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SYNTHESIS OF COMPOUNDS WITH JUVENILE HORMONE ACTIVITY—XII[1]

A STEREOSELECTIVE SYNTHESIS OF 6-ETHYL-10-METHYLDODECA-5-*TRANS*, 9-*CIS*-DIEN-2-ONE, A KEY INTERMEDIATE IN THE SYNTHESIS OF C_{18}-*CECROPIA* JUVENILE HORMONE

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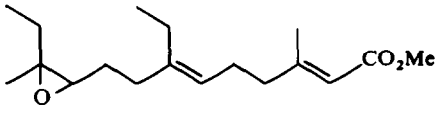
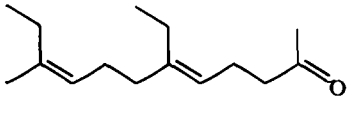
Abstract—A stereoselective synthesis of the title compound (II) as well as that of its lower homolog, 6-ethyl-10-methylundeca-5-*trans*, 9-dien-2-one (III), was accomplished. Both were converted to methyl *dl*-12,14-dihomojuvenate (*dl*-C_{18}-*Cecropia* juvenile hormone, I) and methyl *dl*-14-homojuvenate (IV), respectively. Analogs of the *Cecropia* juvenile hormones with an ethynyl substituent (XVIII and XIX) were also synthesized.

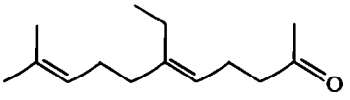
SEVERAL PREVIOUS SYNTHESES of *dl*-C_{18}-*Cecropia* juvenile hormone (I) employed 6-ethyl-10-methyldodeca-5-*trans*,9-*cis*-dien-2-one (II) as the key intermediate.[2-9] Control of the olefin geometry, however, is difficult and the only stereo-controlled synthesis of the ketone (II) hitherto reported is that of Siddall *et al.*[10] We describe here another stereoselective synthesis of ketone II.



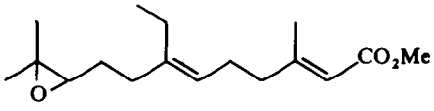
I



II

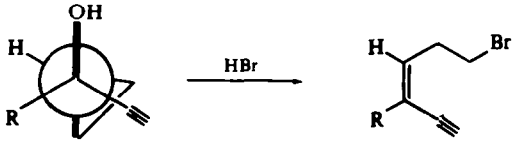


III

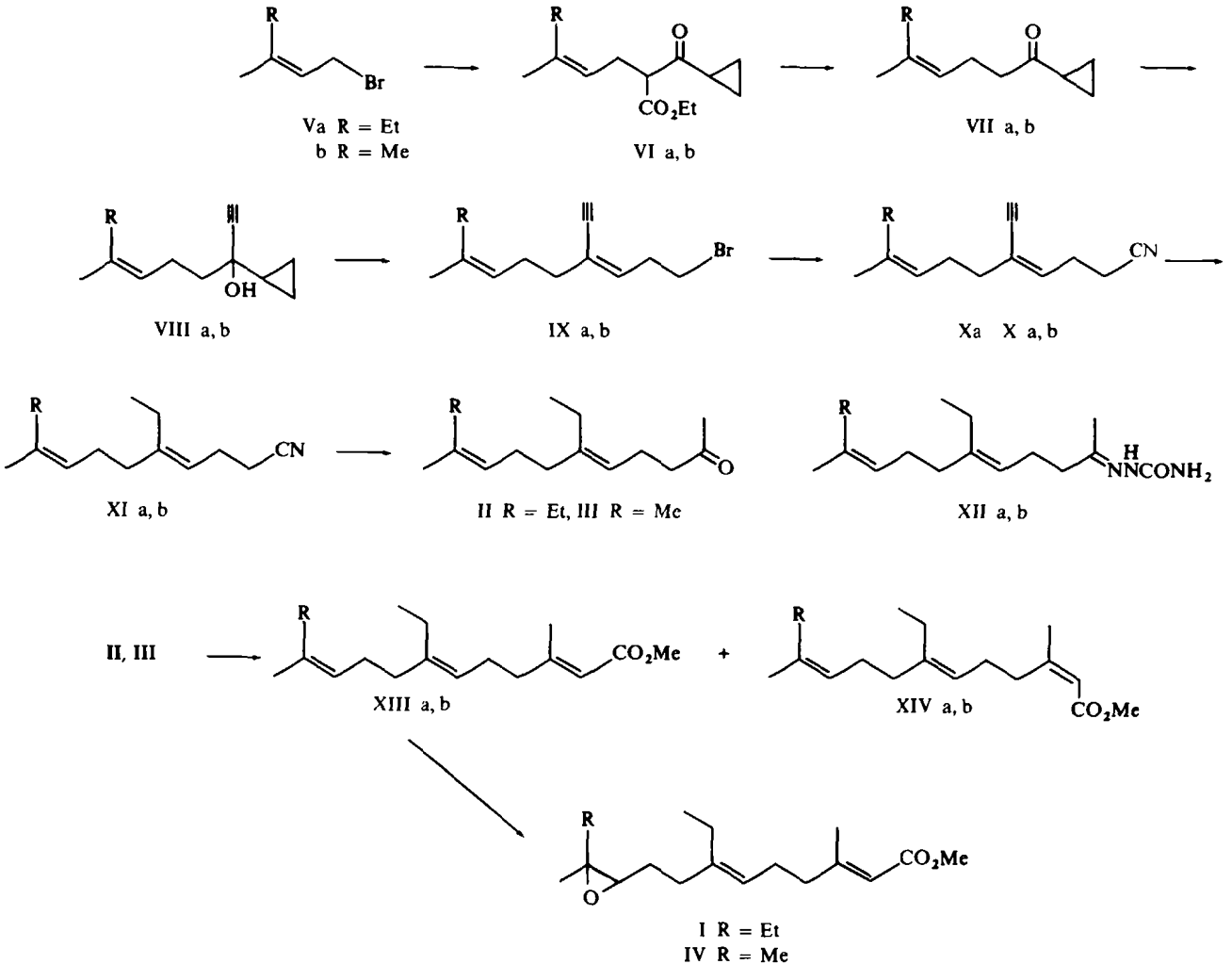


IV

The present synthetic route (Va → I) involves in the key step (VIIIa → IXa) the rearrangement of a cyclopropyl ethynyl carbinol to a homoallylic system. This highly stereoselective construction of a trisubstituted double bond (A → B) was first discovered by Julia[11] and later used by us for the stereoselective synthesis of 4-methylhex-3-*cis*-en-1-ol, a useful starting material in juvenile hormone synthesis.[1]



