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

A STEREOSELECTIVE SYNTHESIS OF *dl*-C_{17}-*CECROPIA* JUVENILE HORMONE

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Abstract—A stereoselective synthesis of the title compound (2) was accomplished using a coupling reaction of a C_6-unit (4) with a C_{10}-unit (8) as the key-step.

A number of publications on the stereoselective total synthesis of the *Cecropia* juvenile hormones (JH) have appeared since 1968,[2] when Corey *et al* announced the first stereoselective total synthesis of *dl*-C_{18}-*Cecropia* JH(I).[3] Here we record another stereoselective synthesis of *dl*-C_{17}-*Cecropia* JH(II) which has been reported in a preliminary form.[4,5] The key-step in the present synthesis is the coupling of a C_6-unit (4) with a C_{10}-unit (8). A synthesis of methyl *trans,trans*-farnesoate was also accomplished by a similar coupling reaction.[1] This same concept was used in an independent synthesis of *dl*-C_{18}-*Cecropia* JH(I) as reported in a preliminary communication by van Tamelen *et al.*[6]

A phenyl sulfide (4) as the C_6-unit was obtained from the bromide (3).[7] Although the C_{10}-unit (8) has previously been prepared,[8,cf 1] we developed an alternative and more efficient route. Geranyl acetate (5) was oxidized to give an aldehyde (6a) stereoselectively.[cf 9] This was treated with KOH-EtOH at $-10°$ and the resulting alcohol (6b) was converted to a tetrahydropyranyl (THP) ether (6c) in the usual manner. Its reduction yielded an alcohol (7). The over-all yield of 7 from 5 was 13%. Stork's method[10] was used for the conversion of the alcohol (7) into the corresponding bromide (8).

The coupling of the two synthons, 4 and 8, was executed by the method of Biellmann and Ducep.[11] This method was used originally in the synthesis of squalene[11] and later by van Tamelen *et al* in their JH[6] and triterpene[12] syntheses. In our case the sulfide (4) in THF was treated with n-BuLi in the presence of diazabicyclo[2.2.2]octane (DABCO) and then alkylated with the bromide (8) in THF to give the desired coupling product (9a) in 58% yield after chromatography over alumina. The THP protective group was removed and the product was purified by chromatography to give an alcohol (9b) in 88% yield. Desulfurization of this phenyl sulfide (9b) was successfully carried out with Li-EtNH_2. Prior to the addition of Li, the alcohol (9b) was converted to the corresponding lithium alkoxide by the addition of n-BuLi to a soln of 9b in EtNH_2 to avoid hydrogenolysis of the allylic OH. The crude 12-homofarnesol (10) was obtained in 33% yield after chromatography over silicic acid. This was oxidatively esterified by Corey's method[13] to give methyl 12-homofarnesoate (11) of 88% purity as checked by GLC in 34% yield. The final purification by preparative GLC afforded pure methyl 12-homofarnesoate (11) identical with an authentic sample[14] on the basis of IR, NMR, MS and GLC. This completed the stereoselective synthesis of *dl*-C_{17}-*Cecropia* juvenile hormone (2), since the conversion of 11 into 2 was well-documented.[5,14] After the completion of this work, a preliminary communication appeared, in which Grieco reported a similar synthesis of synthons 4 and 8 (Ac instead of THP).[15]

EXPERIMENTAL

All b.ps are uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded on a Jeolco 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.

