Application of the Claisen Rearrangement to the Synthesis of Trans Trisubstituted Olefinic Bonds. Synthesis of Squalene and Insect Juvenile Hormone

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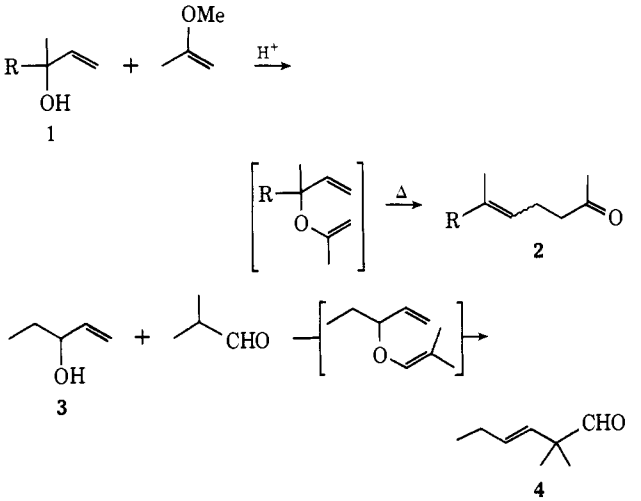
Abstract: A method of predicting the stereochemical outcome of the Claisen rearrangement has been developed. Using the results of this study, we have devised a route to trans trisubstituted olefinic bonds for use in isoprenoid synthesis. This route has been used for the synthesis of squalene and both racemic and optically active forms of the C-18 insect juvenile hormone.

The stereoselective synthesis of trisubstituted olefins has received considerable attention in recent years due to interest in the synthesis of insect juvenile hormone[1] and to Johnson's research into polyolefin cyclizations.[2] While demonstrating that polyolefinic precursors could be cyclized to form steroids,[3] Johnson showed that the ring junction stereochemistry of a product was dependent on the stereochemistry of the olefinic precursor.[4] In a similar vein, it has been shown that the biological activity of insect juvenile hormone and its synthetic mimics was dependent on the stereochemistry of the olefinic bonds.[5] In both studies, the stereochemical purity of the olefinic bonds was of paramount importance.

Many naturally occurring isoprenoids contain trans trisubstituted olefinic bonds having a 1,5 arrangement with respect to one another. A general synthetic route to isoprenoids must therefore combine high stereoselectivity in the formation of the olefinic bond with the ability to build an isoprenoid chain by repetition of the synthetic procedure. While several investigators[6] had adequately solved one or other of these problems, only Cornforth's procedure[7] for the synthesis of squalene had provided a solution to both. Our observations on the stereoselectivity of the Claisen and Cope rearrangements[8] led to the realization that the Claisen rearrangement could form the basis of a simple and convenient route to isoprenoids.[9] This paper describes the development of a highly stereoselective version of the Claisen rearrangement which provided a convenient route to trans trisubstituted olefinic bonds. This procedure has been employed in the synthesis of squalene[10] and insect juvenile hormone.[11]

The Claisen rearrangement had been employed in the preparation of isoprenoids by Saucy and Marbet.[12] They treated a tertiary allylic alcohol **1** with 2-methoxypropene in the presence of an acid catalyst to obtain a γ,δ-unsaturated ketone **2**, from which a new tertiary allylic alcohol could be obtained. The stereochemistry about the newly formed olefinic bond was shown to be about 60% trans and 40% cis. In a single instance, Brannock[13] had shown that a Claisen rearrangement involving the reaction of a secondary allylic alcohol, 1-penten-3-ol (**3**), with isobutyraldehyde gave "an excellent yield of *trans*-2,2-dimethyl-4-heptenal (**4**)." Brannock did not, however, provide a quantitative cis:trans isomer ratio.



We therefore set out to investigate factors which determine the stereoselectivity of the Claisen rearrangement. Variously substituted allylic alcohols were prepared by the addition of a Grignard reagent to a 2-substituted acrolein. Conversion of the allylic alcohols **5a–c** to allyl vinyl ethers **6a–c** was accomplished by mercuric acetate catalyzed transetherification using ethyl vinyl ether.[14] The allyl vinyl ethers were pyrolyzed in sealed tubes to obtain stereoisomeric mixtures of γ,δ-unsaturated aldehydes **7a–c** in quantitative yields. The cis:trans isomer ratios were determined by vapor phase chromatography. In all cases the cis

(1) For two interesting reviews see (a) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970); (b) J. B. Sidall, "Chemical Ecology," E. Sondheimer and J. B. Simeone, Ed., Academic Press, New York, N. Y., 1970, pp 282–289.

(2) W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).

(3) W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Amer. Chem. Soc.*, **90**, 2994 (1968).

(4) W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jacques, and J. K. Crandall, *ibid.*, **86**, 1959 (1964).

(5) K. H. Dahm, B. M. Trost, and H. Roller, *ibid.*, **89**, 5292 (1967).

(6) For recent reviews see (a) D. J. Faulkner, *Synthesis*, **2**, 175 (1971); (b) J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, **25**, 135 (1971).

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

(8) C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2873 (1969).

(9) D. J. Faulkner and M. R. Peterson, *ibid.*, 3243 (1969).

(10) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(11) D. J. Faulkner and M. R. Peterson, *ibid.*, **93**, 3766 (1971).

(12) (a) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967); (b) R. Marbet and G. Saucy, *ibid.*, **50**, 2095 (1967).

(13) K. C. Brannock, *J. Amer. Chem. Soc.*, **81**, 3379 (1959).

(14) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966). In our hands, these reactions were not reproducible.

isomer had a lower retention time than the trans isomer, although the two peaks may overlap. In such cases, reduction of the aldehyde with sodium borohydride followed by acetylation gave a mixture of acetates, which were more easily separated on vapor phase chromatography.

From these cis:trans isomer ratios (Table I) and other data from the literature,[8] Perrin recognized that there was a close agreement between the cis:trans isomer ratio in products from the Claisen rearrangement and the ratio of axial:equatorial conformations of the correspondingly substituted cyclohexane at the temperature of the Claisen rearrangement. By using recommended values of $\Delta G°$, the free-energy change for the conversion of the substituent from the equatorial to the axial conformation on a cyclohexane ring, we were able to predict cis:trans isomer ratios in simple examples of the Claisen rearrangement. Thus, the proportion of trans isomer increased as the bulk of the substituent R_2 was increased and decreased as the reaction temperature was increased.

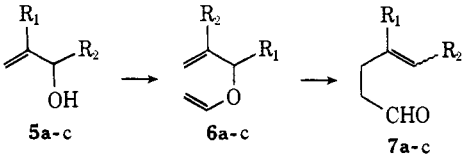
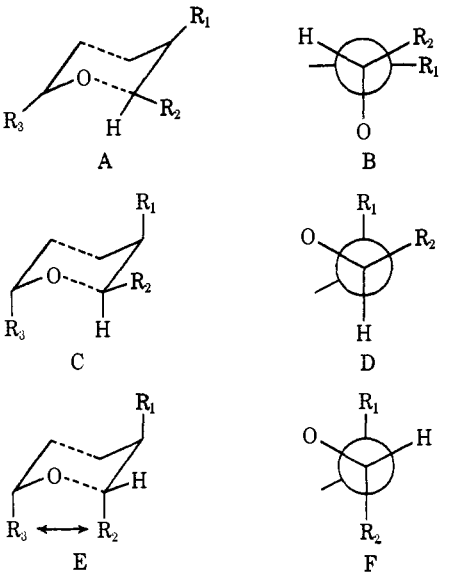


Table I

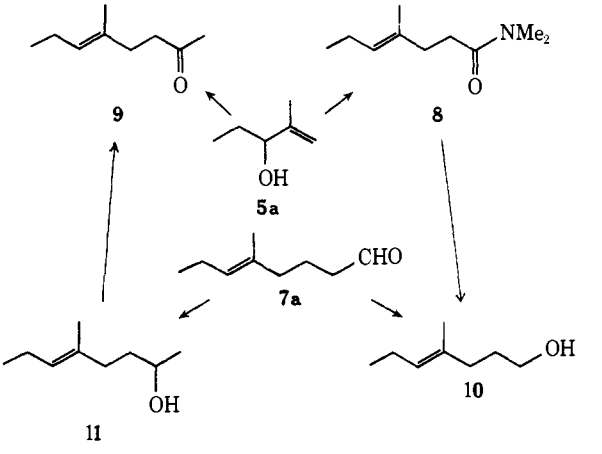
Reaction	R_1	R_2	Temp, °C	Cis:trans ratio (7)	Predicted axial:equatorial ratio
6a → 7a	Me	Et	110	10:90	9:91
6a → 7a	Me	Et	205	14:86	14:86
6b → 7b	Me	*i*-Pr	110	7:93	6:94
6c → 7c	Et	Et	110	10:90	9:91

Using the established[15] chair model (A) for the transition state of the Claisen rearrangement, we would have predicted an interaction between groups R_1 and R_2 (B) such that increasing the bulk of R_1 would have decreased the proportion of trans olefin in the product. Since the cis:trans isomer ratios in products **7a** and **7c** were identical, we suggest a "cyclohexane-like" transition state (C), in which all six centers are tetrahedral and substitutents R_1 and R_3 occupy axial conformations D. The trans olefinic bond results from the transition state C with an equatorial substituent R_2 (D), while the cis olefin results from transition state E with an axial substituent R_2 (F). From the "cyclohexane-like" model, we predicted tht increasing the bulk of the axial substituent R_3 would cause a large 1,3 diaxial interaction in conformer E, thereby increasing the proportion of conformer C in the transition state and increasing the proportion of trans isomer in the product.

Two experiments were sufficient to prove the validity of these arguments. The reaction of allylic alcohol **5a** with dimethylacetamide dimethyl acetal[16] in xylene solution at 140° gave an excellent yield of the amide **8**



which consisted of 99.4% trans olefin and 0.6% cis olefin. Similarly, a mixture of the allylic alcohol **5a**, 2 molar equiv of isopropenyl methyl ether, and catalytic quantities of oxalic acid and hydroquinone was heated in a sealed tube at 110° for 24 hr to obtain a 76% yield of the methyl ketone **9** which contained less than 1% of its cis isomer. This corresponded with the cis:trans isomer ratio which was calculated using ΔG values for a 1,3 diaxial interaction in the cyclohexane system.

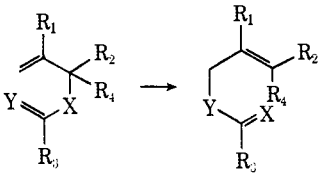


Since the proportion of cis isomer in each case was less than 1%, we felt obliged to confirm that we were observing a true isomer ratio. We therefore converted the aldehyde **7a**, which contained a conspicuous 10% of the cis isomer, into the corresponding alcohol **10** with sodium borohydride in methanol and compared the product with the alcohol **10** produced in an unsuccessful attempt to reduce the amide **8** to the aldehyde using lithium triethoxyaluminum hydride.[17] Comparison of vapor phase chromatography traces confirmed the assignment of cis and trans isomers and the proportion of each in the mixtures. Similarly, reaction of the stereoisomeric mixture of aldehydes **7a** with methylmagnesium iodide and oxidation of the resulting alcohol **11** with Jones reagent gave a mixture of stereoisomeric methyl ketones **9**, in which the 90:10

(15) W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).
(16) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964).
(17) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **86**, 1089 (1964).

