Tetrahedron Letters, Vol. 34, No. 35, pp. 5641-5644, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis and Field Bioassay of the Israeli Pine Bast Scale, *Matsucoccus josephi*, Female Sex Pheromone

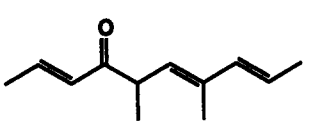
Lev Zegelman[1], Alfred Hassner[1]*, Zvi Mendel[2] and Ezra Dunkelblum[2]

[1]Department of Chemistry, Bar-Ilan University, Ramat Gan 52100
[2]Institute of Plant Protection, Volcani Center, Bet Dagan 50250

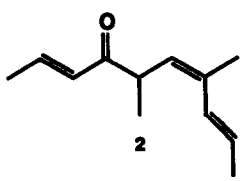
Abstract: We report the first synthesis of the two components of the female sex pheromone of Matsucoccus josephi (2E,4E,8E)-4,6-dimethyl-2,4,8-decatrien-7-one (1) and (2E,4Z,8E)-4,6-dimethyl-2,4,8-decatrien-7-one (2) utilizing the Reformatzky and Wittig reactions as key steps. A mixture of 1 and 2 and the separate isomers were bioassayed in a pine forest indicating that E isomer 1 is much more active than 2 and is also a kairomone for a predator.

The Israeli pine bast scale, *Matsucoccus josephi*, Bodenheimer and Harpaz is a major pest of *Pinus halepensis* and *Pinus brutia* ssp. *eldarica* and has caused severe damage to pine forests in Israel in the last decades (1). The scale is also widespread in the neighboring countries such as Jordan, Lebanon, Cyprus and Turkey (2). The control of the pest is not practical without a convenient and reliable monitoring system, because the scales are often very difficult to detect before inflicting heavy damage to the trees. Pheromone traps are considered to constitute the best means to estimate insect population densities and to discover newly infested areas. This has led us to investigate the structure of the female released pheromone and to develop a simple and efficient synthesis of the racemic pheromone components.

Recently, two components of the sex pheromone of *M. josephi*, in a ratio of 75:25, were isolated and identified as **1** and **2**. The structure of the two isomeric $C_{12}H_{18}O$ compounds was deduced largely from extensive mass spectral data and microreactions. NMR identification was not possible because of the extremely small quantity of natural pheromone (3). To confirm the structures and prepare sufficient amounts of



1



2

pheromone for biological and field tests, a simple synthetic route was designed utilizing cheap commercial starting materials. A retrosynthetic analysis led us to a synthetic route based on a C4 + C3 + C5 approach as outlined in Figure 1. This route provides versatility for synthesis of analogs as well as of chiral compounds.

The commercially available starting materials were crotonaldehyde, ethyl-2-bromopropanoate and *trans*-3-penten-2-ol. The Reformatsky reaction (4) of crotonaldehyde **3** and ethyl 2-bromopropanoate **4**, using a zinc-copper couple as a catalyst (5), was the first step in the synthesis. The hydroxy ester **5** was obtained as

a mixture of two diastereoisomers and was converted to the tert-butyldimethylsilyl (TBS) ether (6). The protected hydroxy ester was reduced with DIBAL (7) to yield directly aldehyde **6**.

