Syntheses of the Insect Juvenile Hormone

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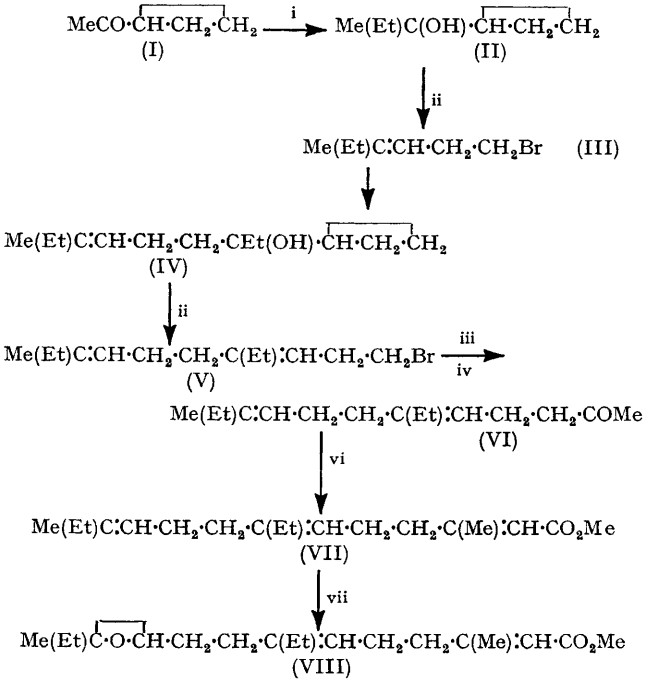
Two syntheses of the insect juvenile hormone are described.

THE morphogenetic activity of the insect juvenile hormone (VIII) ensures the appearance and maintenance of the features characteristic of the larval as opposed to the adult stages of insect development. The hormone also has gonadotrophic effects in the control of ovarian and egg development in the adult female, whilst in certain insects it also activates the prothoracic gland.[1] Consequently when its structure was published,[2] it appeared to be an appropriate synthetic objective, particularly as the descriptions of its biological activity had obvious implications in the control of insect population. At the outset of our work in 1967, there were no reported syntheses, but since then a number of syntheses have appeared.[3] We report two syntheses, which allow structural variation in the alkyl residues, the chain length, and, in the second case, the stereochemistry.

The first synthesis was non-stereospecific but allows for some structural variation (see Scheme 1). Cyclopropyl methyl ketone (I), which is readily available from ethyl acetoacetate and ethylene oxide,[4] underwent a Grignard reaction to give 2-cyclopropylbutan-2-ol (II).[5] Acid-catalysed cleavage[6,7] of the cyclopropane ring gave 1-bromo-4-methylhex-3-ene (III).

[1] V. B. Wigglesworth, *Nature*, 1965, **208**, 522.
[2] H. Röller, K. H. Dahm, C. C. Sweely, and B. M. Trost, *Angew. Chem. Internat. Edn.*, 1967, **6**, 179.
[3] For reviews see C. E. Berkoff, *Quart. Rev.*, 1969, **23**, 372; B. M. Trost, *Accounts Chem. Res.*, 1970, **3**, 120.
[4] G. W. Canon, R. C. Ellis, and J. R. Leal, *Org. Synth.*, 1963, Coll. vol. IV, p. 597.
[5] T. A. Favorskaya, *J. Gen. Chem.* (*U.S.S.R.*), 1947, **17**, 541 (*Chem. Abs.*, 1948, **42**, 1210).
[6] M. Julia, S. Julia, and R. Guegan, *Bull. Soc. chim. France*, 1960, 1072; M. Julia, Fr.P. 76,016/1962 (*Chem. Abs.*, 1963, **59**, 11,252).
[7] S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem. Internat. Edn.*, 1968, **7**, 577.

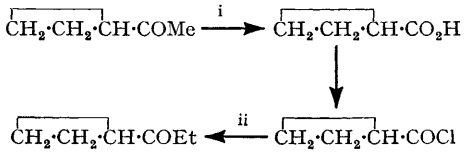
G.l.c. showed that this contained 25·5% of the *cis*- and 74·5% of the *trans*-isomer. A further Grignard reaction between the bromide (III) and ethyl cyclopropyl



SCHEME 1

Reagents: i, EtMgBr; ii, 48% HBr; iii, dry NaCN–Me_2SO; iv, MeMgI; vi, $(EtO)_2P(O)\cdot CH_2\cdot CO_2Me$–NaH; vii, *N*-bromosuccinimide–H_2O–NaOPr^i.

ketone gave the cyclopropyl alcohol (IV). The synthesis of cyclopropyl ethyl ketone [8-10] from cyclopropyl methyl ketone is outlined in Scheme 2. The

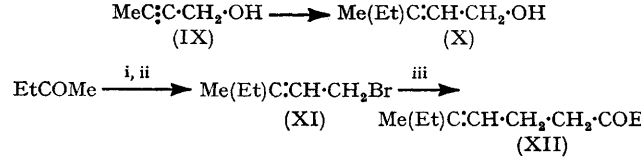


SCHEME 2

Reagents: i, NaBrO–H_2O; ii, Et_2Cd.

