# Pheromone Synthesis, CXCIII[+]

# Simple Synthesis of (±)-Stigmolone (8-Hydroxy-2,5,8-trimethyl-4-nonanone), the Pheromone of *Stigmatella* aurantiaca

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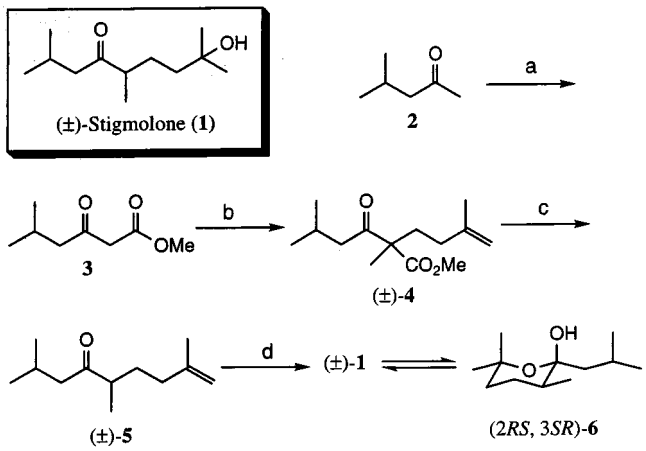
The racemic myxobacterial pheromone (±)-**1** (stigmolone), which induces the formation of the fruiting body of *Stigmatella aurantiaca*, was synthesized from methyl isobutyl ketone (**2**) in 48% overall yield in four steps

*Stigmatella aurantiaca*, a species of myxobacteria, produces a pheromone which induces the formation of its fruiting body. In 1997 Hull et al. isolated and identified the pheromone as 8-hydroxy-2,5,8-trimethyl-4-nonanone (**1**) with unknown absolute configuration at C-5.[1] Our synthesis of both (*R*)- and (*S*)-**1**[2] enabled Morikawa et al. to determine that both enantiomers of **1** are bioactive.[3] More interestingly, they proved the stereochemical heterogeneity of the naturally occurring **1**. Indeed, the natural pheromone is a mixture of (*R*)- and (*S*)-**1**.[3] This means that (±)-**1** is satisfactory for further biological studies of the pheromone. We report in the present paper a simple and efficient synthesis of (±)-**1**. After the completion of this work, Plaga and his co-workers published two papers on the isolation and synthesis of **1**, giving the name "stigmolone" to it.[4][5]

Scheme 1 summarizes our synthetic route to (±)-stigmolone (**1**). Methoxycarbonylation of methyl isobutyl ketone (**2**) furnished the β-oxo ester **3**. By employing potassium *tert*-butoxide in *t*ert-butyl alcohol as the base, **3** was first methylated and further alkylated with 3-methyl-3-butenyl iodide[6] to give (±)-**4** in satisfactory yield. When sodium methoxide or sodium hydride was used as the base, (±)-**4** could not be obtained in good yield. Krapcho demethoxycarbonylation[7] of (±)-**4** with lithium chloride in wet dimethyl sulfoxide (DMSO) afforded the olefinic ketone (±)-**5**. Conventional hydrolytic decarboxylation of (±)-**4** was unsuccessful. Finally, oxymercuration-demercuration[8] of (±)-**5** yielded a mixture of the target molecule (±)-**1** and its hemiacetal (2*RS*,3*SR*)-**6**.[2] The IR, $^1$H- and $^{13}$C-NMR spectral properties of (±)-**1** are in good accord with those of (*R*)- and (*S*)-**1**.[2]

In conclusion, a four-step synthesis of (±)-stigmolone (**1**) was achieved in 48% overall yield based on methyl isobutyl ketone (**2**). The synthesis by Hull et al. was reported to give (±)-**1** in 16% overall yield based on isovaleraldehyde.[5] Our sample of (±)-**1** was supplied to Dr. S. Yamanaka, whose work may reveal more about the biological function of **1**.




