A Synthesis of *dl*-C₁₇-*Cecropia* Juvenile Hormone[†]

By Kenji MORI,* Akira SATO and Masanao MATSUI

Department of Agricultural Chemistry
The University of Tokyo, Bunkyo-ku, Tokyo, 113

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A novel synthesis of *dl*-C₁₇-*Cecropia* juvenile hormone (I) was accomplished.

The C₁₇-*Cecropia* juvenile hormone (methyl 12-homojuvenate, I) was discovered in 1968 by Meyer and his co-workers as the second and minor active principle of *Cecropia* oil.^{1~3)} The proposed structure (I)¹⁾ was confirmed by syntheses.^{4~6)} We previously reported a non-stereoselective synthesis of the hormone (I) leading to a mixture of all the possible stereoisomers.⁷⁾ In this paper we describe a novel synthesis of the pure *dl*-C₁₇-hormone (I). The synthetic scheme is a slight modification of our previous synthesis of the C₁₈-*Cecropia* juvenile hormone⁸⁾ which is based on Julia's cyclopropyl carbinol rearrangement⁹⁾

4-Methylhex-3-*cis*-enyl bromide (II), the starting material, was synthesized from methyl cyclopropyl ketone and acetylene in a highly stereoselective manner as described previously.^{10)**} A Grignard reagent prepared from the bromide (II) and magnesium in tetrahydrofuran was reacted with methyl cyclopropyl ketone to give a crude cyclopropyl carbinol

(III) in 44% yield after distillation. It should be noted that in ether this *cis*-bromide (II) did not yield a stable Grignard reagent and mainly the coupling product was isolated. The crude carbinol was chromatographed over alumina to give a purer carbinol (III, 82% purity with 18% of the dihydro compound) in 26% yield from II. This unsatisfactory result may be due to the steric hindrance caused by the *cis*-ethyl group, for a stereoisomeric mixture of *cis*- and *trans*-4-methylhex-3-enyl bromides gave the carbinols in 61% yield in contrast with the *cis*-bromide (II), when treated with magnesium in ether followed by methyl cyclopropyl ketone. The high yield observed with the stereoisomeric mixture seems to be due to the entrainment effect¹¹⁾ of the more reactive *trans*-bromide.

Treatment of the carbinol (III) with 48% hydrobromic acid gave a stereoisomeric mixture of the bromides (IV) in 89% yield. This, without further purification, was converted into a stereoisomeric mixture of the nitriles (V) by heating with sodium cyanide in DMSO in 63% yield. GLC analysis revealed that this was a mixture of 3-*trans*, 7-*cis*-(58%), 3-*cis*, 7-*cis*-(19%), 3-*trans*, 7-saturated (13%) and 3-*cis*, 7-saturated (4%) cyanides. This indicated that the cleavage of the cyclopropane ring proceeded with a moderate stereoselectivity to give the desired 3-*trans*-material (IV) and the undesired 3-*cis*-isomer in a ratio of 3:1.⁹⁾

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* Address correspondence to this author.

** This bromide (II), however, was contaminated with 3-methylhexyl bromide (17%). This resulted in the subsequent contamination of the synthetic intermediates (III~VI and VI') with the corresponding dihydro compounds. The contaminant was removed partly by GLC purification of the *trans*, *trans*, *cis*-trienoic ester (IX) and completely by TLC purification of the racemic hormone (I).

The mixture of the nitriles was treated with methyl magnesium iodide followed by dilute hydrochloric acid to give a stereoisomeric mixture of ketones (VI) in 67% yield. GLC analysis showed this to be a mixture of 5-*trans*, 9-*cis*-(51%), 5-*cis*, 9-*cis*-(18%), 5-*trans*, 9-saturated (11%) and 5-*cis*, 9-saturated (5%) ketones. The rest (15%) was unknown impurities. This was purified by recrystallization of the corresponding semicarbazone (VII) in the same manner as described in our synthesis of methyl *dl*-14-homojuvenate.^{7,12} The recrystallized semicarbazone (VII), mp 103.5~104.5°C, was boiled with aqueous oxalic acid to give the 5-*trans*, 9-*cis*-ketone (VI') in 83% purity with 15% of the 9-saturated ketone as judged by GLC. The yield of this product from the crude ketone was 21.5%. The structure of the contaminating 6,10-dimethyldodec-5-*trans*-en-2-one was supported by

GC-MS data in which a molecular ion peak of m/e 210 ($=\text{C}_{14}\text{H}_{26}\text{O}$) was observed for the minor component. The above result implies that purification of the ketone as semicarbazone is only effective for the separation of geometrical isomers at the central double bond at C-5. No separation of the desired 9-*cis*-isomer from the dihydro ketone was effected.

