excess of $NaBH_4$ was added. After 15 hr the mixture was diluted with water and extracted with chloroform. Almost pure methyl cholanate (**13**) was obtained: mp 87°; ir ν_{CO} 1740 cm^{-1}; nmr (CCl_4) 215 cps (s, 3, $-OCH_3$).

Reduction of **5** in ether solution with $LiAlH_4$ afforded cholanol (**14**) in high purity: mp 130°; $[\alpha]D$ +24.4 ($CHCl_3$, 1%); ir 3350–3380 (s), 1055 cm^{-1} (w); nmr ($CDCl_3$) 216 cps (t, 2, CH_2, J = 4 cps).

Acetylation of Ketol 6.—The acetylation of ketol **6** to the corresponding ketol acetate **4** could be affected by all known procedures. The dimeric compound **5** resisted acetylation under all conditions.

Registry No.—**3**, 34565-21-4; **4**, 34565-22-5; **5**, 34565-23-6; **6**, 34565-24-7; **7**, 34565-25-8; **8**, 34565-26-9; **11**, 4877-66-1; **12**, 34565-28-1; **13**, 2204-14-0; **14**, 3110-99-4; 24-oxo-25-chlorohomocholane, 34565-31-6.

Mass Spectrometry in Structural and Stereochemical Problems. CCXVIII.[1] The Electron Impact Induced Behavior of Terpenoid Esters of the Juvenile Hormone Class[2]

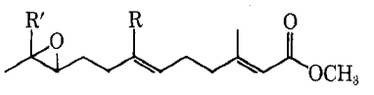
RAYMOND J. LIEDTKE[3] AND CARL DJERASSI*

Department of Chemistry, Stanford University, Stanford, California 94305

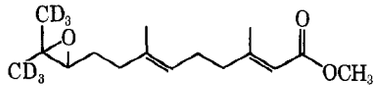
Received November 22, 1971

The 70- and 15-eV mass spectra of methyl 10,11-epoxy-*trans,trans*-farnesoate (III) and three deuterium-labeled analogs, *5,5-d*$_2$ (VI), *8,8,8′,8′,8′-d*$_5$ (V), and *12,12,12,12′,12′,12′-d*$_6$ (IV), have been examined. Generation of the important peaks in the spectra of III at *m/e* 43, 71, 81, 114, and 135 are discussed in light of high resolution and metastable peak data as well as the shift of these peaks in the spectra of the deuterated analogs. The generation of the mass 114 ($C_6H_{10}O_2$) ion by methyl 2,6-dienoates is the subject of further study involving methyl *trans,-trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX), methyl *trans,trans*-3,7-dimethyldeca-2,6-dienoate (XI), their trans,cis isomers, and several specifically deuterium-labeled C-8 or C-8′ analogs. Methyl *trans,trans*-farnesoate (XIII) and several deuterium-labeled analogs are also subjects of investigation. In this latter case, C-12 and C-12′ hydrogen transfer (*via* either a 10-, 12-, or 14-membered transition state) plays a substantial part in the mass 114 ion production.

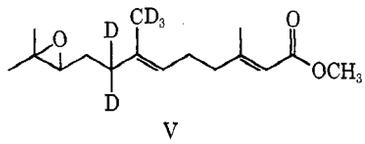
Mass spectrometry played an essential role in the structure elucidation of the first *Cecropria* juvenile hormone I, isolated by Roeller and coworkers,[4] and again in the structure proof of the second hormone II found by Meyer and colleagues.[5] Trost has discussed several of the important mass spectral cleavages of the hormone I in light of the fragments observed in the spectrum of the lower homolog, methyl 10,11-epoxy-*trans,trans*-farnesoate (III),[6] and Meyer, *et al.*,[5] have presented the low-resolution spectrum of the hormone II together with high-resolution mass measurements of some of the fragment ions. The future will see the search for the juvenile hormones of other insects, and, since the acquisition of even a few micrograms of material is very difficult, a clear understanding of the mass spectral behavior of the juvenates[7] is imperative. Because of this and also because of our fundamental interest in the behavior of ionized polyfunctional molecules, we have examined the 70- and 15-eV mass spectra of the methyl 10,11-epoxy farnesoate III and three deuterium-labeled analogs (IV–VI).



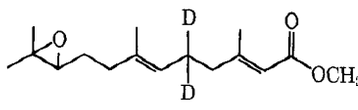
I, R′ = R = C_2H_5
II, R′ = C_2H_5; R = CH_3
III, R′ = R = CH_3



IV



V



VI

Results and Discussion

Peaks in the low mass range dominate the 70-eV spectrum (Figure 1a) of the methyl epoxy farnesoate III; those at *m/e* 43 (66% C_3H_7), 71 (C_4H_7O), 81 (C_6H_9), 114 ($C_6H_{10}O_2$), and 135 ($C_{10}H_{15}$) are particularly intense. None of these fragments arise by simple bond cleavage; as our results show, hydrogen rearrangement is essential in each case. At low ionizing energy (15 eV), fragments in the high mass region of the spectrum (Figure 1b) assume greater importance. One of the more significant peaks is found at *m/e* 248 (M − H_2O) and results from the migration of two hydrogen atoms to the epoxide oxygen. Loss of CH_3OH from the molecular ion generates an ion of mass2 34, which, together with the mass 206 ion [M − (CH_3OH + CO)], serves to identify the ester group. Analysis of the

(1) For preceding paper, see Y. Sheikh, R. J. Liedtke, A. M. Duffield, and C. Djerassi, *Can. J. Chem.*, in press.

(2) Financial assistance by the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged.

(3) National Institutes of Health Predoctoral Fellow, 1968–1971.

(4) H. Roeller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967).

(5) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, **60**, 853 (1968).

(6) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970).

(7) Nomenclature suggested by E. E. van Tamelen; see ref 5.

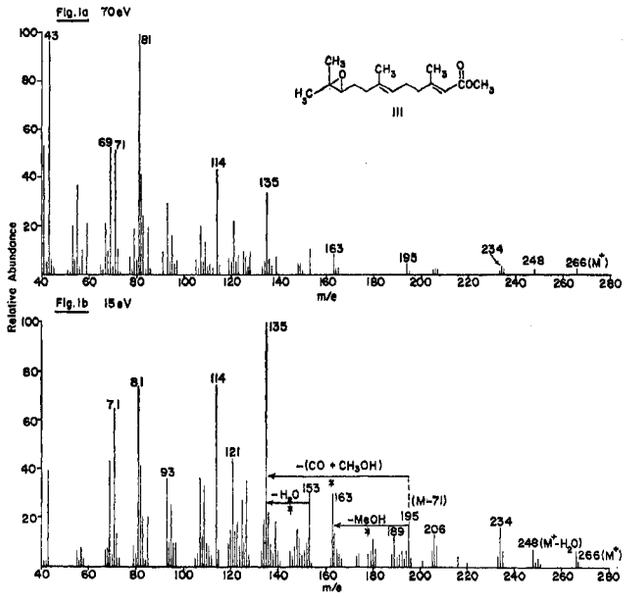


Figure 1.—Mass spectra (70 and 15 eV) of methyl 10,11-epoxy-*trans,trans*-farnesoate (III).

spectra of the deuterium-labeled analogs IV–VI and the high-resolution data presented in Table I makes possible the proposal of plausible mechanistic schemes for the genesis of the more important fragments.

