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STEREOSPECIFIC SYNTHESIS OF A BIOLOGICALLY ACTIVE DEHYDRO DERIVATIVE OF THE C_{18}-JUVENILE HORMONE OF CECROPIA. NEW ROUTES TO A KEY C_{12}-INTERMEDIATE

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Two different stereospecific syntheses of the C_{18}-insect hormone of Cecropia have been reported from this Laboratory previously (1, 2). A critical intermediate in the first of these is 3-ethyl-7-methyl-trans, cis-2, 6-nonadien-1-ol (I). We now outline two new stereospecific routes to this interesting homoisoprenoid structure and also the further transformation to a new, biologically active dehydro derivative of the C_{18}-Cecropia hormone (3).

In the first synthesis of I (see Chart A) the δ-lactone II (4) was converted to the hydroxy methyl ester III (4) in 85% yield by saponification, careful acidification, and esterification of the resulting hydroxy acid with ethereal diazomethane immediately after extraction with ether. Reaction of III with p-toluenesulfonyl chloride--pyridine (4 hr., -10°) and subsequent reduction of the tosyl derivative of III so formed by lithium aluminum hydride in ether produced 3-methyl-cis-2-penten-1-ol (IV) in 71% yield as a colorless liquid (5). Treatment of IV with phosphorus tribromide (2 equiv.) in ether at 0° for 30 min. and 25° for 3 hr. afforded the corresponding bromide which upon alkylation with lithio-1-trimethylsilylpropyne (6, 7) gave the protected ene-yne V (70% from IV) (5). The transformation of V to 3-ethyl-7-methyl-trans, cis-2, 6-nonadien-1-ol (I) was accomplished via VI and VII as previously outlined (1).

Another synthesis of I was carried out as indicated in Chart B. The tosyl derivative of 3-pentyn-1-ol (8) was ethynylated by 3-lithiopropargyl tetrahydropyranyl ether in dioxane at reflux for 12 hr. to give after acid-catalyzed methanolysis octa-2, 6-diyne-1-ol (VIII). As expected, the propargylic triple bond in VIII readily underwent reduction with lithium aluminum hydride--sodium methoxide (9) in tetrahydrofuran at reflux to give after protonolysis the alcohol IX. The organoaluminum intermediate in this process (X) could in principle undergo internal addition to the remaining double bond to give XI. The generation of XI from the diyne VIII in this way would make possible a synthesis of I from VIII in only two laboratory steps: (1) hydride reduction--iodination and (2) replacement of iodine by ethyl (using Et_2CuLi), and this was the underlying rationale for the approach which proved to be successful. In practice both triple bonds of VIII underwent reaction with lithium aluminum hydride--sodium methoxide (mole ratio 1 : 7 : 7) at reflux in dimethoxyethane over a 20-hr. period. Iodination of the resulting organoaluminum intermediate

afforded the desired product, 3,7-diiodo-trans,trans-2,6-octadien-1-ol (XII) (5), along with smaller amounts of the 3,6-diiodo position isomer (ratio 4 : 1). Reaction of XII (obtained in 45% yield after chromatographic purification on silica gel) with 8 equiv. of diethyl copperlithium (10) in ether at -30° followed by a large excess of ethyl iodide [to ethylate any products of iodine-metal exchange (1)] produced the desired dienol I in 60% yield after chromatography.

The identity of I prepared by the two methods described above with material which had been produced by the route reported earlier (1) was confirmed by spectroscopic (i.r., n.m.r., mass spectra) and thin layer chromatographic comparison.

The synthesis of the dehydro C_{18}-Cecropia juvenile hormone XVI (E,E,E isomer) seemed a worthwhile objective, since this substance might be a useful synthetic precursor of the Cecropia hormone itself (requiring only selective reduction of the Δ^4-ethylenic linkage for the conversion) and since XVI also represents a structure of clearly defined geometrical relationship to the hormone which is of interest for biological studies. This new analog was synthesized stereospecifically by the path shown in Chart C. The aldehyde XIII (1), which was prepared by oxidation of I with activated manganese dioxide in hexane at 0° for 20 min. (94% yield), could be condensed with the lithio derivative of the phosphonate XIV stereospecifically under carefully selected conditions to give the tetraene XV in which the newly created double bond is exclusively trans (E). Experimentally, a freshly prepared solution of lithium diisopropylamide in tetrahydrofuran--hexamethylphosphorictriamide (2 : 1) at -65° (11) was treated with 1.03 equiv. of the phosphonate XIV (5, 12) in a little tetrahydrofuran, and then within 1 min. the aldehyde XIII (0.6 equiv.) was added. The solution was stirred at -62 to -68° for 3.25 hr., and the product was isolated by pouring the reaction mixture into aqueous bicarbonate, extracting with ether, with subsequent concentration and chromatography. The tetraene XV (5) was thus obtained in 78% yield and 99% purity (infrared absorption for trans CH=CH at 10.37 μ) (13). Vapor phase chromatographic analysis of the crude reaction product revealed the presence of only traces of isomeric impurities. Epoxidation of XV with 1 equiv. of m-chloroperbenzoic acid in methylene chloride occurred selectively at the terminal double bond to produce XVI (5) in high yield.

Unfortunately, none of the attempts to convert XVI to the C_{18}-Cecropia hormone by selective reduction of the Δ^4-olefinic linkage led to a satisfactory result. Although diimide (produced by thermolysis of anthracene biimine adduct) did react with XVI to form some of the Cecropia hormone, a number of other reduction products also were formed, and other reducing agents were even less successful.