Condensation of the ketone (VI) in *N,N*-dimethylformamide with methyl diethylphosphonoacetate in the presence of sodium methoxide afforded a stereoisomeric mixture of unsaturated esters (VIII and IX) in 86% yield in a ratio of 2:3. These two were separated by preparative GLC to give pure esters VIII and IX. The IR and NMR spectra of the two isomers were similar to but not identical with each other. The greatest difference observed in the NMR spectra was

FIG. 1. NMR Spectrum of *dl*-C₁₇-Cecropia Juvenile Hormone Measured in CCl₄ by a JEOL JNM-4H-100 Spectrometer at 100 MHz.

the down-field shift of a signal due to the methyl group at C-3 of the *trans*-isomer (τ 7.89) compared with that of the *cis*-isomer (τ 8.16). Epoxidation of the *trans*-ester (IX) with *m*-chloroperbenzoic acid in methylene chloride followed by TLC purification afforded the racemic C₁₇-Cecropia juvenile hormone (I) with satisfactory spectral data. Its NMR spectrum shown in the Figure was identical with that of the natural product.^{1,2)}

The biological evaluation of this synthetic material together with others including *dl*-C₁₈-Cecropia juvenile hormone will be reported elsewhere.

EXPERIMENTAL

All mps and bps were uncorrected. IR spectra refer to Nujol mulls for crystalline samples and films for oils and were determined on a JASCO IRA-1 spectrometer. NMR spectra were recorded on a JEOL NM-4H 100 spectrometer at 100 MHz in CCl₄ with TMS as an internal standard. GLC analyses were performed on a YANACO G80 gas chromatograph.

2-Cyclopropyl-6-methyloct-5-cis-en-2-ol (III). A solution of the bromide (II, 61.8 g) in dry THF (200 ml) was added slowly during 2.5 hr to a vigorously stirred suspension of Mg (8.5 g) in THF (200 ml) under N₂ at 30~32°C. After the addition the mixture was stirred and heated at 45°C for 45min. Then it was cooled with ice-water. A solution of methyl cyclopropyl ketone (26 g) in dry THF (150 ml) was added dropwise during 30 min to the stirred and ice-cooled Grignard reagent at 5~10°C. Then the ice-bath was removed. The mixture was stirred at room temperature for 1 hr and then left to stand overnight at room temperature. The mixture was poured into ice and saturated NH₄Cl solution and extracted with ether. The ethereal layer was washed successively with saturated NH₄Cl solution, saturated NaHCO₃ solution, water and saturated NaCl solution, dried (K₂CO₃) and concentrated. The residue was distilled *in vacuo* to give 28.0 g of crude III, bp 98~104°C (9 mmHg). This was chromatographed over alumina (Wako Pure Chemicals, 450 g) in petroleum ether. The eluants used were: petroleum ether, *n*-hexane, *n*-hexane-benzene and benzene-ethyl acetate. Each fraction was checked by GLC, TLC and IR. Fractions containing III were combined and distilled to give 16.4 g (24% from II) of III (82% purity), bp 104~106°C (10 mmHg), n_D^{25} 1.4675; IR $\nu_{\max}$ cm⁻¹: 3400, 3080, 1650, 1020; NMR τ : 9.52~9.88 (4H, m),

9.15 (1H, m), 9.01 (3H, t, $J=7$ Hz), 8.91 (3H, s), 8.34 (3H, s), 4.94 (1H, t, $J=7$ Hz); GLC t_R 4.1 min (82%), 3.0 min (18%), Column, LAC 2R-446 at 153°C, carrier gas, N_2 , 1.3 kg/cm². *Anal.* Found: C, 78.88; H, 12.07. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.16%.

