Synthesis of Compounds with Juvenile Hormone Activity

Part V. Some β -Bisabolene Derivatives[†]

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Some β -bisabolene derivatives, III, XX, XXVII and XXVIII, were synthesized and shown to possess the juvenile hormone activity.

Bisabolene-type compounds are known to possess the juvenile hormone activity as evidenced by juvabione (I),^{1~3)} dehydrojuvabione (II),^{2,4)} *ar*-juvabione^{3b)} and other analogues.^{5~7)}

In continuation of our synthetic work on these compounds,^{3a,4,7)} we planned the synthesis of 2-(4'-carbomethoxycyclohex-3'-enyl)-6-methylhepta-1,5-diene (III) and its derivatives. Although the parent hydrocarbon, β -bisabolene (IV),^{8~10)} and the related alcohol,

lanceol (V)^{10,11)} are found in nature and have been synthesized, neither the ester (III) nor the corresponding alcohol (XXV) has been isolated as a natural product. The molecule III was dissected into four synthons—A, B, C and D. The connection of the four in their alphabetical order afforded the desired product.

The starting material for the synthon A was the known *trans*-4-hydroxycyclohexane-1-carboxylic acid (VI).¹²⁾ Its hydroxyl group was protected by acetylation. The resulting acetoxy acid (VII) was converted into the corresponding acyl chloride (VIII). This was treated with an organocadmium or a Grignard reagent prepared from 4-methylpent-3-enyl bromide¹³⁾ (the synthon B) to give a ketone (IX). Its conversion into an isomeric acetoxy ketone (XV) was accomplished in the following manner.^{cf 14)} A ketol (X), obtained by alkaline hydrolysis of IX, was treated with dihydropyran and *p*-toluenesulfonic acid to give a tetrahydropyranyl ether (XI). Its borohydride reduction yielded an alcohol (XII). The corresponding acetate (XIII) was sub-

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mitted to acid hydrolysis followed by Jones oxidation¹⁵⁾ to afford the desired acetoxy ketone (XV) *via* a diol monoacetate (XIV).

The third synthon, in the form of hydrogen cyanide, was attached to the molecule to give a cyanohydrin (XVI). This was treated with phosphorus oxychloride and pyridine to afford an unsaturated nitrile (XVII). Its alkaline hydrolysis gave a hydroxy acid (XVIII). This was oxidized with the Jones reagent to give a crystalline keto acid (XIX). The corresponding methyl ester (XX) was converted into a ketal (XXI). Its reduction with lithium aluminum hydride gave an alcohol (XXII). A keto acetate (XXIII) was obtained by acetylation and acid hydrolysis of XXII.

The fourth synthon was then attached to the molecule by the Wittig reaction¹⁶⁾ to give an acetate (XXIV). The corresponding alcohol (XXV) was oxidized with manganese dioxide to give an aldehyde (XXVI). This was converted into the final product (III) by the method of Corey and his co-workers.¹⁷⁾

Since some chlorinated esters were known to possess high juvenile hormone activity,^{5,18)} the esters XX and III were treated with hydrogen chloride to give the chlorinated esters, XXVII and XXVIII, respectively.

The biological activity of the four synthetic products, III, XX, XXVII and XXVIII, was tested on newly molted last instar nymphs of *Pyrrhocoris apterus* L. by the courtesy of Dr. W. S. Bowers of USDA Agricultural Research Service. The dichloro ester XXVIII was the most active and might be compared to our synthetic juvabione (I)^{3a)} in activity, while III and XXVII were slightly active. The keto ester XX exhibited intermediate activity. Thus all of the four compounds were shown

to possess the juvenile hormone activity.

