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Pheromone Syntheses: A Tropical Approach. Enantioselective Synthesis of the (2*R*,6*S*,10*S*) and (2*S*,6*S*,10*S*) Isomers of Methyl 2,6,10-Trimethyldodecanoate†

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Abstract—The enantioselective syntheses of two stereoisomers, (2*R*,6*S*,10*S*) and (2*S*,6*S*,10*S*), of methyl 2,6,10-trimethyldodecanoate, out of eight possible isomers, are described, employing the stereoselective hydroboration of (−)-isopulegol (**2**) and (+)-*neo*-isopulegol (**2a**) as the key reaction. Copyright © 1996 Elsevier Science Ltd

Introduction

The preservation of biodiversity is today a very important concern worldwide. There is no doubt that the Brazilian ecosystem is unique in its large number of species of plants and insects. In its tropical climate the flourishing growth of insects is outstanding. The fragile equilibrium of the ecosystem can be easily disturbed by external pressures. Therefore, the understanding of this system is vital for the survival of mankind and studies of insect pheromones can help improve the environment.

Despite the large number of entomologists doing important and fundamental research in the various fields of insect studies, there is not a single independent group working on pheromone isolation and identification in Brazil. Nevertheless, pheromones of economic and scientific importance from Brazilian insect species have been disclosed through scientific collaboration between Brazilian and foreign groups. To mention only a few examples, the following Brazilian insect pheromones have been identified: *Atta sexdens rubropilosa,*[1] *Nezara viridula,*[2] *Acromyrmex subterraneus subterraneus,*[3] and *Migdolus fryanus.*[4]

Furthermore, there are a few Brazilian groups working on pheromone synthesis, including our laboratory; however, the majority of the target molecules are pheromones from insects which are not native to our country. The importance of establishing active and competent groups in this particular area of pheromone isolation and structure determination is clear.

More than a dozen pheromones[5–7] have been synthesized in our laboratory and a few examples are shown in Figure 1.

In this paper we present the enantioselective syntheses of two stereoisomers, (2*R*,6*S*,10*S*)-**1** and (2*S*,6*S*,10*S*)-**1a**, of methyl 2,6,10-trimethyldodecanoate (Fig. 2), which was identified in 1994 as a component of the male-produced pheromone of the Central American stink bug, *Euschistus obscurus*, as well as a minor component of the male-produced South American stink bug *Euchistus heros*. The latter insect is a serious pest in soybean plantations in southern Brazil.[8]

While the carbon skeleton of the pheromone was determined, nothing is known about the stereochemistry of the natural product, thus motivating us to carry out enantioselective synthesis of the various stereoisomers.

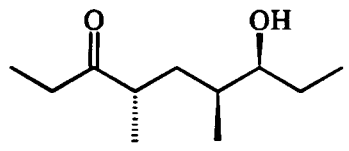
Results and Discussion

The retrosynthetic scheme used in order to enantioselectively obtain both isomers is shown in Scheme 1. Compound **2a** was obtained using Bohlmann's conditions.[9] The diol **3** was obtained through a stereoselective hydroboration reaction of (−)-isopulegol (**2**) according to the procedure described by Schulte-Elte[10] and co-workers, establishing the desired stereochemistry at C-2. The diastereoisomeric ratio obtained in this hydroboration was 8:2 and the two stereoisomers formed were readily separated by flash column chromatography. The transformation[11] of this diol to the aldehyde **10** was performed according to Scheme 2.

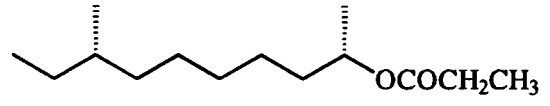
The hydroboration of (−)-isopulegol (**2**) to yield the diol **3** is an important reaction, since in this step a new

†Presented at the 12th Annual Meeting of the International Society of Chemical Ecology, 2–6 Oct., 1995 in Los Andes, Chile.

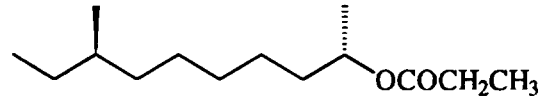
Key words: Pheromone, synthesis, *Euschistus obscurus*, *Euschistus heros*, dodecanoate, methyl 2,6,10-trimethyl-.



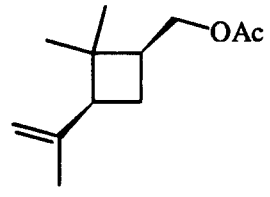
Serricornin (*Lasioderma serricorne* F.)



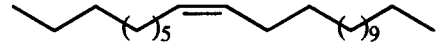
(2S, 8S)-8methyl-2-decanol propanoate



(2R, 8S)
Diabrotica virgifera virgifera Le Conte



(+)-Planococcyl acetate
Planococcus citri (Risso)



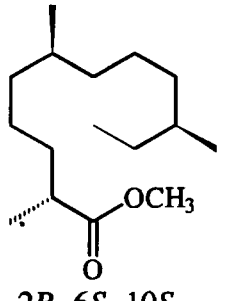
(Z)-9-Tricosene (*Musca domestica*)

Figure 1. Some insect pheromones synthesized in our laboratory.

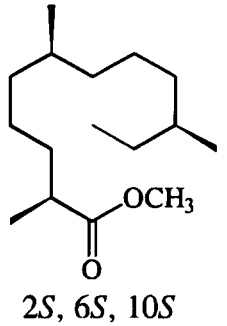
stereogenic center is created (C-2 in the pheromone **1**). At this point, the stereochemistry of this center is established and should be preserved up to the end of the synthesis.

