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Enantioselective Synthesis of All Four Stereoisomers of (2*E*,4*E*)-4,6,10,12-Tetramethyl-2,4-tridecadien-7-one, The Sex Pheromone of *Matsucoccus* Pine Bast Scale

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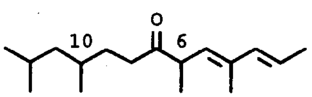
Abstract: A facile enantioselective synthesis of all four stereoisomers of (2*E*,4*E*)-4,6,10,12-tetramethyl-2,4-tridecadien-7-one **1**, the primary sex pheromone of *matsucoccus* pine bast scale is described. The stereochemistry at C-6 and C-10 of **1** was constructed by using optically active citronellal as starting material and by the asymmetric Aldol reaction.

Since the identification of Matsuone **1** as the sex pheromone of the red pine scale *Matsucoccus resinosae* (USA) and two related species *M. matsumurae* (China) and *M.thunbergianae* (Korea),[1] the synthesis of optically active **1** has become an interesting topic due to the critical need for the survey and control program of these insects, and for the investigation of the structure-activity relationship.



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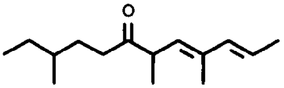

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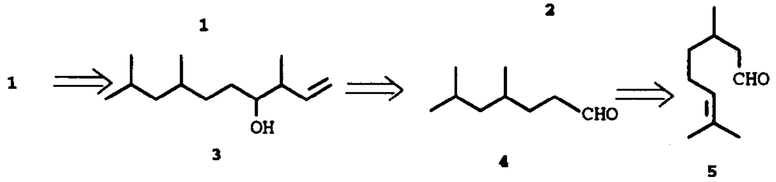
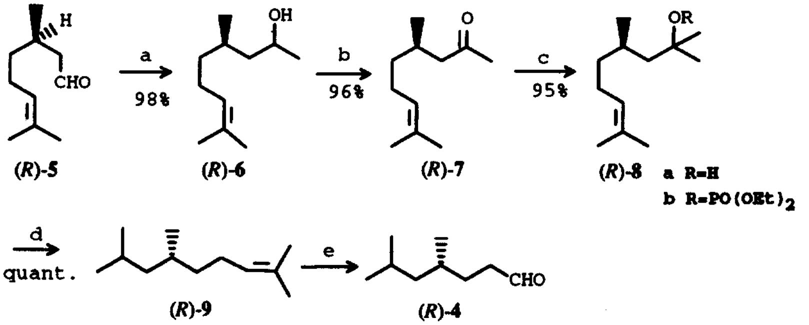


Scheme 1

The relative stereochemistry of this natural pheromone was recently established as 6*R**,10*R** (6,10-*syn*) by Cywin et al.[2] However, the absolute stereochemistry of the natural pheromone **1** is still unknown. In the meantime, a stereoselective synthesis of another pheromone **2** (6,10-*anti*) with its structure very similar to **1** was reported by Mori *et al.*[3] Herein we wish to report our result of the enantioselective synthesis of all four stereoisomers of **1** with the aim to assign the absolute configuration at C-6 and C-10 of the natural pheromone **1** by means of bioassay with the synthetic compounds **1a-d.**

The strategy for the synthesis of the individual stereoisomers of **1**, as shown in scheme 1, was based on the utilization of the commercially available (*R*)-or (*S*)-citronellal[4] as the starting material to build C-7 to C-13 fragment of **1** with the known configuration at C-10 (**5**→**4**). Subsequently, the Aldol type reaction [5] was used to established the anticipated stereochemistry at C-6 of **1** (**4**→**3**).As the hydroxyl group at C-4 of **3** would be finally oxidized to ketone, the control of the stereochemistry at C-7 can be neglected at this stage. The prolongation of **3** to **1** was completed by the Wittig reaction.