3-Methylpent-2-cis-enyl phenyl sulfide (4). Thiophenol (15·7 g) was added to a soln of NaOEt in EtOH prepared from Na (3·1 g) and abs EtOH (100 ml). The mixture was stirred for 30 min at room temp and then cooled to $-15°$ by an ice-salt bath. The bromide 3 (17·5 g) was added dropwise to the stirred mixture kept below $-10°$. After the addition it was stirred for 2·5 h at $-10 \sim -5°$. Subsequently it was concentrated in *vacuo*, poured into water and extracted with ether. The ether extract was washed twice with 5% NaOH aq and then with water, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was distilled to give 15·7 g (73%) of 4, b.p. 107–110°/3mm, n_D^{25}

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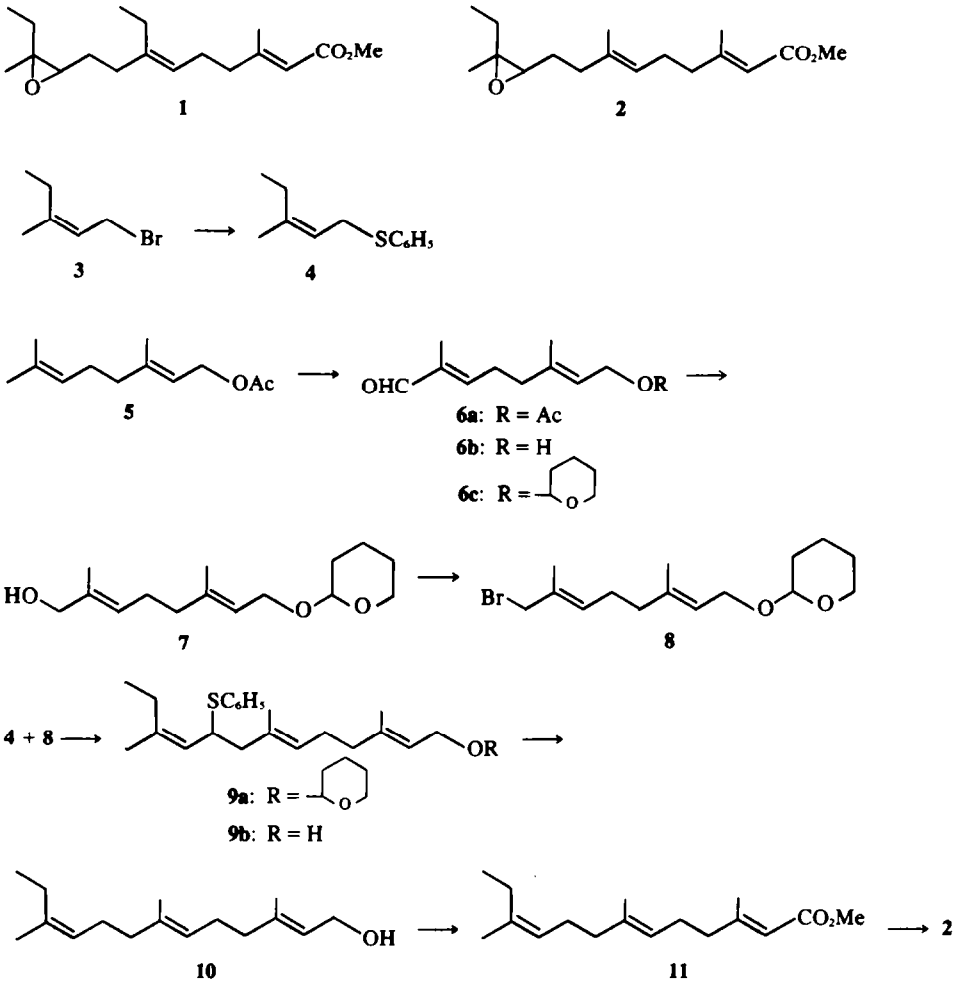

1·5545; ν_{max} 3060, 1660, 1375, 1225, 1090, 1070, 1025, 840, 735, 685 cm^{-1}; δ 0·94 (3H, t, J = 7Hz), 1·70 (3H, s), 1·99 (2H, q, J = 7Hz), 3·95 (2H, d, J = 7Hz), 5·21 (1H, t, J = 7Hz), 6·90 ~ 7·30 (5H, m) ppm. (Found: C, 75·42; H, 7·33. $C_{12}H_{14}S$ requires: C, 75·73; H, 7·41%). Higher reaction temperature caused the isomerization of the *cis*-double bond.