A B


R
Br
Va R = Et
b R = Me
O
CO2Et
VI a, b
VII a, b
OH
VIII a, b
IX a, b
CN
Xa X a, b
XI a, b
II R = Et, III R = Me
H
NNCONH2
XII a, b
II, III
CO2Me
XIII a, b
+
XIV a, b
I R = Et
IV R = Me

The two notable points in the present work are the use of an ethynyl group for the control of olefin geometry and its diimide reduction in a later stage. Except these two, the synthetic scheme is similar to our non-stereoselective synthesis of the *Cecropia* juvenile hormones.[9]

3-Methylpent-2-*cis*-enyl bromide (Va)[1] was condensed with carbethoxymethyl cyclopropyl ketone[9] in the presence of NaOEt in EtOH.* The resulting β-keto ester (VIa) was hydrolyzed and decarboxylated by heating under reflux with aqueous ethanolic $Ba(OH)_2$ to give a cyclopropyl ketone (VIIa). This was treated with sodium acetylide in liquid ammonia to give an acetylenic alcohol (VIIIa). The cleavage of its cyclopropane ring with HBr took place readily to give an unstable acetylenic bromide (IXa) which without distillation, was immediately treated with NaCN in DMSO to give a nitrile (Xa). The stereochemical purity of this nitrile was checked by NMR and shown to be satisfactory as evidenced by a sharp 1H-singlet at δ 3·11 ppm due to the acetylenic proton. GLC analysis also proved the non-existence of the Δ^3-*cis* isomer, although some minor impurities were detected. Thus the expected high stereoselectivity of the rearrangement reaction was shown to be the case.

As the stereo-controlling role of the ethynyl group was over, the acetylenic nitrile (Xa) was reduced with diimide generated from oxygen and hydrazine hydrate in EtOH. The reduction took place fairly regioselectively at the ethynyl group to give a new nitrile (XIa) contaminated with about 20% of an over-reduction product resulting from saturation of the terminal *cis*-double bond. The diimide reduction of the triple bond proceeded rather sluggishly. This caused the partial saturation of the terminal *cis*-double bond prior to complete reduction of the triple bond.† The nitrile (XIa) was treated with MeMgI followed by dilute HCl to give the crude title compound, 6-ethyl-10-methyldodeca-5-*trans*,9-*cis*-dien-2-one (II). It can be further purified as semicarbazone (XIIa), m.p. 111–112°, to remove non-ketonic impurities. The ketone regenerated from the semicarbazone (XIIa) still contained about 20% of the dihydro compound, 6-ethyl-10-methyldodec-5-*trans*-*en*-2-one (MS: *m/e* 224) judging from GC-MS data. This originated from the over-reduction product generated at the stage of diimide reduction. In spite of this contaminant the major part of the product was the stereochemically pure title compound with reasonable NMR data, δ 0·98 (6H, t, J = 7 Hz), 1·66 (3H, s), 2·07 (3H, s), 4·98 (2H) ppm in CCl_4 at 100 MHz. The chemical shift of the Me group at C-10 (δ 1·66) is in good accord with the previous data (δ 1·66).[10]

The remaining steps to *dl*-C_{18}-*Cecropia* juvenile hormone (I) are well-documented.[3–9] Although the first step of this conversion, the introduction of the conjugated ester portion, was non-stereoselective, the two geometrical isomers (XIIIa and XIVa)

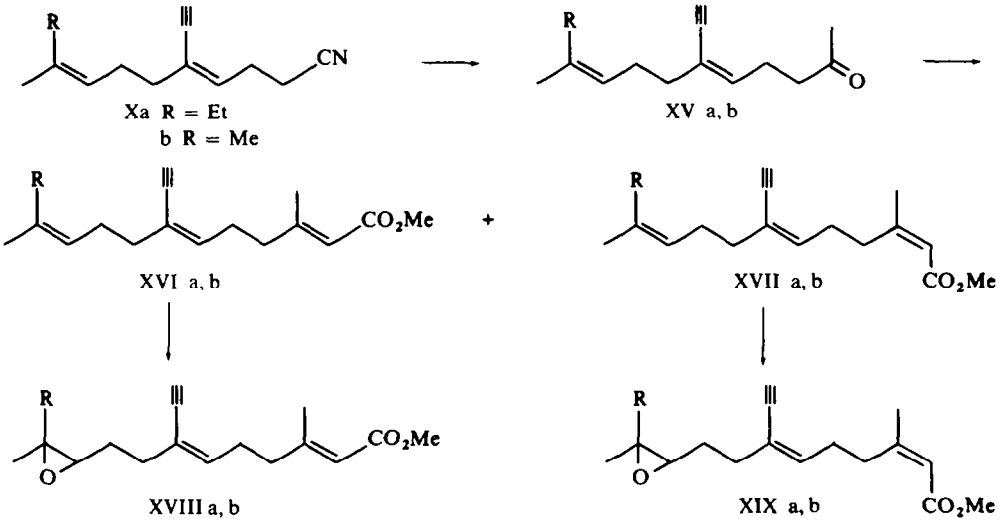
* If the reaction temperature was not kept low, this step caused some isomerization of the terminal *cis*-double bond (about 20%), although the starting bromide (Va) was stereochemically pure.[1] The first synthesis of the racemic C_{18}-hormone (I)[3] also involved this type of alkylation of a β-keto ester with the allyl bromide (Va).

