# Stereoselective Synthesis of the C-18 Cecropia Juvenile Hormone[1]

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Abstract: The stereoselective synthesis of methyl 3,11-dimethyl-10,11-*cis*-epoxy-7-ethyl-2-*trans*,6-*trans*-tridecadienoate (1), the C-18 juvenile hormone of *Hyalophora cecropia*, by two alternative routes is described. The first method proceeds *via* a Claisen condensation of trimethylorthoacetate with methyl 6-hydroxy-3-methyl-7-methylene-2-*trans*-nonenoate (9) and a second method utilized the versatile bifunctional intermediate 25.

The isolation and identification[3] of the juvenile hormones 1 and 2 of *Hyalophora cecropia* prompted us to investigate their stereoselective synthesis. This pair of compounds is responsible, at least in silk moths, for the maintenance of juvenile characteristics in the larvae, and the hormones show gonadotropic, morphogenetic, and prothoracotropic activities.[4] The synthesis of the C-17 hormone 2 is described in the accompanying paper.[5] Here we wish to report two alternate routes to the C-18 hormone 1 based on the recently published ortho ester Claisen rearrangement.[6]

1, R = Et
2, R = Me

3

4
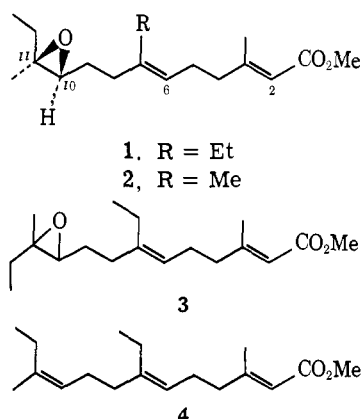
Although the major juvenile hormone 1 produced by the silk moth has been synthesized many times recently with varying degrees of stereoselectivity and utility,[7] we had wished to develop a versatile stereoselective route

via which the racemic hormone 1 and some related analogs could be prepared in quantity. A very useful short synthesis of 1 was recently developed by us and by a group at Stanford University as an alternative synthesis to the approach presented here.[7l] This particular route did allow, for the first time, easy access to both the racemic natural trans,trans,cis hormone 1 and its all trans isomer 3 in very pure form.

The basic problem in the stereoselective preparation of 1 involves the synthesis of trisubstituted double bonds.[8] The trans (or E) configurations of the two double bonds of 1 are crucial for biological activity, in contrast to the observation[9] that the stereochemistry of the oxirane ring appears to be of secondary importance. Both methods presented here incorporate the stereospecific introduction of the *trans*-6-ene double bond, which is essential for high biological activity.

A disadvantage of most published syntheses of 1 is that the oxirane ring is introduced at the last step by selective terminal electrophilic attack[10] on the triene 4, and this can be troublesome when one works on a large scale. The present synthesis was originally designed to overcome this problem by generating the epoxide ring *via* the chloro ketone 14 (Scheme I).[7e,h]

The first scheme proceeded through the known allylic alcohol 9,[7k,l] which was prepared by reaction of

(1) Contribution No. 6 from the Research Laboratory of Zoecon Corp.

(2) Zoecon postdoctoral fellow, 1969–1970.

(3) (a) 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) B. M. Trost, *Accounts Chem. Res.,* 3, 120 (1970); (c) recently the absolute configuration 10R,11S has been established both by asymmetric synthesis (P. Loew and W. S. Johnson, *J. Amer. Chem. Soc.,* 93, 3765 (1971); correction, *ibid.,* 93, 5315 (1971); D. J. Faulkner and M. R. Peterson, *ibid.,* 93, 3766 (1971)), by determination of chirality of the derived 10,11-diol (K. Nakanishi, D. A. Schooley, M. Koreeda, and J. Dillon, *Chem. Commun.,* 1235 (1971)), and also by asymmetric esterification of this diol (A. S. Meyer, E. Hanzmann, and R. C. Murphy, *Proc. Nat. Acad. Sci. U. S.,* 68, 2312 (1971)).

(4) V. B. Wigglesworth, *Quart. J. Microsc. Sci.,* 77, 191 (1934); *ibid.,* 79, 91 (1936); L. I. Gilbert and H. A. Schneiderman, *Nature (London),* 184, 171 (1959).

(5) See accompanying paper, R. J. Anderson, C. A. Henrick, J. B. Siddall, and R. Zurflüh, *J. Amer. Chem. Soc.,* 94, 5379 (1972).

(6) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brochsom, T. Li, D. J. Faulkner, and M. R. Peterson, *ibid.,* 92, 741 (1970).

(7) (a) K. H. Dahm, B. M. Trost, and H. Röller, *ibid.,* 89, 5292 (1967); (b) K. H. Dahm, H. Röller, and B. M. Trost, *Life Sci.,* 7, 129 (1968); (c) B. H. Braun, M. Jacobson, M. Schwarz, P. E. Sonnet,

