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

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

The alkyl 3,7,11-trimethyl-2,4-dodecadienoates 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 (Altosid insect growth regulator; ZR-0515; methoprene; ENT 70460) and we wish to describe here an outline of a procedure which may be used to prepare 1a and related compounds.

Since the 2E, 4E stereoisomer shows considerably higher biological activity than the other three possible stereoisomers, 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 a variety of other methods 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 of all four stereoisomers of 1b (or of the corresponding acids) with benzenethiol gives the same mixture containing ca. 65% of the 2E, 4E isomer, ca. 35% of the 2Z, 4E isomer, and only trace amounts of the two 4Z isomers. Furthermore, as demonstrated below, the 2E, 4E isomer can be readily separated from such an equilibrium mixture and the 2Z, 4E isomer can be recycled.

It has been noted for some time that diethyl and dimethyl 3-methylglutaconates condense with aliphatic and aromatic aldehydes under alkaline conditions (methylene KOH) to give variable yields of 4-alkylidene (or 4-arylidene)-3-methylglutaconic acids. However, the reported yields have been highly variable and the reaction mechanisms of both the condensation and decarboxylation steps have not been clarified. However, the reported yields have been highly variable and the reaction mechanisms of both the condensation and decarboxylation steps have not been clarified.
sation and that both pure Z and E isomers of dimethyl 3-methylglutamate gave the same diacid on condensation with cinnamaldehyde. Wiley and Ellert\textsuperscript{11} found that on acidification of the condensation reaction product both diacids and the previously unnoticed isomeric carboxy-β-lactones (assigned structures such as 5a) were obtained. The 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,\textsuperscript{10c} the preferred method of decarboxylation was found by Cavley, et al.,\textsuperscript{11} to be heating with 2,4-dimethylpyridine in the presence of copper or cupric acetate at 90–120°. However, Wiley and Ellert\textsuperscript{11} obtained poor yields of monoacid and/or β-lactone under these conditions and preferred to decarboxylate in hot acetic acid to give β-lactones, assigned the 5,6-dihydro-2-pyridine structure (cf. 8). We have investigated this reaction sequence in considerable detail and have developed it into a very useful general synthesis of (2Z,4E)- and of (2E,4E)-3-methyl-2,4-dienoic acids.

Results and Discussion

The condensation of dialkyl 3-methylglutrates (3)\textsuperscript{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 98% 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 2E 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 4e in 95% yield in >98% purity. The initial rapid formation of the half-ester indicated that 5c (or 6e) was probably an intermediate in the condensation reaction. On standing, the isolated half-ester lactonized to give a mixture of 5e and 6e. 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° (near to 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,\textsuperscript{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 2Z,4E monoacid 9a by prolonged heating at 100–150° 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\textsuperscript{6,15} 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 2Z,4E 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 2Z,4E monoacid 9a above 160° 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.

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°C 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)] was not necessary (see below).