4, 8-Dimethyldeca-3, 7-cis-dienyl bromide (IV). The alcohol (III, 13.9 g) was added dropwise during 10 min to ice-cooled and vigorously stirred 48% hydrobromic acid (43 ml). The mixture was stirred at 5~10°C for 30 min and then extracted with petroleum ether. The extract was washed with water, $NaHCO_3$ solution and sat. NaCl solution, dried ($CaCl_2$) and concentrated *in vacuo* to give 16.5 g (89%) of crude IV. An analytical sample boiled at 68°C (0.1 mmHg), n_D^{17} 1.4891; IR ν_{max} cm⁻¹: 1660, 1280; NMR τ : 9.25 (3H, t, $J=7$ Hz), 8.34 (3H, s), 7.80~8.20 (6H, m), 7.47 (2H, q, $J=7$ Hz), 6.73 (2H, t, $J=7$ Hz), 4.97 (2H, br). *Anal.* Found: C, 59.91; H, 8.72. Calcd. for $C_{12}H_{21}Br$: C, 58.80; H, 8.59%.

4, 8-Dimethyldeca-3, 7-cis-dienyl cyanide (V). The bromide (IV, 16.5 g) was rapidly added to a stirred solution of NaCN (4.7 g) in dry DMSO (80 ml). Soon after the addition the exothermic reaction took place and crystalline NaBr precipitated. The mixture was stirred and heated at 60°C for 1 hr, left to stand overnight at room temperature, diluted with water and extracted with *n*-hexane. The extract was washed with water and sat. NaCl solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 8.05 g (63%) of V, bp 100~111°C (4 mmHg), n_D^{17} 1.4685; IR ν_{max} cm⁻¹: 2240, 1665; NMR τ : 9.30 (3H, t, $J=7$ Hz), 8.34 (6H, s), 7.85~8.15 (6H, m), 7.62~7.82 (4H, m), 4.92 (2H, m); GLC: t_R 9.8 min (3-*trans*) 58%, 8.8 min (3-*cis*) 19%, 7.7 min (3-*trans*, 7-dihydro) 13%, 7.0 min (3-*cis*, 7-dihydro) 4%. Column, LAC 2R-446 at 168°C, carrier gas N_2 1.1 kg/cm². *Anal.* Found: C, 81.71; H, 11.06; N, 7.08. Calcd. for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32%.

6, 10-Dimethyldodeca-5, 9-cis-dien-2-one (VI). A solution of the nitrile (V, 5.3 g) in dry benzene (20 ml) was added dropwise to a stirred and ice-cooled solution of a Grignard reagent prepared from methyl iodide (9.1 g) and Mg (1.5 g) in dry ether (52 ml). After the addition the mixture was stirred and heated under reflux for 9.5 hr, left to stand overnight at room temperature and poured into ice and dilute hydrochloric acid. After 30 min the mixture was extracted with ether. The extract was washed with water, $NaHCO_3$ solution and sat. NaCl solution, dried ($MgSO_4$) and

concentrated *in vacuo*. The residue was distilled *in vacuo* to give 3.83 g (67%) of crude VI, bp 90~96°C (3 mmHg). GLC: t_R 5.6 min (5-*trans*, 9-*cis*) 51%, 5.4 min (5-*cis*, 9-*cis*) 18%, 4.7 min (5-*trans*, 9-dihydro) 11%, 3.5 min (5-*cis*, 9-dihydro) 5%. Column, LAC 2R-446 at 163°C, carrier gas, N_2 , 1.3 kg/cm².

