

Pheromone synthesis: Part CVII[†] – Synthesis of 2,6-dimethyloctyl formate, a potent mimic of the aggregation pheromone of the flour beetles

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Abstract. A mixture of the four stereoisomers of 2,6-dimethyloctyl formate was synthesized, and found to be a potent mimic of (4*R*,8*R*)-4,8-dimethyldecanal, the aggregation pheromone of the flour beetles, *Tribolium castaneum* and *Tribolium confusum*.

Keywords. Pheromones; pheromone mimics; flour beetles.

1. Introduction

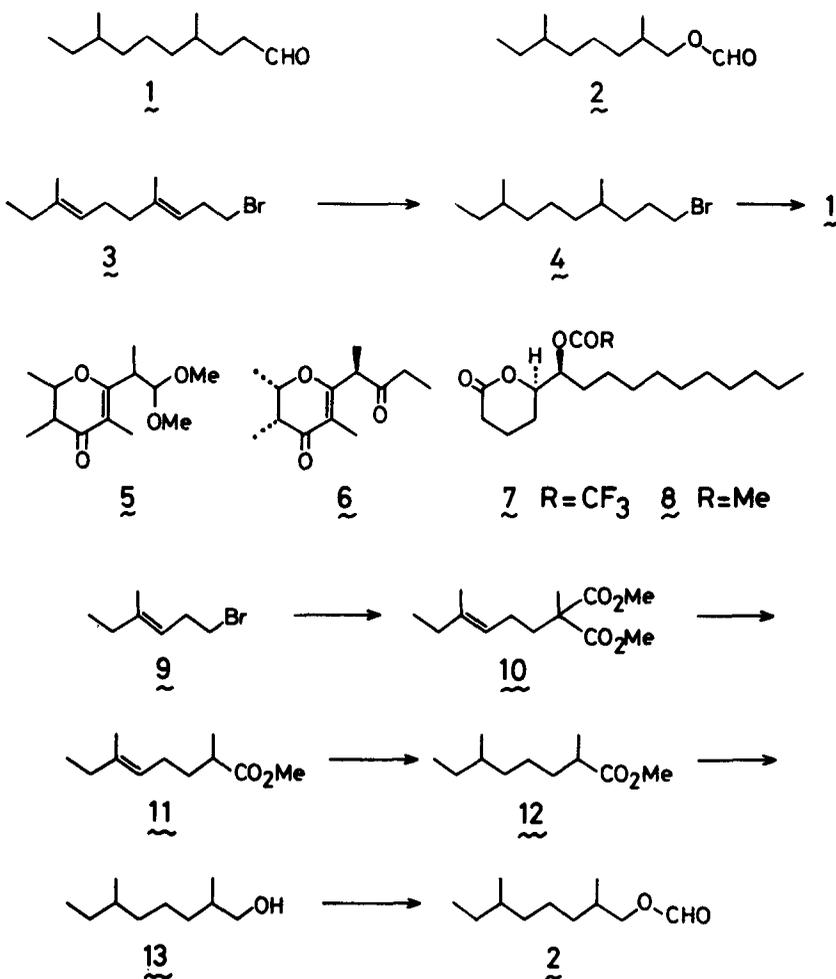
Flour beetles are world-wide pests that infest cereals and cause considerable damage. In 1980 Suzuki isolated and identified 4,8-dimethyldecanal (**1**) as the aggregation pheromone of the flour beetles, *Tribolium castaneum* and *Tribolium confusum* (Suzuki 1980, 1981a). A synthetic diastereomeric mixture of **1** was found to attract the insects, although it was about ten times less active than the natural pheromone (Suzuki 1981b). We synthesized all the four possible stereoisomers of **1** (Mori *et al* 1983, 1985), and (4*R*,8*R*)-**1** was found to be as active as the natural pheromone (Suzuki *et al* 1984). Due to both the chemical interest and the economic importance of the pheromone, several works appeared such as the selective synthesis of (4*R**,8*R**)-**1** (Schreiber and Hulin 1986), a synthesis of (4*RS*,8*S*)-**1** (Bandad and Kulkarni 1986), a synthesis of (4*RS*,8*RS*)-**1** (Breuer *et al* 1982), and the syntheses of some aliphatic aldehydes as the analogues of **1** (Suzuki *et al* 1983, 1984).