We have already noted that pure (2E,4E)-3,4-dienoic acids could be isolated via their S-benzenesulphonium salts. For purification of 10a we 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 2E,4E ammonium salt which was collected. The filtrate from this procedure was recycled to the isomerization step above to convert the unpurified 22,4E acid to an equilibrium mixture of 9a and 10a. The ammonium salt was then acidified and the recovered pure 2E,4E acid converted via its acid chloride (prepared with thionyl chloride in dimethylformamide) into the corresponding ester or thiocarbamate (see Experimental Section). This overall scheme has been used to prepare pure 1a, b, c, and d (purity 90–98% by internal standard gc 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°C 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)-1-tetradecene-1-yl acetate13 with 10% by weight of benzenethiol 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°C).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°C 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 thyl radical addition to the olefinic double bond,22 especially in the case of a resonance-stabilized radical like benzenethiol, is presumably the basis for the thyl-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 investigated for the equilibration of 9a (and of 9b) without solvent, it was found that Na2S (20 mol %; 17 hr at 120°C) and LiSCN (20 mol %; 22 hr at 120°C) gave predominantly the lactone 8a. Butadiene sulfone30,31 (25 mol %; 7 hr at 120°C) and ruthenium trichloride trihydrate (20 mol %; 2 hr at 120°C) gave conjugation to the 5,5-diepoxide and some loss of the 1,4-dioxo group. Heating with thiobenzoic S-acid32 (30 mol %; 24 hr at 120°C), Al2S3 (20 mol %; 19 hr at 120°C), or with diphenyl disulfide (20 mol % plus 10 mol % AIBN; 3 hr at 80°C) gave slow isomerization without attainment of equilibrium under these conditions, whereas heating with dibenzyl disulfide (10 mol % plus 10 mol % AIBN; 5 hr at 120°C) gave rapid equilibration. Diphenyl disulfide did result in equilibration at a higher temperature (20 mol %; 5 hr at 120°C), but benzenethiol, for comparison, gave rapid equilibration with (5 mol % plus 1 mol % AIBN; 2 hr at 80°C) or without (2 mol %; 1 hr at 100°C) the use of AIBN. Heating with sulfur31,33 (20 mol %; 25 hr at 115°C) gave only partial isomerization. Heating with thioecetic S-acid (20 mol %; 6.5 hr at 120°C) 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°C) also gave the equilibrium mixture.

Isomerization of the esters 1a, 1b, 9e, 9f, and 9g was also investigated. Again benzenethiol was a satisfactory catalyst. Thus heating either 1a or 9f with 1% by weight of benzenethiol and 0.5% AIBN at 80°C for 2 hr gave a mixture of 1a and 9f in the ratio 67:33, respectively. Heating the 2,4E 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°C (overnight) did produce isomerization at C-2. Heating the ester 9g (without solvent) with sulfur31,32 (20 mol %; 4.5 hr at 115°C) 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°C (no solvent). Ruthenium trichloride (1 mol %; 15 hr at 115°C) was slower and most other catalysts (no solvent; 115°C) also gave either slow isomerization (e.g., NaSMc, LiSCH3, or KSCH3), no isomerization (e.g., KP or NaOMe), or caused decomposition (e.g., Li or PDCl2).

The configuration of the intermediate 4c was assigned the 22,4E 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 2E 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 (CCl4) 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 5.27 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 22′ 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 isomers possessed 2,5-dienoate (or 5,5-dienoate) structures, but both contained a major fragment (+m/e 64) 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 glutonate route described above is a versatile general method for the preparation of (2E,4E)- and (2Z,4E)-3-methyl-2,4-dienoic acids, and of a variety of esters and related anhydrides. 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 “d” 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 Perkin-Elmer 457 spectrometer equipped with a BOMEM DA-3 Fourier transform infrared spectrometer. 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.

Diethyl Methylglycinate (3a). To a solution of 273 g (1.65 mol) of methyl isodehydroacetate 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 225 g (90%) of 3a, bp 100° (0.5 mm).

Substitution of 300 g (1.16 mol) of ethyl isodehydroacetate for the methyl ester in the above reaction, gave 242 g (86.5%) of a fraction containing 3a and 284 g (1.65 mol) of dimethyl 3-methylglutaconate (analyzed mixture of methyl and ethyl esters). The chemical starting materials were esterified with 1-ethyl-3-p-tolyltriazenylate in ether. Chromatography on preparative thin-layer plates gave 0.50 g of the diester 4f (upper band) and 0.50 g of 5b containing a small amount of 6b: bp (bath, short path) 200° (0.05 mm); ir (CCl4) 1740 and 1735 cm⁻¹; nmr (CDCl3) δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.10 (s, C-11 CH3 + H-12), 1.38 (d, J = 1.5 Hz, C-3 CH3), 3.10 (s, OCH3), 3.20 (s, OCH2), 3.70 (s, OCH3), 5.65 (m, H-2), and 6.70 ppm (t, J = 7.5 Hz, H-5); mass spectrum m/e (rel intensity) M⁺ 340 (100), 325 (29), 308 (30), 277 (3), 276 (3), 261 (7), 244 (10), 229 (8), 183 (60), 153 (18), 123 (8), 73 (100).


