Tetrahedron. Vol. 31, pp. 1846 to 1848. Pergamon Press 1975. Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF THE PINK BOLLWORM SEX PHEROMONE, (*Z, Z*)-7,11-HEXADECADIENYL ACETATE AND ITS (*Z, E*)-ISOMER

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(*Received in Japan* 21 *December* 1974; *Received in the UK for publication* 10 *April* 1975)

Abstract—Two components of the sex pheromone of the pink bollworm moth, (*Z, Z*)-7,11-hexadecadienyl acetate and its (*Z, E*)-isomer, were synthesized employing the Grignard coupling reaction as a key step.

In 1966 Jones *et al.* claimed that the pink bollworm moth, *Pectinophora gossypiella* Saunders, uses (*E*)-10-propyl-5,9-tridecadienyl acetate (propylure) as its female sex pheromone after isolating 1·5 mg of the pheromone from 850,000 virgin female moths.[1] Following this a number of syntheses of propylure were reported, some of them being methodologically unique.[2–4] The challenge of Eiter *et al.*, whose synthetic propylure was biologically inactive,[5] was especially noteworthy, and led to considerable confusion concerning the validity of Jones's claim.

Hummel *et al.* have recently settled this problem by identifying the true sex pheromone as a mixture of (*Z, Z*)- and (*Z, E*)-isomers of 7,11-hexadecadienyl acetate (**1** and **2**).[6] Hummel's synthetic mixture of these two isomers in a 1 : 1 ratio (gossyplure) was highly attractive to male pink bollworm moths. The same conclusion was later reported by Bierl *et al.*[7]

We became interested in the synthesis of this pheromone by the Grignard coupling reaction (**A** + **B** → **C**).[8] Herein we describe in detail a stereoselective synthesis of **1** and **2** employing the coupling of propargyl magnesium bromide (**3**) with halides as the key reaction.[9]

The first synthon, 1-bromo-2-heptyne (**5**), was prepared from 2-heptyn-1-ol (**4**) by treatment with PBr$_3$.[10] The coupling of **5** with propargyl magnesium bromide (**3**), the second synthon, in THF gave a diyne (**6**) in 79% yield. Alkylation (n-BuLi/THF-HMPA)[11] of **6** with the third synthon, 6-bromohexan-1-ol tetrahydropyranyl (THP) ether, gave **7**. The diynol (**8**) was obtained by removal of the THP protecting group. This was hydrogenated over P-2 nickel in the presence of ethylene diamine[12] to give a (*Z, Z*)-dienol (**9**). Acetylation of **9** afforded (*Z, Z*)-7,11-hexadecadienyl acetate (**1**), one component of the pheromone, in 32% over-all yield from the bromide (**5**). The expected (*Z, Z*)-geometry of the product was supported by the absence of an absorption band at $970\,cm^{-1}$ in its IR spectrum.

The (*Z, E*)-isomer (**2**) was synthesized as follows. 2-Heptyn-1-ol (**4**) was reduced with LAH to give (E)-2-hepten-1-ol (**10**).[13] The corresponding bromide (**11**) was treated with propargyl magnesium bromide (**3**) in THF to give an enyne (**12**) in 63% yield. Alkylation of **12** with 6-bromohexan-1-ol THP ether gave **13**. This was converted to the corresponding enynol (**14**), whose hydrogenation over P-2 nickel gave the dienol (**15**). Acetylation of **15** yielded (*Z, E*)-7,11-hexadecadienyl acetate (**2**) in 47% over-all yield from the bromide (**11**). The (*Z, E*)-geometry of the product was supported by the presence of an absorption band at $970\,cm^{-1}$ in its IR spectrum.

The stereochemical homogeneity of our samples was proved by GLC analysis with a 3% PDEAS column. Thus our (*Z, Z*)-pheromone (**1**) was 94·5% pure, while the (*Z, E*)-isomer (**2**) was of 96·3% purity with no contamination of stereoisomers. The impurities were compounds with shorter retention times. On GLC analysis our materials were indistinguishable from authentic samples synthesized by Zoëcon Corporation. It should be added that the two isomers could not be separated by the conventional GLC analysis with OV-17 or LAC-2R-446 columns. However, the separation was possible by means of TLC employing SiO$_2$–AgNO$_3$. This TLC analysis also confirmed the stereochemical homogeneity of our samples. Although the IR spectra of **1** and **2** were definitely different, the NMR spectra were almost indistinguishable, only very small differences being observable in the olefinic region. Even in the presence of Eu(fod)$_3$, the NMR spectra of **9** and **15** were very similar except for small but distinct differences in the olefinic region.

