Epoxidation of IVc with *m*-chloroperbenzoic acid in ether gave only α-epoxide[7] (mp 158–160°), identical with the product from methanol–sodium hydroxide treatment of the bromohydrin[11] a, whereas epoxidation in dichloromethane at 5° allowed hydroxyl-assisted formation of the β-epoxide V[7] (50%, mp 162–163°) from IVc.

Optimal geometry[12] for concerted cleavage of C_{3a}–C_4 and C_5–O bonds is attained in VIa[7] (mp 133–135°), produced in 65% yield by lithium aluminum hydride reduction of V in refluxing dioxane. Treatment of the triol VIa with *p*-toluenesulfonyl chloride (5 equiv) in pyridine at 5° led selectively to the equatorial 5β-tosylate VIb (89%; $\nu_{max}^{CCl_4}$ 1600, 1360, 1180, and 1170 cm^{-1}) which underwent quantitative[13] fragmentation on exposure to sodium hydride in dry tetrahydrofuran at 20° with formation of the *cis*-olefinic ketone VII [$\nu_{max}^{CCl_4}$ 1735 cm^{-1}; nmr 1.67 (d, J = 1.5 Hz, vinylic CH_3) and 5.04 (t, J = 7.5 Hz, vinylic H); semicarbazone[7] mp 144–145°]. Gas chromatographic and nmr analyses of VII did not reveal the presence of any *trans* isomer.

Alkylation of this ketone by ethereal methyllithium to form the diol VIIIa (57%; 3,5-dinitrobenzoate[7] VIIIc mp 91–91.5°) was facilitated by temporary protection of the hydroxyl in VII as a tetrahydropyranyl ether. Reaction of the diol VIIIa with excess *p*-toluenesulfonyl chloride–pyridine was slow but gave cleanly the tosylate VIIIb (95%) which fragmented smoothly in the presence of sodium hydride in dry tetrahydrofuran to generate the central *trans* olefinic bond in *trans,cis*-6-ethyl-10-methyldodeca-5,9-dien-2-one (I; 80% from VIIIb; $\nu_{max}^{CCl_4}$ 1715 cm^{-1}; nmr 1.66 (d, J = 1.5 Hz, vinylic CH_3), 2.12 (s, $COCH_3$), 5.04 (m, 2-vinylic H), homogeneous by gas chromatographic[14] analysis).

Assignment of *cis* geometry to the 9,10 double bond in I is based on the 1.66-ppm chemical shift of the vinylic methyl group. In this series the corresponding *trans* isomers consistently show[3] vinylic methyl signals at 1.59–1.61 ppm.

The stereospecific formation of the central 5,6 double bond in I by fragmentation enables its geometry to be related directly[5] to the configurations of angular ethyl and secondary hydroxyl in VIIIa. Since the *cis* relationship of the latter groups in VIIIa was produced from IIIa by a borohydride reduction whose stereochemical course is well established[8] in such systems, the 5,6 double bond of I can be assigned *trans* geometry.

Acknowledgment. The authors wish to thank Dr. J. H. Fried for helpful discussions.

(15) Syntex Postdoctoral Fellows: (a) 1968–1969; (b) 1967–1968.

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A Highly Stereoselective Synthesis of the Racemic Juvenile Hormone

Sir:

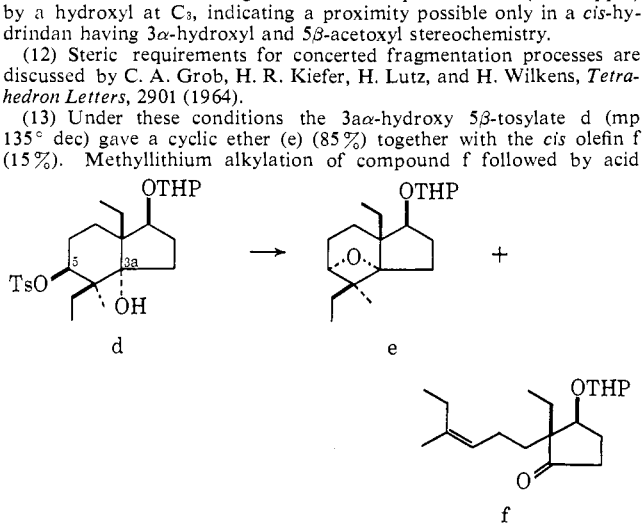
In a series of brilliant investigations Dahm, *et al.*,[1] have shown that the extremely potent substance responsible for arresting develoment at the pupa stage in *Hyalaphora cecropia* is methyl *trans,trans,cis*-10-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (**1**), called the juvenile hormone.[2] Their published work has culminated in a total synthesis of the racemic hormone which, although not stereoselective, made available many of the stereoisomers and set the stage for the next major development, namely a stereoselective synthesis. We are reporting here on the realization of this aim.[3] Our synthesis is based on an application of the highly stereoselective modification of the Julia method for producing *trans*-trisubstituted olefinic bonds[4] which involves in the key step the rearrangement of a cyclopropylcarbinyl to the homoallylic system, as illustrated here by the conversion of the carbinol **5** to the bromide **6**. By this expedient we have developed a scheme which affords the racemic juvenile hormone in 12 steps starting from methyl *trans*-γ-bromo-β,β-dimethylacrylate (**2**)[5] and 1-acetyl-1-ethylcyclopropane (**3**, R = H).[6] At the present stage of development all but two of the steps (see below) proceed in 90% yield or better; thus the hormone is now relatively easily accessible.