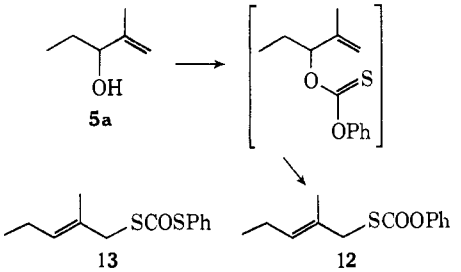
trans:cis isomer ratio was clearly defined on vapor phase chromatography. Again the stereochemical assignments were confirmed.

Having established the value of our transition state model in predicting the stereochemical outcome of the Claisen rearrangement, we sought to determine whether this treatment might be applied to other [3,3] sigmatropic rearrangements. We had previously demonstrated that analysis of the transition state of both Claisen and Cope rearrangements allowed us to predict the stereochemical outcome of these rearrangements provided that R_4 was hydrogen. Where R_2 and R_4

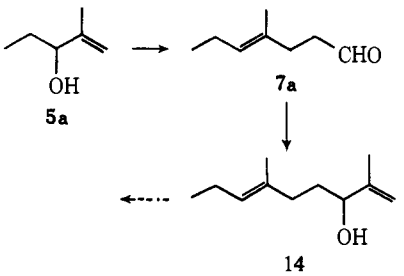


were both alkyl groups, quantitative predictions were less reliable. For example, the combined Claisen and Cope rearrangements investigated by Thomas[18] are too complex to allow an accurate prediction of the cis: trans isomer rations.

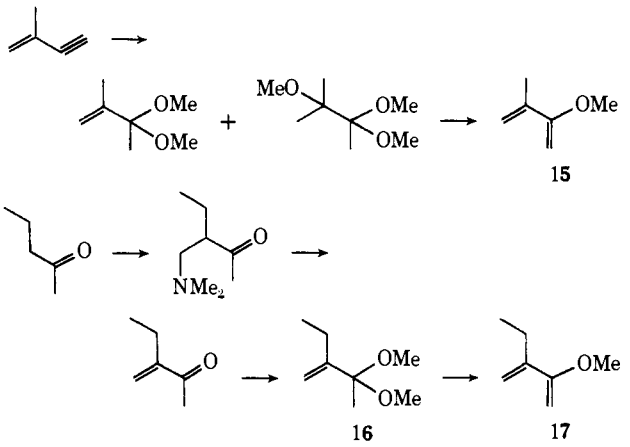
We were particularly interested in the effect of introducing sulfur into the six-membered ring. We expected that the heteroatom would distort the ring and decrease the stereoselectivity of the rearrangement. The allylic alcohol **5a** was treated with phenyl chlorothionoformate and pyridine solution.[19] The thiolcarbonate **12**, formed in 67% yield by rearrangement of the intermediate allylic thionocarbonate, was shown by vpc analysis to contain 96.5% trans olefin and 3.5% cis olefin. Similarly, the reaction between the allylic alcohol **5a** and phenyl dithiochlorocarbonate gave a poor yield of the dithiolcarbonate **13**, which contained >99% of the trans olefin. When we compare the stereoselectivity of the thionocarbonate to thiolcarbonate rearrangement with that of Johnson's orthoester rearrangements,[10] we find that substitution of S for CH_2 in the six-membered ring has indeed caused a decrease in stereoselectivity of olefin formation.



In order to apply the Claisen rearrangement to isoprenoid synthesis, we developed two alternative routes, both of which were capable of repetitive application. Using a suitable allylic alcohol **5a** as a model compound, we prepared the γ,δ-unsaturated aldehyde **7a** using the methods described previously. The aldehyde **7a** was allowed to react with isopropenylmagnesium bromide in tetrahydrofuran at 0° to obtain the allylic alcohol **14**. The overall result of this series of reactions was the addition of an isoprene unit with regeneration of the starting functionality. Since the newly formed trans olefinic bond was contaminated with 10% of the cis isomer and the transetherification reaction proved unreliable, this first route did not appear to be particularly practical.



By adding a five carbon unit, 3-methoxyisoprene (**15**), to the allylic alcohol, we predicted that less than 1% of the cis isomer would be formed in the Claisen rearrangement. At the same time, the overall synthetic procedure would be simplified. The preparation of 3-methoxyisoprene (**15**) was accomplished, following the procedures of Favorskaya and Kotylov–Shahkmatov,[20] by the addition of methanol to 2-methyl-1-buten-3-yne using a mercuric ion catalyst, followed by distillation of the crude product from a mixture of acetic anhydride and pyridine.



Alternatively, this and other 2-alkyl-3-methoxydienes may be prepared from the corresponding α,β-unsaturated ketones. For example, the Mannich base from 2-pentanone, formaldehyde, and dimethylamine was treated with dimethyl sulfate to obtain a salt, which was in turn decomposed with sodium hydroxide to obtain 2-ethyl-1-buten-3-one in good yield.[21] Treatment of ketone with trimethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the corresponding dimethyl ketal, 3,3-dimethoxy-2-ethyl-1-butene (**16**). The dienyl ether, 2-ethyl-3-methoxy-1,3-butadiene (**17**), was prepared by treatment of the ketal **16** with pyridine–acetic acid at elevated temperatures.

The allylic alcohol **5a** and excess 3-methoxyisoprene (**15**) were heated in a sealed tube at 110° for 18 hr to obtain 2,6-dimethyl-1,6-nonadien-3-one (**18**), which was immediately reduced with sodium borohydride in

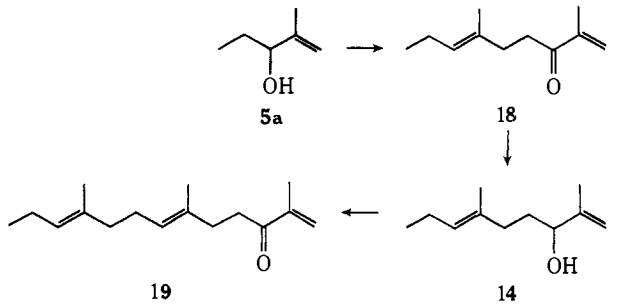
(18) (a) A. F. Thomas, *J. Amer. Chem. Soc.*, 91, 3281 (1969); (b) A. F. Thomas and M. Ozainne, *J. Chem. Soc. C*, 220 (1970).

(19) D. L. Garmaise, A. Uchijama, and A. F. McKay, *J. Org. Chem.*, 27, 4509 (1962).

(20) I. A. Favorskaya and N. N. Kotylov-Shakhmatov, *Zh. Obshch. Khim.*, 27, 2406 (1957).

(21) This result contrasted sharply with the very low yield obtained when the Mannich base was thermally decomposed.

methanol at 0° to obtain 2,6-dimethyl-1,6-nonadien-3-ol (**14**) in 67% overall yield. After comparing this product with the stereoisomeric mixture obtained previously, we concluded that we could not detect the cis isomer. We therefore assume that this reaction was essentially stereospecific. When 2,6-dimethyl-1,6-nonadien-3-ol (**14**) was allowed to react with 3-methoxyisoprene under the conditions described previously, 2,6,10-trimethyl-1,6,10-tridecatrien-3-one (**19**) was formed in 55% yield. The lower yield in this reaction was probably due to the presence of an additional olefinic bond which provided an additional source of side reactions.



In reactions involving 3-methoxyisoprene,[22] we noted that the diene was consumed more rapidly than the allylic alcohol despite the addition of hydroquinone to inhibit free radical polymerization. Following these reactions by vpc, we observed the formation of many by-products, presumably by an acid-catalyzed polymerization. These by-products presented little problem since they were easily separated from the required products by column chromatography. By using the ketal, 3,3-dimethoxy-2-ethyl-1-butene, in place of 3-methoxyisoprene we usually obtained a smaller quantity of by-products, but since the reaction was slower, no real advantage accrued. We feel, therefore, that the choice of reagent should be governed by the relative ease of preparation.

The choice of acid catalyst depends largely on the reagent involved. We found that phosphoric acid was the preferred catalyst for use with vinyl ethers, but oxalic acid should be used with isopropenyl and related ethers. Since oxalic acid was slowly consumed during the pyrolysis reactions we substituted perchlorohomocubanecarboxylic acid,[23] a heat stable acid of similar strength, in reactions involving long reaction times. The use of a weaker acid, 2,4-dinitrophenol, has been suggested by Johnson[24] for use in highly sensitive reactions, but removal of this acid, which must be used in equimolar quantities, was relatively troublesome. Recently, Cookson[25] has suggested the use of *o*-nitrobenzoic acid for sequential Claisen–Cope reactions. It has been our experience that there is no certain way to predict the best acid catalyst for a given reaction but, in general, the weakest acid which catalyzed the reaction gave the highest yields.

Synthesis of Squalene

Squalene was isolated from shark liver oil by Tsujimoto in 1906.[26] The structure of squalene was elucidated by Karrer[27] who showed that squalene was represented by a "tail-to-tail" linkage of two farnasyl units. Using X-ray crystallographic techniques, Nicholaides and Laves[28] showed that squalene possessed the all-trans stereochemistry.

Squalene has been synthesized by the coupling of two farnesyl units[29] and by a Wittig reaction of geranylacetone and the bis(triphenylphosphonium) salt of 1,4-dibromobutane.[30] Cornforth[7b] devised the first synthesis of squalene in which the olefinic linkages were formed in a stereoselective manner. Our route to squalene followed the strategy of Cornforth's synthesis but allowed a considerable improvement in the stereochemical purity of the product. A similar synthetic route employing ethyl orthoacetate as reagent in the Claisen rearrangements was developed by Johnson's group. Both synthetic procedures were presented in a joint communication.[23] Recently, Johnson has disclosed a synthesis of squalene using the Claisen rearrangement of chloro ketals.[31]

Cornforth's strategy for the synthesis of squalene required that the molecule be assembled in a symmetrical manner from the midpoint outwards. In order to use our stereoselective version of the Claisen rearrangement for the synthesis of squalene, we required the bis(allylic alcohol) **20** as starting material. Succindialdehyde, obtained by acid-catalyzed hydrolysis of 2,5-dimethoxytetrahydrofuran, was treated with isopropenylmagnesium bromide in tetrahydrofuran to obtain a 61% yield of the bis(allylic alcohol) **20**. Treatment of the bis(allylic alcohol) **20** with 5 molar equiv of 3-methoxyisoprene (**15**) in toluene solution containing small amounts of oxalic acid and hydroquinone at 140° for 24 hr gave the C-20 tetraenedione **21**, which was immediately reduced with sodium borohydride in methanol at 0° to obtain the C-20 tetraenediol **22** in 57% overall yield.

Repetition of the two-step sequence gave the C-30 hexanediol **23** in 33% overall yield. As had been observed previously, the yield obtained in the Claisen rearrangement decreased as the length of the isoprenoid chain increased. Analysis of the C-30 hexanediol **23** by vapor phase chromatography revealed that the product contained better than 99% all-trans isomer. In order to obtain squalene (**25**) we had to rearrange the terminal double donds and reduce off the functional groups. We had intended to perform the rearrangement with phenyl chlorothionoformate, but we could not find a convenient method of reducing the resulting thiolcarbonate to the corresponding hydrocarbon. We therefore used thionyl chloride in ether at 0°, conditions

(22) Hydroquinone was added to inhibit free radical polymerization of 3-methoxyisoprene.

(23) K. V. Scherer, Jr., G. A. Ungefug, and R. S. Lunt, III, *J. Amer. Chem. Soc.*, **88**, 2859 (1966).

(24) 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).

(25) R. C. Cookson and N. R. Rogers, *Chem. Commun.*, 248 (1972).

(26) M. Tsujimoto, *J. Chem. Ind. Jap.*, **9**, 953 (1906).

