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SIMPLE SYNTHESIS OF SEX PHEROMONES OF CODLING MOTH AND RED BOLLWORM MOTH BY THE COUPLING OF GRIGNARD REAGENTS WITH ALLYLIC HALIDES[a]

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Abstract—The coupling of Grignard reagents with allylic halides was employed for the synthesis of diolefinic pheromones of the codling moth (dodeca-8-*trans*, 10-*trans*-dien-1-ol, **1**) and the red bollworm moth (dodeca-9-*trans*, 11-dien-1-yl acetate, **8**).

The conventional procedure for synthesis of olefinic pheromones mainly depends on the Wittig reaction or on reduction of acetylenes.[1]† However, the steric course of the former is usually uncertain resulting in a mixture of geometrical isomers. Although the latter procedure is generally useful for the stereoselective synthesis of disubstituted olefins, it cannot be used for the preparation of a *trans*-conjugated diene from an enyne.

This prompted us to explore the possibility of employing the Grignard coupling ($A + B \rightarrow C$) for the synthesis of pheromones with *trans*-conjugated diene system (C). The coupling of Grignard reagents with allylic halides was previously achieved in two fashions. One employed transition metal catalysts,[2] while the other employed HMPA as a co-solvent.[3] This latter method seemed preferable, for it was stated to proceed without allylic rearrangement.[3] The success of this procedure depends on the ease of effective separation of C from possible by-products (*cf* Ref 2) and on the degree of retention of the double bond geometry of the starting dienyl halides **2**. These points will be discussed in the following two examples.

Synthesis of the codling moth pheromone. The codling moth, *Laspeyresia* (*Carpocapsa*) *pomonella*, is a notorious pest of apple orchards. Its sex pheromone produced by the virgin female was isolated in 1969 by McDonough *et al.*[4] Later Roelofs *et al.* proposed its structure to be dodeca-8-*trans*, 10-*trans*-dien-1-ol (**1**)[5]. This was soon verified by a synthesis.[6] This Zoëcon synthesis was based on $C_7 + C_5$ principle, starting from crotonaldehyde (C_4 unit), bromocyclopropane (C_3 unit) and tetrahydropyran (C_5 unit).

The present synthesis was based on $C_6 + C_6$ principle employing readily available sorbic acid (**2**) and hexamethylene glycol as starting materials. LAH reduction of sorbic acid (**2**) gave sorbyl alcohol (**3**).[7] This was treated with PBr_3 to give sorbyl bromide (**4**).‡ Another synthon, 6-bromohexan-1-ol tetrahydropyranyl ether (**6**), was prepared from hexamethylene glycol in the usual manner *via* the bromohydrin (**5**). A Grignard reagnet prepared from **6** and Mg in THF was added to a THF-HMPA soln of **4**. The crude product (**7**) was treated with *p*-TsOH-MeOH to give a crude oily pheromone in 65% yield from **4**. This was dissolved in light petroleum and cooled to yield crystals of the pure pheromone (**1**), m.p. 29–30°. Although the yield of the pure crystalline product was rather low and at best a half of the amount of the crude oil, the purification was readily achieved to yield only the *trans*, *trans*-isomer (**1**). The product exhibited entirely identical IR, NMR and GLC data with those of an authentic sample supplied by Dr. C. A. Henrick.

The above synthesis was simpler than the previous one.[6]§ The success was due to the fact that the crystalline product (**1**) was easily separable from oily impurities which were not further examined. The correct geometry of the starting material (**4**) was retained in the final product (**1**).

Synthesis of the major sex pheromone of the red bollworm moth. The red bollworm moth is a major