† In order to overcome this difficulty we tried partial hydrogenation of the ethynyl group to a vinyl group over Lindlar's catalyst. Then, we assumed, the vinyl group would be reduced preferentially with diimide. The partial hydrogenation, however, was unsuccessful with an ordinary small amount of catalyst. With excess catalyst, partial hydrogenation was seemingly successful with appropriate hydrogen uptake. However GLC showed the product to be a mixture of geometrical isomers generated by isomerization over the catalyst.

of the trienoic ester could readily be separated by preparative GLC in a ratio of 3:2. Impurities due to the over-reduction product were mostly removed by this GLC purification. The major product (XIIIa) was epoxidized with *m*-chloroperbenzoic acid. TLC separation of the resulting epoxides gave *dl*-C_{18}-*Cecropia* juvenile hormone (I). This TLC purification completely removed the impurities due to the over-reduction product, as they possessed no double bond at C-10 and hence could not yield C-10 epoxides.* The IR and NMR spectral properties of XIIIa and I coincided with those reported from other laboratories.[3, 8]

In the same manner 6-ethyl-10-methylundeca-5-*trans*,9-dien-2-one (III)[5] was synthesized stereoselectively from isoprenyl bromide (Vb) *via* the intermediates VIb–XIb. The ketone (III) was purified as its semicarbazone (XIIb), m.p. 104–105°. In this case, too, the ketone (III) was accompanied by 20% of 6-ethyl-10-methylundec-5-*trans*-en-2-one (MS: *m/e* 210) judging from GC-MS data. The major product, however, was identical by GLC with our authentic sample prepared previously.[5] The IR and NMR spectral properties were also almost identical with those of an authentic sample in spite of the contamination with the dihydro ketone. Our failure to remove the corresponding dihydro ketones from II or III by semicarbazone formation showed the limitation of this classical technique for the purification of ketones, although it was highly successful in our synthesis of *dl*-juvabione.[14] Conversion of the ketone (III) into methyl *dl*-14-homojuvenate (IV) and its Δ^2-*cis* isomer *via* trienoic esters XIIIb and XIVb has already been reported by us.[5, 9a, 15]

Some juvenile hormone analogs with an acetylenic substituent at C-7 were also synthesized. The acetylenic nitriles (Xa, b) were treated with MeMgI followed by dilute HCl to give acetylenic ketones (XVa, b) in rather low yield (36–38%). These were converted to stereoisomeric mixtures of acetylenic esters (XVIa, b and XVIIa, b) by treatment with methyl diethylphosphonoacetate in the presence of NaOMe in



* The geometrical isomers at C-10 could not be separated by this purification procedure. When 4-methylhex-3-*cis*-enyl cyclopropyl ketone (VIIa) contaminated with about 20% of the *trans*-isomer was used as the starting material, the resulting XIIIa and I also contained about 20% of the all-*trans* isomers judging from the NMR signals due to the Me group at C-11.

DMF. These were separated by prep. GLC into pure Δ^2-*trans*-(XVIa, b) and Δ^2-*cis*-(XVIIa, b) isomers. Their epoxidation with *m*-chloroperbenzoic acid took place regioselectively at C-10 because of the low reactivity of the central double bond conjugated with the ethynyl group. The four products, XVIIIa, b and XIXa, b, were rather unstable and polymerized after storage at room temperature.* A preliminary *Tenebrio* test of these compounds revealed their high juvenile hormone activity. Details of the biological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

All m.ps and b.ps 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 CCl_4 with TMS as an internal standard. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

1-*Carbethoxy*-4-*methylhex*-3-cis-*enyl cycylpropyl ketone* (VIa). Carbethoxymethyl cyclopropyl ketone (60 g) was added to a stirred soln of NaOEt (from 9 g of Na) in EtOH (350 ml) at 5–10° and the mixture cooled with an ice–salt bath. Bromide Va (59 g) was added dropwise during 50 min to the stirred mixture at $-5 \sim -3°$. At the end of the addition NaBr began to precipitate. The mixture was left in the ice–salt bath to gradually reach room temperature then poured into water and extracted with benzene–ether. The extract was washed with water and sat. NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 81·5 g (95%) of VIa, b.p. 110–117°/3 mm. An analytical sample boiled at 114°/3 mm, n_D^{18} 1·4668; ν_{max} 1740, 1702, 1440, 1380, 1195, 1150 cm^{-1}; δ 0·7–1·1 (~4H), 0·95 (3H, t, J = 7 Hz), 1·17 (3H, t, J = 7 Hz), 1·68 (3H, d, J = 1·5 Hz), 2·00 (2H, q, J = 7 Hz), 2·48 (2H, t, J = 7 Hz), 3·40 (1H, t, J = 7 Hz), 4·15 (2H, q, J = 7 Hz), 4·96 (1H, t, J = 7 Hz) ppm. (Found: C, 70·15; H, 9·13. $C_{14}H_{22}O_3$ requires: C, 70·55; H, 9·31%).

4-*Methylhex*-3-cis-*enyl cyclopropyl ketone* (VIIa). A soln of the β-keto ester VIa (81·0 g) in 95% EtOH (180 ml) was mixed with $Ba(OH)_2.8H_2O$ (156 g) and water (700 ml) and then heated at reflux for 17 hr under N_2. After cooling, the mixture was poured into ice water containing HCl to dissolve $BaCO_3$ and extracted with ether. The extract was washed with water, $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated. The residue was distilled *in vacuo* to give 44·7 g (79%) of VIIa, b.p. 82–84°/4 mm, n_D^{18} 1·4660; ν_{max} 1700, 1440, 1380, 1190, 1080, 1005, 895 cm^{-1}; δ 0·65–1·00 (~4H), 0·98 (3H, t, J = 7 Hz), 1·65 (3H, d, J = 1·5 Hz), 5·00 (1H, t, J = 7 Hz) ppm; GLC: *Rt* 6·9 min, Column, 5% LAC 2R 446, 1·5 m × 3 mm i.d. at 140°, Carrier gas, N_2, 0·8 kg/cm². (Found: C, 79·12; H, 10·73. $C_{11}H_{18}O$ requires: C, 79·46; H, 10·92%).