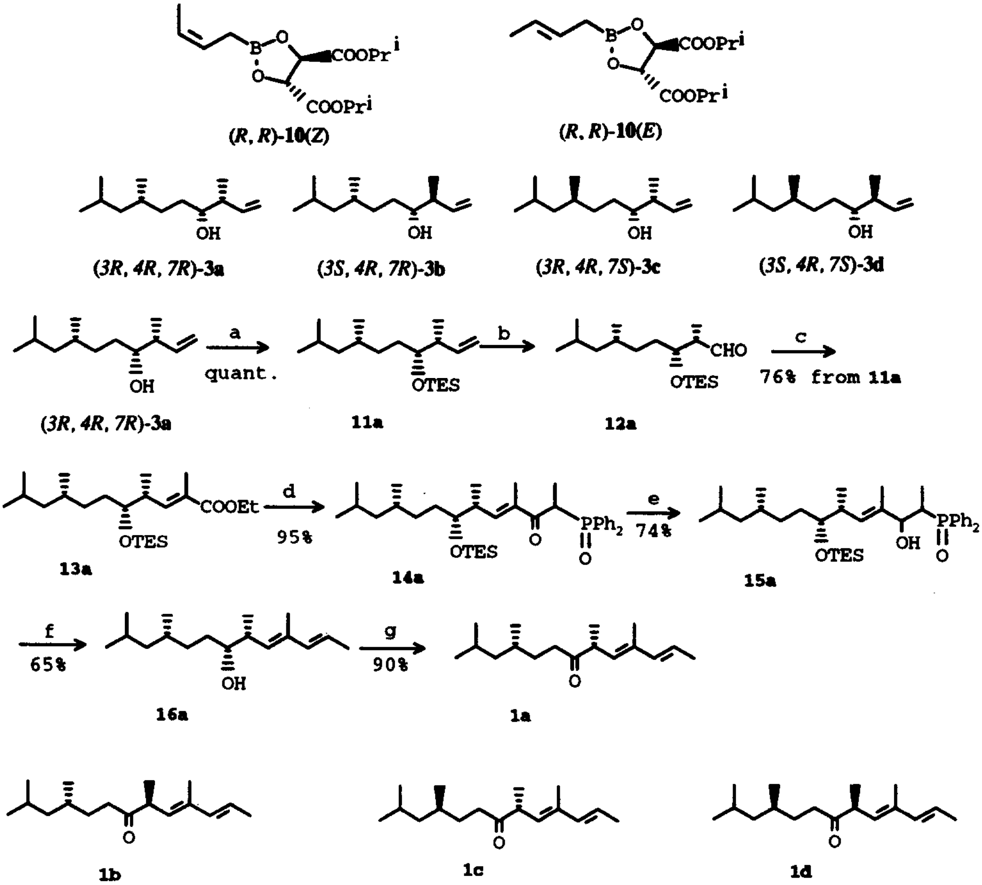
Conditions: a) i. MeMgI/Et$_2$O, ii. H$_3$O$^+$; b) PCC/CH$_2$Cl$_2$, rt; c) i. as in a) step, ii. n-BuLi/THF, -20°C--0°C, iii. ClPO(OEt)$_2$, TMEDA, -20°C --rt; d) Li/EtNH$_2$, -30°C; e) O$_3$/CH$_2$Cl$_2$, -78°C then Ph$_3$P.

Scheme 2

Our synthesis started from (*R*)-**5** to offer (*R*)-**4** over 6 steps (**5**→**9**→**4**)as shown in scheme 2. The yield of each step (from **5**→**9**) was almost quantitative. Ozonolysis of (*R*)-**9** gave the crude aldehyde (*R*)-**4** which was subjected to the Aldol reaction without purification. Preparation of (*S*)-**4** was executed in the same manner as that of (*R*)-**4** from (*S*)-**5**.[6]

Treatment of the freshly prepared aldehyde (*R*)-**4** with the boronate (*R*,*R*)-**10**(*Z*) or (*R*,*R*)-**10**(*E*) prepared according to ref. 5a, b, c (-78°C, MS 4A, toluene, 2hr), provided (3*R*,4*R*,7*R*)-**3a**, (3*S*,4*R*,7*R*)-**3b**, respectively.[6] The d.e. for **3a** and **3b** were >92.8% and >94%, respectively, as determined by GC. The yields from (*R*)-**9** to (3*R*,4*R*,7*R*)-**3a** and (3*S*,4*R*,7*R*)-**3b** were, in general, over 70%. Therefore, the (*R*) or (*S*) configuration at C-6 of Matsuone **1** (ie. the configuration at C-3 of **3**) was settled by employing the (*Z*) or (*E*)-boronate **10**, respectively. In the same manner, the other two isomers (3*R*,4*R*,7*S*)-**3c** (>94% d.e.) and (3*S*,4*R*,7*S*)-**3d** (d.e. 91%) were prepared[6] by the reaction of (*S*)-**4** with (*R*,*R*)-**10**(*Z*) or (*R*,*R*)-**10**(*E*), respectively. Thus, from **3a-d**, all the stereoisomers of **1** were obtained as illustrated by the preparation of **1a** (see Scheme 3).