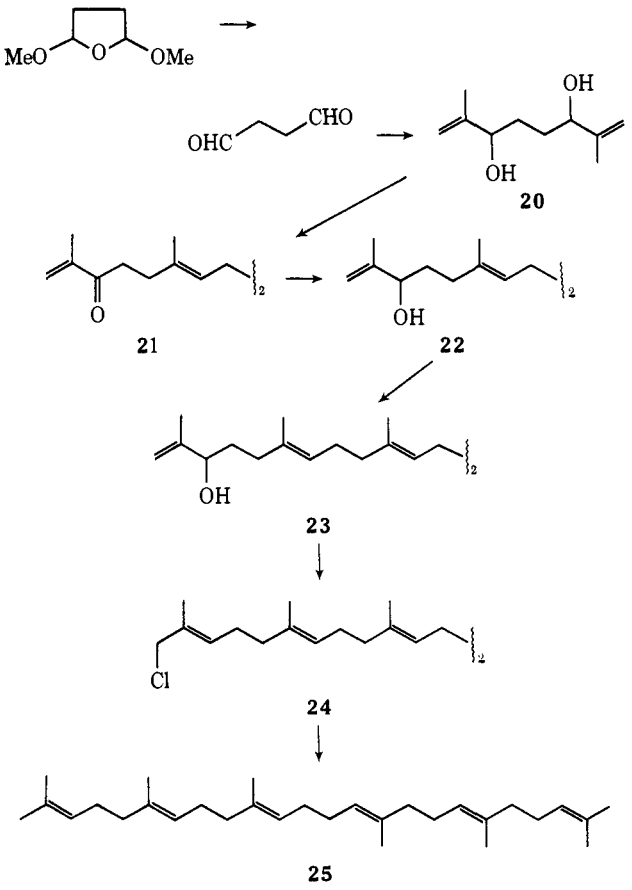
(27) P. Karrer, A. Helfenstein, H. Wehrli, and A. Wettstein, *Helv. Chim. Acta*, **13**, 1084 (1930).

(28) (a) N. Nicolaides and F. Laves, *J. Amer. Chem. Soc.*, **74**, 5204 (1954); (b) *Z. Kristallogr., Kristallgeometrie, Kristallphys., Kristallchem.*, **122**, 283 (1965).

(29) (a) P. Karrer and A. Helfenstein, *Helv. Chim. Acta*, **14**, 78 (1931); (b) O. Isler, R. Ruegg, L. Chopard-dit-Jean, H. Wagner, and K. Bernhard, *ibid.*, **39**, 897 (1956); (c) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969); (d) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969).

(30) (a) S. Trippett, *Chem. Ind. (London)*, 80 (1956); (b) D. W. Dicker and M. C. Whiting, *ibid.*, 351 (1956); (c) *J. Chem. Soc.*, 1994 (1958); see also (d) J. Schmitt, *Justus Liebigs Ann. Chem.*, **547**, 115 (1941); (e) E. H. Farmer and D. A. Sutton, *J. Chem. Soc.*, 116 (1942).

(31) L. Werthemann and W. S. Johnson, *Proc. Nat. Acad. Sci. U. S.*, 1465, 1810 (1970).



which were reported to permit a SNi′ reaction,[32] to obtain a dichloride in which the olefin bonds were rearranged. The crude dichloride **24** was immediately reduced with lithium aluminum hydride in ether to obtain squalene (**25**) in 48% yield after chromatography. Analysis of the squalene by vapor phase chromatography showed a single major peak having an identical retention time with that of authentic squalene obtained from shark liver oil. Minor impurities of unknown structure constituted less than 5% of the product. Although we encountered some relatively low yields in this reaction sequence, the high stereoselectivity of Claisen rearrangement provided ample compensation. We obtained squalene having better than 99% trans isomer at each olefinic linkage in 6% overall yield from the diol **20**. Digeranyl was also obtained by this route.

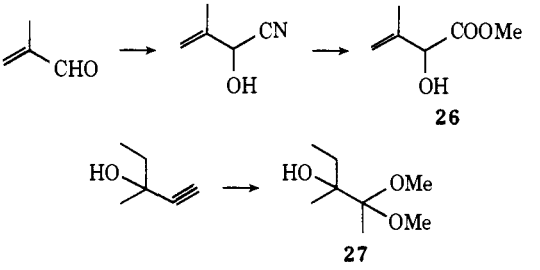
Synthesis of Juvenile Hormone

Since the structure of *Cecropia* juvenile hormone was elucidated in 1967,[33] many synthetic routes to the hormone and closely related compounds have been announced. These synthetic routes fall into two convenient groups: the nonstereoselective syntheses,[34] which were designed to produce large quantities of active material for field testing, and stereoselective syntheses,[35] which have illustrated the efficacy of various methods of stereoselective olefin synthesis.

In 1970, Meyer and Hanzmann[36] isolated an optically active ([α]D ~+7°) mixture of C-18 and C-17 juvenile hormones from the silk moth, *Hyalophora cecropia*. In order to determine the absolute configuration of the natural hormone, we have synthesized optically active forms of juvenile hormone from a starting material of known absolute configuration. A synthesis of juvenile hormone based on the Claisen rearrangement was ideal for this purpose, since the chirality of C-11 can be maintained through the synthesis.

Our strategy for the synthesis of juvenile hormone was to construct three six-carbon units and assemble them using two Claisen rearrangements, during the course of which the olefinic bonds at C-2 and C-6 would be formed. The major drawback of this route was that the stereochemistry of the epoxide ring could not be controlled.

The three six-carbon units, methyl 2-hydroxy-3-methyl-3-butenoate (**26**), 3,3-dimethoxy-2-ethyl-1-butene (**16**), and 2,2-dimethoxy-3-methylpentan-3-ol (**27**), were all readily synthesized. Methyl 2-hydroxy-3-methyl-3-butenoate[37] (**26**) was prepared by acid-catalyzed methanolysis of methacrolein cyanohydrin, the product of addition of sodium cyanide to methacrolein in the presence of acetic acid. 3,3-Dimethoxy-2-ethyl-1-butene (**16**) was formed from the corresponding ketone, 2-ethyl-1-buten-3-one, as shown previously. The final six-carbon unit, 2,2-dimethoxy-3-methylpentan-3-ol (**27**), was obtained from 3-methyl-1-pentyn-3-ol by a mercury(II)-catalyzed addition of methanol.[20]



The reaction of methyl 2-hydroxy-3-methyl-3-butenoate (**26**) and 3,3-dimethoxy-2-ethyl-1-butene (**16**) in toluene containing an acid catalyst at 110° gave a keto ester **28** which was immediately reduced with sodium borohydride in methanol at 0° to obtain methyl 7-ethyl-6-hydroxy-3-methyl-2,7-octadienoate (**29**). Both the yield and stereoselectivity of this reaction were quite variable. Although the reaction usually gave around 85% trans isomer, we obtained better than 98% trans isomer[38] in isolated instances. The least stereoselective experiment gave only 70% trans isomer and

(32) G. M. Young, F. F. Caserio, Jr., and D. D. Brandon, Jr., *J. Amer. Chem. Soc.*, **82**, 6162 (1960).

(33) K. H. Dahm, B. M. Trost, and H. Roller, *ibid.*, **89**, 5292 (1967), and references cited therein.

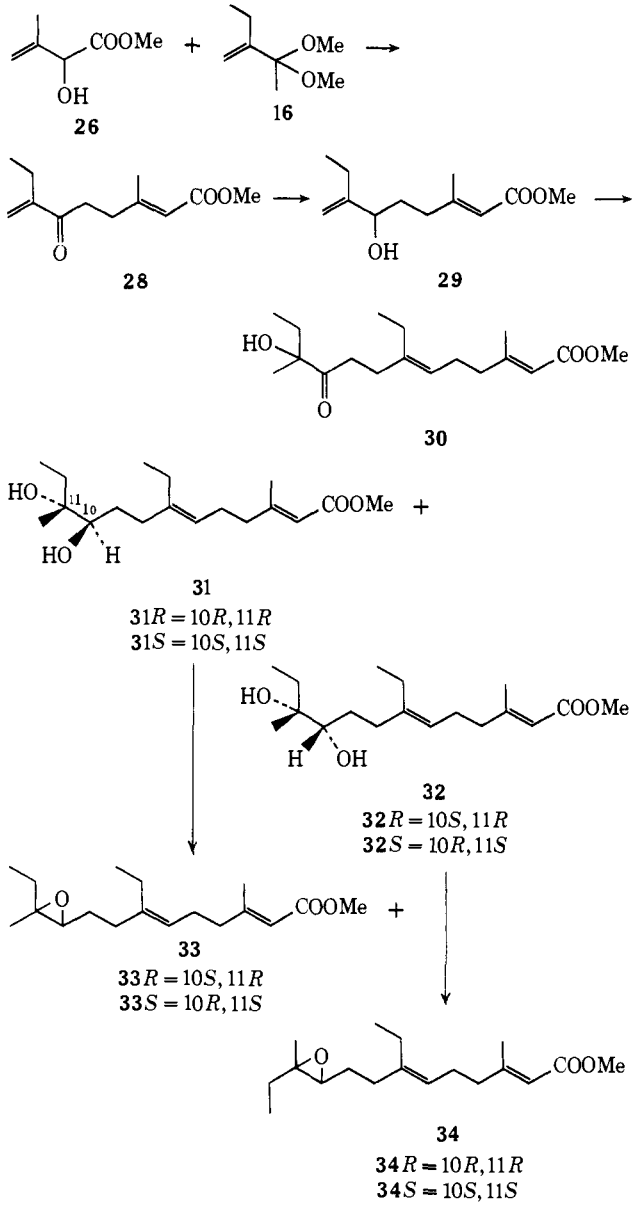
(34) For representative syntheses see (a) J. A. Findlay and W. D. MacKay, *Chem. Commun.*, 773 (1969); (b) H. Schulz and I. Sprung, *Angew. Chem., Int. Ed. Engl.*, **81**, 258 (1969); (c) K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers, *Tetrahedron*, **25**, 1667 (1969); also ref 33.

(35) (a) W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *J. Amer. Chem. Soc.*, **90**, 6225 (1968); (b) R. Zurfluh, E. N. Wall, J. B. Siddall, and J. Edwards, *ibid.*, **90**, 6224 (1968); (c) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968); (d) E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *ibid.*, **92**, 6635 (1970); (e) P. Loew, J. B. Siddall, V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1462 (1970); see also ref 11, 24, and 43.

(36) A. S. Meyer and E. Hanzmann, *Biochem. Biophys. Res. Commun.* **41**, 891 (1970).

(37) See also footnote 9 of ref 24 for an alternative preparation.

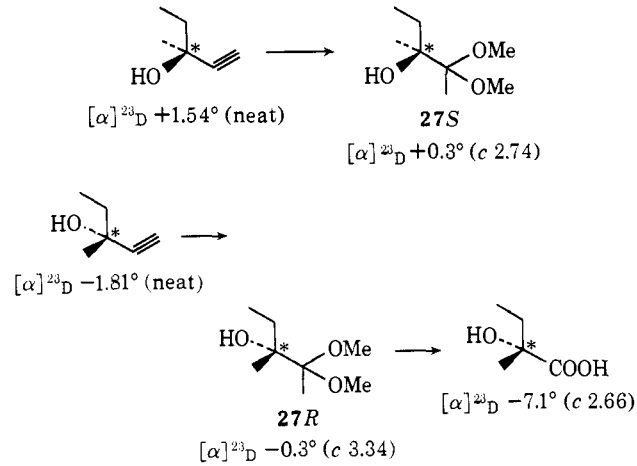
(38) Using the arguments discussed previously, we expected this reaction to be almost stereospecific.



was associated with a higher reaction temperature. Substitution of 3-ethyl-2-methoxybuta-1,3-diene (**17**) for the corresponding ketal **16** did not effect a significant increase in either yield or stereoselectivity. Samples of pure trans keto ester **28** and pure trans hydroxy ester **29** were separately heated at 110° in toluene solution containing oxalic acid without any trace of conversion to the cis isomer. This result indicated that the cis isomer was formed during the formation of the keto ester **28** rather than in a subsequent isomerization. The source of the cis isomer has not been adequately explained.

