Stereoselective Synthesis of the Racemic C-17 Juvenile Hormone of Cecropia[1]

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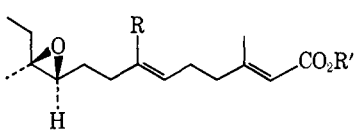
Abstract: The stereoselective synthesis of methyl 3,7,11-trimethyl-10,11-*cis*-epoxy-2-*trans*,6-*trans*-tridecadienoate (**1**), the C-17 juvenile hormone of *Hyalophora cecropia*, is described starting from *trans*-methyl farnesoate. The facile thermal rearrangement of the epoxide **8** to the allylic alcohol **26** allowed a simple stereoselective preparation of the all trans isomer **23**. The homologation of **1** to the C-18 juvenile hormone **2** was carried out *via* alkylation of the allylic esters **34** and **35** with lithium dimethylcuprate.

The natural juvenile hormones of *Hyalophora cecropia*, which are produced and secreted by the corpora allata and are responsible for the persistence of larval characteristics during larval molting, have been identified as **1** and **2**.[3] The synthesis of **2** is described in the accompanying paper[4] and we now wish to present the full details, together with related work, for our synthesis[5] of the minor juvenile hormone **1** which accounts for *ca.* 20% of the endocrine activity of the crude Cecropia extracts.



	R	R'
1	Me	Me
2	Et	Me
3	Me	Et

The synthesis of the C-17 juvenile hormone **1** presents fewer problems than that of the homolog **2**[4] since there are naturally occurring sesquiterpenes such as *trans*-methyl farnesoate, which can provide starting materials containing both the required trans double bonds. The total synthesis of racemic **1** has also been described recently by another group.[6]

trans,trans-Methyl farnesoate (**5**) was prepared from *trans*-geranylacetone (**4**)[7] by reaction with the anion of trimethyl phosphonoacetate. Of the many conditions investigated for this reaction, the simplest and best procedure utilized sodium methoxide in dimethylformamide.[4] Under these conditions, the reaction was initially homogeneous and proceeded readily to completion at room temperature[8] and this method was applicable to large scale runs. Spinning-band distillation of the isomeric mixture readily gave the all trans isomer **5** in high purity. In a similar manner, the corresponding ethyl ester **6** was prepared using triethyl phosphonoacetate.

Selective terminal electrophilic attack on **5** with *N*-bromosuccinimide[9] in aqueous tetrahydrofuran followed by treatment of the bromohydrin **7** with potassium carbonate in dry methanol gave the monoepoxide **8** in 82% yield after careful distillation. This epoxide has been prepared previously by peracid epoxidation of **5** followed by thin layer chromatography[10] and also from **5** by a similar procedure to that described above.[11] Hydration of **8** to the diol **10** and cleavage with sodium metaperiodate gave the aldehyde **11**. By the same route, the corresponding ethyl ester **12** was also prepared.

Reaction of **11** with the ylide **13**, prepared from α-methoxypropyltriphenylphosphonium chloride[12] with *n*-butyllithium at −78° in tetrahydrofuran, gave the enol ethers **14** (mixture of isomers at C-10) which on chlorination with *N*-chlorosuccinimide in buffered aqueous acetone gave the chloro ketone **17** (60% yield from **11**). This was shown to be identical with an authentic sample.[6] The corresponding ethyl ester **18** was also prepared using the ylide **13** and brief treatment of the intermediate enol ether **15** with acid gave the ketone **16**. Transesterification of **15** to **14** could be carried out by heating with dilute sodium methoxide in methanol.

Alkylation of the chloro ketone **17** with methylmagnesium chloride in tetrahydrofuran[13] at −75° gave a mixture of the threo (**19**) and erythro (**20**) chlorohydrins in the ratio of 82:18. A similar result was obtained with the ethyl ester **18**. Thus, as in the case of our synthesis[4] of the homolog **2**, we were unable to reproduce the previously reported[6] high selectivity (*ca.* 95%) in this alkylation reaction. At −95°[14] the

(1) Contribution No. 7 from the Research Laboratory of Zoecon Corp.

(2) Zoecon postdoctoral fellow, 1968–1969.

(3) H. Röller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967); A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, **60**, 853 (1968); B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970).

(4) See accompanying paper, C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Amer. Chem. Soc.*, **94**, 5374 (1972).

(5) J. B. Siddall, "Chemical Ecology," E. Sondheimer and J. B. Simeone, Ed., Academic Press, New York, N. Y., 1970, Chapter 11, p 288.

(6) W. S. Johnson, S. F. Campbell, A. Krishnakumaran, and A. S. Meyer, *Proc. Nat. Acad. Sci. U. S.*, **62**, 1005 (1969).

(7) *trans*-Geranylacetone was supplied by Roche Chemical Division, Hoffmann-LaRoche, Nutley, N. J.

(8) In solvents such as tetrahydrofuran or benzene the reaction with trimethyl phosphonoacetate is heterogeneous and very slow and does not go to completion; *cf.* J. A. Findlay, W. D. MacKay, and W. S. Bowers, *J. Chem. Soc. C*, 2631 (1970).

(9) E. E. van Tamelen and T. J. Curphey, *Tetrahedron Lett.*, 121 (1962); E. E. van Tamelen and K. B. Sharpless, *ibid.*, 2655 (1967); E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

(10) W. S. Bowers, M. J. Thompson, and E. C. Uebel, *Life Sci.*, **4**, 2323 (1965).

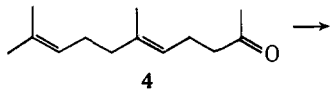
(11) E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966).

(12) *Cf.* D. R. Coulson, *Tetrahedron Lett.*, 3323 (1964).

(13) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959); J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *ibid.*, 2539 (1959).

(14) *Cf.* S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968); W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olson, *ibid.*, **90**, 5277 (1968).

Scheme I



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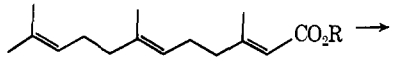
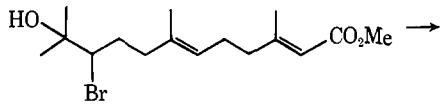


5, R = Me
6, R = Et



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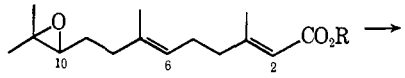
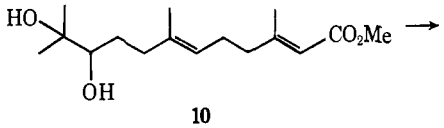


8, R = Me
9, R = Et



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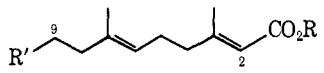
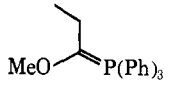


	R′	R
11	CHO	Me
12	CHO	Et
14	EtC(OMe)=CH–	Me
15	EtC(OMe)=CH–	Et
16	EtC(O)—CH_2 –	Et



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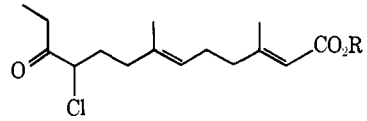
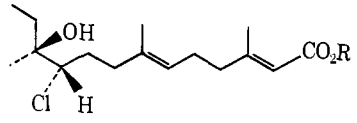
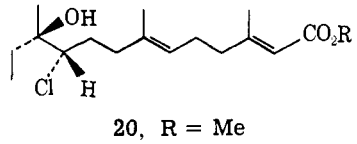


17, R = Me
18, R = Et



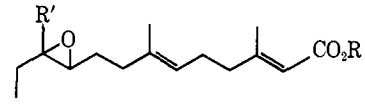
19, R = Me
21, R = Et



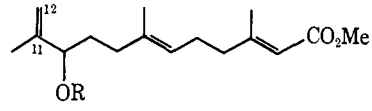
20, R = Me
22, R = Et

reaction was slower but the resulting chlorohydrin mixture still contained *ca.* 14% of the erythro isomer **20**.[4] On a small scale these mixtures of chlorohydrins were separated by preparative thin layer chromatography and brief treatment of each of the pure chlorohydrins with potassium carbonate produced the pure methyl esters **1** and **23**, and the ethyl esters **3** and **24**.

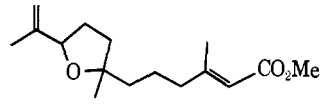
On a larger scale the mixture of chlorohydrins from **17** was converted directly with base to a mixture of the desired hormone **1** and *ca.* 18% of the trans isomer **23**. Alkylation of **17** with ethylmagnesium chloride in tetrahydrofuran at −78°, followed by base treatment, gave the homolog **25**.