The semicarbazone (VII) of 6, 10-dimethyldodeca-5-*trans*, 9-*cis*-dien-2-one (VI'). A solution of the crude ketone (VI, 3.8 g) in 95% ethanol (10 ml) was added to a solution of semicarbazide hydrochloride (2.25 g) and sodium acetate (2.7 g) in a minimum volume of water. The mixture was heated under reflux for 20 min. A small amount of NaCl precipitated. It was dissolved by addition of a small amount of water. An additional several ml of water was added until the solution became turbid while hot. Then several drops of ethanol were added to make the solution clear. It was left to stand overnight at room temperature. The crystalline mass was collected on a filter and washed with a small amount of petroleum ether. It weighed 1.00 g, mp 97~99°C. In the same manner, 3.00 g of semicarbazone (VII) was obtained from 11.86 g of the crude ketone (VI). Ethanol was removed *in vacuo* from the combined mother liquors. The residue was diluted with water and extracted with ether. The extract was washed with $NaHCO_3$ solution, water and sat. NaCl solution, dried (Na_2SO_4) and concentrated *in vacuo* to give 14 g of an oil. This was chromatographed over alumina (Wako Pure Chemicals, 280 g) in *n*-hexane. The eluants used are: *n*-hexane, chloroform and chloroform-methanol (95:5). Later fractions yielded 8.5 g of crude crystals. This was recrystallized from aqueous ethanol to give 1.4 g of VII, mp 95~99°C. The mother liquor of this recrystallization gave 1.1 g of low melting crystals, mp 77~78°C, soluble in petroleum ether. Recrystallization of the first crop (4.0 g) from aqueous ethanol yielded 3.35 g of pure VII, mp 103.5~104.5°C. The mother liquor of this recrystallization and the first crop (1.4 g, mp 95~99°C) from the chromatographic purification were combined. Recrystallization of this material from aqueous ethanol gave 1.65 g of VII, mp 103.5~104.5°C. Thus, 5.00 g of recrystallized semicarbazone (VII), mp 103.5~104.5°C was obtained. IR ν_{max} cm⁻¹: 3060, 3150, 1690, 1580; NMR τ : 9.10 (3H, t, $J=7$ Hz), 8.38 (3H, s), 8.34 (3H, s), 8.12 (3H, s), 4.95 (2H, br), 3.80~4.50 (3H, br. m). *Anal.* Found: C, 67.72; H, 10.10; N, 15.89; Calcd. for $C_{12}H_{27}ON_3$: C, 67.78; H, 10.26; N, 15.83%.

6, 10-Dimethyldodeca-5-*trans*, 9-*cis*-dien-2-one (VI'). A suspension of the crystalline semicarbazone (VII, mp

103.5~104.5°C, 4.90 g) in aqueous oxalic acid solution (4.1 g of C₂H₂O₄·2H₂O in 41 ml of water) was heated under reflux for 1 hr. After cooling, the mixture was extracted with ether. The extract was washed with NaHCO₃ solution, water and sat. NaCl solution, dried (MgSO₄) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 3.29 g of VI' (21.5 % recovery from the crude ketone VI), bp 79~82°C (0.22 mmHg), n_D^{17} 1.4659; IR $\nu_{\max}$ cm⁻¹: 1725; NMR τ : 9.02 (3H, t, $J=7$ Hz), 8.39 (3H, s), 8.34 (3H, s), 4.97 (2H, m); GLC: t_R 5.6 min (5-*trans*, 9-*cis*) 83%, 4.7 min (5-*trans*, 9-dihydro) 15%, Column, LAC 2R-446 at 163°C, carrier gas, N₂, 1.3 kg/cm². GC-MS: Apparatus: Hitachi RMU GC; Column, Carbowax 20M, 3 m×3 mm i.d., (20%) at 150°C; Carrier gas N₂, 1.0 kg/cm². t_R 21.5 min (M⁺ 210), 27.0 min (M⁺ 208, VI'). Anal. Found: C, 80.81; H, 11.55. Calcd. for C₁₁H₂₄O: C, 80.71; H, 11.61%.

Methyl 3, 7, 11-trimethyltrideca-2, 6-trans, 10-cis-trien-1-oate (VIII+IX). Methyl diethylphosphonoacetate (8.0 g) was added to a suspension of NaOMe (2.0 g) in dry DMF (35 ml) and the mixture was stirred for 30 min at room temperature under nitrogen. A solution of the ketone (VI', 3.29 g) in dry DMF (7 ml) was added dropwise to the ice-cooled and stirred enolate. After the addition the bath temperature was gradually raised to 50°C during 1 hr and kept at 50~60°C for 1 hr. The mixture was left to stand overnight at room temperature. The excess Wittig reagent was destroyed by acetone. Then the mixture was poured into water and extracted with ether. The ethereal solution was washed with water and sat. NaCl solution, dried (MgSO₄) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 3.60 g (86%) of VIII+IX, bp 106~114°C (0.25 mmHg), n_D^{17} 1.4815; IR $\nu_{\max}$ cm⁻¹: 1720, 1645; GLC: t_R 10.8 min (2-*trans*) 55%, 8.6 min (2-*cis*) 34%, Column, LAC 2R-446 at 184°C, Carrier gas, N₂, 1.2 kg/cm². Anal. Found: C, 76.61; H, 10.61. Calcd. for C₁₇H₂₈O₂: C, 77.22; H, 10.67%.

