Stereospecific Total Synthesis of the *dl*-C_{18} Cecropia Juvenile Hormone

Sir:

We report herein a novel and stereospecific synthesis of methyl *cis*-10,11-oxido-3,11-dimethyl-7-ethyltrideca-*trans*,*trans*-2,6-dienoate (**1**), a hormonal substance which plays a powerful role in insect development.[1,2] A synthesis of **1** by a route involving three nonstereoselective Wittig condensations and a nonselective epoxidation has been reported previously.[3]

Reduction of *p*-methoxytoluene with 5 atom equiv of lithium in tetrahydrofuran–*t*-amyl alcohol–liquid ammonia (1:1:5) for 1 hr at −33° afforded **2**[4] which was converted to the hydroxy ester **3** by treatment with 1 equiv of ozone in methanol–dimethyl sulfide (10:1)[5] at −78° followed by ethanolic sodium borohydride in excess at −78° for 1 hr. The nmr spectrum[6] of **3** (bp 65–73° (0.2 mm), mass spectrometric mol wt 158.0935) included 1 vinylic H at 5.36 (t, J = 8), 3 methoxy H at 3.62, 2 carbinol H at 3.58 (t, J = 7), 2 H α to carbonyl at 3.02 (d, J = 8), methylene and methyl H attached to C=C at 2.25 (t, J = 7) and 1.77 (d, J = 1.5), respectively; and the infrared spectrum[7] included hydroxyl (2.9 μ), carbonyl (5.74 μ), and C=C (6.01 μ) stretching bands. The homogeneity of **3** was indicated by thin-layer chromatographic (tlc) analysis (R_f 0.45, C_6H_6–EtOAc 3:1) and gas chromatographic (gc) analysis;[8a] the over-all yield from *p*-methoxytoluene was 52%. Reaction of **3** with 1.1 equiv of *p*-toluenesulfonyl chloride–pyridine at 0° for 4 hr afforded an oily tosylate which was reduced with excess lithium aluminum hydride in ether at 25° for 1 hr to give the alcohol **4** (65% from **3**): bp 82–85° (20 mm); molecular ion at *m/e* 114.1044 (calcd 114.1045)[9] (*Anal.* Found: C, 73.65; H, 11.80); homogeneous by tlc and gc[8b] analysis; nmr spectrum including the following peaks: vinylic H at 5.12 (t, J = 7), 2 carbinol H at 3.57 (t, J = 7), 4 methylene H attached to double bond at 2.23 (q, J = 7) and 2.05 (q, J = 7), and 6 methyl H at 1.70 (s) and 0.97 (t, J = 7). The alcohol **4** was converted to the *p*-toluenesulfonate which was then treated with the lithio derivative of propargyl tetrahydropyranyl ether (1.75 equiv) in hexamethylphosphoric amide at 0° for 3 hr to give after acid-catalyzed methanolysis the acetylenic alcohol **5** (30% yield from **4** after chromatographic purification using 4:1 benzene–ethyl acetate and silica gel) (*Anal.* Found: C, 78.78; H, 10.51); homogeneous by gc[8b] and tlc; nmr peaks as expected at 5.11 (1 H, t, J = 7), 4.15 (2 H, s), 3.89 (1 H, s), 2.1–2.4 (4 H, m), 2.06 (2 H, q), 1.69 (3 H, broad s), and 0.96 (3 H, t, J = 7); and hydroxyl absorption at 2.9 μ (film). Reduction of the propargylic alcohol **5** by lithium aluminum hydride (2 mole equiv) in tetrahydrofuran containing sodium methoxide (4 mole equiv) at reflux for 45 min[10] followed by reaction with excess iodine[10] at −60° gave the alcohol **6**, purified by tlc using 8% ethyl acetate in benzene with silica gel adsorbant (*Anal.* Found: C, 42.91; H, 6.26; I, 45.32). The yield of **6**, homogeneous by gc,[8a] was 65% from **5**; *ca.* 6% of the position isomeric[10] 2-iodo alcohol was also formed in the reduction–iodination. The nmr spectrum of **6** contained peaks due to 1 H of the unit –IC=CH– at 5.87 (t, J = 6) and another vinylic proton peak at 5.05 (t, J = 7) in addition to the expected methyl and methylene peaks. Ethylation of **6** was effected by reaction with 4.5 mole equiv of lithium diethylcopper[10–12] in ether at −30° for 2 hr followed by treatment with excess ethyl iodide[11] at 0° for 18 hr to give 78% of pure allylic alcohol **7**: homogeneous by gc[8a,b] and tlc (silica gel, benzene–ethyl acetate 10:1; R_f 0.41 after two developments); molecular ion[9] at *m/e* 182.1669 (calcd 182.1671) (*Anal.* Found: C, 78.67; H, 11.87). The bromide obtained from the reaction of **7** with 1.2 mole equiv of phosphorus tribromide in ether at 0° was alkylated by the 3-lithio derivative of 1-trimethylsilylpropyne[13] to form **8**, which was treated successively with alcoholic silver nitrate[14] and potassium cyanide to give the acetylenic hydrocarbon **9** (80% over-all yield from **7**), further converted by treatment with *n*-butyllithium in ether followed by dry paraformaldehyde[15] to the alcohol **10**: molecular ion at *m/e* 234.1975 (calcd 234.1983); homogeneous by tlc analysis using hexane–ether 3:1 with silica gel (R_f 0.24). The same alcohol (**10**) was prepared from **7** by an alternate sequence consisting of (1) reaction of the bromide **11** with phenylthiomethylcopper[16] to give the sulfide **12**, (2) reaction of **12** with methyl iodide–sodium iodide in dimethylformamide[16] to form the iodide **13**, (3) ethynylation of **13** with lithio propargyl tetrahydropyranyl ether in tetrahydrofuran at reflux,[17] and (4) acid-catalyzed removal of the tetrahydropyranyl group.