alternative route from ethyl 3-oxopentanoate was less satisfactory. Opening of the cyclopropane ring in compound (IV) with 48% hydrobromic acid gave the primary bromide (V), which was shown by g.l.c. to contain 59% of the *cis*- and 41% of the *trans*-3-ene. However this did not readily react under Grignard conditions. It was therefore converted into its nitrile, which was treated with methyl magnesium iodide to give 6-ethyl-10-methyldodeca-5,9-dien-2-one (VI) as a mixture of stereoisomers: *cis*-5,*cis*-9 15·5%; *cis*-5,*trans*-9 43·4%; *trans*-5,*cis*-9 10·8%; and *trans*-5,*trans*-9 30·3% (by g.l.c.). This ketone is an intermediate in a number of other syntheses of the juvenile hormone.[11] Reaction of this ketone with the anion derived from diethyl methoxycarbonylmethylphosphonate gave the ester (VII).[12] G.l.c. showed that this contained 9·8% of the *trans*-2,*trans*-6,*cis*-10-isomer, which possesses the juvenile hormone backbone. However 28·9% of all-*trans*-isomer was also produced, the epoxide of which differs from juvenile hormone in biological activity by a factor of only *ca.* 3. Epoxidation [13] gave a mixture of stereoisomers which showed n.m.r. and mass spectra, g.l.c. behaviour, and biological activity comparable to the published data [14] for the hormone admixed with its stereoisomers. After this work was completed, a comparable sequence was briefly outlined in a flow diagram by another group.[15]

Our second approach made use of an olefin synthesis described [16] by Corey *et al.* and used in his juvenile hormone synthesis [13] which permits the stereospecific construction of *cis–trans* double-bond isomers. 1,3-Dichlorobut-2-ene was converted in two steps into but-2-yn-1-ol (IX) (see Scheme 3). *trans*-Addition of hydrogen iodide by treatment with a heterogeneous mixture of lithium aluminium hydride and sodium methoxide (2 : 1) followed by addition of iodine at −78° gave 3-iodobut-2-en-1-ol. Alkylation of this iodo-alcohol with diethyl copper lithium gave *cis*-3-methylpent-2-en-1-ol (X) in 15% yield from (IX). Although this route is stereospecific, alcohol (X) was not converted into the bromide (XI), since the low overall yield of alcohol precluded its incorporation into a useful synthesis. Hence, the pentenol (X) was also synthesised non-stereospecifically and used as a mixture of isomers. Treatment of ethyl methyl ketone with vinylmagnesium bromide gave 3-methylpent-1-en-3-ol,[17]



SCHEME 3

which on acid hydrolysis gave 1-bromo-3-methylpent-2-ene (XI) (see Schemes 3 and 4). This was used, under carefully defined conditions, to alkylate ethyl 3-oxopentanoate to afford the ketone (XII): *cis*-(27%) and *trans*-(73%) at C-6 (g.l.c.). The second portion of the insect juvenile hormone molecule was prepared from tetra-

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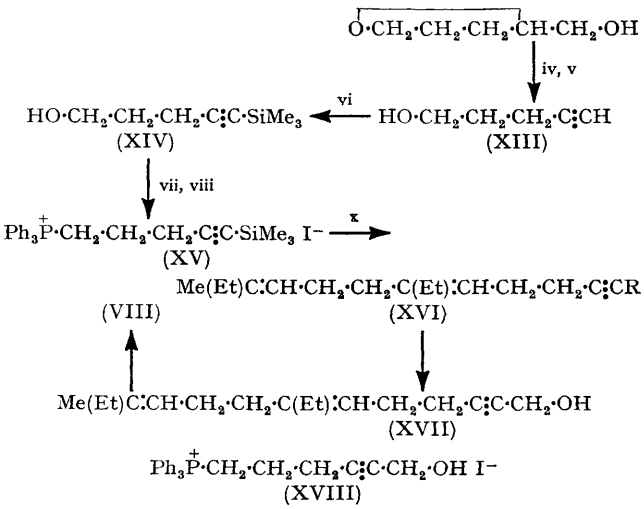
[9] G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1948, 1804.
[10] L. I. Smith and E. R. Rogier, *J. Amer. Chem. Soc.*, 1951, **73**, 4047.
[11] K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers, *Tetrahedron*, 1969, **25**, 1667.
[12] W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.
[13] E. J. Corey, J. A. Katzenellenbogen, W. H. Gilman, S. Q. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, 1968, **90**, 5618.
[14] K. H. Dahn, H. Roller, and B. M. Trost, *Life Sciences, Part II*, 1968, **7**, 129.
[15] B. H. Braun, M. Jacobsen, M. Schwarz, P. E. Sonnet, N. Wakabayashi, and R. M. Waters, *J. Econ. Entomol.*, 1968, **61**, 866.
[16] E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, 1967, **89**. 4245.
[17] D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Amer. Chem. Soc.*, 1954, **76**, 4446.