	R′	R
23	Me	Me
24	Me	Et
25	Et	Me



26, R = H
27, R = Ac



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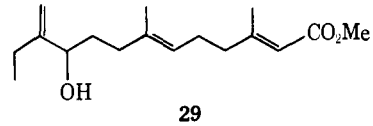

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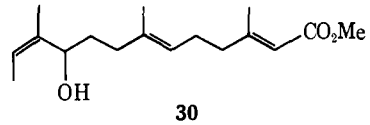

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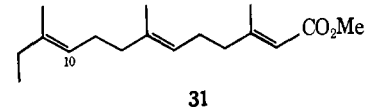

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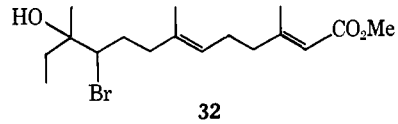

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During this work a facile rearrangement of the epoxide **8** was noticed. Thus it was found that although the epoxide was stable to rapid distillation over a little anhydrous potassium carbonate at less than 125° (0.08 mm), heating **8** in Pyrex glass at about 150–165° (with or without vacuum) caused a smooth rearrangement to the allylic alcohol **26**, which was obtained in quantitative yield. There are many examples, using various reagents,[15] of ring opening of epoxides *via*

(15) (a) Active alumina: E. W. Warnhoff, *Can. J. Chem.*, **42**, 1664 (1964); I. C. Nigam and L. Levi, *ibid.*, **46**, 1944 (1968); V. S. Joshi, N. P. Damodaran, and S. Dev, *Tetrahedron*, **24**, 5817 (1968); P. J. Dunphy, *Chem. Ind. (London)*, 1112 (1970); (b) active silica gel: V. S. Joshi, N. P. Damodaran, and S. Dev, *Tetrahedron*, **27**, 475 (1971); (c) alkyl lithiums: R. Letsinger, J. G. Traynham, and E. Bobko, *J. Amer. Chem. Soc.*, **74**, 399 (1952); (d) aluminum isopropoxide: E. H. Eschinasi, *Israel J. Chem.*, **6**, 713 (1968); E. H. Eschinasi, *J. Org. Chem.*, **35**, 1598 (1970); (e) trilithium phosphate: British Patent 877,139 (1961); (f) diisobutylaluminum hydride: W. Kirchhof, *Chem. Ber.*,

β elimination to give a mixture of allylic alcohols, but this rearrangement proceeds without any added basic or acidic material. In fact, on a small scale (*ca.* 500 mg) addition of anhydrous potassium carbonate completely inhibits the rearrangement. Heating **8** with silica gel produced some rearrangement to **26** but several other unidentified by-products were also produced. Rearrangement of **8** with Woelm neutral alumina (activity I)[15a] in hexane at room temperature gave **26** along with several other minor by-products. Further heating of **26** at up to 180° gave the tetrahydrofuran derivative **28**. Thermal rearrangement of the all trans homolog **23** gave a mixture of the allylic alcohols **29** and **30** in the ratio 0.8:1.

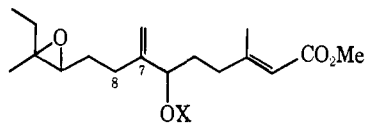
This one-step conversion of epoxide to allylic alcohol under relatively mild conditions enabled us to synthesize stereoselectively the all trans isomer **23**. Thus, acetylation of **26** to **27** followed by alkylation[16] of the allylic acetate with lithium dimethylcuprate in ether stereoselectively gave the all trans triene ester **31** in 90% yield containing only 5% of the cis-10 isomer. The triene was treated with *N*-bromosuccinimide[9] and the resulting bromohydrin **32** converted to **23** (60% overall yield from **31**) with potassium carbonate in methanol. In an attempt to alter the stereoselectivity of the organocuprate alkylation of allylic esters,[16] a study was made of the effect of different ester leaving groups. The results in ether for various esters of **26** are summarized in Table I. With this substrate there

Table I. Alkylation of Esters of **26** with Lithium Dimethylcuprate in Diethyl Ether[a]

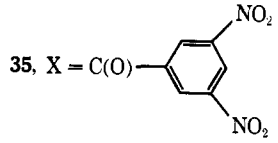
Ester of **26**	Product: Cis	Product: Trans (**31**)	Product: Direct displacement[b]	Cis/trans ratio
3,5-Dinitrobenzoate	30	56	14	0.54
2,4-Dinitrobenzoate	27	60	13	0.45
3,4,5-Trimethoxybenzoate	4	94	2	0.04
2,4,6-Trimethylbenzoate (mesitoate)	2	97	1	0.02
Benzoate	2	96	2	0.02
Trifluoroacetate	27	61	12	0.44
Acetate (**27**)	5	93	2	0.05
Trimethylacetate (pivaloate)	2	97	1	0.02

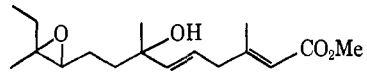
[a] −10° for 0.5 hr. [b] Reference 16.

appears to be a correlation between the acidity of the conjugate acid of the leaving carboxylate group and the stereoselectivity of the alkylation. Several of the ester leaving groups were more stereoselective (*ca.* 97%) for the formation of trans olefin **31** than the acetate used above. A further study into the effects of solvent and temperature was carried out using the 3,5-dinitrobenzoate, which was the least stereoselective leaving group in Table I. It was found that in tetrahydrofuran containing 10% ether as the solvent, the alkylation became selective for the cis olefin (cis:trans ratio was 1.65:1) but the proportion of the product resulting from direct displacement of the ester also increased.[16]



33, X = H
34, X = Ac





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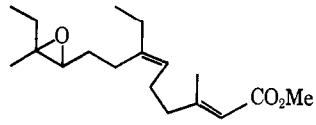

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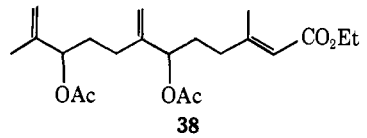

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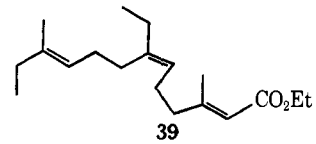

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It was hoped that these results would be applicable to the substrate **33** to enable maximal formation of the central trans olefin by organocuprate alkylation and thus to provide a method for converting the C-17 juvenile hormone into the C-18 hormone **2**. The esters **34** and **35** were prepared from **1** by hematoporphyrin photosensitized oxygenation in methanol, *in situ* reduction with hexamethylphosphorous triamide,[4] preparative thin layer chromatographic separation of **33** (40% overall yield from **1**) from the isomer **36**, and esterification of the former. It is noteworthy that no in-chain 7–8 olefin isomer of **33** could be detected in the product.[4] However, alkylation of the allylic acetate **34** in ether or of the 3,5-dinitrobenzoate **35** in ether–tetrahydrofuran with lithium dimethylcuprate gave essentially identical ratios of the Δ^6 cis and trans isomers of juvenile hormone **37** and **2** (ratio 70:30, respectively), which are separable by glpc. Alkylation of the acetate **34** in ether–tetrahydrofuran or in tetrahydrofuran gave a mixture of **37** and **2** in the ratio of *ca.* 1:1, along with about 10% of direct displacement. Therefore, with the substrate **33**, the effects of the solvent or of the leaving group appear to be less important than with **26**, presumably due to the influence of the terminal epoxide function. The homologation of **1** to **2**, nevertheless, represents the first reported interconversion of the two naturally occurring Cecropia juvenile hormones and provides a route for the introduction of a radioactive label in the C-7 ethyl group of **2**.

93, 2712 (1960); (*g*) *N*-lithiodiethylamide: J. K. Crandall and L.-H. Chang, *J. Org. Chem.*, **32**, 435 (1967); B. Richborn and R. P. Thummel, *ibid.*, **34**, 3583 (1969), and references therein.

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

It is interesting to compare **34** with the substrate **38** which was prepared from **6** in 23% yield, by "one-flask" photosensitized oxygenation in pyridine, *in situ* reduction of the hydroperoxides with trimethyl phosphite, and selective acetylation of the secondary allylic alcohols followed by silica gel chromatography. Methylation[16] of **38** with lithium dimethylcuprate in ether gave ethyl 3,11-dimethyl-7-ethyltrideca-2,6,10-trienoate in quantitative yield as a mixture of the all trans (14%), trans,cis,cis (8%) and trans,cis,trans **39** (76%) isomers.[17] Methylation of **38** in tetrahydrofuran again gave a mixture of isomers but it now also contained the trans,trans,cis isomer as well as products from direct displacement of the ester.

