepared from the alkyl acetoacetates and anhydrous hydrogen chloride in the absence of solvent, by a modification of the procedure of F. R. Goss, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **123,** 327 (1923); *cf.* R. H. Wiley and N. R. Smith, *J. Amer. Chem. Soc.*, **73,** 3531 (1951).
(15) U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1372 (1953); K. Elter and E. Truscheit, German Patents 1,070,175 (Dec 3, 1959), 1,075,598 (Feb 18, 1960); K. Elter, E. Truscheit, and H. Oediger, *Angew. Chem.*, **72,** 948 (1960).
(16) (a) D. S. Sgoutas and F. A. Kummerow, *Lipids*, **4,** 283 (1969); (b) U. T. Bhalerao and H. Rapoport, *J. Amer. Chem. Soc.*, **93,** 4835 (1971).
(17) This compound has been identified as part of the sex pheromone complex of a number of insect species including the female European corn borer and the female redbanded leafroller. The species attracted to this pheromone depends critically on the amount of *E* isomer present; *e.g.*, J. A. Klun, O. L. Chapman, K. C. Mattes, P. W. Wojtkowski, M. Beroza, and P. E. Sonnet, *Science*, **181,** 661 (1973).
(18) C. Mousseboís and J. Dale, *J. Chem. Soc. C*, 260 (1966); see also R. H. Pallen and C. Sivertz, *Can. J. Chem.*, **35,** 723 (1957); I. A. Kopeva, E. I. Tinyakova, B. A. Dolgoplosk, L. I. Red'kina, and E. N. Zavadovskaya, *Vysokomol. Soedin., Ser. A.*, **9,** 645 (1967); *Chem. Abstr.*, **67,** 33124e (1967).
(19) E. J. Corey and E. Hamanaka, *J. Amer. Chem. Soc.*, **89,** 2758 (1967); K. Gollnick and G. Schade, *Tetrahedron Lett.*, 689 (1968).
(20) J. I. Cunneen, G. M. C. Higgins, and W. F. Watson, *J. Polym. Sci.*, **40,** 1 (1959).
(21) M. A. Golub in "The Chemistry of Alkenes," Vol. 2, J. Zabicky, Ed., Interscience, New York, N.Y., 1970, Chapter 9, pp 449–460.
(22) C. Walling and W. Helmreich, *J. Amer. Chem. Soc.*, **81,** 1144 (1959).
(23) U. R. Nayak, A. H. Kapadi, and S. Dev, *Tetrahedron*, **26,** 5071, 5083 (1970); L. H. Hornig, H. Neu, and O. Probst, U. S. Patent 3,642,885 (Feb 15, 1972); see also ref 21, pp 468–474.
(24) E. H. White and H. Scherrer, *Tetrahedron Lett.*, 758 (1961); E. H. White, A. A. Baum, and D. E. Eitel, *Org. Syn.*, **48,** 102 (1968); available from Aldrich Chemical Co. and from Willow Brook Laboratories.
(25) This compound has been identified as the sex pheromone of the oriental fruit moth; W. L. Roelofs, A. Comeau, and R. Selle, *Nature (London)*, **224,** 723 (1969).