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Asymmetric synthesis of phoenicol, ferrugineol and cruentol, aggregation pheromones of *Rhynchophorus* spp.

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Abstract

Syntheses of phoenicol, ferrugineol, and cruentol, aggregation pheromones of *Rhynchophorus* palm weevils, have been achieved with an overall yield of 42, 40 and 41%, respectively (five steps), in high enantiomeric purity.

1. Introduction

Rhynchophorus palm weevils are major pests of coconut and oil palm crops. They produce single isomers of methyl-branched secondary alcohols as aggregation pheromones. *Rhynchophorus phoenicis* (F.), the African palm weevil, produces 3-methyl-4-octanol;[1] Mori et al.[2] achieved the synthesis of all the stereoisomers in order to determine the absolute configuration of the naturally occurring isomer (3*S*,4*S*). Two other Asian palm weevils, *R. ferrugineus* (Oliv.) and *R. vulneratus* (Panz.) produce 4-methyl-5-nonanol;[3,4] its absolute configuration was shown to be (4*S*,5*S*).[5,6] Recently, *R. ferrugineus* has been reported as a new pest in Europe (Granada, Spain).[7] *R. cruentatus* (F.), the palmetto weevil, produces 5-methyl-4-octanol;[8] the absolute configuration of the naturally occurring stereoisomer was established by Oehlschlager et al. as (4*S*,5*S*);[9] Mori et al. carried out its synthesis[10] starting from an enantiomerically pure epoxy alcohol as the source of chirality. Continuing our work on the synthesis of insect pheromones,[11–13] we now report the synthesis of the palm weevil pheromones mentioned above (Scheme 1) based on Evans' methodology.[14–16] This approach involves the use of a chiral oxazolidinone which allows an effective control of the relative and absolute stereochemistry of the aldol reaction.

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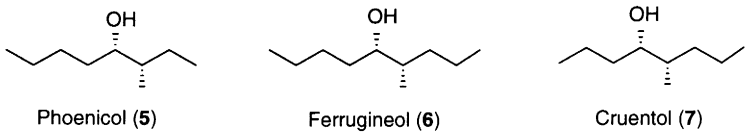
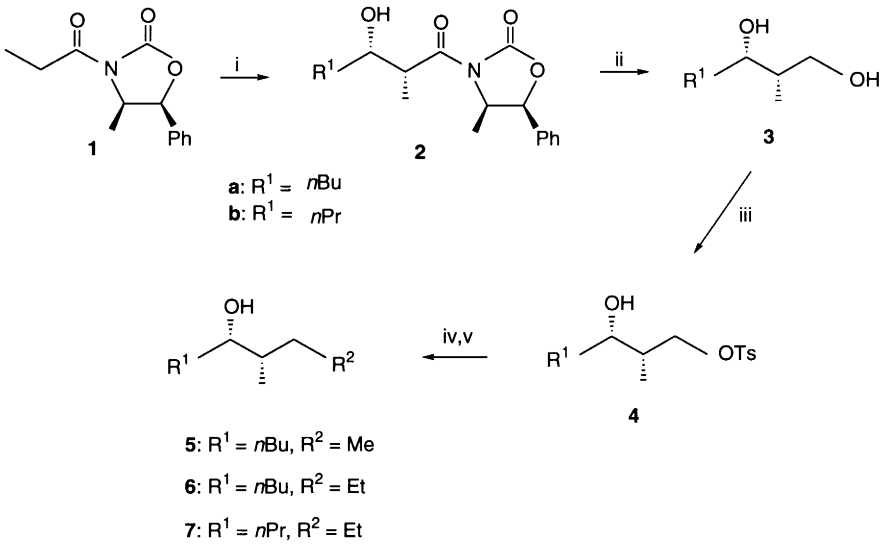