Although a diastereomeric mixture of **1** is known to be less active than (4*R*,8*R*)-**1**, its preparation is far simpler than the synthesis of pure (4*R*,8*R*)-**1**. The simplest synthesis of such a mixture of **1** was the conversion of the bromide **3** to **1** in four steps (Breuer *et al* 1982). Because **3** was readily available from cyclopropyl methyl ketone by the Julia synthesis (Julia *et al* 1960), further simplification of the Breuer synthesis was attempted to prepare **1** from **3** in two steps. Hydrogenation of **3** over platinum oxide in acetic acid gave the saturated bromide **4** in 85% yield.

[†] For Part CVI, see Mori K and Puapoomchareon P 1988 *Liebigs Ann. Chem.* 175
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Oxidation of **4** with dimethyl sulfoxide in the presence of sodium hydrogen carbonate (Kornblum *et al* 1959) directly furnished (4*RS*,8*RS*)-**1** in 26% yield after chromatographic purification and distillation. The product **1**, however, was unstable because of its autoxidation in air. More stable analogues or mimics of **1** must therefore be better suited to be used in pheromone traps.

Research on pheromone analogues and mimics is still in the infant stage. The following recent results, however, are worthy of note. In the case of the drugstore beetle (*Stegobium paniceum*), the pheromone mimic **5** was found to be as active as stegobinone **6**, the genuine pheromone (Kodama *et al* 1986). An analogue **7** of the oviposition attractant pheromone **8** of *Culex* sp. mosquitoes was highly active and more volatile than the natural pheromone (**8**) itself (Pickett *et al* 1986). Bearing these successful cases in mind, we undertook the synthesis of a stable formate analogue **2** instead of the unstable 4,8-dimethyldecanal (**1**). Replacement of the formylmethylene ($-\text{CH}_2\text{CHO}$) group with the formyloxy ($-\text{OCHO}$) group in the case of a lepidopteran pheromone was recorded previously. Thus (*Z*)-9-tetradecenyl formate was thirty times stronger (Preisner *et al* 1975) in eliciting EAG



response than (*Z*)-11-hexadecenal, a constituent of the corn earworm pheromone and tobacco budworm pheromone (Roelofs *et al* 1974; Tumlinson *et al* 1975). The formate, however, did not attract corn earworm males, and actually inhibited the communication between male and female corn earworms and male and female tobacco budworms (Mitchell *et al* 1975).

In order to know whether it would work as a pheromone mimic or as a pheromone inhibitor, we started the synthesis of 2,6-dimethyloctyl formate (**2**) as a mixture of the four stereoisomers. Alkylation of dimethyl methylmalonate with **9** furnished **10**, which was heated with sodium chloride in wet dimethyl sulfoxide (Krapcho and Lovery 1973) to give an unsaturated ester **11**. Hydrogenation of **11** over palladium-charcoal yielded a saturated ester **12**. This was reduced with lithium aluminum hydride to give 2,6-dimethyl-1-octanol (**13**). Esterification of **13** with formic acid afforded the desired formate **2** in 52% overall yield. The pheromone activity of **2** was tested on *Tribolium confusum* by the disc method (Suzuki and Sugawara 1979). At a dose of 1 ng/disc, the formate **2** was inactive, while (*4R,8R*)-**1** was active. When the dose was increased to 10 ng/disc, **2** was found to be active. One hundred ng/disc was the highly effective attractive dose of the formate **2**. At this dose, **2** was as active as the genuine pheromone (*4R,8R*)-**1**.

In summary, we synthesized a new mimic of the flour beetle pheromone. Because the formate **2** is more stable than the aldehyde **1**, **2** can be a useful practical attractant to monitor the population of the flour beetles. It must also be emphasized that the preparation of **2** is quite easy, giving **2** in good overall yield.