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 Varian HA-100 or T-60 spectrometers, and unless otherwise stated, carbon tetarchloride was employed as the solvent, with tetramethylsilane as internal standard. Chemical shifts are reported as δ values in ppm. Infrared spectra were measured either on a Perkin-Elmer Model 237 or on a Unicam SP 200G spectrophotometer. Mass spectra, unless otherwise stated, were measured on an Atlas CH-4 spectrometer, equipped with an E-4B ion source, at 70-eV ionization potential. Vapor-phase chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors.

Methyl 2-*trans*,6-*trans*-Farnesoate (5). To a suspension of 56.2 g (1.041 mol) of sodium methoxide in 500 ml of dimethylformamide under N_2 atmosphere was added 204 g (1.120 mol) of trimethyl phosphonoacetate over 1 hr with stirring and cooling in cold water to maintain the internal temperature at 25–30°. *trans*-Geranylacetone[7] (208 g, 1.071 mol) was then added over 30 min with some cooling and the mixture was stirred for 18 hr at room temperature. The mixture was poured into brine and the product (259 g) was isolated with ether. Glpc analysis showed the presence of 6% starting geranylacetone, 64% methyl 2-*trans*-farnesoate, and 28% methyl 2-*cis*-farnesoate. Distillation *in vacuo* using a stainless-steel spinning-band column gave pure methyl 2-*trans*,6-*trans*-farnesoate (**5**) (130 g): bp 70° (0.02 mm); nmr ($CDCl_3$) δ 1.63 (s, 6, C-7 CH_3 and C-11 CH_3), 1.70 (s, 3, C-11 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.70 (s, 3, CO_2CH_3), 5.13 (m, 2, H-6 and H-10), and 5.73 ppm (m, 1, H-2).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.62; H, 10.35.

The above procedure was found to be the most convenient for the preparation of large quantities of **5**. In a similar way ethyl 2-*trans*-6-*trans*-farnesoate (**6**)[18] was prepared from triethyl phosphonoacetate: bp 97–99° (0.08 mm); nmr ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_2CH_2), 1.63 (s, 6, C-7 and C-11 CH_3), 1.70 (s, 3, C-11 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.15 (m, 2, H-6 and H-10), and 5.73 ppm (m, 1, H-2).

Methyl 10,11-Epoxy-2-*trans*,6-*trans*-farnesoate (8). To a solution of methyl 2-*trans*,6-*trans*-farnesoate (**5**) (165.6 g, 0.662 mol) in 2400 ml of tetrahydrofuran was added 800 ml of water; the solution was cooled to 0° in an ice bath and stirred during the portionwise addition of 129 g (1.095 equiv) of *N*-bromosuccinimide over 30 min. After a further 3.5 hr stirring at 0° the solution was concentrated under reduced pressure, brine was added, and the mixture was extracted several times with ether. The combined ethereal extracts were washed with sodium bicarbonate solution and brine and dried over magnesium sulfate, and the solvent was evaporated to afford 251 g of crude bromohydrin **7**. To a solution of this crude bromohydrin in 3 l. of dry methanol was added 400 g (4 equiv) of anhydrous potassium carbonate under an atmosphere of nitrogen. The mixture was stirred vigorously for 30 min at room temperature; the solid was filtered off under suction and washed with methanol. The combined filtrates were concentrated *in vacuo*, poured into brine, and extracted several times with an ether–hexane mixture to afford 177 g of crude epoxide. Rapid distillation *in vacuo* over a little anhydrous K_2CO_3 gave the epoxide **8**[10,11] (144 g, 81.8% yield): bp 125–126° (0.08 mm); ir (film) 1720, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.27 and 1.32 (s, 2 × 3, C-11 CH_3), 1.65 (s, 3, C-7 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.74 (t, 1, J = 6 Hz, 10-H), 3.72 (s, 3, CO_2CH_3), 5.22 (m, 1, 6-H), and 5.75 ppm (m, 1, 2-H);

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.06; H, 9.79.

In a similar manner, ethyl farnesoate (**6**) was converted to the epoxide **9**: bp 127° (0.10 mm); nmr ($CDCl_3$) δ 1.27 and 1.32 (s, 2 × 3, C-11 CH_3), 1.27 (t, 3, J = 7 Hz, CH_3CH_2), 1.63 (broad s, 3, C-7 CH_3), 2.15 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.70 (t, 1, J = 6 Hz, 10-H), 4.17 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.20 (m, 1, 6-H), and 5.70 ppm (m, 1, 2-H).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.67; H, 10.05.

Methyl 10,11-Dihydroxy-3,7,11-trimethyl-2-*trans*,6-*trans*-dodecadienoate (10). A 66-g sample of epoxide **8** in 550 ml of tetrahydrofuran and 290 ml of water was stirred while 20 ml of 8% perchloric acid was added. After 5 hr brine was added and the mixture extracted several times with ether. The organic phase was washed with dilute sodium bicarbonate and brine, dried (Na_2SO_4), and evaporated to give crude diol (73 g) which was purified by column chromatography on silica gel (420 g, activity III). Elution with ether gave 55 g (78% yield) of pure diol **10**: bp (bath-short path) 85° (0.03 mm); ir (film) 3420, 1720, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.17 and 1.20 (s, 2 × 3, C-11 CH_3), 1.63 (broad s, 3, C-7 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.33 (m, 1, H-10), 3.70 (s, 3, CO_2CH_3), 5.20 (m, 1, H-6), and 5.70 ppm (m, 1, 2-H).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.49; H, 9.73.

Methyl 3,7-Dimethyl-10-oxo-2-*trans*,6-*trans*-decadienoate (11). To a solution of 35 g (0.123 mol) of the diol **10** in 300 ml of tetrahydrofuran was added a solution of 35 g of sodium metaperiodate in 400 ml of water under a nitrogen atmosphere. After stirring for 24 hr at room temperature, brine was added and the mixture was extracted twice with ether. The combined ether extracts were washed with dilute sodium bicarbonate and brine, dried (Na_2SO_4), and evaporated to afford the aldehyde **11**[11] as an oil (23.4 g, 85% yield) (glpc 98% purity); bp (bath) 45° (0.01 mm); ir (film) 2720, 1720, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.63 (broad s, 3, C-7 CH_3), 2.15 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.42 (m, CH_2CHO), 3.70 (s, 3, CO_2CH_3), 5.17 (m, 1, 6-H), 5.68 (m, 1, 2-H), and 9.83 ppm (t, 1, J = 2 Hz, 10-H).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.45; H, 9.17.

The aldehyde is best stored at −10° under argon.

Similarly the epoxide **9** gave the aldehyde **12**: bp (bath) 115° (0.06 mm); ir (CCl_4) 1723, 1715, 1655 cm^{-1}; nmr δ 1.24 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.61 (broad s, 3, C-7 CH_3), 2.10 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.83 (m, H-9), 4.08 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.09 (m, 1, H-6), 5.54 (m, 1, H-2), and 9.68 ppm (t, 1, J = 1.5 Hz, H-10); mass spectrum m/e 238 (M^+) (calcd for $C_{14}H_{22}O_3$: 238.)

α-Methoxypropyltriphenylphosphonium Chloride. A 60.0 g (0.229 mol) portion of triphenylphosphine and 25 g (0.231 mol) of freshly distilled α-chloropropyl methyl ether[19] were dissolved in 150 ml of benzene and allowed to stand at room temperature for 40 hr. The crystals (39 g) were then filtered under suction, washed thoroughly with ether, and dried under high vacuum. The salt melted over a wide range (94–102°): nmr ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, CH_2CH_3), 1.88 (m, 2, CH_2CH_3), 3.63 (s, 3, OCH_3), 6.62 (m, 1, CH), and 7.70–7.85 ppm (m, 15). Additional nmr signals for decomposition products were noted (especially the signal for methanol at 3.45 ppm) within minutes, and by measuring the spectrum a second time after 1 hr it was found that about half of the salt had decomposed in the $CDCl_3$ solution. Attempts to recrystallize the crude salt from dichloromethane–ether gave partial or complete conversion to a hydrate, mp 105–107°. A satisfactory C and H analysis could not be obtained. The crude salt is best stored at −10° and used without attempted purification.

