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Synthesis of the 1,5-dimethylic chiron enantiomers, 3,7,11-trimethyldodec-10-en-1-ol: application to enantiomeric syntheses of tribolure and a marine fatty acid

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Abstract—A convenient synthesis of the title chiron antipodes has been developed starting from (±)-citronellol via a sequential acetylation protocol using two lipases. The different stereoisomers of the chiron were then functionalized by simple routes to (4*R*,8*R*)-dimethyldecanal, an insect pheromone and (5*R*,9*R*)-5,9,13-trimethyltetradecanoic acid, a marine phospholipid fatty acid.

1. Introduction

The 1,5-dimethyl skeleton is ubiquitous among different biologically active natural products. Several insect pheromones,[1a] vitamin E side chain,[1b] various phospholipid fatty acid components[1c,d] of marine origin, etc., are some examples of occurrence of this class of compound. Several of these compounds also act as biological markers[2] and thus, have aroused interest amongst geochemists. Consequently, preparation of this structural feature has drawn a lot of attention. In continuation of our own program on syntheses of insect pheromones and bioactive marine natural products, we were interested in developing a versatile synthetic route for the above structural skeleton. In view of the commercial availability of several enzymes, a chemoenzymatic approach seemed ideally suited for this purpose. Furthermore, we felt that a lipase-catalyzed kinetic resolution would be more flexible, as this would provide all possible diastereomers in reasonable diastereomeric purities.

For this purpose, the compound, 3,7,11-trimethyldodec-10-en-1-ol (**6**, Scheme 1) appeared to be a model target synthon in view of the presence of the designated structural feature and terminal bifunctionality. Hence, we developed a simple enantioselective route for its synthesis and subsequently used it for the synthesis of two compounds possessing the 1,5-dimethyl skeleton viz. (4*R*,8*R*)-dimethyldecanal, **I** and 5,9,13-trimethyltetradecanoic acid, **II**. Compound **I**, commonly known as tribolure, constitutes[3a,b] the aggregation pheromone of the red flour beetle, *Tribolium castaneum* and finds use in effective control of this economically important pest. Interestingly, the racemic pheromone shows[4a,b] very low activity as compared to the natural pheromone and hence its enantiomeric synthesis is extremely important. The acid **II**, on the other hand has been isolated[5] from the phospholipid fraction of the marine sponge, *Cinachyrella alloclada*. To date, the absolute configuration of natural **II** is unknown. We have prepared its (5*R*,9*R*)-isomer only; however, the flexibility of the method would also allow preparation of its other stereoisomers. So far only one synthesis of (±)-**II** has been reported[6] from our laboratory and to the best of our knowledge, this is its first asymmetric synthesis. For the pheromone **I**, although, several syntheses have been reported,[7] this is the first divergent approach for both **I** and **II** from a common intermediate.

2. Results and discussion

2.1. Enzymatic synthesis of the chiron 6

Commercially available (±)-citronellol **1** was acetylated[8] with vinyl acetate using porcine pancreatic lipase (PPL) as the catalyst to furnish the corresponding (*R*)-acetate **2** and (*S*)-**1**. At 30% conversion, (*R*)-**2** (93% ee) and (*S*)-**1** (68% ee) were obtained. A second enzymatic acetylation of the above resolved alcohol (up to 50% conversion) improved its ee to 92% as determined by our earlier procedure.[9] Thus, the enantiopreference of