The alcohol **4** was obtained by selective protection of the primary hydroxyl group from the diol **3** with BnBr.[12] Oxidation of **4** with PCC in CH_2Cl_2 afforded the ketone **5** which was submitted to the Baeyer–Villiger reaction to give the lactone **6**. This was treated with MeOH and H_2SO_4(cat) under reflux (methanolysis), yielding the hydroxy-ester **7**. The corresponding tosylate **8** was reduced with $LiAlH_4$ to the alcohol **9**, which served as the precursor of the key intermediate aldehyde **10**.

The configurations of the C-2 and C-6 centers (in **1**) were determined by X-ray analysis of the crystalline lactone **6**, confirming the desired stereochemistry at those centers, as shown in Figure 3. The aldehyde **10a** was similarly obtained using the aforementioned



2*R*, 6*S*, 10*S*
(1)



2*S*, 6*S*, 10*S*
(1a)

Figure 2. Pheromones of *E. obscurus* and *E. heros*.

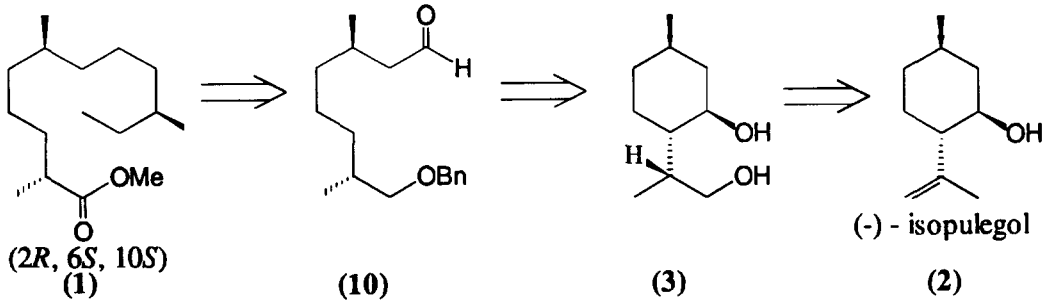
Schulte-Elte[10] method, as shown in Scheme 3. However, we were not able to achieve the same stereoselectivity in the hydroboration of the (+)-*neo*-isopulegol (**2a**) claimed by these authors, in order to obtain the diol **3a** and, in contrast to isomer **3**, we were not successful in efficiently separating the two diastereoisomers formed. Compound **3a**, and all other subsequent intermediates in this synthetic pathway, is a diastereoisomeric mixture at C-2 (in the desired pheromone in a 7:3 ratio) determined by capillary GC.

The aldehyde **10** was transformed in a straightforward manner into the (2*R*,6*S*,10*S*)-methyl 2,6,10-trimethyldodecanoate (**1**), as indicated in Scheme 4. The diastereoisomeric mixture of the alcohol **11** was obtained through the coupling reaction of the aldehyde **10** with the chiral Grignard reagent prepared from commercial (*S*)-(+)-1-bromo-2-methylbutane (**16**).[13] To remove the oxygen function, the tosylate **12** was prepared and reduced with $LiAlH_4$ to the benzyl ether **13**. In this step we faced unexpected difficulties in the preparation of the tosylate **12**. The only way to overcome this problem was to recycle the unreacted alcohol **11** three times, affording an overall yield of 66–70%. The benzyl ether **13** was hydrogenated in EtOH with Pd/C to give the alcohol **14**. The Jones oxidation of the previous alcohol furnished the carboxylic acid **15**, which was treated with diazomethane to give the desired pheromone, methyl (2*R*,6*S*,10*S*)-2,6,10-trimethyldodecanoate (**1**).

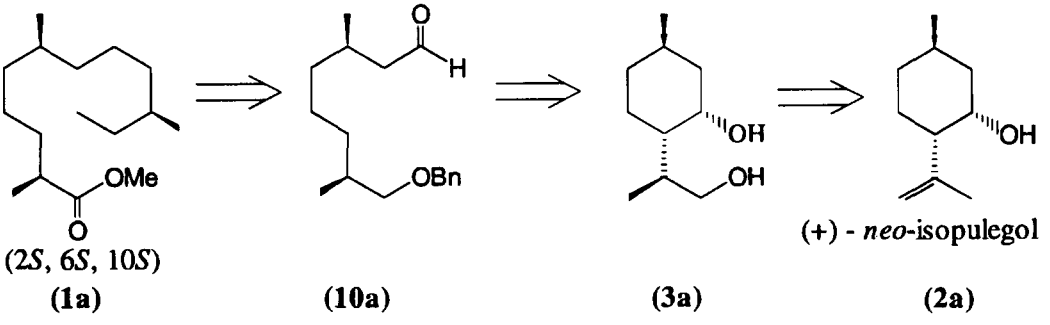
In the same manner as described above, the aldehyde **10a** was transformed into the isomer (2*S*,6*S*,10*S*)-methyl 2,6,10-trimethyldodecanoate (**1a**), as shown in Scheme 5.

The synthetic samples of the stereoisomers of **1** are being tested by Dr Miguel Borges at the CENARGEN,

For the (2*R*,6*S*,10*S*) - isomer (1)



For the (2*S*,6*S*,10*S*) - isomer (1a)



Scheme 1. Retrosynthetic analysis.

Brazil. The results will be reported in a subsequent publication.