Bioassay of our materials at a 1 : 1 ratio of the two isomers was kindly carried out by Prof. H. H. Shorey.[14] Our gossyplure was highly attractive to males of pink bollworm moth, being equally as effective as Prof. Shorey's standard formulations[6] which are known to be of high potency.

The simplicity and high over-all yield of the present stereoselective synthesis renders it an effective preparative method for the pink bollworm sex pheromone,[15] while another reported synthesis[7] suffers from rather low stereoselectivity.

EXPERIMENTAL

All b.ps are uncorrected.

1,5-Decadiyne (**6**). A Grignard reagent (**3**) was prepared from propargyl bromide (18 g), Mg (3 g) and HgCl$_2$ (0·2 g) in dry THF (40 ml). Crude **5** (15·3 g, employed without distillation) was slowly added to the stirred and ice-cooled **3**. The mixture was stirred overnight at room temp. and then heated under reflux for 1 hr. After cooling, the mixture was poured into ice-water and extracted with ether. The ether soln was washed with sat NaCl, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 9·48 g (79%) of crude **6**, b.p. 75–77°/20 mm, containing a small amount of allenic impurities. Although this was pure enough to be used for the next step, a portion of it was purified as follows. The crude **6** (3 g) was dissolved in EtOH (5 ml). To this was added slowly a soln of AgNO$_3$ (4·1 g in 6 ml H$_2$O). The solid ppt was washed with H$_2$O and EtOH. Then a soln of NaCN (5 g in 15 ml H$_2$O) was added to the solid and the mixture was heated under reflux for 3 hr. After cooling, it was extracted with ether. The ether soln was washed with sat NaCl soln, dried

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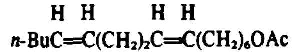
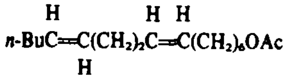


$n\text{-Bu}\overset{H}{C}{=}\overset{H}{C}(CH_2)_2\overset{H}{C}{=}\overset{H}{C}(CH_2)_6OAc$

1



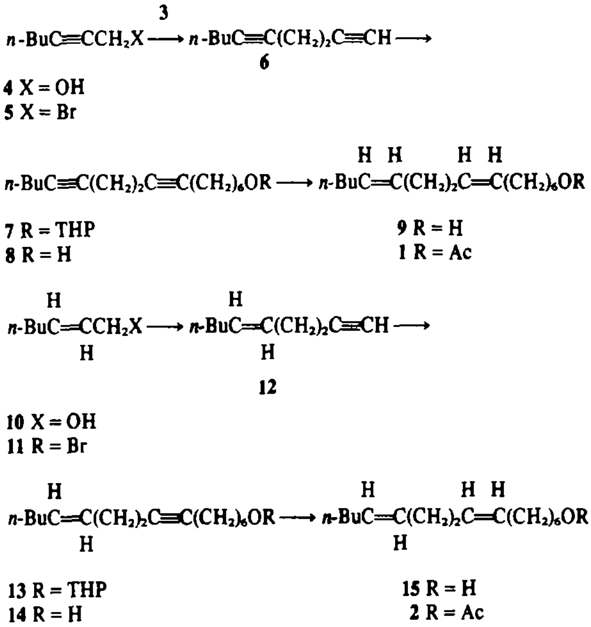
$n\text{-Bu}\overset{H}{C}{=}\underset{H}{C}(CH_2)_2\overset{H}{C}{=}\overset{H}{C}(CH_2)_6OAc$

2

$HC\equiv CCH_2MgBr$

3

$$\underset{A}{RMgX} + \underset{B}{R'X} \longrightarrow \underset{C}{R-R'}$$



$n\text{-BuC}\equiv CCH_2X \xrightarrow{3} n\text{-BuC}\equiv C(CH_2)_2C\equiv CH \longrightarrow$

6

4 X = OH
5 X = Br

$n\text{-BuC}\equiv C(CH_2)_2C\equiv C(CH_2)_6OR \longrightarrow n\text{-Bu}\overset{H}{C}{=}\overset{H}{C}(CH_2)_2\overset{H}{C}{=}\overset{H}{C}(CH_2)_6OR$

7 R = THP
8 R = H

9 R = H
1 R = Ac

$n\text{-Bu}\overset{H}{C}{=}\underset{H}{C}CH_2X \longrightarrow n\text{-Bu}\overset{H}{C}{=}\underset{H}{C}(CH_2)_2C\equiv CH \longrightarrow$