N. Wakabayashi, and R. M. Waters, *J. Econ. Entomol.,* 61, 866 (1968); (d) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.,* 90, 5618 (1968); (e) W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *ibid.,* 90, 6225 (1968); (f) R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *ibid.,* 90, 6224 (1968); (g) H. Schulz and I. Sprung, *Angew. Chem., Int. Ed. Engl.,* 8, 271 (1969); J. A. Findlay and W. D. MacKay, *Chem. Commun.,* 733 (1969); K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers, *Tetrahedron,* 25, 1667 (1969); W. Hoffmann, H. Pasedach, and H. Pommer, *Justus Liebigs Ann. Chem.,* 729, 52 (1969); G. W. K. Cavill, D. G. Laing, and P. J. Williams, *Aust. J. Chem.,* 22, 2145 (1969); (h) W. S. Johnson, S. F. Campbell, A. Krishnakumaran, and A. S. Meyer, *Proc. Nat. Acad. Sci. U. S.,* 62, 1005 (1969); (i) J. B. Siddall, "Chemical Ecology," E. Sondheimer and J. B. Simeone, Ed., Academic Press, New York, N. Y., 1970, Chapter 11, p 288; (j) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.,* 92, 735 (1970); E. E. van Tamelen and J. P. McCormick, *ibid.,* 92, 737 (1970); (k) W. S. Johnson, T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. Li, and D. J. Faulkner, *ibid.,* 92, 4463 (1970); (l) P. Loew, J. B. Siddall, V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci. U. S.,* 67, 1462, 1824 (1970); (m) J. A. Findlay, W. D. MacKay, and W. S. Bowers, *J. Chem. Soc. C,* 2631 (1970); (n) E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.,* 92, 6636 (1970); (o) E. E. van Tamelen, P. McCurry, and U. Huber, *Proc. Nat. Acad. Sci. U. S.,* 68, 1294 (1971).

(8) J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.,* 135 (1971); D. J. Faulkner, *Synthesis,* 175 (1971).

(9) See for example ref 3b, 7a, and 7b.

(10) 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).

Scheme I
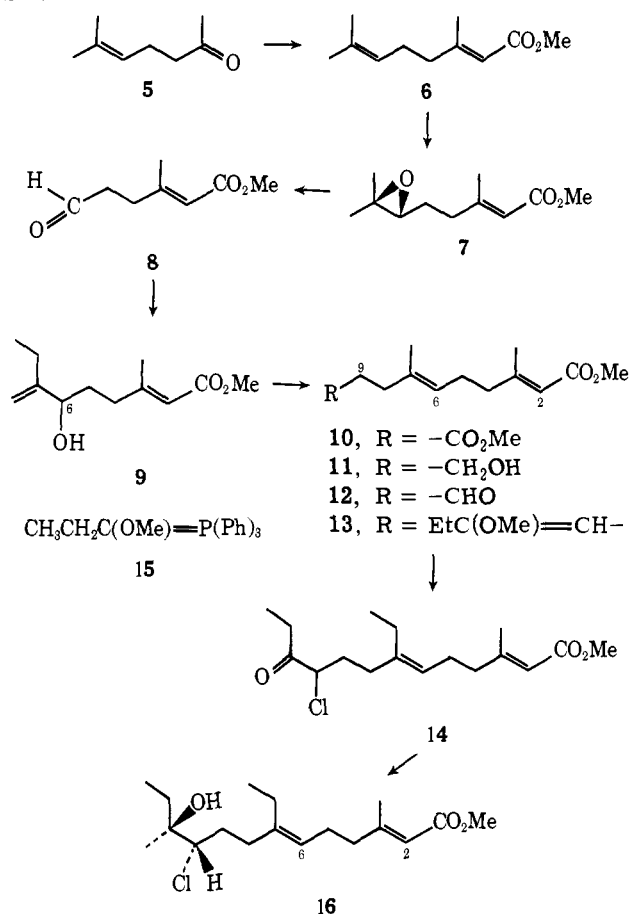
methyl 3-methyl-6-oxo-2-*trans*-hexenoate (8) with 1-butenyl-2-magnesium bromide in tetrahydrofuran at −50°. The aldehyde 8 was obtained from 6-methyl-hept-5-en-2-one (5) via *trans*-methyl geranate (6) as described in the Experimental Section.[7c] Heating 9 with trimethyl orthoacetate at 110° for 3 hr (with acetic acid as catalyst)[6] under conditions for continuous methanol removal produced the diester 10 in 85% yield with glpc analysis indicating greater than 96% of the trans,trans isomer after distillation. Selective reduction of the diester 10 to the hydroxy ester 11 (yield 80%) was carried out with 0.5 mol of lithium aluminum hydride (ether–tetrahydrofuran at −78°),[11] and oxidation of 11 with chromic acid–dipyridine complex[12] in methylene dichloride gave the aldehyde 12 in 90% yield. Attempts to reduce the diester 10 selectively directly to 12 were not successful. Use of 0.25 mol of sodium aluminum hydride (tetrahydrofuran at −50°),[13] 0.25 mol of lithium aluminum hydride (tetrahydrofuran at −78°), or 0.50 mol of lithium diethoxyaluminum hydride (tetrahydrofuran at 0°) gave only partial reduction to a mixture containing mostly 10 and 11. Diisobutylaluminum hydride (1 mol) in toluene at −78° did give some aldehyde 12 but the yield was poor. Use

of 1 mol of lithium diethoxyaluminum hydride at 0° gave a good yield of 11.