Experimental

General

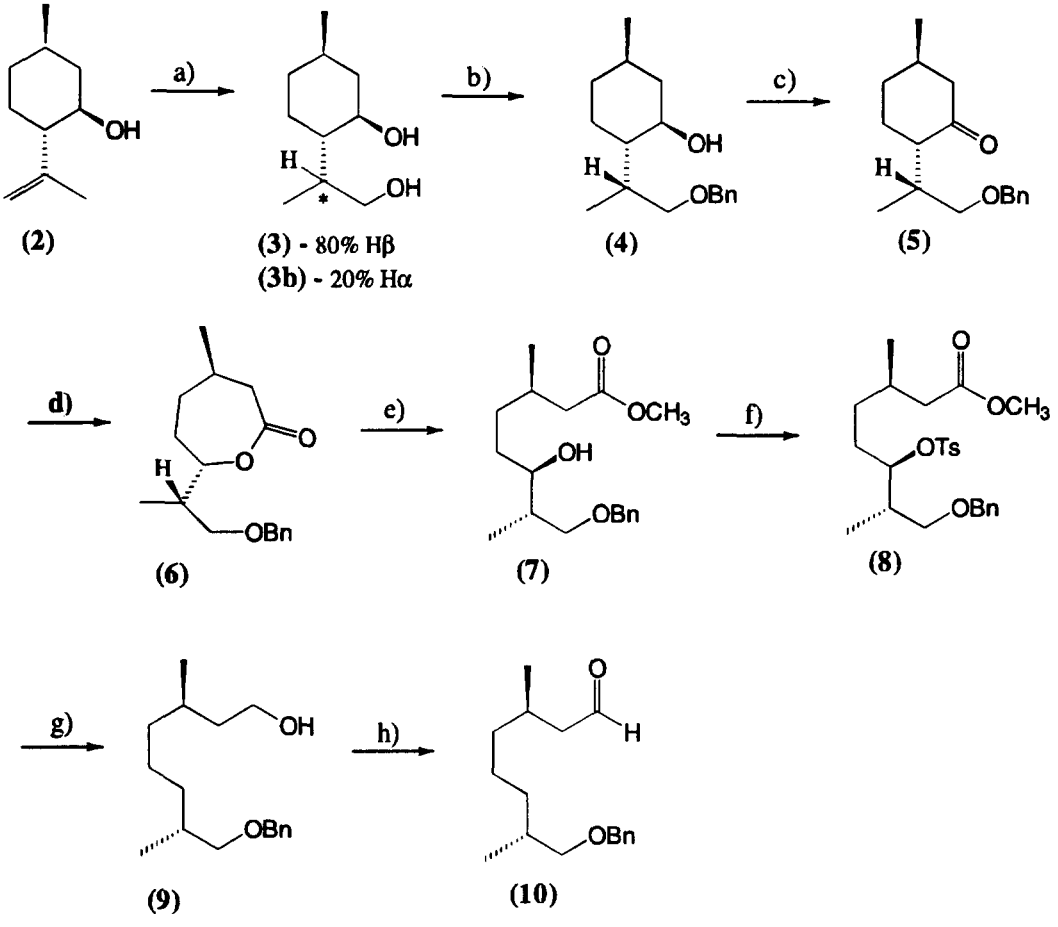
IR spectra refer to films and were measured on a Bomen M-102 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 400 MHz on a Bruker ARX-400 spectrometer. ^{13}C NMR spectra were recorded with TMS as an internal standard at 100 MHz on a Bruker ARX-400 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. GC analysis was performed on an HP-5890 series II gas chromatograph in a Methyl Silicon HP-1 (0.20 mm × 18 m) column or in an HP-Carbowax 20M (25 m × 0.2 mm) column. EI–MS were obtained on a Finnigan-mat GC–MS (column DB-5, 30 m). Column chromatography was carried out in columns packed with Merck Kieselgel 60, Art.-Nr. 7734.

(−)-(1*R*,3*R*,4*S*,8*R*)-*p*-Menthane-3,9-diol (3). $BF_3 \cdot Et_2O$ (9.0 mL, 10.40 g, 73.0 mmol), previously distilled, was added dropwise to a stirred suspension of $NaBH_4$ (1.80 g, 47.4 mmol) in diglyme (32.4 mL) at room temperature under nitrogen. The generated diborane was cannulated into a solution of (−)-isopulegol (**2**) (4.55 g, 29.5 mmol, 5.0 mL) in dry THF (120 mL) under N_2 at 0 °C. After stirring for 3.0 h, H_2O (5.5 mL) was slowly added, followed by H_2O_2 (7.7 mL, 30-vol-%) and aqueous NaOH (7.7 mL, 30%), and stirred for an additional 30 min at room temperature. The reaction mixture was extracted with ether and the separated organic layer was washed with brine and dried ($MgSO_4$). The oil obtained was purified by column chromatography (hexane:ethyl acetate, 1:3) to afford the diol **3** in 74.6% yield (3.78 g) as colorless crystals and the diol **3b** was also obtained (0.95 g), 18.5%, resulting in a 93.0% overall yield (4.72 g). $[\alpha]_D^{30} -18.6°$ (*c* 10.0, $CHCl_3$). IR (ν_{max}, film cm^{-1}): 3370, 2907, 1455, 1034. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86–0.91 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 7.6 Hz, 3H), 0.92–1.01 (m, 1H), 1.32–1.39 (m, 1H), 1.41–1.43 (m, 1H), 1.22 (qd, J = 12.8, 2.8 Hz, 1H), 1.56 (dq, J = 13.2, 3.2 Hz, 1H), 1.61–1.66 (m, 1H), 1.84–1.85 (m, 1H), 1.95 (dtd, J = 12.4, 4.0, 1.6 Hz, 1H), 3.01 (br s, 2H), 3.46 (td, J = 10.4, 4.4 Hz, 1H), 3.59 (dd, J = 10.4, 3.6 Hz, 1H), 3.66 (dd, J = 10.4, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.96, 22.05, 29.43, 31.45, 34.59, 38.56, 44.64, 48.48, 67.14, 70.19.