12

10 X = OH
11 R = Br

$n\text{-Bu}\overset{H}{C}{=}\underset{H}{C}(CH_2)_2C\equiv C(CH_2)_6OR \longrightarrow n\text{-Bu}\overset{H}{C}{=}\underset{H}{C}(CH_2)_2\overset{H}{C}{=}\overset{H}{C}(CH_2)_6OR$

13 R = THP
14 R = H

15 R = H
2 R = Ac

($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1·75 g (58% recovery) of pure **6**, b.p. 77–78°/20 mm, n_D^{15} 1·4583; ν_{max} (film) 3288, 2928, 2852, 2120, 1418, 1342, 1262 cm^{-1}; δ (60 MHz, CCl_4) 0·91 (3H, t, J = 6 Hz), 1·20–1·60 (4H, m), 1·84 (1H, m), 2·0–2·2 (2H), 2·32 (4H); GLC (1·5% OV-17, 1 m, at 50°; Carrier gas N_2, 0·35 kg/cm^2) R_t 5·2 min. (Found: C, 88·42; H, 10·21. $C_{10}H_{14}$ requires: C, 89·49; H, 10·51%).

7,11-*Hexadecadiyn*-1-*ol tetrahydropyranyl ether* (**7**). A soln of n-BuLi (3·8 g in n-hexane 40 ml) was added to a stirred and ice-cooled soln of crude **6** (7 g) in dry THF (50 ml). The mixture was stirred for 15 min at room temp. To this soln was added a soln of 6-bromohexan-1-ol THP ether (28 g) in dry HMPA (80 ml) with ice-cooling and stirring. After 1 hr, the mixture was poured into ice-water and extracted with ether. The ether soln was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 12 g of crude **7**. This was chromatographed over alumina (activity grade II) to give 10·2 g (62%) of **7**, b.p. 180–190°/0·05 mm, n_D^{19} 1·4805; ν_{max} (film) 2950, 2875, 1470, 1459, 1445, 1360, 1330, 1270, 1208, 1148, 1130, 1090, 1040, 915, 880, 823, 770 cm^{-1}; δ (60 MHz, CCl_4) 0·92 (3H, t, J = 6 Hz), 1·12–1·80 (18H), 1·98–2·16 (4H), 2·24 (4H, br. s), 3·06–3·85 (4H, m), 4·46 (1H, br. s). (Found: C, 79·21; H, 10·68. $C_{21}H_{34}O_2$ requires: C, 79·19; H, 10·76%).

7,11-*Hexadecadiyn*-1-*ol* (**8**). *p*-TsOH (1·5 g) was added to a soln of **7** (9 g) in MeOH (60 ml) and the resulting soln was stirred overnight at room temp. MeOH was removed *in vacuo* and the residue was diluted with water. Then it was extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 5·3 g (81%) of **8**, b.p. 153–154°/0·6 mm, n_D^{20} 1·4822; ν_{max} (film) 3300, 2920, 2850, 1450, 1430, 1380, 1335, 1060 cm^{-1}; δ (60 MHz, CCl_4) 0·91 (3H, t, J = 6 Hz), 1·42 (12H, br. s), 1·94–2·20 (4H), 2·26 (4H, br. s), 2·29 (1H, s, –OH) 3·50 (2H, t, J = 6 Hz); GLC (1·5% OV-17, 1 m, at 160°; Carrier gas, N_2, 0·35 kg/cm^2): R_t 11·3 min. (Found: C, 82·05; H, 11·39. $C_{16}H_{26}O$ requires: C, 81·99; H, 11·18%).

(Z, Z)-7,11-*Hexadecadien*-1-*ol* (**9**). P-2 Ni was prepared by the addition of $NaBH_4$ (38 mg) in 95% EtOH (1 ml) to a soln of $Ni(OAc)_2$ (248 mg) in 95% EtOH (10 ml). Then ethylene diamine (180 mg) and **8** (2·0 g) were added. The mixture was shaken under H_2 (1 atm, room temp.) for 1 hr when the H_2 uptake ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and extracted with ether. The ether soln was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1·63 g (81%) of **9**, b.p. 118°/0·2 mm; n_D^{16} 1·4715, ν_{max} (film) 3300, 3000, 2860, 1657, 1450, 1059 cm^{-1}; δ (100 MHz, CCl_4) 0·92 (3H, t, J = 6 Hz), 1·10–1·70 (12H, m), 1·8–2·4 (8H, m), 3·00 (1H, s, –OH), 3·53 (2H, t, J = 6 Hz), 6·15–6·50 (4H, m); GLC (LAC-2R-446, 1·5 m × 3 mm i.d., at 183°; Carrier gas N_2, 0·8 kg/cm^2) R_t 6·7 min. (Found: C, 80·55; H, 12·62; $C_{16}H_{30}O$ requires: C, 80·60; H, 12·68%).