3-*Cyclopropyl*-7-*methylnon*-6-cis-*en*-1-*yn*-3-*ol* (VIIIa). A suspension of sodium acetylide was prepared by bubbling acetylene into a suspension of $NaNH_2$ (from 11 g of Na) in liq NH_3 (1 l) for 1 hr at $-60 \sim -50°$. A soln of the ketone VIIa (44·2 g) in dry ether (200 ml) was added dropwise to the stirred suspension at $-78 \sim -50°$. Then the mixture was stirred for 3·5 hr at $-50 \sim -28°$. To destroy the excess of sodium acetylide, solid NH_4Cl (40 g) was added portionwise to the stirred mixture which was left to stand at room temp to remove NH_3, diluted with water and ether extracted. The extract was washed with sat NH_4Cl soln and sat NaCl soln, dried (K_2CO_3) and concentrated. The residue was distilled *in vacuo* to give 45·0 g (87%) of VIIIa, b.p. 104–105°/4 mm, n_D^{16} 1·4808; ν_{max} 3400, 3300, 2100, 1640, 1080, 1055, 1025 cm^{-1}; δ 0·30–0·65 (~4H, m), 0·98 (3H, t, J = 7 Hz), 1·66 (3H, br. s), 5·60 (1H, t, J = 7 Hz) ppm. (Found: C, 80·84; H, 10·35. $C_{13}H_{20}O$ requires: C, 81·20; H, 10·48%).

3-*Cyclopropyl*-7-*methyloct*-6-*en*-1-*yn*-3-*ol* (VIIIb). This was prepared in the same manner as described above from 4-methylpent-3-enyl cyclopropyl ketone VIIb (94 g)[9] in ether (300 ml) and sodium acetylide (from 17 g of Na) in liq. NH_3 (1 l). The product was distilled *in vacuo* to give 98 g (90%) of VIIIb, b.p. 102–103°/7 mm, n_D^{20} 1·4779; ν_{max} 3400, 3280, 2920, 2090, 1060, 830 cm^{-1}; δ 0·35–0·55 (4H, m), 0·90–1·20 (1H), 1·63 (3H, s), 1·68 (3H, s), 2·28 (1H, s), 5·11 (1H, t, J = 7 Hz) ppm. (Found: C, 80·74; H, 9·98. $C_{12}H_{18}O$ requires: C, 80·85; H, 10·18%).

* The acetylenic epoxide (XVIIIb) could be converted into methyl *dl*-14-homojuvenate (IV) by diimide reduction (N_2H_4–O_2) on a milligram scale. A large scale reduction, however, required a longer reaction period and this caused the conversion of the ester into a hydrazide. Therefore this route to the juvenile hormone was abandoned.

4-Ethynyl-8-methyldeca-3-trans, 7-cis-dienyl bromide (IXa). Alcohol VIIIa (44·7 g) was added dropwise during 15 min to ice-cooled and vigorously stirred 48% HBr (180 ml) at $-3 \sim 0°$. The mixture was stirred at 0–5° for 30 min and extracted with *n*-hexane. The extract was washed with water, sat $NaHCO_3$ soln and sat NaCl soln, dried ($CaCl_2$) and concentrated *in vacuo* to give 60 g (quantitative) of IXa, ν_{max} 3290, 2960, 2100, 1270, 830 cm^{-1}. This could not be distilled because of its instability and was immediately used for the next step.

4-Ethynyl-8-methylnona-3-trans, 7-dienyl bromide (IXb). This was prepared in the same manner as described above for IXa in 99% yield without distillation, ν_{max} 3280, 2920, 2090, 1270, 1215, 1110, 830 cm^{-1}.

4-Ethynyl-8-methyldeca-3-trans, 7-cis-dienyl cyanide (Xa). The bromide IXa (60 g) was added during 5 min to a stirred soln of NaCN (18 g) in dry DMSO (230 ml) at 40°. Soon after addition an exothermic reaction took place and NaBr precipitated. The mixture was stirred and heated at 50–60° for 45 min, poured into ice-water and extracted with *n*-hexane. The extract was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 30·1 g (64%) of Xa, b.p. 110–120°/3 mm. An analytical sample boiled at 116°/3 mm, n_D^{17} 1·4946. This unreasonably high value may be due to contamination with some impurities. ν_{max} 3290, 2250, 2100, 1670, 1640, 840 cm^{-1}; δ 0·97 (3H, t, J = 7 Hz), 1·65 (3H, s), 3·11 (1H, s), 4·98 (1H, br. t), 5·76 (1H, t, J = 7 Hz) ppm; GLC: *Rt* 3·6 min (6%) 4·4 min (2%), 5·0 min (2%), 11·7 min (85%, Xa), 14·2 min (5%), Column, LAC 2R-446 at 180°, carrier gas, N_2, 1·2 kg/cm^2. (Found: C, 82·58; H, 9·46%; N, 6·51. $C_{14}H_{19}N$ requires: C, 83·53; H, 9·51; N, 6·96%).

4-Ethynyl-8-methylnona-3-trans, 7-dienyl cyanide (Xb). This was prepared in the same manner as described for Xa in 68% yield, b.p. 110–120°/3 mm. An analytical sample boiled at 118·5/3 mm, n_D^{20} 1·4921; ν_{max} 3280, 2220, 2080, 830 cm^{-1}; δ 1·60 (3H, s), 1·66 (3H, s), 3·10 (1H, s), 5·01 (1H), 5·74 (1H, t, J = 7 Hz) ppm; GLC: *Rt* 7·9 min (80% purity, Xb), Column, 5% LAC 2R-446, 2 m × 3 mm i.d. at 180° carrier gas, N_2, 1·0 kg/cm^2. (Found: C, 82·01; H, 8·74; N, 6·81. $C_{13}H_{17}N$ requires: C, 83·37; H, 9·15; N, 7·48%).

4-Ethyl-8-methyldeca-3-trans, 7-cis-dienyl cyanide (XIa). Oxygen gas was bubbled into a stirred soln of the acetylenic nitrile Xa (7·2 g) in 85% $N_2H_4.H_2O$ (30 ml) and 99% EtOH (130 ml) for 14 hr at 50°. Periodically an aliquot was taken from the mixture to check the degree of reduction by IR, the end being when absorption at 3290 cm^{-1} due to the ethynyl group disappeared. The mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The extract was washed with water, dil HCl, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 5·25 g (73%) of XIa, b.p. 95–105°/0·2 mm. This was only 70% pure as judged by GLC and did not give a satisfactory analysis. However, spectral data, especially NMR, were in complete accord with the expected structure with correct stereochemistry in spite of some additional absorptions due to impurities. ν_{max} 2230, 1665, 1030, 840 cm^{-1}; δ 0·96 (3H, t, J = 7 Hz), 0·99 (3H, t, J = 7 Hz), 1·65 (3H, s), 4·98 (1H, br), 5·04 (1H, br) ppm; GLC: *Rt* 8·7 min (70%), Column, LAC 2R-446 at 173°, carrier gas, N_2, 1·2 kg/cm^2.