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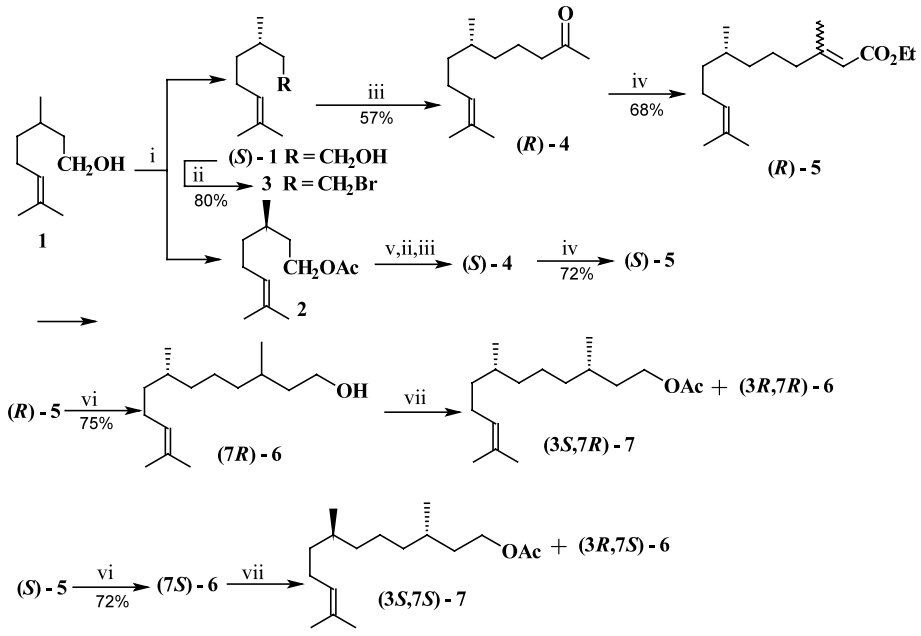


Scheme 1. *Reagents and conditions*: (i) PPL/vinyl acetate/hexane; (ii) $Ph_3P{\cdot}Br_2$/Py/CH_2Cl_2; (iii) NaOMe/MeOH/methyl acetoacetate, alcoholic KOH; (iv) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$; (v) alcoholic KOH; (vi) Li/NH_3/EtOH–ether; (vii) CRL/vinyl acetate/diisopropyl ether.

PPL was found to be opposite to that of pig liver esterase (PLE) which is reported to acylate (*S*)-**1** preferentially.[10] The (*S*)-alcohol was converted[11] to the bromide (*S*)-**3** with triphenylphosphine and bromine. α-Alkylation of methyl acetoacetate with (*S*)-**3** followed by alkaline hydrolysis and acid-catalyzed decarboxylation furnished the ketone (*R*)-**4**. Its Wittig–Horner reaction with triethyl phosphonoacetate cleanly furnished the conjugated ester (*R*)-**5** as an *E*/*Z* isomeric mixture whose composition was not analyzed. Chemoselective reduction[12] of its conjugated ester functionality with Li/NH_3 in the presence of a proton donor directly afforded the key alcohol (3*RS*,7*R*)-**6** (Scheme 1). The (7*S*)-epimer of **6** was likewise prepared from (*R*)-**1**, obtained by alkaline hydrolysis of (*R*)-**2** and subsequent derivatization as above. Synthesis of the target compounds from the C(7)-epimers of **6** warranted their efficient resolution.

For this, we resorted to a lipase-catalyzed acetylation of **6**. Earlier, we have demonstrated[13] that *Candida rugosa* lipase (CRL) could acylate 3-methylalkanols with high degrees of enantioselectivity. Consequently, for the resolution of **6**, first its (7*R*)-isomer was subjected to a CRL-catalyzed acetylation with vinyl acetate in diisopropyl ether to furnish the acetate **7** and the alcohol **6**. At 28% conversion, the acetate and the alcohol were obtained with 97 and 54% enantiomeric excess (ee), respectively. In principle, for enzymatic reactions with moderate enantioselectivity as in the present case, a higher conversion (~70%) provides the substrate with appreciable enantiomeric purity. However, the acetylation of **6** did not proceed beyond ~40% conversion possibly due to the attainment of an equilibrium and there was only a marginal improvement in the % ee of **6**. Hence, we decided to enrich the enantiomeric purity of the partially resolved alcohol (54% ee) via a second CRL-catalyzed acetylation as above. This furnished the alcohol **6** with 96% ee in 35% yield. Following an identical procedure, (7*S*)-**6** was also resolved to give the respective acetate and alcohol with 95 and 93% ee, respectively. The enantiomeric purities of the above compounds were determined by GLC analysis on a WCOT fused silica CP-Chirasil-Dex CB capillary column. Subsequently, the target compounds were synthesized from the appropriate enantiomer of the chiron.

