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Synthesis of Racemic 6,10,14-Trimethylpentadecan-2-ol, a Pheromone of Rice Moth and 5,9,13-Trimethyltetradecanoic Acid, a Component of Marine Sponge from a Common Intermediate

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Abstract—A facile synthesis of *dl*-6,10,14-trimethylpentadecan-2-ol (**1**) a pheromone component of rice moth, *Corcyra cephalonica* Stainton and 5,9,13-trimethyltetradecanoic acid (**2**) a component of marine sponge, *Cinachyrella alloclada* Uliczka, using a common intermediate, hexahydrofarnesol is accomplished. The salient features for **1** are: Grignard coupling of **5** with allylmagnesium bromide and oxymercuration–demercuration whereas for **2** they are: Knoevenagel condensation and subsequent hydrogenation.

The usefulness of pheromones, plant growth regulators and natural insecticides in the Integrated Pest Management programme is well documented.[1] Isolation and characterisation of potentially bioactive principles of marine products is also gaining importance.[2] These methyl branched compounds have some novel biogenetic features as well and are also important as biological markers.[3] Recent work on the identification of 6,10,14-trimethylpentadecan-2-ol[4] (**1**) an insect pheromone of rice moth *Corcyra cephalonica* Stainton and 5,9,13-trimethyltetradecanoic acid[5] (**2**), a component of marine sponge, *Cinachyrella alloclada* Uliczka prompted us to explore their synthesis through a common intermediate viz. hexahydrofarnesol. Yoshinobu *et al.*[6] have reported synthesis of the chiral alcohol **1** wherein the chiral template was the starting material, sulphonation, alkylation and Grignard coupling reactions were the principal steps. Our approach, even though leading to racemic products is facile, and has an additional advantage that the intermediate (hexahydrofarnesol) has been used for the synthesis of a marine natural product also. In principle, the sequence of reactions could lead to chiral products if the appropriate stereoisomer of **4** is used as a starting material.

The *dl*-farnesol on hydrogenation with 10% Pd/C gave almost quantitative yield of hexahydrofarnesol (**4**), a common intermediate for the synthesis of **1** and **2**. For the synthesis of **1**, hexahydrofarnesol was converted into the bromo compound (**5**) with 48% HBr and conc. H_2SO_4. The bromide was subjected to Grignard coupling with allylmagnesium bromide in the presence of Li_2CuCl_4 as catalyst to yield the coupled product (**6**). The terminal olefin in **6** on subsequent reaction with oxymercuration–demercuration afforded the desired racemic compound (**1**).

For the synthesis of compound **2**, the intermediate **4** was oxidised with PCC and the aldehyde thus obtained was condensed with malonic acid in the presence of pyridine and catalytic amount of piperidine to give conjugated acid (**8**), with two carbon homologation. The latter on hydrogenation with 10% Pd/C afforded the desired acid (**2**) and was characterised as its methyl ester.