Methyl 10-Chloro-11-oxo-3,7-dimethyl-2-*trans*,6-*trans*-tridecadienoate (17). An 86-g (*ca.* 0.23 mol) sample of crude phosphonium salt above under an argon atmosphere was cooled to −78° (Dry Ice–acetone bath) and 500 ml of dry tetrahydrofuran was added. The suspension was stirred while 150 ml (0.239 mol) of a solution of *n*-butyllithium in hexane (1.59 *M*) was added over 1 hr. The orange-red colored solution gave a weak positive Gilman-I test so a further

(17) *Cf.* E. E. van Tamelen and J. P. McCormick, *J. Amer Chem. Soc.*, (1970).

(18) *Cf.* B. G. Kovalev, L. A. Yanovskaya, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1876 (1962).

(19) F. Klages and E. Mühlbauer, *Chem. Ber.*, **92**, 1818 (1959).

5 g of salt was added (total 91 g), whereupon the Gilman test was *negative*.[20] A solution of 23 g (0.103 mol) of the aldehyde **11** dissolved in 50 ml of tetrahydrofuran was added over 10 min; the mixture was stirred 1 hr and then set aside 14 hr at −78°. The cooling bath was then removed and the mixture was allowed to come to 0° over 1.5 hr. Water (50 ml) was added and after a further 1 hr the mixture was poured into brine containing dilute sodium bicarbonate and the product isolated by extraction with ether–hexane in the normal manner. The product was stirred with pentane and the insoluble triphenylphosphine oxide was removed by filtration. Evaporation of the pentane filtrate gave an oily product (58 g). The tlc showed it to contain triphenylphosphine, triphenylphosphine oxide, and a mixture of the expected enol ethers **14** (no **11** remaining).

A solution of 16 g of sodium acetate in 100 ml of water was cooled to 0° in an ice–salt mixture and the crude product above dissolved in 400 ml of acetone was added. To the stirred mixture at 0° was added 30 g (0.226 mol) of *N*-chlorosuccinimide portionwise over 1 hr. After the solution was stirred a further 10 min, a solution of 15 g of sodium bisulfite in water (100 ml) was added, the mixture was diluted with brine and extracted with ether–hexane. The extracts were washed with brine, dried ($CaSO_4$), and evaporated. The residue was stirred with pentane and filtered to remove the insoluble triphenylphosphine oxide. Evaporation of the pentane filtrate gave 39 g of an oil which was purified by column chromatography on silica gel (350 g, activity III–IV) to give 18.5 g (60% yield from **11**) of the chloro ketone **17**: bp (bath, short path) 95° (0.025 mm); glpc showed a major peak 96% with two minor peaks (3.4% and 0.7%); ir (CCl_4) 1720–1716 (C=O) 1648 cm^{-1}; nmr δ 1.06 (t, 3, J = 7 Hz, C-12 CH_2), 1.60 (broad s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.63 (m, 2, H-12), 3.60 (s, 3, CO_2CH_2), 4.03 (m, 1, H-10), 5.11 (m, 1, H-6), and 5.56 ppm (m, 1, H-2).

Anal. Calcd for $C_{16}H_{23}O_3Cl$: C, 63.88; H, 8.38. Found: C, 64.00; H, 8.58.

The chloro ketone **17** was shown to be identical (glpc and tlc) with an authentic sample prepared by a different route by Johnson *et al.*[6] The chloro ketone **17** was shown to be stable (as was *also* ethyl farnesoate (**6**)) to excess *N*-chlorosuccinimide under the above *buffered* conditions, whereas triphenylphosphine was rapidly oxidized under these conditions.

Ethyl 11-Methoxy-3,7-dimethyl-2-*trans*,6-*trans*-10-*cis*(*trans*)-tridecatrienoate (15). A 3.31-g (ca. 8.94 mmol) portion of the crude phosphonium salt, maintained under an atmosphere of dry argon, was cooled to −78° and 35 ml of tetrahydrofuran was added. To the resulting magnetically stirred suspension was added 9 ml (14.4 mmol) of 1.6 *M* *n*-butyllithium in hexane over a period of 5 min. The temperature of the mixture was maintained at −78° and after 10 min a solution of 1.21 g (5.08 mmol) of aldehyde ester **12** in 5 ml of cold tetrahydrofuran was added over 5 min. The reaction mixture was then allowed to warm to room temperature for 2.5 hr, after which half-saturated potassium bicarbonate was added and the mixture was extracted with hexane. The hexane extracts were washed with saturated potassium bicarbonate solution and dried over anhydrous sodium sulfate–potassium carbonate. The residue obtained on evaporation of the solvent at reduced pressure was treated with 10 ml of hexane and the insoluble triphenylphosphine oxide was filtered off. Glpc analysis showed the hexane-soluble material to consist of 70–80% of the mixture of enol ethers, 10% starting material, and unidentified products with longer retention time. The crude mixture was submitted to short-path distillation at 100° (bath temperature, 0.025 mm). Column chromatography on basic alumina resulted in partial hydrolysis and only small amounts of pure enol ether **15** were recovered: nmr ($CDCl_3$) δ 1.03 and 1.01 (2 t, 3, J = 7 Hz, CH_2CH_3, trans and cis, respectively), 1.26 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.61 (s, 3, C-7 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.46 and 3.52 (2 s, 3, OCH_3, trans and cis, respectively), 4.15 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 4.40 (m, 1, H-10), 5.13 (m, H-6), and 5.69 ppm (m, H-2). By comparing the intensities of the methoxyl signals the ratio of 10-trans to 10-cis isomers present was estimated to be 75:25, respectively.

Attempted preparative chromatography on silica gel plates resulted in quantitative hydrolysis to the ketone **16** during the isolation process.

Ethyl 11-Oxo-3,7-dimethyl-2-*trans*,6-*trans*-tridecadienoate (16). A 0.090-g sample of crude enol ether **15** was treated at room temperature with 2% perchloric acid in tetrahydrofuran–water (4:1). After 5 min the reaction mixture was poured into 5% aqueous potassium bicarbonate solution and extracted with ether. The ether extracts were washed with water and saturated brine and dried over sodium sulfate. The residue obtained on removal of the solvent was purified by chromatography on 1-m long preparative thin layer plates in hexane–ethyl acetate (85:15), to yield **16**, 0.050 g: bp (bath) 110° (0.03 mm); ir (CCl_4) 1715 (C=O), 1645 cm^{-1}; nmr δ 0.99 (t, 3, J = 7 Hz, terminal CH_3), 1.24 (t, 3, J = 7.5 Hz, $CO_2CH_2CH_3$), 1.59 (s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 4.07 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 5.05 (m, 1, H-6), and 5.57 ppm (m, 1, H-2); mass spectrum m/e 280 (M^+).

Ethyl 10-Chloro-11-oxo-3,7-dimethyl-2-*trans*,6-*trans*-tridecadienoate (18). A mixture of 0.30 g of the above crude enol ether **15** and 0.080 g of sodium acetate in 5 ml of acetone–water (9:1) was cooled down to −20° and stirred while 0.14 g of *N*-chlorosuccinimide was added over a period of a few minutes. After stirring at −20° for 15 min, water and ether were added and the aqueous layer was extracted with ether. The ether extracts were washed with brine, dried, and evaporated under vacuum. The residue was purified by preparative thin-layer chromatography on 1-m long plates using hexane–ethyl acetate (85:15) to give 0.14 g (48% overall yield from the aldehyde **12**) of chloro ketone **18**: bp (bath; short path) 105–107° (0.04 mm); the purity was judged to be 96.4% by glpc analysis; ir (CCl_4) 1718–1716 (C=O), 1646 cm^{-1}; nmr ($CDCl_3$) δ 1.09 (t, 3, J = Hz, terminal CH_3), 1.27 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.60 (s, 3, C-7 CH_3), 2.15 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.68 (q, 2, J = 7.5 Hz, H-12), 4.15 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 4.17 (m, 1, H-10), 5.14 (m, 1, H-6), and 5.64 ppm (m, 1, H-2); mass spectrum m/e 314 (M^+).