The acetylenic alcohol **10** was converted to the allylic alcohol **14** stereospecifically in 53% yield by the method used previously for the stereospecific synthesis of farnesol.[10] Purification of the alcohol **14** and the intermediate iodo alcohol precursor were effected by

(1) The assignment of structures to the Cecropia hormone is due to H. Röller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem. Intern. Ed. Engl.*, **6**, 179 (1967).

(2) For a general discussion see C. M. Williams, *Sci. Am.*, **217**, 13 (1967); *Bioscience*, in press.

(3) (a) K. H. Dahm, B. M. Trost, and H. Röller, *J. Am. Chem. Soc.*, **89**, 5292 (1967); (b) highly ingenious stereoselective syntheses of **1** have been accomplished recently by the Syntex group (J. O. Edwards, J. Fried, and J. Siddall, personal communication) and by W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell (personal communication).

(4) This procedure is superior to that previously described by A. J. Birch [*J. Chem. Soc.*, 593 (1946); 1642 (1947)] which gives substantial amounts of tetrahydro product.

(5) J. J. Pappas and W. P. Keaveney, *Tetrahedron Letters*, 4273 (1966).

(6) Nmr spectra were obtained (in CCl_4 at 60 MHz unless otherwise indicated) for each intermediate and were in every instance in complete accord with the assigned structure. Chemical shifts are expressed in parts per million downfield from tetramethylsilane and coupling constants in hertz. The following peak multiplicity abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

(7) Infrared spectra were obtained for each intermediate (neat or in CCl_4) and were consistent with the structures shown.

(8) The following gc columns (stainless steel 0.125-in. diameter) were used with an F & M Model 810 instrument using silanized neutral support: (a) silicone gum rubber (SE-30); (b) Carbowax 20M containing 2% KOH; (c) diethylene glycol adipate (LAC 446).

(9) Mass spectra were obtained using an Associated Electronic Industries MS 9 instrument with pure samples obtained by preparative gc.

(10) See E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner [*J. Am. Chem. Soc.*, **89**, 4245 (1967)] for the introduction of this method for the stereospecific synthesis of trisubstituted olefins.

(11) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967).

(12) E. J. Corey and G. H. Posner, *ibid.*, **90**, 5615 (1968).

(13) E. J. Corey and H. A. Kirst, *Tetrahedron Letters*, in press.

(14) This elegant method for removal of the trimethylsilyl group from C≡C has been described recently by H. M. Schmidt and J. F. Arens, *Rec. Trav. Chim.*, **86**, 1138 (1967).