Subsequent to the protection of the hydroxyl group of **3a** as TES ether to give **11a**, the ene part of the molecule was subjected to ozonolysis to furnish the crude aldehyde **12a**. The Wittig reaction of the crude **12a** provided **13a** in yield of 76% over two steps (**11a**→**13a**). The geomeric configuration of the double bond of **13a** was confirmed as *E* form by 600MHz ^{1}HNMR, as ^{1}H-^{1}H COSY of **13a** showed no coupling relationship between the vinyl proton and the vinyl methyl group. The ratio of *E*/*Z* was 22.4/1 as proved by GC.[7] The Horner reaction of **13a** followed by DIBAL-H reduction gave **15a** which possessed the same skeleton of the carbon atom as that of the target molecule **1a**. Due to the introduction of two newly formed asymmetric centers, **15a** was found to exist in diastereomeric forms, the ratio of *threo* to *erythro* being 6:1 as revealed by GC.[8] The elimination of diphenyl-phosphate in the presence of NaH and DMF at 40°C, and the concomitant deprotection of the silyl ether offered **16a**. Finally, the alcohol **16a** was oxidized under Swern condition to give **1a** in an overall yield of 19.6% over 15 steps from (*R*)-**4**, $[\alpha]_D$ -93.9° (c 0.5, CHCl$_3$). GC showed that the purity of **1a** was 85% as a major peak. Other two minor peaks, which possessed the same mass fragmentation pattern as that of **1a**, one was from the 2Z form of **1a** (5%), which comes from the *erythro* **15a**, and the other was from uncertain compounds (10%). In the same manner, other three stereoisomers of **1a** were prepared from the corresponding **4**. The purity and $[\alpha]_D$ were 86.0%, +116.0° (c 0.2) for **1b**, 90%, +139.2° (c 0.3) for **1c** and 89.8%, -130.4° (c 0.13)for **1d**,[9] and the overall yields of **1b**-**1d** were ranged from 15% to 19.6%. The bioassays of **1a-d** are under way and the result will be reported elsewhere.



Conditions: a) DMF, Imidazole, TES-Cl, b) O_3/CH_2Cl_2, -78°C, Ph_3P, rt, c) toluene, $Ph_3P{=}C(CH_3)CO_2Et$, 80°C, 36 hrs., d) $Ph_2P(O)C_2H_5$, n-BuLi/THF, -78°C, e) DIBAL-H/Et_2O, -78°C, f) NaH, DMF, 40°C, g) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78°C.

Scheme 3

Acknowledgement

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References and Notes

[1]. Lanier, G.N.; Qi, Y.-T.; West, J.R.; Park, S.C.; Webster, F.X.; Silverstein, R.M. *J.Chem.Ecol.* **1990**, *15*, 1645.

[2]. Cywin, C.L.; Webster, F.X.; Kallmerten, J. *J.Org.Chem.* **1991**, *56*, 2953.

[3]. Mori, K.; Harashima, S. *Tetrahedron Lett.* **1991**, *32*, 5995; Corrigendum: *ibid.* **1992**, *33*, 282.

[4]. (*R*)- and (*S*)-citronellal was purchased from Aldrich Company. (*R*)-(+)-citronellal,96%,Reg.No.34364-1, (*S*)-(-)-Citronellal, 96%,Reg.No.37375-3. (Aldrich Catalog Handbook of Fine Chemicals).

[5]. a. Roush, W.R.; Straub, J.A.; VanNieuwenhze, M.S. *J.Org.Chem.* **1991,** *56* , 1636.
b. Roush, W.R.; Palkowitz, A.D.; Ando, K. *J.Am.Chem.Soc.* **1990,** *112*, 6339.
c. Hoffmann, R.W. *Angew.Chem., Int.Ed.Engl.* **1982,** *21*, 555.

[6]. All new compounds gave satisfactory spectroscopic and microanalytical or high resolution mass data. (3*R*, 4*R*, 7*R*)-**3a**, $[\alpha]_D$ +15.50° (c 2.0, $CHCl_3$); ^{1}HNMR(300 MHz, $CDCl_3$) δ_H: 5.801(1H, ddd, J=14.94, 4.70, 2.68 Hz), 5.148--5.033 (2H, m), 3.450 (1H, m), 2.320 (1H, m), 1.580 (1H, OH), 1.400-1.200 (8H, m), 1.050 (3H, d, J=6.87 Hz)ppm. MS (%): m/z 197 (M-1, 1.7), 180 (M-H_2O, 0.75), 167 (M-CH_3O, 25.02), 83 (49.65), 69 (C_5H_9, 95.01), 57 (100), 43 (94.41). HRMS Cald. for $C_{13}H_{36}O$, 198.1966, Found: 198.3488. (3*S*, 4*R*, 7*R*)- **3b**, $[\alpha]_D$ -3.5°(c 0.9, $CHCl_3$); δ_H: 5.780(1H, ddd, J=17.4, 9.80 and 7.61Hz), 5.100--5.000 (2H, m), 3.450 (1H, m), 2.280 (1H, m), 1.700-1.000 (8H, m), 1.420 (1H, bs, OH), 1.050 (3H, d, J=6.30Hz), 0.880--0.750 (9H, m) ppm. (3*R*, 4*R*, 7*S*)-**3c,** $[\alpha]_D$+23.9°(c 1.2, $CHCl_3$); δ_H: 5.750(1H,ddd,J=18.0, 10.9, 7.2Hz), 5.180- 5.080(2H, m), 3.380 (1H, m), 2.220 (1H, m), 1.700-1.200 (8H, m), 1.630 (1H, bs, OH), 1.060(1H, d, J=7.0Hz), 0.890 (3H, d, J=6.8Hz), 0.85 (6H, d, J=6.8Hz) ppm. (3*S*, 4*R*, 7*S*)-**3d**, $[\alpha]_D$+ 6.03° (c 0.9, $CHCl_3$); δ_H: 5.750 (1H, ddd, J=16.7, 8.0, 2.7 Hz), 5.140-5.080 (2H, m), 3.357 (1H, m), 2.200 (1H, m), 1.600 (1H, bs, OH), 1.400--1.200 (8H, m), 1.040 (3H, d, J=6.0Hz), 0.850 (9H, m) ppm.