Diastereoisomers of Ethyl 10-Chloro-11-hydroxy-3,7,11-trimethyl-2-*trans*,6-*trans*-tridecadienoate (21 and 22). Methylmagnesium chloride (1 *M*) in tetrahydrofuran was cooled to 78°. Four ml of this solution was transferred with a cooled syringe to a solution of 0.15 g (0.5 mmol) of chloro ketone **18** in 5 ml of tetrahydrofuran while under nitrogen and at −78°. After stirring at −78° for 4 hr saturated ammonium chloride solution was added and the resulting mixture was extracted with ether. The extracts were washed with water followed by brine and dried over anhydrous sodium sulfate. The residue (0.15 g) obtained on removal of the solvent was chromatographed on three 1 m × 20 cm plates using hexane–ethyl acetate (88:12). By running the plates four times the diastereomeric chlorohydrins separated from each other. After discarding a very small, overlapping band, the broad faster running band afforded after elution with ether–ethyl acetate 0.105 g (66.5% yield) of the threo diastereoisomer **21** (leading to cis epoxide **3**): ir (CCl_4) 3587 (OH), 1714 (ester C=O), 1645, 1378, 1214, and 1137 cm^{-1}; nmr δ 0.90 (t, 3, J = 7 Hz, terminal CH_3), 1.14 (s, 1, C-11 CH_3), 1.24 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.60 (broad s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.75 (d of d, 1, "J" = 2.5 and 10 Hz, H-10), 4.08 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 5.13 (m, 1, H-6), and 5.55 ppm (m, 1, H-2); mass spectrum m/e 330 (M^+).

The lower band of the above chromatography consisted of the pure erythro diastereoisomer **22** (0.011 g, 7% yield) (leading to trans epoxide **24**): ir (CCl_4) 3581 (OH), 1713 (ester C=O), 1645 cm^{-1}; nmr δ 0.90 (t, 3, J = 7 Hz, terminal CH_3), 1.15 (s, 3, C-11 CH_3), 1.24 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.60 (broad s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.66 (d of d, 1, "J" = 2.0 and 10.5 Hz, H-10), 4.08 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 5.13 (m, 1, H-6), and 5.56 ppm (m, 1, H-2); mass spectrum m/e 330 (M^+).

Ethyl 10,11-*cis*-Epoxy-3,7,11-trimethyl-2-*trans*,6-*trans*-tridecadienoate (3). A 0.40-g sample of the chlorohydrin **21** obtained as the major product in the aforementioned Grignard reaction was allowed to stir for 1 hr at room temperature and under nitrogen with 0.30 g of anhydrous potassium carbonate in 30 ml of methanol. Ether and water were then added and the aqueous layer was extracted with ether. The organic layers were washed with saturated brine and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was submitted to short-path distillation at 95° (bath temperature, 0.045 mm) to give 0.328 g (92% yield) of **3** (96% pure by glpc analysis). The two main impurities having lower retention time were probably the bond migrated exo Δ^3 isomer and the Δ^2 cis isomer: ir (CCl_4) 1714 (ester C=O), 1645, 857 cm^{-1}; nmr δ 0.97 (t, 3, J = 7 Hz, terminal CH_3), 1.18 (s, 3, C-11 CH_3), 1.24 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.62 (broad s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.50 (d of d, 1, "J" = 5 and 7 Hz, H-10), 4.07 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 5.13 (m, 1, H-6), and 5.57 ppm (m, 1, H-2); mass spectrum m/e 294 (M^+).

Ethyl 10,11-*trans*-Epoxy-3,7,11-trimethyl-2-*trans*,6-*trans*-tridecadienoate (24). A 0.035-g sample of the chlorohydrin **22** was treated as above with anhydrous potassium carbonate in methanol to give

(20) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, 47, 2002 (1925).

24 (0.029 g, 95% yield), bp (bath) 90° (0.04 mm) (92% pure by glpc analysis). The main impurity (about 5%) having lower retention time was probably the bond migrated exo Δ^3 isomer ir (CCl_4) 1715 (ester C=O), 1644, 854 cm^{-1}; nmr δ 0.89 (t, 3, J = 7 Hz, terminal CH_3), 1.1 5(s, 3, C-11 CH_3), 1.22 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.60 (broad s, 3, C-7 CH_3), 2.11 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.48 (t, 1, "J" = 6 Hz, H-10), 4.05 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 5.11 (m, 1, H-6), and 5.56 ppm (m, 1, H-2); mass spectrum m/e 294 (M^+).

Methyl 10-Chloro-11-oxo-3,7-dimethyl-2-*trans*,6-*trans*-tridecadienoate (17) from 15. A 0.250 g sample of the crude enol ether **15** was treated for 6 hr at 55° with 1% sodium methoxide in 25 ml of methanol. Ether and half-saturated bicarbonate solution were then added and the aqueous layer was extracted with ether. The organic layers were washed with brine and dried (Na_2SO_4–K_2CO_3). The residue obtained on removal of the solvent at reduced pressure was dissolved in 5 ml of acetone–water (9:1). After addition of 0.10 g of sodium acetate the mixture was cooled to −20°. While the solution was being stirred 0.10 g of *N*-chlorosuccinimide was added over a period of 5 min. After the solution was stirred at −20° for 30 min water and ether were added and the aqueous layer was extracted with ether. The ether extracts were washed with brine, dried, and evaporated under vacuum. The residue was chromatographed on three 1-m long preparative thin-layer plates using hexane–ethyl acetate (85:15), giving 0.075 g of chloro ketone **17**, identical with that obtained above from **11**.

Methyl 10,11-*cis*-Epoxy-3,7,11-trimethyl-2-*trans*,6-*trans*-tridecadienoate (1). To 100 ml of tetrahydrofuran at −78° under argon was added 43 ml (0.136 mol) of a solution of methylmagnesium chloride (3.16 *M*) in tetrahydrofuran. A 10.37 g (0.035 mol) sample of the chloro ketone **17** dissolved in 50 ml of cold tetrahydrofuran (filled syringe was cooled in Dry Ice wrapped in aluminum foil) was then added over 10 min with stirring and the mixture was stirred a further 5.5 hr at −78°. A solution of 10 ml of acetic acid in 40 ml of ether was then added over 10 min at −78° and the mixture was allowed to come to room temperature. Dilution with brine and isolation with ether gave the crude chlorohydrin (11 g). The crude chlorohydrin was dissolved in 350 ml of dry methanol and 15 g of anhydrous K_2CO_3 added under argon with stirring. After 2 hr stirring the mixture was diluted with brine and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4), and evaporated to give 8.8 g of epoxide **1** (90% yield from **17**). The product in redistilled pentane was filtered through a short column (40 g) of Woelm neutral alumina (activity IV) to give 8.7 g of pure **1**. The nmr spectrum (benzene) showed the presence of *ca.* 18% of the epoxide **23**. Analysis by glpc indicated purity of >95% (trans,trans,cis + trans,trans,trans isomers).

The ratio of trans,trans,cis (**1**) to trans,trans,trans (**23**) isomers was established by careful glpc analysis of the intermediate chlorohydrins (Hewlett Packard 402 instrument equipped with a 2 m × 3 mm glass column packed with 3% OV-225 on 100–120 mesh Chromosorb W-AR-DMCS) and of the epoxides (4 m × 3 mm glass column packed with 2% OV-101–1% EPON-1001 on 100–120 mesh Chromosorb W-AW-DMCS) and by nmr integration of **1** in deuteriobenzene.[6]

The reaction of **17** with methylmagnesium chloride was repeated on a small scale and the diastereoisomers **19** and **20** were separated by preparative thin layer chromatography as described above for the ethyl esters: **19**; ir (CCl_4) 3582 (OH), 1718 (C=O), 1645 cm^{-1}; nmr δ 0.90 (t, 3, J = 7 Hz, terminal CH_3), 1.14 (s, 3, C-11 CH_3), 1.60 (broad s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.61 (s, 3, CO_2CH_3), 3.74 (d of d, 1, "J" = 2.5 and 10 Hz, H-10), 5.14 (m, 1, H-6), and 5.58 ppm (m, 1, H-2); mass spectrum m/e 316 (M^+). Pure **19** was converted as above to the epoxide **1**: bp (bath) 85° (0.035 mm) (short-path distillation); ir (CCl_4) 1720, 1648, 1432, and 857 cm^{-1}; nmr δ 0.96 (t, 3, J = 7 Hz, terminal CH_3), 1.17 (s, 3, C-11 CH_3), 1.61 (broad s, 3, C-7 CH_3), 2.12 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.49 (d of d, 1, "J" = 5 and 7 Hz, H-10), 3.59 (s, 3, CO_2CH_3), 5.10 (m, 1, H-6), and 5.56 ppm (m, 1, H-2). Elemental composition was determined by high-resolution mass spectrometry on a MS9 instrument. The calculated mass for $C_{17}H_{28}O_3$ was 280.20383 (found, 280.20383). This mass spectrum was identical with that of the natural hormone.