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

4-Ethoxycarbonyl-5-((2E,4E)-3-methyl-2,4-dienoate) (4e). To a solution of 2.86 g (15 mmol) of 3,7-dimethyl-7-octenal in 48 ml of water was added and the reaction mixture was stirred at 1 hr at room temperature. After cooling the mixture was poured into water and extracted with ether–hexane. The ether layer was washed with 10% Na2CO3, water, and brine and dried (CaSO4). Removal of the solvent in uucuo gave 5.4 g (89% yield) of the diethyl ester 4f: bp (bath, short path) 130° (0.05 mm); nmr (CDCl3) δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.10 (s, C-11 CH3 + H-12), 1.38 (d, J = 1.5 Hz, C-3 CH3), 3.10 (s, OCH3), 3.20 (s, OCH2), 3.70 (s, OCH3), 5.65 (m, H-2), and 6.70 ppm (t, J = 7.5 Hz, H-5); mass spectrum m/e (rel intensity) M⁺ 340 (100), 325 (29), 308 (30), 277 (3), 276 (3), 261 (7), 244 (10), 229 (8), 183 (60), 153 (18), 123 (8), 73 (100).


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 (2e) 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 acetylation, then the dried filter cake of toluene extract could be used directly in the decarboxylation step.

Ethylidyne of the diacid 4e with 1-ethyl-3-p-tolyltriazenylate in ether and purification by silica gel preparative tic gave the corresponding diethyl ester 4f: bp (bath, short path) 130° (0.05 mm); nmr (CDCl3) δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.10 (s, C-11 CH3 + H-12), 1.38 (d, J = 1.5 Hz, C-3 CH3), 3.10 (s, OCH3), 3.20 (s, OCH2), 3.70 (s, OCH3), 5.65 (m, H-2), and 6.70 ppm (t, J = 7.5 Hz, H-5); mass spectrum m/e (rel intensity) M⁺ 340 (100), 325 (29), 308 (30), 277 (3), 276 (3), 261 (7), 244 (10), 229 (8), 183 (60), 153 (18), 123 (8), 73 (100).


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 58° for 8 hr under N2. After cooling the mixture was poured into water and extracted with ether–hexane. The ether layer was washed with 10% Na2CO3, water, and brine and dried (CaSO4). Removal of the solvent in uucuo gave 5.14 g (89% yield) of the diethyl ester 4f: bp (bath, short path) 130° (0.05 mm); nmr (CDCl3) δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.10 (s, C-11 CH3 + H-12), 1.38 (d, J = 1.5 Hz, C-3 CH3), 3.10 (s, OCH3), 3.20 (s, OCH2), 3.70 (s, OCH3), 5.65 (m, H-2), and 6.70 ppm (t, J = 7.5 Hz, H-5); mass spectrum m/e (rel intensity) M⁺ 340 (100), 325 (29), 308 (30), 277 (3), 276 (3), 261 (7), 244 (10), 229 (8), 183 (60), 153 (18), 123 (8), 73 (100).


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 (MgSO4) and the solvent was removed in vacuo to give 4e (446 g) as a viscous oil: nmr (CDCl3) δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.13 (s, C-11 CH3 + H-12), 2.06 (br s, C-3 CH3), 3.22 (s, OCH3), 5.97 (m, H-2), and 6.92 ppm (t, J = 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 acetylation (the CDCl3 nmr spectrum of 4e above contained signals at 2.23 and 5.40 ppm due to 6a). Extraction of the diacid into CCl4 after acification of the disodium salt, followed by washing and drying (CaSO4) of the solution containing no lactone: nmr δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.08 (s, C-11 CH3 + H-12), 2.01 (d, J = 1.3 Hz, C-3 CH3), 3.10 (s, OCH3), 5.85 (m, H-2), and 6.82 ppm (br t, J = 7.5 Hz, H-5).