The acid-catalyzed reaction of the trans hydroxy ester **29** with 2,2-dimethoxy-3-methylpentan-3-ol (**27**) at 110° gave a ketol **30** which was immediately reduced with sodium borohydride in methanol at 0° to obtain a mixture of two diastereoisomeric diol esters **31** and **32** in up to 85% yield. The diastereoisomers could be separated with extreme difficulty using preparative tlc on silica gel. Treatment of the mixture of diol esters **31** and **32** with toluenesulfonyl chloride in pyridine gave a mixture of monotosylates, from which good yields of a mixture of racemic juvenile hormone **33** and the diastereosomeric trans epoxide **34** were obtained by treatment with sodium methoxide in methanol. The mixture of juvenile hormone and its diastereoisomer were converted into the corresponding methyl-d_3 esters for use in assay experiments[39] by repeated equilibrium in sodium methoxide-d_3 in methanol-d_4 solution. Optically active preparations of juvenile hormone and the diastereoisomeric epoxide were prepared using the same route.

3-Methylpent-1-yn-3-ol was resolved into its optical enantiomers using the method of Hickman and Kenyon.[40] The acetylenic alcohol was converted by the action of phthalic anhydride in pyridine, into its phthalate half-ester, which was resolved by fractional crystallization of the brucine salt from acetone–methanol (20:1) solution. The resolved acetylenic alcohols were regenerated from the phthalate half-esters by treatment with 10 *N* sodium hydroxide solution and isolated by steam distillation. (−)-3-Methylpent-1-yn-3-ol, $[\alpha]^{23}D$ −1.81° (neat), was converted into (−)-2,2-dimethoxy-3-methylpentan-3-ol, $[\alpha]^{23}D$ − 0.3° (*c* 3.34), by treatment with methanol containing a mercuric oxide–boron trifluoride etherate–trifluoroacetic acid catalyst. Under similar conditions, (+)-3-methylpent-1-yn-3-ol, $[\alpha]^{23}D$ +1.54° (neat), gave (+)-2,2-dimethoxy-3-methylpentan-3-ol, $[\alpha]^{23}D$ +0.3° (*c* 2.74). In order to determine the optical purity of our samples[41] and also establish their absolute configurations, we converted a sample of (−)-2,2-dimethoxy-3-methylpentan-3-ol into the corresponding ketol, which was oxidized, using sodium hypobromite solution, to (−)-2-hydroxy-2-methylbutyic acid, $[\alpha]^{23}D$ −7.1° (*c* 2.66) [lit.[42] $[\alpha]^{25}D$ −8.5° (*c* 3.0)], of known absolute configuration.[42] Thus (−)-2,2-dimethoxy-3-methylpentan-3-ol possessed the *R* configuration and had an optical purity of 92%. Using the observed rotations for the enantiomeric forms of 3-methylpent-1-yn-3-ol, the (*S*)-(+)-2,2-dimethoxy-3-methylpentan-3-ol was calculated to have an optical purity of 85%.



Both enantiomeric hydroxy ketals **27***R* and **27***S* were allowed to react at 110° with 1.2 equiv of the hydroxy ester in xylene solution containing 2,4-dinitrophenol as the acid catalyst. The resulting ketols **30***R* and **30***S*

(39) M. A. Bieber, C. C. Sweeley, D. J. Faulkner, and M. R. Peterson, *Anal. Biochem.*, 47, 264 (1972).
(40) J. R. Hickman and J. Kenyon, *J. Chem. Soc.*, 2051 (1955).
(41) The literature provides two values for the optical rotation of 3-methylpent-1-yn-3-ol; *cf.* M. L. Capmau, W. Chodkiewiez, and P. Cadiet, *Tetrahedron Lett.*, 1835 (1964), and ref 40.
(42) B. W. Christensen and A. Kajaer, *Acta Chem. Scand.*, 16, 2466 (1962).

were immediately reduced using sodium borohydride in methanol solution at 0° to obtain two diastereoisomeric pairs of diol esters which were partially separated with great difficulty by preparative thin-layer chromatography on silica gel. Each diol preparation was treated with *p*-toluenesulfonyl chloride in pyridine to form the corresponding monotosylates, which were treated with sodium methoxide in anhydrous methanol to obtain the epoxides. The proportions of cis and trans epoxides in each preparation were determined by examination of their 220-MHz spectra, in which the methyl group at C-11 appears as a singlet at 1.17 ppm in the trans epoxide and as a singlet at 1.19 ppm in the cis epoxide. Each epoxide was contaminated with its diastereoisomer owing to our inability to completely separate the diastereoisomers at the diol stage. The observed rotations (Table II) must therefore be related

Table II. Observed Optical Rotations

Composition of sample	$[\alpha]^{25}D$, deg	Concn, *M*
75% **31***R*, 25% **32***R*	+2.8	2.5
75% **31***S*, 25% **32***S*	−1.6	3.0
80% **32***R*, 20% **31***R*	−0.8	3.2
90% **32***S*, 10% **31***S*	+0.3	3.1
75% **33***R*, 25% **34***R*	−7.3	0.5
75% **33***S*, 25% **34***S*	+4.8	1.0
80% **34***R*, 20% **33***R*	−3.6	1.1
90% **34***S*, 10% **33***S*	+0.7	1.2

to the approximate composition of the diastereoisomeric mixtures. There was no doubt, however, that the dextrorotatory C-18 *Cecropia* juvenile hormone had been formed from (*S*)-(+)-2,2-dimethoxy-3-methylpentan-3-ol. Thus the natural hormone of Mayer and Hanzmann must have the 10*R*,11*S* configuration.[43]

Experimental Section

Nmr spectra were obtained on a Varian T-60 or HR-220 spectrometer, mass spectra on a L.K.B. 9000 gas chromatogram–mass spectrometer,[44] infrared spectra on a Perkin-Elmer 700 spectrometer, and optical rotations on a Perkin-Elmer 141 polarimeter. Melting points and boiling points are uncorrected. Gas chromatographic analyses were performed on a Varian Aerograph series 1200 instrument or a Hewlett-Packard 402 instrument.

2-Methylpenten-3-ol (5a). Ethyl bromide (109 g, 1.0 mol) was introduced dropwise into a suspension of magnesium turnings (24.3 g, 1.0 g-atom) in dry ether (300 ml). After the addition was completed, the dark brown solution was boiled under reflux for 0.5 hr, and the flask was cooled in an ice bath. Freshly distilled methacrolein (70 g, 1.0 mol) was added dropwise to the cold solution (0°) which was then stirred for 2 hr at room temperature. The solution was poured into ice-cold ammonium chloride solution and extracted with ether. The extracts were combined, dried over anhydrous sodium sulfate, and distilled to give 2-methyl-1-penten-3-ol: bp 120–122°;[45] yield 53 g (53%); ir (film) 3310 cm^{-1}; nmr (neat) δ 0.60 (t, 3 H, *J* = 6 Hz), 1.41 (s, 3 H), 3.66 (t, 1 H, *J* = 7 Hz), 4.03 (s, 1 H), 4.53 (m, 1 H), 4.64 (m, 1 H).

2,4-Dimethyl-1-penten-3-ol (5b). Isopropyl bromide was substituted for ethyl bromide in the general procedure above: bp 51–53° (22 mm);[46] nmr (neat) δ 0.75 (t, 6 H, *J* = 7 Hz), 1.55 (septet, 1 H, *J* = 6 Hz), 1.57 (d, 3 H, *J* = 2 Hz), 3.53 (d, 1 H, *J* = 7 Hz), 3.59 (s, 1 H), 4.76 (m, 2 H).

2-Ethyl-1-penten-3-ol (5c). 2-Ethyl-2-propenal was substituted for methacrolein in the general procedure above: bp 66–67° (25 mm) (lit.[47] bp 64–65° (25 mm)), nmr (neat) δ 0.65 (t, 3 H, *J* = 6 Hz), 0.82 (t, 3 H, *J* = 8 Hz), 1.45 (q, 2 H, *J* = 7 Hz), 1.85 (q, 2 H, *J* = 7 Hz), 3.80 (t, 1 H, *J* = 6 Hz), 4.13 (s, 1 H), 4.62 (m, 1 H), 4.83 (m, 1 H).

2-Methyl-1-penten-3-yl Vinyl Ether (6a) (*cf.* R. F. Church, *et al.*[14]). 2-Methyl-1-penten-3-ol (3 g, 30 mmol), mercuric acetate (6 g, 19 mmol), which was always freshly recrystallized from ethanol containing a trace of acetic acid, and dry ethyl vinyl ether (150 ml) were boiled under reflux for 18 hr under a nitrogen atmosphere. The solution was allowed to cool, acetic acid (0.5 ml) was added, and stirring was continued for another hour. The mixture was diluted with petroleum ether (250 ml) and extracted twice with 5% potassium hydroxide solution. After drying over anhydrous potassium carbonate, the solvent was evaporated at atmospheric pressure. In order to remove the mercury compounds, the remaining liquid was filtered through alumina (column 1 × 3 cm) and eluted with petroleum ether (150 ml). Distillation of the combined extracts under reduced pressure gave 2-methyl-1-penten-3-yl vinyl ether: bp 42° (40 mm),[48] yield 1.7 g (45%); nmr (neat) δ 0.62 (t, 3 H, *J* = 7 Hz), 1.0–1.6 (2 H), 1.34 (s, 3 H), 3.67 (t, 1 H, *J* = 8 Hz), 3.60 (d, 1 H, *J* = 8 Hz), 3.91 (d, 1 H, *J* = 14 Hz), 4.58 (s, 2 H), 5.92 (q, 1 H, *J* = 7 Hz).

2,4-Dimethyl-1-penten-3-yl Vinyl Ether (6b). 2,4-Dimethyl-1-penten-3-ol was substituted for 2-methyl-1-penten-3-ol in the general procedure above: bp 47° (40 mm); ir (film) 1635 cm^{-1}; nmr (neat) δ 0.52 (d, 3 H, *J* = 7 Hz), 0.67 (d, 3 H, *J* = 7 Hz), 1.2–1.8 (1 H), 1.42 (m, 3 H), 3.47 (d, 1 H, *J* = 7 Hz), 3.68 (d, 1 H, *J* = 6 Hz), 4.04 (d, 1 H, *J* = 14 Hz), 4.73 (m, 2 H), 6.07 (q, 1 H, *J* = 7 Hz).

2-Ethyl-1-penten-3-yl Vinyl Ether (6c). 2-Ethyl-1-penten-3-ol (2.0 g, 18 mmol) and mercuric acetate (5.0 g, 16 mmol) were dissolved in dry ethyl vinyl ether (100 ml) and heated at reflux for 18 hr under nitrogen. Fractional distillation under reduced pressure gave a mixture of 80% 2-ethyl-1-penten-3-yl vinyl ether, and 20% 1-ethoxyethyl acetate (1.72 g).

