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TOTAL SYNTHESIS OF THE RACEMIC FORM OF THE SECOND JUVENILE HORMONE (METHYL 12-HOMOJUVENATE) FROM THE CECROPIA SILK MOTH

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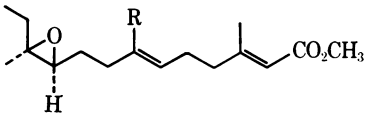
Abstract.—Methyl *cis*-10-epoxy-3,7,11-trimethyl-*trans,trans*-2,6-tridecadienoate has been stereoselectively synthesized in 12 steps starting from methyl *trans*-γ-bromo-β,β-dimethylacrylate and 1-acetyl-1-methylcyclopropane. The final product proved to be identical with the second, less abundant juvenile hormone (methyl 12-homojuvenate) isolated from the Cecropia silk moth. The biological activities of the compound were evaluated in various insects.

Intense interest in juvenile hormone isolated from the lepidopterous Cecropia silk moth has recently culminated in identification of its preponderant component as methyl *cis*-10-epoxy-7-ethyl-3,11-dimethyl-*trans,trans*-2,6-tridecadienoate (**10**).[1] Four syntheses of this compound have so far been reported,[1, 2] three of which are stereoselective.[2]

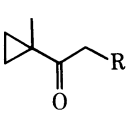
Some four years ago, one of us described the isolation from Cecropia silk moths of two substances, B and E, both of which have similarly high hormonal activity. More recently, compound B was shown to be identical with the juvenile hormone methyl 12,14-dihomojuvenate (**10**); and compound E, although at hand in a very small amount, was identified from spectrometric data as methyl *cis*-10-epoxy-3,7,11-trimethyl-*trans,trans*-2,6-tridecadienoate or methyl 12-homojuvenate (**1**).[3] We now wish to disclose the stereoselective total synthesis of this structure. The identity of the synthetic material with compound E confirms the structure of this natural hormone.

Synthetic Preparation.—The synthesis was carried out in a manner analogous to the previously reported synthesis of the juvenile hormone **10** and the yields were



1, R = CH_3
10, R = C_2H_5

comparable.[2c] Thus, the sodio derivative of the β-keto ester **2** (R = CO_2CH_3) reacted readily with the bromo ester **3** to give the keto diester **4** (R^1 = CO_2CH_3, R^2 = CH_3) (*Analysis:* Found: C, 62.6; H, 7.4). Treatment with barium hydroxide in aqueous methanol followed by acidification effected decarbethoxylation and the keto acid **4**(R^1 = R^2 = H), mp 96–97°, was readily isolated by crystallization (*Analysis:* Found: C, 67.3; H, 8.3). The 60-MHz nuclear magnetic resonance (NMR) spectrum of this substance in deuterochloroform showed absorption for three protons as a doublet (J = 1 Hz) centered at δ 2.16 ppm corresponding to the methyl group at C-3. The keto acid was esterified with diazomethane to give the methyl ester **4**(R^1 = H, R^2 = CH_3) (*Analysis:* Found: C, 68.5, H, 8.6) which on reduction with sodium borohydride in methanol afforded the carbinol **5** (*Analysis:* Found: C, 68.0; H, 9.6). The infrared spectrum showed absorption at 3500 cm^{-1} for a hydroxyl group. Bromination of the carbinol with phosphorus tribromide and lithium bromide in collidine-ether yielded a crude mixture of bromides which, without purification, was treated with zinc bromide in ether to give the rearranged *trans, trans*-bromodienic ester **6** (*Analysis:* Found: C, 52.7; H, 6.9; Br, 28.6). The NMR spectrum showed vinyl methyl absorptions as a doublet (J = 1 Hz) centered at δ 2.16 ppm and a singlet at δ 1.62 ppm, both characteristic of the *trans* configurations of the olefinic bonds.[2c] There was also a very weak absorption at δ 1.70 ppm possibly due to a trace of the *trans,cis* isomer. There is ample precedent that this cyclopropylcarbinyl-homoallylic rearrangement is at least 95 per cent stereoselective.[4]



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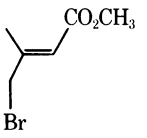

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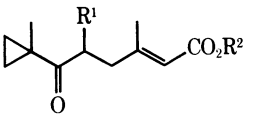

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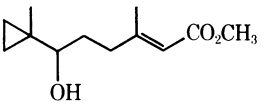

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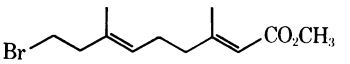

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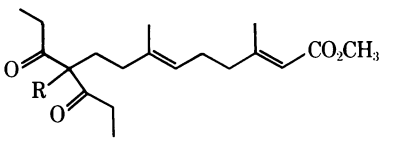
The bromo ester **6** was converted, by treatment with potassium iodide in hexamethylphosphoramide, into the corresponding iodo compound which, without purification, was treated with the lithium enolate of heptane-3,5-dione to give the dione **7** (R = H) (*Analysis:* Found: C, 70.5; H, 9.4). The major byproduct in this reaction appeared to be trienic ester formed by competitive dehydrohalogenation. The dione **7** (R = H) was chlorinated with cupric and lithium chloride in dimethylformamide[5] to give the chloro dione **7** (R = Cl) (*Analysis:* Found: C, 63.7; H, 8.3; Cl, 9.7) which, without purification, was treated with barium hydroxide in ethanol at 0° to afford the chloro ketone **8** (*Analysis:* Found: C, 63.8; H, 8.4; Cl, 11.6).