EXPERIMENTAL

All mp and bp were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for liquids. NMR spectra were recorded at 100 MHz in CCl₄ with TMS as an internal standard unless otherwise stated.

trans-4-Acetoxycyclohexane-1-carboxylic acid (VII). Acetic anhydride (250 ml) was added to a solution of *trans*-4-hydroxycyclohexane-1-carboxylic acid (VI, 156 g) in pyridine (800 ml). The mixture was left to stand at room temp. for 2 days, concentrated *in vacuo* and diluted with ether. The ether solution was washed with dil HCl, dried (MgSO₄) and concentrated to give a crystalline product (VII, 50 g). The oily mother liquor was dissolved in THF (300 ml). The solution was stirred with NaHCO₃ aq (100 g in 500 ml) for 1 hr at room temp and 20 min under reflux. After cooling, the mixture was extracted with ether to remove neutral impurities. The aqueous layer was acidified with dil HCl and extracted with EtOAc. The extract was washed with NaCl aq, dried (MgSO₄) and concentrated to give 44 g of VII. The total amount of VII was 94 g (46%). Recrystallization from EtOAc gave elongated prisms, mp 133~134°C. *Anal.* Found: C, 58.73; H, 7.84. Calcd. for C₉H₁₄O₄: C, 58.05; H, 7.58%. $\nu_{\max}$ ~3200~2600, 1740, 1705, 1266, 1250, 1235, 1045, 1024, 745 cm⁻¹; δ 2.05 (3 H, s), 4.75 (1 H, broad) ppm.

trans-4-Acetoxycyclohexane-1-carboxylic acid chloride (VIII). A suspension of VII (18.6 g) in benzene (60 ml) was mixed with SOCl₂ (40 ml) and heated under reflux for 30 min. The solvent was removed *in vacuo* to give an oily VIII (20.5 g, quantitative). This was employed for the next reaction without further purification.

4-Methylpent-3-enyl 4'-acetoxycyclohexyl ketone (IX). A Grignard reagent was prepared from 4-methylpent-3-enyl bromide (20 g) and Mg (2.9 g) in ether (100 ml). Dry CdCl₂ (22 g) was added to the solution and the mixture was stirred and heated under reflux for 45 min. Ether was distilled off from the mixture and the residue was diluted with dry benzene (150 ml). To this organo-cadmium reagent, VIII (20.5 g) in benzene (50 ml) was added dropwise. After the addition, the mixture was stirred and heated under reflux for 2 hr, left to stand overnight at room temp and

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poured into ice-cooled dil H_2SO_4 . The benzene layer was separated and the aqueous layer was extracted with ether. The combined organic soln was washed with water, 5% Na_2CO_3 aq, and NaCl aq, dried (MgSO_4) and concentrated. The residue was distilled *in vacuo* to give 13.2 g (51%) of IX, bp $130\sim 150^\circ\text{C}/1.0$ mm. An analytical sample boiled at $144\sim 145^\circ\text{C}/0.6$ mm; n_D^{19} 1.4765. *Anal.* Found: C, 68.93; H, 9.02. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_3$: C, 71.39; H, 9.59%, ν_{max} 1738, 1718, 1626 (due to impurities), 1240, 1040 cm^{-1} ; δ 1.62 (3 H, s), 1.66 (3 H, s), 1.96 (3 H, s), 4.62 (1 H, broad), 5.05 (1 H, broad) ppm. The sample could not be purified by distillation alone. No attempt was made to obtain pure IX by chromatographic purification.