The biological activity of the oxidotriene ester XVI was investigated by Professor Carroll M. Williams of Harvard University. He found that this compound was fivefold more active than the C_{18}-Cecropia juvenile hormone on Pyrrhocoris but much less active on A. polyphemus. High juvenile hormone activity was also exhibited by XVI on the order Orthoptera (crickets and grasshoppers). We thank Professor Williams for these data (14).

Chart A

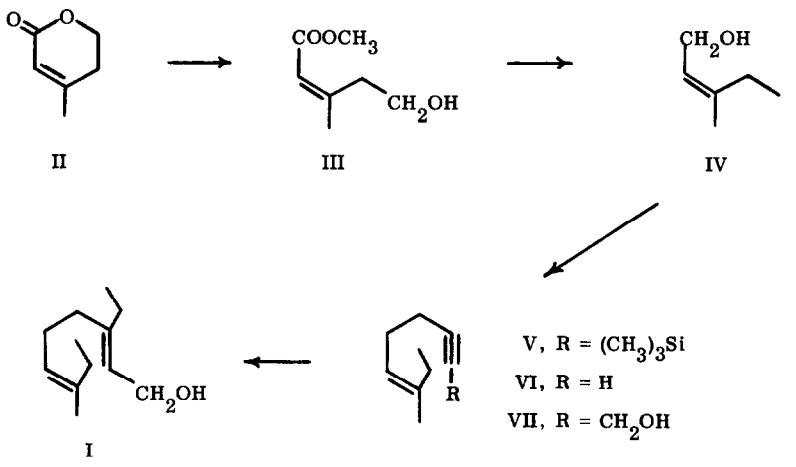


Chart B

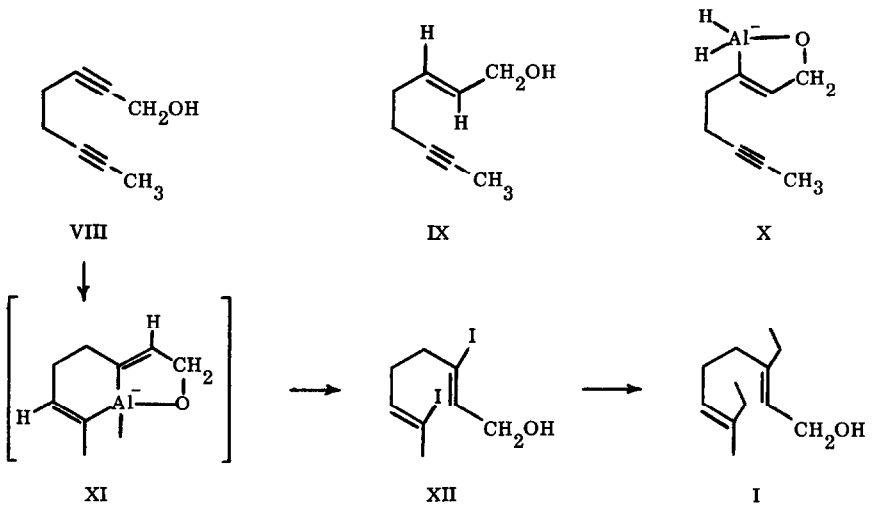
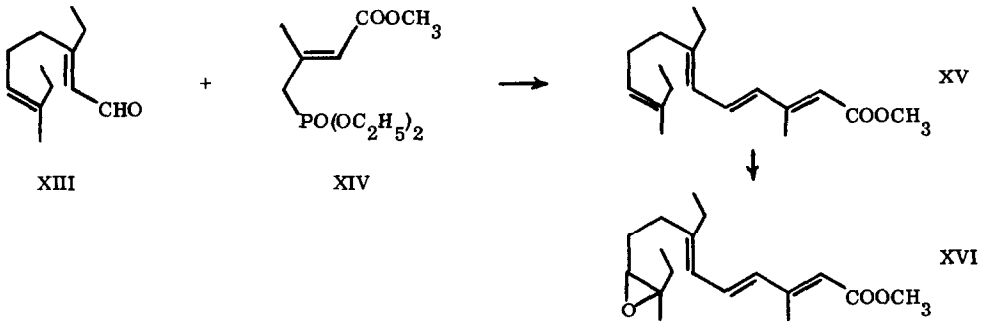


Chart C



XIII XIV XV XVI

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3. These syntheses have been described by one of us previously in a lecture at the International Conference on Insect Juvenile Hormones held at Basle, Switzerland, October 1970.
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11. Prepared from equivalent amounts of diisopropylamine in tetrahydrofuran and n-butyllithium in hexane (Foote Mineral Co.) with subsequent addition of hexamethylphosphoricamide.
12. The E-phosphonate XIV was prepared, inter alia, starting with E-4-hydroxymethyl-2-butenoic acid methyl ester [W. W. Epstein and A. C. Sonntag, J. Org. Chem., 32, 3390 (1967)] by the sequence ROH → RBr [PBr_3, ether] → $RPO(OC_2H_5)_2$ [$P(OC_2H_5)_3$ at 150°]. The reagent XIV had previously been studied as a mixture of E and Z isomers [G. Pattenden and B. C. L. Weedon, J. Chem. Soc., C, 1984, 1997 (1968)].
13. Reaction conditions involving XIII and XIV at higher temperatures, or in a different addition sequence, or without added hexamethylphosphoricamide were invariably found to afford a product consisting of a mixture of stereoisomers of XV. In addition, the condensation of the E-triphenylphosphonium salt analogous to XIV with XIII was found to proceed non-stereospecifically.

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