Wittig reaction of 12 with an excess of the ylide 15[5,14] in tetrahydrofuran at −78° afforded an enol ether 13, which was chlorinated with N-chlorosuccinimide in aqueous acetone buffered with sodium acetate to produce the known chloro ketone 14[7e] (60% yield from 12). Treatment of 14 with excess methylmagnesium chloride in tetrahydrofuran at −78° for 7 hr gave the chlorohydrin 16. However, the product reproducibly contained ca. 18% of the corresponding erythro-chlorohydrin and the previous high stereoselectivity (ca. 95%) reported[7e,h] for this chloro ketone methylation could not be attained.[5] At −95°,[15] the alkylation was considerably slower (ca. 25 hr) but the product still reproducibly contained ca. 14% of the isomeric erythro-chlorohydrin. Although these diastereoisomeric chlorohydrins can be separated with difficulty[5] by silica gel chromatography, on a large scale the isomer mixture was converted directly to the racemic Cecropia juvenile hormone 1 containing ca. 18% of the all trans isomer 3, by treatment with potassium carbonate in methanol. The ratio of trans,trans,cis to trans,trans,trans isomers was established by careful glpc analysis of the intermediate chlorohydrins and of the final epoxides, and supported by the nmr integration of the epoxide mixture in deuteriobenzene.[7e,h] This resulting hormone mixture has high biological activity.[16]

Scheme II

An alternative synthesis proceeded through the versatile bifunctional intermediate 25. Thus, reaction of the cyclopropylcarbinol 17[7b] with aqueous 2 N hydrochloric acid at 60° gave the chloride 18 as a cis,-

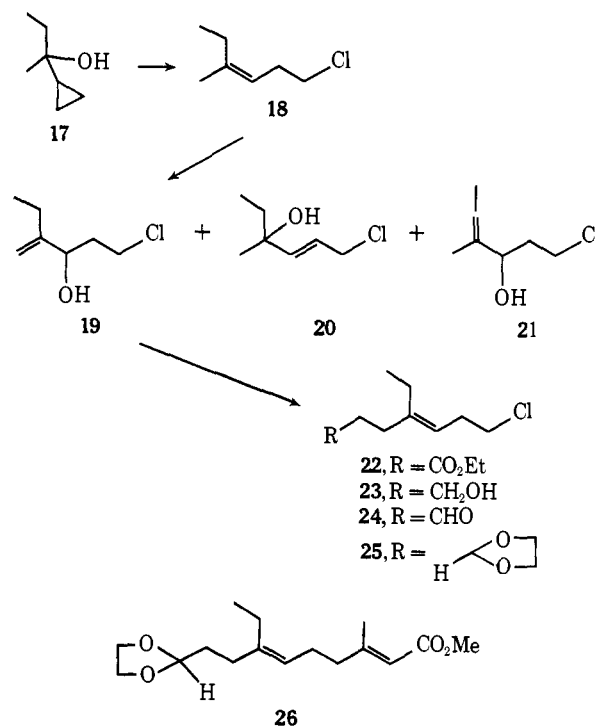(11) Lithium aluminum hydride in ether (ca. 3.7 M) was purchased from Foote Mineral Co.

(12) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); the complex was formed *in situ* by a modification of this method. This improved procedure was subsequently published by R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 35, 4000 (1970).

(13) L. I. Zakharkin, V. V. Gavrilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Lett.*, 2087 (1963); L. I. Zakharkin, V. V. Gavrilenko, and D. N. Maslin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 926 (1964).

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

(15) *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).

(16) Biological tests carried out in Zoecon Corp. by G. B. Staal. The biological activity of this material was essentially indistinguishable from that of pure 1.

trans mixture in 90% yield.[17] Hematoporphyrin-photosensitized oxygenation[18] of **18** in methanol followed by direct *in situ* reduction of the hydroperoxides with 1.05 equiv of hexamethylphosphorous triamide at −25° produced a mixture of the allylic alcohols **19**, **20**, and **21** in the ratio 55:39:6, respectively. Treatment of this mixture with pyridine removed the allylic halide **20** as the pyridinium salt and allowed isolation of the required allylic alcohol **19** in 40% yield from **18**. The small proportion of the in-chain olefin isomer **21** produced during this photosensitized oxygenation is noteworthy.[5,19]

A Claisen type reaction[6] of **19** with triethylorthoacetate smoothly gave the trans ester **22** (90% yield) with less than 4% of the corresponding cis isomer. Reduction of **22** with sodium dihydrobis(2-methoxyethoxy)aluminate to the alcohol **23** and reoxidation with the chromic acid–dipyridine complex[12] gave the aldehyde **24**, which was acetalized to **25** (75% overall yield from **22**). The lithio derivative of **25** (prepared with lithium–1% sodium in ether at −5°) readily formed an organocopper complex with cuprous iodide (1 equiv) and tetramethylethylenediamine (2 equiv), which was added[20] with high stereoselectivity to methyl 2-butynoate to afford **26**. Hydrolysis of the latter then gave the free aldehyde ester **12** identical with material prepared as described above.

These novel synthetic routes, in particular the first method, allow the preparation of juvenile hormone **1** of high biological activity[16] and the second route can be adapted to the synthesis of biologically-active hormone analogs.

Experimental Section

All substances described herein are racemic compounds; the prefix *dl* is omitted. Preparative thin-layer chromatography was carried out with Merck (Darmstadt) silica gel PF-254. Nmr spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200G spectrophotometer. Mass spectra were measured on 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 3-Methyl-6-oxo-2-*trans*-hexenoate (8). In a 12-l. flask was placed 357 g of sodium methoxide (6.607 mol) under nitrogen, and 2.4 l. of dry dimethylformamide was added. To the mechanically stirred mixture was added 1233 g of trimethyl phosphonoacetate over 2 hr with some cooling in ice water to keep the temperature at 35–40° (only mildly exothermic). After a further 20 min, 6-methyl-5-hepten-2-one (**5**) (844 g) was added over 45 min with cooling in ice water (*T*, 30–50°). The cooling bath was then removed; the mixture was stirred for 1 hr and then set aside for 19 hr at room temperature. The mixture was then poured into aqueous brine and extracted with ether–hexane. The combined organic extracts were washed with aqueous brine, dried, and evaporated. The residue was directly distilled on a spinning-band column to give 550 g of pure methyl *trans*-geranate (**6**), bp 80° (0.45 mm).