In analogy with our earlier result[13] on the CRL-catalyzed acetylation of 3-methyl alkanols, we assigned (3*S*)-configurations for the acetates. This was subsequently confirmed by converting one of them, (3*S*,7*R*)-**7** to the pheromone **I**, and comparing its chiroptical data with the reported values of different stereoisomers of **I**. The synthetic pheromone **I** showed a negative optical rotation which can be attributed to the C(4) epimers of the pheromone, (4*R*,8*R*)-**I** or (4*S*,8*R*)-**I**.[7b] Since in the present synthesis, the C(4) stereochemistry was predetermined as *R*, being inherited from that of **1**, the synthesized pheromone would be (4*R*,8*R*)-**I**. Consequently, the configuration at C(3) of the starting acetate **7** must be (*S*). The synthesis warranted conversion of the CH_2OAc group of (3*S*,7*R*)-**7** to CH_3 which altered the Cahn–Ingold–Prelog (CIP) priority sequences and thus, ensured the 8*R*-configuration of **I**.

2.2. Synthesis of compound I

For the synthesis, (3*S*,7*R*)-**7** was hydrolyzed to give (3*S*,7*R*)-**6** which on mesylation and subsequent reductive demesylation with $LiAlH_4$ furnished the hydrocarbon **8**. Its epoxidation with *m*-CPBA to the

corresponding epoxide **9** followed by cleavage with HIO_4 afforded the title pheromone (4*R*,8*R*)-**I** (Scheme 2). The spectral and chiroptical data of the pheromone were commensurate with those reported.[7b]

2.3. Synthesis of compound II

The alcohol (3*R*,7*S*)-**6** was oxidized with pyridinium chlorochromate (PCC) to furnish the aldehyde **10**. Its Wittig–Horner olefination with triethyl phosphonoacetate gave the ester **11** which on catalytic hydrogenation afforded the saturated ester **12**. This on alkaline hydrolysis led to the acid (5*R*,9*R*)-**II** (Scheme 3) whose spectral data were similar to those reported[6] and in conformity with the proposed structure.

3. Experimental

The IR spectra were scanned as thin films with a Perkin–Elmer spectrophotometer model 837. The ^1H NMR spectra were recorded with a Bruker AC-200 (200 MHz) instrument. The optical rotations were measured with a Jasco DIP 360 polarimeter. GLC analyses were carried out with a Shimadzu GC-16A chromatogram fitted with a flame ionization detector. For normal analysis the GLC conditions were a 3% OV-17 column, N_2 (40 ml/min) as the carrier gas and temperature programming 80–240°C @ 4°C/min. The enantiomeric excesses were determined with a WCOT fused silica CP-Chirasil-Dex CB capillary column (10 m×0.25 mm), He (1 ml/min) and temperature programming 80–225°C @ 4°C/min. All anhydrous reactions were carried out under an argon atmosphere using freshly dried solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

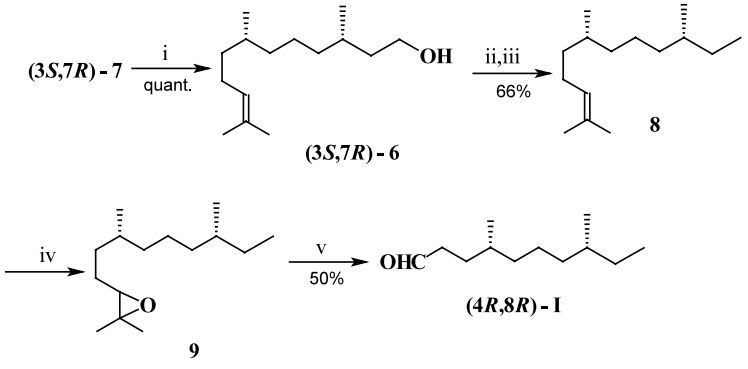
3.1. (*R*)-1-Citronellyl acetate, 2

A mixture of **1** (15.6 g, 0.1 mol), vinyl acetate (12.9 g, 0.15 mol) and PPL (5.0 g) in hexane (100 ml) was stirred for 24 h when 30% conversion was noted. The mixture was filtered, the solid residue washed with EtOAc, the combined extract concentrated and the residue chromatographed (silica gel, 0–10% EtOAc/hexane) to get (*S*)-**1** (9.72 g, 62%) and (*R*)-**2** (4.5 g, 23%). $[\alpha]_D^{22}=+3.5$ (*c* 1.98, $CHCl_3$); IR: 1730, 1480, 1380, 1230 cm^{-1}; ^1H NMR: δ 0.88 (d, $J=7$ Hz, 3H), 1.1–1.4 (m, 4H), 1.58 (s, 3H), 1.62 (s, 3H), 1.8–2.4 (m containing a s at δ 2.1, 6H), 4.1 (t, $J=7$ Hz, 2H), 5.06 (t, $J=6$ Hz, 1H).