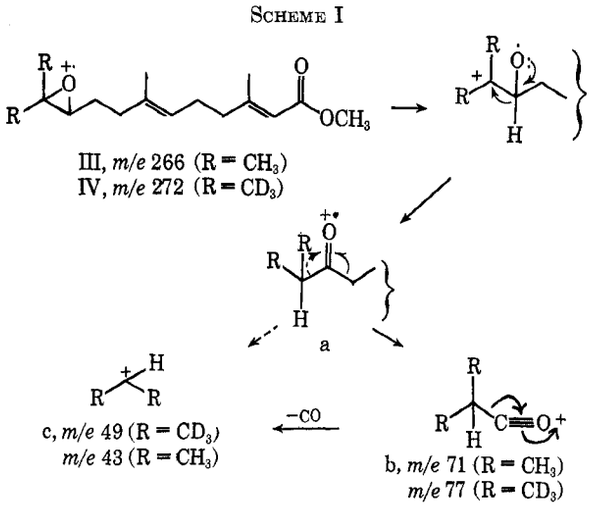
TABLE I

HIGH-RESOLUTION MASS MEASUREMENTS OF IMPORTANT METHYL 10,11-EPOXY-*trans,trans*-FARNESOATE (III) PEAKS AT 70 eV

Peak *m/e*	Composition	Peak *m/e*	Composition
41	100% C_3H_5	93	100% C_7H_9
43	34% C_2H_3O, 66% C_3H_7	95	45% C_6H_7O, 55% C_7H_{11}
53	100% C_4H_5	105	100% C_8H_9
55	11% C_3H_3O, 89% C_4H_7	107	12% C_7H_7O, 88% C_8H_{11}
57	31% C_3H_5O, 69% C_4H_9	109	29% C_7H_9O, 71% C_8H_{13}
59	62% $C_2H_3O_2$, 38% C_3H_7O	114	100% $C_6H_{10}O_2$
67	100% C_5H_7	121	3% C_8H_9O, 97% C_9H_{13}
68	100% C_5H_8	125	42% $C_7H_9O_2$, 51% $C_8H_{13}O$, 7% C_9H_{17}
69	22% C_4H_5O, 78% C_5H_9	127	27% $C_7H_{11}O_2$, 73% $C_8H_{15}O$
71	98% C_4H_7O, 2% C_5H_{11}	135	8% $C_9H_{11}O$, 92% $C_{10}H_{15}$
72	100% C_4H_8O	139	68% $C_8H_{11}O_2$, 32% $C_9H_{15}O$
77	100% C_6H_5	153	100% $C_{10}H_{17}O$
79	100% C_6H_7	163	100% $C_{11}H_{15}O$
81	2% C_5H_5O, 98% C_6H_9	195	100% $C_{12}H_{19}O_2$
82	100% C_5H_6O	206	100% $C_{14}H_{22}O$
83	68% C_5H_7O, 32% C_6H_{11}	234	100% $C_{15}H_{22}O_2$
85	100% C_5H_9O	248	100% $C_{16}H_{24}O_2$
91	100% C_7H_7	266	100% $C_{16}H_{26}O_3$

Peaks at *m/e* 43 and 71.—In the spectrum (not reproduced) of the terminally d_6-labeled methyl epoxyfarnesoate (IV), the *m/e* 71 peak appears nearly quantitatively (>93%) at *m/e* 77, and its generation can thus be pictured as in Scheme I.

SCHEME I



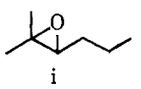
Support of this mechanism comes from the observation that >95% of the hydrocarbon *m/e* 43 fragment shifts to *m/e* 49 in the spectrum of IV (Scheme I).[8]

Peak at *m/e* 81.—The appearance of the base peak in the 70-eV spectrum (Figure 1a) of the methyl 10,11-epoxy farnesoate III at *m/e* 81 is remarkable, since the generation of this hydrocarbon ion (C_6H_9) must involve two carbon–carbon bond cleavages and the additional transfer of one hydrogen atom.[10] From the data listed in Table II, the conclusion can be drawn that the *m/e* 81 species contains carbon atoms 5, 6, 7, 8, 8′, and 9 (for numbering see Scheme II). Furthermore, the shift of the *m/e* 81 peak to *m/e* 85 in the spectrum of the deuterium-labeled epoxy ester V means that hydrogen migration from C-8 or C-8′ is involved.

The mechanisms outlined in Scheme II are in accord with these requirements. As in the generation of the mass 114 ion (see below), the hydrogen migration pictured in path B could equally well be drawn to C-2, or to C-4 with accompanying C-4 hydrogen transfer to the carbonyl oxygen. A mechanism analogous to that given for the generation of ions d and e (paths A, B) has been proposed by Meyerson[11] to explain the facility of ϵ cleavage in certain cis α,β-unsaturated esters.

Peak at *m/e* 135.—Metastable defocusing data demonstrate three important precursors of the mass 135 fragment, namely ions of mass 153, 163, and 195.

(8) It is of interest that in the spectrum of the simple epoxide i, the ion



i

of mass 85 (β cleavage) is more abundant, ratio 5:1, than the ion of mass 71 (α cleavage), whereas in the spectrum (Figure 1) of the methyl epoxy farnesoate III the peak at *m/e* 71 (α cleavage) is the more intense.[9]

(9) The mass spectrometric behavior of simple epoxides has been extensively studied: P. Brown, J. Kossanyi and C. Djerassi, *Tetrahedron, Suppl. 8, Part I*, 241 (1966).

(10) Eight precursors for the *m/e* 81 ions formed in the first field free region were found using the metastable defocusing procedure, but the exact masses of these precursors were not determined.

(11) S. Meyerson, *Int. J. Mass Spectrom. Ion Phys.*, **1**, 309 (1968).

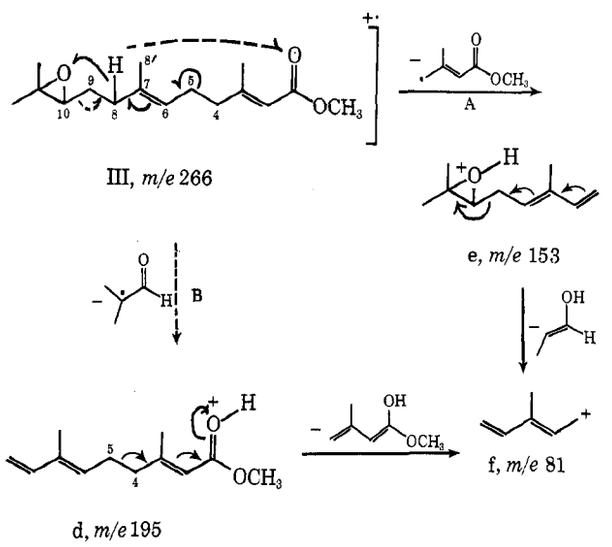
TABLE II

SHIFT OF THE *m/e* 81 PEAK IN THE SPECTRA OF THE DEUTERIUM-LABELED ANALOGS OF METHYL 10,11-EPOXY-*trans,trans*-FARNESOATE

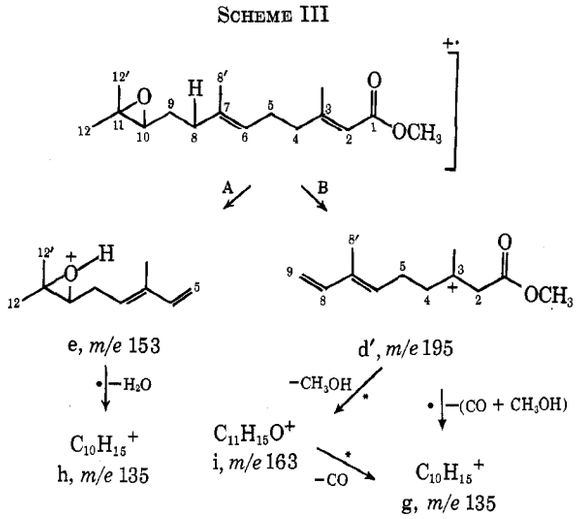
Compd	Intensities[a] of peaks in the *m/e* 77–88 region at 70 eV											
	77	78	79	80	81	82	83	84	85	86	87	88
III	4	1	9	2	48	16	11	1	9	1		
IV	4	1	7	2	59	11	6	3	1	1		
V	1	1	3	3	4	14	5	7	50	9	1	
VI	1	2	3	4	8	16	53	2	12			

[a] Peak intensities are summed, then normalized to 100%; values are rounded to the nearest whole number.