Ketone **3** (R = H) was treated with dimethyl carbonate and sodium hydride. The sodio derivative of the resulting β-keto ester **3** (R = CO_2CH_3) was allowed to react with the bromo ester **2** in tetrahydrofuran at

b show extreme deshielding of the methine proton at C_5 (δ 5.41 ppm) by a hydroxyl at C_3, indicating a proximity possible only in a *cis*-hydrindan having 3α-hydroxyl and 5β-acetoxyl stereochemistry.

(12) Steric requirements for concerted fragmentation processes are discussed by C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkens, *Tetrahedron Letters*, 2901 (1964).

(13) Under these conditions the 3aα-hydroxy 5β-tosylate d (mp 135° dec) gave a cyclic ether (e) (85%) together with the *cis* olefin f (15%). Methyllithium alkylation of compound f followed by acid



hydrolysis gave a diol identical with VIIIa.

(14) F & M Model 402, 4% Carbowax 20M on Diatoport S (2 m × 3 mm) at 130°.

(1) See K. H. Dahm, B. M. Trost, and H. Röller, *J. Am. Chem. Soc.*, **89**, 5292 (1967); *Life Sci.*, 7, 129 (1968), and references cited therein.

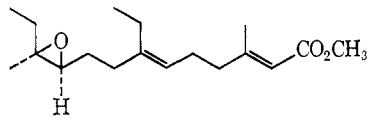
(2) This hormone is extremely active simply on external application to numerous species and shows promise of being a "perfect" insecticide; see, *inter alia*, C. M. Williams, *Sci. Am.*, **198**, (2) 67 (1958); A. S. Meyer, H. A. Schneiderman, and L. I. Gilbert, *Nature*, **206**, 272 (1965).

(3) We have learned by private communication of two recent, highly imaginative stereoselective syntheses of the juvenile hormone, one by E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, and the other by J. O. Edwards, J. Fried, and J. Siddall. We wish to express our thanks to Professor Corey and Dr. Siddall for sending us copies of their manuscripts prior to publication.

(4) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).

(5) I. Ahmad, R. N. Gedye, and A. Nechvatal, *J. Chem. Soc.*, 185 (1968). We prepared the material readily by bromination of β,β-dimethylacrylic acid with N-bromosuccinimide. During the work-up the *cis* bromo acid underwent spontaneous lactonization, leaving the desired *trans* isomer as the only acidic material. The acid was easily esterified by the method of R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(6) This ketone was prepared by the method described for producing 1-acetyl-1-methylcyclopropane (M. Julia, S. Julia, T. S. Yu, and C. Newville, *Bull. Soc. Chim. France*, 1381 (1960)) except that ethyl instead of methyl iodide was used in the alkylation step.



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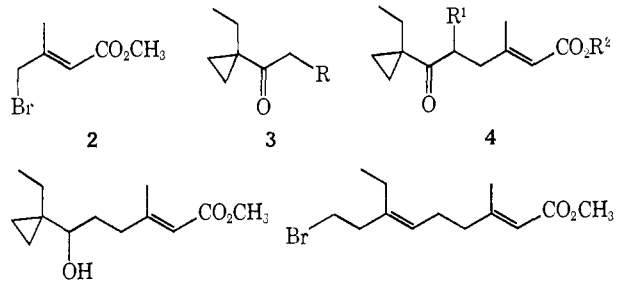
0–23° for 5 hr to give the keto diester **4** ($R^1 = CO_2CH_3$; $R^2 = CH_3$) which, on treatment with barium hydroxide in refluxing aqueous methanol (35 min), underwent hydrolysis and (on acidification) decarboxylation to yield a mixture from which the crystalline keto acid **4** ($R^1 = R^2 = H$), mp 64–65°, was readily isolated in 65% yield. The nmr spectrum (CCl_4) showed a single vinyl methyl absorption at δ 2.18 ppm, characteristic of the *trans* configuration.[1] The keto acid was converted to the methyl ester **4** ($R^1 = H$; $R^2 = CH_3$) with diazomethane. Reduction with sodium borohydride in methanol afforded the carbinol **5** which was transformed, by treatment with phosphorus tribromide and lithium bromide in collidine–ether followed by zinc bromide in ether,[4] into the *trans,trans*-bromodienic ester **6** which proved to contain a maximum of 5% of the *trans,cis* isomer.[7]