(Z, Z)-7,11-*Hexadecadienyl acetate* (**1**). Ac_2O (2 ml) was added to a soln of **9** (1 g) in dry pyridine (3 ml) and the mixture was left to stand overnight at room temp. Then it was poured into ice-water and extracted with ether. The ether soln was washed with 5% HCl aq and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (1·20 g, quantitative yield) was distilled to give 1·04 g (89%) of pure **1**, b.p. 136–137°/0·45 mm, n_D^{26} 1·4575; ν_{max} (film) 3000, 2930, 2860, 1745, 1460, 1365, 1240, 1040 cm^{-1}; δ (100 MHz, CCl_4) 0·92 (3H, t, J = 6 Hz), 1·10–1·68 (12H, m), 1·70–2·20 [11H, m(1·98, 3H, s)], 4·00 (2H, t, J = 6 Hz), 5·16–5·50 (4H, m); GLC (1·5% OV-17, 1 m, at 160°; Carrier gas, N_2, 0·58 kg/cm^2): R_t 10·3 min; GLC (3% PDEAS, 4 m, at 160–190°, 3°/min; Carrier gas He, 60 ml/min): 94·5% pure with two impurities (2·7 and 2·5%, respectively). Coinjection experiment with this column proved the identity of our material with that of Zoëcon Corporation. TLC (20% $AgNO_3$ on Wako gel B-5F, C_6H_6–EtOAc, 5 : 1): R_f 0·64. (Found: C, 77·30; H, 11·52. $C_{18}H_{32}O_2$ requires: C, 77·09; H, 11·50%).

(E)-2-*Heptenyl bromide* (**11**). PBr_3 (11 g) was gradually added to a stirred soln of **10** (10 g) and pyridine (300 mg) in dry ether (60 ml). The reaction was exothermic and the ether refluxed spontaneously. The mixture was stirred and heated under reflux for 2 hr. After cooling, it was poured into ice-water and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residual crude **11** (14·5 g, quantitative yield), ν_{max} (film) 2920, 2845, 1658, 1480, 1430, 1200, 960 cm^{-1}, was employed for the next step without further purification.

(E)-5-*Decen*-1-*yne* (**12**). A Grignard reagent (**3**) was prepared from propargyl bromide (18 g), Mg (3 g) and $HgCl_2$ (0·2 g) in dry THF (40 ml). Crude **11** (14·5 g) was slowly added to the stirred and ice-cooled **3**. The mixture was stirred overnight at room temp and then heated under reflux for 1 hr. Subsequent work-up as in the case of **6** gave 7·5 g (63%) of crude **12**, b.p. 66–67°/16 mm, containing a small amount of allenic impurities. A portion (400 mg) of it was purified as silver salt to give 260 mg of pure **12**, b.p. 69°/18 mm; n_D^{26} 1·4567, ν_{max} (film) 3300, 2925, 2850, 2120, 1465, 1380, 1265, 970 cm^{-1}; δ (60 MHz, CCl_4) 0·89 (3H, t, J = 6 Hz), 1·0–1·6 (4H, m), 1·73 (1H, t, J = 2 Hz), 1·70–2·00 (2H, m), 2·00–2·40 (4H, m), 4·86–5·68 (2H, m); GLC (1·5% OV-17, 1 m, at 50°; Carrier gas N_2, 0·45 kg/cm^2): R_t 3·8 min. (Found: C, 87·45; H, 11·53. $C_{10}H_{16}$ requires: C, 88·16; H, 11·84%).

(E)-11-*Hexadecen*-7-*yn*-1-*ol tetrahydropyranyl ether* (**13**). A soln of n-BuLi (3·2 g in n-hexane 35 ml) was added to a stirred soln of crude **12** (5·5 g) in dry THF (40 ml). The mixture was stirred for 15 min at room temp. To this soln was added a soln of 6-bromohexan-1-ol THP ether (25 g) in dry HMPA (70 ml) with ice-cooling and stirring. After 1 hr at room temp., the mixture was worked up as in the case of **7** to give 13·9 g of crude **13**. This was chromatographed over alumina (activity grade II) to give 11·19 g (86·5%) of **13**, n_D^{19} 1·4756; ν_{max} (film) 2925, 2850, 1463, 1450, 1438, 1350, 1201, 1140, 1120, 1080, 1038, 970, 905, 870, 818 cm^{-1}; δ (60 MHz, CCl_4) 0·93 (3H, t, J = 6 Hz), 1·10–1·80 (18H, m), 1·80–2·32 (8H, m), 3·00–4·00 (4H, m), 4·40–4·59 (1H, br. t), 5·12–5·45 (2H, m). (Found: C, 79·01; H, 11·18. $C_{21}H_{36}O_2$ requires: C, 78·69; H, 11·32%).