Scheme 1. Synthesis of (±)-**1**; reagents: (a) NaH, $CO(OMe)_2$, dry dioxane (95%); (b) (i) *t*BuOK, MeI, *t*BuOH, (ii) *t*BuOK, 3-methyl-3-butenyl iodide, *t*BuOH (83%); (c) LiCl, DMSO, $H_2O$, 170°C (89%); (d) (i) $Hg(OAc)_2$, THF, $H_2O$, (ii) $NaBH_4$, NaOH, $H_2O$ (68%)

## Experimental Section

Boiling points: Uncorrected values. − IR: Jasco A-102. − $^1$H NMR: Jeol JNM-EX 90A (90 MHz) and Bruker DPX 300 (300 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). − $^{13}$C NMR: Bruker DPX 300 (75.5 MHz) ($CDCl_3$ at δ = 77.0 as an internal standard). − MS: Jeol JMS-SX 102A and Hitachi M-80B. − CC: Merck Kieselgel 60 Art 1.07734. − TLC: 0.25 mm Merck silica gel plates (60F-254).

**Methyl 5-Methyl-3-oxohexanoate (3):** To a stirred and heated (under reflux) suspension of NaH (60% in mineral oil, 9.78 g, 245 mmol) in $CO(OMe)_2$ (25.2 mL, 293 mmol) and dry dioxane (60 mL), a solution of **2** (10.5g, 105 mmol) in dry dioxane (15 mL) was slowly added dropwise under argon. The mixture was stirred and heated under reflux for 2 h and cooled. It was then quenched with ice/water, neutralized with 1 M hydrochloric acid and extracted with diethyl ether. The organic layer was washed with water, a satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was distilled to give 15.8 g (95%) of **3** as an oil; b.p. 81°C/10 Torr, $n_D^{25}$ = 1.4146. − IR (film): $\tilde{\nu}$ = 1750 $cm^{-1}$ (s, C=O), 1720 (s, C=O), 1650 (m), 1630 (m). − $^1$H NMR (90 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.5 Hz, 6 H, 5-Me, 6-$H_3$), 1,65−2.44 (m, 3 H, 5-H, 4-$H_2$), 3.41 (s, 2 H, 2-$H_2$), 3.71 (s, 3 H, OMe), 4.95 (s, 0.1 H, 2-H of the enol form), 11,98

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(s, 0.1 H, 3-OH of the enol form). − $C_8H_{14}O_3$ (158.2): calcd. C 60.74, H 8.92; found C 60.57, H 8.68.

**(±)-Methyl 2,5-Dimethyl-2-(3-methyl-3-butenyl)-3-oxohexanoate [(±)-4]:** To a solution of potassium *tert*-butoxide (3.55 g, 31.6 mmol) in dry *tert*-butyl alcohol (18 mL), **3** (5.00 g, 31.6 mmol) was added dropwise at 50°C under argon. Methyl iodide (2.00 mL, 31.6 mmol) was added dropwise to the mixture, and the mixture was stirred and heated under reflux for 1 h. A solution of potassium *tert*-butoxide (3.55 g, 31.6 mmol) in dry *tert*-butyl alcohol (18 mL) was added dropwise to the mixture, and the mixture was heated under reflux for 30 min. Then 3-methyl-3-butenyl iodide (9.30 g, 4.74 mmol) was added dropwise, and the mixture was stirred under reflux for 1 h. It was then poured into ice/satd. ammonium chloride solution and extracted with diethyl ether. The ethereal extract was washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (150 g, hexane/ethyl acetate, 50:1) to give 6.34 g (83%) of (±)-**4** as a colorless oil; $n_D^{25}$ = 1.4434. − IR (film): $\tilde{\nu}$ = 3080 $cm^{-1}$ (m, C=C-H), 1740 (s, C=O), 1710 (s, C=O), 1650 (m, C=C), 890 (m, $=CH_2$). − $^1H$ NMR (90 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.2 Hz, 6 H, 6-$H_3$, 5-Me), 1.20−2.21 (m, 5 H, 5-H 1′-$H_2$, 2′-$H_2$), 1.34 (s, 3 H, 2-Me), 1.73 (br. s, 3 H, 3′-Me), 2.21−2.40 (m, 2 H, 4-$H_2$), 3.72 (s, 3 H, OMe), 4.71 (br. s, 2 H, 4′-$H_2$). − This compound was employed in the next step without further purification.