SCHEME II



SCHEME III



Furthermore, in the spectrum (not reproduced) of the d_6-labeled epoxy farnesoate IV, whereas 60% of the *m/e* 135 peak remains at *m/e* 135, the remaining 40% shifts to *m/e* 141. It is clear then that two structurally unique mass 135 ions (g and h) are generated (Scheme III). Ion h encompasses C-5 through C-12 and its formation from the C-8 protonated epoxide ion e of mass 153 is supported by evidence obtained from the spectrum of the d_5-labeled epoxy farnesoate V. Metastable peaks are observed corresponding to the ejection of HDO and D_2O from the mass 159 fragment but no peak for the elimination of H_2O is visible.[12]

Loss of 60 mass units from a mass 195 precursor to give ion g (C-2 through C-9) is more difficult to rationalize, but appears to involve the sequential and simultaneous expulsion of CH_3OH and CO (Scheme III). The available data does not indicate the origin of the hydrogen atom which migrates in the process of methanol elimination.

(12) In the spectrum of V, the *m/e* 135 peak shifts to *m/e* 138 (~25%), 139 (~25%), and 140 (~50%). Precise calculations and interpretation are not possible, but, if the entire *m/e* 140 peak is assigned to ion g, then it appears that ejection of DHO and D_2O occurs with about equal facility to give ion h.

Ions analogous to g and h should provide valuable structural information pertaining to hormones analogous to I. For example, in the spectrum of I, an ion produced by path A of Scheme III would be expected to appear at *m/e* 163, whereas an ion of mass 149 would result from operation of path B. Indeed, examination of this hormone's 70-eV mass spectrum[6] does confirm these predictions, and no doubt decreasing the ionizing voltage would enhance the abundance of these fragments.

Peak at *m/e* 114.—The generation of the important mass 114 ion involves transfer of one hydrogen atom to the $C_6H_{10}O_2$ charge-retaining fragment. In the spectrum of the *8,8,8',8',8'-d*$_5$-labeled epoxy ester V, roughly 60% of the *m/e* 114 peak shifts to *m/e* 115, thus implicating C-8 and C-8' hydrogen migration to this extent. In contrast (see below) to the case of methyl farnesoate (XIII), C-12 and C-12' hydrogen migration is only of minor importance (~10%). Hydrogen exchange or other mechanistic paths apparently are responsible for the 30% of the transferred hydrogen unaccounted for.

Occurrence of *m/e* 114 Peak in Methyl Dienoates.—An intense *m/e* 114 peak is not unique to the juvenate

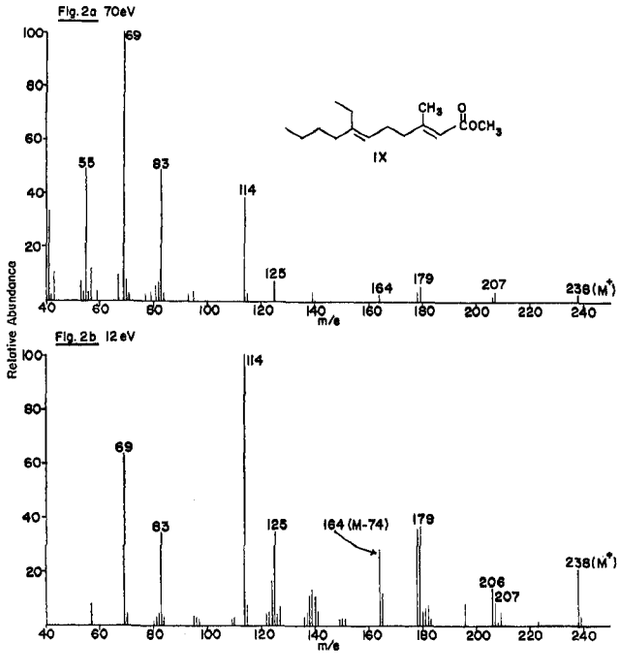
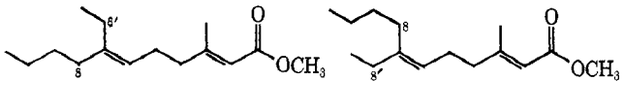


Figure 2.—Mass spectra (70 and 12 eV) of methyl *trans,trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX).

mass spectra. Thomas, *et al.*,[13] have observed that the mass 114 fragment in the spectrum of methyl geranate (VII) shifts to mass 115 in the spectrum of the d_6 terminally labeled analog VIII.

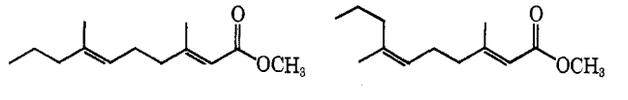
Methyl *trans,trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX) and its trans,cis unsaturated isomer X were



IX X

prepared to examine the behavior of compounds which possess both C-8 and C-8′ hydrogens and which allow specific labeling of one of these positions with deuterium. The 70- and 12-eV spectra (see Figure 2 for the 70- and 12-eV spectra of IX) of these compounds are identical and generation of the mass 114 ion is indeed a favored fragmentation route for these esters, which accounts for the base peak at low ionizing energy. Examination of the spectra of the deuterium-labeled analogs of compounds IX and X reveals that the hydrogens attached to C-8 and C-8′ have equal migratory aptitudes and that a substantial isotope effect (IE = atoms of deuterium transferred/atoms of hydrogen)[14] is operative (see Table III).

Since no preference for hydrogen migration from the C-8 or C-8′ position of the unsaturated ester is apparent, examination of the shift of the *m/e* 114 peak in the spectra of deuterium-labeled analogs of methyl *trans,trans*-3,7-dimethyldeca-2,6-dienoate (XI) and its trans,cis double bond isomer XII will yield information



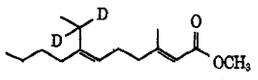
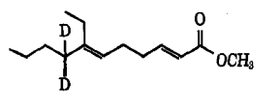
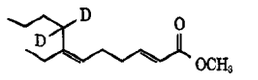
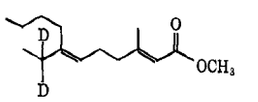
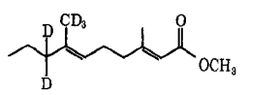
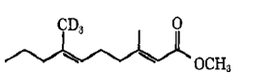
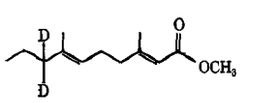
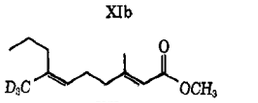
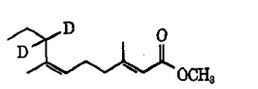
XI XII

(13) A. F. Thomas, B. Willhalm, and R. Müller, *Org. Mass Spectrom.*, **2**, 223 (1969).

(14) J. K. MacLeod and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5182 (1967).

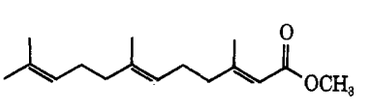
TABLE III

SHIFT OF THE *m/e* 114 PEAK IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED ANALOGS OF METHYL 7-ETHYL-3-METHYLUNDECA-2,6-DIENOATE AND METHYL 3,7-DIMETHYLDECA-2,6-DIENOATE

Compd	Per cent of *m/e* 114 peak which appears at —70 eV— 114	115	—12 eV— 114	115
 IXa	64	36	64	36
 IXb	64	36	62	38
 Xa	65	35	65	35
 Xb	61	39	61	39
 XIc (trans,cis) + (trans,trans)	9	91	11	89
 XIa	78	22	84	16
 XIb	44	56	42	58
 XIIa	76	24	82	18
 XIIb	49	51	44	56

concerning the relative preference of primary allylic *vs.* secondary allylic hydrogen migration (see Table III) after correction for the greater availability of primary hydrogens, and the isotope effect (IE) as well may be estimated. At 70 eV, 76% secondary allylic hydrogen transfer occurs and this value increases to 81% at 12 eV. The calculated IE equals 0.71 at 70 eV and 0.63 at 12 eV.[15]

The spectra (70 and 12 eV) of methyl *trans,trans*-farnesoate (XIII) are shown in Figures 3a and 3b.