Scheme 1. Structures of palm weevil pheromones

2. Results and discussion

The syntheses were carried out as shown in Scheme 2. Thus, following the procedure of Evans for the asymmetric aldol condensations, the boron enolate derived from chiral imide **1** was treated with the corresponding aldehyde at −78°C to afford *syn* adducts **2** in 91 and 81% yield, respectively. Satisfactory spectral and analytical data were obtained and, as expected, the stereoselectivity reached was high: >99% d.e. based on NMR analysis. Cleavage of the oxazolidinone auxiliary was accomplished using lithium borohydride[17] to yield diols **3** (85, 87%) which were converted to the corresponding tosylates **4** (83, 86% yield) under standard conditions. The remaining steps of the synthesis were protection of the secondary hydroxy group as the tetrahydro-2*H*-pyran-2-yl (THP) ether followed by elongation of the carbon chain. Thus, treatment of **4a** with DHP provided the crude protected tosylate which was added to lithium dimethylcuprate. Subsequent removal of the THP group with PPTS furnished the desired phoenicol **5** in 65% yield. In a similar manner, using lithium diethylcuprate, ferrugineol **6** was obtained in 63% yield. Finally, the synthesis of cruentol **7** was accomplished from **4b** and lithium diethylcuprate in 67% yield. The overall yield of pheromones was 42, 40 and 41%, respectively, based on **1**. In all cases the analytical and spectral data were in accord with the literature as well as the specific rotation values for the enantiomerically pure compounds (>99% e.e.).[2,5,10]



Scheme 2. Reagents and conditions: (i) nBu$_2$BOTf/DIPEA, −78°C, R^{1}CHO (91% of **2a**, 81% of **2b**); (ii) $LiBH_4$, Et_2O, 0°C (85% of **3a**, 87% of **3b**); (iii) TsCl/Py, rt, 14 h (83% of **4a**, 86% of **4b**); (iv) DHP, rt, 4 h; (v) Me_2CuLi or Et_2CuLi, then PPTS/MeOH (65% of **5** based on **4a**, 63% of **6** based on **4a**, 67% of **7** based on **4b**)

In summary, an efficient five-step synthesis of phoenicol, ferrugineol, and cruentol has been achieved in high overall yield, suitable for large-scale application and affording high enantiomeric purity pheromones.

3. Experimental

3.1. General

Solvents were dried by distillation from drying agents as follows: THF, Et_2O (Na–benzophenone); dichloromethane (P_2O_5); MeOH (Mg). Column chromatography was performed by using 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions on a Varian Gemini 200. Elemental analyses were performed in a Carlo Erba EA 1108 Analyzer. Mass spectra were recorded on a Finnigan MAT GCQ. Infrared spectra were recorded on a Nicolet 510M FT-IR as films or KBr pellets. Optical rotations were measured in a JASCO-DIP-370 polarimeter.

3.2. (4R,5S)-[(2R,3S)-3-Hydroxy-2-methylheptanoyl]-4-methyl-5-phenyl-2-oxazolidinone **2a**