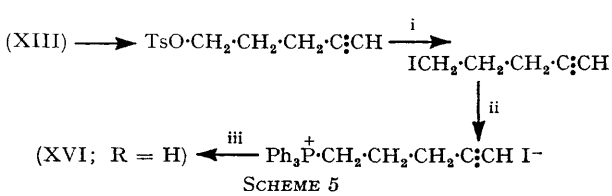
hydro-2-furylmethanol, which was converted into pent-4-yn-1-ol (XIII) *via* the alkyl chloride and treatment of that with sodamide in liquid ammonia (see Scheme 4).[18] In our first experiment the terminal ethynyl group was selectively protected as its trimethylsilyl derivative:[19]



SCHEME 4

Reagents for Schemes 3 and 4: i, $CH_2{:}CH{\cdot}MgBr$; ii, 48% HBr; iii, $MeCH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$; iv, $SOCl_2$; v, $NaNH_2$–NH_3(liq); vi, ethynyl Grignard reagent–Me_3SiCl; vii, $(PhO)_3\overset{+}{P}MeI^-$; viii, PPh_3; ix, (XII)–NaH–Me_2SO.

the alcohol was then converted into its iodide with triphenyl phosphite methiodide[20] and thence with triphenyl phosphine into the phosphonium salt (XV). A Wittig reaction between this salt and the ketone (XII) gave the acetylene (XVI; R = $SiMe_3$) as a mixture of stereoisomers. We were unable to carry out this reaction in good yield. Sodium hydride in pure[21,22] dimethyl sulphoxide gave the best coupling. The silyl group was removed with aqueous silver nitrate[23] and the acetylene was recovered from its silver salt by treatment with potassium cyanide. To improve the yield, an alternative sequence was developed in which the ethynyl group was not protected (*cf.* ref. 24). Pent-4-yn-1-ol



SCHEME 5

Reagents: i, NaI–Me_2CO; ii, PPh_3–C_6H_6, 24 h; iii, (XII)–NaOEt–$HCO{\cdot}NMe_2$.

(XIII) was converted into its toluene-*p*-sulphonate and thence into its iodide in 60% overall yield from the alcohol (see Scheme 5).[25] 5-Iodopent-1-yne was then treated with triphenylphosphine to give the corresponding phosphonium salt. A Wittig reaction with 7-methylnon-6-en-3-one (XII) proceeded in only 30% yield despite considerable variation in the conditions. Treatment of a methyl ketone such as 6-methylhept-5-en-2-one under identical conditions gave a 73% yield of the coupled product. The presence of an acetylene also affects the reaction since coupling of 7-methylnon-6-en-3-one with (4,4-ethylenedioxypentyl)triphenylphosphonium iodide under these conditions proceeded in 82% yield.

Hydroxymethylation of the Grignard derivative of the acetylene (XVI; R = H) gave the ethynyl alcohol (XVII), which was converted into the juvenile hormone by Corey's procedure:[13] *trans*-addition of hydrogen iodide by treatment with lithium aluminium hydride–sodium methoxide–iodine, followed by alkylation of the resulting iodo-olefin with dimethylcopper lithium, afforded an allylic alcohol with the carbon skeleton of the hormone. The alcohol was oxidised under mild conditions, first with freshly prepared manganese dioxide to the aldehyde and then with methanolic sodium cyanide–manganese dioxide–acetic acid to the methyl ester (VII). G.l.c. showed that this contained 21·7% of the required stereoisomer. The mixture was then converted into the terminal epoxide as described before. The product showed n.m.r. and mass spectra comparable to the published spectra of the natural material.

An alternative approach started from the ethynyl alcohol (XVIII). This was prepared by treating the prop-2-ynyltetrahydropyranyl ether with 1-bromo-3-chloropropane. The halogen atoms were replaced by iodine with sodium iodide in acetone. These conditions led to partial removal of the protecting group. Treatment with triphenylphosphine and complete removal of the protecting group with toluene-*p*-sulphonic acid gave the required alcohol. However the Wittig reactions were not successful and this approach was abandoned.

EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP 200 spectrometer for Nujol mulls or neat liquids and u.v. spectra with a Unicam SP 800 spectrometer for ethanolic solutions. N.m.r. spectra were recorded on Varian T60, A60A, and HA100 spectrometers for solutions in deuteriochloroform. Mass spectra were determined with an A.E.I. MS9 or Hitachi–Perkin-Elmer RMU-6 spectrometer. G.l.c. was carried out with a Perkin-Elmer F11 or a Pye 104 machine. Silica gel (B.D.H.) or alumina (Spence grade H) was used for column chromatography. Kieselgel G (Merck) was used for analytical (0·25 mm) and preparative layer chromatography. M.p.s were determinrd on a Kofler hot-stage apparatus.

Materials.—Cyclopropyl methyl ketone had b.p. 111—112° at 760 mmHg (lit.,[4] 110—112° at 760 mmHg).

[18] E. R. H. Jones, G. Eglinton, and M. C. Whiting, *Org. Synth.*, 1963, Coll. vol. IV, p. 755.
[19] M. F. Shostakovskii, A. S. Atavia, and N. V. Egorov, *J. Gen. Chem. (U.S.S.R.)*, 1965, **35**, 813.
[20] J. Landauer and H. Rydon, *J. Chem. Soc.*, 1953, 2224.
[21] E. J. Corey and R. Greenwold, *J. Org. Chem.*, 1963, **28**, 1128.
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[25] G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 1950, 3650.

2-Cyclopropylbutan-2-ol (II) was prepared from cyclopropyl methyl ketone with ethylmagnesium iodide and had b.p. 142—143° at 760 mmHg (lit.,[5] 141·5—143° at 760 mmHg). 1-Bromo-4-methylhex-3-ene (III) was prepared from 2-cyclopropylbutan-2-ol with 48% hydrobromic acid [6,7] and had b.p. 95—96° at 100 mmHg. (lit.,[6] 114—116° at 120 mmHg) (Found: C, 47·0; H, 7·5. Calc. for $C_7H_{13}Br$; C, 47·3; H, 7·4%), $\nu_{max.}$ 2950, 1660, and 860 cm^{-1}, τ 9·00 (3H, t, J 7 Hz), 8·40 (*trans*) and 8·33 (*cis*) (3H, s), 7·99 (*trans*) and 7·96 (*cis*) (2H, q, J 7 Hz), 7·42 (2H, q, J 7 Hz), and 4·88 (1H, m, $w_{\frac{1}{2}}$ 16 Hz).