4-Methylpent-3-enyl 4'-hydroxycyclohexyl ketone (X). a) A soln of IX (232 g) in MeOH (480 ml) was mixed with KOH aq. (80 g in 200 ml) and the mixture was left to stand at room temp. for 2 days. After removal of MeOH *in vacuo*, the residue was diluted with water and extracted with ether. The extract was washed with water and NaCl aq, dried (MgSO_4) and concentrated. The residue was fractionally distilled *in vacuo* to give 120 g (63%) of X, bp $145\sim 150^\circ\text{C}/0.1$ mm. An analytical sample boiled at $144\sim 146^\circ\text{C}/1.0$ mm, n_D^{20} 1.4924. *Anal.* Found: C, 73.98; H, 10.24. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.24; H, 10.54%, ν_{max} ~ 3400 , 1708, 1622, 1065 cm^{-1} ; δ 1.60 (3 H, s), 1.66 (3 H, s), ~ 3.35 (1 H, broad), 3.95 (1 H, broad), 5.04 (1 H) ppm. b) A Grignard reagent prepared from 4-methylpent-3-enyl bromide (98 g) and Mg (14.5 g) in ether (400 ml) was added to a stirred and ice-cooled soln of VIII (from 94 g of VII) in ether (120 ml) containing Cu_2Cl_2 (0.4 g). The stirring was continued for 2 hr at $0\sim 5^\circ\text{C}$ and then for 3 hr at room temp. The mixture was left to stand overnight at room temp and then poured into ice-cooled dil HCl. The ether layer was separated and the aqueous layer was extracted with ether. The extract was washed with NaCl aq, dried (MgSO_4) and concentrated. The oily residue (110 g) was dissolved in MeOH (240 ml) and mixed with KOH aq (40 g in 120 ml). The mixture was left to stand overnight at room temp. Subsequent treatments as described in a) gave 32 g (30%) of X, bp $145\sim 155^\circ\text{C}/0.1$ mm.

4-Methylpent-3-enyl 4'-tetrahydropyranyloxycyclohexyl ketone (XI). A soln of X (115 g) in dry benzene (1 liter) was mixed with dihydropyran (100 ml) and *p*-TsOH (1 g) and left to stand overnight at room temp. The mixture was washed with K_2CO_3 aq and sat NaCl aq,

dried (MgSO_4) and concentrated *in vacuo* to give crude oily XI (195 g) contaminated with some dihydropyran. The IR spectrum of the oil exhibited no OH absorption.

1-(4'-Tetrahydropyranyloxycyclohexyl)-5-methylhex-4-en-1-ol (XII). A soln of XI (195 g) in 95% EtOH (600 ml) was mixed with NaBH_4 (10 g) and KOH aq (0.1 g in 5 ml). The mixture was left to stand overnight at room temp, concentrated *in vacuo*, diluted with water and extracted with ether. The extract was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated to give crude oily XII (190 g) with no carbonyl absorption in its IR spectrum.

1-(4'-Tetrahydropyranyloxycyclohexyl)-1-acetoxy-5-methylhex-4-ene (XIII). Acetic anhydride (300 ml) was added to a soln of XII (190 g) in pyridine (300 ml). The mixture was left to stand at room temp for 2 days and then concentrated *in vacuo* to give an oil (ca. 195 g) with no hydroxyl absorption in its IR spectrum.

1-(4'-Hydroxycyclohexyl)-1-acetoxy-5-methylhex-4-ene (XIV). A soln of XIII (ca. 195 g) in 95% EtOH (300 ml) was mixed with 5% HCl (170 ml). After 3 hr at room temp the mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ether soln was washed with water, NaHCO_3 aq and sat NaCl aq, dried (MgSO_4) and concentrated. The residue was distilled *in vacuo* to give 114 g (85% from X) of XIV, bp $150\sim 160^\circ\text{C}/0.08$ mm. An analytical sample boiled at $150\sim 155^\circ\text{C}/1.5$ mm, n_D^{19} 1.4848. *Anal.* Found: C, 71.40; H, 10.56. Calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_3$: C, 70.83; H, 10.30%, ν_{max} 3400, 1738, 1240, 1045 , 1015 cm^{-1} ; δ 1.60 (3 H, s), 1.66 (3 H, s), 1.98 (3 H, s), 3.35 (1 H, broad), 3.60 (1 H, broad), 4.66 (1 H, broad), 5.02 (1 H, broad) ppm.