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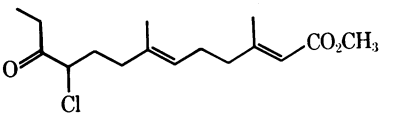

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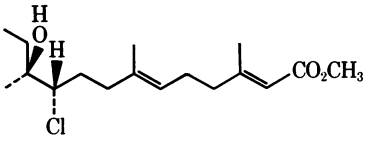

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The reaction of chloro ketones with organometallic reagents has been utilized by Cornforth as the first step in a stereoselective synthesis of trisubstituted olefinic bonds.[6] Several models are available for predicting the stereochemical course of this reaction.[6, 7] When applied to the case at hand, each model predicts that the chloro ketone **8** on treatment with methyl Grignard will give a predominance of that chlorohydrin, namely **9**, which on treatment with base will lead to the desired *cis*-epoxide **1**. We were somewhat disappointed to discover that, when the chloro ketone **8** was treated with methylmagnesium iodide in ether at −78°, the derived epoxides proved to be a mixture of the desired *cis* (65%) and the *trans* (35%) compounds. The isomer ratios were determined, as in the previous work,[2c] by estimating the relative areas of the NMR signals for the methyl group at C-11 at δ 1.19 and 1.17 ppm in carbon tetrachloride solution or at δ 1.26 and 1.215 ppm in benzene solution. The use of methylmagnesium chloride or bromide in ether caused some increase in selectivity (80:20), but a strikingly favorable result was realized when tetrahydrofuran was employed as solvent.[8] Thus, the chloro ketone **8** in tetrahydrofuran was treated with methylmagnesium chloride at −78° overnight and the chlorohydrin **9** isolated (*Analysis:* Found: C, 64.5; H, 9.5). The infrared spectrum showed an absorption at 3580 cm^{-1} for a hydroxyl group. Brief treatment of this chlorohydrin with potassium carbonate in methanol at room temperature converted it into the epoxide (*Analysis:* Found: C, 72.6; H, 10.2) which proved to contain the desired *cis*-isomer (**1**) in a ratio of about 95:5 relative to the *trans* analog.

The gas chromatogram of a sample of this material, which had been applied with a metal-free injector onto a neutral Carbowax 4000 column,[3a] demonstrated the high purity of the synthetic preparation. Only two contaminants, each more volatile than the hormone molecule and totaling 3 per cent of the combined peak areas, were detected. These solutes were retained at ratios relative to 1 of 0.61 (1.1%) and 0.86 (1.9%), suggesting[9] that they may represent the *cis*-2, *cis*-6 and *trans*-2, *cis*-6 isomers of **1**. The slightly less volatile all-*trans* epoxy isomer was only partially resolved from **1**, making it impracticable to gauge its content accurately by the particular analytical procedure.

Physicochemical Comparison between the Synthetic and Natural Hormone.—Gas chromatograms of both preparations revealed exactly coinciding retention times for the principal compounds; no trace of band broadening was noted in mixed chromatograms. The mass spectra, kindly determined by Prof. K. Biemann

and his associates[3a] with a Hitachi RMU 6-D spectrometer, were essentially identical. The small differences in the spectra were of a magnitude compatible with the presence of impurities indicated in both samples and with the fact that the spectra were recorded under not strictly identical conditions because of an elapse of time. The NMR spectra[3a] were identical, except for the absence, in the synthetic specimen, of an unassigned peak at δ 1.27 ppm and shoulder at 2.18 ppm. This would indicate the presence in the natural hormone preparation of minute amounts of contaminants, either in the nature of unresolved companion compounds or, more likely, decomposition products of the hormone resulting from handling of the small quantities of the sensitive compound. At the applied microsampling conditions, the small signal of a minor impurity (all-*trans* epoxide) appearing on the flank of a large resonance 0.02 ppm from the absorption maximum cannot be recognized with certainty. The infrared spectra in the region of 1800–800 cm^{-1} were superimposable.

Biological Evaluation of the Juvenile Hormones.—Natural and racemic synthetic hormone methyl 12-homojuvenate (**1**) were found to be indistinguishably effective morphogenetically in the very sensitive pupal *Galleria* wax[10a] and the *A. polyphemus* injection assays[10b] (these data were obtained by courtesy of Profs. H. A. Schneiderman and L. I. Gilbert, respectively). Substantiating earlier results in these species,[3b] **1** was again equally active as the more plentiful juvenile hormone methyl 12, 14-dihomojuvenate (**10**). The same holds for the capacity of the two hormones to terminate diapause of unchilled, debrained eight-month-old *H. cecropia* and one-month-old *A. polyphemus* pupae.[11]

On the other hand, a difference in potency between **1** and **10** was disclosed when a nonlepidopterous species was the test insect. Upon topical application to *Tenebrio* pupae two to five hours old,[12a] 2 μg of synthetic **1** in 1 μl of acetone induced emergence at the next molt of intermediate forms of a half-pupal, half-adult variety; synthetic and natural **10** brought about the same juvenilizing effect at a three- to fivefold lower dosage. An even greater (about tenfold) difference in their morphogenetic activity was exhibited when the two hormones, dissolved in 1 μl of olive oil, were injected[12b] into the *Tenebrio* pupae. A similar relationship of their potency was noted when the hormones were assayed[12c] at concentration levels more than 1000 times lower. This may be the main reason why the research group that determined the hormone titer in isolation work by means of one of these *Tenebrio* assays[1] did not detect the second juvenile hormone (**1**) in the Cecropia extracts.

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