A Convenient Method for the Preparation of (±)Juvenile Hormone III
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Juvenile Hormone III, Synthesis
Following a different approach methyl (2E,6E)-farnesoate (4) was prepared in three steps from trans-geranylacetone (1). Compound 4 was regioselectively epoxidized to (±)juvenile hormone III.

Since the discovery of juvenile hormone III (JH-III) [1], several non-stereospecific procedures have been used for its synthesis. A common fact was the use of trans-geranylacetone which was transformed into trans-trans methyl farnesoate by Wittig reaction with the appropriate reagent [2]. Monoepoxidation of the farnesoate has been accomplished through the bromohydrin [2, 3] or by peracid oxidation [4]. Recently [5] a new approach has been used for the synthesis of both enantiomers of JH-III producing pure (R)(+)-JH-III and (S)(−)-JH-III in yields of 3.6% and 2.3% respectively.

We now report a convenient preparation of methyl (2E,6E)-farnesoate (4) in three steps from commercially available geranylacetone. Compound 4 was then regioselectively epoxidized to the monoepoxy derivative 5 which resulted identical to racemic JH-III previously described.

Results and Discussion
The reaction of trans-geranylacetone (1) with lithium anion of t-butyl acetate afforded the corresponding hydroxy ester (2) in theoretical yield [6]. Dehydration of 2 to the unsaturated ester 3 was accomplished in 97% yield by treatment with phosphorus oxychloride in pyridine. Compound 3 resulted a mixture of geometric isomers (E/Z = 3.5) as determined by HPLC analysis. Anderson et al. [2] reported a E/Z ratio of 2.3. Transformation of 3 into the methyl ester 4 was conducted on the isomeric mixture without the isolation of the free acid intermediate. At this step the stereoisomeric mixture, obtained in 90% yield, was separated by chromatographic procedures leading to methyl (2E,6E)-farnesoate (4). It is appropriate to point out that in our hands the method employing the anion of trimethylphosphonoacetate [2] gave unreliable results affording compound 4 in 48% yield while the present three steps approach produced 4 in an overall yield of 68%. Regioselective epoxidation of 4 with m-chloroperbenzoic acid gave 10,11-monoepoxy derivative 5 whose spectroscopic properties were identical to those described for JH-III. This epoxidation method has been applied to the syntheses of several juvenile hormone analogues [7].

Experimental
1H and 13C-FT NMR spectra were recorded on a Varian XL-100-15 spectrometer. Mass spectra at 70 eV (direct inlet) on a Varian-MAT CH7-A spectrometer interfaced to a Varian-MAT data system 166 computer.
HPLC analyses were performed with an Altex Ultrasphere ODS 5 μm column (250 × 10 mm) using MeOH–H2O (9:1) as eluent.

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A solution of diisopropylamine (0.7 ml) in THF (10 ml) cooled to −78 °C was treated with n-butyllithium (4.17 ml) and the mixture was stirred for 30 min. t-Butyl acetate (0.68 ml) was added dropwise and the stirring was continued for 30 min. To this solution, trans-geranylacetone (1.0 g) in THF (10 ml) was added and stirred for 90 min at the same temperature. After addition of MeOH (1 ml) the reaction mixture was acidified to pH 1 with 10% HCl, and extracted with CH₂Cl₂. The organic extract was washed with H₂O, dried over MgSO₄, and evaporated giving compound 2 (1.6 g, 100%).

**IR (film):** 3550, 2950, 1710, 1350, 1130 cm⁻¹. ¹H NMR (CDCl₃): δ 1.24 (s, 3H, CH₃ at C-3), 1.48 (s, 9H, [CH₃]₃C), 1.61 (s, 6H, CH₂ at C-7 and at C-11), 1.68 (s, 3H, H-12), 2.00 (m, 8H, H-4, H-5, H-8, H-9), 2.31 (d, J = 15 Hz, 1H, H-2), 2.50 (d, J = 15 Hz, 1H, H-2), 3.70 (s, 1H, OH), 5.11 (t, J = 6 Hz, 2H, H-6, H-10). ¹³C NMR (CDCl₃): δ 15.3 (CH₃ at C-7), 17.5 (CH₂ at C-11), 22.5 (C-5), 25.5 (C-12), 26.5 (C-9 and CH₂ at C-3), 27.9 ([CCH₃]₃C), 39.5 (C-4), 41.7 (C-8), 45.6 (C-2), 70.7 (C-3), 80.9 ([CCH₃]₃C), 123.9 (C-6), 124.2 (C-10), 130.7 (C-11), 134.7 (C-7), 172.0 (C-1). MS (%): 310 (M⁺, 1), 254 (M⁺–31, 57), 236 (M⁺–56–18, 49), 221 (M⁺–56–18–9, 51), 211 (M⁺–56–43, 48), 136 (77), 69 (100).