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The reaction mixture was then stirred at room temperature for 1 hour, then diluted with water and acidified with cold aqueous sulfuric acid, and then extracted with CCl4. The organic layer was washed with water and dried (MgSO4), and then evaporated in vacuo. Partial lactonization to 6c occurred. The residue was dissolved in ether and the solution heated under reflux for 48 hr and then diluted with water and acidified with cold aqueous NaOH. After removal of the organic phase (discarded), the aqueous phase was acidified to pH 1 with a N sulfuric acid and extracted with hexane. The hexane extract was washed twice with water, once with brine, dried (MgSO4), and evaporated in vacuo. A solution of the diacid 6c in ether (45 ml) and water (50 ml) was added, and the mixture was then stirred at room temperature over-night. The solvent was then removed to give 21.02 g (96% yield) of 7a.

Decarboxylation of 4c Directly to 9a. A mixture of 60.6 g (0.194 mol) of the diacid 4c, 0.586 g (0.0048 mol) of cupric acetate monohydrate, and 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 190° and held there for 1 hr. After cooling, ether and water were added and the mixture was then acidified with cold aqueous 3 N H2SO4. The aqueous layer was separated and extracted with ether. The combined ether extracts were washed with aqueous saturated CuSO4 solution, water, and brine and then dried (CaSO4). Solvent removal in vacuo gave 50.8 g of a mixture of the lactones 7a and 8a, and the acid 9a with the starting material.

Heating a sample of the diacid 4c in excess pyridine as the solvent (no added copper salt) at 100° under a N2 atmosphere for 2 hr gave a 20% yield of 7a (plus some 8a) and a 60% yield of 9a. In general decarboxylation using 2,4-dimethylpyridine was found to be faster than when pyridine was used.

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 (0.083 mol) of the lactone 7a, 0.100 mol of ethanol and added to a solution of NaN03 (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 = 3) with 4 N HCl, and the solution was extracted with ether (discarded). The ether extract was washed with water and brine and dried (MgSO4) and the solvent removed to give 21.02 g (96% yield) of 9a.

(2Z,4E)-7,11-Methoxy-2,4-dodecadienoic Acid (9b). A solution of the lactone 7b (1.065 g; 0.0045 mol) prepared from the above procedure gave above 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 N2 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 (Na2SO4) and the solvent removed in vacuo to give 0.92 g (96% 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 (CDCl3) δ 0.88 (J = 6 Hz, C-6 CH3), 1.13 (s, C-11 CH3 + H-12), 2.01 (d, J = 1.3 Hz, C-3 CH3), 3.17 (s, OCH3), 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).

Anal. Calcd for C16H28O3: C, 71.67; 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 to 9c. A 3.50 g mixture of the diacid 4c, 0.001 mol) of the disodium salt 4c, 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 6.3). The solution was heated under reflux for 7 hr (after which the pH was 5.2 and the diacid was consumed). The mixture was then acidified with 4 N HCl, and the solution was extracted with ether (discarded). The aqueous phase was acidified (pH = 3) with 4 N HCl, and the solution was extracted with ether (discarded). The ether extract was washed with water and dried (MgSO4) and the solvent removed to give 0.51 g of a colorless oil which by tlc, glc, and nmr analysis was a 55:45 mixture of 11a 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 washed with MgSO4 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.
ing a sample of the 2Z,4E acid 9a at 120° without solvent both the lactone was precipitated from dichloromethane.

9a, 9c.