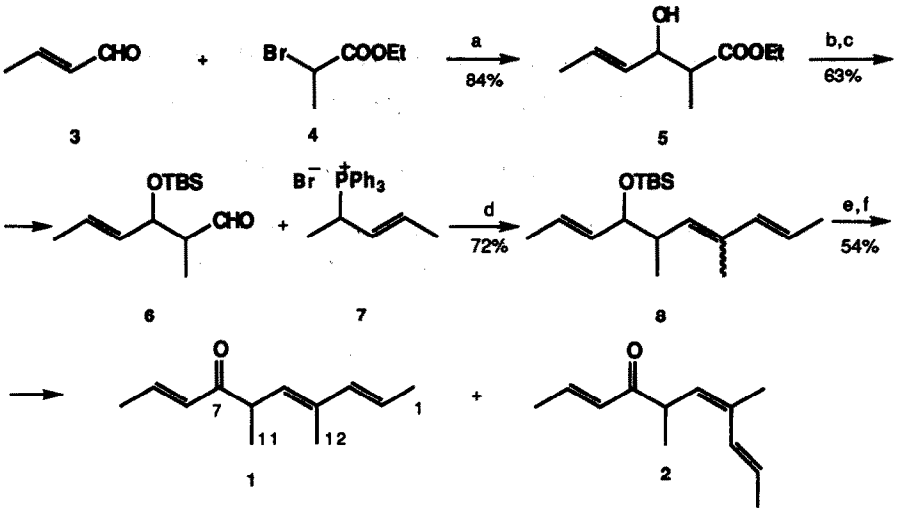


Figure 1. Reagents: (a) Zn-Cu, Et_2O, r.t.; (b) TBSCl, Imidazole, DMF,r.t.; (c) DIBAL, toluene, -78°C; (d) BuLi, THF, 0-10°C; (e) $(n\text{-}Bu)_4NF$, THF, r.t.; (f) PCC, NaAc, CH_2Cl_2, r.t.

The triphenylphosphonium salt **7** was prepared from the commercial *trans*-3-pentene-2-ol *via* the corresponding bromide according to the procedure of Bartelt et al. (8). The bromide was prepared from the alcohol with neat phosphorous tribromide and was used immediately without purification (9). It was treated with triphenylphosphine in refluxing acetonitrile to produce phosphonium salt **7** which was crystallized by washing the product repeatedly with dry ether in a closed vessel, also to remove unreacted starting materials. The phosphonium salt **7**, obtained in 40% yield from the alcohol, is very hydroscopic and must be stored under dry conditions. The identity of **7** was monitored by NMR.

The Wittig reaction (10) of aldehyde **6** and triphenylphosphonium salt **7** gave TBS-ether **8** as a mixture of E and Z isomers. Removal of the TBS protective group (6) from **8** gave the corresponding alcohol mixture. Oxidation of this alcohol with pyridinium chlorochromate (PCC) in the presence of sodium acetate (11) produced a mixture of **1** and **2** in an E:Z ratio of 56:44. The overall yield **1** + **2** from **5** and **7** was 25%.

A modified synthesis of **1** + **2** is described in Figure 2. The hydroxy ester **5** was oxidized with PCC (10) to yield keto ester **9** which was converted to the corresponding ketal and reduced with DIBAL (7) to the ketal

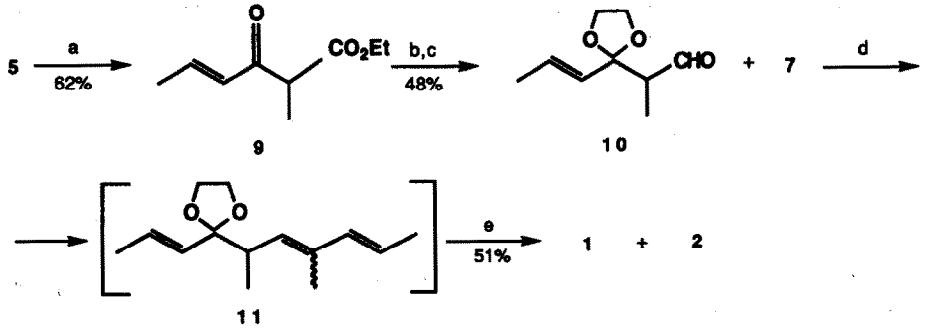


Figure 2. Reagents: (a) PCC, CH_2Cl_2, NaAc, r.t.; (b) $HO(CH_2)_2OH$, TsOH, $CHCl_3$, reflux; (c) DIBAL, toluene, -78°C; (d) BuLi, THF, 0-10°C; (e) aq HCl,THF, r.t.

aldehyde **10** (12). The Wittig reaction (10) of aldehyde **10** and triphenylphosphonium salt **7** gave the ketal pheromone **11** as a mixture of E and Z isomers. There was no necessity to isolate the ketal; it was converted directly under mild acidic conditions to a mixture of the pheromone components **1** + **2** in an E:Z ratio of 62:38. The overall yield of **1** + **2** from **5** and **7** by this route was 15%. The relative advantage of this pathway is that the Wittig reaction leads straight to the pheromone.