G.l.c. was carried out on a Carbowax 20M (50 ft × 0·02 in) column in series with a Carbowax 1540 (50 ft × 0·02 in) column with nitrogen as carrier gas, at a flow rate of 8 ml min^{-1} at 80°. The *cis*-isomer (25·5%) had a retention time (R_t of 41·1 min and the *trans*-isomer (74·5%) 43·2 min.

Cyclopropanecarboxylic acid [9] had b.p. 55° at 2 mmHg (lit.,[9] 97° at 27 mmHg); the acid chloride had b.p. 120° at 760 mmHg (lit.,[10] 114—119° at 760 mmHg) and cyclopropyl ethyl ketone had b.p. 130—131° at 760 mmHg (lit.,[8] 130° at 760 mmHg).

3-Cyclopropyl-7-methylnon-6-en-3-ol (IV).—1-Bromo-4-methylhex-3-ene (28·4 g) and magnesium (3·88 g) in ether (65 ml) were heated under reflux for 1 h. Cyclopropyl ethyl ketone (14·5 g) in ether (75 ml) was added below 10°. The mixture was left overnight and then hydrolysed with cold aqueous ammonium chloride (100 ml). The product was recovered in ether and, on distillation, afforded *3-cyclopropyl-7-methylnon-6-en-3-ol* (28 g), b.p. 82—85° at 2 mmHg (Found: C, 79·1; H, 12·0. $C_{13}H_{24}O$ requires C, 79·6; H, 12·2%), $\nu_{max.}$ 3480 cm^{-1}, τ 9·70 (4H, m), 8·40 (3H, s), and 4·90 (1H, m, $w_{\frac{1}{2}}$ 16 Hz).

1-Bromo-4-ethyl-8-methyldeca-3,7-diene (V).—Ice-cold 48% hydrobromic acid (67 ml) was slowly added to a vigorously shaken suspension of the foregoing alcohol (28 g) in ice (30 g). After 30 min the product was recovered in light petroleum and the extract was thoroughly rinsed with aqueous sodium chloride and sodium hydrogen carbonate. The solvent was evaporated and the residue distilled to afford *1-bromo-4-ethyl-8-methyldeca-3,7-diene* (26 g), b.p. 85—88° at 0·8 mmHg, $\nu_{max.}$ 1660 and 840 cm^{-1}, τ 8·95 (6H, t, J 7 Hz), 8·39 (*trans*) and 8·33 (*cis*) (3H, s), 6·68 (2H, t, J 7 Hz), and 4·86 (2H, m).

5-Ethyl-9-methylundeca-4,8-dienonitrile.—The foregoing bromide (10·3 g) (prepared immediately prior to use) and dry sodium cyanide (4 g) in freshly purified dimethyl sulphoxide (30 ml) were heated at 50° for 30 min and then at 90° for 30 min. The mixture was extracted with light petroleum. The extract was washed thoroughly with water, dried, and the solvent was evaporated. The residue was distilled to afford the *nitrile* (7·3 g), b.p. 88—92° at 1·3 mmHg (Found: C, 82·1; H, 11·1. $C_{14}H_{23}N$ requires C, 81·9; H, 11·3%), $\nu_{max.}$ 2280, 1660, and 860 cm^{-1}, τ 8·95 (6H, t, J 7 Hz), 8·39 (*trans*) and 8·33 (*cis*) (3H, s), and 4·83 (2H, m, $w_{\frac{1}{2}}$ 16 Hz).

6-Ethyl-10-methyldodeca-5,9-dien-2-one (VI).—The preceding nitrile (7·3 g) in ether (100 ml) was added dropwise to a Grignard solution prepared from methyl iodide (25·6 g) and magnesium (4 g) in ether (80 ml). The mixture was stirred for 48 h and then hydrolysed with ice-cold aqueous ammonium chloride (50 ml). Concentrated hydrochloric acid (20 ml) was added and the mixture was heated at 45° for 1 h. The mixture was thoroughly extracted with ether and the extract washed with aqueous sodium hydrogen carbonate and water and dried. The solvent was evaporated and the residue distilled to afford 6-ethyl-10-methyldodeca-5,9-dien-2-one (6·1 g), b.p. 94—95° at 0·4 mmHg (lit.,[11] b.p. 85° at 0·05 mmHg) (Found: C, 80·7; H, 11·8. Calc. for $C_{15}H_{26}O$: C, 81·0; H, 11·8%), $\nu_{max.}$ 1710 and 860 cm^{-1}, τ 9·01 (6H, t, J 7 Hz), 8·39 (*trans*) and 8·33 (*cis*) (3H, s), and 4·85 (2H, m, $w_{\frac{1}{2}}$ 16 Hz). G.l.c. [Carbowax 20M (50 ft × 0·02 in), nitrogen gas flow rate 8 ml min^{-1} at 100°] showed the following results:

Isomer	R_t/min	(%)
cis-9,*cis*-5	25·2	15·5
trans-9,*cis*-5	25·8	43·4
cis-9,*trans*-5	26·6	10·8
trans-9,*trans*-5	27·2	30·3

Methyl 7-Ethyl-3,11-dimethyltrideca-2,6,10-trienoate (VII).—Diethyl methoxycarbonylmethylphosphonate (7 g) was added dropwise to a stirred suspension of sodium hydride (50% suspension in oil; 1·6 g) in anhydrous benzene (20 ml) and the mixture was stirred for 30 min at room temperature until hydrogen was no longer expelled and a clear grey solution was obtained. 6-Ethyl-10-methyldodeca-5,9-dien-2-one (6·5 g) in anhydrous benzene (20 ml) was then added dropwise and the mixture was stirred at room temperature for 20 h. Water (5 ml) was added and the mixture was extracted with light petroleum. The extract was washed with water, dried, and evaporated. The residue was purified by p.l.c. in benzene to give methyl 7-ethyl-3,11-dimethyltrideca-2,6,10-trienoate (6·2 g, R_F 0·68; starting material R_F 0·43) (Found: C, 77·6; H, 10·7%; *m/e*, 278. Calc. for $C_{18}H_{30}O_2$: C, 77·7; H, 11·8%; M, 278), $\nu_{max.}$ 1725, 1655, and 840 cm^{-1}, τ 9·04 and 9·02 (3H, t, J 7 Hz), 8·40 (*trans*) and 8·33 (*cis*) (3H, s, *trans* : *cis* 2·8 : 1), 7·83 (3H, d, J 1 Hz), 6·29 (3H, s), 4·88 (2H, m), and 4·29 (1H, s). G.l.c. [Carbowax 20M (50 ft × 0·02 in), nitrogen; 3 ml min^{-1} and 142°] showed the following results:

Isomer C(10), C(6), C(2)			R_t/min	(%)
c	*c*	*c*	50·4	3·4
t	*c*	*c*	52·8	8·6
c	*t*	*c*	55·2	2·7
t	*t*	*c*	57·6	7·4
c	*c*	*t*	62·4	9·6
t	*c*	*t*	66·0	30·5
c	*t*	*t*	68·6	9·8
	t		72·3	28·9

c = *cis*, *t* = *trans*.

Methyl 10,11-Epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (VIII).—The preceding ester (1·31 g) in dimethoxyethane (5 ml) was added dropwise at 0° to a solution of *N*-bromosuccinimide (0·88 g) in water (3 ml) and dimethoxyethane (20 ml). After 1 hr at 0°, a solution of sodium (0·23 g) in propan-2-ol (8 ml) was slowly added and the mixture was stirred for 30 min. The solution was extracted with ether–light petroleum (3 : 1 v/v; 200 ml). The extract was washed with water, dried, and evaporated. The residue was purified by p.l.c. [hexane–ether (4 : 1)] to give methyl 10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate [2,14] (0·7 g) (R_F 0·42), (Found: C, 73·0; H, 10·2%; *m/e* 294. Calc. for $C_{18}H_{30}O_3$; C, 73·4; H, 10·3%; M, 294), $\nu_{max.}$ 1725, 1655, 1220, and 1145 cm^{-1} τ 9·15—8·85 (6H, m), 8·77 (*trans*) and 8·74 (*cis*) (3H, s), 8·60—8·32 (4H), 8·22—7·80 (12H), 7·84 (3H, d, J 1 Hz), 7·30 (1H, t, J 6 Hz), 6·32 (3H, s), 4·85 (1H, m), and 4·32 (1H, s).

An alternative but less efficient procedure with tetrahydrofuran and methanolic sodium methoxide gave the epoxide in 25% yield. The hormone was tested against *Rhodnius prolixus*, *Schistocerca gregaria*, and *Galleria mellonella* in collaboration with Dr. G. Ellis-Pratt.

trans-3-*Iodobut*-2-*en*-1-*ol*.—Lithium aluminium hydride (3·8 g) and sodium methoxide (10·8 g) in dry tetrahydrofuran (1 l) were heated under reflux under nitrogen for 30 min. But-2-yn-1-ol (3·55 g) was added to the cooled mixture, which was then heated under reflux for a further 3 h. The solution was cooled to −78° and finely powdered iodine (80 g) was added. The mixture was then stirred overnight at −78°. The solvent was evaporated off and water (10 ml) was added. The mixture was extracted with ether, washed with water, aqueous sodium thiosulphate, and water, and dried. The solvent was evaporated off and the product was chromatographed on silica gel to afford 3-iodobut-2-en-1-ol (3·0 g), (*m/e* 198. C_4H_7IO requires *M*, 198) as an unstable oil, $\nu_{max.}$ 3300 and 1650 cm^{-1}, τ 7·5 (3H, m), 7·00 (1H, s), 5·90 (2H, m), and 4·30 (1H, m).

cis-3-*Methylpent*-2-*en*-1-*ol* (X).—3-Iodobut-2-en-1-ol (2·9 g) in ether (20 ml) was added dropwise to a solution of diethylcopper lithium [from copper(I) iodide (14·6 g), ethyl iodide (48 g), and lithium (20 g)] in ether (180 ml) at −30°. The mixture was stirred for 2 h at −30° and then treated with ethyl iodide (10 g) at 0° for 18 h. Methanol (2·0 ml) and then water (5 ml) were added and the inorganic salts were filtered off. The solvent was evaporated and the crude residue was chromatographed on silica gel. Distillation of the fractions eluted with 14% ethyl acetate–light petroleum afforded *cis*-3-methylpent-2-en-1-ol (0·65 g), b.p. 86—87° at 2 mmHg, $\nu_{max.}$ 3300 and 1660 cm^{-1} τ 8·99 (3H, t, *J* 7 Hz), 8·29 (3H, s), 8·15—7·60 (2H), 7·18 (1H, s), 5·82 (2H, d, *J* 8 Hz), and 5·50 (1H, m).