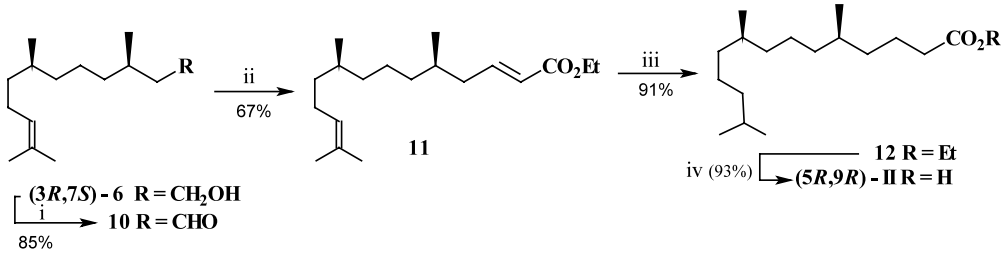
The above alcohol (9.72 g, 0.062 mol) was subjected to another acylation with vinyl acetate (8.0 g, 0.093 mol) for 42 h under the same condition to furnish optically enriched (*S*)-**1** (4.3 g, 44%). $[\alpha]_D^{22}=-4.5$ (*c* 18, MeOH), (lit.[10] $[\alpha]_D^{22}=-4.4$ (*c* 20, MeOH)).

3.2. (*S*)-Citronellyl bromide, 3

To a stirred and cooled (0°C) solution of Ph_3P (15.72 g, 0.06 mol) in CH_2Cl_2 (50 ml) was slowly added Br_2 (10.0 ml, 0.055 mol, 5.5 M in CCl_4). After stirring for 0.5 h, a mixture of (*S*)-**1** (7.8 g, 0.05 mol) and pyridine (4.5 ml, 0.055 mol) in CH_2Cl_2 (25 ml) was added, the cooling bath removed and the mixture stirred for 3 h at ambient temperature. Most of the solvent was removed in vacuo, the residue dissolved in hexane, filtered and



Scheme 2. *Reagents and conditions*: (i) alcoholic KOH; (ii) MsCl/triethylamine/CH_2Cl_2; (iii) $LiAlH_4$/ether/Δ; (iv) *m*-CPBA/CH_2Cl_2; (v) HIO_4/THF–H_2O.



Scheme 3. *Reagents and conditions*: (i) PCC/CH_2Cl_2; (ii) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$; (iii) H_2/Pd–C/EtOH; (iv) alcoholic KOH.

the filtrate concentrated. The residue, thus obtained was diluted with hexane and passed through a pad (6″) of neutral alumina (gr. II) and the eluent concentrated to obtain pure (*S*)-**3**. Yield: 8.75 g (80%); bp: 108–110°C/10 mm; $[\alpha]_D^{22}=-6.3$ (*c* 4.5, $CHCl_3$); IR: 1640, 1480, 1380 cm^{-1}; ^1H NMR: δ 0.93 (d, $J=7$ Hz, 3H), 1.0–1.4 (m, 4H), 1.58 (s, 3H), 1.62 (s, 3H), 1.8–2.2 (m, 3H), 3.54 (t, $J=7$ Hz, 2H), 5.06 (t, $J=6$ Hz, 1H).

3.3. (*R*)-Citronellyl bromide, 3

A solution of **2** (4.5 g, 0.023 mol) in 2N alcoholic KOH (20 ml) was stirred for 6 h at room temperature. Most of the solvent was removed in vacuo, the residue taken in ether and the ether extract washed with water and brine and dried. Removal of solvent followed by column chromatography (0–15% EtOAc/hexane) of the product gave pure (*R*)-**1**. Yield: 3.26 g (91%); $[\alpha]_D^{22}=-4.3$ (*c* 16, MeOH).

As described earlier, bromination of (*R*)-**1** (6.5 g, 0.042 mol) with Ph_3P (13.11 g, 0.05 mol), Br_2 (8.4 ml, 0.046 mol, 5.5 M in CCl_4) and pyridine (3.7 ml, 0.046 mol) in CH_2Cl_2 (50 ml) gave (*R*)-**3**. Yield: 7.0 g (77%). $[\alpha]_D^{22}=+6.15$ (*c* 3.3, $CHCl_3$).