In the same manner, (+)-*neo*-isopulegol (**2a**) afforded the diol **3a** in 95.0% overall yield, in a diastereoisomeric ratio 7:3 by GC, with an identical IR spectrum, $[\alpha]_D^{30} +14.0°$ (*c* 8.6, $CHCl_3$).

(−)-(1*R*,3*R*,4*S*,8*R*)-9-Benzyloxy-*p*-menthan-3-ol (4). The diol **3** (3.0 g, 17.4 mmol) was added dropwise to a stirred suspension of NaH (0.86 g, 18.0 mmol, 50%) in dry THF (70.0 mL) under N_2 at −5 °C. The resulting solution was stirred for 30 min and benzyl bromide (3.1

g, 18.0 mmol, 2.15 mL) was slowly added. After 2.0 h, saturated aqueous NH_4Cl was added and the resulting mixture was extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$), concentrated and the oil obtained was fractionated followed by column chromatographic separation (hexane:ethyl acetate, 3:1) to afford **4** as a colorless oil (3.19 g, 70%). GC, column HP-1 at 70 °C + 7 °C/min, carrier



Scheme 2. Synthesis of aldehyde **10**. Reagents: (a) 1. B_2H_6; 2. H_2O_2, NaOH, THF, 0 °C; (b) 1. separation of diastereoisomers; 2. NaH, BnBr, THF, −5 °C; (c) PCC, CH_2Cl_2, rt; (d) *m*-CPBA/$NaHCO_3$, CH_2Cl_2 rt; (e) MeOH, H_2SO_4 (cat), Δ; (f) TsCL, Py, $CHCl_3$, 0 °C; (g) $LiAlH_4$, Et_2O, rt; (h) PCC, CH_2Cl_2 rt.

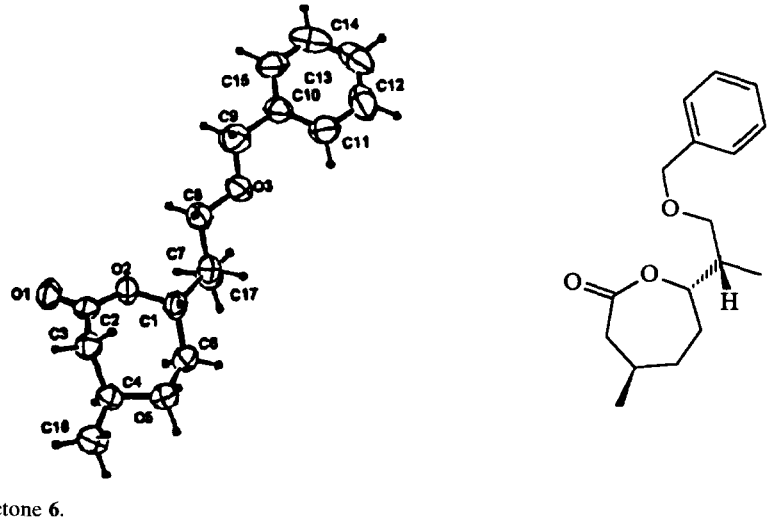
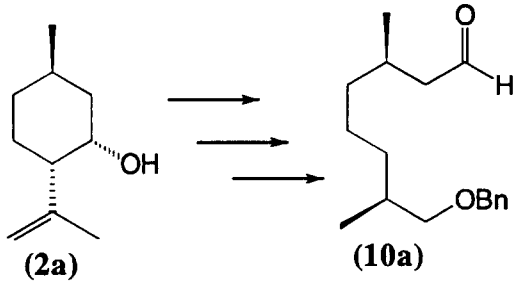


Figure 3. X-ray analysis of lactone **6**.

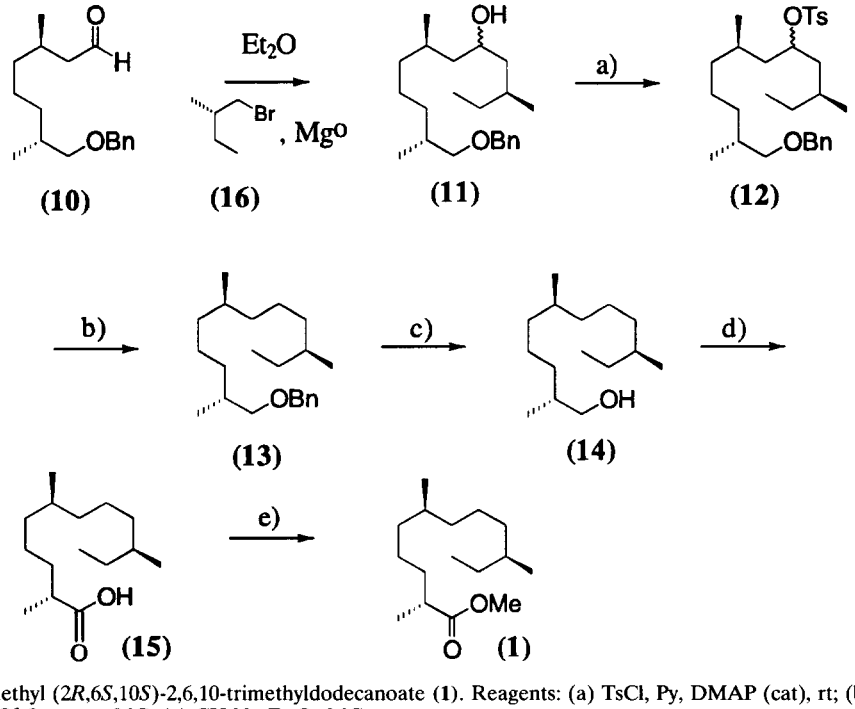
gas: H_2, 1.5 mL/min, $t_R = 16.40$ min. $[\alpha]_D^{30} - 12.4°$ (*c* 14.6, $CHCl_3$). IR ($\nu_{max.}$, film cm^{-1}): 3405, 3030, 2918, 2863, 1453, 1103. ^1H NMR (400 MHz, $CDCl_3$): δ 0.84–0.88 (m, 1H), 0.90–0.98 (m, 1H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H), 1.28–1.34 (m, 1H), 1.39–1.43 (m, 1H), 1.14 (qd, $J = 12.0$, 3.6 Hz, 1H), 1.56 (dq, $J = 12.0$, 3.6 Hz, 1H), 1.63 (dqui, $J = 14.8$, 2.0 Hz, 1H), 1.96 (dtd, $J = 12.0$, 4.0 Hz, 2.0 Hz, 1H), 2.04–2.07 (m, 1H), 3.44 (td, $J = 10.4$, 4.4 Hz, 1H), 3.39 (dd, $J = 9.2$, 3.6 Hz, 1H), 3.50 (dd, $J = 9.2$, 6.4 Hz, 1H), 3.66 (br s, 1H), 4.49 (d, $J = 12.0$ Hz, 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 7.26–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.54, 22.19, 27.91, 31.46, 34.71, 35.50, 43.94, 48.96, 70.43, 73.34, 74.35, 127.72, 128.45, 137.79. MS (70 eV) *m/z* (%): 262 (M^+, 0.01), 244 (0.06), 202 (0.12), 187 (0.11), 153 (22.69), 138 (16.99), 123 (10.17), 107 (17.88), 95 (39.56), 91 (100), 81 (43.80), 69 (29.27), 65 (18.83), 55 (35.25).