7-Methylnon-6-en-3-one was prepared from ethyl 3-oxopentanoate [26] and 1-bromo-3-methylpent-2-ene. It had b.p. 66° at 1·5 mmHg (lit.,[11] 98° at 18 mmHg) (Found: C, 77·9; H, 11·7%; *m/e*, 204. Calc. for $C_{10}H_{18}O$: C, 77·9; H, 11·8%; *M*, 204), $\nu_{max.}$ 1705 and 860 cm^{-1} τ 9·03 and 8·95 (3H, t, *J* 7 Hz), 8·41 (*trans*) and 8·36 (*cis*) (3H, s), and 4·98 (1H, m, $w_{\frac{1}{2}}$ 16 Hz). G.l.c. [Ucon oil HB2000 (50 ft × 0·02 in); nitrogen; 3 ml min^{-1}; 70°] showed the *cis*-isomer 27% (R_t 13·8 min) and the *trans*-isomer 73% (14·2 min).

5-*Trimethylsilylpent*-4-*yn*-1-*ol* (XIV).—Pent-4-yn-1-ol [18] (43 g) in ether (100 ml) was added to an ice-cold solution prepared from ethyl bromide (113·6 g) and magnesium (25 g) in ether (240 ml). After stirring for 2 h, copper(I) chloride (1·2 g) was added, followed by chlorotrimethylsilylsilane (60 g) in ether (100 ml). The mixture was heated under gentle reflux for 14 h, cooled, and hydrolysed with hydrochloric acid (5%). The aqueous layer was extracted with ether and the combined extracts were washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Distillation of the residue afforded 5-*trimethylsilylpent*-4-*yn*-1-*ol*, an oil, b.p. 66° at 1·5 mmHg (Found: C, 61·4; H, 10·2. $C_8H_{16}OSi$ requires C, 61·5; H, 10·2%), $\nu_{max.}$ 3410, 2180, and 1250 cm^{-1}, τ 10·00 (9H, s), 7·82 (2H, t, *J* 6 Hz), 6·50 (2H, t, *J* 6 Hz), and 5·60 (1H, s).

5-*Iodo*-1-*trimethylsilylpent*-1-*yne*.—A mixture of 5-trimethylsilylpent-4-yn-1-ol (15·6 g) and triphenyl phosphite methiodide (51·3 g) was stirred at 85° for 2 h under nitrogen. The fractions which distilled below 74° at 2·2 mmHg were collected, taken up in ether, washed with aqueous sodium hydroxide (5%) and water, and dried. Distillation afforded 5-*iodo*-1-*trimethylsilylpent*-1-*yne*, b.p. 64° at 1·8 mmHg, $\nu_{max.}$ 2180, 1250, 760, and 677 cm^{-1}, τ 10·00 (9H, s), 7·75 (2H, t, *J* 6 Hz), and 6·72 (2H, t, *J* 6 Hz). This was used immediately to prepare the phosphonium salt.

Triphenyl-(5-*trimethylsilylpent*-4-*ynyl*)*phosphonium Iodide* (XV).—Triphenylphosphine (20 g) and 5-iodo-1-trimethylsilylpent-1-yne (22 g) in ethanol (100 ml) were heated under reflux for 12 h. The ethanol was evaporated off *in vacuo* and the product was poured into ethyl acetate (150 ml) to give *triphenyl*-(5-*trimethylsilylpent*-4-*ynyl*)-*phosphonium iodide*, m.p. 233—234° (from chloroform–ethyl acetate) (Found: C, 59·1; H, 5·8. $C_{26}H_{30}IPSi$ requires C, 59·1; H, 5·7%), $\nu_{max.}$ 2175 and 1250 cm^{-1}, τ 10·00 (9H, s), 7·42 (2H, t, *J* 6 Hz), 6·00—6·75 (2H), and 2·60—2·22 (15H). This product was stored over phosphorus pentoxide under vacuum.