**(±)-2,5,8-Trimethyl-8-nonen-4-one [(±)-5]:** To a solution of (±)-**4** (2.50 g, 10.4 mmol) in dimethyl sulfoxide (15 mL) and $H_2O$ (0.2 mL) was added lithium chloride (880 mg, 20.8 mmol). The mixture was stirred at 170°C for 1.5 h. It was then poured into water and extracted with diethyl ether. The ethereal extract was washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane/ethyl acetate, 20:1) and then distilled to give 1.70 g (89%) of (±)-**5** as a colorless oil; b.p. 84−84.5°C/12.5 Torr, $n_D^{25}$ = 1.4189. − IR (film): $\tilde{\nu}$ = 3080 $cm^{-1}$ (m, C=C−H), 1710 (s, C=O), 1650 (m, C=C), 890(m, $=CH_2$). − $^1H$ NMR (90 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.4 Hz, 6 H, 1-$H_3$, 2-Me), 1.06 (d, *J* = 6.9 Hz, 3 H, 5-Me), 1.19−2.68 (m, 8 H, 2-H, 3-$H_2$, 5-H, 6-$H_2$, 7-$H_2$), 1.71 (br. s, 3 H, 8-Me), 4.68 (br. s, 2 H, 9-$H_2$). −This ketone was too volatile to give correct combustion analytical data. − HMRS ($C_{12}H_{22}O$): calcd. 182.1670; found 182.1669.

**(±)-Stigmolone [8-Hydroxy-2,5,8-trimethyl-4-nonanone, (±)-1]:** To a stirred solution of (±)-**5** (1.45 g, 7.96 mmol) in THF (8 mL) and $H_2O$ (8 mL) was added mercury(II) acetate (2.56 g, 7.96 mmol). After addition, the mixture was stirred at room temp. for 6 min. Then sodium hydroxide (3 M, ca. 4 mL) was added to the mixture, and sodium tetrahydroborate (334 mg, 7.96 mmol) in 3 M sodium hydroxide (5 mL) was added slowly. It was then added sodium chloride and the mixture was extracted with diethyl ether. The ethereal extract was washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20 g, hexane/ethyl acetate, 20:1−10:1) to give 689 mg (48%) of (±)-**5** and 565 mg [35%, 68% based on the consumed (±)-**5**] of (±)-**1** as a colorless oil, b.p. 113−115°C/0.4 Torr; $n_D^{23}$ = 1.4485. − IR(film): $\tilde{\nu}$ = 3450 $cm^{-1}$ (s, O−H), 2960 (s, C−H), 2870 (s, C−H), 1710 (s, C=O), 1455 (m, C−H), 1365 (m), 1215 (w), 1170 (m, C−O), 1035 (m), 950 (m), 920 (m), 905 (m). − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.905 (d, *J* = 6.6 Hz, 3 H, 1-$H_3$), 0.909 (d, *J* = 6.6 Hz, 3 H, 2-Me), 1.08 (d, *J* = 7.0 Hz, 3 H, 5-Me), 1.21 (s, 6 H, 8-Me, 9-$H_3$), 1.35−1.47 (m, 3 H, 7-$H_2$, OH), 1.59−1.78 (m, 2 H, 6-$H_2$), 2.09−2.20 (m, 1 H, 2-H), 2.28−2.33 (m, 2 H, 3-$H_2$), 2.43−2.49 (m, 1 H, 5-H). − $^{13}C$ NMR (75.5 MHz, $CDCl_3$): δ = 16.4, 22.5, 22.6, 24.1, 27.2, 29.1, 41.1, 46.7, 50.2, 70.6, 214.4 [signals due to (±)-**1**]; small signals due to (2*RS*,3*SR*)-**6** were also observable; these spectral data are in good accord with those reported for (*R*)- and (*S*)-**1**. − $C_{12}H_{24}O_2$ (200.32): calcd. C 71.95, H 12.08; found C 71.57, H 11.88. − HMRS ($C_{12}H_{24}O_2$ − $H_2O$): calcd. 182.1671; found 182.1670.

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