8 - *Acetoxy* - 2, 6 - *dimethylocta* - 2 - trans - 6 - trans - *dienal* (**6a**). SeO_2 (46 g) was added to a soln of **5** (80 g) in 95% EtOH (600 ml) and the mixture was heated under reflux for 1 h. Then it was filtered through Celite to remove Se. The filtrate was concentrated in *vacuo* to give an oil (87 g). This was dissolved in ether (1 l) and stirred vigorously with active MnO_2 (500 g) overnight at room temp. After filtration through Celite, the filtrate was concentrated *in vacuo* to give an oil (52 g). This was diluted with silicone oil (*ca* 100 g) and distilled *in vacuo* in the presence of a small amount of $CuCl_2$ (*ca* 10 mg) to give 42 g of crude **6a**. Redistillation gave 30 g (34·8%) of pure **6a**, b.p. 97–103°/0·15 mm, n_D^{17} 1·4890; ν_{max} 2700, 1730, 1680, 1640, 1360, 1220, 1020, 940 cm^{-1}; δ 1·71 (3H, s), 1·74 (3H, s), 1·95 (3H, s), 2·10–2·65 (4H, m), 4·46 (2H, d, J = 7Hz), 5·31 (1H, t, J = 7Hz), 6·43 (1H, t, J = 7Hz), 9·30 (1H, s) ppm. (Found: C, 67·26; H, 8·53. $C_{12}H_{18}O_3$ requires: C, 68·54; H, 8·63%).

8 - *Hydroxy* - 2, 6 - *dimethylocta* - 2 - trans, 6 - trans - *dienal* (**6b**). A soln of KOH (8 g) in 95% EtOH (100 ml) was added during 30 min to a stirred soln of **6a** (30 g) in 95% EtOH (100 ml) kept below − 10° by an ice-salt bath. After the addition, the mixture was stirred for 20 min at − 10° and then neutralized with dil HCl. It was diluted with water and extracted with ether. The ether extract was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 24 g (quantitative) of **6b**; ν_{max} ~ 3400, 2710, 1680, 1640, 1380, 1240, 1000, 820 cm^{-1}; δ 1·16 (3H, s), 1·70 (3H, s), 2·00–2·60 (4H, m), 3·13 (1H, s), 4·02 (2H, d, J = 7Hz), 5·35 (1H, t, J = 7Hz), 6·41 (1H, t, J = 7Hz), 9·29 (1H, s) ppm.

8 - *Tetrahydropyranyloxy* - 2, 6 - *dimethylocta* - 2 - trans, 6 - trans - *dienal* (**6a**). 2,3 - Dihydropyran (30 g) and *p*-TsOH (0·1 g) were added to a soln of the crude **6b** (24 g) in dry ether (150 ml) and the mixture was stirred for 9 h. Then it was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (34 g). This was chromatographed over Woelm neutral alumina (activity grade II–III, 300 g) to give 28 g (77%) of pure **6c**; ν_{max} 2700, 1690, 1640, 1370, 1350, 1260, 1190, 1110, 1070, 1015, 900, 860, 805 cm^{-1}; δ 1·30–1·67 (6H, m), 1·69 (3H, s), 1·71 (3H, s), 2·00–2·65 (4H, m), 3·25–4·23 (4H, m), 4·50 (1H, br. s), 5·32 (1H, t, J = 7Hz), 6·35 (1H, t, J = 7Hz),

9·30 (1H, s) ppm. (Found: C, 70·98; H, 9·71. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