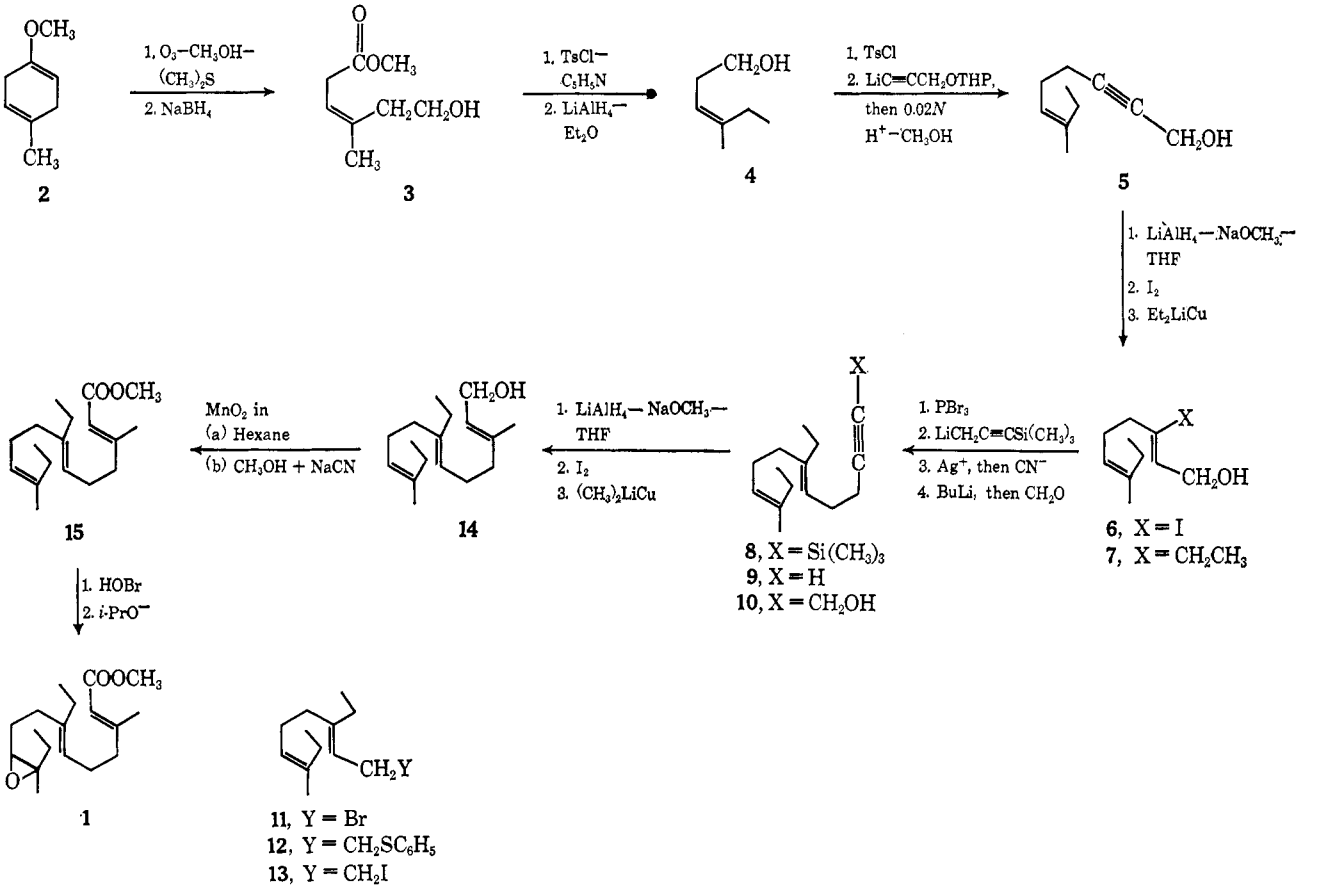
(15) A. Schaap, L. Brandsma, and J. F. Arens, *ibid.*, **84**, 1200 (1965).

(16) For the preparation of phenylthiomethylcopper and its application to the homologation of halides ($RBr \rightarrow RCH_2I$), see E. J. Corey and M. Jautelat, *Tetrahedron Letters*, in press.

(17) We are indebted to Professor W. S. Johnson and Dr. K. E. Harding for the ethynylation procedure which was developed by them for use with homoallylic halides.