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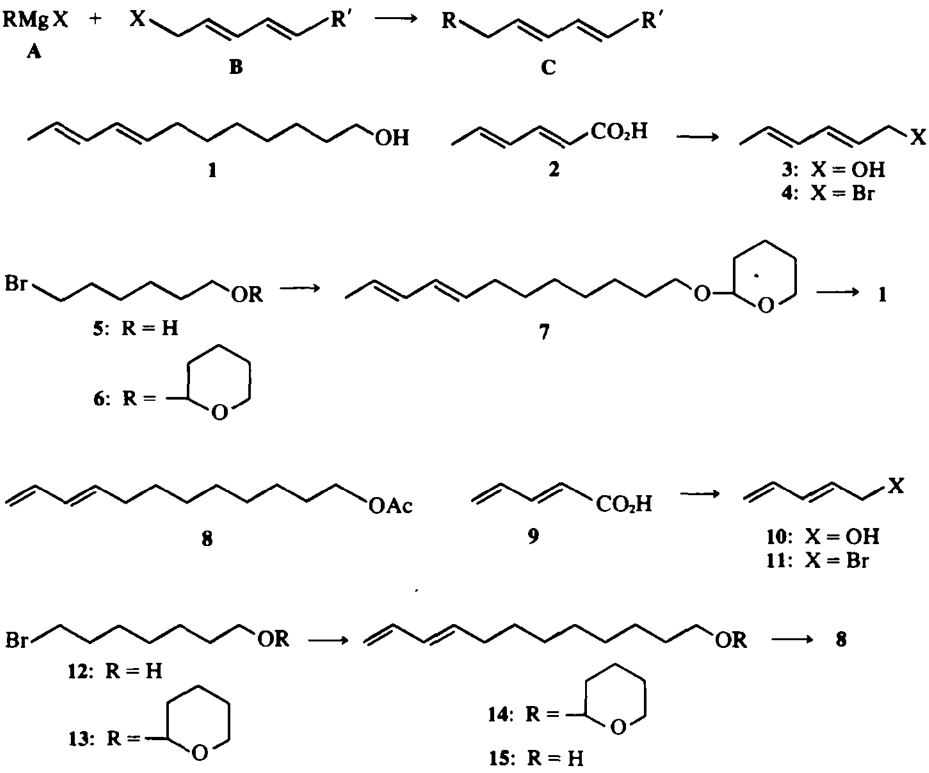
[a] Pheromone Synthesis—II. Part I, K. Mori, *Tetrahedron* **30** (1974). To be published.

† Other available methods include the molecular rearrangements such as the Carroll or Claisen reactions and application of organometallic chemistry such as metal π-allyl complex.

‡ 2-Bromohexa-3,5-diene was the by-product generated by the allylic rearrangement.

§ Dr. J. B. Siddall of Zoëcon Corporation kindly informed us that they also prepared **1** by the same $C_6 + C_6$ route (November 30, 1973).



cotton pest in south-eastern Africa. The most potent of the sex pheromones produced by the virgin female was shown to be dodeca-9-*trans*, 11-dien-1-yl acetate (**8**) by Nesbitt *et al.*[8] Later they synthesized it by the Wittig reaction between 9-oxonon-1-yl acetate and a phosphorane derived from allyl triphenylphosphonium bromide.[9]

Our synthesis was based on $C_5 + C_7$ principle employing pentadienoic acid (**9**) and heptamethylene gylcol as starting materials. Penta-2-*trans*, 4-dienoic acid (**9**)[10] was reduced with LAH to give penta-2-*trans*, 4-dien-1-ol (**10**). This was converted to the corresponding bromide (**11**). Another synthon 7-bromoheptan-1-ol tetrahydropyranyl ether (**13**),[11] was prepared from heptamethylene glycol *via* the bromohydrin (**12**). Penta-2-*trans*, 4-dienyl bromide (**11**) in THF-HMPA was reacted with a Grignard reagent prepared from **13** and Mg in THF. The crude product (**14**) was treated with *p*-TsOH-MeOH to give a crude alcohol in 55% yield from **11**. This was dissolved in light petroleum and cooled in a Dry Ice-acetone bath. The desired alcohol (**15**) crystallized and was collected on a pre-cooled filter. Unfortunately this product was an oil at room temperature (13–14°) and was very difficult to be purified by recrystallization. The yield of the fairly purified alcohol (**15**) was 20 ~ 30% of the amount of the crude product. Conventional acetylation of **15** afforded the pheromone (**8**) as an oil. This was kindly analyzed by Dr. Nesbitt and shown to be of 85% purity with 15% of 9-*cis*-isomer and two very small impurities. The IR and mass spectra of our material was compared with those of Dr. Nesbitt's and shown to be very similar. The NMR spectrum of ours was also in good accord with the structure **8**.

Despite the simplicity of the synthetic scheme, the difficulty in obtaining pure coupling product was so great in this case that the present synthesis of **8** offered little improvement over the Nesbitt synthesis[8] which could yield 80% of 9-*trans* and 20% of 9-*cis* isomers by the Wittig reaction.