8 - *Tetrahydropyranyloxy* - 2, 6 - *dimethylocta* - 2 - trans, 6 - trans - *dien* - 1 - *ol* (**7**). $NaBH_4$ (2 g) was added to a stirred soln of **6c** (28 g) in 99% EtOH (200 ml) at 0–5°. The mixture was stirred for 2 h at room temp, then poured into ice-water and extracted with ether. The ether extract was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 27 g, of an oil. This was chromatographed over neutral alumina and distilled *in vacuo* to give 14·3 g (39% from **6a**) of pure **7**, b.p. 140–143°/0·3 mm, n_D^{13} 1·4938 (another batch: n_D^{16} 1·4926); ν_{max} ~3550, 1660, 1190, 1100, 1070, 1010, 900, 860, 800 cm^{-1}; δ 1·60 (3H, s), 1·64 (3H, s), 3·83 (2H, s), 4·51 (1H, br. s), 5·25 (2H, br. t) ppm. (Found: C, 70·41; H, 9·87. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%).

8 - *Tetrahydropyranyloxy* - 2, 6 - *dimethylocta* - 2-trans, 6 - trans - *dienyl bromide* (**8**). To a soln of **7** (13·8 g) in dry ether (70 ml) and dry HMPA (70 ml) a freshly prepared n-BuLi in ether (1 eq) was added with stirring and ice-cooling. *p*-TsCl (10·7 g) was added portionwise to the stirred soln. Then LiBr (12·6 g) was added and the mixture was stirred overnight at room temp. It was poured into water and extracted with ether. The ether extract was washed with water and NaCl soln, dried ($CaCl_2$) and concentrated *in vacuo*. The residue was chromatographed over Woelm nuetral alumina of activity grade II–III. Elution with C_6H_6 gave 13·8 g (80%) of **8**, ν_{max} 1670, 1385, 1265, 1200, 1160, 1130, 1115, 1080, 1025, 905, 870, 810 cm^{-1}; δ 1·67 (3H, s), 1·73 (3H, s), 3·93 (2H, s), 4·51 (1H, br, s) 5·28 (2H, br. t) ppm. This was employed for the next step without distillation.

Tetrahydropyranyl ether of 3, 7, 11 - *trimethyl* - 9 - *phenylthiotrideca* - 2 - trans, 6 - trans, 10 - cis - *trien* - 1 - *ol* (**9a**). A soln of **4** (10·3 g) and DABCO (6·0 g) in dry THF (50 ml) was stirred and cooled by an ice-salt bath. To this soln at −15°, an exactly equivalent amount of freshly prepared n-BuLi in ether was added dropwise under N_2? The soln turned yellow. It was stirred for 40 min at −10–−15° to complete the formation of the carbanion. A soln of **8** (8·5 g) in dry THF (15 ml) was added dropwise at −10° to the stirred soln and the stirring was continued overnight at room temp. All the operations were carried out under N_2. The mixture was poured into water and extracted with ether. The ether extract was washed with water and NaCl soln, dried ($CaCl_2$) and concentrated *in vacuo*. The residue (17 g) was chromatographed over Woelm neutral alumina (activity grade II–III, 450 g) to give 6·63 g (58%) of **9a**, ν_{max} 3060, 1670, 1580, 1380, 1265, 1140, 1120, 1080, 1030, 910, 870, 750, 690 cm^{-1}; δ 0·78 (3H, t, J = 7·5Hz), 1·58 (s), 1·63 (s), 4·51 (1H, br), 4·80–5·48 (3H, m), 7·0–7·40 (5H, m) ppm. (Found: C, 75·25; H, 9·24. $C_{27}H_{40}O_2S$ requires: C, 75·65; H, 9·36%).

3, 7, 11 - *Trimethyl* - 9 - *phenylthiotrideca* - 2 - trans, 6 - trans - 10 - cis - *trien* - 1 - *ol* (**9b**). A soln of **9a** (6·6 g) and *p*-TsOH (0·1 g) in MeOH (100 ml) was left to stand overnight at room temp. Then it was poured into water and extracted with ether. The ether extract was washed with $NaHCO_3$ soln, water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 5·7 g of an oil. This was chromatographed over Woelm neutral alumina (activity grade II–III, 100 g) to give 4·7 g (88%) of **9b**, ν_{max} ~3320, 3060, 1670, 1580, 1380, 1000, 850, 750, 690 cm^{-1}; δ 0·77 (3H, t, J = 7·5Hz), 1·23 (1H, s, –OH), 1·58 (s), 1·62 (s), 1·90–2·35 (m), 3·70–4·10 (3H, m), 4·80–5·20 (2H, m), 5·33 (1H, t, J = 7Hz), 7·0–7·40 (5H, m) ppm. (Found: C, 76·79; H, 9·24. $C_{22}H_{32}OS$ requires: C, 76·69; H, 9·36%).