6-*Ethyl*-10-*methyldodeca*-5,9-*dien*-1-*yne* (XVI; R = H).—(*a*) Sodium hydride (50% dispersion in oil; 4·8 g) was washed free of oil by flushing with dry pentane under nitrogen. Dimethyl sulphoxide (rigorously purified immediately prior to use [22]) (50 ml) and tetrahydrofuran (purified from sodium and benzophenone) (75 ml) were added and the mixture was stirred at 0° for 1 h (until all the hydrogen was expelled and a clear grey solution remained). Triphenyl-(5-trimethylsilylpent-4-ynyl)phosphonium iodide (52·8 g) was added to give a deep red solution. 7-Methylnon-6-en-3-one (15·4 g) was added and the mixture was stirred for 3 days at 4°. The tetrahydrofuran was evaporated off below 10° and the mixture was then poured on ice (100 g), stirred for 1 h, and extracted with pentane (10 × 100 ml). The extracts were washed with water, dried, and evaporated to give an oil (14·3 g), which was chromatographed on silica gel. Elution with light petroleum afforded an oil (3·8 g), $\nu_{max.}$ 2180 and 1250 cm^{-1}. Elution with 5% ethyl acetate–light petroleum gave 7-methylnon-6-en-3-one (9·1 g). The oil was dissolved in ethanol (15 ml) and a solution of silver nitrate (2·34 g) in water (6 ml) and ethanol (18 ml) was added dropwise. After 1 h potassium cyanide (4·4 g) in water (7 ml) was added and the mixture was stirred for 45 min. The ethanol was evaporated *in vacuo* and the aqueous residue thoroughly extracted with pentane. The extract was washed with water, dried, and evaporated to give an oil which was chromatographed on silica gel. Elution with light petroleum afforded 6-*ethyl*-10-*methyldodeca*-5,9-*dien*-1-*yne* (1·9 g) (Found: C, 87·8; H, 11·9%; *m/e*, 204. $C_{15}H_{24}$ requires C, 88·1; H, 11·8%; *M*, 204), $\nu_{max.}$ 3290, 2120, and 860 cm^{-1}, τ 9·04 and 9·03 (3H each t, *J* 7 Hz), 8·41 (*trans*) and 8·34 (*cis*) (3H, s; *trans* : *cis* 2·62 : 1), and 4·87 (1H, m, $w_{\frac{1}{2}}$ 16 Hz).

5-Iodopent-1-yne was prepared by the method of Eglinton *et al.*[25] and had b.p. 47° at 7 mmHg (lit.,[25] 84—89° at 43 mmHg) (Found: C, 31·3; H, 3·8. Calc. for C_5H_7I: C, 31·0; H, 3·6%). The triphenylphosphonium salt was prepared as before; m.p. 199—200° (lit.,[24] 194—195°) (Found: C, 60·3; H, 5·1. Calc. for $C_{23}H_{22}IP$: C, 60·5; H, 4·9%), $\nu_{max.}$ 3260 and 1600 cm^{-1}, τ 7·85 (1H, t, *J* 2 Hz), 7·38 (2H, t, *J* 6 Hz), 6·50—5·90 (2H, m), and 1·95—2·40 (15H, m).

(*b*) Dimethylformamide (purified over barium oxide) (150 ml) was added dropwise to sodium ethoxide (4·07 g) at 0° under nitrogen and stirred for 1 h. Triphenyl(pent-4-ynyl)phosphonium iodide (27·4 g) was slowly added and the mixture was then stirred for 2 h at 0°. 7-Methylnon-

[26] G. Anderson, I. Halverstadt, W. Miller, and O. Roblin, *J. Amer. Chem. Soc.*, 1945, **67**, 2197.

6-en-3-one (4·62 g) was added dropwise during 1 h and the mixture was stirred at 40° for 48 h. The mixture was concentrated *in vacuo* to 50 ml, poured on ice (150 g), and extracted with pentane (10 × 100 ml). The extracts were washed with water, dried, and evaporated to give an oil which was carefully chromatographed on silica gel. Elution with light petroleum gave successively 6-*ethyl*-10-*methyldodeca*-1,2,5,9-*tetraene* as an oil (0·95 g) (Found: C, 87·9; H, 11·6%; *m/e*, 204. $C_{15}H_{24}$ requires C, 88·1; H, 11·8%; *M*, 204), $\nu_{max.}$ 1960 and 860 cm^{-1}, τ 9·18 (3H, t, *J* 7 Hz), 9·09 (3H, t, *J* 7 Hz), 8·41 (*trans*) and 8·34 (*cis*) (3H, s; *trans* : *cis* 2·62 : 1), and 5·45—4·80 (5H), 6-ethyl-10-methyldodeca-5,9-dien-1-yne (2·2 g), identical with the material obtained before, and 7-methylnon-6-en-3-one (1·6 g).

7-*Ethyl*-11-*methyltrideca*-6,10-*dien*-2-*yn*-1-*ol* (XVII).—6-Ethyl-10-methyldodeca-5,9-dien-1-yne (1·7 g) in ether (5 ml) was added to a solution of ethylmagnesium iodide [from magnesium (0·22 g) and ethyl iodide (1·5 g)] in ether (20 ml). The mixture was heated under reflux under nitrogen for 6 h; acetone–solid carbon dioxide was the coolant in the condenser. Gaseous formaldehyde was slowly introduced by passing dry nitrogen through a flask containing paraformaldehyde (1 g) (dried over phosphorus pentoxide for 2 weeks) at 180°. The mixture was heated under reflux for 6 h and then hydrolysed with 5% hydrochloric acid, and the product was recovered in ether. The solvent was evaporated off and the residue distilled to give 7-*ethyl*-11-*methyltrideca*-6,10-*dien*-2-*yn*-1-*ol* (1·2 g) as an oil, b.p. 115° at 0·09 mmHg (Found: C, 82·4; H, 11·6. $C_{16}H_{26}O$ requires C, 82·0; H, 11·5%), $\nu_{max.}$ 3380, 2220, 1665, and 840 cm^{-1}, τ 9·04 (3H, t, *J* 7 Hz), 9·03 (3H, t, *J* 7 Hz), 8·41 (*trans*) and 8·34 (*cis*) (3H, s; *trans* : *cis* 2·7 : 1), 5·79 (2H, s), and 4·87 (2H, m, $w_{\frac{1}{2}}$ 16 Hz).