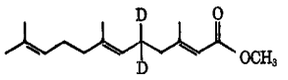
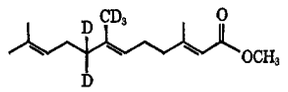
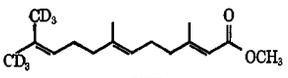
XIII

(15) This IE is estimated reasonably assuming no substantial IE on subsequent decompositions of the *m/e* 114 and 115 ions.

Analysis of the mass spectra (Table IV) of several deuterated analogs of XIII shows, remarkably, that

TABLE IV

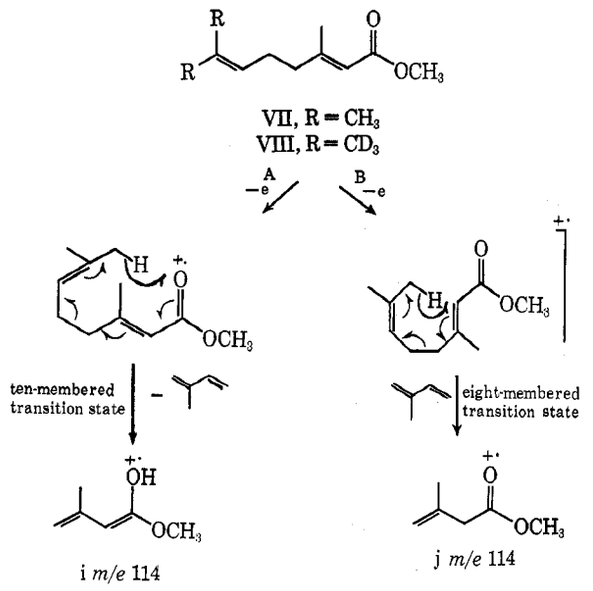
SHIFTS OF THE *m/e* 114 PEAK IN THE SPECTRA OF DEUTERIUM-LABELED ANALOGS OF METHYL FARNESOATES

Compd	Per cent of *m/e* 114 peak which appears at —70 eV— 114	115	—12 eV— 114	115
 XIIIa	100	0	100	0
 XIIIb	67	33	50	50
 XIIIc	47	53	73	27

at 70 eV most of the hydrogen transferred in the process of mass 114 ion production originates from the terminal C-12 and C-12′ positions. On the other hand, transfer from C-8 and C-8′ is the favored route at low ionizing energy. At 70 eV, 86% of the migrating hydrogen is accounted for, but only 77% at 12 eV. The difference from 100% is probably due to a small isotope effect and some hydrogen migration from positions other than those labeled. A small amount of hydrogen randomization could also contribute to this result.

Possible Mechanistic Pathways to the *m/e* 114 Peak.—In analogy to the McLafferty rearrangement exhibited by carbonyl-containing compounds and olefins, the hydrogen atom could be transferred to the carbonyl oxygen through a ten-membered transition state as shown (Scheme IV, path A) for methyl geranate

SCHEME IV



producing a dienolic ester ion of mass 114 (i). Alternatively, transfer to the C-2 carbon atom (eight-membered transition state) would generate the enone ion j (Scheme IV, path B).

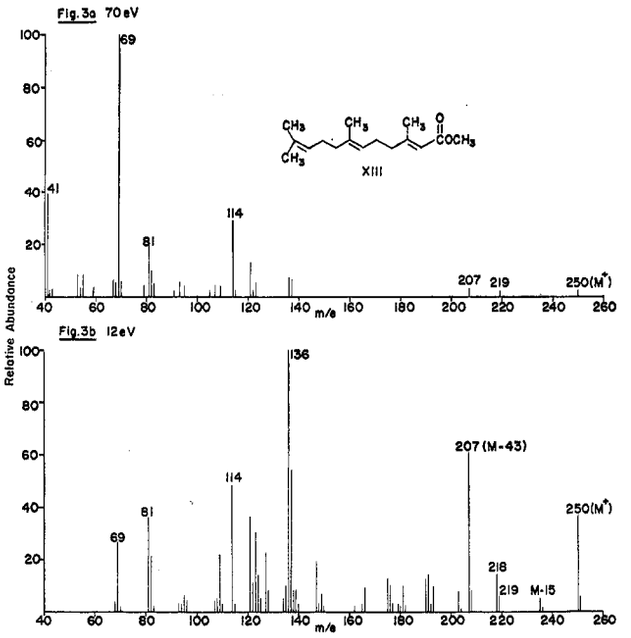
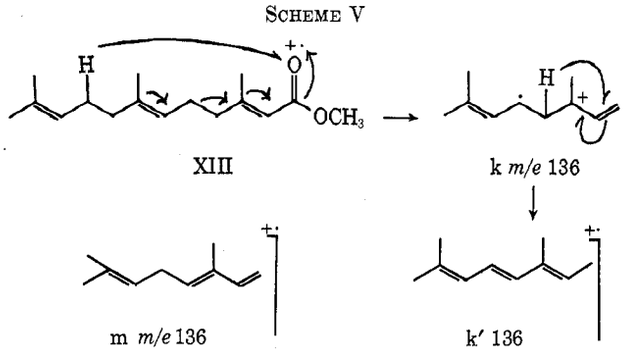


Figure 3.—Mass spectra (70 and 12 eV) of methyl *trans,trans*-farnesoate (XIII).

Thomas and coworkers[13] propose yet another possibility which involves first movement of the α,β double bond to the β,γ position *via* migration of a C-4 allylic hydrogen atom to the carbonyl oxygen, and then transfer of a hydrogen from C-8 or C-8′ to C-4, giving the dienolic ester ion i. Either our mechanism or that of Thomas would account for the terminal hydrogen migration observed in the case of methyl farnesoate (XIII).

The *m/e* 136 Peak in Methyl Farnesoate (XIII).—The mass 136 hydrocarbon ion ($C_{10}H_{16}$) which accounts for the base peak at 12 eV in the spectrum (Figure 3b) of methyl *trans,trans*-farnesoate (XIII), results from elimination of a mass 114 neutral fragment by the molecular ion. This mass 136 ion might be expected to arise by the same processes (*cf.* Scheme IV) involved in the generation of the mass 114 species, the charge being retained in this case by the hydrocarbon fragment. However, in the spectrum of the d_5 ester XIIIb, the *m/e* 136 peak appears at *m/e* 141, whereas it moves to *m/e* 142 in the spectrum of the d_6 ester XIIIa (Table V). Thus, *a fundamentally different mechanistic pathway must be involved in the production of the ion of mass 136.* A plausible suggestion appears in Scheme V.