tlc, and the product **14** so obtained was 97% pure by gc analysis[8c] and exhibited fully consistent nmr and infrared spectra; the molecular ion for a purified sample occurred at *m/e* 250.2290 (calcd 250.2297). The transformation of the alcohol **14** to the methyl ester **15** was carried out in 70% yield by a new method[18] in one preparative step which involved stirring of **14** with excess manganese dioxide in hexane at 0° for 30 min (to form the corresponding aldehyde (molecular ion at *m/e* 248.2132; calcd 248.2140)), filtration, removal of hexane under reduced pressure, addition of excess methanol, sodium cyanide (5 equiv), acetic acid (1.5 equiv), and manganese dioxide, and stirring at 25° for 12 hr. The infrared and nmr spectra of **15** were entirely analogous to those of methyl farnesoate; a sample purified by tlc showed the molecular ion at *m/e* 278.2239 (calcd 278.2246). Selective 10,11 epoxidation of **15** was accomplished in 52% yield by reaction with 1.1 equiv of N-bromosuccinimide in dimethoxyethane–water (1.5:1) at 0° for 30 min to form an intermediate bromohydrin followed by reaction with 1.1 equiv of sodium isopropoxide in isopropyl alcohol at 0° for 30 min.[19] The product so obtained was purified by tlc using hexane–ether 4:1 on buffered (pH 8) silica gel to give *dl*-**1**, molecular ion at *m/e* 294.2186 (calcd, 294.2195) (*Anal.* Calcd: C, 73.43; H, 10.27. Found: C, 73.18; H, 10.42). The nmr, infrared, and mass spectra of **1** were identical with those of the naturally derived C-18 Cecropia juvenile hormone.[1,20]

The biological effects of synthetic *dl*-**1** were strictly comparable to those produced by natural Cecropia hormone in all insect species treated. With pupae of the polyphemus silk worm (*Antheraea polyphemus*) 0.05 μg of synthetic hormone injected in 50 μl of chemically pure olive oil was completely effective in blocking maturation. Metamorphosis of the bugs *Pyrrhocoris apterus* and *Oncopeltus fasciatus* was completely inhibited by topical application of 0.5 μg of synthetic **1** in 1 μl of acetone. With *Tenebrio mollitor* the critical topical dose for response was 0.1 μg applied in 1 μl of acetone.[21]



The above stereospecific synthesis of C-18 Cecropia hormone (**1**) includes five novel synthetic processes which are of quite general utility: (1) the stereospecific synthesis of **4** from a benzenoid precursor, (2) the stereospecific conversion of propargylic alcohols to trisubstituted olefinic carbinols *via* organoaluminum[10] and copper[11,12] reagents, (3) selective propynylation,[13] (4) the "one-flask" conversion of allylic alcohols to conjugated esters,[18] and (5) the two-step homologation of primary halides.[16]

Investigations are continuing on other synthetic routes to **1** and related insect hormones as well as on the resolution of **1**.

(18) E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).

(19) For an analogous oxidation of methyl farnesoate, see E. E. van Tamelen, M. A. Schwartz, E. Hessler, and A. Stone, *Chem. Commun.*, 409 (1966).

(20) We thank Dr. H. Röller and associates for a copy of the mass spectrum of natural C-18 Cecropia juvenile hormone in advance of publication; see H. Röller and K. H. Dahm, *Recent Progr. Hormone Res.*, **24**, 651 (1968).

(21) We thank Professor Carroll M. Williams for carrying out these biological tests.

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Anodic Hydroxylation of Aromatic Compounds

Sir:

We report the first unequivocal evidence for anodic hydroxylation of aromatic compounds under voltammetric conditions. These hydroxylations take place at low potentials in aqueous solutions. The reaction details can be examined by quantitative electrochemical techniques and can provide valuable comparisons with hydroxylations of physiological significance.

To best illustrate the style of reaction, Figure 1A shows the cyclic voltammetry for the oxidation of 1,5-dihydroxynaphthalene in 2 *M* perchloric acid at a carbon paste electrode. (The electrochemical techniques and electrodes used are all conventional and have been described.[1] The initial oxidation peak N is at +0.54 V *vs.* sce, but there is practically no reversible reduction current for the corresponding quinone. Instead, a rapid follow-up chemical reaction has occurred and new reduction product is seen at peak J. On the second and subsequent scans, the new, reversible redox system (peaks J, J′) is well defined. This new redox system is readily identified as that of juglone–hydrojuglone (5-hydroxy-1,4-naphthoquinone–1,4,5-trihydroxynaphthalene). A controlled potential oxidation of 1,5-dihydroxynaphthalene at a potential corresponding to peak N yields a quinone whose nmr, ir, and uv spectra are identical with those of authentic juglone. Raising the pH of such a solution to about 12 gives an epr spectrum identical with that of the juglone semiquinone. Finally, the cyclic voltammetry of authentic 1,4,5-trihydroxynaphthalene (Figure 1B) matches perfectly that of the follow-up couple, J, J′. Clearly, in the over-all oxidation of 1,5-dihydroxynaphthalene, a hydroxyl group is inserted in position 4 of the naphthalene ring. The resulting 1,4,5-trihydroxynaphthalene is more easily oxidized than the starting material and first appears in the cyclic voltammetry as a reduction peak of juglone.