(−)-(1*R*,4*S*,8*R*)-9-Benzyloxy-*p*-menthan-3-one (5). The alcohol **4** (3.1 g, 11.83 mmol) was quickly added to a suspension of PCC (6.2 g, 28.76 mmol) in dry CH_2Cl_2 (180.0 mL) at room temperature. After 2 h, dry ether (20.0 mL) was added and the mixture of ether and CH_2Cl_2 was filtered through Celite®, silica gel and charcoal and then concentrated. The oil was purified by column chromatography (hexane:ethyl acetate, 2:1) to afford the ketone **5** (2.85 g, 93%). GC, $t_R = 15.96$ min. (HP-1) under the same conditions as for the analysis of compound **4**. $[\alpha]_D^{30} - 10.5°$ (*c* 36.8, $CHCl_3$). IR (ν_{max}, film cm^{-1}): 3029, 2940, 1708, 1453, 1101. ^1H NMR (400 MHz, $CDCl_3$): δ 1.001 (d, $J = 6.4$ Hz, 3H), 1.012 (d, $J = 6.8$ Hz, 3H), 1.326–1.382 (m, 1H), 1.422 (qd, $J = 12.4$, 3.2 Hz, 1H), 1.793–1.850 (m, 1H), 1.868–1.882 (m, 1H), 1.957 (dd, $J = 13.2$, 1.2 Hz, 1H), 2.025–2.071 (m, 1H), 2.163 (hept, $J = 6.4$ Hz, 1H), 2.310–2.369 (m, 2H), 3.381 (dd, $J = 9.2$, 6.0 Hz, 1H), 3.474 (dd, $J = 9.2$, 5.2 Hz, 1H), 4.458 (d, $J = 12.2$ Hz, 1H), 4.496 (d, $J = 12.2$ Hz, 1H), 7.259–7.343 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.51, 22.34, 29.50, 32.67, 34.11, 35.51, 51.01, 52.22, 72.95, 73.04, 127.41, 127.51, 128.28, 138.73. MS (70 eV) *m/z* (%): 260 (M^+, 0.76), 202 (12.49), 169 (12.87), 158 (4.27), 151 (10.93), 139 (9.93), 112 (48.53), 91 (100), 69 (25.88), 55 (36.52).

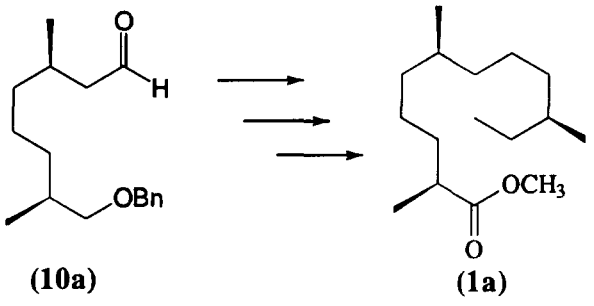


Scheme 3. Synthesis of aldehyde **10a**.

(3*R*,6*S*)-3-Methyl-6-[(1′*S*)-1′-methyl-2-benzyloxymethyl]-ε-caprolactone (6). Ketone **5** (1.9 g, 7.3 mmol) was added to a stirred solution of *m*-CPBA (3.75 g, 7.5 mmol, 35%) in CH_2Cl_2 containing a suspension of solid $NaHCO_3$ (3.0 g, 43.0 mmol). After stirring for 18 h at room temperature, aqueous KI (15.0 mL, 40%) and aqueous $NaHSO_3$ (15.0 mL, 40%) were added to reduce excess oxidant. The resulting two phase system was stirred for 5 min. After separation the organic phase was washed with brine, dried and concentrated to afford the pure lactone **6** in 90% yield (1.80 g). GC, $t_R = 18.21$ min. (HP-1) under the same conditions as for the analysis of compound **4**. IR (ν_{max}, film cm^{-1}):



Scheme 4. Synthesis of methyl (2*R*,6*S*,10*S*)-2,6,10-trimethyldodecanoate (**1**). Reagents: (a) TsCl, Py, DMAP (cat), rt; (b) $LiAlH_4$, Et_2O, rt; (c) H_2, Pd/C, EtOH, 25 psi; (d) [O] Jones, −5 °C; (e) CH_2N_2, Et_2O, 0 °C.