The mixture was saponified in 5 ml of 20% potassium hydroxide for 10 min, then extracted with petroleum ether, and fractionally distilled at reduced pressure to give pure 2-ethyl-1-penten-3-yl vinyl ether: bp 58–59° (40 mm); yield 0.9 g (36%); ir (film) 1640, 1190 cm^{-1}; nmr (neat) δ 0.58 (t, 3 H, *J* = 7 Hz), 0.90 (t, 3 H, *J* = 8 Hz), 1.31 (q, 2 H, *J* = 7 Hz), 1.8–2.1 (2 H), 3.65 (d, 1 H, *J* = 7 Hz), 3.76 (t, 1 H, *J* = 6 Hz), 4.00 (d, 1 H, *J* = 13 Hz), 4.75 (m, 2 H), 6.05 (q, 1 H, *J* = 7 Hz).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.92; H, 11.52.

4-Methyl-4-heptenal (7a). 2-Methyl-1-penten-3-yl vinyl ether (1.7 g, 13.5 mmol) was sealed in a nmr tube and heated at 110–120°. The reaction was followed to completion by nmr. After 18 hr the crude product was transferred to a flask and purified by evaporative distillation to give 4-methyl-4-heptenal, bp 70–72° (25 mm), yield 1.3 g (77%). The cis:trans isomer ratio, 10:90, was determined by glc with a 6 ft × 0.25 in. column of 1% OV-1 on 100–120 mesh Chromosorb W.

The allyl vinyl ether (400 mg, 32 mmol) was sealed in a nmr tube and heated at 205° for 20 hr. 4-Methyl-4-heptenal was isolated and contained some higher boiling material, yield 312 mg (78%). Glc on the same column showed the cis:trans isomer ratio to be 14:86; ir (film) 2740, 1725 cm^{-1}; nmr (CCl_4) δ 1.00 (t, 3 H, *J* = 7 Hz), 1.67 (s, 3 H), 2.08 (m, 2 H), 2.38 (m, 4 H), 5.19 (t, 1 H, *J* = 7 Hz), 9.75 (s, 1 H).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.15; H, 11.15.

4,6-Dimethyl-4-heptenal (7b). Crude 2,4-dimethyl-1-penten-3-yl vinyl ether (435 mg) was sealed in a glass tube and heated for 40 hr at 110–120°. Evaporative distillation gave pure aldehyde; bp 60–70° (20 mm); yield 183 mg. The cis:trans isomeric ratio was 6:94 as determined by glc; ir (film) 1730 cm^{-1}; nmr (neat) δ 0.85 (d, 6 H,

(43) Using optically active samples of juvenille hormone prepared by P. Loew and W. S. Johnson [*J. Amer. Chem. Soc.*, **93**, 3765 (1971)], Nakanishi, *et al.*, have independently assigned the same absolute configurations: K. Nakanishi, D. A. Schooley, M. Koreeda, and J. Dillon, *Chem. Commun.*, 2253 (1971).

(44) The L.K.B. 9000 gas chromatogram-mass spectrometer was purchased with a grant from the National Science Foundation (GP-18245).

(45) H. A. Bruson and J. W. Eastes, *J. Amer. Chem. Soc.*, **59**, 2011 (1937).

(46) S. Mima, *Osaka Kogyo Gijutsu Shikensho Kiho*, **14**, 30 (1963).

(47) M. B. Green and W. J. Hickenbottom, *J. Chem. Soc.*, 3262 (1957).

(48) Microanalyses were not performed in vinyl ethers **6a** and **6b** owing to their contamination with the Claisen rearrangement products. Compound **6c** was analyzed to prove the absence of 1-ethoxymethyl acetate.

J = 6 Hz), 0.94 (q, 1 H, J = 6 Hz), 1.40 (d, 3 H, J = 2 Hz), 2.18 (m, 4 H), 4.84 (d, 1 H, J = 9 Hz), 9.60 (m, 1 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.99; H, 11.51.

4-Ethyl-4-heptenal (7c). 2-Ethyl-1-penten-3-yl vinyl ether (395 mg, 2.8 mmol) was sealed in a nmr tube and heated for 65 hr at 110–120°. Evaporative distillation gave 4-ethyl-4-heptenal. The cis:trans isomer ratio, 10:90, was determined by glc (see above): ir (film) 1730 cm^{-1}; nmr (neat) δ 0.68 (t, 3 H, J = 8 Hz), 0.72 (t, 3 H, J = 8 Hz), 1.8–2.2 (4 H), 2.17 (m, 4 H), 4.95 (t, 1 H, J = 8 Hz), 9.60 (m, 1 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.21; H, 11.30.

***N,N*-Dimethyl-4-methyl-4-heptenamide (8).** 2-Methyl-1-penten-3-ol (2.5 g, 250 mmol) and 1-*N,N*-dimethylamino-1-methoxyethylene (4.0 g, 396 mmol) were dissolved in xylene (50 ml) and the solution was heated at 140° for 14 hr while methanol was allowed to distil. The solvent was removed by distillation and the residue distilled *in vacuo* to obtain the amide: bp 86–87° (0.7 mm); yield 3.675 g (87%); ir 1630, 1620 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz), 1.66 (bs, 3 H), 2.00 (m, 2 H), 2.41 (s, 4 H), 3.01 (s, 3 H), 3.09 (x, 3 H), 5.30 (bt, 1 H).

5-Methyl-5-octen-2-one (9). Claisen Route. 2-Methyl-1-penten-3-ol (1.17 g, 12 mmol) and methyl isopropenyl ether (1.72 g, 14 mmol) were sealed in a glass tube containing oxalic acid (50 mg) and hydroquinone (10 mg) and heated 15 hr at 110–120°. Direct evaporative distillation gave 5-methyl-5-octen-2-one: bp 80° (25 mm); yield 1.25 g (76%); ir (film) 1705 cm^{-1}; nmr (neat) δ 0.93 (t, 3 H, J = 8 Hz), 1.62 (s, 3 H), 2.09 (s, 3 H), 2.00–2.75 (6 H), 5.27 (t, 1 H, J = 6 Hz). Glc showed the product to have a cis:trans isomeric ratio of 1:99.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.91; H, 11.49.

Grignard Route. 4-Methyl-4-heptenal (250 mg, 20 mmol; cis:trans isomer ratio of 10:90) in ether solution was added dropwise to methylmagnesium iodide, which had been prepared in dry ether from methyl iodide (300 mg, 23 mmol) and magnesium (55 mg, 23 g-atoms). The mixture was stirred for 1 hr, poured onto ice, and extracted with ether. The extracts were combined, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was evaporatively distilled to obtain 5-methyl-5-octen-2-ol (**11**): bp 70–80° (25 mm); yield 235 mg (84%); ir (film) 3380 (broad) cm^{-1}; cis:trans isomer ratio 10:90.

5-Methyl-5-octen-2-ol (117 mg, 0.82 mmol) was dissolved in cold acetone (5 ml) and titrated with Jones reagent (0.55 g of chromium trioxide dissolved in 1.5 g of water and 1 g of concentrated sulfuric acid) until the yellow color persisted for 5 min. The product was isolated and purified by evaporative distillation to give 5-methyl-5-octen-2-one, yield 73 mg (63%), cis:trans isomer ratio 10:90.

4-Methyl-4-heptenol (10). From Amide 8. Lithium aluminum hydride (320 mg, 8.4 mmol) was suspended in dry ether (25 ml) and the suspension cooled to 0°. Ethyl acetate (1.11 g 12.6 mmol) was added to the stirred suspension, which was then allowed to warm to room temperature over 2 hr. Addition of the amide **8** (1.0 g 6.0 mmol) was followed by a further 2 hr stirring at room temperature. After addition of water (1 ml), the products were partitioned between ether and dilute hydrochloric acid (to remove amines). The ether layer was washed with water and dried over anhydrous sodium sulfate and the solvent removed by evaporation. The product was distilled using a Kugelrohr apparatus at 80° (20 mm). A mixture of 80% alcohol **10** and 20% aldehyde **7a** was obtained. The mixture was dissolved in dry ether (20 ml) and lithium aluminum hydride (excess) was added. After the suspension had been stirred for 1 hr at room temperature, water (1 ml) was added and the ether layer decanted and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 4-methyl-4-heptenol: yield 330 mg (44%); nmr ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz), 1.65 (bs, 3 H), 1.5–2.4 (m, 6 H), 2.60 (s, 1 H), 3.68 (t, 2 H, J = 7 Hz), 5.30 (bt, 1 H, J = 7 Hz).

From Aldehyde 7a. 4-Methyl-4-heptenal (350 mg, 2.8 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (1 g) in dry ether (25 ml). After 1 hr the solution was cooled and excess hydride destroyed with ethyl acetate. The product was partitioned between 3 *N* hydrochloric acid and ether. The ether extracts were dried over anhydrous sodium sulfate and the solvent evaporated to yield an oil. The oil was purified by bulb-to-bulb distillation using a Kugelrohr oven to give 4-methyl-4-heptenol: bp 85° (20 mm), yield 327 mg (93%), cis:trans 10:90.

Phenyl 2-Methyl-2-pentenyl Thiolcarbonate (12). A solution of 2-methyl-1-penten-3-ol (1.2 g, 1.2 mmol) in pyridine (10 ml) was cooled to −20°, and phenyl chlorothionoformate (2.2 g, 1.28 mmol) was added with stirring. After 1 hr the product was poured into water and the organic material was extracted with ether. The ether layers were washed with 2 *N* sodium hydroxide solution, water, 3 *N* hydrochloric acid, and water again. The combined ether layers were dried over anhydous sodium sulfate and the solvent was evaporated. The residue was distilled to obtain the thiolcarbonate as a pale yellow oil: bp 110° (1 mm); yield 1.77 g (67%); cis:trans ratio 3.5:96.5 by vpc; ir (CH_2Cl_2) 1725 cm^{-1}; nmr ($CDCl_3$) δ 0.91 (t, 3 H, J = 7 Hz), 1.71 (bs, 3 H), 2.13 (m, 2 H), 3.63 (s, 2 H), 5.57 (bt, 1 H, J = 7 Hz), 7.3 (m, 5 H).

Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.1; H, 6.78. Found: C, 66.31; H, 6.88.

Phenyl 2-Methyl-2-pentenyl Dithiolcarbonate (13). Phenyl dithiochloroformate was substituted for phenyl chlorothionoformate in the previous procedure. The dithiolcarbonate was obtained in 30% yield as a yellow oil: ir (CH_2Cl_2) 1640 cm^{-1}; vpc analysis revealed a cis:trans ratio of 1:99.

2-Methoxy-3-methyl-1,3-butadiene (3-Methoxyisoprene) (15). The catalyst, consisting of red mercuric oxide (1.5 g), trichloroacetic acid (0.2 g), boron trifluoride etherate (1 ml), and methanol (1 ml), was placed under nitrogen in a three-necked flask fitted with a thermometer, reflux condenser, and a dropping funnel. After an initial addition of methanol (50 ml), 2-methyl-1-buten-3-yne (33 g, 0.5 mol) in methanol (20 ml) was added to the catalyst over a 15-min period. The reaction flask was cooled in a water bath to maintain the temperature below 40°. The solution gradually turned green, then dark purple. The reaction, shown by glc to be complete after 16–24 hr, was quenched by adding 0.5 g of sodium methoxide. The mixture was stirred 1 hr and partitioned between ether and water. The ether layer was dried over anhydrous sodium sulfate and distilled[49] to obtain 2,2-dimethoxy-3-methyl-3-butene [bp 95–100° (lit.[20] bp 117–120°); yield 8.0 g (12%; 90% pure by glc); ir (film) 2950, 1150, 1055 cm^{-1}; nmr (neat) δ 1.00 (s, 2 H), 1.54 (m, 3 H), 2.85 (s, 6 H), 4.75 (m, 1 H), 5.06 (m, 1 H)] and 2,2,3-trimethoxy-3-methylbutane [bp 65–77° (22 mm) (lit.[26] bp 69° (22 mm)); yield 36.7 g (45%; 90% pure by glc); ir (film) 2950, 1110 cm^{-1}].