7-*Ethyl*-3,11-*dimethyltrideca*-2,6,10-*trien*-1-*ol*.— Lithium aluminium hydride (475 mg) and sodium methoxide (1·35 g) were heated under reflux in tetrahydrofuran (125 ml) under nitrogen for 30 min. The foregoing alcohol (XVII) (1 g) in tetrahydrofuran (5 ml) was added and the solution was heated under reflux for 3 h. The mixture was cooled to −78° and iodine was added in small portions until a permanent brown colour remained. Stirring was continued for 14 h at −78°. The solvent was evaporated off and aqueous sodium thiosulphate was added. The mixture was extracted with ether and the extract washed with water, dried, and evaporated to give the iodo-alcohol (1 g) as a yellow oil. This was dissolved in ether (5 ml) and added to a solution of dimethylcopper lithium [from copper(I) iodide (2·92 g)] in ether (10 ml) and stirred at 0° for 24 h. Water (1 ml) was added and the mixture was extracted with ether. The extracts were washed with water and dried. The solvent was evaporated off and the residue distilled to give an oil which was purified by p.l.c. (silica gel; 25% ethyl acetate–light petroleum): the product had R_F 0·20 and the iodo-alcohol R_F 0·25. 7-*Ethyl*-3,11-*dimethyltrideca*-2,6,10-*trien*-1-*ol* (260 mg) was recovered as an oil (Found: C, 81·3; H, 12·0%; *m/e*, 250. $C_{17}H_{30}O$ requires C, 81·5; H, 12·0%; *M*, 250), τ 9·04 (3H, t, *J* 7 Hz), 9·03 (3H, t, *J* 7 Hz), 8·41 (*trans*) and 8·34 (*cis*) (6H, s; *trans* : *cis* 1·84 : 1), 5·84 (2H, d, *J* 6 Hz), 4·87 (2H, m), and 4·64 (1H, m).

Methyl 7-*Ethyl*-3,11-*dimethyltrideca*-2,6,10-*trienoate* (VII).—7-Ethyl-3,11-dimethyltrideca-2,6,10-trien-1-ol (120 mg) in hexane (0·5 ml) was added to fresh manganese dioxide [27] (1·5 g) in hexane (8 ml) and stirred at 0° for 30 min. The solvent was evaporated off. Sodium cyanide (164 mg), glacial acetic acid (60 mg), and manganese dioxide (1·5 g.) in methanol (15 ml.) were added and the mixture was stirred at 25° for 14 h. Water (0·5 ml) was added and the solution was extracted with ether. Evaporation of the solvent and chromatography of the product on silica gel afforded methyl 7-ethyl-3,11-dimethyltrideca-2,6,10-trienoate (53 mg) (Found: C, 77·6; H, 10·7%; *m/e*, 278. Calc. for $C_{18}H_{30}O_2$: C, 77·6; H, 10·8%; *M*, 278), $\nu_{max.}$ 1720 and 830 cm^{-1}, τ 9·04 (3H, t, *J* Hz), 9·03 (3H, t, *J* 7 Hz), 8·41 (*trans*) and 8·34 (*cis*) (3H, s), 7·82 (3H, d, *J* 1 Hz), 6·30 (3H, s), 4·88 (2H, m), and 4·30 (1H, s). G.l.c. [Carbowax 20M (50 ft × 0·02 in); nitrogen; 3 ml min^{-1}; 142°] showed:

Isomer C(10), C(6), C(2)			R_t/min	% (Average)
c	*c*	*c*	50·4	<0·5
t	*c*	*c*	52·8	<0·5
c	*t*	*c*	55·2	<1
t	*t*	*c*	57·6	<1
c	*c*	*t*	62·4	20·4
t	*c*	*t*	66·1	26·6
c	*t*	*t*	69·1	21·7
t	*t*	*t*	72·6	31·3

c = *cis*, *t* = *trans*

The terminal epoxide was prepared as described earlier and used in the same test system.

(6-*Hydroxyhex*-4-*ynyl*)*triphenylphosphonium Iodide* (XVIII).— 1-(Tetrahydro-2-pyranyloxy)-6-chlorohex-2-yne [28] [b.p. 117 °C at 0·25 mmHg (lit.,[28] 110—114 at 0·14 mmHg)] (10 g) and sodium iodide (7·7 g) were heated under reflux for 6 h in freshly purified acetone (50 ml). The solution was filtered and the solvent was evaporated off. The iodo-acetylene (1 g) and triphenylphosphine (880 mg) were heated under reflux in dry benzene (20 ml) for 24 h and the solvent was evaporated off. The residue was taken up in ether (50 ml) and heated under reflux with toluene-*p*-sulphonic acid (110 mg) for 30 min. The product was collected and washed thoroughly with hot benzene to give (6-*hydroxyhex*-4-*ynyl*)*triphenylphosphonium iodide* (0·76 g) as white flakes, m.p. 190—192° (from chloroform–ethyl acetate) (Found: C, 59·4; H, 5·0. $C_{24}H_{24}IOP$ requires C, 59·3; H, 4·9%), $\nu_{max.}$ 3380, 1590, 745, and 690 cm^{-1}, τ 5·82 (2H, t, *J* 2 Hz) and 1·85—2·50 (15H, m).

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