To a cooled (0°C), stirred solution of imide **1** (1.17 g, 5 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise di-*n*-butylboryltriflate (1.19 ml, 5.5 mmol) followed by freshly distilled DIPEA (1.05 ml, 6 mmol). The mixture was maintained at 0°C for 30 min and then cooled to −78°C. Freshly distilled valeraldehyde (0.58 ml, 5.5 mmol) was added in one portion and the mixture was held at −78°C for 30 min, allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was then quenched by the addition of 4 ml of phosphate buffer solution (pH 7) and MeOH (12 ml). This cloudy solution was treated with 12 ml of methanol:30% aqueous hydrogen peroxide solution (2:1) and the resulting mixture was stirred for an additional hour at rt. The organic solvents were removed in vacuo and the resulting slurry was extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford, after flash chromatrography (EtOAc:hexane, 1:3), 1.45 g (91%) of **2a** as a white solid: mp 98–99°C (hex.); $[\alpha]_D^{25}$ +11.3 (*c* 1, CH_2Cl_2); IR (KBr): ν=3455 (OH), 1782 (C=O), 1688 (C=O) cm^{-1}; ^1H NMR: δ=0.92 (d, *J*=6.6 Hz, 3H), 0.94 (t, *J*=6.4 Hz, 3H), 1.26 (d, *J*=7.0 Hz, 3H), 1.18–1.63 (m, 6H), 2.91 (d, *J*=2.9 Hz, 1H), 3.80 (dq, *J*=2.6 and 7.0 Hz, 1H), 3.96–4.00 (m, 1H), 4.76–4.89 (m, 1H), 5.71 (d, *J*=7.3 Hz, 1H), 7.26–7.51 (m, 5H); ^{13}C NMR: δ=10.19, 14.10, 14.45, 22.71, 28.22, 33.61, 42.14, 54.76, 71.50, 78.92, 125.54, 128.69, 128.79, 133.04, 152.52, 177.38; anal. calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.53; H, 7.80; N, 4.41.

3.3. (4R,5S)-[(2R,3S)-3-Hydroxy-2-methylhexanoyl]-4-methyl-5-phenyl-2-oxazolidinone **2b**

Prepared as described for **2a**, starting from **1** (1.17 g, 5 mmol) and using butyraldehyde (0.5 ml, 5.5 mmol), **2b** was obtained as an oil (1.24 g, 81%): $[\alpha]_D^{25}$ +13.1 (*c* 1.4, CH_2Cl_2); IR (neat): ν=3508 (OH), 1778 (C=O), 1698 (C=O) cm^{-1}; ^1H NMR: δ=0.91 (d, *J*=6.6 Hz, 3H), 0.97 (t, *J*=7.0 Hz, 3H), 1.25 (d, *J*=7.0 Hz, 3H), 1.30–1.66 (m, 4H), 2.93 (br s, 1H), 3.79 (dq, *J*=2.6 and 7.0 Hz, 1H), 4.00 (m, 1H), 4.75–4.89 (m, 1H), 5.71 (d, *J*=7.3 Hz, 1H), 7.30–7.50 (m, 5H); ^{13}C NMR: δ=10.22, 14.05, 14.42, 19.25, 36.03, 42.16, 54.73, 71.22, 78.89, 125.51, 128.66, 128.75, 133.02, 152.51, 177.29; MS (70 eV): *m/z* (%)=118 (80.73), 134 (69.83), 172 (63.03), 233 (100), 306 (M) (0.52).

3.4. (2S,3S)-2-Methyl-1,3-heptanediol **3a**

To a cooled solution (0°C) of **2a** (1.28 g, 4 mmol) in Et_2O (80 ml) was added water (1 ml) followed by $LiBH_4$ (0.23 g, 10.4 mmol). The solution was stirred for 1 h at 0°C and then for 1 h at rt. Aqueous NaOH solution (1N, 44 ml) was added dropwise, and the mixture was stirred for 1 h at rt. The aqueous layer was extracted with EtOAc (4×40 ml), the combined organic layers were dried ($MgSO_4$), filtered,

and concentrated in vacuo. Purification of the crude product by flash chromatography (EtOAc:hexane, 1:10→1:1) yielded **3a** as an oil: 0.5 g (85%); $[\alpha]_D^{25}$ −6.7 (*c* 2.4, CH_2Cl_2); IR (neat): ν=3357 (OH) cm^{-1}; ^1H NMR: δ=0.91 (d, *J*=7.3 Hz, 3H), 0.92 (t hidden, *J*=6.2 Hz, 3H), 1.26–1.53 (m, 6H), 1.71–1.87 (m, 1H), 2.72 (br s, 1H), 2.95 (br s, 1H), 3.70 (d, *J*=5.5 Hz, 2H), 3.79–3.83 (m, 1H); ^{13}C NMR: δ=10.04, 14.08, 22.74, 28.42, 33.70, 39.01, 67.03, 74.41.