1-(4'-Oxocyclohexyl)-1-acetoxy-5-methylhex-4-ene (XV). To a soln of XIV (110 g) in acetone (1.2 liters) was added Jones reagent (100 ml) at $0\sim 5^\circ\text{C}$ during 30 min. After 30 min MeOH was added to destroy the excess oxidant. The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ethereal soln was washed with water, NaHCO_3 aq and sat NaCl aq, dried (MgSO_4) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 81 g (74%) of XV, bp $135\sim 150^\circ\text{C}/0.08$ mm. An analytical sample boiled at $140\sim 144^\circ\text{C}/0.08$ mm, n_D^{20} 1.4775. *Anal.* Found: C, 71.71; H, 9.54. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_5$: O, 71.39; H, 9.59%, ν_{max} 1728,

1240, 1015 cm^{-1} ; δ 1.58 (3 H, s), 1.67 (3 H, s), 2.00 (3 H, s), 4.67 (1 H, broad), 5.04 (1 H, broad) ppm.

1-(4'-Cyano-4'-hydroxycyclohexyl)-1-acetoxy-5-methylhex-4-ene (XVI). To a stirred and ice-cooled soln of XV (81 g) in 95% EtOH (430 ml) powdered KCN (70 g) was added followed by AcOH (76 ml). After the addition, the mixture was stirred for 30 min at 0~5°C and then for 30 min at 40~50°C. The excess HCN was removed *in vacuo* after the addition of 2~3 drops of conc HCl. The mixture was diluted with water and extracted with ether. The ether extract was washed with dil HCl and sat NaCl aq, dried (MgSO_4) and concentrated to give 90 g of crude oily XVI, ν_{max} ~3400, 2270 (w), 1720, 1690, 1240, 1050 cm^{-1} . This was employed for the next reaction without further purification.

1-(4'-Cyanocyclohex-3'-enyl)-1-acetoxy-5-methylhex-4-ene (XVII). To an ice-cooled soln of XVI (90 g) in pyridine (360 ml) was added POCl_3 (90 g). The dark-colored mixture was left for 2 days at room temp, heated under reflux for 30 min and finally poured into ice-water containing conc HCl (600 ml). The mixture was extracted with ether. The ethereal soln was washed with dil HCl, water, NaHCO_3 aq and sat NaCl aq, dried (MgSO_4) and concentrated. The residue was distilled *in vacuo* to give 69 g (83% from XV) of XVII, bp 140~160°C/1.5 mm. An analytical sample boiled at 145°C/0.08 mm, n_D^{28} 1.4902. *Anal.* Found: C, 73.97; H, 9.13; N, 5.11. Calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$: C, 73.53; H, 8.87; N, 5.36%. ν_{max} 2200, 1742, 1648, 1605, 1240, 1015 cm^{-1} ; δ 1.55 (3 H, s), 1.65 (3 H, s), 1.98 (3 H, s), 4.70 (1 H, broad), 5.00 (1 H, broad), 6.52 (1 H, broad) ppm.

1-(4'-Carboxycyclohex-3'-enyl)-5-methylhex-4-en-1-ol (XVIII). A soln of the crude XVII (69 g) in diethylene glycol (300 ml) was mixed with KOH aq (80 g in 250 ml) and the mixture heated under reflux for 42 hr. After cooling, the mixture was diluted with water and extracted with ether to remove neutral impurities. The alkaline aqueous layer was acidified with conc HCl (170 ml) and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated to give oily crude XVIII (63 g, 99%), ν_{max} (film)~3400, ~3200~2600, 1690, 1645 cm^{-1} . This was employed for the next step without further purification.

4-Methylpent-3-enyl 4'-carboxycyclohex-3'-enyl ketone (XIX). To a soln of XVIII (63 g) in acetone (500 ml)