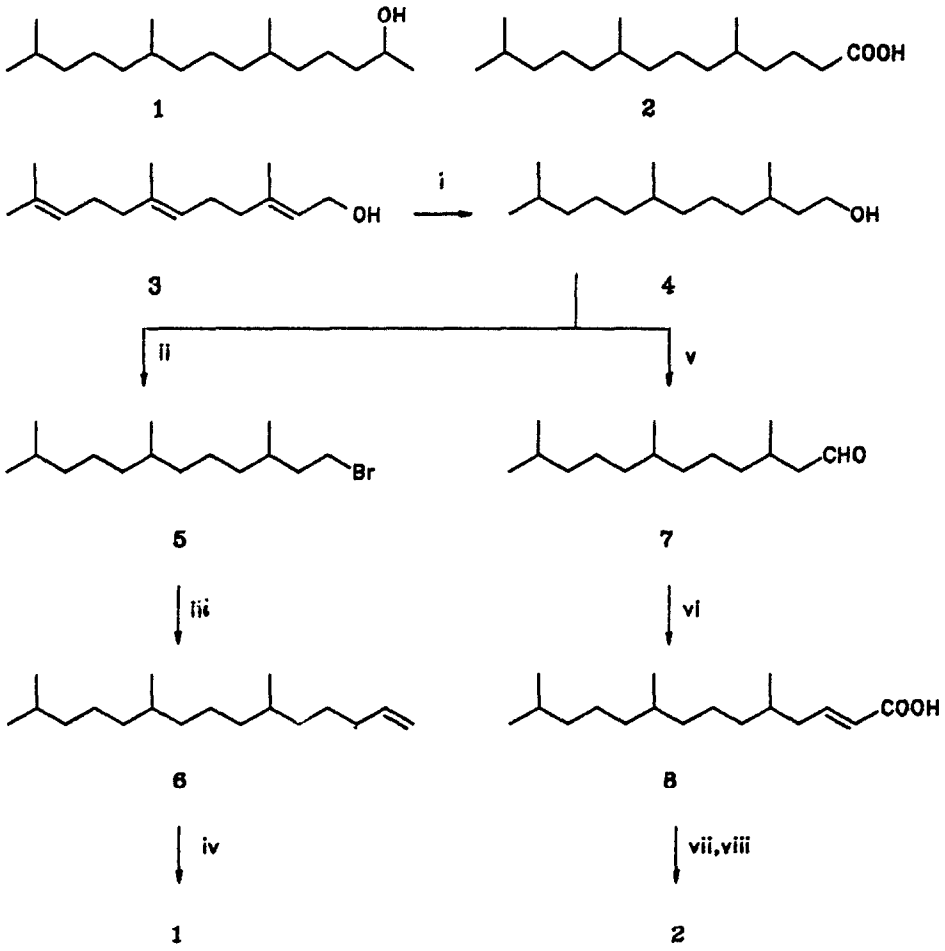
The physical and spectral properties of some of the intermediates and final products **1** and **2** are compatible with the reported data.[4,6]

Experimental

The IR spectra were recorded as thin films on a Perkin–Elmer infracord spectrophotometer model 737 and are expressed in cm^{-1}. The PMR spectra were recorded on a Varian E-360 60 MHz instrument and values are given in ppm (δ-scale). GLC was carried out on a Shimadzu 16A model gas chromatogram using a FID detector, 3% OV-17 on gas chrom Q (80–100 mesh) and N_2 as a carrier gas. Mass spectra were recorded on a Shimadzu QP-1000A Mass Spectrometer in EI (70 eV) mode. Anhydrous solvents were prepared by standard procedures prior to use. The organic extracts were dried over anhydrous Na_2SO_4. Column chromatography was carried out with 100–200 mesh silica gel and neutral aluminium oxide (Acme Synthetic Chemicals).

3,7,10-Trimethyldodecan-1-ol (4)

To a hydrogenation flask containing 10% Pd/C (0.1 g), ethanol (50 ml) and glacial acetic acid (2–3 drops), farnesol (20 g, 89 mmol) was added and hydrogenation was carried out at a pressure of 40 psi at room temperature for 8 h. The contents of the flask were filtered on a celite bed with a thickness of 1 inch. **4** (19 g, 95%) was obtained after evaporation of the solvent and removal of acetic acid by applying high vacuum. This was subjected to column chromatography on neutral alumina (280 g) with ethyl acetate:hexane (5:100) to give pure **4**. IR ν_{max}(film): 3400, 2930, 2920, 2890, 1470, 1385, 1375, 1065; PMR (δ): 0.87 (d, 12H, 4 x -CH–C$\underline{H}_3$), 1.20 (bs, 14H, -CH_2), 1.75 (m, 3H, 3 x -CH), 3.6 (t, 2H, -C$\underline{H}_2$OH), 4.2 (bs, 1H,



Scheme I.
i. H_2/10% Pd-C/EtOH
ii. 48% HBr/conc. H_2SO_4
iii. CH_2=$CHCH_2MgBr$/THF/Li_2CuCl_4
iv. $Hg(OAc)_2$/THF/H_2O, alk. $NaBH_4$
v. PCC/CH_2Cl_2
vi. Malonic acid/Py/piperidine
vii. H_2/10% Pd-C/MeOH
viii. MeOH/PTS

-CH_2OH), GLC: 3% OV-17, N_2 flow rate, 40 ml/min, 140 °C — 0 min, 140–230 °C, 8 °C/min, 230 °C — 1 min, r_t = 5.42 min, MS (EI, 70 eV) : 227 [0.7%, $(M - 1)^+$].