(10a) (1a)

Scheme 5. Synthesis of methyl (2*S*,6*S*,10*S*)-2,6,10-trimethyldodecanoate (**1a**).

3030, 2917, 1728, 1454, 1102. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J=6.8 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.31–1.38 (m, 1H), 1.66–1.78 (m, 2H), 1.79–1.87 (m, 1H), 1.89–1.98 (m, 2H), 2.45 (dt, J=13.2, 2.0 Hz, 1H), 2.54 (dd, J=13.2, 11.6 Hz, 1H), 3.36 (dd, J=9.2, 5.2 Hz, 1H), 3.49 (t, J=9.2 Hz, 1H), 4.48 (s, 2H), 4.50–4.52 (m, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.26, 24.00, 30.32, 32.14, 37.32, 39.43, 42.50, 71.81, 73.20, 79.05, 127.69, 128.42, 138.30, 175.00.

Methyl (3*R*,6*S*,7*R*)-8-benzyloxy-6-hydroxy-3,7-dimethyloctanoate (7). Concentrated H_2SO_4 (5 drops) was added to the lactone **6** (0.8 g, 2.9 mmol) in MeOH (10.0 mL), and the mixture was refluxed for 10 min. After cooling, saturated aqueous $NaHCO_3$ was added, most of the MeOH was evaporated and the residue was extracted with ether. Washing (brine), drying ($MgSO_4$) and concentrating gave the hydroxy ester **7** (0.89 g, quant.). GC, t_R = 19.25 min. (HP-1) under the same conditions as for the analysis of compound **4**. $[\alpha]_D^{30}$ −1.10° (*c* 3.6, $CHCl_3$). IR (ν_{max}, film cm^{-1}): 3481, 3030, 2920, 1732, 1451, 1093, 1006. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.4 Hz, 3H), 1.16–1.25 (m, 1H), 1.41–1.45 (m, 2H), 1.49–1.55 (m, 1H), 1.86–1.91 (m, 1H), 1.96–1.99 (m, 1H), 2.12 (dd, J=14.8, 8.4 Hz, 1H), 2.32 (dd, J=14.8, 6.0 Hz, 1H), 2.62 (br s, 1H), 3.52 (d, J=6.0 Hz, 1H), 3.53 (d, J=4.8 Hz, 1H), 3.66 (s, 3H), 3.73 (td, J=6.8, 2.4 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.53 (d, J=12.0 Hz, 1H), 7.26–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.66, 19.80, 30.48, 31.26, 33.31, 37.74, 41.53, 51.41, 73.45, 74.31, 74.79, 127.63, 127.73, 128.46, 137.99, 173.73. MS (70 eV) *m/z* (%): 290 (M^+, 0.13), 276 (0.41), 248 (0.12), 230 (0.55), 184 (1.97), 152 (6.77), 127 (12.72), 108 (22.06), 91 (100), 81 (17.40), 69 (15.77), 55 (14.54).

Methyl (3*R*,6*S*,7*R*)-8-benzyloxy-3,7-dimethyl-6-*p*-toluene-sulfonyloxyoctanoate (8). Tosyl chloride (1.0 g, 5.2 mmol) was added in small portions (1 h) to the ester **7** (0.80 g, 2.6 mmol) in dry pyridine (7.8 mmol, 0.65 mL) and chloroform (5.0 mL), with magnetic stirring at 0 °C. After 5 h, ether was added and the solution was thoroughly washed with aqueous HCl (10%), satd aq $NaHCO_3$, dried and concentrated to afford the tosylate **8**; 0.84 g (70%). IR (ν_{max}, film cm^{-1}): 2928, 1735, 1451, 1358, 1178, 1100, 1009. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, J=6.8 Hz, 3H), 0.89 (d, J=7.2 Hz, 3H), 1.02–1.11 (m, 1H), 1.19–1.31 (m, 1H), 1.61–1.67 (m, 2H), 1.84 (hept, J=6.4 Hz, 1H), 1.98–2.03 (m, 1H), 2.03 (dd, J=15.2, 8.0 Hz, 1H), 2.18 (dd, J=15.2, 6.0 Hz, 1H), 2.42 (s, 3H), 3.24 (d, J=6.4 Hz, 2H), 3.65 (s, 3H), 4.31 (d, J=12.0 Hz, 1H), 4.39 (d, J=12.0 Hz, 1H), 4.81 (td, J=10.0, 3.2 Hz, 1H), 7.26–7.36 (m, 7H), 7.77 (d, J=8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.98, 19.46, 21.60, 29.38, 30.03, 31.95, 36.52, 41.25, 51.43, 71.68, 72.95, 84.46, 127.55, 127.69, 127.86, 128.33, 129.65, 129.81, 134.68, 138.35, 144.38, 173.30.