was added Jones reagent (60 ml) at 0~5°C. After 30 min MeOH was added to destroy the excess oxidant. The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated. The residue was distilled *in vacuo* to give 43 g (68%) of XIX, bp 190~200°C/1.5 mm. An analytical sample boiled at 165~168°C/0.08 mm, n_D^{31} 1.5080; *Anal.* Found: C, 70.88; H, 8.80. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3$: C, 71.16; H, 8.53%. ν_{max} ~3400~2600, 1690, 1640, 1290 cm^{-1} . After standing in a refrigerator it partly crystallized. The semisolid mass was triturated with pet. ether and the crystals were collected by filtration. The pure XIX weighed 8.7 g (13.8%). This was recrystallized from ether-pet. ether to give leaflets, mp 78~79°C. *Anal.* Found: C, 71.21; H, 8.47. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3$: C, 71.16; H, 8.53%. ν_{max} ~3300~2600, 1702, 1685, 1640, 1260, ~935 cm^{-1} ; δ 1.62 (3 H, s), 1.67 (3 H, s), 4.64 (1 H, broad), 5.01 (1 H, broad), 11.29 (1 H, s) ppm. The mother liquor (34 g) after removal of the crystalline XIX was dissolved in 95% EtOH (100 ml) and mixed with a soln of semicarbazide hydrochloride (30 g) and KOAc (28 g) in water (100 ml). The mixture was heated under reflux for 30 min. The separated semicarbazone was collected on a filter and washed with ether to give 13.2 g of crystals. Recrystallization from EtOH gave small prisms, mp 196~198°C. *Anal.* Found: C, 61.69; H, 7.94; N, 14.48. Calcd. for $\text{C}_{15}\text{H}_{23}\text{O}_3\text{N}_3$: C, 61.41; H, 7.90; N, 14.33%. ν_{max} 3470, ~3200~2600, 1690, 1650, 1580, 1260, ~950 cm^{-1} . The same semicarbazone was also obtained from pure XIX.

4-Methylpent-3-enyl 4'-carbomethoxycyclohex-3'-enyl ketone (XX). The crystalline XIX (8.2 g) was esterified with CH_2N_2 and the product was distilled *in vacuo* to give 8.2 g (94%) of XX. An analytical sample boiled at 150~153°C/1.8 mm, n_D^{19} 1.4950. *Anal.* Found: C, 71.93; H, 8.84. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_3$: C, 71.97; H, 8.86%. ν_{max} 1730 (sh), 1715, 1654, 1622, 1250, 1075, 1035, 915 cm^{-1} ; δ 1.58 (3 H, s), 1.63 (3 H, s), 3.63 (3 H, s), 4.98 (1 H, broad), 6.89 (1 H, broad) ppm.

4-Methylpent-3-enyl 4'-carbomethoxycyclohex-3'-enyl ketone ethylene ketal (XXI). To a soln of XX (7.0 g) in anhyd 1, 2-dichloroethane (100 ml) ethylene glycol (6 ml) and *p*-TsOH (0.1 g) were added and the mixture stirred and heated for 2 hr. During that period anhyd 1, 2-dichloroethane (ca. 300 ml) was gradually added while an equal amount of the water-containing solvent was distilled off from it. After cooling, the

soln was washed with K_2CO_3 aq, dried over K_2CO_3 and concentrated. The residue was distilled *in vacuo* to give 5.4 g (65%) of XXI, bp $150\sim 165^\circ\text{C}/0.1$ mm. An analytical sample boiled at $160\sim 165^\circ\text{C}/0.1$ mm, n_D^{20} 1.4960. *Anal.* Found: C, 69.50; H, 8.90. Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_4$: C, 69.36; H, 8.90%. ν_{max} 1718, 1655, 1250, 1080, 1042, 940, 720 cm^{-1} ; δ 1.55 (3 H, s), 1.62 (3 H, s), 3.56 (3 H, s), 3.80 (4 H, s), 4.95 (1 H, broad), 6.75 (1 H, broad) ppm.