To 328 g (1.8 mol) of methyl *trans*-geranate (**6**) in 500 ml of dichloromethane, cooled in an ice water bath, was added over 1.5 hr a suspension of 403 g of technical 85% *m*-chloroperoxybenzoic acid in 3500 ml of dichloromethane with mechanical stirring

(*T*, 20–30°). After the solution was stirred for 1 hr further at 5–10°, excess aqueous sodium sulfite was added and after 15 min (negative starch–I$_2$ test) the mixture was filtered through a large coarse-sintered glass funnel and the insoluble acid washed with more dichloromethane. The filtrate was washed with aqueous sodium sulfite, aqueous NaHCO$_3$, and brine, dried, and evaporated to give 350 g of monoepoxide **7**.

To a solution of 400 g of the crude epoxide **7** in 1500 ml of tetrahydrofuran was added 800 ml of water followed by a solution of 10 ml of 70% perchloric acid in 90 ml of water. After the solution was stirred for 2 hr at room temperature, solid sodium chloride and saturated brine were added, and the mixture was extracted with ether. The organic layer was washed with brine, dried, and evaporated to give 400 g of the diol. To this diol in 1.25 l. of tetrahydrofuran was added a solution of 450 g of sodium metaperiodate in 2 l. of water with mechanical stirring under a nitrogen atmosphere with cooling in ice-water. After the solution was stirred for 20 hr at room temperature, solid sodium chloride and saturated brine were added and the mixture was extracted with ether. The ether layer was washed with brine, saturated NaHCO$_3$, and brine, and dried and the solvent was removed to give 280 g of the aldehyde **8**[7c] (stored at −10° under N$_2$): bp 60° (0.015 mm); ir (CCl$_4$) 2710, 1725, 1650, 1231, 1157 cm^{-1}; nmr (CDCl$_3$) δ 2.18 (d, 3, *J* = 1.5 Hz, C-3 CH$_3$), 2.57 (m, H-4 and H-5), 3.72 (s, 3, COOCH$_3$), 5.73 (broad s, 1, H-2), and 9.86 ppm (CHO).

Anal. Calcd for C$_8$H$_{12}$O$_3$: C, 61.52; H, 7.75. Found: C, 61.41; H, 7.65.

Methyl 6-Hydroxy-3-methyl-7-methylene-2-*trans*-nonenoate (9). To 40 g of magnesium turnings and a crystal of I$_2$ under N$_2$ was added 1.5 l. of dry tetrahydrofuran and 1 g of 2-bromo-1-butene. Gentle warming started the reaction and then 177 g of pure 2-bromo-1-butene (purified by spinning-band distillation) was added over 2.5 hr and the mixture was stirred overnight.

A solution of 165 g of the aldehyde **8** in tetrahydrofuran (750 ml) under argon was cooled to −45° and the above Grignard solution added portionwise over 2.5 hr with mechanical stirring. After the solution was stirred a further 4 hr at −40° (positive Gilman test[21]), saturated aqueous NH$_4$Cl was added dropwise and then the cooling bath was removed. Dilution with saturated aqueous NH$_4$Cl and extraction with ether followed by washing of the organic layer with aqueous NaHCO$_3$ and brine, drying, and solvent removal, gave the crude product (200 g); glpc analysis always showed the presence of some starting aldehyde **8**. Careful distillation gave the allylic alcohol **9**: bp 92–93° (0.015 mm); ir (CCl$_4$) 3595, 1720, 1650, 1235, 1158, 918 cm^{-1}; nmr (CDCl$_3$) δ 1.06 (t, 3, *J* = 7 Hz, CH$_3$CH$_2$), 1.92 (q, 2, *J* = 7 Hz, CH$_3$CH$_2$), 2.18 (d, *J* = 1.5 Hz, C-3 CH$_3$), 3.67 (s, COOCH$_3$), 4.07 (t, 1, *J* = 7 Hz, H-6), 4.93 (d, C=CH$_2$), and 5.70 ppm (broad s, H-2).

Anal. Calcd for C$_{12}$H$_{20}$O$_3$: C, 67.89; H, 9.50. Found: C, 67.78; H, 9.45.

The crude allylic alcohol **9** had a tendency to polymerize on distillation and so in several experiments crude **9** was converted directly to the diester **10** which could be purified readily by distillation.

Preparation of Diester 10. To a mixture of 350 g of the crude allylic alcohol **9** and 925 g of trimethyl orthoacetate was added 6 ml of acetic acid and the mixture was stirred and heated in an oil bath at 110° for 8.5 hr while a slow nitrogen stream was passed over the surface of the solution so that the methanol was distilled out as it formed. The excess reagent was then removed *in vacuo* and the residue rapidly distilled on a spinning-band column to give 300 g of **10**: bp 109–110° (0.02 mm); ir (film) 1740, 1720, 1650 cm^{-1}; nmr (CDCl$_3$) δ 0.98 (t, 3, *J* = 7 Hz, C-7 CH$_2$CH$_3$), 2.18 (d, 3, *J* = 1.5 Hz, C-3 CH$_3$), 2.38 (H-9), 3.72 (s, 6, CO$_2$CH$_3$), 5.13 (m, 1, H-6), and 5.70 ppm (m, 1, H-2).