3.4. (6*R*)-6,10-Dimethylundec-9-en-2-one, 4

To a stirred solution of NaOMe (0.018 mol) [prepared from Na (0.414 g, 0.018 mol)] in anhydrous MeOH (20 ml) was added methyl acetoacetate (2.2 g, 0.019 mol). After 0.5 h, (*S*)-**3** (3.6 g, 0.016 mol) and a catalytic amount of NaI in MeOH (10 ml) was introduced into it and the mixture heated under reflux for 6 h. After cooling, most of the solvent was removed in vacuo, the residue taken in ether and the ether layer washed with water, brine and dried. After concentration, the product was taken in 2N alcoholic KOH (30 ml) and stirred under reflux for 1 h. It was brought to room temperature, acidified with aqueous dilute H_2SO_4 and heated under reflux further for 3 h to ensure completion of decarboxylation. The mixture was extracted with ether, the extract washed with water and brine and dried. After concentration, the residue was purified by column chromatography (silica gel, 0–10% ether/hexane) to furnish pure (*R*)-**4**. Yield: 1.86 g (57.8%); $[\alpha]_D^{22}=+2.2$ (*c* 1.6, $CHCl_3$); IR: 1720, 1640, 1470, 1380 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 3H), 1.3–1.5 (m, 7H), 1.58 (s, 3H), 1.62 (s, 3H), 2.0 (s, 3H), 2.1–2.2 (m, 2H), 2.4 (t, $J=6$ Hz, 2H), 5.06 (t, $J=7$ Hz, 1H). Anal. calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.71; H, 12.22.

3.5. (6*S*)-6,10-Dimethylundec-9-en-2-one, 4

Alkylation of methyl acetoacetate (3.7 g, 0.032 mol) with (*R*)-**3** (6.0 g, 0.027 mol) as above using NaOMe (0.03 mol) in MeOH (60 ml) gave (*S*)-**4**. Yield: 2.95 g (55%); $[\alpha]_D^{22}=-2.4$ (*c* 0.98, $CHCl_3$).

3.6. Ethyl (7*R*)-3,7,11-Trimethyl-2(*E*/*Z*),10-dodecadienoate, 5

To a stirred and cooled (0°C) suspension of pentane-washed NaH (0.501 g, 10.44 mmol, 50% suspension in oil) in THF (30 ml) was added triethyl phosphonoacetate (2.55 g, 11.38 mmol) in THF (20 ml). After 0.5 h, the ketone (*R*)-**4** (1.86 g, 9.48 mmol) in THF (20 ml) was introduced into it and the mixture stirred for 24 h at room temperature. The mixture was diluted with water, the organic layer separated and aqueous portion further extracted with ether. The combined organic extract was then washed with water and brine and finally dried. Solvent removal followed by column chromatography of the residue over silica gel (0–10% EtOAc/hexane) afforded (*R*)-**5**. Yield: 1.72 g (68%); $[\alpha]_D^{22}=+2.6$ (*c* 1.1, $CHCl_3$); IR: 1715, 1650, 1480, 1380 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 3H), 1.1–1.4 (m, 10H), 1.60 (s, 3H), 1.65 (s, 3H), 2.0 (s, 3H), 2.2–2.3 (m, 4H), 4.1 (q, $J=7$ Hz, 2H), 5.06 (t, $J=7$ Hz, 1H), 5.6 (s, 1H). Anal. calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.78; H, 11.47%.

3.7. Ethyl (7*S*)-3,7,11-Trimethyl-2(*E*/*Z*),10-dodecadienoate, 5

Wittig–Horner reaction between (*S*)-**4** (2.1 g, 10.71 mmol) and triethyl phosphonoacetate (2.90 g, 12.95 mmol) using NaH (0.58 g, 12.10 mol) in THF (40 ml) gave (7*S*)-**5**. Yield: 2.05 g (72%); $[\alpha]_D^{22}=-2.1$ (*c* 1.2, $CHCl_3$).