2,2,3-Trimethoxy-3-methylbutane (18.6 g, 112 mmol) was added dropwise to a hot (140°) mixture of pyridine (50 ml), acetic anhydride (50 ml), and acetic acid (5 ml) in a flask fitted with a dropping funnel and a distillation apparatus (7 in. Vigreux column). The dropping rate and the oil-bath temperature were adjusted to maintain the head temperature below 100° during the distillation. (If the distillate still contained ketal, the distillate was reintroduced and distilled again.) The distillate was poured into ether and washed several times with water. The organic layer was repeatedly extracted with copper sulfate solution to remove the remaining pyridine as a water-soluble, royal blue complex. The organic layer was washed with water, dried over sodium sulfate, and distilled to obtain the dienyl ether: bp 93–95° (lit.[20] bp 99°); yield 8.7 g (77%); nmr (neat) δ 1.45 (m, 3 H), 3.20 (s, 3 H), 3.72 (m, 1 H) 3.85 (m, 1 H), 4.52 (m, 1 H), 5.00 (m, 1 H).

2,6-Dimethyl-1,6-nonadien-3-ol (14). Grignard Route. 2-Bromopropene (750 mg, 5.2 mmol; Columbia Chemicals) and magnesium turnings (150 mg, 6.1 mg-atoms) in solution were boiled under reflux (in dry tetrahydrofuran) under nitrogen for 1 hr and then stirred for 2 hr at room temperature. After the brown solution was cooled in an ice bath, 4-methyl-4-heptenal (500 mg, 4.0 mmol; cis:trans isomer ratio of 10:90) in dry solvent was added dropwise, and the mixture was stirred 1 hr. The solution was poured into cold ammonium chloride and extracted with petroleum ether. The organic layer was dried and the solvent removed under reduced pressure. Evaporative distillation gave 2,6-dimethyl-1,6-nonadien-3-ol, bp 80° (5 mm), yield 192 mg (25%, 85% pure by glc).

Claisen Route. 2-Methyl-1-penten-3-ol (213 mg, 2.1 mmol), 3-methoxyisoprene (474 mg, 4.8 mmol), hydroquinone (10 mg), and oxalic acid (5 mg) were heated to 110° for 18 hr under a nitrogen atmosphere in a sealed tube. The crude dienone was dissolved in methanol (5 ml) and cooled to 0° using an ice bath. Sodium borohydride (200 mg, 4 mmol) was added over 10 min to the stirred solution, and the stirring was then continued for 2 hr while the solution was allowed to warm to room temperature. The product was partitioned between ether and brine and the combined ether

(49) In most experiments the product was not distilled and the mixture of dimethoxy and trimethoxy compounds was used directly in the next step to give up to 65% overall yield of 3-methoxyisoprene.

phase and washings were dried over anhydrous sodium sulfate. The solvent was evaporated and the resulting oil distilled to obtain the dienol: bp 80–90° (10 mm); yield 240 mg (67%); ir (film) 3310 (broad), 1660 cm^{-1}; nmr (CCl_4) δ 0.62 (t, 3 H, J = 7 Hz), 1.28 (s, 3 H), 1.40 (s, 3 H), 1.6–2.2 (6 H), 2.36 (s, 1 H), 3.49 (t, 1 H, J = 6 Hz), 4.48 (s, 1 H), 4.62 (s, 1 H), 4.84 (t, 1 H, J = 7 Hz).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.70; H, 12.04.

The product was shown to contain less than 1% cis isomer by vpc analysis.

A sample of the intermediate dienone, 2,6-dimethyl-1,6-nonadien-3-one (**18**), gave the following spectra: ir (film) 1680 cm^{-1}; nmr (CCl_4) δ 0.83 (t, 3 H, J = 8 Hz), 1.50 (s, 3 H), 1.72 (s, 3 H), 1.8–2.8 (6 H), 5.04 (t, 1 H, J = 8 Hz), 5.60 (m, 2 H).

2,7-Dimethyl-1,7-octadiene-3,6-diol (20). A Grignard reagent was prepared by adding 2-bromopropene (23.6, 1.95 mmol; Columbia Chemicals) to a suspension of magnesium turnings (6 g, 250 mg-atoms) in dry tetrahydrofuran. After stirring 1 hr, the solution was cooled, and freshly distilled succindialdehyde (6.6 g, 87 mmol; bp 64–64° (15 mm)) in tetrahydrofuran (50 ml) was added dropwise. The mixture was stirred 2 hr at room temperature, poured into ammonium chloride solution, and extracted with ether. The extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residual oil was distilled under reduced pressure to give 2,7-dimethyl-1,7-octadiene-3,6-diol as very viscous oil: bp 102–120° (14 mm); yield 9.1 g (61%); ir (film) 3425, 1650, 905 cm^{-1}; nmr ($CDCl_3$) δ 1.70 (s, 6 H), 3.14 (s, 2 H), 4.04 (t, broad, 2 H), 4.81 (m, 2 H), 4.92 (m, 2 H), 1.6–2.0 (m, 4 H). A sample of the diol was crystallized from hexane–ether solution, mp 85–87°.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 10.55; H, 10.66. Found: C, 10.78; H, 10.73.

6,10-*trans*-2,6,11,15-Tetramethyl-1,6,10,15-hexadecatetraene-3,14-dione (21). A solution of 2,7-dimethyl-1,7-octadiene-3,6-diol (255 mg, 1.5 mmol), 3-methoxyisoprene (441 mg, 4.5 mmol), perchlorohomocubanecarboxylic acid (25 mg), and hydroquinone (10 mg) in xylene (55 ml) was heated to 140° under a nitrogen atmosphere. After 6 hr and again at 12 hr, portions of 3-methoxyisoprene (147 mg, 1.5 mmol) in xylene (10 ml) were added. After 24 hr, the reaction mixture was cooled and the solvent was evaporated. The residue was chromatographed on a column (20 × 2 cm) of neutral alumina (grade 3) using 5% ether in hexane to elute the C-20 dione: yield 267 mg (60%); ir (CH_2Cl_2) 1670, 1630 cm^{-1}; nmr ($CDCl_3$) δ 1.62 (s, 6 H), 1.87 (s, 6 H), 2.02 (m, 4 H), 2.24 (m, 4 H), 2.80 (m, 4 H), 5.20 (t, broad, 2 H), 5.81 (m, 2 H), 6.00 (m, 2 H).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.75; H, 10.15.

6,10-*trans*-2,6,11,15-Tetramethyl-1,6,10,15-hexadecatetraene-3,14-diol (22). The C-20 dione (267 mg) from the previous experiment was dissolved in methanol (20 ml) and the solution was cooled to 0°. Sodium borohydride (250 mg, 6.6 mmol) was added in portions to the stirred solution which was allowed to warm to room temperature over 2 hr. The mixture was poured into brine and the organic material extracted with ether. The combined ether extracts were dried over sodium sulfate and the solvent was evaporated to give the C-20 diol as a clear oil. A sample was distilled for analysis: bp 90° (2 × 10^{-5} mm); yield 262 mg (57% from C-10 diol); ir (film) 3350 cm^{-1} (broad); nmr (CCl_4) δ 1.50 (s, 6 H), 1.57 (s, 6 H), 1.8–2.1 (112 H), 2.15 (s, 2 H), 3.80 (t, 2 H, J = 6 Hz), 4.70 (m, 2 H), 4.74 (m, 2 H), 5.00 (t, 2 H).

6,10,14,18-*trans*-2,6,10,15,19,23-Hexamethyl-1,6,10,14,18,23-tetracosahexaene-3,22-diol (23). The C-20 diol (694 mg, 2.4 mmol) and 3-methoxyisoprene (0.6 g, 6.2 mmol) were dissolved in dry xylene (50 ml) containing hydroquinone (23 mg) and oxalic acid (31 mg) and the solution was heated under nitrogen at 150°. After 2 hr another portion (10.6 g, 6.1 mmol) of 3-methoxyisoprene in dry xylene (15 ml) was introduced. Six hours later, the reaction was cooled. After removal of the solvent under reduced pressure (25 mm), the residue was chromatographed (alumina activity III, eluent, 5% ether in hexane) to obtain the hexaenedione: yield 400 mg (40%); ir (film) 1680, 800 cm^{-1}; nmr (CCl_4) δ 1.41 (s, 12 H), 1.67 (s, 6 H), 1.8–2.6 (20 H), 5.00 (t, broad, 4 H), 5.30 (m, 2 H), 5.76 (m, 2 H).

The C-30 dione (400 mg, 0.9 mmol) was dissolved in cold (0°) methanol, and sodium borohydride (1150 mg, 3.9 mmol) was slowly added. The solution was stirred at 0° for 1 hr and at 25° for 2 hr, then poured into water, and extracted with hexane. The organic phase was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give the hexaenediol: yield 333 mg (82%; 33% from the C-20 tetraenediol); ir (film) 3400 (broad), 910 cm^{-1}; nmr (CCl_4) δ 1.50 (s, 12 H), 1.60 (s, 6 H), 1.8–2.2 (20 H), 2.47 (s, 2 H), 3.83 (t, 2 H, J = 8 Hz), 4.63 (m, 2 H), 4.76 (m, 2 H), 5.01 (t, broad, 4 H); mass spectrum m/e 424 (M − 18), 406 (M − 36).

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.48; H, 11.22

Squalene (25). The C-30 diol (115 mg, 0.26 mmol) was dissolved in cold ether (20 ml), and cooled thionyl chloride (0.14 ml, 1.4 mmol) was added dropwise. The reaction mixture was stored overnight at −20° and evaporated under reduced pressure. The residual oil was dissolved in dry tetrahydrofuran, and lithium aluminum hydride (100 mg, 2.6 mmol) was added. The solution was boiled under reflux for 4 hr, cooled, and poured into ether. The ether phase was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave crude squalene. The product was chromatographed on silica gel using hexane as eluent to obtain a sample of squalene, which was identical in all respects (vpc, ir nmr, mass spectrum) with an authentic sample, yield 50 mg (48%).

Methyl 2-Hydroxy-3-methyl-3-butenoate (26).[50] Sodium cyanide (40 g, 0.82 mol) and dry ether (500 ml) were placed in a 1-l. three-necked flask fitted with a reflux condenser and 2 dropping funnels. Acetic acid (48 ml, 0.85 mol) and freshly distilled methacrolein (33 g, 0.47 mol) were separately, but simultaneously, added over 30 min to the vigorously stirred suspension, while the temperature of reaction mixture was maintained at 20° with a water bath. The mixture was stirred overnight and filtered under vacuum to remove the sodium acetate The solvent was removed under reduced pressure to obtain the crude cyanohydrin which contained some unreacted aldehyde (10–15%). No attempt was made to purify the cyanohydrin: ir (film) 3440 (broad), 2250 cm^{-1}; nmr (neat) δ 1.67 (s, 3 H), 4.83 (m, 1 H), 4.85 (s, 1 H), 5.10 (m, 1 H).