The organic layer was washed with brine and dried (CaSO₄) and the solvent removed to give 147 g (90% yield) of 11-hydroxy-3,7,11-trimethyl-2,4-dodecadienoate: bp 156° (0.09 mm); nmr (CCl₄) δ 0.88 (d, 3, J = 6 Hz, C-7 CH₃), 1.10 (s, C-11 CH₃), 1.10 (s, C-11 CH₃) and acidified with 4 N HzSO₄ with stirring. After 15 min the organic layer was washed with brine and dried (CaSO₄) and the solvent was removed to give 180 g (76 mol) of 10b as a crystalline solid, mp 42-44° (lit. mp 44°). Analysis by gic (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, and also the pure 2E,4E acid 10c (by film) 1687, 1643 and 1610 cm⁻¹ (m, nmr (CCl₄)) δ 0.88 (d, J = 6 Hz, C-7 CH₃), 1.17 (s, C-11 CH₃ + H-11), 1.22 (t, 3, J = 7 Hz, C-3 CH₃), 1.29 (m, C-2 CH₃), 2.10 (s, OCH₃), 4.83 (br s, H-1), 5.57 (m, H-4), and 6.11 ppm (d, J = 16 Hz, H-3, H-5); mass spectrum (70 eV) m/e (rel intensity) 224 (100), 209 (1), 192 (6), 177 (7), 149 (16), 136 (8), 123 (13), 123 (25), 121 (13), 109 (20), 107 (27), 95 (10), 93 (15), 81 (20), 73 (100), 69 (27), and 58 (10).

Equilibration of the 2Z,4E Acid 9a. To 123 g (0.46 mol) of 9a was added with stirring under N₂, 1.23 g (11 mmol) of benzethionol and the mixture was heated at 100° in an oil bath for 1 hr (reaction was followed by glc analysis of diazomethane methylated alkylos). To the mixture was then added 60 g of odorless hydrocarbon solvent (37 g (0.05 mol) of hexane, 37 g (0.05 mol) of octane and 37 g (0.05 mol) of isopropyl methylether). After thorough mixing the aqueous layer was separated and acidified with 4 N HzSO₄ and then was extracted with hexane. The organic layer was washed with water and brine and dried (MgSO₄) and the solvent removed at 15°C (up to 60°C) to give 117.3 g (96%) of a mixture containing 35% 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 benzethionol removal, the temperature of the pot was kept below 102°C 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 % benzethionol plus 1 mol % 2,2'-azobis(isobutyl nitrite) with heating at 80°C for 2 hr, to give a mixture of 9a:10a in the ratio 52:48, respectively.

Equilibration of (Z)-11-Tetradec-1-en-y1 acetate. A mixture of 10.36 g of (Z)-11-tetradec-1-en-1-y1 acetate12 and 0.104 g of benzethionol was added to 100 ml of an oil bath at 100°C under a N₂ atmosphere. After cooling, 15 ml of Soltrol 130 (a mixture of hydrocarbons; bp 176-190°C) from Philadelphia Chemical Co.) and the solution distilled in vacuo at 3 mm (up to 90°C) to remove the benzethionol. The residue was then cooled and to it was added hexane (100 ml), water (400 ml), and 37 g (0.55 mol) of 58% NH₄OH. After thorough mixing the aqueous layer was separated and acidified with 4 N HzSO₄ and then was extracted with hexane. The organic layer was washed with water and brine and dried (MgSO₄) and the solvent removed at 1 mm (up to 60°C) to give 117.3 g (96%) of a mixture containing 32% of 9a and 68% of 10a (determined by glc analysis of a diazomethane treated aliquot, on OV-101 or PDEAS).

To a solution of 85.4 g (0.36 mol) of 10b in 500 ml of water was added 850 ml of hexane.C 275 g (0.1 mol) of N₂H₄SO₄ with stirring. After 15 min the organic layer was washed with brine and dried (CaSO₄) and the solvent was removed to give 180 g (76 mol) of 10b as a crystalline solid, mp 42-44° (lit. mp 44°). Analysis by gic (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, and also the pure 2E,4E acid 10c (by film) 1687, 1643 and 1610 cm⁻¹ (m, nmr (CCl₄)) δ 0.88 (d, J = 6 Hz, C-7 CH₃), 1.17 (s, C-11 CH₃ + H-11), 1.22 (t, 3, J = 7 Hz, C-3 CH₃), 1.29 (m, C-2 CH₃), 2.10 (s, OCH₃), 4.83 (br s, H-1), 5.57 (m, H-4), and 6.11 ppm (d, J = 16 Hz, H-3, H-5); mass spectrum (70 eV) m/e (rel intensity) 224 (100), 209 (1), 192 (6), 177 (7), 149 (16), 136 (8), 123 (13), 123 (25), 121 (13), 109 (20), 107 (27), 95 (10), 93 (15), 81 (20), 73 (100), 69 (27), and 58 (10).