The retention time of **3a**, **3b**, **3c**, **3d** were determined by GC as 15.86, 8.09, 10.74 and 12.76 min, respectively. GC condition: FFAP 50m x 0.2mm, column temp. programmed from 150°C (stopped for 1min) to 230°C at the rate of 5°C per minute.

[7]. Introduction of the diene part of **1a** by the treatment of the crude **12a** with the Wittig reagent $Ph_3=C(CH_3)CH=CHCH_3$ (r.t. 12hr) failed. A complicated mixture was obtained under this condition.

[8]. GC conditions:column FFAP 50mx0.2mm, column temp. programmed from 150°C (stopped for 1 min) to 230°C at the increased rate of 8°C per min.

[9]. (6*R*,10*R*)-**1a**, $[\alpha]_D$ -93.9° (c 0.5, $CHCl_3$); ^{1}HNMR(600 MHz, $CDCl_3$) δ_H: 6.309 (1H, d, J=17.04), 5.738 (1H, m) 5.205 (1H, d, J=9.76Hz), 3.462(1H, m), 2.436(2H, t, J=7.79Hz), 1.86(3H, s), 1.778(3H, d,J=7.12Hz), 1.157(3H, d, J=6.79Hz), 1.70-1.20 (8H, m), 0.86 (3H, d, J=6.61Hz), 0.83(3H, d, J=6.47Hz), 0.82 (3H, d, J=6.47Hz) ppm. Ms(%): m/z 250(M, 1.2), 141(M-C_8H_{13}, 5.0), 109 (C_8H_{13}, 100.0), 81 (C_6H_9, 20.0), 67 (C_5H_7, 36.0), 57(C_4H_9, 21.0), 55(C_4H_7, 27.0), 43 (C_3H_7, 59.0), 41 (C_3H_5, 50.0).

(6*S*,10*R*)-**1b**, $[\alpha]_D$+139.2° (c 0.3, $CHCl_3$); δ_H: 6.05 (1H, d, J=15.0Hz), 5.50(1H, dq, J=15.0, 6.0Hz),5.20(1H, d, J=8.0Hz), 3.40 (1H, dq, J=8.0, 6.8Hz), 2.26 (1H, ddd, J=15.0, 9.0, 5.7Hz), 2.15 (1H, ddd, J=15.0, 8.9, 5.7Hz), 1.70 (3H, d, J=2.0Hz), 1.65 (3H, dd, J=6.5, 1.2Hz), 1.60-1.15 (8H, m), 1.03 (3H, d, J=6.8 Hz) ,0.85-0.70 (9H, m) ppm.

(6*R*,10*S*)-**1c**, $[\alpha]_D$ -130.4°(c 0.13, $CHCl_3$); δ_H: 6.05 (1H, d, J=15.0Hz), 5.50(1H, dq, J=15.0, 6.0Hz), 5.20(1H, d, J=8.0Hz), 3.40 (1H, dq, J=8.0, 6.8Hz), 2.26 (1H, ddd, J=15.0, 9.0, 5.7Hz), 2.15 (1H, ddd, J=15.0, 8.9, 5.7Hz), 1.70 (3H, d, J=2.0Hz), 1.65 (3H, dd, J=6.5, 1.2Hz), 1.60-1.15 (8H, m), 1.03 (3H, d, J=6.8Hz), 0.85-0.70 (9H, m) ppm.

(6*S*,10*S*)-**1d**, $[\alpha]_D$+116°(c 0.2, $CHCl_3$); δ_H: 6.05 (1H, d, J=15.0Hz), 5.62 (1H, dq, J=15.0, 6.7Hz), 5.50(1H, d, J=10.0Hz), 3.50 (1H, dq, J=10.0, 6.7Hz), 2.50 (1H, ddd, J=15.5, 9.2, 6.0Hz), 1.90 (3H, s), 1.70 (3H, d, J=6.8Hz), 1.39 (3H, d, J=6.7Hz),1.70-1.20 (8H, m), 0.86-0.80(9H, m)ppm.

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