4-Methylpent-3-enyl 4'-hydroxymethylcyclohex-3'-enyl ketone ethylene ketal (XXII). A soln of XXI (5.3 g) in ether (50 ml) was added dropwise to a suspension of LAH (1.8 g) in ether (50 ml). The mixture was stirred at room temp for 5 hr. Then the excess hydride was destroyed by the addition of EtOAc . Dilute H_2SO_4 (6 ml conc $\text{H}_2\text{SO}_4 + 50$ ml H_2O) was added to the mixture. After stirring for 10 min at room temp, the ether layer was separated and the aqueous layer was extracted with ether. The combined ethereal soln was washed with sat NaCl aq, dried (MgSO_4) and concentrated to give 4.6 g (94%) of oily XXII. An analytical sample boiled at $160\sim 162^\circ\text{C}/0.1$ mm, n_D^{19} 1.5032. *Anal.* Found: C, 72.29; H, 10.12. Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_3$: C, 72.14; H, 9.84%. ν_{max} 3360, 1680 (w), 1660 (w), 1045 cm^{-1} ; δ 1.56 (3 H, s), 1.64 (3 H, s), 3.36 (1 H, broad), 3.76 (2 H, s), 3.82 (4 H, s), 5.00 (1 H, m), 5.51 (1 H, broad) ppm.

4-Methylpent-3-enyl 4'-acetoxymethylcyclohex-3'-enyl ketone (XXIII). A soln of XXII (4.5 g) in pyridine (25 ml) was mixed with Ac_2O (25 ml) and left to stand overnight at room temp. The mixture was concentrated *in vacuo*. The residue was acidified with dil HCl and heated for 5 min on a boiling water bath. After cooling, the mixture was extracted with ether. The extract was washed with NaHCO_3 aq and sat NaCl aq, dried (MgSO_4) and concentrated to give 4.1 g (91%) of oily XXIII. An analytical sample boiled at $142\sim 145^\circ\text{C}/0.1$ mm, n_D^{20} 1.4850. *Anal.* Found: C, 72.53; H, 9.13. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_3$: C, 72.69; H, 9.15%. ν_{max} 1730, 1710, 1220, 1015 cm^{-1} ; δ 1.59 (3 H, s), 1.65 (3 H, s), 1.96 (3 H, s), 4.30 (2 H, s), 4.95 (1 H, m), 5.63 (1 H, broad s) ppm.

2-(4'-Acetoxymethylcyclohex-3'-enyl)-6-methylhepta-1, 5-diene (XXIV). To a soln of sodium methylsulfinyl methylide (from 200 mg of 50% NaH) in DMSO (25 ml) was added triphenylmethylphosphonium bromide (2.6 g) under N_2 with ice-cooling. The mixture was stirred for 10 min to yield an orange-red soln of the

Wittig reagent. A soln of XXIII (1 g) in DMSO (4 ml) was added to the reagent. The mixture was stirred for 3 hr at room temp, poured into ice-water and extracted with *n*-hexane. The extract was washed with 80% MeOH aq, dried (MgSO_4) and concentrated *in vacuo* to give 0.8 g (80%) of XXIV. An analytical sample boiled at $128\sim 130^\circ\text{C}/0.1$ mm, n_D^{20} 1.4884. *Anal.* Found: C, 77.99; H, 9.79. Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_2$: C, 77.82; H, 9.99%. ν_{max} 3070, 2920, 1742, 1645, 1430, 1370, 1220, 1015, 954, 880 cm^{-1} ; δ 1.58 (3 H, s), 1.66 (3 H, s), 1.97 (3 H, s), 4.30 (2 H, s), 4.66 (2 H, s), 5.00 (1 H, m), 5.63 (1 H, broad) ppm.

2-(4'-Hydroxymethylcyclohex-3'-enyl)-6-methylhepta-1, 5-diene (XXV). A soln of XXIV (2.9 g) in MeOH (20 ml) was mixed with KOH (1 g) in MeOH (10 ml) and left to stand overnight at room temp. The mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The extract was washed with sat NaCl aq, dried (MgSO_4) and concentrated to give 2.3 g (94%) of XXV. An analytical sample boiled at $125^\circ\text{C}/0.06$ mm, n_D^{20} 1.5030. *Anal.* Found: C, 81.20; H, 11.05. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76; H, 10.98%. ν_{max} ~ 3300 , 3080, 2900, 1640, 1430, 1370, 1050, 980, 910, 880, 820 cm^{-1} ; δ 1.58 (3 H, s), 1.65 (3 H, s), 2.01 (broad s), 3.30 (1 H, broad), 3.76 (2 H, s), 4.64 (2 H, s), 5.00 (1 H, broad), 5.53 (1 H, broad s) ppm.