2. Experimental

All boiling points were uncorrected. IR spectra were measured as films on a Jasco A-102 spectrometer. ¹H NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer.

1-Bromo-4,8-dimethyldecane (**4**): Platinum oxide (8 mg) in acetic acid (2 ml) was shaken under hydrogen for 30 min. To this was added a solution of **3** (502 mg) in acetic acid (2 ml), and the mixture was shaken under hydrogen for 6 h. It was then filtered and the filtrate was poured into aqueous sodium carbonate. The resulting mixture was extracted three times with *n*-hexane. The extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was distilled to give 432 mg (85%) of **4**, b.p. 83°C/1.6 Torr, n_D^{24} 1.4500; IR ν_{\max} cm⁻¹ 1462 (*s*), 1380 (*m*), 1258 (*w*), 1210 (*w*); NMR δ (CCl₄) 0.6–1.0 (9H, *m*), 1.0–1.5 (12H, *m*), 1.5–2.1 (2H, *m*), 3.30 (2H, *t*, *J* = 6.3 Hz). Analysis, found: C, 57.94; H, 9.99. Calculated for C₁₂H₂₅Br: C, 57.83; H, 10.11%.

4,8-Dimethyldecanal (**1**): To a mixture of dry dimethyl sulfoxide (42 ml) and sodium hydrogen carbonate (10 g) was added **4** (4.2 g) at 150°C under argon, and the mixture was stirred for 10 min at 150–160°C. After cooling, the mixture was poured into water, and extracted three times with ether. The ether solution was washed with water and brine, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel (30 g). Elution with *n*-hexane-ether (20:1–0:1) gave **1**, which was distilled to give 803 mg (26%) of pure

1, b.p. 83–85°C/8 Torr, n_D^{22} 1.4304; IR ν_{\max} cm^{-1} 2710 (*m*), 1730 (*s*); NMR δ (CCl_4) 0.6–1.1 (9H, *m*), 1.2–2.1 (12H, *m*), 2.30 (2H, *t*, $J = 6\text{ Hz}$), 9.85 (1H, *t*, $J = 1.8\text{ Hz}$); GLC column, 5% PEG 20 M, 2 m \times 4 mm at 150°C; carrier gas, nitrogen, 1.0 kg/cm^2 ; R_t 5.3 min (single peak); MS (70 eV; m/z) 184 (M^+), 140 ($\text{M}^+ - 44$). Analysis, found: MS (m/z) 184.1842. Calculated for $\text{C}_{12}\text{H}_{24}\text{O}$ 184.1828.

Dimethyl methyl-(4-methyl-3-hexenyl)malonate (10). Sodium hydride in mineral oil (60%, 3.5 g) was washed three times with *n*-pentane (each 5 ml). To this was added dropwise, under ice-cooling and stirring, a solution of dimethyl methylmalonate (13 g) in dry tetrahydrofuran (30 ml) at 0–10°C. The resulting almost clear solution was stirred for 10 min at room temperature. Then a solution of **9** (13 g) in dry tetrahydrofuran (13 ml) was added dropwise to the stirred solution at room temperature. After the addition, the mixture was stirred and heated under reflux for 8 h. The stirring was continued overnight at room temperature. The mixture was subsequently poured into saturated aqueous ammonium chloride and extracted with ether. The ether solution was washed with water and brine, dried with magnesium sulfate, and concentrated *in vacuo* to give 19.7 g of crude **10**, IR ν_{\max} cm^{-1} 1735 (*s*), 1260 (*s*), 1235 (*s*), 1160 (*s*), 1110 (*s*), 870 (*m*). This was employed in the next step without further purification.