SCHEME V



It could be the case that the ion k or the ionized triene k′ has a lower ionization potential than the expelled

TABLE V

SHIFT OF THE m/e 136 PEAK IN THE SPECTRA OF DEUTERIUM-LABELED METHYL FARNESOATES

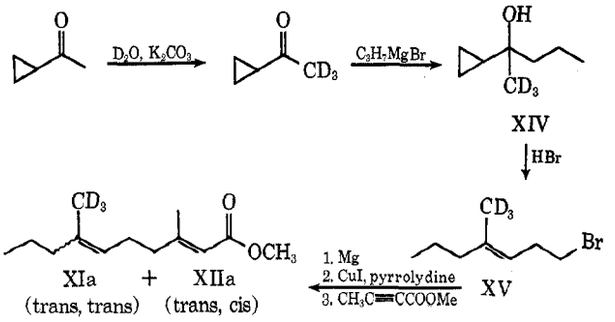
Compd	Intensities of ions in the m/e 133 to 144 region at 12 eV[a]											
	133	134	135	136	137	138	139	140	141	142	143	144
XIII	1	2	6	56	25	2	4	2	1			
XIIIb						1[b] 2	4 3	2 6	55	26	1	
XIIIc			4	2	1	2	5	4	5	53	24	1
XIIIa			2	2	7	53	26	3	4	2	1	

[a] Peak intensities are summed, then normalized to 100%. [b] Upper number is oxygen-containing fragment, lower number hydrocarbon fragment.

neutral mass 114 species and thus carries the positive charge. On the other hand, ion m apparently has a higher ionization potential than the mass 114 species (i or j). Similar reasoning has been used to explain the fact that the McLafferty rearrangement of hexanal involves site-specific γ-hydrogen transfer, whereas formation of the complementary olefin ion of mass 56 involves not only γ-hydrogen transfer but also δ-hydrogen migration.[16]

Synthesis of Labeled Compounds.—Several methods were employed to synthesize the deuterium-labeled methyl 2,6-dienoates. One procedure started with an appropriate cyclopropyl alkyl ketone, *e.g.*, cyclopropyl methyl ketone (Scheme VI). Preparation of

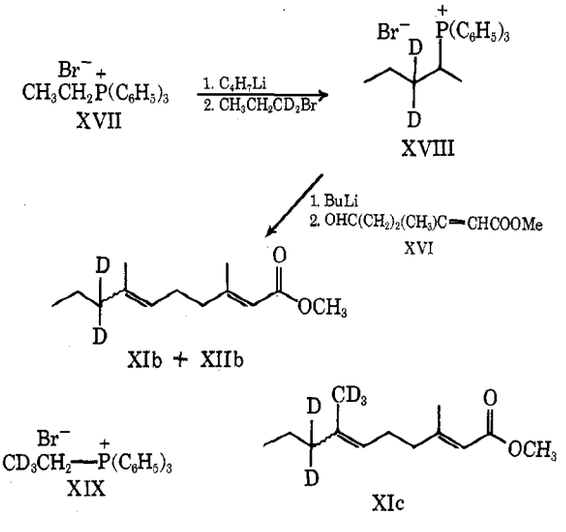
SCHEME VI



the homoallylic bromide XV (70% trans) was accomplished according to the conditions of Julia.[17] Conjugate addition[18] of the corresponding organocopper reagent to methyl 2-butynoate at −78° gave the dienoates XIa and XIIa in fair yield.

Another highly versatile method (Scheme VII) made use of the trans aldehydo unsaturated ester XVI. Alkylation of the ylide derived from the phosphonium salt XVII (butyllithium) with *1,1-d*$_2$-1-bromopropane gave the labeled secondary phosphonium salt XVIII

SCHEME VII



(Scheme VII). Addition of another equivalent of butyllithium followed by the reaction of the resulting phosphorane with XVI produced a mixture of trans and cis 6,7 double bond isomers XIb and XIIb. Beginning with the deuterium-labeled phosphonium salt XIX and following these procedures, the methyl dienoate XIc was produced.

The deuterium-labeled methyl epoxy farnesoates were made from the corresponding deuterated methyl farnesoates (XIIIa–c) by reaction with *N*-bromosuccinimide in water–tetrahydrofuran, purification (tlc), and treatment with a fourfold excess of dry potassium carbonate. The syntheses of the labeled farnesoates are outlined in Schemes VIII–X.

Experimental Section

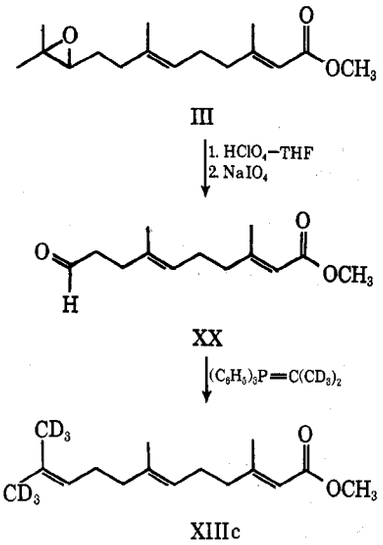
Mass spectra of the α,β-unsaturated esters and epoxy farnesoates were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°) and by Mr. R. Conover on an Atlas CH-4 instrument using an E-4B ion source and direct insertion probe (samples adsorbed on charcoal). Spectra of compounds run on both of these instruments were essentially identical. Metasta-

(16) S. Meyerson, C. Fenselau, J. L, Young, W. R. Landis, E. Selke, and L. C. Leitch, *Org. Mass Spectrom.*, **3**, 689 (1970).

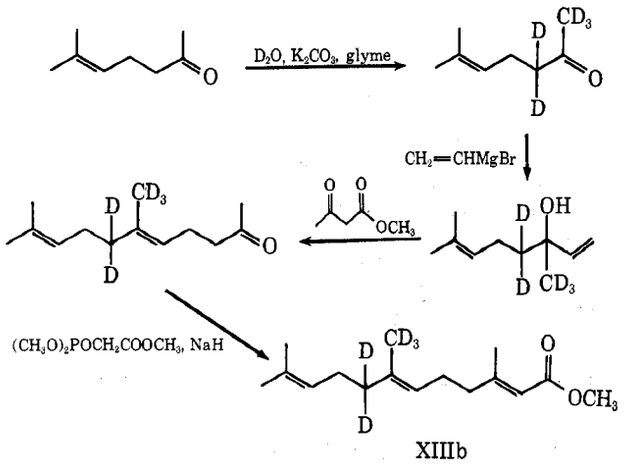
(17) M. Julia, S. Julia, T. S. Yu, and C. Newville, *Bull. Soc. Chim. Fr.*, 1849 (1961).

(18) J. B. Siddall, M. Biskup, and J. H. Fried, *J. Amer. Chem. Soc.*, **91**, 1853 (1969).

SCHEME VIII



SCHEME IX

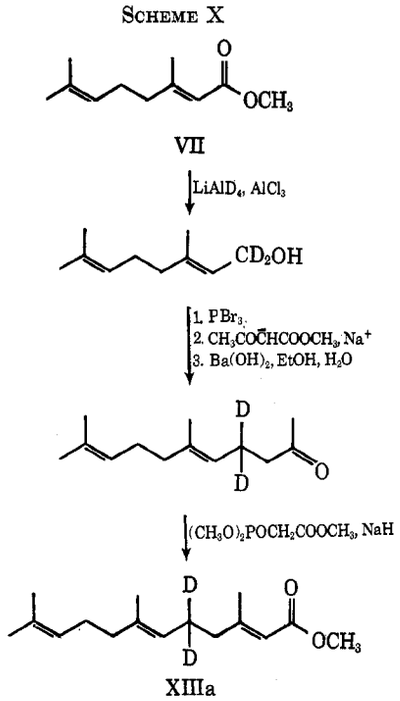


ble transitions in the first field-free region were observed with the aid of the defocusing procedure.[19] The 2,6-dienoates were submitted for mass spectral measurement only after purification by vapor phase chromatography (unless otherwise noted a 6 ft × 0.25 in., 3% OV 25 on Gas-Chrom Q column, or a 6 ft × 0.25 in., 5% Carbowax 20M on Chromosorb W column were used, both columns glass). The methyl epoxy farnesoates were purified by tlc.

Infrared characterization was carried out using a Perkin-Elmer Model 700 spectrophotometer. Nmr spectra were obtained with either a Varian Model T-60 spectrometer or a Varian HA-100 spectrometer (measured by Mr. M. Bramwell) and are recorded in δ values with carbon tetrachloride as solvent and tetramethylsilane as an internal reference standard. The spectral characteristics not explicitly stated of all compounds used in this study were found to be in agreement with the material's assigned structure. The elementary composition of all new compounds was determined by mass spectral molecular weight determination.