The two isomeric components **1** and **2** were separated by preparative GLC on a 2 m x 4 mm column of OV1 5% on CWHP using a thermal conductivity detector. The Z isomer eluted first. The purity of the separated isomers was at least 95%, as verified on an analytical 30 m x 25 mm capillary RTX225 column. The NMR data of **1** and **2** confirmed the structure of the two pheromone components (13). The most significant differences in the chemical shifts, between the E isomer **1** and the Z isomer **2**, were observed for the vinylic protons at C3 and C5. This is in accord with the data for the E and Z isomers of the *Matsucoccus feytaudi* sex pheromone, which have similar diene moieties (14). The IR and MS data (15) were also in accord with structures **1** and **2** and were identical with those of the natural compounds (3b). The E/Z stereochemistry of the double bond in position 4, formed in the Wittig reaction, in **1** and **2** was further established by a Diels Alder reaction of the mixture with tetracyanoethylene in dichloro methane at 25^0 C. After 24 hours only the E isomer **1** reacted to produce a diastereoisomeric mixture of two cycloadducts (16), whereas the Z isomer **2** remained in the reaction solution. It is known that conjugated dienes with the E,E geometry react much faster with tetracyanoethylene than the corresponding E,Z isomers (17).

The reported yields (not optimized) are of purified materials, either by distillation or silica column chromatography. All intermediate products were characterized by NMR, IR and MS spectra.

A preliminary field test with the synthetic pheromone as a mixture (56% E + 44% Z) and the separated isomers **1** and **2** was conducted in a pine forest, using triangular sticky traps and rubber septa as dispensers for the pheromone (18). The results (Table 1) indicate that the isomeric pheromone mixture is highly active

Table 1: Trap catch of *Matsucoccus josephi* males and *Elatophilus hebraicus* with pheromone components, test in Harel Forest, April 7-28 (21 days), with four replicas for each treatment[x]

BAIT[y]	DOSE	CATCH/TRAP/MJ Mean ± S.E.[z]	CATCH/TRAP/EH Mean ± S.E.[z]
1	100 µg	263.75 ± 25.48ab	9.00 ± 1.79ab
2	100 µg	53.25 ± 13.73c	2.50 ± 0.86b
1 + 2	100 µg	137.25 ± 10.04b	4.75 ± 1.93ab
1 + 2	200 µg	405.00 ± 77.95a	12.00 ± 2.38a
CONTROL	-	0d	0c

[x]MJ = mean catch/trap of the scale *Matsucoccus josephi*, males only, during the entire test; EH = mean catch/trap of the predator *Elatophilus hebraicus*, both males and females, during the entire test.

[y]Isomeric purity of 1 and 2 was 95%, ratio of 1 + 2 was 56:44.

[z]The variable number of insects/trap/test was anlyzed using ANOVA on square root $\sqrt{x+1}$ transformed data. Different letters indicate significant differences according to Newman-Keuls test at $P<0.05$.

and attracts large numbers of *M. josephi* males. However, it seems that the activity is due mainly to the E isomer **1**. The relatively low catch of males in traps baited with isomer **2** may be due to low activity of this isomer or due to the 4-5% of **1** in the separated material. Fortunately, the Z isomer **2** is not an inhibitor - this

is evident from the fact that a mixture of 200 µg of 1 + 2 is statistically as active as 100 µg of the E isomer 2. Further, a laboratory bioassay in a petri dish (3a) also indicated that the main activity of the pheromone is due to the E isomer 1. In view of the preliminary field results, it is clear that the synthetic mixture of 1 + 2 can be used for monitoring. Interestingly, the pheromone is also a kairomone of *Elatophilus hebraicus*, an obligatory predator of *Matsucoccus* spp. Both sexes of the predator are attracted by the pheromone. Again the E isomer seems to be the active component (the numbers are relatively low due the late seasonal appearance of the predator). This observation of a scale pheromone being also a kairomone is unique.

Further chemical work is in progress to prepare the chiral pheromone components and biological work to determine the role of the various isomers as pheromone components or as kairomones.

Acknowledgements: *We wish to thank the Ministry of Science for supporting the project, Grant 4000-2-92. and to Mrs. Miriam Harel, Mrs. Fabienne Assael and Mr. Shlomo Tam for their technical assistance. We are grateful to Dr.R.J. Bartelt (USDA, Peoria, Ilinois) for supplying details of the preparation of phosphonium salt 7 and for its NMR spectrum, and to Drs. E. Semon and J.L. Le Quere (INRA, Dijon) for GC-IR spectra of 1 and 2.*