The minor chlorohydrin **20** was not characterized but was converted directly to the epoxide **23**; nmr (CCl_4) δ 0.90 (t, 3, J = 7 Hz, terminal CH_3), 1.15 (s, 3, C-11 CH_3), 1.62 (broad s, 3, C-7 CH_3), 2.13 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.49 (t, 1, J = 6 Hz, H-10), 3.60 (s, 3, CO_2CH_3), 5.10 (m, 1, H-6), and 5.56 ppm (m, 1, H-2).

Methyl 3,7-Dimethyl-10,11-epoxy-11-ethyl-2-*trans*,6-*trans*-tridecadienoate (25). To a solution of 1.0 g of the chloro ketone **17** in tetrahydrofuran (15 ml) at −78° was added dropwise a cold solution of ethylmagnesium chloride (5 equiv) in tetrahydrofuran (18 ml). After stirring for 5.5 hr at −78° a solution of acetic acid (2 ml) in ether (10 ml) was added dropwise. After a further 15 min the mixture was diluted with brine and extracted with ether. The organic layer was washed with brine and dried, and the solvent removed. The crude chlorohydrin was dissolved in dry methanol (40 ml), anhydrous potassium carbonate (5 g) was added, and the mixture was stirred 2 hr at room temperature. Dilution with brine and extraction with ether gave the crude epoxide (0.88 g) which was dissolved in redistilled pentane and filtered through a short column (20 g) of Woelm neutral alumina (activity IV). Evaporation of the pentane eluate gave 0.6 g of **25**: nmr δ 0.92 (t, J = 7 Hz, terminal CH_3), 1.00 (t, J = 7 Hz, terminal CH_3), 1.67 (s, 3, C-7 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.73 (t, 1, "J" = 6 Hz, H-10), 3.72 (s, 3, CO_2CH_3), 5.18 (m, 1, H-6), and 5.72 ppm (m, 1, H-2).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.21; H, 10.42.

Methyl 10-Hydroxy-3,7,11-trimethyl-2-*trans*,6-*trans*-11-dodecatrienoate (26). In a typical conversion, 6.15 g of epoxide **8** was heated under N_2 at 165° for 8.5 hr in a 50-ml, round-bottom flask (Pyrex 7740 glass) equipped with a condensor. Allylic alcohol **26** (6.07 g, 99% yield) was recovered in 90% purity: bp (bath, short-path) 63° (0.01 mm); ir (film) 3440 (–OH) 3060, 1720, 1650, 910 cm^{-1}; nmr ($CDCl_3$) δ 1.62 and 1.73 (s, 6, C-7 and C-11 CH_3), 2.16 (s, 3, C-3 CH_3), 3.70 (s, 3, $-CO_2CH_3$), 4.04 (t, 1, J = 6 Hz, H-10), 4.85 and 4.95 (2, H-12), 5.16 (m, 1, H-6), and 5.70 ppm (broad s, 1, H-2).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.07; H, 9.68.

When the epoxide **8** is heated above 165°, at temperatures up to 180°, the cyclic ether **28** is recovered in good yield: bp 110–113° (0.02 mm); ir 3065 (H_2C=C), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) 1.22 (s, 3, CH_3CO–), 1.73 (s, 3, CH_3C=C), 2.16 (s, 3, CH_3C=CCOOR), 3.70 (s, 3, $-COOCH_3$), 4.36 (m, 1, –CHO–), 4.82 and 5.03 (m, 2, H_2C=C), and 5.71 ppm (broad s, 1, C=CHCOOR); mass spectrum (70 eV) m/e 266 (M^+).

Methyl 10-Acetoxy-3,7,11-trimethyl-2-*trans*,6-*trans*-11-dodecatrienoate (27). A 2.90-g (10.9 mmol) sample of **26** was dissolved in 15 ml of pyridine and 12 ml of acetic anhydride and stirred overnight at room temperature under argon. Ice water was added dropwise and then the solution was poured over ice and ether added. After consecutive washes of the ether layer with 5% HCl, saturated $NaHCO_3$ solution, and saturated NaCl solution, the organic phase was dried over $MgSO_4$. Removal of solvent gave 2.91 g of allylic acetate **27** (87% yield): bp (bath) 75° (0.03 mm); ir 1740 (acetate C=O), 1720 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.62 (s, 3, C-7 CH_3), 1.73 (d, 3, J = 1 Hz, C-11 CH_3), 2.08 (s, 3, $COCH_3$), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.71 (s, 3, $-CO_2CH_3$), 4.96 (m, 2, H-12), 5.16 (t, 1, J = 7 Hz, H-10), and 5.73 ppm (broad s, 1, H-2).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.02; H, 9.26.

Methyl 3,7,11-Trimethyl-2-*trans*,6-*trans*,10-*trans*-tridecatrienoate (31). To 2.66 g (14 mmol) of anhydrous cuprous iodide in 40 ml of anhydrous ether under argon at −15° was added 16.8 ml of methyllithium solution (1.65 *M* in diethyl ether, 27.8 mmol). After a negative Gilman test[20] was obtained, 2.85 g (9.25 mmol) of allylic acetate **27** in 10 ml of ether was added. After 1 hr at −10°, the reaction mixture was poured into saturated NH_4Cl solution and ether was added. The organic phase after filtration was washed with saturated NaCl solution and dried ($MgSO_4$). Trienoic ester (2.12 g) was isolated in 87% yield (glpc analysis of the product indicated 93% of **31** along with 5% of the Δ^{10} cis isomer): nmr ($CDCl_3$) δ 0.97 (t, 3, J = 7 Hz, 13-H), 1.62 (s, 6, C-7 and C-11 CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.70 (s, 3, $-CO_2CH_3$), 5.13 (m, 2, H-6 and H-10), and 5.72 ppm (broad s, 1, H-2).

Methyl 10,11-*trans*-Epoxy-3,7,11-trimethyl-2-*trans*,6-*trans*-tridecadienoate (23). Trienoic ester **31** (2.0 g, 7.6 mmol) was dissolved in 50 ml of distilled tetrahydrofuran and 20 ml of water at 2°, and 1.49 g (9.35 mmol) of *N*-bromosuccinimide was added in portions. After the mixture was stirred for 3 hr at 0–5°, ether was added and the organic layer was washed with saturated sodium bicarbonate and saturated sodium chloride. The ether layer was dried ($MgSO_4$), the solvent was removed, and 2.05 g of crude bromohydrin **32** was isolated. Silica gel chromatography of the crude reaction product (elution with 18% ether in hexane) gave 1.63 g of pure bromohydrin **32**: ir (film) 3480 (–OH), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz, 13-H), 1.30 (s, 3, C-11 CH_3), 1.63 (s, 3, C-7 CH_3). 2.20 (s, 3, C-3 CH_3), 3.74 (s, 3, CO_2CH_3), 4.00 (m, 1, H-10), 5.24 (m, 1, H-6), and 5.75 ppm (s, 1, H-2).

To 1.60 g (4.44 mmol) of bromohydrin **32** in 25 ml of anhydrous methanol under argon was added 1.38 g (10 mmol) of dry potassium carbonate. After the solution was stirred for 15 min, hexane and water were added, the organic layer was washed with saturated NaCl solution and dried (Na_2SO_4), and the hexane was removed to give 1.23 g of epoxide **23**: bp (bath, short path) 67° (0.01 mm); ir 1720, 1650, 1230, 1150, 880 cm^{-1}; nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz, terminal CH_3), 1.23 (s, 3, C-11 CH_3), 1.62 (d, 3, J = 1 Hz, C-7 CH_3), 2.20 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.68 (t, 1, J = 6 Hz, H-10), 3.70 (s, 3, CO_2CH_3), 5.17 (m, 1, H-6), and 5.70 ppm (broad s, 1, H-2).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.68; H, 9.97.