4-Ethyl-8-methylnona-3-trans, 7-dienyl cyanide (XIb). This was prepared in the same manner as described for XIa in 68% yield, b.p. 120–130°/6 mm. An analytical sample boiled at 126–128°/6 mm. This was 71% pure as judged by GLC and hence gave a poor analysis. However, its NMR data were in complete accord with the expected structure with correct stereochemistry in spite of additional signals due to impurities. ν_{max} 2950, 2900, 2230, 1100, 830 cm^{-1}; δ 0·99 (3H, t, J = 7 Hz), 1·58 (3H, s), 1·66 (3H, s), 5·04 (2H) ppm; GLC: *Rt* 9·7 min (71%), Column, LAC 2R-446 at 160°, carrier gas N_2, 1·0 kg/cm^2.

6-Ethyl-10-methyldodeca-5-trans, 9-cis-dien-2-one (II). A soln of the nitrile XIa (5 g) in dry benzene (30 ml) was added dropwise to a stirred and ice-cooled soln of Grignard reagent prepared from MeI (12 g) and Mg (2 g) in dry ether (85 ml). After addition the mixture was stirred and heated under eflux for 7·5 hr under N_2, left to stand overnight at room temp and poured into ice and dil HCl. The mixture was ether extracted, the extract was washed with water, $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 3·75 g (70%) of crude II, b.p. 100–104°/0·1 mm, n_D^{20} 1·4821 (high value due to impurities). This crude ketone II (3·0 g) was dissolved in 95% EtOH (20 ml) and mixed with a soln of semicarbazide hydrochloride (2·1 g) and NaOAc (2·5 g) in water (10 ml). The mixture was heated under reflux for 15 min and left to stand overnight at room temp. The precipitated crystalline *semicarbazone* XIIa (2·4 g, 64% yield from the crude ketone) was collected on a filter and washed with a small amount of aqueous EtOH and pet. ether. Recrystallization from EtOAc–pet. ether gave XIIa as leaflets, m.p. 111–112°; ν_{max} 3460, 3190, 1690, 1575, 1220, 1110, 760 cm^{-1}; δ ($CDCl_3$) 0·96 (6H, t, J = 7 Hz), 1·66 (3H, s), 1·80 (3H, s), 1·97, 2·25, 5·05 (2H, br. s), 5·68 (2H, br), 8·26 (1H, s) ppm. (Found: C, 68·77; H, 10·43; N, 15·10. $C_{16}H_{29}ON_3$ requires: C, 68·77; H, 10·46; N, 15·04%). This semicarbazone XIIa

(2·3 g) was suspended in a soln of oxalic acid ($C_2H_2O_4.2H_2O$, 2 g) in water (20 ml) and heated under reflux for 1·5 hr when crystalline XIIa disappeared. After cooling, the mixture was ether extracted. The extract was washed with water, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 1·5 g (81% from XIIa) of II, b.p. 95–96°/0·1 mm, n_D^{18} 1·4682. This contained about 20% of the dihydro ketone as shown by GC–MS. However, the following physical data were in good accord with the published values for I, although additional peaks due to the dihydro ketone were observed. ν_{max} 1715, 1160, 840 cm^{-1}; δ 0·98 (6H, t, J = 7 Hz), 1·66 (3H, s), 2·07 (3H, s), 4·98 (2H, br. t, J = 7 Hz) ppm; GLC: *Rt* 8·1 (20% dihydro ketone without Δ^9), 10·5 min (80%, II), Column, LAC 2R-446 at 170°, carrier gas, N_2, 1·2 kg/cm^2; GC-MS: Apparatus, Hitachi RMU GC; column, 3% Carbowax 20M on Diasolid L (80 mesh), 3 m × 3 mm i.d. at 160°, carrier gas, N_2, 1·1 kg/cm^2, *Rt* 8·1 min (M^+ 224), 10·2 min (M^+ 222 = II). (Found: C, 80·84; H, 11·53. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

6-*Ethyl*-10-*methylundeca*-5-trans, 9-*diene*-2-*one* (III). This was prepared in the same manner as described for II in 50% yield as crude product. This crude ketone (III, 8·0 g) yielded 5·1 g (51%) of *semicarbazone* XIIb. Recrystallization from EtOAc–pet. ether yielded leaflets, m.p. 104–105°; ν_{max} 3460, 3200, 1695, 1580, 1220, 1105, 760, 720 cm^{-1}; δ ($CDCl_3$) 0·95 (3H, t, J = 7 Hz), 1·58 (3H, s), 1·67 (3H, s), 1·80 (3H, s), 1·98, 2·26, 5·06 (2H, br. s), 5·65 (2H, br), 8·25 (1H, s) ppm. (Found: C, 68·10; H, 10·26; N, 15·90. $C_{15}H_{27}ON_3$ requires: C, 67·88; H, 10·26; N, 15·83%). This semicarbazone XIIb (3·5 g) gave 2·2 g (81% from XIIb) of III, b.p. 92–94°/0·1 mm, n_D^{20} 1·4650. This contained about 20% of a dihydro ketone (III, without a double bond at C-9) as shown by GC–MS. However, the following physical data were in good accord with those of our authentic III, although some additional peaks due to the dihydro ketone were also observed. ν_{max} 1710, 1150, 820 cm^{-1}; δ 0·96 (3H, t, J = 7 Hz), 1·57 (3H, s), 1·65 (3H, s), 2·02 (3H, s), 5·00 (2H, br) ppm; GLC: *Rt* 3·1 min (20%, dihydro ketone), 4·2 min (80%, III), Column, LAC 2R-446 at 180°, carrier gas, N_2, 1·2 kg/cm^2. The retention time of III was identical with that of an authentic sample. GC–MS: Apparatus, Hitachi RMU GC; Column, 3% Carbowax 20M on Diasolid L (80 mesh), 3 m × 3 mm i.d. at 160°, carrier gas, N_2, 1·1 kg/cm^2; *Rt* 5·6 min (M^+ 210), 7·8 min (M^+ 208). (Found: C, 80·40; H, 11·42. $C_{14}H_{24}O$ requires: C, 80·71; H, 11·61%).