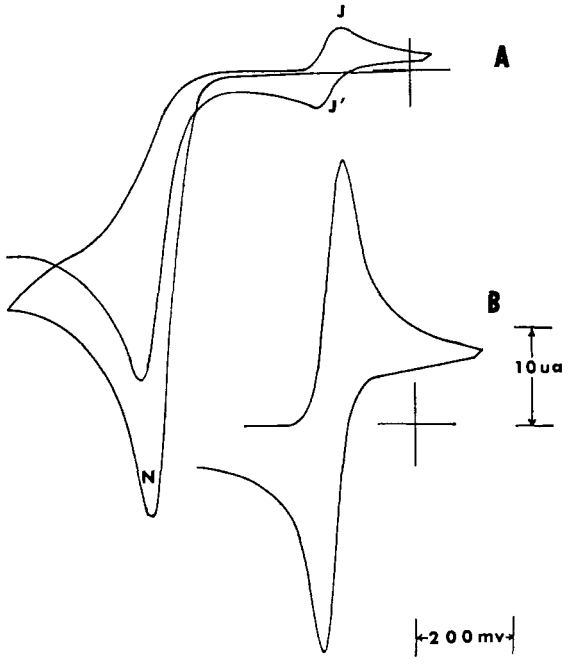
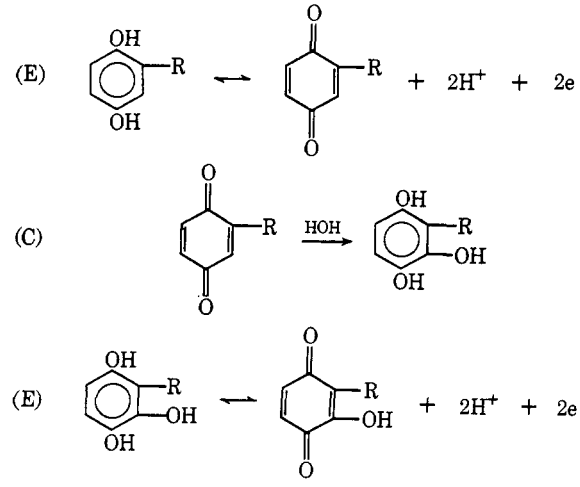


Figure 1. Cyclic voltammetry of anodic hydroxylation of 1,5-dihydroxynaphthalene: (A) cyclic polarogram of 1,5-dihydroxynaphthalene in 2 *M* $HClO_4$; (B) cyclic polarogram for oxidation of 1,4,5-trihydroxynaphthalene, same conditions.

The wider scope of such reactions is shown by a series of 2-substituted hydroquinones. If the 2 substituent is electron withdrawing like COOH, CHO, NO_2, hydroxylation occurs in an over-all process



For 2-nitrohydroquinone, after controlled potential electrolysis, a carbon–hydrogen analysis and mass spectrum of the 2,4-dinitrophenylhydrazine derivative of the quinone formed shows unquestionable proof of OH insertion. No hydroxylation occurs if the 2 substituent is Cl, CH_3, OH, or H. In this case the reaction only involves a two-electron oxidation to the ordinary benzoquinone (whereas a total of four electrons are found in the controlled potential coulometry of the COOH, CHO, and NO_2 derivatives). In acetonitrile all derivatives give a simple two-electron oxidation (if water is added to the acetonitrile, hydroxylation reappears for the above three compounds).

These reactions are typical 1,4-nucleophilic additions to quinones, but they have never been seen previously under these mild electrochemical conditions. We have not proven unequivocally that the hydroxyl group enters position 3 of the substituted hydroquinones. The nmr spectra of the products are not definitive enough for this proof. However, for the hydroquinone-2-carboxylic acid the cyclic voltammetry of the follow-up product is identical with that of authentic 2,3,6-trihydroxybenzoic acid. Molecular orbital calculations also show the 3 position to be that of highest positive charge, and hence the most reactive site for nucleophilic attack. The 1,4 addition of thiols to similar 2-substituted benzoquinones was shown to occur in the 3 position.[2]

(1) For typical applications of the electrochemical techniques to anodic oxidations, see Z. Galus, H. Y. Lee, and R. N. Adams, *J. Electroanal. Chem.*, **5**, 17 (1963).

(2) H. S. Wilgus, E. Frauenglass, E. T. Jones, R. F. Porter, and J. W. Gates, *J. Org. Chem.*, **29**, 594 (1964).