3,7,10-Trimethyl-1-bromododecane (5)

To a round bottom flask containing 48% hydrobromic acid (11.92 g, 147 mmol), 3–4 drops of conc. H_2SO_4 was added by cooling the flask in an ice bath. Finally hexahydrofarnesol (**4**) (2 g, 8.9 mmol) was added dropwise. The contents of the flask were refluxed in an oil bath for 6 h and subjected to the usual work up. Pure **5** was obtained by column chromatography on neutral alumina (30 g) with ethyl acetate:hexane (5:100). Yield: 1.3 g (65%), IR ν_{max} (film): 2960, 2940, 2880, 1470, 1380; PMR (δ): 0.85 (d, 12H, 4 x -CH_3), 1.21 (bs, 14H, -CH_2), 1.75 (m, 3H, -CH), 3.36 (t, 2H, -CH_2Br), MS (EI, 70 eV): 290 (44.2%, M^+), 292 [30.0, $(M + 2)^+$]

6,10,14-Trimethylpentadec-1-ene (6)

Grignard coupling of allylmagnesium bromide [prepared from allyl bromide (0.423 g, 3.5 mmol) and magnesium turnings (0.101 g, 4.2 mmol)] with 3,7,10-trimethyl-1-bromododecane **5** (1.0 g, 3.5 mmol) in THF (70 ml) in the presence of Li_2CuCl_4 (0.175 ml, 0.020 mmol) under Ar atmosphere afforded 6,10,14-trimethylpentadec-1-ene **6** after the usual work up. Pure **6** was obtained by column chromatography on silica gel (15 g) with ethyl acetate:hexane (5:100). Yield: 0.450 g (45%); IR ν_{max} (film): 2960, 2930, 2870, 1640, 1460, 1375, 990, 910, 725; PMR (δ): 0.90 (t, 12H, 4 x -CH_3), 1.2 (s, 16H, -CH_2), 1.7–1.9 (m, 3H, -CH–CH_3), 2.30 (bt, 2H, -CH_2-

CH=C$\underline{H}_2$), 4.9 (bd, 2H, CH=C$\underline{H}_2$), 5.45–6.1 (m, 1H, -C$\underline{H}$=CH_2), MS (EI, 70 eV): 252 (9.4%, M^+).

6,10,14-Trimethylpentadecan-2-ol (1)

A solution of 6,10,14-trimethylpentadec-1-ene **6** (0.45 g, 1.8 mmol) in THF (9 ml) was added to a stirred solution of $Hg(OAc)_2$ (0.572 g, 1.8 mmol) in H_2O (3 ml). The mixture was stirred for 4 h at room temperature and then cooled to 0 °C. To the cooled solution was added NaOH (5 ml, 3N), followed by a solution of $NaBH_4$ (0.150 g, 3.95 mmol) in NaOH (5 ml, 3N). After being stirred overnight at room temperature, the mixture was diluted with H_2O and filtered and the filtrate was extracted with ether. Usual work up of the extract gave crude product, which was purified by column chromatography on silica gel (7.5 g) with ethyl acetate:hexane (10:100) to give pure (*dl*)-6,10,14-trimethylpentadecan-2-ol (**1**). Yield: 0.27 g (60%); IR ν_{max} (film): 3420, 2970, 2940, 2860, 1470, 1460, 1125, 1075, 740; PMR(δ): 0.89 (d, 12H, 4x -CH–C$\underline{H}_3$), 1.0(d, 3H, -CH(OH)–C$\underline{H}_3$), 1.25 (bs, 16H, CH_2), 1.32–2.30 (m, 6H, 3 x C$\underline{H}$ & -CH_2OH), 3.6–3.85 (m, 1H, C$\underline{H}$(OH)–CH_3); MS (EI, 70 eV): 270 (0.80%, M^+), 252 (0.8).