In conclusion the Grignard compling is a convenient method for the preparation of insect pheromones. In a certain case it is superior to other methods, while in another case only moderately successful. None the less it is worth while to add this reaction to the list of useful methods in pheromone synthesis.

EXPERIMENTAL

All b.ps and m.p. were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 or 100 MHz with TMS as an internal standard. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

Hexa-2-trans, 4-trans-*dienyl bromide* (*sorbyl bromide*, **4**). PBr_3 (15·0 g) was added during 30 min to a stirred and cooled soln of **3** (10·0 g) in dry ether (100 ml) at −5 ~ 0°. The stirring was continued for 1 h at −10 ~ −5°. The mixture was poured into ice-water and extracted with ether. The extract was washed with H_2O, sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was fractionally distilled *in vacuo* to give 5·6 g (34%) of pure **4**, b.p. 60 ~ 61°/12 mm, n_D^{15} 1·5443; ν_{max} 3020 (m), 2960 (m), 2920 (m), 2840 (m), 1660 (s), 1440 (m), 1380 (w), 1340 (w), 1305 (vw), 1250 (vw), 1205 (vs), 1180 (w), 1120 (w), 1050 (w), 985 (vs), 930 (w), 775 (w) cm^{-1}; δ (60 MHz, CCl_4) 1·76 (3H, d, J = 6 Hz), 3·90 (2H, d, J = 7 Hz), ~5·0– ~6·4 (4H, m); MS: *m/e* 162, 160 (M^+), 81, 79, 53, 41, 39. (Found: C, 44·90; H, 5·33. C_6H_9Br requires: C, 44·74; H, 5·63%).

Dodeca-8-trans, 10-trans-*dien*-1-*ol* (**1**). A small portion of a soln of **6** (15·9 g) in THF (20 ml) was added to a stirred suspension of Mg (1·5 g) in THF (15 ml). A small amount of I_2 was added to start the reaction. Then the rest of **6** was added slowly during 30 min. The formation of the Grignard reagent was completed by stirring under N_2 for 1·5 h at 40 ~ 45°. This Grignard soln was added during 30 min to a stirred and ice-cooled soln of **4** (8·4 g) in THF (13 ml) and HMPA (12 ml) at 0 ~ 10° under N_2. The mixture was left to stand overnight at room temp, poured into ice-water and extracted with ether. The ether extract was washed with H_2O and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in MeOH (200 ml) containing *p*-TsOH (0·4 g). The mixture was heated for 1 h at 50 ~ 60°, made alkaline with K_2CO_3 and concentrated *in vacuo*. Subsequently it was diluted with H_2O and extracted with ether. The ether extract was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 6·2 g (65%) of crude **1**. This solidified when cooled. Recrystallization from light petroleum gave 2·7 g (28%) of needles, m.p. 29 ~ 30°. ν_{max} 3320 (m), 3020 (m), 2920 (s), 2830 (s), 1630 (w), 1440 (m), 1380 (m), 1055 (m), 985 (s), 920 (w) cm^{-1}; ν_{max} (nujol) 3300 (m), 3020 (m), 2920 (s), 2900 (s), 2850 (s), 1630 (w), 1490 (m), 1480 (m), 1460 (m), 1390 (w), 1380 (w), 1350 (w) 1330 (w), 1240 (w), 1170 (vw), 1060 (m), 1055 (m), 1030 (w), 990 (s), 930 (w), 785 (w), 770 (w), 730 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1·34 (10H, br), 1·53 (1H, s, –OH), 1·74 (3H, d, J = 6 Hz), 2·05 (2H, br. d), 3·63 (2H, t, J = 7 Hz), ~5·35– ~6·20 (4H, m; 5·40, 5·47, 5·53, 5·61, 5·68, 5·74, 5·90, 5·95, 6·07, 6·10); MS: *m/e* 182 (M^+), 164, 82, 81, 79, 69, 68, 67, 55, 53, 41, 31; GLC (5% LAC-2R-446 Column, 1·5 m × 3 mm i.d. at 150°; Carrier gas N_2, 0·85 kg/cm^2): Rt 10·6 min. (Found: C, 78·89; H, 12·00. $C_{12}H_{22}O$ requires: C, 79·06; H, 12·16%). The spectral data were identical with those of an authentic sample. GLC co-injection experiment by Dr. C. A. Henrick with 3% OV-17 at 140° also proved the identity.