2-(4'-Formylcyclohex-3'-enyl)-6-methylhepta-1, 5-diene (XXVI). To a soln of crude XXV (2.2 g) in *n*-hexane (100 ml) was added MnO_2 (12 g). The mixture was stirred under N_2 for 23 hr at room temp and then filtered. The filtrate was concentrated *in vacuo*. The residue boiled at $114\sim 115^\circ\text{C}/0.05$ mm to give 1.7 g (77%) of XXVI, n_D^{19} 1.5085. *Anal.* Found: C, 81.85; H, 9.94. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$: C, 82.51; H, 10.16%. ν_{max} 3080, 2900, 2720, 1685, 1648, 1158, 882, 765 cm^{-1} ; δ 1.60 (3 H, s), 1.66 (3 H, s), 2.05 (broad s), 4.70 (2 H, s), 5.00 (1 H, m), 6.65 (1 H, m), 9.33 (1 H, s) ppm.

2-(4'-Carbomethoxycyclohex-3'-enyl)-6-methylhepta-1, 5-diene (III). A soln of XXVI (500 mg) in MeOH (50 ml) was mixed with MnO_2 (5.75 g), NaCN (820 mg) and AcOH (0.3 ml). The mixture was stirred overnight at room temp and then filtered. The filtrate was concentrated *in vacuo*, diluted with water and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated *in vacuo* to give III (400 mg, 73%). An

analytical sample boiled at 134~136°C/0.1 mm, n_D^{20} 1.4922. *Anal.* Found: C, 77.06; H, 9.92. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74%. $\nu_{\max}$ 3070, 2910, 1715, 1640, 1425, 1370, 1295, 1240, 1190, 1075, 1030, 880 cm^{-1} ; δ 1.58 (3 H, s), 1.66 (3 H, s), 3.60 (3 H, s), 4.68 (2 H, s), 5.00 (1 H, broad), 6.85 (1 H, broad) ppm.

4-Chloro-4-methylpentyl 4'-carbomethoxycyclohex-3'-enyl ketone (XXVII). An ice-cooled soln of XX (0.3 g) in MeOH (10 ml) was saturated with dry HCl gas, left to stand for 30 min at 0~5°C and then poured into ice-water. The mixture was extracted with pet. ether. The extract was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated *in vacuo* to give 0.3 g of XXVII. $\nu_{\max}$ 1710, 1650, 1255, 1090 cm^{-1} ; δ 1.55 (6 H, s), 3.61 (3 H, s), 6.80 (1 H, broad) ppm. This could not be purified because of its instability.

2-(4'-Carbomethoxycyclohex-3'-enyl)-2, 6-dichloro-6-methylheptane (XXVIII). An ice-cooled soln of III (0.2 g) in MeOH (6 ml) was saturated with dry HCl gas, left to stand for 30 min at 0~5°C and then poured into ice-water. The mixture was extracted with pet. ether. The extract was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated *in vacuo* to give 0.2 g of XXVIII. $\nu_{\max}$ 1710, 1650, 1255, 1085, 1035 cm^{-1} ; δ 1.55 (9 H, s), 3.61 (3 H, s), 6.79

(1 H, broad) ppm. This could not be purified because of its instability.

Bioassay. Data are based on topical treatment of last instar nymphs of *Pyrrhocoris apterus*. (10 insects per assay)

Compound	Dosage (μg)			
	0.01	0.1	1.0	10.0
XX	A	A	A	NA
III	A	A	A	A+NC
XXVII	A	A	A	A+NC
XXVIII	A	A	A+NC	SN

A=Normal adults (no activity).

A+NC=Adults with nymphal cuticle on the abdomen (very little activity).

NA=Nymphal-adult intermediate (intermediate activity).

SN=Supernumerary nymphs (high activity).

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