(+)-(3*R*,7*R*)-8-Benzyloxy-3,7-dimethyloctan-1-ol (9). The tosylate **8** (1.3 g, 2.8 mmol) from above, used without further purification, was dissolved in dry ether (80.0 mL) and reduced with $LiAlH_4$ (0.975 g, 25.6 mmol) by stirring at room temperature for 4 h. Excess hydride was destroyed with water (1.0 mL), NaOH 15% (1.0 mL) and adding more water (4.0 mL). The suspension was filtered through Celite®, dried and concentrated. The product obtained by ether extraction was chromatographed (hexane:ethyl acetate, 3:1), affording the alcohol **9** in 66% yield (0.49 g). GC, t_R = 16.60 min. (HP-1) under the same conditions as for the analysis of compound **4**. $[\alpha]_D^{30}$ +3.57° (*c* 2.8, $CHCl_3$). IR (ν_{max}, film cm^{-1}): 3371, 3031, 2912, 1456, 1106. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, J=6.4 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H), 1.07–1.15 (m, 2H), 1.25–1.43 (m, 6H), 1.54–1.61 (m, 2H), 1.76 (oct, J=6.4 Hz, 1H), 3.24 (dd, J=9.2, 6.8 Hz, 1H), 3.31 (dd, J=9.2, 6.4 Hz, 1H), 3.61–3.70 (m, 2H), 4.48 (d, J=12.4 Hz, 1H), 4.52 (d, J=12.4 Hz, 1H), 7.26–7.35 (m, 5H).^{13}C NMR (100 MHz, $CDCl_3$): δ 17.11, 19.60, 24.23, 29.40, 33.43, 33.83, 37.28, 39.99, 61.19, 72.96, 76.03, 127.42, 127.54, 128.31, 138.78. MS (70 eV) *m/z* (%): 264 (M^+, 3.34), 246 (0.18), 155 (1.22), 137 (3.24), 107 (36.88), 91 (100), 83 (15.95), 69 (36.73), 55 (27.99).

(+)-(3*R*,7*R*)-8-Benzyloxy-3,7-dimethyl-octanal (10). Alcohol **9** (0.35 g, 1.32 mmol) was added to a suspension of PCC (0.85 g, 3.96 mmol) in dry CH_2Cl_2 (50.0 mL). After 2 h, dry ether (10.0 mL) was added and the mixture of ether and CH_2Cl_2 was filtered through Celite®, silica gel and charcoal and then concentrated. The oil was rapidly purified through filtration on silica to afford the aldehyde **10** (0.31 g, 90%). GC, t_R = 15.49 min. (HP-1) under the same conditions as for the analysis of compound **4**. $[\alpha]_D^{30}$ +6.70° (*c* 8.5, $CHCl_3$). IR (ν_{max}, film cm^{-1}): 2926, 2717, 1724, 1457, 1098. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H), 1.09–1.13 (m, 1H), 1.19–1.23 (m, 1H), 1.25–1.32 (m, 3H), 1.34–1.46 (m, 1H), 1.76 (oct, J=6.8 Hz, 1H), 1.99–2.09 (m, 1H), 2.22 (ddd, J=16.4, 7.6, 2.4 Hz, 1H), 2.38 (ddd, J=16.4, 5.6, 2.0 Hz, 1H), 3.25 (dd, J=9.2, 6.4 Hz, 1H), 3.31 (dd, J=9.2, 6.4 Hz, 1H), 4.48 (d, J=12.0 Hz, 1H), 4.51 (d, J=12.0 Hz, 1H), 7.33–7.35 (m, 5H), 9.75 (dd, J=2.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.08, 19.92,

24.26, 28.10, 33.41, 33.65, 37.11, 51.12, 72.98, 75.91, 127.44, 127.54, 128.32, 138.75, 203.16. MS (70 eV) *m/z* (%): 262 (M^+, 0.69), 123 (3.75), 107 (29.51), 91 (100), 55 (18.07).

In the same manner, aldehyde **10a** was obtained in an 84% yield, with a diastereoisomeric ratio of 7:3 by GC. Both isomers have identical IR and MS spectra.

(+)-(2*R*,6*R*,8*RS*,10*S*)-1-Benzyloxy-2,6,10-trimethyldodecan-8-ol (11). A Grignard reagent was prepared as usual from (*S*)-(+)-1-bromo-2-methylbutane **(16)** (0.151 g, 1.0 mmol, 0.12 mL) and Mg (0.024 g, 1.0 mmol) in dry ether (10.0 mL). A solution of aldehyde **10** (0.160 g, 0.6 mmol) in dry ether (1.5 mL) was added to the organomagnesium reagent at 0 °C and stirred for 3.5 h at the same temperature. A solution of saturated NH_4Cl was added and the reaction mixture was extracted with ether, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (hexane:ethyl acetate, 9:1) and the alcohol **11** was obtained in a 74.3% yield (0.15 g) as a colorless oil. GC, t_R = 20.81 and 21.07 min. (HP-1) under the same conditions as for the analysis of compound **4**. $[\alpha]_D^{30}$ +4.0° (*c* 6.5, $CHCl_3$). IR (ν_{max}, film cm^{-1}): 3393, 2913, 1457, 1096. ^1H NMR (400 MHz, $CDCl_3$): δ 0.85–0.93 (m, 12H), 1.09–1.16 (m, 5H), 1.19–1.47 (m, 8H), 1.54–1.62 (m, 2H), 1.75–1.77 (m, 1H) [3.31 (dd, *J*=8.8, 6.0 Hz, 1H), 3.24 (dd, *J*=8.8, 6.4 Hz, 1H)], [3.32 (dd, *J*=8.8, 6.0 Hz, 1H), 3.24 (dd, *J*=8.8, 6.8 Hz, 1H)], 3.75–3.80 (m, 1H), 4.50 (s, 2H), 7.26–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (11.29, 11.34), (17.07, 17.13), (18.88, 19.31), (19.89, 20.41), (24.12, 24.24), (28.89, 30.31), (29.20, 29.42), (30.84, 31.01), (33.41, 33.45), 33.87, (36.61, 38.07), (45.24, 45.45), (45.77, 45.89), (67.29, 67.97), 72.96, 76.03, 127.41, 127.53, 128.31, 138.79. MS (70 eV) *m/z* (%): 316 (M^+, 0.62), 141 (9.69), 91 (100), 69 (17.66), 55 (17.13) (identical for the two isomers).