Anal. Calcd for C$_{15}$H$_{24}$O$_4$: C, 67.13; H, 9.02. Found: C, 67.31; H, 9.06.

Methyl 7-Ethyl-10-hydroxy-3-methyl-2-*trans*,6-*trans*-decadienoate (11). A solution of 49.61 g (0.185 mol) of the diester **10** in 250 ml of dry tetrahydrofuran under argon was cooled to −78° and 26.15 ml (0.101 mol) of a 3.86 *M* solution of LiAlH$_4$ in ether[11] was added slowly with stirring over 1.5 hr. After a further 2.5 hr at −78° the low-temperature cooling bath was removed and the mixture stirred at 0° (ice bath) for 2 hr. Dilution with acidic brine followed by extraction with ether, washing the organic layer with brine, drying, and removal of solvent gave 45 g of residue. This was chromatographed on silica gel (activity III; 1010 g), and elution

(17) When concentrated hydrochloric acid was used, formation of the dichloride predominated; *cf.* M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960).

(18) C. S. Foote, *Accounts Chem. Res.*, 1, 104 (1968).

(19) *Cf.* G. W. K. Cavill and I. M. Coggiola, *Aust. J. Chem.*, 24, 135 (1971); these authors could not detect any of the analogous in-chain olefin isomer from the photosensitized oxygenation of α-farnesene.

(20) M. Biskup, J. B. Siddall, and J. H. Fried, *J. Amer. Chem. Soc.*, 91, 1853 (1969); E. J. Corey, and J. A. Katzenellenbogen, *ibid.*, 91, 1851 (1969).

(21) H. Gilman and F. Schulze, *ibid.*, 47, 2002 (1925).

with 10% ether–benzene gave 36 g (81% yield) of pure **11**: ir (film) 3390, 1720, 1650 cm^{-1}; nmr (CDCl$_3$) δ 0.97 (t, 3, J = 7 Hz, C-7 CH$_2$CH_3), 2.18 (d, 3, J = 1.5 Hz, C-3 CH$_3$), 3.60 (t, 2, J = 7 Hz, H-10), 3.70 (s, 3, CO$_2$CH_3), 5.12 (m, 1, H-6), and 5.70 ppm (m, 1, H-2).

Anal. Calcd for C$_{14}$H$_{24}$O$_3$: C, 69.96; H, 10.07. Found: C, 69.90; H, 10.15.

Oxidation of 11. To a mechanically stirred suspension of 61.4 g of dry chromic acid and 40 g of powdered CaSO$_4$ in dichloromethane (1500 ml) was added 100 ml of pyridine with cooling in ice water. After 20 min, a solution of the alcohol **11** (24.2 g) in dichloromethane (100 ml) was added; the mixture was stirred 1 hr in the ice bath and 1 hr at room temperature. The solution was decanted from the insoluble residue and the latter rinsed several times with more dichloromethane. The combined organic layer was washed with aqueous NaHCO$_3$, water, aqueous HCl, and brine, and dried and the solvent was removed to give 22 g (91.7%) of the pure aldehyde **12**. A small sample was short-path distilled: bp (bath) 85–88° (0.04 mm); ir (CCl$_4$), 2702, 1727, 1652, 1232, 1156 cm^{-1}; nmr (CDCl$_3$) δ 0.98 (t, J = 7 Hz, CH$_2$CH_3), 2.18 (d, J = 1.5 Hz, C-3 CH$_3$), 3.72 (s, COOCH$_3$), 5.11 (H-6), 5.69 (H-2), and 9.83 ppm (t, 1, J = 1.5 Hz, H-10).

Anal. Calcd for C$_{14}$H$_{22}$O$_3$: C, 70.55; H, 9.31. Found: C, 70.41; H, 9.11.

Methyl 10-Chloro-7-ethyl-3-methyl-11-oxo-2-*trans*,6-*trans*-tridecadienoate (14). To 60 g of α-methoxypropyltriphenylphosphonium chloride[5] suspended in dry tetrahydrofuran (450 ml) under N$_2$ at $-78°$ was added 100 ml of 1.59 M n-butyllithium in hexane over 10 min with mechanical stirring. After 1 hr at $-78°$ (negative Gilman test[21]), a solution of 18.7 g of aldehyde **12** in 60 ml of tetrahydrofuran was added and the mixture was stirred overnight at $-78°$. The cooling bath was then removed and the mixture was allowed to come to 10°. Water (250 ml) was added and then after 1 hr the mixture was poured in saturated NaCl–NaHCO$_3$ and extracted with ether–hexane. The extracts were washed with aqueous NaHCO$_3$ and dried (CaSO$_4$–K$_2$CO$_3$) and the solvent was removed. The residue was stirred with pentane, filtered from Ph$_3$PO, and the filtrate evaporated to give 41 g of crude product.