3.8. (3*RS*,7*R*)-3,7,11-Trimethyl-10-dodecen-1-ol, 6

The ester (7*R*)-**5** (1.7 g, 6.39 mmol) in ether–ethanol mixture (125 ml, 7:3) was added to liquid NH_3 (50 ml). To this stirred mixture was added excess Li metal (0.88 g, 0.126 mol) in pieces until the blue color persisted for 1 h. After 3 h, the ammonia was removed, water was carefully added into the mixture and the organic layer separated. The aqueous layer was reextracted with ether and the entire organic extract washed with water followed by brine. After drying the solvent was removed in vacuo and the residue chromatographed (silica gel, 0–15% EtOAc/hexane) to furnish pure (3*RS*,7*R*)-**6**. Yield: 1.08 g (75%); $[\alpha]_D^{22}=+5.9$ (*c* 4.1, $CHCl_3$); IR: 3360, 1480, 1380 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 6H), 1.3 (br. s, 12H), 1.60 (s, 3H), 1.63 (s, 3H), 2.1–2.2 (m, 2H), 2.81 (br. s, D_2O exchangeable, 1H), 3.68 (t, $J=6$ Hz, 2H), 5.06 (t, $J=7$ Hz, 1H). Anal. calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.62; H, 13.52%.

3.9. (3*RS*,7*S*)-3,7,11-Trimethyl-10-dodecen-1-ol, 6

Reduction of the ester (7*S*)-**5** (2.0 g, 7.52 mmol) with Li metal (1.05 g, 0.15 mol) in ether–ethanol mixture (125 ml, 7:3) and liquid NH_3 (50 ml) followed by isolation as above and column chromatography (silica gel, 0–15% EtOAc/hexane) of the product gave (3*RS*,7*S*)-**6**. Yield: 1.23 g (72%); $[\alpha]_D^{22}=+2.2$ (*c* 3.9, $CHCl_3$).

3.10. (3*S*,7*R*)-3,7,11-Trimethyl-10-dodecenyl acetate, 7

A mixture of (3*RS*,7*R*)-**6** (1.2 g, 5.3 mmol), vinyl acetate (0.688 g, 8.0 mmol) and CRL (0.3 g) in diiso-

propyl ether (25 ml) was stirred at room temperature until 28% conversion (cf. GLC). It was filtered, the solid residue washed with ether and the extract concentrated in vacuo to give a mixture. From this, the individual components viz. (3*S*,7*R*)-**7** (0.313 g, 22%) and (3*R*,7*R*)-**6** (0.87 g, 72.5%) were isolated by column chromatography (silica gel, 0–15% EtOAc/hexane). (3*R*,7*R*)-**6**: $[\alpha]_D^{22}=+2.5$ (*c* 1.02, $CHCl_3$). Its spectral properties were similar to those of (3*RS*,7*R*)-**6**. (3*S*,7*R*)-**7**: $[\alpha]_D^{22}=-5.2$ (*c* 0.88, $CHCl_3$); IR: 1730, 1480, 1380, 1230 cm^{-1}; ^1H NMR: δ 0.88 (d, $J=6$ Hz, 6H), 1.3 (br. s, 12H), 1.58 (s, 3H), 1.62 (s, 3H), 2.1–2.3 (m containing a s at δ 2.14, 5H), 4.12 (t, $J=6$ Hz, 2H), 5.06 (t, $J=7$ Hz, 1H). Anal. calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.18; H, 11.86%.

3.11. (3*S*,7*R*)-3,7,11-Trimethyl-10-dodecen-1-ol, 6

A solution of (3*S*,7*R*)-**7** (1.2 g, 4.48 mmol) in 2N alcoholic KOH (25 ml) was stirred for 18 h. Most of the solvent was removed in vacuo, the residue taken in ether and the ethereal extract washed with water and brine. After drying, the organic extract was concentrated in vacuo and the residue was chromatographed (silica gel, 0–15% EtOAc/hexane) to furnish (3*S*,7*R*)-**6**. Yield: 1.0 g (~quantitative); $[\alpha]_D^{22}=-4.6$ (*c* 0.98, $CHCl_3$).