Thermal Rearrangement of 23. The epoxide **23** (50 mg) was heated in a small Pyrex glass tube under N_2 at 165° for 12 hr (reaction was followed by glpc). The ratio of **29** to **30** in the product was *ca.* 0.8:1. The isomers were separated by preparative tlc chromatography on silica gel. **29**: ir (CCl_4) 3600, 3070, 1720, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (t, 3, J = 7 Hz, CH_3CH_2–), 1.61 (s, 3, CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, CH_3C=CCO_2Me), 3.70 (s, 3, CO_2Me), 4.06 (t, 1, J = 6 Hz, –HCOH), 4.85 and 5.04 (H_2C=C), 5.16 (m, 1, C=CH), and 5.70 ppm (broad s, 1, H-2); mass spectrum (70 eV) *m/e* 262 (M − H_2O). **30**: ir (CCl_4) 3600, 1720, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.62 and 1.67 (CH_3C=C), 2.16 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.70 (s, 3, CO_2Me), 3.97 (t, 1, J = 6 Hz, HCOH), and 5.70 ppm (broad s, 1, H-2); mass spectrum (70 eV) *m/e* 262 (M − H_2O).

Esters of the Allylic Alcohol 26. All of the ester derivations of the allylic alcohol **26** in Table I, with exception of the trifluoroacetate, were prepared by dissolving the alcohol in an excess of pyridine, adding the corresponding acid chloride, and following the reaction by tlc. For example, 200 mg (0.76 mmol) of alcohol **26** and 440 mg of 3,5-dinitrobenzoyl chloride (1.90 mmol) were dissolved in 8 ml of pyridine under argon at 0°. After 1.25 hr, water was added portionwise and the mixture extracted using ether. After successive acid (5% hydrochloric acid), base (saturated $NaHCO_3$), and neutral (saturated brine) washing of the ether layer and drying ($MgSO_4$), solvent removal gave 302 mg of the 3,5-dinitrobenzoate (87% yield).

The trifluoroacetate was prepared very simply by adding an excess of trifluoroacetic anhydride to 100 mg (0.38 mmol) of allylic alcohol **26** at room temperature under argon. After 2 hr, the excess anhydride and the acid were removed under vacuum and the residue was short-path distilled (bath 70°, 0.01 mm) to give 127 mg (0.35 mmol) of the pure trifluoroacetate (92% yield).

Each of the esters was completely characterized: R = $CF_3C(O)$–; ir (film) 3070, 1780 ($CF_3C(O)O$), 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.63 and 1.77 (s, 6, CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, CH_3C=CCOOR), 3.72 (s, 3, $COOCH_3$), 5.07 (broad s, 2, H_2C=C), 5.32 (t, 1, J = 6 Hz, H-10), and 5.72 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{23}F_3O_4$: C, 59.66; H, 6.95; F, 15.73. Found: C, 59.49; H, 6.75; F, 15.85.

R = $(CH_3)_3CC(O)$–: bp (bath) 100° (0.0075 mm); ir (film) 3060 (H_2C=C), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.23 (s, 9, $(CH_3)_3CO$), 1.63 and 1.73 (CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.71 (s, 3, $COOCH_3$), 4.96 (broad s, 2, H-12), 5.15 (t, 1, J = 6 Hz, H-10), and 5.72 (broad s, 1, H-2).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.80; H, 9.67.

R = $C_6H_5C(O)$–: bp (bath) 120° (0.01 mm); ir (film) 1720 (C=O) and 720 cm^{-1}; nmr ($CDCl_3$) δ 1.65 and 1.83 (s, 6, CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.72 (s, 3, $COOCH_3$), 4.96 and 5.06 (broad s, 2, H-12), 5.45 (t, 1, J = 6 Hz, H-10), 5.71 (broad s, 1, H-2), 7.52 (m, 3, aromatic H), and 8.15 ppm (m, 2, ortho aromatic H).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.45; H, 8.32.

R = 3,4,5-trimethoxybenzoyl: bp (bath) 140° (0.0075 mm); 1730 and 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.65 and 1.82 (s, 6, CH_3C=C), 2.17 (broad s, 3, C-3 CH_3), 3.70 (s, 3, $COOCH_3$), 3.95 (s, 9, CH_3), 4.97 and 5.06 (broad s, 2, H-12), 5.42 (t, 1, J = 6 Hz, H-10), 5.70 (broad s, 1, H-2), and 7.36 ppm (s, 2, aromatic).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.98; H, 8.07.

R = 2,4,6-trimethylbenzoyl: bp (bath) 125° (0.005 mm); ir (film) 3070 (H_2C=C) and 1720 cm^{-1} (C=O); nmr δ 1.62 and 1.78 (s, 6, CH_3C=C), 2.16 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.30 (s, 9, aromatic CH_3), 3.70 (s, 3, $COOCH_3$), 5.00 and 5.10 (broad s, 2, H-12), 5.45 (t, 1, J = 6 Hz, H-10), 5.70 (broad s, 1, H-2), and 6.89 ppm (s, 2, aromatic).

Anal. Calcd for $C_{28}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.20; H, 8.72.

R = 2,4-dinitrobenzoyl: ir (film) 1730 and 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.67 and 1.78 (s, 6, CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.70 (s, 3, $COOCH_3$), 5.06 (broad s, 2, H-12), 5.46 (t, 1, J = 6 Hz, H-10), 5.70 (broad s, 1, H-2), 8.00 (d, 1, J = 8 Hz, aromatic H-6), 8.59 (d of d, 1, J = 8 Hz, J = 2 Hz, aromatic H-5), and 8.82 ppm (d, 1, J = 2 Hz, aromatic H-3).

Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 59.99; H, 6.13; N, 6.08. Found: C, 60.14; H, 5.89; N, 6.17.

R = 3,5-dinitrobenzoyl: ir (film) 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.67 and 1.85 (s, 6, CH_3C=C), 2.17 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.70 (s, 3, $COOCH_3$), 5.10 (broad s, 2, H-12), 5.52 (t, 1, J = 6 Hz, H-10), 5.67 (broad s, 1, H-2), and 9.20 ppm (m, 3, aromatic).

Photosensitized Oxygenation of 1. The hormone **1** (1.90 g, 6.80 mmol) and 60 mg of hematoporphyrin were dissolved in 60 ml of methanol and the solution illuminated (two 15-W fluorescent lamps) in a Pyrex glass chromatography column for 28 hr while oxygen was bubbled through the solution. After cooling the resulting solution to −20°, 1.23 g (7.50 mmol) of hexamethylphosphorous triamide was added dropwise. After 0.5 hr, most of the methanol was removed and ether and water were added. The organic phase was washed with water and dried and the solvent was removed. The residue (2 g) was chromatographed on four preparative tlc plates (1 m × 20 cm, 1.3 mm PF silica gel) and developed with ether–hexane (2:1). The uppermost band (760 mg) was the desired allylic alcohol **33** while the lower band (620 mg) was the isomeric alcohol **36**.

Both allylic alcohol isomers were fully characterized. **33**: ir (CCl_4) 3590 and 3440 (–OH), 1720 (C=O), 1650 (C=C) and 920 cm^{-1} (H_2C=C); nmr ($CDCl_3$) δ 1.00 (t, 3, J = 7 Hz, CH_3CH_2–), 1.28 (s, 3, CH_3CO–), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.78 (t, 1, "J" = 6 Hz, H-10), 3.70 (s, 3, $COOCH_3$), 4.12 (t, 1, J = 6 Hz, H-6), 4.95 and 5.12 (broad s, 2, H_2C=C), and 5.74 ppm (broad s, 1, H-2).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.72; H, 9.34.

For isomer **36**: ir (CCl_4) 3580 and 3480 (–OH), 1720 (C=O) and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.00 (t, 3, J = 7 Hz, CH_3CH_2–), 1.28 and 1.32 (s, 6, CH_3COH and CH_3CO), 2.16 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.84 (m, H-10 and H-4), 3.72 (s, 3, $COOCH_3$), and 5.69 ppm (m, 3, HC=CH and H-2).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.76; H, 9.42.

Esters of 33. To 100 mg (0.34 mmol) of **33** in 1.5 ml of anhydrous pyridine was added 0.75 ml of acetic anhydride, and the solution was stirred at room temperature under argon for 6 hr. Water was added along with ether, and the ether layer was washed with dilute potassium carbonate solution and saturated brine and dried, and the solvent was removed to give 110 mg of acetate **34** (96% yield): ir (CCl_4) 3070, 1740, 1720, and 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (t, 3, J = 6 Hz, CH_3CH_2–), 1.28 (s, 3, CH_3CO), 2.06 (s, 3, OAc), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 2.75 (t, 1, "J" = 6 Hz, H-10), 3.70 (s, 3, $COOCH_3$), 5.00 and 5.10 (broad s, 2, H_2C=C), 5.22 (t, 1, H-6), and 5.70 ppm (broad s, 1, H-2).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.38; H, 8.79.