To a mixture of 30 g of sodium acetate in 150 ml of water and 400 ml of acetone cooled in an ice–salt bath was added N-chlorosuccinimide (30 g) with stirring, followed by the dropwise addition of the crude enol ether **13** above dissolved in acetone (100 ml) over 0.5 hr ($-5°$). After 1 hr at $-5°$ a solution of 20 g of sodium bisulfite in 100 ml of water was added and then dilution with brine and extraction with ether–pentane gave the crude chloro ketone. The residue was stirred with pentane and decanted and the pentane-soluble material (37 g) was chromatographed on silica gel (activity III; 700 g). Elution with 50% benzene–hexane and benzene gave 14.9 g (60.3%) of the chloro ketone **14**:[7e] nmr (CDCl$_3$) δ 0.97 (t, 3, J = 7 Hz, C-7 CH$_2$CH_3), 1.10 (t, 3, J = 7 Hz, C-12 CH$_3$), 2.18 (d, 3, J = 1.5 Hz, C-3 CH$_3$), 2.69 (m, 2, H-12), 3.70 (s, 3, CO$_2$CH$_3$), 4.17 (t, 1, H-10), 5.13 (m, 1, H-6), and 5.68 ppm (m, 1, H-2).

Anal. Calcd for C$_{17}$H$_{27}$O$_3$Cl: C, 64.85; H, 8.65. Found: C, 64.68; H, 8.58.

Juvenile Hormone (1). To a solution of 1.8 g of the chloro ketone **14** in 50 ml of tetrahydrofuran under N$_2$ at $-78°$ (Dry Ice–acetone bath) was added dropwise with stirring a cold (*ca.* $-40°$) solution of excess methylmagnesium chloride (4 equiv) in tetrahydrofuran (30 ml) over 15 min. After the solution was stirred for 7 hr at $-78°$, saturated aqueous NH$_4$Cl (10 ml) was added dropwise; the mixture was diluted with brine and extracted with ether to give 1.9 g of chlorohydrin **16**. To a solution of this crude chlorohydrin in methanol (25 ml) was added 4 g of dry K$_2$CO$_3$ and the mixture was stirred for 2 hr. Dilution with brine and extraction with ether gave 1.7 g of product. This was taken up in redistilled pentane and filtered through 3 g of Woelm neutral alumina (activity IV) to give 1.50 g of *dl*-hormone **1**, identical (ir, nmr, tlc, glpc) with authentic material.[71]

Analysis by glpc indicated purity of >95° (**1** + **3**). The ratio of trans,trans,cis (**1**) to all trans (**3**) isomers was established as 82:18 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.[7b]

Slow addition of a cold solution of the chloro ketone **14** in tetrahydrofuran *to* excess Grignard reagent at $-78°$ gave identical results.

A reaction was also run in dilute tetrahydrofuran with both solutions precooled and then mixed at $-95°$ (methylene dichloride–liquid N$_2$ bath). After 25 hr at $-95°$ excess Grignard was destroyed at $-95°$ and the mixture worked up as above to give a mixture of **1** and **3** in the ratio 86:14.

cis- and *trans*-**1-Chloro-4-methyl-3-hexene (18).** To a 22.8-f portion (0.20 mol) of the tertiary alcohol **17**[7b] was added 200 ml og aqueous 2 N hydrochloric acid[17] (0.40 mol) with vigorous stirring at room temperature within 5 min. Stirring was continued for 1 hr while the mixture was heated to 60° and then for 3 hr at 55–65°. The reaction mixture was then cooled and poured into ice and extracted with pentane. The pentane extracts were washed with water, 10% potassium bicarbonate solution, and brine and dried. The crude chloride isomer mixture, obtained on removal of most of the solvent by distillation through a 2-ft Vigreux column, was distilled to give 20.1 g (76% yield) of **18**, bp 135–140°, which by vpc was 94% pure (cis:trans $\approx$ 25:75): ir (film) 1665, 725, 665 cm^{-1}; nmr (CDCl$_3$) δ 1.00 (t, 3, J = 7.5 Hz, H-6), 1.64 (s, trans C-4 CH$_3$), 1.71 (d, J = 1.5 Hz, cis C-4 CH$_3$), 2.04 (q, 2, J = 7.5 Hz, H-5), 2.47 (q, 2, J = 7.5 Hz, H-2), 3.51 (t, 2, J = 7.5 Hz, H-1), and 5.17 ppm (H-3).

In another comparable run the crude product was filtered through Merck silica gel in pentane, and then distilled to give a sample with bp 92.5–94° (96 mm), which was 98% pure by glpc analysis.

Anal. Calcd for C$_7$H$_{13}$Cl: C, 63.39; H, 9.88; Cl, 26.73. Found: C, 63.53; H, 9.75; Cl, 26.68.

5-Chloro-2-ethylpent-1-en-3-ol (19). A 47.3-g portion (0.357 mol) of the chloride isomer mixture **18** and 70 mg of hematoporphyrin were dissolved in 700 ml of anhydrous methanol. The photosensitized oxygenation was conducted in a water-jacketed reaction flask into which the oxygen was dispersed at a convenient rate by means of two extracoarse gas dispersion tubes. The solution was irradiated externally with a Sylvania "Sungun" Type DWY 625-W tungsten–iodine lamp, installed 10 cm below the bottom of the flask. Efficient water cooling of the jacket was essential to keep the reaction temperature at 28° during the 15-hr reaction period (reaction followed by glpc). The oxygen then was replaced by nitrogen and the three isomeric hydroperoxides were reduced to the allylic alcohols **19, 20,** and **21,** by addition (over 45 min) of 61.2 g of hexamethylphosphorous triamide (0.375 mol, 1.05 equiv) under nitrogen to the reaction mixture cooled to $-25°$. The solution was stirred for 75 min at -25 to 15° and then freed from methanol *in vacuo* (bath temperature 30°). Ice and 2 N hydrochloric acid were added to the residue and the aqueous layer was extracted with ether. The combined extracts were carefully washed with water, saturated sodium bicarbonate solution, water, and brine and dried. The residue (44.2 g of yellow oil) obtained on evaporation of the solvent *in vacuo* consisted of **19, 20,** and **21** in the ratio 55:39:6, as estimated by glpc analysis. It was used without purification in the selective pyridinium salt formation described below.