The crude cyanohydrin was dissolved in dry methanol (250 ml) and dry hydrogen chloride was bubbled into the solution for 15 min. The solution was boiled under reflux for 6 hr, cooled, and poured into cold ammonium chloride solution. The organic material was extracted with dichloromethane and the combined extracts were dried over sodium sulfate. The solvent evaporated and the residue distilled under reduced pressure to obtain methyl 2-hydroxy-3-methylbutenoate: bp 114–6 (19 mm); yield 27.4 g (45%); ir (film) 3500 (broad), 1735 cm^{-1}; nmr ($CDCl_3$) δ 1.42 (s, 3 H), 3.40 (s, 3 H), 4.05 (s, 1 H), 4.30 (s, 1 H), 4.63 (m, 1 H), 4.69 (m, 1 H).

2-Ethyl-1-buten-3-one.[51] A mixture of 2-pentanone (240 g, 2.8 mol), dimethylamine hydrochloride (229 g, 2.8 mol), and formalin (226 g, 2.8 mol; 37% solution) was acidified to pH 1, heated at reflux for 3 hr, cooled, and extracted with ether to remove unreacted 2-pentanone. The solution was made basic with 12 N sodium hydroxide and the Mannich base, N,N-dimethyl-2-ethyl-3-oxobutylamine, was extracted with ether. The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was distilled to give the Mannich base: yield 226 g (56%); ir (film) 1700 cm^{-1}; nmr (neat) δ 0.70 (t, 3 H, J = 6 Hz), 1.30 (q, 2 H, J = 8 Hz), 1.92 (s, 3 H), 2.00 (s, 6 H), 2.2–2.4 (3 H).

This Mannich base (11.7 g, 82 mmol) was dissolved in benzene (50 ml), cooled to 0°, and treated with dimethyl sulfate (10.5 g, 83 mmol) in benzene (25 ml). After stirring for 1 hr at room temperature, the two phases were separated A water washing of the organic phase (later discarded) was combined with the aqueous phase and made basic with 20% sodium hydroxide solution (15 ml). After vigorous stirring for 1 hr, the aqueous solution was extracted with ether. The extracts were washed with 3 N hydrochloric acid and water, dried over anhydrous sodium sulfate, and fractionally distilled to give 2-ethyl-1-buten-3-one: bp 60–62° (25 mm); yield 6.0 g (75%); ir (film) 1660 cm^{-1}; nmr (neat) δ 0.63 (t, 3 H, J = 7 Hz), 1.75 (q, 2 H, J = 8 Hz), 1.91 (s, 3 H), 5.38 (m, 1 H), 5.67 (m, 1 H).

2-Ethyl-3,3-dimethoxy-1-butene (16). 2-Ethyl-1-buten-3-one (4.0 g, 41 mmol) and trimethyl orthoformate (4.4 g, 42 mmol) were dissolved in dry methanol (20 ml) containing toluenesulfonic acid monohydrate (30 mg). Tlc showed that the reaction started very slowly and then accelerated to completion; total time was 1 hr. The reaction was quenched with sodium methoxide. The mixture was poured into dichloromethane and the organic phase washed

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(51) G. S. Mironov, M. I. Faberov, and I. M. Orlova, *Zh. Prikl. Khim. (Leningrad)*, **36**, 654 (1963); *J. Appl. Chem. USSR*, **36**, 622 (1963).

twice with water. The organic layer was dried, concentrated, and distilled to give the dimethyl ketal: bp 78–79° (84 mm), also bp 130–132° (760 mm); yield 3.6 g (61%); nmr (neat) δ 1.00 (t, 3 H, J = 7 Hz), 1.24 (s, 3 H), 2.02 (q, 2 H, J = 7 Hz), 3.04 (s, 6 H), 4.92 (m, 1 H), 5.28 (m, 1 H).

2-Ethyl-3-methoxy-1,3-butadiene (17). 2-Ethyl-3,3-dimethoxy-1-butene (40 g, 0.28 mol) was added dropwise into a hot mixture of pyridine (100 ml), acetic anhydride (100 ml), and acetic acid (10 ml) in a flask fitted with a dropping funnel and a distillation apparatus (7-in. Vigreux column). The dropping rate and the oil bath temperature, 140°, were adjusted to maintain the head temperature around 110–115°. The distillate was poured into ether and washed several times with water. The organic layer was repeatedly extracted with copper sulfate solution to remove the remaining pyridine as a water-soluble, royal blue complex. The organic layer was washed with water, dried over sodium sulfate, and distilled to obtain the dienyl ether: bp 113–114°; yield 21.0 g (68%); ir (film) 1580 cm^{-1}; nmr (neat) δ 0.70 (t, 3 H, J = 7 Hz), 1.82 (q, 2 H, J = 7 Hz), 3.08 (s, 3 H), 3.60 (m, 1 H), 3.80 (m, 1 H), 4.43 (m, 1 H), 5.00 (m, 1 H)

Methyl 2-*trans*-7-Ethyl-6-hydroxy-3-methyl-2,7-octadienoate (14). Methyl 2-hydroxy-3-methyl-3-butenoate (1.0 g, 7.7 mmol), 3-ethyl-2-methoxy-1,3-butadiene (2.0 g, 18 mmol), oxalic acid (50 mg), and hydroquinone (50 mg) were placed in a sealed container under nitrogen. The mixture was heated to 110° for 20 hr, cooled, and poured into ether. The ether solution was washed with a salt–sodium bicarbonate solution and dried over anhydrous sodium sulfate. The ether was evaporated and the residue dissolved in methanol (10 ml). Sodium borohydride (200 mg, 19 mmol) was added in portions to the cooled (0–5°) solution and the solution was stirred for 2 hr. The mixture was partitioned between brine and dichloromethane, and the organic phases were dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product chromatographed on silica gel (50 × 2 cm) using 10% ether in hexane as eluent. The hydroxy ester was obtained as a colorless oil: yield 810 mg (50%); ir (film) 3450 (broad), 1710, 1640 cm^{-1}; nmr ($CDCl_3$) δ 1.03 (t, 3 H, J = 8 Hz), 2.14 (s, 3 H), 3.60 (s, 3 H), 4.02 (t, 1 H, J = 6 Hz), 4.78 (s, 1 H), 4.96 (s, 1 H), 5.63 (s, 1 H)

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50 Found: C, 68.09; H, 9.74.

2,2-Dimethoxy-3-methylpentan-3-ol (27) (*cf.* Froning, *et al.*[52]). The catalyst, mercuric oxide (1.5 g), trifluoroacetic acid (2 ml), and methanol (5 ml) were placed in a flask fitted with a reflux condenser and a dropping funnel. Dry methanol (100 ml) was added, followed by a solution of freshly distilled 3-methyl-1-pentyn-3-ol (100 g, 1.02 mol) in dry methanol (100 ml). During the addition the mixture was cooled on a water bath. After stirring overnight, the dark green solution was treated with sodium methoxide (2 g), poured into water, and extracted with ether. The extracts were dried over anhydrous sodium sulfate and the solvent was then evaporated under reduced pressure. Distillation of the orange residue gave 2,2-dimethoxy-3-methylpentan-3-ol: bp 80–82° (22 mm); yield 91.3 g (57%); ir (film) 3350 (broad), 1150 cm^{-1}; nmr (neat) δ 0.96 (s, 3 H), 1.07 (s, 3 H), 0.7–1 7 (m, 5 H), 2.53 (s, 1 H), 3.12 (s, 3 H), 3.14 (s, 3 H)

Methyl 2,6-*trans*-10,11-Dihydroxy-3,11-dimethyl-7-ethyl-2,6-tridecadienoate (31). Methyl 2-*trans*-7-ethyl-6-hydroxy-3-methyl-2,7-octadienoate (210 mg, 1 mmol), 2,4-dinitrophenol (134 mg, 0.7 mmol), and 2,2-dimethoxy-3-methylpentan-3-ol (802 mg, 5 mmol) were heated for 7 hr (followed by glc) at 110° under nitrogen. The solution was cooled and chromatographed on Florisil (column 2 × 8 cm; eluent, hexane) to obtain the crude ketol. The ketol prepared in another experiment, purified by column chromatography on silica gel, gave the following data: ir (film) 3500 (broad), 1705, 1640 cm^{-1}; nmr (CCl_4) δ 1.07 (s, 3 H), 1.94 (m, 3 H), 3.38 (s, 3 H), 4.80 (t, broad, 1 H), 5.34 (s, broad, 1 H); mass spectrum m/e 310 (M^+)

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.83; H, 9.94.

The crude ketol was reduced in cold methanol (15 ml) with sodium borohydride (50 mg, 1.3 mmol) for 1 hr. After stirring at room temperature for 2 hr, the methanol solution was partitioned between water and ether. The organic layer was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. Column chromatography on silica gel (eluent, 25% ether in hexane) gave 152 mg of pure C-17 dihydroxy ester (49%) and 184 mg of impure product.

Normal yields were ~50%, but yields of only 10–20% were obtained when impure C-11 hydroxy ester was used as starting material. This same reaction, run on a large scale using 10.5 g of C-11 hydroxy ester, 20 g of dihydroxy ketal, and a catalytic amount of dinitrophenol (80 mg), gave 6.0 g of recovered C-11 hydroxy ester and 5.2 g of all-trans C-18 dihydroxy ester; yield 37%; 85% based on starting material consumed; ir (film) 3500 (broad), 1705, 1635 cm^{-1}; nmr ($CDCl_3$) δ 1.06 (s, 3 H), 2.12 (m, 3 H), 2.66 (s, broad, 2 H), 3.63 (s, 3 H), 5.03 (t, broad, 1 H), 5.60 (s, broad, 1 H); mass spectrum m/e 312 (M^+). No cis isomer was detected.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32 Found: C, 69.35; H, 10.44.

Methyl 2,6-*trans*-10,11-Epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (33 and 34). The C-17 dihydroxy ester **31** (326 mg, 1.05 mmol) and toluenesulfonyl chloride (271 mg, 1.3 mmol) were dissolved in pyridine (3 ml) and allowed to stand overnight in a stoppered flask. The mixture was poured into ice water, acidified to pH 6 with 3 N hydrochloric acid, and extracted with ether. The extracts were washed with sodium bicarbonate solution, dried over sodium sulfate, and concentrated under reduced pressure. Sodium methoxide (75 mg, 1.4 mmol) was added to a methanol solution (5 ml) of the residue. After standing in a stoppered flask for 2 hr, the mixture was poured into water and extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, evaporated under reduced pressure, and chromatographed on Florisil (column 1 × 10 cm; eluent, 10% ether in hexane) to give methyl 2,6-*trans*-10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate, yield 149 mg (48%). Some starting dihydroxy ester (65 mg (20%)) was recovered. The product consisted of two isomeric epoxides: 53% trans,trans,trans, and 47% trans,trans,cis (*Cecropia* juvenile hormone); nmr ($CDCl_3$) δ 0.93 (t, 6 H, J = 8 Hz), 1.17 (s, 3 H), trans isomer, and 1.20 (s, 3 H), cis isomer, 2.13 (m, 3 H), 2.64 (t, 1 H, J = 6 Hz), 3.42 (s, 3 H), 5.00 (t, broad, 1 H), 5.55 (s, broad, 1 H); mass spectrum m/e 294 (M^+).

Anal. Calcd for $C_{10}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.68; H, 10.24.