Penta-2-trans, 4-*dien*-1-*ol* (**10**). This was prepared in the same manner as described for sorbyl alcohol[7] starting from **9**, m.p. 72°, δ (60 MHz, CCl_4) ~5·40– ~7·56 (Complex 5H m, 5·40, 5·45, 5·48, 5·59, 5·75, 6·00, 6·18, 6·35, 6·46, 6·50, 6·62, 6·80, 7·12, 7·30, 7·38, 7·56), 12·35 (1H, s). The alcohol (**10**) showed the following properties: b.p. 86 ~ 88°/66 mm, n_D^{15} 1·4815; ν_{max} ~ 3300 (vs), 3080 (m), 3035 (m), 3000 (m), 2970 (m), 2920 (s), 2850 (s), 1810 (w), 1660 (m), 1605 (s), 1420 (m), 1365 (m), 1310 (m), 1275 (w), 1225 (m), 1170 (m), 1090 (vs), 1005 (vs), 970 (s), 955 (s), 905 (vs), 810 (w) cm^{-1}; δ (60 MHz, CCl_4) 4·02 (2H, d, J = 6 Hz), ~4·90– ~6·60 (5H, complex m). (Found: C, 70·85; H, 9·62. C_5H_8O requires: C, 71·39; H, 9·59%).

Penta-2-trans, 4-*dienyl bromide* (**11**). PBr_3 (5·5 ml) was added to a stirred soln of **10** (8·4 g) in dry ether (100 ml) at 0 ~ 5° under N_2. The mixture was stirred for 1 h at 5 ~ 10°, poured into ice-water and extracted with ether. The ether soln was washed with H_2O, sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 9·7 g (71%) of **11**, b.p. 54 ~ 55°/34 mm, n_D^{13} 1·5442; ν_{max} 3080 (w), 3030 (w), 3005 (w), 2960 (w), 1825 (w), 1640 (w), 1600 (m), 1440 (w), 1420 (w), 1300 (w), 1210 (s), 1115 (w), 1065 (w), 1005 (s), 950 (m), 915 (s), 875 (w), 835 (w) cm^{-1}; δ (60 MHz, CCl_4) 3·95 (2H, d, J = 6 Hz), ~4·90– ~6·70 (5H, complex m). (Found: C, 39·91; H, 4·82. C_5H_8Br requires: C, 40·56; H, 5·45%).

7-*Bromoheptan*-1-*ol* (**12**). A mixture of heptane-1,7-diol (10 g), 48% HBr (50 ml) and H_2O (15 ml) was kept at 70 ~ 80° and extracted continuously with toluene for 16 h in the same manner as described for the preparation of 6-chlorohexan-1-ol.[12] The toluene soln was concentrated and the residue was distilled to give 10 g (70%) of **12**, b.p. 111 ~ 112°/4 mm, n_D^{12} 1·4802; ν_{max} ~ 3300 (s), 2920 (s), 2840 (s), 1460 (m), 1440 (m), 1250 (m), 1050 (s), 730 (m) cm^{-1}. (Found: C, 43·61; H, 7·82. $C_7H_{15}OBr$ requires: C, 43·09; H, 7·75%).

7-*Bromoheptan*-1-*ol tetrahydropyranyl ether* (**13**). *p*-TsOH (0·1 g) was added to a soln of **12** (10 g) and dihydropyran (7 g) in dry ether (50 ml) and the mixture was kept at 20 ~ 30° for 2 h. Then it was washed with K_2CO_3 aq, dried (K_2CO_3) and concentrated *in vacuo* to give 14 g (97%) of **13**, ν_{max} 2920 (s), 2840 (s), 1135 (s), 1120 (s), 1080 (s), 1030 (s), 980 (m), 900 (m), 870 (m), 815 (m) cm^{-1}. This was employed for th next step without further purification.