A sample of the crude alcohol mixture from another run was chromatographed on preparative thin-layer plates developed with hexane–ethyl acetate (88:12). By running the plates three times, the allylic alcohols **19** and **20** were completely separated from each other. On elution with ether, the faster running band provided chloro alcohol **19**, which by glpc analysis proved to be >96% pure: bp (bath, short path) 49–53° (9 mm); ir (film) 3350, 3070, 1650, 915 cm^{-1}; nmr (CDCl$_3$) δ 1.09 (t, J = 7.5 Hz, CH_3CH$_2$–), 1.80–2.33 (m, H-2 and H-5), 3.68 (dt, J = 7 Hz, J = 2 Hz, H-1), 4.35 (t, J = 6.5 Hz, H-3), 4.94 and 5.12 ppm (4-CH$_2$).

Anal. Calcd for C$_7$H$_{13}$OCl: C, 56.56; H, 8.82; Cl, 23.86. Found: C, 56.41; H, 8.92; Cl, 23.68.

The more polar band consisted of 85% allylic chloride **20** (with three impurities in relative amounts of 10, 1, and 4%): ir (film) 3400 cm^{-1}; nmr (CDCl$_3$) δ 0.89 (t, J = 7 Hz, H-6), 1.29 (4-CH$_3$), 1.2–1.8 (m, H-5), 4.10 (dd, J = 4 Hz and J = 2 Hz, H-1), and 5.80–5.79 ppm (m, 2 and H-3).

The selective pyridinium salt formation of **20** in the presence of **19** and **21** was achieved by heating the entire crude alcohol mixture (44.2 g) above, in 100 ml of dry pyridine (about 4 equiv) under nitrogen at 50° for 9 hr (reaction followed by glpc). This solution was then poured into ice and extracted with ether. The extracts were washed with 2 N hydrochloric acid, water, saturated NaHCO$_3$, water, and brine, and dried, and the solvent removed. The crude chloro alcohol was fractionally distilled to give 20.1 g (38% overall yield from **18**) of pure **19**, bp 57–59° (0.75 mm). The chloride **19** was shown to be stable to pyridine under the above conditions.

One small fraction from this fractional distillation, which contained 15% of **21** besides 80% of **19**, was chromatographed on silica gel. By elution with petroleum ether–ethyl acetate (9:1), a

fraction containing 75% **21** (as estimated by glpc analysis) was obtained. which on further purification by preparative glpc gave a pure sample of **21**: ir (film) 3350, 1665 cm^{-1}; nmr (CDCl$_3$) δ 1.55–1.76 (7 H, OH and 4- and 5-CH$_3$), 3.62 (dt, J = 7 Hz and 1.5 Hz, H-1), 4.25 (t, J = 7 Hz, H-3), and 5.07–5.80 ppm (m, H-5).

The photosensitized oxygenation of **18** was also carried out as above but in pyridine as the solvent, and also with rose bengal as the sensitizer (in methanol or pyridine). The reduction of the hydroperoxides could also be carried out with trimethyl phosphite or with aqueous sodium borohydride. However, the above described procedure was found to give the best yield of **19** with fewer byproducts.

Ethyl 7-Chloro-4-ethyl-4-*trans*-heptenoate (22). A mixture of 19.4 g (0.131 mol) of the allylic alcohol **19**, 148 g (7 equiv) of triethyl orthoacetate, and 0.6 ml (0.06 equiv) of propionic acid was heated in an oil bath at 116–118° with stirring for 7 hr with a slow stream of argon being allowed to pass over the surface of the liquid such that ethanol plus some triethyl orthoacetate slowly distilled off. After cooling, the reaction mixture was poured into ice and extracted with ether. The organic layer was washed with saturated aqueous NaHCO$_3$ and brine and dried, the solvent was removed, and the residue was fractionally distilled to give 25.4 g (89% yield) of the trans ester **22**: bp 94–96° (0.6 mm) (the glpc analysis showed the presence of <3% of cis isomer); ir (film) 1735, 1665 cm^{-1}; nmr (CDCl$_3$) δ 0.98 (t, J = 7.5 Hz, CH_3CH$_2$), 1.25 (t, J = 7.5 Hz, -CO$_2$CH$_2$CH_3), 3.49 (t, J = 7 Hz, H-1), 4.14 (q, J = 7 Hz, CH$_3$CH_2O-), and 5.17 ppm (t, J = 7 Hz, H-3).

Anal. Calcd for C$_{11}$H$_{19}$O$_2$Cl: C, 60.40; H, 8.76; Cl, 16.21. Found: C, 60.36; H, 8.87; Cl, 16.26.