3.12. (3*S*,7*S*)-3,7,11-Trimethyl-10-dodecenyl acetate, 7

Esterification of (3*RS*,7*S*)-**6** (1.08 g, 4.78 mmol), vinyl acetate (0.62 g, 7.2 mmol) and CRL (0.2 g) in diisopropyl ether (20 ml) was carried out until 30% conversion (cf. GLC). Usual isolation as above gave (3*S*,7*S*)-**7** (0.320 g, 25%) and (3*R*,7*S*)-**6** (0.702 g, 65%). (3*R*,7*S*)-**6**: $[\alpha]_D^{22}=+1.8$ (*c* 0.88, $CHCl_3$); (3*S*,7*S*)-**7**: $[\alpha]_D^{22}=-5.9$ (*c* 1.22, $CHCl_3$).

3.13. (3*R*,7*S*)-3,7,11-Trimethyl-10-dodecen-1-ol, 6

Esterification of the above (3*R*,7*S*)-**6** (1.0 g, 4.42 mmol), vinyl acetate (0.57 g, 6.6 mmol) and CRL (0.2 g) in diisopropyl ether (20 ml) was carried out until 40% conversion (cf. GLC). Usual isolation as above gave (3*R*,7*S*)-**6** (0.340 g, 34%). $[\alpha]_D^{22}=+3.3$ (*c* 1.12, $CHCl_3$).

3.14. (6*R*,10*R*)-2,6,10-Trimethyl-2-dodecene, 8

To a cooled (0°C) and stirred mixture of (3*S*,7*R*)-**6** (0.6 g, 2.65 mmol) and triethylamine (0.5 ml, 3.4 mmol) in CH_2Cl_2 (25 ml) was added mesyl chloride (0.232 ml, 3.0 mmol) in drops. After 1 h, when the reaction was complete, the mixture was poured in ice cooled water containing NH_4Cl (10%). The organic layer was separated, the aqueous portion extracted with $CHCl_3$, the total organic extract washed with aqueous saturated NH_4Cl solution and dried. The solvent was removed to get the corresponding mesylate which was directly used for the next step. IR: 1640, 1480, 1380, 1180 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 6H), 1.29 (br. s, 12H), 1.54 (s, 3H), 1.60 (s, 3H), 2.1–2.2 (m, 2H), 2.9 (s, 3H), 4.31 (t, $J=6$ Hz, 2H), 5.06 (t, $J=7$ Hz, 1H).

The above mesylate in ether (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.197 g, 5.2 mmol) in ether (30 ml) and the mixture gently heated under reflux for 6 h. Excess hydride was decomposed by dropwise addition of aqueous saturated Na_2SO_4 solution, the supernatant decanted from the crystalline mass and the solid washed with ether. The combined organic extract was carefully concentrated to obtain pure **8** after column chromatography (silica gel, pentane). Yield: 0.37 g (66%); $[\alpha]_D^{22}=-6.2$ (*c* 0.84, $CHCl_3$); IR: 1480, 1380 cm^{-1}; ^1H NMR: δ 0.8–1.0 (m, 9H), 1.34 (br. s, 12H), 1.58 (s, 3H), 1.62 (s, 3H), 2.1–2.2 (m, 2H), 5.06 (t, $J=7$ Hz, 1H). Anal. calcd for $C_{15}H_{30}$: C, 85.63; H, 14.37. Found: C, 85.79; H, 14.19%.

3.15. (4*R*,8*R*)-4,8-Dimethyldecanal, I

To a cooled (0°C) and stirred solution of **8** (0.3 g, 1.43 mmol) in CH_2Cl_2 (15 ml) was added *m*-CPBA (0.538 g, 1.72 mmol) in portions. After stirring for 3 h at the same temperature, the mixture was kept at 0°C for 18 h. Then the mixture was filtered to remove the solid precipitate and the extract successively washed with aqueous $NaHSO_3$, water, aqueous $NaHCO_3$ (10%), water, brine and dried. Concentration of the extract gave the crude epoxide **9** which was directly used for the next step. IR: 1480, 1380, 1230 cm^{-1}; ^1H NMR: δ 0.88 (d, $J=6$ Hz, 6H), 0.93 (d, $J=6$ Hz, 3H), 1.3 (br. s, 14H), 1.54 (s, 3H), 1.58 (s, 3H), 3.28 (t, $J=5.5$ Hz, 1H).