Methyl 2,6-dimethyl-5-octenoate (11). Sodium chloride (5.9 g) and water (3.2 ml) were added to a solution of **10** (19.7 g) in dimethyl sulfoxide (55 ml). The mixture was stirred and heated under reflux for 20 h. After cooling, the mixture was poured into water and extracted with ether. The ether solution was washed with water and brine, dried with magnesium sulfate, and concentrated *in vacuo* to give 13.7 g of crude **11**. This was chromatographed over silica gel (150 g). Elution with *n*-hexane-ethyl acetate (100:1–70:1) gave **11**, which was distilled to give 9.7 g (72% from **9**) of pure **11**, b.p. 110–111°C/25 Torr, n_D^{24} 1.4351; IR ν_{\max} cm^{-1} 1740 (*vs*), 1200 (*s*), 1160 (*s*), 845 (*m*); NMR δ (CCl_4) 0.96 (3H, *t*, $J = 7\text{ Hz}$), 1.11 (3H, *d*, $J = 7\text{ Hz}$), 1.56 (3H, *s*), 1.2–2.6 (7H, *m*), 3.60 (3H, *s*), 5.03 (1H, *t*, $J = 7\text{ Hz}$). Analysis, found: C, 71.09; H, 10.74. Calculated for $\text{C}_{11}\text{H}_{20}\text{O}_2$: C, 71.69; H, 10.94%.

Methyl 2,6-dimethyloctanoate (12). Palladium-charcoal (10%, 0.7 g) was added to a solution of **11** (5.0 g) in methanol (50 ml), and the mixture was shaken under hydrogen at atmospheric pressure and room temperature. At the end of the hydrogen uptake, the catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was distilled to give 4.7 g (93%) of **12**, b.p. 114–116°C/35 Torr, n_D^{24} 1.4176; IR ν_{\max} cm^{-1} 1740 (*s*), 1200 (*m*), 1170 (*s*); NMR δ (CCl_4) 0.7–1.0 (6H, *m*), 1.09 (3H, *d*, $J = 7\text{ Hz}$), 1.1–1.9 (9H, *m*), 2.1–2.6 (1H, *m*), 3.59 (3H, *s*). Analysis, found: C, 71.17; H, 11.64. Calculated for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C, 70.92; H, 11.90%.

2,6-Dimethyl-1-octanol (13). A solution of **12** (4.0 g) in dry ether (10 ml) was added dropwise to a stirred and ice-cooled suspension of lithium aluminum hydride (0.85 g) in dry ether (45 ml). After stirring for 1 h, the excess hydride was destroyed by the successive addition of water (0.85 ml), 15% aqueous sodium hydroxide (0.85 ml) and water (2.55 ml). After stirring for 30 min, the mixture was filtered, and the filter-cake was washed with ether. The combined ether solution

was concentrated *in vacuo*. The residue was distilled to give 3.2 g (95%) of **13**, b.p. 117–119°C/26 Torr, n_D^{24} 1.4321; IR ν_{\max} cm^{-1} 3350 (s), 1040 (s); NMR δ (CCl_4) 0.7–1.0 (9H, m), 1.0–1.9 (10H, m), 3.11 (1H, s, OH), 3.26 (2H, d, $J = 6$ Hz). Analysis, found: C, 76.29; H, 13.81. Calculated for $\text{C}_{10}\text{H}_{22}\text{O}$: C, 75.88; H, 14.01%.

2,6-Dimethyloctyl formate (2). A solution of **13** (0.856 g) in formic acid (> 98% purity, 10 ml) was stirred and heated at 65–70°C for 30 min. The mixture was then carefully added portionwise to ice and aqueous sodium hydrogen carbonate, and extracted with ether. The ether solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried with magnesium sulfate, and concentrated *in vacuo* to give 1.0 g of crude **2**. This was chromatographed over silica gel (20 g). Elution with *n*-hexane-ether (100:1 – 50:1) gave **2**. This was distilled to give 0.817 g (81%) of pure **2**, b.p. 109–111°C/23 Torr, n_D^{24} 1.4215; IR ν_{\max} cm^{-1} 1730 (s), 1180 (s); NMR δ (CCl_4) 0.89 (3H, t, $J = 6$ Hz), 0.94 (3H \times 2, d, $J = 6$ Hz), 1.0–2.1 (10H, m), 3.92 (2H, d, $J = 6$ Hz), 7.99 (1H, s). Analysis, found: C, 70.80; H, 11.89. Calculated for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C, 70.92; H, 11.90%.

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