**t-Butyl 3,7,11-trimethyl-dodeca-2(E,Z),6E,10-dienoate (3)**

Compound 2 (400 mg) in pyridine (10 ml) was cooled to −15 °C and treated dropwise with POCl₃ (5 ml). The mixture was stirred at 0 °C for 90 min at the same temperature. After addition of m-chloroperbenzoic acid (105 mg) in CH₂Cl₂ (5 ml), cooled to 0 °C and treated dropwise with a solution of m-chloroperbenzoic acid (105 mg) in CH₂Cl₂ (5 ml). The mixture was stirred at 0 °C for 6 h. It was washed with NaCO₃ solution, with H₂O, and dried (MgSO₄). Evaporation of the solvent gave a residue that was purified by column chromatography (silica gel, toluene–EtOAc 9:1) affording unreacted compound 4 (65 mg) which was purified further by HPLC (MeOH–H₂O 8:2 as eluent).

**IR (film):** 2950, 1720, 1215, 1130 cm⁻¹. ¹H NMR (CDCl₃): δ 1.26 (s, 3H, CH₃ at C-7), 1.30 (s, 3H, H-12), 1.62 (s, 3H, CH₃ at C-7), 1.70 (m, 4H, H-8, H-9), 2.10 (m, 4H, H-4, H-5), 2.70 (t, J = 6 Hz, 1H, H-10), 3.69 (s, 3H, OCH₃), 5.14 (t, J = 6 Hz, 1H, H-6), 5.67 (br. s, 1H, H-2). ¹³C NMR (CDCl₃): δ 15.8 (CH₃ at C-7), 17.4 (CH₃ at C-11), 18.6 (CH₂ at C-3), 25.4 (C-12), 25.8 (C-5), 26.5 (C-9), 28.0 ([CCH₃]₃C), 39.5 (C-8), 40.7 (C-4), 78.9 ([CCH₃]₃C), 117.1 (C-2), 122.8 (C-6), 123.9 (C-9), 130.8 (C-11), 135.5 (C-7), 157.4 (C-3), 165.8 (C-1). MS (m/z, %): 292 (M⁺, 1), 236 (M⁺–56–80, 193 (M⁺–56–43, 68), 136 (61), 69 (100).

**Methyl 10(R,S)-11-epoxy-3,7,11-trimethyl-dodeca-2(E),6,E-dienoate (5)**

Compound 4 (120 mg) was dissolved in CH₂Cl₂ (5 ml), cooled to 0 °C and treated dropwise with a solution of m-chloroperbenzoic acid (105 mg) in CH₂Cl₂ (5 ml). The mixture was stirred at 0 °C for 6 h. It was washed with NaCO₃ solution, with H₂O, and dried (MgSO₄). Evaporation of the solvent gave a residue that was purified by column chromatography (silica gel, toluene–EtOAc 9:1) affording unreacted compound 4 (65 mg) which was purified further by HPLC (MeOH–H₂O 8:2 as eluent).

**IR (film):** 2950, 1720, 1215, 1130 cm⁻¹. ¹H NMR (CDCl₃): δ 1.26 (s, 3H, CH₃ at C-7), 1.30 (s, 3H, H-12), 1.62 (s, 3H, CH₃ at C-7), 1.70 (m, 4H, H-8, H-9), 2.10 (m, 4H, H-4, H-5), 2.70 (t, J = 6 Hz, 1H, H-10), 3.69 (s, 3H, OCH₃), 5.14 (t, J = 6 Hz, 1H, H-6), 5.67 (br. s, 1H, H-2). ¹³C NMR (CDCl₃): δ 15.8 (CH₃ at C-7), 17.4 (CH₃ at C-11), 18.6 (CH₂ at C-3), 25.4 (C-12), 25.8 (C-5), 26.5 (C-9), 28.0 ([CCH₃]₃C), 39.5 (C-8), 40.7 (C-4), 78.9 ([CCH₃]₃C), 117.1 (C-2), 122.8 (C-6), 123.9 (C-9), 130.8 (C-11), 135.5 (C-7), 157.4 (C-3), 165.8 (C-1). MS (m/z, %): 292 (M⁺, 1), 236 (M⁺–56–80, 193 (M⁺–56–43, 68), 136 (61), 69 (100).

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