Methyl *trans*-3-Methyl-6-oxohex-2-enoate (XVI).—In a dry 1-l. flask (nitrogen) were placed dimethylformamide (250 ml) and sodium methoxide (17.1 g, 0.95 equiv). Trimethyl phosphonoacetate[20] (60 g) in dimethylformamide (50 ml) was added over 15 min, the mixture was stirred for 15 min, and then 6-methylhept-5-en-2-one[20] (40 g) in 50 ml of dimethylformamide was added. After stirring overnight, the mixture was poured into 90% brine–water and extracted with ether. The organic material was washed with brine and dried over sodium sulfate. Methyl geranate (14 g, 99% trans) was isolated by spinning band distillation.

SCHEME X



To methyl *trans*-geranate (VII) (10 g) in 30 ml of dichloromethane at 0° was added *m*-chloroperbenzoic acid (12.3 g, 10% excess) and the reaction was worked up after 30 min by pouring into 10% sodium sulfite. The organic material was separated, washed with 5% potassium bicarbonate and brine, and dried over magnesium sulfate, and the solvent was evaporated. The crude epoxy geranate (10 g) was dissolved in tetrahydrofuran (50 ml) and water (50 ml). Perchloric acid (3%, 4 ml) was added; and after 30 min sodium chloride (20 g) was added, the organic material separated, and the aqueous phase was extracted three times with ether. The combined organic extracts were washed with saturated sodium carbonate and brine and dried over magnesium sulfate. Evaporation of the solvent gave the corresponding crude diol (10 g). The diol was dissolved in 50 ml of tetrahydrofuran (nitrogen), and sodium periodate (11 g in 75 ml of water) was added at 0°. The mixture was stirred at 0° for 1 hr and at 25° for 0.5 hr. Brine and ether were added and the organic material was separated, washed with sodium bicarbonate and brine, and dried over calcium chloride. Distillation gave 5.5 g of methyl *trans*-3-methyl-6-oxohex-2-enoate (XVI), bp 150–152 (aspirator pressure), one peak by vpc.[21]

Methyl *trans,trans*-3,7-Dimethyldeca-2,6-dienoate (XI) and Methyl *trans,cis*-3,7-Dimethyldeca-2,6-dienoate (XII).—Cyclopropyl methyl ketone (12 g) was added to propylmagnesium bromide (10% excess) and the mixture was stirred for 3 hr and worked up in the usual fashion to yield 13 g of 2-cyclopropylpentan-2-ol (XXI),[22] bp 78–80° at aspirator pressure. The alcohol XXI was treated with 49% hydrobromic acid[17] to give 1-bromo-4-methylhept-3-ene (XXII),[22] yield 13.7 g after distillation. A better purification procedure involves eluting the bromide from a column of acid-washed alumina with hexane.

In a dry flask (argon) was placed magnesium (1.77 g, 73 mmol) and ether (3 ml); a little of the bromide XXII was added and the reaction began quickly. Ether (110 ml) was added and the remaining bromide (12 g, 62.8 mmol) in ether (100 ml) was added dropwise over 2 hr; the mixture was stirred overnight. Titration of an aliquot according to the procedure of Watson and Eastham[23] indicated a 65% yield (0.22 *M* solution). To 100 ml of the 0.22 *M* homoallylic Grignard reagent at −10° were added copper iodide (5 g, 1.2 equiv) and pyrrolidine (1.88 g, 1.2 equiv);

(19) (a) K. R. Jennings, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davies, Ed., United Trade Press, London, 1967, p 105; (b) T. W. Shannon, T. E. Mead, C. G. Warner, and F. W. McLafferty, *Anal. Chem.*, **39**, 1748 (1967).

(20) Available from the Aldrich Chemical Co.

(21) The procedures used were suggested by Dr. Clive Henrick of the Zoecon Corp., who also supplied an authentic sample of the material.

(22) J. Kulesza, J. Gora, and K. Katarzyna, *Riechst., Aromen. Koerperpflegem.*, **19**, 192, 194, 199–200 (1969); *Chem. Abstr.*, **71**, 102020q (1969).

(23) S. Watson and J. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

this mixture was stirred at 20° for 1 hr (Gilman test can be used) and cooled to −78°. Methyl 2-butynoate (1 equiv) was then added, and the mixture was stirred at 78° for 1 hr and worked up by first the slow addition of methanol (−78°) and then pouring into saturated ammonium chloride. The mixture was filtered, and the organic material in the filtrate was separated and washed with water and brine. Evaporation of the solvent gave 4.5 g of crude product which was best purified by column chromatography (silica gel, 3% ether–hexane) giving a mixture of the four possible double-bond isomers of methyl 3,7-dimethyldeca-2,6-dienote (2.4 g); the trans α,β-unsaturated isomers (XI and XII) predominated (85%). The main two peaks (XI and XII) overlapped on vpc; these were collected together. Nmr indicated the presence of the trans 6,7 double bond compound XI (73%) and the cis 6,7 isomer XII (27%). Repetitive vpc runs made separation of XI and XII possible. XI had ir λ_{max}^{neat} 1720, 1646 cm^{-1}; nmr δ 0.85 (t, 3 H, CH_3CH_2), 1.37 (m, 2 H, CH_3CH_2), 1.59 [s, 3 H, $C_3H_7(CH_3)$=C], 1.95 (t, 2 H, $CH_3CH_2CH_2C$=C), 2.16 [m, 7 H, $CHCH_2CH_2(CH_3)C$=C], 3.67 (s, 3 H, $COOCH_3$), 5.08 [m, 1 H, C_3H_7 $(CH_3)C$=CH], 5.66 (broad s, 1 H, CH-$COOCH_3$); M^+ 210. The chemical shift of the C-7 methyl group allows the assignment of the 6,7 double bond stereochemistry.[24]

The deuterium-labeled methyl dienoates XIa and XIIa were prepared in an analogous manner starting with cyclopropyl d_3-methyl ketone.

Methyl *trans,trans* 8,8-d_2-3,7-Dimethyldeca-2,6-dienoate (XIb) and Methyl *trans,cis*-8,8-d_2-3,7-Dimethyldeca-2,6-dienoate (XIIb).—To ethyltriphenylphosphonium bromide (1.1 g, 3.22 mmol) in 50 ml of ether (distilled from lithium aluminum hydride) under argon was added butyllithium (1 equiv, 1.6 *M* in hexane). After 2 hr at 25°, 1,1-d_2-1-bromopropane[25] (1.3 equiv) was added. The red phosphorane reacted slowly, but after 2 days at reflux the solution was essentially clear with a white precipitate of the labeled secondary phosphonium salt present. Addition of butyllithium (1 equiv) generated the corresponding dark red ylide, to which was added the aldehydo ester XVI (1 equiv); an immediate white precipitate formed. The mixture was stirred overnight (25°), hexane was added, and this mixture was filtered and finally extracted with water and brine and dried over magnesium sulfate. Evaporation of the solvent and bulb-to-bulb distillation gave a mixture (~1:1) of the deuterium-labeled methyl dienoates XIb and XIIb (350 mg). These were separated by preparative vpc: XIb M^+ 212 (99% d_2), 211 (1% d_1); XIIb M^+ 212 (99% d_2), 211 (1% d_1).

In a similar manner, starting with (2,2,2-d_3-ethyl)triphenylphosphonium bromide,[26] methyl 8,8,8′,8′,8′-d_5-3,7-dimethyldeca-2,6-dienoate (XIc) was prepared. This material, after preparative vpc, was submitted for mass spectral analysis as a mixture of the trans,cis and trans,trans isomers, M^+ 215 (98% d_5), 214 (2% d_4).