A solution of 197 g (0.77 mol) of the ammonium salt of 10a in 350 ml of water was added 856 g of hexane.C 275 g (0.1 mol) of N₂H₄SO₄ with stirring. After 15 min the organic layer was washed with brine and dried (CaSO₄) and the solvent was removed to give 180 g (76 mol) of 10b as a crystalline solid, mp 42-44° (lit. mp 44°). Analysis by gic (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, and also the pure 2E,4E acid 10c (by film) 1687, 1643 and 1610 cm⁻¹ (m, nmr (CCl₄)) δ 0.88 (d, J = 6 Hz, C-7 CH₃), 1.17 (s, C-11 CH₃ + H-11), 1.22 (t, 3, J = 7 Hz, C-3 CH₃), 1.29 (m, C-2 CH₃), 2.10 (s, OCH₃), 4.83 (br s, H-1), 5.57 (m, H-4), and 6.11 ppm (d, J = 16 Hz, H-3, H-5); mass spectrum (70 eV) m/e (rel intensity) 224 (100), 209 (1), 192 (6), 177 (7), 149 (16), 136 (8), 123 (13), 123 (25), 121 (13), 109 (20), 107 (27), 95 (10), 93 (15), 81 (20), 73 (100), 69 (27), and 58 (10).

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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 (CaSO4) and the solvent was removed to give 97.8 g (96% yield) of crude product. Analysis by gc showed it to be 97.5% pure 1d: bp (bath, short path) 121° (0.01 mm); ir (film) 1725, 1640, and 1615 cm-1; nmr (CDCl3) δ 0.88 (d, J = 6 Hz, C-7 CH3), 1.01 (d, J = 7 Hz, C-10 CH3), 1.12 (d, J = 6 Hz, C-3 CH3), 2.45 (t, J = 2.5 Hz, C≡C=CH), 4.74 (d, J = 2 Hz, OCH2C≡C=CH), 5.76 (m, 1, H-2), and 6.17 ppm (m, 2, H-4 and H-5).


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

Isomerization of Dimethyl Ester 4f. To 2.01 g of the ester 4f was added 0.065 g of benzenethiol and 0.046 g of 2,2'-azobis(isobutyronitrile) [AIBN] and the mixture heated at 88° for 2.5 hr under N2. Analysis by gc showed the presence of 48% of 4f, 34% of 12, and 12% of 13. Further addition of 0.065 g of benzenethiol and 0.007 g of AIBN were added and the mixture heated again at 80° for 2 hr. Analysis by glc showed the presence of 48% of 4f, 34% of 12, and 12% of 13. Further addition of 0.065 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 isomer 12, and 13% of the isomer 13. A further 0.065 g of benzenothiol in high vacuum) showed the presence of 40% of 4f, 36% of 12, and 13% of 13. A further 0.065 g of benzenethiol was added and the mixture heated again at 80° for 2 hr. Glc analysis (after removal of ether-pentane (1:4) gave two fractions, the first containing 12 and 13 in the ratio 3:1:69 and the second fraction containing 12 and 13 in the ratio 77:22, respectively. Attempted separation of a portion of this mixture by bp liquid chromatography on LiChrosorb (30 μm) in ether–pentane (1:4) gave two fractions, the first containing 12 and 13 in the ratio 81:19 and the second fraction containing 12 and 13 in the ratio 89:11, respectively. 12: nmr (CDCl3) δ 0.93 (d, J = 6 Hz, C-7 CH3), 1.10 (s, C-11 CH3 + H-12), 2.22 (d, J = 1.5 Hz, C-3 CH3), 3.10 (s, OCH3), 3.70 (s, CO2CH3), 3.73 (s, CO2CH3), 5.54 (m, H-1), and 6.76 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 gc-f.