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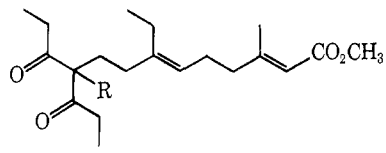
5 6



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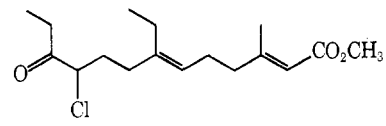

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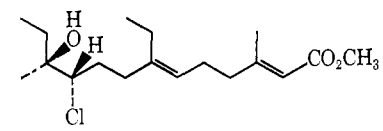

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The bromo compound **6** was converted, by treatment with sodium iodide in hexamethylphosphoramide for 6 hr at room temperature, into the corresponding iodo compound[8] which, without purification, was allowed to react for 4 days with an excess of the lithium enolate of heptane-3,5-dione in refluxing tetrahydrofuran containing 5% hexamethylphosphoramide. The resulting dione **7** (R = H), which was separated (in 45% yield) by Florisil chromatography from some trienic ester (formed by dehydrohalogenation), was chlorinated by the Kosower method[9] (cupric and lithium chloride in dimethylformamide) to give the chloro dione **7** (R = Cl). This last substance, on treatment at 0° for 25 min with barium hydroxide in ethanol, underwent deacylation to give the chloro ketone **8** which was readily purified by preparative vpc.[10] When the chloro ketone **8** was treated with excess methylmagnesium chloride in tetrahydrofuran at −75° the Grignard reagent reacted only with the keto group to give the racemic chlorohydrin **9**, contaminated with a maximum of 8% of its diastereoisomer (see below).[11] The chlorohydrin, on stirring for 10 min at room temperature with anhydrous potassium carbonate in methanol, was converted into the epoxide **1** (*Anal.* Found: C, 73.3; H, 10.4). The 100-Mc nmr spectrum (CCl_4) of this product was indistinguishable from that of the authentic juvenile hormone[1] except that our specimen showed an additional weak signal at δ 1.17 ppm corresponding to the methyl group at C-11 of the *trans* epoxide.[1] The area under this signal was 5–8% of that under the methyl signal at δ 1.19 ppm for the *cis* isomer.[12] Therefore our product is contaminated with a maximum of 8% of the *trans,trans,trans* isomer[13] and, as shown above, 0–5% of the *trans,cis,cis* isomer. The mass spectrum fragmentation pattern as well as the vpc behavior of our product was indistinguishable from that of the authentic material.

Acknowledgment. We wish to express our thanks to Professor B. M. Trost for supplying us with a comparison specimen of the authentic racemic juvenile hormone and for conducting some of the vpc comparisons. We also thank Professor A. Meyer for conducting some preliminary vpc analyses. We are grateful to the U. S. Public Health Service and the National Science Foundation for support of this research.

(7) A sample of this bromodienic ester was converted, by treatment with sodium acetate in dimethylformamide (see ref 4), into the corresponding acetoxydienic ester. The 100-Mc nmr spectrum of this material in CCl_4 showed absorption for two protons as a triplet (J = 7 Hz) centered at δ 4.01 ppm corresponding to the protons on the carbon holding the acetoxy group. A weak absorption appeared as a second triplet centered at δ 3.99 ppm due to the *trans,cis* isomer. The relative areas under these two triplets were estimated to be 96 and 4%.

(8) An alternative, more direct approach to the iodo compound involved application of a procedure developed by B. Staskun in our laboratory, *i.e.*, the carbinol **5** was treated with *o*-phenylene phosphorochloridite in pyridine according to E. J. Corey and J. E. Anderson, *J. Org. Chem.* 32, 4160 (1967), and the resulting crude phosphite ester was in turn treated with zinc iodide in ether giving the iododienic ester in about 75% yield. A sample was converted to the acetate and analyzed as described in ref 7. The results indicated that the product contained only a trace of the *trans,cis* isomer.

(9) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, 28, 630 (1963).

(10) This treatment, which is probably unnecessary, removed a small amount of lower retention time material which we suspect, but have not yet proved, contained the few per cent of unwanted *trans,cis* isomer (see above).

(11) *Cf.* J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112, 2539 (1969).

(12) In benzene solution, a larger (0.04 ppm) separation of the methyl signals was observed, permitting a more accurate estimation of the *cis*:*trans* isomer ratio.

(13) This isomer also has a very high biological activity.[1]

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The Nature of the Tin–Transition Metal Bond[1]

Sir:

The discovery of synthetic techniques leading to tin–transition metal compounds has resulted in an