*3.5. (2S,3S)-2-Methyl-1,3-hexanediol **3b***

Under the same conditions described for **3a**, by reduction of **2b** (1.22 g, 4 mmol), the title compound was isolated as an oil: 0.46 g (87%); $[\alpha]_D^{25}$ −4.8 (*c* 1.5, CH_2Cl_2); IR (neat): ν=3359 (OH) cm^{-1}; ^1H NMR: δ=0.90–0.99 (m, 6H), 1.27–1.60 (m, 4H), 1.71–1.88 (m, 1H), 2.48 (br s, 1H), 2.66 (br s, 1H), 3.72 (d, *J*=5.1 Hz, 2H), 3.80–3.87 (m, 1H); ^{13}C NMR: δ=10.14, 14.13, 19.41, 36.22, 39.10, 67.14, 74.25.

*3.6. (2S,3S)-2-Methyl-1-tosyloxy-3-heptanol **4a***

To a cooled solution (0°C) of **3a** (292 mg, 2 mmol) in dichloromethane (15 ml) was added pyridine (0.66 ml, 8 mmol) and then tosyl chloride (0.44 g, 2.3 mmol). The mixture was stirred for 14 h at room temperature. The reaction was quenched with water (15 ml) and then diethyl ether (15 ml) was added. The aqueous phase was extracted with diethyl ether (3×15 ml) and the combined organic phases were washed with 2N HCl (5×10 ml), brine (5 ml), dried with magnesium sulfate and concentrated in vacuo. This crude product was purified by flash chromatography (EtOAc:hexane, 1:10→1:1) yielding **4a** as an oil: 500 mg (83%); $[\alpha]_D^{25}$ −4.3 (*c* 2.07, CH_2Cl_2); IR (neat): ν=3375 (OH), 1355, 1172 (S=O) cm^{-1}; ^1H NMR: δ=0.82 (d, *J*=6.9 Hz, 3H), 0.89 (t, *J*=6.5 Hz, 3H), 1.14–1.51 (m, 6H), 1.72 (br s, 1H), 1.89 (m, 1H), 2.45 (s, 3H), 3.69 (m, 1H), 3.88 (dd, *J*=6.0 and 9.6 Hz, 1H), 4.07 (dd, *J*=7.9 and 9.6 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 2H), 7.79 (d, *J*=8.4 Hz, 2H); ^{13}C NMR: δ=9.51, 14.09, 21.70, 22.68, 28.33, 34.11, 37.74, 70.48, 72.78, 127.79, 129.76, 132.85, 144.68.

*3.7. (2S,3S)-2-Methyl-1-tosyloxy-3-hexanol **4b***

Prepared as described for **4a**, starting from **3b** (264 mg, 2 mmol) the title compound was isolated as an oil (492 mg, 86%): $[\alpha]_D^{25}$ −5.1 (*c* 1.6, CH_2Cl_2); IR (neat): ν=3528 (OH), 1356, 1171 (S=O) cm^{-1}; ^1H NMR: δ=0.86 (d, *J*=7.0 Hz, 3H), 0.92 (t, *J*=7.1 Hz, 3H), 1.22–1.58 (m, 5H), 1.91–2.00 (m, 1H), 2.46 (s, 3H), 3.73 (m, 1H), 3.90 (dd, *J*=6.0 and 9.5 Hz, 1H), 4.09 (dd, *J*=7.7 and 9.5 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 2H), 7.81 (d, *J*=8.4 Hz, 2H); ^{13}C NMR: δ=9.53, 14.03, 19.33, 21.66, 36.53, 37.78, 70.22, 72.77, 127.78, 129.77, 132.89, 144.69.

