Efficient Synthesis of (±)-4-Methyloctanoic Acid, Aggregation Pheromone of Rhinoceros Beetles of the Genus Oryctes (Coleoptera: Dynastidae, Scarabaeidae)

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(±)-4-Methyloctanoic acid and its ethyl ester are aggregation pheromones of many rhinoceros beetles of the genus Oryctes and are investigated for the control of these pests by olfactory trapping. A simple, economical, and high-yield (>50%) synthesis of (±)-4-methyloctanoic acid and its ethyl ester is presented starting from n-hexanal. The key step in this sequence is an orthoester Claisen rearrangement for the elongation of the carbon chain by two.

KEYWORDS: Pheromone synthesis; rhinoceros beetles; Oryctes elegans; Oryctes rhinoceros; Oryctes monoceros; 4-methyloctanoic acid; ethyl-4-methyloctanoate; Claisen rearrangement

INTRODUCTION

Rhinoceros beetles of the genus Oryctes are the main pests of coconut and date palm plantations in Southeast Asia, North Africa, and some Pacific islands (1–3). Adult beetles burrow galleries in the fresh and growing point of palms for feeding. The damage is particularly severe when apical buds in young trees or the fruit stalks in producing trees are attacked. Despite the use of high doses of insecticides (e.g., carbofuran and cypermethrin) against most rhinoceros beetles (4), efficient and acceptable methods of controlling these insects are still lacking, because adults spend more of their life hidden in galleries and rapidly colonize new feeding and breeding sites, flying easily away from the initial colony. The idea to manipulate adult populations by luring beetles into traps with specific attractants was investigated in the 1970s (5). The attractant chosen at that time, ethyl chrysanthemate, was rapidly abandoned because of insufficient catches. More recently, it was reported (1–3) that the main male pheromone emitted from most of the Oryctes species is a blend of 4-methylheptanoic acid (1) and its ethyl ester (2) (Figure 1) and that these species appear to use 1 and 2 differently and modulate the released amounts under certain circumstances. Furthermore, it has been demonstrated that the ethyl 4-methylheptanoate (2) is the aggregation pheromone of the tropical Oryctes rhinoceros (1, 2) and of Oryctes monoceros (6–8), whereas 4-methylpropionic acid (1) is the aggregation pheromone of Oryctes elegans (3). Both substances have been studied (1–3) in adequate traps and proved to be powerful attractants in operational programs to control the major pest in oil palm plantations.

Besides its activity as a pheromone, 4-methylheptanoic acid is also cited in the literature for its contribution to the aroma of various foods (9–11). However, no information about the absolute configuration of this naturally occurring substance is available.

Field experiments revealed that synthetic pheromones 1 and 2 in their racemic forms are very efficient attractants, indicating that chirality is not a critical point in the pheromone activity of Oryctes species (1, 3, 9–11).

A prerequisite for the application of aggregation pheromones in large trapping areas is the availability of cheap 4-methylheptanoic acid (1) of high purity in sufficient quantities. To date, different approaches have been reported for the synthesis of racemic 4-methyloctanoic acid and its esters. Among the most general ones are (a) reaction of 4-ketopentanoic acid or its ethyl ester with the appropriate Grignard reagent for the elongation of the chain (12); (b) reductive desulfurization of thioesters of N-tert-butylmalonic acid (13); (c) methylation of N-tert-butylmalonic acid (13); (d) conjugate addition of organocuprates to 3-ethylpentanoic acid (16) or Ni-catalyzed coupling of alkylidienes with ethyl acrylate (7); and, finally, (e) chain elongation of 2-methylhexanoic acid via malonic ester synthesis (15) or by reduction and elongation of the chain by the Wittig reaction (16). Concerning the optically active 4-methylheptanoic acid, one asymmetric synthesis has been reported (16), and two others used enantiopure 2-alkyl-branched acids (17) or natural citronellol (1) as starting material.

Figure 1. Aggregation pheromones of rhinoceros beetles.
Efficient Synthesis of 4-Methyloctanoic Acid

MATERIALS AND METHODS

All reagents and solvents were purchased from Sigma-Aldrich and were used as supplied. Thin-layer chromatography (TLC) was performed on 0.25 mm precoated silica gel 60 F 254 aluminum sheets and column chromatography on silica gel 60 (0.063–0.2 mm) as well as silica gel 60 (0.063 mm), products of Merck & Co. (Darmstadt, Germany). IR spectra were obtained in CCl₄ solutions (5%) on a PerkinElmer 247 spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on a Varian Mercury 200 MHz spectrometer, with anhydrous Na₂SO₄, and concentrated under reduced pressure. The reaction mixture was cooled to room temperature, poured into ice water (150 mL) containing NaHCO₃ (1.0 g), and extracted with diethyl ether (3 × 50 mL). The organic phase was washed with water, dried with Na₂SO₄, and concentrated under reduced pressure.