(2*R*,6*R*,8*RS*,10*S*)-1-Benzyloxy-2,6,10-trimethyl-8-*p*-toluenesulfonyloxydodecane (12). Tosyl chloride (0.18 g, 0.62 mmol) was added in small portions (1 h) to a magnetically stirred solution of the alcohol **11** (0.105 g, 0.31 mmol) in dry pyridine (20.0 mL) with a small amount of DMAP (0.031 mmol), at room temperature. After 20 h, the reaction mixture was extracted with ether. The organic phase was thoroughly washed with aqueous 10% HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated to afford the tosylate **12** and unreacted alcohol. After separation through a short silica gel column filtration (hexane) the alcohol was recycled twice, affording the tosylate **12** (0.084 g, 70%), used in the next step without further purification.

(2*R*,6*S*,10*S*)-1-Benzyloxy-2,6,10-trimethyldodecane (13). The tosylate **12** (0.25 g, 0.50 mmol) was dissolved in dry ether (15.0 mL) and reduced with $LiAlH_4$ (0.20 g, 5.2 mmol) by stirring at room temperature for 2.5 h. Excess hydride was destroyed with water (0.20 mL), NaOH 15% (0.20 mL) and adding more water (0.80 mL). The suspension was filtered through Celite®, dried and concentrated. The product obtained by ether extraction was used in the next step without purification.

(2*R*,6*S*,10*S*)-2,6,10-Trimethyldodecan-1-ol (14). A mixture of benzyl ether **13** (0.07 g, 0.22 mmol) and 10% Pd/C (0.015 g) in 3.0 mL of 95% ethanol was hydrogenated at room temperature and 25 psi in a Parr® apparatus for 5.0 h. The mixture was filtered through Celite®, and the filtrate evaporated at reduced pressure to afford 0.044 g of alcohol **14**, in a 44% overall yield from **12**. GC, t_R = 11.31 min. (HP-1) under the same conditions as for the analysis of compound **4**. ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, *J*=6.8 Hz, 6H), 0.86 (t, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.4 Hz, 3H), 1.06–1.10 (m, 4H), 1.24–1.39 (m, 12H), 1.61 (oct, *J*=6.0 Hz, 2H), 3.42 (dd, *J*=10.4, 6.4 Hz, 1H), 3.51 (dd, *J*=10.4, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.42, 16.55, 19.27, 19.68, 24.37, 24.51, 29.37, 32.75, 33.42, 34.42, 35.78, 36.97, 37.26, 37.49, 68.48.

(2*R*,6*S*,10*S*)-2,6,10-Trimethyldodecanoic acid (15). Jones CrO_3 (1.0 mL) was added to a solution of the alcohol **14** (0.015 g, 0.06 mmol) in acetone (5.0 mL) and the mixture was magnetically stirred for 30 min at −5 °C. The excess CrO_3 was destroyed with MeOH and the mixture was concentrated in vacuo, diluted with water and extracted with ether. The ether extract was washed with H_2O and satd NaCl solution, dried with $MgSO_4$ and concentrated. The residue obtained was used directly in the next step.

(−)-Methyl (2*R*,6*S*,10*S*)-2,6,10-trimethyldodecanoate (1). The residue **15** in ether (5.0 mL) was treated with ethereal CH_2N_2, at 0 °C, until the reaction mixture turned yellow. The solution was stirred for 30 min, concentrated and the residual oil was chromatographed over silica gel (hexane:ethyl acetate, 9.5:0.5), yielding 8.7 mg of pheromone **1**, (87%), overall yield from **14**. GC, column HP-20M at 70 °C+4 °C/min, carrier gas: H_2, 1.5–2.0 mL/min, t_R = 9.16 min. $[\alpha]_D^{30}$ −8.33° (*c* 2.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, *J*=6.8 Hz, 3H), 0.84 (d, *J*=7.2 Hz, 3H), 0.85 (t, *J*=7.2 Hz, 3H), 1.01–1.10 (m, 3H), 1.14 (d, *J*=6.8 Hz, 3H), 1.16–1.43 (m, 13H), 2.44 (sext, *J*=7.2 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.41, 17.03, 19.26, 19.65, 24.45, 24.66, 29.45, 32.64, 34.10, 34.41, 36.82, 36.95, 37.34, 39.46, 51.46, 177.46. MS (70 eV) *m/z* (%): 256 (M^+, 2.55), 241 (0.71), 225 (0.86), 166 (6.84), 157 (15.28), 129 (5.97), 101 (43.51), 97 (17.46), 88 (100), 69 (17.91), 55 (25.57).

In the same manner, the ester **1a** was obtained in 65% yield, as a diastereoisomeric mixture, 7:3, *S:R* at C-2, by GC. GC, t_R=9.23 min and 9.16 min. (HP-20M) under the same conditions as for the analysis of compound **1** $[\alpha]_D^{30}$ +4.20° (*c* 3.2, $CHCl_3$). The ^1H NMR

and MS spectra were identical to those of compound **1**. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.43, (17.03, 17.14), (19.20, 19.26), (19.59, 19.65), 24.46, 24.69, (29.45, 29.56), 32.63, 34.14, 34.41, 36.82, (36.90, 36.94), 37.37, 39.48, 51.47, 177.47.

The MS of compounds **1** and **1a** were identical to that of the natural pheromone.[8]

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