Methyl *trans,trans*-7-Ethyl-3-methylundeca-2,6-dienoate (IX) and Methyl *trans,cis*-7-Ethyl-3-methylundeca-2,6-dienoate (X).—These compounds were prepared by procedures analogous to those employed to make the methyl dienoates XI and XII. The starting material, cyclopropyl butyl ketone, was prepared by the addition of butyllithium to the lithium salt of cyclopropanecarboxycyclic acid in glyme.[28] Treatment of cyclopropyl butyl ketone in glyme with deuterium oxide and potassium carbonate at reflux (three successive times) gave cyclopropyl α,α-d_2-butyl ketone. This labeled ketone was the precursor of methyl *trans,trans*-8,8-d_2-7-ethyl-3-methylundeca-2,6-dienoate (IXb) and methyl *trans,cis*-8,8-d_2-7-ethyl-3-methylundeca-2,6-dienoate (Xb): XVIb M^+ 240 (99% d_2), 239 (1% d_1); Xb M^+ 240 (99% d_2), 239 (1% d_1).

In order to unequivocally assign the 6,7 double bond stereochemistry of the dienoates IX and X, the trans,trans isomer IX was synthesized stereoselectively.[29] Propyl bromide (0.4 ml, 10% excess) was added to lithium wire (58 mg) in 5 ml of dry ether (argon) at −10° until the lithium disappeared (about 2 hr). After further cooling to −25°, cuprous iodide (2 mmol) was added, giving a black solution of dipropylcopper lithium. The acetate ester of methyl *trans*-6-hydroxy-7-ethyl-3-methylocta-2,7-dienoate[30] (0.5 mmol) was next added, giving (after work-up in the usual fashion with saturated ammonium chloride) in 90% yield the trans,trans dienoate (less than 10% of the trans,cis isomer was present).

Methyl *trans,trans*-8′,8′-d_2-7-Ethyl-3-methylundeca-2,6-dienoate (IXa) and Methyl *trans,cis*-8′,8′-d_2-7-Ethyl-3-methylundeca-2,6-dienoate (Xa).—The deuterium-labeled methyl dienoates IXa and Xa were prepared following an analogous method to that used for the methyl dienoates XI and XIIb. The phosphorane derived from *n*-pentyltriphenylphosphonium bromide (butyllithium) was alkylated with 1,1-d_2-1-iodoethane (12 hr, 25°); another equivalent of butyllithium was added and finally the aldehydo ester XVI. Work-up followed as usual and the isomers IXa and Xa were separated by repetitive vpc: IXa M^+ 240 (98% d_2), 239 (2% d_1); Xa M^+ 240 (98% d_2), 239 (2% d_1).

Methyl *trans,trans*-Farnesoate (XIII).—6-Methylhept-5-en-2-one was added to a solution of vinylmagnesium bromide[31] (10% excess) in tetrahydrofuran to give 3-hydroxy-3,7-dimethylocta-1,6-diene (XXIII). The alcohol XXIII was heated (200°) overnight with a 1.5-fold excess of methyl acetoacetate according to the conditions of Carroll.[32] Distillation gave in 60% yield 6,10-dimethylundeca-5,9-dien-2-one (XXIV).

Sodium hydride (497 mg of 55% dispersion, 11.1 mmol) was washed with pentane under argon; dimethylformamide (4 ml) was added and then trimethyl phosphonoacetate (1.88 g, 10.3 mmol). This mixture was stirred for 1 hr and the ketone XXIV (2.0 g, 10.3 mmol) was added in 3 ml of dimethylformamide. After stirring for 6 hr, the mixture was poured into 90% brine, the aqueous layer was extracted with ether, and the organic material was combined, washed with water and brine, and dried. Distillation (bulb-to-bulb, 1 Torr) gave methyl farnesoate as a mixture of four isomers. Methyl *trans,trans*-farnesoate (XIII) was purified by preparative vpc: nmr δ 1.57 (s, 6 H, CH_3C=C), 1.65 (s, 3 H, CH_3C=C), 1.96 [s, 4 H, $CHCH_2CH_2(CH_3)C$=C], 2.12 [m, 7 H, $CH_2CH_2(CH_3)C$=CHCO], 3.59 (s, 3 H, $COOCH_3$), 5.02 (broad s, 2 H, C=CH), 5.55 (s, 1 H, C=CH$COOCH_3$); M^+ 250.

In a similar manner, using 1,1,3,3-d_5-6-methylhept-5-en-2-one as a starting material, methyl 8,8,8′,8′,8′-d_5-*trans,trans*-farnesoate (XIIIb) was prepared, M^+ 255 (95% d_5), 254 (5% d_4).

Methyl 8,8,8′,8′,8′-d_5-10,11-Epoxy-*trans,trans*-farnesoate (V).—Methyl *trans,trans*-farnesoate (66.3 mg, 0.26 mmol, purified by vpc) was dissolved in tetrahydrofuran (5 ml), and water (~3 ml) was added until the solution was cloudy; tetrahydrofuran was again added dropwise until the solution was clear. *N*-Bromosuccinimide (49.2 mg, 5% excess) was added and the mixture was stirred (argon) for 2.5 hr. Solid sodium chloride and ether were added, and the organic material was separated, washed with water and brine, and dried. Purification by tlc (40% ether–hexane) gave 54 mg (58%) of the corresponding terminal bromohydrin. The bromohydrin (54 mg) was dissolved in anhydrous methanol (5 ml) and anhydrous potassium carbonate (83 mg, fourfold excess) was added. After stirring (argon) for 1 hr, ether, water, and hexane were added, and the organic material was separated, washed with water and brine, and dried. Purification by tlc gave the deuterium-labeled methyl epoxy farnesoate V (37 mg) as a clear oil: one peak by vpc (4 ft, 3% w/w PDEAG 100/120 CHSBW-AW-DMCS, glass, 160°); nmr δ 1.18 (s, 3 H, epoxy CH_3), 1.21 (s, 3 H, epoxy CH_3), 1.51 (d, 2 H, epoxy CH_2), 2.14 [m, 7 H, $CHCH_2CH_2(CH_3)C$=CH], 2.47 (t, 1 H, epoxy H), 3.59 (s, 3 H, $COOCH_3$), 5.12 (m, 1 H, C=CH), 5.58 (broad s, 1 H, $CHCOOCH_3$); M^+ 227 (>95% d_5).

Methyl 5,5-d_2-10,11-Epoxy-*trans,trans*-farnesoate (VI).—*trans*-1,1-d_2-3,7-Dimethylocta-2,6-dien-1-ol (XXV) was prepared by aluminum deuteride reduction of methyl *trans*-geranate. The d_2 alcohol XXV was converted to its bromide (phosphorus tribromide) and used to alkylate the sodium enolate of methyl acetoacetate in tetrahydrofuran. Decarbomethoxylation was effected by treatment with barium hydroxide to give *trans*-4,4-d_2-

(24) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

(25) Prepared from propionic acid by lithium aluminum deuteride reduction and conversion of the resulting alcohol to its bromide using 48% hydrobromic acid and sulfuric acid.

(26) Prepared by treating 2,2,2-d_3-ethyl bromide[27] with triphenylphosphine.

(27) R. Liedtke and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6814 (1969).

(28) T. M. Bare and H. O. House, *Org. Syn.*, **49**, 81 (1969).

(29) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970).

(30) Prepared by the addition of the vinyl Grignard reagent derived from 2-bromobut-1-ene to the aldehydo ester XVI at −78° and treatment of the resulting allylic alcohol with acetic anhydride in pyridine.

(31) H. L. Normant, *Bull. Soc. Chim. Fr.*, 728 (1957).

(32) (a) M. F. Carroll, *J. Chem. Soc.*, 507 (1941); (b) W. Hoffman, H. Pasedach, and H. Pommer, *Justus Liebigs Ann. Chem.*, **729**, 52 (1969).