Preparation of the 3,5-dinitrobenzoate was achieved by dissolving 195 mg (0.85 mmol) of 3,5-dinitrobenzoyl chloride in 3 ml of dry pyridine and adding 50 mg (0.17 mmol) of **33**. After 1.5 hr water was added, the solution was stirred for another 1 hr, and then ether–hexane (1:9) was added and the organic phase washed repeatedly with water. After drying and solvent removal, the crude residue was applied to one 20 × 20 cm silica gel plate (1.3 mm PF) and developed with 20% ethyl acetate in hexane. In this manner, 43 mg (51% yield) of **35** was isolated: ir (CCl_4) 3080, 1720 (broad), 1650, 1630, 1340 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (t, 3, J = 7 Hz, CH_3CH_2–). 1.28 (s, 3, CH_3CO), 2.23 (C-3 CH_3), 2.78 (t, 1, "J" = 6 Hz, H-10), 3.68 (s, 3, $COOCH_3$), 5.16 and 5.30 (broad s, 2, H_2C=C), 5.60 (t, 1, J = 6 Hz, H-6), 5.74 (broad s, 1, H-2), and 9.22 ppm (m, 3, aromatic).

Alkylation of 34 and 35. Formation of Juvenile Hormone (2). Several different reaction conditions were tried and a typical example is given below.

To 122 mg of cuprous iodide (0.64 mmol) was added 3 ml of dry ether, the suspension cooled to −10° under argon, and 0.73 ml (1.20 mmol) of methyllithium (1.65 M CH_3Li in ether) added. A negative Gilman test[20] was obtained after a few minutes. Addition of 30 mg of acetate **34** (0.09 mmol) in 0.5 ml of ether gave immediate

formation of yellow solid. After 0.5 hr at −10° the suspension was poured into saturated ammonium chloride solution and additional ether was added. The organic phase was washed with saturated sodium bicarbonate and saturated brine and dried, and the solvent was removed to give 26 mg (98% yield) of the olefinic esters **2** and **37** (in the ratio 32:68, respectively). The products were identified by glpc, mass spectrum, tlc, ir, and nmr comparisons with authentic samples.

Alkylation of **35** with lithium dimethylcuprate in ether–tetrahydrofuran (1:5) for 17 hr at 0° gave a very similar ratio of **2** and **37**. Reaction of the acetate **34** in tetrahydrofuran–ether (6:1) or in pure tetrahydrofuran at −10° gave a mixture of **2** and **37** in the ratio of *ca.* 1:1 along with *ca.* 10% of the product from direct displacement of the ester.[16] A small sample of pure **2** was obtained from the latter reaction product by micropreparative glpc, and the mass spectrum was shown to be identical with that of an authentic sample.

Photooxygenation of 6. A 2.4-g sample of **6** in 50 ml of dry pyridine was placed in a glass chromatography column and 50 mg of hematoporphyrin was added. The mixture was irradiated with two 15-W fluorescent lamps while dry oxygen was passed through the solution for 10 hr (the reaction was followed by tlc). The solution was then cooled to 5° and 2.35 g of trimethyl phosphite added dropwise. After 1.5 hr at 5°, acetic anhydride (5.2 g) was added and the solution was left for 2 hr at room temperature. Ice was then added, followed by ice-cold aqueous HCl and extraction with ether. The ether layer was washed with water, brine, saturated $NaHCO_3$, and brine and dried, and the solvent was removed. The residue (2.5 g) was chromatographed on preparative tlc silica gel plates to give 0.80 g (23.4% yield) of **38**: ir (CCl_4) 3080, 1740, 1720, 1650, 1375, 1245, 1155, 920 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (t, 3, J = 7 Hz, CH_3CH_2), 1.77 (d, 3, J = 1 Hz, CH_3C=), 2.10 (s, 6, OAc), 2.18 (d, J = 1.5 Hz, C-3 CH_3), 4.17 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.02 (d, 4, CH_2=C), 5.18 (m, CHOAc), and 5.69 ppm (broad s, 1, H-2); mass spectrum (70 eV) *m/e* M^+ 380.

Ethyl 3,11-Dimethyl-7-ethyltrideca-2,6,10-trienoate (39). To a suspension of cuprous iodide (210 mg, 1.10 mmol) in 5 ml of ether at −10° under argon was added 1.27 ml (2.10 mmol) of methyllithium in ether (1.65 *M*). After a negative Gilman test[20] was obtained, 26 mg (0.055 mmol) of the acetate **38** in ether (1 ml) was added. After 0.5 hr at −10° the mixture was diluted with saturated NH_4Cl and the product (18 mg) recovered with ether. Analysis by glpc (comparison with authentic samples) showed the presence of 14% all trans, 8% trans,cis,cis, and 76% of the trans,cis,trans triene **39**: nmr ($CDCl_3$) δ 0.99 (t, 6, J = 7 Hz, CH_3CH_2C=C), 1.27 (t, 3, J = 7 Hz, CH_3CH_2O), 1.61 (s, 3, CH_3C=C), 2.18 (d, 3, J = 1.5 Hz, C-3 CH_3), 4.16 (q, 2, J = 7 Hz, CH_2O), 5.11 (CH=C), and 5.68 ppm (broad s, 1, H-2).

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Stereoselective Total Synthesis of (±)-Zizaene[1]

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Abstract: 1-(3′-Phenylpropyl)bicyclo[2.2.1]heptan-*exo*-2-yl acetate (**9**), obtained by rearrangement of the adduct (**7**) from 3-phenyl-1-propylmagnesium bromide and norcamphor, was converted stereoselectively, by way of unsaturated keto acetate **14**, to the 1′β methyl homolog (**17b**). The relative stereochemistry at the 1′ position was established independently with nmr spectral data from the δ-lactone (**22**) resulting from oxidative cleavage of the side chain phenyl group. The acetoxy acid (**19a**), produced by ozonolysis of the benzene ring in **17b**, was transformed through a sequence of functional group alterations, into a diazopentylnorcamphor intermediate (**3**) which cyclized spontaneously to 1,2,3,4,5,6β,7,8aα-octahydro-3α-methyl-8*H*-3aα,6-methanoazulen-8-one (**4a**). Reduction–methylation of the corresponding *n*-butylthiomethylene derivative (**30b**) of **4a** followed by epimerization at position 5 afforded (±)-13-norzizan-6-one (**32**). Introduction of the exocyclic methylene group into this sterically hindered ketone was achieved by addition of phenylthiomethyllithium, and then reductive elimination of the corresponding benzoate (**30b**) with lithium in liquid ammonia affording (±)-zizaene (**1**).

Zizaene (tricyclovetivene, **1**)[4–6] is the parent hydrocarbon of a small family of tricyclic sesquiterpenes found in vetiver oil. Degradative and spectral investigations with the more abundant zizanoic acid (**2**)[7–9] provided evidence for the 3a,6-methanoperhydroazulene ring system, a tricyclic carbon skeleton previously unknown among natural sesquiterpenes.[10] The structures of its various cogeneric relatives zizaene,[4d,8b] zizen-12-ol (khusimol),[7a,8b,11] ziz-

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(2) A. P. Sloan Foundation Fellow, 1971–1973.

(3) University of Illinois Fellow, 1970–1971; Johnson and Johnson Fellow, 1971–1972.

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(5) For a review on early isolation and structural investigations, see N. T. Anh and M. Fetizon, *Amer. Perfum. Cosmet.*, **80**, 41 (1965). Unfortunately most of the structures contained therein have been revised subsequent to the publication of this article. See also N. H. Anderson, *Photochemistry*, **9**, 145 (1970).

(6) Alternative names appearing in the literature include tricyclovetivene,[4b] khusinene,[4c] and khusene.[8c]

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(10) Other types of methanoperhydroazulene sesquiterpenes are well known: 1,4-methanoperhydroazulene (longifolene), 3a,7-methanoperhydroazulene (cedrene, cyperene), and 4,8-methanoperhydroazulene (α-caryophyllene alcohol). The B/C/D rings of the tetracyclic gibberellin diterpenes describe a 3a,6-methanoperhydroazulene.

(11) D. C. Umarani, K. G. Gore, and K. K. Chakravarti, *Tetrahedron Lett.*, 1255 (1966); *Perfum. Essent. Oil Rec.*, **60**, 307 (1969).