The crude product was purified by column chromatography on silica gel (81: petroleum ether/diethyl ether) to give 6 (7.94 g, 76%; purity by GC = 98%) as a colorless oil: IR, cm⁻¹ 1736, 1645; ¹H NMR δ 0.80–0.91 (m, 3H, J = 7.2 Hz), 1.05–1.48 (m, 4H), 1.96–2.06 (m, 2H), 2.30–2.47 (m, 4H), 4.10 (q, 2H, J = 7.2 Hz), 4.67 (s, 1H), 4.71 (s, 1H); ¹³C NMR δ 13.90, 14.18, 22.36, 29.88, 30.81, 32.74, 35.92, 60.24, 109.0, 148.22, 173.31; EI-MS, m/z (%): 184 (M⁺, 3), 142 (21), 110 (19), 96 (70), 60 (100), 41 (98), 57 (59). Anal. Calc. for C₁₃H₂₉O₃: C, 71.69; H, 10.94. Found: C, 71.54; H, 10.85.

Ethyl 4-Methyleneoctanoate (2). A mixture of pure ethyl 4-methyleneoctanoate (6.50 g, 16.3 mmol) in ethanol (15 mL) and 10% Pd/C (10 mg) was stirred under H₂ at room temperature. The reaction was completed in 3 h, and the catalyst was filtered through Celite and washed with diethyl ether. The combined filtrates were concentrated under reduced pressure to give pure acid (2.78 g, 92%; purity by GC = 98%) as a colorless oil: IR, cm⁻¹ 1735; ¹H NMR δ 0.86–0.92 (m, 6H), 1.26 (t, 3H, J = 7.2 Hz), 1.16–1.75 (m, 9H), 2.25–2.34 (m, 2H), 4.12 (q, 2H, J = 7.2 Hz); ¹³C NMR δ 14.07, 14.20, 19.26, 22.9, 29.12, 31.88, 32.13, 32.34, 36.30, 60.13, 174.14; All spectroscopic data are in accordance with the literature data (1). 4-Methyloctanoic Acid (1). The ethyl ester 2 (2.65 g, 14.2 mmol) was saponified by refluxing with alcoholic potassium hydroxide (1.6 g of KOH, 12 mL of water and 35 mL of ethanol) for 2.5 h. The reaction mixture, after cooling, was added into water (60 mL) and was extracted with diethyl ether (2 × 25 mL) to remove any remaining ester 2 and neutral impurities as well. The aqueous phase was acidified to pH 2 with the addition of 10% HCl (3 mL) and was extracted with diethyl ether (3 × 20 mL). The organic phase was washed with water, dried with anhydrous Na₂SO₄, and concentrated under reduced pressure to give pure acid 1 (2.14 g, 95%; purity by GC = 99%) as a colorless oil: IR, cm⁻¹ 1710; ¹H NMR δ 0.84–0.90 (m, 6H), 1.10–1.52 (m, 8H), 1.56–1.80 (m, 1H), 2.29–2.38 (m, 2H), 11.45 (s, 1H); ¹³C NMR δ 14.07, 19.21, 22.91, 29.09, 31.59, 31.88, 32.27, 36.27, 180.58; EI-MS, m/z (%): 129 (M⁺–29, 3), 101 (27), 99 (32), 83 (17), 73 (60), 60 (30), 57 (100), 55 (55), 43 (77), 41 (50). The mass spectrum is in accordance with the literature data (3).

RESULTS AND DISCUSSION

Hexanal, a common cheap aldehyde, was the starting material of our synthesis. Mannich reaction (23) of hexanal (3) with formaldehyde and dimethylammonium chloride gave 2-methyloctanal (4) (88%). This was subsequently reduced by sodium borohydride in methanol, to give the allylic alcohol 5 in high yield (90%). The Claisen rearrangement (24) of the intermediate formed by the presence of propionic acid gave the ethyl 4-methyleneoctanoate (6) (76%). This new compound, identified by its spectroscopic data, is the key element of the present approach. Finally, hydrogenation of an ethanolic solution of 6 in the presence of 10% Pd/C gave ethyl 4-methyloctanoate (2) in high yield (92%). Saponification of the ethyl ester 2 gave 4-methyloctanoic acid (1) almost quantitatively and in high purity.
Although no efforts have been made to optimize the yields, the above reactions gave sufficient quantities of products that can be easily purified either by distillation or by a rapid column chromatography.

In conclusion, a facile procedure for the preparation of ethyl 4-methyloctanoate (2), the aggregation pheromone of O. rhinoceros and O. monoceros, and 4-methyloctanoic acid (1), a major component of the aggregation pheromone of O. elegans, is reported herein. Both substances can be easily prepared in four–five simple steps from hexanal in >50% yields. The starting material and other reagents used are common and inexpensive, and the reactions are suitable for a large-scale preparation.

LITERATURE CITED