Resolution of (±)-3-Methyl-1-pentyn-3-ol.[40] Racemic 3-methyl-1-pentyn-3-ol (82 g, 0.835 mol), pyridine (130 g, 1.65 mol), and phthalic anhydride (130 g, 0.878 mol) were heated 7 hr at 90°. The cooled solution was acidified with 3 N hydrochloric acid and extracted with saturated sodium bicarbonate solution (2 × 100 ml). The organic layer was washed with water, dried over sodium sulfate, and distilled to give the starting alcohol (17.1 g (21%)). The aqueous bicarbonate phase was carefully acidified with 3 N hydrochloric acid and extracted with chloroform. The chloroform phase was dried and evaporated to give crystals of phthalate ester, mp 89–93°. On recrystallization from benzene, the crude orange product gave colorless crystals of the ester, mp 93–96° g (27%) (lit.[40] 45.5%, mp 97–98°).

The phthalate ester (54.0 g, 0.22 mol) and (−)-brucine (89.0 g 0.22 mol; freshly recrystallized from acetone) were dissolved in a hot acetone–methanol solution (20:1) and fractionally recrystallized six times. Crystals from the third recrystallization melted at 109–130°, from the fifth at 115–135°, and from the sixth at 135–150° (lit.[40] mp 148–149°). This crude brucine salt was decomposed in dilute hydrochloric acid and the resolved phthalate extracted with ether. Recrystallization from hexane–ether solution gave (*S*)-(+)-phthalate: mp 109–110°; yield 4.9 g; $[\alpha]^{25}_{578}$ +38.2° (*c* 5.02, EtOH), (lit.[40] mp 112–113°; $[\alpha]^{19}_{578}$ +44.0° (*c* 5.00, EtOH)).

The mother liquor from the first recrystallization was concentrated and worked up as described above to give (−)-phthalate; mp 104–106°, yield 11.1 g, $[\alpha]^{25}_{578}$ −30.8° (*c* 5.01, EtOH) (lit.[40] mp 112–113°, $[\alpha]^{18}_{589}$ −22.3° (*c* 5.00 EtOH)).

The (+)-phthalate (4.0 g, 16.3 mmol) was dissolved in 10 N potassium hydroxide (2.4 g dissolved in 4.4 ml of water), allowed to stand 0.5 hr, and poured into ether. The ether extract was washed with water, dried over sodium sulfate, and distilled to give the (*S*)-(+)-3-methyl-1-pentyn-3-ol, bp 121–123°, yield 1.3 g (87%), $[\alpha]^{25}_{589}$ +1.54° (neat) (lit.[40] bp 120–121°, $[\alpha]^{21}_{589}$ +2.22°).

The (−)-phthalate (11.1 g, 22.2 mmol) was dissolved in a 10 N potassium hydroxide solution and treated as just described to obtain (*R*)-(−)-3-methyl-1-pentyn-3-ol, bp 120–121°, yield 3.6 (82%), $[\alpha]^{25}_{578}$ −1.81° (neat).

(*S*)-(+)-2,2-Dimethoxy-3-hydroxy-3-methylpentane (27*S*). (*S*)-(+)-3-Methyl-1-pentyn-3-ol (1.3 g, 1.32 mmol) was dissolved in dry methanol (15 ml) containing a catalyst of mercuric oxide (0.2 g), trifluoroacetic acid (1 ml), boron trifluoride etherate (1 ml), and methanol (1 ml). The reaction was followed on glc. When the

(52) J. E. Froning and G. F. Hennion, *J. Amer. Chem. Soc.*, **62**, 653 (1940).

hydroxy acetylene had completely reacted, the reaction was quenched with sodium methoxide, stirred 1 hr, and poured into water. The organic layer was dried over sodium sulfate and distilled to give the hydroxy ketone (bp 65–75° (17 mm), yield 0.3 g) and hydroxy ketal (bp 76–80° (17 mm), yield 0.4 g).

The hydroxy ketone was ketalized overnight with trimethyl orthoformate in methanol and a trace of toluenesulfonic acid monohydrate. This procedure gave an additional 0.2 g of ketal. The total yield of (*S*)-(+)-2,2-dimethoxy-3-hydroxy-3-methylpentane, bp 76–80° (17 mm), was 0.6 g (28%), $[\alpha]^{25}_{589}$ +0.3° (*c* 2.74, $CHCl_3$)

(*R*)-(−)-2,2-Dimethoxy-3-hydroxy-3-methylpentane (27*R*). (*R*)-(−)-3-Methyl-2-pentyn-3-ol (3.6 g, 36.8 mmol) was treated in the same manner to obtain hydroxy ketone and the desired ketal. Ketalization of the ketone yielded more ketal to give (*R*)-(−)-3-hydroxy-2,2-dimethoxy-3-methylpentane, bp 81–83° (18 mm), total yield 2.5 g (42%), $[\alpha]^{25}_{589}$ −0.3° (*c* 3.34, $CHCl_3$).

(*R*)-(−)-2-Hydroxy-2-methylbutanoic Acid. (−)-Hydroxy ketal (364 mg, 2.2 mmol) was dissolved in dioxane (25 ml) and water (1 ml) containing toluenesulfonic acid (10 mg). Glc of the mixture showed that hydrolysis was complete. Sodium hypobromite solution was prepared by adding several grams of bromine to cold sodium hydroxide solution (2.3 g, 20 ml water) and added dropwise to the ice-cooled dioxane solution until the yellow-green color persisted. The solution was stored overnight at 0°, then acidified to pH 6 with 3 *N* hydrochloric acid. The ether extracts of the solution were dried over sodium sulfate and evaporated. Recrystallization of the residue from benzene gave (−)-2-hydroxy-2-methylbutyric acid: mp 73–73°, yield 133 mg (50%), $[\alpha]^{25}_{589}$ −7.1° (*c* 2.66, $CHCl_3$) (lit.[42] mp 73.5–74.5°, $[\alpha]^{25}_{589}$ −8.5 (*c* 3.0 $CHCl_3$), *R* configuration).

Methyl (10*R*,11*S*)-2,6-*trans*-10,11-Dihydroxy-3,11-dimethyl-7-ethyl-2,6-tridecadienoate (32*S*) and Methyl (10*S*,11*S*)-2,6-*trans*-10,11-Dihydroxy-3,11-dimethyl-7-ethyl-2,6-tridecadienoate (31*S*). (*S*)-(+)-3-Hydroxy-2,2-dimethoxy-3-methylpentane (400 mg, 2.47 mmol), methyl 7-ethyl-6-hydroxy-3-methyl-*trans*-2,7-octadienoate (1.5 g, 6.7 mmol), and 2,4-dinitrophenol (20 mg) were dissolved in xylene (2 ml) and heated 24 hr under nitrogen. The solution was poured into ether (25 ml), extracted with dilute sodium hydroxide solution, washed with water, and dried over sodium sulfate. After removal or the solvent under reduced pressure, the residue was chromatographed on preparative tlc (silica gel PF-254; 50% ether in hexane). The plate was developed five times and three adjacent bands were removed, extracted with ether, and concentrated to give the (10*R*,11*S*)-dihydroxy ester **32*S*** (yield 78 mg (10%); $[\alpha]^{25}_{589}$ +0 3° (*c* 3.12, $CHCl_3$)), the (10*S*,11*S*)-dihydroxy ester **31*S*** (yield 81 mg (11%); $[\alpha]^{25}_{589}$ −1.6° (*c* 3.09, $CHCl_3$)), and a mixture of the two dihydroxy esters (yield 103 mg). Total yield or the recovered ester was 262 mg (23%).

Methyl (10*S*,11*R*)-2,6-*trans*-10,11-Dihydroxy-3,11-dimethyl-7-ethyl-2,6-tridecadienoate (32*R*) and Methyl (10*S*,11*R*)-2,6-*trans*-10,11-Dihydroxy-3-,11-dimethyl-7-ethyl-2,6-tridecadienoate (31*R*). (*R*)-(−)-3-Hydroxy-2,2-dimethoxy-3-methylpentane (848 mg, 5.24 mmol) and methyl 7-ethyl-6-hydroxy-3-methyl-*trans*-*trans*-2,7-octadienoate (946 mg, 4.46 mmol) were allowed to react and purified as in the previous preparation to give the (10*S*,11*R*)-dihydroxy-ester **32*R*** (yield 163 mg (10%); $[\alpha]^{25}_{589}$ −0.8° (*c* 3.26, $CHCl_3$)), the (10*R*,11*R*)-dihydroxy ester **31*R*** (yield 127 mg (8%), $[\alpha]^{25}_{589}$ +2.8° (*c* 2.54, $CHCl_3$)), and a mixture of both (yield 227 mg). The total yield was 517 mg (37%).

Methyl (10*R*,11*S*)-10-*cis*-2,6-*trans*-3,11-Dimethyl-10,11-epoxy-7-ethyl-2,6-tridecadienoate (33*S*). The (10*S*,11*S*)-dihydroxy ester (81 mg, 0.26 mmol) was allowed to react overnight with *p*-toluenesulfonyl chloride (203 mg, 1.07 mmol) in pyridine (2 ml). The mixture was poured into ether, diluted with water, acidified with 3 *N* hydrochloric acid, and extracted several times with ether. The extracts were washed with water and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was chromatographed on Florisil (column 1 × 6 cm; eluent, 20% ether in hexane) to obtain the (10*S*,11*S*)-dihydroxy ester (23 mg, 28%) and the (10*R*,11*S*) epoxy ester, yield 14 mg (18%), $[\alpha]^{25}_{D}$ +4.8° (*c* 1.0), cis:trans epoxide ratio 75:25.

Methyl (10*S*,11*R*)-10-*cis*-2,6-*trans*-3,11-Dimethyl-10,11-epoxy-7-ethyl-2,6-tridecadienoate (33*R*). The (10*R*,11*R*)-dihydroxy ester (127 mg, 0.42 mmol) was allowed to react overnight with *p*-toluenesulfonyl chloride (209 mg, 1.07 mmol) in pyridine (2 ml) and further treated as described above to give the (10*R*,11*R*)-dihydroxy ester (31 mg, 24%) and the (10*S*,11*R*)-epoxy ester, yield 50 mg (42%), $[\alpha]^{25}_{D}$ −7.3° (*c* 0.5), cis:trans epoxide ratio 75:25.

Methyl (10*R*,11*R*)-2,6,10-*trans*-3,11-Dimethyl-10,11-epoxy-7-ethyl-2,6-tridecadienoate (34*R*). The (10*S*,11*R*)-dihydroxy ester (163 mg, 0.53 mmol) was allowed to react overnight in *p*-toluenesulfonyl chloride (252 mg, 1.34 mmol) in pyridine (2 ml) and further treated as described above to give the (10*S*,11*R*)-dihydroxy ester (19 mg, 12%) and the (10*R*,11*R*)-epoxy ester, yield 112 mg (73%), $[\alpha]^{25}_{D}$ −3.6° (*c* 1.12), cis:trans epoxide ratio 20:80.

Methyl (10*S*,11*S*)-2,6,10-*trans*-3,11-Dimethyl-10,11-epoxy-7-ethyl-2,6-tridecadienoate (34*S*). The (10*R*,11*S*)-dihydroxy ester (78 mg, 0.25 mmol) was allowed to react overnight with *p*-toluenesulfonyl chloride (173 mg, 0.94 mmol) in pyridine (2 ml) and further treated as described above to obtain the (10*R*,11*S*)-dihydroxy ester (33 mg, 42%) and the (10*S*,11*S*)-epoxy ester, yield 36 mg (48%), $[\alpha]^{25}_{D}$ +0.7° (*c* 1.2), cis:trans epoxide ratio 10:90.

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