Methyl 3,11-*dimethyl*-7-*ethyltrideca*-2,6-trans, 10-cis-*trienoate* (XIIIa + XIVa). Methyl diethylphosphonoacetate (2·1 g) was added to a suspension of NaOMe (0·54 g) in dry DMF (10 ml) and the mixture was stirred for 30 min at room temp under N_2. A soln of the ketone II (0·95 g) in dry DMF (8 ml) was added dropwise to the ice-cooled and stirred phosphonate soln at 0–5°. The mixture was stirred at 0–5° for 1 hr and at 50–60° for 1 hr, left to stand overnight at room temp, poured into water and ether extracted. The ethereal extract was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 1·032 g (87%) of XIIIa + XIVa, b.p. 121–122°/0·1 mm, n_D^{21} 1·4810; ν_{max} 1725, 1645, 1220, 1140, ~1040, 840 cm^{-1}; δ 0·96 (6H, t, J = 7 Hz), 1·64 (3H, s), 3·60 (3H, s), 5·00 (2H, br.), 5·56 (1H, s) ppm; GLC: *Rt* 9·7 min (40%, Δ^2-*cis*), 13·0 min (60%, Δ^2-*trans*), small additional peaks at 7·5, 11, 14·3 min, Column: LAC 2R-446 at 183°, carrier gas, N_2, 1·35 kg/cm^2. (Found: C, 77·14; H, 10·73. Calcd. for $C_{18}H_{30}O_2$: C, 77·65; H, 10·86%).

GLC separation of the two isomers (XIIIa and XIVa). The mixture (XIIIa + XIVa) described above was separated by GLC: Column, LAC 2R-446, 3 m × 0·6 cm i.d. at 220°; carrier gas, N_2, 1·0 kg/cm^2. *Methyl* 3,11-*dimethyl*-7-*ethyltrideca*-2-trans, 6-trans, 10-cis-*trienoate* (*XIIIa*) showed the following physical properties: ν_{max} 1720 (vs), 1640 (s), 1420, 1370, 1350 (This absorption is stronger than that at 1370 cm^{-1}.), 1220 (vs), 1140 (vs), 1060, 850 cm^{-1}; δ 0·97 (6H, t, J = 7 Hz), 1·64 (3H, s), 1·96, 2·13 (including a signal due to Me at C-3), 3·61 (3H, s), 5·00 (2H, br), 5·57 (1H, br. s) ppm; GLC: *Rt* 16·3 min, Column, LAC 2R-446 at 170°, carrier gas, N_2, 1·2 kg/cm^2. (Found: C, 77·86; H, 11·27. $C_{18}H_{30}O_2$ requires: C, 77·65; H, 10·86%).

Methyl 3,11-*dimethyl*-7-*ethyltrideca*-2-cis,6-trans,10-cis-*trienoate* (XIVa) showed the following physical properties: ν_{max} 1720 (vs), 1645 (s), 1440, 1370 (This absorption is stronger than that at 1350 cm^{-1}.), 1120 (s), 1150 (vs), 1070, 850 cm^{-1}; δ 0·97 (6H, t, J = 7 Hz), 1·65 (3H, s), 1·87 (3H, s, Me at C-3), 1·96, 2·13, 3·61 (3H, s), 5·00 (1H), 5·08 (1H), 5·56 (1H, br. s) ppm; GLC: *Rt* 13·2 min, Column, LAC 2R-446 at 170°, carrier gas, N_2, 1·2 kg/cm^2. (Found: C, 77·62; H, 11·01. $C_{18}H_{30}O_2$ requires: C, 77·65; H, 10·86%).

Methyl 3,11-*dimethyl*-7-*ethyldodeca*-2,6-trans,10-cis-*trienoate* (XIIIb + XIVb). This stereoisomeric mixture was prepared in the same manner as described for XIIIa + XIVa in 83% yield from III, b.p. 120–128°/0·1 mm, n_D^{19} 1·4812; ν_{max} 1730, 1650, 1225, 1150 cm^{-1}; δ 0·96 (3H, t, J = 7 Hz), 1·57 (3H, s), 1·65 (3H, s), 1·96, 2·12, 3·60 (3H, s), 5·00 (2H), 5·56 (1H, s) ppm; GLC: *Rt* 12·8 min (40%, Δ^2-*cis*), 16·2 min (60%, Δ^2-*trans*), Column, LAC 2R-446, 3 m × 0·6 cm i.d. at 220°, carrier gas, N_2, 1·0 kg/cm^2 or *Rt* 12·8 min (40%), 16·2 min (60%), Column, SE-30, 0·75 m × 3 mm i.d. at 160°, carrier gas, N_2, 1·0 kg/cm^2. (Found:

C, 77·40; H, 10·74. Calcd. for $C_{17}H_{28}O_2$: C, 77·22; H, 10·67%). Separation of these two isomers and their epoxidation were previously recorded by us.[15]

dl-C_{18}-*Cecropia juvenile hormone* (I). A soln of *m*-chloroperbenzoic acid (Aldrich, 85% pure, 64·5 mg) in purified CH_2Cl_2 (1·0 ml) was added to a soln of the *trans, trans, cis*-trienoic ester XIIIa (80 mg) in purified CH_2Cl_2 (0·6 ml) at 0–5°. The mixture was left to stand overnight in a refrigerator, diluted with CH_2Cl_2, washed with 5% Na_2CO_3 soln, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. This was purified by prep. TLC (Merck, Silica gel GF 254, 20 × 20 cm × 0·5 mm) developed with benzene–EtOAc (15:1). *dl*-C_{18} juvenile hormone (I) was obtained from a band at R_f 0·41–0·53 as 39·6 mg (47%) of an oil. Twelve mg of the starting material XIIIa was recovered. The *dl*-C_{18} juvenile hormone (I) showed the following spectral properties which were identical with the recorded data: ν_{max} 1720, 1640, 1230, 1150, 850 cm^{-1}; δ 0·98 (6H, t, J = 7 Hz), 1·19 (3H, s), 2·12 (3H, s), 2·50 (1H, t), 3·60 (3H, s), 5·05 (1H, br), 5·55 (1H, br. s) ppm; MS: *m/e* 294 (M^+).