6,10-dimethyldeca-5,9-dien-2-one. This ketone was converted to the labeled methyl farnesoate XIIIa as described above for XIIIb and then to the terminal epoxy farnesoate VI also as described above for V. VI had nmr δ 1.18 (s, 3 H, epoxy CH_3), 1.21 (s, 3 H, epoxy CH_3), 1.51 (m, 2 H, epoxy CH_2), 1.61 (d, 3 H, $CH_3C{=}C$), 2.14 [m, 7 H, $CH_2C{=}CHCD_2CH_2(CH_3)C{=}C$], 2.47 (t, 1 H, epoxy H), 3.59 (s, 3 H, $COOCH_3$), 5.12 (broad s, 1 H, C=CH), 5.58 (m, 1 H, $CHCOOCH_3$); M^+ 268 (>98% d_2).

Methyl *12,12,12,12',12',12'*-d_6-10,11-Epoxy-*trans,trans*-farnesoate (IV).—d_6-Acetone was reduced with lithium aluminum hydride and the resulting alcohol was converted to *1,1,1,3,3,3*-d_6-2-bromopropane according to the conditions of Wiley.[33] The bromide was mixed with an equimolar amount of triphenylphosphine and heated at 130° for 2 days to give (*1,1,1,3,3,3*-d_6-isopropropyl)triphenylphosphonium bromide (XXVI) in 30% yield. Methyl 10,11-epoxy-*trans,trans*-farnesoate[34] was converted to methyl *trans,trans*-3,7-dimethyl-9-oxonona-3,6-dienoate (XX) as described above for XVI. The aldehydo ester XX (0.5 g) was added to the dark red ylide (1 equiv), derived from the phosphonium salt XXVI in ether, and the mixture was stirred at reflux overnight. Work-up in the usual manner and bulb-to-bulb distillation (0.5 Torr) gave the d_6-labeled methyl farnesoate. After purification by preparative vpc, this *trans,trans*-farnesoate was converted to the 10,11-epoxy compound IV (as described above for V): nmr same as for VI except for absence of the methyl singlets at δ 1.18 and 1.21, and the presence of nine allylic protons at δ 2.14; M^+ 272 (91% d_6), 271 (9% d_5).

(33) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chang, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(34) A generous sample was provided by Dr. Clive Henrick, Zoecon Corp.

Registry No.—III, 5299-11-6; IV, 34603-22-0; V, 34635-39-7; VI, 34603-23-1; IXa, 34603-24-2; IXb, 34603-32-2; Xa, 34603-25-3; Xb, 34603-24-2; XI, 34603-26-4; XIb, 34603-27-5; XII, 34603-28-6; XIIb, 34635-40-0; XIII, 3675-00-1; XIIIb, 34603-30-0; XVI, 24603-31-1.

Acknowledgment.—We wish to thank Drs. John Siddall, John Diekman, Clive Henrick, and Loren Dunham of the Zoecon Corporation, not only for helpful discussion but for providing details of several synthetic procedures as well as several very valuable synthetic intermediates.

Stereospecific Synthesis of (20*S*,22*R*)-17α,20,22-Trihydroxycholesterol and (20*S*,22*S*)-17α,20,22-Trihydroxycholesterol[1]

R. C. NICKOLSON[2] AND MARCEL GUT*

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received December 22, 1971

Addition of vinyl Grignard to the known 16α,17α-oxidopregnenolone acetate followed by reduction of the epoxide, conversion of the product to a 3,5-cyclo steroid, and epoxidation of the remaining double bond yields a C-22 epimeric mixture of epoxides which, when condensed with *sec*-butyllithium and reconverted to the 3β-hydroxy-Δ^5-sterols, yield the title compounds.

Interest in the preparation of compounds which are postulated intermediates in the catabolism of cholesterol to C_{21} and C_{19} hormones has led numerous investigators to synthesize cholesterol derivatives possessing hydroxyl groups at C-17, C-20, and C-22. Specifically, the syntheses of (22*R*)-22-hydroxycholesterol and its C-22 epimer,[3-5] 20α-hydroxycholesterol,[6] 20β-hydroxycholesterol,[7] and (20*R*,22*R*)- and (20*R*,22*S*)-20,22-dihydroxycholesterol[8,9] have been described previously.

In recent years, the suggestion that cholesterol can be enzymatically cleaved between C-17 and C-20 to yield dehydroepiandrosterone[10-12] has prompted the synthesis of side-chain hydroxylated cholesterols which could serve as substrates for this transformation. Compounds of importance in this series include 17α,-20α-dihydroxycholesterol, its C-20 epimer,[13] and 17α-hydroxycholesterol.[14] We now describe the synthesis of (20*S*,22*R*)-17α,20,22-trihydroxycholesterol (**21**) and (20*S*,22*S*)-17α,20,22-trihydroxycholesterol (**23**), sterols which could conceivably undergo desmolytic cleavage between C-20 and C-22 to yield 17α-hydroxypregnenolone. Alternatively, oxidative cleavage between C-17 and C-20 could occur to yield dehydroepiandrosterone, as suggested for a direct biosynthetic pathway from cholesterol to the C_{19} hormones.[10]

The stereospecific introduction of hydroxyl groups at C-17, C-20, and C-22 of the cholesterol side chain presents a problem of some complexity. Of immediate interest was the preparation of a 17,20-glycol possessing a two-carbon, unsaturated side chain which, after epoxidation, can be treated with a suitable alkyllithium to produce the desired 17,20,22-hydroxylation pattern (see Scheme I). The preparation of 17α,20-dihydroxysterols can be easily accomplished by the addition of Grignard reagents to 17α-hydroxypregnenolone acetate **29**. However, this method of preparation is unsuitable for our purposes, as the only alcohol obtained has been

(1) This work was supported by the U. S. Public Health Service Grant AM-03419 from the Institute of Arthritis and Metabolic Diseases and a contract from the Atomic Energy Commission AT(30-1)918.

(2) Taken in part from a dissertation by R. C. Nickolson in partial fulfillment of the requirements for the Ph.D. degree in organic chemistry, Clark University, Worcester, Mass. 01610.

(3) K. Tsuda and R. Hayatsu, *Chem. Pharm. Bull.*, **6**, 680 (1958).

(4) K. Tsuda and R. Hayatsu, *J. Amer. Chem. Soc.*, **81**, 5987 (1959).

(5) H. Mori, K. Shibata, K. Tsuneda, M. Sawai, and K. Tsuda, *Chem. Pharm. Bull.*, **16**, 1407 (1968); E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, **34**, 103 (1969).

(6) V. Petrow and I. A. Stewart-Webb, *J. Chem. Soc.*, **46**, 75 (1956).

(7) A. Mijares, P. I. Cargill, J. A. Glasel, and S. Lieberman, *J. Org. Chem.*, **32**, 810 (1967).

(8) K. Shimizu, M. Gut, and R. I. Dorfman, *J. Biol. Chem.*, **237**, 699 (1962).

(9) N. K. Chaudhuri, R. Nickolson, H. Kimball, and M. Gut, *Steroids*, **15**, 525 (1970).

(10) R. A. Jungmann, *Biochim. Biophys. Acta*, **164**, 110 (1968).

(11) S. Burstein, H. Zamoscianyk, N. Co, M. Adelson, D. S. M. Prasad, A. Greenberg, and M. Gut, *ibid.*, **231**, 223 (1971).

(12) R. B. Hochberg, H. Mickan, and S. Lieberman, *ibid.*, **231**, 208 (1971).

(13) N. K. Chaudhuri, J. G. Williams, R. C. Nickolson, and M. Gut, *J. Org. Chem.*, **34**, 3759 (1969); for information concerning the metabolism of these 17,20-dihydroxycholesterols see S. Burstein, H. L. Kimball, N. K. Chaudhuri, and M. Gut, *J. Biol. Chem.*, **243**, 4417 (1968).

(14) N. K. Chaudhuri, R. C. Nickolson, and M. Gut, *Steroids*, **16**, 495 (1970).