GLC separation of the trienoic esters (VIII+IX). The mixture (550 mg) gave after GLC separation 38 mg of methyl 3,7,11-trimethyltrideca-2-*cis*, 6-*trans*, 10-*cis*-trienoate (VIII) and 108 mg of methyl 3,7,11-trimethyltrideca-2-*trans*, 6-*trans*, 10-*cis*-trienoate (IX). GLC: Column, PEG 20M 20% on Celite 545 (60~80 mesh), 10 ft×3/8 inch. Column temp. 225°C. Injection temp. 265°C. Carrier gas N₂, 26 kg/cm². The *cis*, *trans*, *cis*-ester (VIII) showed the following physical properties. n_D^{21} 1.4760; IR $\nu_{\max}$ cm⁻¹: 1720, 1645; NMR τ : 9.07 (3H, t, $J=6.5$ Hz), 8.42 (3H, s), 8.38 (3H, s), 8.16 (3H, s), 6.43 (3H, s), 4.98 (2H, m), 4.46

(1H, br. s); GLC: t_R 6.2 min (91% pure), Column LAC 2R-446, Column temp. 193°C, Carrier gas, N₂, 1.3 kg/cm². Anal. Found: C, 76.76; H, 10.99. Calcd. for C₁₇H₂₈O₂: C, 77.22; H, 10.67%. The *trans*, *trans*, *cis*-ester (IX) showed the following properties. n_D^{21} 1.4842; IR $\nu_{\max}$ cm⁻¹: 1720, 1645; NMR τ : 9.07 (3H, t, $J=6.5$ Hz), 8.44 (3H, s), 8.39 (3H, s), 7.89 (3H, s), 6.43 (3H, s), 5.00 (2H, m), 4.48 (1H, br. s); GLC: t_R 8 min (95% pure), Column LAC 2R-446, Column temp 193°C, carrier gas, N₂, 1.3 kg/cm². Anal. Found: C, 77.61; H, 10.57. Calcd. for C₁₇H₂₈O₂: C, 77.22; H, 10.67%.

Methyl dl-12-homojuvenate (dl-C₁₇-Cecropia juvenile hormone, I). A solution of *m*-chloroperbenzoic acid (Aldrich Chemical Co., 85% pure, 67.4 mg) in purified methylene chloride (5.2 ml) was added to a solution of the *trans*, *trans*, *cis*-trienoic ester (IX, 88 mg) in methylene chloride (2.6 ml) at 0~5°C. The mixture was left to stand overnight in a refrigerator, diluted with methylene chloride, washed with 5% Na₂CO₃ solution, dried (MgSO₄) and concentrated *in vacuo* to give 89 mg of an oil. This was purified by preparative TLC (Merck, Silica gel GF₂₅₄, 20 cm×20 cm×0.5 mm) developed with benzene-ethyl acetate (15:1). *dl*-C₁₇-Juvenile hormone (I, 31 mg) was obtained from a band at *R_f* 0.50. The starting trienoic ester (IX, 18 mg) was recovered from a band at *R_f* 0.73. The 7,10-diepoxy (4 mg) was obtained from a band at *R_f* 0.27. The racemic C₁₇-juvenile hormone (I) showed the following spectral properties which were identical with the recorded data. IR $\nu_{\max}$ cm⁻¹: 1720, 1640; NMR τ : 8.98 (16-Me, 3H, t, $J=6$ Hz) 8.76 (15-Me, 3H, s), 8.34 (14-Me, 3H, s), 7.83 (13-Me, 3H, s), 6.35 (CO₂Me, 3H, s), 4.90 (C=CH at C-6, 1H, m), 4.41 (C=CH at C-3, 1H, m); MS (Hitachi RMH-2, 002, 70 eV): *m/e* 55 (C₄H₇), 57 (C₄H₉), 67 (C₅H₇), 81 (C₆H₉), 85 (C₅H₉O), 95 (C₇H₁₁), 99 (C₆H₁₁O), 114 (C₆H₁₀O₂), 121 (C₉H₁₃), 123 (C₉H₁₅), 135 (C₁₀H₁₅), 280 (M⁺, C₁₇H₂₈O₃).

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