6-*Ethynyl*-10-*methyldodeca*-5-trans,9-cis-*dien*-2-*one* (XVa). A soln of the nitrile Xa (23·0 g) in dry benzene (100 ml) was added dropwise to a stirred and ice-cooled soln of a Grignard reagent prepared from MeI (47 g) and Mg (7·9 g) in dry ether (180 ml) under N_2. After addition the mixture was stirred and heated under reflux for 7 hr, left overnight at room temp and poured into ice and dil HCl. The mixture was ether extracted, the ethereal extract washed with water, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 9·25 g (38%) of crude XVa, b.p. 96–103°/0·2 mm. Redistillation gave a purer sample, b.p. 103°/0·2 mm, n_D^{18} 1·4971. GLC analysis revealed the purity was low and hence it did not afford correct analysis. Impurities seemed to be non-ketonic, for this crude ketone gave a pure ester (XVIa + XVIIa) in the next step after rectification. ν_{max} 3280, 1710, 1150, 1030, 840 cm^{-1}; δ 0·96 (3H, t, J = 7 Hz), 1·64 (3H, s), 2·05 (3H, s), 1·8–2·2 (11H), 2·95 (2H, d, J = 6 Hz), 3·02 (1H, s), 4·97 (1H, br), 5·70 (1H, t, J = 7 Hz) ppm. GLC: *Rt* 3·5 min (26%), 4·1 min (6%), 7·6 min (62%) and minor peaks, Column, LAC 2R-446 at 180°, carrier gas, N_2, 1·2 kg/cm^2.

6-*Ethynyl*-10-*methylundeca*-5-trans,9-*diene*-2-*one* (XVb). This was prepared in the same manner as described for XVa in 36% yield, b.p. 114–121°/5 mm, n_D^{17} 1·4988; ν_{max} 3280, 2900, 2080, 1710, 1430, 1350, 1150, 820 cm^{-1}; δ 1·60 (3H, s), 1·67 (3H, s), 2·05 (3H, s), 3·03 (1H, s), 5·01 (1H), 5·70 (1H, t, J = 7 Hz) ppm; GLC: *Rt* 5·3 min (70% purity), 5 minor peaks, Column, LAC 2R-446 at 180°, carrier gas, N_2, 1·0 kg/cm^2 (too impure for correct analysis).

Methyl 3,11-*dimethyl*-7-*ethynyltrideca*-2,6-trans,10-cis-*trienoate* (XVIa + XVIIa). Methyl diethylphosphonoacetate (18·9 g) was added to a suspension of NaOMe (4·8 g) in dry DMF (80 ml) and the mixture stirred for 30 min at room temp under N_2. A soln of the ethynyl ketone XVa (8·75 g) in dry DMF (20 ml) was added dropwise to the ice-cooled sodium enolate at 0–5°. After addition the bath temp was kept at 0–5° for 1 hr, gradually raised to 50° during 1 hr and kept at 50–60° for 1 hr. The mixture was left overnight at room temp, poured into water and extracted with ether. The ethereal soln was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 6·80 g (62%) of the ester (XVIa + XVIIa), b.p. 115–126°/0·2 mm. An analytical sample boiled at 123°/0·2 mm, n_D^{17} 1·4976; ν_{max} 3280, 1730, 1650, 1225, 1150 cm^{-1}; δ 0·97 (3H, t, J = 7 Hz), 1·64 (3H, s), 1·88, 2·10, 2·14, 2·98 (0·35H, s), 3·04 (0·65H, s), 3·62 (3H, s), 4·98 (1H, br), 5·59 (1H, br. s), 5·68 (1H, br) ppm; GLC: *Rt* 12·4 min (35–40%, Δ^2-*cis*), 16·2 min (65–60%, Δ^2-*trans*), Column, LAC 2R-446 at 190°, carrier gas, N_2, 1·2 kg/cm^2. (Found: C, 78·77; H, 9·45. $C_{18}H_{26}O_2$ requires: C, 78·79; H, 9·55%).

GLC separation of the two isomers (XVIa + XVIIa). The mixture (XVIa + XVIIa) described above was separated by GLC: Apparatus, F & M 775, Column, 20% Polydiethylene glycol adipate on Chromosorb P (40–80 mesh), 2 m × 16 mm, Column temp, 200°; carrier gas, He 300 ml/min. A pure *trans,trans,cis*-ester XVIa (370 mg) and *cis,trans,cis*-ester XVIIa (173 mg) was obtained from 6·45 g of the mixture. *Methyl* 3,11-*dimethyl*-7-*ethynyltrideca*-2-trans,6-trans,10-cis-*trienoate* (XVIa) showed the following physical properties: ν_{max} 3280, 1720, 1640, 1220, 1140, 850 cm^{-1}; δ 0·94 (3H, t, J = 7 Hz), 1·61 (3H, s), 2·07, 2·10, 3·02 (1H, s), 3·58 (3H, s), 4·96 (1H, br), 5·55 (1H, s), 5·60 (1H, t, J = 6 Hz) ppm. *Methyl* 3,11-*dimethyl*-7-*ethynyltirdeca*-2-cis,6-trans,10-cis-*trienoate* (XVIIa) showed the following physical properties: ν_{max} 3280, 1720, 1640, 1240, 1185, 1150, 845 cm^{-1}; δ 0·94 (3H, t, J = 7 Hz), 1·61 (3H, s), 1·85 (3H, s), 2·03, 2·08, 2·95 (1H, s), 3·58 (3H, s), 4·95 (1H, br. s), 5·55 (1H, s), 5·70 (1H, t, J = 7 Hz) ppm.