*3.8. Phoenicol [(3S,4S)-3-methyl-4-octanol] **5***

To a stirred solution of the tosylate **4a** (390 mg, 1.3 mmol) DHP (0.24 ml, 2.6 mmol) and PPTS (0.13 g, 0.52 mmol) in dichloromethane (10 ml) were added at room temperature. The mixture was stirred for 4 h and then diethyl ether (20 ml) was added. The organic solution was washed with water (10 ml), $NaHCO_3$ (3×10 ml), brine (5 ml), dried with magnesium sulfate and concentrated in vacuo. This crude product was used in the next step without further purification. Methyllithium in diethyl ether (1.6 M, 8.13 ml, 13 mmol) was added to a cooled suspension of copper(I) iodide (1.23 g, 6.5 mmol) in dry diethyl ether (20 ml) at 0°C under nitrogen. This mixture was stirred for 30 min and then cooled to −78°C. To this was added a solution of the above-described tosylate in dry diethyl ether (5 ml). The reaction mixture

was stirred for 2 h at rt and then poured at 0°C into a mixture of satd. aq. ammonium chloride solution and 29% aq. ammonia solution (4:1). The aqueous layer was extracted with diethyl ether (3×15 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The obtained oil was dissolved in MeOH (5 ml) and PPTS (0.1 g, 0.4 mmol) was added. The reaction mixture was refluxed for 4 h. The methanol was removed under atmospheric pressure and after the usual workup the residue was chromatographed over silica gel (*n*-pentane:diethyl ether, 100:1→10:1) and distilled to give **5** as a colorless liquid (122 mg, 65%): $[\alpha]_D^{25}$ −21.9 (*c* 1.23, Et_2O) {lit.[2] $[\alpha]_D^{20}$ −20.7 (*c* 1.01, Et_2O)}; IR (neat): ν=3407 (OH) cm^{-1}; ^1H NMR: δ=0.84–0.98 (m, 9H), 1.15–1.53 (m, 10H), 3.49–3.57 (m, 1H); ^{13}C NMR: δ=11.93, 13.21, 14.12, 22.83, 26.09, 28.49, 34.26, 40.00, 74.88; MS (70 eV): *m/z* (%)=143 (M−1) (1.68), 69 (100).

3.9. Ferrugineol [(4S,5S)-4-methyl-5-nonanol] ***6***

Prepared as described for **5**, starting from **4a** (390 mg, 1.3 mmol) and using ethyllithium the title product was isolated as a colorless liquid: 130 mg (63%); $[\alpha]_D^{25}$ −28.0 (*c* 1.0, Et_2O) {lit.[5] $[\alpha]_D^{19}$ −26.5 (*c* 0.88, Et_2O)}; IR (neat): ν=3416 (OH) cm^{-1}; ^1H NMR: δ=0.83–0.92 (m, 9H), 1.12–1.47 (m, 12H), 3.48 (br s, 1H); ^{13}C NMR: δ=13.56, 14.12, 14.37, 20.50, 22.83, 28.51, 34.20, 35.64, 37.92, 75.16; MS (70 eV): *m/z* (%)=157 (M−1) (2.61), 69 (100).

3.10. Cruentol [(4S,5S)-5-methyl-4-octanol] ***7***

Prepared as described for **5**, starting from **4b** (372 mg, 1.3 mmol) and using ethyllithium the title product was isolated as a colorless liquid: 126 mg (67%); $[\alpha]_D^{25}$ −32.5 (*c* 1.32, Et_2O) {lit.[10] $[\alpha]_D^{19}$ −33.1 (*c* 1.14, Et_2O)}; IR (neat): ν=3420 (OH) cm^{-1}; ^1H NMR: δ=0.86–0.98 (m, 9H), 1.14–1.56 (m, 10H), 3.47–3.54 (m, 1H); ^{13}C NMR: δ=13.60, 14.21, 14.39, 19.49, 20.52, 35.63, 36.69, 37.97, 74.91; MS (70 eV): *m/z* (%)=143 (M−1) (0.74), 55 (100).

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