3,7,11-Trimethyldodecanal (7)

In a three necked round bottom flask fitted with a reflux condenser and a guard tube, was suspended pyridinium chlorochromate (PCC) (1.34 g, 6.25 mmol) in anhydrous CH_2Cl_2 (40 ml). A solution of hexahydrofarnesol (**4**) (1.0 g, 4.35 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to the stirred solution at room temperature and stirring was continued for 1.5 h. After completion of the reaction, dry ether (50 ml) was added to the reaction mixture and the supernatant was decanted. The insoluble residue was washed three times, each time with dry ether (20 ml). The combined organic extract was passed through a bed of celite and the solvent was removed by distillation, to obtain crude 3,7,11-trimethyldodecanal. Pure (**7**) was obtained by passing it through a column of silica gel (15 g) using ethyl acetate:hexane (5:100). Yield: 0.70 g (70%); TLC of **7** using 5% ethyl acetate in hexane gave a single yellow spot when sprayed with 5% methanolic 2,4-dinitrophenylhydrazine hydrochloride solution; IR ν_{max} (film): 2960, 2940, 2820, 1715, 1470, 1380, 1170, 1130, 940.

5,9,13-Trimethyltetradec-2-enoic acid (8)

To a round bottom flask containing malonic acid (0.322 g, 3.09 mmol) and pyridine (20 ml), 3,7,11-trimethyldodecanal (**7**) (0.70 g, 3.09 mmol) was added dropwise with stirring at 0 °C. A guard tube was inserted at the mouth of the flask and the contents were left at room temperature for 60 h. The contents were then heated until evolution of CO_2 ceased (8 h). The reaction mixture was stirred with equal volume of water, which was followed by the addition of 25% HCl (100 ml). The crude product (**8**) was obtained by extracting it with $CHCl_3$ following the usual work up. Yield: 0.595 g (85%). Methyl ester: quantitative yield. IR ν_{max} (film) 2950, 2920, 2850, 1745, 1660, 1470, 1380, 1160, 985, 970; PMR (δ): 0.90 (d, 12H, CH_3), 1.25 (bs, 12H, CH_2), 1.4–2.6 (m, 5H, 3C$\underline{H}$–CH_3, CH_2), 3.60 (s, 3H, $COOCH_3$), 6.0 (d, J = 17 Hz, CH=C$\underline{H}$–COOMe), 7.09 (dt, 1H, -CH_2–C$\underline{H}$=CH–COOMe); MS (EI, 70eV), 282 (1.7%, M^+), 251 (1.6), 166 (4.4), 158 (4.8), 157 (4.7), 143 (18.9), 142 (15.0), 125 (19.6), 111 (17.9), 96 (18.4), 85 (38), 69 (35), 57 (45.9), 55 (55.2), 43 (100).

5,9,13-Trimethyltetradecanoic acid (2)

In the hydrogenation flask containing 10% Pd/C (100 mg) and CH_3OH (10 ml) was added **8** (0.1 g, 0.373 mmol) and hydrogenation was carried out for 5 h. The reaction mixture was filtered and the solvent was evaporated to obtain 5,9,13-trimethyltetradecanoic acid (**2**). This was converted to its methyl ester by refluxing it with methanol and *p*-toluenesulphonic acid (PTS). Pure **2** was obtained by passing it on a column of silica gel (10 g) using ethyl acetate:hexane (5:100). Yield: 0.095 g (95%); IR ν_{max} (film): 2940, 2920, 2860, 1740, 1470, 1380, 1170, 725; PMR (δ) : 1.86 (d, 12H, 4 x -CH–C$\underline{H}_3$), 1.23 (bs, 18H, -CH_2), 1.8–2.5 (m, 3H, -CH–C$\underline{H}_3$), 3.66 (s, 3H, -$COOCH_3$); GLC: 3% OV-17, N_2 flow rate, 40 ml/min, 150 °C — O min, 150–250 °C, 8 °C/min, 250 °C — 5 min, r_t = 7.642 min, MS (EI, 70 eV) 284 (2.9%, M^+), 253 (0.8), 170 (3.8), 169 (3.8), 158 (2.0), 157 (2.0), 144 (18.9), 130 (13.4), 129 (13.0), 98 (13.1), 97 (12.5), 87 (25.6), 74 (77.8), 57 (49.7), 55 (52.5), 43 (100), 41 (74.6).

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