To a stirred and cooled (0°C) solution of **9** in THF–H_2O (20 ml, 2:1) was added H_5IO_6 (0.498 g, 2.18 mmol) in portions. After stirring for 1 h, the mixture was extracted with ether, the ether layer washed with aqueous $NaHSO_3$, water and brine and finally dried. Removal of solvent followed by column chromatography over silica gel (0–10% ether/hexane) furnished the pheromone **I**. Yield: 0.132 g (50%); $[\alpha]_D^{22}=-7.2$ (*c* 1.4, $CHCl_3$) (lit.[7b] $[\alpha]_D^{22}=-7.4$ (*c* 2.04, $CHCl_3$)); IR: 2720, 1720 cm^{-1}; ^1H NMR: δ 0.8–1.0 (m, 9H), 1.1–1.5 (m, 12H), 2.3 (t, $J=6$ Hz, 2H), 9.8 (t, $J=1.5$ Hz, 1H).

3.16. (3*R*,7*S*)-3,7,11-Trimethyl-10-dodecenal, 10

To a stirred solution of (3*R*,7*S*)-**6** (0.591 g, 2.62 mmol) in CH_2Cl_2 (30 ml) was added PCC (0.850 g, 3.9 mmol) in one lot. After stirring for 3 h, when the reaction was complete (cf. TLC), the mixture was diluted with ether (30 ml) and the supernatant passed through a pad (2″) of silica gel. Concentration of the extract in vacuo furnished pure **10**. Yield: 0.498 g (85%). $[\alpha]_D^{22}=+3.9$ (*c* 1.4, $CHCl_3$); IR: 2720, 1720, 1480, 1380 cm^{-1}; ^1H NMR: δ 0.88 (d, $J=6$ Hz, 6H), 1.3–1.8 (m containing two s at δ 1.55 and 1.60, 16H), 2.1–2.3 (m, 4H), 5.06 (t, $J=7$ Hz, 1H), 9.78 (t, $J=1.5$ Hz, 1H).

3.17. Ethyl (5*R*,9*S*)-5,9,13-Trimethyl-2(*E*),10-tetradecadienoate, 11

As described earlier, Wittig–Horner reaction between triethyl phosphonoacetate (0.695 g, 3.10 mmol) and **10** (0.498 g, 2.22 mmol) using NaH (0.139 g, 2.90 mmol,

50% suspension in oil) as the base afforded pure **11** after chromatographic purification (silica gel, 0–10% ether/hexane). Yield: 0.44 g (67%); $[\alpha]_D^{22}=+5.8$ (*c* 0.68, $CHCl_3$); IR: 1715, 1650, 1480, 1380, 980 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 6H), 1.3 (br. s, 13H), 1.54 (s, 3H), 1.58 (s, 3H), 2.1–2.4 (m, 4H), 4.2 (q, $J=7$ Hz, 2H), 5.06 (t, $J=7$ Hz, 1H), 5.61 (d, $J=15.6$ Hz, 1H), 6.1 (dt, $J=15.6$, 5.5 Hz, 1H). Anal. calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.59; H, 11.88%.

3.18. (5*R*,9*R*)-5,9,13-Trimethyltetradecanoic acid, II

A mixture of **11** (0.44 g, 1.5 mmol) was hydrogenated over 10% Pd–C (0.1 g) in EtOH (20 ml) to give the ester **12**. Yield: 0.406 g (91%); $[\alpha]_D^{22}=+4.8$ (*c* 0.8, $CHCl_3$); IR: 1730, 1480, 1380 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 12H), 1.3 (br. s, 22H), 2.34 (t, $J=7$ Hz, 2H), 4.1 (q, $J=7$ Hz, 2H). Anal. calcd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83. Found: C, 76.59; H, 12.75.

A solution of the ester **12** in 2N alcoholic KOH (10 ml) was stirred for 12 h. Most of the solvent was removed in vacuo, the residue acidified with 5N aqueous HCl and extracted with ether. The ethereal extract was washed with water and brine. After drying, the organic extract was concentrated in vacuo and the residue was chromatographed (silica gel, 0–20% EtOAc/hexane) to furnish (5*R*,9*R*)-**II**. Yield: 0.342 g (93%); $[\alpha]_D^{22}=+3.6$ (*c* 1.26, $CHCl_3$); IR: 3700–2500, 1710, 1480, 1380, 980 cm^{-1}; ^1H NMR: δ 0.9 (d, $J=6$ Hz, 12H), 1.32 (br. s, 19H), 2.26 (t, $J=7$ Hz, 2H), 11.2 (br. s, D_2O exchangeable, 1H).

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