References and Notes

1. a) F.S. Bodenheimer, S. Newmark, *The Israeli pine Matsucoccus*. Kiryat Sefer, Jerusalem, **1955**, b) Mendel Z. Liphschitz, N., J. Exp. Bot. **1988**, 951.
2. Z. Mendel, *Entomol. Gener.* **1992**, *17*, 299.
3. a) Z. Mendel, E. Dunkelblum and D. Robison, *J. Chem. Ecol.* **1990**, *16*, 2341; b) E. Dunkelblum, Z. Mendel, F. Assael, M. Harel, L. Kerhoas and J. Einhorn, *Tetrahedron Letters* **1993**, *34*, 2805.
4. L.E. Rice, M.C. Boston, H.O. Finklea, B.J. Suder, J.O. Frazier and T. Hudlicky, *J. Org. Chem.* **1984**, *4*, 1845.
5. a) E. Santaniello and A. Manzocchi, *Synthesis* **1978**, 698; b) E. Le Goff, *J. Org. Chem.* **1964**, *29*, 2048.
6. K. Mori, M. Itoh and R. Brossut, *Liebigs Ann. Chem.* **1990**, 1249.
7. L.I. Zacharkin and I.M. Khorlina, *Tetrahedron Letters* **1962**, *14*, 619.
8. R.J. Bartelt, P.F. Dowd, R.D. Plattner and D. Weisleder, *J. Chem. Ecol.* **1990**, *16*, 1015.
9. Several other methods, including Br_2-Ph_3P, PBr_3-HBr, CBr_4-Ph_3P, $SOCl_2$ and TsCl were tried unsuccessfully for the conversion of *trans*-3-penten-2-ol into the corresponding halide or tosylate.
10. P.E. Sonnet, *Org. Prep. Proc. Int.* **1974**, *6*, 269.
11. E.J. Corey and W. Suggs, *Tetrahedron Letters* **1975**, *31*, 2677.
12. Varying amounts of the corresponding ketal alcohol were also obtained; while purifying the aldehyde by column chromatography, the alcohol was also separated and reoxidized to the aldehyde with PCC (11).
13. NMR (300 MHz, $CDCl_3$) for 1: δ 6.87 (dq, J = 16, 7 Hz, H-9), 6.16 (dq, J = 16, 2 Hz, H-8), 6.07 (bd, J = 16 Hz, H-3), 5.68 (dq, J = 16, 7 Hz, H-4), 5.25 (bd, J = 10 Hz, H-5), 3.61 (dq, J = 10, 7 Hz, H-6), 1.86 (dd, J = 7, 2 Hz, 3H, H-1), 1.81 (d, J = 1.5 Hz, 3H, H-12), 1.77 (dd, J = 7, 2 Hz, 3H, H-10), 1.17 (d, J = 7 Hz, 3H, H-11); for 2: δ 6.90 (dq, J = 16, 7 Hz, H-9), 6.47 (bd, J = 16 Hz, H-3), 6.19 dq, J = 16, 2 Hz, H-8), 5.82 (dq, J = 16, 7 Hz, H-2), 5.11 (bd, J = 10 Hz, H-5), 3.68 (dq, J =10, 7 Hz, H-6), 1,87 (dd, J = 7, 2 Hz, 3H, H-10), 1.84 (bd, J = 7 Hz, 3H, H-1), 1.82 (d, J = 1.5 Hz, 3H, H-12), 1.17 (d, J = 7 Hz, 3H, H-11).
14. J. Einhorn, P. Menassieu, C. Malosse and P.H. Ducrot, Tetrahedron Letters **1990**, *31*, 6633.
15. The capillary GC-MS of 1 and 2 was identical: m/z 178 (M^+, 8), 163 (3), 109 (100), 91 (7), 81 (16), 79 (10), 77 (6), 69 (42), 67 (36), 55 (9). High resolution MS of a mixture of 1 and 2 gave m/z of 178.1370, calculated for $C_{12}H_{18}O$: 178.1357. The gas phase IR (GC-IR) of 1 and 2 were practically identical with the exception of slight shifts in some of the bands. The main bands for 1 are: 2978, 2930; 1705 and 1639 (conjugated ketone), 1454, 1042 and 962 cm^{-1} (trans disubstituted double bonds); for 2: 2980, 2932; 1705 and 1637 (conjugated ketone), 1452, 1038 and 962 cm^{-1} (trans disubstituted double bonds).
16. Analyzed by capillary GC-MS; m/z 306 (M^+, 2), 291 (1), 109 (6), 98 (8), 69 (100) and 41 (18).
17. K.E. O'Shea and C.S. Foote, *Tetrahedron Letters*, **1990**, *31*, 841.
18. E. Dunkelblum, Y. Ben-Dov, Z. Goldschmidt, J.L. Wolk and L. Somekh, *J. Chem. Ecol.* **1987**, *13*, 863.

(Received in UK 8 June 1993; accepted 9 July 1993)