7-Chloro-4-ethyl-*trans*-4-hepten-1-ol (23). To a stirred solution of sodium dihydrobis(2-methoxyethoxy)aluminate (0.25 mol) in tetrahydrofuran (40 ml) and ether (330 ml) at −20° was added over 1 hr a solution of the ester **22** (22.9 g, 0.102 mol) in ether (200 ml). After 5 hr at −15 to −10°, cold 2 N aqueous NaOH (250 ml) was added portionwise with cooling. The two layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine and dried, and the solvent was removed. Distillation of the residue gave 17.5 g of the alcohol **23**: bp 71° (0.10 mm); ir (film) 3320, 1660 cm^{-1}; nmr (CDCl$_3$) δ 0.96 (t, J = 7.5 Hz, CH_3CH$_2$-), 1.5–2.7 (7 H, -OH and allylic -CH$_2$-), 3.51 (t, J = 7 Hz, H-1), 3.65 (t, J = 6 Hz, H-7), and 5.17 ppm (t, J = 7 Hz, =CHCH$_2$-).

Anal. Calcd for C$_9$H$_{17}$OCl: C, 61.18; H, 9.70; Cl, 20.07. Found: C, 61.06; H, 9.51; Cl, 19.86.

7-Chloro-4-ethyl-*trans*-4-hepten-1-al (24). To a mechanically stirred suspension of 63 g (6 equiv) of CrO$_3$ and 10 g of anhydrous calcium sulfate powder in 3 l. of dry dichloromethane at 3–5° was added slowly 101.5 ml (12 equiv) of pyridine. After a further 15 min, a solution of 18.4 g of the alcohol **23** in 200 ml of dichloromethane was added over 30 min. Stirring under an argon atmosphere was continued at 3–5° for 1.5 hr and at 5–16° for 2 hr further. Then ice and saturated aqueous KHCO$_3$ were added, the two phases were separated, and the aqueous layer was extracted

with CH$_2$Cl$_2$. The combined organic layers were washed with cold aqueous KHCO$_3$, water, cold 2 N HCl, water, and brine, dried, and the solvent was removed. The brown residue was taken up in ether, filtered through a little Celite, and dried (CaSO$_4$), and the solvent removed to give 17.5 g of the aldehyde **24**. A small sample was short-path distilled: bp (bath) 65° (1.4 mm); ir (film) 2810, 2710, 1720, 1660 cm^{-1}; nmr (CDCl$_3$) δ 1.00 (t, J = 7.5 Hz, CH_3CH$_2$-), 3.51 (t, J = 7 Hz, H-1), 5.17 (t, J = 7 Hz, H-3), and 9.85 ppm (-CHO).

Anal. Calcd for C$_9$H$_{15}$OCl: C, 61.88; H, 8.66; Cl, 20.30. Found: C, 62.03; H, 8.78; Cl, 20.26.

Acetalization of 24. To a solution of 17.2 g of the chloro aldehyde **24** in 600 ml of benzene was added 52 ml of ethylene glycol and 200 mg of p-toluenesulfonic acid and the mixture was stirred and refluxed 15 hr with a Dean–Stark water separator. The reaction mixture was then poured into ice-cold aqueous KHCO$_3$ and the organic phase was washed with brine and dried, and the solvent was removed. The residue was distilled to give 16.2 g of the acetal **25**: bp 79–80° (0.12 mm); nmr (CDCl$_3$) δ 0.99 (t, J = 7.5 Hz, CH_3CH$_2$-), 3.52 (t, J = 7 Hz, H-1), 3.8–4.0 (m, -OCH_2CH_2O-), 4.91 (t, J = 4.5 Hz, H-7), and 5.18 ppm (t, J = 7 Hz, H-3).

Anal. Calcd for C$_{11}$H$_{19}$O$_2$Cl: C, 60.40; H, 8.76; Cl, 16.21. Found: C, 60.31; H, 8.53; Cl, 16.13.

Methyl 7-Ethyl-3-methyl-10-oxo-2-*trans*,6-*trans*-decadienoate (12). To 0.165 g of lithium (1% sodium) in 15 ml of ether at −10° under argon was added 2.58 g of the chloro acetal **25** and the mixture was stirred at −10°–0° for 3 hr. The solution was then cooled to −30° and 2.20 g of cuprous iodide, 2.75 g of tetramethylethylenediamine, and 50 ml of dry ether were added. After the solution was stirred for 1 hr, the Gilman test[21] was negative and the reaction was cooled to −78° and 1.12 g of methyl 2-butynoate was added. After 2 hr at −78°, methanol (5 ml) was added dropwise and then the mixture was diluted with saturated aqueous NH$_4$Cl and extracted with ether in the usual way. The product was purified by preparative thinlayer chromatography (developed in hexane–ethyl acetate, 85:15) to give 1.5 g (45%) of **26**: bp (bath short path) 106–107° (0.03 mm); ir (CCl$_4$) 1721, 1650, 1591, 1152 cm^{-1}; nmr (CDCl$_3$ (0.97 (t, J = 7 Hz, CH$_2$CH_3), 2.18 (d, J = 1.5 Hz, C-3 CH$_3$), 3.72 (s, COOCH$_3$), 3.94 (s, 4, OCH_2CH_2O), 4.90 (t, J = 6 Hz, H-10), 5.15 (m, 1, H-6), and 5.74 ppm (H-2).

Anal. Calcd for C$_{16}$H$_{26}$O$_4$: C, 68.05; H, 9.29. Found: C, 67.95; H, 9.09.

The acetal (93.5 mg) was dissolved in 5 ml of distilled tetrahydrofuran and 5 ml of 0.5 N HCl was added. The reaction was stirred at room temperature for 70 hr, then worked up by pouring into saturated sodium chloride solution and extracted with pentane. The pentane was washed with 10% NaHCO$_3$, water, and brine, dried, and evaporated to give the aldehyde **12**, identical (ir, tlc, glpc, nmr) with that prepared from **11**.