Dodeca-9-trans, 11-*dien*-1-*ol* (**15**). A Grignard reagent was prepared from **13** (14 g) and Mg (1·4 g) in dry THF (35 ml) under N_2. This was added to a stirred and cooled soln of **11** (9·0 g) in THF (35 ml)-HMPA (40 ml) at – 10 ~ 0° during 30 min under N_2. The mixture was left to stand at room temp (10°) for 16 h. Subsequently it was poured into ice-water and extracted with ether. The extract was washed with H_2O, and sat NaCl aq, dried (K_2CO_3) and concentrated *in vacuo*. The residue (**14**, *ca* 20 g) was dissolved in MeOH (200 ml) containing *p*-TsOH (0·3 g). The soln was heated at 35 ~ 45° for 2 h, made alkaline with K_2CO_3 and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with ether. The ether soln was washed with sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The remaining oil was distilled to give 5·0 g (55%) of crude **15**, b.p. 95 ~ 110°/0·1 mm. This was dissolved in a small amount of light petroleum and cooled in a Dry Ice-acetone bath to yield needles of pure **15**. This was collected on a pre-cooled filter. It was an oil at room temp (13 ~ 14°) and distilled to give 1·3 g of fairly pure **15**, b.p. 111·5 ~ 112·5·/0·3 mm, n_D^{14} 1·4788; ν_{max} ~ 3300 (s), 3080 (m), 3030 (m), 3005 (m), 2920 (s), 2850 (s), 1800 (w), 1650 (m), 1605 (m), 1470 (m), 1445 (m), 1430 (m), 1380 (m), 1360 (m), 1310 (w), 1060 (s), 1000 (s), 950 (m), 895 (s), 730 (m) cm^{-1}; δ (100 MHz, CCl_4) 1·1 ~ 1·7 (12 H), 2·01 (2H, t, J = 6 Hz), 3·49 (2H, t, J = 6 Hz), 3·96 (1H, s), 4·80–6·40 (5H, complex m, 4·85, 4·92, 4·94, 5·00, 5·07, 5·09, 5·45, 5·51, 5·60, 5·67, 5·73, 5·83, 5·94, 6·03, 6·06, 6·14, 6·21, 6·23, 6·30, 6·40); GLC (SE-30, 2 m, 70° → 170°/2° per min progr.; Carrier gas He, 60 ml/min) Rt 53 min (10%) 65·2 min (90%). (Found: C, 78·57; H, 11·80. $C_{12}H_{22}O$ requires: C, 79·06; H, 12·16%).

Dodeca-9-trans, 11-*dien*-1-*yl acetate* (**8**). Ac_2O (3 ml) was added to a soln of **15** (1·0 g) in dry C_5H_5N (3 ml). The soln was left to stand overnight at room temp, poured into H_2O and extracted with ether. The extract was washed with dil HCl, sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1·1 g (90%) of **8**, b.p. 110°/0°3 mm, n_D^{11} 1·4637; ν_{max} 3080 (w), 3030 (sh), 3000 (sh), 2920 (vs), 2840 (vs), 1740 (vs), 1650 (w), 1605 (w), 1470 (m), 1440 (m), 1395 (m), 1370 (s), 1250 (vs), 1035 (s), 1000 (s), 950 (m), 895 (m), 730 (w) cm^{-1}; δ (100 MHz, CDCl$_3$) 1·2 ~ 1·8 (12H, m, 1·32), 2·02 (3H, s), 2·0 ~ 2·2 (2H), 4·06 (3H, t, J-6 Hz), 4·85 ~ 6·50 (5H, complex m, 4·85, 4·99, 5·14, 5·15, 5·55, 5·60, 5·70, 5·75, 5·81, 5·92, 6·02, 6·12, 6·15, 6·23, 6·30, 6·32, 6·39, 6·50); MS: *m/e* 224 (M$^+$), 182, 164, 141, 135, 121, 107, 96, 81, 80, 79, 68, 67, 55, 54; GLC (Carbowax 20M, 120° → 180°/4° per min progr; Carrier gas N$_2$, 65 psi): Rt 8·4 min (4%, impurity), 11·4 min (86%, **8**), 11·8 min (10%, impurity); GLC (SE-30, 2 m, 120° → 190°/2° per min progr; Carrier gas He, 60 ml/min): Rt 35·8 min (~ 10%, impurity), 38·0 min (~4% impurity), 45·4 min (~85%, **8**). Dr. B. F. Nesbitt kindly informed us in his letter of February 28, 1974, that this material was of 85:15 *trans*:*cis* isomer content by their method of analysis.[8,9] (Found: C, 74·18; H, 10·21. $C_{14}H_{24}O_2$ requires: C, 74·95; H, 10·78%).

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