(E)-11-*Hexadecen*-7-*yn*-1-*ol* (**14**). *p*-TsOH (1·5 g) was added to a soln of **13** (9 g) in MeOH (60 ml) and the resulting soln was stirred overnight at room temp. Subsequent work-up as in the case of **8** gave 6·2 g (93·5%) of **14**, b.p. 103–104°/0·06 mm, n_D^{21} 1·4743; ν_{max} (film) 3350, 2925, 2850, 1458, 1430, 1378, 1300, 1080, 1060, 1037, 970 cm^{-1}; δ (60 MHz, CCl_4) 0·94 (4H, t, J = 6 Hz), 1·12–1·78 (12H, m), 1·78–2·32 (8H, m), 2·28 (1H, s, –OH), 3·54 (2H, t, J = 6 Hz), 5·28–5·54 (2H, m); GLC (1·5% OV-17, 1·0 m, at 160°; Carrier gas N_2, 0·35 kg/cm^2): R_t 8·2 min. (Found: C, 80·83; H, 12·13. $C_{16}H_{28}O$ requires: C, 81·29; H, 11·94%).

(Z, E)-7,11-*Hexadecadien*-1-*ol* (**15**). P-2 Ni was prepared by the addition of $NaBH_4$ (57 mg) in 95% EtOH (1 ml) to a soln of $Ni(OAc)_2$ (372 mg) in 95% EtOH (14 ml). To this were added ethylene diamine (270 mg) and **14** (3 g). The mixture was shaken under H_2 (1 atm, room temp.) for 1 hr when the H_2 uptake ceased. Subsequent work-up as in the case of **9** gave 2·81 g (93%) of **15**, b.p. 121–122°/0·35 mm, n_D^{20} 1·4691; ν_{max} (film) 3300, 3000, 2925, 2860, 1657, 1450, 1059, 970 cm^{-1}; δ (100 MHz, CCl_4) 0·91 (3H, t, J = 7 Hz), 1·04–1·70 (12H, m), 1·70–2·28 (8H, br. s), 2·39 (1H, s, –OH), 3·55 (2H, t, J = 6 Hz), 5·08–5·60 (4H, m); GLC (LAC-2R-446, 1·5 m × 3 mm i.d., at 183°; Carrier gas N_2, 0·8 kg/cm^2): R_t 6·7 min. (Found: C, 80·45; H, 12·60. $C_{16}H_{30}O$ requires: C, 80·60; H, 12·68%).

(Z, E)-7,11-*Hexadecadienyl acetate* (**2**). Acetylation of **15** (700 mg) with Ac_2O (1·5 ml) and pyridine (3 ml) gave **2** in quantitative yield. An analytical sample boiled at 135–136°/0·5 mm, n_D^{26} 1·4570; ν_{max} (film) 3000, 2930, 2860, 1740, 1460, 1365, 1240, 1040, 970 cm^{-1}; δ (100 MHz, CCl_4) 0·92 (3H, t, J = 6 Hz), 1·10–1·76 (12 H, m), 1·76–2·24 [11H, m (1·98, 3H, s)], 3·99 (2H, t, J = 6 Hz), 5·10–5·54 (4H, m); GLC (1·5% OV-17, 1·0 m, at 160°; Carrier gas N_2, 0·58 kg/cm^2) R_t 10·3 min; GLC (3% PDEAS, 4 m, at 160–190°, 3°/min; Carrier gas He, 60 ml/min): 96·3% pure with three impurities (1·0, 0·6 and 1·7%). Coinjection experiment with this column proved the identity of our material with that of Zoëcon Corporation. TLC (20% $AgNO_3$ on Wako gel B-5F, C_6H_6–EtOAc 5:1): R_f 0·79. (Found: C, 77·05; H, 11·59. $C_{18}H_{32}O_2$ requires: C, 77·09; H, 11·50%).

Acknowledgements—Thanks are due to Drs. J. B. Siddall and C. A. Henrick (Zoëcon Corporation, Palo Also, California) for their hospitality and GLC analysis during K.M.'s visit to their laboratories. We thank Prof. H. H. Shorey (University of California, Riverside) for the bioassay.

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