Methyl 3,11-*dimethyl*-7-*ethynyldodeca*-2,6-trans,10-*trienoate* (XVIb + XVIIb). This was prepared in the same manner as described for XVIa + XVIIa in 50% yield, b.p. 116–127°/0·2 mm. An analytical sample boiled at 122°/0·2 mm, n_D^{17} 1·4997; ν_{max} 3280, 2910, 2080, 1710, 1650, 1225, 1150, 850 cm^{-1}; δ 1·60 (3H, s), 1·67 (3H, s), 1·89, 2·10, 2·16, 2·99 (0·4H, s), 3·04 (0·6H, s), 3·62 (3H, s), 5·01 (1H), 5·59 (1H), 5·70 (1H) ppm. GLC: *Rt* 8·5 min (37%, Δ^2-*cis*), 11·7 min (63%, Δ^2-*trans*), Column, LAC 2R-446 at 190°, carrier gas,

He, 1·0 kg/cm². (Found: C, 77·75; H, 9·15. $C_{17}H_{24}O_2$ requires: C, 78·42; H, 9·29%).

GLC separation of the two isomers (XVIb + XVIIb). The mixture (XVIb + XVIIb) described above was separated by GLC: Apparatus, F & M 775, Column, 20% Polydiethylene glycol adipate on Chromosorb P (40–80 mesh), 2 m × 16 mm, Column temp, 210°; carrier gas, He, 300 ml/min. A pure 2-*trans*-ester XVIb (1·120 g) and 2-*cis*-ester XVIIb (516 mg) was obtained from 7·7 g of the mixture. *Methyl* 3,11-*dimethyl*-7-*ethynyldodeca*-2-trans,6-trans,10-*trienoate* (XVIb) showed the following physical properties: ν_{max} 3280, 1730, 1650, 1230, 1150, 860 cm^{-1}; δ 1·58 (3H, s), 1·65 (3H, s), 2·08, 2·13 (3H, s), 3·01 (1H, s), 3·60 (3H, s), 5·00 (1H), 5·58 (1H,s), 5·62 (1H, t, J = 7 Hz) ppm. *Methyl* 3,11-*dimethyl*-7-*ethynyldodeca*-2-cis-6-trans,10-*trienoate* (XVIIb) showed the following physical properties: ν_{max} 3280, 1725, 1650, 1220, 1150, 850 cm^{-1}; δ 1·58 (3H, s), 1·65 (3H, s), 1·87 (3H, s), 2·07, 2·13, 2·96 (1H, s), 3·60 (3H, s), 5·00 (1H, br), 5·58 (1H, s), 5·72 (1H, t, J = 7 Hz) ppm.

dl-10-*Epoxide of methyl* 3,11-*dimethyl*-7-*ethynyl*-2-trans,6-trans,10-cis-*trienoate* (XVIIIa). The *trans,trans,cis*-ester XVIa (118 mg) in CH_2Cl_2 (2 ml) was epoxidized with *m*-chloroperbenzoic acid (Aldrich, 85% pure, 95 mg) as described for I to give 106 mg (85%) of XVIIIa, ν_{max} 3280, 1720, 1640, 1220, 1140, 850 cm^{-1}; δ 0·95 (3H, t, J = 7 Hz), 1·17 (3H, s), 2·10 (3H, s), 3·10 (1H, s), 3·60 (3H, s), 5·56 (1H, br. s), 5·70 (1H, t, J = 6 Hz) ppm.

dl-10-*Epoxide of the* 2-cis,6-trans,10-cis *ester* (XIXa). This was prepared from 66 mg of XVIIa in the same manner as described for XVIIIa, ν_{max} 3280, 1720, 1640, 1230, 1180, 1140, 840 cm^{-1}; δ 0·97 (3H, t, J = 7 Hz), 1·18 (3H, s), 1·88 (3H, s), 3·00 (1H, s), 3·60 (3H, s), 5·58 (1H, br. s), 5·80 (1H, t, J = 7 Hz) ppm.

dl-10-*Epoxide of methyl* 3,11-*dimethyl*-7-*ethynyl*-2-trans,6-trans,10-*trienoate* (XVIIIb). This was prepared from XVIb (480 mg) in the same manner as described for XVIIIa in 91% yield (465 mg of XVIIIb), ν_{max} 3280, 1730, 1650, 1230, 1150 cm^{-1}; δ 1·24 (6H, s), 2·15 (3H, s), 3·10 (1H, s), 3·62 (3H, s), 5·60, (1H, s), 5·74 (1H, t, J = 7 Hz) ppm.

dl-10-*Epoxide of the* 2-cis,6-trans-10-*trienoic ester* (XIXb). This was prepared from XVIIb (500 mg) in the same manner as described for XVIIIa in 97% yield (516 mg of XIXb), ν_{max} 3280, 1720, 1650, 1240, 1150 cm^{-1}; δ 1·21 (3H, s), 1·23 (3H, s), 1·88 (3H, s), 3·01 (1H, s), 3·61 (3H, s), 5·60 (1H, s), 5·73 (1H, t, J = 7 Hz) ppm.

Diimide reduction of XVIIIb; *methyl* dl-14-*homojuvenate* (IV). The ester XVIIIb (105 mg) in 95% EtOH (5 ml) was mixed with 85% $N_2H_4 \cdot H_2O$ (1 ml). O_2 was bubbled into this soln for 50 min at room temp after which an absorption due to acetylenic group at 3280 cm^{-1} in the IR had disappeared almost completely. The mixture was diluted with water and extracted with pet. ether. The extract was washed with water and sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo* to give 62 mg (60%) of oily IV, ν_{max} 2910,1710, 1640, 1220, 1140, 860 cm^{-1}; δ 0·98 (3H, t, J = 7 Hz), 1·20 (3H, s), 1·23 (3H, s), 2·14 (3H, s), 2·50 (1H, t, J = 7 Hz). 3·60 (3H, s), 5·04 (1H, br.), 5·55 (1H, br. s) ppm. The IR and NMR spectra were identical with those of the authentic sample. TLC: Kieselgel G nach Stahl, benzene: EtOAc = 15:1. R_f 0·42 (cf. XVIIIb: R_f 0·39, XVIb: R_f 0·62).

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