3, 7, 11 - *Trimethyltrideca* - 2 - trans, - 6 - trans, 10 - cis - *trien* - 1 - *ol* (12 - Homofarnesol, **10**). A soln of **9b** (4·1 g) in dry $EtNH_2$ (60 ml) was stirred and cooled by a dry-ice-acetone bath to −30°. An equivalent amount of freshly prepared n-BuLi in ether was added dropwise to the soln. Then finely cut Li (100 mg) was added in one portion and the resulting blue soln was stirred for 2 h at −20°. MeOH was slowly added to destroy excess Li. Then the soln was poured into water and extracted with ether. The ether extract was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil (2·1 g) was chromatographed over sliicic acid (Mallinckrodt, 100 g) to give 920 mg (33%) of crude **10**, ν_{max} ~3320, 1670, 1440, 1380 cm^{-1}; δ 0·94 (t, J = 7Hz), 1·50–1·70 (d), 1·80–2·30 (m), 3·99 (d, J = 6Hz), 5·0 (br. d), 5·31 (t, J = 7·0Hz) ppm. This crude alcohol was employed for the next step without further purification, for our experience in the synthesis of methyl *trans,trans*-farnesoate[1] made us to believe that purification in a later stage would be more effective. This crude **10** presumably contained a double bond position isomer with a double bond at C-9,10.[cf.1]

Methyl 3, 7, 11 - *trimethyltrideca* - 2 - trans, - 6 - trans, 10 - cis - *trienoate* (Methyl 12-homofarnesoate, **11**). Active MnO_2 (6·5 g) was added to a soln of **10** (920 mg) in n-hexane (50 ml) and the mixture was stirred for 5 h at 0–5°. Then it was filtered through Celite and the filtrate was concentrated *in vacuo* to give a crude aldehyde, ν_{max} 2780, 1680, 1640, 1380, 1200, 1120 cm^{-1}. This was dissolved in MeOH (20 ml) and mixed with active MnO_2 (4·5 g), NaCN (610 mg) and AcOH (230 mg). The mixture was vigorously stirred overnight at room temp. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether. The ether soln was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (570 mg) was chromatographed over silicic acid (Mallinckrodt, 25 g) to give 357 mg (34%) of **11**. An analytical GLC revealed that this contained 88% of **11** together with 12% of a by-product. GLC: Rt 6·0 min (12%), 8·8 min (88%, **11**), Column, 5% LAC 2R 446, 1·5 m × 3 mm i.d. at 180°, Carrier gas, N_2, 1·2 kg/cm^2. Preparative GLC yielded 39 mg of pure **11** from 350 mg of the crude material (Column, PEG 20M, 20% on Celite 545, 10 ft × 3/8 in at 220°, Carrier gas, N_2, 30 kg/cm^2). ν_{max} 1725, 1650, 1380, 1360, 1220, 1140, 1020, 860 cm^{-1}; δ 0·93 (3H, t, J = 7Hz), 1·56 (3H, s), 1·61 (3H, s), 2·11 (3H, s), 3·58 (3H, s), 5·00 (2H, br), 5·54 (1H, br. s) ppm; MS m/e 264·2080 (M^+, $C_{17}H_{28}O_2$ requires 264·390). The spectral data were identical with those of an authentic sample.[14] The identity was also proved by GLC exhibiting a single peak upon co-injection.

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